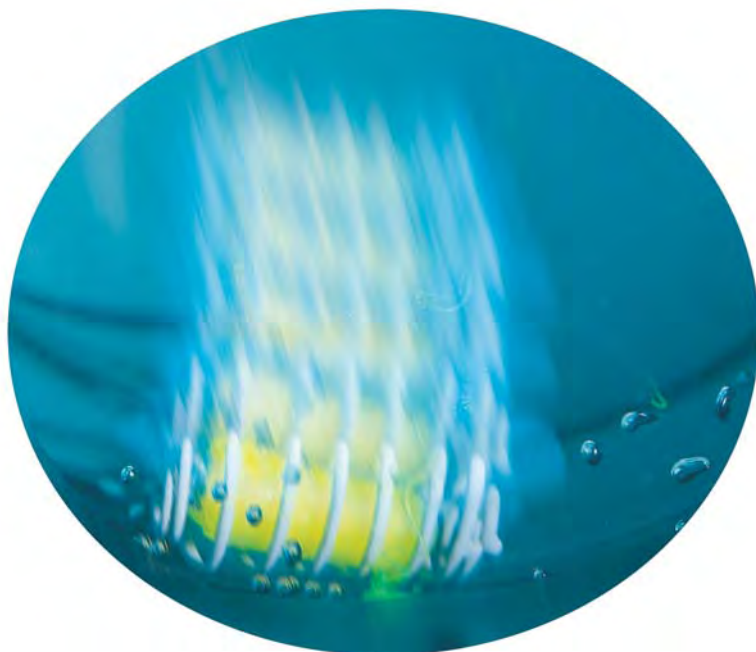


# SUSTAINED RELEASE FORMULATION WITH LIPID BASED EXCIPIENT

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BULLETIN TECHNIQUE GATTEFOSSÉ  
**2004**

# SUSTAINED RELEASE FORMULATION WITH LIPID BASED EXCIPIENT

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## FOREWORD/PREFACE

Jacques Moyrand/Duncan Q.M. Craig.....4-5

LIST OF PARTICIPANTS .....6-7

## PART I

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### LIPID MATRICES FOR SUSTAINED RELEASE - AN ACADEMIC OVERVIEW

Pr Duncan Q.M. CRAIG.....9

### SUSTAINED RELEASE FORMULATIONS WITH LIPID DERIVED EXCIPIENTS; BIG PHARMA PERSPECTIVES - WHY AND WHEN

Pr Elizabeth B. VADAS .....21

### SUSTAINED RELEASE LIQUID FILLED HARD GELATIN CAPSULES IN DRUG DISCOVERY AND DEVELOPMENT: A SMALL PHARMACEUTICAL COMPANY'S PERSPECTIVES

Dr Stephen K. DORDUNOO.....29

## PART II

---

### STRUCTURAL AND THERMAL CHARACTERISATION OF LIPIDIC EXCIPIENTS AND CARRIERS BY X-RAY DIFFRACTION COUPLED TO DIFFERENTIAL MICROCALORIMETRY

Pr Michel OLLIVON.....41

### POLYMER-COATED LIPID NANOSTRUCTURES AS CARRIERS FOR ORAL PEPTIDE DELIVERY

Dr Maria José ALONSO.....51

### CONTROLLED RELEASE OF ACRIVASTINE AND PSEUDOEPHEDRINE USING LIPID-BASED COMPRITOL® AND HYDROPHILIC METHOCEL®

Dr Xiaochen GU .....63

### GASTRIC RETENTION RESERVOIR SYSTEMS UTILIZING SOLID AND SEMISOLID CARRIERS.....

Dr Jose G. ROCCA.....73

### MELT EXTRUSION-BASED DOSAGE FORMS: EXCIPIENTS AND PROCESSING CONDITIONS FOR PHARMACEUTICAL FORMULATIONS

Dr Marcus E. BREWSTER.....85

### PHYSICAL CHARACTERIZATION AND SCALE-UP MANUFACTURE OF GELUCIRE® 50/13 BASED CAPSULE FORMULATIONS

Laurence F. ROBINSON.....97

### PELLETISATION WITH MELTABLE BINDERS

Dr Torben SCHÆFER.....113

## INFORMATION

### BIBLIOGRAPHY ON GATTEFOSSÉ'S PRODUCTS 2003-2004 REVIEW

Dr Vincent JANNIN.....125

## FOREWORD

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**"Contributing to the progress  
of pharmaceutical science  
through the exchange of skills"**

This daring and ambitious challenge succinctly sums up the *raison d'être* of the *Académie des Alpilles*:

- to provide a platform for academics, researchers and industrialists who wish to pool their knowledge, their results and their experience.
- to encourage the encounter of ideas in a climate of respect of individuals, beliefs and academic or professional backgrounds.
- to lay down lines of action along which to direct new work, and open up areas of reflection in some insufficiently tackled fields.

The 38th session of the Academy remained true to its founding principles.

Our company is proud to have been able, on this occasion, to welcome leading specialists at the Mas Bellile, all of them desirous of acquiring values that over the years have forged the international reputation of the *Académie des Alpilles*.

*Jacques MOYRAND*  
*Chairman of the board*  
*Gattefossé Holding*

## PREFACE

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The development of new delivery systems remains a topic of persistent interest to both industry and academia due to the combination of both the intellectual challenges involved and the clear commercial relevance. More specifically, lipid-based controlled release systems have attracted and will continue to attract attention for a number of reasons, these including (in general terms) their low toxicity, reasonable cost and favourable handling properties. However, as with all drug delivery approaches it is essential to take a holistic view of their use and development, incorporating the fundamental science underpinning the approach, the practical viability of the manufacturing process at both bench and production scale and the overall feasibility of producing a commercial product in an environment of strict regulation and tightly managed timelines. Given these multiple considerations, it is useful in the extreme to bring together academics and industrialists with a common interest in lipid-based drug delivery to discuss the opportunities and barriers to using this approach from a range of perspectives. This was the intention of the 38th Gattefossé Meeting at *St Rémy de Provence*, whereby academics with expertise bases in materials science, drug release and technology development came together with colleagues from industry who are fully conversant with the practicalities of bringing new delivery systems to the market as well as having specific tales to tell in terms of their own experiences in developing lipid-based systems. This Bulletin Technique represents the contributions from the invited speakers to the conference and can be loosely considered to consist of three main areas. Firstly, three overviews are given outlining perspectives from academic and industrial viewpoints. Secondly, some new advances in the development of lipid-based dosage forms are outlined and thirdly the current thinking in terms of processing is described. Clearly it is not possible to capture the many stimulating discussions that accompanied the presentations but these papers will provide a strong indication of not only the specific topics and ideas but also of the value of taking a multiple perspective approach when considering this important and topical issue. Hopefully, therefore, the sum of these papers will represent a total that is even greater than the individual parts and will allow the reader to gain new insights into the possibilities, perils and many opportunities for developing lipid-based dosage forms.

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## 38<sup>th</sup> Académie des Alpilles de Saint-Rémy de Provence

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GATTEFOSSÉ

# LIPID MATRICES FOR SUSTAINED RELEASE – AN ACADEMIC OVERVIEW

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## Summary

Lipid-based dosage forms have been extensively used within the pharmaceutical sciences for topical, oral, rectal and parenteral delivery for a number of years. More recently there has been interest in using lipids and lipid derivatives for oral controlled release purposes, including application for both sustained delivery and enhanced absorption purposes. In this article some of the general considerations pertinent to the use of lipids in dosage forms will be outlined, including the benefits and drawbacks of using these materials. The paper will then focus on two lipid-based excipients, Gelucire® 50/13 and Gelucire® 44/14, both of which are compositionally similar but differ greatly in terms of their performance. Four issues will be explored with regard to these excipients; the effect of drug addition on the structure and performance of Gelucire® 50/13, the storage stability of Gelucire® 50/13 dispersions, the incorporation of a liquid drug into Gelucire® 44/14 and the mechanism by which absorption enhancement may occur on dispersion of drugs in this material. The intention of the paper is to provide a discussion of the some of the less widely explored, but nevertheless important issues associated with the use of these excipients in practice.

## Keywords

*Gelucire® 50/13, Gelucire® 44/14, lipid, stability, microscopy, thermal analysis, controlled release.*

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## 1. Introduction – Lipids as Delivery Systems

Lipids and lipid-based materials have been extensively used within the pharmaceutical sciences for many years. Traditionally, these materials have been used as creams for topical delivery or emulsions for oral delivery, either as a vehicle for lipid soluble drugs or as a means of delivering drugs which are themselves oily in nature. Other applications have included the use of lipids as suppository bases, whereby the low melting points of commonly used materials allow effective release of the drug on application. However, in recent years there has been a proliferation of newer drug delivery applications, including what are now established approaches including liposomal drug delivery systems [1] and lipids for injection [2] through to sophisticated drug solubilisation systems [3], stearic acid microspheres for taste masking [4], self-emulsifying drug delivery systems [5] and solid lipid nanoparticles [6]. In addition there has been great interest in chemically conjugating lipids to drug molecules for specific cellular delivery or targeting purposes [7]. The interested reader is referred to two issues of *Advanced Drug Delivery Reviews*, one of them being very recent, for more details of these and other approaches currently under investigation [8,9]. A further area of interest, that will form the focus of this article, is the use of lipids of oral controlled delivery purposes. In particular, this discussion will outline a number of issues associated with two lipid-based excipients, Gelucire® 50/13 and Gelucire® 44/14, described in more detail below

Before going into detail with regard to these two materials, it is perhaps helpful to make some comments with regard to the use of lipids in a general sense, both in terms of their advantages and limitations. Advantages include the relatively low toxicity and cost of these materials along with their favourable regulatory status and familiarity to the manufacturing industry. These favourable aspects must, however, be considered in the context of the choice of lipid, as any derivatised lipid will be subject to extensive testing to establish regulatory status, besides

which the terms 'lipid' is commonly used to cover fatty acids, glycerides and related materials including phospholipids. The breadth of materials included in this term is therefore extremely wide and the above advantages, whilst true for the most commonly used materials such as stearic and palmitic acids and common oil-derived glycerides, cannot be taken as being universally applicable by any means. Other advantages, stated with the same rider as above, are the simplicity of many lipid-based delivery systems. Davis [10] has repeatedly and compellingly put forward the case for avoiding over-engineering of dosage forms; the possibility of simply dispersing the active within a lipid matrix with a minimum of processing and additional excipients is a very attractive one. Furthermore, the processing properties of lipids are reasonably well understood, with their low melting points lending them to a range of manufacturing techniques, some of which are covered by other articles within this publication. Finally, and from an academic point of view perhaps the most interesting facet of these materials, is that they may be used for a wide range of delivery outcomes including, intriguingly, both sustained release and enhanced absorption. Indeed, the structure-performance relationship for these materials is still, in our view, poorly understood, perhaps confounded by the familiarity of these materials which leads to the (incorrect) assumption that their behaviour *in vivo* or indeed *in vitro* is simple.

Allied to these advantages are a number of drawbacks associated with the use of lipids. There are problems associated with the chemical and physical stability of many lipids, with glycerides being prone to rancidity on storage via a complex free radical reaction. From a delivery viewpoint, there are also several reports of changes in dissolution profile on storage, an issue which is explored in more detail below. Whether these changes are relevant in an *in vivo* setting is a pertinent question and one which merits further exploration, although the fact that such changes may occur at all is sometimes sufficient to raise concerns with regard to the practical applicability of some lipid-based delivery systems. Other issues include the fact that simple dosage form manufacturing approaches such as

tableting and capsule filling are not easily applicable to many (but not all) lipid systems, rendering it necessary to consider alternative approaches that are by definition more costly and slower. Similarly, the natural sources of virtually all the less expensive lipids result in concerns being raised regarding interbatch variation. Two interrelated further concerns are the complex biological fate of lipids, with enzymatic degradation being an integral aspect of their digestion, although the role of such degradation in drug absorption is still poorly understood [8]. This has also led to a paucity of truly predictive *in vitro* tests for lipid dosage forms as it is not yet clear how the conditions of the gastrointestinal tract are best mimicked for these dosage forms.

Overall, lipid delivery systems do offer some extremely exciting possibilities for delivery but perhaps represent a field whereby integration of academic and industrial study is particularly important. In the light of this consideration, the remainder of this article will focus on a limited number of recent academic studies whereby we believe that 'academic' areas of interest transpose onto practical issues associated with using the materials in question in a practical setting. Please note that the article is not intended as being an extensive review but rather a tying together of three interrelated studies in order to highlight the importance of certain general issues, notably the importance of thorough physical characterisation of these dosage forms. On that basis the data and text are derived from the original papers [11-13] and the interested reader is referred to these publications for more details of the individual studies.

## **2. The effect of drug incorporation on the solid structure of Gelucire® 50/13**

As mentioned above, the remainder of the article will focus on a limited number of studies [11-13] that exemplify certain issues associated with the use of lipid-based dosage forms. In each case, the discussion will revolve around the use of Gelucire®, a family of lipid-based excipients comprising mono-, di- and triglycerides mixed with mono- and diesters of fatty acids and polyethylene glycol (PEG). These materials are

derived from natural lipids but are derivatised so as to confer a degree of hydrophilicity to what would otherwise be prohibitively hydrophobic excipients. The derivatisation methods include direct esterification or, more usually, alcoholysis whereby coconut, palm or palm kernel oil is hydrolysed and the fatty acids removed by fractional distillation. These fatty acids are then esterified with PEG (usually of the molecular weight range 300 to 1500) at 230°C under a nitrogen atmosphere. The two most widely studied materials are Gelucire® 50/13 and Gelucire® 44/14, the first number corresponding to the melting point of the material and the second to the hydrophile-lipophile balance (HLB) number that reflects the proportion of water soluble to lipid soluble moieties in each material. Gelucire® 50/13 contains a large proportion of PEG mono- and diesters with palmitic (C16) and stearic (C18) acid, while Gelucire® 44/14 is composed largely of esters of lauric acid (C12) [14]. Despite their compositional similarities, these two materials exhibit markedly differing *in vitro* properties, with Gelucire® 44/14 forming a microemulsion system on contact with water that appears to lead to enhanced absorption [15] while Gelucire® 50/13 swells in water and forms a barrier to drug release [16]; these differences will be discussed in subsequent sections of this article.

A number of studies have investigated the *in vitro* and *in vivo* release characteristics of drug dispersions in Gelucire® 50/13, both alone and in combination with other bases [17-19], and their effectiveness as controlled release matrices is now reasonably well established. A number of studies have also been performed on the physical properties of the bases, examining issues such as the effect of cooling rate on the thermal properties of lipids [20,21]. However, less work has been performed on the solid-state structure of the drug and lipid, particularly with in terms of the physical distribution of the drug within the matrix and the possible influence of the drug and lipid on their respective solidification processes. Here we describe the effect of incorporating two model drugs, paracetamol and caffeine, into Gelucire® 50/13 matrices on the solid-state structure of the dispersions and the

corresponding release profiles [11]. These two drugs were selected due to their similarities in terms of water solubility and molecular weight, hence one would reasonably expect corresponding similarities in their incorporation and release behaviour; the discussion below highlights the salient points but the interested reader is referred to the original article for further details.

Dispersions were prepared using a standard melt-cooling protocol to produce systems containing 10% paracetamol or caffeine and the dispersions examined in comparison with the unloaded matrices using differential scanning calorimetry, hot stage microscopy, dissolution rate studies and a series of studies where factors such as dimensional change, water uptake and dry weight loss were monitored as a function of exposure time in the dissolution medium. A point to highlight early on is the necessity to consider the heat-cool protocol employed; in this case we used a standardised maximum temperature of 75°C, a temperature that is above the melting point of the Gelucire® but below the melting points of the two drugs. There is little information available as to whether it is necessary or indeed desirable to dissolve the drug in the molten lipid, or indeed whether such as process results in the drug remaining in solution on cooling; this issue will be discussed in more detail below for the systems under discussion here but, in our opinion, merits further exploration.

Initial DSC studies indicated the familiar pattern for Gelucire® 50/13 comprising two main peaks at circa 36°C and 44°C, with two minor peaks seen at circa 49°C and 56°C (Figure 1a). The interested reader is referred to a paper by the group of Ollivon included in this Bulletin which provides some extremely interesting X ray diffraction data which may, for the first time, allow us to relate the peaks to specific chemical and physical entities. However for the purposes of the present discussion it is pertinent to note that the DSC traces for the caffeine dispersions were effectively indistinguishable from those of the Gelucire® 50/13, indicating no change to the structure on the scale of scrutiny interrogated by DSC, i.e. on the breaking of solid-solid bonds on a multiple molecular scale. The paracetamol

systems, however, showed a marked alteration in peak size distribution, with a greater preponderance of the lower melting peak. Over and above the mechanism responsible for this alteration, it is clear that the percentage in the liquid state at any given temperature within the melting range will be lower for the paracetamol systems. This may be illustrated by use of solid fat content diagrams, whereby the proportion melted is plotted as a function of temperature (Figure 1b). One may see from this diagram, that the proportion in the liquid state at 37°C (the temperature of the subsequent dissolution experiments) will be greater than for the caffeine systems. One may intuitively expect the dissolution rate to therefore be greater for the paracetamol systems; this (incorrect) assumption is discussed in more detail below.

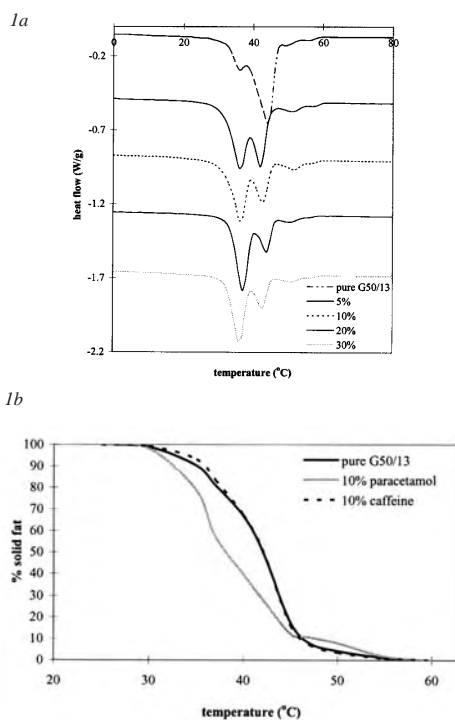


Figure 1: a) DSC response for Gelucire® 50/13 alone and dispersions containing up to 30% paracetamol b) Solid fat content for Gelucire® 50/13 alone and dispersions containing 10% caffeine and 10% paracetamol (reproduced from [11]).

Further insights into the solid state structure may be derived from hot stage microscopy studies. The Gelucire® 50/13 alone crystallised on cooling initially as large spherulites at circa 55-45°C

(designated Form 111). These spherulites were rapidly covered with smaller spherulites (Form 11) as the temperature was lowered and a few oil-streak like structures (Form 1) were observed at circa 40°C. It is suggested that the Form 11 and 111 correspond to the two main DSC peaks, although more work is required in order to assign these structures with more certainty, particularly given the difficulty in directly correlating HSM with DSC data given the differences in experimental conditions involved. Over and above such considerations, however, a series of interesting observations arose with regard to the effect of drug addition. In the first instance, the paracetamol particles appeared to nucleate the formation of the Form 11 (small spherulite) systems, with a lower predominance of the larger Form 1 crystals observed; this correlates well with the DSC data whereby the lower melting peak became dominant in the presence of the paracetamol. While the caffeine particles did not appear to significantly influence the Gelucire® 50/13 recrystallisation process, it was noted that the caffeine crystals seen suspended in the mix changed shape to form needle-like structures (Figure 2).

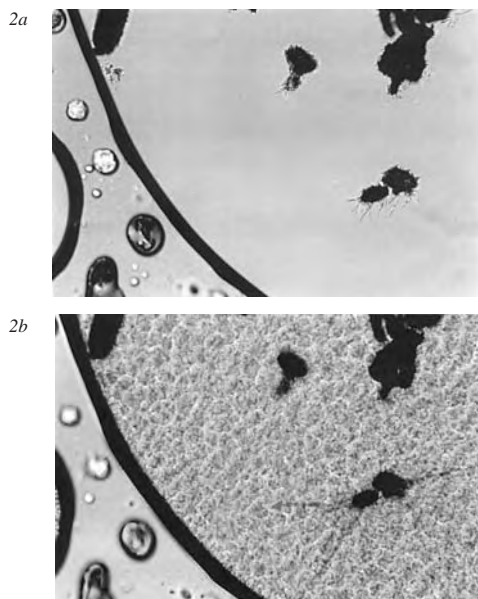


Figure 2: Hot stage differential interference contrast images of a) 5% caffeine in Gelucire® 50/13 at 50°C during cooling. Note needle shaped crystals starting to emerge from the caffeine particle b) 5% caffeine in Gelucire® 50/13 at 50°C during heating. Note extensive formation of needle-shaped crystals of caffeine. Horizontal length of images represents 1.4 mm. (reproduced from [11]).

Such structures are commonly associated with the enantiotropic Form 1 caffeine which is normally only found after heating to 140°C; this being the case the implication is that the manufacturing process has resulted in the generation of an unstable polymorph of the drug.

Perhaps surprisingly given the lower melting profile, the dissolution rate for the paracetamol was slower than for the caffeine systems (Figure 3). Kinetic analysis of the data using the standard models [22-24] indicated that the paracetamol systems showed a (slightly) greater preponderance towards diffusion than erosion than did the caffeine systems. Examination of the data obtained from direct measurement of erosion, water uptake and diameter change showed some trends with, for example, the water uptake being lower for both drug-loaded systems and the erosion being slightly higher for the caffeine. One intriguing observation, however, was the effect of paracetamol on the change in diameter with time. For Gelucire® 50/13 alone, a maximum is seen at circa three hours, after which the diameter decreases; the paracetamol systems showed only a steady increase, possibly reflecting the lower influence of the erosion mechanism for this material.

Overall the study has indicated that the presence of incorporated drugs may have a profound influence on the structure and behaviour of Gelucire® 50/13 matrices. In the first instance, the DSC and HSM studies indicated that although the caffeine does not appear to significantly influence the solidification of the lipid, the form of the caffeine itself may be altered by the incorporation process. The paracetamol, however, is clearly altering the structure of the Gelucire® base, increasing the proportion of the material in the lower melting form, with evidence from the microscopy studies that the drug particles acted as nucleation sites. The question therefore arises as to why paracetamol may act as a nucleating agent for the lower melting form with no such effect being seen for caffeine, despite similarities in solubility and molecular weight. We suggest that the difference may lie in the surface energies of the two drugs, with paracetamol having a higher

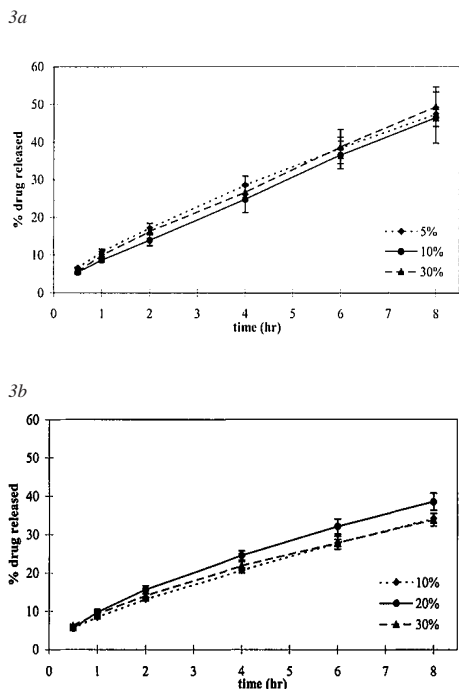


Figure 3: Dissolution profiles of a) caffeine and b) paracetamol in Gelucire® 50/13 at 37°C as a function of drug loading (reproduced from [11]).

contact angle with water than caffeine (59° and 43° respectively [25]), combined with the empirical observation that the molten Gelucire® appeared to spread readily over the caffeine but not the paracetamol particles. It is well known that the reactivity of the surfaces of heterogeneous nucleants may profoundly influence the nature of the associated crystalline species [26]; while merely a suggestion at present the role of surface energy and spreading may be an avenue worth exploring in more detail in the future.

The dissolution data indicated that the drug release from the caffeine systems was more rapid than for the paracetamol dispersions and that erosion was more predominant for the former. This is in many ways counter-intuitive, as one would reasonably expect a matrix with a greater molten content to show a greater release rate and a greater tendency to erode. Our suggestion is that the increased ‘molten’ content results in greater resistance of the surface to disintegration, either due to the greater flexibility

of the surface during swelling or the formation of a cohesive layer on sorption of water into the liquid fraction. Consequently, both the erosion process itself and the decrease in diameter caused by erosion may be expected to be less marked for these systems, as was indeed observed experimentally. However, the study does highlight two important points, namely that the effect of the drug on the matrix and *vice versa* should be considered when formulating products using Gelucire® 50/13, and secondly that there appears to be correlation between the release properties and the solid state structure but not one that is immediately obvious in nature. As will be seen in the next section, a more profound understanding of this relationship would be of great use in predicting and hence controlling the behaviour of drug dispersions in Gelucire® 50/13.

### 3. The performance stability of Gelucire® 50/13 dispersions

Despite the effectiveness of Gelucire® 50/13 as a controlled release excipient, there have been concerns regarding the performance stability of this material, particularly in the context of dissolution rate changes on storage. Whether these changes, when they occur, are of biological relevance or not is a relevant question. However, the perception of instability may lead to a reluctance to develop such dispersions commercially, hence it is of use to consider the current knowledge base in this regard. The effect of storage on the structure and properties of lipids has been extensively studied within the food science literature, with the majority of emphasis having been placed on changes in polymorphic form. Glyceride polymorphs are often denoted as  $\alpha$ ,  $\beta'$  and  $\beta$  in order of stability, with changes between these forms having been frequently observed, particularly at elevated temperatures (e.g. [27]). Consideration of the polymorphic transitions is often complicated by the multicomponent nature of naturally occurring lipids, with segregation of components within complex lipids also having been noted [28].

Several studies have indicated that the Gelucire® show ageing effects. Bodmeier et al [19] investigated the characteristics of propranolol and theophylline dispersions in Gelucire® 50/13, particularly in the context of exploring the possibility of the drug recrystallising from the base on storage. Sutananta et al [20,21] examined the effect of preparation conditions on the structure and storage stability of a range of Gelucire®, noting, for example, that materials containing triglyceride only (Gelucire® 43/01) assumed a stable conformation after 14 days on flash cooling from the melt, while the slow cooled form altered slowly to an equilibrium structure over a period of months. Remunan et al [29] examined formulations of nifedipine in Gelucire® 50/13 and noted that alterations in dissolution on storage were exacerbated by high temperatures and humidities, suggesting that the changes were due to the formation of nifedipine microcrystals. Similarly Dennis et al [17] studied ketoprofen in Gelucire® 50/13 and 50/02 and noted an increase in dissolution rate on storage which, interestingly, was not mirrored by changes in the *in vivo* absorption rate. There is, however, no common consensus regarding the mechanism underpinning these alterations in performance.

In this section of the article, a study into the stability of the caffeine and paracetamol dispersions in Gelucire® 50/13 described above is outlined [12]. In particular, an attempt has been made to correlate the solid state properties of the dispersions with associated changes in dissolution, the intention being to establishing a mechanistic basis for understanding the causes of such instability. The dissolution profiles of the dispersions were obtained on storage for up to 180 days at 25°C and 37°C, with increases in release rate seen for both drugs at both temperatures. The increases were more marked for the paracetamol systems and were also accelerated by storage at higher temperatures. More specifically, the time taken for 50% of the drug to dissolve ( $t_{50\%}$ ) for the caffeine dispersions decreased from 8.70 hours for the freshly prepared systems to 6.97 hours after 180 days. The values decreased from 13.32 hours to 7.45 hours for the paracetamol systems over the same time period, reflecting the more rapid initial rate

for the paracetamol and the greater proportional increase on storage. At 37°C the  $t_{50\%}$  values decreased from 8.70 to 5.02 hours for the caffeine (a 42% decrease) and 13.32 to 5.29 hours (a 60% decrease) for the paracetamol dispersions after 180 days storage (Figure 4). It is interesting to note that the equivalent kinetic analysis of the data to that used in the previous section indicated an increased preponderance of the erosion as opposed to the diffusion mechanism on storage. Overall, therefore the changes appear to be accelerated by the presence of paracetamol and elevated temperatures, with an alteration of mechanism to a more erosion-dominated release process being in evidence.

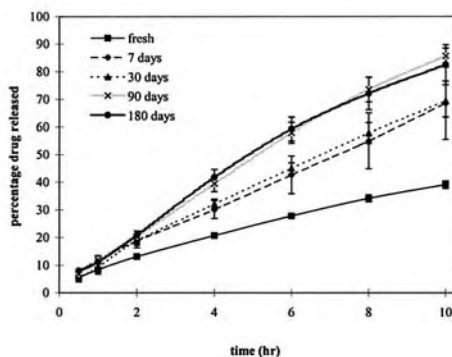


Figure 4: Dissolution profiles of 10% paracetamol dispersions in Gelucire® 50/13 on storage at 37°C (reproduced from [12]).

One may reasonably anticipate that such changes may be mirrored by changes in DSC profile. This was found to be the case to some extent but there was by no means a clear correlation. Interestingly, the systems stored at 20°C did not show significant alterations in thermal response, although for the systems stored at 37°C a general increase in melting profile was observed for all three systems, as indicated by the solid fat profile (Figure 5). In our view it is the negative result at 20°C that is the more interesting data set, as it indicates that DSC is not an effective predictor of dissolution rate change, despite the earlier indications that these profiles so in themselves alter with storage. Instead we found a much closer correlation with surface morphology changes, as measured by scanning electron microscopy (SEM). Here we saw evidence of the formation of small crystallites on the surface of the dispersions that grew into leaf-shaped

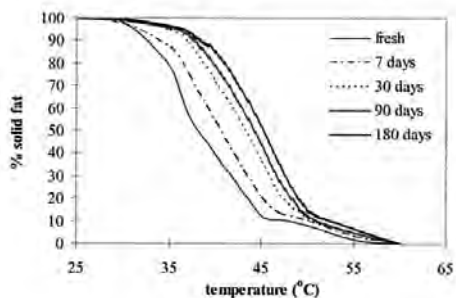
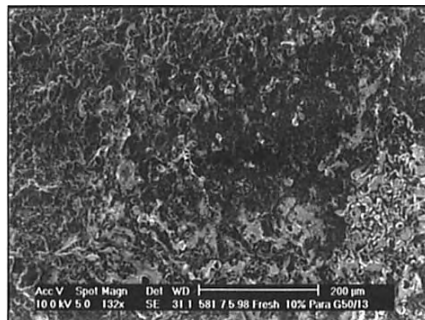


Figure 5: Thermal response of 10% paracetamol dispersions in Gelucire® 50/13 on storage at 37°C, shown as the solid fat content as a function of temperature (reproduced from [12]).

structures, with the effect being more rapid at elevated temperatures and for systems containing paracetamol (Figure 6). Such surface alterations are well recognized in the confectionary industry and may lead to visible imperfections on the surface of products such as chocolate. The development of large crystals on storage of fat systems is known as ‘blooming’ and is generally (but not universally) associated with crystal habit alterations associated with polymorphic changes [30]. For example, the blooming effect in chocolate is thought to be due to the transformation from the  $\beta_2$  to the more stable  $\beta_1$  form. However, blooming has also been associated with migration of lipids to the surface rather than polymorphic transformation as such [31], this effect being exacerbated by a low temperature solid fat content distribution, thus aiding diffusivity of lipid components. Indeed, soft lipid products are known to be more susceptible to bloom [32]. In the context of the current study, it is reasonable to suggest that the samples are undergoing a process analogous or identical to blooming, with the lower SFC paracetamol systems showing more rapid effects. We also suggest that this process may be associated with the observed changes in dissolution, (also noting that there appears to be a much better correlation between the dissolution data and the SEM than the DSC data). Our suggestion is that the physical integrity of the matrices is being compromised which may in turn lead to a greater erosion and a higher release rate. This being the case, the implication is that the stabilisation of the matrices lies in the prevention of blooming.

6a



6b

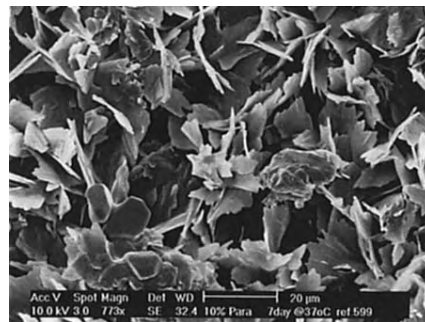


Figure 6: SEM images of 10% paracetamol dispersions in Gelucire® 50/13 a) freshly prepared b) on storage for 7 days at 37°C (reproduced from [12]).

#### 4. The incorporation of a liquid drug into Gelucire® 44/14

Gelucire® 44/14 is unusual amongst the Gelucire® as, for reasons that have not yet been elucidated, this material appears to promote rapid drug release and bioavailability rather than sustained release, thus rendering this excipient suitable for the formulation of poorly soluble and/or poorly absorbed drugs. This is exemplified by the studies of Dordunoo et al [33] who reported increases in the dissolution rate of temazepam and triamterene when formulated in Gelucire® 44/14 compared to polyethylene glycol dispersions. Similarly, Serajuddin et al [34] showed improved dissolution of a poorly soluble drug, REV 5901 ( $\alpha$ -pentyl-3-(2-quinolinylmethoxy) benzenemethanol) when dispersed in Gelucire® 44/14 compared to polyethylene glycols. Studies have also indicated improved oral absorption of drugs dispersed in Gelucire® 44/14 [35-37], although again the mechanism involved remains uncertain. In the particular study outlined here [13], our interest was twofold. Firstly we wished to examine of the use of this material as a means

of formulating a liquid for which oral bioavailability is an issue, namely vitamin E (or more specifically Vitamin E Preparation USP); the formulation of liquid drugs and nutraceuticals remains a persistent challenge, usually necessitating the use of liquid filled softgel capsules. The possibility of preparing a solid dosage form from a liquid preparation with a concomitant high loading is therefore of some interest. Secondly we wished to explore the mechanism of bioavailability enhancement, if indeed such an improvement was manifested. The study involved solid state characterisation of the dispersions, a human bioavailability study and a microscopic investigation into the release process.

In the first instance we used a combination of thermal and microscopic techniques to study dispersions of Vitamin E in Gelucire® 50/13 at loadings up to 50% w/w. These included polarising light microscopy and differential interference contrast microscopy, both of which indicated that the Vitamin E and Gelucire® 44/14 were phase separated at all concentrations studied. This was in itself a surprising result, as during the manufacturing process the two components appeared to be fully miscible immediately upon melting of the Gelucire® 44/14. However, to further verify whether this was the case we used conventional DSC to study the melting profile of the Gelucire® 44/14, finding that the shape of the DSC trace remained essentially unchanged on addition of the Vitamin E. Again, this strongly indicates phase separation of the Gelucire® 44/14 and Vitamin E, as one would expect a change in melting profile of the former if a solid solution had formed between the two components. Finally we used Tzero DSC in modulated mode to examine the effect of incorporation on the glass transition of the Vitamin E. An earlier study had [38] had indicated that the same Vitamin E preparation shows a glass transition around -60°C, hence one may be able to ascertain whether phase miscibility had taken place by measuring the T<sub>g</sub> as a function of loading. Where such measurement was possible, given the subtlety of the transition, the results indicated that the T<sub>g</sub> remained unchanged on loading the Vitamin E into the Gelucire® 44/14, again indicating phase separation. Taken together, these three indicate that the level

of miscibility between the solid Gelucire® 44/14 and Vitamin E was in fact very small or negligible. It was also interesting to note that the capsules prepared containing the two components did not leak after prolonged storage; our suggestion is that the Gelucire® 44/14 forms a solid mesh that effectively encapsulates the Vitamin E and prevents extensive leakage, possibly by capillary forces.

A human volunteer study was then carried out comparing the bioavailability of Vitamin E (or more specifically  $\alpha$ -tocopherol) from the Gelucire® 44/14 formulation to that from a proprietary product containing equivalent amounts of active. Six healthy adult male volunteers participated in a standard two period, two sequence crossover study. The oral absorption of  $\alpha$ -tocopherol from the Gelucire® 44/14 formulation was considerably higher than from the commercial product, with a more rapid onset (Figure 7).

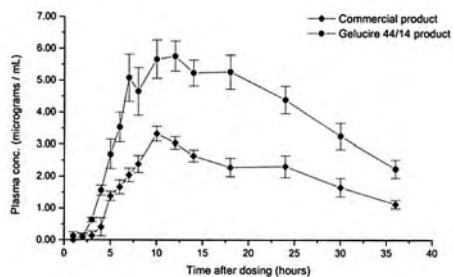


Figure 7: The mean ( $\pm$  sem) plasma  $\alpha$ -tocopherol concentration versus time profiles of the commercial and Gelucire® 44/14 formulations (reproduced from [13]).

This very encouraging result also raised an important question, namely what is the mechanism associated with the increase in bioavailability? The prevailing opinion at the time of writing is that Gelucire® 44/14 works as a solid self emulsifying drug delivery system, forming an emulsion 'spontaneously' or with minimal agitation on contact with water [39], whereupon absorption enhancement may occur via the routes mentioned briefly earlier in this article and discussed in greater depth elsewhere [8,9]. This being the case, it is intuitively difficult to see how a phase

separated system would show absorption enhancement, as the  $\alpha$ -tocopherol would not be expected to become incorporated into the emulsion droplets. In order to address this, confocal laser scanning microscopy studies were conducted to examine the behaviour of the Gelucire® 44/14 on contact with water, using the fluorescent dye rhodamine (base) as a model drug. Examination of the dispersions indicated that almost full miscibility was obtained, with a small number of rhodamine particles remaining distinct. The system appeared to be forming particles with an approximate diameter of 10 $\mu$ m that were then released into the aqueous medium. However, two unexpected observations were made. In the first instance, two distinct interfacial regions were observed, with the outer region remaining approximately constant in thickness (~200 $\mu$ m) through the experiment. The inner region extended into the solid phase at approximately 20 $\mu$ m/minute under the experimental conditions used here. Examination of the colour intensity showed a clear decreasing gradation from the solid to the aqueous phase between adjacent layers, indicating that the two interfacial regions corresponded to hydrated layers with a greater proportion of water in the outer layer. The second observation related to the small crystals of rhodamine remaining in the solid dispersion. It was noted that when the inner interfacial layer came into contact with this region the lipophilic base dispersed into the hydrated layer. Our suggestion is that a hydrated layer forms between the Gelucire® 44/14 and water, into which the drug may dissolve and hence become incorporated into the emulsion droplets.

## 5. Overall comments

This article is intended to provide a discussion of some of the issues associated with the use of lipid-based excipients by focussing on a limited number of studies [11-13] that illustrate a range of pertinent considerations. These include the necessity of considering the effect of the drug on the lipid and *vice versa*, the possibility of microscopic rather than molecular changes being associated with performance instability and the possibility of complex lipid-water interactions being responsible for bioavailability enhancement

from Gelucire® 44/14 (the physical structure of the dispersions being surprisingly simple in this case). However underpinning all the examples given is the need to understand the physical structure of the system rather than being content to simply know the drug loading; while it is appreciated that lipids will inevitably be structurally complex there are a number of methods outlined here and also described in other papers within this publication that allow the operator to gain a useful insight into the nature of the drug, the lipid and degree of interaction between the two. It is our view that, while physical characterisation may not have received the attention it deserves, it does not provide all the answers to the questions associated with mechanism and stability. It does, however, provide one of the essential pieces of the jigsaw corresponding to the issue of how we go from solid dosage form to biological response. Indeed, it is hoped that this article has demonstrated that without understanding the physical structure of these systems it is difficult to understand their biological activity.

## 6. Acknowledgement

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# SUSTAINED RELEASE FORMULATIONS WITH LIPID DERIVED EXCIPIENTS; BIG PHARMA PERSPECTIVES – WHY AND WHEN

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## Summary

Sustained release formulations allow modulating drug delivery to achieve the desired clinical effects. In general, a research based large pharmaceutical company with integrated discovery and development functions will consider an immediate release dosage form for first introduction to man of a newly discovered molecule. The goal is to advance the new chemical entity (NCE) rapidly through preclinical toxicology enabling testing of the molecule in man to assess safety, tolerability and pharmacokinetics. There are several critical aspects of the NCE, which need to be evaluated prior to making a decision whether a sustained release formulation is a clinical and therapeutic necessity. Absorption characteristics, pharmacokinetics, pharmacodynamics, metabolism, clearance and clearance mechanisms, potential food effects are some of the critical attributes of the molecule that will have a bearing on the decision. Unless a formulation with sustained release characteristics is an absolute requirement to achieve the desired clinical effect, the first clinical formulation and the first market entry are likely to be immediate release dosage forms. Depending on the solubility and permeability of the NCE, the immediate release formulation may contain lipid based excipients to enhance absorption characteristics and improve bioavailability.

A sustained release formulation is often part of the product life cycle management and it is likely to be a second market entry providing patients with improved delivery characteristics. These characteristics include reduced dosing frequency and may include reduced side effects while maintaining therapeutic plasma and/or tissue levels.

The choice of the type of sustained release formulation will depend primarily on the biological and physicochemical properties of the molecule. However, if the molecule is amenable to two or three different formulation approaches, it is likely that the pharmaceutical company will chose the one which represents an in-house technology or one which allows the utilization of available manufacturing capacity.

The choice of lipid derived excipients for sustained release formulations, if feasible, can offer several advantages. While providing the desired release characteristics, these excipients may offer a simultaneous enhancement of bioavailability. Furthermore, they may provide flexibility in the choice of manufacturing technologies including direct compression, wet granulation, melt granulation or hot melt coating.

In the increasingly complex world of health care delivery the judicious choice of appropriate delivery systems, excipients and manufacturing technologies can provide therapeutic benefits to patients and a competitive edge to pharmaceutical companies.

## Keywords

*Business environment, drug delivery, physicochemical characterization, delivery mechanism.*

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## Introduction

To understand the perspective of a large, research based pharmaceutical company regarding sustained release formulations in general and those, which use lipid based excipients in particular; we need to look at the current state of the industry and the economic/market pressures it faces. We must also look at the state of the science pertaining to lipid based sustained release formulations.

