

1992-1993

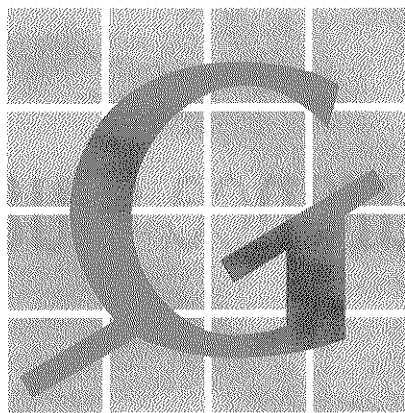


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BULLETIN TECHNIQUE

GATTEFOSSÉ REPORT

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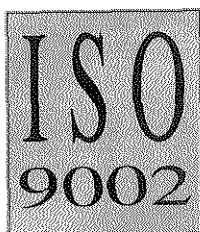
GATTEFOSSÉ REPORT

Santé,

Beauté,

Assurance Qualité,

Gattefossé.



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EDITORIAL

"La Connaissance a pour objectif l'Assurance,
l'Intelligence a pour Objectif l'Invention."

Le philosophe Michel SERRES résume par cette réflexion une problématique familière du galéniste.

Comment à la fois conjuguer l'absolue nécessité de sécurité attendue par le consommateur, et introduire l'élément inconnu et nouveau qui transforme l'ordre établi en innovation ?

En effet, le monde pharmaceutique n'échappe pas à la loi du marché qui impose nouveauté et par conséquent, rupture avec la tradition.

C'est autour de cette réflexion essentielle pour l'avenir de toute entreprise pharmaceutique que se sont déroulées les Journées Galéniques de St-Rémy de Provence 1992, démontrant ainsi que pour Gattefossé, l'innovation s'inscrit dans la continuité.

EDITORIAL

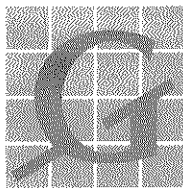
*"The Aim of Knowledge is Assurance,
the Aim of Intelligence is Invention."*

By this thought the philosopher Michel SERRES sums up a problem familiar to Galenists.

How can we juggle between the total safety expected by consumers, and the introduction of new, unknown, innovating elements which may transform the established order ?

The world of pharmaceuticals cannot avoid market law demands for new products and the resulting breaks with tradition.

This reasoning, essential for the future of all pharmaceutical companies, was behind the "Journées Galéniques de St-Rémy de Provence 1992", showing once again that Gattefossé innovation is an ongoing process.



GATTEFOSSÉ

SOFTGEL FORMULATION PROGRESS

PROGRES DES FORMULATIONS EN CAPSULES MOLLES

P. METZIGER - R.P. SCHERER - FRANCE

Connue depuis plus d'un siècle, la capsule molle n'a guère évolué jusqu'au début des années soixante dix avec l'encapsulation de solvants hydrophiles.

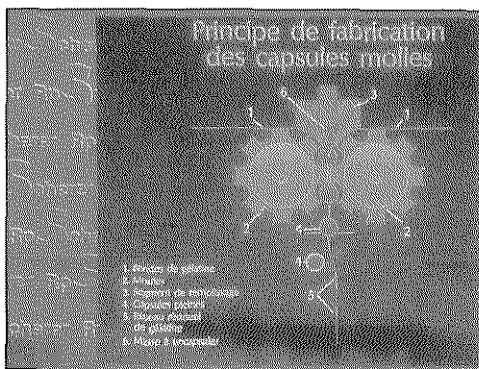
Ces solvants ont permis de véhiculer les principes actifs soit sous forme dispersée ou mieux encore sous forme dissoute.

Plus récemment, R.P. Scherer a développé des systèmes solvants brevetés très performants permettant ainsi non seulement d'améliorer les performances des molécules mais aussi de prolonger leur protection industrielle.

L'apparition de ces nouveaux systèmes a nécessité la mise au point de nouvelles tuniques pour les capsules molles afin de limiter les échanges entre l'enveloppe de la capsule molle et son contenu.

THE ROTARY DIE PROCESS

Figure I

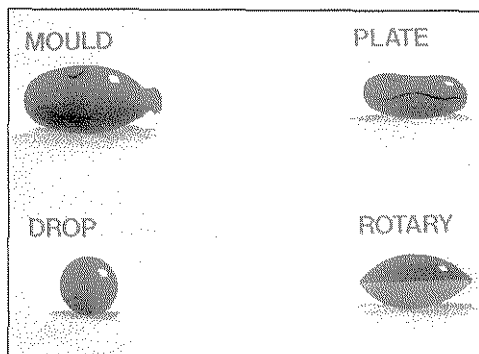


The manufacturing process uses *the rotary die method*, invented in 1933 by Robert Pauli Scherer whose first encapsulation machine is now housed in the Smithsonian Institution in Washington, D.C. Today softgels are produced on modern encapsulation machines running around the clock. The process consists in two

gelatin ribbons with calibrated thickness, formed from the molten gelatin mass and led to the die rolls. Accurately metered volumes of liquid fill material are injected between these gelatin ribbons. The injection of the liquid forces the gelatin ribbon to expand into the die pockets that determine the softgel shape. The formed softgel is heat sealed and automatically cut out between the two dies.

It exists other methods for the manufacturing of softgels out of the rotary die process:

Figure II



• The mould method:

This is the original method invented by Mr. Mothes in Paris in 1833. He used a leather mould with mercury inside. He dipped this into the molten gelatin. After the gelatin has set, he allowed the mercury to run out and then could pull the moulded capsule off, fill it with liquid and seal it with gelatin. This is a very laborious, inaccurate method with little variation in shape and size possible.

• The plate method:

This was invented to enable manufacturing chemists to produce larger numbers of capsules. The method consists of a metal plate with raised shoulders around holes which are the shape of the desired capsules. A thin sheet of gelatin is placed on the plate, the liquid poured onto the gelatin, another sheet placed on top of this and finally another of the metal plates placed on top. This pile was then pressed, forcing the oil to flow away from the high-pressure areas of the shoulders around the holes, the shoulders cut the gelatin, formed the seams and the capsules could be then stripped out. The method produced capsules of varying fill content and size and wasted much of the fill.

• The drop method:

This was an old Scherer patent but was not pursued because the rotary die method offers greater versatility and accuracy. Limitations with the drop method are that solids cannot be put into the fill or the shell and there is an upper limit to the size of capsule, about 9 round maximum (i.e. 0.5 ml/capsule). This method can only make round capsules.

Only the *rotary die method*, however, offers the possibility to have high volume productions in a large range of shapes (round, oval, oblong, tube, round-tube, twist-off tube, suppository,...), sizes (from 0.05 ml to 30 ml) and colors. The process also allows to fill liquids as well as solids preliminary put into solution or suspension.

A large part of R.P. Scherer's activity is devoted to the pharmaceutical industry, as well for

prescription products in the different therapeutic indications as for OTCs. The other segments of activity which have been developed more recently are the Health and Nutritional and Toiletry products and in a less large extent products for the food industry.

ADVANTAGES OF THE SOFTGEL VERSUS OTHER DOSAGE FORMS

The softgel is

- Economical
- Contains the correct dose
- Stable
- Elegant,
- Easy to administer
- Safe
- Therapeutically effective
- Protects its content against oxidation and hydrolysis

DEVELOPMENT ACTIVITIES

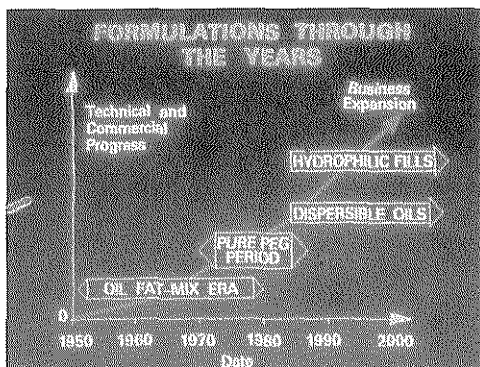
Additionally to its manufacturing activity, R.P. Scherer is also largely involved in the development of formulation technology both for shell and fill to enhance this dosage form according to the most modern advances in technology. Developments are performed by considering:

- the chemical characteristics to be studied: activity, degradation products, impurities, stability.
- the physical characteristics of the active ingredient which are needed to be known: particle size, particle shape, polymorphic form, bulk density, hygroscopicity, flow, freezing point, compression characteristics
- the biopharmaceutical characteristics on the finished product: solubility, dissolution rate, pka, partition coefficient, bioavailability, to assure the right efficiency, safety and performance of the product.

• Softgel formulations

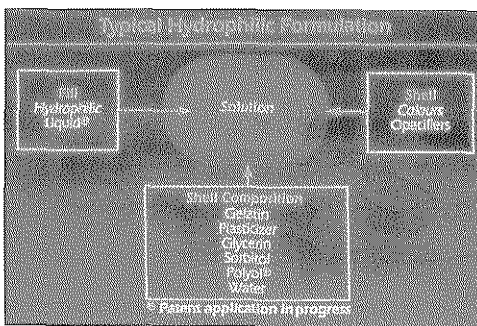
Softgel production started with liquids as fill material. Later on oily solutions or suspensions of pulverulent active ingredients have been used. Such formulations were based, additionally to oily excipients, on suspension agents such as waxes or hydrogenated oils as well as on products with surface active power such as soja lecithin. These formulations continue to be used nowadays.

Figure III



Hydrophilic solvents started to be used in the 70's, not without some stability problems due to the exchange between shell and fill. The major advantage of these solvents was the possibility to dissolve an active ingredient which enables high absorption rates to be achieved. New proprietary formulations of softgel shells have been developed by R.P. Scherer to limit this phenomenon of exchange between the hydrophile shell and the hydrophile content. Stability problems are therefore totally cleared up.

Figure IV



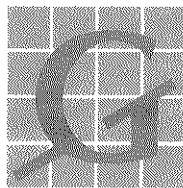
• Scherersol systems®

These are the result of the most recent developments to allow dissolution of active ingredients. These systems which are proprietary formulations, give the softgel product both a biopharmaceutical advantage due to

- optimal bioavailability
- more consistent absorption of drug
- more consistent delivery of drug
- higher accuracy of single doses
- higher consistency of doses from batch to batch
- possibility of lower dose or more effective treatment.

and a commercial advantage due to a longer protection of some active ingredients.

Nevertheless, there remains one excipient to be rather incompatible which is water. Therefore Gattefossé have developed anhydrous microemulsions which are currently tested in softgels and are still to be improved since the least exchange between one of the excipients and the microemulsion can lead the emulsion to break. These criterias are to be taken into consideration for the development and the presentation of microemulsions in softgels, which is the ideal dosage form for unit doses of liquids.



GATTEFOSSÉ

ORAL ANHYDROUS NON IONIC MICROEMULSIONS ADMINISTRATED IN SOFTGEL CAPSULES

MICROEMULSIONS ANHYDRES NON IONIQUES POUR VOIE ORALE PRESENTEES SOUS FORME DE CAPSULES MOLLES

E. GEORGAKOPOULOS - N. FARAH - G. VERGNAULT
GATTEFOSSÉ s.a. - FRANCE

D*epuis quelques années, le monde pharmaceutique s'intéresse aux microémulsions en tant que système promoteur d'absorption tant pour la voie orale que topique cutanée.*

Les capsules molles constituent, à priori, une forme séduisante et pratique pour présenter ces formulations de façon unitaire. Cependant, un certain nombre de problèmes de compatibilité ont dû être résolus afin de permettre cette présentation.

La formulation de microémulsions anhydres n'apporte cependant pas la solution à cette incompatibilité et une nouvelle orientation de ces formulations a dû être retenue.

INTRODUCTION

Historical review

(1) (2) (3) (4) (5) (6)

The first known formulation which can be considered as a microemulsion was elaborated in 1928. At this date, in the name of Miracal wax Company, RODAWALD finalised a floor wax which shows surprising properties.

It is only in 1940 that the scientific community began to be largely interested by this system, and the vulgarisation of the word "Microemulsion" appeared only in 1959.

After having been used in the petroleum assisted recuperation, microemulsions are considered by the pharmaceutical field as the new drug delivery system since a few years. (7) (8) (9)

General properties of micro-emulsions (10) (11) (12), (13) (14)

Microemulsions are liquid systems, macroscopically homogeneous, transparent, with low viscosity, thermodynamically stable, isotropic, composed of a polar phase, an organic phase (non miscible with the first one), and surfactant and cosurfactant compounds.

Their formation is spontaneous and do not require any important energy.

These characteristics are due to the specific microstructure of these systems which are composed of microdroplets of dispersed phase (15 to 200 nm) into the continuous phase.

The alternance of Surfactant and CoSurfactant molecules induce a dramatic decrease of interfacial tension. The length of the cosurfactant molecule as well as the medium ionic strength play a very important role in the size of the microemulsion existence field.

INTERESTS OF MICROEMULSION FOR ORAL USE

Today many pharmaceutical industries or universities are performing studies on the use of microemulsions for oral route specially for the absorption of peptides. (15)

Solubilizing properties

One of the most important interest of microemulsion is their high solubilization power. It is possible to dissolve poorly soluble active drugs in aqueous phase as well as in oily phase.

This property was largely used for the formulation of injectable products or blood substitutes (fluorocarbons as hemoglobin carriers) (20).

In addition, with the specific studies of microemulsion, it will be possible to dissolve in the same preparation incompatible drugs or lipophilic and hydrophilic drugs (21) (22).

Mechanism of oral absorption of microemulsions (16) (17) (18) (19)

Ritschel tried to elucidate the mechanism of absorption of molecules such as Ciclosporine, vasopressine and insulin orally or rectally administered in microemulsions.

After absorption of the preparation, the gastrointestinal fluid dilutes the microemulsion and gives larger size droplet aggregates forming a fine emulsion.

In the presence of bile salts, the emulsion will be partially digested and the remaining forms mixed micelles in which bile salts act as cosurfactant. Some mixed micelles can be obtained with the association of long chain and medium chain fatty acids.

All particles penetrate in the aqueous layer and the mucin, and will be absorbed following different ways : pynocytosis, diffusion or endocytosis.

Due to their structure, mixed micelles can dissolve a part of the lipids of the membrane or follow the way of facilitated transport. By the way of capillaries, the active drug can reach the mesenteric veins and the portal vein or can be absorbed by the general blood circulation going through the lymphatic system.

WHICH KIND OF EXCIPIENTS FOR ORAL ROUTE FORMULATION

Toxicity requirements

All the excipients used for the oral microemulsion formulation have to be exempt of toxicity for this route.

Generally, tri, di and mono glycerides are digested, metabolised and assimilated as well as food quality lipids.

Hydrolysis of esters of polyglycols gives fatty acids which are metabolised and assimilated. The remained polyglycols are rejected intact in the case of high molecular weight molecules.

However, it is wellknown that fatty acids with odd number of carbon atoms, or having very short chain or ramified chain are very difficult to be assimilated by the organism and have to be banished for the oral route.

ANHYDROUS MICRO-EMULSIONS FORMULATION

Constraints due to the softgel capsules

As you certainly know, softgel capsule needs specific formulations. The shell is composed of gelatin and plasticizers like glycerin, sorbitol, polyols, and contains about 6 to 10% of constitutive water.

In addition, it is possible to include also thickeners as hydrogenated vegetable oils, beeswax, colloidal silicon dioxide.

A lot of products can interact with the shell of the softgel.

Among these products, water seems to be the more problematic compound. Also, high concentration of propylene glycol alters the shell and formulated microemulsions must contain low quantities (below 20%) of this product.

Due to these obligations, we have developed anhydrous microemulsions in which aqueous phase is replaced by hydrophilic product or microemulsions with very low quantities of water which are able to absorb or to give up water from or to the capsule shell.

Substitution products for useful microemulsion phases

• Substitution of aqueous phase

In our case, microemulsion aqueous phase can be substituted by PEG 300, PEG 400, polyglycerol, propylene glycol or derivatives of diethylene glycol (e.g. TRANSCUTOL®).

• Selected lipophilic phase

This phase contains only products with clearly defined status and toxicity. They are essentially vegetable oils, fatty acid esters or modified vegetable oils. We have tested LABRAFAC® LIPOPHILE, Corn Oil, and LABRAFIL® M 1944 CS.

• Cosurfactant (CoS)

Selected products are derivatives of polyglycerol especially PLUROL® OLEIQUE (polyglycerol

Oleate) as well as polyglycol monocaprylate and caprylocaprate.

• Surfactant (S)

Tested surfactants are characterised by their very low aggressivity and toxicity. Their uses are wellknown since a long time in the field of topical microemulsions.

Among the most famous, LABRASOL®, non ionic surfactant compound of saturated polyglycolized glycerides as well as TRANSCUTOL®, diethylene glycol mono ethyl ether, show a very good compatibility with softgel capsule shell.

Other products like glycerolysed vegetable oils have been tested (MAISINE®, OLICINE® and PECEOL®).

Results - Pseudoternary diagrams

Non ionic surfactants used for the microemulsion formulation are issued from oleochemistry.

Among the retained products as substitutes of the aqueous phase, PEG and polyglycerol do not present enough larger fields of existing microemulsion.

• Couple LABRASOL® PLUROL® OLEIQUE (S-CoS) (fig. 1)

With this couple, microemulsions with corn oil are obtained for ratio S/CoS where Cosurfactant proportions are relatively high ($R < 1$).

In the other cases it is impossible to obtain microemulsions. On another hand, LABRAFAC® LIPOPHILE, used as oily phase with the same couple, gives larger microemulsion existence field for ratio up to 4.

• Couple TRANSCUTOL® - PLUROL® OLEIQUE (S - CoS) (fig. 2)

In this case, we obtain microemulsion existence field with corn oil only for the ratio 2, in opposition to LABRAFAC® LIPOPHILE which allows better results especially for ratio 6.

• Couple PECEOL®/PLUROL®
OLEIQUE (fig. 3)

This couple allows the formation of wide and very interesting field of existing microemulsions.

