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An Investigation into the Effects of Preparation Conditions and Storage on the Rate of Drug Release from Pharmaceutical Glyceride Bases

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Abstract

The effects of preparation conditions on the release of theophylline from Gelucires 50/13 and 55/18 have been investigated. Samples were prepared by melting physical mixes under controlled conditions, followed by either slow or fast (ambient) cooling to the solid state.

A rapid cooling rate was shown to result in a slower release rate for 2% w/w dispersions in Gelucire 55/18, with the slow- and fast-cooled systems resulting in drug release via a diffusion and a mixed diffusion/erosion mechanism, respectively. At higher drug loading (30% w/w), the cooling rate did not effect the release characteristics. The erosion of Gelucire 50/13 was found to be more rapid for slowly cooled samples.

Viscosity measurements were used as a means of assessing the chemical stability of the Gelucires, with evidence being found for degradation of Gelucire 55/18 on storage following heat treatment, while Gelucire 50/13 appeared to be stable.

The effects of storage on the dissolution profiles of ambiently cooled systems were studied, with drug release from both bases increasing on ageing for up to 180 days.

The Gelucires are a family of glyceride-based products which comprise mixtures of mono-, di- and triglycerides with polyethylene glycol (PEG) esters of fatty acids. These materials have attracted interest as bases for controlled-release dosage forms, as the presence of the hydrophobic glycerides and more hydrophilic PEG esters within the same base result in a wide range of overall hydrophobicities and hence drug-release rates, depending on the choice of base. However, due to the physical and chemical complexities of these systems, it has proven difficult to develop a fundamental understanding of their behaviour. Recently, a series of studies has attempted to relate the physical structure (Sutananta et al 1994a, b) and dissolution behaviour (Sutananta et al 1995) of a range of Gelucire systems to their chemical structures. In particular, it has been emphasized that in order to understand the properties of these materials, it is extremely helpful to have some knowledge of the chemical compositions of the bases, as the Gelucires may range from being composed entirely of glycerides (e.g. Gelucire 54/02) to containing only PEG esters (Gelucire 55/18). The properties and uses of Gelucire bases have been recently reviewed (Craig 1994).

Several studies have examined the drug release properties of the Gelucire bases, with many investigations attempting to relate the physical and chemical properties of the Gelucire to the dissolution rate (e.g. Howard & Gould 1987; Bodmeier et al 1990; Kopcha et al 1990; Prapaitrakul et al 1991; Sutananta et al 1995). Sutananta et al (1994a, b) recently studied changes in the morphology of Gelucire bases using differential scanning calorimetry, demonstrating that the thermal history of the samples had a profound effect not only on the immediate morphology of the materials but also on the physical stability. The extent to which the morphology is related to the dissolution characteristics is not yet understood. A further consideration is the physical stability of Gelucire bases, particularly in terms of changes in the rate of drug release from the various bases on storage. Such effects are well recognized in the field of suppository formulation (e.g. de Blaey & Rutten-Kingma 1976; Moes & Jaminet 1976; Liversidge et al 1981; Yoshino et al 1981) and has been noted for a range of Gelucire bases (Doelker et al 1986; Dordunoo et al 1991; Remunan et al 1992). However, the mechanisms involved are not clear.

In this investigation, the effects of preparation conditions (particularly drug loading and rate of cooling of the melt) and storage of dispersions of theophylline in Gelucires 50/13 and 55/18 will be described. Gelucire 50/13 contains a mixture of glycerides and PEG esters, while Gelucire 55/18 contains only PEG esters (Sutananta et al 1994b). Gelucire 50/13 therefore serves as an example of a typical Gelucire base containing both types of major component, while Gelucire 55/18 allows identification of the role of PEG esters in any observed phenomena.

Materials and Methods

Anhydrous theophylline (Sigma, Poole) and Gelucires 50/13 and 55/18 (Gattefosse, St Priest) were used as received. Samples for dissolution studies were prepared in a manner

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similar to that described in a previous study (Sutananta et al 1995). This method involved heating the Gelucire at 3°C min^{-1} to 75°C, at which temperature the sample was held for 30 min. The drug was then added at a concentration of either 2% or 30% w/w and maintained at 75°C for a further 30 min. The mixture was then either poured into aluminium moulds (previously held at room temperature) and allowed to cool under ambient conditions, or alternatively samples were slow cooled in the oven at 10°C h^{-1}, again in aluminium moulds. In each case, excess material was cut off from the moulded tablets to produce discs with a diameter of 1·25 cm and height of 0·62–0·68 cm. The matrices were kept for 12–24 h over silica gel before testing. For stability studies, the samples were kept at room temperature (≈ 18–24°C) over silica gel. The relative humidity in the cabinets was 0–10%.

