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An Evaluation of the Mechanisms of Drug Release from Glyceride Bases

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Abstract

A series of dispersions containing theophylline in Gelucires 43/01, 54/02, 50/02, 50/13 and 55/18 was prepared and the physical structures studied using differential scanning calorimetry. The dissolution, erosion and swelling profiles of the drug dispersions were assessed.

Gelucire 43/01 and 54/02 systems were found to release the drug by a simple diffusion mechanism, with no evidence for erosion or swelling being noted. Gelucire 55/18, however, showed a more complex mechanism involving both diffusion and erosion. On increasing the drug load within the matrices, the predominance of the erosion mechanism increased. Drug release from Gelucire 50/13 matrices took place principally by erosion, although the process was dominated by swelling and subsequent disintegration of the matrix, rather than simple dissolution of the base as was found for Gelucire 55/18. Gelucire 50/02 matrices also exhibited swelling, although drug release occurred predominantly via diffusion.

The study, therefore, demonstrates that Gelucires may release incorporated drugs by a number of mechanisms depending on the chemical composition of the base.

Glycerides are naturally-occurring substances composed of fatty acid esters of glycerol. These materials have been used pharmaceutically for a number of years, notably as suppository bases and solvents. More recently, glyceride-based materials have been used as controlled-release matrices. In particular, a number of studies have been conducted on Gelucires, which are mixes of mono-, di- and triglycerides with polyethylene glycol esters of fatty acids. Gelucires are classified by two numbers, the first referring to the approximate melting point of the base and the second to the HLB (hydrophilic-lipophilic balance) value. The values of these parameters depend on the composition of the base, particularly the ratio of glycerides to the more polar polyethylene glycol esters.

A number of studies have investigated the mechanisms by which drugs are released from Gelucire bases, the majority using models based on the Higuchi equations (Higuchi 1961, 1963) for diffusion-controlled release (Dennis & Kellaway 1987; Howard & Gould 1987; Dennis 1988; Kopcha et al 1990, 1991; Baykara & Yuksel 1991; Prapaitrakul et al 1991). However, while these models are appropriate for Gelucires with a low HLB (< 7), release rates from bases with high HLB values are faster and are thought to involve both diffusion and erosion mechanisms (Howard & Gould 1987; Kopcha et al 1990, 1991), although very few studies have been conducted which have actually measured erosion rates. Furthermore, Gelucires may swell in the dissolution medium, particularly those with high HLB values (Dennis 1988; Bodmeier et al 1990; Nadkarni & Laskar 1991; Prapaitrakul et al 1991).

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There are, therefore, a number of mechanisms which may be involved in drug release from Gelucires which are almost certainly dependent on the composition of the base used. Furthermore, the release characteristics may be dependent on the method of measurement. For example, when release experiments were performed on high HLB Gelucires using discs whereby only one surface was exposed to the dissolution medium, the release of a drug was predominantly by diffusion (Kopcha et al 1990, 1991; Prapaitrakul et al 1991). The investigators reported that the matrices were intact at the end of the experiments. However, when dispersions of the same drug in the same Gelucire (50/13) were filled into capsules and tested using a USP or BP dissolution method, disintegration of the matrices was reported (Dennis 1988; Bodmeier et al 1990); hence the erosion mechanism became more important. Clearly, therefore, the method by which the base is introduced to the dissolution medium may affect the release mechanism.

Previous studies (Sutananta et al 1994 a,b) have examined the relationship between the composition of the base, the preparation conditions and the thermal behaviour of these systems. In this study, an investigation into the mechanisms of drug release from a range of Gelucire bases has been performed with a view to clarifying the relationship between the composition of the base and the release characteristics. This has been performed by measuring not only the drug dissolution rate but also the rate of swelling and erosion of the bases.