S. LABRASOL®
CoS. PLUROL® OLEIQUE
O. LABRAFAC® LIPOPHILE
W. PROPYLENE GLYCOL

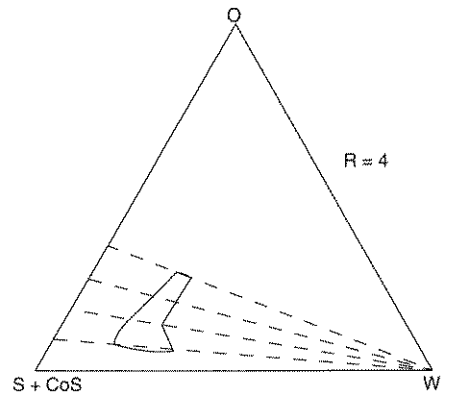
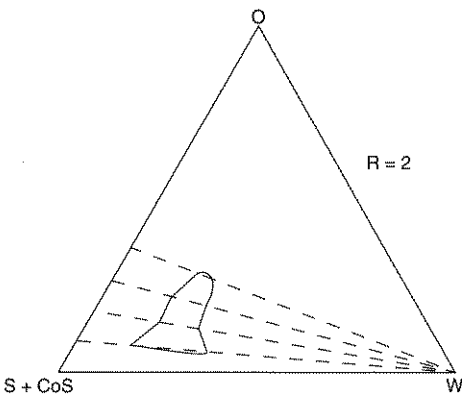
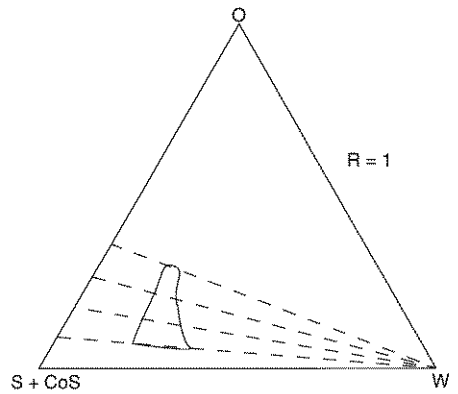
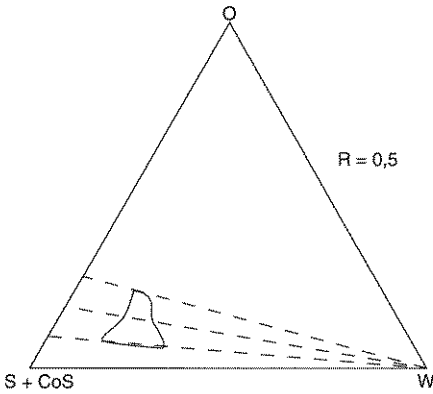
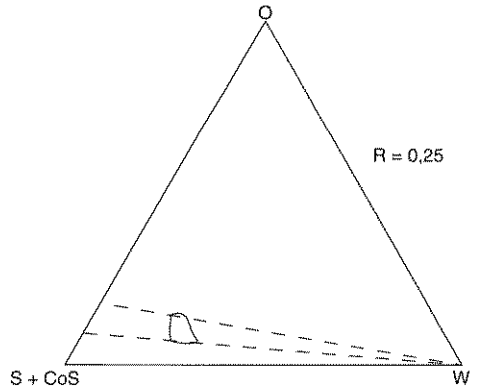


FIGURE 1 : Couple LABRASOL® / PLUROL® OLEIQUE (S-CoS)

S. TRANSCUTOL®
 CoS. PLUROL® OLEIQUE
 O. LABRAFAÇ® LIPOPHILE
 W. PROPYLENE GLYCOL

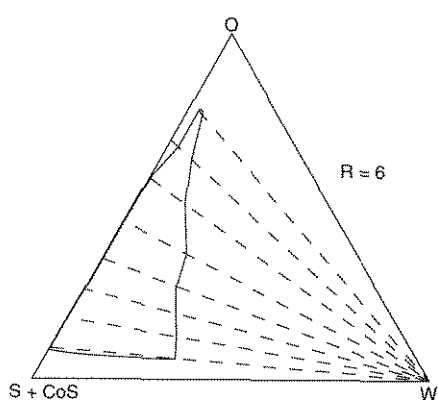
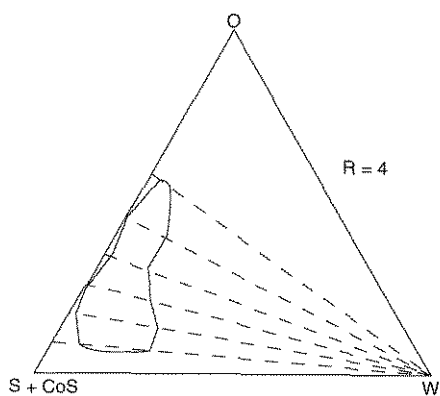
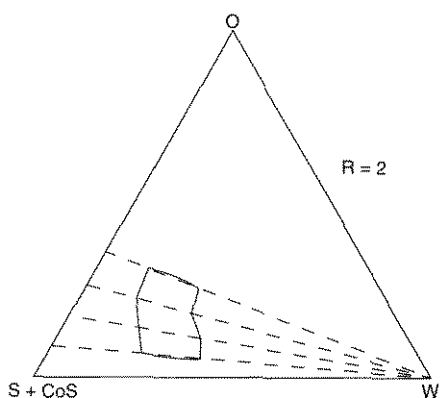
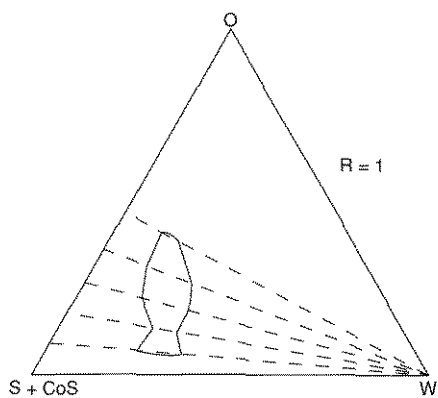
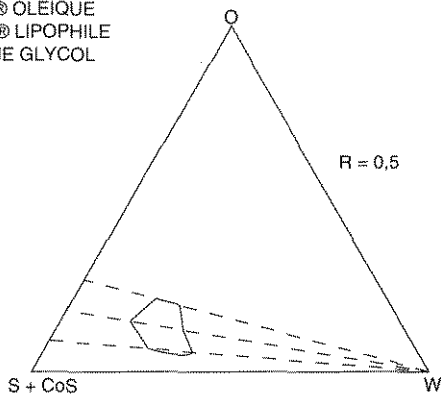
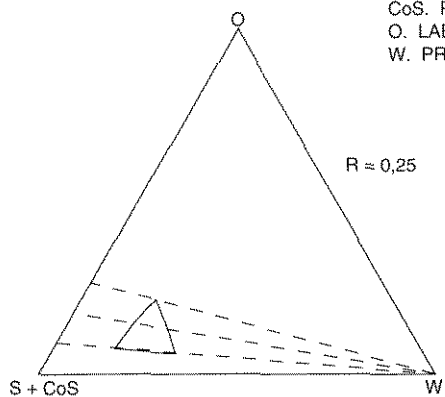


FIGURE 2 : Couple TRANSCUTOL®/PLUROL® OLEIQUE (S - CoS)

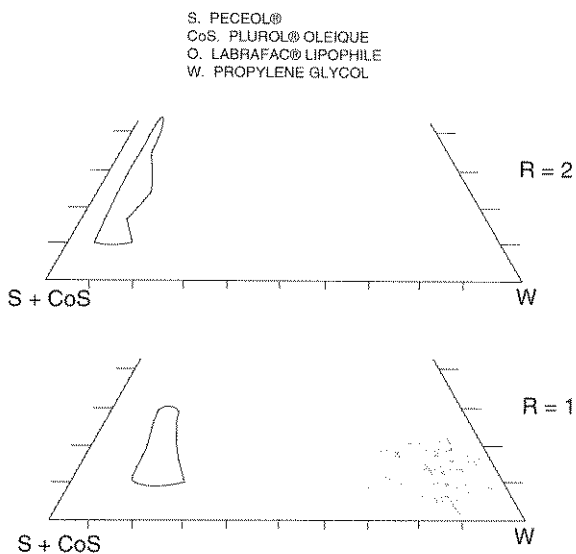


FIGURE 3 : Couple PECEOL/PLUROL® OLEIQUE (S - CoS)

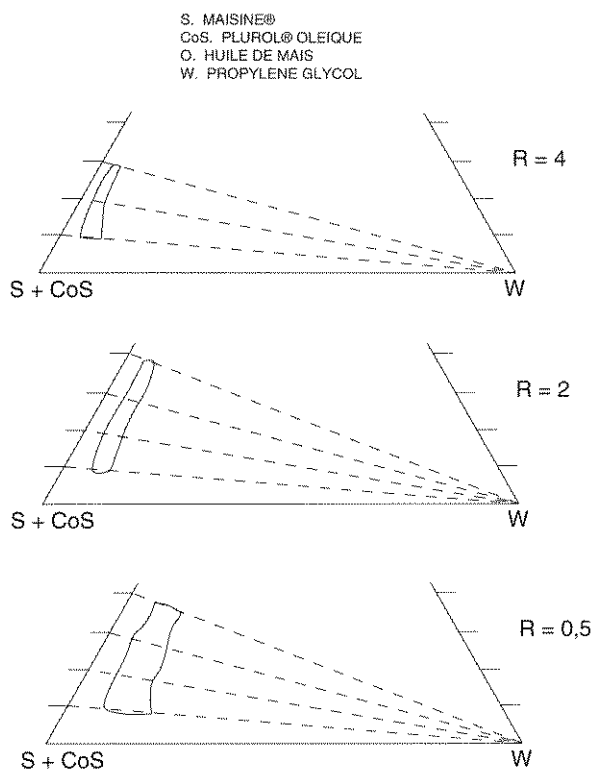


FIGURE 4 : Couple MAISINE® / PLUROL® OLEIQUE (S - CoS)

• Other couples (Figure 5)

The couples OLICINE®/PLUROL® OLEIQUE, MAISINE®/PLUROL® OLEIQUE give interesting microemulsion existence field but these formulations cristallize at room temperature during storage.

The cristallization problem of this kind of products is discussed in literature (23). In order to avoid this drawback, it is possible to use them associated with 10% of TRANSCUTOL®.

FIGURE 5 : MAISINE® WITH 10% TRANSCUTOL®

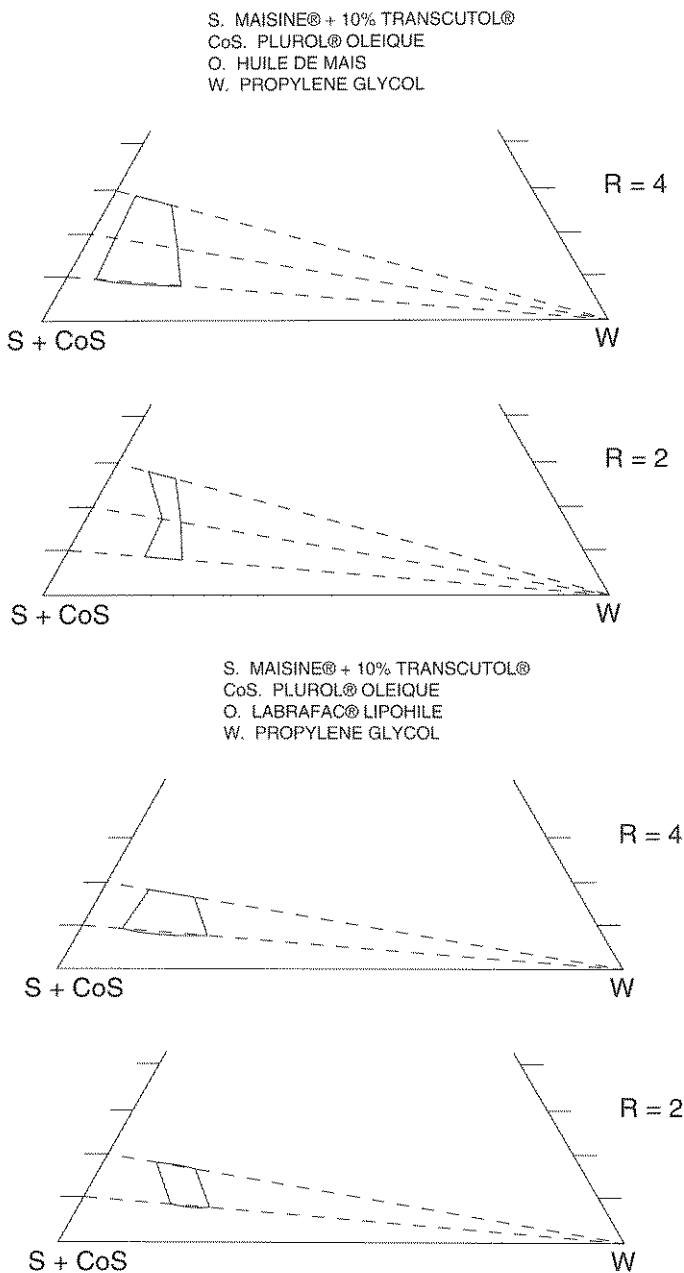


Table 1 : Various Winsor's System density (d_{20}^{20})

FORMULA	TA + CoTA	TA + CoTA + oil	MICROEMULSION	INFERIOR PHASE	INFERIOR PHASE	SUPERIOR PHASE	SUPERIOR PHASE
1	1.0292	1.0052	1.0211	Transparent	1.0477	Translucent	0.9860
2	1.0353	1.0077	1.0129	Transparent	1.0475	Translucent	0.9835
7	1.0353	1.0169	1.0182	Translucent	1.0961	Transparent	0.9932
9	1.0420	1.0232	1.0212	Translucent	1.0450	Transparent	0.9900
12	1.0992	1.0290	1.0298	Translucent	1.0956	Transparent	0.9867
14	1.0551	1.0319	1.0326	Translucent	1.0448	Transparent	0.9807
35	1.0034	0.9894	0.9896	Translucent	1.0349	Transparent	0.9775
36	0.9982	0.9795	0.9820	Translucent	1.0288	Transparent	0.9665
29	0.9982	0.9814	0.9900	Translucent	1.0204	Transparent	0.9663
30	0.9944	0.9764	0.9819	Transparent	1.0208	Transparent	0.9567
31	0.9930	0.9751	0.9802	Transparent	1.0163	Transparent	0.9555

WINSOR SYSTEMS

A lot of methods can be used to characterise microemulsion. We have retained a very simple method which needs no expensive equipment and which is based on Winsor concept.

Winsor concept reminder (24)

A few years ago, Winsor has classified the different phases which can be obtained on a pseudoternary diagram into 4 subsectors.

a) Winsor I

In this two phase system, the inferior one rich in surfactant is the microemulsion, and the other one, poor in surfactant is the oily phase.

b) Winsor II

This system is also biphasic, but in this one the inferior phase, poor in surfactant, is hydrophilic and the superior phase, rich in surfactant, is the microemulsion.

c) Winsor III

Winsor III system has 3 phases. The superior one is the oily phase, the inferior one is the aqueous phase, and the medium one is the microemulsion.

d) Winsor IV

Winsor IV system corresponds to the microemulsion.

Characteristic of formulated microemulsions

Theoretical approach

When large excess of hydrophilic phase is added to the microemulsion, two kinds of behaviour can be observed.

1 - Hydrophilic phase is incorporated very easily and dilutes the system. The original system is a solution.

2 - If after repose, we obtain a Winsor II system, the original mix corresponds to a microemulsion which is a thermodynamically stable system, with a minimum energy level and which refuses the destabilisation by the excess of hydrophilic

phase. The same study can be performed with excess of oily phase. In this case we obtain a Winsor I system.

Presentation of results (Table 1)

All the tested formulations gave Winsor II systems. As you can observe by comparison between the density values of inferior phase against propylene glycol density values, some components of the microemulsions have been partially solubilized in the propylene glycol.

This fact is confirmed by the evolution of the microemulsion density. The superior phase we obtain corresponds to the optimum combination of the 4 components of the microemulsions.

CONCLUSIONS

The formulation of anhydrous microemulsion using non ionic surfactant for oral use in softgel capsule is possible.

However, some stability problems appear with migration of shell water inside the fill without collapse of the microemulsion.

The water migration can induce major modification of the shell characteristics, and the development of microemulsion containing small quantities of water which can establish an equilibrium with the shell water seems to be a good alternative to this problem.

This study has been performed with "placebo" microemulsion. Active drug will play an important role especially peptides which exhibit large steric hindrance, need specific pH, etc...

For the future, in collaboration with R.P. Scherer France, the development of microemulsions for softgel capsules will be carried on in order to optimize the first obtained results.

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OPTIMISATION DES EMULSIONS MULTIPLES : AXES DE DEVELOPPEMENT

MULTIPLE EMULSIONS : NEW DEVELOPMENTS

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Multiple emulsions W/O/W constitue new vesicular systems. The aim of this lecture is to present the results of different studies performed in order to improve the knowledge and the control of the emulsification process.

Due to the large number and diversity of parameters, mathematical matrix have been used. Significant responses, considered as characteristics of given multiple emulsion, and manufacturing formulation variables show, quantify and elucidate the role and the importance of the studied parameters.

Comme à l'occasion d'autres découvertes, l'intérêt des émulsions multiples (EM) a été mis en évidence fortuitement. Ainsi, il y a plusieurs dizaines d'années, un chercheur, administrant à des animaux un vaccin présenté sous forme d'émulsion à phase continue huileuse, donc de viscosité assez élevée, eut l'idée, pour en faciliter l'injection, de la disperser extemporanément dans de l'eau. L'administration en fut facilitée, comme prévu, mais il observa en outre un phénomène inattendu: les animaux traités avec cette dispersion manifestèrent tous un taux d'anticorps supérieur à celui obtenu avec le vaccin présenté sous forme d'émulsion à phase continue huileuse. Dispersée dans l'eau, cette dernière avait donné, après simple agitation manuelle de la seringue, une EM H/L/H (Hydrophile/Lipophile/Hydrophile). L'antigène alors encapsulé, avait vu sa libération ralentie du

fait de la deuxième interface L/H formée, entraînant en conséquence une augmentation d'efficacité.

Ce résultat encouragea la recherche dans le domaine thérapeutique. Ainsi, ce type de système fut-il exploré par voie parentérale pour améliorer l'action de certains PA, tels des anticancéreux, et par voie orale pour permettre l'administration de divers dérivés telle l'insuline, dès lors préservée de l'action des sucs digestifs. Cependant, malgré certains résultats prometteurs, ces recherches furent peu à peu délaissées, du fait notamment de la stabilité précaire de ces systèmes qui n'excédait généralement pas une période de quelques jours à quelques semaines, ainsi que du manque de fiabilité et de reproductibilité de leur obtention. Depuis quelques années, la recherche médicale s'orientant de plus en plus vers la mise au point de systèmes à action prolongée (targetable

delivery systems), l'étude des EM a repris. Elles font actuellement l'objet d'assez nombreuses publications portant notamment sur des essais de libération réalisés *in vitro* mais aussi et même principalement *in vivo*. Parmi les principales classes de substances actives encapsulées en phase interne et étudiées sous différentes formes dans les 5 dernières années, citons les anti-inflammatoires, antimétaboliques, vasodilatateurs, substituts du sang, antiparasitaires, anesthésiques, antalgiques...<1-15>

Ces émulsions destinées, comme il y a plusieurs décennies, à la voie orale et/ou parentérale, semblent bien être de bons systèmes pour une libération prolongée de ces principes actifs.

Par voie cutanée, en revanche, les EM ne font l'objet que de très rares travaux publiés <16,17> et leur effet après application sur la peau est encore à évaluer. Les EM font cependant l'objet d'un engouement indéniable de la part des chercheurs de l'industrie cosmétique qui espèrent trouver des formes nouvelles, plaisantes, faciles d'emploi et hautement performantes.

Leur emploi dans ce domaine, pourrait être aussi étendu que celui des 2 émulsions simples dont elles dérivent, et au moins équivalent à d'autres systèmes vésiculaires, tels les liposomes, dont elles sont proches ; elles semblent en effet présenter à peu près les mêmes propriétés que ces derniers. Ainsi, elles protégeraient une substance active fragile, elles permettraient d'avoir, dans une même préparation, des substances actives incompatibles, et surtout, elles pourraient entraîner une libération contrôlée de la substance active introduite en phase interne avec, en conséquence, une certaine substantivité après application sur la peau, et donc, une plus grande efficacité.

A ce jour, si de très nombreux brevets existent <18>, moins de 6 formules d'EM ont été commercialisées. Ceci est dû notamment à une stabilité encore très limitée et à un comportement mal connu après application sur la peau.

En ce qui concerne nos travaux, nous tentons, pour l'essentiel, de comprendre les phénomènes d'émulsification, afin d'augmenter la stabilité de ces préparations, et nous nous efforçons d'appréhender leur mécanisme de libération, afin d'optimiser puis de maîtriser leurs propriétés potentielles. Après une définition succincte de ces systèmes, nous nous limiterons ici à une présentation de quelques uns de nos résultats concernant leur **obtention** et leur **caractérisation** par le biais des **plans d'expérience**.

DÉFINITION

Les EM sont des émulsions dans lesquelles une phase dispersée renferme une autre phase dispersée. Par exemple, une émulsion H/L/H est un système dans lequel des globules d'eau sont encapsulés dans des globules d'huile, ces derniers étant eux-mêmes dispersés dans une phase aqueuse. De façon symétrique, il existe des EM de type L/H/L présentant une phase huileuse interne dispersée dans des globules aqueux, eux-mêmes dispersés dans une phase huileuse externe.