A fully integrated, research based, large pharmaceutical company, or “big pharma” company has a strong focus on discovering, developing and ultimately marketing novel, disease modifying molecules. These companies have large discovery groups comprised of scientists engaged in biological target identification and validation and in the synthesis of molecules that interact with the targets. There are also large groups of scientists whose areas of expertise are in toxicology, drug metabolism, materials science, formulation development, process chemistry and chemical engineering, that is, scientist whose responsibility is preclinical development. Big pharma is also characterized by having strong clinical research groups whose goal is to design and lead a streamlined clinical development program for the molecule leading to regulatory approval worldwide. Beside the discovery and development components described above, big pharma is comprised also of regulatory groups as well as extensive manufacturing capabilities, large marketing departments and global sales forces. The goal of the company is to achieve regulatory approval and quick market penetration of its new chemical entities. Hence, big pharma, in contrast to a small drug discovery or drug delivery company, is a very complex organization with multiple divisions, multiple interfaces and multiple layers of decision making bodies.

The competitive pressures currently facing the pharmaceutical industry must be taken into account also if we are to understand the big pharma perspectives. In the last few years the innovative pharmaceutical industry has been characterized by diminished numbers of drug

approvals, weak pipelines and many clinical candidate failures, some in late stage clinical development. There are significant price pressures on the pharmaceutical industry around the world due to the rapidly increasing overall cost of delivering quality health care. In addition, there are regulatory pressures on the industry: more stringent regulatory requirements to demonstrate clinical safety of the new therapeutic agent along with more stringent GMP compliance requirements. Many of the large pharmaceutical houses also are facing patent expirations and rapid market erosion of major products due to generic entries in the market.

These pressures have resulted in an unprecedented wave of mergers and acquisitions in the pharmaceutical industry in the last few years resulting in the creation of even larger, more complex behemoths. Instead of stronger pipelines and the promised synergies and efficiency gains within these mega companies, there is increased complexity, often conflicting cultures, and redundancies in most areas of the company including extra manufacturing capacity. More importantly, there are many more layers of decision making and an increasing tendency to avoid risks of any kind.

From a scientific point of view one of the important questions is whether enhanced efficiency and effectiveness of both discovery and development endeavours can be encouraged in the current big pharma environment. This paper is a review of certain aspects of lipid based sustained release formulations, their advantages, and the potential barriers to using them.

## New Chemical Entities- First Formulations.

New chemical entities (NCEs) fall into two major categories. If a molecule is designed to interact with a new biological target, or if it exerts its influence on the target by a new mechanism of action, it maybe classified as a “proof of concept” molecule. If the target is validated and the mechanism of action is elucidated with other molecules already on the market or in clinical development, companies

may chose to set themselves the goal of discovering “second generation” compounds with better safety and improved therapeutic profiles.

If the company is dealing with a proof of concept molecule, it will often employ a development strategy, which allows for advancing the molecule rapidly into the clinic to demonstrate safety, tolerability, validate the new target and/or the new mechanism of action. Usually, this strategy calls for a minimalist approach to preclinical development, particularly in the area of formulation development. Even if the molecule is anticipated to have less than ideal pharmacokinetics in man, the company will start with an immediate release (IR) formulation for an orally active synthetic small molecular weight compound.

If the proof of concept molecule is safe, well tolerated and its efficacy and general clinical profile warrant full development, the pressure on development scientists, including those working on formulations, becomes enormous to support the “first to market” approach. It is logical then to ask whether other dosage form(s) should be contemplated at this stage alongside the discovery and development of a second generation compound. It is very rare for a pharmaceutical company, big or small, not to search for a second generation or back-up compound. The second generation compound is expected to have a better therapeutic profile than the primary molecule; improved safety, improved efficacy, better pharmacokinetics to name a few. Many large pharmaceutical companies also develop multiple dosage forms of their molecules. These alternate dosage forms maybe designed to provide better absorption properties, more convenient dosing, improved pharmacokinetics or reduced side effects, or they maybe designed for special patient populations such as the elderly or the very young, if use of the drug is warranted in these populations. However, these approaches generally form part of the patent life cycle management and most, if not all, pharmaceutical companies will use an IR formulation as the first market entry for an orally active new molecule.

## **The use of sustained release formulations**

Oral formulations with modified release characteristics are developed when drug administration using an immediate release formulation is non-ideal. The two major reasons for developing a sustained release formulation are (1) the drug molecule has a short half-life in man resulting in having to dose multiple times daily to maintain therapeutic plasma levels at all times or (2) the drug molecule may have a narrow therapeutic index with undesirable side effects associated with its peak plasma concentrations. An interesting example of the second case is azythromycin, a molecule, which absorbs rapidly from the upper GI tract and has a long elimination half-life. A drug with a long half-life is generally not considered a candidate for sustained release formulations. However, if the molecule has a narrow therapeutic index with side effects associated with peak plasma levels, as is the case with azythromycin, modulation of the serum concentration-time profile may provide significant benefits to patients by reducing undesirable side effects. Gandhi et al., have shown that the high peak plasma concentrations associated with the IR formulation of azythromycin can be reduced significantly by an experimental controlled release formulation [1].

The choice of how to modulate the release characteristics depends on many factors beside the biological properties of the therapeutic agent. The physicochemical characteristics of the molecule are important determinants in the choice of excipients, the type of dosage form and manufacturing processes. These characteristics include aqueous and non-aqueous solubility, lipophilicity, pH solubility, pKa, pH stability and solid state properties such as melting point and the existence of solvates, hydrates and crystal polymorphism. Thus the formulation scientist is faced with a very complex, multifaceted problem comprised of biological, chemical and physical components.

## Types of sustained release formulations.

There is a bewildering array of sustained release formulations described in the pharmaceutical literature. A cursory survey of publications in the last 2 years in a single journal, the Journal of Controlled Release, indicates a very diverse and active field of research in the areas of sustained release and controlled release. Some of the formulations described in the journal use the following approaches to modulate drug delivery, generally with the goal of having sustained and preferably well controlled plasma profiles:

- Liposomes, liposome-surfactant and liposome-polymer combinations
- Microemulsions
- Formulations based on natural polymers, alginate, chitosan, guar gum, crosslinked amylose
- Polylactic acid microspheres
- Polymer and copolymer micelles
- Polymer network hydrogels
- Thermoresponsive hydrogels
- Swellable polymer matrices
- Erodible polymer matrices
- Biodegradable and bioerodible polymers
- Osmotic delivery systems

This is not a complete list; it merely serves to illustrate some of the options and choices available to the formulation scientist. If one is looking to improve development effectiveness, it is imperative to have a full understanding of the material properties of the molecule to be delivered from a sustained release formulation along with an understanding of its interaction with the biological environment so that the right formulation choices will be made. A molecule that is readily soluble in an acidic environment and is well absorbed from the upper GI tract but is poorly soluble and poorly absorbed at near neutral or slightly basic pH is unlikely to be a good candidate for a sustained release formulation such as an erodible polymer matrix. However, such a molecule may benefit from formulation approaches using excipients, which can slow GI

transit time. It is equally important to have a full understanding of the types of excipients, formulations and manufacturing processes, which are compatible with and can accommodate the chemical, physical and mechanical properties of the molecule. This understanding ultimately should result in a stable, well tolerated and efficacious dosage form with the desired *in vivo* release profiles.

## Sustained release formulations with lipid based excipients

The use of lipid based excipients can provide a high degree of flexibility to obtain sustained release characteristics for a large variety of molecules. Yet there are relatively few marketed products containing these excipients in sustained release formulations. In contrast, there are some very important therapeutic successes in improving the absorption characteristics of drugs characterized by poor aqueous solubility and delivering them effectively via the oral route by using lipid based formulations. Cyclosporin, ritonavir and saquinavir represent the most notable examples of the important role self-emulsifying or microemulsion based lipid formulation can play in effective drug delivery.

While there are relatively few sustained release formulations with lipid based excipients on the market, there is significant research activity in elucidating the role these excipients play in drug delivery. Specific areas of research include the physicochemical characterization of lipid based excipients, evaluation of formulation approaches, manufacturing technologies, and *in vitro* and *in vivo* characterization of sustained release formulations. There is also active research to elucidate the mechanisms of drug absorption from lipid based formulations. The last area of endeavour is not focused specifically on sustained release formulations; rather it deals with bioavailability enhancement and drug absorption from lipid based formulations in general. These areas of research are very important to the formulation scientist. In a complex and risk averse environment the ability to knowledgeably and cogently argue for the development of one type of formulation versus another is critical.

It is not within the scope of this discussion to provide an extensive historical review of the scientific literature. However, there are several important papers published in the last 5-10 years in each of the areas of research mentioned. A few representative papers will be cited; beyond their scientific merit they also provide extensive bibliographies of their field of endeavour.

One of the most important aspects of formulating with lipid based excipients is a thorough knowledge of their complex solid state properties and an understanding how these excipients respond to mechanical and thermal stress encountered during pharmaceutical processing. In the early nineties Sutananta et al., have carried out an extensive series of studies to characterize the effect of preparation conditions on the structure and mechanical properties of pharmaceutical glyceride bases, demonstrating the polymorphic complexity of Gelucire® [2]. These authors have also evaluated the physical stability of Gelucire® upon aging [3]. Their work represents the most systematic physicochemical characterization of lipid based excipients in the literature. Beside the characterization of the complex thermal behaviour of these excipients, they have also demonstrated the utility of a number of instrumental techniques, which are commonly available in pharmaceuticals or material science laboratories [4].

Understanding the physical state of excipients and possible changes upon storage with time and under different environmental conditions is of primary importance to the formulation scientist. Lack of understanding of the physical characteristics of excipients may result in failure of the dosage form to meet prescribed quality attributes and may deter the formulator to use the excipients in the future. It is interesting to contemplate how much we need to know about the properties of excipients we use, such as Gelucire® and the two most commonly used lipid based excipients in sustained release formulations, Compritol® and Precirol®. Craig has addressed this question fairly recently in a thought provoking manner [5]. It is this author's opinion that while our understanding of the physicochemical properties and behaviour of these excipients is extensive, further work is desirable in this area

particularly in the current big pharma environment characterized by low tolerance for risk, increased regulatory requirements and the need for speed in development. This type of research could be carried out in a collaborative manner among scientists from academe, the pharmaceutical industry and the excipient company.

Beyond the knowledge of the physicochemical characteristics of lipid based excipients we also must have an understanding of how they interact with the GI tract since this interaction is an important component of the behaviour of the dosage form and its delivery characteristics. The problems associated with the oral delivery of drugs having poor aqueous solubility have resulted in significant use of lipid based excipients along with intensive research into the mechanism by which these excipients can enhance absorption characteristics. Humbertson and Charman have reviewed the impact of the GI tract on lipids and lipid based formulation extensively [6]. They explored the digestion of lipids, intracellular lipid processing and the effects of lipids on intestinal permeability. In a follow up paper Porter and Charman proposed a framework for the *in vitro* assessment of oral lipid based formulations [7]. A very recent paper by Risovic et al., proposes a potential mechanism by which Pecenol™ may increase the gastrointestinal absorption of amphotericin B [8]. In addition to the papers cited here there are many others, which deal with the mechanism of bioavailability enhancement and the *in vivo* behaviour of IR dosage forms containing poorly water soluble drugs and lipid based excipients.

The question arises whether the concepts developed to explain the bioavailability enhancement and delivery characteristics of the lipid based IR dosage forms can be applied to lipid based sustained release formulations and if yes, to what extent? The scientific literature in this regard is rather limited and it is another area where research opportunities exist. Do we fully understand both the *in vitro* release characteristics and the *in vivo* absorption processes from lipid based sustained release formulations? Do we have guidelines, which would help predict dosage form behaviour and assist the formulator

in making the right formulation choices? Perhaps one of the difficulties to find generally applicable non-empirical guidelines for formulating sustained release dosage forms with lipid based excipients lies in the flexibility these excipients offer. There are a large number of different types of dosage forms one can design, coupled with a variety of manufacturing technologies one can exploit. There are oral dosage forms such as granules, tablets and capsules where the lipids are used in combination with a variety of other excipients as the matrix and there are dosage forms where the lipids are used as coating materials to modulate drug release. In addition to the variety of dosage forms, one can use a number of different processes to manufacture the dosage forms. Process itself can have profound effects on release characteristics. Eliassen et al., studied the rheology dependent processing behaviour of Gelucire® 50/13, Stearate 6000WL 1644 and PEG 3000 during melt agglomeration in a high shear mixer [9]. Duclos et al., examined the drug release characteristics of a model drug from monolithic hard gelatine capsules made by using 3 different polyol behenates of similar melting points but different HLB values [10]. There are several papers, which deal with more general concepts of either release characteristics of a certain type of lipid based formulation or describe the fundamentals of the manufacturing process. Two examples of these more general, concept oriented papers are those by Bummer and Achanta and coworkers. The paper by Bummer describes the physical chemical considerations of drug delivery as they apply to one of the many lipid based formulation with sustained drug delivery characteristics: solid lipid nanoparticles (SLN) [11]. The paper by Achanta et al., deals with the development of hot melt coating technologies and the fundamental aspects of the technology [12].

Pouton has devised a classification system for lipid formulations used for oral drug delivery [13]. He classified formulations as non-emulsifying, self-emulsifying and self-microemulsifying systems. A classification system of lipid based sustained release formulations would be a potentially useful

guidance to formulation scientists in view of the numerous possibilities in terms of composition, process and presentation form, that is; monolithic, particulate or coated dosage forms. This diversity is further complicated by the potential for different mechanisms of drug release of these sustained release formulations.

## Conclusions

The use of lipid based excipients offers enormous potential for the development of sustained release formulations. They are well tolerated excipients with low toxicity, relatively low cost and they are amenable to several conventional processes used throughout the industry. If a molecule has the appropriate biological profile to make it a candidate for modulated release, lipid based excipients may represent an opportunity for rapid and effective dosage form development and the flexibility to use existing manufacturing technologies and exploit available production capacity. These formulations also represent important intellectual property for the pharmaceutical company.

In spite of the many advantages offered by lipid based sustained release formulations, their very flexibility manifested by a wide choice of formulations and manufacturing approaches may represent one of the barriers in the big pharma environment to the adoption of this formulation approach. The choice of the formulation and associated manufacturing technology most appropriate for a specific molecule may not be obvious and requires significant experimentation. The major emphasis within the research component of the company is on the discovery of NCEs with the business goal of rapid, streamlined development leading to regulatory approval and market introduction in the shortest possible time frame. In the product development area the complex physical behaviour of lipid based excipients, their perceived variability and the need to select the most appropriate type of formulation/manufacturing process are major concerns. The technical decisions made regarding product development must serve both the therapeutic needs of patients and the business needs of the company. In the current business

environment it is often easier to fall back on less complex or known formulation strategies that may have been used successfully and may already be familiar to many in the company.

The fast adopters of lipid based sustained release formulations are likely to be smaller drug companies and drug delivery companies where the decision making process is more streamlined and the business decision makers are often scientists themselves with an appreciation for the inherent risks associated with using relatively new materials or using them in a new context. To facilitate adoption of lipid based sustained release formulation approaches throughout the industry, it would be desirable to have a classification system according to formulation types, release mechanisms and manufacturing processes. Such a classification system would present the inherent potential and flexibility of these formulations in an organized and systematic manner and would encourage companies to make wider use of them.

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GATTEFOSSÉ

# SUSTAINED RELEASE LIQUID FILLED HARD GELATIN CAPSULES IN DRUG DISCOVERY AND DEVELOPMENT: A SMALL PHARMACEUTICAL COMPANY'S PERSPECTIVES

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## Summary

The drug, a high dose experimental drug with low melting point and short biological half-life was formulated into liquid filled hard gelatin capsules as a controlled release formulation for oral administration. The aim was to simplify the dosing regimen and improve patient compliance and gastric tolerance. The drug, formulated in an oil/wax matrix was physically and chemically stable and demonstrated prolonged release profiles; the higher the proportion of the wax, the slower the drug release. The formulation was simple to prepare, used approved excipients and provides opportunity for both immediate and controlled products for pre-clinical investigation, clinical trial supplies as well as for commercialization.

## Keywords

*Neuroimmunophilin ligands, sustained release, capsules, liquid-filled, lipids.*

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## 1. Introduction

Guilford Pharmaceuticals Inc. is a fully integrated pharmaceutical company engaged in the research, development and commercialization of products that target the hospital market. Presently, Guilford markets two commercial products, GLIADEL® Wafer, for the treatment of brain cancer, and AGGRASTAT® Injection, a glycoprotein GP IIb/IIIa receptor antagonist used for the treatment of acute coronary syndrome (ACS). Guilford's clinical product pipeline includes a novel anesthetic, AQUAVAN® Injection, and drugs for treating Parkinson's disease and post-prostatectomy erectile dysfunction.

### 1.1 Neuroimmunophilin Ligand

Neuroimmunophilin Ligands (NILs) belong to a class of neuroprotective and neuro-regenerative drugs that Guilford is evaluating for the potential treatment of central and peripheral nerve disorders [1]. In preclinical models, neuroimmunophilin ligands have been shown to repair and regenerate damaged nerves without affecting normal, healthy nerves. These neuroimmunophilin ligands may have application in the treatment of a broad range of diseases, including Parkinson's disease, brain and spinal cord injury, multiple sclerosis, and peripheral nerve injuries including post-prostatectomy erectile dysfunction. Preclinical data also suggest that a separate class of neuroimmunophilins, known as cyclophilin ligands, may also have potential utility in the treatment of degenerative disorders of the nervous system, including retinal disorders, such as age-related macular degeneration.

### 1.2 Parkinson's Disease

Parkinson's disease is a chronic, progressive degenerative disorder that involves a specialized region of the brain that controls muscle tone and coordination and affects over one million people in the United States [2]. Most patients are affected in mid-life and usually develop hand tremors, muscle rigidity, and postural instability, among the many manifestations of the disease. The disease is caused by the degeneration of nerve cells that use dopamine as a chemical messenger. Treatment currently consists of administering drugs that increase the amount of

dopamine in the affected regions of the brain or substitute for the lost dopamine. Unfortunately, there are no current treatments that can reverse, or even slow down, the progressive degeneration of the affected dopamine nerve cells.

### 1.3 Post Prostatectomy Erectile Dysfunction (PPED)

The American Cancer Society estimates that approximately 190,000 American men will be diagnosed with prostate cancer this year. Of these, the cancer will be localized in 70% of patients, and a significant proportion will undergo prostatectomy for treatment. Potential complications of surgery include urinary incontinence and sexual dysfunction. In a retrospective study of patient outcomes, published in the Journal of the American Medical Association, the incidence of sexual dysfunction reported at eighteen months following prostatectomy ranged from 60 percent to 85 percent [3].

### 1.4 Historical perspectives of liquid filling of hard gelatin capsules

Gelatin capsules have been defined as "solid preparations with hard or soft shells of various shapes and capacities, usually containing a single dose of medicament" [4].

The use of the capsule as a pharmaceutical dosage form dates back into antiquity. The Ebers Papyrus dating from about 1500 B.C. states *inter alia* that "medicines for internal application are given in the form of infusions, pills... capsules, powders, potions and inhalations". Later, in 1730 A.D. a Viennese pharmacist, de Pauli, fashioned oblate capsules with the object of covering up the "bad taste" of the pure turpentine he prescribed for podagra [5,6]. Gelatin capsules were introduced into modern pharmaceutical armamanta early in the nineteenth century by Mothes who, together with Dublanc, took out a French patent [French Patent 5648] in March 1834. These capsules were also liquid-filled with the oleoresin of copaiba [6].

Leakage of contents had been a serious drawback for hard gelatin capsules filled with

liquids or semi-solid materials and sealing of the capsules had been suggested as a preventive measure [7,8 French Patent 5648 and Cade]. The leakage problem with these capsules was suggested as the reason for the slow trend away from liquid filling [9, François and Jones 1979]. This trend was, however, speeded up with the advent of the rotary die process, perfected in 1930, for making soft gelatin capsules which met the demand for a leak-proof capsule for liquid medicaments [9]. Thereafter, the interest in oil and paste filling into hard gelatin capsules was limited to the patent literature. A Japanese patent application was filed in 1963 to prepare a non-leaky product by using silica to gel the oily contents [9].

Another approach was patented by a French company, which suggested the use of thermosetting substances, which could be hot-filled into the capsules and would set into a solid on cooling [9]. Banding and dot sealing of hard gelatin capsules were also used to avoid spillage, resulting from the opening of the two halves of the shell during handling. These also adequately eliminated the problem of leakage in liquid-filled capsules but the process was time consuming and costly [9].

Walker and al. [10] described a process of filling molten and thixotropic substances into hard gelatin capsules. François & Jones [9] also gave an account on the use of thixotropic materials in hard shells. These molten or thixotropic formulations, by their very nature, remain as solids or immobile plugs on storage. Though these attempts are primarily directed at eliminating leakage of the filled materials, there are several other advantages including ease of formulation/manufacture, weight and content uniformity and increases in chemical and physical stability and improved bioavailability. Other advantages of liquid filling of hard gelatin capsules have been extensively reviewed in the literature [11,12].

### *1.5 Sustained release formulations*

The concept of sustained release formulations was developed to eliminate the need for multiple dosage regimens, particularly for those drugs requiring reasonably constant blood levels over a long period of time [13, 14]. In addition, it has

also been adopted for those drugs that need to be administered in high doses but where too rapid a release is likely to cause undesirable side effects. For example, in controlled clinical trials, a serious ulceration with mortality rates as high as 27% occurs when potassium chloride is released rapidly in the gastrointestinal tract [15]. This ulcerogenic effect may be minimized using a controlled release dosage form and a microencapsulated controlled release product was found to produce higher incidence of lesions compared with a matrix-type formulation [16].

Sustained release dosage form may also lead to a reduction in healthcare cost [17]. The total cost of therapy of the controlled release product could be comparable or lower than the immediate-release product. With reduction in side effects, the overall expense in disease management also would be reduced.

Also, modified release dosage forms, be it temporal or spatial, are used as part of product life cycle management and maximizing brand equity; they are introduced after product launch or way into the commercial life of a product to extend the period of product exclusivity [17].

The scientific and patent literature is replete with various approaches to achieve a sustained release dosage form. Basically, most of the approaches can be categorized as:

- Manipulating particle size
- Embedding drug in a matrix
- Coating drug or the dosage form containing the active ingredient (including osmotically active ingredients/excipients)
- Forming complexes of the drug with materials such as ion exchange resins
- Using different salt forms of the drug with varying solubility and/or dissolution profiles.

## **2. The Drug: Neuroimmunophilin ligand (GPI 1485)**

GPI 1485 is an experimental neuroimmunophilin ligand in development for the treatment of Parkinson's Disease and post-prostatectomy

erectile dysfunction. As with new compounds in early clinical development, the final physical properties of the API such as bulk density, particle size, crystal form, and degree of crystallinity, have not been completely defined. These physical properties, which may change on scale up, may affect processing and the bioavailability of the final dosage forms.

This drug is a high dose experimental drug with low melting point and short biological half-life. A short half life compound is preferable to long half-life compound in early phase clinical development of a first in class, new chemical entity in view of the shorter time to termination of treatment in case of severe adverse effect(s). However, short biological half-life requires frequent dosing which may impair patient compliance with dosing during clinical trials with obvious efficacy implications. For these short half-life drugs, sustained release formulations may simply dosing regimen, improve patient compliance and make termination of treatment easier.

In this study, sustained release liquid filled of hard gelatin capsules was adopted as a means to facilitate processing, provide clinical trial supplies, reduce cost of development, and to obtain a formulation capable of commercial production with minimal scale up effort. Another aim was to simplify the dosing regimen, improve patient compliance and increase gastric tolerance. In its final form, the hard gelatin capsules contain a solid/semi-solid plug of the drug and carriers to minimize leakage on storage. The formulation must be simple to prepare, uses approved excipients, cost effective and provides opportunity for both immediate and controlled release products.

### **2.1 Carriers**

Many pharmaceutical excipients are claimed to be suitable for liquid filling of hard gelatin capsules [18, 19]. The physical properties of these carriers can be liquids, semi-solids or solids. The liquids may be natural, semi-synthetic or synthetic oils. They include oils such as arachis, maize, cottonseed, fractionated coconut oil and dimethicone. The semi-solids and solids include beeswax, Gelucire<sup>®</sup>,

spermaceti, ceresin, hard and soft paraffin, theobroma oil, cetyl and stearyl alcohols, and polyethylene glycols. While the carrier oils would need thickeners, the solids and semi-solids may be used alone. Labrafil<sup>®</sup> and Precirol Ato 5<sup>®</sup> were selected as oil and wax carriers, respectively, based on history of use in controlled release dosage forms as well as commercial availability.

### **2.2 Dose calculation of GPI 1485**

Currently, GPI 1485 is administered four times a day. This was not only inconvenient but there is high potential for patient non-compliance. In addition, very low trough drug levels were observed due to the short half-life of the drug. Using preliminary median pharmacokinetic data, it was estimated that a dose of 1.5 g would maintain the target plasma concentration over a 12-hour period. Therefore, dosage strength of 750 mg of drug (2 capsules to be administered twice daily) was chosen as ideal for development.

## **3. Aims and scope of this study**

The present study was intended to:

- Determine the suitability of Labrafil<sup>®</sup> alone and with Precirol Ato 5<sup>®</sup> as carriers for GPI 1485
- Determine the dissolution properties of the dispersions and the effects of the type of carrier and drug:carrier ratio
- Optimise the drug release from the dispersions using dissolution data and
- Estimate the chemical stability of the drugs and the carriers.

### **3.1 Materials used in the study**

GPI 1485 (Lot 17GM01); Labrafil<sup>®</sup> M 2125 CS (Lot 22380) from Gattefossé; Labrafil<sup>®</sup> M 1944 CS (Lot 23689) from Gattefossé; Precirol Ato 5<sup>®</sup> (lot 22997) from Gattefossé; Propylene Carbonate (Sigma-Aldrich); propylene glycol, PEG 400; Transcutol<sup>®</sup> (diethylene glycol monoethyl ether) and polysorbate 80. Size 00 and 00el and hydroxypropylmethyl-cellulose (HPMC) capsules.

## 4. Methods

### 4.1 General preparation of liquid filled hard gelatin capsules

The drug and carrier(s) in fixed ratios were weighed and placed in an oven at about 100°C (fusion temperature) for about 10 minutes (holding time) to melt/dissolve. The molten material was stirred, cooled to about 75°C (filling temperature) and filled into size 00el (or as appropriate) capsules (pure drug was filled at 85°C) to contain 750 mg of drug. Sustained release formulations were prepared using various proportions of Labrafil® (oil) and Precirol® Ato (wax) to obtain capsules with various drug release rates. In addition, capsules with biphasic drug release profiles were also designed to mimic some of the peaks in the plasma concentration observed for the current immediate release dosage form for comparative evaluation in pre-clinical efficacy models to determine the most appropriate drug release profile for this drug. This approach was based on the premise that, in some cases where drug partition into some body compartments such as the brain is dependent on the diffusion gradient, the peak concentration (steepest gradient between the brain and plasma concentration) biphasic administration may drive more drug into the brain than would be expected from a low continuous rate of input. This bi-layer formulation has an immediate release portion containing approximately a quarter to a third of the drug overlaid with the rest of the drug as a sustained release. The immediate release portion contains the 92.5% drug and 7.5% propylene carbonate, Transcutol®, PEG 300 or other pharmaceutically acceptable liquid. The sustained release fraction contains the drug and 2:1 or 1:1 Labrafil® and Precirol Ato 5® ratios.

Content weights of 900 to 1,000 mg corresponding to 83 to 75% of drug, respectively, were investigated, to allow the use of standard size 00 capsules instead on the 00el required for the 1,000 mg capsules.

### 4.2 Characterization of filled capsules

#### 4.2.1 Differential Scanning Calorimetry

The filled capsules were characterized using differential scanning calorimetry (DSC) to

determine melting temperature of the drug-carrier dispersions. Briefly, about 5 mg of the content of the capsules was weighed into aluminium sample pans and scanned using Differential Scanning Calorimeter (TA Instruments) at 10°C min<sup>-1</sup> from 0 to 100°C. The onset temperature (T<sub>o</sub>) of the endothermic peak (the melting point) and the enthalpy of fusion (ΔH) were both recorded.

#### 4.2.2 Thermogravimetric Analysis (TGA)

About 20 mg of the contents of the capsules was added to the sample pan (previously equilibrated) of the Thermogravimetric Analyser (TA Instruments) and scanned at 10°C min<sup>-1</sup> from ambient until degradation is complete. The onset temperature of decomposition (T<sub>d</sub>) was measured and compared with that of pure drug and carriers.

#### 4.2.3 Dissolution methods

The dissolution of the drug from filled capsules was determined using USP Paddle method (Apparatus II) and sinkers for the capsules. The dissolution medium for immediate release formulations was 1000 ml of 0.1N hydrochloric acid (HCl) at 37°C. For controlled release formulations, the dissolution medium was 750ml of 0.1N HCl at 37°C for 3 hours and thereafter the pH was adjusted to 6.8 with 250 ml of 0.2M tribasic sodium phosphate solution previously equilibrated at 37°C.

#### 4.2.4 Stability testing

Preliminary physical stability, as measured by changes in dissolution profiles, of the filled capsules on storage was investigated at room temperature, 25°C/60% RH and 40°C/75% RH. The dissolution medium used was 1000 ml of 0.1M HCl at 37°C.

## 5. Results

### 5.1 The Capsule shell

Usually a hard gelatin capsule contains 14-16% moisture, which acts as a plasticizer for gelatin. A hygroscopic material, when filled into the capsule, could extract moisture from the shell thereby inducing embrittlement. The potential

for this is checked by storing capsules filled with the product under various conditions of relative humidity from 2.5 to 65% and measuring the weight change or the breaking force of the emptied shell before and after filling. In addition, gelatin being a protein derivative does not tolerate high filling temperatures. Attempts to fill the current formulation into hard gelatin capsules caused the capsule shells to crack. Therefore, hydroxypropylmethylcellulose (HPMC) capsules were used to accommodate the high fill temperatures of about 70-75°C employed. Capsules made with hydroxypropylmethylcellulose (HPMC) are commercially available from various vendors. These capsules must comply with the USP disintegration test. The shell dissolution of various empty capsules had been described in the literature [20]. However, our investigations showed that only one supplier's product (out of three) passed the USP disintegration test. During dissolution testing on capsules prepared using the HPMC capsules from other suppliers, films were formed around the filled material and served as a dissolution rate limiting membrane, producing zero order release profiles irrespective of composition. When the capsule shells were removed, dissolution of the plug was similar to profiles obtained with capsule prepared using the well made, disintegrating HPMC capsules.

## 5.2 Dissolution of GPI 1485 and effect of carriers

### 5.2.1 Immediate release capsules

Figure 1 show the dissolution profiles of pure GPI 1485 into 0.1M HCl as a powder and after processing into hard gelatin capsules. The GPI 1485 powder showed an initial fast dissolution, which slowed after about 10 minutes probably due to the effect of particle size. The GPI 1485 in liquid filled hard gelatin capsules showed a more gradual release profile with  $T_{80\%}$  (time for 80% of the drug to be dissolved) of about 75 minutes. Addition of 7.5% propylene carbonate allowed the fill material to be filled at a lower temperature (about 5°C) without affecting dissolution of the drug (Figure 2). Similar observation was made for capsules containing 7.5% of other liquids such propylene glycol, PEG 400 or Transcutol®

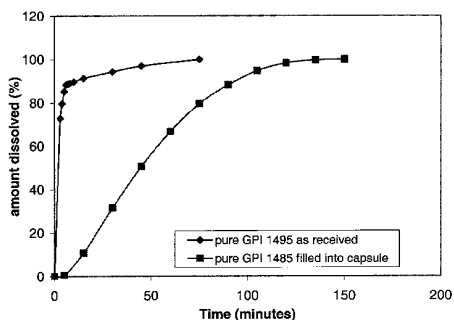


Figure 1: Dissolution profiles of pure drug powder as received and pure drug heated to 85°C and liquid filled into HPMC capsules.

(diethylene glycol monoethyl ether) and polysorbate 80.

Storage of the capsules filled with the GPI 1485 or GPI 1485:PC in the ratio of 92.5:7.5 at 25°C/60%RH for about 38 days did not show any signs of ageing as measured by the dissolution studies (Figure 2). However, storage at 40°C/75%RH for 72 hours showed a slight slowing of dissolution compared with storage at 25°C with  $T_{80\%}$  of 60 and 75 minutes for 25°C/60RH and 40°C/75RH, respectively. In addition, capsules containing 92.5 drug and 7.5% PC showed signs of leakage on storage at 40°C for about 38 days. Leakage was not observed in samples stored at 25°C or at 40°C for 10 days, which suggests that this formulation can accommodate short-term (up to 10 days) temperature excursions to up 40°C without leakage. Furthermore, no leakage was observed for capsules stored at 30°C/75RH.

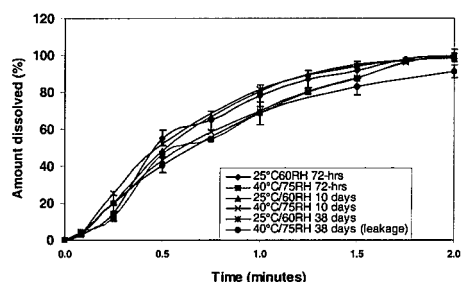


Figure 2: Effect of storage on dissolution of capsules filled with a mixture containing 92.5% GPI 1485 and 7.5% propylene carbonate showing little change in dissolution with time.

### 5.2.2 Controlled release formulation of GPI 1485

As seen above, filling of GPI 1485 was performed at very high temperatures (80-85°C) and during screening for pharmaceutically acceptable solvents to reduce the filling temperature of GPI 1485, it was discovered that unlike solvents such as triethylcitrate, propylene glycol, propylene carbonate Transcutol®, PEG400 and polysorbate 80, Labrafil® M2125 CS extended the release of the drug; and this effect was increased by addition of Precirol Ato 5®. Figure 3 show dissolution profiles of liquid filled capsules containing 75% drug and various proportions of Labrafil® M 2125 CS and Precirol Ato 5®. Similar profiles were observed when Labrafil® M 1944 CS was used instead of Labrafil® M 2125 CS. The dissolution of GPI 1485 from a formulation containing 75% GPI and 25% Labrafil® showed a extended release profile with the  $T_{80\%}$  of about 4.5 hours compared with 1 hour for the liquid filled pure drug. When a portion of Labrafil® was replaced with Precirol® Ato, the rate of dissolution gradually reduced with increase in proportion of Precirol Ato 5® with about 80% of drug released in about 22 hours for a formulation containing 75% drug 5% Labrafil® and 25% Precirol Ato 5®. Formulations containing 75% drug and 25% Precirol® gave  $T_{80\%}$  in excess of 24 hours (Table 1). Square-root of time plot of the data from capsules (e.g. figure 4 for 1:1 Labrafil®: Precirol®) showed linearity over the first 9 hours and subsequently slowed down (after about 80% of the drug was released) indicating that dissolution is diffusion controlled.

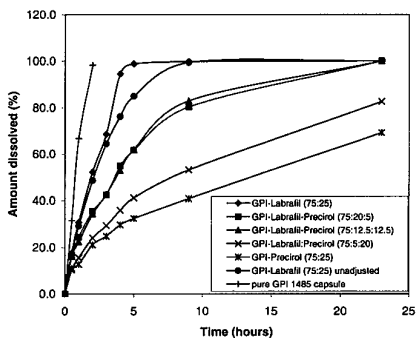


Figure 3: Effect of Labrafil® and Precirol Ato 5® on dissolution of GPI 1485 from liquid filled hard gelatin capsules.

Table 1: Effect of Composition of GPI 1485, Labrafil® and Precirol Ato 5® on time required for 80% of the drug to be dissolved ( $T_{80\%}$ ).

Composition (%)	$T_{80\%}$ (hours)
100:0:0	1.0
75:25:0	4.5
75:20:5	8.0
75:12.5:12.5	8.3
75:5:25	22.0
75:0:25	> 24.0

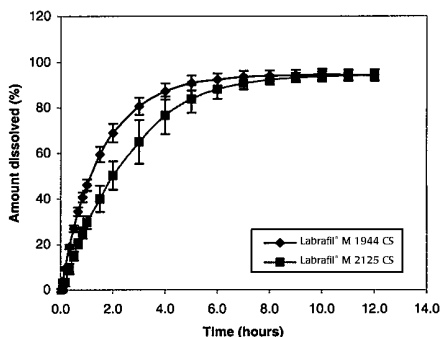


Figure 4: Effect of Labrafil® type on dissolution of GPI 1485 from capsules containing 83.3% drug and 16.7% of Labrafil® (900 mg total weight).

Root time plot of drug release from capsules containing 1:1 ratio of Labrafil and Precirol ato 5

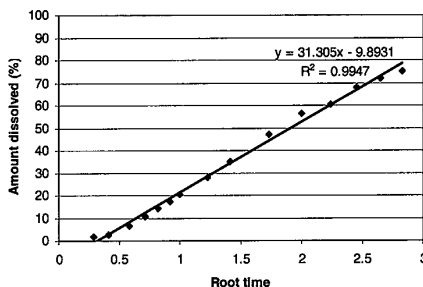


Figure 5: Square root of time plot of dissolution data from capsules containing 75% drug and 1:1 ratio of Labrafil® and Precirol® Ato.

In an attempt to optimize the content weight, capsules containing various amounts of a 1:1 blend of Labrafil® and Precirol Ato 5® were prepared. Dissolution of drug from these capsules showed that the fill weight could be reduced to about 830 mg (i.e. 750 mg of drug,

40 mg of Labrafil® and 40 mg of Precirol Ato 5®) with very little change in dissolution profiles (Figure 6). Table 2 shows theoretical weights of the current formulations that can be filled into various sizes of hard gelatin or HPMC capsules.

Table 2: Approximate volumes and fill weights of various capsules sizes containing dispersions of GPI 1485

Size	Approx. voL. (ml)	density	Max. fill wt (mg)
000	1.37	1.28	1.75
00el	0.98	1.28	1.25
00	0.95	1.28	1.22
0	0.68	1.28	0.87
1	0.5	1.28	0.64
2	0.37	1.28	0.47
3	0.3	1.28	0.38
4	0.21	1.28	0.27
5	0.13	1.28	0.17

The reduction in fill weight to about 830 mg allows the use of size 0 instead of size 00 capsules for preparing extended release capsule formulations suitable for 2 or 3 times daily dosing.

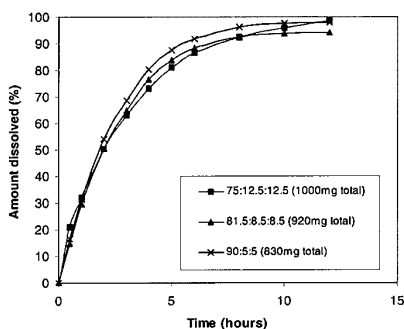


Figure 6: Effect of content weight on release of drug from capsules containing drug and 1:1 Labrafil®:Precirol® ratio.

### 5.2.3 BiPhasic dissolution

Capsules were prepared to contain the immediate release formulation (GPI 1485 with 7.5% propylene carbonate) and sustained release formulation containing the drug and 1:1 ratio of

Labrafil®:Precirol Ato 5®. The aim was to formulate a dosage form, which produces a fast release of the drug over the first 2-4 hours and a slower release over the next 2-8 hours. From the previous pharmacokinetic data (not shown), this drug release profile is expected to provide the initial target plasma concentration and maintain this concentration for 10-12 hours and thereby allowing a twice-daily dose administration. Figure 7 shows the dissolution profile of a prototype of the biphasic capsule formulation.

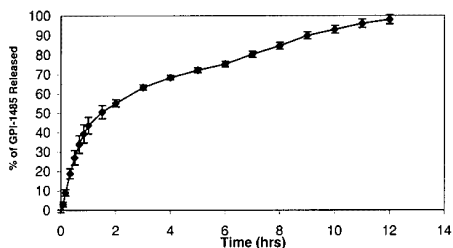


Figure 7: Dissolution profile of a prototype biphasic release formulation.

The pH-dependency of dissolution of GPI 1485 from the liquid-filled capsules depended on the composition. As seen in Figure 3, capsules containing drug: Labrafil® showed increased dissolution at higher pH. Addition of the wax reduced the extent of increase and there was no significant changes when dissolution was conducted in 0.1M HCl or phosphate buffer at pH 6.5 for compositions with at least 5% Precirol® (e.g. Figure 8).

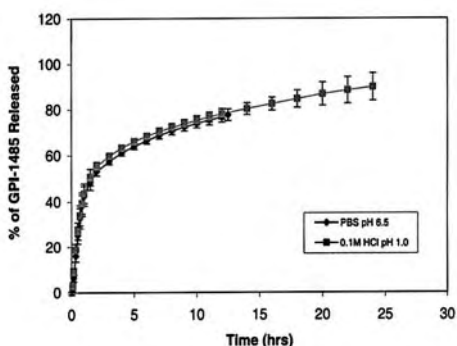


Figure 8: Dissolution of a biphasic formulation containing 250 mg of drug as an immediate release formulation and 500 mg as a controlled release formulation containing GPI 1485, Labrafil® 5% and Precirol® 20% showing pH-independent dissolution profiles.

### 5.3 Thermal analysis

#### 5.3.1 Differential Scanning Calorimetry (DSC)

Both the melting temperature and the enthalpy of fusion were determined using DSC. The melting temperature is used as a guide in determining the fusion temperature of the formulation during processing into capsules and also as initial alert for possible leakage of contents from filled capsules. Generally, the fusion temperature used was about 5°C above the melting temperature of the formulations. The enthalpy of melting which measures the degree of crystallinity of the dispersion was used to monitor the physical stability of the dispersions and significant increases in enthalpy values on storage may be used as an indication of physical stability of the dispersion or may explain any changes in dissolution of the drug from its dispersion in the carriers [21]. Usually, enthalpy values of freshly prepared dispersions are low (meta-stable forms) and gradually increase on storage. A rapid conversion to maximum enthalpy indicates rapid ageing and suggests long-term physical stability of the product.