The rheological properties of the Gelucire bases were investigated using a Carrimed CSL 500 Controlled Stress Rheometer (TA Instruments Ltd) with a cone and plate measuring system (4 cm, 2° and gap = 56 μ). The Standard Peltier System installed in the rheometer allowed the temperature to be accurately controlled (± 0·1°C) from 15 to 99·9°C. Continuous shear flow technique was used to measure the viscosities and flow characteristics of molten Gelucire bases at various temperatures. Approximately 6–8 g Gelucire base was used in each measurement, with samples being either slow- or flash-cooled in liquid nitrogen before measurement or storage, as described in a previous study (Sutananta et al 1994a). The sample was placed on the rheometer plate and left to equilibrate at the required temperature for 5 min before measurement took place. Maximum torques of 20 and 200 μN m were used for Gelucires 50/13 and 55/18, respectively. Fresh sample that had not been previously subjected to shear was used for any repeated measurement. Samples were stored as above up to 580 days after preparation. The measurements were performed in duplicate, with further repeats showing a coefficient of variation within 6%. Dissolution and erosion rate studies were performed using the apparatus described previously (Sutananta et al 1995). For all studies, a rotation speed of 100 rev min^{-1} was used, with distilled water at 37°C being the dissolution medium.

Results and Discussion

The effects of sample preparation conditions

The effects of cooling conditions on the dissolution rate of theophylline from Gelucire 55/18 are shown in Fig. 1 for dispersions containing 2% drug. The proportion of drug released from the slowly cooled matrices during the first four hours was higher than those from ambiently cooled systems, although no significant differences in release rate were seen for matrices containing 30% drug. Furthermore, after four hours the fractions of drug released from both slow and ambiently cooled 2% systems were similar. The data were fitted to the model outlined in a previous study (Sutananta et al 1995), whereby the dissolution profiles may be described by two sets of exponents. Firstly, the dissolution profiles may be modelled using the equation:

$$M_t/M_\infty = k_1 t + k_2 t^{1/2} \quad (1)$$

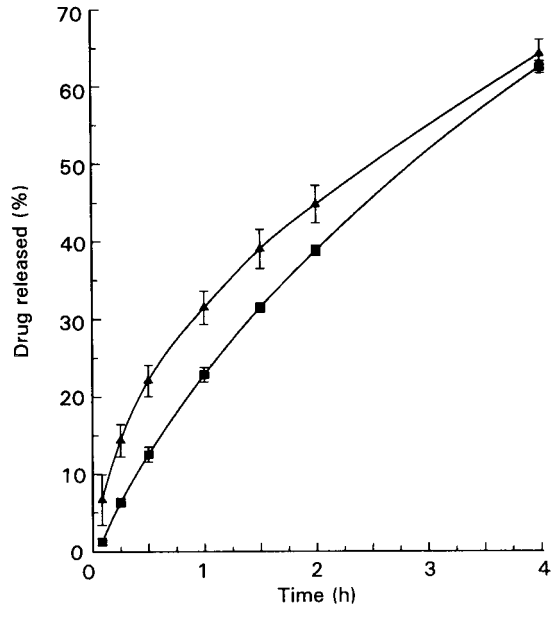

FIG. 1. The effect of cooling rate on the release of theophylline from Gelucire 55/18 matrices containing 2% drug. ■ Ambiently cooled matrices, ▲ slowly cooled matrices.

where M_t/M_∞ is the fraction of drug released and k_1 and k_2 are constants describing the rate of erosion and diffusion respectively. Similarly, the data may also be modelled by:

$$M_t/M_\infty = kt^n \quad (2)$$

where k is a constant and the exponent n gives an indication of the mechanism of drug release, with n = 0·5 indicating a diffusion mechanism and n = 1 indicating erosion of the matrix, assuming a slab-shaped matrix. Intermediate values indicate a combination of the two mechanisms. The values for the slow and ambiently cooled samples are given in Table 1. At 2% drug loading, the exponent n and the ratio k_1/k_2 indicated that the release of drug from slow and ambiently cooled Gelucire 55/18 was dominated by diffusion and mixed kinetics (diffusion and dissolution/erosion of polymer), respectively. This may be associated with the changes in the degree of crystallinity of the two samples, as previous studies have indicated that the slowly cooled material has a higher heat of fusion (ΔH_F) value than rapidly cooled samples (Sutananta et al 1994a). The higher

Table 1. Kinetic parameters describing the dissolution profiles of theophylline from slowly and ambiently cooled Gelucire 55/18 matrices.