Ces émulsions étant constituées d'au moins deux liquides non miscibles, leur réalisation nécessite la présence d'émulsifiants. En s'orientant à l'interface, les molécules de ces derniers, appelés respectivement ADS I et ADS II forment un film assurant pendant un temps plus ou moins long une certaine stabilité du système. Dans le cas d'EM de type H/L/H par exemple, les molécules de l'ADS I à tendance lipophile s'orientent à l'interface interne H/L et celles de l'ADS II à tendance hydrophile à l'interface externe L/H, formant ainsi deux films monomoléculaires: les parties apolaires de chaque émulsifiant sont dans l'huile et leurs parties polaires soit dans la phase aqueuse interne, soit dans la phase aqueuse externe. Il s'ensuit que les émulsifiants se disposent selon une couche bimoléculaire aux interfaces, formant alors avec l'huile l'enveloppe même de la vésicule. Cette disposition est identique à celle, mieux connue, des liposomes; mais dans ces derniers, l'enveloppe est constituée des seuls émulsifiants, l'huile elle-même étant absente.

OBTENTION

Contrairement à d'autres systèmes vésiculaires, les EM n'exigent pas, pour leur formation, de constituants particuliers.

Les huiles les plus fréquemment utilisées dans les formes cosmétiques sont facilement émulsionnables dans ces systèmes: hydrocarbures, huiles végétales, esters, et d'autant plus que leur viscosité est élevée. Les agents de surface sont également d'un usage courant; ce sont pour l'essentiel des émulsifiants non ioniques à liaison éther ou ester. Il faut citer plus particulièrement les esters de sorbitane polyoxyéthylénés ou non, les alcools gras oxyéthylénés, les copolymères à longue chaîne d'oxyde d'éthylène et d'oxyde de

propylène, les esters de polyglycerol, les esters de saccharose et les agents de surface polymères.

Dans nos EM, nous avons pu introduire, à côté des constituants de base, de nombreux épaississants, soit en phase aqueuse, soit en phase huileuse, afin d'augmenter leur viscosité, voire leur stabilité. Ils correspondent respectivement à des polymères hydrophiles (gomme xanthane, dérivés de la cellulose, composés carboxyvinyliques...) ou à des substances lipophiles (cires, acides ou alcools gras, sels ou dérivés d'aluminium, dérivés de silicones...). D'autres matières premières, pour l'essentiel des électrolytes, des conservateurs et des actifs tels le lactate de sodium, l'urée, l'acide hyaluronique, ont pu être également ajoutés sans trop nuire à la stabilité des préparations <19-21>.

A condition de respecter certaines conditions concernant le rapport entre les taux de l'ADS I et de l'ADS II, le HLB de leur mélange, et de ne pas dépasser une certaine concentration des additifs, la nature des constituants ne semble pas exercer une action importante sur le caractère multiple et la stabilité des émulsions. En revanche, le protocole opératoire, ainsi que les principaux paramètres de fabrication tels la température, la durée d'agitation, la vitesse de cisaillement, ont une influence considérable. C'est pourquoi nous étudions divers procédés de fabrication parmi lesquels le procédé à double étape (appellation insuffisamment précise en toute rigueur puisque les autres procédés nécessitent également une double phase), le procédé par dispersion d'une phase lamellaire ou d'un isotrope huileux dans l'eau et enfin le procédé par inversion de phase (dénomination impropre puisqu'il ne s'agit pas vraiment d'une inversion de phase). Ces quatre protocoles sont conduits de façon pratiquement identique:

* Dans un premier temps, on réalise, soit une émulsion simple à phase continue huileuse, soit une phase lamellaire, soit un isotrope huileux. Ces systèmes sont réalisés à 70-80°C, l'eau, l'huile et les deux émulsifiants étant mélangés à l'aide d'un agitateur à turbine de type centrifète pendant environ 30 minutes.

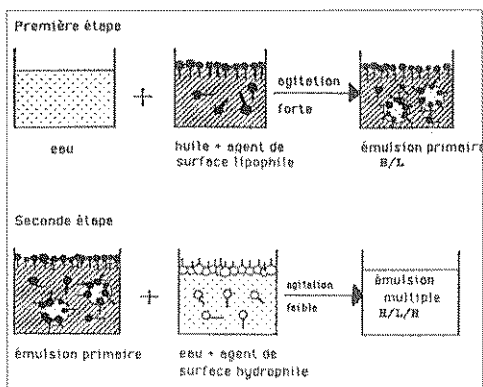
* Dans un second temps, l'émulsion à phase continue huileuse est versée lentement dans la phase aqueuse, pour le protocole appelé par double étape, tandis que pour les trois autres procédés, c'est l'eau qui est introduite progressivement soit dans la phase lamellaire, soit dans l'isotrope huileux, soit dans l'émulsion à phase continue huileuse. La dispersion est

réalisée également à l'aide d'agitateur à turbine, le plus souvent à une température de 60 à 70°C pendant une durée d'environ 30 minutes.

Bien évidemment chaque protocole présente des avantages et des inconvénients. Parmi ceux les plus facilement mis en évidence, il faut retenir que:

(i) Le procédé par double étape (figure 1) présente comme avantage d'avoir un déroulement bien maîtrisé. Il est possible, en théorie du moins, de fixer la quantité d'eau interne. Il a pour inconvénient d'être peu reproductible, ne serait-ce qu'à cause de la deuxième émulsification qui constitue une étape critique. En effet, l'émulsion primaire H/L, très visqueuse, est difficile à disperser, et lors de cette étape, il y a risque de rupture de certains globules d'huile nouvellement formés avec, en conséquence, le mélange d'une partie de l'eau interne avec l'eau externe.

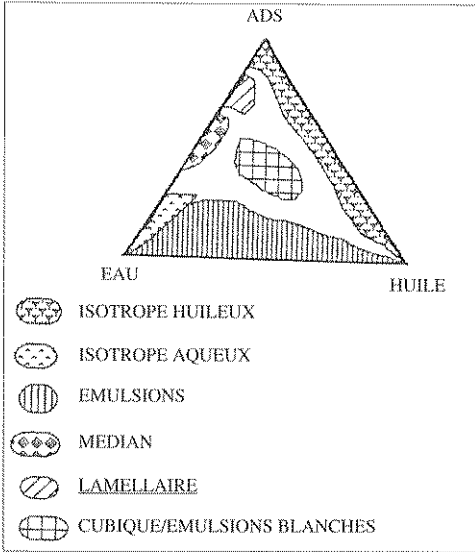
Figure n°1 : Représentation schématique de l'obtention d'une émulsion multiple H/L/H par double étape.



(ii) Le procédé par dispersion dans l'eau d'une phase lamellaire (figure 2) présente comme avantage de ne faire appel qu'à une seule émulsification; la phase de départ est une phase anisotrope et thermodynamiquement stable. Une limitation à ce procédé provient du fait que tous les ADS ne forment pas de phase lamellaire. Lorsque celle-ci existe, le HLB est souvent élevé, et ceci n'est pas souhaitable pour assurer la stabilité d'une EM. Enfin, la quantité d'huile incorporée dans la phase lamellaire est toujours faible, difficilement supérieure à 10%.

(iii) Le procédé par dispersion dans l'eau d'un isotrope huileux (figure 2) présente à peu près le même avantage: il n'y a qu'une seule émulsification; la phase de départ est une phase pure, stable et simple à obtenir. L'inconvénient

Figure 2 : Diagramme de phase eau-agent de surface-huile



principal réside dans la faible incorporation d'eau solubilisée dans les micelles inverses, là aussi difficilement supérieure à 10%.

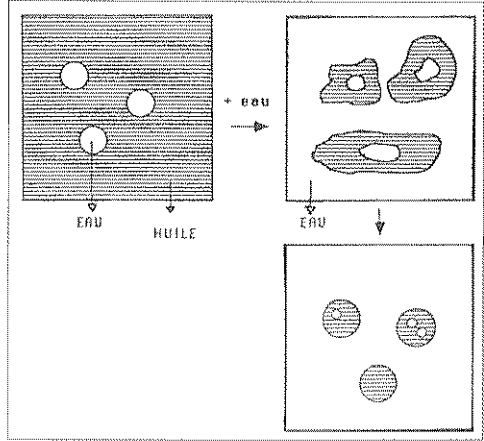
Les limites communes à ces deux procédés tiennent aux quantités élevées en ADS. De plus, du fait de la dispersion dans l'eau de phases dans lesquelles l'eau initiale n'est pas émulsionnée, il est difficile de savoir si de l'eau, apportée par la dispersion, s'est encore solubilisée, et, si tel est le cas, de connaître la quantité totale en phase interne.

(iv) Le procédé par inversion de phase (figure 3) présente comme avantage d'être facile à réaliser et de fournir un taux parfaitement connu de phase interne comme par le procédé par double étape. De plus, à la différence de ce dernier, il est reproductible. Il présente toutefois l'inconvénient de comporter lui aussi deux émulsifications, et surtout d'avoir une mise au point délicate. En effet, un très léger excès d'eau suffit à transformer l'EM en émulsion simple aqueuse.

Le protocole par double étape conduit dès maintenant sous certaines conditions de formulation (nature et concentration des émulsifiants, valeurs des fractions volumiques des phases aqueuses interne et externe...) et de fabrication (température et modalités d'agitation...) à des EM H/L/H stables sur plus de deux ans pour la formule type <22>:

Paraffine fluide	19%
Émulsifiant lipophile	3,2%
Émulsifiant hydrophile	0,8%
MgSO ₄	0,56%
Eau déminéralisée	qsp 100%

Figure 3 : Représentation schématique de l'obtention d'une émulsion multiple H/L/H par inversion de phase.

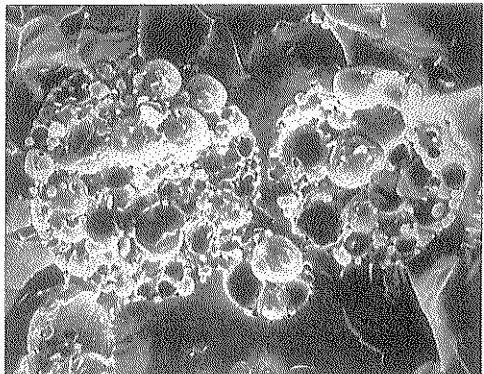


CARACTÉRISATION

Macroscopiquement, rien ne distingue une émulsion multiple d'une émulsion simple. Aussi comprend-on qu'il est possible de réaliser sur les EM tous les contrôles classiques (sens, mesure de la stabilité à différentes températures et à la centrifugation, analyse granulométrique...) mais qu'en plus, il est indispensable d'effectuer des contrôles spécifiques pour préciser notamment le caractère multiple, le taux d'encapsulation et l'"identité" même des EM.

* Pour le contrôle du caractère multiple, le recours à différents examens microscopiques simples ou plus élaborés (microscopie à balayage après cryofracture par exemple) permettent de noter la présence ou l'absence de globules d'eau

Figure 4 : Cliché d'une émulsion multiple obtenue au microscope électronique après cryofracture.



à l'intérieur des globules d'huile (figure 4), et d'évaluer leurs tailles respectives (généralement, dans notre cas, de quelques micromètres pour les premiers à une dizaine de micromètres pour les seconds), ainsi que leur forme.

* Pour le taux d'encapsulation, encore appelé rendement, il peut être fait appel à différentes méthodes physicochimiques. L'objectif est de s'assurer que la substance introduite en phase interne n'a pas migré dans la phase externe.

Cet essai est réalisé juste après la fabrication et répété au cours du temps. Il peut être réalisé par conductimétrie directement sur l'émulsion si la substance encapsulée est de nature électrolytique ou encore par une autre méthode de dosage approprié après dialyse par exemple.

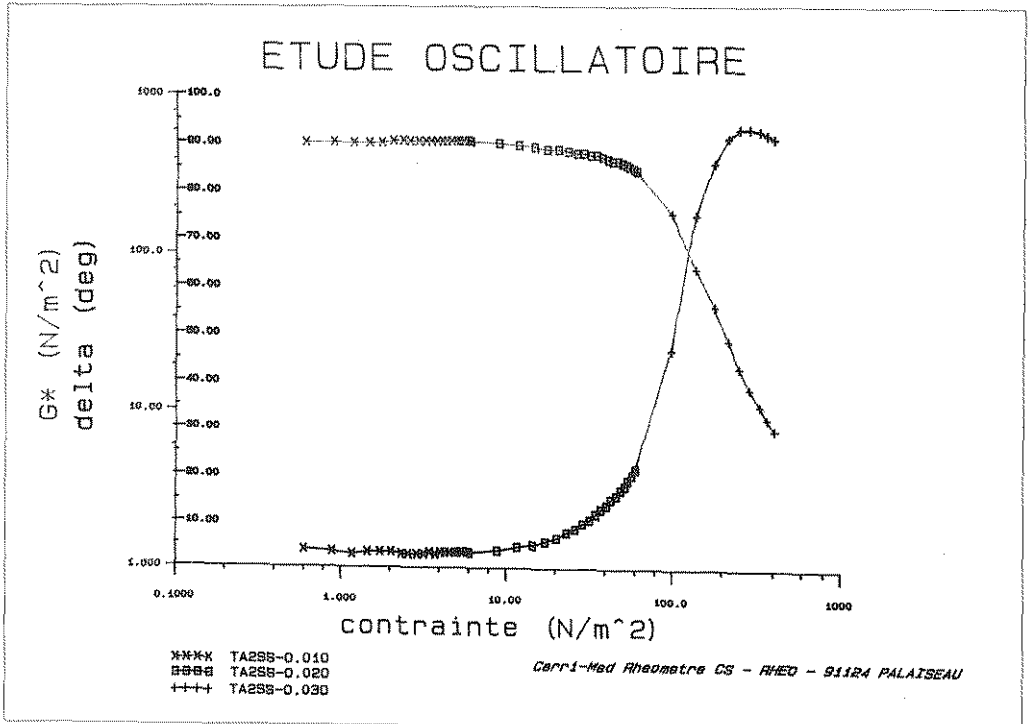
* Pour une connaissance plus approfondie des EM, le recours à des analyses rhéologiques <23> constitue un moyen de caractérisation d'importance primordiale. Leur très grande diversité leur permet en effet :

(i) de caractériser la structure initiale de l'EM, en utilisant l'analyse viscoélastique oscillatoire non destructive (régime linéaire de microcisaillement), qui fournit une signature précise de la structure au repos (figure 5),

(ii) de suivre son évolution au cours du temps, soit par la même analyse oscillatoire, soit par l'utilisation de tests d'écoulement permanent (tracés de rhéogrammes), au cours desquels l'application d'un cisaillement croissant, constant et décroissant, permet de simuler un vieillissement accéléré et de mettre en évidence certaines phases de l'évolution temporelle de l'EM (floculation, rupture, inversion de phase...). A titre d'exemples, les figures 6 et 7 représentent les rhéogrammes d'EM qui subissent respectivement une déstructuration et une inversion de phase. A l'inverse, la figure 8 représente le rhéogramme d'une EM stable.

Ayant à notre disposition d'une part différents procédés d'obtention à optimiser (notamment, dans un premier temps celui par inversion de phase) et à comparer en fonction des caractéristiques des EM obtenues, et d'autre part de bons outils de caractérisation, les recherches sur les EM peuvent être efficacement poursuivies. Afin de la mener au mieux, la technique que nous utilisons actuellement est celle des plans d'expérience (analyse statistique de régression multiple).

Figure 5 : Définition du régime oscillatoire linéaire.



MISE EN OEUVRE D'UNE ANALYSE PAR PLANS D'EXPÉRIENCE

Cette analyse permet d'obtenir des relations quantitatives avec précision et avec un minimum d'essais, entre les variables de fabrication-formulation et les réponses de caractérisation les plus significatives.

Les tableaux I et II ainsi que les figures 9 et 10 illustrent, sur un exemple précis, le principe et la mise en oeuvre d'une telle analyse. Il s'agit d'un plan pour lequel 3 variables de fabrication-formulation des EM ont été définies : le temps d'agitation t , la fraction volumique F_v et la concentration en émulsifiant hydrophile c . Le tableau I fournit l'intervalle de variation de ces 3 variables, en valeurs réelles, ainsi qu'en valeurs centrées réduites de façon à pouvoir comparer quantitativement leur influence respective. Le tableau II présente la structure du plan hybride étudié correspondant. Chacun des 11 points qui le constituent est caractérisé par des "réponses" qui sont principalement:

* le diamètre moyen des globules multiples D_m , ainsi que leur écart-type, tels qu'ils sont mesurés par analyse microscopique

* le rendement de l'EM, déterminé par analyse conductimétrique

* certaines grandeurs rhéologiques oscillatoires, telles le déphasage contrainte/déformation δ , le module de cisaillement G^* et la contrainte critique $(\tau_0)_c$

* des grandeurs rhéologiques obtenues lors d'analyse en écoulement, comme le seuil d'écoulement τ_s ou encore la viscosité pour une valeur donnée de la contrainte.

Dans un souci de simplification, nous ne considérerons ici que deux réponses parmi les plus significatives, à savoir la contrainte critique $(\tau_0)_c$ et le diamètre moyen D_m .

De façon à caractériser l'influence du vieillissement sur l'EM, l'étude du plan a été renouvelée à différents âges: t_{-1} (juste après fabrication), t_0 (24 heures après la fabrication), t_1 (1 semaine après la fabrication).

Le logiciel d'analyse statistique (LUMIÈRE)

fournit les meilleurs ajustements quantitatifs reliant les réponses aux variables; il s'agit de développements de type polynomial de la forme:

$$Y = A_0 \quad \text{constante}$$

$$+ A_1 F_v + A_2 t + A_3 c \quad \text{termes linéaires}$$

$$+ A_{12} F_v t + A_{13} F_v c + A_{23} t c \quad \text{termes d'interaction d'ordre 1}$$

$$+ A_{123} F_v t c \quad \text{terme d'interaction d'ordre 2}$$

$$+ A_{11} (F_v)^2 + A_{22} (t)^2 + A_{33} (c)^2 \quad \text{termes quadratiques}$$

$$+ \dots$$

Le tableau III fournit les valeurs des coefficients de la régression aux différents âges ainsi que l'intervalle de confiance de l'ajustement. On observe de façon générale une très bonne qualité d'ajustement caractérisée par des intervalles de confiance le plus souvent supérieurs à 95%. Les figures 8 à 10 résument graphiquement certaines conclusions de l'analyse.

Pour l'essentiel, on peut noter:

(i) Pour l'évolution de $(\tau_0)_c$ en fonction de F_v à t_{-1} (figure 9), un profil très caractéristique qui comporte deux zones de variation significatives:

* pour les valeurs réelles de F_v inférieures à 0,73 (0,5 en valeur centrée réduite), $(\tau_0)_c$ présente des valeurs très faibles et pratiquement constantes; le profil parabolique observé pour les faibles valeurs de F_v est lié au développement polynomial utilisé et doit être interprété comme un palier.

* pour les valeurs réelles de F_v supérieures à 0,73, $(\tau_0)_c$ augmente très rapidement.

Ce comportement s'explique par l'analyse théorique qui prévoit que le seuil d'écoulement d'une émulsion de particules sphériques homogènes ne se manifeste que pour des fractions volumiques supérieures à 0,74.

(ii) Pour l'évolution du diamètre moyen D_m en fonction de F_v à t_0 , pour 3 temps d'agitation différents (figure 10) :

* une décroissance de D_m avec F_v . Ce comportement pourrait s'expliquer par le processus de fabrication: lorsque F_v croît, la viscosité de l'émulsion augmente si bien que l'agitateur, qui travaille à vitesse de rotation inchangée, fournit une puissance mécanique plus importante, ce qui pourrait se traduire, toutes choses égales par ailleurs, par une diminution des tailles des particules.