DSC studies showed that capsules filled with molten GPI 1485 aged very quickly with the fill material attaining initial physical state within 7 days storage at ambient temperature (Figures 9-14). It is anticipated that storage of the filled capsules at an elevated temperature may accelerate the ageing of formulation. The thermal analysis data also supported the dissolution data, which showed that ageing of the fill material occurred quickly and remained constant thereafter. The DSC data also showed that addition of 7.5% PC decreased the onset temperature of the melting endotherm and also suggests a potential for leakage of the fill material from the capsules on storage at high temperatures such as 40°C/75RH (Figure 11). The temperature of the melting endotherm increased on storage, the magnitude of which depended on the storage temperature; the higher the storage temperature the faster the ageing (see table 3). This supports the statement above that curing may be accelerate at high temperature storage conditions.

Table 3: Effect of composition and storage conditions on the extrapolated onset temperature of melting ( $T_o$ ) of dispersions containing GPI 1485.

Sample	$T_o$
Pure GPI 1485	83.8
Pure GPI 1485 (second run)	78.03
Liquid filled GPI 1485 (1 week)	81.98
Liquid filled GPI 1485 (2 weeks)	83.89
Liquid filled GPI 1485/PC (92.5:7.5) 24 hours	61.09
Liquid filled GPI 1485/PC (92.5:7.5) 10 days at 25°C/60%RH	67.51
Liquid filled GPI 1485/PC (92.5:7.5) 10 days at 40°C/75%RH	76.66

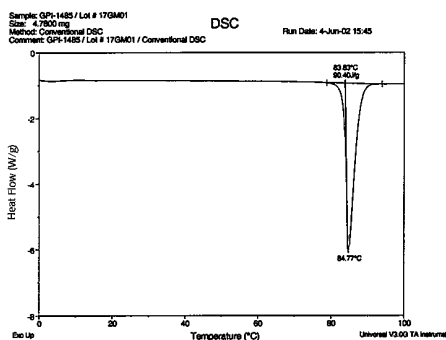


Figure 9: DSC scan on pure GPI 1485.

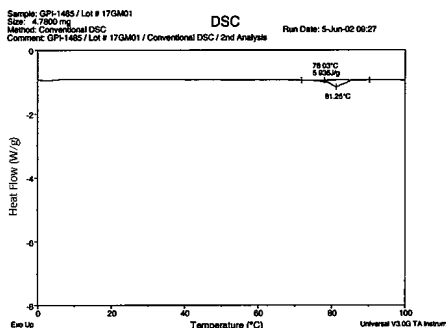


Figure 10: DSC scan of GPI 1485; repeat run after rapid cooling at 50°C min<sup>-1</sup> from 100 to 0°C showing the formation of an unstable form.

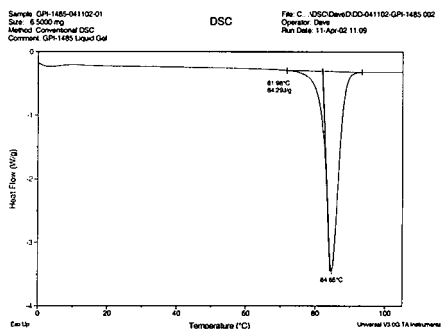


Figure 11: DSC scan of GPI 1485 liquid filled into hard gelatin capsules (1 week sample) showing a fairly rapid conversion into the original crystalline form as shown by the enthalphy values.

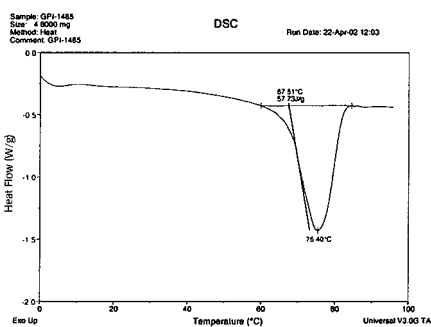


Figure 14: DSC scan of GPI 1485-PC 92.5:7.5 liquid filled into hard gelatin capsules and stored at 25°C/60RH for 10 days showing slower ageing (lower onset melting temperature) compared with storage at 40°C/75RH.

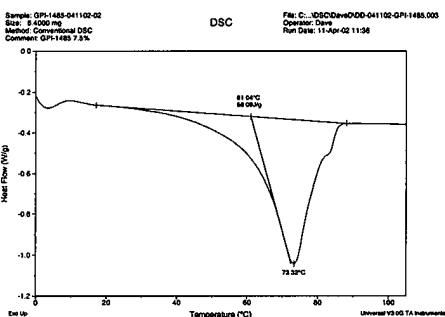


Figure 12: DSC scan of contents of hard gelatin capsule containing 92.5% GPI 1485 and 7.5% PC (24 hour-old) indicating potential for leakage above 30°C

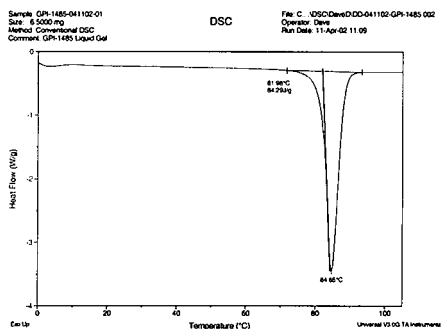


Figure 13: DSC scan of contents of hard gelatin capsule containing GPI 1485/PC 92.5:7.5 stored at 40°C/75RH for 10 days showing elevation of onset melting temperature of storage.

### 5.3.2 Thermogravimetric Analysis (TGA)

TGA measures the weight loss of the drug-carrier systems as a function of temperature, or time of heating or both. Usually, loss of surface-adsorbed solvent can be distinguished from solvent in crystal lattice and from degradation losses [22]. When decomposition of a drug or carrier is accompanied with generation of gaseous materials (and therefore weight loss) TGA may be used to determine the compatibility of the drug and carriers used in the formulation. The decomposition temperature may decrease, remain the same or increase depending on the interaction of the drug and the carriers. Lowering of the decomposition temperature below that of both the drug and carrier(s) is an indication of incompatibility.

Figure 15 is a representative TGA scan of GPI 1485. Under the experimental conditions, the extrapolated onset of decomposition is about 216°C with about 94% of the drug degraded at 300°C and 99% at 400°C. However, as seen in the scan, the actual onset of decomposition (the temperature at which the scan departs from the baseline) is about 150°C. The difference between the extrapolated onset temperature and the actual decomposition temperature may be a function of factors such as the particle size of the material being analysed and the heating rate. Generally, the smaller the particle size and size distribution, the smaller the difference between these two values. In addition, the lower the heating rate, the closer are the extrapolated and actual

decomposition temperatures. Our data showed that addition of excipients such as propylene carbonate (boiling point 242°C), Labrafil® or Precirol Ato 5® did not significantly reduce the extrapolated onset temperature of decomposition of the drug indicating that these excipients are compatible with the drug.

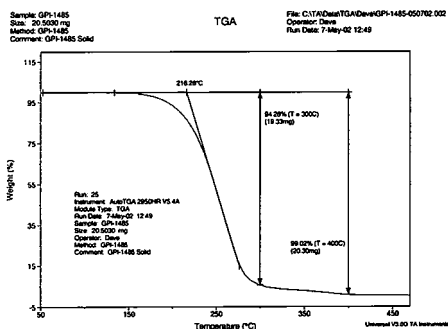


Figure 15: Representative TGA scan of GPI 1485 showing that the drug is stable below 150°C

## 6. Conclusions

Our studies showed that capsule formulations containing GPI 1485 and various proportions of Labrafil® and Precirol Ato 5® may be prepared and filled into size 0 or 00 capsules. These formulations were observed to be physically and chemically stable on storage at 25°C/60RH for over 18 months. Liquid filled HPMC capsule formulations containing GPI 1485 are simple to prepare and provide a cost effective process for preparing clinical trial supplies as well as commercialization.

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GATTEFOSSÉ

# STRUCTURAL AND THERMAL CHARACTERISATION OF LIPIDIC EXCIPIENTS AND CARRIERS BY X-RAY DIFFRACTION COUPLED TO DIFFERENTIAL MICROCALORIMETRY

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## Summary

A new technique coupling X-ray diffraction and DSC has been used recently for the structural and thermal characterisation of synthetic and natural triglyceride mixtures as well as that of polyoxyethylene glycol glycerides (Gelucire® 50/13) used as sustained-release matrix forming agent in pharmaceutical applications. Physical properties of Gelucire® were studied by coupled time-resolved synchrotron X-ray diffraction and Differential Scanning Calorimetry combined with Infrared Spectroscopy and Polarized Light Microscopy as a function of temperature. With these techniques, structures formed upon cooling or melting of newly melted or stabilized Gelucire® 50/13 are characterized. All endotherms and exotherms observed were attributed to the transition or the melting of either the main phase formed by polyoxyethylene glycol derivatives or to that of a secondary phase formed by the excess of glycerides and characterized by long spacings corresponding to a double fatty acid chain length. The fatty esters of polyoxyethylene glycol (PEG) polymorph conformations corresponding to long spacings ranging from 90 to 120 Å are all provided by the same lamellar phase with the PEG chains under a helical conformation but with a more or less important tilt of the PEG chains. The rate of crystallization was found to be crucial for the formation of these polymorphs. Therefore a slow crystallization rate will induce the formation of a 120 Å lamellar phase presenting a higher melting point and consequently a better stability in time and in temperature. Inversely a rapid crystallization rate will enhance the formation of a 90 Å lamellar phase. We show however the easy possibility of a rapid transition toward the most stable form. Possible interdigitation of fatty acid chains in both lamellar phases is discussed.

## Keywords

*Polyoxyethylene glycol, Gelucire® 50/13, sustained-release, structure, crystallization, melting.*

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## I - Introduction

Semisolid matrixes are often used in the composition of hard gelatin capsules, for modified drug release. The choice of excipient depends on the type of drug and also on the profile of release required [1]. Such excipients are frequently made from lipids and for this reason an important variety of excipient is available. Gelucire® 50/13 (the two numbers correspond respectively to the drop point and the HLB value) consists of a mix of mono-, di-, triacyl glycerol (around 20% in weight) and monoacyl polyoxyethylene glycols and diacyl polyoxyethylene glycols labelled respectively MPEG and DPEG. These compounds have several capabilities, including amongst others: drug encapsulation whatever the drug form is liquid or viscous, unstable or strongly hydrophobic and above all they are susceptible to change the drug release. In fact, by changing the HLB value and the melting point of the Gelucire® 50/13, the amount of drug released per unit of time can be controlled. As drug release is dependent on the stability of the crystalline structures formed, it is of prime importance to characterize any possible structural evolution of the excipient. Indeed, through the control of drug release characterization and understanding of drug and excipient polymorphism is coming out as one of the main issue in pharmaceutical science.

Glycerides and polyoxyethylene glycol (PEG) are subject to an extensive literature including a variety of experimental [2, 3] and theoretical tools and models derived from computational results based on molecular simulation [4, 5]. Glycerides display a complex polymorphism of monotropic type meaning that transitions between polymorphic varieties are irreversible. This polymorphism has been studied for more than one century and is not yet fully understood. Briefly, the hydrocarbon chains of fatty acids laterally pack according to a limited number of subcells of hexagonal, orthorhombic or triclinic symmetries in the order of stability and compacity that are easily characterized by one (4.15 Å), two (e.g. 4.2 and 3.8 Å) or at least three (4.6 Å and e.g. 3.85 Å and 3.70 Å) main lines at wide angles by X-ray diffraction [6-9]. These lateral packings results in longitudinal stackings

of molecules giving birth to long spacings corresponding to 1, 2, 3, 4 or 6 chain lengths observed at small angles by X-ray diffraction [10-12].

The description of the packing of PEG chains is not simple and was only clarified recently. WAXS patterns which are directly related to the lateral organization of the molecules directly reflect as for glycerides the chain packing subcell adopted. Several structures have been proposed [13, 14, 15]. Evans et al. [15] and Takahashi et al. [16] have observed a zigzag conformation. In this case, the fibre period is 7.12 Å for two ethylene oxide (EO) units under tension. Takahashi et al. [2, 17] or Neyertz et al. [4] have shown that PEG can also crystallize in a slightly distorted helical structure noted (7/2) helix. In that case crystalline PEG subcell is monoclinic and its cell parameters are  $a=8.05$  Å,  $b=13.04$  Å,  $c=19.48$  Å (fibre axis) and  $\beta=125.4^\circ$ . This unit cell contains two left and two right-handed helical chains, each containing seven  $-(\text{CH}_2-\text{CH}_2-\text{O})-$  monomer units. A value of 2.78 Å per monomer along the chain axis is found in such conformation.

X-ray diffraction allows the study of the structure and the polymorphism of both the lipid and polymer compounds. Wide angle X-ray scattering (WAXS) region informs on short reticular distances between chains while small angles (SAXS) domain corresponds to long spacing in the chain direction. DSC by temperature and enthalpy of transition measurement highlights energetic phenomena that occur during the heating or the cooling of the sample. By coupling these two techniques it is possible to link the structural changes to phase transitions. Infrared Spectroscopy is a complementary technique to the X-ray diffraction and has also been intensively used to determine chain positioning and conformation of glycerides and PEG at the molecular level [18].

In this study, the thermal and structural evolutions of glycerides and mono- and diacyl polyoxyethylene glycols have been characterized by the combined use of coupled X-Ray diffraction and Differential Scanning Calorimetry [19], Polarized Light Microscopy and Infrared Spectroscopy [20]. All characterisations were recorded as a function of temperature.

The aim of the study, only part of which is presented here (more details are given in ref. [21]), is to get a complete structural representation of Gelucire® 50/13, in particular at the molecular scale of PEG chains, as a function of temperature and thermal history of the sample. Then, first objective is to find experimentally all possible polymorphs of Gelucire® 50/13 and secondly to control the formation of these polymorphs under particular experimental conditions. For instance, understanding the thermal and structural variations of these compounds with time might allow us to prevent it by an adequate thermal treatment.

## II - Materials and methods

MICROCALIX is a new instrument that allows simultaneous time-resolved synchrotron X-Ray Diffraction as a function of Temperature and high sensitivity DSC recordings from the sample microsample [19]. The design of the microcalorimeter with X-ray transparent windows and glass or quartz-contained sample capillary allows time-resolved synchrotron X-Ray Diffraction recording together with calorimetry. However, both techniques microcalorimeter and X-ray diffraction are working independently when required. Microcalorimetry and XRDT scans can be performed at any heating rate comprised between 0.01 and 10°C/min with a 0.01°C temperature resolution in the -30/+230°C temperature range. However, maximum cooling rates are T dependent and 10°C/min rates cannot be sustained below 30°C. Conversely, microcalorimeter can also be used as a temperature controlled sample-holder for X-ray purposes not recording microcalorimetry signal. Isothermal microcalorimetry is also possible when time dependent thermal event such as metastable state relaxation, is expected. Temperature and enthalpy calibration of MICROCALIX was obtained using lauric acid as secondary standard.

X-ray diffraction measurements were performed at the D22 and D24 beam lines of the synchrotron ring storage LURE-DCI, University of Paris Sud, Orsay, France using the two different MICROCALIX cells designed for these lines. The Position Sensitive Detectors (PSD) of SAXS and WAXS were calibrated with both silver

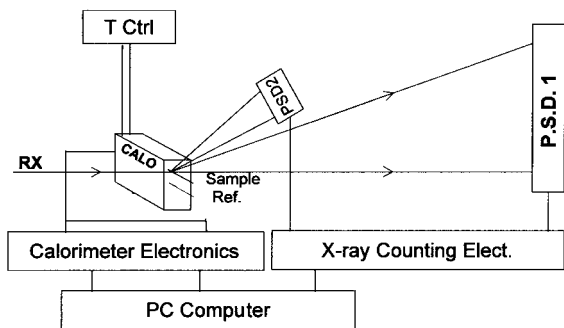
behenate and tristearin. All the figures presented are expressed as a function of the scattering vector,  $q$  ( $\text{\AA}^{-1}$ ) =  $2\pi/d$  ( $d$  is the period of Bragg law) and sample temperature ( $^{\circ}\text{C}$ ). On these two experimental set-ups X-ray diffraction pattern and DSC were collected simultaneously. The high resolution, the high flux and the long distance between sample and detector (2m at D22, 3m at D24) allow to investigate a large range of scattering vectors with a linear response, which in turn permit to access to scattering vector compatible with the largest periods observed. While D24 only allowed single PSD detector, D22 beam line permitted simultaneous SAXS, WAXS and DSC measurement (Figure 1). The sample to detector distance has been chosen to cover a domain of  $q$  ( $\text{\AA}^{-1}$ ) ranging from  $0.02\text{\AA}^{-1}$  to  $0.16\text{\AA}^{-1}$  in SAXS and about  $1.0\text{\AA}^{-1}$  to  $2.0\text{\AA}^{-1}$  in WAXS allowing precise determination of long and short spacings of the long chain compounds examined. For each X-ray pattern, mathematical treatments were performed using IGOR 4.01 in order to determine position, maximum intensity and half width at middle height, of each diffraction peak [22].

Crystallization of Gelucire® 50/13 was monitored by Polarized Light Microscopy (PLM) using a Nikon Eclipse E600 (Champigny, France) microscope equipped with a lab-made temperature-controlled stage. This stage allows T scan from 100°C down to -30°C at any rate between 10 and 0.1K/min thanks to T control by Peltier modules. About 0.5 mg sample was placed between glass cover plates, melted for 10 min at 60°C and cooled from 60°C to 0°C at 1K/min. The description of IR measurements is given elsewhere [21].

## III - Results and discussion

Samples of Gelucire® 50/13 were supplied as small pellets by Gattefossé (France) and were analyzed without any special thermal treatment (as received) after gentle manual grinding. Gelucire® 50/13 consists of a mixture of mono-, di-, triacyl glycerol and mono-, diacyl polyoxyethylene glycols (MW 1500).

Polarized Light Microscopy of Gelucire® 50/13 on cooling from 60°C shows first a completely



### Simultaneous DSC/WAXS/SAXS design



Figure 1: Schematic drawing and photo of MICROCALIX setup (photo taken at LURE D24 station). RX coming from left are passing through the calorimeter cell and its sample capillary-contained. Cryostat assures T control, while calorimeter electronics (facing in photo) and PC computer simultaneously collect DSC and X-ray data thank to PSDs.

melted sample. At cooling rate of 1K/min. first crystals appeared at 47°C while homogeneous distribution of small crystals was obtained at 45°C (not shown) but not at vicinity of the very first crystals that appeared branched as shown Figure 2 (centre of image). No change is observed on further cooling until about 25°C, the small crystals keeping surrounded by liquid phase. Then, a second crystallisation develops very fast everywhere in the sample leading to a homogeneous distribution of small crystal (Figure 2, insert). The mean size of the crystals is estimated visually to about 5µm.

Figure 3 represents the 3D evolution of both SAXS and WAXS patterns as a function of

temperature of an untreated sample of Gelucire® 50/13 during its heating at a rate of 1°C per minute between 20°C to 60°C. Figures 4 and 5 represent subsequent crystallization and second melting recorded in the same conditions. The bottom moiety of each figure represents the evolution of the position and of the intensity (symbol size is proportional to line intensity) of each peak observed.

All recordings are characterized by similar SAXS and WAXS main lines. However, some minor differences can be detected between each 3D plots. Analysis of such plots will allow to tentatively interpret the DSC recordings of Figures 3 to 5 as well as some previous observations [1]. As previously reported, the occurrence and vanishing of the main lines observed allows to delimit the domain of existence of the different crystalline phases and to relate them to the transitions recorded by DSC. In this respect the most striking behaviour is that recorded upon crystallization. Figure 4 shows that the weak but distinct lines at  $1.49\text{Å}^{-1}$  (4.2Å) and  $0.127\text{Å}^{-1}$  (49.5Å) are strongly correlated together and to the small exotherm observed at  $T_{\text{onset}} = 47^\circ\text{C}$  by DSC. The long spacing value of 49.5 Å corresponds exactly that of a form of triglycerides with hexagonal packing of hydrocarbon chains and 2L stacking

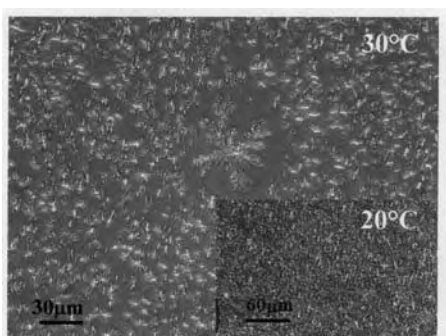


Figure 2 Polarized Light Microscopy of Gelucire® 50/13. Photos taken at 30°C and 20°C on cooling from melt.

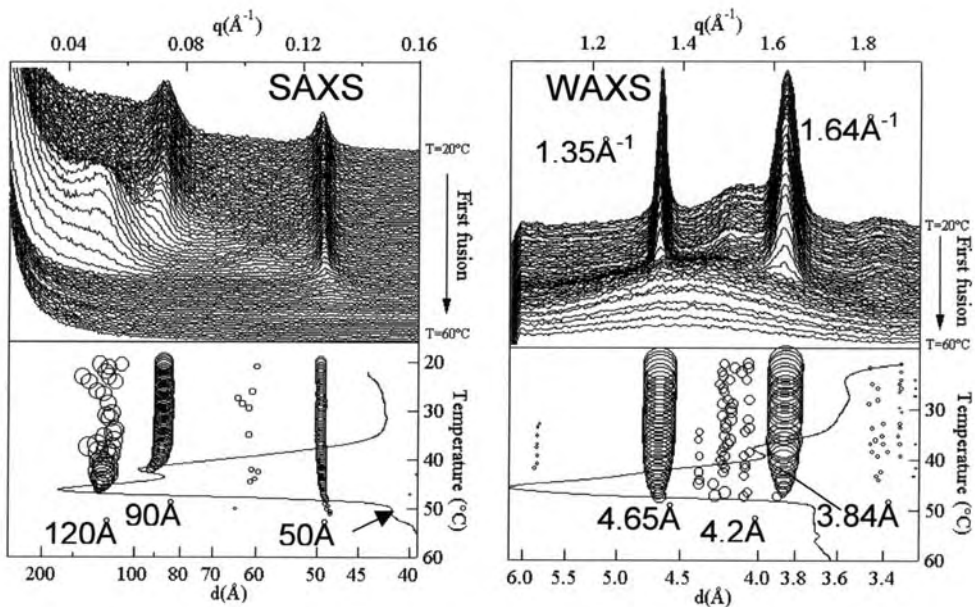


Figure 3: Evolution (3D plot) of SAXS and WAXS patterns as a function of temperature during first melting of an untreated Gelucire® 50/13 sample (top). Plane spacings deduced by IGOR automatic analysis from line positions (circle centre position) and intensity (size of the symbol) are shown in the bottom as a function of T for each peak observed in SAXS and WAXS. DSC curves recorded simultaneously with SAXS or WAXS are superimposed.

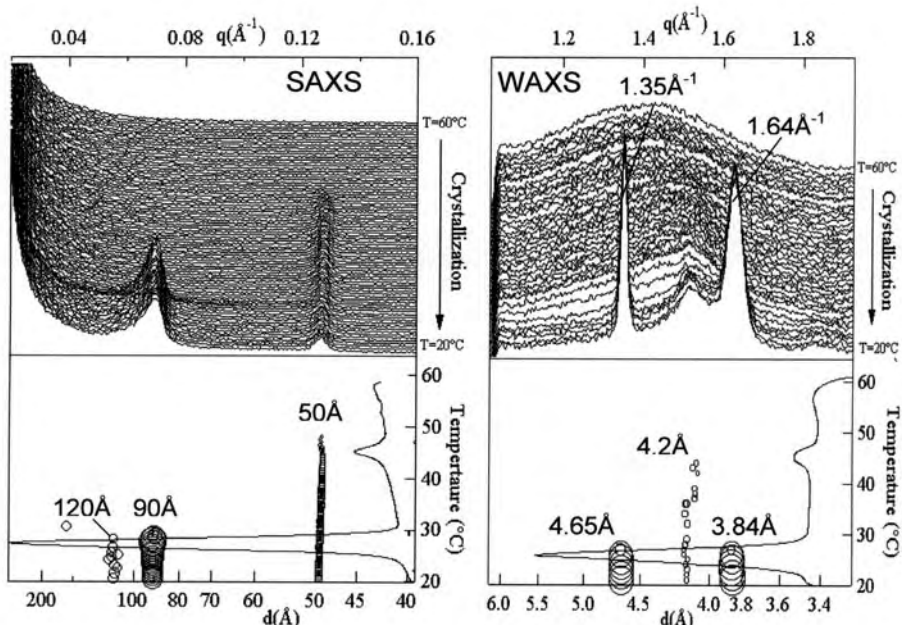


Figure 4: Evolution (3D plot) of SAXS and WAXS patterns as a function of temperature during first crystallization of Gelucire® 50/13 sample following melting of Figure 3 (top). Plane spacings deduced by IGOR automatic analysis from line positions (circle centre position) and intensity (size of the symbol) are shown in the bottom as a function of T for each peak observed in SAXS and WAXS. DSC curves recorded simultaneously with SAXS or WAXS are superimposed.

of molecules (Small, Chapman etc.) taking into account the fatty acid composition of Gelucire® 50/13. This crystallization is likely related to that first observed between 47 and 45°C by PLM. To note is the slight increase of stacking period (about 50 Å) observed at the very beginning of the crystallization which might be related to the very first branched crystals observed by PLM. This first crystallization appears independent of the main one of Gelucire® 50/13 observed at  $T_{\text{onset}}$  = about 29-30°C and characterized by a sharp strong exotherm by DSC (Figure 4).

This main crystallization is related to the occurrence of two strong lines at  $1.35\text{\AA}^{-1}$  (4.65 Å) and  $1.64\text{\AA}^{-1}$  (3.84 Å) at wide angles corresponding to that at  $0.07\text{\AA}^{-1}$  (90Å) which is accompanied by a weak broad line at about  $0.055\text{\AA}^{-1}$  (114Å). Surprisingly the line at 4.65 Å is very sharp while that at 3.84 Å is twice broader and slightly asymmetric (Figure 4). At  $T > 50^\circ\text{C}$ , melted chains display an intense broad line centred at about  $1.4\text{\AA}^{-1}$  (4.5 Å), clearly visible on Figures 3 to 6. This broad bump is attributed to a liquid crystalline organisation of the PEG chains similar to that observed for hydrocarbon chains at similar  $q$  values.

Both meltings (Figures 3 and 5) are similar. They do not correspond exactly to the reverse of crystallization process but for the minor fraction which melts about at its crystallization  $T$  (melting of this fraction is indicated by arrows on SAXS bottom moieties of Figure 3 and 5 and corresponds to small single or double endotherms). While crystallization of the main phase occurred at  $T < 30^\circ\text{C}$ , its melting  $T$  is  $40 < T < 50^\circ\text{C}$ . There is about a 10-20°C supercooling  $T$  domain. Moreover, surprisingly, the melting is accompanied by i) a progressive shift of the main small angle ii) corresponding to an important increase of the stacking period from 90 to about 120 Å iii) not accompanied by any change in the wide angle lines then no change of the lateral packing is observed. The change observed at small angles is related to the double peak or the shoulder observed on the main peak by DSC.

Moreover, the intensity of the line at about  $120\text{\AA}$  (a weak second order of which is also observed on figures 3 and 5) depends on the melting. This

line is more important for the stabilized (first fusion) than for a sample recently crystallized (second fusion). Then, a solid state evolution within the sample is expected. Comparison of SAXS of Figures 3 and 5 shows that the heating to  $T > 40^\circ\text{C}$  triggers in the stabilized sample a transition more important than the one observed in the fresh one. The origin of this transition is discussed below and more in detail elsewhere [21].

#### • *Molecular packing of low MW PEG compounds.*

In order to help solving the molecular packing of mono-, diacyl polyoxyethylene glycols, a sample of PEG (MW = 1500) was examined in the same conditions than Gelucire® 50/13. Figure 6 shows the X-ray diffraction evolutions as well as DSC. The WAXS signature is identical to that of Gelucire® 50/13 showing that POE chains of Gelucire® 50/13 packs in the same subcell (shown Figure 7). However, the long spacing observed is significantly different. At room temperature, SAXS patterns show three sharp peaks,  $0.064\text{\AA}^{-1}$  and  $0.128\text{\AA}^{-1}$  and  $0.189\text{\AA}^{-1}$  (not shown) ( $d(\text{\AA}) = (2*\pi)/q(\text{\AA}^{-1}) = 96.7\text{\AA}$  and  $49.0\text{\AA}$  and  $33.2\text{\AA}$ ). They can be ascribed respectively to the first, the second and the third order of a single phase. It follows that at room temperature, PEG 1500 presents a single lamellar phase with a long structure of  $96.7\text{\AA}$ . This value is even larger than the value observed for Gelucire® 50/13 while the molecule length of this last should be longer by one or two acyl chains.

Calculation (not shown) of the X-ray pattern corresponding to the molecular packing presented Figure 7 using Carine 3.1 software yielded both a sharp line at  $1.35\text{\AA}^{-1}$  (4.65 Å) and a series of lines at  $1.60 < q < 1.67\text{\AA}^{-1}$  close enough to overlap and produce the broad line of WAXS pattern of Gelucire® 50/13 observed. Some additional minor lines are also observed at wide angles [21]. The final melting of PEG 1500 as observed by SAXS and WAXS as well as by DSC resembles to that observed for Gelucire® 50/13. As expected from “pure” compound the SAXS lines are sharper for PEG than for Gelucire® 50/13 allowing observation of a second order line at  $48.5\text{\AA}$ . The WAXS line at  $4.2\text{\AA}$  attributed to glyceride

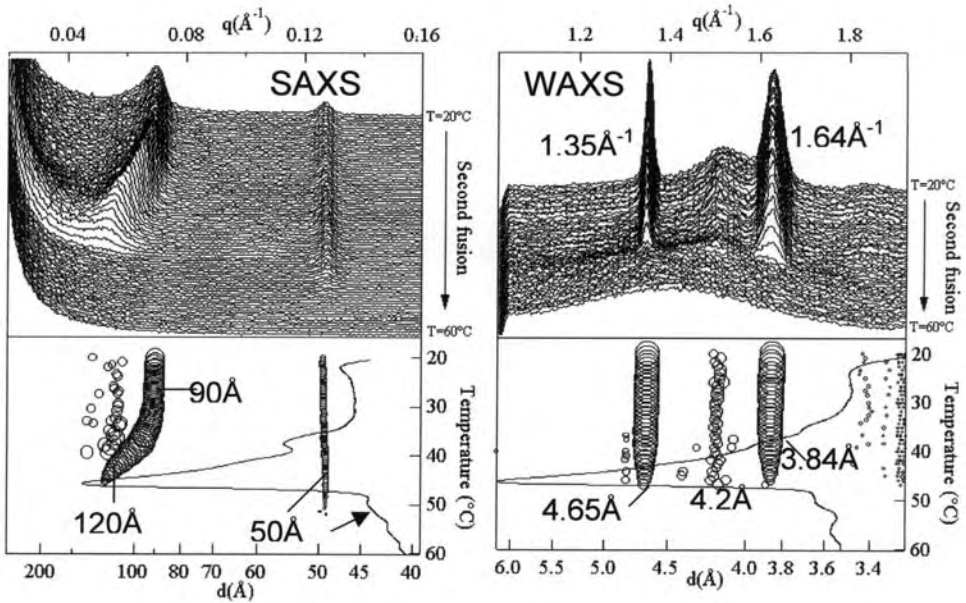


Figure 5: Evolution (3D plot) of SAXS and WAXS patterns as a function of temperature during second melting of the Gelucire® 50/13 sample following crystallization of Figure 4 (top). Plane spacings deduced by IGOR automatic analysis from line positions (circle centre position) and intensity (size of the symbol) are shown in the bottom as a function of T for each peak observed in SAXS and WAXS. DSC curves recorded simultaneously with SAXS or WAXS are superimposed.

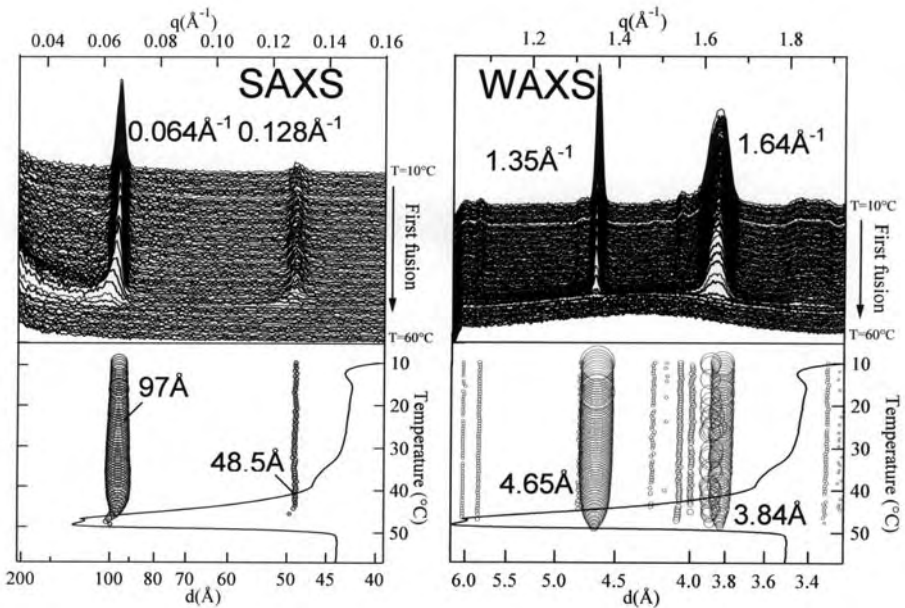


Figure 6: Evolution (3D plot) of SAXS and WAXS patterns as a function of temperature during first melting of a PEG 1500 sample (top). Plane spacings deduced by IGOR automatic analysis from line positions (circle centre position) and intensity (size of the symbol) are shown in the bottom as a function of T for each peak observed in SAXS and WAXS. DSC curves recorded simultaneously with SAXS or WAXS are superimposed.

mixture is absent in PEG (Figure 6) and replaced by the weak sharp lines as expected from calculation. This further confirms the coexistence of a glyceride phase with the PEG one.

Infrared spectroscopy which has been used extensively to characterize lipids [9, 18] and the different conformations of PEG, helical or zigzag [15, 23], was recorded as a function of T in order to identify the various species formed and their transitions. It appeared clearly that several bands are temperature dependent. Such behaviour was also observed for Gelucire® 50/13. This confirms that the PEG moiety of this last adopts in the solid state the same conformation than pure PEG.

#### • *Molecular packing of Gelucire® 50/13 compounds.*

The origin of the SAXS lines observed allowed us to tentatively propose a molecular packing of PEG phase in Gelucire® 50/13. WAXS recordings above clearly show that the PEG moiety of Gelucire® 50/13 adopts a lateral packing identical to that of “pure” PEG 1500. It is nowadays well accepted that the “pure” PEG adopts a helical conformation with repeating *trans*, *trans* and *gauche* conformation as shown Figure 7. It is likely that the PEG moiety of Gelucire® 50/13 is also helically packed. This packing and the tilt of the helix axis relatively to the plane of diffraction  $hkl = 001$  depends on temperature. The conformation observed at high temperature just before melting is that showing the larger period (about 120 Å). Such period could not correspond to single straight PEG chain ( $\beta=90^\circ$ ) since a PEG molecule of MW = 1500 is expected to be only about 94 Å long (79.5 Å for  $\beta=125.4^\circ$ ). Such behaviour has also been observed in alkanes for which the rotator phase preceding melting also displays vertical chains (Small, 1986) while the low temperature packing corresponds to tilted chains.

A similar behaviour is expected for the PEG moiety of Gelucire® 50/13 which is composed of a mixture of mono and di acylated PEG (in about equal proportions). On another hand, the period of about 120 Å could not correspond to the addition of two hydrocarbon chain lengths and one PEG 1500. Then, this period was necessarily attributed to the sum of a single hydrocarbon and

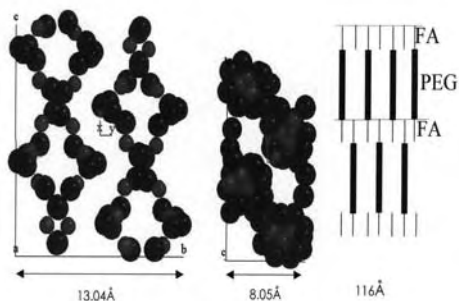


Figure 7: Schematic models of the molecular packings of PEG and PEG derivatives. From left to right, illustration of the packing of PEG as obtained from Carine 3.1, the helices are seen laterally (left) and from top (middle), only carbon (black) and oxygen (red) atoms are drawn. The right view represents the probable interdigitation of hydrocarbon chains at both extremities of the PEG helices of the Gelucire® 50/13. Bold lines represent PEG helix while narrow ones figure hydrocarbon chains of fatty acids (FA).

a single PEG helix as illustrated on Figure 7. In this packing taking into account the volume occupied by the hydrocarbon chains as well as their distribution on PEG chain ends we found that the hydrocarbon chains are likely interdigitated.

The smaller period at about 90 Å observed at low temperature corresponds to a tilt of PEG helix, if not of both chains. In fact the mechanism by which chains stand up at high temperature could be relatively more complex and operating step by step as discussed in [21].

#### IV - Conclusion

Investigation of the structures made by excipients in the anhydrous state is of prime importance regarding the difficulty encountered by pharmaceutical companies to formulate poorly water-soluble drugs. Such structural studies should also be made in excess water to get the basis for improving their dissolution rate as well as for the control of drug delivery [24, 25, 26].

By using coupling of time-resolved synchrotron X-ray diffraction and DSC, we have established the thermal behaviour of Gelucire® 50/13 and related it to structural evolutions occurring as a function of time and temperature. Several

lamellar phases and the helical conformation of the PEG 1500 moiety of Gelucire® 50/13 have been identified.

From a methodological point of view, the scanning of temperature systematically applied to all the techniques used for characterization including X-ray diffraction coupled to DSC, PLM and infrared spectroscopy, enabled us to identify the transitions and phase changes observed during heating and cooling of Gelucire® 50/13. Especially, the complex DSC recordings received for the first time to our knowledge a tentative explanation based on both evolution of molecular packing and the coexistence of at least two phases within Gelucire® 50/13.

Although this could be guessed from the thermal behaviour described above, a more detailed study has shown that a slow cooling rate favours the formation of a unique lamellar phase of 120 Å having the higher melting point. Conversely, a rapid cooling rate produces a mix of lamellar phase of different periods 90 Å and 120 Å, while, quenching leads to even different periods [21].

Interestingly, figures 3 and 5 show that whatever the cooling rate (even quenching) it is always possible to reach the most stable form at 120 Å by heating up again the excipient above 36°C during a few minutes.

Nevertheless the nature and value of the tilt of mono and diacyl polyoxyethylene are still unknown. Structural studies by X-ray diffraction on pure mono or diacyl polyoxyethylene and molecular simulation are under way in this respect.

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# POLYMER-COATED LIPID NANOSTRUCTURES AS CARRIERS FOR ORAL PEPTIDE DELIVERY

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## Summary

Over the last decade we have assisted to a biotech revolution that is leading to the development of an important number of macromolecules with a great therapeutic potential. As a consequence, there is an increasing necessity to define specific formulation strategies for these delicate compounds. In our group, we have attempted to develop new nanocarriers for oral peptide administration. Among them, those consisting of a lipid core surrounded by a hydrophilic coating have resulted very promising. The lipid core was either liquid (Miglyol® 812 oil) or solid (tripalmitin) and the coating was a non-charged polymer such as polyethyleneglycol (PEG) or a positively charged polysaccharide i.e. chitosan. We first demonstrated that these polymer-coated nanostructures have an improved stability in the gastrointestinal fluids. Following this, we tested the ability of these new nanostructures to enhance the systemic absorption of the model peptide salmon calcitonin (sCT), after oral administration. The results indicated that, irrespective of the nature of the core, the chitosan-coated systems provided an enhanced and prolonged hypocalcemic response to sCT. In contrast, the PEG-coated lipid systems were not successful at increasing the response to sCT. The studies performed in the Caco-2 model cell line indicated that, irrespective of the coating, the nanostructures were internalized into the monolayer, however, only those coated with chitosan caused a significant reduction of the transepithelial resistance. Consequently, these results suggest that the superiority of the chitosan-coated nanostructures as compared to the PEG-coated nanostructures, could be related to inherent properties of chitosan, i.e. its favourable interaction with the mucus overlaying the intestinal mucosa and, possibly, its ability to open the tight junctions between epithelial cells.

## Keywords

*Nanoparticles, nanocapsules, lipid-based carriers, oral peptide delivery, chitosan, PEG.*

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## 1. Introduction

Overcoming the low bioavailability of drugs that have low permeability through biological membranes is one of the most prominent pharmaceutical problems [1]. The advent of the biotech revolution has stressed even more this limitation as an increasing number of molecules with high therapeutic potential are dumped because of their poor biopharmaceutical properties [2]. Peptides and proteins are the molecules that best exemplify these biopharmaceutical properties: together with their poor permeability, these molecules are extremely labile to the action of proteolytic enzymes [3]. The combination of these two biopharmaceutical barriers (low permeability through the epithelia and degradation) constrains the oral bioavailability of peptides to values usually below 1%. One of the most appealing strategies to improve the oral absorption of these delicate macromolecules has been the association or inclusion of peptides in submicrometer-size carriers [4,5,6]. The challenge, however, has been the definition of the characteristics of the carrier that will lead to an optimized transport and, an adequate delivery of the associated peptide. Among the materials chosen for the design of these nanocarriers, the lipids have played an important role.

### *1.1 From lipid excipients to nanostructured lipid carriers*

Lipids comprise a rather heterogeneous group of molecules that are characterized by the presence of aliphatic chains. Lipids have been used for pharmaceutical preparations due to their excellent biocompatibility and their wide spectrum of physicochemical characteristics, which make them useful for multiple applications [7]. To this date, waxes, mono-, di- and triglycerides, fatty acids, cholesterol derivatives or phospholipids are the most common classes of lipids used in traditional pharmaceutical formulations such as lipid emulsions, intramuscular depot injections, matrix tablets or suppositories.

