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Research Papers

BIOPHARMACEUTICAL STUDIES OF FATTY SUSPENSION SUPPOSITORIES II. INFLUENCE OF PARTICLE SIZE AND CONCENTRATION ON IN VITRO RELEASE OF READILY WATER-SOLUBLE COMPOUNDS

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SUMMARY

The influence of particle size and concentration of lithium sulphate, as a readily water-soluble compound, on the in vitro release rate from fatty suppository vehicles is described. The results show a good correlation with the apparent viscosity of the suspension suppositories at 37°C. This indicates that the release may be described by a three-step model, i.e. transport of particles to the vehicle/water interface, transport through that interface, and finally dissolution. In the case of readily water-soluble compounds the first step, i.e. sedimentation, acts as rate-limiting. Thus small particles are released at a lower rate than larger particles.

INTRODUCTION

In the first part of this series (Rutten-Kingma et al., 1979) we discussed the spreading of suppositories in the rectum of the rat, together with the factors influencing this process. The results showed that drug particles up to approximately 100 μm and in concentrations up to 20% m/m did not seem to influence the spreading in situ, eliminating this as a complication of the release model proposed. This model described the release of suspended drugs from a non-aqueous medium in three steps: (1) transport of the particles to the interface between the melted suppository and the rectal fluid, (2) transport across this interface and (3) dissolution of the particles in the rectal fluid. It should hold for fatty suppositories as well as for suspensions in oil.

Step 1 may then be considered as a sedimentation process, step 2 as a wetting process and step 3 as a dissolution process. Depending on the physical and chemical

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properties of the drug the rate-limiting step for the release may be situated in any one of them.

The particle size of the active compound is important for two reasons. Firstly, the apparent viscosity of the suppository mass is influenced by the number of suspended particles, which will be determined by the particle concentration as well as by the particle size; secondly the settling time is also directly proportional to the particle size. Thus both concentration and particle size will be of influence on the first step of our model.

Weiss-Fogh (1961) has shown for testosterone that very small particles (2–5 μm) suspended in Witepsol H suppository mass are released faster than particles of approximately 150 μm. Based on these data no definite conclusion about the rate-limiting step can be given; this can still be dissolution in the rectal fluid as well as dissolution in the suppository mass, since testosterone is a poorly water-soluble compound. Since testosterone is not released from cocoa butter suppositories at all, in which it dissolves completely, it is most likely that in the case of Witepsol the dissolution in the rectal fluid is the rate-limiting step since otherwise the release from cocoa butter should have been the more rapid one. The same can be true for the study of Kraml et al. (1962) with oral griseofulvine suspensions in sesame oil. After administration of micronized particles higher blood levels were obtained than after administration of larger particles. Cid (1974) and also Parrott (1975) have found the same effect for particles of acetylsalicylic acid in suppositories. Cid demonstrated higher blood levels in rabbits with particles of 50–150 μm than with particles of 150–200 μm and 300–420 μm. Also, the extent of absorption was significantly larger for the particles of 50–150 μm. In the case of Parrott's study, powdered acetylsalicylic acid was released faster than from pellets which had a specific surface approximately 40 times smaller than the particles used. Kata and Kedvessey (1968) studied the influence of particle size for aminophenazone which dissolves partly in their suppository vehicle (Witepsol H35). Small particles (<150 μm) were released faster in vitro then larger particles (320–800 μm). Buckwalter and Dickison (1958) have demonstrated an influence of particle size for procaine-penicillin G in oil suspensions. A plasma concentration level above the minimal effective concentration was found for micronized particles (<5 μm), suspended in sesame oil gelled with 2% aluminium monostearate, over a longer period than for particles of ~150 μm. However, the plasma concentration level of the latter suspension reached higher values than the first suspension. For better water-soluble compounds Kassem et al. (1975) have published the results of an investigation of noramidopyrine-methanesulfonate-sodium in vitro. Since at best only 4% of the drug was released after 1 h the observed differences cannot be easily interpreted. Bevernage et al. (1973) reported the results of a preliminary investigation in our laboratory in which small particles (sodium chloride in vitro and lithium sulphate in rats) were released slower than larger particles from suppositories. Schoonen et al. (1976) reported on the in vitro release of salicylic acid and phenobarbital and their sodium salts of different particle sizes. Their results support the possibility of release through sedimentation or through diffusion as the main governing steps, readily soluble compounds following the former and fat soluble compounds the latter, in the main. Particle size influences were especially apparent with the readily soluble compounds. Nour-El-Din et al. (1977) have published data on the influence of particle size and concentration for chlorphenamine maleate from cocoa butter. Their data were somewhat inconclusive, with a tendency for

the largest particles (~500 μm) to be released somewhat slower than the smallest ones (~125 μm) studied, but they have not studied micronized powders.

