

# Bulletin Technique

Fondation Gattefossé

# 2012

Melt techniques  
in solid dosage  
forms & GI modeling  
*in the spotlight*



## AAPS - LIPID BASED DRUG DELIVERY AWARDS SPONSORED BY GATTEFOSSÉ

### Congratulations to the 2012 winners:

- Graduate Student Award:  
**Yan Yan Yeap**, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Australia.  
In acknowledgement for her work on the absorption pathways of lipids and poorly water soluble drugs after oral administration and more specifically, lipid based colloidal assemblies.
- Graduate Student Travelship Award:  
**Josimar Oliveira Eloy**, University of Sao Paulo, Brazil.  
For the poster presented at AAPS on solid dispersions containing ursolic acid in Gelucire 50/13: a strategy to enhance *in vitro* dissolution and trypanocidal activity.

We also thank all the researchers who submitted their papers for the awards.

These awards are presented at the American Association of Pharmaceutical Scientists annual congress.

For further information please refer to the AAPS website:  
[http://www.aaps.org/About\\_AAPS/Annual\\_Meeting\\_\\_\\_Exposition\\_Awards/](http://www.aaps.org/About_AAPS/Annual_Meeting___Exposition_Awards/)

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## PREFACE

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The Gattefossé Foundation was established in 2008 to provide a conduit for the company's staff and family share holders to express their corporate, intellectual and philanthropic values and those of the company's founders.

The Foundation's actions are focused on three key missions; support of research and development; dissemination of scientific knowledge and involvement in community and social initiatives. To find out more please visit our website: <http://www.gattefosse.com/en/gattefosse-foundation>

The annual Journées Galéniques, held in St. Rémy de Provence, France began in the 60's. The ethos of the meeting was (and still is) the open sharing of data, eclectic discussion and acute listening on the part of the participants; these being drug development researchers (both academic and corporate) from around the world. The ultimate aim of the meeting, that remains the same today, is to catalyze advancements in medicines and healthcare.

This year's meeting - the 46<sup>th</sup> - was dedicated to progress being made in the processing technologies used to make dosage forms and also advances in our understanding of how gastrointestinal physiology affects the performance of oral medicines. These two areas will certainly drive improvements in the quality, efficacy and safety of finished medicines and ultimately benefit the end users – the patients.

As President of the Gattefossé Foundation, I am delighted to share with you the content of this meeting, and I extend my sincere gratitude to the Chairman – Prof Kleinebudde – and to all the authors for their contribution.

Lastly, whether you are a corporate, academic, or student researcher, I hope you find these articles of use, interest and possibly inspiration for your research projects.

*Sophie Gattefossé - Moyrand  
President of the Gattefossé Foundation*

## FOREWORD

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### MELT TECHNIQUES IN SOLID DOSAGE FORMS & GI MODELING IN THE SPOTLIGHT

Melt techniques and GI modeling were the central topics of the 46<sup>th</sup> edition of the Journées Galéniques de Saint-Rémy de Provence sponsored by the Gattefossé Foundation. Widely known experts presented cutting edge knowledge to a small audience during three days. The intimate atmosphere of the meeting and the liberal timetable allowed intensive discussions. Perfect hosting, an ideal format of the meeting and high-level scientific exchange made the Journées Galéniques an unforgettable event for all participants. Basic contents of the presentations are provided in this issue of the Bulletin Technique Foundation Gattefossé.



Prof. Dr. Peter Kleinebudde

Melt techniques can be used for quite different purposes in the design of new solid dosage forms. By choosing appropriate formulations and processes it is possible to enhance dissolution rate, solubility and bioavailability of APIs or to modify drug release, especially achieving a prolonged release profile. Both aspects are important and they are addressed. Among the available techniques melt extrusion seems to be of highest importance. It is important to assess in an early stage, whether melt extrusion is appropriate to handle a problematic API. A comprehensive strategy for the evaluation was presented. In some cases the use of supercritical fluids in melt extrusion can be beneficial to broaden the applicability of this technique for drug delivery. As a temporary plasticiser supercritical CO<sub>2</sub> allows lower extrusion temperatures helping the processing of thermo labile compounds by widening the process window. Melt extrusion as a continuous manufacturing process has many advantages to be used in the frame of Quality by Design. A fictive example is used to demonstrate a development strategy.

Other upcoming techniques beside melt extrusion like the Kinetisol™ technique were also presented. Kinetisol™ allows the formation of solid dispersions by imparting high shear and friction forces without the need of plasticisers. This technique is particularly useful for high melting point APIs as shown in some case studies.

Other new techniques like co-extrusion and injection moulding are not yet fully exploited for the production of solid dosage forms. Recent examples were shown to demonstrate the state-of-the-art. Melt-spray-congeal microspheres can be used for different purposes like taste masking, sustained release and improved stability.

For all peroral solid dosage forms the assessment of gastrointestinal transit is of major importance. Imaging techniques have made major improvements in the last years. The knowledge about factors responsible for transit times in different parts of the GI tract has expanded dramatically. This is of high relevance for the development of solid dosage forms. Recent advances in the understanding of GI hydrodynamics is driving the development of more relevant *in vitro* dissolution methods. Mechanical stresses can influence the dissolution profile dramatically and they are included in new dissolution equipment. The modeling of drug release from solid dosage forms has also improved. Mechanistic models for different dosage forms are available now and they are of high predictive power. The new findings are relevant for future dosage form development and will lead to the revision of current concepts.

A critical assessment of melt techniques and the impact of new insights in GI tract fate of solid dosage forms were helpful to make better decisions, and progress in both fields is extremely dynamic.

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# 46<sup>TH</sup> JOURNÉES GALÉNIQUES DE SAINT-RÉMY DE PROVENCE

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# FROM HOT STAGE MICROSCOPY TO HOT MELT EXTRUSION - APPROACHES TO PREDICT PRODUCT PERFORMANCE, STABILITY AND PROCESSABILITY

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## Abstract

There are many drug delivery technologies that may enhance the bioavailability of a poorly water soluble drug. The ranking of the solubilization technologies is a balance between performance (both *in vitro* and *in vivo*) and efforts/costs necessary to implement the technology. In order to minimize front loading, i.e. resources expenditure prior to the selection of a front runner technology, an effective and predictive selection process needs to be in place. For hot melt extrusion (HME) this selection process can start with a micro scale performance evaluation on a hot stage microscope (HSM). A batch size of 400 mg can provide sufficient materials to assess drug product attributes like solid state properties, solubility enhancement and physical stability as well as process related attributes such as processing temperature in a twin screw extruder (TSE). Prototype formulations will then be fed into a 5 mm TSE (app. 1-2 g) to confirm performance from the HSM under additional shear stress. Small stress stability testing might be performed with these samples or a larger batch (20-40 g) made by the 9 or 12 mm TSE. Simultaneously, numeric process simulations are performed using process data and rheological and thermal properties of the formulations. Further scale up work to 16 mm and 18 mm TSE confirmed and refined the simulation model. Thus at the end of lab scale development, not only the clinical trial supply is manufactured but also one can form a sound risk assessment to support further scale up even without decades of process experience.

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## Keywords

*Computational process simulation, hot melt extrusion, hot stage microscopy, hot melt extrusion.*

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## 1. Introduction

At the transition of a new chemical entity (NCE) from research into development the available amount of drug substance is usually the limiting factor in pharmaceutical development. Work packages like excipient compatibility, development of an oral solution and selection of a solid oral formulation approach compete for around 50 g of API. In combination with an API exhibiting poor aqueous solubility and consequently insufficient bioavailability, material sparing selection tools for enabling technologies are therefore mandatory. Amorphous solid dispersion prepared by hot melt extrusion, where the API is molecularly dispersed and physically stabilized in a polymeric matrix is one effective enabling tool to overcome poor solubility and bioavailability [1].

However, the hot melt extrusion process predominantly used in the plastics industry works with batch sizes of around 1 kg/hour on the lower end, which is still far too much material for early drug product development. It is therefore inevitable to employ a strategy which includes the elements of screening, equipment miniaturization and numeric simulation at continuous performance control in order to successfully develop a melt extruded solid dispersion product with the limited material resources available in early drug product development.

## 2. Polymer selection and first performance evaluation of solid dispersions

The first obstacle in designing a solid dispersion is the selection of an appropriate polymer irrespective of the manufacturing process. Ideally the API should “dissolve” in the polymer and must not degrade in combination with the polymer or other excipients and the applied process conditions. At the same time the polymer needs to minimize molecular mobility of the API within the matrix in order to preserve the dissolution performance connected to the amorphous solid state throughout the shelf life of the drug product [2,3]. A selection tool ideally provides information on all of the above mentioned characteristics of solid dispersions. While chemometric prediction tools, like the various solubility parameters [4-11], have the potential of selecting a matching polymer [12,13] without API consumption, the prediction accuracy is often poor and the complexity is limited to binary mixtures [14-16]. Slightly more API is necessary when miscibility is experimentally assessed using differential scanning calorimetry (DSC). In particular, mDSC reveals glass transitions and/or melting points for solid state characterization which facilitates not only polymer selection but also gives some rough estimates on physical stability and processing temperature during hot melt extrusion [17-21]. However, DSC is limited in the information it can provide about drug product performance, in particular dissolution performance. Similarly to casted films as a screening tool for spray dried dispersions [22] hot stage microscopy (HSM) in combination with polarized light mimics most elements in hot melt extrusion. The heat ramp of the hot stage table facilitates the observation of drug dissolution (rate and extent) in the polymeric matrices. As a result loading capacity of the matrix, solid state and processing temperature in the melting zone of the extruder can be closely estimated [Figure 1].

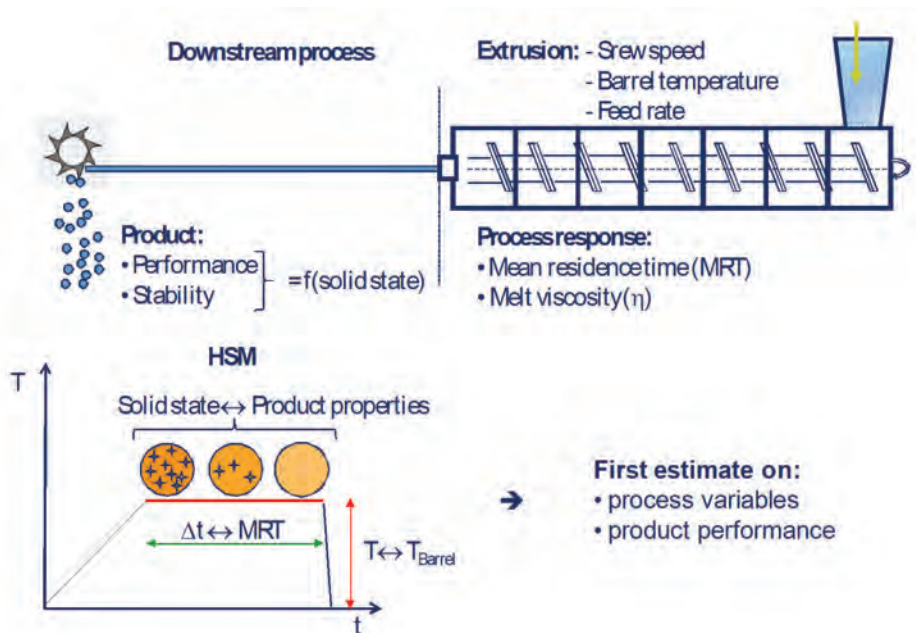


Figure 1. Schematic correlation of hot melt extrusion with hot stage microscopy.

In a first step of screening we aim to select a suitable matrix to enhance initial solubility and provide sufficient physical stability. In a second optimization / refinement step supersaturation can be prolonged - when necessary - by dispersing additional functional excipients into the matrices selected in the first step.

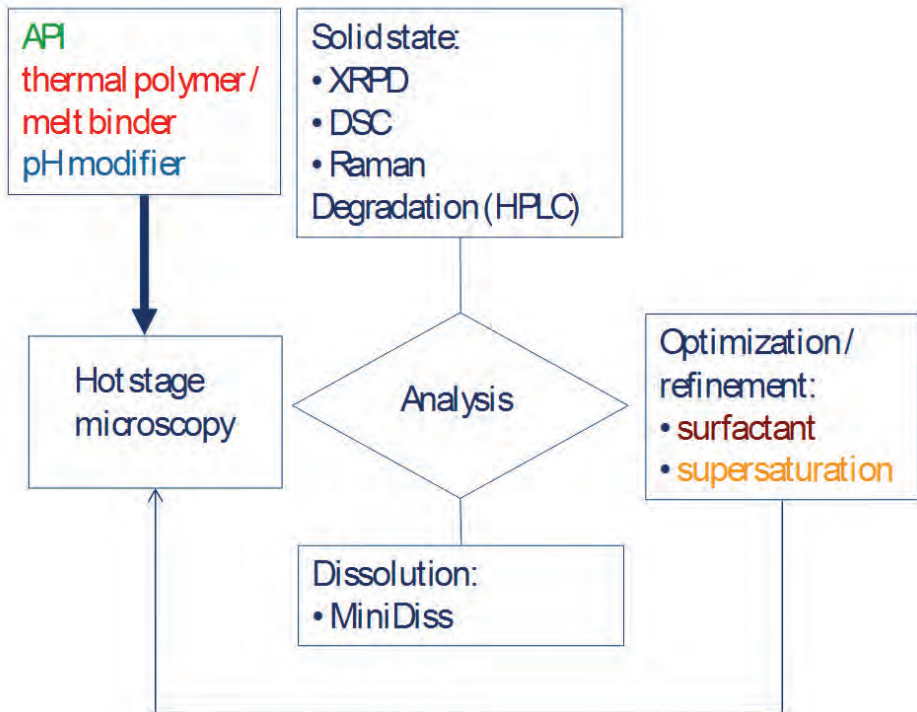


Figure 2. Screening / selection approach for solid dispersions to be produced by hot melt extrusion.

Following the melt experiment, the melt on the microscope slide can be directly assessed in terms of solid state (XRPD or Raman) and its dissolution properties further analyzed. As many authors have pointed out [23-25] it is crucial to perform such dissolution tests in non sink conditions and / or pH / buffer change tests. Since the amount of API on the microscope slide is limited, the dissolution tests were consequently performed in a self made miniaturized apparatus II (MiniDiss) at volumes in between 15 and 20 mL where the round microscope slides ( $\varnothing = 15$  mm) holding the melt were directly added to the vessel [Figure 3].

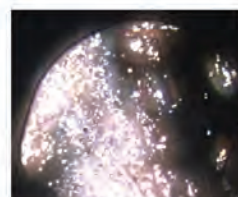
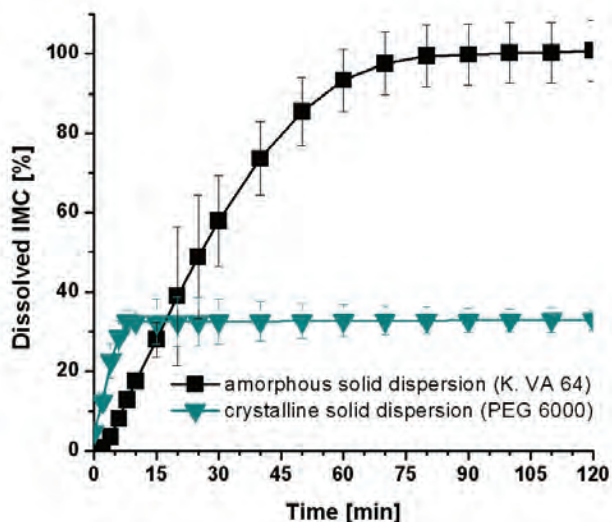


Figure 3. Dissolution and microscopic image of indomethacin solid dispersions molten on microscopic slides using copovidone ■ and PEG 6000 ▼ as a matrix polymer. Samples equivalent to 2.2 mg of IMC were placed in each dissolution vessel of the MiniDiss (paddle 74 rpm). The test was performed in triplicate at  $37 \pm 2^\circ\text{C}$ , in 20 ml of 0.05 M phosphate buffer, pH 5.5.

Similarly to casted films, a stress test on physical stability could be applied using the hot stage microscope. The HSM table is maintained at an elevated but constant temperature (40 or  $60^\circ\text{C}$ ) and moisture conditioned air (75% rh) was purged through the heating chamber. Pictures were taken automatically at a predefined interval in order to detect the onset of recrystallization.

### 3. Transition into hot melt extruders

HSM provides a good indication of the solid state properties and dissolution / physical stability performance of a formulation made by solid dispersion using hot melt extrusion. However, degradation and shelf life stability are strongly influenced by the imparted energy during production. The imparted energy is the sum of conducted heat (from microscope or extruder barrel) and viscous (dissipated) energy caused by shear stress of the extrusion screws. It was obvious that the energy distribution of a HSM experiment could hardly represent the pattern of imparted energies from an extrusion process. So for further development of representative samples for stress stability studies, formulation selection studies in animals and analytical assay development miniaturized extrusion was inevitable. As vendors did not supply small scale extruders by the time we started our investigations we developed extruders with screw diameters from 5 to 12 mm for batch sizes in the range of 0.5 – 100 g in collaboration with the company ThreeTec [Figure 4]. All extruders were equipped with modular screws with the exception of the 5 mm extruder.

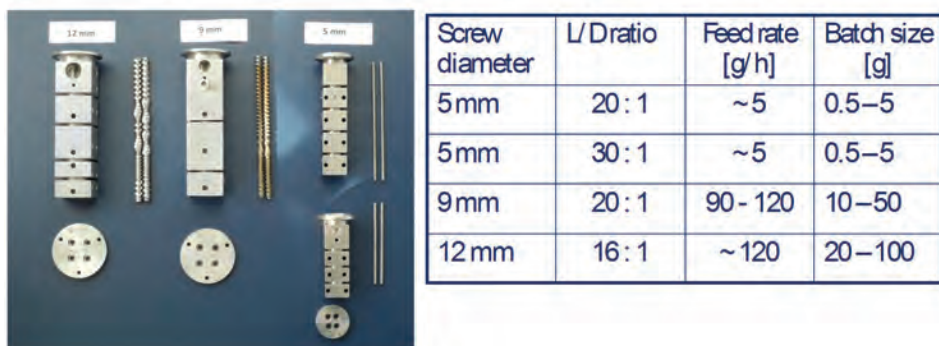


Figure 4. Barrels, screws and dies of small scale extrusion equipment and respective L/D ratios, feed rates and batch sizes.

Before transferring formulations from HSM to the mini-extruders it was important to know the operating space in terms of viscosity in order to obtain - on the one hand - solid extrudate strands and - on the other - still extrude below the maximum motor load of the extruder. With the correlation of temperature dependent viscosity data (complex viscosity  $\eta^*$  measured in oscillation) and the observed extrusion performance, we could specify an operating window for our extruders (5 to 18 mm) in the range of  $\sim 100 - 20\,000$  Pa\*s [Figure 5]. The viscosity range therefore, determined the temperature range as shown exemplarily for the three excipients Eudragit E, copovidone and isomalt. Whereas the polymers needed a temperature above  $130 - 140$  °C when processed without plasticizer in order to extrude without clogging the extruder, the disaccharide isomalt could only be processed below  $120$  °C otherwise liquid would have run out of the die. The higher end of the temperature scale for the polymers is usually determined by either polymer or API degradation.

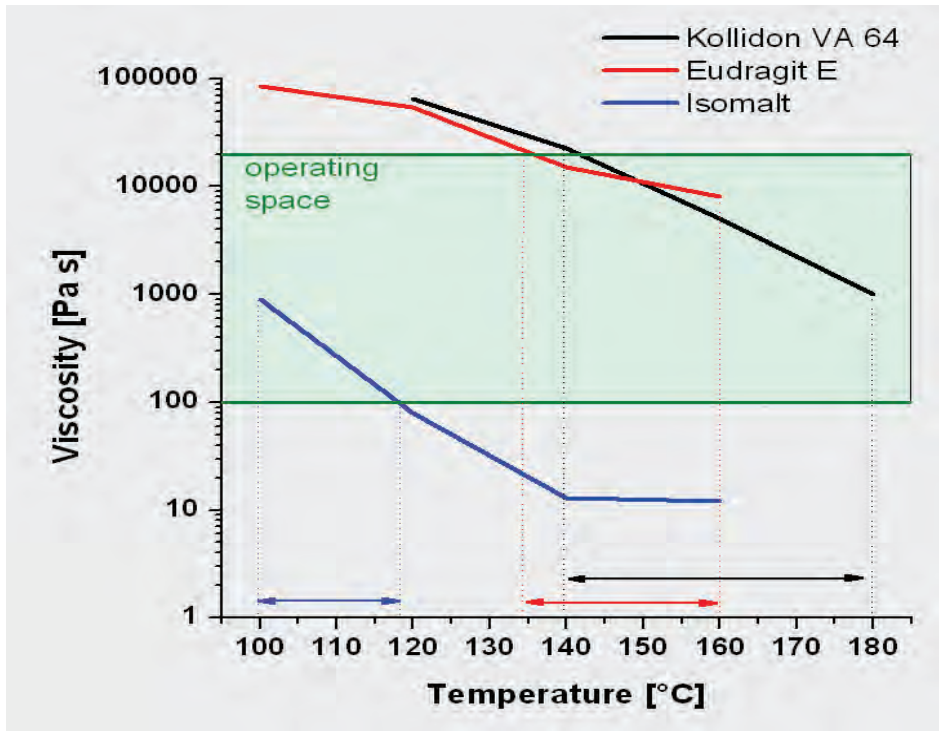


Figure 5. Viscosity and temperature dependent operating space for melt extrusion processes (5 – 18 mm).

The initial "extrudability" check for the top HSM candidates involved determining the melt viscosity of the formulations at the HSM 'melt' temperature. When the measured viscosity was in between 100 – 20 000 Pa\*s the formulation was directly processed in the smallest extruder (5 mm) else a suitable plasticizer (e.g. PEG) was added. The temperature at the main melt zone of the extruder (middle of the extrusion barrel) was set to the HSM melt temperature while the temperature at the feeding zone was kept as cool as possible to avoid clogging the zone with molten polymer. The die temperature was chosen to be close to the melting temperature at the start of the process and was further decreased until desired extrusion strand properties were achieved. Simultaneous recording of all temperatures and motor load of the mini extruders facilitated a first assessment of the processability of the test formulation [Figure 6].

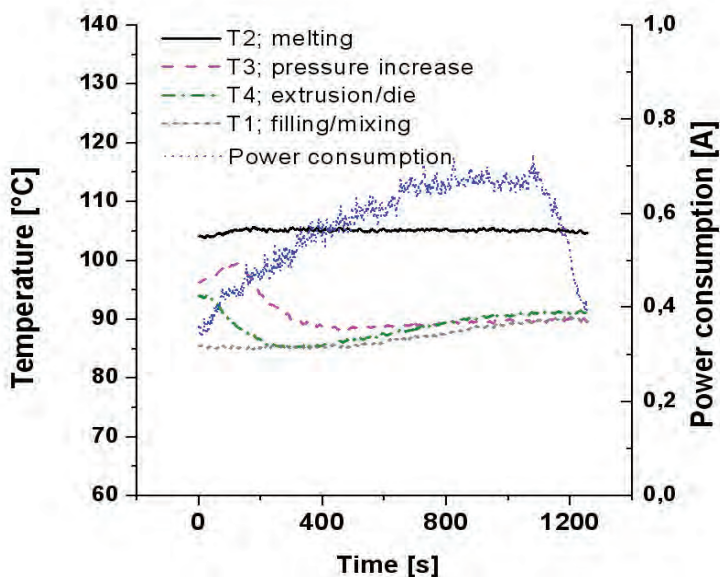


Figure 6. Process chart of mini extruder with 4 separated heating zones and motor load instrumentation.

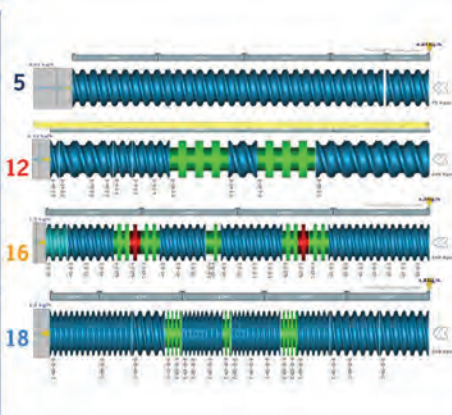
In this step only about 2 g of material is needed to carry out the process which provides sufficient product for subsequent analysis. Once the mechanical process parameters of the extrusion set-up are determined, dissolution studies using the MiniDiss for comparison with the HSM results were performed and solid state properties confirmed.

#### 4. Scale-up between 5 mm and 18 mm twin screw extruders and process simulation

As processability of the formulation at given temperatures was proven in the 5 mm extruder scale, the production of larger batch sizes by 9 mm or 12 mm TSE was easily feasible. Batch sizes here usually ranged between 20 g and 40 g enabling compulsive characterization in terms of dissolution properties, assay and degradation, solid state and stability studies with additional testing conditions. Also further stress stability studies or formulation selection studies in animals could be supplied. In parallel to the extrusion on a 9 mm or 12 mm TSE, the material obtained is further characterized (e.g. heat capacity, heat enthalpy, viscosity, heat conductance) to allow numeric extrusion simulations [26]. Together with the experimental data from 5 mm and 12 mm extrusion runs, first simulations could be conducted in order to identify any critical energy distribution (heat and dissipated energy) dependent on screw element, barrel temperature and time. This theoretical assessment of the extrusion process was of great importance as the extruder characteristics and screw design within the equipment was not consistent [Table 1].

Table 1. Characteristics and screw design of extrusion equipment.

Screw diameter	5 mm	12 mm	16 mm	18 mm
Number of flights	2	2	2	2
Screw clearance [cm]	0.05	0.15	0.05	0.05
Ratio L/D	16.6	15.33	25	38.3
Screw portion L/D	Solid conveying	X	4.5	6.5
	Mixing/Kneading	X	4.7	7
	Melt conveying	16.6	6	11.4



Data obtained from further scale up work to 16 mm and 18 mm TSE confirmed and validated the simulation model (see section 4) and serves to minimized risks in a subsequent scale up to production scale. The technical process variables could be adopted from 12 mm TSE for larger TSE. For example, indomethacin/ copovidone solid dispersions showed that temperatures derived from HSM correlated well with barrel temperature settings at all scales [Figure 7].

Extruder	Feed rate	Die plate
5 mm	0.08 g/min	2 x 1.0 mm
12 mm	2 g/min	2 x 1.0 mm
18 mm	15 g/min	2 x 1.0 mm
18 mm	15 g/min	8 x 0.8 mm

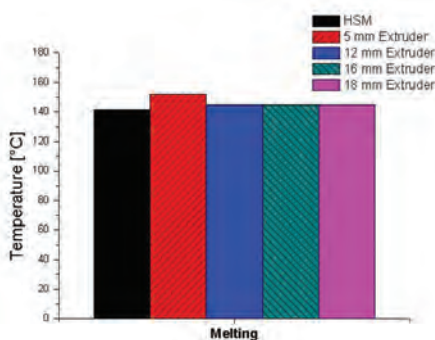


Figure 7. Feed rate, die plate and extrusion processing temperatures for melting and melt temperature resulting from hot stage microscopy for indomethacin/ copovidone solid dispersions.

The analyses were identical for products obtained with the 16 mm or 18 mm TSE and with the smaller scale TSE to ensure consistent and full characterization. The *in vitro* dissolution properties (Figure 8) and solid state properties of solid dispersions of indomethacin with copovidone produced by HSM and TSE were similar for all screw scales. These control loop combination ensured a high quality level and reproducibility of the process and the final product properties.

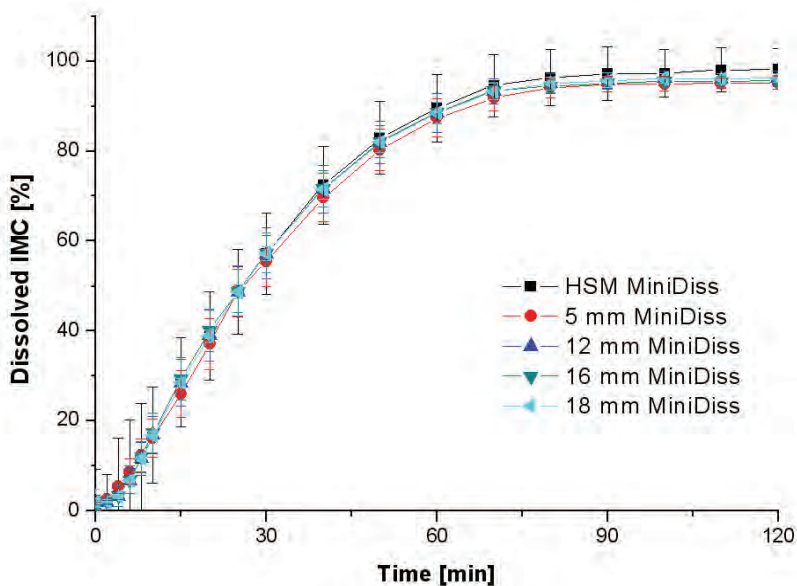


Figure 8. Dissolution of Indomethacin solid dispersions molten on microscopic slides compared to extrudates obtained by 5 mm, 12 mm and 18 mm Extrusion using copovidone as a matrix polymer. Samples equivalent to 2.2 mg of IMC were placed in each dissolution vessel of the MiniDiss (paddle 74 rpm). The test was performed in triplicate at  $37 \pm 2$  °C, in 20 ml of 0.05 M phosphate buffer, pH 5.5.

## 5. Computational process simulation and scale up assessment

With respect to the results presented in Table 1, it seemed rather strange that the differences in the extruder set-up did not result in larger variations in product properties. However, would it be safe to conduct extrusion scale-up solely on temperature settings? What risks are attributed to various shear stresses, residence times and temperature peaks in the melt, hardly to be controlled by the barrel temperature settings? To answer those questions computational process simulations were performed for the upscale of the indomethacin/ copovidone solid dispersion extrusion with emphasis on energy distributions, mean residence times (MRT) and temperature distribution along the screw [26-29]. Global results of the simulations showed that in this “lucky case” of the indomethacin / copovidone mixture, all extrudates left the extruders at identical final product energy [Figure 9]. This fact is concurrent with the observed material properties which showed practically no difference in terms of dissolution performance and solid state. As one could expect from geometrical considerations, imparted material energy by conduction decreased with increasing extrusion scale as the barrel surface ratio to barrel volume was decreasing. Accordingly, energy by (viscous) dissipation tends to increase with TSE scale caused by higher shear forces of larger screw diameters. Comparing the imparted energy of material processed with the 16 mm TSE with all

others scales, a remarkable difference was revealed. The extrudate out of the 16 mm TSE experienced a higher energy intake at similar final energy content. Computations showed that the kneading elements with the 16 mm TSE are more effective and hence cause more shear stress compared - for instance - to those of the 18 mm screw. This means more energy was imparted by dissipation and therefore the amount of excessive energy had to be exhausted by conduction, i.e. by cooling. This explained the negative value for the total conducted energy for this simulation.

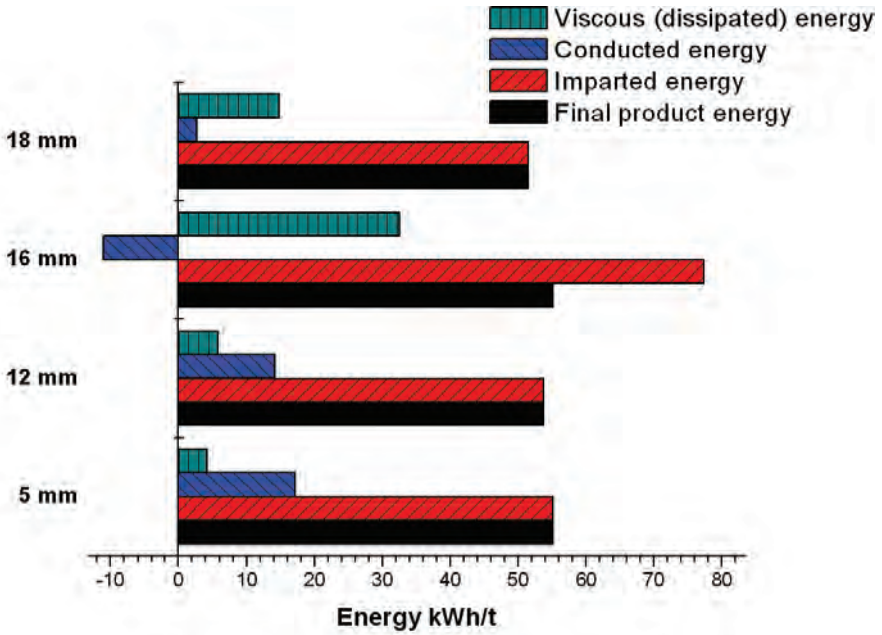


Figure 9. Comparison of final product energy, imparted energy, conducted energy and viscous (dissipated) energy of Indomethacin solid dispersions with copovidone obtained by extrusion on a 5 mm, 12 mm, 16 mm and 18 mm scale.

Following the evolution of temperature along the screws for all scales revealed huge differences which could be visualized by simulation [Figure 10]. For the 5 mm TSE barrel temperatures were set slightly higher than for larger scales in order to avoid a torque overload of the extruder. Accordingly, the melt temperature was higher along the screw. Nevertheless, due to the lower temperature setting in the last barrel segment the final product temperature became comparable to those on larger scales.

The simulations described also illustrate very clearly the influence of the different screw profiles on the melt temperature. As suspected the temperature of the melts was strongly influenced by the restrictive elements and their position along the screw. At positions with restrictive elements the calculated temperatures increased

the most. At these positions the local residence times of the material was long. At the same time and location along the screw the extruder barrel was usually completely filled which allowed a higher rate of energy conduction and subsequently viscous dissipation increased.