In the last decades, a better understanding of the interactions of lipids at the cellular level has considerably increased the interest for these materials as drug transmucosal carriers. In fact,

electron spin resonance and NMR studies have shown that monoglycerides and fatty acids interact causing a disorder in the lipid membranes that is supposed to be related to their capacity to permeate the epithelia [8]. Moreover, some lipids have exhibited an affinity for the SH-proteins, which are known to play a role in transmembrane transport and tight junction permeability [9]. More recently, it has also been shown that some lipids can also interact with P glycoprotein and cytochrome P 450, thereby facilitating intracellular drug delivery [10].

However, maybe the most unique characteristic of lipid based formulations is their ability to be digested in the intestine, thus producing micelles that can enter the organism through the intestinal lipid transport system [7]. Drugs incorporated in the micelles resulting from lipid digestion may be internalized through this pathway [11]. The absorption enhancing properties of lipid excipients have already been tested for oral insulin delivery [12,13]. This early works provided some proof-of-concept of the possibility to achieve higher oral bioavailability of peptides if administered with lipid promoters.

The new challenges faced by lipid formulations have stimulated the design of more advanced drug delivery systems, particularly submicrometric carriers, whose high surface/volume ratio maximizes the interactions with the biological environment. Moreover, some of these nanocarriers, i.e. liposomes and solid lipid nanoparticles, have shown their ability to cross the intestinal epithelium, probably through an endocytic pathway [14,15].

### *1.2 Liposomes in oral peptide delivery*

The capacity of liposomes to encapsulate hydrophilic macromolecules has been suggested as a way to protect them in the gastrointestinal tract [16]. However, in order to achieve this protective effect, it is critical to preserve the liposome integrity in this hazardous environment. Since the early works from Dapergolas et al. [17] it is well known that liposomes made of phospholipids with a phase transition temperature above 37°C are more stable in the GI tract than those composed of lipids in a liquid-crystalline state (such as natural phospholipids).

A step further in the development of oral liposomes has been based upon the optimization of their surface characteristics. For example, the modification of the surface of liposomes with protective coatings such as mucin or PEG resulted in enhanced oral insulin effect compared to uncoated liposomes. *In vitro* experiments confirmed that these liposome formulations were able to protect the peptide more efficiently against its degradation in intestinal fluids [16]. Nevertheless, the beneficial effect of these coatings should not only be attributed to its protective capability, as a subsequent study has also shown that these polymers increased the residence time of the liposomes in the GI tract. More concretely, mucin-coated liposomes displayed an extended gastric retention and PEG-coated liposomes an increase in the residence time in the small intestine [18]. Liposomes coated with other type of mucoadhesive polymers such as Carbopol® or chitosan have also shown to enhance the absorption of orally administered peptides [19,20].

The surface charge of liposomes also seems to have an important role in the capacity of liposome formulations to promote the oral peptide absorption, however, the optimal value of that parameter remains unclear. Some papers have indicated that the presence of anionic lipids improves the intestinal absorption of insulin [21,22], while others have reported the same effect, either for insulin or calcitonin for cationic liposomes [16,23].

### ***1.3 Microemulsions and nanoemulsions in oral peptide delivery***

Microemulsions and nanoemulsions are dispersed systems of two immiscible liquids. Microemulsions can also be defined as colloidal dispersions of liquids thermodynamically stabilized by a layer of surface-active molecules. Nanoemulsions are not thermodynamically stable, however, their coalescence can be hindered for prolonged periods of time if they are properly stabilized. With an already marketed oral Cyclosporine A formulation (Sadimmune Neoral®), increased attention has been paid to the possibility of formulating peptides orally by including them in submicrometric emulsions. Nevertheless, up to

date, the most successful results have been obtained with small peptides such as desmopressin [24], vasopressin [25] or the fibrinogen antagonist peptide SK&F 106760 [26]. This positive behaviour has been understood as a consequence of the lipid absorption promoting effect. This hypothesis has been further supported by the fact that composition, rather than emulsion droplet size was found to be the main factor responsible for the enhanced peptide absorption. Indeed, the presence of a polyoxyethylene derivative (Cremophor EL) was considered essential to achieve those high peptide oral bioavailabilities [27].

Despite the encouraging data obtained for Cyclosporine A and the SK&F 106760 peptide, the success of the submicron emulsion for oral delivery of high molecular weight peptides remains to be a challenge. Some improvements in the absorption of peptides, i.e. salmon calcitonin, have been observed for submicron emulsions which were coated with a mucoadhesive polymer such as Carbopol® [24]. This improved absorption of the associated peptide was attributed to the enzyme inhibitory action of this polymer [28]. More recent studies [29] have confirmed that the presence of Carbopol® as a coating was critical for the efficacy of the formulation.

### ***1.4 Polymeric nanocapsules in oral peptide delivery***

Nanocapsules are carriers comprising an inner lipid reservoir and an outer polymeric wall. Insulin-loaded polycyanoacrylate nanocapsules have been reported, so far, some of the most outstanding results in animal models. Significant reductions in the glycemia of diabetic rats were produced and maintained for prolonged periods of time, when that nanocapsule formulation was administered orally [30]. The extent and duration of the pharmacological effect was explained by the penetration of the nanocapsules through the mucosa and the further release of the peptide from the internalized formulation [31]. Unfortunately, the results obtained in the dog model, although positive, were not as promising as those previously reported with rats [32].

## 2. New polymer-lipid nanostructures for oral peptide delivery

Although over the last years some breakthrough technologies have led to a new perspective of oral peptide delivery, renewed efforts are still needed to obtain a clinically useful carrier system. Lipid-based carrier systems are not an exception and still have to face important challenges to optimize their performance.

First, lipids are labile materials, very susceptible to enzymatic degradation in the intestine. As a consequence, lipid drug delivery systems are usually destroyed before reaching the adequate site for peptide absorption, thus losing their ability to protect and enhance the transport of the peptide. Finally, it is generally accepted that the capacity of transport of lipid carriers, even though significant, may be insufficient at this stage to achieve a clinically useful effect.

In order to advance a further step in the development of a useful peptide delivery system for the oral route, we have designed new carrier systems based on a lipid core-polymer coat structure. The polymeric coating was intended to optimize the interaction of the delivery system with the biological environment present in the gastrointestinal tract. Hence, we selected polymer coatings that were supposed to prevent aggregation and destruction of the delivery systems, to confer mucoadhesive properties to the carriers or to enhance transepithelial permeability.

A schematic illustration of the nanostructures prepared is depicted in Figure 1. Since the composition of the core is supposed to affect drug incorporation and release [33], we have proposed three different cores for the nanostructures: a solid lipid (tripalmitin), a liquid

lipid (Miglyol® 812) or a solid-liquid lipid mixture (tripalmitin/Miglyol® 812).

Regarding the polymer coating, two hydrophilic polymers have been selected: PEG and chitosan. The selection of PEG is based on the results of previous studies performed by our group, which have shown that a PEG coating around PLA nanoparticles greatly enhanced their stability in simulated gastrointestinal fluids [6]. Similarly, studies performed by Olbrich et al. have shown that a coating with ethylene oxide derivatives (Poloxamers) around the lipid nanoparticles protected them from degradation by pancreatic enzymes [34]. Moreover, it has been indicated that a PEG coating may favour the interaction of colloidal carriers with mucosal surfaces [18,35]. However, while the protective effect of PEG is well understood, its possible role in enhancing the interaction of nanosystems with epithelia remains unclear. Nevertheless, whether this improved interaction is simply a consequence of the enhanced stability of the nanoparticles in contact with biological fluids, or is additionally helped by some specific mechanisms, the clear observation is that the PEG-coated PLA nanoparticles are able to cross the nasal mucosa up to a more important extent than those non-coated [36,37].

On the other hand, the selection of the polysaccharide chitosan as a coating for transmucosal nanocarriers is justified by its interesting biopharmaceutical behaviour. From the point of view of drug delivery, some important features of this material are its mucoadhesiveness [38] and its capacity to increase the permeability of epithelia [39]. In addition, previous studies from our group have shown that chitosan-based nanosystems are able to interact with mucosal surfaces, thus facilitating

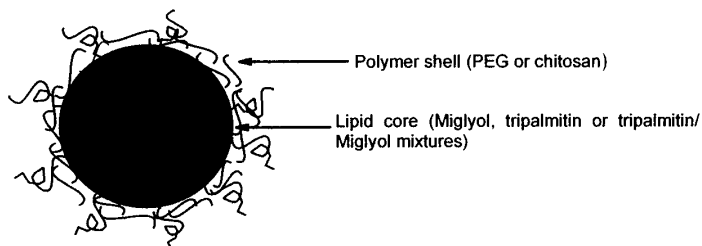


Figure 1: Illustration of the proposed architecture of the designed polymer-coated lipid nanostructures.

the interaction and transport of the associated active compound across these surfaces. More specifically, chitosan nanoparticles were able to enhance the transport of insulin across the rabbit nasal mucosa up to a much greater extent than chitosan solutions [40]. Similarly, low molecular weight chitosan nanoparticles elicited an interesting capacity for the transport of antigens across the nasal mucosa [41]. In addition, besides their favorable behaviour for the nasal transport of macromolecules, chitosan nanoparticles exhibit an affinity for the ocular mucosa. Recent studies aimed at studying the residence time of these nanoparticles in the ocular mucosa, following topical administration, indicated that the interaction of chitosan with the cornea and conjunctiva was enhanced and prolonged when presented in a nanoparticulate form [42]. All these studies provided evidence of the benefits of chitosan nanosystems as compared to other forms of presentation of chitosan.

Taking this previous information into account the aim of the present paper was not simply to review the state-of-the-art of the potential of lipid-based colloidal systems for oral peptide administration but to specifically emphasize the latest advances from our work regarding the design and evaluation of polymer-coated lipid nanosystems.

## 2.1 Preparation and characterization of polymer-coated lipid nanostructures

PEG-coated tripalmitin (or PEG-coated tripalmitin/Miglyol®) nanoparticles were prepared in a single step by a modified double emulsion-solvent evaporation method [43]. In this technique, hydrophilic drugs such as peptides may be incorporated to the nanoparticles in the inner aqueous phase. The PEG coating was formed due to the addition of the modified fatty acid PEG-stearate to the organic phase.

On the other hand, chitosan-coated nanocarriers have been prepared following different procedures depending on the nature of the core. Chitosan-coated solid lipid nanostructures were prepared by the double emulsion-solvent evaporation technique, indicated above [43]. When using this procedure, chitosan can be

either added to the external aqueous phase of the double emulsion or once the lipid cores were precipitated [44]. Alternatively, chitosan-coated submicron emulsions were prepared according to the solvent displacement-solvent evaporation technique, as previously reported [45]. As in the case of the solid cores, chitosan can be added before or after the solvent evaporation takes place. Irrespective of the technique, a critical ingredient for the formation of the chitosan-coated systems was the presence of lecithin, which was added to the organic phase in both procedures. Indeed, an ionic complex between lecithin and chitosan is formed at the interface of the colloidal system, thus facilitating the attachment of chitosan onto the surface of the system.

Lipid cores (non-coated) showed particle sizes around 200 nm upon preparation and strongly negative surfaces (Table 1). The coating of the tripalmitin cores with PEG produced a negligible effect on the particle size whereas the zeta potential shifted towards more neutral values [43]. As described for other PEG-coated systems, this change is a consequence of the extension of the shear plane of the colloidal system [46]. The formation of a chitosan coating around the lipid cores led to an increase in the particle size, accompanied by an inversion of the zeta potential from negative to positive values (Table 1) [47]. Both, the size increase and the inversion of the zeta potential, support the successful formation of a chitosan layer surrounding the lipid cores.

Table 1: Hydrodynamic diameter (analyzed by photon correlation spectroscopy) and zeta potential (analyzed by laser Doppler anemometry) of the studied nanostructures (Mean  $\pm$  SD., n=3). Data from: <sup>1</sup>Prego et al. [54] and <sup>2</sup>García-Fuentes et al. [47].

Formulation	Size (nm)	Zeta Potential (mV)
Nanoemulsion <sup>1</sup>	195.8 $\pm$ 1.1	-52.0 $\pm$ 1.1
Nanocapsules <sup>1</sup>	266.6 $\pm$ 7.6	+34.8 $\pm$ 0.6
Tripalmitin cores <sup>2</sup>	200.0 $\pm$ 2.3	-50.3 $\pm$ 1.8
PEG-coated tripalmitin nanoparticles <sup>2</sup>	226.4 $\pm$ 7.5	-34.8 $\pm$ 2.8
PEG-coated tripalmitin/Miglyol® nanoparticles <sup>2</sup>	207.4 $\pm$ 19.1	-36.6 $\pm$ 2.5
Chitosan-coated tripalmitin nanoparticles <sup>2</sup>	537 $\pm$ 16	+29.2 $\pm$ 6.2

The size and the morphology of the PEG- and chitosan-coated systems were visualized by transmission electron microscopy (Figure 2). All the nanostructures presented a spherical shape. In the case of PEG-coated nanoparticles, a difference in the staining was appreciated between the inner and the outer part of the nanoparticles, being this a possible indication of the core-coat structure of the systems. Unfortunately, this difference in staining could not be observed for chitosan-coated tripalmitin nanoparticles although the change in particle size was clearly visible in the micrographs. This dissimilarity between micrographs could be related not only to the different nature of the coating polymers but also to the high chitosan molecular weight as compared to that of PEG. This observation led us to suggest that the chitosan may be forming a more compact polymer layer compared to that of the PEG.

NMR analysis has allowed us to confirm that the PEG-coated nanostructures are mainly composed of a triglyceride core and a small amount of surfactants and surface modifying molecules (i.e. lecithin, PEG-stearate) [48]. On the other hand, the core-coat model proposed for these structures was fully confirmed in the case of PEG-tripalmitin nanoparticles. NMR experiments aimed to analyze the relaxation of the chemical groups of nanoparticle suspensions and their spin-population effects with the water protons confirmed the presence of PEG protruding towards the external phase and the presence of a solid lipid core comprising mainly the triglycerides. Moreover, quantitative NMR analysis has confirmed the possibility of

modulating the PEG coating density of these carriers by controlling the amount of PEG-stearate added in the preparation procedure [48].

The NMR characterization of nanoparticles having a tripalmitin/Miglyol® core indicated that there were significant amounts of the oil incorporated within the nanoparticles matrix. Moreover, the presence of Miglyol® as separated liquid domains associated to the nanoparticles was confirmed by NMR relaxation analysis and the observed restricted diffusion dynamics of the entrapped oil. A further confirmation of this structure was obtained from differential scanning calorimetry (DSC) and x-ray diffraction spectroscopy [49].

## 2.2 Stability in simulated gastrointestinal fluids

Taking into account that the designed lipid nanostructures were intended for oral drug delivery, the assessment of their stability in gastrointestinal fluids was critical. Indeed, lipid nanoparticles have shown important particle aggregation in gastric media and a marked degradation in simulated intestinal fluid with enzymes [50,51]. Interestingly, the aggregation of the lipid cores in gastric medium has been found to be dependent on the mechanism of particle stabilization. Thus, we previously prepared lipid cores that were stabilized only with lecithin (uncoated cores), a surfactant that confers on the system a distinctly negative charge at neutral pH. At low pH, the surface charge of the lipid nanostructures was significantly reduced due to the less important ionization of the negatively charged phospholipids, thus leading to the

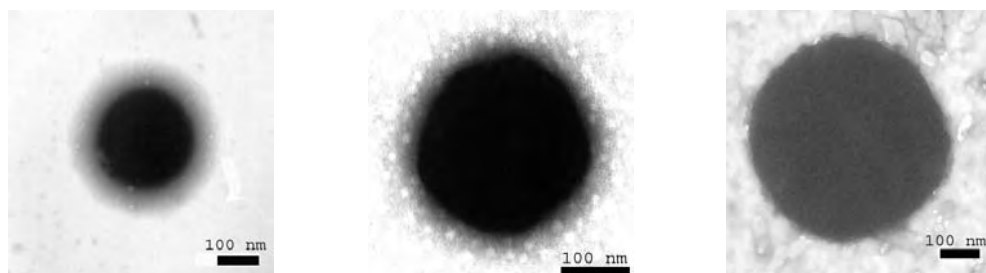


Figure 2: Transmission electron microscopy pictures of different lipid nanostructures: PEG-coated tripalmitin nanoparticles (left), PEG-coated tripalmitin/Miglyol® nanoparticles (center) and chitosan-coated tripalmitin nanoparticles (right).

aggregation of the nanoparticles in simulated gastric medium (Figure 3) [43]. The importance of the pH of gastric medium in the aggregation processes was also assessed by incubating the formulations in an inorganic acid solution (pH 1.2), without enzymes. As can be appreciated in Figure 3, the addition of a second ionic stabilizing surfactant (sodium cholate) did not enhance the stability of tripalmitin cores neither in inorganic medium nor in simulated gastric medium. On the contrary, by coating the lipid cores with polymers with steric stabilizing properties such as the PEG-stearate or the poloxamer 188, completely stabilized the formulations in both media [43,52]. As indicated before, previous experiments performed in our group with polyester nanoparticles also support the key role of PEG in providing enhanced stability to the nanoparticles formulations incubated in simulated gastric media [6].

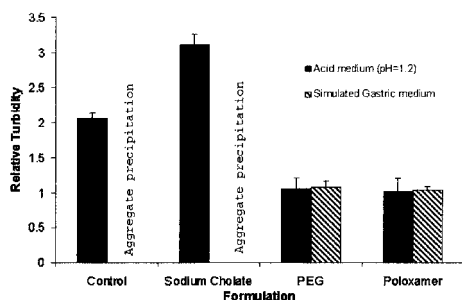


Figure 3: Relative turbidity (expressed as the ratio between the optical density value after 1 h of incubation with respect to the initial value) of tripalmitin cores (control) and tripalmitin cores stabilized with different surfactants in an inorganic acid medium and in simulated gastric medium (mean  $\pm$ SD, n=3). Adapted with permission from García-Fuentes et al. (2002) [43].

The results of our experiments also showed that, as expected, the lipid cores undergo an important degradation in intestinal medium (Figure 4). In fact, the capacity of pancreatic lipase to degrade lipids is accelerated in these formulations as the lipid is highly dispersed and, therefore, presents an important surface area for interaction with enzymes. However, protection of the lipid cores by a hydrophilic polymer coating capable of hindering the interaction with lipolytic enzymes, such as that of provided by PEG-stearate or poloxamer 188, reduced significantly the degradation.

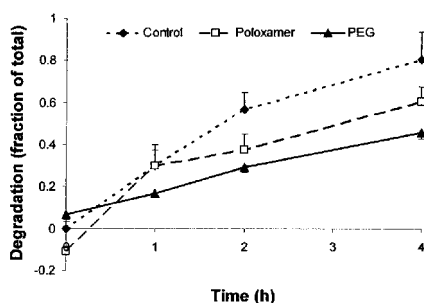


Figure 4: Degradation of tripalmitin cores (control) and PEG- or poloxamer-coated tripalmitin nanoparticles in simulated intestinal medium (mean  $\pm$ SD, n=3). Graph from García-Fuentes et al. (2002) [43].

Although the charge and solubility of chitosan are pH-dependent due to the presence of amine groups, our stability studies have evidenced that it may also enhance the stability of lipid nanostructures in gastrointestinal fluids [47,53]. More specifically, the results from our studies showed that chitosan-coated lipid nanostructures are stable in simulated gastric fluids. Moreover, chitosan also protected the lipid cores against enzymatic degradation in simulated intestinal medium [47].

### 2.3 Peptide loading and release

A major goal in designing these lipid nanostructures was to achieve a sufficient loading of the peptide in the carriers while maintaining their active structure. Specific nanoparticle preparation methods were developed for this aim. In the case of nanocapsules, the peptide sCT was easily associated upon incorporation in the organic phase, using the nanoprecipitation technique. This smooth nanoencapsulation method resulted in high peptide encapsulation efficiencies (>98%) with preservation of peptide integrity [54]. On the other hand, peptides such as insulin or sCT were loaded in solid lipid (tripalmitin) nanoparticles using a modified double emulsion method. When using this approach, the peptide was dissolved in the inner aqueous phase of the double emulsion. This method has allowed us to increase markedly the capacity of these solid lipid matrixes to incorporate peptides such as insulin (encapsulation efficiency>45%) [43] and sCT (encapsulation efficiency>90%) [47]. As in the case of the nanocapsules, no signs of peptide degradation were detected by reverse phase high performance liquid chromatography (Figure 5).

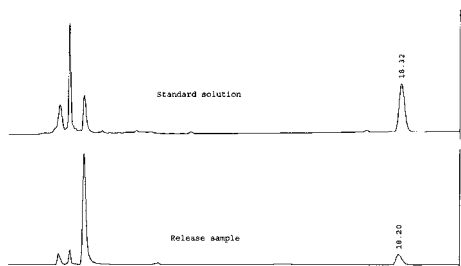


Figure 5: Reverse phase high performance liquid chromatograms of salmon calcitonin (retention time= 18-18.5 min) in a standard buffer solution (top) or after being released from a PEG-coated tripalmitin nanoparticle formulation (bottom).

This important association efficiency can be explained by the affinity of these peptides by the lipids. Indeed, it is known that phosphatidylglycerol, which present in our particles, shows a particularly strong interaction with this macromolecule [55]. On the other hand, insulin has already been shown to associate to lipid-based carriers such as polycyanoacrylate nanocapsules [30]. Moreover, as indicated in the introductory section, there is a significant number of references which have shown the efficient incorporation of peptides within lipid submicron emulsions [24,25]. Furthermore, in order to corroborate this, theoretically possible, interaction we have performed some adsorption experiments which have confirmed that our negatively charged nanostructures were able to adsorb high amounts of sCT following a Langmuir-type isotherm [47].

The release of the peptide sCT from the lipid nanostructures was slightly dependent on the lipid core. In the case of solid and solid-liquid mixtures, the release profile of sCT followed a biphasic pattern consisting of an initial burst (20% of the amount encapsulated) followed by a continuous and slow release [47]. The burst release was attributed to the surface-associated peptide whereas the second slow phase would correspond to the peptide entrapped in the lipid matrix. On the other hand, the burst release effect was reduced when the carriers were coated with the polymer chitosan (10% of the amount encapsulated) [47]. This reduction in the burst effect has been attributed to the lower amount of peptide on the surface of the nanostructures. In the case of the oily nanostructures, only the chitosan-coated systems showed a detectable

release of sCT. The release process from these systems followed a biphasic pattern similar to that of the chitosan-coated solid nanostructures, although only negligible amounts of the peptide were released after the initial burst.

In conclusion, we have developed nano-encapsulation techniques that make feasible the association of peptides to lipid systems. By means of these techniques, lipid nanostructures are able to load peptides and release them in a controlled manner.

#### 2.4 Studies in the Caco-2 cell model

Studies in the Caco-2 cell model were aimed at gaining information about the mechanism of interaction of the designed polymer-coated lipid nanostructures with the intestinal epithelium.

We have previously reported a study showing the capacity of PEG-coated polyester nanoparticles and chitosan nanoparticles to be internalized in the Caco-2 cell model [56]. The results from this work showed that the uptake of chitosan nanoparticles was higher than that of PEG-polyester nanoparticles, a result that was even more remarkable when both formulations were compared in the MTX-E12 cells, a model of mucus secreting cells. Interestingly, within the range of concentrations studied (31.25-1000 µg/ml), the association of chitosan nanoparticles to the monolayer was saturable and temperature dependent.

These results are different from those obtained for polymer-coated lipid nanostructures in the Caco-2 model cell line. Indeed, the amount of fluorescent particles associated to the cells was similar independently of the polymer coating [57]. On the other hand, when we compared the behaviour of the chitosan nanocapsules with that of the chitosan-coated tripalmitin nanoparticles, we observed an important difference in the amount of carrier associated to the cells, being it higher for the solid lipid cores [54,57]. However, these surprising results should be cautiously interpreted due to the different source of chitosan used to form the coating of the structures and also the fact that both systems were assayed separately.

We have also checked the capacity of our polymer-coated nanostructures to modify the permeability of the cell monolayers. In this sense, it is known that chitosan has a capacity to cause a dose-dependent decrease in the transepithelial electric resistance (TEER) [39] while PEG is supposed to be inert in terms of cellular interaction. In agreement with this, we observed that PEG-coated lipid cores did not cause a reduction in the TEER of Caco-2 cell monolayers in the range of concentrations investigated (220-330  $\mu\text{g}/\text{cm}^2$ ). In contrast, chitosan-coated lipid nanostructures induced a dose-dependent drop in the TEER of Caco-2 monolayers reaching significant reductions for the range of concentrations (83-330  $\mu\text{g}/\text{cm}^2$ ) [54,57]. The values of the reduction of the TEER were additionally supported by the observation of enhanced paracellular transport of the macromolecular marker dextran-Texas Red<sup>®</sup> (Mw = 3000 Da). However, it should be added that these values were, in the case of nanocapsules, close to those that compromised cell viability (220  $\mu\text{g}/\text{cm}^2$ ). Therefore, it could be expected that this change in the epithelium permeability could only be seen when an important amount of particles are accumulated onto the epithelium.

Reductions in the TEER similar to those of the chitosan-coated lipid nanostructures have been observed for chitosan solutions when the concentrations of the polymer were within the same range [58]. Interestingly, we observed that, as in the case of chitosan solutions, the normal TEER values were slowly recuperated after the exposure to the chitosan-coated nanostructures. Indeed, values within 10% of the original value of TEER were achieved after 8 h of recuperation and after 24 h, all monolayers had returned to the initial resistance level [54,57].

### **2.5 *In vivo* efficacy of polymer-coated lipid nanosystems as oral peptide carriers**

Keeping in mind that the main goal of our work was to design new peptide carriers for oral delivery, it was important for us to assess the ability of the new polymer-coated nanostructures to increase the transport of peptides across the intestinal mucosa. For this purpose, we chose sCT as a model compound [54,57]. A control

experiment showed that sCT in solution was unable to reduce the serum calcium levels. Similarly, significant reductions in serum calcium levels could not be achieved after the oral administration of sCT included in the control nanoemulsion or in the PEG-coated tripalmitin nanoparticles. However, significant hypocalcemic responses were observed for sCT when included in the chitosan-coated lipid nanostructures. More importantly, this significant reduction in the serum calcium levels (25-27% reduction at 1 h post-administration for both chitosan-coated lipid nanostructures) was maintained for at least 24 h [54,57]. Interestingly, the positive behaviour of these new systems should not be simply attributed to the presence of chitosan but to their intrinsic nanostructural composition. In fact, Takeuchi et al. observed that the polymer itself in solution was ineffective at improving the intestinal calcitonin absorption [20]. In addition, we have recently evaluated *in vivo* the efficacy of chitosan microspheres (identical dose of chitosan and sCT) and found that they were unsuccessful at reducing the serum calcium levels [59]. Therefore, the general conclusion from these studies is that the efficacy of the new nanostructures presented in this report can not be assigned to their individual components, but to the way these components are nanostructured.

The mechanistic explanation for the positive behaviour of the chitosan-coated lipid nanostructures as compared to that of non-coated or PEG-coated lipid systems is not perfectly defined yet, although some preliminary hypothesis can be established from the *in vitro* experiments. First, the enhanced stability provided by the polymeric coatings seems to be a relevant issue for peptide delivery. Chitosan, a polymer with well defined mucoadhesive properties, not only provides better colloid stability but possibly enhances the interaction of the nanostructures with the mucosal surfaces [19,38]. At this stage, increasing evidence points to the process of mucoadhesion as a way of gaining better access to the underlying epithelium [56]. Finally, taking into account the results from the Caco-2 experiments, one could attribute the success of the chitosan-coated lipid nanostructures to their ability to reduce the TEER. However, we should underline that sCT co-administered with

chitosan solutions that show similar reduction in the TEER do not produce any significant hypocalcemic effect. In addition, it should be noted that the marked reductions in the TEER were observed for high doses of chitosan-coated lipid nanostructures while doses in animal were far below this limit. In conclusion, the positive behaviour of chitosan-coated lipid nanostructures seems to be determined by a combination of functions from the carrier that may include better peptide protection, improved carrier stability and enhanced interaction between drug and the mucosal surfaces.

### 3. Conclusions

This article reports the design and characterization of new polymer-coated lipid-based nanostructures for oral drug delivery. Among the systems prepared, chitosan-coated lipid nanostructures have shown the capacity to improve the oral efficacy of sCT. The positive behaviour of this system should be most probably attributed to a combination of factors that contribute to the protection of the peptide in the gastrointestinal tract and enhances its interaction with the epithelium of the intestine. Among them, the mucoadhesive properties of chitosan can have a major role at improving the efficacy of orally administered peptides.

### 4. Acknowledgements

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## Summary

For treatment of allergic rhinitis, antihistamine acrivastine with decongestant pseudoephedrine in Semprex<sup>®</sup>-D conventional capsules requires frequent dosing every 6 hours. This study was designed to develop a controlled release matrix tablet of acrivastine and pseudoephedrine and compare 5 different types of matrix excipients for their *in vitro* controlled release profiles. Compritol<sup>®</sup> 888 Ato, Eudragit<sup>®</sup> RS, Methocel<sup>®</sup> K100M, Polyox<sup>®</sup> WSR301 and Precirol Ato 5<sup>®</sup> were used alone or in varying combinations for the formulation of controlled release matrix tablets. *In vitro* drug dissolution and mathematical modeling were used to characterize drug release rate and extent. All tablet formulations yielded quality matrix preparations with satisfactory tableting properties. Due to the aqueous solubility of pseudoephedrine and the size of the dose, none of the matrix excipients used alone prolonged drug release significantly to meet the projected twice-daily administration frequency. The use of two excipients in combination, however, significantly decreased the dissolution rate of both active ingredients. A combined lipid-based Compritol<sup>®</sup> and hydrophilic Methocel<sup>®</sup> produced optimal controlled drug release for longer than 8 hours for both acrivastine and pseudoephedrine.

## Keywords

*Acrivastine, pseudoephedrine, controlled release matrix tablet, dissolution, mathematical modeling.*

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## Introduction

Acrivastine, [(E)-3-(6-[3-pyrrolidino-1-(4-tolyl)-prop-1E-enyl]-2-pyridyl)-acrylic acid], is a second-generation, non-sedating H<sub>1</sub>-antihistamine that was derived from the first-generation antihistamine triprolidine [1]. It has specific antihistaminic activity for the treatment of allergic rhinitis with reduced potential for the sedative side effects that characterize triprolidine and other first-generation antihistamines [2]. Semprex®-D capsule contains 8 mg of acrivastine and 60 mg of the decongestant pseudoephedrine hydrochloride, a commonly used antihistamine-decongestant combination that relieves rhinorrhea, sneezing, itching, and nasal congestion.

Frequent dosing, 3-4 times daily, is normally required for acrivastine, as the compound has a relatively short plasma elimination half-life of 1.5-2 hours [3]. This contrasts unfavorably with the other second-generation, non-sedating antihistamines such as fexofenadine and loratadine that are taken no more than once or twice daily, due mainly to their long *in vivo* half-lives [3-5]. A controlled release formulation of acrivastine and pseudoephedrine would maintain effective plasma concentrations of both active ingredients for longer than 8 hours, subsequently reducing drug administration to a twice or even once daily regimen.

Both acrivastine and pseudoephedrine are appropriate candidates for controlled release preparations, because controlled release approaches are able to considerably improve *in vivo* performance and reduce administration frequency for both compounds. While extended release or controlled release dosage forms of pseudoephedrine have been available for years [6,7], formulating a relatively simple and straightforward solid controlled release formulation for acrivastine and pseudoephedrine still faces several technical challenges. Concurrent presence of two active ingredients in the formulation increases the complexity and difficulty in formulation development and drug dissolution. Optimization of drug release rates of both acrivastine and pseudoephedrine from the same preparation to achieve a satisfactory overall controlled release pattern will be solely dependent on the formulation techniques and the

excipient selections. In addition, physicochemical properties of acrivastine are distinctly different from those of pseudoephedrine. Acrivastine is relatively insoluble in most pharmaceutical solvents, but pseudoephedrine is readily soluble in almost all solvents. There are also specific treatment requirements for each medication. As a decongestant, pseudoephedrine is required to produce a prompt relief to the nasal congestion and maintain its pharmacological action over a prolonged period of time. Acrivastine as an antihistamine should produce constant antihistaminic activity over the complete administration course. It will therefore require special formulation technology to coordinate drug release profiles of the active ingredients to achieve the most optimal therapeutic goals.

The extensive availability of synthetic, biocompatible and biodegradable pharmaceutical excipients as tablet additives and the successful application of highly sophisticated techniques to produce various controlled release tablets have been well documented and established both in laboratory research and in industrial manufacture [8-10]. These technologies exhibit many advantages over traditional tableting processing, yielding high production efficiency and versatility, ease of automation and cost-saving benefits. Matrix tablet preparation is one of the most widely used dosage forms within controlled release techniques in pharmaceutical manufacturing standards, as drug release rates are controlled mainly by the type and proportion of excipients used in the preparations, and no complex production procedures such as coating and pelletization are required.

It was hypothesized that appropriate selection of pharmaceutical excipients and manufacturing techniques would modify drug release profiles for both acrivastine and pseudoephedrine from the same matrix tablet formulation to achieve a sustained drug release for up to 8-12 hours. This projected dissolution rate would enable a twice daily dosing regimen. To test this hypothesis, 5 different types of matrix excipients were used to prepare controlled release matrix tablets of acrivastine and pseudoephedrine, and their *in vitro* controlled release characteristics were evaluated.

## Materials and Methods

The pharmaceutical excipients used in the study were received as gifts from various sources. They were the water-soluble, hydrophilic polymers Methocel® K100M (hydroxypropyl methylcellulose, The Dow Chemical Company, Midland, MI, USA) and Polyox® WSR301 (polyethylene oxide, Union Carbide Corporation, Danbury, CT, USA), the water-insoluble, acrylic resin Eudragit® RS (methacrylic acid esters, Röhm Pharm, Darmstadt, Germany), and the water-insoluble, lipid-based excipients Compritol® 888 Ato (glyceryl behenate NF, Gattefossé, Lyon, France) and Precirol Ato 5® (glyceryl palmitostearate, Gattefossé, Lyon, France). Acrivastine was received as a gift from Celltech Pharmaceuticals (Rochester, NY, USA), and pseudoephedrine hydrochloride was purchased from Medisca Pharmaceutique Inc. (Montreal, QC, Canada). Other tablet additives used included magnesium stearate and ethanol (Fisher Scientific, Fair Lawn, NJ, USA).

Each tablet formulation contained 20 mg of acrivastine and 150 mg of pseudoephedrine hydrochloride, with the projected administration frequency of once every 12 hours. The compositions of the matrix tablet formulations are listed in Table 1. Some formulations contained one single matrix excipient to control drug release, while other formulations contained a combination of two matrix excipients as controlled release mechanism. Wet granulation

with ethanol was used to prepare the granules before tableting.

Tablets were prepared by using a Manesty® single-punch tablet press (Liverpool, UK). A set of 7/16 punches and die was used for the tableting and the compression force was set at 50 kg for all tablet formulations.

*In vitro* dissolution tests were carried out on a VanKel® 600 Dissolution Apparatus (Palo Alto, CA, USA) using USP Apparatus I. The dissolution medium was distilled water. The dissolution temperature was maintained at  $37\pm 0.5^\circ\text{C}$  and the rotation speed was set at 50rpm. Samples were collected from the dissolution medium every 30 minutes for up to 8 hours. Each sample volume removed was replaced by an equal volume of fresh dissolution medium. Six replicates were tested for each batch of the tablet formulations. Dissolution samples were filtered and diluted to appropriate concentrations for drug analysis.

Concentrations of acrivastine and pseudoephedrine were simultaneously measured using an HPLC assay developed in our laboratory [11]. In brief, a Waters® HPLC system (Milford, MA, USA) comprised of a 600S Controller, a 616 Solvent Delivery Pump, a 717 Autosampler, and a 996 Photodiode Array Detector was used with a C<sub>18</sub> Nova-Pak® column (4 µm, 3.9x150 mm). The mobile phase was composed of acetate buffer (pH 4.0):acetonitrile:methanol (45:47:8) and was delivered at a flow rate of 0.8 mL/min.

Table 1. Matrix Tablet Formulations of Acrivastine and Pseudoephedrine

Excipients	Formulation (mg/tablet)						
	A	B	C	D	E	F	G
Acrivastine	20	20	20	20	20	20	20
Pseudoephedrine	150	150	150	150	150	150	150
Eudragit® RS	75	-	-	-	-	-	-
Compritol® 888 Ato	-	75	-	-	-	40	130
Precirol Ato 5®	-	-	75	-	-	-	-
Methocel® K100M	-	-	-	75	-	140	200
Polyox® WSR301	-	-	-	-	75	-	-
Magnesium stearate	5	5	5	5	5	5	5
Total weight	250	250	250	250	250	355	505

The detection wavelength for both compounds was 214 nm. Under these HPLC conditions, pseudoephedrine and acrivastine were eluted from the column at 2.0 and 2.5 minutes respectively. The detection limit was 5 ng for acrivastine and 10 ng for pseudoephedrine respectively, and no interference was found from any tablet excipients or additives.

Mathematical modeling of drug release characterization used two well-known equations from Hixson-Crowell [12,13] and Peppas-Ritger [14,15]. The Hixson-Crowell Cube Root Kinetics Equation describes the relationship between drug release and dissolution time using Equation 1,

$$\left(\frac{W_d}{W_i}\right)^{1/3} = 1 - k_1 t \quad (1)$$

where  $W_d$  is dry weight of the tablet at designated times after immersion in the dissolution medium,  $W_i$  is initial dry weight of the tablet,  $k_1$  is the erosion rate constant of the tablet, and  $t$  is the dissolution time. When drug dissolution is considerably slower than tablet erosion, a modified Hixson-Crowell Equation could be used, which more accurately correlates the drug dissolution profile,

$$\left(1 - \frac{Q_d}{A}\right)^{1/3} = 1 - k_2 t \quad (2)$$

where  $Q_d$  is dissolved drug amount at time  $t$ ,  $A$  is the total drug amount in the matrix, and  $k_2$  is apparent rate constant of drug dissolution. Dissolution data from dissolution studies were fitted linearly using Equation 2.

The Peppas-Ritger Equation was developed to describe the influence of polymeric hydration and swelling on drug release rate. The equation has been modified by Korsmeyer et al [16] to simplify the relationship between drug diffusion from the matrix tablet and the dissolution time through Equations 3 and 4,

$$\frac{M_t}{M_\infty} = kt^n \quad (3)$$

$$\log\left(\frac{M_t}{M_\infty}\right) = \log k + n \log t \quad (4)$$

where  $M_t/M_\infty$  is the fraction of drug release,  $k$  is a release rate constant,  $n$  is the diffusional release exponent indicative of the drug release mechanism, and  $t$  is the dissolution time. Dissolution data of the study ( $M_t/M_\infty \leq 0.6$ ) were correlated linearly using Equation 4.

The time required for 50% of the drug to be released ( $DT_{50\%}$ , hours) and dissolution efficiency (DE, %) [17,18] of the formulations were also obtained to compare differences in drug release rate and extent.  $DT_{50\%}$  was obtained directly from the dissolution-time curves. Dissolution efficiency was calculated from the following equation,

$$DE (\%) = \frac{AUC_{dissolution(0 \rightarrow 8hr)}}{100\% \times 8hr} \times 100 \quad (5)$$

## Results

All tablet formulations possessed satisfactory tableting properties such as good mixing/granulating characteristics, flowability and compressibility. The manufacturing process was simple and straightforward with conventional granulation and mixing procedures. No complex processing was required for the production of matrix tablets of acrivastine and pseudoephedrine.

Figure 1 shows drug release from Tablet Formula A that was composed of 30% Eudragit®. Dissolution of pseudoephedrine was slightly retarded for up to 2 hours, while dissolution of acrivastine was prolonged for 5 hours. Figure 2 shows drug release from Tablet Formula B that was composed of 30% Compritol®.

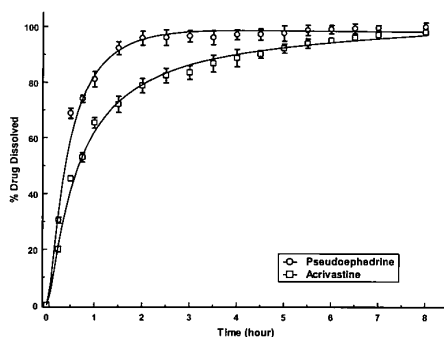


Figure 1. Dissolution profiles of acrivastine and pseudoephedrine from Tablet Formula A (Eudragit® RS).

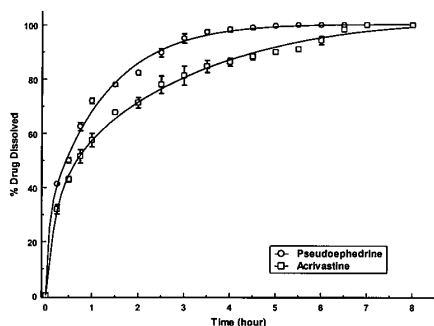


Figure 2. Dissolution profiles of acrivastine and pseudoephedrine from Tablet Formula B (Compritol® 888 Ato).

Drug release was extended to 4 hours and 8 hours for pseudoephedrine and acrivastine respectively. Figure 3 shows drug release from Tablet Formula D that was composed of 30% Methocel®. Dissolution of pseudoephedrine and acrivastine was prolonged for up to 7 and 8 hours respectively.

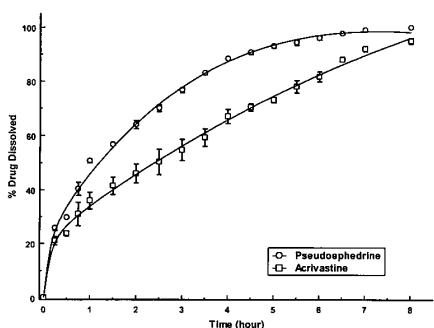


Figure 3. Dissolution profiles of acrivastine and pseudoephedrine from Tablet Formula D (Methocel® K100M).

Figure 4 shows drug release from Tablet Formula E that was composed of 30% Polyox®, which had sustained dissolution profiles of pseudoephedrine and acrivastine for up to 6 and 8 hours respectively. Drug dissolution data from Tablet Formula C (Precirol®, dissolution figure not shown) were similar to that of Formula B, as they are both lipid-based matrix excipients. None of the above formulations was able to sustain the dissolution of both active ingredients to the extent that met the designed objective of drug administration once every 12 hours. Dissolution of pseudoephedrine was routinely faster than that of acrivastine, mainly due to its greater solubility.