Taking all this together, poorly water-soluble compounds seem to show a release rate which is determined by the dissolution step, while for readily soluble ones this is mainly so by their sedimentation behaviour. Therefore the release rate of the latter may well be favoured by increasing particle sizes. Without any doubt the use of a variety of vehicles and active substances has also added to the existing confusion. To clarify this situation more information would be most welcome.

In this paper we present our results on the release of readily water-soluble compounds, lithium sulphate and sodium chloride, from fatty vehicles, varying both the particle size and concentration. In subsequent papers results obtained in rats and in man will be presented.

MATERIALS AND METHODS

To determined the influence of the viscosity of the suppository mass on the release rate, sodium chloride, particle size <5 μm, was used as a model compound. The suppositories (≈2.6 g) were prepared by thoroughly mixing the sodium chloride particles (3% m/m) and the suppository mass manually at 37°C, and moulding this mixture at 34°C. As suppository vehicles cocoa butter and Witepsol H15 were chosen.

In the experiments studying the influence of the concentration and the particle size on the release rate suppositories were prepared, weighing approximately 200 mg, containing lithium sulphate as a model compound in Witepsol H5 as vehicle. Two size fractions of the lithium sulphate were isolated, one of 20–30 μm by wet-sieving in ethanol and one of 90–125 μm by means of an Alpine air jet sieve. Microscopical control of the fractions showed that both obeyed the fraction limits for at least 80%. Suppositories

TABLE 1

MEAN CONTENT AND STANDARD DEVIATION OF LITHIUM SULPHATE SUPPOSITORIES IN WITEPSOL H5

Particle size	Mean content (mg)	m/m%	S.E. (mg)	s_{rel} (%)
20–30 μm	1.78	1.0	0.026	1.5
	3.66	2.1	0.048	1.3
	7.40	4.1	0.104	1.4
	15.41	8.4	0.324	2.1
	24.65	12.1	0.273	1.1
	35.33	17.4	0.283	0.8
90–125 μm	1.85	1.1	0.024	1.3
	3.56	2.0	0.043	1.2
	7.18	4.0	0.065	0.9
	15.11	8.2	0.106	0.7
	22.75	12.2	0.682	3.0
	29.90	15.7	0.508	1.7

were prepared with different percentages of lithium sulphate. The thoroughly mixed masses were moulded with the aid of a hypodermic syringe at 34°C.

In Table 1 the mean content of the suppositories and the standard deviations are summarized. An in vitro dissolution technique derived from the one described by Kerckhoffs and Huizinga (1967) was used with the suppository rotated in a horizontal position at 56 rpm. As a semipermeable membrane Visking dialysis tubing 18/32 was used.

The rheological behaviour of the suppository masses was determined with a concentric cylinder rotational viscosimeter (Epprecht). The suspensions were homogenized at 37°C and transferred into the preheated system. All suspensions with particles <10 μm were measured twice. Because of sedimentation during the measurement of the particles of 90–125 μm the change in the shear rate was measured, along certain time intervals at various deformation rates. By extrapolation to time zero of the plots of shear rate versus time the real shear rate was estimated.

RESULTS AND DISCUSSION

The influence of viscosity of the vehicle was studied by performing release experiments with the sodium chloride suppositories at 35.5, 37.0, 38.5, 43.0 and 46.0°C. The results are shown in Fig. 1.

For both vehicles, i.e. cocoa butter and Witepsol, the release rate increases with temperature, thus with decreasing viscosity. Equalizing the viscosity by choosing different temperatures for the release experiment does not equalize the release rates. At the same viscosity the release from cocoa buffer is faster than from Witepsol, i.e. cocoa butter/Witepsol combinations of 46°C/38.5°C, 43°C/37°C and 37°C/35.5°C, respectively. At