The melt temperature along the 12 mm screw was constantly increasing after the first kneading element. Compared to the evolution of temperature after the first kneading element of the 18 mm screw the temperature increase was rather low along those elements. Only after the second restrictive element the melt temperature had almost reached the final temperature. This was in accordance with the global results as more energy was imparted due to conduction. Further the kneading elements proved not to be as efficient as those of the 16 mm screw or the second set of kneading elements of the 18 mm screw. The 16 mm and 18 mm screws used in study both contained 90° kneading elements, whereas the 12 mm screw had only 30° kneading disks. Chan and Dufresne reported that a configuration of 90° kneading disks is the most efficient in terms of melting and temperature increase with a high filling ratio [30], which could be shown for the 18 mm screw. Before the last kneading block with a 90° element a conveying screw with a smaller pitch increased the degree of fill and the temperature increase was superior compared to the first kneading block where only 30° and 60° kneading disks were placed, i.e. the first kneading block was not adequately effective to impart sufficient energy to increase melt temperature.

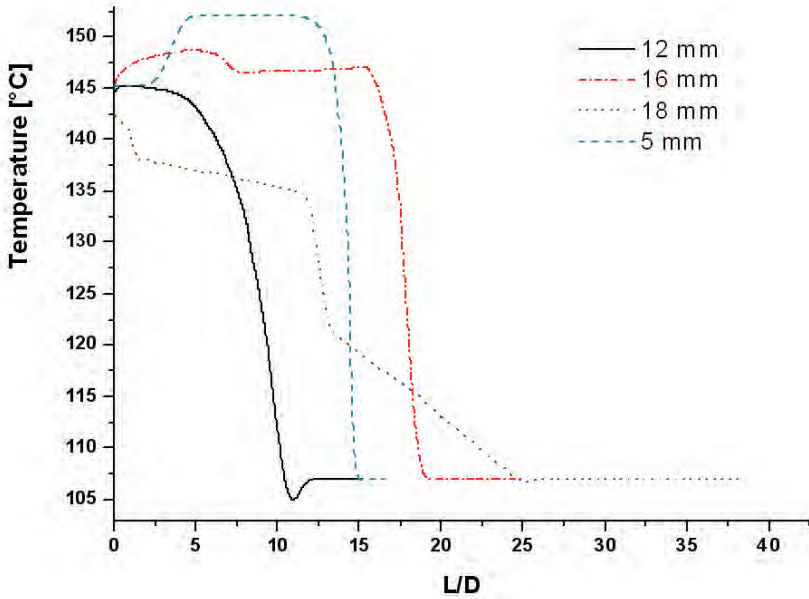


Figure 10. Simulated temperature evolution over screw length/screw diameter on the 12 mm, 16 mm and 18 mm extrusion scale.

MRT calculations allowed us to estimate how long the processed material is experiencing thermal and mechanical burden during the process. The MRT varied from 310 seconds for the 12 mm extruder and 138 and 84 seconds for the 16 mm and 18 mm TSE respectively [Figure 11].

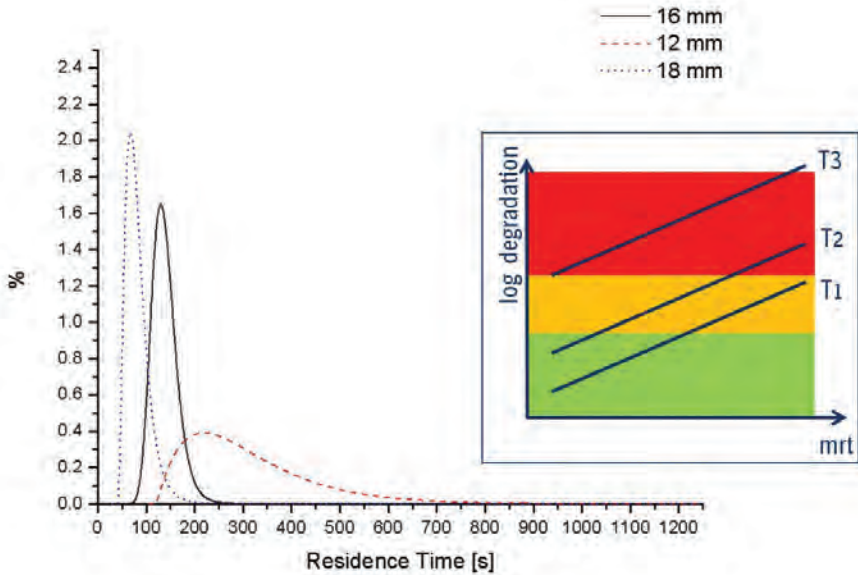


Figure 11. Simulated Residence Time Distributions on the 12 mm, 16 mm and 18 mm extrusion scale.

Mean residence times for 16 mm and 18 mm extrusion showed a narrow and almost Gaussian distribution, also indicating good mixing efficiency [31]. However, for the 12 mm extrude the peak showed a broad distribution in combination with pronounced tailing towards longer residence times resulting in a high MRT-variance. The flat distribution function and the long MRT can be explained with two major effects. As mentioned above the kneading blocks were not very effective to increase the degree of fill and flow velocity. Secondly, the wide screw clearance (0.15 mm instead of 0.05 mm) facilitated a possible “back flow” of the melt contributing to the strong peak tailing. Considering that possible degradation processes are time and temperature dependent MRT calculations can help to identify degradation processes and to judge whether larger scales are less prone to cause them.

Overall computational extrusion process simulations showed a high potential to identify high energy intake spots due to screw elements or high MRT. Thus, for future projects inefficient screw designs for scale-up can be identified and avoided, product quality can be optimized and scale feasibility be judged.

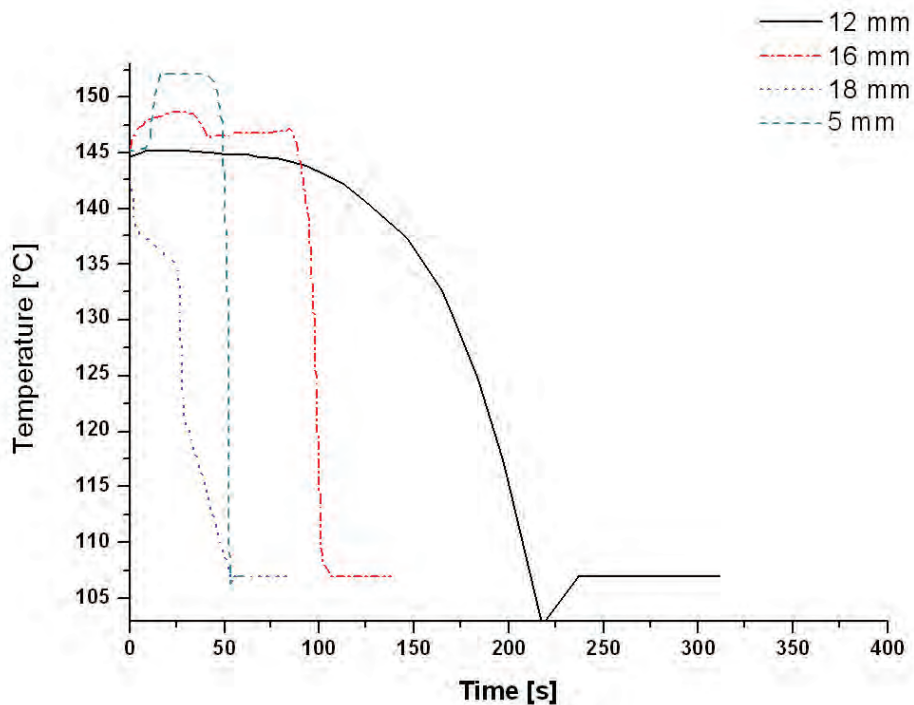


Figure 12. Evolution of temperature as a function of time for extrusion of Indomethacin/copovidone solid dispersions at the 5 mm, 12 mm, 16 mm and 18 mm extrusion scale.

The accuracy of the simulations with Ludovic was assessed with extrusion experiments with copovidone on the 18 mm TSE [Table 1]. Simulated MRT and simulated final melt temperatures are in good accordance to the experimentally obtained values. The accuracy of Ludovic was also described in literature [27, 29, 32].

Table 2. Simulated end experimental Mean Residence Times and melt temperatures for extrusion experiments at various throughput rates and screw speeds on the 18 mm TSE.

Speed [rpm]	Q [kg/h]	MRT (Simulation/Experiment)	T melt (Simulation/Experiment)
200	1.5	58/55	188/194
250	2.1	42/40	190/195
300	2.7	34/30	192/198
350	3.3	28/22	194/200
400	3.9	24/18	197/201

## 6. Summary

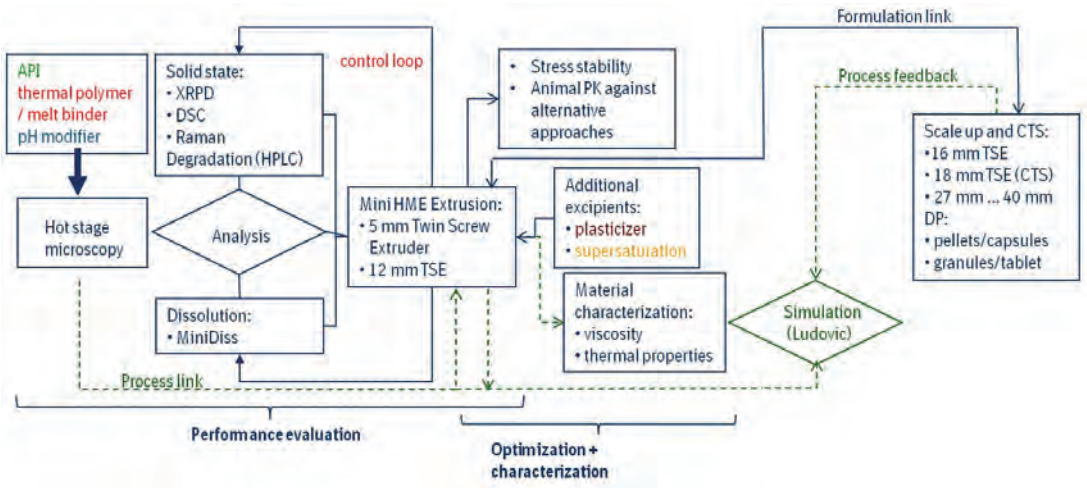


Figure 13. Process development flowchart.

An efficient screening and process development approach for dosage form development can be proposed. As API polymer miscibility and physical stability prediction is questionable especially for ternary or higher order mixtures, HSM offers an ideal, fast and easy mean to estimate product performance including solid state, physical and chemical stability and degradation. Identified formulations from HSM can be further prepared on a small lab scale extruders and further scales to 16 mm and 18 mm TSE [Figure 13].

The combination of an experimental screening assay like hot stage microscopy, miniaturized extrusion equipment and computational process simulations proved to be a very efficient tool for early drug product development. In this way the extrusion emerges from a black box with temperature and screw speed settings towards a transparent and well-designed process.

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# THE USE OF SUPERCRITICAL FLUID TECHNOLOGY TO BROADEN THE APPLICABILITY OF HOT MELT EXTRUSION FOR DRUG DELIVERY APPLICATIONS

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## Abstract

Hot melt extrusion is generally accepted as a technique to prepare solid dispersions for improving aqueous solubility and oral bioavailability. A major drawback of hot melt extrusion is its limitation to thermally stable compounds and excipients, as well as the difficulty to further formulate the glassy melt extrudate into a suitable dosage form such as a tablet or a capsule. Therefore, the aim of this research approach was to explore and investigate the possibilities of pressurized CO<sub>2</sub> and hot melt extrusion, to broaden the applicability of this technique for drug delivery. The influence of injecting a pressurized gas as a temporary plasticizer for thermally labile products was investigated, as was the ability to form a foam upon expansion of the pressurized gas post-die. The novelty of this project lies in the use of hot melt extrusion combined with sub- and supercritical fluid technology, to expand the processing window of the technique and to influence the macroscopic morphology and performance of the solid dispersion.

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## Keywords

*Carbon dioxide, controlled release, hot melt extrusion, increased aqueous solubility, plasticizer, solid dispersion, supercritical fluids.*

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## 1. Introduction

The utilization of supercritical fluids (SCFs) for the processing of pharmaceutical dosage forms has gained considerable interest in the last decade. SCFs can be used, generally, (a) to extract substances from natural sources, (b) as solvents or anti-solvents for particle engineering, encapsulating drugs into polymeric carriers, resolving racemic mixtures of active compounds or fractionating mixtures of polymers or proteins, (c) as reaction medium for chemical reactions, and (d) to reduce bacterial counts [1-3]. The most popular SCF in pharmaceutical applications is carbon dioxide. It is non-toxic, non-flammable, tasteless, inert and inexpensive, which makes it a useful substitute for organic solvents. Also, SCFs based on carbon dioxide are environmentally friendly, whereas conventional pharmaceutical processes are often associated with both the emission of organic solvents and with difficulties of removing residual solvents. Furthermore, the mild operating conditions (supercritical temperature 31°C and critical pressure 73.8 bar) associated with sub- and supercritical carbon dioxide can be especially favorable to bio-molecules, such as proteins involved in pharmaceutical applications. As the critical point of a substance is approached, its isothermal compressibility approaches infinity, and thus, its molar volume, or density, changes dramatically. A SCF can provide the solvent capacity of classical solvents, while providing higher diffusional capacity through its proximity to the gas state. Close to the critical point, density changes are considerable and thus the solubility of a substance can be tailored by fine tuning the pressure and temperature. The same holds true for the diffusivity and the viscosity of the SCF.

Particle formation/engineering is currently one of the most popular applications of SCFs in the area of pharmaceuticals, which has been extensively reviewed by Jung et al. and Knez [4, 5]. This application can be further subdivided into three main research areas: (a) the preparation of powders of active substances to improve or modify their therapeutic action or to enhance their solubility (micronisation), (b) the production of polymers as a matrix for drug impregnation, and (c) the preparation of drug-based polymeric carrier systems as drug delivery systems with improved bioavailability (i.e., solid dispersions) or controlled release characteristics.

On the other hand, one commonly applied pharmaceutical method to prepare solid dispersions is via hot melt extrusion using an intermeshing co-rotating twin screw extruder. Numerous pharmaceutical applications of hot melt extrusion are described in the literature as reviewed by Breitenbach and Verreck and Brewster [6, 7]. A variety of excipients can be used in the processes. Traditional extrusion carriers include pharmaceutical polymers such as polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), polyvinylpyrrolidone (PVP), polyvinylpyrrolidone-vinylacetate (PVPVA 64) and Eudragit® E100 as well as various small organic molecules (i.e., mannitol, citric acid, cyclodextrins).

Although the process can be applied to poorly soluble drugs like itraconazole [8, 9], for a number of active substances (and excipients), hot melt extrusion cannot be used due to thermal lability of formulation components and subsequent loss

of drug/excipient activity or functionality [10]. This is a major drawback of the hot melt extrusion process. Another downside is the difficulty to further formulate the glassy melt extrudate into a suitable dosage form such as a tablet or a hard gelatine capsule [11]. Often the extrudate strands or films obtained post-die are further milled to pellets, granules or powder. These extrudates can be very difficult to mill to obtain a suitable particle size distribution. High energy mills are often required resulting in low yields and possible transformations of the amorphous drug phase to the crystalline state. In order to reduce thermal degradation and to improve process-ability, a plasticizer is often added to the formulation to reduce its viscosity during melt extrusion. Plasticizers are typically ingredients with low molecular weight, and can be either in the solid or the liquid/liquefied state. They add to the free volume of the main constituent of the formulation, i.e., the polymeric carrier, and thereby increase flexibility in the local liquid structure of the polymer. Plasticizers reduce polymer-polymer secondary chain bonding and provide for higher molecular mobility. As such, they reduce bulk properties like tensile strength, hardness, density, melt viscosity, glass transition temperature, and at the same time increase parameters like elongation at break, toughness and dielectric constant. Added plasticizers usually remain in the final product, thus affecting its properties and performance. Typically, conventional plasticizers such as triacetin or PEG are used in a concentration range of 5 up to 30% w/w of the extrudable mass [12-14]. This means that when a plasticizer is used, the total extrudate mass to be formulated into the final dosage form increases [15].

When assessing the interaction of supercritical carbon dioxide with polymers, one important effect of carbon dioxide is plasticization of amorphous and semi-crystalline polymers. This plasticization occurs through two mechanisms as described by Chiou et al. [16]. First, carbon dioxide is absorbed between the polymer chains causing an increase in free volume and a decrease of chain entanglement. Second, carbon dioxide acts as a molecular lubricant which reduces melt viscosity. One such example of carbon dioxide acting as a plasticizer is described by Kikic et al. [17], who describe the plasticization effect for poly(2,6-dimethylphenylene oxide), polyacrylic acid and PVP-VA 64, measured using an inverse gas chromatographic technique. This and other examples show that pressurized gases lower the melt viscosity of numerous amorphous and semi-crystalline polymers.

Based on these observations, SCFs can be applied during polymer processing and more specifically during hot melt extrusion. Elkovitch et al. and Royer et al. reported on the viscosity reduction of polystyrene PS and PMMA induced by supercritical carbon dioxide when measured in a single screw extruder equipped with a slit die to measure the viscosity [18-21]. They reported a viscosity reduction of 70% for PMMA and up to 50% for PS. Further, they investigated blends of PMMA and PS in a twin-screw melt extruder and observed that the blending improved due to the reduced viscosity of the two polymers subsequent to injecting supercritical or subcritical carbon dioxide [19]. Lee et al. investigated the viscosity reduction of polyethylene/polystyrene (PE/PS) blends and also observed a significant plasticization effect when measured in a twin screw extruder equipped with a slit die [22].

They further studied foam formation that was observed when the extruded polymer/gas mixture exited the die. It was found that pore size could be altered by changing pressure and carbon dioxide concentration. Other groups have also investigated foam formation upon CO<sub>2</sub> loss at the die of a melt extruder. Park et al. and Han et al., for example, studied the continuous micro-cellular foam formation of PS using a single screw extruder [23-25].

It is the objective of this work to explore and investigate the combined possibilities of supercritical CO<sub>2</sub> and hot melt extrusion to expand the applicability of these techniques in drug delivery. The influence of injecting a pressurized gas as a temporary plasticizer (being not present in the final product) for thermally labile products will be investigated, as will the ability to form a foam upon expansion of the pressurized gas (making down-stream processing easier). The following polymers were used in this work: PVP-VA 64, Eudragit® E100 and ethyl cellulose 20 cps (EC). Itraconazole and p-aminosalicylic acid were used as model compounds.

## **2. Equipment set-up for injection of pressurized carbon dioxide with pharmaceutical polymers**

Examples described above demonstrate that injection of a pressurized gas in both a single screw as well as a twin screw extruder should be feasible.

The extruder set-up and screw configuration that were used in our experiments are shown in Figures 1 and 2. As discussed by Mollan [26], intermeshing co-rotating twin-screw extruders possess excellent mixing capabilities which make them the extruder of choice to prepare solid dispersions. A Leistritz Micro 18 co-rotating intermeshing twin-screw extruder was used for the experiments (Leistritz, Germany). As a consequence of its design, this type of extruder can never be completely filled with polymer inside the barrel. Injecting carbon dioxide could cause leakage of the gas resulting in an insufficient build up of pressure inside the barrel. Therefore, the screw configuration was carefully considered in order to be able to mix the CO<sub>2</sub> with the polymer melt at appropriate pressures. As suggested by Lee et al. [22], a number of different aspects should be taken into account to design the extruder set up and screw configuration including, (a) at the injection port of the carbon dioxide, the pressure fluctuations should be minimized to obtain a stable injection. Therefore, transport elements instead of kneading elements should be used at the injection port, (b) injected carbon dioxide should not be allowed to leak from upstream orifices, requiring the use of a melt seal using reversing elements, (c) the pressure downstream should be maintained at a sufficiently high level to ensure that the carbon dioxide remains dissolved in the polymer. This can be obtained by providing high die resistance, and (d) complete dissolution of carbon dioxide can be designed in the process by using kneading elements to improve mixing downstream of the pressurized gas introduction.

According to these suggestions, a number of different extruder set ups and screw configurations were tested and optimized, as depicted in Figures 1 and 2 [27].

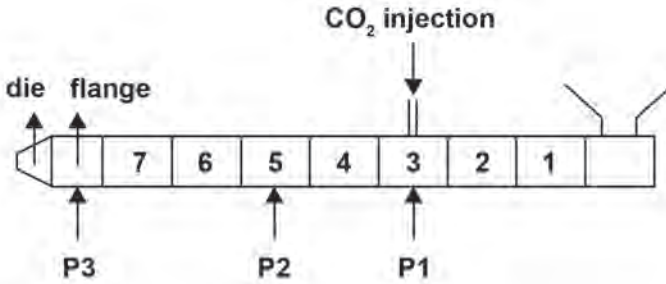


Figure 1. Schematic set up of the Leistritz twin screw extruder. Carbon dioxide was injected in segment 3. Further downstream, the barrel is completely sealed. Pressurized carbon dioxide is released to atmospheric pressure upon exiting the die.

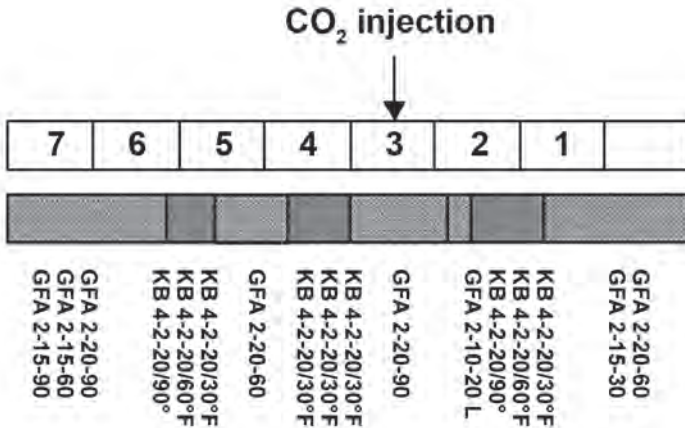


Figure 2. Schematic set up of the screw configuration. The descriptions represent the properties of the transport elements (GFA) and kneading blocks (KB), respectively, as well as the length and angle of each element.

Carbon dioxide was injected in barrel segment 3. Proximal to the CO<sub>2</sub> injection port, one melt seal was obtained in segment 2 using a reversing transport element, and further downstream, another melt seal was obtained at the die plate. To better distribute the carbon dioxide in the polymer, two mixing zones were provided downstream of carbon dioxide introduction after the first melt seal. To insure creation of a robust melt seal, the barrel segments 1 and 2 were kept at increased temperature to guarantee a polymer melt in this zone. Using this extruder set-up and screw configuration it was feasible to inject carbon dioxide under sub- and supercritical conditions and foaming was observed at the die of the extruder (see Figure 3).



Figure 3. Extrusion of PVP-VA 64 with injection of carbon dioxide at a pressure of 55 bar. Foaming at the die of the extruder.

As shown in Table 1, based on the minimal temperature settings during melt extrusion of the polymers PVPVA 64, EC and Eudragit® E100, it can be observed that CO<sub>2</sub> acts as a plasticizer, and upon expansion of the gas which occurs upon exiting the extruder, it is not present in the final extrudate.

Table 1. The minimal temperature settings at which maximum torque was obtained with and without carbon dioxide injection as well as the maximal CO<sub>2</sub> pressure under these conditions. Feed rate = 1 kg/hr and screw speed = 100 rpm.

Polymer	T <sub>set, minimal</sub> (°C) without CO <sub>2</sub>	T <sub>set, minimal</sub> (°C) with CO <sub>2</sub>	Δ <sup>1</sup>	P <sub>max, CO<sub>2</sub></sub> (bar)
PVPVA 64	150	120	30	55
Eudragit® E100	130	115	15	45
EC	140	75	65	125

<sup>1</sup>: Δ = Difference between the minimal temperature settings without carbon dioxide injection and with carbon dioxide injection.

Size exclusion chromatography was performed to evaluate the effect of injecting carbon dioxide on the molecular weight of the polymers, but no effect was observed. The thermal properties of the polymers before and after CO<sub>2</sub> injection were not different, except for EC, where the crystalline fraction of the polymer was influenced as a function of the carbon dioxide pressure [27]. Due to the observed foaming, both specific surface area, as well as porosity was increased after carbon dioxide injection during hot melt extrusion.

This is shown in Figure 4 for EC, wherein the pore size is influenced by the CO<sub>2</sub> pressure and extrusion temperature. This change in porosity resulted in improved milling efficiency for all 3 polymers [27].

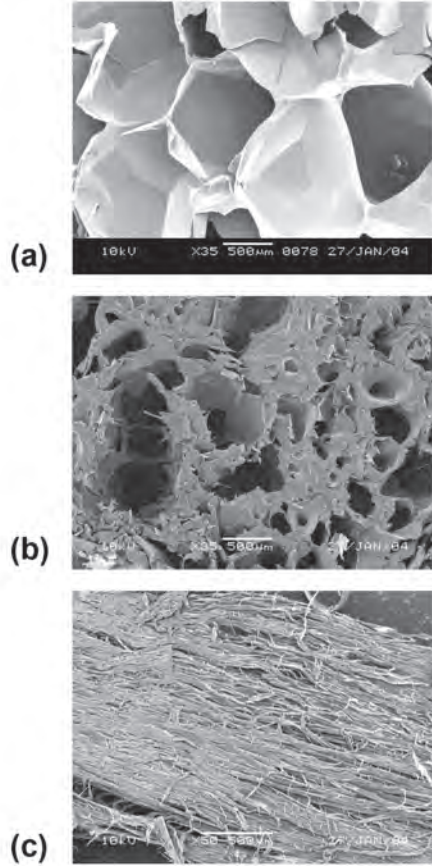


Figure 4. Scanning electron microscopy (SEM) of EC as a function of pressure and temperature during the hot melt extrusion process. All size bars are 500 μm. (a)  $T=130^{\circ}\text{C}$ ,  $P=39$  bar, (b)  $T=130^{\circ}\text{C}$ ,  $P=60$  bar, (c)  $T=100^{\circ}\text{C}$ ,  $P=100$  bar.

### 3. The effect of injecting carbon dioxide as a temporary plasticizer and foaming agent during hot melt extrusion of itraconazole and PVPVA 64

In the next set of experiments, the same extruder set-up and screw configuration were used as with the pure polymers. The aim of these experiments was to investigate whether carbon dioxide acted as a temporary plasticizer and foaming agent in the presence of model drug substances. Itraconazole was melt extruded with PVPVA 64 at 10 and 40% w/w concentrations. Since itraconazole is thermally stable, it was selected as a test compound to evaluate the influence of injecting carbon dioxide on the properties of the solid dispersion. Also, previous investigation showed that itraconazole transforms into the glassy state with the formation of a chiral nematic mesophase when cooled from the melt [28, 29]. This phase transition occurs reproducibly, but disappears when itraconazole is mixed and melted with PVPVA 64. This resulted in the formation of amorphous dispersions and glass solutions [9, 30, 31]. The typical thermal characteristics of itraconazole therefore enable an evaluation of whether the mixing behavior of the solid dispersion will be influenced by the injection of carbon dioxide during hot melt extrusion. Table 2 gives a comparison of the minimal temperature settings during the melt extrusion process as a function of the  $T_g$  for pure PVPVA 64 and itraconazole/PVPVA 64 10 and 40% w/w.

Table 2. Comparison of the minimal temperature settings during hot melt extrusion versus  $T_g$  for pure PVPVA 64 and itraconazole/PVPVA 64 10 and 40 % w/w solid dispersions.

	PVPVA 64 <sup>1</sup>	10% w/w	40% w/w
$T_g$ (°C) <sup>2</sup>	109	104	90
$T_{set, min}$ (°C) <sup>3</sup>	150	125	110
$T_{set, min, CO_2}$ (°C) <sup>4</sup>	120	115	105
$T_{set, min, CO_2} - T_g$ (°C)	11	11	15

<sup>1</sup>: from previous work, <sup>2</sup>: average glass transition temperature of the sample (n=2), <sup>3</sup>: minimal temperature settings during hot melt extrusion without injection of carbon dioxide (feed rate = 1 kg/hr, screw speed = 100 rpm), <sup>4</sup>: minimal temperature settings during hot melt extrusion with injection of carbon dioxide (feed rate = 1 kg/hr, screw speed = 100 rpm)

These results indicate that both itraconazole as well as carbon dioxide act as a plasticizer for PVPVA 64. However, the total plasticizing effect of both components is comparable for all three system, i.e., the minimal temperature settings during extrusion are between 11°C and 15°C above the glass transition temperature of the samples. This indicates that there is a limiting value above the  $T_g$  of the amorphous system, below which there is no further temperature reduction possible during hot melt extrusion. Evaluation of the thermal properties of the solid dispersion with modulated-differential scanning calorimetry (DSC) showed that all solid dispersions extruded at temperatures above the melting point of itraconazole demonstrated behavior consistent with the Fox equation suggesting that the formation of glass solutions is not influenced by the injection of  $\text{CO}_2$  [32]. The 40% w/w solid dispersions extruded below the melting point of the active substance did show the presence of crystalline itraconazole whether  $\text{CO}_2$  was injected or not, indicating the formation of a phase separated solid dispersion. This was also confirmed by powder X-ray diffraction and infrared spectrophotometry. The dissolution of the itraconazole/PVP-VA 64 10% w/w extrudates with and without carbon dioxide injection was assessed and compared to the physical mixtures (Figure 5).

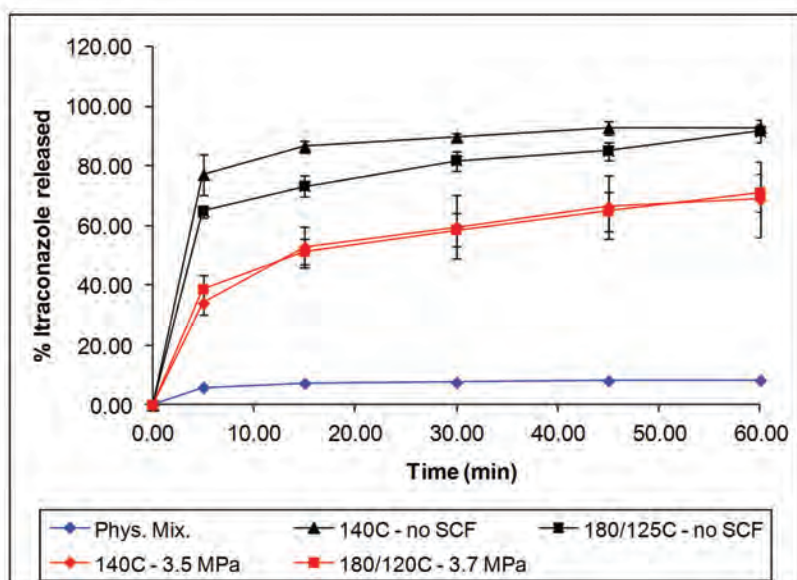


Figure 5. Dissolution of itraconazole/PVP-VA 64 10% w/w with and without carbon dioxide injection. The dissolution of a 50 mg dose was measured in 500 ml of SGF at 37°C. The dissolution was assessed using a paddle rotating at 100 rpm (USP II apparatus). Error bars represent the standard deviation based on measurements in triplicate.

The data obtained show that dissolution of itraconazole can be controlled by temperature and pressure during the hot melt extrusion process. The dissolution of all samples was enhanced compared to the physical mixture. The dissolution rate for the different solid dispersions is comparable, but the initial dissolution (initial wetting) is faster for the extrudates without carbon dioxide injection. It was observed that after injection of carbon dioxide, the specific surface area, porosity and water sorption were increased for both the 10 and 40% w/w samples. Since density did not change while porosity increased, only surface pores were measured which was confirmed by an increased specific surface area. This may explain, at least in part, the difference in the initial wetting during dissolution measurement. Since the carbon dioxide treated samples are more hygroscopic, water penetrates faster causing agglomeration due to the presence of the hydrophobic itraconazole. This was also visually observed during dissolution measurement [32]. Furthermore, and similar to the situation with the pure polymers, milling efficiency was improved when extrusion was performed with the injection of carbon dioxide.

Based on the results obtained thus far, it can be stated that carbon dioxide acts as a temporary plasticizer and foaming agent for a number of pharmaceutical polymers as well as drug loaded solid dispersions with itraconazole and PVPVA 64 and similarly observed for itraconazole and EC [33].

#### 4. Melt extrusion of the thermally labile compound p-amino salicylic acid with EC using pressurized CO<sub>2</sub> as a temporary plasticizer

The aim of the subsequent experiments was to explore the possibility of combining supercritical carbon dioxide with melt extrusion during manufacturing of solid dispersions of the thermally labile compound, p-aminosalicylic acid (p-ASA), and EC and to evaluate the ability of the carbon dioxide to act as a temporary plasticizer. p-ASA melts at 147°C with decomposition. A temperature/degradation profile was constructed as can be seen in Table 3 [34].

Table 3. Thermal degradation profile for p-ASA under atmospheric conditions.

Temperature (°C)	Time (minutes)	% p-ASA intact
140	5	0
130	5	0
120	5	72.7
110	5	98.5
110	10	96.7
100	10	98.9
80	10	99.4

This table shows that the active substance does not thermally degrade below 100-110°C when kept 10 minutes under atmospheric conditions. In other words, the temperature inside the extruder should not exceed 110°C for too long a period in order to prevent degradation of the active substance. The minimal temperature settings obtained during melt extrusion with and without carbon dioxide injection are presented in Table 4.