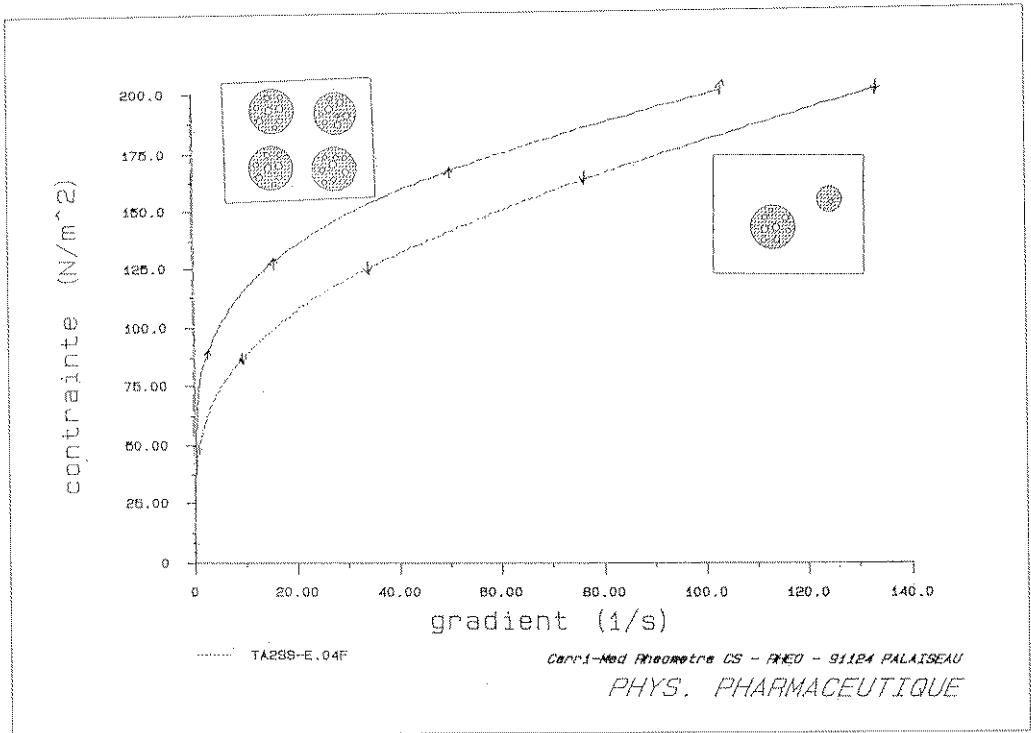
* une diminution de D_m avec le temps d'agitation; là encore ce comportement pourrait s'expliquer par une augmentation de l'énergie mécanique mise en jeu.

Cette analyse est trop spécifique et limitée pour en tirer des conclusions de portée générale. Toutefois l'exemple présenté permet d'ores et déjà d'illustrer la mise en oeuvre et la puissance d'analyse et de prévision de la méthode des plans d'expérience appliquée à l'étude des EM. Cette technique, développée de façon systématique doit permettre:

* d'obtenir les conditions optimales de fabrication-formulation assurant un rendement maximal ou une stabilité maximale ou encore le meilleur compromis rendement-stabilité

* de définir les conditions particulières permettant d'obtenir une EM de caractéristiques données (élasticité, viscosité, granulométrie...)

Figure 6 : Rhéogramme traduisant une déstructuration sous l'effet du cisaillement.



CONCLUSION

Certaines propriétés des EM étaient bien connues depuis plusieurs dizaines d'années, mais ni leur obtention ni leur caractérisation n'étaient maîtrisées. Des progrès très importants et même décisifs ont été réalisés récemment dans ces deux domaines. Il reste à confirmer et à mettre à profit par des études rigoureuses l'intérêt des EM, voire leur supériorité par rapport à des émulsions simples, notamment en tant que système à action prolongée. Certaines études de libération réalisées *in vitro* et *in vivo* montrent en effet une libération de la substance active introduite en phase interne qui se prolonge sur huit à dix heures. Cette libération

se ferait soit par rupture des globules huileux, soit par diffusion, soit par les deux mécanismes à la fois.

Mettant à profit ces propriétés, de nombreux brevets ont été déposés dès 1980 pour des formes cosmétiques qui revendiquent entre autres des qualités hydratantes, anti-rides, solaires, parfumantes à action prolongée. Depuis 1991, trois crèmes - deux EM H/L/H et une EM L/H/L- ont été mises sur le marché français. Tout laisse penser que de très nombreuses autres suivront d'autant qu'elles possèdent un toucher très agréable et qu'elles sont directement applicables sur la peau: point n'est besoin, comme d'autre systèmes vecteurs, de les disperser dans un véhicule après leur obtention.

Tableau n°I : Intervalles de variation des trois variables : fraction volumique, temps d'agitation et concentration en agent de surface hydrophile.

FRACTION VOLUMIQUE = Fv					
Valeurs réelles	0,6	0,63	0,7	0,77	0,8
Valeurs centrées réduites	-2	-1,41	0	+1,41	+2
TEMPS D'AGITATION = t (minutes)					
Valeurs réelles	5	9,4	20	30,6	35
Valeurs centrées réduites	-2	-1,41	0	1,41	2
CONCENTRATION EN ADS HYDROPHILE = c (%)					
Valeurs réelles	1,5	2	2,5	3	3,5
Valeurs centrées réduites	-2	-1	0	1	2

Tableau n°II : Structure du plan hybride.

N° d'expérience	Temps d'agitation t	Fraction volumique Fv	Concentration TA hydrophile c
1	0	0	-2
2	0	0	+2
3	-1,41	-1,41	+1
4	+1,41	-1,41	+1
5	-1,41	+1,41	+1
6	+1,41	+1,41	+1
7	-2	0	-1
8	+2	0	-1
9	0	-2	-1
10	0	+2	-1
11	0	0	0

Tableau n°III : Valeurs des coefficients de regression

	$(\tau_0) c$ (Pa)			Dm (μm)		
	t-1	t0	t1	t-1	t0	t1
A0	15,28	14,86	17,75	4,03	4,28	4,47
A1	10,39	10,38	14,85	-0,71	-0,40	-0,35
A2				-0,38		-0,38
A3						
A11	7,86	8,01	8,81			-0,27
Intervalle de confiance dans la régression (%)	99,94	99,99	99,98	94,49	99,08	98,69

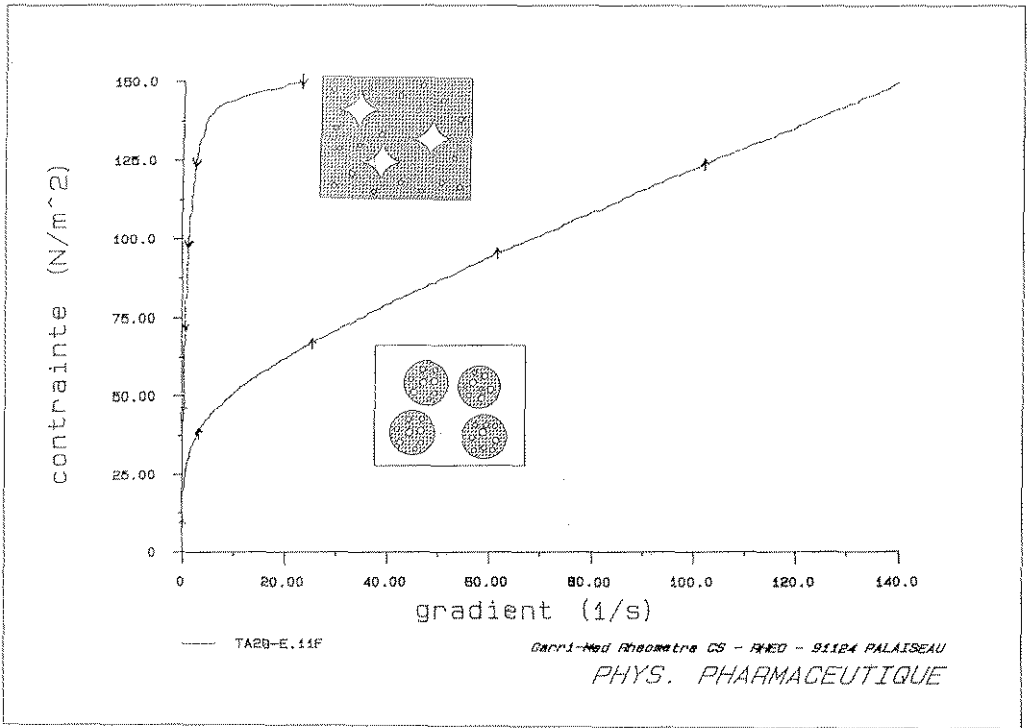


Figure 7 : Rhéogramme traduisant une inversion de phase sous l'effet du cisaillement.

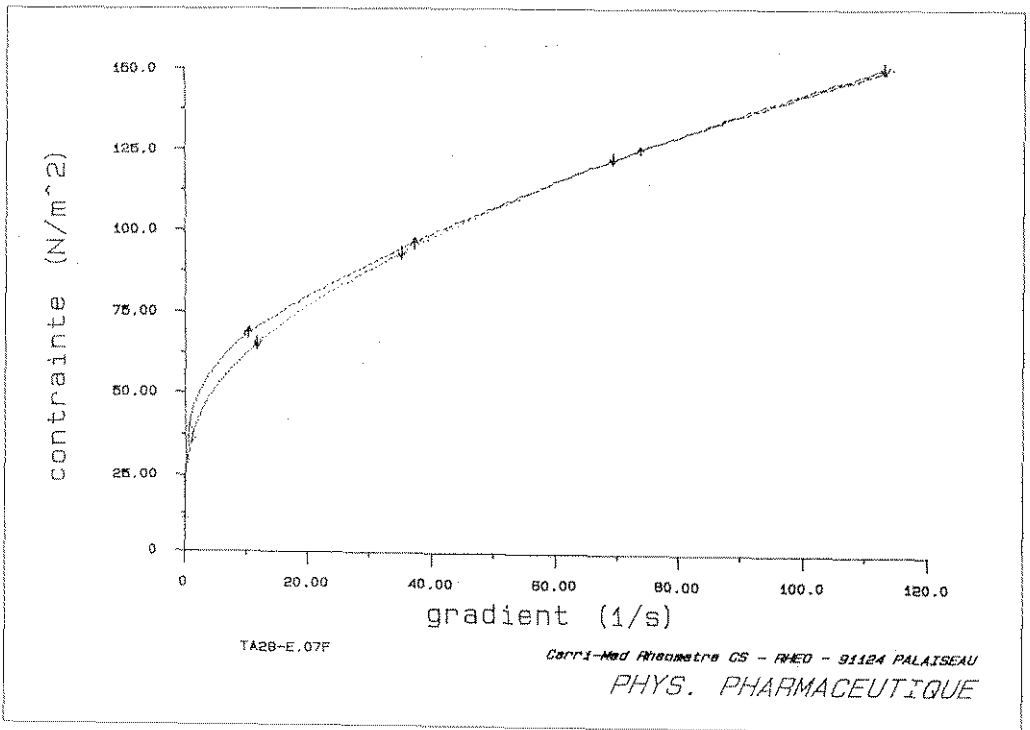


Figure 8 : Rhéogramme traduisant une stabilité sous l'effet du cisaillement.

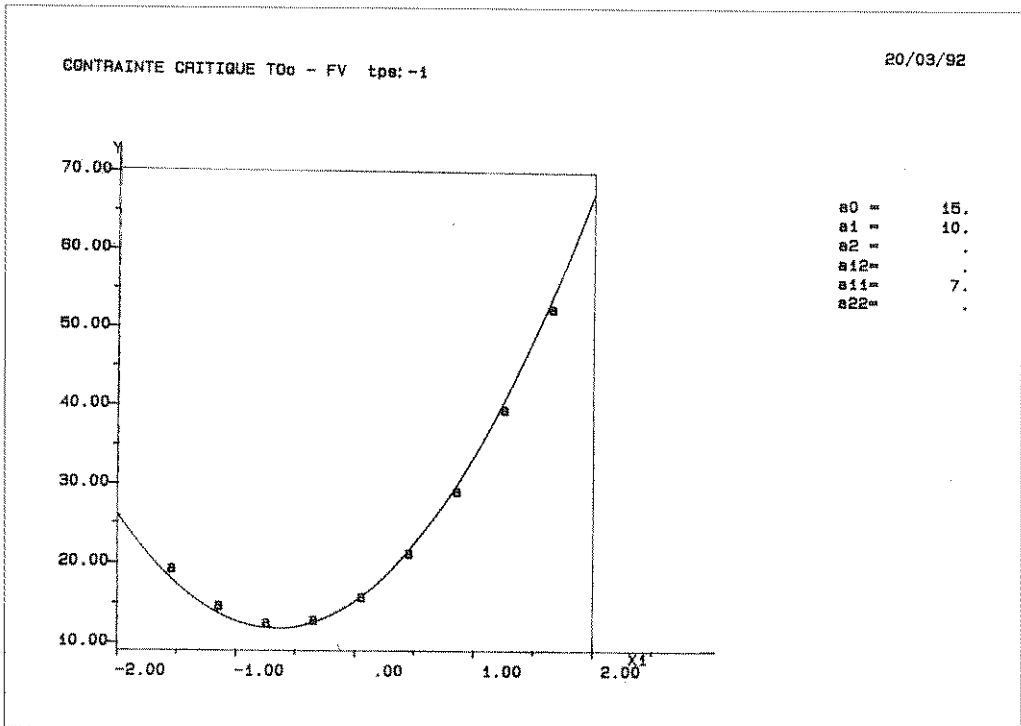


Figure 9 : Graphe de l'évolution de la contrainte critique en fonction de la fraction volumique

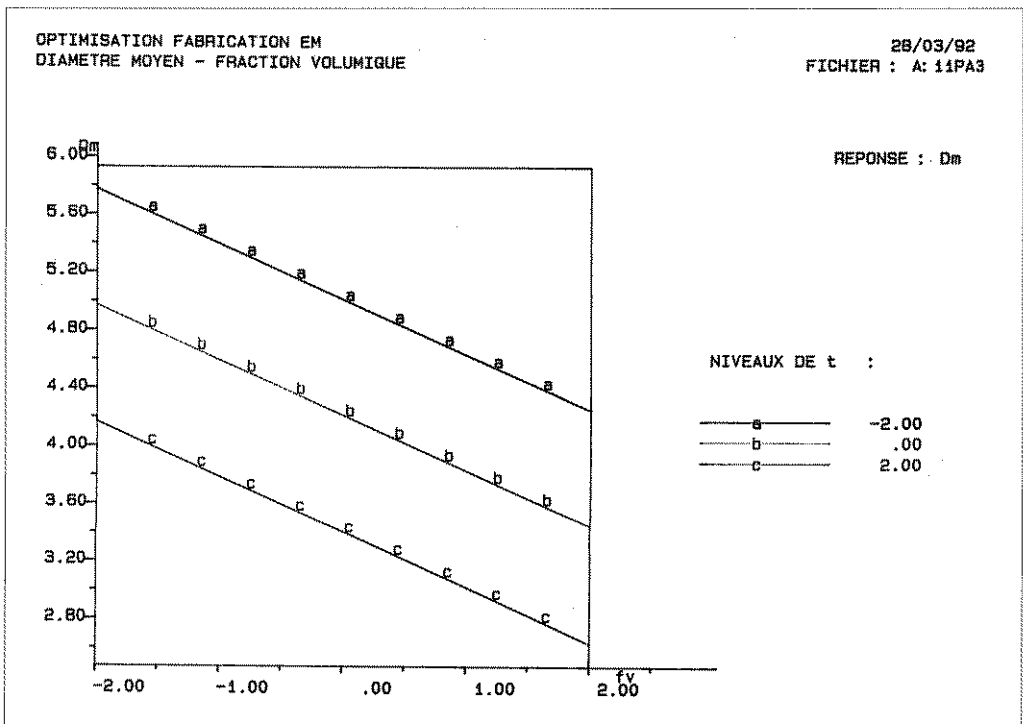
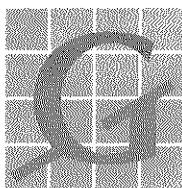


Figure 10 : Graphe de l'évolution du diamètre moyen en fonction de la fraction volumique.

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GATTEFOSSÉ

RECENT OPHTHALMIC LIQUID DOSAGE FORMS

NOUVELLES FORMES LIQUIDES A USAGE OPHTHALMIQUE

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La plupart des traitements employés pour les maladies oculaires sont topiques. Le principe actif est donc délivré très près de l'organe cible. La formulation de ces préparations va modifier la qualité du contact de la molécule avec le segment antérieur de l'oeil et jouer un rôle majeur sur le temps de résidence de la molécule sur le globe oculaire.

Dans cette présentation, sont décrits les différentes approches de formulation afin d'améliorer les performances des traditionnelles gouttes ophtalmiques.

Drugs intended to treat eye diseases are essentially delivered by topical administration. Several important consequences result from this intimate contact of the active ingredient with the target organ. The distribution by which a systematically administered product is carried to the organ/tissue/receptor(s) through the blood flow is of little or no importance. However, assuming an intra-ocular site of action, the properties governing the passage through the membranes, e.g. corneal epithelium, are critical. Amongst these properties size, polarity, charge(s) and partition coefficient are of importance for the transcorneal route. It should be noted that although this route is described as the most common, absorption via non corneal routes might exist (1). Once a drug is administered from a drop instilled on the surface of the eye, several events occur which drastically reduce its eventual ocular bioavailability. A blinking reflex might occur, inducing part of the dose to be expelled from the precorneal area. There may be an excess of delivered liquid due to the fact that the conjunctival cul-de-sac can barely contain

amounts larger than 15 -18 μ l (2), so that both normal drainage in the lacrymal duct and overflow onto the cheek will decrease the actual amount delivered. The remaining part of the active ingredient will be diluted by the tear flow, either from the normal tear turnover, or from a larger one induced by irritation to the drug/vehicle system. Moreover, a part of the drug could be metabolized, bound to tear proteins, or partly lost through conjunctival absorption. Conjunctival absorption, absorption following elimination by naso-lacrymal pathways and ultimately disposition through the pharynx, followed by gastro-intestinal absorption of residual quantities, cause systemic levels which may generate side effects. Aqueous humor turnover into ocular blood flow, tissue binding and drug metabolism are responsible for the disappearance of intraocular drugs.

The most critical factor in preventing drugs from penetrating the eye or from remaining on the surface of the eyeball, is the precorneal drainage by tears. As the dosage form is placed into the precorneal area, e.g. by instillation, the role of the pharmacist is to design a formulation

resistant to dilution and drainage by the tears. Competition between the transcorneal absorption, which is rather low, and the loss of drug in the front of the eye, which in comparison is enormous, has been called the parallel elimination loss pathway (3). A typical example, e.g. pilocarpine, would give the following K constants:

$$K \text{ loss} \approx 0.2 - 0.5 \text{ min}^{-1}$$

$$K \text{ absorption} \approx 0.01 - 0.001 \text{ min}^{-1}$$

hence K apparent losses = K loss.

Therefore, two potential avenues towards improving the balance between absorption and loss can be seen; either increase absorption or decrease elimination. The ratio between the two coefficients could lead to the conclusion that increasing penetration might result in substantially higher intraocular levels. Attempts were made to favor the paracellular pathways and other mechanisms of drug absorption (4). Our group studied the effect of Azone® (N dodecylazacycloheptan-2 one) on the transcorneal penetration of the sulfonamide L-643,799, a topically active carbonic anhydrase inhibitor (5) (Table 1).

Although the results obtained in rabbits were encouraging, it was found that they were linked to changes in the corneal endothelium and therefore associated with a potentially toxic effect of the penetration enhancer (6). Presently there are no approved penetration enhancers for the eye.

Table 1 :
Effect of 1% Azone® on ocular levels of L-643,799

	Area under Curve $\mu\text{g}\cdot\text{hr/g}$ or ml	
	Vehicle 1.5% HEC	Vehicle 1.5% HEC+ 1% AZONE®
Cornea	288.4	374.7
Aq. Humor	17.2	32.6
Iris + C. Body	80.0	62.7
HEC : Hydroxyethylcellulose Azone® : N dodecylazacycloheptan-2 one, Nelson Labs.		