Cooling rate	Drug loading (%)	n	k_1	k_2	k_1/k_2	T50 (h)
Slow	2	0·52	0·30	31·19	0·01	2·34
	30	0·89	9·37	6·51	1·44	3·62
Ambient	2	0·71	5·45	18·82	0·29	2·74
	30	0·87	9·69	6·97	1·39	3·61

T50 = time required for 50% of drug to be released from the matrices.

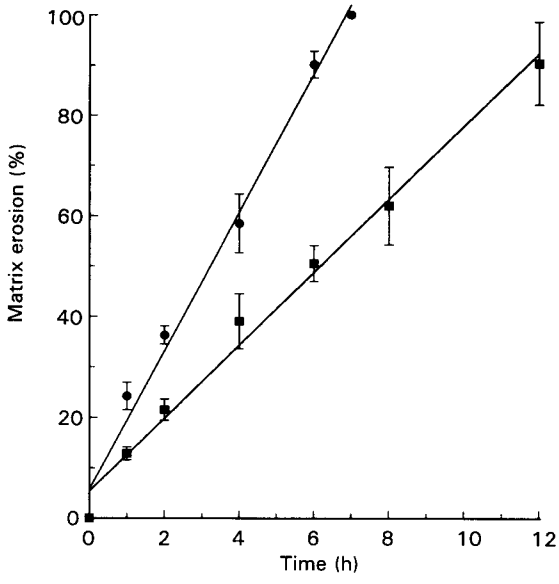

FIG. 2. The effect of cooling rate on the erosion of Gelucire 50/13 matrices. ■ Ambiently cooled matrices (correlation coefficient = 0·995, erosion rate = 7·2% h^{-1}); ● slowly cooled matrices (correlation coefficient = 0·995, erosion rate = 13·8% h^{-1}).

lattice strength of the slowly cooled samples would result in greater energy being required to break the bonds between the Gelucire chains, hence reducing the predominance of the erosion mechanism. However, given the structural complexity of the Gelucires, other factors such as the distribution of crystallites and crystal composition of the material may also play a role in determining the mechanism of drug release.

When 30% of drug was included, both the values of n and k_1/k_2 ratios were similar for the slow and ambiently cooled samples, indicating similar mechanisms of drug release in both cases. The value of n of 0·87 and 0·89 at this drug loading indicates that the release was dominated by the erosion of the polymer; hence it is reasonable to suggest that the presence of the larger proportion of drug resulted in disruption to the matrix structure, leading to a predominance of the erosion mechanism. As this process may be more associated with the presence of the drug than the disintegration of the matrix structure, the dissolution at 30% drug loading was therefore not as dependent on cooling rate as was found for the lower drug concentration. Fig. 2 shows the erosion profiles of Gelucire 50/13. This parameter was measured following the observation (Sutananta et al 1995) that for this Gelucire, the drug-release process is dominated by erosion. The erosion rate of the slowly cooled matrices was almost twice that of the ambiently cooled materials (13·8 and 7·2% h^{-1}, respectively); hence these materials also showed differences in performance, depending on the cooling rate used. The percentage water uptake of slow-cooled Gelucire 50/13 matrices is compared with that of ambiently cooled samples in Table 2. It was noted that over time periods up to 6 h, the water uptake was very similar, even though the erosion rate of the slowly cooled Gelucires was faster. The dependence of the erosion process on cooling rate is therefore associated with disintegration rather than swelling of the matrices. This is in agreement with previous studies (Sutananta et al 1995) which suggested that drug release from Gelucire 50/13 occurred predominantly via surface disintegration rather than swelling. However, other investigations (Sutananta et al 1994a) have indicated that the heat of fusion of slow-cooled Gelucire 50/13 is greater than that of fast-cooled samples, hence one might expect a more rapid erosion for the faster cooled material. The reason for this discrepancy may lie in differences in the microstructure of these materials, with previous evidence (Sutananta et al 1994a) suggesting that slow- and fast-cooled materials undergo different segregation processes, whereby the various constituents of the base crystallize into either mixed or separate microscopic regions. It is therefore possible that structural differences on a microscopic scale could account for changes in the erosion rate.