Materials and Methods

Materials

Anhydrous theophylline (Sigma, Poole) was used as received ($< 300\,\mu m$). Five Gelucires (Gattefosse, St Priest) were used throughout the study, these being 43/01, 50/02,

50/13, 54/02 and 55/18. Gelucire 43/01 is a mixture of triglycerides, while Gelucire 54/02 is a mixture of di- and triglycerides and contains 8–17% of monoglycerides. Gelucire 50/02 and 50/13 are mixtures of glycerides and polyethylene glycol (PEG) esters of fatty acids, with 50/13 having a higher HLB value owing to a higher proportion of PEG esters. 50/02 has a wider range of fatty acid compositions, ranging from C12 to C18, while 50/13 is composed principally of palmitate (C16) and stearate (C18) esters and also contains free PEGs. Gelucire 55/18 contains only polyethylene glycol 6000 esters and does not contain glyceride species. It is obtained from a direct esterification of fatty acids with PEG 6000. The proportions of glycerides to PEG esters have been summarized in a previous study (Sutananta et al 1994b).

DSC characterization of Gelucire-drug mixtures

Gelucires containing 2 to 70% w/w concentrations of anhydrous theophylline were subjected to DSC investigation. Physical mixtures were heated to 75°C, held for 1 h and cooled under ambient conditions. Ten milligrams of sample were scanned from −20°C to 300°C at the speed of 20°C min^{-1} using a Perkin-Elmer DSC7. Samples were also examined microscopically using an Olympus BH-2 polarizing microscope (Olympus Ltd, London).

Sample preparation for dissolution, erosion and swelling studies

Samples were fabricated into flat-faced moulded tablets (diam. 1·25 cm, height 0·62–0·68 cm). A glass mortar containing an accurately weighed amount of Gelucire was heated in the programmable oven from 30 to 75°C at 3°C min^{-1} and maintained at 75°C for 30 min. Theophylline (from 2 to 30% w/w) was dispersed in the Gelucire and the mixture held for a further 30 min at 75°C, then stirred to ensure homogenous dispersion of drug and poured into an aluminium mould (previously at room temperature 21°C). After solidification the excess solid was cut away. The matrices were stored for 12–24 h over silica gel and the diameter and height measured before testing. The average weights of the matrices used in the dissolution tests were between 0·85 and 0·95 g.

Dissolution studies

The dissolution of theophylline from the matrices was conducted in the USP rotating baskets apparatus (PTW S Dissolution test instrument, Pharmatest) in 1000 mL distilled water at 37 ± 0·5°C with a rotation speed of 100 rev min^{-1}. At pre-selected time intervals up to 24 h, 3–4 mL dissolution medium was automatically withdrawn and the drug content was analysed spectroscopically at 272 nm. Six tablets were used for each measurement. The single-surface disc method was not used since it may prevent the bases from swelling and disintegrating, thus altering the release characteristics.

On testing Gelucire 50/13, a milky solution was obtained resulting from the erosion of the matrices. This resulted in interference with the spectroscopic reading and required extra filtration through a 0·45 μm cellulose acetate membrane. The membrane did not absorb any measurable amount of drug. Gelucire 55/18 dissolves in water but does not interfere with the spectroscopic reading of theophylline.

Measurement of matrix erosion and swelling

Measurements of matrix erosion and swelling were carried out on the tablets containing no drug. Six tablets (weighed to 0·0001 g, mass = X) were placed in the dissolution apparatus and subjected to the conditions used in the dissolution test described above. Each basket was taken out at preselected time intervals, excess water was removed and the basket placed on a small aluminium pan, allowed to stand for 3 min at room temperature (21°C), then weighed to 0·001 g (Mass = Y) and dried at 80°C to a constant weight (mass = Z). These three weights, therefore, give the initial dry weight (X), the wet weight after being immersed in water for a given time interval (Y) and the corresponding dry weight (Z), weights Y and Z including that of the dry basket and small aluminium pan. The diameters of the matrices were also measured immediately after samples were taken out of the dissolution medium.