Figure 5 and Figure 6 show drug release from Tablet Formulas F and G respectively that were

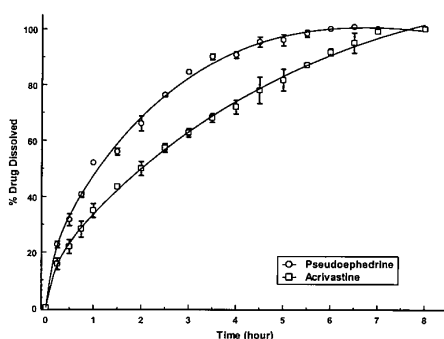


Figure 4. Dissolution profiles of acrivastine and pseudoephedrine from Tablet Formula E (Polyox® WSR301)

composed of lipophilic Compritol® and hydrophilic Methocel® in various proportions. Drug release was significantly prolonged for both acrivastine and pseudoephedrine. Formula F appeared to achieve our design objectives in terms of drug release. At 8 hours, the overall drug dissolution was 68% for acrivastine and 85% for pseudoephedrine respectively.

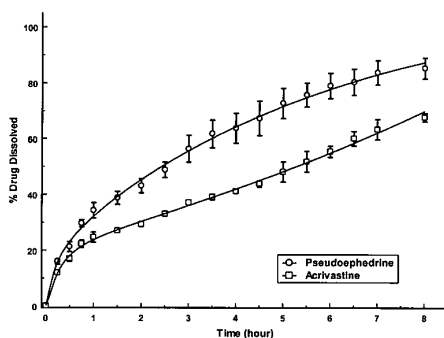


Figure 5. Dissolution profiles of acrivastine and pseudoephedrine from Tablet Formula F (Compritol® 888 Ato + Methocel® K100M, I).

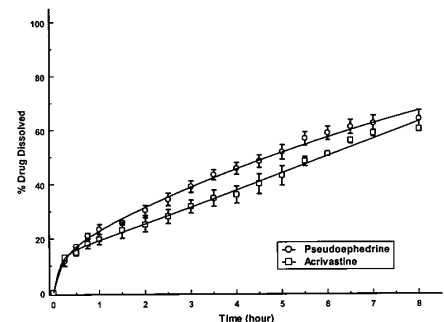


Figure 6. Dissolution profiles of acrivastine and pseudoephedrine from Tablet Formula G (Compritol® 888 Ato + Methocel® K100M, II)

Table 2. Results of Linear Regression of Acrivastine and Pseudoephedrine Release Using the Hixson-Crowell Cube Root Kinetics Equation [Eq. (2)].

Formulation	Acrivastine			Pseudoephedrine		
	$k_2$ (1/h)	y-intercept	$r^2$	$k_2$ (1/h)	y-intercept	$r^2$
Formula A	0.074	0.806	0.928	0.283	0.875	0.931
Formula B	0.090	0.864	0.963	0.106	0.762	0.960
Formula C	0.089	0.848	0.965	0.145	0.831	0.986
Formula D	0.068	0.954	0.980	0.102	0.921	0.992
Formula E	0.101	1.003	0.950	0.114	0.912	0.990
Formula F	0.033	0.956	0.986	0.055	0.935	0.991
Formula G	0.029	0.965	0.987	0.033	0.952	0.988

Table 3. Results of Linear Regression of Acrivastine and Pseudoephedrine Release Using the Peppas-Ritger Equation [Eq. (4)]

Formulation	Acrivastine			Pseudoephedrine		
	$n$	$k$	$r^2$	$n$	$k$	$r^2$
Formula A	0.843	0.693	0.956	0.846	1.049	0.913
Formula B	0.426	0.578	0.999	0.401	0.699	0.972
Formula C	0.449	0.570	0.995	0.417	0.709	0.973
Formula D	0.409	0.348	0.985	0.480	0.469	0.943
Formula E	0.569	0.339	0.998	0.535	0.475	0.978
Formula F	0.454	0.231	0.983	0.499	0.321	0.988
Formula G	0.464	0.205	0.959	0.495	0.230	0.991

Table 4. Dissolution Parameters of the Formulations

Formulation	Acrivastine		Pseudoephedrine	
	DT <sub>50%</sub> (hr)	DE (%)	DT <sub>50%</sub> (hr)	DE (%)
Formula A	0.88	81.95	0.47	91.38
Formula B	0.65	80.38	0.35	88.72
Formula C	0.80	81.60	0.50	89.05
Formula D	2.25	62.98	1.13	77.81
Formula E	2.00	68.42	1.06	80.48
Formula F	5.25	41.99	2.44	59.82
Formula G	6.00	37.67	4.88	43.40

Table 2 lists dissolution parameters of acrivastine and pseudoephedrine from various tablet formulations using the Hixson-Crowell Cube Root Kinetics Equation [Eq. (2)]. Table 3 lists dissolution parameters of acrivastine and pseudoephedrine from various tablet formulations using the modified Peppas-Ritger Equation [Eq. (4)]. Table 4 lists  $DT_{50\%}$  and DE of both acrivastine and pseudoephedrine from various tablet formulations. Rankings in dissolution parameters from mathematical modeling were variable among Formulations A-E. However, rankings of dissolution rate from Formula F and Formula G were identical in all calculations.

## Discussion

The extreme aqueous solubility of pseudoephedrine compared to that of acrivastine was one of the major factors to be considered in controlling release of the medications from the matrix tablet. Since the proportion of pseudoephedrine, 150 mg, in the formulation is significantly larger than that of acrivastine, 20 mg, and pseudoephedrine is readily soluble as a hydrochloride salt, selecting appropriate matrix excipient in the formulation is critical to the success of the formulation development. Both water-insoluble and water-soluble matrix excipients were investigated in the study, with the goal of finding the optimal excipient type and amount that would be able to modify the overall drug release rate consistent with the design objectives.

Of the five matrix excipients evaluated in this study, Eudragit® is an insoluble resin that allows slow permeation of water into the matrix and drug diffusion out of the matrix. Compritol® and Precirol® are lipid-based insoluble wax excipients that control drug release by slow matrix erosion and drug diffusion. Drug release from these insoluble matrix materials is mainly dependent upon the rate and extent of water permeation and aqueous solubility of the drug compounds that are embedded in the matrix. Methocel® and Polyox® are hydrophilic, gel-swelling polymers that regulate water penetration to control release of the medications. Drug release is mainly dependent upon the rate

and extent of water penetration into the tablet matrix and the relative aqueous solubility of both the matrix material and the drug compounds embedded in the matrix. Different drug release mechanisms were involved in controlling drug dissolution from these selected tablet formulations, depending on the type and ratio of the matrix material in the formulations. They included diffusion, dissolution and a combination of both diffusion and dissolution.

The apparent dissolution rate constant ( $k_2$ ) from various tablet formulations ranged 0.029-0.101 hr<sup>-1</sup> for acrivastine and 0.033-0.283 hr<sup>-1</sup> for pseudoephedrine respectively (Table 2). The linear correlation ( $r^2$ ) was larger than 0.95 for all formulations except Formula A, indicating satisfactory curve fitting of the dissolution data. Differences in this rate constant resulted from the use of different types of matrix excipients. The dissolution rate constant from Polyox® was larger than that of Methocel®, suggesting that water permeability and gel relaxation of Polyox® are more significant. For insoluble matrix materials tested in the study, drug dissolution appeared to be mainly dependent upon the aqueous solubility of the active ingredients. Tablets made of Eudragit® as a matrix excipient had a significantly larger rate constant for pseudoephedrine than lipid-based matrix Compritol® and Precirol®, indicating its larger water permeability and weaker bonding with water-soluble components. Li et al [19] evaluated the controlled release of pseudoephedrine using Eudragit® resin as either matrix or coating excipient. Dissolution of pseudoephedrine from sustained release formulations was mostly prolonged for up to 6 hours. Williams et al [20] also reported dissolution results for the controlled release of alprazolam from Methocel® matrix tablets. The study concluded that the hydrated gel layers were more permeable for alprazolam release when the tablets contained soluble excipients, resulting in faster rates of dissolution. Dissolution of pseudoephedrine in our study facilitated the penetration of water into the matrix interior, promoting diffusion of acrivastine from the tablets. This might be the main reason why no single excipient was able to prolong drug dissolution of both acrivastine and

pseudoephedrine significantly to meet our design objectives.

According to the Peppas-Ritger Equation, the value of diffusional release exponent  $n$  dictates the drug dissolution mechanism. Drug release in zero-order, non-Fickian (anomalous) diffusion and Fickian diffusion is represented by  $0.89 < n < 1.0$ ,  $0.45 < n < 0.89$  and  $n = 0.45$ , respectively. The  $n$  values from various tablet formulations ranged 0.409-0.843 for acrivastine and 0.401-0.846 for pseudoephedrine respectively (Table 3). The linear correlation ( $r^2$ ) was mostly larger than 0.95, representing satisfactory curve fitting of the dissolution data. Dissolution of acrivastine from Formula C, F and G appeared to observe a Fickian diffusion mechanism, as  $n$  values were very close to 0.45. Dissolution of acrivastine from other formulations and dissolution of pseudoephedrine from all formulations indicated combined mechanisms of anomalous diffusion and matrix relaxation/erosion. Rankings in dissolution rate constants for both active ingredients from this modeling were very similar, Formulas A, B, C > Formulas D, E > Formulas F, G. Zhang and Schwartz [21], and Barthelemy et al [22] studied dissolution of various compounds with Compritol® as matrix material for controlled release formulations. Their results suggested that drug release from Compritol® matrix followed the Fickian diffusion mechanism, which was consistent with what we have found in formulations C, F and G that contained the lipid-based matrix excipients Compritol® or Precirol®.

Combined use of lipid-based Compritol® and hydrophilic Methocel® sustained drug release significantly compared to any formulation that was composed of only single matrix excipients. The dissolution profiles were characterized from dissolution rate constants obtained from Equations 2 and 4, and dissolution parameters  $DT_{50\%}$  and DE. Formula F and Formula G had the lowest values among all test formulations. Dissolution of the highly soluble pseudoephedrine was well prolonged with the combined use of two different types of matrix excipients. In addition, increase in the proportions of matrix materials in the formulation further

retarded the drug release rate and extent. Hydrophilic polymers such as Methocel® rely on water absorption to produce gel swelling and matrix relaxation, which subsequently facilitate drug dissolution and diffusion from the matrix. When a lipid-based excipient is concurrently present in the same matrix, its lipophilicity is able to reduce water uptake rate by the matrix. Consequently, drug dissolution and diffusion from tablet matrix is reduced to produce a sustained release pattern for a prolonged period of time. This formulation strategy worked satisfactorily for pseudoephedrine, even when there was a large amount of pseudoephedrine embedded in the tablet matrix. The combination of lipophilic and hydrophilic matrix materials in the formulation did not appear to significantly affect the dissolution characteristics of acrivastine, due probably to its lower aqueous solubility. Dissolution of acrivastine itself might have a similar rate profile as that of matrix hydration and erosion, resulting in satisfactory controlled release of acrivastine for up to 8 hours. Tiwari et al [23] studied controlled release of tramadol hydrochloride using both hydrophilic (hydroxypropyl methylcellulose) and hydrophobic (hydrogenated castor oil) matrix excipients. The study found that combined use of hydrophilic and hydrophobic excipients was not desirable because immediate tablet disintegration and drug dissolution took place. We did not observe such phenomena in our dissolution studies.

## Conclusion

To achieve controlled release dissolution for both the antihistamine acrivastine and the decongestant pseudoephedrine hydrochloride that would be suitable for a twice daily administration regimen, no single water-soluble or water-insoluble matrix excipient studied was able to achieve the required drug release rate profiles *in vitro*, mainly due to large proportion of pseudoephedrine present in the matrix and its high aqueous solubility. However, the combination of lipid-based Compritol® 888 Ato and hydrophilic Methocel® K100M in the formulation achieved the dissolution profiles

that met the formulation objectives in terms of controlled drug release over 8-12 hours. This formulation will be further tested *in vivo* in an animal model for its pharmacokinetic and pharmacodynamic characteristics.

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# GASTRIC RETENTION RESERVOIR SYSTEMS UTILIZING SOLID AND SEMISOLID CARRIERS

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## Summary

The majority of drugs cannot be delivered orally with once daily formulations, as they are not well absorbed throughout the whole gastrointestinal (GI) tract. Kos has developed a gastric retention delivery system via the use of a superporous hydrogel (SPH). The SPH platform provides controllable gastric retention by maintaining the dosage form, which may be a solid or semisolid, in the GI tract regardless of the physiological environment, motility or diseased state of the subject. Superporous hydrogels (SPH) are cross-linked hydrophilic polymers, which have demonstrated desirable gastric retention properties in *in vivo* animals studies and are undergoing further studies for proof of principle in humans. Pharmaceutical reservoir systems such as mixtures of high melting point glycerol esters fatty acids have been created in the SPH platforms, where the delivery of the medicament is modulated by the carrier.

## Keywords

*Oral absorption, gastrointestinal transit, gastric retention, super porous hydrogels.*

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## Introduction

In oral drug delivery there are many phenomena that can disrupt the effective delivery of drugs with maximum potency and efficacy to the GI tract; motility, diseased state, caloric contents of ingested meal, stress level are to name a few. Since there is no real control over gastric emptying from the stomach, variability in transit time, location and absorption of compounds is often expected and can result in insufficient dose levels and irregular plasma concentration profiles. It has now become abundantly apparent from studies on regional absorption within the last decade or so that all drugs are not absorbed throughout the whole GI tract, and absorption windows exist for most. The transport mechanism of the drug is the defining characteristic as to whether the drug will encounter regional absorption across the epithelial membrane. For example, compounds exhibiting transcellular transport have absorption independent of regional locality, and compounds transported through paracellular transport show preferential upper GI tract absorption due to narrowing of tight junctions further down the GI tract. The ultimate aim of any oral gastric retention dosage strategy is to maximize the duration of the compound in the highest region of the GI tract, and allow sufficient duration and opportunity for improved bioavailability and optimum therapeutic levels. There is a wide range of therapies and compounds which can potentially benefit from these systems including those locally delivered to the stomach.

## Physiology and Gastrointestinal Motility

The GI tract is approximately 9 meters long, and consists of the esophagus, stomach, duodenum, jejunum, ileum, appendix, colon and rectum. The wall of the gastrointestinal tract has the same general structure throughout most of its length from the esophagus to the anus, but with regional variations. Furthermore, factors such as pH, nature and volume of gastric secretions, and gastric mucosa are important in drug release and absorption. The stomach is an organ with a

capacity for the storage and mixing. The antrum region is responsible for the mixing and the grinding of gastric contents. The mucus spreads and covers the mucosal surface of the stomach as well as the rest of the GI tract. The thickness of the mucus layer varies throughout the GI tract, with the stomach having a greater thickness than the small intestine.

The walls of the stomach are lined with millions of gastric glands, which together secrete 400-800 ml of gastric juice following each meal. There are three kinds of cells that are found in the gastric glands; parietal cells, peptic cells, and mucus cells. These cells are associated with different functions of the GI tract, for example parietal cells secrete hydrochloric acid and intrinsic factor; mucus cells secrete mucus and bicarbonate. The peptic cells synthesize and secrete pepsinogen, the precursor to the proteolytic enzyme pepsin. Pepsin cleaves peptide bonds, favoring those on the C-terminal side of tyrosine, phenylalanine, and tryptophan residues. Its action breaks long polypeptide chains into shorter lengths. Secretion by the gastric glands is stimulated by the hormone gastrin. Gastrin is released by endocrine cells in the stomach in response to the arrival of food.

The gastrointestinal tract is always in a state of motility (Macheras *et al.*, 1995). This may be occurring in the interdigestive (fasted state) or the digestive (fed state). The key function of the digestive motility is of cleaning up the residual content of the upper GI tract. It is commonly called the migrating motor complex (MMC) and is organized in cycles of activity and quiescence. Each cycle lasts 90-120 minutes and consists of four phases. The concentration of the hormone and motilin in the blood controls the duration of the phases. In the interdigestive or fasted state, every 90 to 120 minutes, an MMC wave migrates from the stomach down the GI tract. A full cycle consists of four phases, beginning in the lower esophageal sphincter/gastric pacemaker and propagates over the whole stomach, the duodenum, jejunum and finishing at the ileum. Figure 1 describes features of the different phases.

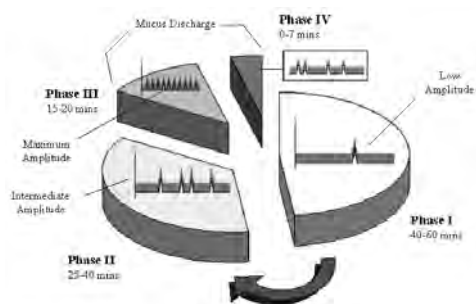


Figure 1. Illustration of the motility pattern of the fasted state, illustrating the relative phase durations, amplitude of the contractions showing one complete cycle.

Phase I is a relatively docile phase, lasting for approximately 40-60 minutes as there are minimal contractions or secretions taking place. Phase II is characterized by irregular contractions and bile secretion. The pressure of the stomach reportedly rises to approximately 5-40 mmHg during these contractions (Deshpande *et al.*, 1996). Phase III is termed the “housekeeper wave” as the powerful contractions in this phase tend to empty the stomach of its fasting contents and indigestible debris. Mucus discharge takes place during this phase. Phase IV is a short transitional period between phases III and I. The phase activity moves along the esophagus, stomach, antrum, duodenum, jejunum, ileum and cecum. It takes approximately 2 hours for the phase to move from the stomach to the ileocecal junction.

The administration and subsequent ingestion of food rapidly interrupts the MMC cycle and the digestive phase is allowed to take place (Meyer, 1987). The upper part of the stomach stores the ingested food initially where it is gradually compressed by the phased contractions. The digestive or fed state is observed in response to meal ingestion. It resembles the fasting phase II and is not cyclical, but continuous, providing food remains in the stomach. Large objects are retained by the stomach during the fed pattern but are allowed to pass during phase III of the interdigestive MMC. It is thought that the sieving efficiency (*i.e.* the ability of the stomach to grind the food into smaller size) of the stomach is enhanced by the fed pattern and/or by

the presence of food. The fasted-state emptying pattern is independent of the presence of any indigestible solids in the stomach. Patterns of contractions in the stomach occur such that solid food is reduced to particles of less than 1 mm diameter that are emptied through the pylorus as a suspension. The duration of the contractions is dependent on the physiochemical characteristics of the ingested meal.

With all the constraints in GI physiology, variability in motility and inter-subject differences, effective oral delivery of drugs is challenging. For this reason, there has been considerable focus by researchers over the last 2 decades in development of systems designed to function independent of any type of variability related to the function or state of the GI tract. Due to narrow absorption windows for many active pharmaceutical ingredients, maintaining the dosage form in the upper GI tract and increasing its transit time can be beneficial by sustaining drug plasma levels prior to passage from the region of absorption. Gastric retention is an approach whereby the dosage form is designed to resist gastric emptying by some means or mechanism and maintain in the stomach for prolonged periods of time.

## Gastric Retention Approaches

Over the last 2 decades there have been a multitude of approaches in gastric retention based on some well-established principles to prevent the dosage form from exiting the pylorus during gastric emptying. Figure 2 shows the approaches based on expansion mechanisms. Utilizing this technique, the device is intended to expand once in the presence of the gastric fluids based on a chemical, physical or mechanical driven property.

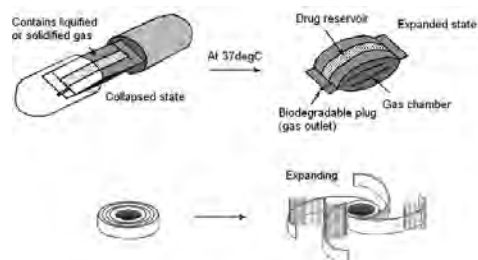


Figure 2. Gastroretentive dosage forms based on expansion approaches.

Another more classical approach to gastric retention is utilizing the buoyancy principle (Figure 3). This is where the dosage form is instilled with components resulting in reduced density than the gastric fluids, providing buoyancy. Gas generation or effervescence is another approach where bubbles formed from carbon dioxide are entrapped within the dosage form and provide buoyancy. Another idea that has been well used in known anti-reflux medicaments is utilizing the formation of a floating 'raft' based on combined gelling and effervescence processes.

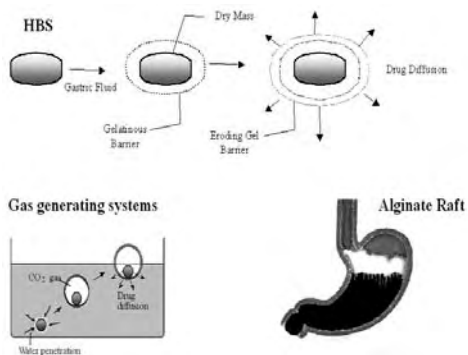


Figure 3. Gastric retention dosage forms based on the floating approach.

Another approach to achieve gastric retention is utilizing technologies based on swelling mechanisms. Here the dosage form will swell to a size larger than the pylorus, and is physically unable to pass through to the duodenum, thus achieving gastric retention. There are very few companies that have focused efforts on designing gastric retention technologies (Rocca *et al.*, 2002). DepoMed, Inc. have developed technology consisting of a swellable tablet that swells following ingestion and achieves sufficient size to resist gastric emptying, while simultaneously providing controlled release of the drug. They have several products in late clinical trials and undergoing FDA approval. SkyPharma have a tri-layer tablet consisting of a hydrophilic core, swellable layer and erodable layer. They have developed Xatral in combination with Sanofi-Synthelabo, with

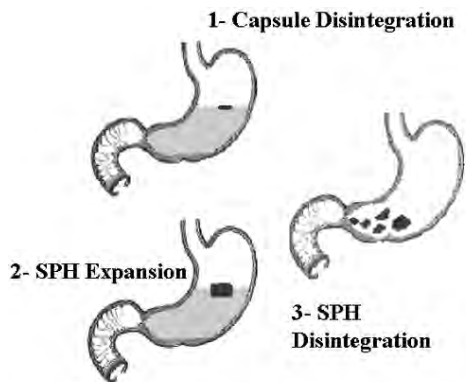


Figure 4. Gastric retention approach utilizing Kos superporous hydrogel.

gastric retention claimed for 6 hours. Kos Pharmaceuticals have developed the Superporous hydrogel as a platform for gastric retention with fast swelling kinetics. Figure 4 shows the Kos swelling-based platform technology.

## Kos Technology

Superporous Hydrogels were developed by Dr. Kinam Park at Purdue University. They are cross-linked hydrophilic polymers, which following the absorption of fluids, have the innate capacity to swell rapidly and sizably within a short time. The hydrogels consist of densely concentrated small pores that can connect to produce capillary channels, through which water can be absorbed. The resulting superporous hydrogel quickly absorbs water and swells dramatically, much faster and to a greater extent than a normal conventional hydrogel. By modification of the different aspects of the hydrogel synthesis, such as monomer content and crosslinker type and other components, the SPH properties can be controlled to enable different mechanical strength, swelling ratio and disintegration time. Figure 5 shows micrographs of the SPH, which illustrate the macroporous structure and surface porosity, a property which results in a fast initial absorption. The pores are well distributed within the SPH structure with sizes 10-200 microns.

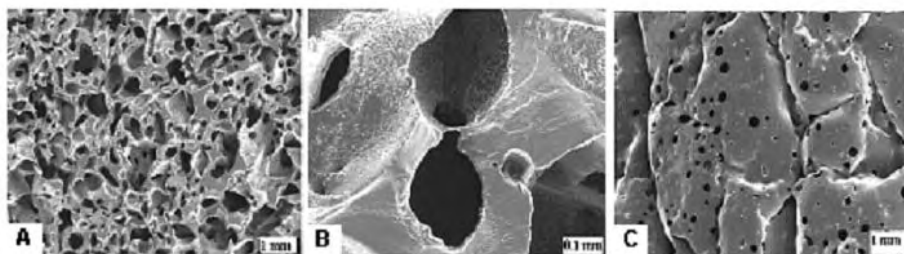


Figure 5. Micrographs of a superporous hydrogel showing the cross-sectional view (A and B) and surface (C).

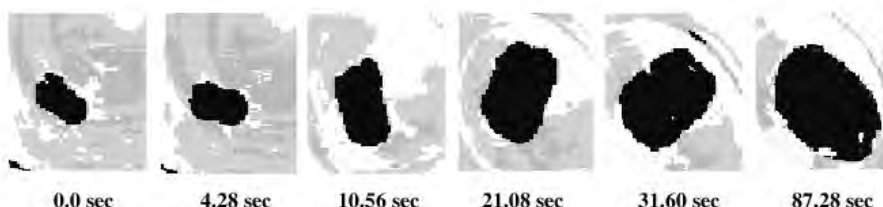


Figure 6. Swelling of a typical superporous hydrogel.

The unique swelling features of a typical superporous hydrogel are shown in Figure 6. A typical SPH can absorb water or aqueous medium and swell to its equilibrium swelling capacity in less than 2 min. Gastric retention requires the device to be large enough to not be able to pass through the pyloric sphincter.

When Kos licensed the SPH technology for oral drug delivery, the hydrogels were found to lack mechanical strength and contain certain toxic constituents requiring replacement. There was found to be a fine line between rapid swelling, sufficient mechanical strength and flexibility. The research carried out by Kos spanned 3 generations of hydrogels, each with successive improvements in physical properties and *in vitro* characteristics. Animal studies in the pig were carried out to confirm the proof of concept, followed by *in vivo* evaluation.

The building blocks of the first generation SPH were selected from amongst highly hydrophilic (acrylamide) or ionic (salts of acrylic acid or sulfopropyl acrylate) monomer species. Since the corresponding polymers were rigid in structure, hence the final product was also rigid and brittle after complete drying. Flexibility was instilled through external plasticization by using different types of low-high melting plasticizers. Since there was no direct control over the

flexibility of the SPH, there was not sufficient control over the final SPH properties. In the dried state, the first generation SPHs were hard and brittle resulting in considerable handling difficulties (Table 1). In the swollen state, they resembled a mass of water-swollen gel particles, which were adhered by weak strands of the same water-swollen gel. Table 1 summarizes the properties of the SPH with digital images of the dry and swollen gels.

With the second generation of SPH, the use of an interactive matrix-swelling additive was exploited. This was accomplished through incorporation of a water-absorbent hydrophilic crosslinked structure into the formulation of the first generation SPH as described in table 2.

The matrix swelling additive (MSA) polymers function as a dynamic reactor, and diffusion of polymer chains of the MSA and the synthetic polymer chains into one another results in an interpenetrated network structure (IPN). Since the whole structure is microscopically heterogeneous, this IPN-type structure (IV) is called a non-integrated IPN. Although general features of this SPH generation remain the same as their first counterpart, this type of modification results in better mechanical properties for the SPH compared with the first generation (see Table 1).

Table 1. Swelling, mechanical strength and physical properties of generations of superporous hydrogel.

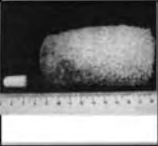

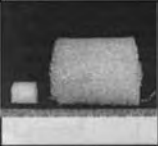






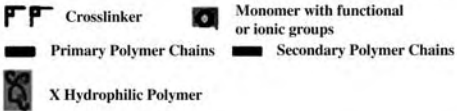
Generation	Swelling	Mechanical Strength	Properties				
			Swelling		Swollen state	Dry state	Handling Machining Processing
			Capacity	Rate			
1st			Very High	Very Fast	Weak	Rigid	Difficult
2nd			High	Very Fast	Stronger than first gen.	Rigid	Difficult
3rd			Medium	Very Fast	Very Strong	Rigid-Flexible	Easy

Table 2. Structural differences of different generations of superporous hydrogels.

Generation	Structure	Properties
1 <sup>st</sup>		<ul style="list-style-type: none"> <li>- Simple hydrogel structure</li> <li>- A simple hydrophilic polymer chain is crosslinked using a chemical crosslinker.</li> <li>- Foaming takes place at the time of crosslinking</li> <li>- Porous macrostructure is produced</li> </ul>
2 <sup>nd</sup>		<ul style="list-style-type: none"> <li>- A water-absorbent already-crosslinked hydrophilic polymer is used as an additive during synthesis</li> <li>- The filler can swell in the reacting medium and interacts with the primary polymer chains.</li> <li>- Foaming and crosslinking take place simultaneously.</li> </ul>
3 <sup>rd</sup>		<ul style="list-style-type: none"> <li>- A water-soluble hydrophilic polymer (natural or synthetic) is added to the reacting mixture, followed by is crosslinked using another crosslinker.</li> <li>- The final product structure resembles an integrated hydrogel hybrid.</li> </ul>
Legend		

Desire for better mechanical properties of SPHs motivated the research activities toward formulation of stronger superporous hydrogels. These third generation hydrogels were modified versions from second generation in which the non-integrated IPN structure of the latter was changed into an integrated one for the former via use of a crosslinkable water-soluble polymer (see Table 2). Depending on the type of crosslinking polymer used and its corresponding treatment, there is large variety of third generation superporous hydrogels, preparable with their properties ranging from high modulus to highly elastic and rubbery (in their water-swollen states) (see Table 1). Depending on the starting materials and the processing conditions, elastic SPHs with exceptional resilience, elongation, extensibility and mechanical strength could be prepared. Figure 7 illustrates the third generation hydrogels produced with good elastic properties.



Figure 7. Third generation of superporous hydrogels displaying elastic properties.

### SPH *in vitro* characteristics

Superporous hydrogels were produced with different swelling and mechanical properties. The *in vitro* properties of the gels could be tailored by modification of the formulation type.

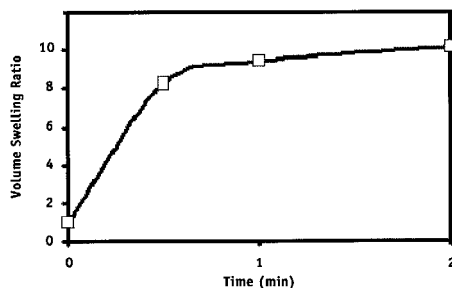


Figure 8. Swelling profile of superporous hydrogel in SGF at 37 °C.

Figure 8 illustrates the swelling profile of a typical SPH in simulated gastric fluid (SGF) at 37 °C. Swelling of the gel is linear until reaching the maximum swelling capacity (approximately 8 times volume increase) followed by a plateau.

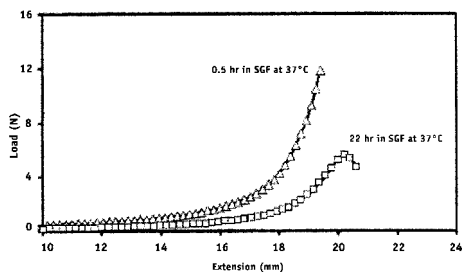


Figure 9. Mechanical properties of a superporous hydrogel in SGF at 37 °C.

Figure 9 shows the mechanical properties of a typical SPH with control over the disintegration. After 0.5 hours incubation in SGF, the gel is still strong and with resistance of compression loads up to 12 N (not shown in the figure). Prolonged retention results in decreased mechanical properties, such that the SPH fails under 6 N compression load following retention for 22 hours. This illustrates the control over the retention of the SPH, which could be achieved in the stomach, as mechanical integrity is vital for gastric retention, coupled with sufficient disintegration allowing safe passage through the GI tract.

### SPH *in vivo* studies

The first stage of any *in vivo* campaign is to achieve a proof of concept. Once hydrogels were

optimized and formulated with non-toxic constituents, good *in vitro* mechanical strength and fast swelling characteristics, the next stage of the SPH platform development was *in vivo* animal studies. Different models of animals were considered for these studies, and the pig model was chosen as the one most suitable to assess gastric retention, due to factors based on size and function, i.e. ion transport and gastrointestinal motility.

Two animal studies were carried out using hydrogels with different swelling capacities and mechanical strength, to determine the control over gastric retention based on the disintegration of the SPH.

No noteworthy incidences were observed during or after dosing. The gels were administered in the fed and fasted states. Formulations with different swelling characteristics and flexibility were dosed. Gels were recovered from the stomach intact after 6 hours in the fasted and fed states. Some formulations had properties enabling them to remain intact up to 24 hours. Disintegration of hydrogels was believed to begin after 6 hours (Figure 10).

The animal study gave authentication of the proof of concept, as gels were retained after 6 hours in both fed and fasted conditions. The effect of mechanical strength on retention of the gels was also realized, as it was found that duration of gastric retention could be mediated by changes in the formulation.

## SPH platform design

The SPH is a delivery platform for a drug delivery system. Therefore, design of the SPH to enable the drug/dosage form to be contained within was vital. A number of methods were considered in the design of a suitable platform. In this two-layer design (Figure 11A), two sheets of SPH are pressed together to encapsulate a deposit of active ingredient. One method involves having individual sheets of PHEMA poly(acrylic acid) copolymer on separate rollers, with inclusion of a wetting agent. The illustration (Figure 11B) shows how the outer layers can be attached to the inner layer (e.g. if outer layer PHEMA, inner layer would be poly(acrylic acid)). The inner layer has a hole in it which when sealed with the outer layers acts as a cavity in which the active ingredient could be deposited. Any excess space is filled with superporous hydrogel grain. Figure 11C is a further modification of the two-layer approach. Here, the dosage form contains many altering layers of PHEMA, and polyacrylic polymers. In between these layers are microparticles containing the active ingredient.

The plug design approach consists of formulation of the SPH with a hollow centre (Figure 11D). In this compartment, the drug delivery system, e.g. tablet will be contained. The reservoir will be closed utilizing a plug and sealed with an appropriate adhesive. This delivery strategy was used as the choice method to contain a drug delivery system within the SPH platform.

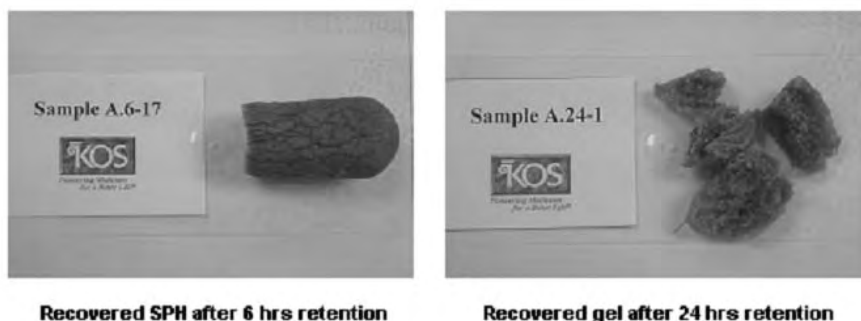


Figure 10. Recovered gels from *in vivo* animal studies after 6 and 24 hrs retention.

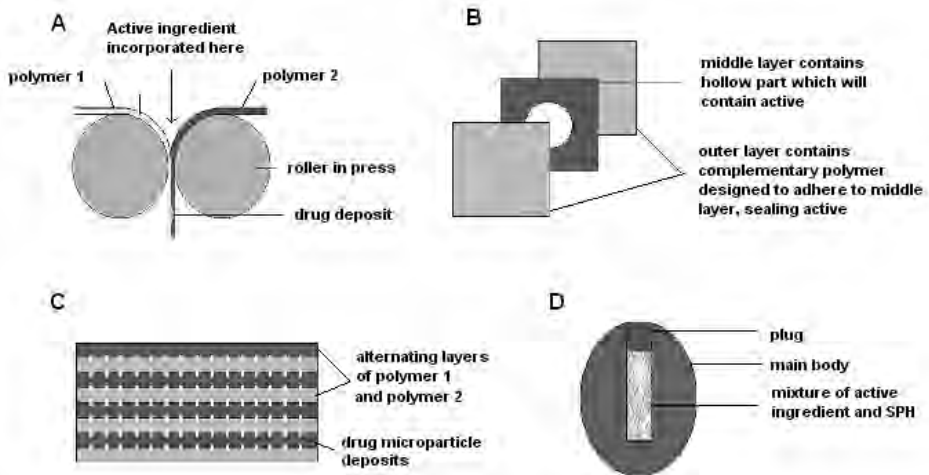


Figure 11. (A) Two-layer approach and (B) three-layer approach, (C) multi-layer approach and (D) plug system for design of SPH platform.

## Solid or semi-solid carriers in SPH platform

Solid or semi-solid carriers have potential in the SPH platform in the delivery of active agents. A suitable carrier may be one that is solid at room temperature (e.g. 25 °C), but is easily liquefied at elevated temperatures, e.g. 30-80 °C, and is inert in the selected API. A carrier may be a long chain fatty acid, wax, polysaturate or glyceride. The API would be combined with the carrier in its liquid form forming an injectable medicament mixture. The injectable mixture would then be injected into the SPH shell or reservoir using conventional techniques (Figure 12). With the former, the mixture would transverse through the

pores of the SPH toward the centre and form a solid medicament core following cooling. Thus, the solid compartment remains intact until reaching the stomach, where upon swelling of the SPH the API is released.

## Example of loading a semi-solid carrier into the SPH platform

To demonstrate the feasibility of SPH platforms for semi-solid carriers, an acid-soluble active ingredient was incorporated into a wax matrix containing Compritol® 888, Polysorbate 80, Methocel E-10P and Olive oil. The drug concentration was set at 20wt%. The wax, surfactant and the oil were mixed

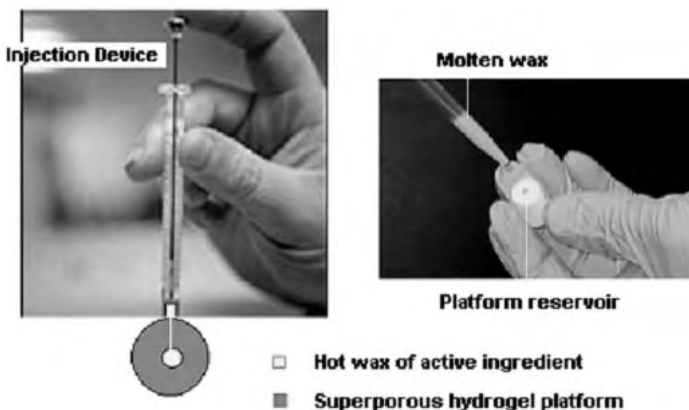


Figure 12. Illustration of the injectable SPH system.

at about 70 °C, followed by addition of Methocel and drug. The mixture was then well dispersed. Using a disposable syringe, the molten wax (250 mg) was loaded into the reservoir of the Kos SPH (Figure 12) and also into a HPMC capsule (used as control). The final wax-loaded SPH platform was assembled according to the procedure developed at Kos. Table 3 shows a typical wax-based formulation, which was combined with the SPH platform.

Table 3. Semi-solid formulations utilizing Compritol®.

	Compritol® 888
Wax (Gattefossé)	31.3
Polysorbate 80 (Jeen Intl)	1.2
Methocel E-10P (Dow)	3.8
Olive oil (Croda Inc)	63.7

Compritol® 888 is atomized glyceryl behenate, synthesized by esterification of glycerol by behenic acid (C22 fatty acid). The product is then atomized by spray-cooling. Compritol® 888 is composed of mono, di and triglycerides of behenic acid, the diester fraction being predominant. It is utilized as lubricant in tablet and capsule preparations, as a controlled release agent and a coating agent.

Figure 13 (right) shows the wax-loaded swollen SPH platform after 48 hrs retention in the dissolution medium (0.01 HCl). Pictures on the left demonstrate the size of the SPH platform in its swollen state. This size is achieved after about 2 min in the dissolution medium.

Figure 14 shows the release profiles of the active ingredient imbedded into two different matrices (wax and wax/SPH systems). Once HPMC capsule is disintegrated, the active ingredient is quickly released and dissolved in the dissolution medium. After about 1 hr, the concentrations of the active ingredient in the dissolution medium are about 100 and 30% respectively for the wax and the wax/SPH systems. While the active compound is almost completely released from the wax system, its release continues in a linear trend from the wax/SPH system, so that a release of about 80% is finally achieved after 48 hrs.

In another experiment, Gelucire® 43/01 replaced the Compritol® 888 and a same wax-based formulation was loaded into the same SPH platform.

Gelucire® 43/01 are glycerol esters of saturated C12-C18 fatty acids esters. It is a waxy carrier that protects active ingredients from light, moisture and oxidation

Having similarly formulated, the Gelucire®-based wax formulation was a thinner paste than a Compritol®-based one. As shown in Figure 15, drug release from the wax contained in the capsule and in the SPH platform follows a similar trend. Similarity of the drug release profiles can be accounted for in terms of lower-melting point of the wax and thinness of the final paste, by which the wax/SPH interaction is minimized.

These two experiments have shown that the drug release profile can be extensively modified by changes in the wax components of the wax formulations. Similarly, any change including the type of SPH, pore size of the SPH, size of the SPH reservoir and also the type of active ingredient may significantly affect the drug release profile from the SPH platform. The release profile of the drug can be modified by formulators based on the requirements of the particular drug candidate. Here it has been shown that the technology is achievable with an effective method of incorporation. Even though the SPH platform may have an effect on the drug release profile from the wax formulations, the major objective of using the SPH is to achieve gastric retention for the wax-based or semi-solid formulations with the aim of allowing more exposure time in the stomach.

## Conclusions

The continual advancement in oral drug delivery necessitates the need for improved techniques to ensure those drugs with absorption windows or local actions are delivered effectively to the GI tract with sufficient therapy. Additionally the physiology and variability of the GI tract both in itself and between subjects, has ensued the search for systems that can function independent

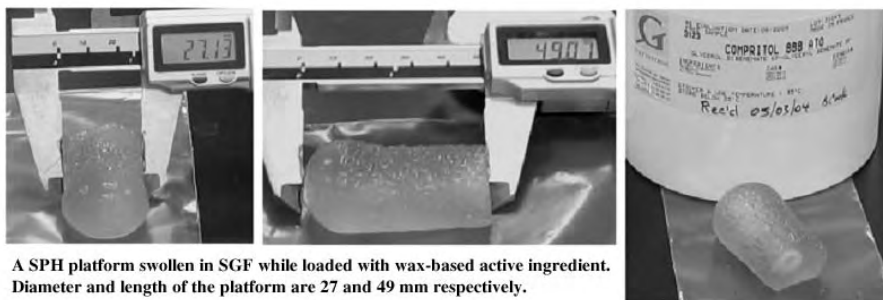


Figure 13. Images showing wax-loaded SPH platforms following immersion in SGF.