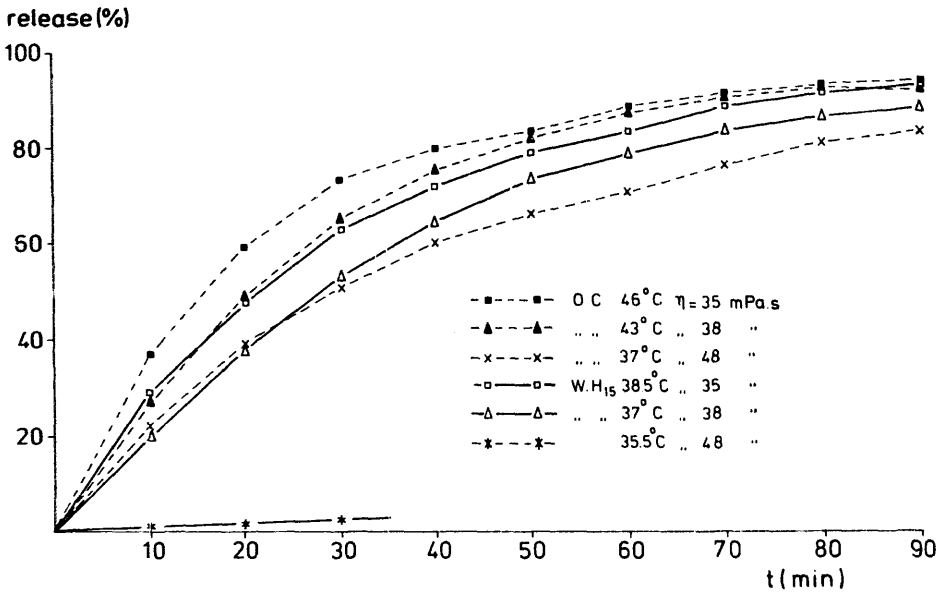

Fig. 1. The release of sodium chloride from cocoa butter (O.C) and a semisynthetic vehicle ($W.H_{15}$) at various temperatures and viscosities.

35.5°C the Witepsol suppository is not fully melted, which means that hardly any release can occu.. Also the differences in melting time between both vehicles may influence the results, since Witepsol takes approximately twice as long as cocoa butter. This parameter was excluded in the experiments shown in Fig. 2, in which the suppositories were melted prior to the release experiments. In order to prevent preliminary sedimentation the masses were kept homogenized until the release experiment started.

Now the two isoviscous masses show essentially the same release rate, while the more viscous one shows a slower release. Qualitatively this is in agreement with the predictions based on a sedimentation-determined release. Quantitatively the effect of viscosity is more pronounced than would be predicted by Stokes' law, which is not surprising since the systems involved do not comply with the prerequisites for the application of this law. Apparently other parameters are involved too, increasing the sedimentation rate.

By increasing the concentration of suspended particles the apparent viscosity of the suppository increases, while an influence of particle size on the apparent viscosity may also be expected (Roscoe, 1953). Therefore the viscosity of a number of lithium sulphate suspensions in Witepsol H5 was measured at 37°C.

In Fig. 3 the viscosity at 37°C is plotted versus the concentration of lithium sulphate. With the exception of the 20% suspension of particles <10 μm, the rheological behaviour was Newtonian. As expected, the viscosity of the suspension with the smaller particles increases faster with increasing concentration than the viscosity of the other suspensions. The viscosity of the 20% suspension, particles <10 μm, was calculated at a high shear stress where the influence of the non-Newtonian behaviour was negligible, estimating the viscosity at the low side. From these data an influence of particle concentration on the

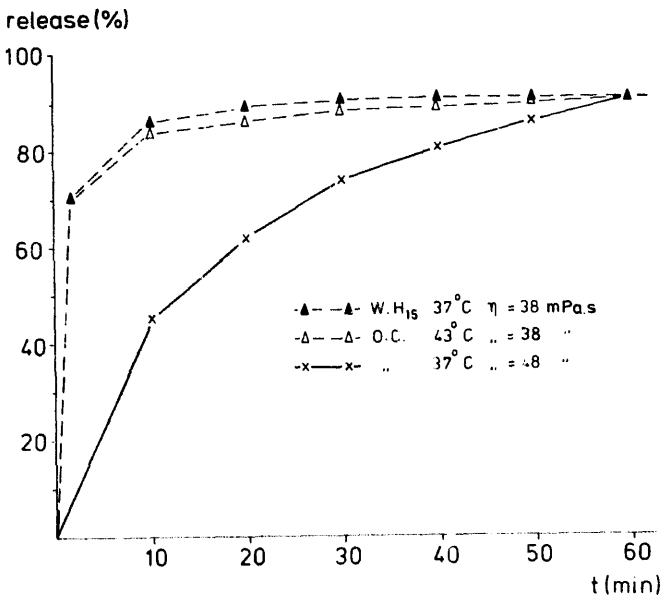

Fig. 2. The release of sodium chloride from cocoa butter (O.C.) and a semisynthetic vehicle ($W.H_{15}$), both premelted, at various temperatures and viscosities.