*Table 4. Minimal temperature settings for hot melt extrusion of p-ASA/EC 10% w/w with and without CO<sub>2</sub> injection. The screw speed and feed rate were maintained at 100 rpm and 1 kg/hr, respectively.*

Nr.	T <sub>1-2</sub> <sup>a</sup>	T <sub>3</sub>	T <sub>4</sub>	T <sub>5</sub>	T <sub>6</sub>	T <sub>7</sub>	T <sub>die</sub> <sup>b</sup>	T <sub>flange</sub> <sup>c</sup>	torque	P <sub>pump</sub>	%p-ASA (n=3 ± RSD)
	(°C)	(°C)	(°C)	(°C)	(°C)	(°C)	(°C)	(°C)	(%)	(bar)	
<b>Without CO<sub>2</sub> injection</b>											
1	180	115	115	115	115	115	115	115	87-100	-	36.4 ± 0.6
2	130	130	130	130	130	130	130	130	78-93	-	83.7 ± 0.2
3	130	130	130	130	130	130	130	130	75-91	-	83.3 ± 0.3
<b>With CO<sub>2</sub> injection</b>											
4	130	80	80	80	80	80	80	80	88-100	90	87.9 ± 0.2
5	130	80	80	80	80	80	80	80	86-100	90	86.4 ± 1.1
6	125	90	90	90	90	90	90	90	86-100	75	89.6 ± 1.1
7	110	110	110	105	105	100	100	95	85-100	75	96.3 ± 0.8

<sup>a</sup>: Temperature settings of barrel segments 1 and 2, <sup>b</sup>: Temperature settings of the die, <sup>c</sup>: Temperature settings of the flange.

The results show that CO<sub>2</sub> acted as a plasticizer for p-ASA/EC 10% w/w. The optimal conditions that allowed for CO<sub>2</sub> to be injected were at supercritical pressure resulting in a processing temperature decrease of approximately 30°C. HPLC analysis was performed after hot melt extrusion to evaluate the influence of CO<sub>2</sub> as a plasticizer on the thermal degradation of p-ASA. The results in Table 4 show that the percentage of p-ASA which is had not degraded after hot melt extrusion, has significantly increased when using CO<sub>2</sub> as a plasticizer. Without carbon dioxide injection, almost 65% degradation occurs when the first two barrel segments are kept at increased temperature. Even when the temperature of the initial barrel elements are maintained at reduced temperature, approximately 17% degradation occurred. When CO<sub>2</sub> was injected, the extent of degradation was less than 5%. These experiments demonstrate that the hot melt extrusion of p-ASA with EC became possible as a result of the injection of CO<sub>2</sub>, a temporary plasticizer, which is not present in the final product.

## 5. Conclusions

Using the pure polymers, an optimal extruder configuration and screw design were developed for a co-rotating intermeshing twin-screw melt extruder, which allowed for, (a) the injection of pressurized carbon dioxide, (b) the build up of pressure inside the extruder, (c) an intimate mixing between active compound, polymer and carbon dioxide so that the pressurized gas can dissolve in the drug/polymer mixture and (d) the formation of a foam upon expansion of the carbon dioxide. This configuration also provided a method to establish a condition of steady state (no pressure drops, i.e., no leakage of carbon dioxide) accompanied with significant foaming upon release of the pressure. As such, CO<sub>2</sub> was applied as a temporary plasticizer for the pharmaceutical polymers PVPVA 64, Eudragit® E100 and EC. Also, the post-die morphology was changed to a foam extrudate after CO<sub>2</sub> treatment, which improved the milling efficiency of the polymer samples.

Carbon dioxide also acted as a plasticizer under subcritical conditions in the case of solid dispersions containing itraconazole and PVP-VA 64 10% and 40% w/w. Again, the morphology was converted to a foam extrudate after CO<sub>2</sub> treatment, which resulted in an increased specific surface area, porosity and hygroscopicity. As a consequence, milling efficiency of the extrudates was improved and dissolution rate could be impacted. Similar observations were made for the itraconazole/EC 10% and 40% w/w solid dispersions.

The test compound, p-ASA is thermally labile and thermal investigation showed that the compound should be maintained between 80°C and 110°C, under atmospheric conditions and for a period of less than 10 minutes to retain adequate stability. Supercritical CO<sub>2</sub> acted as a temporary plasticizer during the hot melt extrusion of solid dispersions of p-ASA/EC (10 % w/w), allowing a reduction in processing temperature. HPLC showed that without carbon dioxide injection, approximately 17% of p-ASA decomposed, while this was less than 5% with CO<sub>2</sub> injection.

These experiments clearly showed that injecting pressurized carbon dioxide broadens the applicability of hot melt extrusion to the processing of thermally labile compounds.

## 6. Acknowledgements

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# WHY HOT MELT EXTRUSION AND QUALITY BY DESIGN ARE MADE FOR EACH OTHER - AND WHICH OBSTACLES THEY STILL HAVE TO OVERCOME IN THE PHARMACEUTICAL INDUSTRY

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## Abstract

Despite the obvious benefits of a QbD-driven drug development approach, implementation of the new paradigm has so far been slow and rudimentary in the pharmaceutical industry. Potential annual savings of 20 – 30 billion \$ were predicted by McKinsey in 2009. The author's own survey in autumn 2011 revealed, that among the companies that had adopted QbD in Europe, only 52% felt that they had gained from the approach. Even they could, however, not measure the actual return on investment (ROI) and 13% of the adopters believed that their expectations were not going to be fulfilled at all. This is directly associated with the substantial costs and complexity of applying QbD to traditional, multi-step manufacturing technologies.

In August 2011, the US FDA's "Advancing Regulatory Science at FDA – a Strategic Plan" started promoting Quality by Design and highlighted continuous processing technologies (e.g. hot melt extrusion), the use of process analytical technology and the development of new statistical approaches. Hot melt extrusion has now finally made its way into the manufacturing technologies for oral drug products after extensive use over the last decades in other industries. Establishing hot melt extrusion as a continuous manufacturing technology for oral drug products certainly still faces substantial challenges, but when 'married' to QbD, this technology will provide new opportunities for the development and manufacturing of modern dosage forms via a fully understood process, enabling improved manufacturing efficiency, and continuous, real time assessment of the process and product quality. The coupling of HME and QbD will improve the quality of drug products and thus patients' safety by a process amendable to continuous improvement throughout product lifecycle.

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## Keywords

*Continuous processing, control strategy, design space, hot melt extrusion, quality by design, return on investment (ROI).*

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## 1. The state of the pharmaceutical industry today

The dilemma of today's pharmaceutical industry is quite obvious.

Consistent cuts by the health care providers in the budgets for drug reimbursement, imposed fixed prices and maximum treatment costs, large discounts and discounted contracts enforced on the pharmaceutical companies, and the legal obligation of hospitals, physicians and pharmacists to constantly lower expenditure for drugs have finally caused a stagnation of profits and profit growth for the pharmaceutical industry.

Generic companies compete with proprietary companies gaining advantage from their higher efficiency in the production of these drug products compared to the originator itself. Additionally most of the big proprietary companies have not been able to maintain their product pipeline at the same level as in the past and therefore can not compensate the financial losses of expiring patents of block busters by the introduction of new, potential block buster products.

The development of new drug compounds and drug products is a long, expensive and highly regulated process and traditionally prone to high failure rates during the 4 to 8 years it takes to bring one new drug compound onto the market. Out of 100 drug compounds that go into phase I development (first in human studies) only 1 compound will actually obtain approval to be marketed as a new drug product. Drop out rates are even higher at the preclinical stage, when less than 1% of all screened compounds makes it successfully through the preclinical Good Laboratory Practice (GLP) toxicity phase [1]. Therefore, the number of new drug products that were submitted and obtained regulatory approval has dropped consistently over the last 15 years as the pipelines of most companies are depleted. This drop in the number of submitted New Molecule Entities per year was so dramatic that the US FDA, as the biggest regulatory authority, openly expressed its concern about the future shortage of new drugs. While 45 New Drug Applications (NDA) were submitted in 1996, only 22 were submitted in 2002 and the number for all submitted NDAs and Biological Applications together for 2010 was down again to 23 from a high of 38 in 2005 [2].

Development costs for a new drug product are also immense and often exceed 1 billion US\$ [3] for a new drug in a chronic indication. The company needs to cover these costs by the large profits it makes from the few successfully authorised products while these are protected by intellectual property rights and thus free from generic competition and price reductions. Due to the high competitiveness and complexity of the modern pharmaceutical markets superior competitiveness really means being able to demonstrate superior differentiation at superior cost efficiency and doing so sustainably in a constantly changing "macro-environment" [4].

The perceived value proposition of the product, i.e. the drug compound in its specific application form, its dosage form and its packaging will be different for each customer in the pharmaceutical business, and strongly influenced by their role in the buying transaction and their use of the product. For example :

- National health authorities: seek excellence of marketed drug products in terms of efficacy and safety for patients and require high quality of conformity and consistency.
- Health care systems: seek maximisation of the perceived value at the lowest possible price position for a specific product as compared to alternative treatment options.
- Physicians, hospitals, (pharmacies): seek efficacious and safe treatment for their patients at reduced resources to do so; thereby reducing their own service costs or increasing their service efficiency.
- Patients: seek product excellence, i.e. efficacious, safe drugs that are convenient, easy to use, and allow them to maximise quality of life [5].

## 2. The new paradigm in the pharmaceutical industry - Quality by Design (QbD)

Despite the immense development costs and stringent regulatory requirements for the production and quality control of drug products there is still a high rate of failure in both the development of new drugs and even the manufacturing of market supplies for approved drug products. In 2007 the average batch rejection rate in the pharmaceutical industry ranged around 6.7% corresponding to 3s. [6] This means that 6.7% of all manufactured batches did not fulfil the defined quality criteria as they showed either deviations during analytical testing or could not be manufactured at the required process conditions. In other words, as F. Erni explained it during a conference in London, “a failure rate of just 1% (0.7% corresponds to 4s!) means that there would be 2 unsafe landings every day at London Heathrow or 6 hours of unsafe drinking water every month!” [6]

This highlights the other dilemma of R&D in the pharmaceutical industry quite strikingly – despite the high costs spent during the development, the immense quality systems in place, and the high regulatory burden during the development and manufacturing of drug products, the outcome still lags behind the standards of other industries. The lack of consistent quality and reliability common in commercial scale drug manufacturing highlights the inadequate investigation of the impact of material attributes and process parameters on the relevant drug product attributes during the product development stages. While many scientific investigations are carried out most of them fail to provide relevant criteria to ensure consistent quality performance during manufacturing throughout a product’s life cycle. This results in batch failures or low yields as a consequence of system immanent variability and changes in these systems during a product’s life cycle.

The new paradigm of Quality by Design was thus created to emphasize that quality must be built in, it cannot be improved by additional testing and inspection alone [7]. This can be achieved by better utilization of modern science throughout product lifecycle management, with the implementation of Quality Risk Management (QRM) a key enabler, Pharmaceutical Quality System (PQS), and appropriate Knowledge Management (KM). Therefore, QbD can be summarised as an integrated approach to development, manufacturing and quality - for both the industry and the regulators.

At the 2008 AAPS conference, A. Selen from the US FDA gave a description of quality with patients being at the heart of the concept (8), describing quality as... [8]

- Products: which are designed to meet intended use and consistently deliver the desired/intended dose.
- Manufacturing processes: designed to consistently meet product critical quality attributes and suitable for continuous monitoring and updates, and allow for consistent quality over time (life cycle).
- Understanding the main sources of variability associated with starting materials and processes, due to methodology and assumptions, product-patient interface and the patient his or herself.

Although QbD was rolled out by the authorities mainly to increase their value proposition of new drug products and to foster increased value for patients, the different needs and expectations from the other members of the buyer circle also need to be considered when evaluating the competitive advantage QbD can generate via superior product quality.

In 2009 M. Lösch from McKinsey published an article discussing the benefits of QbD and its potential to generate substantial cost savings for CMC (Chemistry, Manufacturing, Controls) activities during development, which "account for 15 to 30% of overall R&D expenditures" [9]. Translating this to the published development costs of 1.2 billion \$ per NDA this represents approximately 180 – 360 million \$ alone for each new drug product on the market – without considering the number of candidates that failed to make it to the market. He further claims that optimised practises in this area "would reduce COGS (Cost of Goods Sold) by 10 to 20%, which could deliver \$15 billion to \$25 billion of annual savings on the industry's \$145 billion to \$166 billion COGS". In addition to value gained through operational efficiency, companies can find value in reducing compliance remediation costs and improving product development-enabled sales, such as novel dosage forms or line extensions." Improved CMC activities as directed by QbD can, in his opinion, also "increase revenue by ensuring smooth scale-up and product launch, and make it easier for companies to create differentiated products" [8].

Furthermore companies can also build up a competitive advantage by implementing QbD at the very start of development and by expanding the use of QbD elements and tools for a QbD-driven CMC development as clinical development progresses. This allows the increasing efforts and resources needed for QbD to be aligned with

an increased probability of clinical success. The author thus proposes in Table 1 a schedule for maximising the benefits of QbD while at the same time limiting the costs, building up profitability and sustainable profit growth for the development of drug products. In alignment with the proposal of the ICH Q-IWG Integrated Training Programme as to the set up of a QbD driven development this stepwise approach may facilitate the roll out and make it more attractive also for smaller companies with limited resources, while not compromising on its benefits [10].

*Table 1. QbD-driven development – how QbD can evolve and grow over the course of development by a stepwise use of tools which avoids expensive front loading and is thus applicable for both innovators, generic companies, and contract manufacturers (CMOs).*

<b>Development Phase</b>	<b>Essential QbD Elements according to a Minimalism approach</b>	<b>Major Intent / Pursued Benefit</b>
Pre-clinical	QTTP, QRM	Maximise exposure at acceptable tolerability
Phase I	as above + CQAs, Control Strategy	Optimised bioavailability and tolerability for volunteers; no impediment of outcome by instability
Phase IIa	as above + CPP, CMA, Knowledge Management	Understand impact of material attributes and major process parameters
Phase IIb	as above + DOE, PAT, Design Space, PQS	Establish multivariate & multidimensional design space; understand robustness of performance and manufacturing process
Phase III	as above + transfer design space to scale-up, (RTRT), Design validation	Determine validity and transfer leanings to larger scale and final process location
Validation	as above + validation conformation	Understand extent of variability, sources of variability and impact on CQAs
Transfer to Commercial Production	as above + Validation verification, Continual Improvement	Establish capable process and determine opportunities for optimisations within Design Space, starting Continual Improvement and life cycle management

*QTTP = Quality Target Profile, CQA = critical Quality Attribute, CPP = Critical Process Parameter, CMA = Critical Material Attribute, DOE = Design of Experiment, PAT = Process Analytical Technology, RTRT = Real Time Release Testing.*

A strong business case for QbD emerges with substantial savings for the industry without tangible increases in the costs or timelines for the development of new drug products. A similar finding was also stated for the ROI of QbD during a joint FDA and EMEA Workshop on QbD [11]. This claims that a reduction of Cost of Goods Sold (COGS) and capital expense, increased technical development productivity, improved quality (and lower risk), and increased sales can account for up to US\$20 - \$30 billion of profit growth for the industry.

### 3. The state of adoption of QbD in the summer of 2011

To further investigate the current status of the roll out of QbD throughout the pharmaceutical industry, I started a survey using a questionnaire with 12 questions as to the current status of QbD, the different approaches pursued for the roll-out of a QbD-driven development approach and the experiences made to date, including problems, benefits, and future returns expected from this shift of paradigm in various pharmaceutical companies [12].

The survey was posted at [www.zommerang.com](http://www.zommerang.com) [13] with a link to the survey provided in the discussion forum of the Quality by Design Group on LinkedIn [14]. The survey was also emailed directly to colleagues in the pharmaceutical industry. Completion of the on-line survey could be done anonymously and was open from August 2011 to November 2011. A total of 39 of completed surveys were analysed together by combining both versions of the questionnaire and adjusting the calculation of responses for the slight differences between both versions.

Out of 39 companies, including innovators and CROs, manufacturing either small molecules (SMOLs) or biopharmaceuticals, and in some cases medical devices, 31 companies had actually adopted the paradigm of QbD – although the extent of QbD implementation varied between individual companies. As depicted in Figure 1, adopters were not exclusively those in SMOLs and even most of the CROs had rolled-out QbD - at least to some extent!

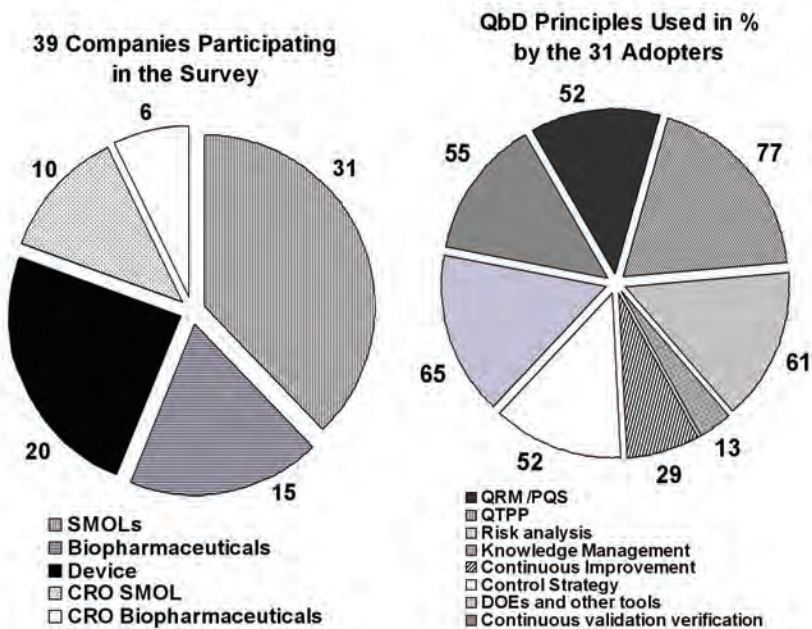


Figure 1. Survey on the state of QbD adoption in summer 2011: Analysis of the answers to the questions: Who participated in the survey and who has rolled out QbD in the 31 adopters out of the 39 responders?

However, Figure 1 shows that the extent of the roll-out differed considerably between the companies. While the majority of adopters had implemented the use of QTPPs (77%), Design of Experiments and other tools (65%) or risk analysis (61%) during development, only very few had actually implemented Continuous Improvement (CI =29%) and Knowledge Management (13%) which are essential parts of a robust PQS and one of the key enablers of QbD.

When asked how the QbD initiative had been started within the corporation it is clear that pharmaceutical development or other departments within the technical or CMC development area were key promoters of the QbD in the majority of all cases.

Altogether, it would appear that in most companies QbD is rolled-out without an integrated, cross functional system approach, and often lacks the active participation of senior management to promote the paradigm shift. In most cases the roll-out is driven by the scientific desire of the concerned functions, and lack management commitment and the integration into the existing quality systems and other corporate programmes. This also explains why certain elements of QbD, in particular those that are associated with integrated systems such as QRM, and PQS with its KM and CI, are noticeably absent from many of the roll-outs.

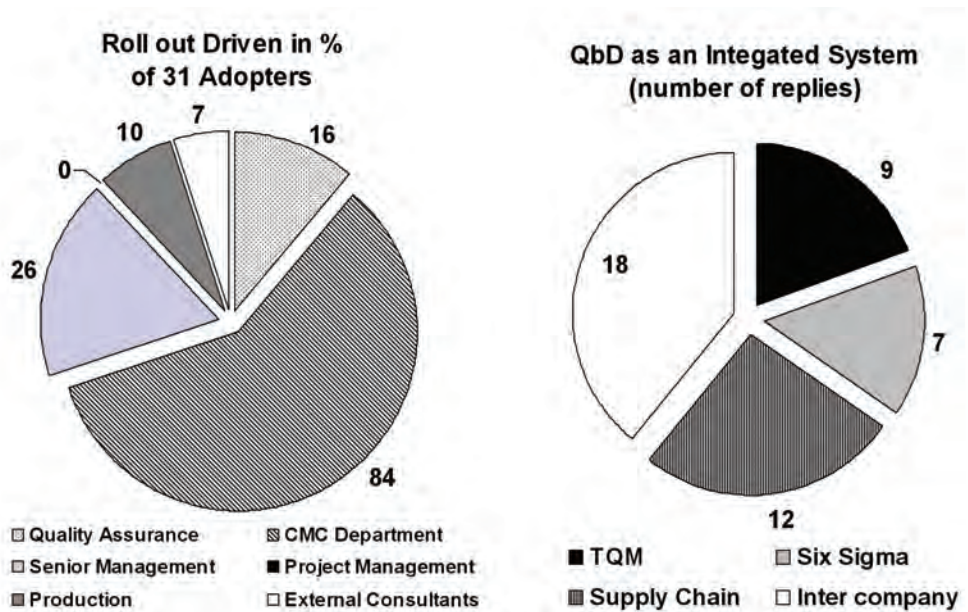


Figure 2. Survey on the state of QbD adoption in summer 2011: Analysis of the answers to the questions: Who have been the drivers of the roll out and how much is QbD integrated within the organisation?

Pursuing QbD as an integrated approach is essential to fully benefit from it, but this then also needs to include the complete supply chain, including suppliers of raw materials, contract research organisations or manufacturers to which all or part of the manufacturing has been outsourced and of course all internal functions of the supply chain starting at R&D through to the commercial scale production of drug products. However, only 12 responses out of 31 adopters of QbD stated to have included their suppliers and CROs/CMOs into this approach and not all of them having included both. Internal integration of the value chain functions and supporting functions has been achieved at a wider extent according to 18 positive responses, but this is still often limited to the technical development functions (4x) and/or production (3x).

Question 7 of the survey focused on the reasons for QbD implementation, i.e. what benefits the company hoped to obtain in doing so. As Figure 3 demonstrates, most companies rolled-out QbD to either improve the quality of their drug products, which are going to be marketed (> 50%), and/or to receive regulatory benefits in return for providing additional information derived from the QbD approach in the dossier (> 25%), and/or to increase the success rate of projects either during development or during filing.

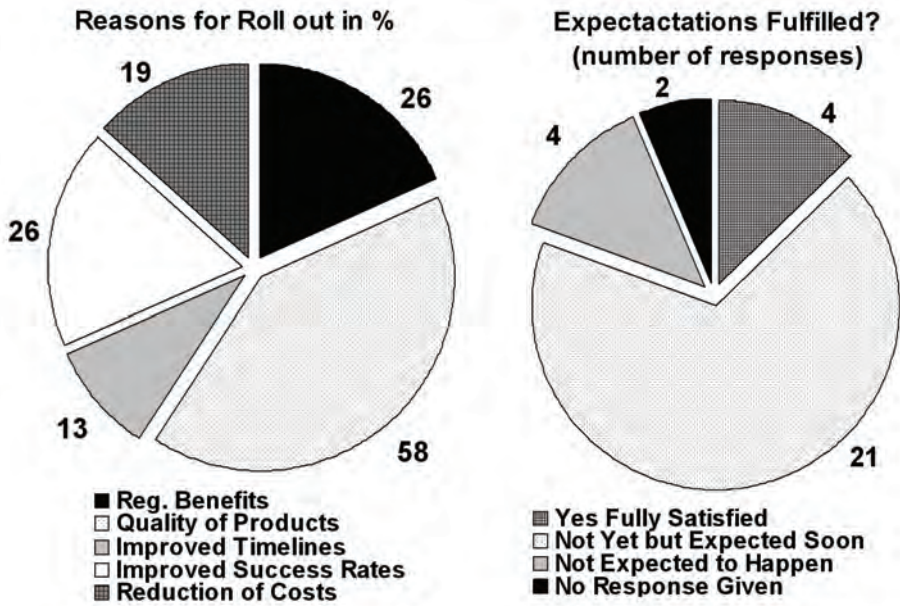


Figure 3. Survey on the state of QbD adoption in summer 2011: Analysis of the answers to the questions: What were the reasons for the roll out of QbD and have these expectations been fulfilled?

The huge potential of QbD to actually reduce development timelines, improve success rates and reduce costs in development and production were important factors in the decision to adopt a QbD-driven development strategy in 58% of respondents, although these factors were by no means the main drivers.

When asked whether their expectations from the roll-out of QbD had been fulfilled, the huge majority stated that they still expected this to happen within the next 1-2 years, though obviously the type of expectations differed depending on the motivations for the initial roll-out. Only for 4 out of 31 adopters actually considered the QbD approach to be a full success fulfilling their expectations. Another 2 companies reported full satisfaction with the achieved improvements in the quality of their drug products but they were still waiting for cost reductions and regulatory benefits to materialise. Surprisingly, some of these fully satisfied responses came from companies which focus on generic drug products, device/combination product development, contract development or biopharmaceutical product development and often appear to be most hesitant to adopt the QbD philosophy because of the increased costs and resources required.

However, all of the satisfied companies shared a common feature; they had all implemented PQS, QRM, Control Strategy, the new validation approach and in one case even a formal Knowledge Management system. Obviously it is this degree of integration which enables companies to fully benefit from the new approach and see their expectations fulfilled, while others are still struggling to see the benefits over the costs and resources needed to roll-out QbD.

In summary, four major hurdles to seeing the full return on the investment (ROI) from the roll-out of QbD were identified.

- Lack of integration into the company's structure and culture = internal mindset is missing.
- Lack of economic drivers for implementation = high initial costs.
- Majority of adopters see no immediate payback for costs faced by the roll-out of QbD = regulatory benefits not received due to still substantial deficiencies in QbD applications at the regulatory authorities.
- Minority of adopters perceive actual ROI but still can not measure it = missing metrics to calculate ROI.

Clearly, there is still substantial work needed to resolve these obstacles and more successful models of QbD adaptation are needed to promote a further spread of this initiative throughout the industry. None of the survey responders had tried to combine the QbD approach with the paradigm of Minimalism [15], which describes focussing on the most critical and thus most important activities at a time. A better understanding of the relationship between the implementation of QbD, development cost reduction and improved success rate is highly desirable and has been approached but still remains poorly understood.

The basic principle of “Doing the Right Things at the Right Time Right” can however be strongly supportive of QbD as it enables companies to achieve customer delight via excellent quality and at the same time delivers cost reduction - by reduced drug manufacturing costs and by overall cost reduction for R&D when product development success rates increase.

#### **4. Hot Melt Extrusion (HME) – a manufacturing technology for the 21st century**

The findings of the survey highlight many issues that industry needs to tackle, and technologies like Hot Melt Extrusion may provide answers to some of the challenges.

Traditional pharmaceutical manufacturing processes consist of many steps, which are interlinked but can not be controlled as a single unit operation i.e. they were not designed for QbD and therefore struggle with this approach. Design of experiment (DoE) for such processes requires a large number of separate batches and huge quantities of API resulting in substantial costs and increased time and material for statistical investigations of quality attributes and process parameters. This is hard to justify in front of tight budgets!

Continuous manufacturing processes are made for continuous process control, they adapt easily to QbD and DOE investigations can be made by changing input parameters within the same run! This makes the application of QbD tools easy. HME as a continuous manufacturing process provides not only major technological advantages but is actually very favourable to a QbD approach. Thereby, quality can be improved and consistently met while reducing the investments needed (time, costs, etc...); this enables maximisation of the ROI providing an economically convincing argument.

Beyond the ideal fit with a QbD driven development, HME also provides further opportunities, such as...

- Use of other excipients as compared to conventional processes may assist in avoiding patent infringement.
- New opportunities for life-cycle management and prolongation of a product's patent protection.
- Anti-counterfeiting by "difficult to copy" images and shapes via HME and specific downstream processing (e.g. mould injection).
- Novel dosage forms can be manufactured directly after compounding when combining the extruder with suitable downstream equipment (e.g. Extrudetten).
- Reduced manufacturing costs for a single step, well controlled process.

- Continuous manufacturing with greatly improved potential for process monitoring and control (online or inline PAT, feed forward and backward controls).
- Improved dissolution and oral bioavailability for poorly soluble compounds.
- Improved stability of amorphous compounds embedded in polymer matrices: choice of formulation and control of process parameters.
- Design of sophisticated (sustained or controlled) release profiles
- Transient excipients, e.g. supercritical CO<sub>2</sub> can be incorporated temporarily during the process and removed at the end.
- Online reactions can be triggered during extrusion (e.g. change of salt or modification).
- Dosage forms showing abuse deterrence and reduced risk of mis-administration.

However, despite these numerous advantages there are still also many obstacles and persistent prejudices which need to be addressed adequately if HME is going to become a standard technology for the future.

- “Intellectual Property” landscape is rather complex and many people are afraid that there is no freedom to operate.
- Lack of pharmaceutically qualified and suitable downstream processing equipment.
- Manufacturers of extruders and downstream equipment are still in the process of getting used to working with pharmacists and their rather different expectations from the supplier of machines.
- Most production sites still do not have a good understanding of the HME process – let alone commercial scale equipment installed.
- HME is still considered as an exploratory technology or a technology of last resorts – to be employed only if nothing else works.
- Limited number of suitable carriers for HME (ie. approved in oral dosage forms or having GRAS status); required quantities in the formulation may exceed maximum daily intakes and previously approved quantities.
- Continuous processing does require a different approach and controls to ensure product quality during processing, which deviates significantly compared with traditional pharmaceutical processes and controls.

This is where HME greatly benefits from a QbD driven approach to development and manufacturing of pharmaceutical dosage forms. The following case study shows how this symbiosis of HME and QbD could be exploited for the development and manufacturing a pharmaceutical dosage form. This example also aims to demonstrate how the principles of a simplified QbD approach can be applied to HME following the proposed scheme of Table 1.

#### 4. HME and QbD combined

A hypothetical case study is applied to the development of “Product Capsule X” manufactured via a hot melt extrusion process which serves to demonstrate how amendable HME is for such a systematic, science-based methodology.

The requirements which Capsule X is supposed to comply with are summarised in a task list which also builds the initial QTPP when translated into specific requirements: A solid oral dosage form (capsule) for 3 dose strengths of very low doses of 250 µg, 500 µg and 1000 µg with identical, relative composition and the same capsule size for all 3 dose strengths is desired. Differentiation between dose strengths only via capsule colour of small capsules to assists ingestion (compliance). Drug release is immediate and capsules can be stored at room temperature (zone I and II), having a shelf life of at least 2 years, thereby exhibiting a stable drug product despite instability of drug compound = sensitive to hydrolysis and prone to oxidation and starting decomposition at  $\geq 100^{\circ}\text{C}$ .

Such a QTPP is summarised in Table 2 and needed at the very start of any development activities, but can evolve throughout a product’s life-cycle, whenever there is new knowledge available as to patients’ needs or the availability of new requests or technologies.

Table 2. Initial QTPP for Capsule X.

Dosage form and dose strength	Immediate release capsule with 250µg, 500µg or 1000µg API X as extrudate pellets filled into capsules at different fill weights to provide the same relative composition for all dose strengths
Specifications to ensure safety and efficacy throughout shelf life	Assay Uniformity of Dosage Unit (Content Uniformity) Dissolution and Disintegration Purity and degradation Water content
Description and mechanical robustness of dosage form	Robust capsule with sufficient mechanical stability during transportation and handling; reduced rigidity despite low water content of capsule shell
Appearance	Capsules of colour A, B, C , capsule size 4 to assist ingestion and compliance; Total fill weight of pellets at 1000µg drug substance X is 100 mg;

Based on the information available on the drug substance and the prior knowledge on hot melt extrusion processes it appears feasible to achieve the QTPP via a dosage form of hard capsules, filled with pellets cut from HME extrudates. However, during the initial risk analysis and screening of dosage forms it is then confirmed that the drug substance X needs to be present as a crystalline suspension in the polymer matrix to ensure chemical stability.

As a next step the CQAs need to be defined as linked to the patient interface = Efficacy, Safety, and Compliance.

CQAs are initially determined based on Prior Knowledge but also may evolve during further development! This needs to be kept in mind when selecting the composition and the manufacturing process for this drug product. The initial risk analysis for the selected manufacturing process is then made to identify the impact of material attributes and process steps on the CQAs of Capsule X as depicted in Figure 4, which categorises all process steps and materials either into critical, potentially critical or uncritical with regard to the agreed specifications for the CQAs. Due to the relevance of assay, uniformity of dosage unit, water content, crystallinity of the drug substance, and chemical stability after storage for the patient interface the further discussion of the case focuses on these as most important CQAs. As visible from Figure 4 the hot melt extrusion process is believed to exhibit quite significant risks with respect to the CQAs, which need appropriate mitigation before reaching an acceptable risk level. In particular, the CQAs associated with the manufacturing process, processing conditions and parameters which affect dosage form homogeneity and stability of the drug compound. The drug compound needs to be embedded in the polymer matrix as suspended crystals in order to protect it from oxidative degradation. Additionally, water content and processing conditions need to be optimised to avoid hydrolytic or thermal decomposition.

CQA	Drug Substance			Excipients Type, amount, material attributes	Manufacturing Process				
	Purity	PSD	Water Content		Blend 1+2	HME	Pellets	Capsules	Packaging
In-vivo availability						■			
Dissolution									
Disintegration									
Assay									
Related substances	■								
Uniformity of dosage unit									
Water content									
Drug substance crystallinity						■			
Mechanical capsule stability									
Storage stability chemical	■					■			
Storage stability physical						■			

Figure 4. Initial Risk analysis to evaluate impact of manufacturing steps on CQAs using prior knowledge; ■ = high risk; ■ = medium risk; □ = low or no risk.

The description and composition of the drug product as presented in module 3.2.P.2.1 of the CTD is summarised in Table 3 for all 3 dose strengths.

Table 3. Composition of Capsules X, 250µg, 500 µg and 1000µg.