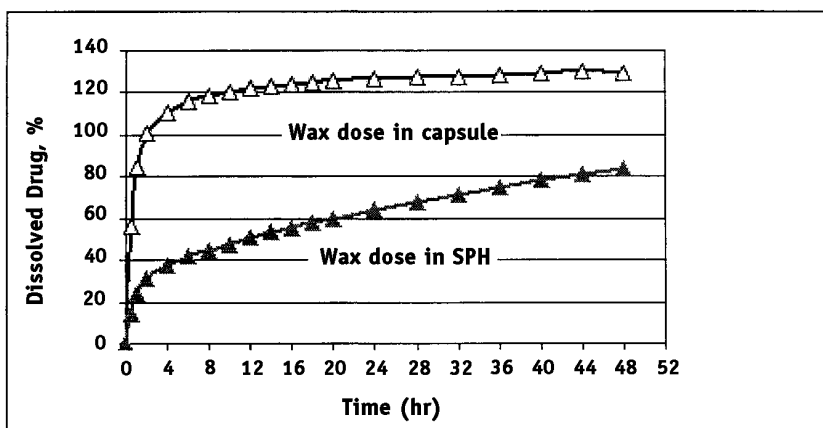


Figure 14. Typical drug release from wax (Compritol® 888) formulations and wax-carriers (Compritol® 888) in SPH

(USP II Apparatus Paddle type, 900 ml of 0.01N HCl @ 37 °C, 100 rpm, pH 2; Standard: Solution of active ingredient in 0.01 HCl (50 mg/l); Equipment: HP8453 UV/VIS @280 nm).

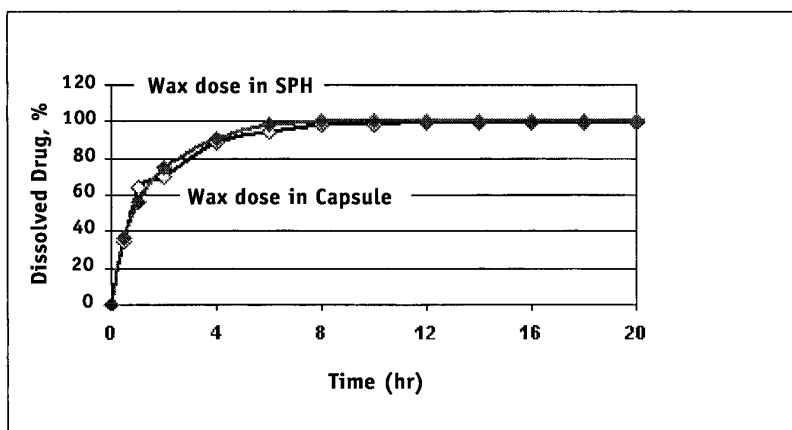


Figure 15. Typical drug release from wax (Gelucire® 43/01) formulations and wax-carriers (Gelucire® 43/01) in SPH

(USP II Apparatus Paddle type, 900 ml of 0.01N HCl @ 37 °C, 100 rpm, pH 2; Standard: Solution of active ingredient in 0.01 HCl (50 mg/l); Equipment: HP8453 UV/VIS @280 nm)

of the local environment and remain in the GI tract irrespective of the physiological state of the subject. The superporous hydrogel is one of the few methods studied for gastric retention, which has been adapted in an industrial setting. The technology constitutes a swelling system able to retain in the stomach for defined periods of time based on fast swelling, mechanical strength and disintegration properties. The reservoir nature of the SPH platform has the ability to incorporate a wide range of drug delivery systems within, such as tablets, liquids, solids or semi-solids. Wax based formulations were also assessed for their feasibility in incorporation within the platform as semi-solid carriers.

## Acknowledgements

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# MELT EXTRUSION-BASED DOSAGE FORMS: EXCIPIENTS AND PROCESSING CONDITIONS FOR PHARMACEUTICAL FORMULATIONS

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## Summary

Melt extrusion is a useful tool to aid in the preparation of orally bioavailable formulations for poorly water-soluble drugs through the generation of solid dispersions. Likewise, this technique can be applied to the difficult task of sustained and/or controlled release of drugs and drug candidates which are either water-soluble or limited in their aqueous solubility. Various oral dosage forms which have been developed for the market demonstrate the utility of these approaches and include a melt extruded tablet for itraconazole (Sporanox<sup>®</sup>, Korea). In addition, a verapamil product based on the Meltrex<sup>®</sup> technology of Soliqs (a division of Abbot) is available on the Polish market. While traditional extrusion carriers include pharmaceutical polymers as well as various monomers, use of lipids/surfactants either as carriers or additives can be very useful. As the complexity of drug candidates increase, these techniques will become increasingly important enabling technologies for generating useful drug delivery systems.

## Keywords

*Hot melt extrusion, solid dispersion, increased aqueous solubility, controlled release, sustained release, Gelucire<sup>®</sup>.*

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## 1. Introduction

Current pharmaceutical research has a number of drivers including the nature of the drugs being developed and the need for generating adequately bioavailable dosage forms. Drug discovery has evolved over the years such that high throughput screening techniques have become routine. These approaches put a type of evolutionary pressure on emerging drug candidates, which has led to a systematic increase in molecular weight, lipophilicity and a decrease in water solubility for lead compounds over time [1-3]. This, in turn, has had a significant impact on what is required from formulators in that the number of formulation options has to be increased to address the larger number of challenges being presented.

For a drug to be orally available, the compound must dissolve and be absorbed through the gut in such a way so as to generate adequate drug levels at the pharmacologically active site so that the desired action(s) is obtained in a reproducible manner. Retrospective studies show that > 40% of drug failures in development can be traced to poor biopharmaceutical properties namely poor dissolution or poor permeability [1]. In recognition of the importance of these factors, the FDA and other drug regulatory organizations have defined a Biopharmaceutical Classification System (BCS) in which drugs are divided into 4 types based on their solubility and permeability characteristics [4-6]. Soluble, permeable drugs are termed Class 1 compounds with oral bioavailability only being limited by their ability to reach appropriate sites of absorption in the GI tract. Class 2 drugs are poorly soluble but permeable through the gut meaning that oral bioavailability is limited by dissolution rate and, as a consequence of the Noyes-Whitney equation, drug solubility. Class 3 compounds are soluble but poorly permeable meaning that oral bioavailability is limited by the barrier properties of the GI tract. Finally, Class 4 compounds are both insoluble and poorly permeable combining the limitations of both Class 2 and 3 materials. Thus, high throughput discovery methodologies are selecting, more and more, for difficult Class 2 compounds. Importantly, the number of

Class 3 compounds is also on the rise as proteins, peptides along with their small molecular weight biomimics fall into this category. One additional comment is that not all Class 2 compounds are cut from the same bolt of cloth. Poor aqueous solubility can have various causes and these factors may dictate what formulation approach is required to provide for orally bioavailable systems [2]. Solubility can be controlled, for example, by log P meaning that methods to improve wettability may be paramount. Alternatively, poor aqueous solubility may be associated with a high melting point meaning that crystal lattice forces are responsible. These two factors give rise to the terms “greaseballs” (compounds whose solubility is log P-limited) and “brick dust” (compounds whose solubility is melting point-limited). A qualitative indication of whether a compound falls into the “greaseball” or “brick dust” category can be assessed using the empirical relationships of Yalkowsky [7,8] such as:

$$\text{Log } S_w = -\log P - 0.01 T_m + 1.05$$

where Log  $S_w$  is the log of the aqueous solubility, log P is the log of the octanol-water partition coefficient and  $T_m$  is the melting point for the drug.

A significant aspect of pharmaceutical research in the last few years and, likely in the foreseeable future, has been strongly targeted to overcome issues related to the formulation of Class 2 compounds. Generally, the search for such methods have been guided by the (modified) Noyes-Whitney equation which defines dissolution rate ( $dC/dt$ ) as [9,10]:

$$\frac{dC}{dt} = \frac{D \times A \times (C_s - C_t)}{h \times V}$$

where D is the diffusion coefficient, h, the diffusion layer thickness at the solid-liquid interface, A, the surface area of drug exposed to the dissolution media, V, the volume of the dissolution media,  $C_s$ , the saturation solubility of the drug and  $C_t$ , the drug concentration at time, t. That is, dissolution rate can be increased by increasing the surface area of the drug (via micro-

or nanosizing), by decreasing the diffusional layer thickness (through improving wettability by e.g. addition of surfactants or by hydrodynamic parameters) and by altering the solubility of the drug (through formation of supersaturated drug solution via solid dispersion, complexation approaches or by manipulation of the solid form to give more soluble salts, polymorphs or amorphous material). Solid solution and dispersion technology is especially useful in this regard as it combines a number of factors identified by the Noyes-Whitney relationship [11-13]. Specifically, the drug substance is (a) often obtained in the amorphous state meaning that crystal lattice forces have been overcome and solubility is improved, (b) the theoretical drug particle size is reduced to the smallest size possible, that is to the isolated, dissolved molecules, and, (c) based on an appropriate selection of the drug carrier, wettability is increased and a microenvironment conducive to dissolution is generated. Balancing these attractive elements are a number of disadvantages, chief of which includes the physical stability of the drug in the cast or melt-processed polymeric carrier. The amorphous state is of high energy relative to the crystalline state and tends to recrystallize over time. Stabilization is possible but methods are specific to the formulation of interest. These stabilizing approaches will be discussed in Section 2.3 below.

Two common methods exist to prepare solid dispersions: (a) the solvent method, and (b) the hot melt method [12,13]. With the solvent method, the drug and carrier are dissolved in a common organic solvent, followed by removal of the solvent by evaporation. This can be done, for instance, by spray-drying, whereby the solution is pumped into a chamber through a spraying nozzle, and is then distributed into a fine mist of droplets. The solvent is rapidly evaporated from these small droplets and particles are collected in a cyclotron. The hot melt method consists of melting the carrier and drug whereby the solid dispersion is formed upon cooling of the melt. In some cases it is sufficient to only melt the carrier with the crystalline drug subsequently dissolving or dispersing in the molten polymer.

Different approaches exist to perform the hot melt method, but during the last decade, hot melt extrusion has gained increasing popularity [14,15]. Hot melt extrusion is a common processing technique in the polymer industry. About 35 years ago, the process was adapted for pharmaceutical applications by Speiser [16]. However, only in the last decade has the process gained significant interest such that it is now generally accepted in pharmaceutical industry as a valuable technique to prepare solid dispersions and sustained/controlled release dosage forms. One of the major advantages of melt extrusion is the absence of any solvents to produce a solid dispersion, compared to the solvent method whereby expensive explosion proof equipment and solvent recovery systems are needed [17]. The major drawback of hot melt extrusion is that it is limited to thermally stable products. However, in many cases the application of hot melt extrusion can be expanded through the use of plasticizers.

## 2. Types of solid dispersions

A complete understanding of the types of solid dispersion obtained upon melt extrusion is extremely important with respect to selecting the most stable dispersion (both physically and chemically), as well as during process scale-up to detect any changes as a consequence of changing the process parameters. It may well be that even the slightest change in the type of solid dispersion may cause a major change in the performance of the final product, ultimately impacting oral bioavailability. Therefore, in this section, a brief overview will be given of the different types of solid dispersions [13,18,19].

### 2.1 Simple eutectic mixtures

Simple eutectic mixtures show complete miscibility in the liquid state but only to a very limited extent in the solid state. In a eutectic composition, both components crystallize simultaneously in very fine crystals. They are usually prepared by rapid cooling (quenching) of the melt.

## 2.2 Solid solutions

Solid solutions can be compared to liquid solutions as they consist of a single phase. The drug particle size is reduced to the smallest size possible, that is to the molecular level and the dissolution rate is solely dependent on the dissolution rate of the carrier.

Solid solutions can be classified based on miscibility (continuous or discontinuous) or they can be classified based on the way in which the solute/solvent molecules are distributed in the matrix (interstitial, substitutional or amorphous).

### 2.2.1 Continuous solid solutions

In this kind of system, the individual components show complete miscibility in all concentrations. This would suggest that the hetero-molecular bonding strength is stronger relative to the homo-molecular bonding strength. These type of solid solutions have thus far not been reported in literature.

### 2.2.2 Discontinuous solid solutions

In discontinuous solid solutions, the solubility of one component in the other is limited. In other words, only in a small area of the phase diagram are hetero-molecular forces stronger relative to the homo-molecular interactions.

### 2.2.3 Substitutional crystalline solid solutions.

In substitutional crystalline solid solutions, solvent molecules are replaced by solute molecules in the crystal lattice. These types of solid solutions can only be formed when the diameter of the solute molecules differs by less than 15% of the solvent molecule diameter.

### 2.2.4 Interstitial crystalline solid solutions

In interstitial crystalline solid solutions, the dissolved molecules occupy the interstitial spaces of the solvent molecules in the crystal lattice. As with substitutional crystalline solid solutions, the size of the solute molecules is an important parameter in determining whether this type of arrangement will form. The diameter of the solute molecules should not be greater than 0.6 times the diameter of the solvent molecules

and the volume of the solute molecules should not exceed 20% of that for the solvent.

Based on these constraints, it is clear that most of crystalline solid solutions are interstitial, given the high molecular weight of the polymeric carriers and the relatively low molecular weight of the active substance.

## 2.3 Amorphous solid solutions

An amorphous or glass solution is a homogeneous, glassy system whereby the solute molecules are dispersed molecularly but irregularly within the amorphous solvent. Amorphous solutions are characterized by a glass transition region ( $T_g$ ) which is the temperature at which mobility in the system changes from low to high. Amorphous solutions are formed by either (rapid) cooling of the melt or (rapid) evaporation of a solution. Upon cooling (or evaporation), the drug is frozen or vitrified into the glassy state in the amorphous solvent molecules, thereby stabilizing the amorphous drug substance. Since many pharmaceutical polymeric carriers are amorphous in nature, this type of solid solutions are most likely to be formed. This being the case, glass solutions will be discussed in a bit more detail. It should again be mentioned that the amorphous state is a metastable state. The tendency of these systems to recrystallize increases as molecular mobility increases which occurs as the storage temperature approaches the glass transition region. Based on the determination of the relaxation enthalpy as a function of temperature, a storage temperature of 50 K below the glass transition of the system has been repeatedly shown to generate a thermodynamically stable product within a shelf-life consistent with a marketable pharmaceutical drug product [20-22]. However, this does not take into account kinetic effects which may occur during real-time stability studies. Therefore, close monitoring of the amorphous solution during stability investigation is of extreme importance. Besides the stabilizing effect of the amorphous drug associated with vitrification in a polymeric carrier, intermolecular interactions such as hydrogen bonding or complexation may further stabilize the amorphous solution [23]. Therefore,

these events must be evaluated during preparation and stability investigation as well.

The theoretical glass transition of the amorphous solution can be calculated according to the Fox equation (assuming ideal mixing and equal densities) [24]:

$$\frac{1}{T_{g_x}} = \frac{w_1}{T_{g_1}} + \frac{w_2}{T_{g_2}}$$

In this equation,  $T_{g_1}$  and  $T_{g_2}$  are the glass transition temperature of the active substance and the carrier respectively, while  $w_1$  and  $w_2$  are the weight fractions of drug and carrier in the amorphous solution. Although the Fox equation assumes equal densities, it is useful to calculate the expected theoretical glass transition temperature and thus test the hypothesis that an amorphous solution is formed. Deviations from the theoretical value may indicate the existence of intermolecular interactions or the formation of a phase separated system.

When equal densities do not apply for the system, the theoretical value for the  $T_g$  of a binary mixture (assuming ideal mixing) can be calculated using the Gordon-Taylor / Kelly-Bueche equation [25,26]:

$$T_{g_x} = \frac{T_{g_1}w_1 + T_{g_2}Kw_2}{w_1 + Kw_2}$$

in which  $T_{g_1}$  and  $T_{g_2}$  are the glass transition temperature of drug and carrier, respectively,  $w_1$  and  $w_2$  are the weight fractions of the drug and carrier in the amorphous solution, respectively, and  $K$  is a constant which can be calculated using the Simha-Boyer rule [27]:

$$K \cong \frac{\rho_1 T_{g_1}}{\rho_2 T_{g_2}}$$

where  $\rho$  is the density of the amorphous solid.

#### **2.4 Amorphous precipitations in a crystalline carrier**

In this type of solid dispersions, the solute molecules are dispersed in the amorphous state

into crystalline solvent molecules. Again, for the amorphous drug substance, the metastable state may cause stability-related issues and therefore close monitoring during stability investigation is required.

#### **2.5 Complex formations**

These are dispersions whereby a complex is formed between the solute molecules and the solvent molecules. Due to the complex formation, these dispersions may be more stable compared to systems without intermolecular interaction.

#### **2.6 Combinations of solid dispersions**

Usually, a solid dispersion formed between the active substance and the carrier does not entirely belong to any of the previous classes and thus is often a combination of different types of solid dispersions.

### **3. Process and equipment**

The hot melt extrusion process can be divided into a number of unit-operations including: feeding the products, melting the components, mixing/dispersing the drug in the excipients, venting the volatile substances and pressurizing the molten mass [15,28,29]. Important considerations during the process include: the product flowability, the shear forces inside the extruder barrel, the residence time in the extruder at increased temperature, the pressure developed by the screw(s), cooling of the extrudate upon exiting the die and shaping of the extrudate in the final form. The process can be controlled by the following main process parameters: the temperature settings of the barrel, the feeding rate and the screw speed. These parameters will result in a certain viscosity in the extruder, which is reflected by the torque. In other words, the torque is a measure of the resistance that the motor experiences as a consequence of the viscosity inside the barrel. For each parameter setting and type of equipment, the specific energy (SE) can be calculated and is an important value to be considered e.g. when scaling-up the process or when changing the equipment [28]:

$$SE(KWhr/kg) = \frac{MotorPower(KW) \times Torque(\%) \times \left( \frac{ScrewSpeed(rpm)}{MaxScrewSpeed(rpm)} \right)}{FeedRate(kg/hr)}$$

The simplest of the extruder designs is the single screw extruder. Basically, the single screw extruder, working under flood feeding principle, provides for a continuous bed of material transported throughout the barrel and transmitting pressure from the die back to the hopper (see Figure 1).

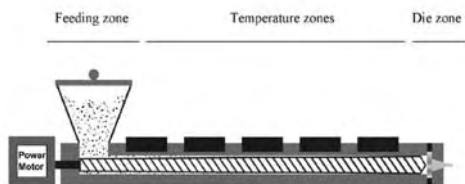


Figure 1: Schematic presentation of a single screw extruder

The die-plate, connected to the end of the barrel, determines the shape of the extruded products. The barrel is heated through the means of electrical or liquid-based (oil, steam) heaters. Besides the heat supplied by the barrel, there will be friction between the rotating screw(s) and the wall of the barrel, generating a substantial amount of additional heat. Extruder screws and barrel are usually modular, i.e. interchangeable barrel sections or screw configurations, which allows for the modification from low to high shear extrusion.

The twin-screw extruder has two screws arranged side by side. These shafts are driven through a splitter/reducer gearbox and rotate in the same direction (co-rotating) or in the opposite direction (counter-rotating). The screws are often intermeshing, which means that each agitator element interacts with both the surface of the corresponding element on the adjacent shaft, and the internal surfaces of the barrel.

The screws of the twin-screw extruder are modifiable by using transport elements (used to convey the product) and kneading elements (used to mix the product) as shown in Figure 2.

These kneading elements can be placed in different angles, providing more or less mixing, and thus higher or lower shear force effects.

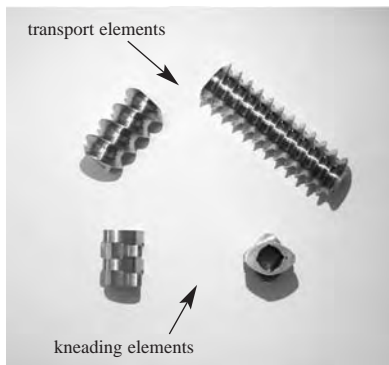


Figure 2: Transport and kneading elements.

In general, co-rotating shafts have better mixing capacities as the surfaces of the screws move towards each other. Therefore, co-rotating twin-screw extruders are preferred to counter-rotating instruments when solid dispersions and mixing/dissolving drug into polymeric carrier(s) are considered. Also the screw configuration is of importance for generating solid dispersions/sustained release dosage forms, since the mixing zone also determines the degree of mixing.

Co-rotating twin-screw extruders work according to the starve fed feeding principle. In other words, separate feeding systems are necessary, wherein the loss-in-weight system is used most frequently to obtain an accurate feeding of the pharmaceutical ingredients (see Figure 3).

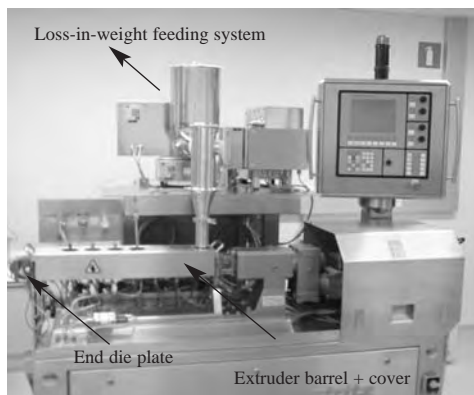


Figure 3: Typical co-rotating twin screw extruder set up with loss-in-weight powder feeding system.

The end die-plate determines the shape of the extrudate leaving the extruder. An annular die results in the formation of a strand or a rod while a slit die results in a film shaped extrudate. Besides these shapes, more complex shapes can be obtained as well, such as tubes, tapes, etc.

Upon exiting the die, different possibilities exist to further process the extrudate. The extrudate can be directly shaped into dosage forms using two calendar rollers. In this case, the extrudate film or strand is compressed between two rollers with pre-shaped molds, resulting in the on-line production of tablet-shaped extrudates. These tablets are then further cooled downstream using a cooling conveyer. Another possibility is the formation of granules or pellets by either a hot or a cold cut (see Figure 4). A hot cut is performed using a cutting knife placed immediately behind the die, while a cold cut is performed after cooling the extrudate strand on a cooling conveyer. The strand is then removed from the conveyer by twin rollers and cut into pellets using a rotating cutting knife. The pellets can then be used immediately (e.g. filled into hard gelatin capsules) or further milled and processed into oral tablets by conventional techniques and equipment. A third possibility is to produce a film, for instance, for transdermal applications. A film can be produced by a series of rollers that pull and compress the film to a certain thickness.



Figure 4: Examples of extrudate shapes: extrudate powder (left), granules (middle) and strands (right).

#### 4. Pharmaceutical Applications

Numerous pharmaceutical applications of hot melt extrusion are described in the literature and have been extensively reviewed by Breitenbach [15]. A variety of excipients can be used to

perform the process. Traditional extrusion carriers include pharmaceutical polymers such as polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), polyvinylpyrrolidone (PVP), polyvinylpyrrolidone-vinylacetate (PVP-VA 64) and Eudragit E100 as well as various monomers (i.e., mannitol, citric acid, cyclodextrins).

One such example is given by Verreck et al. and Six. et al., who describe hot melt extrusion of the poorly water-soluble antifungal drug itraconazole [30-33]. The compound is insoluble in water ( $S \sim 1$  ng/ml at neutral pH and  $S = 6$   $\mu$ g/ml in 0.1 N HCl at pH 1), has an ionization constant of 4.0 and a very high octanol-water partition coefficient ( $\log P > 5$ ) [34]. Importantly, itraconazole is thermally stable above 200°C. According to the biopharmaceuticals classification system, itraconazole is an extreme example of a class II compound meaning that its oral bioavailability is determined by dissolution rate in the GI tract [4-6]. Verreck and co-workers describe the hot melt extrusion process of itraconazole with HPMC 2910 5 mPa. s in a drug/carrier ratio of 40/60 w/w [31,32]. This combination resulted in the formation of an amorphous dispersion, which was physically and chemically stable for at least 2 years when packed into aluminum bags. Process-wise, extrudate strands were formed and cooled on a cooling conveyer after which the strands were cut into pellets. These pellets were further milled to obtain a powder with a particle size below 250 micron. This extrudate powder was then mixed with other classical tableting ingredients and compacted into fast disintegrating tablets. Both dissolution and bioavailability were significantly enhanced for this drug substance relative to the unformulated drug when melt extruded with HPMC in a drug/polymer ratio of 40/60 wt% [30]. The tablets with a 100 mg dose were introduced on the Korean market as Sporanox® 100 mg tablets. Six and co-workers also investigated hot melt extrusion applications for itraconazole [35-37]. They assessed binary dispersions with Eudragit E100 and PVP-VA 64, respectively, as well as ternary dispersions using combinations of Eudragit E100 and PVP-VA 64. With PVP-VA, itraconazole formed an amorphous solution over the entire concentration

range, but dissolution was poor with 45% itraconazole dissolved after 3 hours. With Eudragit E100, phase separation occurred above a drug loading of 13%, but dissolution from the amorphous solution at drug loadings below 13% was good with 80% dissolved after 30 minutes. However, after a two hour dissolution measurement, precipitation from the supersaturated solution occurred. Based on these results, ternary solid dispersions were prepared containing itraconazole, PVP-VA 64 and Eudragit E100. In these extrudates, no free crystalline or glassy clusters of itraconazole were observed. In other words, all itraconazole was mixed with one of both polymers. With an Eudragit E 100/PVP-VA 64 polymer ratio of 70/30 w/w or 80/20 w/w (and 40 w/w drug loading of itraconazole), a dissolution of 85% after 30 minutes was obtained without precipitation during the time course of the measurement. An *in vivo* bioequivalence study in human volunteers with extrudates consisting of itraconazole/HPMC, itraconazole/Eudragit E100 and itraconazole/Eudragit E100/PVP-VA 64, in comparison with the commercial Sporanox® 100 mg capsules was subsequently performed. The extrudates were milled to a fine powder and filled into hard gelatin capsules. It was shown that the binary solid dispersions with either HPMC or Eudragit E100 were bioequivalent to Sporanox®, while the ternary system with Eudragit E100/PVP-VA 64 showed less exposure after oral administration. It was assumed that the dissolution rate for Eudragit E100/PVP-VA 64 was “too” fast and that supersaturation was reached early allowing for *in vivo* precipitation to occur in the GI tract prior to drug absorption.

Another drug substance, verapamil, has also been developed and patented using hot melt extrusion for the treatment of hypertension, coronary heart disease and arrhythmia. The hydrochloric salt of verapamil can be melt extruded with a variety of polymeric carriers (both traditional as well as non-traditional polymers/excipients) to produce different release profiles. One such example for verapamil describes the use of a water-swelling graft copolymer consisting of methyl methacrylate

and poloxamer 188 with calendaring post-extrusion to obtain oblong shaped tablets [38]. The *in vitro* release of verapamil. HCl was 40% in 8 hours. Another sustained release application using a copolymer for sustained release is sodium 5-sulfoisophthalate/isophthalic acid/hexamethylenediamine/ε-caprolactam (16.67:16.67:33.33:33.33) copolymer which was employed to generate a 500 mg calendared tablet. This system released 10% of its drug content after 8 hours [39]. A faster release was obtained using a copolymer of vinylpyrrolidone/stearyl methacrylate (90:10) (55% in 8 hours), a copolymer of vinylformamide/vinylpyrrolidone (50:50) copolymer (100% in 2 hours) and poly(N-vinylcaprolactam) (100% in 1 hour) [40-42]. Additionally, mixtures of different excipients have been used to develop verapamil. HCl calendared tablets including copolyvidone, isomalt and lecithin (33.33/13.67/ 50/3 w/w) which were prepared by extrusion at a nozzle temperature of 110°C. These tablets released 86% of the verapamil within 20 min [43]. An alternative mixture consisted of verapamil. HCl, HPC, HPMC and hydrogenated soybean lecithin (49/38/10/3 w/w) [44]. In these formulations, lecithin is added to prevent sticking of the extrudate to the calender molds and to decrease the plasticity of the melt. These examples show that the release of verapamil. HCl can be sustained and/or controlled by the choice of the proper carrier and/or excipients.

Besides these two examples, a number of references can be found in literature describing the use of hot melt extrusion either to increase the aqueous solubility of drugs or drug candidates or to develop a sustained and/or controlled release formulation. The hot melt extrusion of theophylline monohydrate for controlled release applications is relevant in this context. This drug substance was extruded with corn starch as the matrix forming agent, sorbitol as a plasticizer and glyceryl monostearate as a lubricant (30/53/15/2 w/w) [45]. The drug release was retarded with a dissolution profile of 80% after 8 hours. This experimental formulation was tested in an *in vivo* study with the commercial formulation Xanthium® as the reference. The results showed that the extruded

formulation manifested a lower  $C_{\max}$  and  $T_{\max}$  compared to the reference formulation. The dosage form was further characterized towards *in vitro* release by investigating the influence of extrusion process parameters [46]. Two design of experiments were performed which concluded that the effect of the process parameters on the extrudate characteristics were minimal. In a subsequent study, the influence of the formulation composition was investigated [47]. Both the concentration as well as the type of the various excipients was investigated. Changing the composition of the extrudates did not change the water content or porosity after extrusion, but did influence the mechanical strength and dissolution profiles. The concentration of the plasticizer and lubricant as well as the type of starch and lubricant seem to impact these two parameters. All release profiles showed *in vitro* sustained release, but the effect was expected to be too low to give superior *in vivo* performance compared to the commercial reference.

Another example is described by Mehuys et al [48,49]. They investigated hot melt extrusion for sustained release formulations of propranolol, theophylline hydrate and hydrochlorothiazide, three drugs with different solubility characteristics. The concept developed involved a matrix-in-cylinder system to produce zero order drug release. Basically, the matrix-in-cylinder system consists of a hot melt extruded non-erodible tube surrounding a core matrix containing HPMC, Gelucire® 44/14 and drug, also prepared by hot melt extrusion. The hollow tube consists of ethyl cellulose as the carrier material and dibutyl sebacate as the plasticizer. Drug release was erosion-controlled and independent of drug solubility. A sustained release was obtained due to the HPMC present in the formulation and release was tunable by changing the length of the tube. The propranolol system was evaluated *in vivo* in dogs as well as in healthy volunteers and was compared to a commercially available sustained release formulation of Inderal®. These studies showed that the bioavailability of propranolol increased 4-fold compared to the commercial sustained release formulation. It was suggested by the authors that Gelucire® 44/14 promotes lymphatic

uptake, resulting in avoidance of liver first pass metabolism and consequently in an improved bioavailability.

Hulsmann and co-workers also describe the use of Gelucire® 44/14 as an adjuvant during the hot melt extrusion process to enhance dissolution properties [50]. They added Gelucire® 44/14 to various extruded formulations to increase the dissolution rate of 17 $\beta$ -estradiol. In their work, they have investigated different formulation components including PEG 6000, PVP K30 or PVP-VA 64 as polymers and Sucroester® WE15 or Gelucire® 44/14 as additives. The extrusion was performed below the melting point of the drug using a single screw extruder. The extrudate strands were crushed using a mortar and pestle to either a particle size fraction below 100 micron or above 400 micron. All solid dispersions resulted in a significantly higher drug release compared to the compound alone and various physical mixtures of the drug and polymers. The highest release was obtained using a composition consisting of 17 $\beta$ -estradiol, PVP K30 and Gelucire® 44/14 10/50/40 w/w. X-ray diffraction was performed to evaluate the physical state of 17 $\beta$ -estradiol in the solid dispersion. Data suggested that crystalline 17 $\beta$ -estradiol was present in the melt extruded material. The authors suggested that the higher dissolution rates were obtained by improved wettability of the drug substance. In contrast with the physical mixture, it was assumed that the dispersed drug particles in the solid dispersion are surrounded by the water-soluble polymeric carrier and also by the amphiphilic additives. The excipients readily dissolve or disperse in contact with the dissolution medium, resulting in better wetting of the drug particles by the dissolution medium.

Montousse et al. describes the investigation of different types of Gelucire® on the extended release properties of theophylline [51]. Both Gelucire® 50/02 as well as Gelucire® 55/18 were processed by extrusion-spheronization to obtain extended-release spheres. Although extrusion-spheronization differs from melt extrusion, the Gelucire® 50/02 and 55/18 were molten during the extrusion process to be able to incorporate the theophylline. It was observed that the more

hydrophobic Gelucire® (i.e., 50/02) behaved as an inert matrix and released theophylline very slowly compared with the more hydrophilic Gelucire® 55/18, which acted as a hydrophilic matrix. The process of extrusion-spheronization was easier with Gelucire® 50/02 compared with the 55/18 product. When ethanol was used as a wetting agent during the process, the release rate of theophylline was increased with Gelucire® 50/02 but reduced with Gelucire® 55/18. The use of castor oil to attenuate the rate of ethanol evaporation improved extrusion and spheronization. Castor oil decreased the drug release rate with Gelucire® 50/02 but increased it for the Gelucire® 55/18 matrix. The authors explain these phenomena based on the different solubilities of theophylline, Gelucire® 50/02, and Gelucire® 55/18 in ethanol and castor oil. By adding microcrystalline cellulose (Avicel CL 611) to the granulation matrix, the extrusion process was enhanced. The experiments indicated that the best formulation was obtained using Gelucire® 55/18 and AvicelCL611 which was wetted by a mixture of ethanol and castor oil. The mechanism of drug release was investigated. It was suggested that regardless of the formulation, the mechanism of theophylline release appeared to be Fickian in nature.

Another example showing Fickian release is given by Prapaitrakul and co-workers, who describe the use of glyceryl fatty acid esters, polyethylene glycol fatty acid esters or a mixture of the two to modify the release of chlorpheniramine maleate [52]. Matrix disks containing either one or a mixture of these excipients were prepared by hot melt extrusion. This group showed that the release could be modified by changing the hydrophilic-lipophilic balance (HLB) from a value of 1 to 14.

## 5. Conclusion

It is clear that hot melt extrusion today has proven to be a useful tool for the production of solid dispersions. This is clear from the pharmaceutical products that have reached the market and from the number of references that can be found in literature. It should be noted that not only are oral applications possible, but parenteral and topical dosage form can also be configured using this technique.

In the case of oral applications, hot melt extrusion is a feasible technique to increase aqueous solubility and bioavailability as well as to develop sustained and/or controlled release formulations. The main advantage of the technique is the absence of (organic) solvents, while the main drawbacks are associated with limitation in applications to thermally stable active compounds and excipients. Although most systems involve binary solid dispersions comprising drug dispersed in a polymeric carrier, the future may lie in the combination of different excipients such as polymeric carriers, solubilizers and surfactants to obtain the proper release profiles. Since modern pharmaceutical pipelines are presenting greater and greater formulation challenges, broader and more complex drug delivery systems are needed to circumvent issues related to bioavailability and timed drug release. Hot melt extrusion can play a major role in solving these issues.

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GATTEFOSSÉ

# PHYSICAL CHARACTERISATION AND SCALE-UP MANUFACTURE OF GELUCIRE® 50/13 BASED CAPSULE FORMULATIONS

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## Summary

Extensive physical characterisation work was carried out to correlate the physical properties of the formulation wax vehicles (Gelucire® 50/13 and Precirol®) with the stability issues (dissolution variability) observed on some wax-filled capsules.

Techniques included, DSC, XRD, SEM, to examine the crystal structure of the waxes. The drug distribution and particle size were determined using sulphur mapping and hot stage microscopy respectively. MRI was utilised to investigate the formulation hydration and erosion rates. Dissolution testing assessed the physical stability of uncured and cured capsules stored at different ICH conditions. Results showed that the changes in dissolution behaviour after storage under ambient conditions were related to changes in the crystalline structure of Gelucire® 50/13. The physical stability was greatly improved by curing the wax filled capsules, by converting Gelucire® 50/13 from its metastable form I to its stable form I'.

Process scale-up trials showed that the use of electrically heated grids greatly reduced the melting time of the two waxes.

The drug dispersion process was very robust with high shear mixing, but with low shear mixing homogeneity results were highly dependent on stirring speed, paddle design and batch size. Vacuum was essential to avoid aeration of the active wax blend.

Capsule filling was successfully scaled-up using the Qualifill semi-automated capsule filler. The H&H capsule filler was also evaluated as it offers greater output.

## Keywords

*Gelucire® 50/13, Precirol®, physical characterisation, scale-up, stability, capsule.*

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## 1. Introduction

A sustained release capsule formulation of a low dose drug (<10 mg) containing two waxy semi-solid excipients, Gelucire® 50/13 and Precirol® was developed.

Although the use of semi-solid excipients has been shown to enhance the dissolution/bioavailability of several drugs, very few formulations have been marketed owing to physical stability issues [1], [2], [3], [4], [5], [6]. Waxy excipients can exist as metastable systems and can exhibit physical changes upon aging. The conversion of the excipient(s) into a more stable polymorphic form is an example of such changes, and can lead to changes in the drug release from the dosage form [7], [8], [9], [10].

The objective of this work was to carry out extensive physical characterisation work to gain a thorough understanding of the solid phase formed after cooling the wax fill, and subsequent changes upon aging. Developing a greater understanding of the pharmaceutical glyceride bases, Gelucire® 50/13 and Precirol®, and subsequently the drug product, helped to offer a possible solution to physical stability issues.

Scale-up trials were performed with the aim to define a robust process. Different ways of melting the waxes, low shear and high shear mixing for the preparation of the active wax blend, and capsule filling were fully characterised. A reliable process was identified and could be recommended for production scale batches.

## 2. Excipients, Formulation, Process and Storage Conditions

### 2.1. Gelucire® 50/13

Gelucire® 50/13 is a well defined mixture of mono, di and triglycerides, mono and di fatty acid esters of polyethylene glycol, and free polyethylene glycols.

Gelucire® 50/13 can increase the solubility and bioavailability of poorly soluble drugs and is used as a sustained release excipient due to its high melting point (approximately 50°C). It has a Hydrophilic Lipophilic Balance (HLB) value of 13, and the drug release is controlled by erosion [11], [12].

Gelucire® 50/13 is a waxy excipient and can undergo changes in its crystalline structure with time [13]. It is able to exist in three crystalline forms, which are illustrated in Figure 1.

### 2.2. Precirol Ato 5®

Precirol® is composed of mono, di and triglycerides of palmitostearic acid and is therefore an hydrophobic waxy excipient (HLB value of 2). Due to its relatively high melting point (55°C) and low HLB value, it can be used as a controlled release agent, from which the drug is slowly released by diffusion/erosion.

Precirol® was added to Gelucire® 50/13 to slow down the drug release rate, by obtaining a more diffusional drug release mechanism. There is a simultaneous influence of the melting point and the HLB on dissolution rate. Generally, the lower the HLB value and the higher the melting point of the wax blend, the slower the release rate [14], [15], [16], [17], [18], [19], [20], [21], [22].

### 2.3. Formulation and Process

A size 2 wax filled capsule containing 4%w/w of drug X, 46%w/w of Gelucire® 50/13 and 50%w/w of Precirol® proved to possess adequate *in vitro* sustained release characteristics, and *in vivo* performance with good bioavailability and prolonged plasma levels.

Gelucire® 50/13 and Precirol® were heated to 70°C-75°C for a short period of time to destroy any crystalline structure. The two waxy excipients were mixed together to form a

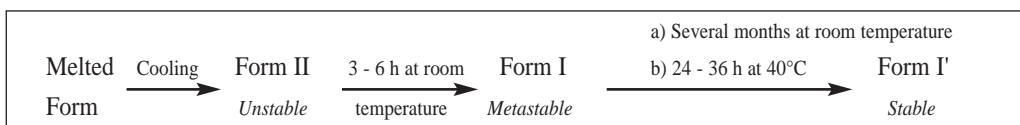


Figure 1. Crystalline forms of Gelucire® 50/13

single uniform phase. The wax blend temperature was decreased to 50-55°C and 4%w/w of drug X was added to the molten mixture and stirred until a uniform suspension was obtained. Approximately 269 mg of the mixture was filled into size 2 hard gelatin capsules.

The same process was utilised to prepare matching placebo capsules which were used as a control for the physical characterisation work.

## **2.4. Storage Conditions**

Gelucire® 50/13 and Precirol®, untreated or cured at 40°C for different periods of time, were fully characterised.

Active and placebo formulations freshly prepared or cured for different periods of time at 40°C were extensively examined. The uncured and cured formulations were also stored for several months under different conditions of Relative Humidity (RH) and temperature, to look at changes upon aging.

## **3. Method and Equipment**

### **3.1. Physical Characterisation**

#### **3.1.1. Differential Scanning Calorimetry (DSC)**

DSC traces were collected using a Perkin Elmer Differential Scanning Calorimeter, Power Compensation DSC7.

Samples in crimped aluminium pans were heated from 20°C to 80°C at 5°C / min (unless stated).

#### **3.1.2. X-Ray Diffractometry (XRD)**

Powder patterns were obtained using a Bruker D8 Advance X-Ray Powder Diffractometer configured with a Cu anode (40 kV, 40 mA), variable divergence slit, primary and secondary Soller slits, and a position sensitive detector. The samples were packed into Si sample cups which were rotated during data collection. Data were acquired over the range 2-35 degrees 2-theta using a step size of 0.0145 degrees 2-theta (time per step: 0.5 s).

#### **3.1.3. Scanning Electron Microscopy (SEM) and Digital Elemental Distribution Maps (Sulphur Mapping)**

The base of the capsule was cut off with a scalpel, and the remaining contents pushed out of the capsule shell from below using a stick. The upper part of the wax fill was cut off and mounted onto an aluminium specimen support using silver paint. After allowing the paint to dry, samples were sputter-coated with platinum for 2x 30s at 20mA (Emitech K575 sputter coater) prior to imaging at 1kV in a Hitachi S-4700 field emission scanning electron microscope.

X-ray spectra and digital elemental distribution maps were collected from points or areas of interest on the same samples at typically 8kV, using a PGT IMIX energy dispersive X-ray spectrometer with a PGT PRISM ultra-thin window detector.

#### **3.1.4. Hot stage microscopy**

A small amount of capsule fill was placed on a half-length microscope slide and a cover glass applied. The fill was spread into a thin layer by gentle pressure on the cover glass on a hot plate at 50°C. The slide was then transferred to a Linkam THM600 hot stage on a Zeiss Axioplan transmitted light microscope with polarising optics. Melting of the wax to reveal drug particles was achieved by raising the hot stage temperature up to 70°C. Images were captured and calibrated against a certified stage micrometer to obtain an accurate scale bar. Particle size measurements were made by reference to the scale bar.