If DB is the weight of a dry basket and small aluminium pan, matrix erosion and water uptake can be expressed, in percentage, as:

$$\text{matrix erosion} = [X - (Z - DB)] \times 100/X \quad (1)$$

$$\text{water uptake} = (Y - Z) \times 100/(Z - DB) \quad (2)$$

Results and Discussion

The physical state of theophylline in Gelucire matrices

Microscopic examination of the dispersions containing 2–30% w/w theophylline in all the Gelucires studied indicated that the theophylline was dispersed as particles throughout the molten bases (up to 75°C). When the melts were solidified, discrete drug particles in the bases were still evident. These indicated that the dissolution of the drug in the bases was incomplete at the drug concentrations of 2% w/w or greater.

A typical partial phase diagram of the theophylline-Gelucire systems obtained from the DSC studies is shown in Fig. 1 for Gelucire 50/13. The DSC curves of the Gelucire matrices containing 5–70% of drug showed two separate melting endotherms at low and high temperatures corresponding to the melting of Gelucires and the drug,

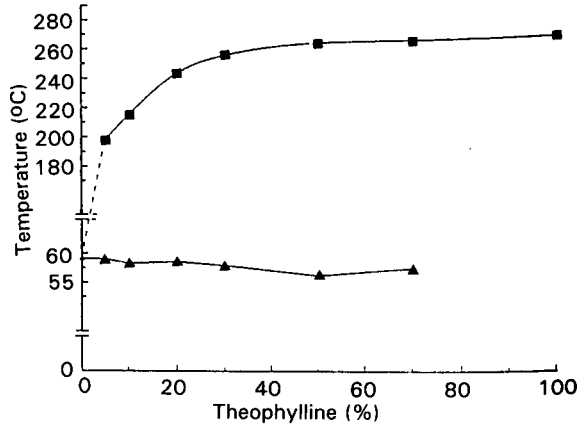

FIG. 1. Partial phase diagram of Gelucire 50/13-theophylline systems. ■ Liquidus temperatures, taken from the peak maximum of the drug melting endotherm; ▲ solidus temperature from T_b, the temperature at which the endotherm corresponding to the Gelucire returns to the baseline.

respectively. The liquidus temperatures were taken from the peak maximum at the drug melting endotherm and the solidus temperature from T_b, the temperature at which the endotherm corresponding to the Gelucire returns to the baseline. This solidus temperature was chosen as a result of the complex nature of the melting endotherms (Sutananta et al 1994a) which precluded the use of a single peak temperature or an unequivocal melt onset temperature.

The phase diagrams were of the monotectic type (Craig 1990; Craig & Newton 1991), whereby a depression in the melting point of the higher melting (drug) component is observed at low drug contents. Such phase diagrams have been associated with simple binary mixes of the two components, the decrease in drug melting point being due to the drug effectively dissolving in the base at elevated temperatures. At the lowest drug contents studied, the endotherm or the drug became indistinguishable from the baseline due to peak broadening, rather than due to any interaction between the drug and base in the solid state. Both the microscopy and DSC results, therefore, indicate that the drug is simply dispersed through the Gelucire matrices in particulate form.

The mechanisms of drug release from Gelucire matrices

Fig. 2 shows the release profiles of Gelucires containing 30% theophylline. The amounts of drug released from Gelucires 43/01, 54/02 and 50/02 matrices were 1·7, 1·4, and 9·7% of drug loading in 20 h, respectively, while the drug was completely released from Gelucires 55/18 and 50/13 in 10 and 20 h. This diversity, therefore, suggests a relationship between the composition of the Gelucire and the drug release rate. This will, therefore, be discussed in relation to each base.