Function	Specification	Name	Capsule Filling	Capsule X 250µg	Capsule X 500µg	Capsule X 1000µg
			%	Quantity in mg		
Active Ingredient	Separate specification	x	1.0	0.250	0.500	1.000
Polymer	EP, NF	Basic Butylated Methacrylate Copolymer	72.5	18.125	36.250	72.500
Plasticizer	EP, NF + PSD	Stearic Acid	10.0	2.500	5.000	10.000
Inert filler	EP, NF + PSD	Calcium phosphate	10.0	2.500	5.000	10.000
Antioxidant	EP, NF	Butylated hydroxytoluene	0.5	0.125	0.250	0.500
Lubricant	EP, NF + PSD	lubricant	5.0	1.250	2.500	5.000
Total	EP, USP		100.0	25.000	50.000	100.000
Capsule shell size 4	EP, NF + water content	Hypromellose Colouring agent A Colouring agent B Colouring agent C		x	x	x

Following the risk assessment, the composition of the extrudate is based on a suspension of the drug substance in Eudragit EPO, which is plasticised to allow processing at low temperatures. Antioxidant is added to protect the drug substance from oxidation during processing and storage and calcium phosphate is used as an insoluble filler. Extrudate pellets are then filled into HPMC capsules, which can be processed under low humidity conditions without increased brittleness and have a lower water content than gelatine capsules.

The Manufacturing Process Development as presented in module 3.2.P.2.3 of the CTD focuses on the determination of the CPPs and their impact on the CQAs for the individual process steps. Scientific investigations (simulations, modelling, DOEs, PAT,...) are proposed for all process parameters to generate scientific knowledge and process understanding and include the investigation of interactions between material attributes and CPPs. If appropriate, a Design Space can be defined for all parameters and attributes. The control space within the design space has to be defined with a sufficiently high probability to ensure that all CQAs can be met consistently. The generated model then needs to be verified to demonstrate the validity of the established Knowledge Space, Design Space und Control Space also for later scale up steps and technology transfers. Thereby this phase of development essentially also defines Stage I of the process validation (= Process Design) according to the latest validation guidance of the US FDA [16]. The flow chart of the selected manufacturing process of Capsule X is depicted in Figure 5, while more details on the specifics of the HME step are described in Figure 6.

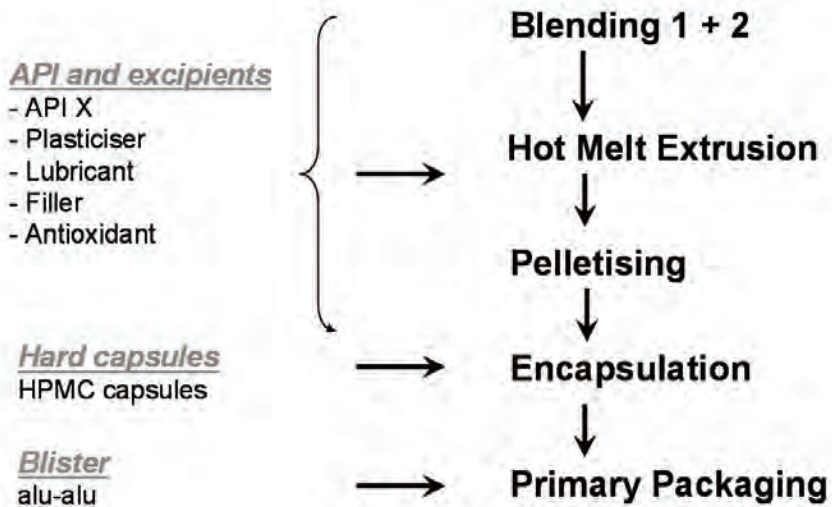


Figure 5. Manufacturing process – flow chart summary.

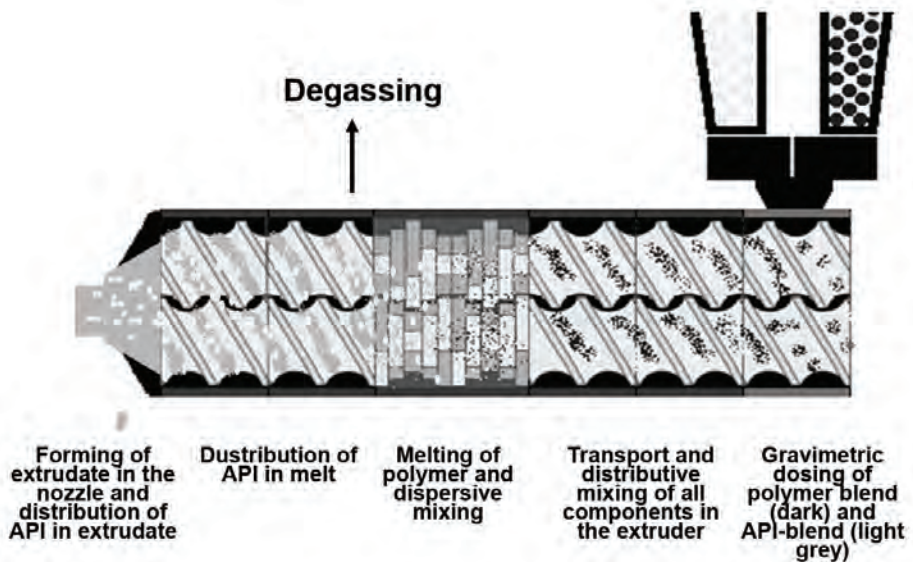


Figure 6. Schematic depiction of extrusion process for crystalline API dispersed in polymer matrix with split feeding of polymer blend and API blend via separate gravimetric dosing.

The extrusion step itself can be described as five separate phases of material transformation inside the extruder, which are specific for the very process and product and thereby also determine the impact of each phase on the critical quality attributes.

Dosing of the polymer blend and API blend are done by separate gravimetric dosing to avoid segregation of the powder blend and aid content uniformity of the 1% active in the formulation. The API and antioxidant are blended with the inert filler and dosed, while polymer is dosed as a blend with the plasticizer and lubricant.

Initially both blends are mixed in the extruder by distributive mixing during transport into the melting zone, where intensive mixing and melting of the polymer results in a melt with the API dispersed in its crystalline form. Melting or dissolution of the API in the polymer needs to be avoided by the process configuration and extrusion parameters. The melt suspension is further mixed, degassed to remove potentially destabilising moisture from the product and then transported into the nozzle, where a strand of homogeneous dimensions needs to be formed and discharged from the nozzle at a constant speed in order to enable downstream cutting to result in equally sized extrudate pellets of 2 mm depicted in Figure 7.

The CPPs and their interactions with material attributes need to be investigated together for all manufacturing steps as proposed in Table 4. How this can be broken down further into the five phases inside the extruder for the HME process is outlined in Figure 8.

Linking the CPPs to the CQAs allows differentiation between really critical parameters, posing the risk of negatively impacting efficacy, safety or compliance, and other risks, which are not critical to the quality and can thus be adjusted according to process requirements.

CQAs, CPPs and the risks of the individual HME “process phases” in Figure 8 demonstrate how to break down a complex process into individual steps and correlating the various categories of process parameters with the criticality of the process and its impact on the CQAs.

Table 4. CPPs of the manufacturing process steps of Capsule X.

Process	Operation	Material	CPP
Process 1	Blending 1	lubricant, active pharmaceutical ingredient X, butylated hydroxytoluene	Speed, volume, time, type of blender
Process 2	Blending 2	Stearic acid, calcium phosphate, basic butylated methacrylate copolymer	Volume, time, speed
Process 3	HME	Blend 1 Blend 2	<b>Free Volume, screw design, die design, screw speed, feed rate, temperature of barrels, temperature of melt, specific thermal energy, specific mechanic energys residence time, pressure, peak temperature (hot spots), torque</b>
Process 4	Pelletisation	-	Speed, temperature
Process 5	Encapsulation	Hypromellose capsules	Speed, .....
Process 6	Packaging	Alu-alu blister (specification, size to volume ratio (head space))	Pressure, speed, die, ...

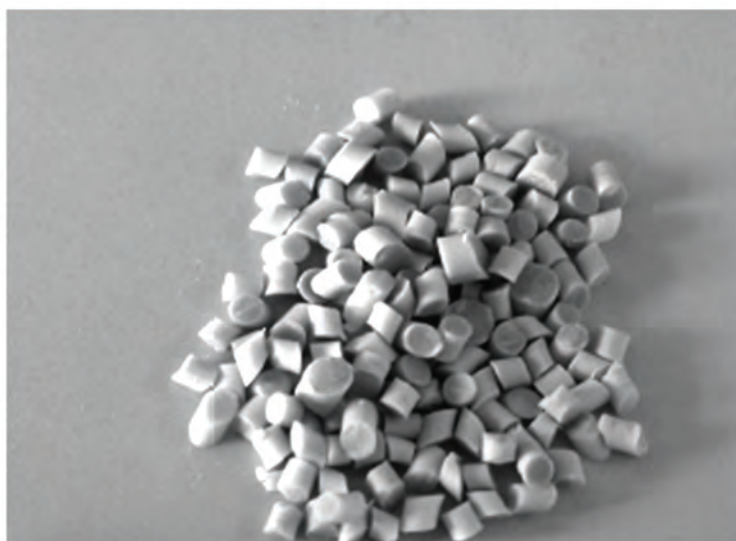


Figure 7. Extruded pellets of crystalline drug substance X, dispersed in the polymer matrix and ready for filling into capsules.

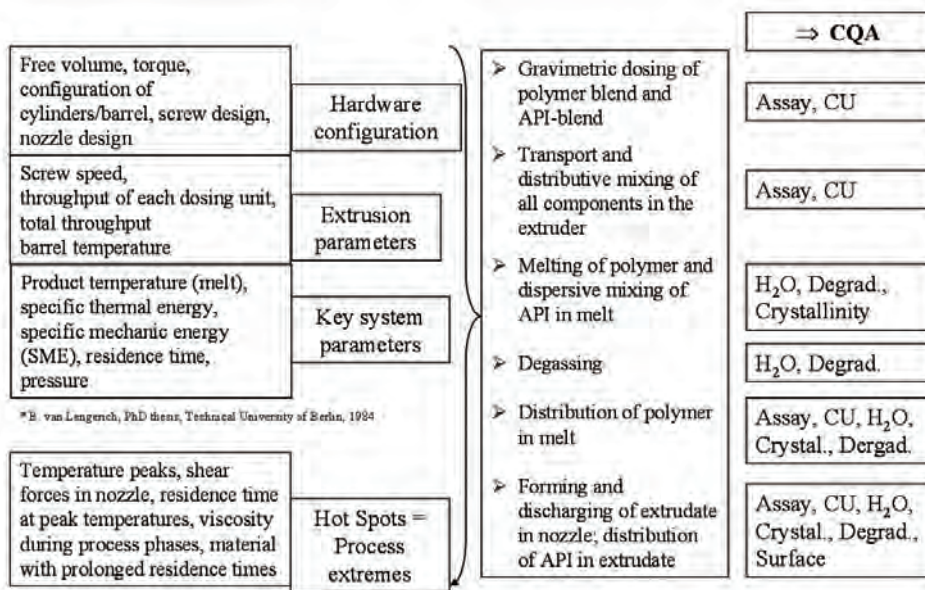


Figure 8. How to define the different types of parameters and their impact on the CQAs during hot melt extrusion.

The most critical quality attributes for Capsule X extrudate are assay, content uniformity, water content, crystallinity, purity of drug substance and surface of the extrudate. However, these are potentially impacted to a different extent during the individual phases of the extrusion process and thus need to be investigated / assured differently during these phases. While assay and content uniformity remain critical throughout the complete extrusion process, stability is closely connected to crystallinity and thus most influenced during the phase of polymer melting and distribution of drug substance in the melt. Surface appearance is not a direct attribute for the final dosage form but impacts the quality of the intermediate extrudate pellets, as uniformity of dosage units of capsules is determined by the flow properties and homogeneity of the extrudates and the cutting of these into equally sized pellets. Therefore, the shaping of and discharge of extrudate in the nozzle is the most critical phase for this quality attribute.

Hardware parameters include the configuration of the extruder and need to be adapted to the process and formulation requirements in order to allow processing of the melt at moderate temperature. This requires an extruder with high torque load and a screw design which aids distribution of the drug substance in the melt without generating excessive shear, which can negatively impact drug stability. Once the configuration has been defined this will be kept constant for the further investigation or varied deliberately in combination with parameters in order to investigate the interactions e.g. with the process parameters. The direct process parameters of the extrusion process are straight forward to identify and can be varied either in separate runs or within one run in order to investigate their impact on the CQAs. However, they are always specific to the type of extruder and its scale and size.

Much more important however are the composite process parameters, which result from the interaction of direct process parameters with the selected hardware configuration and the individual formulation. These have also been defined as “key system parameters” by Lengerich [17] since they allow a scale independent assessment and optimisation of process performance and its impact on the CQAs.

Finally, temporary hot spots exist and need to be identified for HME processing, as they may have huge impact on quality even though their occurrence may be limited to seconds. This is particularly important when investigating the impact of process parameters on crystallinity and degradation. Hot spots need to be considered and eventually eliminated by the set-up and direct process parameters or tightly controlled throughout the process.

Mitigation strategies and suitable tools (such as DOEs, PAT, modelling, simulations, etc...) can be applied to identify the CPPs. These then these need to be defined in order to ensure the integrity of CQAs.

This all needs to be part of an integrated system or governance structure and applied to the QbD systems of Design Space, Scale-up, Control Strategy, Process Validation, Knowledge Management and Continual Improvement (Figure 9)

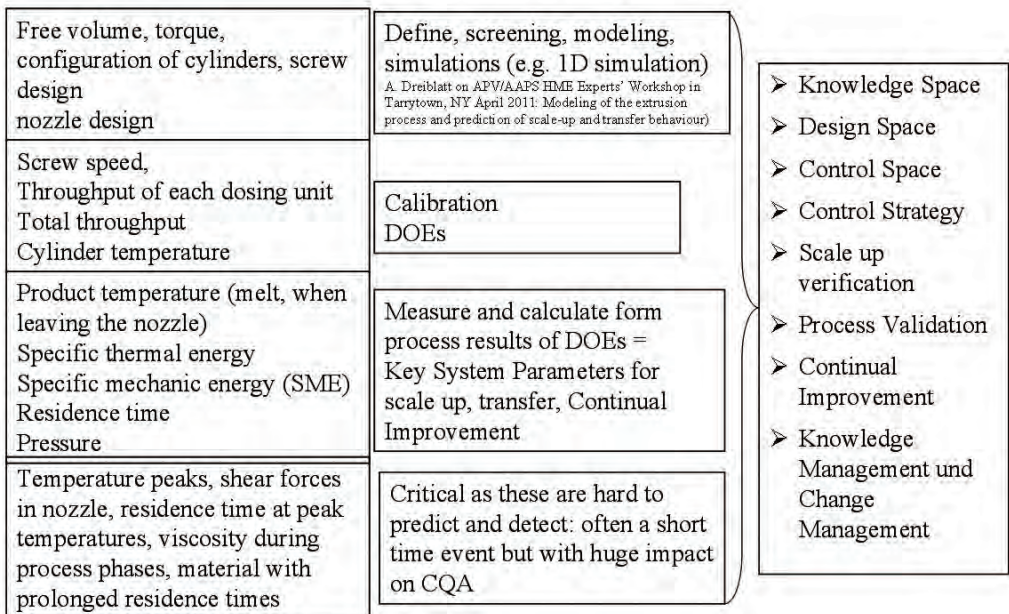


Figure 9. Investigating CPPs for hot melt extrusion within a QbD driven development Design Space for CQA: Key System Parameters are more adequate then traditional process parameters when evaluating the impact of the manufacturing process on the CQAs [18].

For Capsule X the Design Space is generated as an outcome of the investigations for the key process parameters of specific mechanical energy (SME), residence time, pressure at the nozzle and product temperature, with product temperature being the most important of these parameters. Extruder configuration and process inputs were optimised to ensure that the drug product at the nozzle does not exceed the limit of 60°C. A multidimensional Design Space (Figure 10) can be used as part of the Control Strategy and is best defined by the key system parameters and process extremes rather than the conventional extrusion parameters, as only the former two will be suitable to explain and understand the impact of the HME manufacturing process on the CQAs.

Temporary process extremes need to be investigated additionally during scale-up to verify that the established Design Space is also valid for the larger scale as to their impact on the CPPs and CQAs. However, in most cases these will eventually require continued process verification during commercial scale manufacturing, e.g by monitoring the product temperature at the nozzle during extrusion.

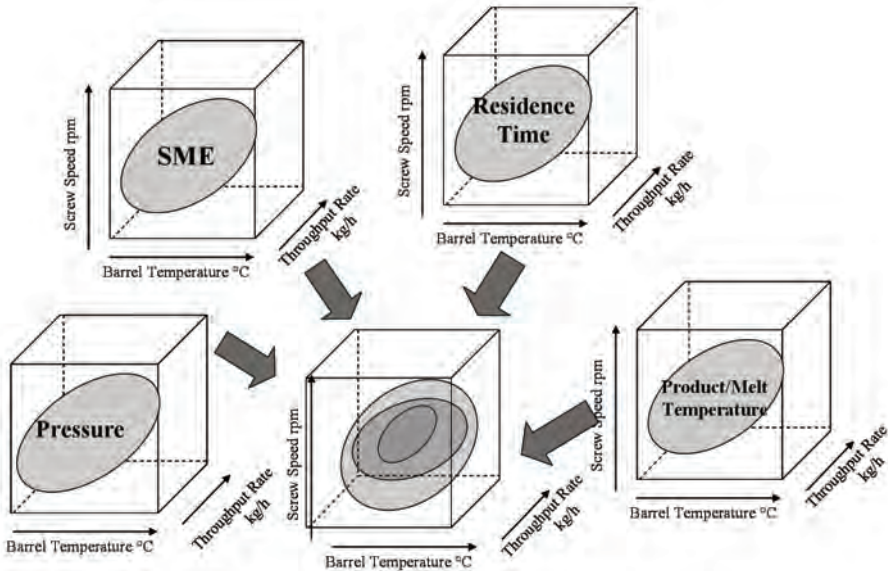


Figure 10. Generating a Design Space for the hot melt extrusion process from key system parameters.

Material specifications, product specification, Design Space, continuous process verification, PAT tools, and traditional in-process-controls are then combined to build the Control Strategy, which via an iterative risk management process ensures in its final version, that all remaining risks have been reduced to a level ensuring that the provided quality will consistently meet patients' requirement and meet all CQAs.

For Capsule X good storage stability can thus be ensured at conditions which prevent softening of polymer as this could trigger dissolution of the drug substance in the polymer followed by degradation of the dissolved drug substance (kinetically controlled dissolution of traces of drug substance triggers oxidative degradation). Therefore, monitoring of product temperature of extrudate leaving nozzle need to be part of the Control Strategy. Figure 11 summarises how the iterative risk analysis, risk mitigation steps and the resulting Control Strategy ensure that the resulting composition and manufacturing process for Capsule X does result in a product meeting CQAs consistently throughout its lifetime as demonstrated during process qualification and continued process verification [16].

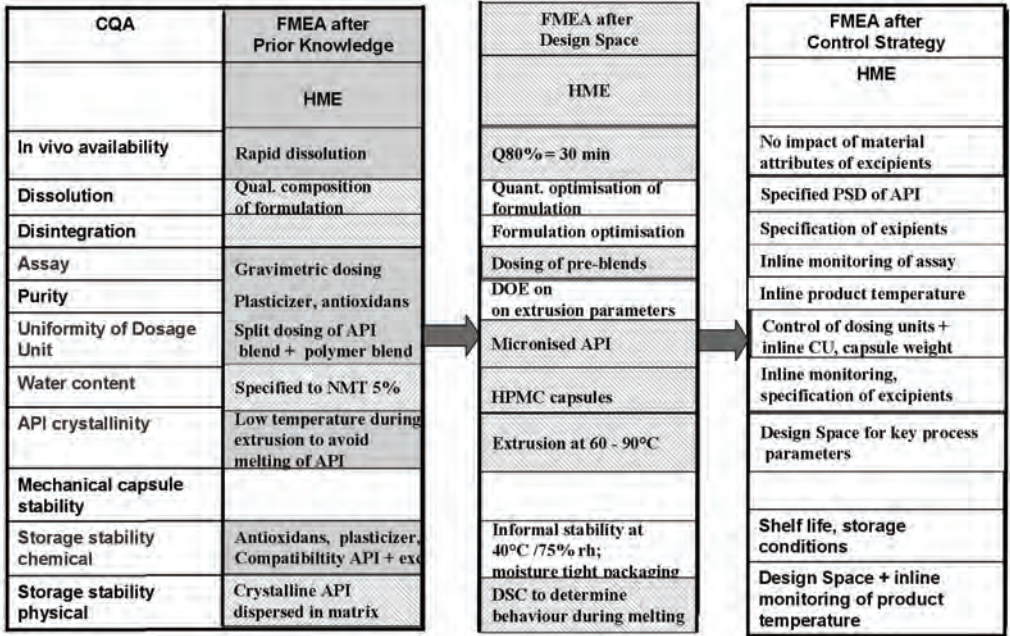


Figure 11. Iterative risk management using Failure –Mode – Effect - Analysis (FMEAs) to verify risk reduction during development and the effectiveness of the employed mitigations; high risk = dark, medium risk = stripes; low risk = no filling.

## 5. US FDA's strategic plan – can HME and QbD finally fulfil expectations?

The new approach to support the adoption of QbD is also trying to promote new manufacturing technologies, which are more amendable to the systematic development and monitoring approach, and to promote new PAT technologies and statistical tools as summarised in the FDA's strategic plan in August 2011 aiming to "Support New Approaches to Improve Product Manufacturing and Quality" [19]

In particular the agenda points of the plan are to...

- Investigate the effects of continuous manufacturing on product quality,
- Examine specific novel manufacturing technologies to determine how they impact product failure rates,
- Evaluate the role of excipient ingredients and complex dosage forms on product safety, efficacy and quality,
- Promote two state of the art manufacturing strategies – Process Analytical Technology, and Quality by Design approaches – for impact on manufacturer's ability to maintain constant quality,
- Investigate feasibility and value of using emerging and improved analytical technologies like NMR, mass spectrometry, or NIR or Raman spectroscopy for evaluating product quality of pharmaceutical agents, and evaluate whether these technologies should replace existing methods [19],

These points appear to concur that Hot Melt Extrusion and QbD fit perfectly into this concept and should therefore stand a better chance of being recognised and adopted as a modern manufacturing technology and a standard approach for development and manufacturing in the pharmaceutical industry.

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# KINETISOL™: A NOVEL PROCESS FOR THE PRODUCTION OF PHARMACEUTICAL SOLID DISPERSION SYSTEMS

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## Abstract

KinetiSol™ is a new fusion-based process that was recently developed to rapidly form solid dispersions by imparting high shear and friction forces without external heat input. KinetiSol™ enables rapid processing of heat labile APIs and polymers, since these materials are subjected to elevated temperatures for only a few seconds. No solvents or plasticizers are required for KinetiSol™, although plasticizers have been shown to function as pore formers to increase drug release rates. The absence of a plasticizer has been demonstrated to enhance solid state stability by producing solid dispersions with higher glass transition temperatures.

The KinetiSol™ process has been effective in forming amorphous molecular dispersions of APIs having melting points in excess of 200°C. Single phase systems of poorly water-soluble drugs were demonstrated to have superior dissolution rates and oral bioavailabilities when compared with similar formulations prepared by hot melt extrusion. The presence of concentration enhancing polymers in samples processed by KinetiSol™ has resulted in higher supersaturated concentrations of poorly water-soluble drugs in aqueous media. Specific targeting of drug supersaturation to the intestinal lumen has been achieved by the use of pH-dependent carrier polymers in formulations processed by KinetiSol™. Four case studies involving BCS II and BCS IV compounds are presented.

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## Keywords

*Amorphous dispersions, hot-melt extrusion, itraconazole, KinetiSol™, meloxicam supersaturation, thermal process.*

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## 1. Introduction

For pharmaceutical scientists developing a new chemical entity into a commercial dosage form, the three most difficult challenges to overcome include solubility, permeability and stability. During the past several years, hot melt extrusion has been reported in the literature by numerous scientists as a successful process to form amorphous solid dispersions of poorly water soluble drugs as a method to increase dissolution rate and provide supersaturation of the active moiety in aqueous media [1-3]. In the hot melt extrusion process, the powder blend of drug and functional excipients is introduced into a barrel containing rotating screws that convey the powder into a melt or molten mass where shear forces are imparted into the mixture, compounding the material until a homogenous mass is achieved [4]. Although this manufacturing method has many advantages over solvent based methods, drug substances are exposed to elevated temperatures for prolonged periods of time, usually between 1-2 minutes, although residence times as long as 10 minutes have also been reported [5-7]. Since many new BCS II and BCS IV compounds have a melting point in the 200°C to 300°C range, the majority of polymeric carriers employed to solubilize these moieties suffer from stability issues at these high temperatures. Therefore, processing these compounds by melt extrusion will have its limitations.

When drugs are thermally processed with polymers and other optional adjuvants there are at least three possible outcomes. The composition resulting from the process may contain crystalline drug where the drug is dispersed in the formulation. Another outcome is seen with many drug products that will contain solubilized drug where the compound melts and is miscible with the polymeric carrier in the formulation. Alternately, the drug is crystalline and dissolves in the formulation during processing. In the latter case, a molecular dispersion of the active pharmaceutical ingredient provides a thermodynamically stable or metastable amorphous solid solution which enhances the dissolution rate, and in some cases, may result in supersaturated concentrations of the poorly water soluble compound in aqueous media.

KinetiSol™ is a novel high-energy manufacturing process that has been used to prepare molecular dispersions of crystalline drugs in polymeric carriers. This new fusion-based manufacturing process utilizes a combination of frictional and shear energies to rapidly produce polymeric solid dispersions of poorly water soluble APIs. Processing times are generally less than 30 seconds and elevated temperatures above 100°C are maintained for extremely short durations, typically in the 3-10 second range. As reported in the scientific literature, KinetiSol™ has been successfully employed to produce hydrophilic solid dispersions as well as plasticizer-free solid dispersions containing temperature sensitive polymers, including both cellulosic and acrylic polymers [8-12]. The KinetiSol™ process utilizes rapidly rotating blades to impart shear and frictional energies onto processed materials within a cylindrical chamber. A rapid increase in temperature to the desired setpoint for ejection from the chamber minimizes thermal exposure to both the drug substance and the excipient materials. During processing, the temperature of the materials in the chamber is monitored in real time using a computer controlled system and the finished product

is automatically discharged when the required endpoint is reached. A photograph of a GMP Unit is seen in Figure 1.



*Figure 1. GMP Unit, Photo Courtesy of Dispersol LLC, Georgetown, Texas.*

The discharged material is rapidly collected for either post processing or for immediate processing into suitable dosage forms. The high energy of mixing with KinetiSol™ can produce homogenous systems. Processing can be achieved without a plasticizer for compositions using polymers with high glass transition temperature. Application of the technology to high melting point and/or heat sensitive compounds is also effective. DiNunzio et al have demonstrated the advantages of KinetiSol™ over HME, including the preparation of plasticizer-free solid dispersions containing temperature-sensitive polymers, such as Eudragit® L100-55 [10]. Additionally, the short residence time of the operation allows for successful processing of heat-sensitive active ingredients, as was demonstrated using the model compound hydrocortisone [12].

Like HME, the basis of KinetiSol™ was established in another industry (plastics processing) prior to its adaptation for pharmaceutical manufacturing. The viability of the KinetiSol™ process for production of pharmaceutical systems was first established at a commercial scale and then subsequently scaled down to accommodate pharmaceutical laboratory environments and to minimize active pharmaceutical ingredient consumption during formulations development. In the plastics industry, the process is operated semi-continuously, generating product outputs on the order of 1,000 kg/hr. Similar operating principles will be applied to high volume cGMP pharmaceutical manufacturing. Low volume manufacturing is currently conducted in batch mode with batches processed in rapid succession by easily removed and replaced product contact parts.

## 2. Properties of solid dispersions of DS901, a broad spectrum anti-cancer agent

DS901 has demonstrated compelling efficacy in aggressive cancer cell models. The compound is currently being targeted for colon cancer. DS901 has an aqueous solubility of less than 2 µg/mL and the solubility is independent of pH. The melting point is 295°C and efforts to solubilize this molecule using HME have been unsuccessful. The Caco-2 permeability was less than  $1 \times 10^{-6}$  cm/s, suggesting a BCS IV compound. The LogP, however, was 8.1, suggesting a BCS II. KinetiSol™ processing profiles for oral compositions, including DS901, a surfactant, dioctyl sodium sulfosuccinate (DSS) along with four different polymers, HPMCAS-LF (a), HPMCAS-MF (b), Soluplus® in combination with Eudragit® L100-55 (c) and Eudragit® L100-55 (d), are seen in Figure 2. The recovery of DS901 from all formulations exceeded 99%. The ejection temperatures utilized to obtain amorphous compositions are seen in the figure.

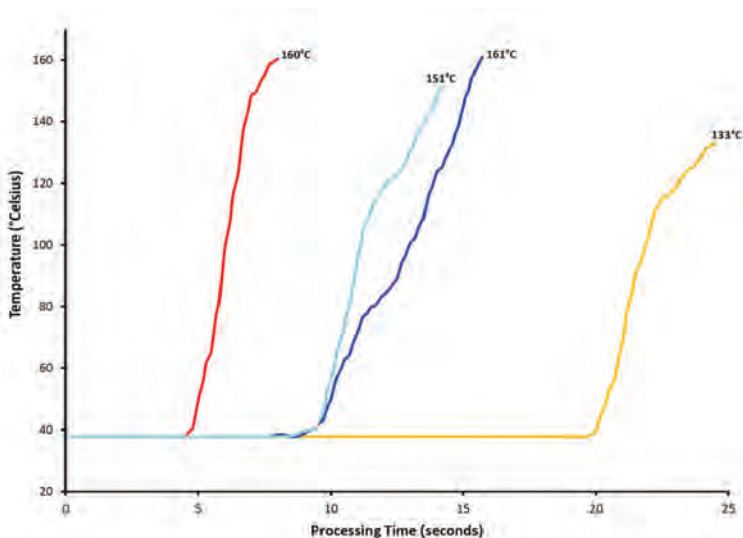


Figure 2. KinetiSol™ Processing Profiles for DS901 with four polymeric carriers.

All formulations were processed for less than 5 seconds above 100°C and all compositions resulted in molecular dispersions of the anti-cancer compound in each polymeric carrier. Dissolution data demonstrated that the composition containing DS901 and the HPMCAS-LF with the surfactant DSS, was the lead formulation [13]. When dosed at 50mg per kg in male Sprague-Dawley rats, peak blood levels were 20 times higher than the pure API. These results demonstrate that the KinetiSol™ formulations generated substantial supersaturation of DS901 in simulated intestinal fluids and substantially enhanced the oral bioavailability of DS901. Studies are ongoing to optimize the formulation prior to future studies in rats and beagle dogs.

### 3. Solid dispersions of ROA, an experimental anti-inflammatory compound

ROA is acid labile and decomposes at its melting point of 230°C. The compound is BCS II and has a solubility in simulated gastric fluid of 3 µg/mL and a solubility in FaSSIF of 7 µg/mL. Eudragit® L100-55 and HPMCAS-LF were the two polymers selected to prepare molecular dispersions of ROA. In order to understand the mechanism by which ROA degrades, studies were undertaken to evaluate its stability over a pH range of 1-11 at 60°C in aqueous buffers. The compound was found to be more stable as the pH is increased and decomposition of ROA was described by pseudo first-order kinetics [4]. The TGA profiles for individual components and compositions containing each of the enteric polymers are seen in Figure 3. ROA was found to degrade at a faster rate in the presence of the enteric polymers, indicating a strong interaction between the API and Eudragit® L100-55 and HPMCAS-LF.

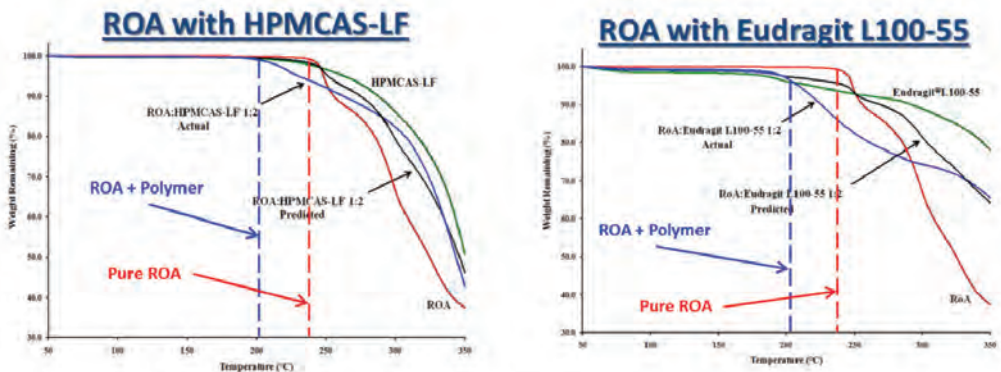


Figure 3. Thermogravimetric analysis of solid dispersions and physical mixtures containing HPMCAS-LF and Eudragit® L100-55, courtesy of reference 4.

The KinetiSol™ temperature profiles are shown in Figure 4. Both compositions were exposed to temperatures above 100°C for less than 5 seconds before being ejected from the unit and passed through chilled plates prior to collection. Hughey and co-workers demonstrated that the high frictional forces inherent in the KinetiSol™ process were effective in allowing processing at reduced temperatures while still rendering the material substantially amorphous [4].

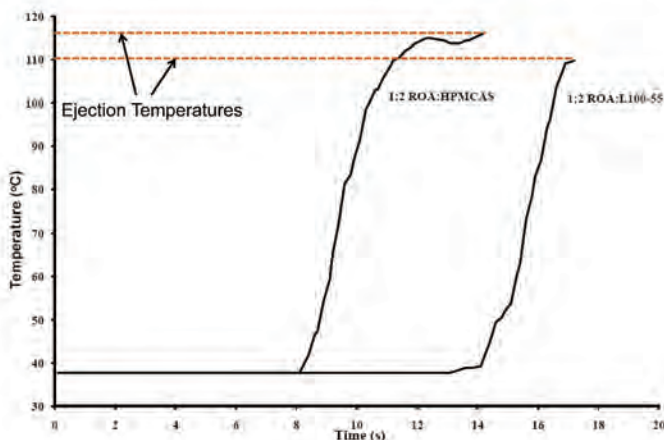


Figure 4. KinetiSol™ processing profiles demonstrating the rapid increase in temperature during the manufacture of ROA solid dispersions. [4]

The X-ray powder diffraction (XRPD) profiles for both KinetiSol™ and HME compositions, along with recoveries of the API in these compositions are seen in Figure 5. The API:HPMCAS-LF (1:2) sample processed by KinetiSol™ appeared to be amorphous and a recovery of 99.4% ROA was obtained with this processed material.

