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Drug Release from Suppositories[1]

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Abstract: Many studies have been carried out over the past decades on suppositories and their drug release properties. The present state of knowledge is reviewed with the conclusion that our current understanding of the *in vivo* performance of suppositories is deficient. It is therefore not possible to rely on *in vitro* data to predict *in vivo* performance. Suggestions are presented for future studies that are required to enhance our knowledge of suppositiories as drug delivery systems.

Suppositories have been in use as drug dosage forms for a very long time and have been the subject of research ever since. Especially in the past decade basic research has been carried out resulting in an impressive increase in knowledge regarding this system and its application. Since *in vivo* performance still seems rather unpredictable, e.g. with regard to spreading behavior in combination with first pass metabolism, the question remains whether there is still a role for suppositories in modern drug therapy. This is essential with the appearance of sophisticated controlled release systems with many attractive features. The answer to such a question will also have to take into account the cost-benefit ratio and the expected progress in resolving the most crucial remaining uncertainties for the system in question.

In this paper the present status of (suspension) suppositories is discussed, with special emphasis on gaps in our current knowledge. An attempt is made to analyze future research directions and the progress to be expected from this research.

General Aspects

In 1973 Bevernage and Polderman (1) published an overview of the factors involved in the release of drugs from suppositories. This overview is reproduced in Table I.

As a follow up Polderman and his coworkers have published a widely known schematic description of the vicissitudes of a

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Tabel I. Factors influencing availability from fatty suspension suppositories [adapted from (1)].

Rectal environment	Drug substance	Vehicle
Amount*	solubility	composition
composition*	surface properties	furion behavior
pH*	particle size	surface tension
buffer capacity*	drug concentration	rheol. behavior
surface tension*	pK_a	
viscosity*		
luminal pressure		

* of rectal fluid

suppository in the rectum. This description with its inherent oversimplifications has proven to be useful in understanding the problems of drug absorption in the rectum and has also served as a stimulus for further investigations.

The underlying concept was that suspension suppositories have to undergo several changes before the contained drug could become bioavailable. This is represented in Fig. 1.

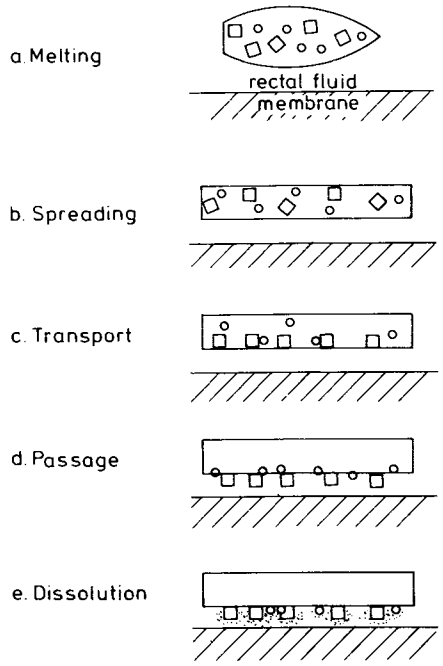

Fig. 1 Processes involved in the release from fatty suspension suppositories [adapted from (2)].

However, in such a schematic overview several essential parameters remain hidden, since they have already been inserted during the formulation stage. This will have to be included in the analysis of the consecutive processes represented in Fig. 1.

Discussion

Melting

This phase change is mainly determined by physico-chemical parameters such as the type of vehicle (chemical composition), amount of solid (suspended) material present, drug particle size and age of the vehicle. This already indicates that the process itself is not a simple phase change, and certainly not a clear-cut abrupt change at one (fixed) temperature. The melting process has to be considered as a rather gradual change of a product being completely solid macroscopically (but already heterogeneous) into a product which contains solid and dissolved drug in a viscous liquid carrier. It would even be more realistic to state that at the temperature of interest in the *in vivo* situation, i.e. 37 °C, a complicated mixture exists containing both solid and liquid vehicle. Even then the solid and liquid phases are not clearly defined. Experimental work on phase transitions using various techniques, e.g. DSC[5], NMR and dilatometry give different answers (3).