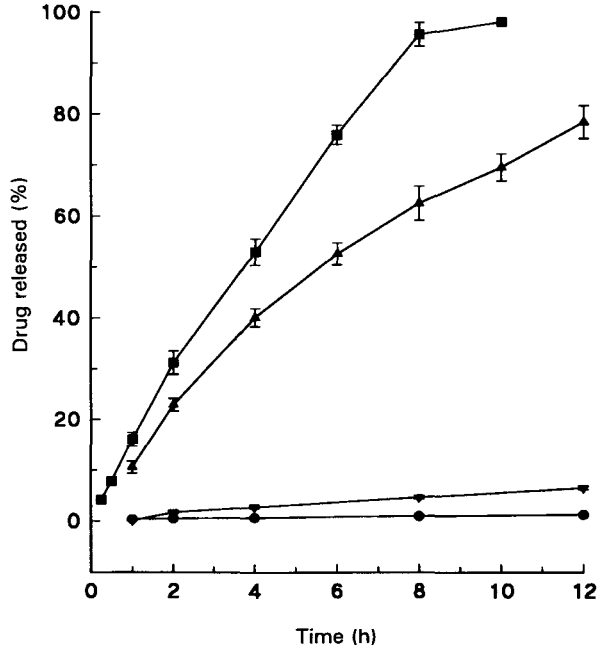

FIG. 2. The release profiles of various Gelucire matrices containing 30% w/w theophylline. For clarity, the release from Gelucire 54/02 is not shown but the amounts released were less than 1·5% in 12 h. ■ 55/18; ▲ 50/13; ▼ 50/02; ● 43/01.

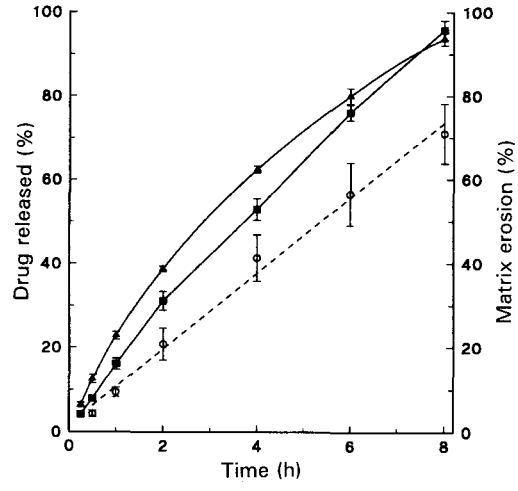

FIG. 3. The release and the erosion profiles of theophylline from Gelucire 55/18. Solid line, drug release from Gelucire 55/18 matrices containing 2% (▲) and 30% (■) drug; broken line, a regression line of the weight loss of pure 55/18 matrices during dissolution. The release from matrices containing 5, 10, 15 and 20% drug lie between those of 2 and 30% but are not shown, for clarity.

Gelucires 43/01 and 54/02. Gelucire 43/01 contains only triglycerides, while Gelucire 54/02 contains a mixture of glycerides. In either case, these matrices will be highly hydrophobic and may be expected to release the drug at a very slow rate, as indeed was found to be the case (Fig. 2). It is likely that the dissolution of drug particles at the surface of the matrices allowed the establishment of channels through the tablet, from which the drug was slowly released. No evidence was found for swelling or erosion and a linear relationship was found between the fraction of drug released vs $t^{\frac{1}{2}}$ ($r < 0.999$), indicating a diffusion-controlled release.

Gelucire 55/18. In terms of composition, the opposite extreme to Gelucires 43/01 and 54/02 is Gelucire 55/18,

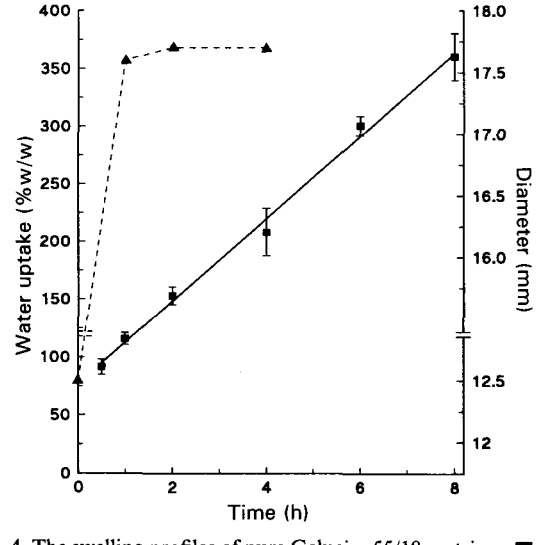

FIG. 4. The swelling profiles of pure Gelucire 55/18 matrices. ■ The amount of water in the swollen matrices (% w/w of dry base), ▲ diameter of swollen matrices. The correlation coefficient (r) of the regression line of the water uptake profile is >0·998.