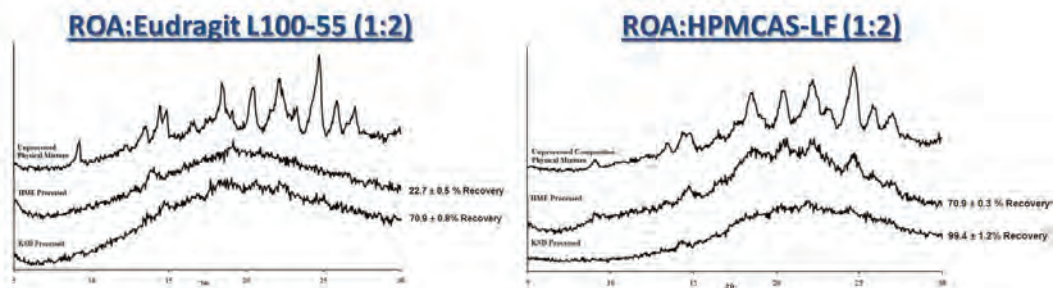


Figure 5. XRPD Analysis-KinetiSol and HME compositions, courtesy of reference 4.

Non-sink dissolution analysis of all compositions showed rapid supersaturation after pH adjustment to approximately 2-3 times the equilibrium solubility of ROA, which was maintained for at least 24 hours. The results of the study demonstrated that KinetiSol™ was an effective method of forming dissolution-enhanced amorphous solid solutions where HME was not a feasible alternative [4]. There was an improvement in ROA recovery with KinetiSol™ versus hot melt extrusion in both polymer systems.

## 4. KinetiSol™ processing of meloxicam

Meloxicam (MLX) is a nonsteroidal anti-inflammatory drug with a melting point of 270°C. It is thermally labile and has a solubility in hydrochloric acid of 0.9 µg/mL. The solubility in purified water is 12 µg/mL and the drug is classified as a BCS II compound. Hughey and co-workers reported on the properties of molecular dispersions of MLX when processed by KinetiSol™ dispersing [9]. The goals of these experiments were to identify polymeric carriers in order to produce single phase solid dispersions of MLX that were chemically stable and demonstrated enhanced dissolution rates and solubilities of the compound in aqueous media. The results of the polymer screening studies with Meloxicam and povidone (PVP), co-povidone, and Soluplus® demonstrated that MLX was most soluble in the Soluplus® systems. TGA studies with the physical blends (1:3, MLX:polymeric carrier) demonstrated that MLX decomposition occurred at temperatures greater than 40°C below the melting point of MLX, possibly due to amorphous MLX being formed in the drug:polymer blend during the experiment [Figure 6]. Degradation at temperatures lower than suggested by TGA have been reported in the literature with other drug:polymer compositions [4]. Amorphous systems prepared by hot-melt extrusion required processing temperatures at 175°C and yielded only 88% potency. Utilizing KinetiSol™ it was possible to reduce processing temperatures by 65°C and minimize residence time to lower impurity formation during production, achieving a product with over 97% potency.

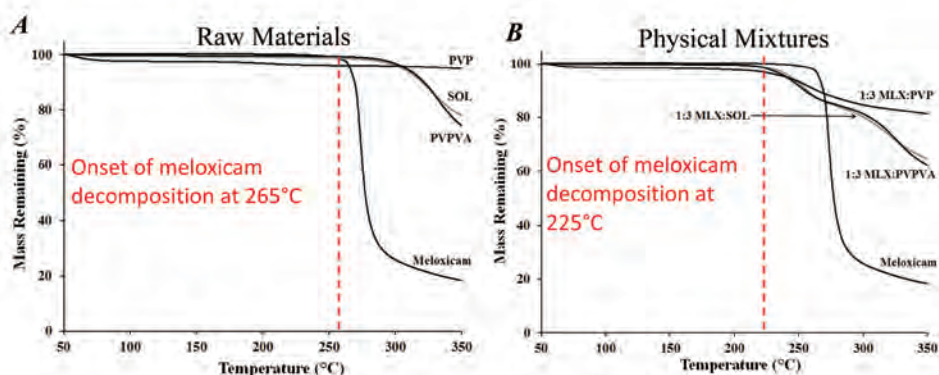


Figure 6. A. Thermogravimetric analysis of raw material and unprocessed crystalline mix (MLX). B. Thermogravimetric analysis of 1:3 physical mixtures, courtesy of reference 9.

The non-sink dissolution profiles for the KinetiSol™ composition and MLX generic tablets were compared to MLX powder and are shown in Figure 7. A significant increase in the amount of drug in solution in the KinetiSol™ solid dispersions is observed for both the acidic media and purified water [9].

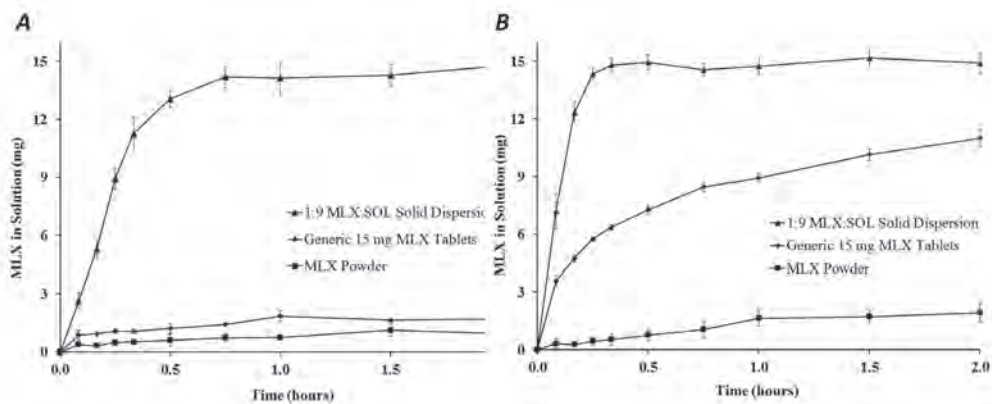


Figure 7. Non-sink dissolution analysis of KinetiSol™ composition versus generic tablet and MLX powder. USP 34 Apparatus II, Paddle speed = 50 rpm. In (A) 0.1N HCl or (B) water at 37°C, n=3, courtesy of reference 9.

## 5. Properties of molecular dispersions of itraconazole.

Itraconazole (ITZ) is a broad spectrum anti-fungal BCS II compound with a melting point of 170°C. The solubility in 0.1N HCl is approximately 4-6 µg/mL and in water is 1-4 ng/mL. Unlike the three previous compounds having melting points above 200°C and not being able to be processed by hot melt extrusion, itraconazole has a melting point of 170°C and can be processed by melt extrusion. It is a weak base that is more soluble in acid than in neutral pH, but in both media it displays extremely low solubilities. The dissolution profiles of itraconazole from Sporanox® pellets was reported by DiNunzio and co-authors and is seen in Figure 8 [8]. Miller and co-workers demonstrated that hot melt extrusion utilizing excipient carriers under appropriate extrusion conditions, deaggregated and dispersed engineered drug particles of itraconazole into an excipient matrix without altering the properties of the individual drug particles and thereby improved and modulated the dissolution properties of the engineered drug particles [1]. In a follow-up manuscript, these same authors reported supersaturated dissolution conditions for itraconazole from both IR and enteric polymers [2]. The Eudragit® L100-55 formulation exhibited substantially greater ITZ release than the HP-55 and the HP-55S formulations in both acidic and the pH 6.8 media of dissolution testing [2].

composition	$C_{max}$ (mg)	$t_{max}$ (min)	AUC <sub>dissolution</sub> (mg·min)			$t_{1/2}$ (min)
			acid	neutral	total	
Sporonox pellets	36.7 ± 1.6	120 ± 0	3023.6 ± 207.9	225.8 ± 23.1	3249.4 ± 222.6	6.7 ± 2.4

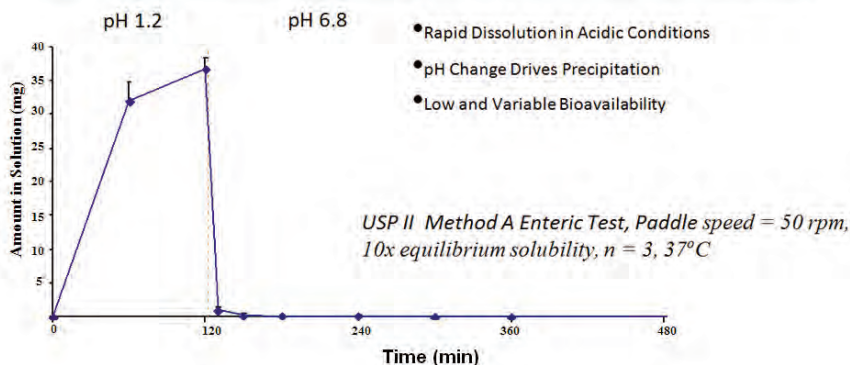


Figure 8. Dissolution properties of Sporonox® pellets, courtesy of reference 8.

More recently, DiNunzio and co-workers [11] compared KinetiSol™ processed and melt extruded itraconazole solid dispersions. As seen in Figure 9, these workers reported that the KinetiSol™ processed material provided faster *in vitro* dissolution rates in comparison to the HME processed material, which was related to a single phase system formed with KinetiSol™ versus a biphasic system seen in the DSC profile from the HME samples.

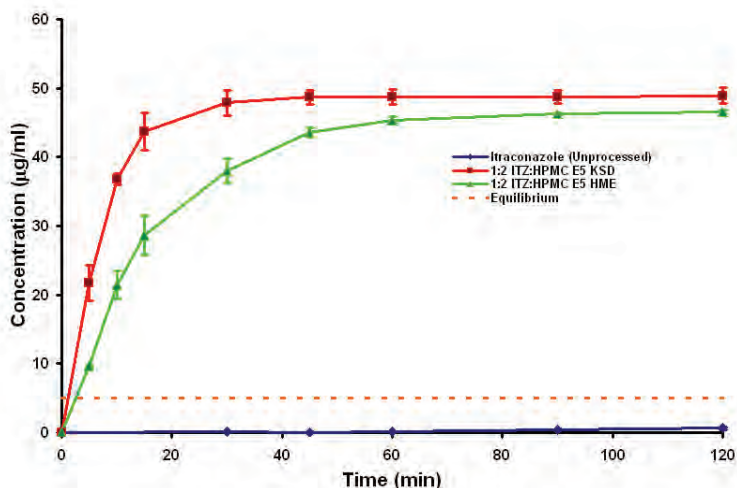


Figure 9. Supersaturated dissolution profile of HME (▲) and KinetiSol™ (■) processed solid dispersions. Each vessel ( $n = 3$ ) contained 50.0 µg/mL ITZ equivalent corresponding to 10 times the equilibrium solubility of ITZ in the acid phase. Testing was conducted for 2h in 900 mL of 0.1N HCl, courtesy of reference 11.

## 6. Conclusions

KinetiSol™ has been demonstrated to be a viable method of producing amorphous solid dispersions of poorly water soluble drugs, particularly those with high melting points and those with chemical instabilities at elevated temperatures. Processing occurred at lower temperatures and samples are exposed to shorter residence times, thus reducing the thermal stress on both the API and the carrier polymers. Plasticizers are not required, although the presence of a plasticizer has been shown to increase the dissolution rate and supersaturated concentrations of some poorly water soluble compounds.

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# (CO-)EXTRUSION AND INJECTION MOULDING AS MANUFACTURING TOOLS FOR ORAL SOLID DOSAGE FORMS

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## Abstract

Hot melt extrusion (HME) is a well-established technique in the plastic industry. In the pharmaceutical field it is investigated as an application to develop solid pharmaceutical dosage forms, more specifically matrix systems where the drug can be dispersed or dissolved.

Co-extrusion is defined as the simultaneous extrusion of two or more materials creating a multi-layered extrudate while injection moulding permits the manufacturing of very complex shapes and allows to accurately control the three-dimensional structure of the processed materials.

This article provides an overview of the conventional HME, co-extrusion and injection moulding processes, type of equipment, the polymers processed, advantages and disadvantages of the techniques. The integration of suitable PAT tools to facilitate understanding of the process and material behavior is also described. Finally structural polymethacrylate modifications and their impact on thermal behavior and release characteristics for injection moulded tablet formulations of ibuprofen as a model drug will be presented.

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## Keywords

*Bioavailability, hot melt extrusion, hydrochlorothiazide, ibuprofen, injection moulding, metoprolol tartrate, mini-matrix, plasticizer, polymer, process analytical technology, quality by design, sustained release.*

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## 1. Introduction

Originating from the plastic and rubber industry in the second half of the 19<sup>th</sup> century, hot melt extrusion (HME) has over the last years been introduced as a manufacturing technique in the pharmaceutical industry (Figure 1).

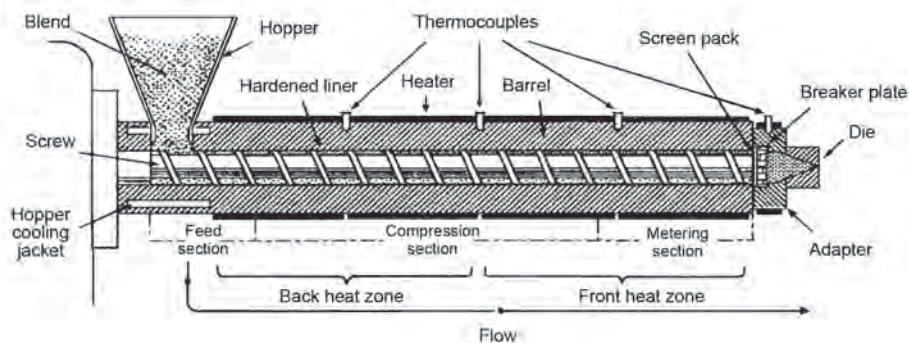


Figure 1. Schematic of an extruder illustrating various functional zones including the hopper, solid conveying zone, melting zone, metering zone and die. N. Follonier et al., *J. Control. Release* 36 (1995) 243-250.

Due to the advantages offered by HME, interest in this technique within the pharmaceutical industry has grown over the last 10 – 15 years. Although extensively used to manufacture medical devices, often in combination with injection moulding, the number of drugs on the market which are manufactured by HME is limited.

To streamline the development of drug products, regulatory authorities have driven the investment in new manufacturing techniques highlighting continuous production, quality by Design (QbD) and Process Analytical Technologies (PAT) as important tools to simplify, control and understand the manufacturing process. Based on these criteria, HME offers many advantages over conventional pharmaceutical production techniques e.g. continuous process with possible implementation of PAT-tools, limited number of processing steps, possibilities for process automation, solvent-free process, manufacturing of wide range of dosage forms possible via post-processing techniques (pelletisation, milling, calendering, injection moulding, etc...), drug release profiles can be adapted: solid solutions might in some cases help to improve dissolution characteristics and bioavailability of poorly soluble drugs while on the other hand sustained-release formulations can also be formulated [1-4].

The main disadvantages of HME are related to the thermal processing, limiting its application to thermostable compounds, and costs mainly due to equipment investment.

Injection moulding (IM) can be considered as an extension of HME and consists of a repetitive cyclical process in which polymers are heated and gradually melted in the injection unit of an injection molding machine, which resembles, in principle, an extrusion process (Figure 2).

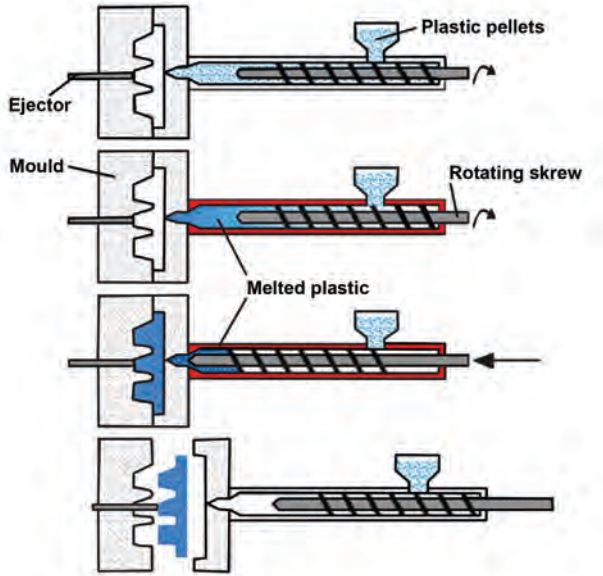


Figure 2. Image of a single stage injection moulding machine.

The molten material is then transferred by means of an injection step into a closed and shape-specific mold cavity. After solidification, the article is recovered by opening the mold to release the product. Currently, injection moulding has been applied for a plethora of pharmaceutical medical applications varying from the development of oral drug delivery dosage forms to the design of complicated stents or implants. The high precision of the IM process, the ability for mass production due to short production time, and the possibility to accurately control the three dimensional structure of the product, favour IM for the production of a variety of medical devices, medical implants and stents, bone analogue composites, tissue-engineered scaffolds and vaginal rings.

Although IM has significant potential as a novel drug delivery technology, a paradigm shift in pharmaceutical solid dosage form manufacturing will require a fundamental and extensive evaluation of this process to determine the effects of both process and formulation factors on product performance [5].

## 2. Materials used in HME

The basic requirements for pharmaceutical grade polymers to be used in HME are a thermoplastic behavior, a glass transition temperature low enough to allow processing at not too high temperature, an excellent thermal stability and no toxicity. Thermoplastic polymers commonly used in HME for immediate release and sustained release formulation are shown in Table 1.

*Table 1. Thermoplastic polymers commonly used to prepare immediate and sustained-release dosage forms via HME.*

Immediate release	Sustained release
Polyethylene oxide (PEO)	Ethylcellulose (EC)
Hydroxypropyl methyl cellulose (HPMC)	Ethylene vinyl acetate (EVA)
Hydroxypropyl cellulose (HPC)	Polyvinyl acetate (PVA)
Vinylpyrrolidone/vinyl acetate copolymer (Kollidon® VA)	Poly(lactic-co-glycolic acid) (PLGA)
Dimethylaminoethyl methacrylate copolymer (Eudragit® E)	Polycaprolactone (PCL)
PEG 6000 / vinylcaprolactam / vinylacetate copolymer (Soluplus®)	Silicone
	Ammonium methacrylate copolymers (Eudragit® RS/RL)

In addition plasticizers are often required to reduce the glass transition temperature and so the processing temperature (Table 2).

*Table 2. Commonly used plasticizers during hot-melt extrusion of pharmaceutical formulations.*

Phtalate esters (dimethyl, diethyl, dibutyl, dioctyl phthalate) Citrate esters (triethyl, tributyl, acetyl triethyl, acetyl tributyl citrate)
Fatty acid esters (butyl stearate, glycerol monostearate)
Sebacate esters (dibutyl sebacate)
Vitamin E TPGS
Polyethylene glycol, propylene glycol, polyethylene oxide
Triacetin
Surfactans (polysorbates, docusate sodium, polyethylene glycol monostearate)
Carbon dioxide

Although a plasticizer is intentionally added to the API/polymer blend, APIs themselves can be effective plasticizers e.g. lidocaine for Eudragit E, ibuprofen for ethylcellulose, ketoprofen for polyethyleneoxide.

### 3. HME and active ingredients

The use of HME to produce solid dispersions in order to improve the dissolution properties of drugs has long been recognized. The ideal type of solid dispersion for increasing dissolution is a solid solution in which the amorphous drug has a lower thermodynamic barrier to dissolution. In addition, the intimate presence of hydrophilic excipients can increase wetting and lead to supersaturation in the diffusion layer. When a drug is dispersed in the crystal form in an amorphous polymer, a solid crystalline suspension is formed, typically used for sustained release purposes. While solid crystalline suspensions are thermodynamically stable, solid glass suspensions have a higher tendency for recrystallization.

To obtain a stable formulation and avoid recrystallization, the selection of a suitable carrier showing specific interactions with the drug is essential. Several studies have identified ion-dipole interactions and intermolecular hydrogen bonding between drugs and polymers inducing a better stability of the solid dispersions. Supersaturation of poorly soluble drugs upon release increases the risk of drug recrystallization. Hydrophilic polymers have been used to inhibit crystal formation e.g. PVP and hydroxypropyl methylcellulose. Controlled drug release is possible via different mechanisms using matrix-forming polymers with a variety of physicochemical properties. These matrix systems can be manufactured via HME using swellable, poorly soluble or insoluble carriers to reduce drug release from the matrix (e.g. polyethylene oxides, ethylcellulose, ethylene vinyl acetate).

In the next paragraphs data generated in our research unit using multiple-unit matrix systems formulated by extrusion and coextrusion as well as single-unit systems manufactured by injection moulding are reviewed [6].

### 4. HME mini-matrices manufactured via conventional HME

In a first approach sustained-release mini-matrices were developed by hot melt extrusion of an ibuprofen (IBP)/ethylcellulose (EC) mixture with the addition of xanthan gum (XG) to tailor drug release [7,8]. The combination of ethylcellulose and a hydrophilic component offers the flexibility to tailor drug release. Xanthan gum addition yielded formulations having a nearly zero-order drug release without burst effect and complete drug release *in vitro* within 24hrs. The higher ability of xanthan-gum to control drug release in comparison with HPMC originates from their different hydration properties.

Table 3. Composition (% w/w) of the hot-melt extruded formulations.

	10 % XG	20 % XG	30 % XG
Ibuprofen	60	60	60
Xanthan gum (XG75)	10	20	30
Ethylcellulose	30	20	10

Table 3 shows the composition of the hot-melt extruded formulations. Prior to hot-melt extrusion the formulations were dry blended in a planetary mixer. Hot-melt extrusion was performed using a lab scale intermeshing co-rotating twin-screw extruder with a length-to-diameter ratio of 25/1. Extrusion was performed at a temperature of 50°C for all heating zones along the barrel. This rather low extrusion temperature, far below the glass transition temperature of EC (130°C) can be explained by the plasticizing effect of ibuprofen favourably affecting the stability of both the drug and the polymer. Changing the XG/EC ratio allowed modification of the drug release rate as increasing concentrations of XG enhanced drug release after 24hr; only 50 % IBP was released from formulations containing 10 % XG, whereas the total drug load was released within this time from mini-matrices containing 20 and 30 % XG. In this case due to the swelling of XG, the structure of the mini-matrices was opened, creating pores through which IBP was released (Figure 3).

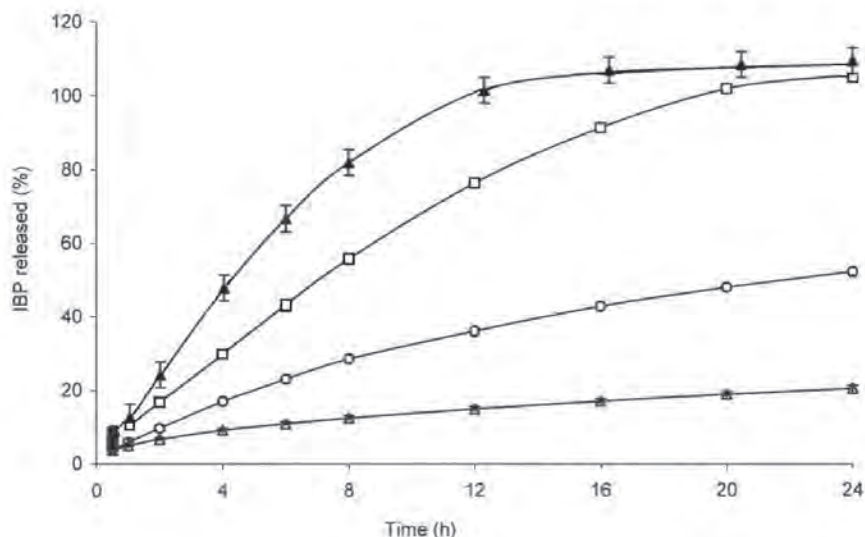


Figure 3. Influence of xanthan gum concentration on the dissolution profiles (mean  $\pm$  standard deviation (S.D.),  $n=6$ ) of mini matrices containing 60 % IBP, EC and XG: ( $\Delta$ ) 0 % XG, ( $\circ$ ) 10 % XG75, ( $\square$ ) 20 % XG75, ( $\blacktriangle$ ) 30 % XG75.

Drug release from the mini-matrices was mainly diffusion-controlled, while swelling played an important role to obtain complete drug release within 24hr.

An oral dose of 300 mg IBP was administered to dogs either as an immediate release preparation (suspension), as a sustained release formulation available on the market or as the experimental mini-matrices.

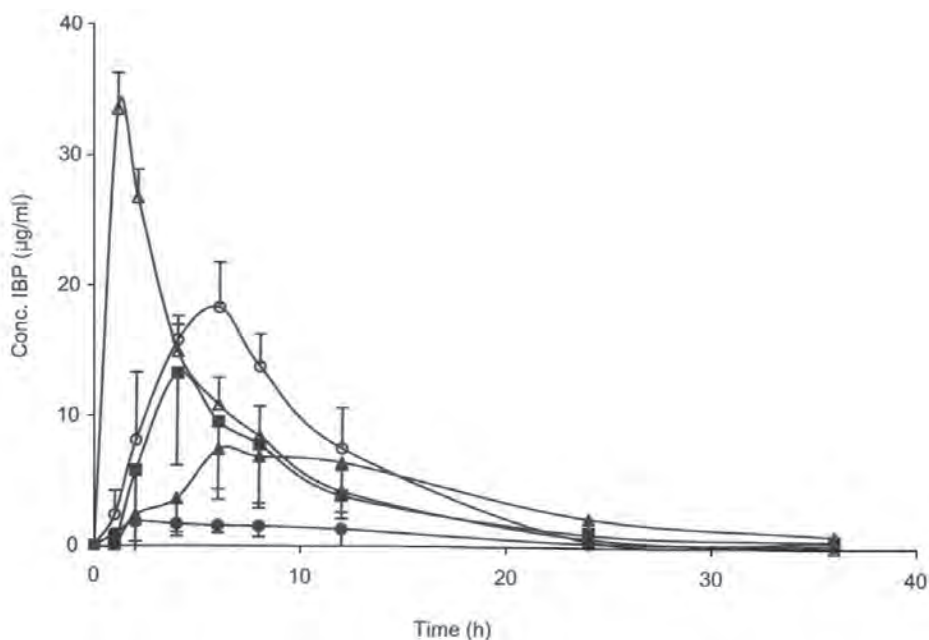


Figure 4. Mean plasma concentration-time profiles ( $\pm$  S.D.,  $n=6$ ) after oral administration of 300 mg ibuprofen to dogs: (●) 10 % XG75 mini-matrices, (▲) 20 % XG75 mini-matrices, (■) 30 % XG75 mini-matrices, (○) Ibu-Slow® 600 ( $\frac{1}{2}$  tablet), (△) Junifen® (15 ml).

Figure 4 shows the mean plasma concentration/time profiles after oral administration and the pharmacokinetic parameters are reported in Table 4.

Table 4. Mean pharmacokinetic parameters ( $\pm$  S.D.,  $n=6$ ) after oral administration of 300 mg ibuprofen to dogs as 10 % XG75 mini-matrices, 20 % XG75 mini-matrices, 30 % XG75 mini-matrices, Ibu-Slow® 600 ( $\frac{1}{2}$  tablet) and Junifen® (15 ml).

Dosage form / test sample	$C_{max}$ ( $\mu\text{g/ml}$ )	$T_{max}$ (h)	$AUC_{0-36h}$ ( $\mu\text{g.h/ml}$ )	$HVD_{t50\%C_{max}}$ (h)
10 % XG75	$3.0 \pm 0.5^a$	$5.7 \pm 3.9^{a,b}$	$34.8 \pm 8.8^a$	$10.6 \pm 3.8^{a,b}$
20 % XG75	$9.8 \pm 2.3^b$	$6.3 \pm 2.9^{a,b}$	$129.7 \pm 40.0^b$	$9.5 \pm 4.0^{a,b}$
30 % XG75	$15.8 \pm 4.6^{b,c}$	$3.7 \pm 0.8^b$	$134.9 \pm 32.6^b$	$6.9 \pm 2.1^b$
Ibu-Slow® 600 ( $\frac{1}{2}$ tablet)	$18.4 \pm 5.7^c$	$4.3 \pm 2.0^{a,b}$	$186.2 \pm 39.8^b$	$8.5 \pm 1.8^b$
Junifen® (15 ml)	$32.1 \pm 3.7^d$	$1.0 \pm 0.0^a$	$175.4 \pm 46.9^b$	$3.1 \pm 0.4^a$

a, b, c, d: means in the same column with different superscript are different at the 0.05 level of significance.

The formulations with 20 and 30 % XG showed a pronounced sustained release profile. It was interesting to observe that during the initial phase of the profiles a slower absorption was seen for the mini-matrices containing 20 % XC. This delayed onset of action could be seen as an advantage since it could favourably affect the clinical effect of an ibuprofen dose administered in the evening by preventing the morning stiffness typically associated with rheumatoid arthritis.

Due to the specific drug-matrix interaction, the low-melting ibuprofen was identified as a plasticizer for EC. Consequently, the characteristics of EC mini-matrices containing ibuprofen are not predictive of the extrusion and dissolution properties of EC mini-matrices containing non-plasticizing drugs. Therefore ibuprofen was substituted by metoprolol tartrate (MPT) a drug with a higher melting point (123°C). The MPT concentration was 30 % (w/w) and dibutylsebacate was used as a plasticizer (EC/DBS ratio 2/1; w/w). The extrusion temperature was 60°C for all heating zones. XG was added to all formulations and increasing XG concentrations yielded a faster drug release while a zero-order release was only obtained at  $\leq 5$  % (w/w) XG. (Figure 5).

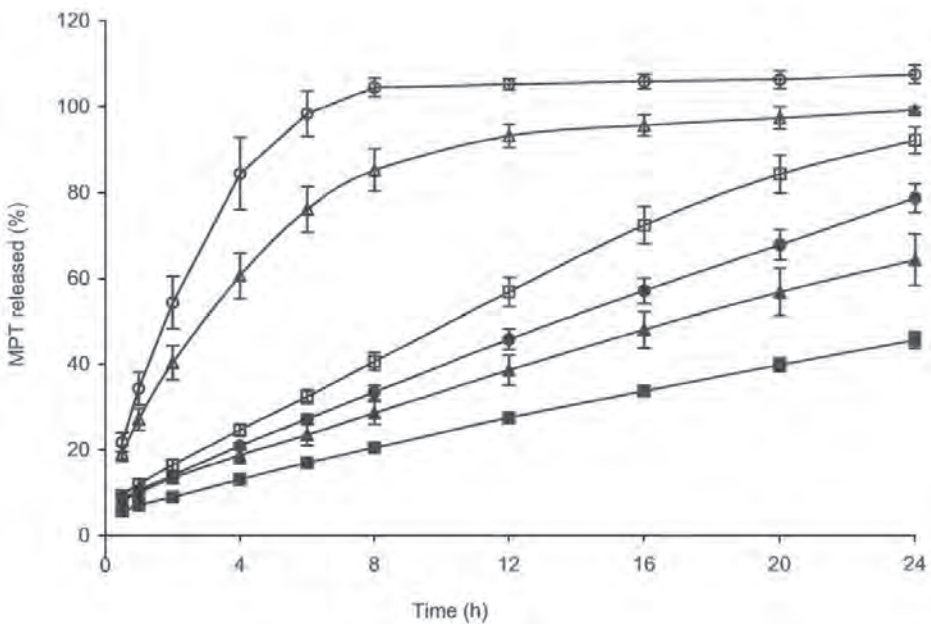


Figure 5. Influence of xanthan gum concentration on the dissolution profiles (mean  $\pm$  S.D.,  $n=6$ ) of mini-matrices containing 30 % (w/w) MPT, XG, EC and DBS (EC/DBS 2/1, w/w). XG concentration (w/w): (■) 0 %, (▲) 1 %, (●) 2.5 %, (□) 5 %, (△) 10 %, (○) 20 %.

Modifications of the process parameters (screw design, powder feed rate and screw speed) had no influence on release characteristics confirming the robustness of the process. However, a drawback of this robustness is that it offers limited flexibility for optimization of drug release. Therefore, polyethylene oxides were used as an alternative to xanthan gum [9]. MPT concentration was again fixed at a concentration of 30 % (w/w). The concentration of PEO varied between 0 and 7 % (w/w). The remaining part of the formulation consisted of EC/DBS in ratio of 2/1 (w/w). Extrusion was performed at 70°C for the five heating zones along the barrel. At low PEO concentration (1 - 2.5 %) no effect of PEO Mw on drug release was observed. Although a slower drug release is described from hydrophilic matrices containing higher Mw PEO due to the increasing viscosity of the polymer (a higher Mw increases gel strength, which tends to decrease the diffusion of the drug), drug release from matrices containing 5 and 10 % PEO 100K was significantly slower in comparison to the PEO 1M and 7M mini-matrices (Figure 6).