#### **3.1.5. Magnetic Resonance Imaging (MRI)**

Water penetration and disintegration of cured and uncured capsules were evaluated using Magnetic Resonance Imaging (MRI), by detecting the distribution of mobile hydrogen atoms in water.

Individual capsules were scanned repeatedly in flowing media, so that water penetration and changes in capsule shape and properties, could be measured over time.

The capsule was scanned in the horizontal bore high field 7 Tesla 300 MHz Bruker Biospec

instrument, in flowing (ca. 10ml/min) media. The water penetration was measured in terms of the change in the cross sectional area of the unpenetrated and penetrated zones of the capsule. Cross sections were recorded at initial timepoint, after 2h in Simulated Gastric Fluid (SGF), and at different timepoints after the switch to Simulated Intestinal Fluid (SIF). The medium switch from SGF to SIF occurred at the 2 hour timepoint.

### 3.1.6. Dissolution

Dissolution was performed using USP Apparatus 2 (rotating paddles) at 50 rpm.

The dissolution medium was an aqueous solution of sodium chloride and hydrochloric acid, pH 1.5. The medium was titrated to pH 7.4 by addition of aqueous sodium dodecyl sulfate and an aqueous solution of sodium acetate and tris(hydroxymethyl)methylamine after 2 hours of dissolution. Samples were collected at discrete timepoints and assayed for drug content by HPLC.

### 3.1.7. Dissolution Medium Appearance

Dissolution media were observed visually.

## 3.2. Scale-up

### 3.2.1. Wax Melting

Two methods were assessed to melt the waxes.

The first method consisted of heat transmission in the heated jacketed vessels (Brogli mixer and Becomix mixer type RW15) set up at 80°C.

The second method used a fast melter (electrically heated stainless steel grid) supplied by SEBA, with a surface area of 480 cm<sup>2</sup>. The grid was set up at a temperature of 100°C or 300°C.

### 3.2.2. Low Shear Mixing

Low shear mixing was assessed in the Becomix and the Brogli vessels. Process factors such as paddle design (propeller, anchor, paddle with scrapers blades as can be seen in Figures 2, 3, and 4), stirring speed, vacuum (on or off) and batch size were evaluated.

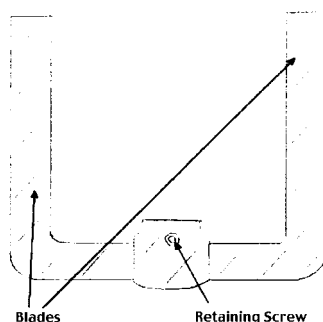


Figure 2. Anchor type paddle (side view)

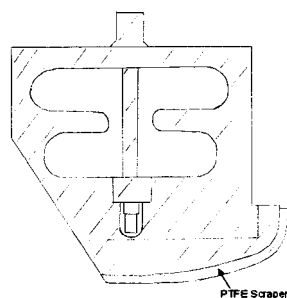


Figure 3. Large paddle with scraper blades (side view)

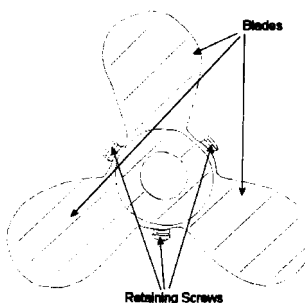


Figure 4. Propeller type paddle (top view).

A batch size of 5 kg was initially assessed. Several more batches were produced at the 10 kg level, varying the paddle design and speed. Finally, one batch was produced at the 20 kg level, the maximum scale possible in the Brogli vessel. Batches were tested for drug content uniformity and dissolution.

### 3.2.3. High shear mixing

High shear mixing was carried out in the Becomix mixer in order to assess factors such as method of homogenisation (continuous or

pulsed), batch size and vacuum (on or off). The pulsed homogenisation consisted of 1 min of high shear mixing before the sampling timepoints of 10, 20 and 30 minutes. Batches were tested for drug content uniformity and dissolution.

### 3.2.4. Capsule filling

Capsule filling studies were principally carried out with a Quali-fill oil and paste filler used in conjunction with a Quali-fill Model 8S, from Shaefer Technologies. The fill volume was set to achieve a deposition of 269 mg into size 2 capsules, and the filling temperature was about 50 to 52°C.

Some familiarisation work was also carried out with the Harro Hofliger KFM III capsule filling machine, used in conjunction with the liquid dosing system.

## 4. Results and Discussion

### 4.1 Physical characterisation

#### 4.1.1. DSC

##### • Gelucire® 50/13

Uncured Gelucire® 50/13 (Figure 5) exhibited two characteristic peaks, a premelting transition at approximately 37°C, followed by a larger melting endotherm at approximately 43°C. This profile corresponded to Gelucire® 50/13 Form I.

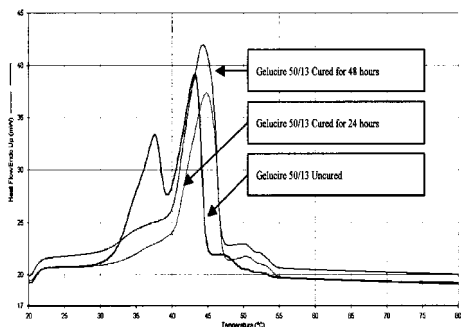


Figure 5. DSC curves of Gelucire® 50/13 Forms I and I' showing the differences in their thermal behaviour.

After curing at 40°C for 24 hours, a very small pretransition and a large main transition close to 45°C were seen and this profile corresponded to Gelucire® 50/13 Form I'. The decrease in magnitude of the pretransition, combined with the temperature shift of the main transition peak to a higher temperature, indicated a more stable form was obtained. No difference was seen between the 24 and 48-hour cured samples (only slight differences in magnitude of response was noticed). This confirmed that Gelucire® 50/13 achieved its most stable form after 24 hours curing. The same results were obtained with a scan speed of 2°C/min, indicating no problem of resolution. Results were reproducible when the experiment was repeated 3 times, showing the robustness of the method.

##### • Precirol Ato 5®

Uncured and cured Precirol® exhibited a single melting endotherm at approximately 54°C.

Several scan speeds (5°C/min and 2°C/min) detected one form only of Precirol®. There was no evidence of form changes over 48 hours curing.

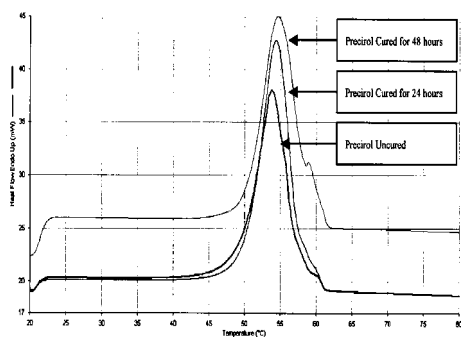


Figure 6. DSC curves of Precirol® showing the similarities in their thermal behaviour.

##### • Placebo Capsules

Placebo capsules were analysed as uncured samples, cured 24-hour and cured 48-hour samples.

Figure 7 shows that the uncured placebo capsules produced a poorly resolved profile. The complex nature of the Precirol®/Gelucire® 50/13

mixture added complication in interpreting the DSC traces.

The placebo capsules produced a profile with three peaks when cured. The first two peaks corresponded to the Gelucire® 50/13 region of the thermogram and were well resolved. The small premelt transition of Gelucire® 50/13 on its own (seen in Figure 5) appeared to be accentuated by the presence of Precirol®.

Figure 7 clearly illustrates the ability of DSC to differentiate cured and uncured placebo samples, by interpretation of peak shape, magnitude and position in the thermogram of the thermal events.

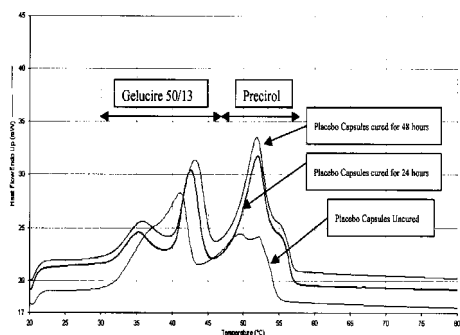


Figure 7. DSC Curves of Placebo Capsules containing Gelucire® 50/13 and Precirol®.

### • Active Capsules

A batch of capsules was divided into sub-batches and cured at 40°C for various lengths of time, ranging from 2 hours up to 4 weeks. The sub-batches were analysed to determine whether differences in crystal form, caused by length of curing, could be detected by DSC. Figures 8, 9 and 10 illustrate the profiles obtained.

In general, DSC showed a gradual change in the profiles obtained with respect to curing time, from a profile resembling Form I (at 2 hours), to a profile indicating Form I' (at 16 hours and beyond).

Samples at 2 hours had a profile that was neither concordant with an uncured sample nor a cured sample. Three peaks could be seen but they were not well resolved.

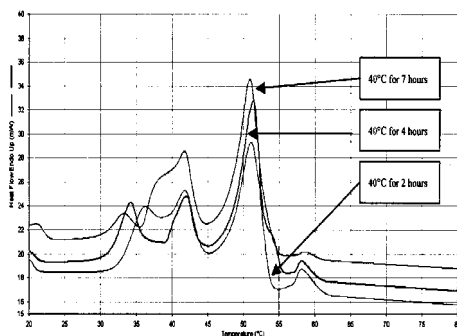


Figure 8. Effect of curing time (2, 4 and 7 hour curing).

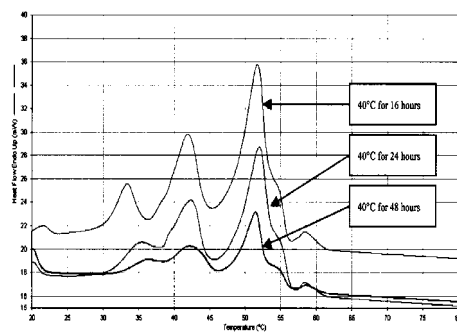


Figure 9. Effect of curing time (16, 24 and 48 hour curing).

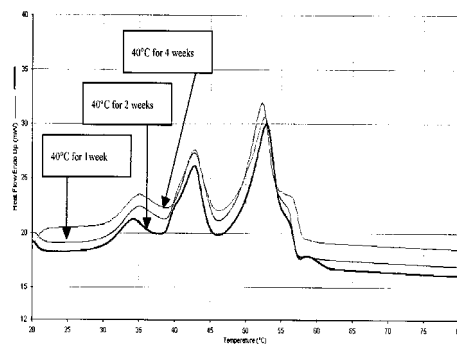


Figure 10. Effect of curing time (1, 2 and 4 week curing).

Samples at 4 hours were inbetween uncured and cured profiles, although in this instance three clear peaks could be seen. The presence of the first two peaks (corresponding to Gelucire® 50/13) and the very small difference in the magnitude between the two peaks, indicated that Gelucire®

50/13 was still present as Form I, and therefore had insufficient curing time to reach the most stable form I'.

After 7 hours curing, the peak shape was not entirely concordant with a completely cured sample. The magnitude difference between the first two peaks increased indicating that Gelucire® 50/13 started to convert from Form I to Form I'.

At 16 hours, the magnitude of difference between the first two peaks corresponding to Gelucire® 50/13 increased. The peak shape was also concordant with a completely cured sample, implying that after 16 hours at 40°C Form I' was obtained. A curing time of 16 hours was therefore the shortest amount of time required to convert the unstable Form I of Gelucire® 50/13 to its stable Form I'.

From 16 hours onwards, the peak shape did not alter significantly. The difference in magnitude between 16, 24 and 48-hour samples was due to the difference in sample weight. Results also indicated that no further transition or degradation in crystal structure occurred at extended lengths of curing time.

Although 16 hours appeared to have been a sufficient curing time to obtain the stable form of Gelucire® 50/13, 24 hours would provide a safe-zone, to eliminate any possibility that 16 hours would be on the edge of curing performance.

Active capsules from two separate batches (A and B) were analysed and compared, to determine if different batches would produce different DSC profiles.

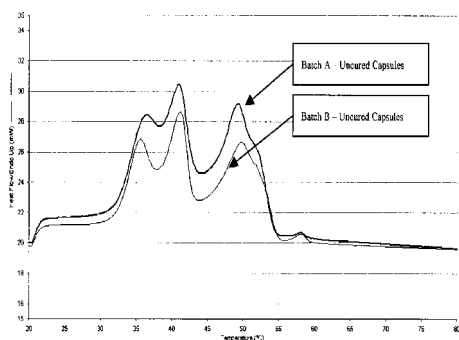


Figure 11. Comparison of DSC profiles for different active batches.

Figure 11 revealed a high level of similarity between the batches. Peaks occurred at the same temperature in both batches and difference in magnitude was due to difference in sample weights. The peaks corresponding to Gelucire® 50/13 could clearly be seen and indicated that it was present as Form I. The Precirol® peak could also be identified easily.

This confirmed that batch to batch reproducibility was satisfactory.

Figures 12 and 13 illustrate the effect of different storage conditions (5°C, 25°C/60%RH, 30°C/60%RH, 40°C/75%RH) on uncured samples, stored in HDPE bottles for six months.

The Gelucire® 50/13 region of the profiles revealed that freshly prepared active capsules and stored capsules for six months at 5°C or 25°C/60%RH were uncured. This was determined by the presence of the shoulder on the main melting endotherm of Gelucire® 50/13.

At 30°C/60%RH, the profile as a whole began to resemble a cured profile (with Gelucire® 50/13 closer to Form I') but was not identical. It seems reasonable to assume that a period of six months at 30°C began to cure the samples, but was not sufficient to cure them completely.

The samples stored at 40°C/75%RH, produced a profile that showed a shift to higher temperatures of all the main peaks for Gelucire® 50/13 and Precirol®. However, peak shape was severely distorted in some places and did not follow the trend of other storage conditions. This was thought to be due to the high humidity present at this storage condition.

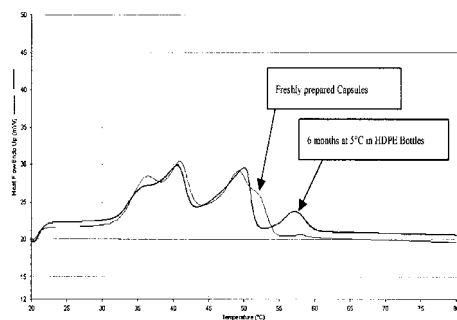


Figure 12. Effect of storage conditions (Freshly prepared and 5°C capsules).

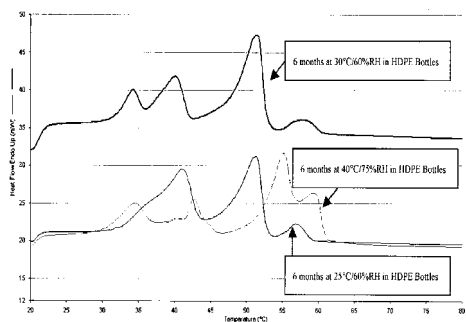


Figure 13. Effect of storage conditions (25°C/60%RH, 30°C/60%RH and 40°C/75%RH capsules).

The profile for samples stored at 40°C dry, showed a shift in all the peaks towards higher temperatures when compared to the 40°C/75%RH samples. This may indicate conversion to a more stable form. The 40°C samples were, in effect, cured for six months at 40°C.

#### 4.1.2. XRD

The X-Ray diffraction patterns changed when uncured capsules were exposed to different storage conditions for six months.

Figure 14 illustrates that identical XRD traces were obtained for an active capsule freshly prepared or stored for 6 months at 5°C, implying no polymorphic change of the excipients at this particular storage condition.

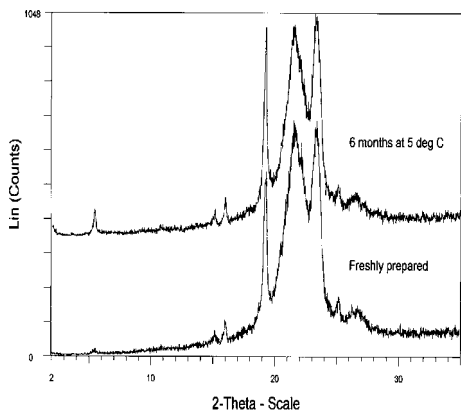


Figure 14. Effect of storage conditions (capsules freshly prepared and stored at 5°C).

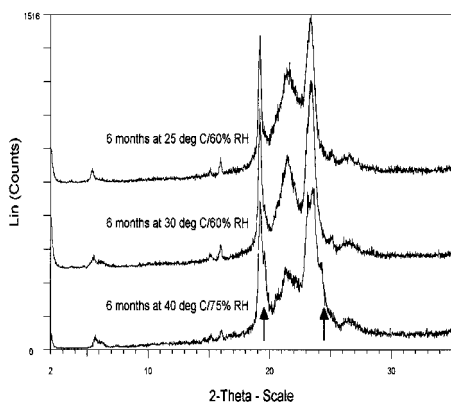


Figure 15. Effect of storage conditions (25°C/60%RH, 30°C/60%RH, and 40°C/75%RH).

For capsules stored at 30°C/60%RH, a small diffraction peak at 19.6° (2θ) could be observed (Figure 15). When the sample was stored at 40°C/75%RH, it was found to have changed even more, as two characteristic diffraction peaks at 19.6° (2θ) and at 24.2° (2θ) were present.

The appearance of the above two diffraction peaks was temperature and time dependent. It was found that the longer the period of exposure at 40°C, the greater was the intensity of the diffraction peaks at 19.6° (2θ) and 24.2° (2θ), as can be seen in Figure 16.

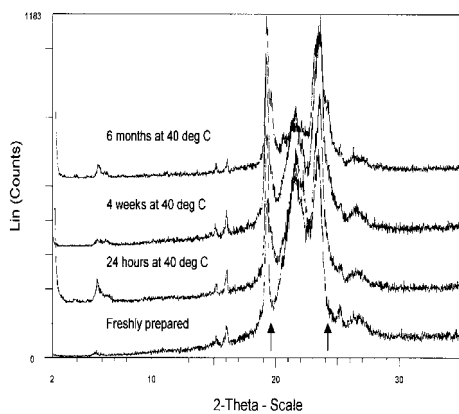


Figure 16. Active capsules - Effect of curing time at 40°C.

Figure 17 shows that humidity had no effect, as XRD traces were identical for samples stored at 40°C/75%RH or 40°C dry for four weeks.

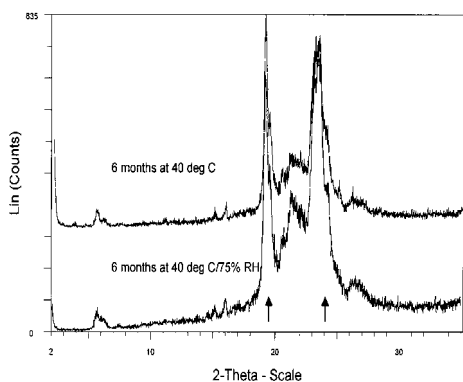


Figure 17. Effect of humidity

Uncured samples spiked with 1% w/w water and stored for almost two months at room temperature, did not show the above two characteristic diffraction peaks, implying no polymorphic transition by addition of water.

The drug did not affect the crystal forms of the glyceride vehicles, as results were very similar for placebo and active capsules, as seen in Figure 18.

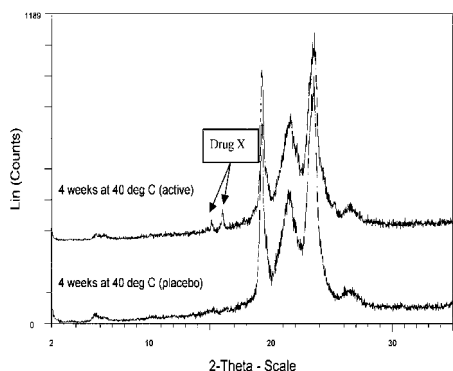


Figure 18. Effect of drug substance X.

The different XRD patterns, with unknown additional diffraction peaks indicate polymorphic changes of one or both excipients. It seems reasonable to presume that the intermediary pattern obtained at 30°C/60%RH was a mixture of forms.

Finally, XRD results showed no polymorphic changes for drug X at any storage conditions.

#### 4.1.3. SEM

##### • Surface appearance by SEM of uncured capsule and sulphur mapping

SEM images revealed a uniform, granular surface for capsules freshly prepared and uncured.

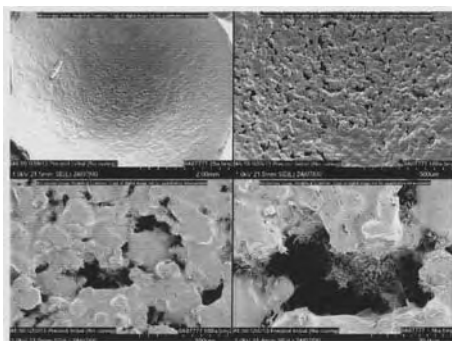


Figure 19. Surface appearance of contents of an uncured capsule.

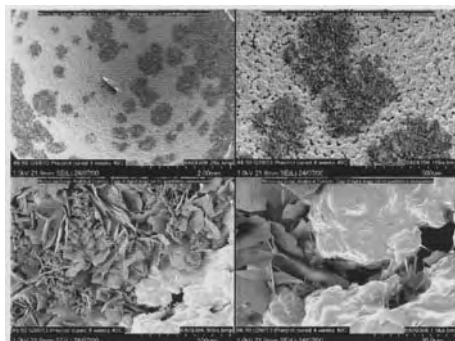


Figure 20. Surface appearance of contents of a capsule cured for 4 weeks at 40°C.

Some dark patches could be seen on the surface of a cured capsule fill, indicating a modification of the wax fill during curing.

The dark patches formation was more pronounced with longer curing times, and was not visible up to 48 hours curing. After a week of exposure at 40°C, a few patches were detectable. At the four week timepoint, dark patches were abundant, as can be seen in Figure 20. This was seen for both the placebo and active capsules.

The results show that the dark patches formation was temperature and time dependent. It was excipient and not drug related. Results from the

digital elemental distribution maps show no significant presence of crystals containing sulphur, implying no polymorph of drug X (sulphur being present in the drug substance and not in the excipients).

The dark patches were not humidity related, as the addition of 1% of water (w/w) to the wax blend did not induce the dark patches formation.

#### 4.1.4. Hot Stage Microscopy

After heating to 70°C and melting the wax components (Gelucire® 50/13 and Precirol®), the drug crystals, present in suspension in the wax blend, could be easily detected by microscopic observation. Results indicated no change from initial in drug particle size for capsules stored at 5°C, 25°C/60%RH, and 40°C/75%RH. There was therefore no drug crystallisation on storage at the above conditions.

#### 4.1.5. MRI

MRI was an effective method for studying cured and uncured capsules. Different aspects such as the dissolution medium ingress, capsule disintegration, fissuring of the penetrated zone could clearly be seen (Figure 21).

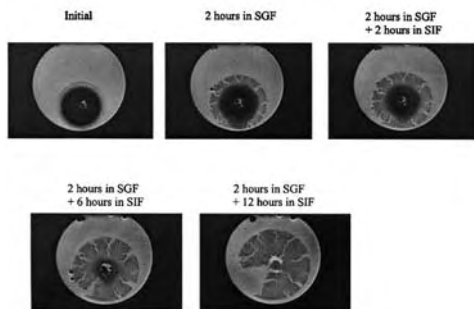


Figure 21. Magnetic resonance images at different timepoints.

The measurement of the cross sectional area of penetrated and unpenetrated material as a function of time was very similar for uncured and cured capsules (24 hours at 40°C), as seen in Figure 22. The hydration rate into the inner part of cured and uncured capsules was comparable. The erosion rate of an uncured or cured capsule was very similar. All results indicate that curing did not affect the formulation performance in the dissolution medium.

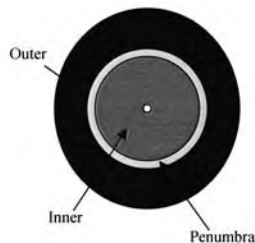


Figure 22. Comparison of cross sections areas (outer, penumbra and inner) for uncured and cured capsules.

#### 4.1.6. Dissolution

Uncured capsules stored at 25°C/60%RH (Figure 23) showed a significant increase in variability levels from initial to the 6 month timepoint. This was not seen at 30°C/60%RH (Figure 24).

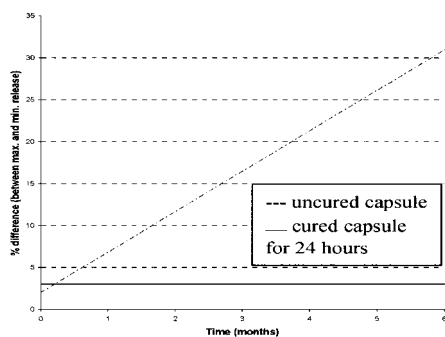


Figure 23. Storage for 6 months at 25°C/60%RH - Dissolution variability (n=6) at the 16 hour dissolution timepoint.

All capsules cured for different periods of time (7, 16, 24, 48 and 72 hours) and stored at 25°C/60%RH showed consistently low variability (below 15%). Dissolution results for the cured samples remained consistent throughout the stability timepoints (0, 3, 6 months) at both 25°C/60%RH and 30°C/60%RH conditions.

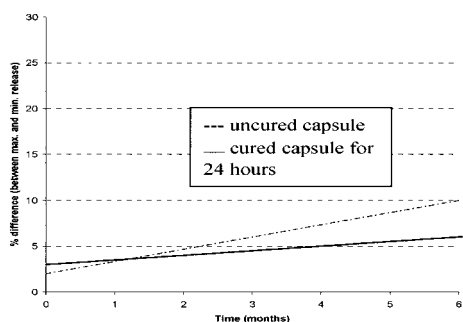


Figure 24. Storage for 6 months at 30°C/60%RH - Dissolution variability (n=6) at the 16 hour dissolution timepoint.

At 30°C/60%RH, for the uncured capsule, a slight general increase (10%) in variability after six months was observed (Figure 24). Dissolution results showed that capsules cured for 24 hours and above were physically stable.

It seems reasonable to presume that the dissolution variability observed for uncured capsules was due to Gelucire® 50/13 being not converted to its most stable polymorphic form. The inter-sample variability could also be due to a mixture of forms I and I'. Variability was higher in the 25°C/60%RH samples than for 30°C/60%RH. Capsules were probably cured slowly when stored at 30°C/60%RH.

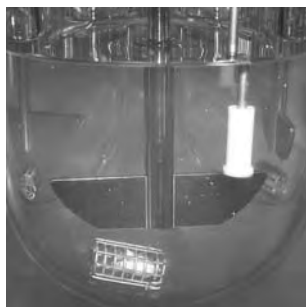
#### 4.1.7. Dissolution Medium Appearance

The dissolution media of uncured capsules or capsules cured for a shorter period of time than 24 hours all had a degree of cloudiness, as seen in Picture 1.



Picture 1. Cloudy dissolution medium

Storage of the capsules for at least 24 hours at 40°C was associated with a dissolution medium remaining clear during the entire dissolution run, as can be seen in Picture 2.



Picture 2. Clear dissolution medium.

The dissolution medium appearance was cloudy, slightly cloudy or clear for a capsule stored at 25°C/60%RH, 30°C/60%RH or 40°C/75%RH respectively. These findings indicate that a change in the dosage form occurred upon storage at a relatively high temperature (e.g. Gelucire® 50/13 being converted to its most stable form).

The dissolution medium appearance was the same for a placebo or an active capsule stored at the same condition for the same period of time. The drug substance was therefore not responsible for the cloudiness of the dissolution medium.

## 4.2. Scale-up

### 4.2.1. Wax melting

The use of the jacketed vessels to melt the waxes by heat transmission was possible at small scale (batch scale not greater than 5 kg), but it was a lengthy process of approximately 3 to 4 hours. The melting time was overnight when batches were greater than 10 kg.

A more practical solution was identified by using heating grids supplied by SEBA, also called fast melters. When the wax came into contact with the hot grid it instantly liquified and drained through the holes into the collecting vessel. It took on average 9 minutes to melt approximately 2.5 kg of Gelucire® pellets or Precirol® pastilles when the grid was set at 100 or 300°C. Temperature did not affect the melting rate of Gelucire® 50/13 and Precirol®, but at 300°C the wax had degraded to a sticky viscous material. Therefore customised grids with a large surface and set up at 100°C were identified to melt efficiently large batches of Gelucire® 50/13 or Precirol® in a short period of time.

## 4.2.2. Low Shear Mixing

Table 1. Scale-up batches prepared using low shear mixing.

Batch identification	Scale (kg)	Mixer type	Paddle type	Paddle speed (rpm)	Mixing time (mins)	Content uniformity (% RSD)
A	5	Becomix	Becomix	50	60	2
B	5	Becomix	Becomix	50	60	3
C	5	Becomix	Becomix	150	60	1
D	5	Brogli	Propeller	200	45	2
E	10	Brogli	Propeller	100	overnight	drug sedimentation
F	10	Brogli	Anchor	50/100	30	15
G	10	Brogli	Anchor	100	30	7
H	10	Brogli	Anchor	200	30	1
I	10	Brogli	Anchor	200	30	1
J*	10	Brogli	Anchor	200	30	3
K	10	Brogli	With scrapers	100	30	1
L	10	Brogli	With scrapers	50	30	2
M	20	Brogli	With scrapers	50	30	7

\* Batch E re-processed

The results show that all three factors (paddle design, stirring speed, and batch size) were important for the preparation of a visually smooth, uniform blend. Of these, the paddle design was the most critical.

The propeller type paddle (as seen in Figure 4) gave acceptable content uniformity results at 200 rpm at 5 kg scale (batch D). However, at a 10 kg scale with a stirring speed reduced to 100 rpm, the drug sedimented out, and was not re-suspended even after stirring overnight. This can be attributed to the propeller paddle poor mixing characteristics for batches larger than 5 kg. Batch E was kept liquid and re-processed with the anchor type paddle (Figure 2) at 200 rpm to give batch J. Content uniformity values of around 3% were achieved within 30 minutes of stirring, demonstrating that incorrectly processed batches can be recovered with suitable mixing.

The anchor paddle design demonstrated better mixing characteristics than the propeller. Batches H and I produced at 200 rpm showed

excellent content uniformity (with RSDs below 2%) after 30 minutes and good reproducibility. However, batches produced at 100 rpm were not as good (RSD of 7% after 30 minutes stirring), and required overnight mixing to achieve good content uniformity.

The paddle with scraper blades (seen in Figure 3) provided the best mixing characteristics. Batches K and L produced at the 10 kg level, with either 50 or 100 rpm mixing speeds both gave excellent content uniformity and smooth blend appearances. However, when scaled up to the 20 kg level (batch M), the 50 rpm stirring speed gave poorer content uniformity results (7% RSD after 30 minutes), and a gritty appearance. After continued stirring for 15 hours the blend appearance was much smoother with excellent content uniformity values (RSD below 1%).

The paddle design had a major effect on the mixing efficiency, especially when working at the maximum capacity of the Brogli mixer. The higher the paddle speed, the tighter the relative standard deviation for content uniformity.

A large paddle with scrapers that mixed throughout the entire blend and a stirring speed of 100 rpm was identified to produce a satisfactory product.

Deaeration was a critical factor to ensure effective capsule filling. The use of vacuum during stirring ensured the mixture to be filled easily into capsules.

Eight different batches, prepared in the Brogli mixer, were analysed for dissolution. The results (Figure 25) indicate that the reproducibility between batches was acceptable, although a scatter of drug release rates in the acid phase (first two hours of dissolution) was observed. The slope of the dissolution profile, from the 2 hour to the 16 hour timepoints was similar for all batches, indicating reproducible drug release mechanism at pH 7.4 (mainly erosion).

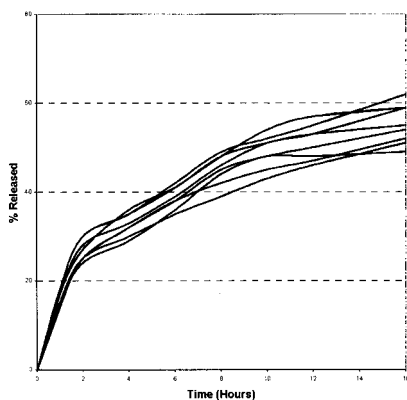


Figure 25. Dissolution profiles of blends prepared in the Brogli vessel and filled into capsules.

Table 2. Scale-up batches prepared using high shear mixing

Batch identification	Scale (kg)	Paddle speed (rpm)	Homogeniser frequency/Speed (rpm)	Mixing time (mins)	Content uniformity (RSD)
N	5	50	Continuous 2500	30	1
O	5	50	Continuous 2500	30	1
P	8	50	Continuous 2500	30	1
Q	5	50	Pulsed (1 min) 2500	30	2
R	8	50	Pulsed (1 min) 2500	30	0.5

#### 4.2.3. High Shear Mixing

The continuous and pulsed homogenisation processes gave excellent content uniformity results, as seen in Table 2. Blends looked visually very smooth for both processes.

Pulsed homogenisation appeared to be slightly less consistent than continuous homogenisation, and was also more difficult to perform. Blockages occurred when the wax blend remained static and did not recirculate through the homogenisation head.

Continuous homogenisation was a more robust process. The RSD values were consistently around 1% for homogenisation times of 30 minutes, on batch sizes of up to 8 kg (maximum capacity of the Becomix vessel). Similar and excellent content uniformity results were achieved for batch sizes of 5 and 8 kg.

As for low shear mixing, vacuum was a critical factor to deaerate the wax blend while homogenisation/stirring occurred. Without any vacuum the wax blend was foamy and could not be filled into capsules.

Dissolution results from different batches prepared in the Becomix vessel, plotted in Figure 26, indicate that reasonable reproducibility was achieved, using high shear mixing. A much better control of the drug release rate in the acid phase was observed, when compared to low shear mixing. Different lots of Gelucire® 50/13 and Precirol® were used to prepare the above batches, indicating consistent batch to batch performance.

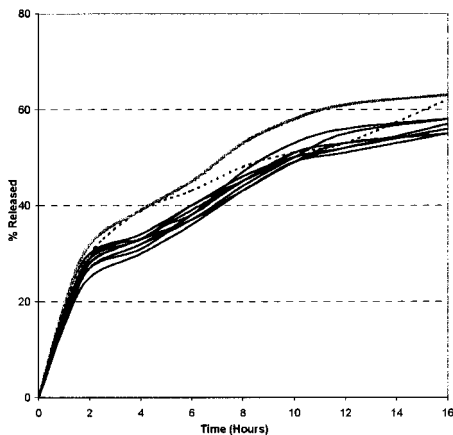


Figure 26. Dissolution profiles of blends prepared in the Becomix vessel and filled into capsules.

Precirol® was supplied as a powder for all batches, except for the batch represented by the dotted line which was prepared with Precirol® pastilles. The similarity in dissolution profiles indicate that the two forms of Precirol® (atomised and pastilles) had very similar drug control release performance.

#### 4.2.4. Comparison of dissolution profiles obtained for capsules prepared by high and low shear mixing

The Gelucire®/Precirol® formulation offered a robust drug release mechanism, as high shear or low shear manufacturing methods led to identical dissolution profiles.

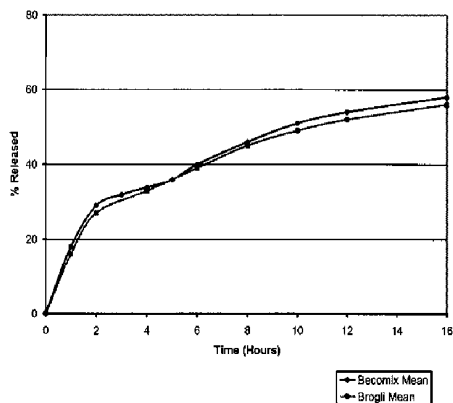


Figure 27. Mean dissolution data of scale-up batches prepared in a Becomix or a Brogli vessel.

#### 4.2.5. Capsule filling

Capsule filling trials were initially conducted using a Quali-fill oil and paste filler used in conjunction with a Quali-fill model 8S.

The Quali-fill flawlessly performed the tasks of separating and closing the capsules. The design allowed several capsules to be filled at once whilst remaining vertical, before rotating the dies position to allow the next row of capsules to be filled. This feature allowed the maximum amount of time for the capsules to set prior to being ejected.

Successful filling was achieved with the water bath temperature set to 60°C, a wax blend of 55°C-56°C and the nozzle temperature set to 55°C. Capsules produced by this process were filled evenly into the shell. Weight uniformity was excellent, with RSDs usually below 1%. However, the output was limited due to the manual operations to be performed.

The H&H KFMIII capsule filling machine used in conjunction with a liquid dosing system had a certain amount of success in producing capsules to the required standards. Insufficient testing was performed to fully assess the problems that were encountered, of which the most problematic was the machine stopping regularly. The machine managed generally to operate for 30 minutes before stoppages started occurring. The most common problem was caused by capsule shells sticking due to wax product fouling the dies. However, the actual causes were probably due to incorrectly positioned/mismatched stations and running the machine too fast.

The first successful 30 mins filling of the wax blend into capsules was achieved with temperatures for the melting pot and dosing head between 49 and 51°C. At this temperature, the blend set almost instantaneously, allowing capsules to be filled evenly before the capsule ejection. The filling temperature of the blend was critical to achieve successful capsule filling at a reasonable output. A temperature close to the crystallisation point was necessary to avoid any wax dripping and to achieve almost instantaneous blend solidification.

Capsules produced over periods of 30 minutes had very low weight variation, with RSD values of approximately 0.6%.

## 5. Conclusion and Perspectives

The physical characterisation results obtained by various techniques were complementary. They showed that the changes in dissolution behaviour after storage under ambient conditions were related to polymorphic changes of Gelucire® 50/13. The physical stability was greatly improved by curing the capsules, and consequently by converting Gelucire® 50/13 from its metastable form I to its stable form I'. At 40°C, part of the semi-solid system is liquid, and rearrangement of the molecules to reach the most stable form is expected to be easier.

An acceptable shelf-life can be expected for capsules cured for 24 hours at 40°C before storage.

DSC was found to be the most reliable and reproducible screening method to ensure that the manufactured dosage form reached its stable form. DSC had a distinct ability to detect the state of crystallinity within a given formulation, and to indicate subtle changes in the extent of curing.

From the process scale-up trials, it is recommended to use fast melters (heating grids) to greatly reduce the melting time of the waxes.

High shear mixing under vacuum is the method of choice to disperse the drug in suspension, as it was found to be a very robust process.

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GATTEFOSSÉ

# PELLETISATION WITH MELTABLE BINDERS

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## Summary

Melt pelletisation is a process by which pelletisation is obtained through the addition of either a molten binder or a solid binder which melts or softens during the process. High shear mixers are advantageous for melt pelletisation, because the high shearing forces make it easier to obtain a uniform distribution of the molten binder as well as a spheronization of the agglomerates. A conventional fluidized bed granulator is unsuitable for melt pelletisation due to the lack of shear forces, whereas a rotary fluidized bed has been found suitable. An optimum choice of the physical properties of the solid particles as well as the meltable binder is essential in order to obtain that proper balance between deformability and strength of the agglomerates that is a prerequisite of preparing pellets. Hydrophilic meltable binders are favourable for formulations where a rapid release is desirable, especially for an incorporation of solid dispersions in pellets. Lipidic binders are suitable for production of matrix pellets with prolonged release properties.

## Keywords

*Melt pelletisation, high shear mixer, fluidized bed granulator, particle size, binder content, binder viscosity, agglomeration mechanisms, solid dispersion, prolonged release.*

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## 1. Introduction

In a melt agglomeration process, a binder being solid at room temperature is added to a mixture of a drug substance and excipients either in a molten state or as a solid binder which melts or softens during the process. Melttable binders are normally having a melting point between 50 and 100°C. During the process, the product temperature is kept within or above the melting range of the binder. The molten or softened binder acts like a binder liquid causing an agglomeration by forming liquid bridges between the initial particles. At the end of the process, dry agglomerates are obtained by cooling the agglomerates to a temperature below the melting range of the binder.

Melt agglomeration is a rather simple process. It is favourable compared with conventional wet agglomeration since the drying step of the process is eliminated. Further, the liquid addition step is eliminated if the melttable binder is admixed in a solid state. The elevated temperature during the process might be a disadvantage, however, when processing heat sensitive materials.

Melttable binders might be hydrophilic like polyethylene glycols (PEGs) or lipidic like fatty acids, fatty alcohols, glycerides, and waxes. The binder concentration applied is typically 15-30% m/m of the solid materials but might be lower as well as higher.

A melt agglomeration process might result either in granules of a rather wide size distribution and an irregular shape or in pellets. Pellets are agglomerates of a narrow size distribution and a spherical shape typically having a mean size within the range from 0.3 to 2 mm. A melt pelletisation process is a melt agglomeration process being controlled in such a way that pellets are obtained as the final product.

## 2. Equipment for melt pelletisation

In order to obtain pellets instead of granules, the shear forces during the process have to be rather high. High shear forces will typically cause a uniform distribution of the binder, a narrowing of the agglomerate size distribution, and a

spheronization of the agglomerates [1]. This is why melt pelletisation has primarily been carried out in high shear mixers [2,3]. The shear forces in a high shear mixer depend on the inclination and shape of the impeller blades [2,4,5] and can be varied by varying the impeller speed.

High shear mixers for melt pelletisation are normally equipped with a heating jacket but heating of the product to the melting point of the binder might take place solely by means of heat of friction caused by the impeller rotation [1]. The high shear forces in a high shear mixer might also be a disadvantage since the formation of heat of friction makes it difficult to control the product temperature which might become too high [6]. Further, the high shear forces result in a densification of the agglomerates. This densification will increase the liquid saturation of the agglomerates, i.e. the degree of filling of the intragranular pores and voids with binder liquid. In order to make pellets, the liquid saturation has to be close to 100% [3]. A marked densification during the process will make it difficult to control the liquid saturation and thus give rise to a higher risk of overwetting.

In a high shear mixer, the melttable binder can be added by a melt-in as well as a pour-on or pump-on procedure [7,8]. By the melt-in procedure, the solid binder is added at room temperature as powder, beads or flakes which after melting by heating become uniformly distributed due to the high shear forces. By the pour-on or pump-on procedure, the molten binder is added by pouring or pumping it into the mixer bowl. Normally, the high shear forces make it unnecessary to atomize the molten binder in order to obtain a uniform distribution.