which contains only PEG stearates. The release profiles of theophylline from Gelucire 55/18 matrices containing 2 and 30% drug are shown in Fig. 3 together with the erosion profile of pure matrices, while Fig. 4 shows the amount of water entering the pure matrices (in % w/w of dry base) and the change in matrix diameter during dissolution testing, which gives an indication of the swelling behaviour of the bases. It may be seen from Figs 3 and 4 that the mechanism by which the drug is released may involve both swelling and erosion processes. It is helpful to consider the kinetics of both processes in order to develop an analysis which may indicate the relative importance of the two mechanisms.

In swellable matrices, the release of the drug is controlled by one or more of the following processes: the diffusion of water into the matrix; the swelling due to hydration of the matrix or the relaxation of the polymer chains (often referred to as Case II transport); diffusion of the drug through the swollen matrix and through the existing pores, if any; and the dissolution or erosion of the matrices. The overall profile depends on which process or combination of processes dominate the release. A simple expression that may be used to model these processes is that suggested by Beren & Hopfenberg (1978):

$$\frac{M_t}{M_\infty} = k_1 t + k_2 t^{\frac{1}{2}} \quad (3)$$

where M_t/M_∞ is the fraction released in time t, and k_1 and k_2 are constants describing the constant rate process (erosion) and diffusion-controlled release mechanisms, respectively. The advantage of this expression is that it separates the effects of two simultaneous processes and that k_1 and k_2 have a meaningful physical interpretation. Equation 3 includes, in k_1, the effect of polymer relaxation, the so-called Case II transport. The phenomenon is generally attributed to structural changes induced in the polymer by the penetrant (Peterlin 1979, 1980), which cause the polymer to swell. If this process is the rate-limiting step, the release of drug from the matrix will be zero order and is called relaxation-controlled, swelling-controlled or Case II transport process (Korsmeyer & Peppas 1983; Peppas & Korsmeyer 1986). However, Hopfenberg (1976) suggested that the most simple relaxation process might be dissolution of the polymer. Therefore, k_1 can be associated with the dissolution as well as relaxation of polymer chains. Lee (1980, 1981) formulated a drug release model from erodible matrices which has diffusion contribution (but no swelling component) and came to the same empirical form as equation 3.

It can be seen from equation 3, that the release can be approximated by $t^{\frac{1}{2}}$ (k_2), zero order (k_1) or mixed kinetics (k_2 and k_1) if it is controlled by diffusion, Case II transport (or dissolution of the polymer) and a mixture of the two (anomalous or non-Fickian transport), respectively. In addition, the simple power law expression shown in equation 4 may be used to correlate and evaluate release data (Langer & Peppas 1981):

$$\frac{M_t}{M_\infty} = kt^n \quad (4)$$

where k is a constant and n is a release exponent, indicative of the mechanism of drug release. For a slab $n = 0{\cdot}5$, $0{\cdot}5 < n < 1$ or $n = 1$ indicates Fickian diffusion, anomalous transport or Case II transport kinetics, respectively. For a cylinder and a sphere, n is 0·45 instead of 0·5, and 0·89 replaces 1. The equation generally holds for $M_t/M_\infty \leqslant 70\%$ of drug released (Peppas & Korsmeyer 1986).

The release of the drug from the Gelucire 55/18 matrices could be approximated by the $t^{\frac{1}{2}}$ model; i.e. graphs of the percentage drug released vs $t^{\frac{1}{2}}$ were linear ($r > 0{\cdot}98$ in all cases from 2–30% drug loading). It is, however, clear from the evidence shown in Fig. 4 that the release may be controlled by both the erosion and swelling of the tablets, hence the relative importance of the two processes was mathematically assessed by fitting the dissolution data to equations 3 and 4. The exponent n from equation 4, was the slope of a linear regression line of a logarithmic plot of percentage drug released against time ($r > 0{\cdot}99$ in all cases). The values k_1 and k_2 in equation 3 were obtained from non-linear regression curve fitting (through the origin) of the graphs of percentage drug released against $t^{\frac{1}{2}}$.