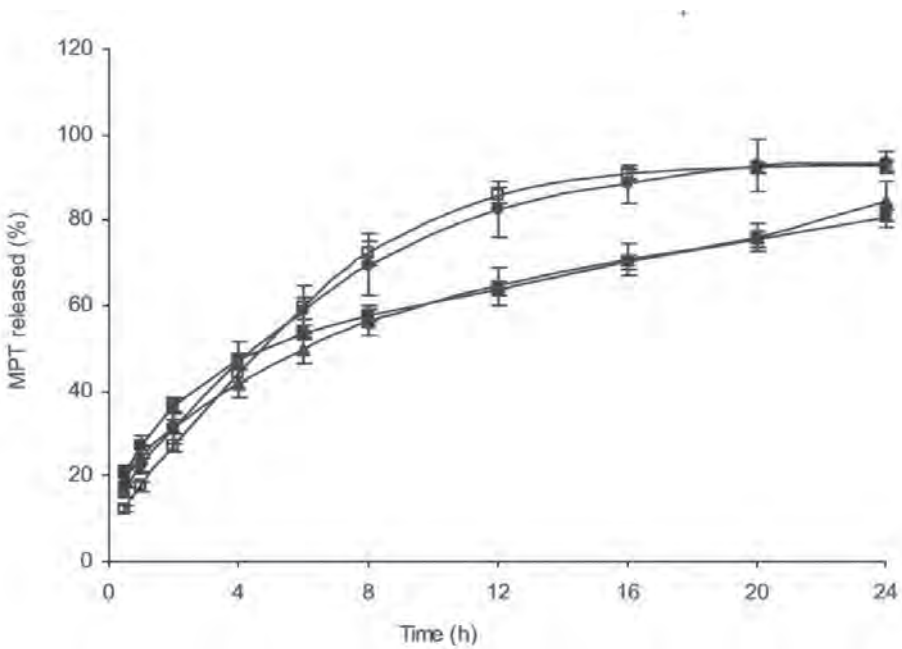


Figure 6. Influence of PEG/PEO MW on the dissolution profiles (mean  $\pm$  S.D., n=6) of mini-matrices containing 30 % (w/w) MPT, EC/plasticizer (2/1, w/w) and 10 % (w/w) hydrophilic polymer: (■) PEG 6000, (▲) PEO 100.000, (●) PEO 1.000.000, (□) PEO 7.000.000.

This might be due to the faster release of lower Mw PEO (in comparison with the release of high Mw PEO), resulting in a rearrangement of EC, thus modifying the porous network inside the matrix and hindering drug release. The dissolution conditions provided sufficient mobility for the EC polymer chains as the MTDSC analysis showed that T<sub>g</sub> of EC in combination with DBS was 40°C (ratio EC/DBS: 2/1).

An oral dose of 200 mg metoprolol tartrate was administered to dogs either as an immediate release preparation, as a sustained release formulation (both available on the market) or as the experimental mini-matrices. Only formulations with 5 and 20 % PEO (Mw 1M) were administered to the dogs.

*Table 5. Mean pharmacokinetic parameters (± S.D., n=6) after oral administration of 200 mg metoprolol tartrate to dogs as 5 % PEO 1M mini-matrices, 20 % PEO 1M mini-matrices, Lopresor® 100 (2 tablets) and Slow-Lopresor® 200 Divitabs® (1 tablet).*

	C <sub>max</sub> (µg/ml)	T <sub>max</sub> (h)	AUC <sub>0-36h</sub> (µg.h/ml)	HVD <sub>t50%Cmax</sub> (h)	F <sub>rel</sub> * (%)
5 % PEO 1.000.000	5.9 ± 2.1	2.2 ± 0.4	51.5 ± 22.6	4.3 ± 1.2	66.2 ± 31.0
20 % PEO 1.000.000	21.3 ± 7.9	2.7 ± 0.5	113.5 ± 54.9	3.7 ± 1.0	148.2 ± 87
Lopresor® 100 (2 tablets)	31.8 ± 4.6	1.3 ± 0.5	151.3 ± 51.4	2.9 ± 1.2	-
Slow-Lopresor® 200 Divitabs® (1 tablet)	13.3 ± 2.8	3.2 ± 1.0	87.8 ± 35.8	4.9 ± 1.2	-

-: Not applicable.

\*: Using Slow-Lopresor® 200 Divitabs® (1 tablet) as reference.

Table 5 shows the mean pharmacokinetic parameters (± SD; n=6) after oral administration of the mini-matrices and the marketed formulations. T<sub>max</sub> and HVD<sub>50%</sub> values showed no significant difference in comparison with the SR reference formulation (p>0.05). The sustained release effect of the experimental formulations was limited and relative bioavailabilities of 66 and 148 % were obtained for 5 and 20 % PEO 1.000.000 mini-matrices, respectively. An increasing PEO concentration of 5 to 20 % enhanced drug release, which was reflected in the higher AUC and F<sub>rel</sub>.

As indicated before the majority of polymers require a plasticizer to improve the processability of the formulations made by HME. This results in several restrictions related to polymer/plasticizer miscibility, plasticizer concentration, interactions with drug and polymer. In contrast, ethylene vinyl acetate (EVA) does not require a plasticizer to obtain good quality extrudates. EVA is a copolymer of ethylene and vinyl acetate. While polyethylene is a semicrystalline polymer with alternating crystalline lamellae and amorphous domains, the incorporation of VA comonomer units

(typically the VA content varies between 9 and 40 %) into a polyethylene backbone chain induces differences in crystallinity and crystalline structure, melting point, glass transition temperature, affecting the flexibility and thermoplastic characteristics of EVA. In the pharmaceutical field it has been used for the development of films, stent coating, implantable devices, vaginal rings, etc...

Table 6. General properties, thermal behavior and crystallinity of 4 different types of EVA (ELVA – Dupont).

General properties	DSC: Thermal behavior and crystallinity					
	Polymer Type	% VA	MW	T <sub>g</sub> (°C)	Melt Onset Temp. (°C)	T <sub>m</sub> (°C)
<b>EVA40</b>	40	64 900	-28.7 ± 0.3	34.9 ± 0.3	42.8 ± 0.0	13.7
<b>EVA28</b>	25	101 600	-28.6 ± 0.5	38.6 ± 1.1	72.8 ± 0.9	17.1
<b>EVA15</b>	15	151 200	-25.3 ± 0.5	70.0 ± 0.1	91.1 ± 0.1	29.4
<b>EVA9</b>	9	578 200	-26.9 ± 1.2	80.2 ± 0.1	98.6 ± 0.2	33.1

Table 6 gives the general properties, thermal behavior and crystallinity of the four different types of EVA used. It should be noted that the T<sub>g</sub> is not significantly affected by the VA content ranging between -25.3°C for EVA 15 and -28.7 % for EVA 40. Such a low T<sub>g</sub> is responsible for the polymer rubbery state at room temperature. Depending on the VA content, the extrusion behavior of the EVA grades differed: while EVA 40 and EVA 28 could already be processed at a temperature of 60°C (with higher torque registered for EVA 28), a temperature of 100 and 110°C was required for EVA 15 and 9, respectively. Molecular weight measurements showed that EVA samples which contained a lower VA content presented a higher molecular weight responsible for an increase of polymer melt viscosity. Therefore, higher process temperatures aided the extrusion process by lowering the flow viscosity of the polymers with lower VA content.

Mini-matrices (2 mm length; 2 mm diameter) were produced via HME using metoprolol tartrate as a model drug using a co-rotating twin-screw mini-extruder (Haake MinLabs II Micro Compounder, Thermo Electron, Karlsruhe, Germany) [10].

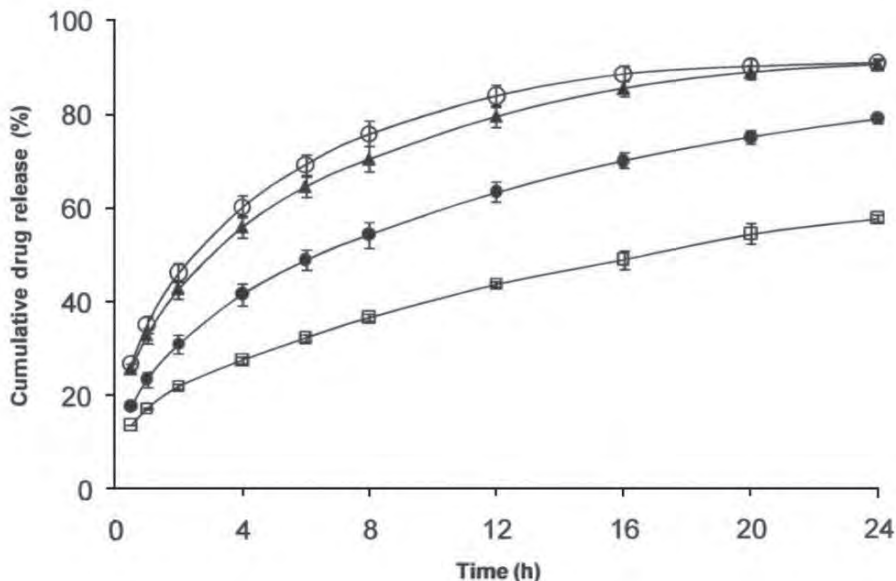


Figure 7. Cumulative drug release of MPT from EVA40 (□), EVA28 (▲), EVA15 (o) and EVA9 (●) matrices (EVA/MPT, w/w, 50/50) (n=3).

Drug release from EVA/MPT matrices (50/50; w/w) was affected by the EVA grades (Figure 7) as the release decreased in the following order: EVA 15, 28, 9 and 40.

All matrices showed a small burst release. Porosity measurements indicated similar values for all matrices formulated with different EVA grades, ranging from 5.2 (EVA 28) to 8.9 (EVA 15). X-ray tomography confirmed that larger pores were located in the center of the matrices while a higher concentration of small pores was registered just below the surface, probably due to compression of the material during passage through the die. Although 50 % of the EVA matrices were composed of drug and at least 60 % drug was released after 24hrs, a limited increase in porosity was observed for EVA 9, 15 and 28 after 24hrs dissolution testing. In case of EVA 40 even a small reduction of porosity was observed after dissolution. X-ray tomography of EVA 40 matrices indicated that the matrix was characterized by a significant structural change after dissolution as pore structure had partially collapsed. It was suggested that EVA 40 matrix was initially structurally supported by drug crystals. When the drug has leached from the matrix, the structure collapses, resulting in a reduction of the number of pathways available for drug release. The lower dissolution rate from EVA matrices compared to the other EVA grades, despite its lower crystallinity, is due to molecular rearrangement of this EVA grade. So EVA 40 experiences two distinct events during drug release: plastic recovery of the polymer and molecular rearrangement. As a result the sustained drug release capacity is increased.

In order to further understand the flexible structural behavior of the hot-melt extruded EVA formulations and its influence on drug release, PEO was added to these matrices [11]. The addition of PEO of variable Mw (100K, 1M and 7M) to MPT/EVA blends affected the HME processability. While EVA/MPT mixtures (50/50; w/w) could be processed into smooth-surfaced extrudates over a temperature range from 60 to 110°C, the incorporation of 5 % PEO 7M required a higher minimal process temperature (90-110°C).

The effect of PEO addition on MPT release from EVA extrudates also depended on the VA content. While drug release after 24hrs from EVA 40 matrices increased from 36 to 85 % upon addition of 10 % PEO 7M, the release only increased from 57 to 77 % in the case of EVA 28. In contrast, the addition of 5 % PEO 7M to EVA 15 and 9 showed lower drug release. This decrease might be attributed to the creation of a highly viscous PEO solution/ gel phase, instantly formed within the pores so acting as a diffusion barrier. Due to the lower flexibility of EVA 9&15, swelling of both formulations was limited. In case of the more flexible EVA 28 and 40, the higher flexibility allowed higher water influence thus limiting a potential increase in viscosity of the liquid filling the pores.

To investigate the influence of VA content and PEO in the mini-matrices different formulations containing 200 mg metoprolol tartrate were administered to dogs (n=6). The slow drug release from EVA 40/MPT matrices (60/40; w/w) was correlated with a low bioavailability. The addition of PEO 7M to the EVA 40 matrix enhanced drug release and bioavailability. The PEO concentration (5 & 15 %) did not have any influence on bioavailability however the 5 % PEO formulation tended to sustain plasma levels over a longer period. Substitution of EVA 40 by EVA 28 had no significant influence on the plasma drug concentration time profile (Figure 8).

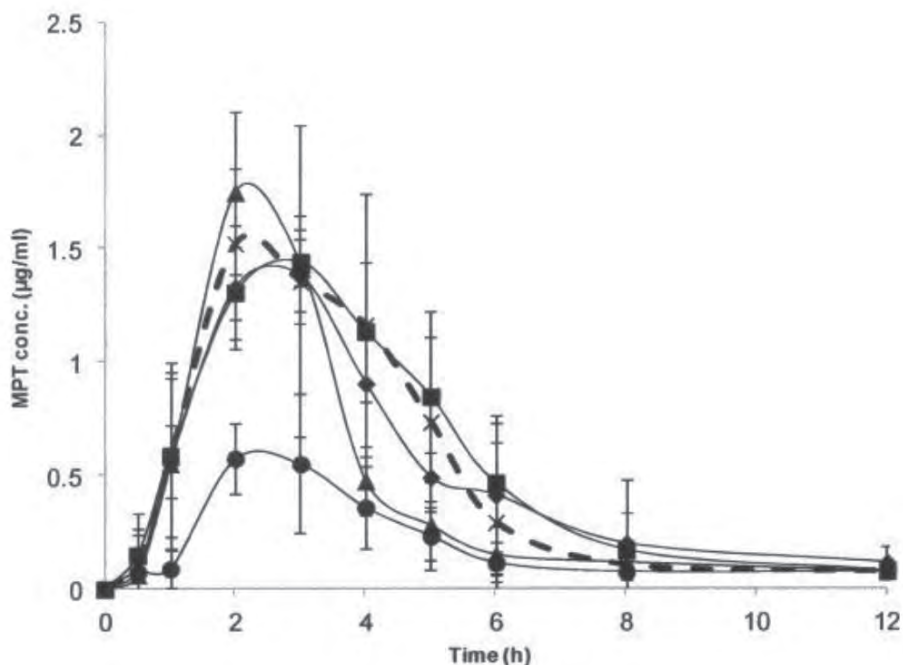


Figure 8. Plasma concentration-time profiles (mean  $\pm$  S.D.,  $n=6$ ) after oral administration of 200 mg metoprolol tartrate to dogs and Slow-Lopressor<sup>®</sup> 200 Divitabs<sup>®</sup> (X): EVA 40/MPT (50/50, w/w) containing 50 % PEO 7M (■) or 15 % PEO 7M (▲), EVA28/MPT (55/40, w/w) containing 5 % PEO 7M (◆), and EVA 40/MPT (60/40, w/w), free of PEO (●).

## 5. HME minimatrices manufactured via co-extrusion

Coextrusion of polymers is widely applied in the plastic industry. However, this technique has been barely applied in the pharmaceutical industry. The manufacturing of oral drug delivery systems via co-extrusion offers the opportunity to combine different drugs with different release profiles. The biggest challenge of the co-extrusion process is to find good polymer combinations, taking into account optimal drug release characteristics as well as some technical considerations (e.g. similar extrusion temperature, melt viscosity, adhesion between layers [12]).

The combination of hydrochlorothiazide (HCT) and metoprolol tartrate (MPT) as immediate and sustained release model drugs was selected. Co-extrusion was performed using a Prism Eurolab 16 co-rotating, fully intermeshing twin-screw extruder (Thermo Fisher Scientific, Germany). In this case all co-extruded formulations consisted of a polycaprolactone core and PEO/PEG 4000 coat and were processed at a temperature of 70°C. The core of the coextrudate had a diameter of 3 mm, surrounded by a coat of 0.5 mm thickness, resulting in a total extrudate diameter of 4 mm. The length of the mini-matrices was 2 mm.

The ratio PEO/PEG was 1/1 allowing a good quality extrudate and 100 % HCT release in less than 60min. X-ray diffraction and DSC revealed the crystalline state of MPT in the capronolactone core while HCT remained dissolved in the coat. The dissolution rate of MPT from the core is controlled by the drug/carrier ratio as the release rate increased at higher MPT content. A formulation containing 45 % MPT and 10 % HCT was selected for *in vivo* testing. Figure 9 shows the dissolution profiles of both drugs while Figure 10 shows the plasma concentration time profiles after oral administration of 200 mg MPT and 25 mg HCT to dogs.

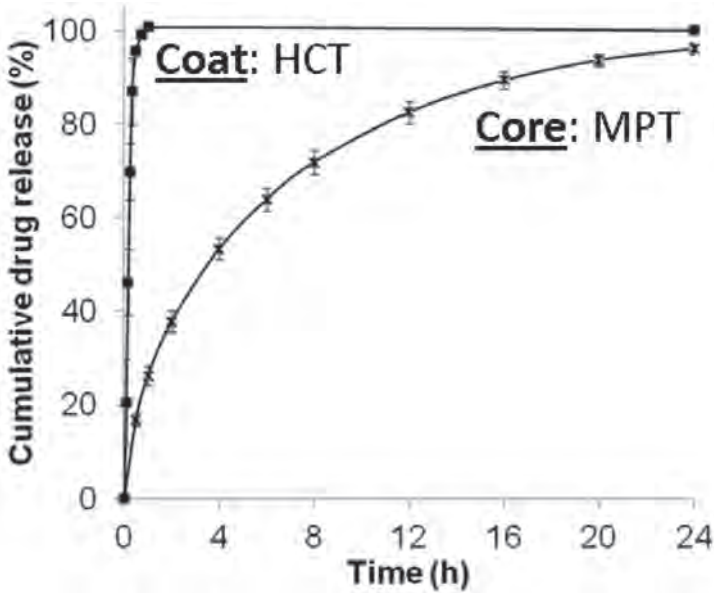


Figure 9. Dissolution profiles of both MPT and 25 mg HCT from co-extrudates (n=6).

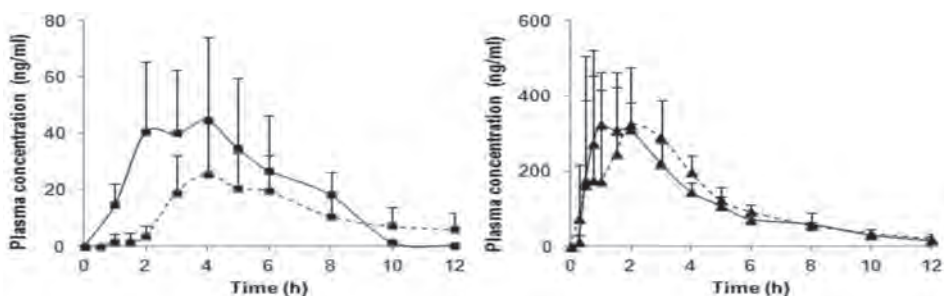


Figure 10. MPT (■) and HCT (▲) plasma concentration-time profiles (mean ± S.D., n=6) after oral administration of 200 mg metoprolol tartrate and 25 mg hydrochlorothiazide to dogs: Zok-Zid® (2 tablets) (dotted line), experimental co-extruded mini-matrices with a core consisting of 45 % (w/w) MPT and a coat consisting of 10 % (w/w) HCT (full line).

The bioavailability data of HCT of both formulations were comparable (no statistical significant difference;  $p > 0.05$ ). Although there was a trend that MPT bioavailability of the test formulation was higher than the reference, the difference was also not statistically significant ( $p > 0.05$ ). This study showed that co-extrusion seems a promising technique to produce fixed-dose combination mini-matrices.

## 6. Injected moulded matrix tablets

The feasibility of polymethacrylate (Eudragit RL and RS) as matrix carrier for the manufacturing of sustained release matrix tablets containing metoprolol tartrate as a highly water soluble drug was investigated (13). Eudragit RL and RS were plasticized with triethylcitrate and next blended with metoprolol-salt. These mixtures were extruded using a co-rotating twin-screw mini-extruder (Thermo Scientific Hakke MiniLab II Micro Compounder, Thermo Scientific, Germany), 4 of the molten extrudates were collected in a heated reservoir and shaped into tablets using a lab-scale injection moulder (Haake Minijet System, Thermo Electron, Germany). An injection pressure of 800 bar during an injection phase of 10s followed by an after pressure of 600 bar (5s) was used to prepare the matrix tablets. The temperature of the mould was set at 20°C. After cooling, biconvex tablets (diameter 10 mm; height 5 mm) with a mass of approximately 375 mg were obtained.

Formulations composed of 70/30 % Eudragit RL/MPT showed the fastest drug release, substituting part of Eudragit RL by RS resulted in slower drug release, all following first-order release kinetics. Drug load only affected drug release of matrices composed of Eudragit RS (Figure 11).

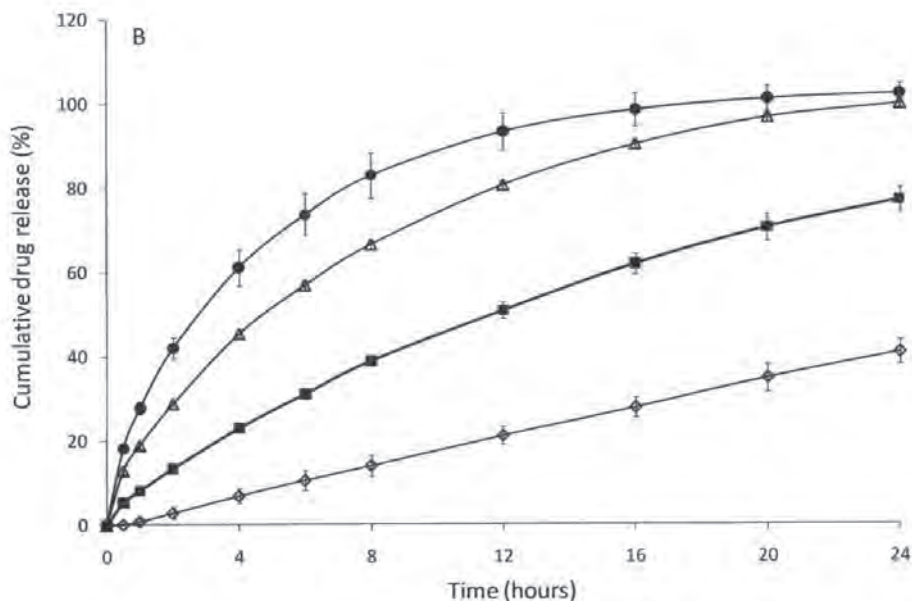


Figure 11. Influence of MPT concentration on drug release. Dissolution profile (mean  $\pm$  S.D.,  $n=6$ ) of formulations containing Eudragit RS with various metoprolol tartrate concentrations: 10 % (empty diamond), 20 % (■ filled square), 30 % ( $\Delta$  empty triangle), 40 % w/w (● filled circle) MPT.

The water uptake of matrices containing Eudragit RL was almost five times higher than Eudragit RS based tablets. These differences in drug release are most likely attributed to the different amounts of quaternary ammonium groups, which account for differences in water permeability and hence dissolution properties. The drug release data provided a good fit with the Ritger-Peppas model and anomalous transport was depicted as the main drug release mechanism, confirming that both diffusion and swelling contributed to the overall drug release process. In order to investigate the influence of metoprolol salts on drug release, IM tablets containing Eudragit RS 30 % (w/w) and metoprolol tartrate, fumarate and succinate were prepared. Tablets composed of the tartrate salt provided the fastest drug release, whereas drug release from metoprolol fumarate was the slowest (Figure 12).

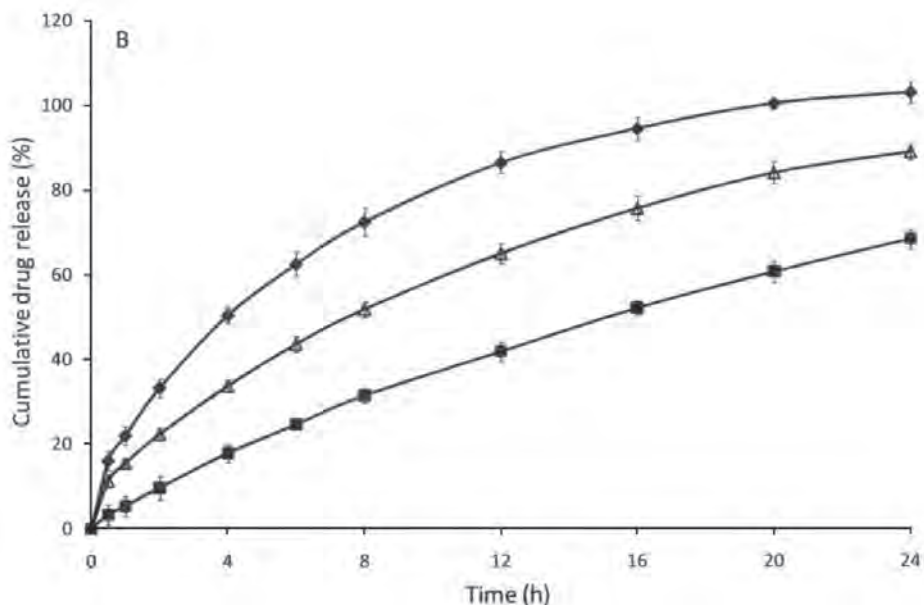


Figure 12. Influence of metoprolol salt on drug release. Dissolution profile (mean  $\pm$  S.D.,  $n=6$ ) of formulations containing 70 % Eudragit RS (■) with 30 % metoprolol salt: tartrate (♦ filled diamond), succinate ( $\Delta$  empty triangle), fumarate (■ filled square).

These differences can not only be attributed to differences in intrinsic water solubilities (aqueous solubility at 37°C of tartrate, fumarate and succinate salts is 3.63, 472 and 276 mg/ml, respectively) since the tartrate salt is more soluble than the succinate but provided slower release rates. However, it was reported that in the presence of anions, the chloride counterion of the quaternary ammonium group exchanged with these anions affecting the permeability of the polymer and hence the drug release profile. From our data faster drug release rates were seen for tartrate > succinate > fumarate. These anions exchanged with the chloride counterion and altered the permeability of the tablet and thus its hydration, resulting in different release rates.

During an *in vivo* bioavailability study in dogs the following formulations were administered: an injected moulded tablet containing 30 % MPT and 70 % Eudragit RS (F1 dose administered 110 mg); injection-moulded tablet containing 50 % MPT and 50 % Eudragit RS (F2 dose administered 186 mg); one half tablet slow-Lopressor® 200 Divitabs (ref. formulation) (F3 dose administered 100 mg). Doses administered were different due to the fixed size of the moulded tablets. However the pharmacokinetic profile was normalized for dose administered. Tablets containing 30 % MPT and 70 % Eudragit RS (F1) resulted in significantly lower pharmacokinetic parameters compared to the reference formulation with a relative bioavailability of 42 %. Tablets with a higher drug load (F2) (50/50 MPT Eudragit S) and having a faster drug release *in vitro* (100 % after 4hrs) yielded similar pharmacokinetic parameters as reference formulation with a relative bioavailability of 130 % (Figure 13).

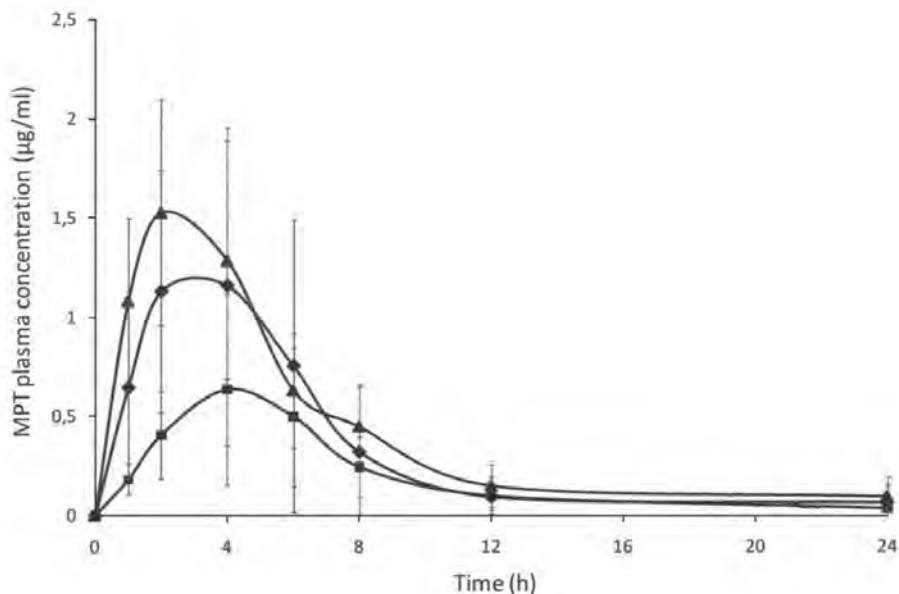


Figure 13. Plasma concentration-time profiles (mean  $\pm$  S.D.,  $n=6$ , normalised for dose) after oral administration to dogs: one half tablet Slow-Lopressor® 200 Divitabs® (◆ filled diamond), formulation 1 (■ filled square, 30 % w/w MPT and 70 % Eudragit RS), formulation 2 (▲ filled triangle, 50 % w/w MPT and 50 % Eudragit RS).

Although injection-moulded tablets were produced at temperatures below the melting point of the drug a single  $T_g$  between the  $T_g$  of the drug and the carrier was observed during thermo-analysis of the IM tablet. At low drug concentrations (10-20 % w/w) the experimental  $T_g$  corresponded with the theoretical values calculated by the Gordon-Taylor equation; however for higher drug concentrations, negative deviations were observed, indicating a possible interaction between MP salts and Eudragit. This could also confirm the plasticizing effect of the drug in the polymer. This was also confirmed by dynamical mechanical analysis of injected-moulded bars, showing a clear reduction in  $T_g$  for increasing drug concentration irrespective of the salt type.

Finally, it should be noted that visual inspection of moulded tablets revealed that some transparent tablets gradually turned cloudy/opaque during 1 year storage at ambient conditions. Evidence of recrystallization was found in these formulations as a melting peak of metoprolol was observed during thermo-analysis. Metoprolol tartrate provided the most stable formulations, as no recrystallization was observed during storage, even at high drug loadings. These data suggested that molecular interactions between drug and polymer have a significant impact in preventing drug recrystallizations. These findings were confirmed with X-ray diffraction measurements.

## 7. Raman spectroscopy as a PAT tool to study material behavior during HME

PAT aims at designing, analyzing and controlling manufacturing processes based on timely in-line, on-line and at-line measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process materials, with the goal of ensuring final product quality. In the context of Quality by Design, PAT can then be an efficient tool to obtain real-time information of all critical process aspects and to guide processes towards their desired state (using feed-forward and feed-back control algorithms), hence ensuring the quality of each end product and possibly allowing real-time release and avoiding batch losses. The implementation of PAT systems in pharmaceutical production processes is strongly encouraged by the most important pharmaceutical regulatory authorities (e.g. FDA and European Medicines Agency, EMA). The aim within the pharmaceutical industry to shift towards continuous processing strengthens the need to invest in PAT. Today, extruders allow in-line monitoring and control of the process parameters barrel and die temperature, melt pressure in the extruder and die, feed rate, screw speed and motor load. In-line monitoring and control of quality parameters corresponding to the extruded product itself, such as drug load and solid state, are generally not performed. Besides real-time product quality evaluation, this might increase the understanding of the product behavior during extrusion [14].

The results described below show that Raman spectroscopy allows continuous estimation of the drug concentration in the polymer-drug melt in the die and (Figure 17) monitoring the polymer-drug behavior throughout the entire extrusion barrel.

Metoprolol tartrate (MPT) (Esteve Quimica, Barcelona, Spain) was chosen as a model drug. It has a melting temperature ( $T_m$ ) around 120°C. Eudragit® RLPO (Evonik, Germany) was used as polymer to form the matrix systems. For the development of a calibration model allowing in-line API quantification, four different polymer-drug mixtures, containing 10 %, 20 %, 30 % and 40 % (w/w) API, respectively, were extruded. Eudragit® RSPO (Evonik, Germany) was used for the barrel monitoring study.

Hot-melt extrusion was performed with a Prism Eurolab 16 co-rotating, fully intermeshing twin screw extruder (Thermo Fisher Scientific, Germany). The temperature of each segment of the extruder and of the die can be controlled separately.

Raman spectra were collected with a Raman Rxn1 spectrometer (Kaiser Optical Systems, Ann Arbor, MI, USA). A fibre-optic Raman Dynisco probe was used to monitor the extrusion process in-line, both in the extrusion die and in the modular barrel. The laser wavelength was the 785 nm line from a 785 nm Invictus NIR diode laser. The analyzed spectral region was 50 – 1800  $\text{cm}^{-1}$ , since this region contained all useful drug and polymer information.

In-line drug concentration monitoring ; 10 %, 20 %, 30 % and 40 % MPT (API) – Eudragit RL PO (polymer) mixtures were extruded. The concentration variations are visible in the collected Raman spectra (Figure 14). PCA on all in-line collected spectra showed that two principle components covered nearly all spectral variation. The first principal component captures 97 % of the variation, i.e. the variation caused by concentration differences. The second principal component represents only 1 % of extra variation. This variation is most likely not related to the differences in API concentration. The PC1 versus PC2 scores plot (Fig. 15) shows a clear distinction between the spectra of the different mixtures and confirms that PC1 captures the variation caused by differences in API-polymer concentration. Saerens et al. developed and validated a PLS model, regressing the MPT concentrations versus the in-line collected Raman spectra, allowing real-time API concentration determination in the extrusion die [15].