Fluidized bed granulators have also been used for melt agglomeration [9-11]. In a fluidized bed, the product temperature is much easier to control by controlling the temperature of the fluidizing air. However, the low shear forces in a fluidized bed are a disadvantage. Although excellent granules can be produced by melt agglomeration in a fluidized bed, the spheronization of the agglomerates has been found to be insufficient for melt pelletisation since the shear forces are too low [12]. If the melt-in procedure is applied, the binder particle size is

critical, because it affects the agglomerate size [9]. A suitable alternative is to add the binder in a molten state by atomization through a heated nozzle [10,11].

Recently, it has been found that the advantages of the high shear mixer and the fluidized bed granulator can be combined by using a rotary fluidized bed granulator, i.e. a fluidized bed equipped with a rotating friction plate, for melt agglomeration [12]. The friction plate gives rise to shear forces which are sufficiently high for melt pelletisation, and the product temperature can be properly controlled by the inlet air temperature. The shear forces depend on the design of the friction plate. Grooved plates were found to improve the sphericity compared with a smooth plate. The pellet size obtained in a rotary fluidized bed granulator is primarily controlled by the binder concentration and the rotation speed of the friction plate, a higher binder concentration as well as a higher speed giving rise to larger pellets (Figure 1). Further, a longer massing time was found to increase the pellet size.

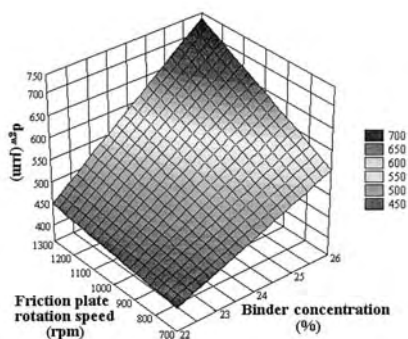


Figure 1: Effects of friction plate rotation speed and binder concentration on the agglomerate size ( $d_{gw}$ ) by melt pelletisation of lactose monohydrate with PEG 3000 in a rotary fluidized bed granulator. Massing time: 12 min. (from Ref. [12] with permission from Elsevier Science B. V.).

The shear forces are normally lower in a rotary fluidized bed than in a high shear mixer. Consequently, the sphericity of pellets produced in a high shear mixer has been found to be slightly better when compared with pellets from a rotary fluidized bed [12].

### 3. Formulation variables

In order to render a melt pelletisation of a specific formulation possible, it is necessary to make a proper choice of the formulation variables related to the solid materials as well as the meltable binder (Table 1).

Table 1: Formulation variables

Solid	Meltable binder
Particle size distribution	Type
Particle shape	Concentration
Surface area	Viscosity
Surface structure	Particle size distribution
	Particle shape

Agglomerate growth and spheronization during the process depend on the deformability and the strength of the agglomerates [3]. A sufficiently high deformability is a prerequisite of an agglomerate growth by coalescence between smaller agglomerates as well as of a spheronization. The deformability becomes primarily increased by increasing the liquid saturation of the agglomerates. The liquid saturation depends on a combination of the amount of binder liquid and the densification of the agglomerates. As mentioned above, the liquid saturation has to be about 100% for melt pelletisation to occur. Further, a lower viscosity of the molten binder will increase the deformability. Thus, PEG 2000 resulted in perfectly spherical pellets by melt pelletisation of lactose in a high shear mixer, whereas spheronization was found to be impossible with PEG 20,000 because of the markedly higher viscosity of the latter [13].

The deformability is related to a rearrangement of the solid particles within the agglomerates. Therefore, a higher intragranular porosity and lower cohesive forces between the solid particles will increase the deformability. This means that weaker granules are more deformable. On the other hand, the agglomerate strength has to be sufficiently high to avoid a breakage of the agglomerates since breakage will cause agglomerates of a wider size distribution and an irregular shape [14]. It is important, therefore, to

make a choice of formulation variables that results in a proper balance between deformability and strength.

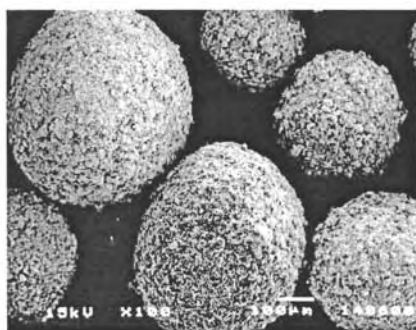
### 3.1 Properties of solid materials

A lower mean particle size of the initial particles results in stronger agglomerates [15]. This makes the pelletisation properties of the formulation very dependent on the mean particle size and the size distribution of the solid materials. Figure 2 shows that pellets could be produced in a high shear mixer from small (5  $\mu\text{m}$ ) calcium carbonate particles with PEG 1500 as the meltable binder. The results obtained with PEG 20,000 indicate that a combination of small particles and a highly viscous binder makes the agglomerates so strong that spheronization is impossible in accordance with the above-mentioned results.

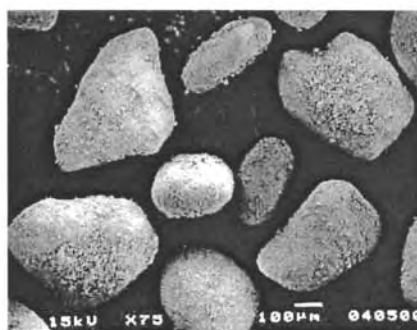
It appears from figure 3 that an 80  $\mu\text{m}$  calcium carbonate powder cannot be melt pelletised with

PEG 1500. Because of the large particle size, the agglomerates are so weak that breakage occurs. This is seen to result in porous agglomerates of irregular shape and wide size distribution. If PEG 20,000 is used as meltable binder instead, breakage is avoided due to a higher agglomerate strength caused by the higher binder viscosity. Although the larger particle size of the calcium carbonate increases the deformability, this is still too low for a smoothing of the agglomerates to occur. Due to such interactions between solid particle size and binder viscosity, it will be possible to make pellets from particles within rather wide size limits by choosing a meltable binder with a viscosity that results in the right balance between deformability and strength of the agglomerates [16].

The shape of the initial particles might also affect the pelletisation properties of the formulation. Interlocking between particles of an irregular shape will increase the agglomerate strength [17].

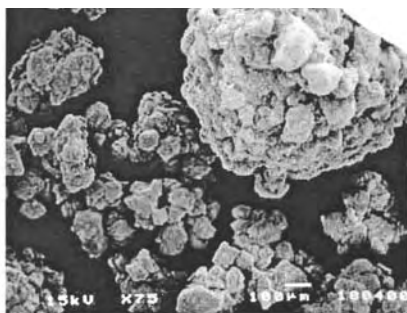


PEG 1500

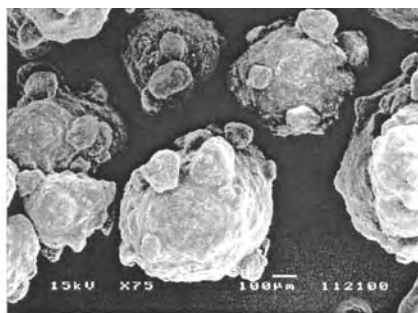


PEG 20,000

Figure 2: SEM micrographs of agglomerates produced in a high shear mixer from a calcium carbonate powder with a mean particle size of 5  $\mu\text{m}$ . Meltable binder: 15.5% m/m of either PEG 1500 or PEG 20,000 (modified from Ref. [16]).



PEG 1500



PEG 20,000

Figure 3: SEM micrographs of agglomerates produced in a high shear mixer from a calcium carbonate powder with a mean particle size of 80  $\mu\text{m}$ . Meltable binder: 9.5% m/m of either PEG 1500 or PEG 20,000 (modified from Ref. [16]).

On the other hand, rounded particles of corn starch have been found to decrease the strength [3]. Particles of a platelike or needlelike shape might be difficult to melt pelletise since such particles are prone to cause irregular agglomerates [18].

### 3.2 Properties of meltable binders

The effect of binder viscosity on the pelletisation properties of a formulation has been discussed above. Table 2 shows examples of viscosities of molten binders. The binders having viscosities > 100 mPas are all hydrophilic. It seems that lipidic binders generally have rather low viscosities. This might explain why the melt pelletisation properties of hydrophilic meltable binders in high shear mixers have been found to be better than those of lipidic binders [14]. The high viscosities of the hydrophilic binders counteract a breakage of the agglomerates and this will promote a pelletisation. When using lipidic binders, the agglomerate growth is often affected by a marked breakage.

Table 2: Examples of viscosities (mPas) of molten binders at 70 °C (from Ref. [13,14,19,20])

Stearic acid	8
Stearyl alcohol	10
Glycerol palmitostearate (Precirol Ato 5®)	26
Glycerol monostearate	36
Gelucire® 50/13	49
PEG 2000	101
PEG 3000	222
Stearate 6000 WL 1644	414
PEG 6000	938
Poloxamer 188	1450
PEG 10,000	4660
PEG 20,000	26500

Figure 4 shows how the size distribution of agglomerates produced with stearic acid as the meltable binder is affected by the impeller rotation speed in a high shear mixer. The agglomerate strength is rather low because of the low viscosity of the stearic acid (Table 2). At 600 rpm, a slight increase in the content of

agglomerates in the smaller size fractions is seen indicating a breakage. Breakage becomes more evident at higher impeller speeds indicated by a change from a monomodal to a bimodal size distribution [7]. In order to avoid breakage with low viscosity binders, it might be necessary to decrease the impeller speed. This might result in agglomerates that are less spherical than those produced with hydrophilic binders at high impeller speed.

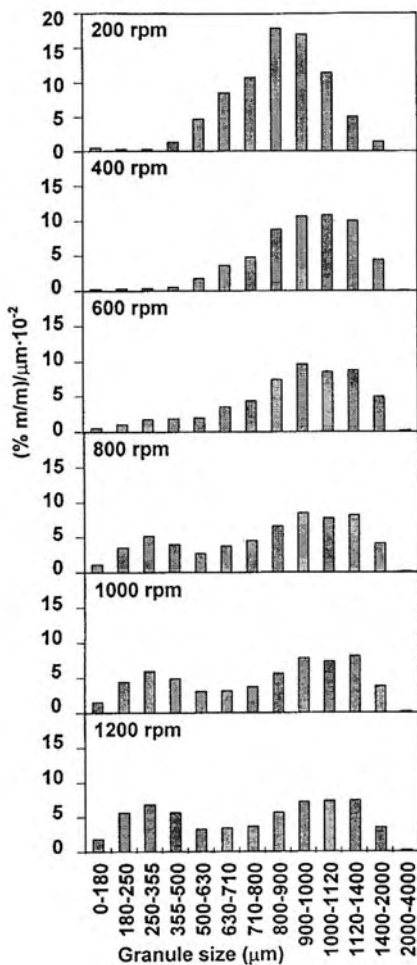


Figure 4: Effect of impeller speed in a high shear mixer on the agglomerate size distribution by melt agglomeration of lactose monohydrate. Meltable binder: 23% m/m of stearic acid (from Ref. [14] with permission from Elsevier Science B. V.).

Further, lipidic binders have been found to give rise to more adhesion of material to the bowl than hydrophilic binders [21]. Adhesion will reduce

the yield of product and will counteract pelletisation, because a simultaneous adhesion and detachment of material will counteract a narrowing of the size distribution as well as a spheronization of the agglomerates. A lining of the bowl with polytetrafluoroethylene (PTFE) has been found to be efficient in preventing adhesion in comparison to metal surfaces [5]. An addition of surfactants might also reduce the adhesion. Sucrose stearates were found to lower the adhesion markedly when added to a formulation with hydrogenated cottonseed oil as the meltable binder [22].

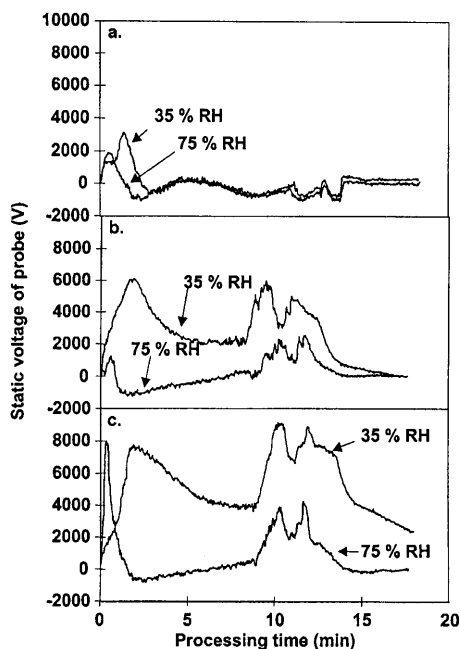


Figure 5: Effects of type of binder and relative air humidity (RH) on the static voltage achieved during processing in melt agglomeration experiments with lactose monohydrate in a high shear mixer. Meltable binder: 23% m/m of (a) PEG 3000, (b) stearic acid/glycerol monostearate (20:3), (c) stearic acid (from Ref. [21] with permission from Elsevier Science B. V.).

Figure 5 indicates that adhesion problems are related to electrostatic charging. PEG 3000 (Figure 5a) resulted in a low level of static voltage. The PEGs are generally causing a low amount of adhesion. The highest level of static voltage is observed with stearic acid (Figure 5c) which was found to cause the highest amount of

adhesion in the experiments. An addition of glycerol monostearate to the stearic acid is seen to reduce the electrostatic charging (Figure 5b). It is further illustrated that a high air humidity in the room can reduce the electrostatic charging.

### 3.3 Amount of binder

As mentioned above, the amount of binder has to be chosen in order to cause a liquid saturation of the agglomerates that is close to 100%. This means that only slight variations in the concentration of meltable binder, typically  $\pm 0.5$ -1% m/m of the amount of solid material, are possible for a specific formulation being pelletised in a specific equipment. Pellets might be produced with a very low binder content if the solid material is soluble in the meltable binder [23,24].

For certain formulations, it might be favourable to be able to incorporate a high amount of binder. When solid dispersions are incorporated in agglomerates by melt agglomeration, a high binder content might be necessary in order to obtain an adequate drug content [25]. For the production of prolonged release products by melt agglomeration, a high binder content might be advantageous in order to obtain a complete embedding of the drug in the meltable binder [26].

#### 3.3.1 Effect of shear forces

Since the liquid saturation depends on the densification of the agglomerates during the process, it will be possible to incorporate a higher amount of binder by using process conditions giving rise to less densification, i.e. to more porous agglomerates. It is to be expected, therefore, that it will be possible to incorporate a larger amount of binder by using an equipment giving rise to lower shear forces. Accordingly, the maximum binder concentration that could be used in a melt agglomeration process with a 350 mesh lactose and PEG 3000 as the meltable binder was found to be 22% m/m in a high shear mixer, 28% m/m in a rotary fluidized bed granulator, and 30% m/m in a conventional fluidized bed granulator [12]. If a higher binder content is obtained by reducing the shear forces, less spherical agglomerates are to be expected, however.

### 3.3.2 Effect of agglomeration mechanisms

The amount of binder that can be incorporated depends on the mechanism of agglomerate formation and growth. Figure 6 shows that agglomerates can be formed by two different mechanisms. By the distribution mechanism, the surface of the initial solid particles is wetted by the binder liquid, and nuclei are formed by a coalescence between the wetted particles. By the immersion mechanism, nuclei are formed by immersion of the solid particles being captured in the surface of a droplet of binder liquid. Which of these mechanisms will be the dominant one will depend on the ratio between the size of the solid particles and the droplets [11,27]. Distribution will be the dominant mechanism if the droplets are smaller than the solid particles or of a similar size, whereas immersion will dominate if the droplets are larger than the solid particles. In a melt-in process, the binder droplet size will depend on the particle size of the solid binder.

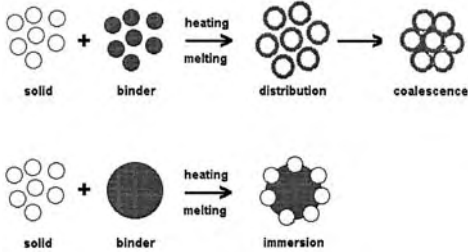


Figure 6: Agglomeration mechanisms in melt agglomeration. (a) Distribution mechanism. (b) Immersion mechanism (from Ref. [27] with permission from Elsevier Science B. V.).

If high shear forces are involved in the process, the initial droplets will normally become reduced in size due to comminution. Consequently, the distribution mechanism will be the typical mechanism of agglomerate formation in a high shear mixer. No comminution of droplets will occur in a conventional fluidized bed. In this equipment, therefore, the mechanism will depend solely on the ratio between the solid particle size and the initial droplet size (Figure 7). In the agglomerates formed by distribution, the initial lactose particles are clearly seen. The agglomerates

formed by immersion are seen to be denser, because small lactose particles are immersed in a larger binder droplet.

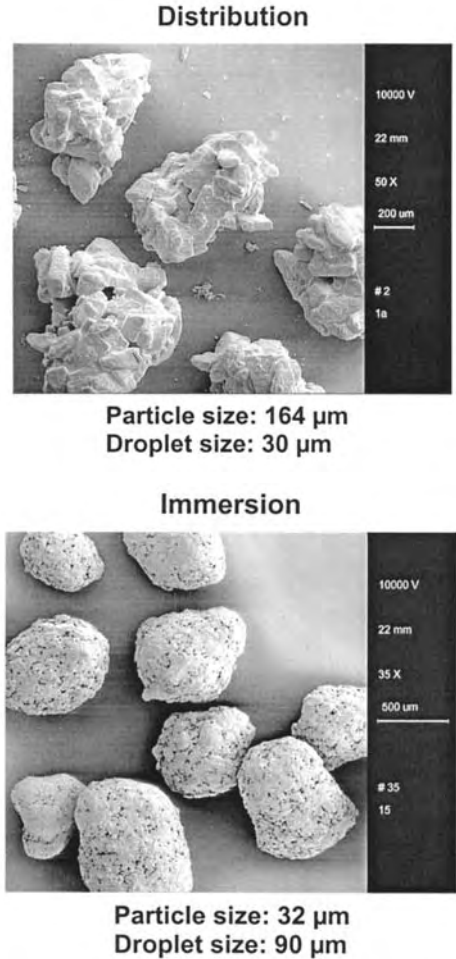


Figure 7: Effects of particle size of lactose monohydrate and binder droplet size on the agglomeration mechanisms in a fluidized bed granulator. Meltable binder: 11.5% m/m of PEG 3000 (from Ref. [11] with permission from Elsevier Science B. V.).

Immersion might also occur in a high shear mixer if the binder viscosity is so high or the impeller speed is so low that a comminution of droplets occur only to a limited degree. Figure 8 shows the effect of binder particle size on the agglomerate growth by melt-in experiments in a high shear mixer at the lowest impeller speed (400 rpm) that ensured an appropriate movement of the mass. The low impeller speed made it possible to incorporate 28% m/m of meltable binder, whereas only 23% m/m could be incorporated if the

impeller speed was increased to 1200 rpm. It is seen that the PEG powder gives rise to a markedly higher agglomerate growth than the PEG beads. A PEG fine powder having a mean particle size of 55  $\mu\text{m}$  was found to give rise to a total overwetting shortly after melting of the PEG. This indicates that the distribution mechanism dominates with the fine powder and the immersion mechanism with the beads. For the powder, distribution and immersion are supposed to occur simultaneously.

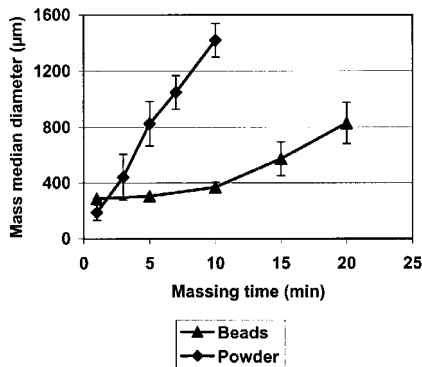


Figure 8: Effect of binder particle size on the agglomerate size by melt agglomeration of lactose monohydrate in a high shear mixer at low impeller speed (400 rpm). Meltable binder: 28% m/m of PEG 6000 (modified from Ref. [25]).

Immersion will cause a slower agglomerate growth rate, because the surface of the agglomerates is covered with solid particles. During massing, the solid particles will penetrate into the binder droplet, and molten binder will slowly become squeezed to the surface due to densification. This makes it possible to immerse further solid particles into the surface until all the initial particles have been captured. The surface wetness, therefore, will be insufficient for an appreciable coalescence between agglomerates. These results indicate that it will be possible to incorporate a higher amount of binder by increasing the binder particle/droplet size. Immersion, however, is expected to give rise to an inhomogenous binder distribution since the agglomerates will contain a central core having a higher binder content.

### 3.3.3 Effect of product temperature

A highly viscous binder liquid will counteract a densification of the agglomerates and promote

agglomerate formation and growth by immersion making it possible to incorporate more binder. For a meltable binder having a low viscosity in a molten state, it will be possible to increase its viscosity markedly by keeping it in a semisolid state. This can be done by keeping the product temperature within or slightly below the melting range of the binder. In order to keep the meltable binder in a semisolid state, it has been shown to be advantageous to use a binder with a wide melting range [28]. Using a semisolid or highly viscous binder, however, might make it more difficult to obtain a spheronization of the agglomerates.

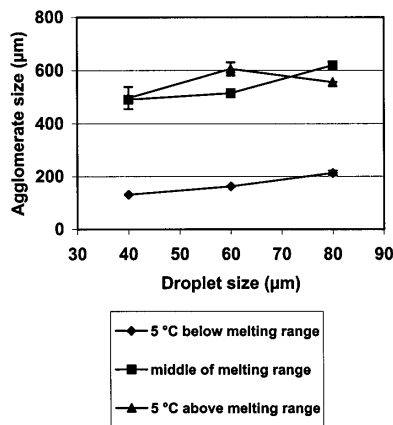


Figure 9: Effects of binder droplet size and approximate product temperature on the agglomerate size by melt agglomeration of lactose monohydrate in a fluidized bed granulator. Meltable binder: 27.5% v/m of PEG 3000 (modified from Ref. [10]).

Figure 9 illustrates that agglomerate growth can be counteracted by decreasing the product temperature in a fluidized bed granulator. Molten PEG was added through a heated nozzle. A rapid solidification of the PEG is supposed to take place when the product temperature is kept below the melting range of the PEG. Immersion of solid particles in the droplet surface will be possible until the solidification has been completed. The size of these nuclei will depend on the droplet size. Because the binder is highly viscous or has become solidified, the surface deformability of the agglomerates will be so low that practically no agglomerate growth by coalescence will occur. Nuclei might grow in size by collisions with further binder droplets being added but if these droplets solidify rapidly,

this will be more a coating than an agglomeration. Thus, Figure 9 indicates that an incorporation of a very high binder content might be possible by keeping the product temperature sufficiently low.

In a high shear mixer, it was found to be possible to vary the content of a meltable wax within the range of 18.75-50% m/m by controlling the product temperature in such a way that a complete melting of the wax was avoided [29]. Accordingly, pellets with a binder content up to 45% m/m were obtained in high shear mixers by an addition of a molten binder followed by a continued massing at a temperature below the melting point [26,30]. Pellets having binder contents from 18 to 80% m/m were prepared in a high shear mixer by using a mixture of two meltable binders and keeping the product temperature so low that the binder with the highest melting point was incorporated in the unmelted state [6]. As previously mentioned, it might be difficult, however, to control the product temperature in a high shear mixer.

#### 4. Pharmaceutical applications

Melt pelletisation can be applied for agglomeration of moisture sensitive drugs as an alternative to the use of toxic solvents. If the pellets have to be rapidly disintegrating, a hydrophilic meltable binder has to be used. Melt pelletisation might be favourable for incorporation of solid dispersions into agglomerates and for the preparation of prolonged release products.

##### 4.1 Solid dispersions

The preparation of solid dispersions can be combined with a melt agglomeration process where the carrier acts as a meltable binder resulting in an enhanced drug dissolution rate [31,32]. In a high shear mixer, it was found to be possible to produce pellets containing solid dispersions of diazepam by using PEG 3000 as well as Gelucire® 50/13 [8]. Pellets were prepared by a melt-in as well as a pump-on procedure. When the pump-on procedure was applied, the diazepam was dissolved or dispersed in the molten binder.

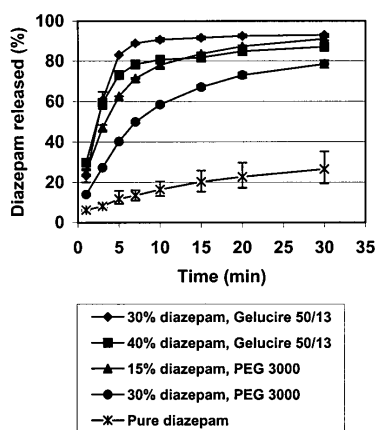


Figure 10: Effects of meltable binder and drug concentration (% m/m of the amount of binder) on the dissolution of diazepam from pellets prepared by melt pelletisation using a pump-on procedure in a high shear mixer. Meltable binder: 22% m/m of PEG 3000 or Gelucire® 50/13 (modified from Ref. [8]).

It appears from Figure 10 that the dissolution rate from the pellets containing PEG 3000 as well as Gelucire® 50/13 is markedly higher than the dissolution rate of pure diazepam. This is because the diazepam is dissolved or finely dispersed in the meltable binder. Gelucire® 50/13 is seen to cause a higher dissolution rate than PEG 3000 probably due to surface active and self-emulsifying properties [33,34]. The concentration of diazepam was varied at two levels for each binder. These levels were chosen on the basis of phase diagrams in such a way that the lower concentration is likely to result in a solid solution and the higher in a solid dispersion. For Gelucire® 50/13 as well as PEG 3000, the lower diazepam concentration is seen to cause the highest dissolution rate probably because a larger part of the diazepam is dissolved in the binder at a lower concentration. Further, the product temperature during the process and the procedure for cooling of the pellets were found to affect the dissolution rate in a complex way [8].

Admixing of the meltable binders by the melt-in procedure resulted in dissolution profiles that were similar to those seen in Figure 10. This indicates that the shear forces in a high shear mixer are so efficient that it is unnecessary to dissolve/disperse the drug in the molten binder before the binder addition.

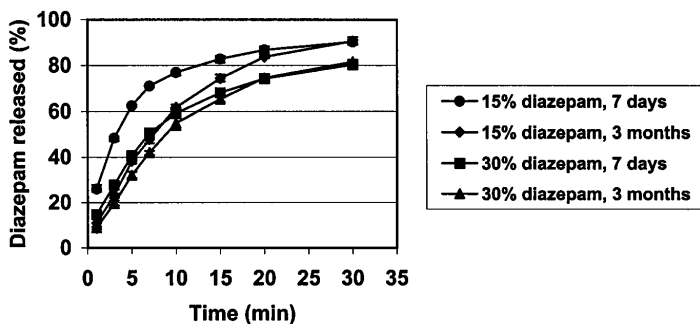


Figure 11: Effect of storage on the dissolution rate of diazepam from pellets prepared by melt pelletisation using a pump-on procedure in a high shear mixer. Meltable binder: 22% m/m of PEG 3000 (modified from Ref. [35]).

A general problem related to solid dispersions is that the dissolution rate might change during storage [36]. Figure 11 shows that storage for three months at room temperature of the pellets from Figure 10 resulted in a decrease in dissolution rate when PEG 3000 was applied as the meltable binder. Storage for three months did not result in significant changes in dissolution rate when Gelucire® 50/13 was applied.

#### 4.2 Prolonged release formulations

Pellets having prolonged release properties have been produced in high shear mixers by using different lipidic meltable binders [2,5,6,19,26,30,37-39]. The meltable binder forms a matrix from which the drug becomes slowly released. The dissolution profile obtained depends on the choice of meltable binder and on the binder concentration. Prolonged release pellets have been prepared with drug loadings up to 70-75% m/m of highly hydro-soluble as well as less water soluble drugs [6,37].

Figure 12 shows examples of dissolution profiles obtained from pellets containing paracetamol as

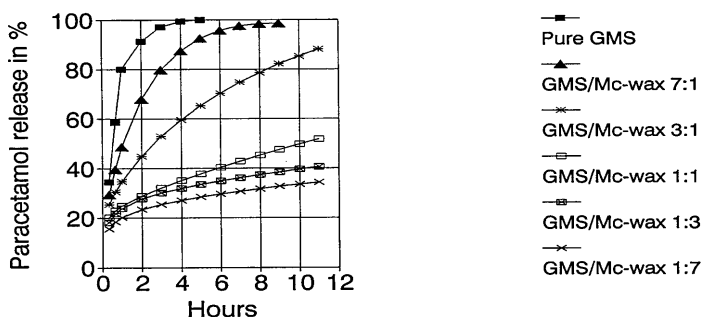


Figure 12: Effect of binder composition on the dissolution rate of paracetamol from pellets prepared by melt pelletisation in a high shear mixer. Meltable binders: glycerol monostearate (GMS) and microcrystalline wax. Binder content: 23% v/m (modified from Ref. [19]).

the drug and a mixture of glycerol monostearate and microcrystalline wax as meltable binder. It appears that it is easy to change the dissolution profile by changing the mixing ratio between glycerol monostearate and wax. The wax is more hydrophobic than the glycerol monostearate and a higher wax content, therefore, results in a lower dissolution rate. Using pure wax as the meltable binder was impossible because of a marked adhesion to the bowl.

#### 5. Conclusions

Pelletisation with meltable binders is possible in high shear mixers as well as rotary fluidized bed granulators. More melt pelletisation studies in rotary fluidized beds are necessary, however, to clarify the general applicability of this equipment for melt pelletisation. In conventional fluidized bed granulators, the shearing forces are so low that a spheronization of the agglomerates is difficult.

In order to optimize a formulation for melt pelletisation, it is important to choose a meltable

binder with appropriate physical properties. The viscosity of the molten binder is especially important since it affects the deformability, the strength as well as the densification of the agglomerates. Further, the particle size/droplet size of the binder might be essential since it can effect the mechanisms of agglomerate formation and growth and the intragranular binder distribution.

Melt pelletisation is a suitable and simple process for incorporation of solid dispersions in pellets and for preparation of pellets with prolonged release properties. In both cases, a high binder content in the pellets might be advantageous. The binder content can be increased by using lower shear forces during the process and/or by using a highly viscous binder. It might be difficult, however, to obtain sufficiently spherical pellets with a high binder content since lower shear forces as well as high binder viscosity counteract a spheronization of the agglomerates.

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# BIBLIOGRAPHY ON GATTEFOSSÉ'S PRODUCTS 2003-2004 REVIEW

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Gattefossé has reviewed a selection of published references found in the literature that talk about Gattefossé's excipients. This review includes information found from June 2003 to June 2004.

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Nowadays, the main objectives of pharmaceutical science are enhancing the bioavailability and maintaining the efficient plasma concentration of active ingredients over time by the oral route. In both cases, lipid excipients as well as lipid drug delivery systems offer some solutions to those biopharmaceutical problems. These two applications – bioavailability enhancement and controlled release – provide most of the literature on Gattefossé's products this year. Nevertheless some innovative papers were published on topical or nasal route as well as process-oriented applications.

## 1. Oral route

### 1.1 Bioavailability enhancement

Solubilizing excipients such as non-ionic surfactants and self-emulsifying drug delivery systems (SEDDS) are classically used in order to improve the oral bioavailability of class II active ingredients (low solubility - high permeability) (Gursoy and Benita, 2004).

Labrasol® (PEG-8 caprylic/capric glycerides) and Gelucire® 44/14 (PEG-32 lauric glycerides) are all-in-one self-emulsifying surfactants allowing enhanced bioavailability. The formulation of piroxicam - a class II drug - with both these surfactants permits a 2-fold increase of its oral bioavailability on healthy human volunteers due to their solubilizing properties (Yüksel, 2003; Yüksel, Karatas et al., 2003). The use of Gelucire® 44/14 with a large amount of a liquid drug – 50% (w/w) of  $\alpha$ -tocopherol – also provokes a 2-fold increase of its bioavailability on healthy humans compared to a commercial product (Barker, Yap et al., 2003).

The use of Labrasol® and Gelucire® 44/14 with a co-surfactant – Capryol® (propylene glycol monocaprylate) – leads to a 3-fold increase of the area under the curve (AUC) of another poorly-water soluble active ingredient – simvastatin - in beagle dogs (Roulot-Marchaud and Jannin, 2003). Other SEDDS formulations of simvastatin with Capryol® 90, a powerful solvent of that active substance, confirm the

increase of its bioavailability in beagle dogs (Kang, Lee et al., 2004).

In addition to solubilizing properties, non-ionic surfactants can promote drug absorption *via* physiological effects. These effects, sometimes called indirect effects, can be the fluidization of the cell membrane, the opening of tight junction, the inhibition of the gastric emptying, the p-glycoprotein or the pancreatic lipase activity, or a combination of these effects.

As a matter of fact, Labrasol® increases the bioavailability of two class III drugs (high solubility – low permeability) in dogs: gentamicin (Rama Prasad, Eaimtrakarn et al., 2003) and compound UK81252 (Chang and Shojaei, 2004). The absorption of these active substances is limited to the transcellular and paracellular pathway respectively. Labrasol® appears to cause a disruption/fluidization of the cell membrane and/or the tight junction opening, hence allowing the absorption of these drugs. Hopefully, another study on the reversibility of absorption enhancing effect of Labrasol® for low molecular weight heparin in rats, proves that the membrane quickly recover its barrier function (in less than half an hour) (Rama Prasad, Minamimoto et al., 2004).

However, many physiological effects can induce drug absorption at the same time. For compound UK81252, a 7-fold greater AUC is observed due to the tight junction opening as well as the inhibition of the gastric emptying by Labrasol®. The bioavailability enhancement of gentamicin is due to the combined effect of increased paracellular transport and p-glycoprotein inhibition by Labrasol®. The inhibition of p-glycoprotein – a membrane carrier – by Labrasol® has been confirmed *in vitro* by the analysis of digoxin transport by everted gut sacs. Indeed, Labrasol® enhances the digoxin uptake into the sac contents by 5.1-fold (Cornaire, Woodley et al., 2004).

The effect of lipid excipients on lipase activity should also be considered. For example, Gelucire® 44/14 and Peceol® (glyceryl monooleate) inhibit the pancreatic lipase activity *in vitro* (Subramanian and Wasan, 2003).

Finally understanding how lipid excipients perform *in vivo* is of major importance in order to ascertain their ultimate success (Strickley, 2004).

The transformation of semi-solid formulations of Gelucire® 44/14 into solid forms has also been evaluated by two techniques this year: cryogenic grinding and melt granulation.

The powder formed by cryogenic grinding keeps the physical, solubilizing and self-emulsifying properties of the native excipient (Chambin, Jannin et al., 2004a; Chambin, Jannin et al., 2004b). However, it must be stored below 0°C to avoid re-agglomeration of the product.

Pellets of piroxicam obtained by melt pelletization also keep the solubilizing and self-emulsifying properties of Gelucire® 44/14 as they increase the dissolution rate and apparent solubility of the active ingredient (Blachez, Roulot-Marchaud et al., 2003)

### 1.2 Controlled release

Controlled release of active substances with lipid excipients can be achieved by various techniques: molding, melt granulation, hot-melt coating or spray chilling for example.

Molding is the easiest method to produce controlled release systems with lipids. The formulation can be liquid or solid and can be moulded in various recipients: capsules, tablets or even ethylcellulose cylinders.

Liquid mixes of Labrafil® M 1944 CS (PEG-6 oleyl glycerides) and Precirol ATO 5® (glyceryl palmitostearate) into hard gelatin capsules permit the controlled release of a new chemical entity with short half-life (Dordunoo, 2003). It is noteworthy that the suitable concentration of Precirol ATO 5® – the matrix forming agent – is of 5% which is very low for a 12-hour sustained release profile.

Gelucire® 50/13 (PEG-32 stearyl glycerides) matrices of either paracetamol or caffeine obtained by tablet molding allow a sustained release of both drugs for more than 8 hours (Khan and Craig, 2003a; Khan and Craig, 2003b). However, the nature of the drug

influences the structure of the matrix and its release properties. As a matter of fact paracetamol induces more profound structure changes than caffeine after incorporation into Gelucire® 50/13 (as seen by differential scanning calorimetry and hot-stage microscopy). The dissolution rate of paracetamol matrices is lower than the corresponding caffeine systems due to a lower tendency to erosion-controlled release. Altering the thermal properties (i.e. solid fat content at 37°C) of Gelucire® 50/13 can lead to modified swelling behaviour of the matrix during dissolution.

An innovative molding system has been proposed for Gelucire® 44/14 and hydroxypropylmethylcellulose mix, a formulation with sustained release properties. That mix is moulded in ethylcellulose pipe to prevent the core from hydrodynamic and mechanical stresses *in vitro*. That system allows a controlled release of various model drugs over 24 hours with a zero-order drug release (Mehuys, Vervaeet et al., 2004b). In addition the length of the pipe can modify the drug release of the active ingredient. The evaluation of that system in dogs demonstrates its efficiency as the release of propranolol hydrochloride is sustained for 24 hours with a 4-fold increase of its oral bioavailability versus a commercial formulation (Mehuys, Vervaeet et al., 2004a). That increase is due to the absorption enhancing properties of Gelucire® 44/14 and especially the promotion of the lymphatic uptake.

Many lipid excipients can be used as meltable binders for the preparation of sustained release formulation by melt granulation. Among others, Gelucire® 50/13, Precirol ATO 5® and Compritol® 888 ATO (glyceryl behenate) allow the formation of granules by high-shear melt granulation process (Ochoa, 2003). After compaction these granules exhibit a sustained release of theophylline over more than 20 hours. Gelucire® 50/13 is the most promising binder and tablets formulated with it present an *in vitro* release profile similar to the commercial product.

Precirol ATO 5® or Gelucire® 50/02 (PEG-6 stearyl glycerides) are also used as coating

agents by hot-melt coating in order to control the release of propranolol hydrochloride pellets (Sinchaipanid, Junyaprasert et al., 2004). The increase of the concentration of Precirol ATO 5<sup>®</sup> or the coating thickness induces a slower drug release. On the contrary the addition of Gelucire<sup>®</sup> 50/02 - a more hydrophilic coating agent - increases the drug release at any coat thickness.

Some hydrophilic polymers such as Poloxamer 407 can be added to Precirol ATO 5<sup>®</sup> in order to control the release of active substances. Such matrix-type formulations possess higher dissolution rate compared to lipid matrix systems. A formulation of felodipine with that mix of excipients processed by spray-chilling presents a zero-order drug release over 7 hours (Savolainen, Herder et al., 2003).

## 2. Topical route

Microemulsion systems can be used as drug delivery vehicles through the topical route. The mixture of Labrasol<sup>®</sup> as a surfactant, Plurol<sup>®</sup> oleique (polyglyceryl-6 dioleate) as a co-surfactant, isopropyl myristate as an oily phase and water allows the formulation of low-irritant microemulsion vehicles (with an increased oil to surfactant/co-surfactant ratio). The investigation of the microstructure changes with the addition of water by conductivity and rheological measurements shows a structural inversion from oil-continuous to water-continuous over bi-continuous structure (Djordjevic, Primorac et al., 2004).

The permeation enhancer properties of Transcutol<sup>®</sup> (diethylene glycol monoethyl ether) has also been confirmed both *in vitro* with hydrogel patches containing triclosan and *in vivo* in humans with 4-hydroxy-benzonitrile as a model drug.

A concentration lower than 5% (w/w) of Transcutol<sup>®</sup> in hydrogel patches of triclosan allows an enhanced skin accumulation of the drug without a concomitant increase of its transdermal permeation (Lee, Kim et al., 2003).

In addition the synergistic effect of Transcutol<sup>®</sup> and sucrose laurate (Sucroester<sup>®</sup>) on the *stratum*

*corneum* modification thus permitting the penetration of 4-hydroxy-benzonitrile has been demonstrated (Ayala-Bravo, Quintanar-Guerrero et al., 2003).

## 3. New applications for lipids

### 3.1 Nasal route

A microemulsion system containing Labrafil<sup>®</sup> M 1944 CS as an oily phase administrated by nasal route increases the bioavailability of nimodipine in rats (Zhang, Jiang et al., 2004). That formulation permits to solubilize a large amount of active substance, shows no nasal ciliotoxicity and transports a fraction of the drug directly into the brain. In addition, the microemulsion is sprayable and physically stable for 3 months.

### 3.2 Sub-cutaneous implants

Glycerides possess potential for use as subcutaneous implants due to their good biocompatibility on subcutaneous injection and their well-known controlled release properties. Matrix implants of lysozyme - a model protein - with Precirol ATO 5<sup>®</sup> can be prepared either by compression or by melting (Pongjanyakul, Medlicott et al., 2004). Both techniques permit a sustained release of the protein with retention of the lysozyme activity. Implants produced by compression are more porous than those obtained by melting which allow the entry of the water needed for the release of the protein. However more hydrophilic components can be introduced in the matrices produced by the melt process in order to increase the percentage of drug release.

### 3.3 Intraarticular administration

Biodegradable microspheres formulated with poly(D,L-lactide-co-glycolide) and Labrafil<sup>®</sup> M 1944 CS permits to obtain a sustained-release of ibuprofen in the intraarticular cavity (Fernandez-Carballido, Herrero-Vanrell et al., 2004). The addition of Labrafil<sup>®</sup> M 1944 CS as a biodegradable oil into the microspheres leads to a lower initial ibuprofen burst and prolongs the release rate from 24 hours to 8 days.

### 3.4 New lubricant technology

Compritol® 888 ATO is classically used as a solid-phase lubricant in oral solid dosage formulations. Compritol® 888 ATO can also be sprayed onto a powder by hot-melt coating (Gattecoat® process). Use likewise, the excipient exhibits a better repartition at the surface of the powder and confirms its good lubricant capacity (Jannin, Bérard et al., 2003; Andrès, Jannin et al., 2004).

### 3.5 Orally disintegrating tablets

Orally disintegrating tablets can be produced by melt granulation with Superpolystate® (PEG-6 stearate) an hydrophilic binder (Abdelbary, Prinderre et al., 2004). Superpolystate® provides two kinds of advantage as a binder: tablets possess good physical properties as hardness and low friability and melt and solubilize rapidly in the mouth without residues.

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