Thus, the activity of scientists designing ophthalmic formulations has mainly been concentrated on modifying the excipients of active ingredient vehicle(s) in order to decrease the precorneal losses. However, the degree of freedom available to the development pharmacist is very narrow. The eye is very

sensitive to irritation and very few excipients, especially the more recent ones, have a well established history of ophthalmic use. To be able to determine the basic parameters of the drug or to appreciate the influences of any vehicle, the formulation pharmacist needs a system. Equipments have been described using membranes or excised corneas to separate donor and acceptor compartments, thereby enabling transfer rates to be measured. However, due to established knowledge and ease of local administration, *in vivo* testing has been by far the most commonly used procedure. The albino rabbit is the most frequent animal used to assess the bioavailability of ophthalmic drugs. The parameters measured can be drug levels in tear fluid or eye tissues, or a pharmacological response e.g. miosis, mydriasis or intraocular pressure.

Rabbits and humans do not have identical eye physiology. The blinking rate and tear physiology are of special concern when studying ophthalmic formulations (2). Pharmacological response and non-invasive techniques like the decay of fluorescence and of radioactivity can be used in man and compared to data obtained in rabbits. There is a general consensus that only a low percentage of the instilled dose is actually available to the eye tissues, hence the need for better systems to carry the drug to the receptors. Ideally, these systems should improve the availability expressed as area under the curve of drug concentration vs time both in terms of eye tissue levels and duration of activity. However, this might be seen as being too idealistic and a compromise between these two parameters has to be reached.

Petrolatum ointments, as well as solutions in oil such as peanut oil or sesame oil, have been described as prolonging to some extent the activity of several drugs (7). Nowadays, ointments are perceived as forms of limited use i.e. for bedtime administration since, like oily solutions, they induce some blurring of vision. The widespread use of plastic vials is also not well suited to accommodate vehicles based on oils. Microemulsions (8), nanoparticles and liposomes (9,10) are described as discontinuous lipidic phases entrapping the active ingredients and dispersed in a continuous aqueous phase. Although very attractive, they have not yet been demonstrated to give sufficiently improved, permanent results to justify the development of an industrial process.

The use of viscosifiers added to simple aqueous solutions has been and is still being extensively studied and many of their individual contribution(s) have been scrutinized in animal models and man (11, 12). Our group has studied the effect of vehicle viscosity on the ocular bioavailability in rabbits of L-653,328, a non-selective beta blocking drug (13). We observed a clear concomitant increase in ocular drug bioavailability expressed as area under the curve for cornea, aqueous humor and iris + ciliary body, with increase in viscosity of the instillate (see Table 2).

*Table 2 :
Maximum concentrations of L-652,698 observed in rabbit ocular sites after instillation of 1% L-653,328 in HEC solutions of different viscosities*

% HEC	Viscosity (cps)	Cornea (µg/g)	Aq. Humor (µg/g)	Iris + Ciliary Body (µg/g)
0	1	73.7	4.69	7.99
0.2	9.8	64.5	4.22 ^a	8.79
0.25	15.6	84.3 ^b	4.23	10.45
0.3	22.5	86.5 ^b	5.69	12.32
0.35	35.2	103.0 ^b	5.68	12.10
0.4	51.1	113.5	6.33 ^a	11.60
0.5	105.6	98.7 ^b	7.93	15.89 ^a

^a Maximum at 1 h
^b Maximum at 10 min
All other values occurred at 0.5 h post-instillation

The actual contribution of each different viscous polymer is also dependent on the individual properties of each active ingredient. Drugs like pilocarpine or beta blockers, which easily penetrate corneal barriers, might need less contribution from the vehicle compared to topical carbonic anhydrase inhibitors. Effectively, these entities can exhibit pKa, hydro and lipophilicity which are far from ideal. Although it was stated (3) that changes of 1 to 3 orders of magnitude are needed to improve ocular drug bioavailability, one might think that since the bioavailability of ophthalmic drugs is very low (a few percent of the administered dose) (2), even a 2-fold increase would be considerable.

The investigations conducted on polymers in various fields of biopharmacy led to the

potential interest of bioadhesion in the delivery of ophthalmic drugs (14). Bioadhesive polymers have been found to attach themselves to the mucin layer of the conjunctival surface by non-covalent bonds (3). Our group has studied the respective roles of viscosity and bioadhesion using timolol as a model drug and polyacrylic acid (PAA) as a bioadhesive polymer (15). The regular formulation of 0.5% Timoptol® was compared with a formulation based on PAA, a timolol polyacrylate formulation and a polyvinyl alcohol non-bioadhesive formulation. The three polymer-containing formulations had the same viscosity, as measured with a Rheomat 30 rotary viscosimeter. The results, expressed as area under the curve, are shown in Table 3 and they show that mucoadhesion could have a role in ocular drug delivery. From our experience with polyacrylic acid and timolol polyacrylate (15), we concluded that the improvement in drug bioavailability was, under these conditions, modest and of the same order of magnitude as that already reported using viscosifying agents.

Cyclodextrins were described as increasing the bioavailability of some drugs (16), especially poorly soluble ones (17). The topically active carbonic anhydrase inhibitor L-671,152 has a reduced solubility above pH 6. The addition of 30 mg/ml of beta-cyclodextrin (BCX) allowed us to solubilize L-671,152 in a standard ophthalmic vehicle at 20 mg/ml and 15 mg/ml (as base) at pH 6.5 and 7.0, respectively (18). However, the formulations containing beta-cyclodextrin induced lower ocular concentrations of the drug in rabbits, although previous results have shown that, below pH 7, the ocular penetration of L-671,152 increases concomitantly with pH up to neutrality. Dialysis studies of solution (B) showed that only 51% unbound L-671,152 compared to solution (A) and these values were in excellent agreement with the ratio of the areas under the curves (Figure 1). One might speculate that the fraction of the drug entrapped in the cyclodextrin was not released fast enough, compared to the precorneal elimination of the formulation, resulting in a overall decrease of the ocular bioavailability of L-671, 152.

Aqueous gels exhibit advantages over ointments and viscous aqueous solutions in terms of retention of the active ingredients on the corneal surface and manufacturing technology. Pre-formed aqueous gels of very high viscosity have already been used (19), but these gels are not

easily dispensed and induce blurred vision, suggesting a bedtime administration. Phase transition gelling systems consist of viscous solutions in the vial and are transformed into a gel in the conjunctival cul-de-sac. Several properties can be used to effect this phase transition e.g. change in temperature (20), pH (21), or ion concentration. Our group has investigated the latter mechanism and has developed an ophthalmic vehicle based on GELRITE®². GELRITE® is a polysaccharide low-acetyl gellan gum which gives a viscous aqueous solution in deionized water and forms clear gels in the presence of mono- and divalent cations. The ion concentration necessary to induce gelation varies with the cation. The concentration of sodium in tears of 2.6 g/l is particularly suited to cause gelation of the material when topically instilled into the conjunctival cul-de-sac. When comparing 0.25 %

timolol solutions made in hydroxyethylcellulose and GELRITE® formulations of equivalent viscosity in the rabbit, it was found that GELRITE® produced significantly higher intraocular levels at all time points (Figure 2). Moreover, scintigraphic studies showed that the tracer retention can be more pronounced in man than in rabbit (23). Finally, controlled clinical studies have demonstrated that a GELRITE® vehicle can be of significant use in improving the activity of timolol in man (24). Gelling vehicles such as GELRITE®-based formulations, have a definite potential as new liquid dosage forms in ophthalmology.

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Many thanks to Marjorie Cremont for preparing the manuscript.

Table 3 :
AUC (0-4 h) of timolol concentrations in ocular tissues of albino rabbits after instillation of various 0.5% formulations^a

	(A) Timoptol®	(B) PAA	(C) PAA Timolol	(D) PVA	Statistics ^b
Cornea	29.9	55.9	56.3	73.2	<u>ABCD</u>
Aq. Humor	2.71	4.06	5.03	7.29	<u>ABCD</u>
Iris + Ciliary Body	3.51	4.80	7.93	6.43	<u>ABCD</u>

^a Expressed in $\mu\text{g. h. ml}^{-1}$ or mg. h. g^{-1}

^b Treatments compared separately for each region. Each ocular site had statistically significant differences among treatments ($P < 0.001$). Areas were placed in ascending order and compared statistically by the Newman-Keul test. Those not statistically higher ($P > 0.05$) are connected by a solid line.

² GELRITE® is a trademark of Merck & Co. Inc., Kelco Division, USA.

Figure 1

Effect of Beta-Cyclodextrin on the Ocular Bioavailability of L-671,152

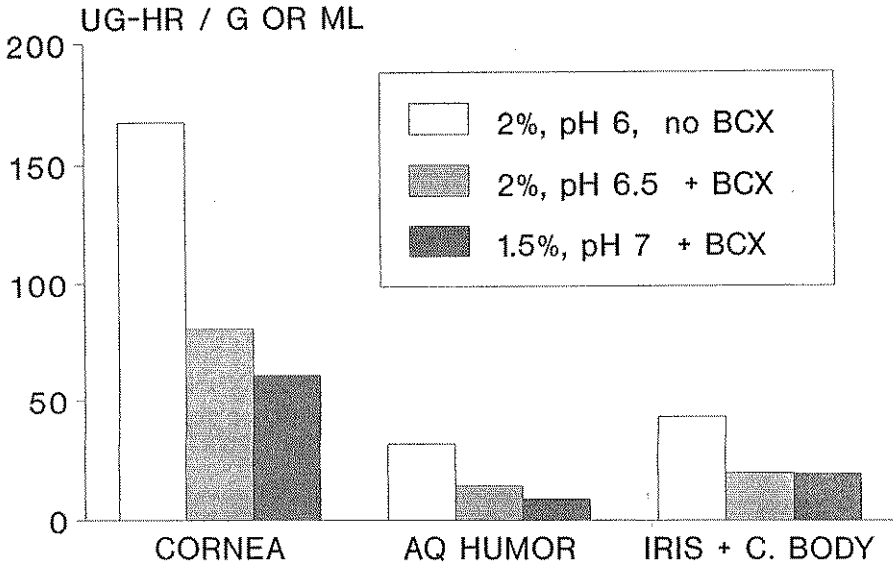
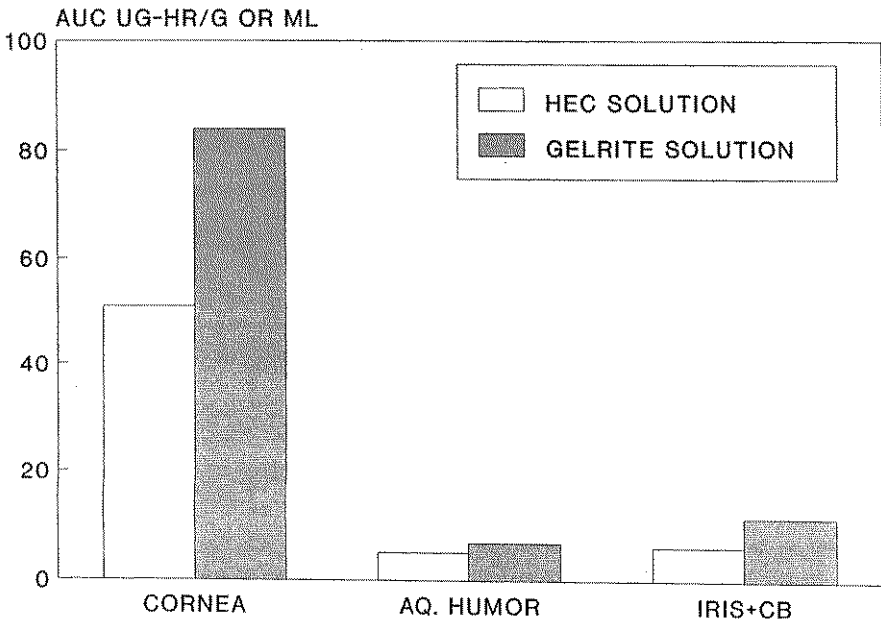


Figure 2

OCULAR LEVELS OF TIMOLOLO FOLLOWING INSTILLATION OF 0.25% IN VARIOUS VEHICLES



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PHYSIOLOGICAL & BIOPHARMACEUTICAL CONSIDERATIONS IN LIQUID DOSAGE FORM DELIVERY

CONSIDERATIONS PHYSIOLOGIQUES ET BIO- PHARMACEUTIQUES DANS L'ADMINISTRATION DES FORMES LIQUIDES.

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Les formulations liquides sont largement développées pour l'administration tant par voie orale, pulmonaire, oculaire que topique.

L'absence d'étape de désintégration et/ou de dissolution, favorise une réponse rapide après administration de la forme.

Cependant, dans le cadre d'une administration orale, le temps de résidence gastrique est très variable et est très largement influencé par la prise concomitante ou non de nourriture.

La technique de gamma scintigraphie, permettant de suivre la distribution de molécules marquées dans le corps, a permis aux scientifiques de mieux appréhender le devenir de la forme galénique in vivo.

L'influence des repas sur l'absorption des molécules est étudiée et notamment leur effet sur le temps d'apparition du C max.

Les résultats comparatifs d'études de gamma scintigraphie sur des aérosols avec CFC et sans CFC sont également présentés.

Liquid and suspension formulations are widely used to achieve an immediate effect following dosing. The rapidity of action results from the relatively large area available for absorption compared to solid dosage forms and the avoidance of a lag phase needed to complete disintegration of the dosage form. All routes of administration are utilised for liquid formulations although for the purposes of this text, we will consider just two routes: oral and pulmonary delivery. These areas have been

chosen to illustrate the manner in which liquid and suspension formulations may be evaluated *in vivo*. The examples chosen illustrate work carried out in our laboratories to evaluate and to optimise drug formulations in man. The data collected are based on the application of gamma scintigraphy to follow the behaviour of radionuclide-labelled preparations. A considerable advantage of this technique is that the dosimetry associated with the investigation of deposition and transit carried out using

scintigraphy is usually much less than by fluoroscopy. The absorbed dose equivalents are measured in millisieverts (mSv) and the whole body dose equivalent from a gastrointestinal transit study using a Tc-99m-labelled formulation would typically be less than 0.5 mSv. It follows that due to the low dosimetry, there are an increasing number of publications in which scintigraphy has been utilised to monitor transit of dosage forms, replacing old X-ray methodology.

BEHAVIOUR OF DOSAGE FORMS IN THE UPPER GASTROINTESTINAL TRACT

Information concerning the oesophageal transit of conventional drug formulations is still somewhat sparse (Spiller 1986, Wilson and Washington 1989) although the problems associated with oesophageal injury resulting from the administration of oral dosage forms are well documented. Drug induced oesophagitis has been recognised as being a particular problem following the administration of osmotically-active solutes such as potassium chloride and ferrous salts, and acidic or basic drugs including quinidine-sulphate and non-steroidal anti inflammatory agents (Kikendall et al, 1983).

Scintigraphic studies of the oesophageal transit of liquid and solids provide a more physiological means of assessing oesophageal transit and are capable of demonstrating oesophageal spasm, stasis and gastric reflux (Ham et al 1985, Klein et al 1984, Svedberg 1982, Tolin et al., 1979). The method is quantitative, noninvasive and involves minimal discomfort to patients. A logical extension of this diagnostic procedure is to assess the transit of radio labelled tablets and capsules. Fisher and co-workers pioneered the application of this technique to look at transit of dosage forms (Fisher et al., 1982), complementing the valuable data acquired by other workers over a number of years using formulations containing barium sulphate (Channer et al., 1986). The X-ray techniques have been criticised as it is appreciated that the density of units containing contrast agents will usually be greater than conventional formulations; however, the scintigraphic findings have generally confirmed that oesophageal retention is surprisingly common, particularly in the elderly.

Table 1 :
Oesophageal Transit of Pharmaceutical Formulations
(Data adapted from Wilson & Washington, 1989)

Formulation	Median Transit Time (s)	Posit° Ref.
Oval (14mm x 9mm) Film-coated	> 300	Supine (2)
Oval (14mm x 9mm)	> 300	Supine (2)
Various sizes & shapes	8	Supine (3)
Oval (14mm x 9mm) Film-coated	3	Erect (2)
Oval (12mm x 8mm)	3	Erect (4)
Various	4	Erect (5)
Capsules		
Hard gelatin, Size 2	10	Supine (2)
Hard gelatin, Size 2	10	Supine (2)
Hard gelatin, Size 2	8	Supine (2)
Hard gelatin, Size 0	45	Supine (2)
Hard gelatin, Size 0	9	Supine (2)
Hard gelatin, Size 4	9	Erect (4)
Hard gelatin, Size 2	9	Erect (2)
Hard gelatin, Size 2	3	Erect (2)
Hard gelatin, Size 0	3	Erect (2)
Hard gelatin, Size 0	9	Erect (2)
Liquid,		
20 ml	10	Supine (1)

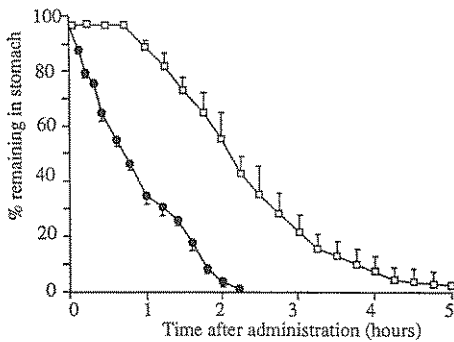
(1) Mison et al.; 1988, (2) Channer and Virjee 1985, (3) Hey et al.; 1982, (4) Perkins et al.; unpublished (d) Channer and Virjee, 1986.

As can be seen from the table, the degree of retention is related both to the characteristics of the formulation and whether the subject is erect or supine. In a recent cross-over study where we compared the oesophageal transit of small oval tablets and capsules in elderly subjects (n=24, mean age = 69), retention occurred in 22% of subjects taking the capsule but none swallowing the tablet (Perkins et al., unpublished observations). This data was useful in selecting the appropriate dosage form for an incorporated material which had a risk of causing ulceration. In the latter study the subjects were erect; when the subject is supine, the incidence of retention is far higher. In situations where oesophageal clearance is compromised and the subject is bed-ridden, palatable liquid and suspension formulations offer the physician a significant advantage in the avoidance of oesophageal injury.

GASTRIC RESIDENCE TIMES OF LIQUID AND SUSPENSION DOSAGE FORMS

The time for which a dosage form remains in the stomach is extremely variable and is greatly influenced by the concomitant intake of food. The digestion of food causes a release of secretagogues and activation of the myenteric network. This causes an increase in duodenal wall pressure which opposes the emptying of solids by decreasing the calibre of the opening of the pylorus, allowing a slow steady supply of nutrients into the small intestine. During digestion, the stomach squirts a small amount of semi-solid chyme into the duodenum at the end of the contraction, expelling triturated particles. For a suspension, gastric emptying will be slowed by food, and the emptying follows an exponential pattern (Figure 1).

Figure 1 :
Gastric emptying of 20 ml suspension when given to a group of fasted (●) or fed (□) volunteers.
(mean + or - s.d.; n=12).



As can be seen, the gastric half time for 20 ml suspension is increased from 1 hour on an empty stomach to over two hours when taken with a meal of calorific value of 1700 kJ and a volume of 400 ml. Small volumes of liquid administered orally also empty exponentially. The retention time can be as little as within 5 minutes in a fasted volunteer but this is greatly influenced by posture. Larger isotonic loads, with a moderate calorific value (350-400 kJ) have a gastric half-time of between 0.75 - 1 hour.