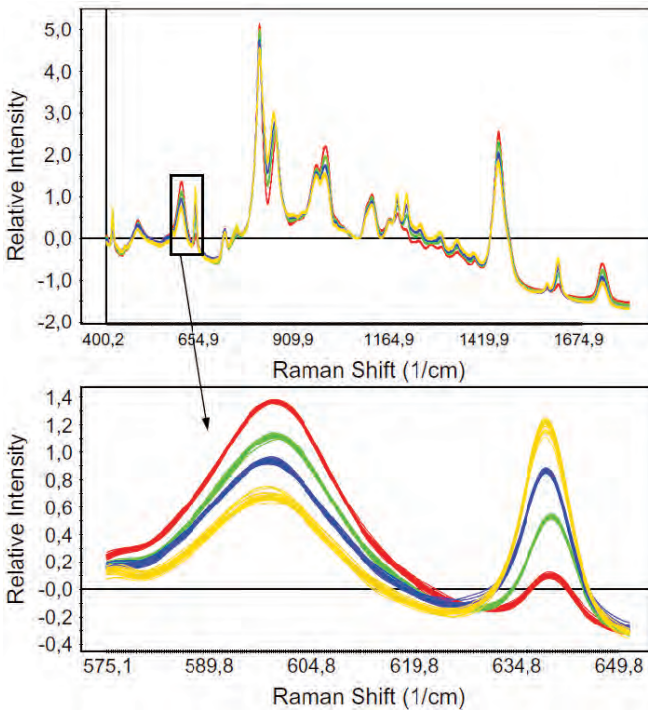


Figure 14. In-line collected Raman spectra of different MPT – Eudragit RL PO mixtures. Red = 10 % MPT, green = 20 % MPT, blue = 30 % MPT, yellow = 40 % MPT.

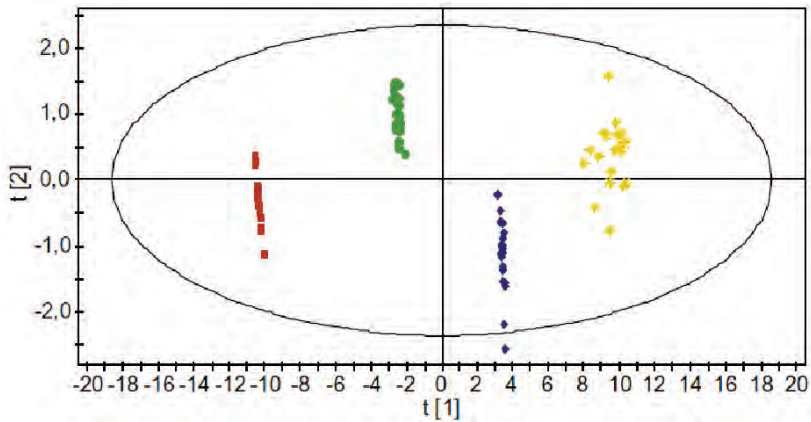


Figure 15. PC1 versus PC2 scores plot of the in-line collected Raman spectra. Red = 10 % MPT, green = 20 % MPT, blue = 30 % MPT, yellow = 40 % MPT.

The Raman probe was positioned in every segment of the modular extrusion barrel (Figure 16 & 17), and principal component analysis was performed on all in-line collected spectra. MPT concentration (10 and 40 % w/w), barrel temperature (100 and 140°C, and 120 and 140°C for 40 % and 10 % MPT, respectively) and screw speed (80 and 160 rpm) were varied during measurements.

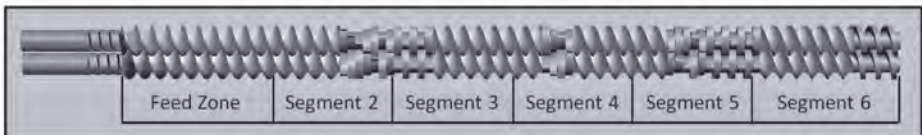


Figure 16. Modular barrel and screw design.



Figure 17. Experimental setup with Raman Dynisco probe mounted in segment 2.

When extruding with a high drug load, most spectral changes occur between barrel segments 2 and 3, where a first kneading zone is situated. The variation between other segments further down the barrel was smaller. A lower drug load shows the same variation between segments 2 and 3, with an extra difference in spectra between 5 and 6, caused by the formation of a solid solution due to additional shear forces, which is not possible with a 40 % MPT load. The main variation in spectra when extruding at 140°C (40 % MPT, 160 rpm) lies between segments 2 and 3, whereas at 100°C (40 % MPT, 160 rpm), below  $T_m$  of MPT, spectral differences can only be seen after segment 5 (Figure 18).

This is a logic consequence of the selected screw configuration. When extruding at temperatures higher than  $T_m$  of MPT, the first kneading zone appears to be enough to melt the drug, and no more large changes occur further down the barrel, since the MPT concentration is too high to form a solid solution. At temperatures lower than  $T_m$  of MPT, extra mixing zones will have a large influence on the polymer-drug behavior and on the solid state of the end product. The MPT does not melt after the first mixing zone, but starts to melt after the third one, due to shear forces.

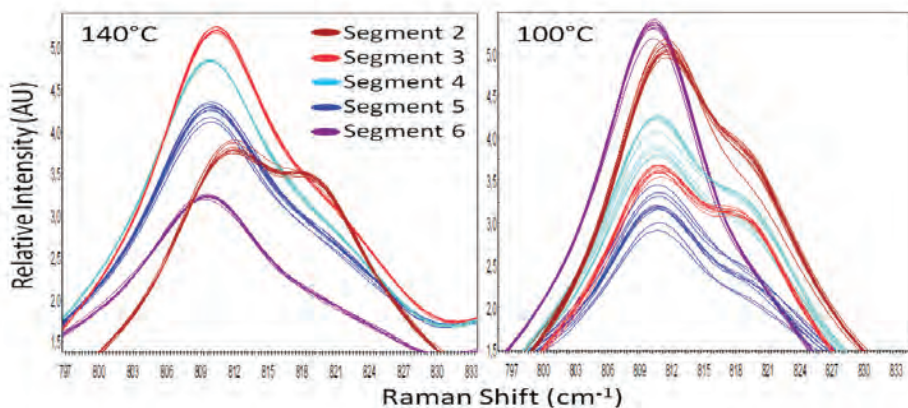


Figure 18. Influence of barrel temperature profile.

The third process parameter which was varied during extrusion was the screw speed. At a lower screw speed, and at 140°C, the variation within segments 3 to 6 is larger than at a higher screw speed for all MPT concentrations. A lower screw speed increases the residence time and lowers shear forces, resulting in a lower temperature. Therefore, more mixing zones (shear forces) are required to obtain similar end product characteristics. At 100°C, the variation caused by screw speed differences is much smaller, since the MPT does not melt at this temperature. Even a screw speed of 160 rpm, which raises the melt temperature, is not enough to melt the MPT.

## 8. Conclusion

HME and IM represent relatively new, but very promising manufacturing techniques for a wide range of drug delivery systems. They have both become an attractive alternative to traditional processing techniques since they offer many advantages including a fully automated and continuous production set-up, design flexibility, absence of water or organic solvents and implementation possibilities for PAT tools.

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# THE MECHANISM OF RELEASE OF AZITHROMYCIN FROM MICROSPHERES

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## Abstract

Zmax<sup>®</sup> is a single-dose antibiotic approved in the United States and Japan for treatment of acute bacterial sinusitis and community-acquired pneumonia. Zmax<sup>®</sup> is modified-release azithromycin microspheres combined with sugar, flavors, and an alkalinizing compound in an oral formulation that is resuspended before dosing. This paper discusses the mechanism of azithromycin release from the modified-release microspheres, which contain Compritol<sup>®</sup> and a poloxamer. Based on azithromycin and poloxamer dissolution tests and microscopy, azithromycin is released from the microspheres after dissolving in liquid-filled pores that are formed following rapid dissolution of the poloxamer.

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## Keywords

*Azithromycin, Compritol<sup>®</sup>, mechanism of release, melt-spray-congeal, microspheres, modified release, poloxamer.*

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## 1. Introduction and summary

Melt-spray-congeal (MSC) microspheres are manufactured by conveying a molten wax or glyceride feed-stream containing suspended crystalline active pharmaceutical ingredient (API) to a spinning disk or rotary atomizer. The 50 µm-to-300 µm spherical microspheres that are produced by this process can be included in capsule, tablet, or sachet formulations.

MSC microspheres have been formulated for modified release applications [1], to improve the chemical stability of excipient-sensitive API [2], and to taste mask bitter API [3]. The microspheres can be utilized as manufactured or can be subsequently coated using fluid bed coating technology to optimize API release rates, improve stability, or to improve palatability.

Zmax<sup>®</sup> is a single-dose antibiotic that was approved in the United States in 2005 for acute bacterial sinusitis and community-acquired pneumonia [4,5]. It was subsequently approved for the Japanese market in 2009. The 2-g active dose is administered as a resuspended sachet of modified-release azithromycin microspheres in a pH-modifying powder that contains sugar and flavors.

The azithromycin microspheres are composed of azithromycin dihydrate, Compritol<sup>®</sup> ATO 888 (Gattefosse) as a matrix material, and a poloxamer, Lutrol<sup>®</sup> F-127<sup>†</sup> (BASF), as a dissolution enhancer. The microspheres are manufactured using a melt-spray-congeal (MSC) process [6]. In this process, a molten mixture of Compritol<sup>®</sup> and the poloxamer, containing crystalline azithromycin dihydrate in suspension, is pumped from an extruder onto a spinning disk. The melt subsequently ligates and forms microspheres, which congeal and are then collected.

During product development, work was performed to develop a fundamental understanding of the microspheres and their drug-release mechanism. The results of these efforts are reported in this paper.

These studies involved investigation of the three most probable mechanisms for drug release from azithromycin microspheres:

- (1) erosion of the matrix,
- (2) diffusion of drug through the matrix, and
- (3) diffusion of the drug through pores in the microspheres.

Based on our work, the primary mechanism of release from azithromycin microspheres appears to be diffusion through liquid-filled pores that are formed by dissolution of the poloxamer from the Compritol<sup>®</sup> matrix. These pores are formed in the solid matrix as the water-soluble components azithromycin and the poloxamer dissolve when exposed to aqueous media.

## 2. Results and discussion

In determining the mechanism of azithromycin release from MSC microspheres, our work was focused on three main areas:

- (1) microscopic evaluation of microspheres to determine if erosion of the solid matrix plays a role in azithromycin release;
- (2) dissolution tests to differentiate between diffusion of the azithromycin through liquid-filled pores and diffusion through the solid matrix; and
- (3) dissolution tests to determine the effect of dissolution-medium pH on azithromycin release.

### 2.1 Microscopic evaluation

To determine whether erosion of the matrix plays a role in the release of azithromycin from microspheres, microspheres were observed using microscopy before and after dissolution. Figure 1a shows a scanning electron micrography (SEM) image of a microsphere before it was placed in dissolution medium. As the figure shows, the microsphere was relatively spherical, smooth, and had few surface pores. Figure 1b shows an SEM image of a microsphere after dissolution testing. Overall, the microsphere remained largely intact and had small surface pores.

Further microscopic examination of the microspheres during release - following complete release of the azithromycin - was performed to understand microsphere morphology. Figure 2 shows an SEM image of microsphere cross sections after dissolution testing. As the figure shows, the microspheres have large voids where azithromycin crystals have dissolved and many smaller pores, likely where smaller crystals of azithromycin and/or the poloxamer have dissolved. Based on the microscopic evidence that shows the microspheres remain largely intact during dissolution, we conclude that drug release via matrix erosion is not significant.

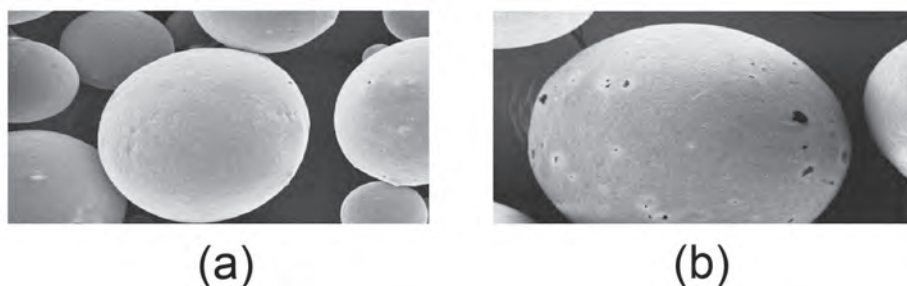


Figure 1. SEM images of azithromycin microspheres before (a) and after (b) complete drug release.

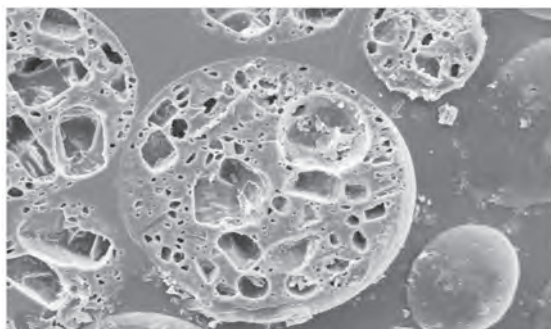


Figure 2. SEM image of cross sections of azithromycin microspheres.

## 2.2 Dissolution tests

Experiments were performed to differentiate between diffusion of the drug through the solid Compritol® matrix and diffusion through liquid-filled pores. Since the dependence of the diffusion rate on temperature is significantly smaller for diffusion through a liquid than through a solid [1], the temperature dependence of the dissolution rate was investigated.

As shown in Figure 3, the dissolution rate - represented by the dose dissolved at 30 minutes - had a very weak dependence on temperature, indicating diffusion through liquid-filled pores. If release occurred via diffusion through the solid matrix, an exponential dependence on temperature would have been observed. These results confirm the microscopy observations which suggest that diffusion through pores was likely.

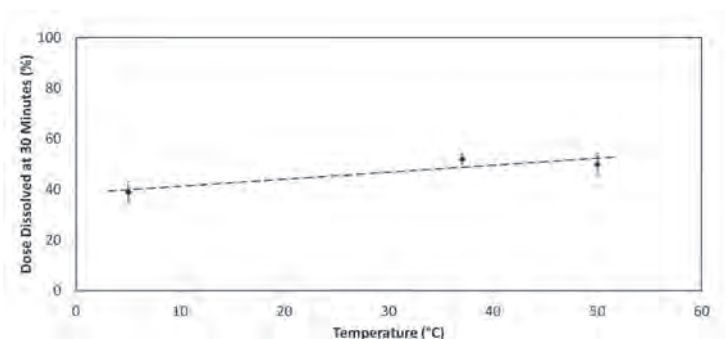


Figure 3. Dose dissolved at 30 minutes as a function of temperature for azithromycin microspheres.

To confirm the reliance of azithromycin dissolution on the poloxamer, the release of both components from microspheres was measured as a function of time by measuring the amount of each component remaining in the microsphere. As shown in Figure 4, the poloxamer rapidly dissolves from the microspheres. Release of the poloxamer was incomplete, likely because a fraction of the poloxamer is dissolved in the water-insoluble Compritol® matrix.

As Figure 4 also shows, the azithromycin dissolves more slowly. Based on the data for both components, we believe that pores are formed by the dissolution of the poloxamer and then filled with the liquid dissolution media, in which the azithromycin dissolves. As the azithromycin dissolves, an additional pore network is formed for the drug to dissolve and exit the microsphere.

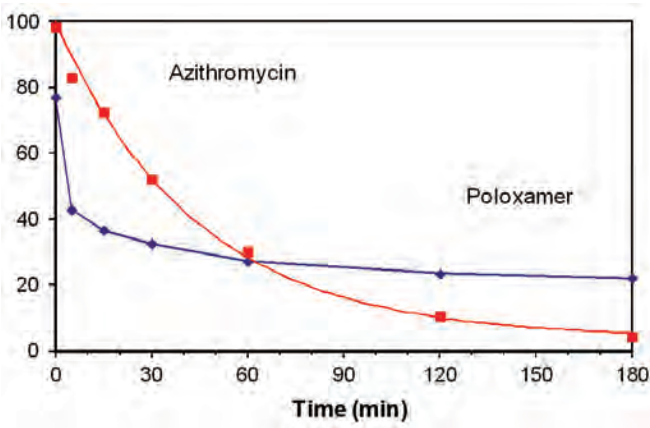


Figure 4. Residual azithromycin and poloxamer in azithromycin microspheres as a function of time following dissolution at pH 6.8.

### 2.3 Effect of pH on release rate

To confirm the hypothesis that liquid-filled pores were the pathway for azithromycin dissolution, tests were also performed to determine the effect of pH on release rate. Figure 5 shows the solubility of azithromycin as a function of pH.

As these data show, azithromycin solubility is highly pH dependent, decreasing significantly as pH is increased from 6 to 7.

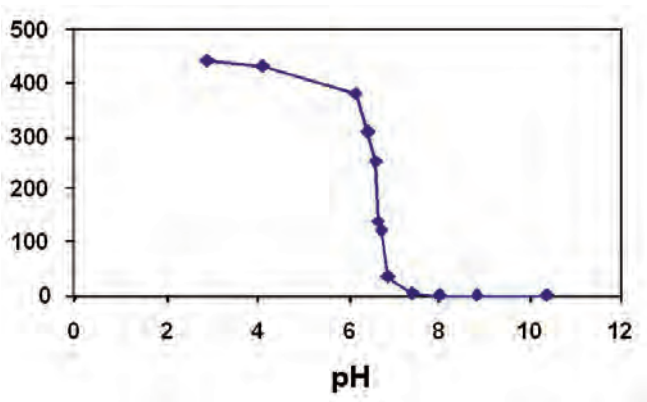


Figure 5. Azithromycin solubility as a function of pH.

Since the solubility of azithromycin is pH dependent, the release of azithromycin from the microspheres is expected to be pH dependent. Dissolution tests were conducted to confirm this.

As the data in Figure 6 show, dissolution of azithromycin decreases as the pH increases - consistent with the proposed mechanism of azithromycin dissolving via liquid-filled pores.

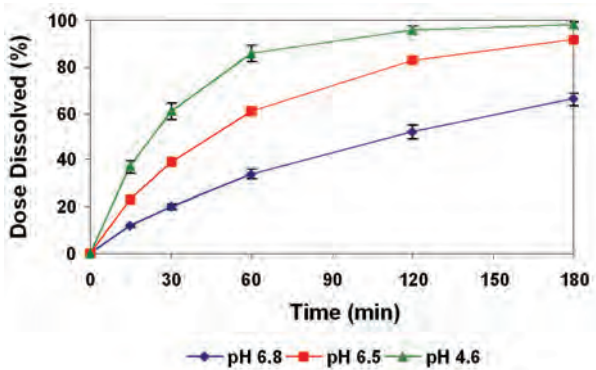


Figure 6. Dissolution performance of azithromycin microspheres as a function of medium pH.

### 3. Summary

Based on the studies described here, we conclude that azithromycin is released from the microspheres via diffusion through liquid-filled pores. The pores are formed in the microsphere as the water soluble components - first poloxamer and then azithromycin - dissolve from the water-insoluble Compritol® matrix.

## 4. Acknowledgments

Pfizer, Inc. is acknowledged for funding this work. Numerous Pfizer and Bend Research scientists and engineers contributed to this product development program and are acknowledged for bringing this product to market. Tanya Hayden, Leah Appel and Marshall Crew (Bend Research Inc.) and Eric Eisenhart, Julian Lo, and Scott Herbig (Pfizer Inc.) are specifically acknowledged for their contributions to this mechanism of release work.

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# GI (HYDRO)DYNAMICS: APPLYING WHAT WE KNOW TODAY TO THE CHARACTERIZATION OF SOLID DOSAGE FORMS

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## Abstract

A major weakness in drug development to date is our inability to predict whether two oral formulations of the same drug in the same dose strength will behave the same way *in vivo* in man. Today, therefore the development of new devices and procedures for the predictive characterization of the behavior of oral drug dosage forms is indispensable.

However, despite increasing knowledge on the conditions dosage forms experience in the gastrointestinal (GI) tract, the development of such devices and procedures remains a major challenge. For example the highly dynamic conditions of media exchange and also physical stresses during GI transit are frequently ignored factors in the development of realistic dissolution test set-ups.

The following article explores some of the dynamic variables and reviews some of the current advances in biorelevant dissolution test device development with emphasis on the approach taken by our research group.

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## Keywords

*Biorelevant dissolution tests, dissolution stress test, gastrointestinal hydrodynamics, IVIVC, predictive dissolution testing.*

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## 1. Introduction

Today oral drug therapy remains the most accepted and the most convenient form of drug administration, especially for long-term chronic therapy. However, the mechanisms of oral drug absorption are far from being fully understood. There are many “unknowns” that determine oral drug absorption and dosage form behaviour. This means that reliable predictions of the extent and rate of drug absorption and the influences of drug formulation and intake conditions are mostly impossible. This inability to predict *in vivo* biopharmaceutic behavior holds true either for *in vitro* test systems as well as *in silico* methods.

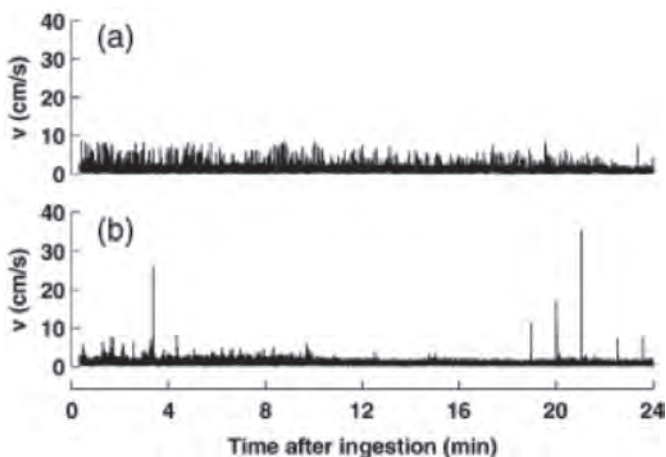


Figure 1. Velocity patterns of a non-disintegrating capsule during residence in different parts of the stomach of the identical volunteer. (a) Proximal stomach, (b) distal stomach. Reprinted with permission from [1].

However, some of the “unknown” parameters influencing drug availability from solid oral dosage forms are not necessarily “unknown” but rather ignored in compendial dissolution or disintegration tests. Such a disregard of *in vivo* parameters applies very frequently to the (hydro)dynamic conditions dosage forms meet in the GI tract. Most of the conventional test systems are based on constant test parameters. However, real life conditions after dosage form intake are not static but highly dynamic in both pre- and postprandial states. A very well-known, but mostly ignored example for the highly dynamic conditions in the GI tract is the motility pattern of the proximal GI tract under fasting conditions. This complex motility results in highly dynamic flow patterns of the GI fluids as well as complex transport and movement patterns of dosage forms (Figure 1). This can be demonstrated applying real time imaging techniques such as magnetic marker monitoring (MMM) [1, 2].

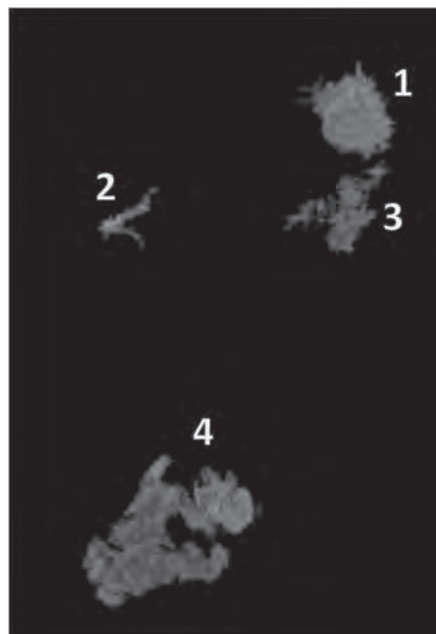


Figure 2. Distribution of water in the GI tract of a healthy volunteer under fasting conditions obtained by magnetic resonance imaging (frontal view). In this example gastrointestinal water is present in the stomach (1: 27 mL) and three “water pockets” that are located in the duodenum (2: 3 mL), in the proximal jejunum (3: 11 mL) and the terminal ileum (74 mL).

A further example for the complex *in vivo* situation is the highly discrete distribution of water throughout the intestinal tract that is characterized by the existence of regions filled with water (“water pockets”, Figure 2). Furthermore, we are able to demonstrate that non-disintegrating dosage forms are not necessarily in permanent contact with such “water pockets” throughout their gastrointestinal transit [3].

## 2. Dynamic biorelevant dissolution test devices

Today, several attempts have been made to develop and establish *in vitro* test devices and protocols that accurately simulate the complex conditions that are present along the GI tract [4]. These approaches follow two main strategies. In the first strategy novel devices are designed that are intended to simulate the functionality of the intestinal organs as close to reality as possible and as complete as required. Usually this results in quite complex designs. The most popular and most advanced systems are the TIM-1 system for the simulation of the upper GI tract (Figures 3 and 4) [5], the TIM-2 system for the simulation of the colon [6] and the dynamic gastric model (DGM) that mimics the stomach (Figure 5) [7].

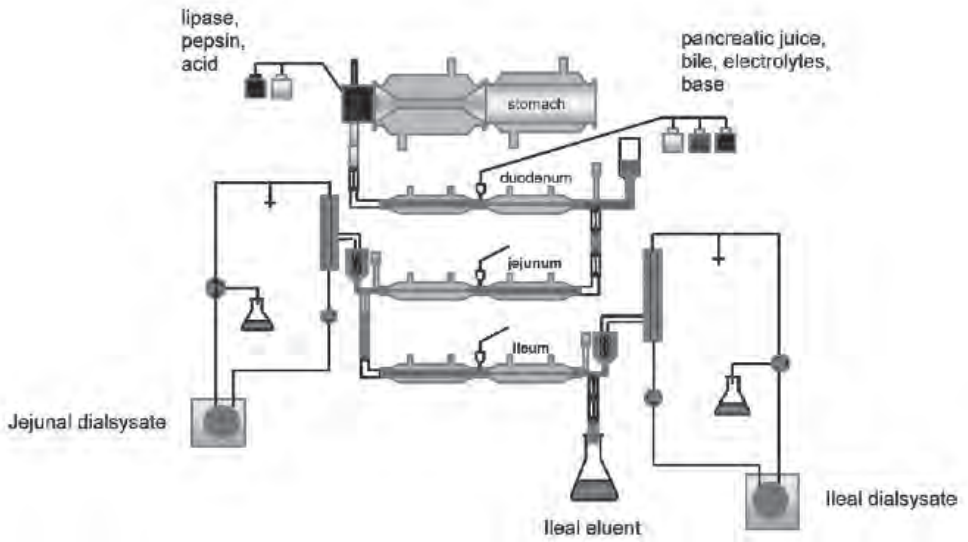


Figure 3. Systemic schematic of TIM-1: A simulator for the stomach and small intestine. Reprinted with permission from [4]. Copyright 2010 American Chemical Society.

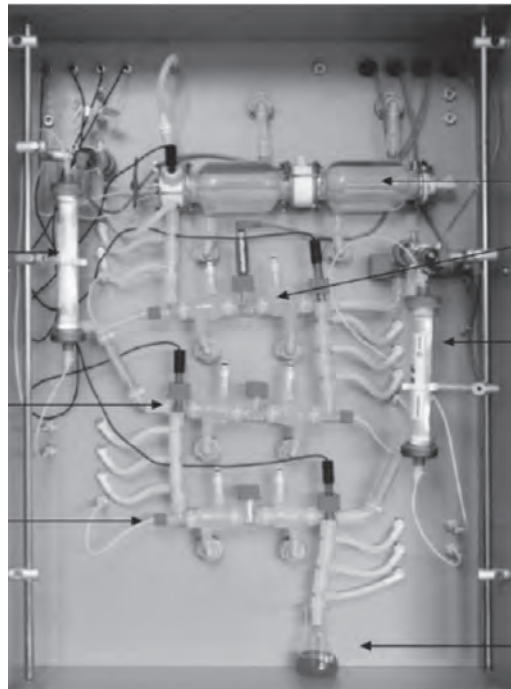
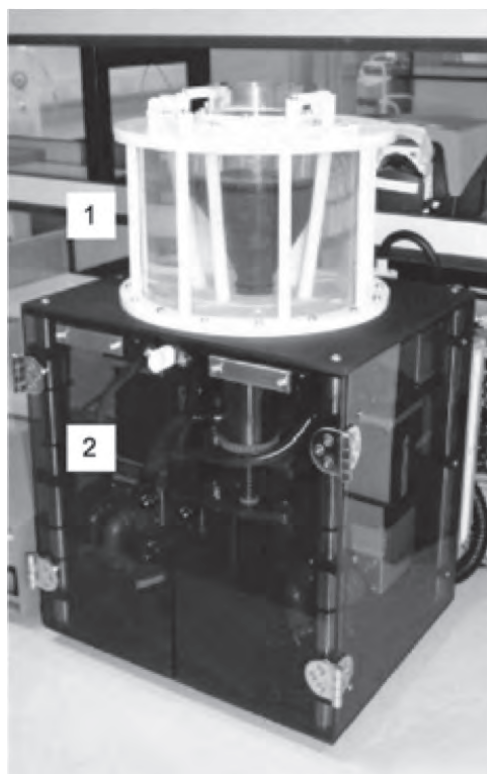


Figure 4. TIM-1: A simulator for the stomach and small intestine. Reprinted with permission from [4]. Copyright 2010 American Chemical Society.



*Figure 5. DGM: A simulator for the stomach. Reprinted with permission from [4]. Copyright 2010 American Chemical Society.*

The second strategy is the creation of test systems and test protocols that enable the simulation of segregated biorelevant conditions. This can be achieved in many different ways as it has been reviewed recently [4]. The advantage of the first strategy is that such devices have, in principle, the potential to generate predictive data on the pharmaceutical availability during all stages of drug development, from the compound to the final formulation. The disadvantage is the high complexity that necessarily results in extensive and time-consuming experiments. The second strategy has the advantage of simplicity. It enables the consecutive simulation of different biorelevant factors that impact oral drug delivery systems during the GI passage. The simple strategy allows investigation of the impact of selected physiological factors of biorelevant intensity on the drug delivery processes. In such a way the critical parameters for the tested formulation can be identified in a combination of a basic experiments. However, the test apparatus and protocols used in the second strategy are typically not suitable for the prediction of drug bioavailability, i.e. blood plasma levels, but for the prediction of the pharmaceutical availability depending on the drug delivery system. Accordingly, they can be seen as formulation test tools.

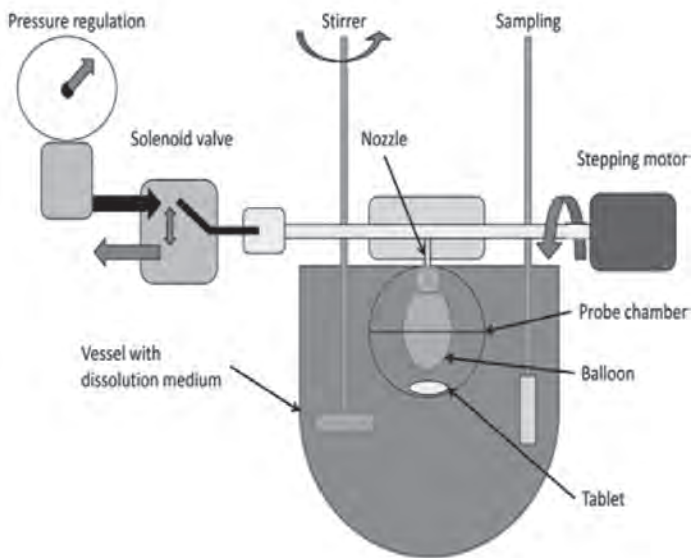


Figure 6. Schematic of the dissolution stress test device.

In our laboratories we are pursuing the second strategy. Our first approach was the development of the dissolution stress test device (Figures 6, 7), a dynamic biorelevant test device that maintains major elements of the compendial dissolution test setups (USP Apparatuses 1 and 2) but adds the functionality of applying pressure of biorelevant intensity as well as enforcing dosage form movement (transport) patterns of physiological frequency and velocity [8, 9, 10].



Figure 7. Dissolution stress test device: Prototype in development by ERWEKA.

### 3. Experiences with the dissolution stress test device

The exposure of oral dosage forms to biorelevant hydrodynamic conditions and mechanical forces of physiological intensity enables the identification of formulation failures due to gastrointestinal stresses (dose dumping behaviour) as it has been observed for diclofenac extended release tablets (Figure 8) [8, 11].

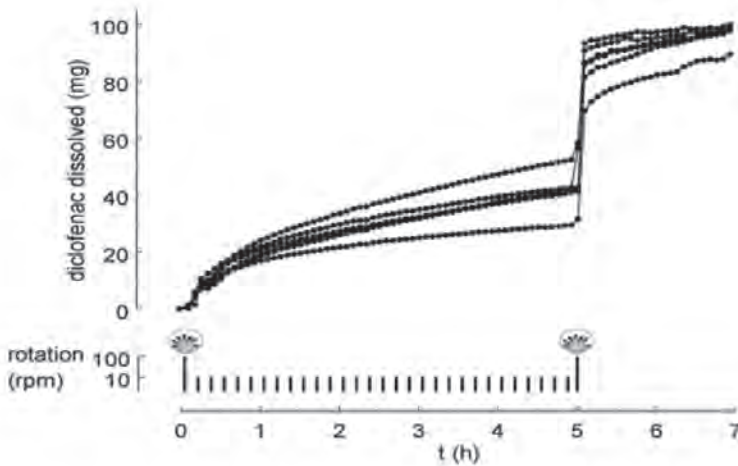


Figure 8. Dissolution profile of diclofenac extended release tablets (Voltaren retard, 100 mg diclofenac) under biorelevant stress test conditions [8].

We have also observed that the susceptibility of modified release dosage forms towards episodes of biorelevant gastrointestinal mechanical and hydrodynamic stresses is often dependent on the dissolution medium. This is illustrated in figures 9 and 10. In these experiments dose dumping from test amitriptyline tablets under stress test conditions has only been observed after five hours incubation in compendial phosphate buffer of pH 6.8 (Figure 9) but when the same tablets are incubated in simulated intestinal fluid (FeSSIF) dose dumping occurs within the first hour (Figure 10).