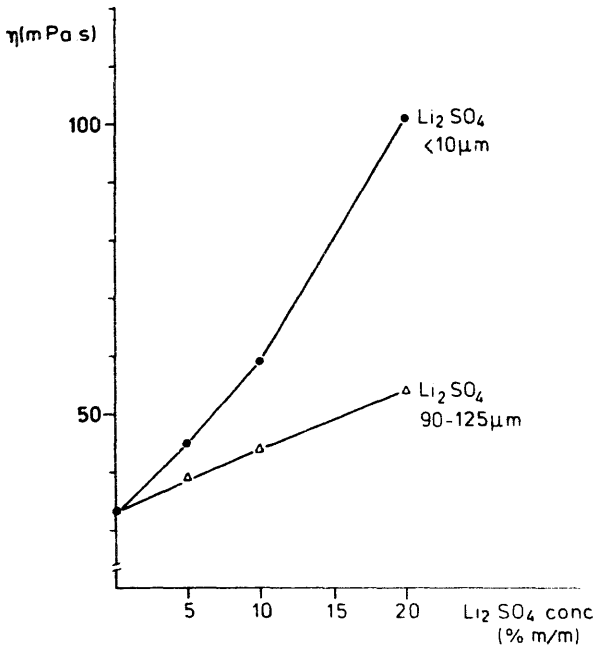

Fig. 3. The relation of particle concentration and apparent viscosity of lithium sulphate suppositories prepared with a semisynthetic vehicle.

release rate could be expected because of the increased viscosity. This effect should become more important with decreasing particle size.

In Fig. 4 the results of the release rate experiments of suppositories with varying concentrations of lithium sulphate and different particle sizes (20–30 μm vs 90–125 μm) are summarized. The time of 50% release is plotted against the concentrations (% m/m) of lithium sulphate in the suppositories. The results are the mean of 9 determinations.

With an increasing particle concentration (4–16%) a statistically significant ($P = 0.05$) decrease in release rate is found, when the particles of 20–30 μm are considered. This is also true for the particles of 90–125 μm. For concentrations of 1 and 2%, lower release rates are observed, especially for the smaller particles. These findings may be explained assuming a sedimentation-determined release. For the two lower concentrations this would mean a sedimentation rate related to their dimensions while for the higher concentrations this is not so. In that case the sedimentation rate is related to the dimensions of agglomerates that are formed between particles, thus resulting in an increased release rate. Increasing the concentration above 4% then introduces the retarding effect of an increased viscosity and hinders settling. The model is also supported by the fact that the larger particles are released considerably faster than the smaller ones at every concentration, although the effects are less pronounced since the number of particles, which essentially determines the viscosity, is much lower in the range of m/m concentrations studied. It is also clear, however, that the differences observed do not quantitatively conform to predictions based on a purely sedimentation-determined process.

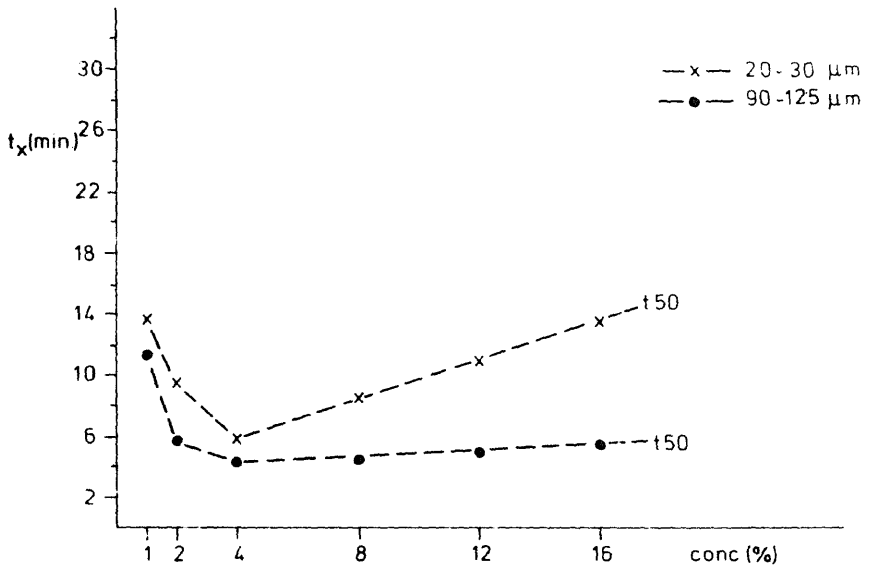

Fig. 4. The relation between release rate and particle concentration of lithium sulphate suppositories prepared with a semisynthetic vehicle.

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