From a scientific point of view it is desirable to enhance our understanding of the melting process of suppository bases as a function of parameters such as particle size of drugs, physicochemical properties of drug molecules, composition and purity of the suppository base and interactions between drug molecules and the suppository base. Results obtained until now provide information on a semi-macroscopic scale. However, a true understanding of the melting process can only be obtained by interpretation of data at the microscopic and molecular scale. Therefore, appropriate techniques include highly sensitive DSC, adiabatic calorimetry and ^{13}C-NMR.

Although most drugs do not affect the melting behavior of a suppository, exceptions are known. The most explicit example is the change in melting behavior of aged aminophylline suppositories (4). Therefore one should investigate the melting behavior of suppositories, since an influence on bioavailability may occur.

Spreading

The flow behavior of dispersions has not been studied in any detail. Especially for coarse disperse systems information is lacking, and no theoretical insights exist. The only information available about spreading of suppository masses comes from experimental observations, both *in vitro* and *in vivo* (5, 6, 7). From these studies it became clear that spreading behavior is influenced by drug particle size, nature of the vehicle (e.g. hydroxyl number, viscosity) and pressure on the vehicle.

Since the spreading behavior of a suppository is of importance for the bioavailability of the suspended drug, especially in case of a large first-pass effect, studies in this field have to be carried out *in vitro* as well as *in vivo*. For the *in vitro* situation it would be attractive to design an experimental set-up in which it is possible to distinguish quantitatively between various suppository formulations. Formulations of different behavior could then be tested *in vivo* by following the spreading behavior using a labeled tracer of the base material and taking blood samples for the determination of the amount of drug absorbed.

It may thus be possible to find an *in vivo* correlation between spreading and bioavailability and to determine those parameters that affect this correlation.

Sedimentation

The model shown in Fig. 1 suggests that if spreading takes place, the layer of molten material may become very thin. In such a situation sedimentation of drug particles takes place

[5] DSC: Differential Scanning Calorimetry.

over 100 to 500 micrometers, and hence, the path length of particles (usually 30–90 micrometers) to the base-rectal fluid interface may be very small. The spreading behavior of differently sized particles is expected to be different, and it is known from several studies that large particles performed relatively well compared with small ones (8). *In vitro* this is easily explained and confirmed experimentally. *In vivo*, however, this process cannot be monitored separately, and thus no definite conclusions can be drawn at present. Since particle size is of great importance in formulation, regarding the spreading of the dispersed particles, it seems essential to pursue this matter further. For that purpose existing *in vitro* models would have to be adapted to include spreading in thin layers and measuring the release towards a viscous sublayer. It has to be decided whether the spreading has to be carried out under a certain pressure and what the composition of the viscous sublayer should be. Although some work regarding pressure in the rectum has been done (7), it is still not known what the pressure pattern in the human rectum is. The same uncertainty exists for the composition of the sublayer. Thus the first step in research in the field of "sedimentation" should be *in vivo* investigations concerning the above mentioned omissions.

Transport through the fat/water interface

Particles, dispersed in an oily phase, upon approaching an oil/water interface seldom show problems in passing this interface. Apparently there are little wetting problems. This was observed in an *in vitro* set-up for various compounds, e.g. glass, sodium chloride, chloramphenicol, paracetamol, several methylxanthines and phenobarbital. These compounds were suspended in liquid paraffin and passed the interface with an aqueous layer spontaneously and rapidly in relation with sedimentation and/or dissolution. Only addition of Span 20 as an example could prevent this passage. However, such a spontaneous wetting cannot occur from a physical-chemical point of view unless gravitation or similar forces add the extra energy required. Therefore (very) small particles could remain unwetted, although there can be an additional energy source *in vivo* from pressure exerted by the rectal wall. Attention should be given to the influence of the viscosity of the aqueous layer (viz. mucous *in vivo*). Under these conditions a retarded wetting seems likely. The kinetics of wetting (suppository on mucus) would seem to be a most challenging research subject, in which many variables are included such as composition of the suppository, spreading force, influence of additives and interactions (as crystallization).