The effects of ageing

Viscosity studies. The viscosities of molten Gelucires 55/18 and 50/13 were assessed, the samples having been previously subjected to a heating and cooling cycle. These studies were conducted with a view to assessing the chemical stability of the samples to the different heat treatments, although a number of studies have discussed the melt viscosities of the Gelucires with regard to their subsequent processing (e.g. Bourret et al 1994). The graphs of shear rate against shear stress showed a linear relationship in all cases (r = 0·9997–1·0000) indicating Newtonian behaviour for these molten Gelucires. As a result, the viscosity of each system may be described by a single figure. The viscosity of Gelucire 55/18 was independent of thermal history, as shown in Table 3. However, the viscosity decreased on storage, possibly due to

Table 2. Water uptake in % w/w of water in dry base of slow- and ambient-cooled Gelucire 50/13 matrices during dissolution testing.

Time (h)	Water uptake (%)	
	Slow-cooled	Ambient-cooled
1·0	43·8 ± 3·3	48·3 ± 3·3
2·0	63·9 ± 5·2	66·4 ± 3·8
4·0	104·6 ± 11·6	108·8 ± 15·4
6·0	186·5 ± 30·2	143·3 ± 6·6
8·0	e	178·7 ± 6·4
12·0	e	308·2 ± 32·5

e = matrices completely eroded within 7 h.

Table 3. Viscosities of molten Gelucire 55/18 (Pa s) at 60 and 70°C after ageing for various periods of time following slow or fast cooling from the melt.

Sample	Storage time (days)		
	0	90	580
Slow-cooled 55/18			
60°C	1·82	1·81	0·54
70°C	1·35	1·33	0·40
Fast-cooled 55/18			
60°C	1·82	1·83	0·42
70°C	1·35	1·36	0·33

degradation of the base. Gelucire 50/13 showed no change in viscosity over the period under study, being 0·054 Pa s initially and 0·052 Pa s after 220 days; hence there is no evidence for degradation of this base.

The degradation of Gelucire 55/18 could be a result of two chemical reactions: the hydrolysis of PEG esters into PEG and fatty acids, or the breakup of the polymer (PEGs) chains into lower molecular weight fragments. Both processes would result in a reduction in the viscosity of the subsequent melts. However, Chatham (1985) suggested that long melting periods at high temperatures seem to be required before appreciable degradation of PEG chains occurs. Below 100°C, degradation of polymer chains is minimal. It is therefore more likely that hydrolytic breakdown of the ester linkage is occurring. While more work is required to clarify the mechanism involved, the study clearly shows that Gelucire 55/18 is not stable following the heating and cooling process used in this study.