The upper size limit for solid particles to escape from the stomach in the fed mode is around 5 mm, provided that the unit is resistant to gastric disruption. The emptying of large inert particles, however, may depend on their deformability by antral contractions, since it has been observed that hard nondeformable spheres empty more slowly than softer compliant spheres. (Schlegel et al. 1966). For both solutions and suspensions,

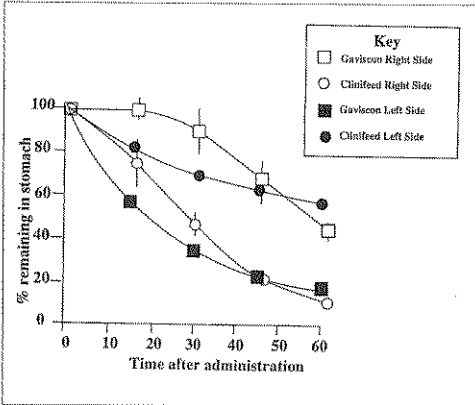
the components of a meal control the rate of gastric emptying. The major inhibitory factor is the calorific value of the meal (carbohydrate and fats) whereas the protein content influences acid secretion through local secretagogue action.

Under fasted conditions, the calibre of the pylorus is usually sufficient to allow emptying of liquids whereas non-disintegrating objects are retained until the onset of the house-keeper sequence, (Code & Martlett, 1975). This migrating myoelectric activity occurs regularly during fasted periods or within three hours of the gastric emptying of a meal being complete. The rise in peristaltic activity through Phase III increases the chances of large indigestible objects being emptied into the duodenum. Shape of a tablet does not appear to be an important factor influencing emptying in the fasted state, and workers have found that no differences in the rate of emptying of enteric-coated tablets over a large size range, with 80% emptying of the dose forms over the first 2 hours following dosing. (Park et al., 1984)

For solutions and suspensions, retention will also depend on density and posture. To illustrate this importance of the interaction of these two variables, the gastric emptying of a floating raft system is presented. Raft systems have been considered by several workers as possible platforms for extending drug release over several hours, allowing drug to percolate through the duodenum. Gaviscon®, a raft-forming alginate product is widely prescribed for the treatment of oesophagitis and it was of interest to examine the retention of this product using scintigraphic techniques. The aim of the study was to mimic the situation when the patient retires at night. Previous studies (Malmud et al., 1979; May et al., 1984) had shown that alginate-based formulations tend to float on the other stomach contents when taken with a liquid meal (Clinifed). The gastric emptying of two radio labelled antacid preparations was monitored by radio labelling the Gaviscon with indium-113m and the liquid meal with technetium-99m labelled diethylenetriaminepentaacetic acid (Bennett et al., 1985) Subjects were placed in 3 postures on different occasions; supine, lying on their left sides and lying on their right sides. The raft-forming alginate formulation emptied faster than the food in subjects lying on their left sides, and slower in subjects lying on their right sides. (Figure 2)

Figure 2 :

Gastric emptying of Tc-99m labelled meal and In-113m labelled Gaviscon with subjects lying on their right or left sides. Bars show the range of observations (n=3) (Adapted from Bennett et al., 1984).



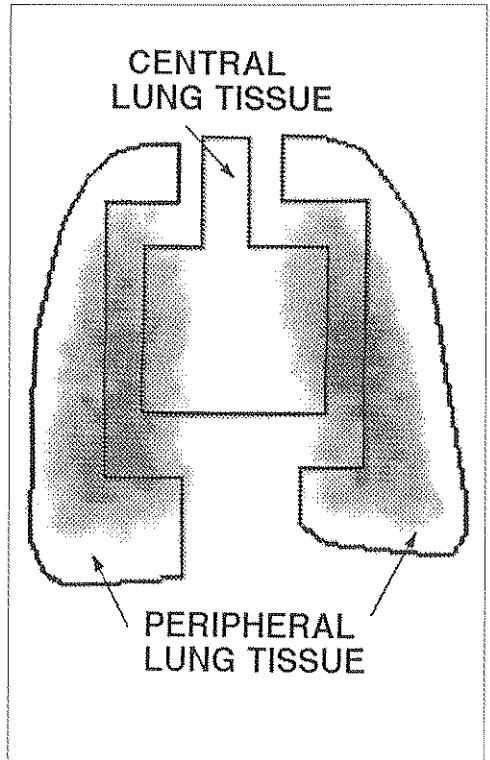
With subjects lying on their right sides the floating alginate layer was towards the greater curvature of the stomach and thus away from the pylorus. Only when the volume of stomach contents was relatively low was the alginate able to pass into the duodenum. The opposite situation occurred in the subjects when they lay on their left sides. Part of the alginate layer was between the food and the pylorus, and thus emptied preferentially. In the supine posture, all 3 preparations had similar access to the pyloric antrum and emptied at approximately equal rates. Thus the efficiency of a raft-based system for prolonged delivery is probably not suitable for nocturnal dosing.

PULMONARY DELIVERY

Liquids and suspensions are also used for the administration of drugs by other routes for example the lung using devices capable of generating an aerosol cloud. The effectiveness of pulmonary drug delivery from a device is a function of the amount of drug delivered to the appropriate site in the lung. In general terms, aerosols with a mass median aerodynamic diameter (MMAD) of 3-5 μm are considered optimal for drug delivery to the upper airways and small bronchi whereas a lower MMAD of 0.8-3 μm is considered optimal for the treatment of parenchymal disease. Nebulisers are widely used to deliver drugs to the alveoli and smaller airways and gamma scintigraphy has been useful in determining the respirable fraction from different instruments.

Pulmonary delivery with metered dose inhalers have also been investigated using technetium-99m labelled particulates including Tc-99m labelled Teflon spheres (Newman et al., 1982). Gamma scintigraphy was used by our laboratories around the same time for the assessment of salbutamol deposition using a technetium-99m labelled phenyl arsonium complex in dogs (Malton et al., 1982) but there was insufficient toxicity data to proceed to man. Two recent introductions have caused us to re-evaluate the delivery of drug by metered dose inhaler; the introduction of highly lipophilic β_2 -adrenoreceptor agonist drug, tulobuterol, used in the treatment of asthma and the availability of a new imaging agent, technetium-99m labelled hexamethyl propylene amine oxime ($^{99\text{m}}\text{Tc-HMPAO}$). Tulobuterol base is sufficiently lipophilic to dissolve in trichlorofluoromethane (propellant 12), a component of the propellant mixture contained within a M.D.I. The high lipophilicity of $^{99\text{m}}\text{Tc-HMPAO}$ which also dissolves in propellant 12 allows us to safely mimic the behaviour of such drugs in man and study the deposition following actuation of a metered dose inhaler (Ashworth et al., 1991).

Figure 3a



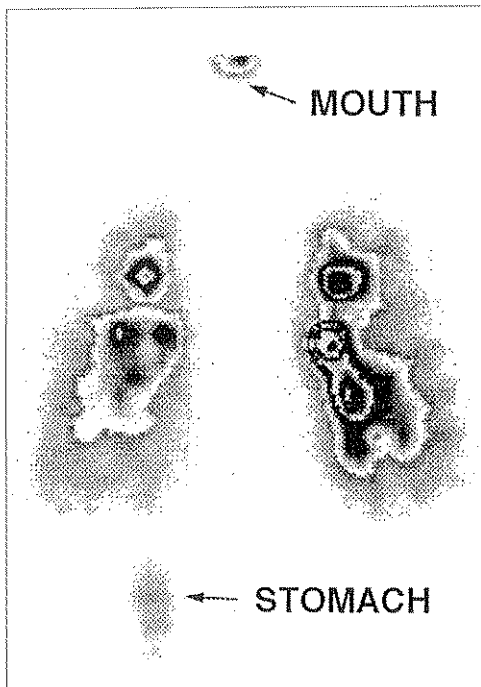


Figure 3b

Figure 3a and 3b :

Krypton-81m (a) and Tc-99m HMPAO (b) images for subject taking part in a study of the behaviour of metered dose inhalers (from Harnor et al., in press).

Fig. 3a shows inner and outer regions of interest used to assess extent of peripheral deposition.

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The technique we use is to image the periphery of the lungs by inhaling the shortlived gamma emitter krypton-81m ($T_{1/2}=13$ seconds). With the subject remaining in front of the gamma camera, the subject inhales from a metered dose inhaler containing the radio labelled preparation. The deposition pattern of the aerosol can then be compared with the image obtained for the gas and the extent of peripheral deposition assessed (Figure 3)

In the first study (Ashworth et al., 1991), the effects on deposition of varying the size of the delivery orifice and the attachment of a spacer were assessed. Without the spacer, on average, 39% of the dose was deposited in the lungs, with 15% penetrating into the small airways and alveoli. Attachment of the spacer to the mouthpiece increased the mean lung deposition to 57% and reduced oropharyngeal deposition. The second study (Harnor et al., in press) examined the deposition patterns for high vapour pressure (HVPA) and low vapour

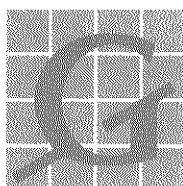
pressure (LVPA) aerosols. The deposition showed that a lower proportion of the dose was swallowed for HVPA compared with LVPA. Additionally, the results obtained confirm previous observations that greater than 40% of the marker achieves pulmonary deposition when dissolved in the propellant phase.

CONCLUDING REMARKS

The techniques now available to the pharmaceutical scientist are able to graphically and quantitatively demonstrate the behaviour of liquid and suspension formulations in man. The availability of scintigraphy in an increasingly large number of laboratories throughout Europe will lead to more informative trials and no doubt, to the development of new applications for liquid and suspension dose forms.

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GATTEFOSSÉ

SELF-EMULSIFYING DRUG DELIVERY SYSTEMS (SEDDS) FOR IMPROVING *IN VITRO* DISSOLUTION AND ORAL ABSORPTION OF LIPOPHILIC DRUGS

SYSTEMES THERAPEUTIQUES AUTO-EMULSIONNANTS

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Les SEDDS sont des mélanges isotropes d'huile et de tensio-actif non ionique. Leur intérêt majeur est de former une émulsion H/E fine (sous faible agitation) lorsqu'ils sont mis en présence d'un milieu aqueux. Cette propriété est mise à profit pour améliorer la vitesse et l'ampleur de la dissolution de molécules faiblement hydrosolubles ainsi que pour obtenir une meilleure reproductibilité des concentrations plasmatiques. Dans cette étude, les SEDDS formulés avec des glycérides polyglycolysés associés à différentes huiles, sont évalués en retenant comme critère la distribution de taille des globules huileux formés, la vitesse de dissolution des PA dans la phase aqueuse, et le coefficient de partage de la molécule dans ces systèmes.

Les études *in vitro* ont mis en évidence les performances d'un glycéride polyglycolysé de HLB 10. Les études *in vivo* (chez le chien) ont confirmé ces résultats et ont démontré que les SEDDS, non seulement amélioreraient la biodisponibilité des molécules mais limitaient aussi les variabilités inter-sujets.

INTRODUCTION

Self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of an oil and a non-ionic emulsifier. One feature of these mixtures is their ability to form fine oil-in-water emulsions with only gentle agitation when exposed to aqueous media. This property makes SEDDS good candidates for the oral delivery of hydrophobic drugs. After oral administration of soft gelatin capsules, SEDDS readily disperse in the stomach to form a fine emulsion; in this case, the digestive motility of the stomach and the intestine can provide the agitation necessary for self-emulsification (1,2). At a given temperature, self-emulsification occurs when the entropy change that favors dispersion is greater than the energy required to increase the surface area of the dispersion (3). The performance of SEDDS is dependent upon two main factors:

a) the ability of the self-emulsifying mixture to form an emulsion of fine particles (i.e. $< 5\mu\text{m}$) with a uniform size distribution; and b) the polarity of the resulting oil droplets to promote a fast rate of release of the drug into the aqueous phase. The efficiency of emulsifiers in SEDDS is commonly related to their ability to form fine droplet size of the emulsion on exposure to water, having polarity favoring faster rate of the drug release (2,4,5). For drugs subject to dissolution rate limited absorption, SEDDS may offer improvement in the rate and extent of absorption, as well as in the reproducibility of the blood level-time profile (4,5). SEDDS containing medium chain monoglycerides (Capmul MCM90) and PEG-25 Trioleate (Tagat TO) have been reported to form small (submicron) droplet oil-in-water emulsions (4,6,7).

THEORETICAL CONSIDERATIONS

The efficiency of SEDDS depends on two main factors: 1) uniform fine particle size of oil droplets on exposure to aqueous media; and 2) the polarity of the resulting oil droplets. Both properties control the rate of release of the drug from the oil to the aqueous phase.

Once exposed to the aqueous phase, SEDDS form oil-in-water (O/W) emulsions. The resulting o/w emulsions produced by SEDDS tend to be thermodynamically more stable than

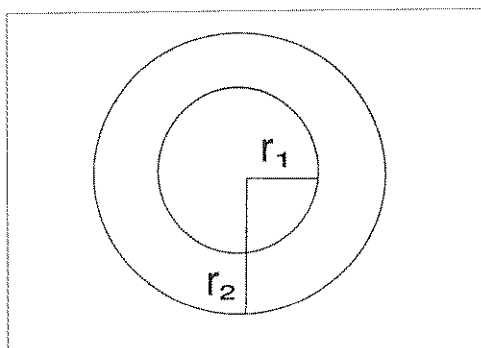
regular emulsions. There are two factors that favor emulsion stability in the case of SEDDS: 1) relatively small volume of the dispersed oil phase, and 2) narrow range of droplet size distribution. For a given combination of components, emulsions with small, uniform droplet size will take longer to break. Larger droplets are less unstable than smaller droplets due to their larger area to volume ratio, and so will tend to grow at the expense of the smaller droplets (8).

The smaller droplets will have a larger interfacial surface area per unit volume. The diffusion path for a drug will decrease with the reduction of the radius of the droplets.

Another important factor for the performance of SEDDS is the polarity of the oil droplets. The polarity of the oil droplets is governed by the hydrophile-lipophile balance (HLB), the chain length and degree of unsaturation of the fatty acid, the molecular weight of the hydrophilic portion and the concentration of the emulsifier. The combination of small droplets together with the appropriate polarity (lower $PC_{O/W}$ of the drug) of the droplets will permit an acceptable rate of release of the drug. Polarity of the oil droplets is also estimated by the oil/water partition coefficient ($PC_{O/W}$) of the lipophilic drug.

A schematic representation of the drug release from emulsion is shown in Figure 1. The amount of drug diffused at time t , Q_t , from the oil droplet to the aqueous environment is primarily a function of the radius of the droplet, r , which is a reflection of the surface area and the partition coefficient, K (polarity), which reflects the affinity of the drug for oil and/or water and the type of forces formed. A picture of an ideal SEDDS indicating its maximum efficiency on exposure to water is shown in Figure 2.

Figure 1 : Drug Diffusion from Oil Droplet.



$$Q_t = f(1/r^*K)$$

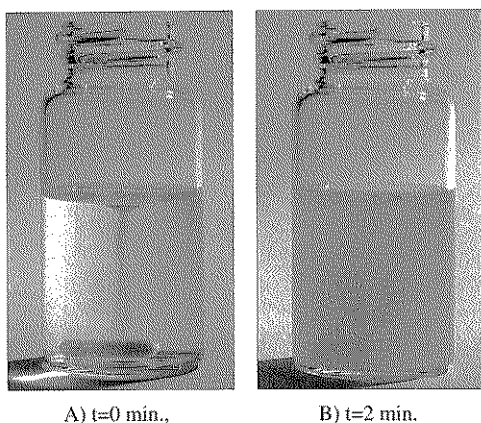
Q_t = Amount of Drug Diffused at time t

r = Radius of the Droplet

K = Partition Coefficient

Figure 2 :

Photograph of an ideal Self-Emulsification.



A) $t=0$ min.,

B) $t=2$ min.

EXPERIMENTAL

Materials

Lipophilic model drug: Ro 15-0778, a naphthalene derivative, with low water solubility, < 0.01 mg/ml, and high peanut oil solubility, 95 mg/ml_o

Vegetable oils : Peanut Oil (Ruger, Irvington, NJ and Croda, New York, NY), Neobee M5 (Stepan Co., Maywood, NJ).

Non-ionic emulsifiers: A) Glyceryl Monocaprylate/caprate (Capmul MCM90, 90% monoglycerides of medium chain fatty acids, C₈-C₁₀) (Karishmans USA, Inc. Columbus, OH) and B) Polyglycolized glycerides, see TABLE I.

Non-ionic surfactants : A) Polysorbate 80 (ICI Corp., Wilmington, DE) and B) PEG-25

Glyceryl Trioleate (Tagat TO) (Goldschmidt Chemical Corp., Hopewell, VA).

All materials were used as received.

Formulation for SEDDS : The formulation of oil solution for SEDDS is shown in TABLE II. A 500 mg formulation was filled manually with a syringe in a soft gelatin capsule and the resulting hole was sealed with heat.

Methods

Release Rate Determination: USP XXII, Dissolution Apparatus 2 (Van-Kel Industries, Inc.) was employed to obtain the release of the drug from the oil to aqueous systems. Soft gelatin capsules containing the SEDDS were placed in copper coils to keep them at the bottom of the dissolution vessel, which was filled with 900 ml of 5% aqueous solution of Alkamuls EL-719 (from Rhône-Poulenc) at 37°C. A fine emulsion is formed by gentle agitation provided by the Teflon-coated dissolution paddle, rotating at 50 rpm. The emulsion was filtered through a 0.2 μ m millipore filter and analyzed by UV at 298 nm. (UV DU®-65 Spectrophotometer).

Emulsion Particle Size Measurement: The particle size of the emulsions obtained were determined using a Malvern Particle Size Analyzer, Model No. 2600, 63 mm lens (Malvern, UK). The particle size distributions of the resultant emulsions were compared with the apparent volume-average diameters of 50 percentile D(v,0.5). Efficient emulsification was arbitrarily defined (in the same fashion as Charman, et al.(4)) as a system which produced mean emulsion droplet diameters (MEDD) values of D(v,0.5) $< 5\mu$ m.

Partition Coefficient : Equal amounts of formulation and aqueous solution of 5% Alkamuls EL-719 were mixed for 1 hour on a Glas-Col Laboratory Rotator, Speed 4, centrifuged and each phase diluted appropriately and analyzed for drug content by UV spectrophotometry at 298 nm.

Table I :
POLYGLYCOLYZED GLYCERIDES

Emulsifier PEG Glyceride	Oil/Main Fatty Acid in Glyceride	HLB
Labrafil® M 2125 CS	Corn oil/ Linoleic Acid, C _{18:2}	3-4
Labrafil® M 1944 CS	Apricot Kernel oil/ Oleic Acid, C _{18:1}	3-4
Labrafac® Hydro	MCT/ Caprylic & Capric Acids	4-5
Labrafac® CM 6 BM 290	MCT/ Caprylic & Capric Acids	6
Labrafil® WL 2609 BS	Corn Oil/ Linoleic Acid, C _{18:2}	6-7
Labrafac® CM 8 BM 284	MCT/ Caprylic & Capric Acids	8
Labrafac® CM 10 BM 287	MCT/ Caprylic & Capric Acids	10
Labrafil® M 10 BM 355	Corn Oil/ Linoleic Acid, C _{18:2}	10
Labrafil® NA 10 BM 369	Apricot Kernel oil/ Oleic Acid, C _{18:1}	10
Labrasol®	MCT/ Caprylic & Capric Acids	14

MCT = Medium Chain (C₈-C₁₀) Triglycerides from coconut oil.

Table II :
Formulation of SEDDS

Ingredients	I	II	III
	% W/W	% W/W	% W/W
Lipophilic Drug (Ro 15-0778)	5	5	5
Polyglycolized Glycerides	5-60	-	-
Medium Chain Mono- and diglycerides (Capmul MCM90)	-	17	-
PEG-25 Glyceryl Trioleate	-	-	30-60
Polysorbate 80	-	5	-
Peanut oil/Neobee Oil, q.s.	100	100	100

RESULTS AND DISCUSSION

Polyglycolized Glycerides (PGG) were investigated for their utility in SEDDS. A comparison of the efficiency of PGG in SEDDS was made with previously investigated SEDDS containing medium chain monoglyceride (Capmul MCM90) and PEG (25) Trioleate (Tagat TO).