The calculated parameters describing the dissolution process are shown in Table 1. The values of n increased with higher percentage drug loading. At 2% drug loading, the n-value was 0·71, which indicated that the release of drug was controlled by both diffusion and swelling/dissolution (erosion) of the polymer. At 20 and 30% drug loading, where $n = 0{\cdot}87$, the predominant mechanism of drug release was swelling/dissolution of the matrix and hence release was nearly constant between 1 and 8 h. The same conclusion could be drawn from the analysis of data using k_1 and k_2 from equation 3. The values of k_1, a term related to constant rate processes, increased with drug loading, while k_2, a term related to diffusion, decreased at higher drug concentrations in the matrix. As a result, the ratio k_1/k_2, which indicated the relative importance of erosion to diffusion, increased with percent drug loading.

Table 1. Kinetic parameters calculated from dissolution data of theophylline from Gelucire 55/18 matrices.

Drug loading (%)	Exponent n from equation 2	Exponents from equation 1			T50 (h)
		k_1	k_2	k_1/k_2	
2	0·71 ± 0·02	5·45	18·82	0·29	2·74 ± 0·24
5	0·72 ± 0·01	4·92	19·67	0·25	2·88 ± 0·22
10	0·77 ± 0·02	6·63	11·83	0·56	3·10 ± 0·20
15	0·80 ± 0·01	7·77	11·75	0·66	3·17 ± 0·13
20	0·87 ± 0·03	8·82	7·94	1·11	3·43 ± 0·15
30	0·87 ± 0·02	9·69	6·97	1·39	3·61 ± 0·23

T50 is the time that 50% w/w of the drug was released from the matrices.

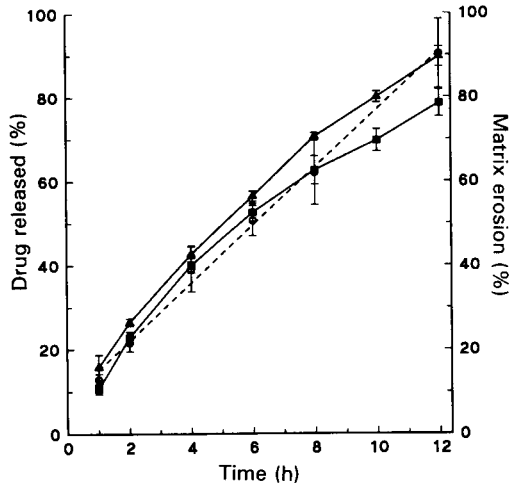

FIG. 5. The release and the erosion profiles of Gelucire 50/13. Solid line, the release profile of Gelucire 50/13 matrices containing 2% (▲) and 30% (■) drug; broken line, weight loss of pure 50/13 matrices during dissolution (correlation coefficient of the regression line, $r > 0.998$).

Release from Gelucire 50/13 matrices. Unlike Gelucire 55/18 which contains PEG 6000 esters, Gelucire 50/13 contains 20% glycerides and 80% PEG esters; hence these matrices contain both hydrophobic and hydrophilic components. The PEG backbones, however, are of shorter chain length (molecular weight $\approx$ 1500) than Gelucire 55/18. Fig. 5 shows the release profiles of the matrices containing 2% and 30% theophylline together with the weight loss of the pure matrices during dissolution. Fig. 6 shows the swelling profiles of the matrices in terms of water uptake and diameter of the tablets.