Dissolution

The dissolution of pure compounds or simple mixtures in pure liquids in hydrodynamically well-defined systems (e.g. a rotating disk) is fairly well understood (9). However, changing systems, liquid mixtures or using more complex systems directly causes problems with the calculations and predictions from dissolution experiments. The release process of drug from an oily phase to an aqueous phase is without any doubt an example of a very complex system and hence is largely understood qualitatively but not quantitatively (e.g. (E)SCRD situations). Here again simulation *in vitro* fails because of lack of precise (or even fairly rough) information about the *in vivo* situation. Factors such as hydrodynamics, composition and properties of the dissolution medium (pH, buffer capacity, viscosity) are largely unknown. Therefore, to proceed in the understanding of bioavailability, *in situ* experiments have to be carried out, in order to determine the above mentioned factors. Only then can progress in the control of bioavailability be expected. This statement can be generalized for many biosites, although the knowledge of the rectal environment seems especially poor. Only systems whose rate limiting step lies elsewhere and can be controlled, avoid the problem of an unpredictable bioavailability.

Transport of released drug in situ

So far this process has been treated separately in the literature, and research in this field is scarce. It will be clear that the influence of the dosage form can be considered of no importance, unless adjuvants are involved or emulsification occurs. In such situations some influence of the original formulation might still remain. Data concerning the transport *in situ* show the importance of parameters such as pH, buffer capacity and (surface active) adjuvants on the bioavailability from solutions.

It appears that, as in the upper part of the intestinal tract, the pH-partition theory is of limited value, and pH gradients have to be considered (10). Furthermore the properties of the mucus layer, including its network structure and binding sites, might well play an important role in the approach of a drug molecule towards the membrane. It has been hypothesized that a "deep" compartment may be present, from which absorption continues after removal of the instilled drug solution. Presently, however, these assumptions are supported only sparsely by experimental evidence (11). Hence, much effort is required in this field, and it can be expected that such investigations might become useful in assessing the therapeutic relevance of (micro)-enemas.

Absorption

At present there are only very global indications of the parameters governing the membrane transport. The partition coefficient is regarded as the most important parameter determining drug uptake. However, it still is not clear which *in vitro* system is the best (or most representative) for the *in vivo* situation (e.g. oil/water, octanol/water, octanol/buffer etc.).

Active transport and rectum wall metabolism seem not very likely contributing factors, but these factors have not yet been extensively studied. Much interest has arisen lately in the area of absorption promotors. Although a certain success has been achieved for certain normally unabsorbable molecules, it still remains to be seen whether absorption promotors will gain general acceptance, since the mode of action of these compounds is questionable. Recent results indicate that the absorption-promotion in some cases occurred by breakdown of the villi, which seems a rather crude way of reaching the goal of enhanced drug absorption.

Conclusions

The several steps of rectal drug bioavailability have been studied in some detail, especially in the last decades. Most of the work has been carried out *in vitro* and in some areas (sedimentation, passage through an interface, dissolution) a rather solid knowledge has been built up. However, it is questionable whether the available *in vitro* test models (12) are suited to predict the *in vivo* situation. For the separate investigation of the influence of a single parameter on the release rate of a drug from a suppository, several experimental

set-ups can be used. The influence of parameters such as particle size, nature of the suppository base and presence of surface-active agents on the release can be measured, and results are used in the formulation process. It is therefore possible to adapt a few standards for *in vitro* test procedures, e.g. a modified USP XX paddle set-up for testing the release of a drug from a suppository (13). It has to be clear, however, that *in vitro* test models permit only a rather rough distinction between different formulations.

From this discussion it is clear that the main research has to be done above all in the *in vivo* situation. Too many parameters are unknown (e.g. composition of the rectal fluid, buffering capacity in the rectum, spreading behavior). Before an *in vitro/in vivo* correlation can be determined, much basic research work still needs to be done. For those who are involved in the development of rectal drug delivery systems, suppositories can still be attractive because of price and the relatively easy manufacturing process; however, from a biopharmaceutical standpoint too many uncertainties remain. In order to improve the reliability of suppositories fundamental research as indicated above has to be undertaken.

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