The formulations used in the evaluation of PGG in SEDDS over a range of PGG content are described in Table II. Figures 3 and 4 show the effect of fatty acid chain length and the effect of molecular weight of PEG in the glyceride, respectively, on the release of the drug. A long chain length of fatty acid in the glyceride (Labrafil® WL 2609 BS) leads to a more lipophilic environment, whereas a medium chain length of the fatty acid in the glyceride (Labrafac® CM 10 BM 287 or simply Labrafac® CM 10) offers a less lipophilic system. The arrangement of the lipophilic portion of the PGG with the oil phase and the polar heads with water gives an energetically more favorable situation than complete solution in either phase, and therefore, tends to be more efficient in releasing the drug. Also, within the same fatty acid chain length but with different molecular weights of PEG, e.g. Labrafil® WL 2609 BS was less lipophilic than Labrafil® M 2125 CS resulting in a different rate of drug release.

Figure 3

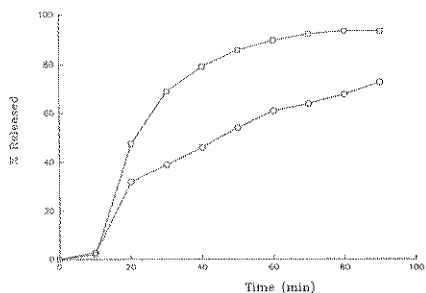


Figure 3. Effect of fatty acid chain length in Polyglycolized Glycerides on the release of Ro 15-0770. (○) Labrafil WL 2609 BS ($C_{18:2}$); (□) Labrafac CM 10 BM 287 (C_8-C_{10}).

The achievement of “adequate” polarity of the resulting oil droplets permits an acceptable rate of release of the drug. Figure 5 illustrates the polarity in terms of HLB; PGG with an HLB about 10 gives the best results in terms of drug release. However, an HLB around 10 (Figure 6) needs to meet some qualifications, i.e. it should

be obtained by appropriate combination of fatty acid and PEG. Labrafac® CM 10 provides a faster drug release than either Labrafil® M 10 or Labrafil® NA 10 due to the medium chain length (C_8-C_{10}) of the fatty acid present in its composition. Drug release was slightly faster with Labrafil® M 10 than with Labrafil® NA 10. This can be explained by the degree of unsaturation present in the fatty acid chain length between Labrafil® M 10 ($C_{18:2}$) and Labrafil® NA 10 ($C_{18:1}$). Unsaturation present in the fatty acid molecule is predisposed to be more polarizable.

Figure 4

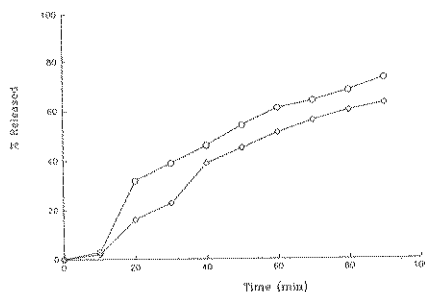


Figure 4. Effect of Molecular Weight of PEG in Polyglycolized Glycerides on the Release of Ro 15-0770. (○) Labrafil WL 2609 BS ($C_{18:2}$, PEG 450); (□) Labrafil M 2125 CS ($C_{18:2}$, PEG 300).

Figure 5

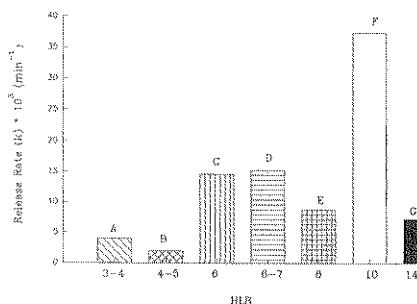


Figure 5. Comparison of different HLB on the Release Rate of Ro 15-0770 at 90% of Emulsifier. A. Labrafil M 2125 CS; B. Labrafac Hydra; C. Labrafac CM 8 BM 330; D. Labrafil WL 2609 BS; E. Labrafac CM 8 BM 284; F. Labrafac CM 10 BM 287; G. Labrafac.

Figure 7 illustrates the role of the emulsifier (Labrafac® CM 10) concentration for efficient SEDDS. The higher the concentration of the emulsifier is the smaller the droplet size of the emulsion and the faster the release rate of the drug. Figure 8 shows the relationship of partition coefficient with release rate as a function of the emulsifier Labrafac® CM 10 concentration. The results indicate that the formation of a fine particle size emulsion together with lower partition coefficient ($PC_{O/W}$) of the drug from these oil droplets are the prerequisites for the optimum efficiency of SEDDS in terms of drug release.

Figure 6

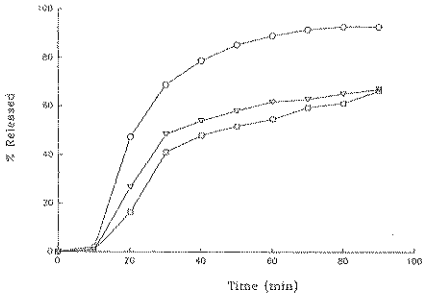


Figure 6. Effect of Fatty Acid Chain Length and Saturation of Fatty Acid Present in the Glyceride, on the Drug Release, at 60% Emulsifier Concentration and HLB of 10. (O) Labrafac CM 10 BM 287 (C₈-C₁₀); (∇) Labrafac M 10 BM 355 (C₁₈); (□) Labrafac NA 10 BM 388 (C₂₂).

Figure 9

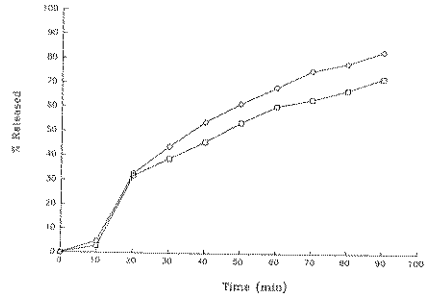


Figure 9. Effect of Lipophilic Vehicle on the Release of Ro 15-0778. (∇) Neobee Oil; (□) Peanut Oil.

It was observed that drug release from formulations containing Peanut Oil or Neobee M5 was slightly different (Figure 9). This difference is explained in terms of the compositions of the two oils: Peanut Oil contains saturated and unsaturated C₁₈ fatty acids, whereas Neobee M5 contains medium chain saturated C₈-C₁₀ fatty acids.

Figure 7

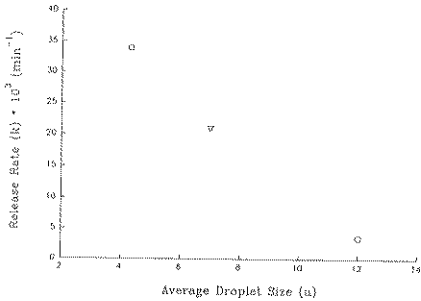


Figure 7. The influence of emulsifier concentration in SEDDS containing Labrafac CM 10 BM 287 on the release rate of Ro 15-0778 and droplet size of the emulsifier. (□) 60%; (∇) 40%; (○) 20%.

Additional experiments were conducted to corroborate the influence of each component on the efficiency of SEDDS and to provide information indicating the best formulation (small- droplet size, maximum *in vitro* dissolution). A phase diagram can be used to establish the optimum concentrations of the drug, oil and emulsifying agent (Figure 10). In region A, good self-emulsification occurs, this area represents an isotropic mixture. A good emulsification is related to the mutual solubility existing between the oil in water and vice-versa. Region C is especially dependent on the emulsifier, since, polyglycolized glycerides are predisposed to form liquid crystal dispersions with the oil. This leads to a more difficult penetration of the water into this system, and hence, the efficiency of SEDDS is diminished. In region B, poor SEDDS are expected because the drug concentration exceeds its solubility.

Figure 10

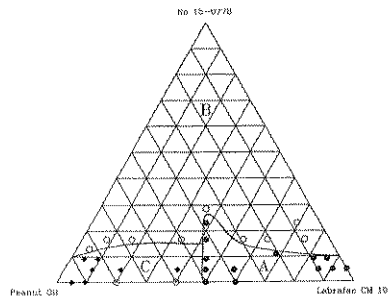


FIGURE 10 Phase Diagram for Peanut Oil/Labrafac CM10/Ro 15-0778 system (●) region A: good and efficient self-emulsifying systems. (○) region B: poor self-emulsifying systems. (◆) region C: intermediate self-emulsifying systems

Figure 8

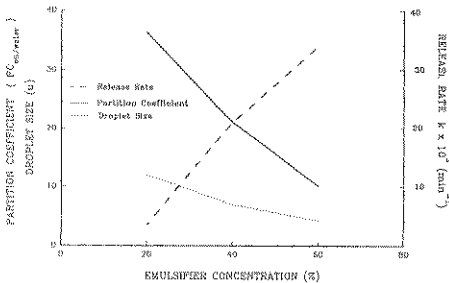


Figure 8. Effect of Concentration of Emulsifier, Labrafac CM 10 BM 287, on Partition Coefficient, Droplet Size and the Release Rate of Ro 15-0778.

Figure 11 shows that Glyceryl Monoesters appear to be comparable to Polyglycolized Glycerides (PGG) as effective emulsifiers for SEDDS when an auxiliary surfactant, for the formation of efficient SEDDS, is added.

The presence of an auxiliary surfactant Polysorbate 80 was necessary to assist Capmul MCM90 in enhancing the release of the lipophilic drug from SEDDS. Capmul MCM90 alone even at higher concentrations, does not provide for efficient SEDDS. In contrast, the addition of an auxiliary surfactant was not required for Labrafac® CM 10 or Tagat TO. This behavior could be attributed to the fact that Capmul MCM90 is less hydrophilic emulsifier (HLB about 5) consisting of only one mole of glycerol and saturated fatty acid. When Polysorbate 80 [polyoxyethylene (20) sorbitan monooleate] is added, a more hydrophilic environment is attained resulting in a reduction of the surface tension between the oil and water, and "adequate" polarity. In the case of Labrafac® CM 10 and Tagat TO, the presence of a satisfactory chain length of PEG in the molecule provides adequate lipophile-hydrophile balance.

The efficiency of SEDDS for *in vitro* dissolution and *in vivo* absorption was compared to three other dosage forms: i) a 1.2% drug solution in

PEG 400; ii) a tablet of the micronized drug; and iii) a capsule of 55% wet-milled spray dried powder at a 200 mg dose level. *In vitro* dissolution profiles of these dosage forms and SEDDS are shown in Figure 12. A single oral dose of 200 mg of each formulation was orally administered to non-fasted male beagle dogs. The plasma concentration vs. time profiles are shown in Figure 13. The superior performance of SEDDS compared to the other dosage forms is clearly apparent. *In vivo* absorption data showed at least three-fold greater C_{max} and AUC with SEDDS than with the other dosage forms (Table III). Even though the *in vitro* dissolution rate from PEG 400 solution was faster than that of SEDDS, *in vivo* absorption data showed greater C_{max} and AUC with SEDDS. Drug in solution in PEG 400 could possibly have precipitated out during *in vivo* administration. During *in vitro* dissolution studies, precipitation was not observed due to the presence of surfactant in the dissolution medium. These data clearly demonstrated the utility of SEDDS in improving oral absorption of lipophilic drugs.

Figure 11

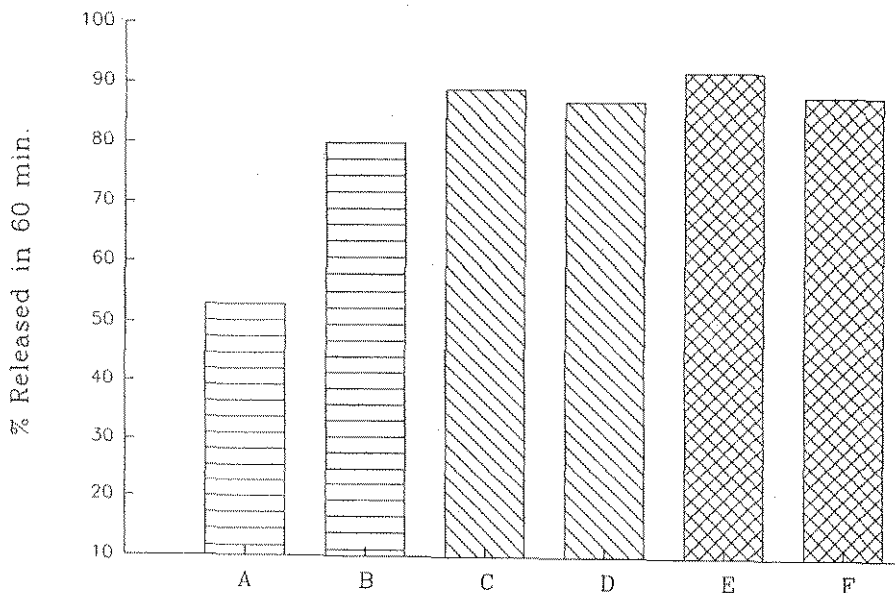


Figure 11. Effect on drug release after the addition of 5% of Polysorbate 80 to the emulsifier. A. Capmul MCM90 (17%); B. Capmul MCM90 (17%) + Polysorbate 80; C. Labrafac CM 10 (60%); D. Labrafac CM 10 (60%) + Polysorbate 80; E. Tagat TO (60%); F. Tagat TO (60%) + Polysorbate 80.

Figure 12

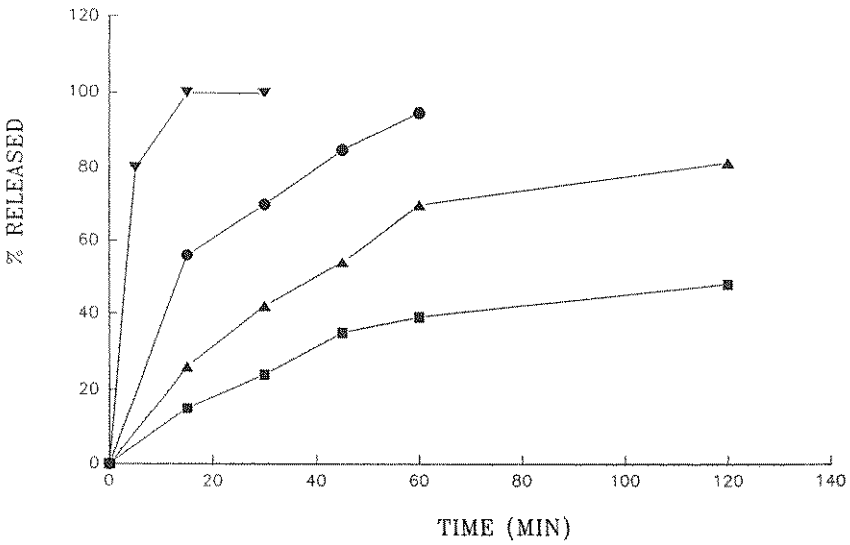


Figure 12. In vitro dissolution profiles of the drug from different formulations. (●) SEDDS; (▼) 1.2% Solution in PEG 400; (▲) Capsule containing wet-milled spray dried powder; (■) Tablet containing micronized drug.

Figure 13

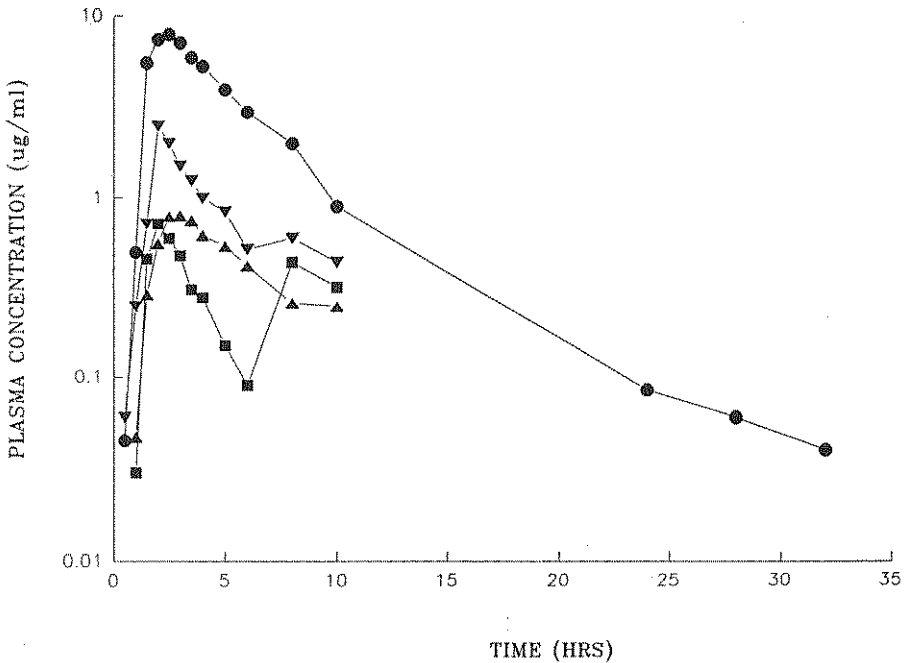


Figure 13. Mean Plasma Concentration of Ro 15-0778 in non-fasted dogs after oral administration of four different formulations. (●) SEDDS; (▼) 1.2% solution of PEG 400; (▲) Capsule containing wet-milled spray dried powder; (■) Tablet containing micronized drug.

Table III :
Pharmacokinetic parameters of Ro 15-0778 from different formulations in non-fasting dogs.

FORMULATION	C _{max} µg/ml	t _{max} hours	AUC µg Hr/ml	% RELATIVE BIOAVAILABILITY
Self-Emulsified Solution (SEDDS)	5.57	2.50	29.77	389.0
Drug Solution in PEG 400 (Control)	1.44	2.00	7.64	100.0
Capsule Form. of Wet-Milled Spray Dried Powder	0.78	3.00	2.69	35.3
Tablet Form. of Micronized Drug	0.58	2.00	1.32	17.2

CONCLUSIONS

Polyglycolized Glycerides (PGG) with varying fatty acid and polyethylene glycol (PEG) chain lengths have shown their ability to produce the self-emulsification of oil in water. The performance of self-emulsifying drug delivery systems (SEDDS) is governed by two main factors: a) the ability of the self-emulsifying mixture to form an emulsion with uniform fine particle size droplets (i.e., < 5µm); and b) the polarity of the resulting oil droplets which permits a faster rate of release of the drug into the aqueous phase.

The chain length and unsaturation of the fatty acid, as well as the molecular weight and concentration of PEG in the emulsifier, influence the droplet particle size and droplet polarity in the emulsion and thus the drug release. An HLB of the emulsifier, around 10, gives the best results in terms of drug release. However, this HLB needs to meet some qualifications, i.e., it should be obtained by an appropriate combination of fatty acid(s) and PEG.

In addition to the above factors, small particle size and drug release rate, the partition

coefficient (Table III) was found important parameter to be considered for the evaluation of the efficiency of SEDDS. The smaller the particle size of the oil droplets and the lower the $PC_{O/W}$, the more efficient will be the SEDDS.

SEDDS containing PGG, such as Labrafac® CM 10, were comparable to those with Capmul MCM90 plus Polysorbate 80, and PEG-25 Glyceryl Trioleate (Tagat TO) for their efficiency and stability.

In *in vivo* absorption studies in dogs for a lipophilic drug, SEDDS gave at least a three-fold greater C_{max} and AUC than either the drug in solution, a tablet of micronized drug or a capsule of wet-milled spray dried powder.

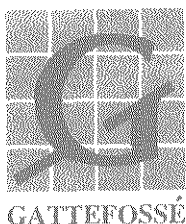
The data presented have shown that SEDDS provide a most efficient way of improving the oral absorption of a lipophilic drug.

ACKNOWLEDGMENTS

The authors wish to thank Dr. A. S. Railkar for her support in dissolution studies, Dr. F.C. Chen for micromeritic assistance and Ms. M. Bachynsky for her helpful discussion.

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INFORMATIONS DIVERSES/ MISCELLANEOUS INFORMATIONS

DERMSEARCH

A NEW RESEARCH HUB FOR BIOPHARMACY
AND PHARMACEUTICAL TECHNOLOGY IN THE CLAUDE BERNARD
UNIVERSITY

The Lyon I University Pharmaceutical Technology research laboratory has joined forces with a British Pharmaceutical Chemistry laboratory to set up a technological hub providing assistance to manufacturers active in the sector for the development of new products.