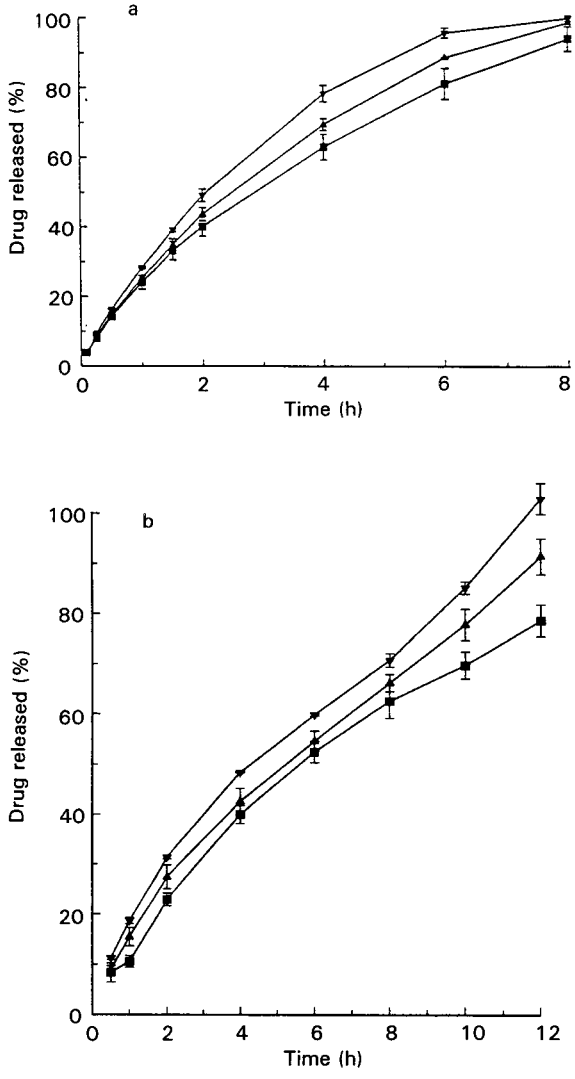

FIG. 3. The effect of ageing on the release of theophylline from ambiently cooled Gelucire 55/18 (a) and Gelucire 50/13 (b) matrices containing 30% drug. ■ 1, ▲ 60, ▼ 180 days.

Table 4. T50 (h) of the release of drug from various ambient-cooled Gelucire matrices after ageing for various periods of time.

Sample (drug loading)	Storage time (days)		
	1	60	180
55/18 (2%)	2·7 ± 0·2	2·5 ± 0·2	2·1 ± 0·1
55/18 (30%)	3·6 ± 0·2	3·2 ± 0·2	2·8 ± 0·2
50/13 (30%)	5·6 ± 0·3	5·2 ± 0·3	4·1 ± 0·1

Dissolution studies

Fig. 3 shows the release profiles of ambiently cooled Gelucire 55/18 and 50/13 matrices after storage for various periods of time, while Table 4 lists the time taken for 50% of the drug to be released from these matrices. It was observed that the release rate increased after ageing for 180 days. In the case of Gelucire 55/18, the value of n was found not to change on storage, indicating that the mechanism of drug release did not in itself alter on ageing. The decrease in viscosity noted previously indicates that this base may undergo degradation during ageing either by hydrolysis or breakage of PEG chains. As both routes of degradation lead to products with higher water solubilities than PEG esters, the drug release rate may be expected to increase on storage, which was indeed observed. Moreover, the decrease in the viscosity of the gel might increase the diffusion coefficient of the drug in swollen polymer and hence result in more rapid diffusion of the drug. The increase in dissolution rate from Gelucire 55/18 seen on storage may, therefore, be at least partially associated with chemical changes in the base.

The more rapid release from aged Gelucire 50/13 matrices is more likely to be attributable to changes in the physical structure of the base. Previous studies have shown a decrease in tensile strength of the matrix on storage (Sutananta et al 1994b), although examination of the dissolution properties of the slow- and fast-cooled samples has indicated that changes in the dissolution behaviour may not necessarily correlate with changes in tensile strength. Examination of the effect of storage on the thermal properties of Gelucire 50/13 (Sutananta et al 1994b) indicates that the endotherm profiles of both slowly and rapidly cooled base alter on storage. While there is no obvious direct correlation between the shape of the DSC traces and the dissolution behaviour, samples with a higher ΔH_F (i.e. slow cooled samples compared with fast cooled samples, aged samples compared with fresh) have a faster release rate. While it is not possible to state whether this is a causal relationship at this stage, the observation does lend support to the hypothesis that there is an association between the erosion rate and microstructure of Gelucire 50/13.

Conclusion

This study has examined the relationship between the preparation and storage conditions of Gelucires 55/18 and 50/13 and the dissolution of theophylline from these bases. The rate of cooling from the melt has an effect on drug release from both systems. In particular, a marked difference in the mechanism of release from Gelucire 55/18 at low drug loadings was noted, which was related to differences in the

crystal structure of the samples, while release from slow-cooled Gelucire 50/13 was greater than that of fast-cooled systems, this effect being ascribed to changes in the distribution of constituents within the sample. In both cases, therefore, it is possible to relate the dissolution rate and mechanism to the physical structure, as investigated in previous studies using DSC (Sutananta et al 1994a, b). Ageing effects were noted for both bases, although evidence was obtained for changes in the chemical composition of Gelucire 55/18 over and above any changes in physical structure. Again, however, at least in the case of Gelucire 50/13, the observed effects could be related to alterations in the physical structure. The study has therefore highlighted the importance of considering the processing conditions, the chemical composition and the physical structure of Gelucire bases in order to understand the dissolution behaviour of drugs from these systems.

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