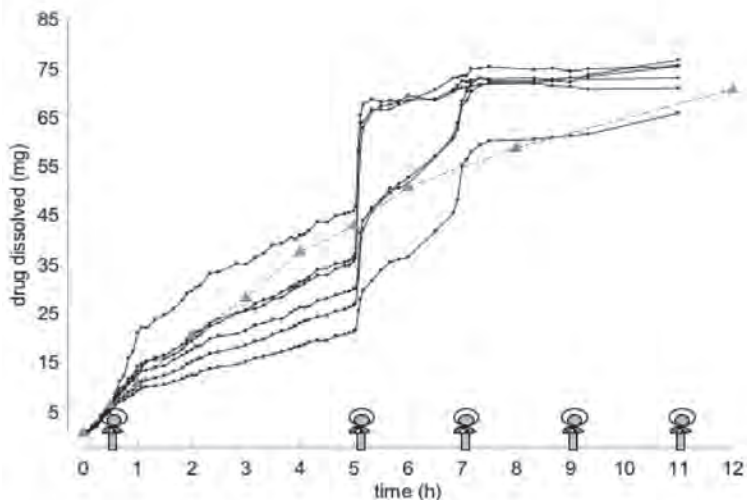


Figure 9. Dissolution profile of six amitriptyline extended release tablets (75 mg amitriptyline) under biorelevant stress test conditions in phosphate buffer pH 6.8. The triangles connected with the dashed line represent the mean ( $n = 6$ ) dissolution profile obtained using the same dissolution medium and USP apparatus 2 at a stirring rate of 100 rpm.

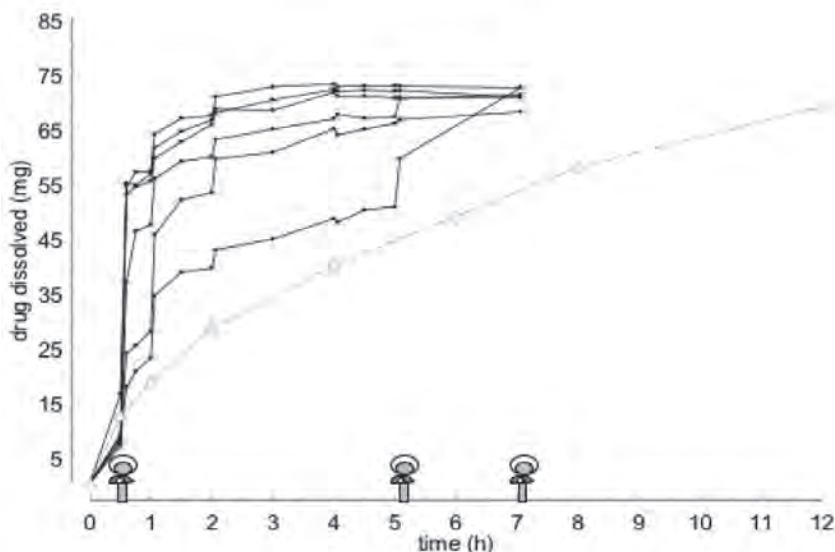


Figure 10. Dissolution profile of six amitriptyline extended release tablets (75 mg amitriptyline) under biorelevant stress test conditions in FeSSIF. The triangles connected with the dashed line represent the mean ( $n = 6$ ) dissolution profile obtained using the same dissolution medium and USP apparatus 2 at a stirring rate of 100 rpm.

## 4. Future developments

In the dissolution stress test device previously described (Figure 7) the aim is to simulate the conditions oral dosage forms meet during longer periods of gastrointestinal transit, as is the target for modified release dosage forms. As a next step we are currently working on an extension of the dissolution stress test device to enable the characterization of immediate release dosage forms under biorelevant (hydro)dynamic conditions. As such our primary targets are the development of an accessory to the dissolution stress test apparatus and the implementation of test programmes that enable the characterization of the behaviour of oral immediate release formulations under gastric and duodenal conditions. This requires the simulation of parameters including hydrodynamics, media volume, gastrointestinal motility and transport, and the challenge is to find a simple approach that is as close to *in vivo* reality as possible. The result of this development is the so-called “dynamic open flow through test apparatus” which is an accessory module to our stress test apparatus (Figure 11).

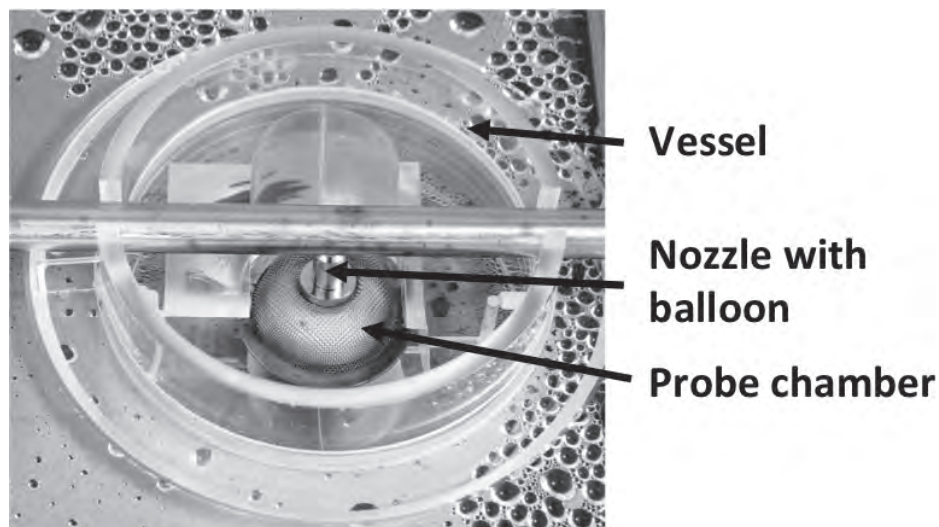


Figure 11. Dynamic open flow through test apparatus

## 5. Conclusions

With the increasing knowledge on the physiological conditions dosage forms meet in the gastrointestinal tract significant advances have been made in the design of both biorelevant test equipment and media. Despite the many hurdles and current “unknowns” it is our ultimate goal to contribute to the development of *in vitro* test set-ups that have the potential to replace *in vivo* studies at least in the field of bioequivalence testing.

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# ASSESSMENT OF GASTROINTESTINAL TRANSIT IN FORMULATION DEVELOPMENT: METHODOLOGY & INTERPRETATION

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## Abstract

Oral drug delivery remains the mainstay of patient treatment although the candidate drugs of the new millennium are becoming increasingly difficult to formulate for good systemic absorption. There are sharp transitions in the luminal environment moving from mouth to stomach, stomach to duodenum and ileum to caecum and these impact on dispersion of the dosage form and solubility of the active pharmaceutical ingredient. Food, posture, disease and time of dosing, all cause changes in the length of time that the dosage form will spend in these different environments. The pattern of transit also impacts on exposure. For example, considering a slowly absorbed material, a prolonged retention in one area of the gut may lead to increases in absorption, particularly if absorption promoters are employed. This environmental control cannot be mimicked in a conventional dissolution apparatus.

If we can relate the phases of drug absorption in patients or animals to position in the gut, each data set will yield immensely more valuable information, essential during early formulation development. The central issue is that once the dose has been swallowed, the investigator needs a tool to image the formulation. We now have an impressive array of interior imaging modalities, from miniature endoscopes, through to camera capsules and exterior technologies including scintigraphy, MRI and magnetic moment imaging. Surgeons have explored these techniques and developed standardized protocols for assessment. Pharmaceutical scientists have taken the system one stage further with purpose-built regionally positioned release systems. This short article considers the advantages and limitations of the approaches and considers future avenues for development in the technology.

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## Keywords

*Caplet, coating, gamma imaging, gastric emptying, gastrointestinal transit, tablet.*

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## 1. Introduction

Formulation performance is governed by a multitude of influences within a living environment. These include changes in pH, changes in ionic composition, the degree of agitation, pressure stress and propulsion. These effects show large spatial and sometimes temporal changes along the g.i. tract, not reflected under compendial conditions in a conventional dissolution apparatus and *in vivo-in vitro* relationships become unreliable or difficult to establish. Clearly, methods are needed that would allow the formulation dispersion to be seen in the body such that each plasma concentration time profile could be understood. The 'black box amplifier' between the dissolution stage of the formulation and the plasma kinetics had to be understood.... and pharmaceutical sciences turned to clinical science as a source of robust, discriminating technology that could measure whole gut transit [1,2].

The rise of the use of imaging techniques preceded the development of physiologically based models in pharmacokinetics as techniques such as gamma scintigraphy provided information that discriminated between the behaviour of single matrix, dispersing and disintegrating systems in man. Previous drug absorption screens had been largely dependent on laboratory procedures such as the perfused Doluisio loop or everted sac models. The rise in diagnostics provided agents that could be easily incorporated into formulations based on simple kits using [<sup>99m</sup>Tc] sodium pertechnetate as a starting material as it was available on demand from a Mo-99 generator, supplied as a portable item to the hospital radiopharmacy. More exotic pharmaceuticals included the [<sup>125</sup>I] iodinated substrates and derivatives produced by the same process but labelled with [<sup>123</sup>I] or [<sup>131</sup>I] which provided gamma-labelled formulations that could be imaged in animals [3]. Before the wider use of positron emission tomography, drugs which could be produced with the stable nuclide substituted by an unstable, gamma emitting radionuclide were rare (such as [<sup>125</sup>Sb]-sodium stibogluconate [4]. The need to study targeting specificity was acute in the development of cancer chemotherapy constructs. As techniques tended to use planar 2D imaging, it was easiest to image a flank tumor, subtracting the circulating activity from a region of interest constructed over the contralateral limb.

Gamma scintigraphy allowed multiple labels to be imaged with satisfactory information from 2D images at low dosimetries, and therefore food-formulation interactions to be studied. As gamma imaging became mature, progress was being made in the field of magnetic resonance imaging in which proton relaxation could be imaged, giving highly detailed maps of tissue and some formulations particularly oils [5]. The availability of sensitive Hall effect transistors allowed the development of portable magnetic moment imaging which supplemented the exquisitely sensitive highly shielded systems. A recent review with Professor Weitschies has compared the imaging modalities in research and for further information, the reader is referred to this article [6].

## 2. Using imaging to identify transit issues in the gastrointestinal tract

The complexity provided by the dynamic interactions between control systems in the gut, provides a fascinating arena of study. Food, posture, disease and time of dosing all cause changes in the length of time that the dosage form will spend in these different environments. The pattern of transit also impacts on exposure, which may not be desired. The ability of tablets to transit the oesophagus is related to several properties of the formulation including size, surface area, shape and coating. The tendency of a tablet to stick increases with surface area, and coated tablets tend to be less sticky than uncoated tablets [7, 8]. Published literature on the impact of modern tablet coatings on oesophageal transit is minimal. Channer and Virjee (1985) showed that the clearance of plain, sugar-coated, enteric-coated and film-coated tablets in 34 patients was strongly influenced by coating and by posture [9]. The authors reported 100% clearance of film-coated tablets in 13 seconds; whereas full clearance of the plain uncoated formulation was observed in only 60% of subjects at this time. The findings also confirmed their earlier report that oval coated tablets showed the fastest oesophageal transit in the erect position, even when swallowed with low volumes of water.

In a scintigraphic study of modern coating materials, solid oral dosage forms were given with a minimum amount of water to allow the effect of coatings on oesophageal transit to be studied. Data from part of the study is presented in Figure 1.

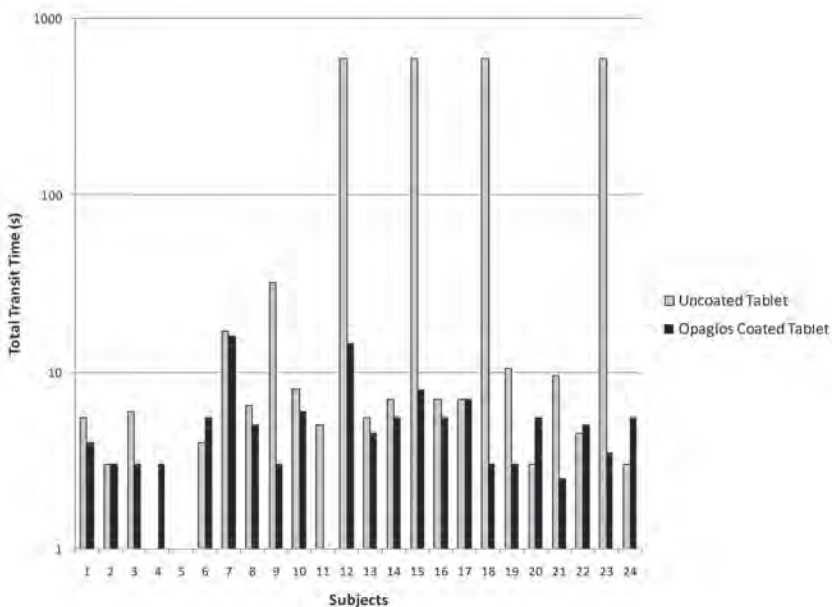


Figure 1. Oesophageal transit times in 24 subjects comparing uncoated and coated caplet-shaped tablets (unpublished data).

Different industry standard film coatings (Opaglos® 2, Opadry® and Opadry® II 85; Colorcon) were used with caplet tablets. 30ml was selected as the volume of water for dosing as this volume has been shown to detect formulations prone to oesophageal adhesion and also represents minimal volumes of water that patients may ingest with the risedronate tablet [10]. The data illustrates the potential dangers to patients, associated with uncoated tablets. This is a concern as health providers may be unaware of the issues associated with cheaper generic supplies. A proportion of the elderly public will have swallowing difficulties. Ekberg & Feinberg measured oesophageal function in 56 asymptomatic patients (without dysphagia) and found normal clearance in only 16% of the cohort, mean age 83 years [11]. The worst problems occur with buoyant dosage forms, since elderly patients lack the ability to swallow the water and the capsule simultaneously [12].

### 3. Stomach to intestine transfer

It is often assumed that drugs can be absorbed from the stomach, but few drugs undergo significant absorption directly through the gastric mucosa into the systemic circulation. Certainly, partitioning is likely to occur as a function of the pH-pKa relationship and thus there may be luminal loss when the pyloric sphincter is occluded, but the usual source of a rise in blood levels whilst the unit is in the stomach is emptying of the dissolved or finely disintegrated phase through the pyloric sphincter. Drugs with high solubility in the gastric milieu and high permeability provide points for discussion, since gastric emptying must be faster than dissolution if a simple relationship between dissolution and absorption is to be observed. In this situation, postural effects will become important, for example lying down causing the fundus to sink into the abdomen which prevents emptying. Periodic turning movements and intake of water will cause the appearance of transient, early peaks. Some individuals on the collected plasma concentration-time profiles display a bimodal curve as illustrated in Figure 2 especially if the subjects have access to water *ad libitum*. The dissolved drug will be emptied from the stomach into the duodenum as the water empties.

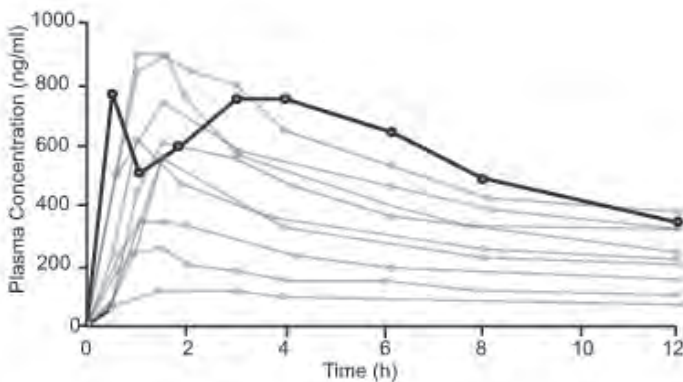


Figure 2. Appearance of a bimodal trend in one individual due to early gastric emptying (probable cause, intake of water) following dosing with 100 mg development formulation (moderately soluble base in conventional tablet).

Deliberate retention, or more correctly gastroretention can be achieved with swelling dosage forms. This might be useful for drugs with a narrow absorption window at the upper gastrointestinal tract; for example, bases that precipitate on transfer to the jejunum. In the examination of a large number of scintiscans collected after the intake of labelled food, there are obvious differences between stomach shapes as shown in Figure 3. These anatomical differences become important in the transit of single units and in particular, those that swell slowly in the stomach. In the steerhorn shaped stomach, as shown in the right of the figure, there is more chance of an early exit compared to a J-shaped stomach during propagation of a contractile wave.



*Figure 3. Differences in gastric anatomy and phase of a meal affect stomach shape. Scintiscan on the left shows fundal relaxation with the bulk of the meal held in the upper stomach. A typical 'J' shape is noted. The scintiscan on the right illustrates a tablet given to a fasted individual, positioned in the body of the stomach. Note the shallowness of the profile – a 'steerhorn' shaped stomach.*

The opposite situation, attempting to increase the rate of gastric emptying, is important to achieve early relief of pain with mild analgesics. These materials generally fall into BCS class 1 and therefore gastric emptying and not dissolution rate is the controlling variable with regard to the onset of drug action. In the design of a faster onset drug delivery system, relaxation of the duodenum was achieved by incorporating sodium bicarbonate into the formulation. It was expected that this would help empty the stomach in the fasted condition, but it was surprising to us that it occurred in the fed mode [13]. The reason was that the effervescence allowed the material to spread to the greater curvature of the stomach and the acid secretion created a pathway around semi-solid components of the meal. This phenomenon, referred to as 'magenstrasse' by German radiologists, allows the earlier emptying of the liquid slightly ahead of the bulk of the meal as illustrated in Figure 4.

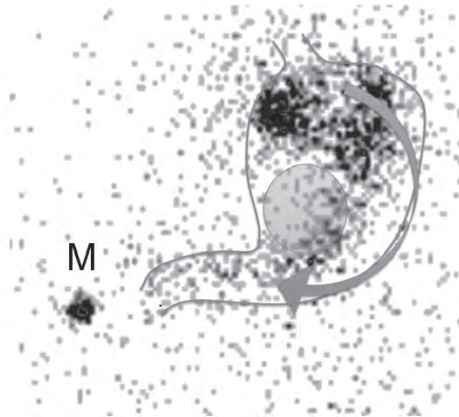


Figure 4. The mass of food has consolidated and the effervescent tablet disperses at the top of the stomach. The contents then move around the unlabelled food. From reference 13.

It would be useful to establish a more reproducible emptying of tablets and we have previously observed that a light meal stabilises the emptying pattern of non-disintegrating tablets in young volunteers. In developing a model for gastroparesis, we needed a model meal that would reduce inter and intra-subject gastric emptying rates to a minimum, allowing treatment modalities to be examined [14]. At Nottingham, we had previously used a liquid parenteral meal to provide reproducible pH conditions and emptying rates to study the behaviour of antacids and anti-reflux agents. Figure 5 illustrates that highly reproducible emptying rates can be achieved with a standard portion of Clinutren®, given fasted or 3 hours after a light meal (Goodman et al., in preparation). The key parameters are that sufficient calories are given to evoke the fed mode and the liquified medium calories meal contains no solids to be processed during the formation of chyme.

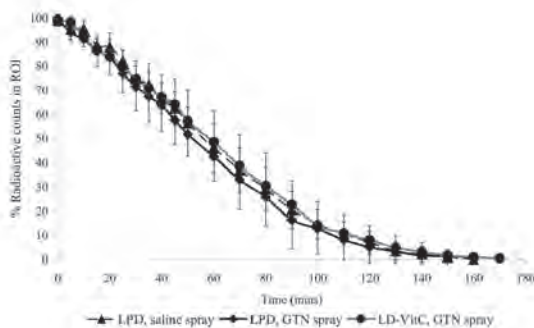


Figure 5. Emptying curves of Tc-99m labelled enteral feed, given after various unsuccessful attempts to induce a gastroparesis. From Goodman et al., in preparation.

The transit time in the duodenum is very fast (typically less than 5 minutes), and measurements by magnetic moment imaging or gamma show that after a fat load, transit of the meal slows at the jejunum, leaving the duodenal segment empty [15]. The role of the duodenum as a sampling zone for gastric contents and adjustment of the duodenal bulb-gastric pressure difference would be compromised if this segment of the gut did not clear. Stasis of small intestinal contents is observed at various times during the day and this may contribute to increased drug absorption if efflux or degradative mechanisms are overwhelmed. As the food-formulation matrix move down the g.i. tract towards the ileocaecal junction, the materials lose water and the area occupied is seen to reduce until quite tight bunching is seen at the ileocaecal junction. On taking a meal, the contents spread out again in the caecum. The formulation is subjected to mild crushing force during the transit through the ileocaecal junction and softened formulations may be broken at this point causing an increase in surface area of undissolved drug particles leading to a second or late peak in plasma drug levels. The entry into the large bowel is triggered by gastro-colic activity and large migrating movements across the bowel allow the entry of materials from the small intestine to empty. Colon activity is therefore a key determinant of small intestinal exposure and since the colon activity decreases at night, formulations taken later in the day have an increased small bowel exposure time.

In conclusion, imaging has provided a wealth of understanding concerning the relationship of gastrointestinal physiology with drug absorption. No one technique is 'best' since all shed light on the vagaries of inter and intra-subject behaviour.

## 4. Acknowledgements

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# MODELING DRUG RELEASE FROM SOLID DOSAGE FORMS IN THE GI TRACT

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## Abstract

A brief overview is given on the current state of the art of mathematical modeling of drug release from solid pharmaceutical dosage forms within the gastro intestinal tract (GI tract). An introduction into the basic mass transport phenomena is provided, including diffusion, swelling and dissolution. Two specific examples are described in more detail: A polymeric matrix tablet and a lipid extrudate. Based on a thorough physicochemical characterization of the systems before and after exposure to the release medium, adequate mathematical theories can be identified and used to quantitatively describe drug release. Importantly, such models should be mechanistically realistic and allow predicting the effects of key formulation parameters on the resulting drug release kinetics. In these cases, *in silico* simulations can help saving time and costs during product optimization.

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## Keywords

*Extrusion, controlled drug release, diffusion, dissolution, mathematical modeling, prediction, swelling, tablet.*

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## 1. Introduction

To be able to accurately control the rate at which a drug leaves a solid dosage form within the GI tract, the active ingredient is generally embedded within a matrix former. Often polymers are used for this purpose. However, lipids also offer a great potential to precisely control drug release. Upon contact with aqueous body fluids after administration, different types of mass transport phenomena can be involved in the control of drug release. Very often, the following processes play a role [1]:

### A: Diffusion

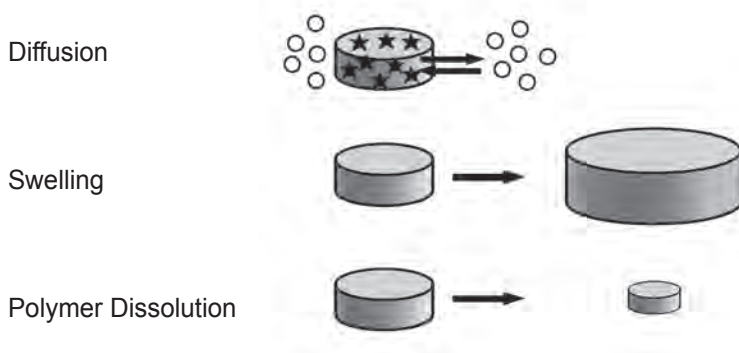
Importantly, different species can be diffusing: Water (represented as white circles in Figure 1) diffuses into the system (e.g. a cylindrical matrix tablet), drug (represented as black stars in Figure 1) diffuses out of the device, and optionally water-soluble excipients can also diffuse into the surrounding bulk fluid.

### B: Swelling

Many polymers used for oral controlled drug delivery significantly swell upon contact with water. The two main consequences for subsequent drug release are: a) an increase in the lengths of the diffusion pathways to be overcome (slowing down drug release, Figure 1), and b) an increase in the macromolecular mobility and, hence, also in drug mobility (accelerating drug release). Depending on which of these two phenomena is more pronounced in a specific system, the overall drug release rate is decreased or increased compared to a non-swelling device.

### C: Polymer dissolution

Often, water-soluble polymers (such as hydroxypropyl methylcellulose - HPMC) are used as matrix formers for oral controlled drug delivery [2]. In these cases, the matrix former itself starts to dissolve upon contact with the aqueous body fluids, resulting in decreased diffusion pathway lengths (Figure 1) and, thus, increased drug release rates compared to a non-dissolving matrix.



*Figure 1. Schematic presentation of the phenomena, which are most frequently involved in the control of drug release from solid dosage forms in the GI tract. The white circles represent water molecules, the black stars drug molecules.*

In certain solid dosage forms, only one of these phenomena is dominant and determines the overall release rate. In other cases, a combination of two or even all of these processes (and optionally other phenomena) might be of major importance [3]. For the mathematical modeling of drug release from advanced drug delivery systems it is decisive to consider all major phenomena and to neglect those which do not significantly contribute; the simpler the theory, the easier it is to be applied and the less parameters are required for quantitative predictions.

In order to identify which are the crucial mass transport processes controlling drug release from a specific type of dosage form, the latter should first be characterized as thoroughly as possible before and after exposure to relevant release media. This should ideally include the monitoring of potential dimension changes, the measurement of the dry and wet mass of the systems, drug release kinetics, glass transition temperature (if applicable), mechanical properties and inner and outer morphology. Based on these experimental results, appropriate, mechanistically realistic mathematical models can then be identified. These models should be fitted to sets of experimental data to have a first idea of their applicability. If good agreement is obtained between theory and experiment, these fittings can be used to determine the system specific parameters, e.g. the diffusion coefficient of the drug within a polymeric matrix. Once all these parameters are known (in case of simple models only very few parameters are required), the model should be used to quantitatively predict the effects of specific formulation and/or processing parameters on the resulting drug release kinetics. These theoretical predictions should then be compared with experimental results, obtained only after the predictions were made. Observing good agreement between such theoretical predictions and independent experiments is a much more reliable indication for the validity of the model than obtaining good agreement between model fittings (during which at least one parameter was adapted) and experimental data.

Two specific examples will be presented in more detail: a polymeric matrix tablet and a lipid extrudate.

## **2. Case study: Kollidon® SR-based matrix tablets**

Kollidon® SR is a formulation consisting of 80 % poly(vinyl acetate) (PVAc), 19 % poly(vinyl pyrrolidone) (PVP), sodium lauryl sulfate and colloidal silicon dioxide in powder form. Different types of tablets consisting of Kollidon® SR and 0-60 % freely water-soluble diprophylline were prepared by direct compression [4]. The systems were characterized by drug release measurements in 0.1M HCl and phosphate buffer pH 7.4, monitoring of changes in the tablet's height and diameter, morphology as well as dry mass loss upon exposure to the release media. Based on these results, the following equation has been identified, quantifying drug diffusion in radial and axial direction in a cylindrical tablet with initial homogeneous drug and excipient distribution [5]:

$$\frac{M_t}{M_\infty} = 1 - \frac{32}{\pi^2} \cdot \sum_{n=1}^{\infty} \frac{1}{q_n^2} \cdot \exp\left(-\frac{q_n^2}{R^2} \cdot D \cdot t\right) \cdot \sum_{p=0}^{\infty} \frac{1}{(2 \cdot p + 1)^2} \cdot \exp\left(-\frac{(2 \cdot p + 1)^2 \cdot \pi^2}{H^2} \cdot D \cdot t\right) \quad (1)$$

where  $M_t$  and  $M_\infty$  are the absolute cumulative amounts of diprophylline released at time  $t$  and infinite time, respectively;  $q_n$  are the roots of the Bessel function of the first kind of zero order [ $J_0(q_n)=0$ ];  $R$  and  $H$  denote the radius and height of the cylinder. Equation 1 is an analytical solution of Fick's second law of diffusion considering the given initial and boundary conditions in this particular case.

Importantly, good agreement between theory and experiment was obtained when fitting Equation 1 to different sets of experimentally determined drug release kinetics, irrespective of the initial drug loading (up to 40 %) and type of release medium (data not shown). Based on these fittings, the apparent diffusion coefficient of diprophylline in these tablets could be determined and Equation 1 could be used to theoretically predict the impact of the tablet height on the resulting drug release kinetics (illustrated as curves in Figure 2).

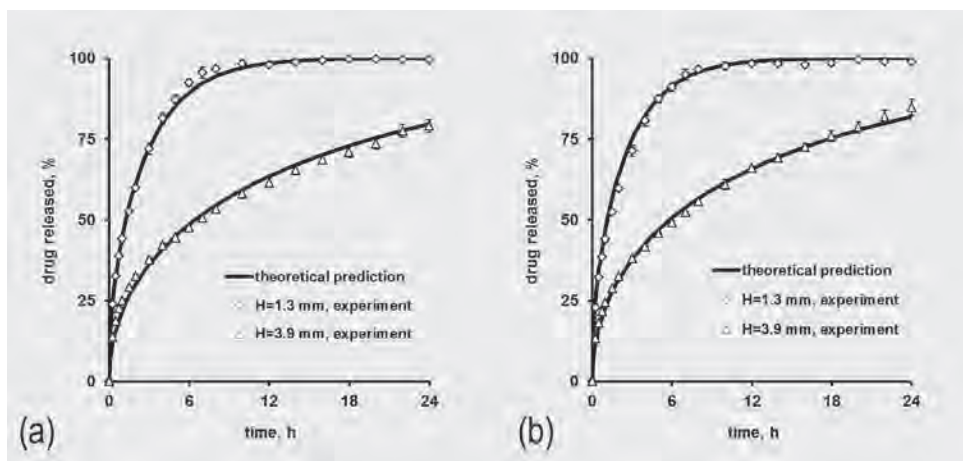


Figure 2. Theoretical prediction (curves, Equation 1) and independent experimental verification (symbols): Effects of the initial tablet height (indicated in the diagrams) on diprophylline release from Kollidon® SR-based tablets in: (a) 0.1 M HCl and (b) phosphate buffer pH 7.4 (drug loading: 20 %, initial tablet diameter: 11.3 mm). Adapted from [4]

Interestingly, these theoretical predictions could be verified by independent experiments (symbols in Figure 2), obtained only after the theoretical predictions were made. The observed good agreement (curves and symbols) indicates that indeed drug diffusion in radial and axial direction in the cylindrical tablets is the release rate controlling process in these systems. Also, it becomes obvious that such *in silico* simulations can help reduce time and costs during product optimization.

### 3. Lipid extrudates

Cylindrical extrudates were prepared consisting of the freely water-soluble drug diprophylline, the lipid matrix former glycerol tristearate and the pore former polyethylene glycol (PEG) or crospovidone [6]. The blend ratio was 50:45:5% w/w/w. The extrudates had a diameter of 0.6, 1, 1.5, 2.7 and 3.5 mm, respectively. They were manufactured using a twin screw extruder at 65 °C and subsequently cut into cylinders of different length. Diprophylline release was measured in a USP basket apparatus in water at 37 °C. Furthermore, the extrudates were characterized by Scanning Electron Microscopy (SEM), Differential Scanning Calorimetry (DSC) before and after exposure to the release medium. Assuming the same release mechanism and initial and boundary conditions as in Example 1 (Kollidon® SR-based matrix tablets), Equation 1 might also be applied in this case. Fitting this equation to sets of experimentally measured diprophylline release kinetics indeed led to good agreement between theory and experiment (data not shown), and allowed determination of the respective apparent drug diffusivities. Knowing these values, Equation 1 could be used to quantitatively predict the impact of the system dimensions on the resulting drug release kinetics. Figure 3 shows for example the theoretically predicted effects of varying the extrudates' radius from 0.6 to 3.5 mm. The curves show the theoretical predictions, which could be confirmed by independent experimental data (symbols). Thus, also in this case diffusion in radial and axial direction is likely to be the dominant mass transport process and product optimization can be facilitated using *in silico* simulations.

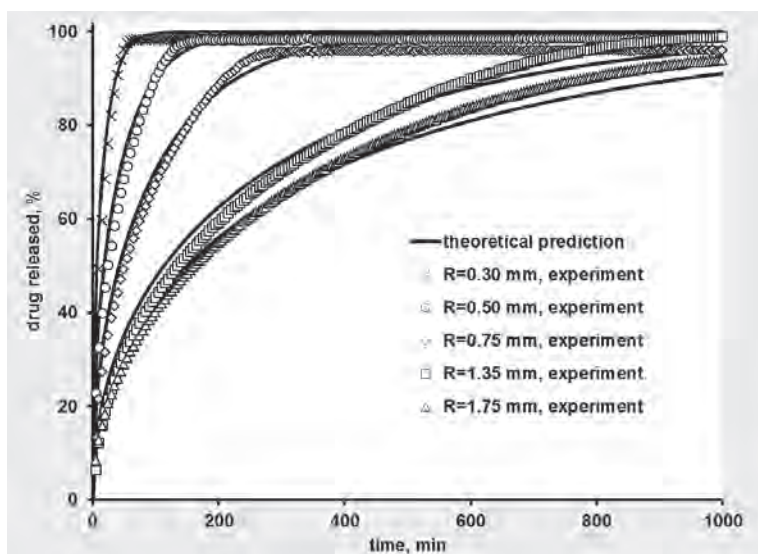


Figure 2. Theoretical predictions (curves, Equation 1) and independent experimental results (symbols): Diprophylline release from solid lipid extrudates in water at 37 °C ( $n = 3$ , standard deviation < 2%, not shown). The systems consisted of 50 % drug, 45 % glycerol tristearate and 5% poly(ethylene glycol) (PEG 20000) and were cylindrical in shape. The radius was varied from 0.3 to 1.75 mm (as indicated). Adapted from [6].

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GATTEFOSSÉ is an independent multinational company which creates, develops and manufactures specialized ingredients for the pharmaceutical and personal care industries.

Present in almost 50 countries worldwide, GATTEFOSSÉ provides extensive expertise in lipochemistry, biology and extraction from natural sources.

GATTEFOSSÉ offers the pharmaceutical industry innovative functional lipidic excipients for bioavailability improvement, sustained release formulation, lubrication, taste-masking, solubilization and penetration enhancement.