Pr. Françoise Falson and Pr. Jonathan Hadgraft, Directors of DERMSEARCH, explain how they have built it:

Pr F. Falson:

“The research laboratory that I created in Lyon I specialises in absorption modulators which permit controlled diffusion of active substances in cutaneous structures.

This work started previously with H.M. Gattefossé in the Transdermal research unit that I conducted in the laboratory of Professeur F. Puisieux (Paris XI University). Taking a Professor position in UCB Lyon 1 in 1990, I transposed my work creating a laboratory in good agreement with the traditional Ecole Lyonnaise de Dermopharmacie et Cosmétologie.

From 1935, many scientific persons have been interested with skin in Lyon: Dr. H. Jonquières, Pr. Thiers, Pr J. Cotte, E. Mahler, H. M. Gattefossé and Pr. J. Thivolet who recently created l’Institut de la Peau.

The aim of our research is to evaluate the interactions of the components of the dosage form and the skin by measuring partition coefficients and rate of diffusion into the cutaneous structures. Formulation or Bioformulation, as I like to say, enables these physico-chemical parameters to be modified and then predicts modulation of the percutaneous absorption.

To increase our scientific resources, we have recently decided to join forces with Professor Jonathan Hadgraft in the Welsh School of Pharmacy in Cardiff. The British laboratory will make a vital contribution to enhance

understanding of the fundamental principals of diffusion with model of molecule interactions.

Set up jointly EZUS, Filiale de Valorisation de la Recherche de l’Université Lyon I, DERMSEARCH is a new technology hub designed to pool the complementarity facilities of both laboratories; it constitutes a driving force in the field of pharmaceutical technology.

It is really my pleasure to introduce you Jonathan Hadgraft and let him talk about his research.”

Pr. J. Hadgraft:

“My father had an interesting education, at school he was more interested in the arts subjects and was progressing through the school in Bedford to the form VI arts when his father became ill. He had to give up his ideas of a University education and a career in architecture and instead took a position in a local pharmacy shop. He progressed within the pharmacy profession, obtained a position within the Industry and as a result of his outspoken attitudes was asked to leave the company as a result of writing a letter to the Pharmaceutical Journal. He was given a temporary position within the Pharmaceutical Society and at a very young age was appointed chief pharmacist at the Royal Free Hospital. It is perhaps coincidental that he and I were similar ages when we were appointed to fairly senior positions. I was interviewed for my current Chair in Pharmaceutical Chemistry when I was 33.

My father had an interest in basic chemistry and

was studying for a BSc in chemistry part time. Unfortunately ill health prevented him from taking the degree and instead he took the Royal Society of Chemistry's equivalent professional qualification. As the chief pharmacist at the Hospital he was anxious to continue a research programme and combine his pharmaceutical and chemical skills.

My first recollection of the research that my father was conducting on skin permeation was when he took me along to one of the lectures he was giving at a meeting of the Pharmaceutical Society. It was at a time that he was collaborating with Dr Sarkany, a dermatologist at the Royal Free Hospital in London. The particular interest was in the formulation of corticosteroids and how formulation effects could alter the subsequent therapeutic activity. The steroids were of great interest clinically and also they had the advantage that their skin permeation could be monitored using their ability to create local vasoconstriction. I was fascinated by the way in which he was able to interpret the results of his biological experiments with simple explanations based on the underlying chemistry.

My interest in chemistry had been kindled at an early age when my father and I would conduct simple experiments in the garden using a primus stove as our Bunsen burner. He showed me examples of water of crystallisation using salts of copper, how nitrogen dioxide was released from lead nitrate when it was heated, the production of hydrogen from zinc and hydrochloric acid and the different forms of sulphur. Other gases were also produced, some to the dismay of my mother such as hydrogen sulphide, oxygen rekindled a glowing splint, sulphur dioxide and chlorine were not too pleasant. However my interest was raised and I thought that I would like to become either an analytical chemist or a geochemist; I also had a great interest in geology.

When it became time to decide on University education, I decided that I wanted to study pure chemistry and I was lucky enough to gain a place at Oxford University. During the summer vacations it was difficult for me to get a temporary job and my father arranged for me to be paid by the Dermatology department at the Royal Free Hospital with some money that had been obtained from the Dunhill Trust. I conducted a small research project using methyl nicotinate and measured the times of onset of erythema as a function of the formulation. The work resulted in

my first publication jointly with my father and Dr Sarkany and which appeared in the British Journal of Dermatology.

J. Hadgraft, J.W. Hadgraft and I. Sarkany.

The effect of glycerol on the percutaneous absorption of methyl nicotinate.

Brit. J. Derm. (1972) 87, 30-36

The first summer vacations research was very interesting but it generated many unresolved questions. We discussed these and I returned the following year and produced some more data which was published in the Journal of Pharmacy and Pharmacology and which I presented at the British Pharmaceutical Conference in London, my first public presentation which gave me the idea that I would really like to continue research and pursue an academic career.

J. Hadgraft, J.W. Hadgraft and I. Sarkany.

The effect of thermodynamic activity on percutaneous absorption.

J. Pharm. Pharmacol (1973) 25, 122P-123P.

The fourth year of the degree scheme in Oxford is devoted to research and I worked on the rates at which molecules transfer across liquid liquid interfaces. I saw the relevance of this to understanding how molecules cross biological membranes including the skin. I stayed on at Oxford to continue these studies for my D.Phil. About the same time my father left London for a position at the Regional Health Authority in Cambridge and his research into percutaneous absorption ceased. However he continued to be interested in the work I was conducting and gave me all the relevant literature he had on the subject. One of the papers that he had written in 1956 was particularly impressive since he had identified what he felt were the ideal characteristics of a skin permeant "Maximum percutaneous absorption occurs when the medicament combines lipoid solubility with a moderate solubility in water".

J.W. Hadgraft and G.F. Somers.
Percutaneous absorption
J. Pharm. Pharmacol (1956) 8, 625-634.

Little was he aware back in the mid fifties that these same parameters would be the subject of many investigations into transdermal drug delivery.

The work that I have been conducting since my D.Phil. has concentrated on the application of simple physicochemical factors to understand skin penetration. It is important to have a fundamental knowledge since it is from this that the rational choice of skin permeants, their enhancers and their formulation can be made.

Often the work that we have conducted has concentrated on simple single solvent systems. Attempts have been made to minimise the number of variables by keeping the model formulations as simple as possible. In the original work that we conducted on methyl nicotinate we used simple mixtures of glycerol and water. This has enabled us to tease out the different factors that are important and answer many questions which would have been impossible if we had used industrially relevant multi-component systems. It was an approach that Boyd Poulsen was also using with the classic studies that he conducted on the effects of simple propylene glycol mixtures on the release and percutaneous absorption of the two steroids, fluocinolone acetonide and its acetate ester. However it is important to make the jump to industrially relevant formulations and to find out how some of the more complex mixtures work. This is where the links with the group at Lyon have been important. The transition from a binary to a ternary system is quite complex. The data for the ternary system Transcutol®, Labrafac® Hydrophilic and propylene glycol diperlagonate are available for some permeants but the number of variables is so large that it is still proving difficult to interpret the data with a degree of confidence that I would like. I am sure that the data will reveal the ways in which formulations are optimised in terms of basic physicochemical properties. We should be able to consider some basic factors of the permeant e.g. its solubility parameter, partition coefficient and molecular size and shape and choose a combination of solvents which will optimise its release and permeation through the skin.

It is often forgotten that the drug or active cosmetic needs to be incorporated into an acceptable formulation which will both aid its release to the skin surface and promote its transfer into and across those layers of the skin

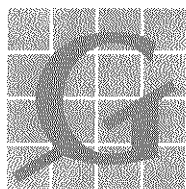
which are relevant to the therapeutic effect for which it is designed. The relevance of the release to the skin surface can again be seen in a paper published by my father many years ago where he demonstrated the effect of particle size on the ability of a corticosteroid preparation to induce vasoconstriction. The smaller the particle size, as induced by micronisation, the greater the specific surface area and hence the faster the dissolution rate. In the case of the steroid under investigation, fluocinolone acetonide, the dissolution rate must have been comparable or less than the skin permeation rate since significant particle size effects were seen.

C.W. Barrett, J.W. Hadgraft, G.A. Caron and I. Sarkany.
The effect of particle size and vehicle on the percutaneous absorption of fluocinolone acetonide.
Brit. J. Derm. (1965) 77, 576-578.

Subsequent to this work one of my research students has investigated the effect of particle size and good *in vitro in vivo* correlations were found in an animal model using salicylic acid as the skin permeant.

K. Al-Khamis, S.S. Davis and J. Hadgraft.
***In vitro-in vivo* correlations for the percutaneous absorption of salicylates.**
Int. J. Pharm.(1987)40,111-118

Recent advances in instrumentation have provided a large armament of techniques with which we can probe formulation effects and skin lipid biophysics. It is unfortunate that these were not available to my father since I am sure he would have made great advances with their help. Clearly instrumental advances are progressing at a fast rate and their use in the future will give us even more insight into the mechanisms of skin penetration and its enhancement. Over the past two or three years the developments in molecular graphics have been dramatic and these will be used to design tailor made molecules as formulation excipients. This is an area where it is important for the academic and industrial research groups to collaborate and interact. For maximum progress it is important for academics to realise that their work is not so esoteric lacking in applied nature that is not of interest to the industrialists. Equally it is important for the industry to appreciate the merit in gaining a fundamental knowledge of the skin permeation process and help in the funding of this. By doing this financial benefits in the long term will be great."



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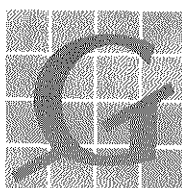
INFORMATIONS DIVERSES/ *MISCELLANEOUS INFORMATION*

PROGRES DANS LE TRAITEMENT DES GRANDS BRULES

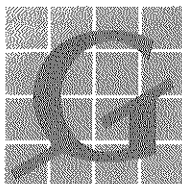
Journée annuelle de l'Information scientifique de l'Académie des Sciences, Paris le 15 Décembre 1992.

Mr JP. HELME, Président de l'Institut des Corps Gras, a présenté l'aspect Bio-chimique de la peau et les modifications chimiques qu'entraînent les "brûlures".

Mme le Docteur Rosy ELOY, chirurgien, spécialiste du domaine des Bio-matériaux, membre associé du CADAS et qui a collaboré aux tous premiers travaux du GERP, a fait un exposé scientifique de synthèse concernant ce Rêve ou cet Espoir de reconstruire un Epiderme sur un Substitut Homologue pour la couverture définitive des Grands Brûlés.



GATTEFOSSÉ



GATTEFOSSÉ

HOMMAGE A MADAME LE PROFESSEUR ALICE VERAIN

Discours de Mme le Professeur Y. Pourcelot, réalisé le 12/02/93 au Ministère de la Santé, Paris.

Madame le Professeur Alice VERAIN nous a quitté le Mardi 2 Juin au matin. Comment peut-on le croire ?

Elle nous a quitté au moment même où se tenait le Congrès International de Technologie Pharmaceutique auquel elle avait projeté d'assister. Elle nous a quitté (un an, jour pour jour) après avoir eu la grande joie d'être nommée aux fonctions de Docteur Honoris Causa de L'Université de Genève, distinction qui lui a fait si chaud au coeur et qu'elle a reçue entourée de toute sa famille et de ses nombreux amis et collègues. Quelle belle fête !...

L'Association Francophone des Enseignants de Pharmacie Galénique regrette aujourd'hui la disparition d'une Présidente exceptionnelle dont l'immense carrière a été au service du Médicament, de la Santé Publique, et de la Pharmacie Galénique (Pharmacotechnie - Biopharmacie - Génie Pharmaceutique), et ce au plan Régional, National et Européen, mais également une belle carrière au service des autres, elle possédait une telle foi en Dieu...

Qu'il s'agisse de sa mission universitaire (aux plans industriel, officinal ou hospitalier), de ses contrats avec l'industrie pour l'Enseignement et la Recherche, de son esprit d'ouverture avec la création du Génie Pharmaceutique (DEA et livre de la collection Galenica), de son travail incessant dans le cadre du Ministère de la Santé et du Groupe Qualité Europe, de l'Académie de Pharmacie, du Centre Européen de l'aromatisation et des colloques Pharmapole - CEE qu'elle avait créée. Quel enthousiasme, quel dynamisme, quelle volonté, quelle compétence, quelle joie de vivre, en un mot quel exemple pour nous tous.

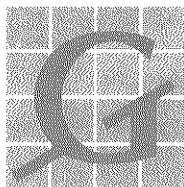
Ses nombreux élèves actuellement en poste dans l'industrie, dans l'Université, en milieu hospitalier ou officinal garderont le souvenir d'une "Très Grande Dame de la Pharmacie" qui demeure très présente dans leur mémoire, qui était attentive à chacun, prompte à rendre service, volontaire et se fixant inlassablement de nouveaux objectifs à atteindre dans les différents secteurs d'activités.

Ses rares journées de repos, mais également ses grands moments de joie étaient les fêtes de Noël en famille à la Tronche, les étés à la Verrière dans la maison familiale de la Drôme entourée de son mari, ses enfants et petits enfants, offrant toujours table ouverte à ses amis. Elle repose maintenant, précisément dans cette campagne de la Drôme, au milieu des fleurs, des senteurs et des paysages auxquels elle était tant attachée.

Quelle émotion en écrivant ces quelques lignes qui font revivre brièvement cette immense vie ! Certains collègues ont même dit : "Madame Véraïn a vécu au moins trois vies en une..."

Que Monsieur Véraïn, ses enfants et petits enfants soient assurés de la profonde sympathie de tous les galénistes de notre Association.

Y. POURCELOT



GATTEFOSSÉ

HOMMAGE A MONSIEUR LE PROFESSEUR JEAN COTTE

Lors du départ de Monsieur le Professeur Jean COTTE de la Faculté de Pharmacie Lyon I, ses collègues, Parents et Amis ont été conviés à une cérémonie amicale dans les locaux de la Faculté de Pharmacie, Avenue Rockefeller à Lyon.

Ci-contre le discours prononcé par Madame Martini, Professeur de Cosmétologie à la Faculté de Pharmacie, à cette occasion.

En hommage au Professeur Jean COTTE
Le 14 décembre 1992

Je vous ai rencontré il y a plus d'une vingtaine d'années à un colloque organisé par la Société Gattefossé. Vous étiez "oh combien dynamique" et vous exposiez vos idées sur l'avenir de la cosmétologie. Vous organisiez déjà régulièrement en compagnie du Professeur THIERS et de Monsieur H.M. GATTEFOSSE des journées de formation et d'information pour les Industriels et vous vous apprêtiez à mettre sur pieds un enseignement de cosmétologie dans le cadre de l'Institut de Pharmacie Industrielle.

Séduite par l'originalité de l'idée, j'ai proposé mes services qui ont été acceptés. Les premiers T.P. ont eu lieu dans les laboratoires d'application de la Société Gattefossé qui nous ont beaucoup aidés, après quoi, en 1973, nous volions de nos propres ailes non pas à la Faculté mais conjointement avec le C.T.C. qui développait alors les travaux de recherche sur le collagène et la peau.

Une salle de T.P. a été mise à notre disposition équipée par nos soins et nous avons pu accueillir entre 6 et 8 étudiants pour l'obtention d'un DESS de Pharmacie Industrielle, option cosmétologie.

Ceci pour dire que vous avez été pionnier en la matière, bientôt suivi et copié, sans état d'âme, par deux autres facultés de Pharmacie.

Les étudiants formés étaient très appréciés. C'était l'époque faste où les offres d'emploi couvraient la totalité des formations.

Fort de ce succès, et cette fois en association avec la Faculté de Châtenay Malabry, vous avez proposé un DEA de biologie cutanée et cosmétologie qui, pendant un certain temps a été, si l'on peut dire une "spécialité pharmaceutique". 6 à 8 étudiants étaient ainsi initiés à la recherche. Beaucoup d'entre eux ont complété leur cursus par une thèse de 3ème cycle et ont trouvé à s'employer avec des fortunes diverses.

Au cours du temps, les choses ont évolué, pas toujours comme nous l'aurions souhaité pour diverses raisons que je ne détaillerai pas ici mais qui résultent en un mot du peu de cas qu'ont toujours fait les instances universitaires locales de la cosmétologie.

En revanche, cet état d'esprit ne régnait pas ailleurs et la plupart des Facultés de Pharmacie, en particulier les plus importantes, se sont lancées sur les traces lyonnaises, parfois avec succès, de telle façon qu'il existe actuellement de multiples formations : BTS, DUT, DU, DESS, DEA attestant de l'intérêt qu'a suscité l'idée première.

C'est évidemment une belle réussite et nous croyons pouvoir penser que le leadership est

encore lyonnais. Mais c'est surtout parce que vous êtes universellement reconnu par la profession pour votre compétence, l'originalité de vos idées et votre soutien sans faille aux niveaux les plus élevés, nationaux et internationaux.

J'ajouterai à titre personnel puisqu'on a bien voulu me demander de dire ces quelques mots que ces vingt années de travail en commun m'ont permis d'apprécier plusieurs de vos qualités que je juge peu communes et irremplaçables. Je n'en citerai que 3 :

- d'abord une capacité exceptionnelle de synthèse et de clarification. Le texte le plus touffu, la situation la plus embrouillée sont immédiatement décortiqués et exposés en 3 ou 4 points essentiels.

- ensuite un dynamisme à toute épreuve et je dis bien à toute épreuve, vous permettant de tracer un sillage que les autres n'ont plus qu'à suivre, situation fort confortable lorsque les nageurs

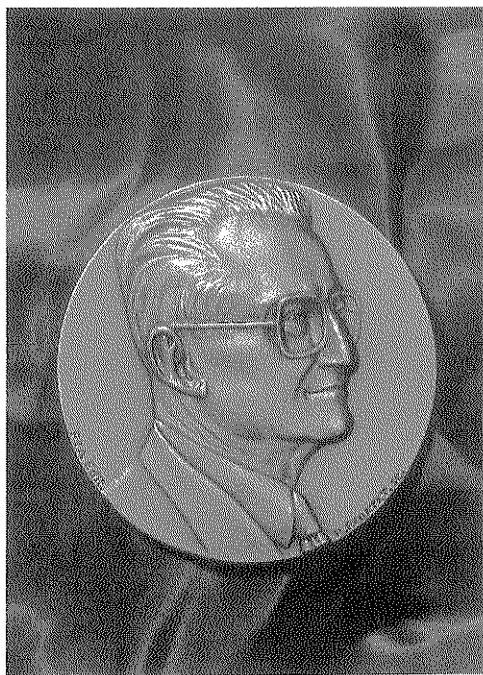
sont accrochés au bateau, mais encore faut-il ne pas décrocher.

- enfin, une faculté de confiance inébranlable dans vos collaborateurs et même vos collaboratrices puisque chacun a pu remarquer que vous étiez principalement entouré de femmes et que vous sembliez vous en accommoder très bien.

Je terminerai en disant que vous pouvez être fier de vous, de votre carrière et de la multitude de vos réalisations.

Fier aussi de votre famille, de votre épouse, oh combien admirable, de vos enfants, de leur présent et de leur avenir.

Bref, vous avez tout réussi et je pense que c'est pour vous une immense satisfaction. Nous espérons tous que vous accepterez d'être pour nous un modèle pendant encore de nombreuses années puisque vous entamez maintenant une énième carrière.



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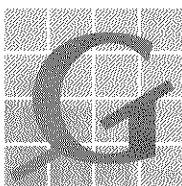
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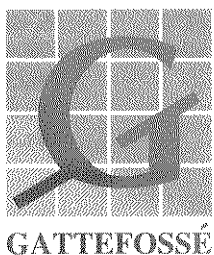
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