On immersion in water, the matrices swelled and also exhibited surface erosion, as shown in Fig. 6. The swelling, however, was not as extensive as in Gelucire 55/18 as seen from the smaller increase in diameter, which reached a maximum after 2 h and then decreased. In addition, no

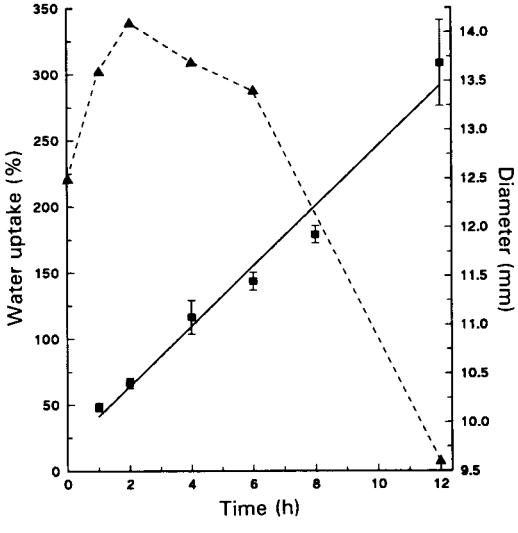

FIG. 6. The swelling profiles of pure Gelucire 50/13 matrices. ■ The amount of water in the swollen matrices (% w/w of dry base), ▲ diameter of swollen matrices. The correlation coefficient (r) of the regression line of the water uptake profile is 0·988.

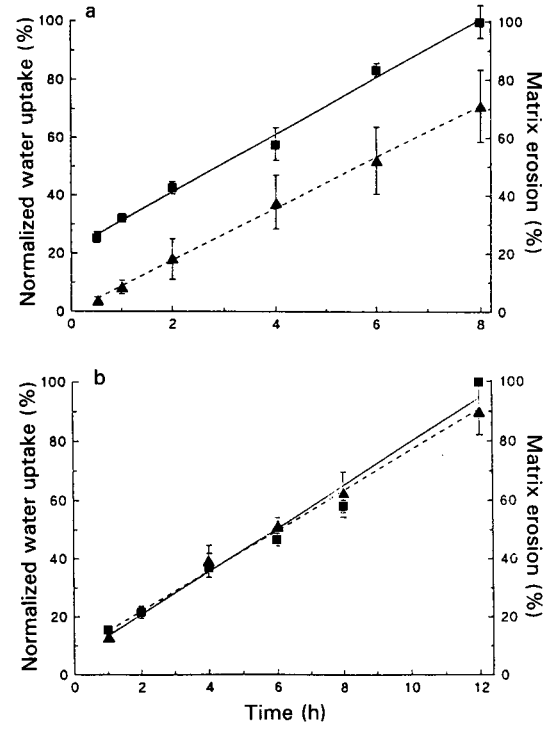

FIG. 7. Normalized water uptake and the erosion profiles of pure Gelucire matrices 55/18 (a) and 50/13 (b). The normalized water uptake expresses the amount of water in the matrices (in % w/w of the dry matrices) at any time as percentage of the amount of water in the matrices at the end of the dissolution test. Broken line, erosion; solid line, normalized water uptake profile.

transparent gel layer could be seen. Instead, the erosion occurred through the disintegration of the masses at the surface of the matrices. The difference between the swelling of Gelucire 55/18 and 50/13 can be clearly seen when the percentage water uptake and the erosion profiles are plotted on the same scale as shown in Fig. 7. It can be seen that the water uptake of Gelucire 50/13 matrices totally determined the matrix weight loss, indicating that the erosion of

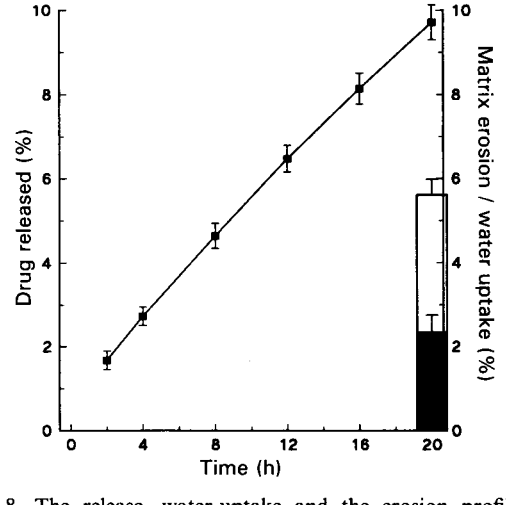

FIG. 8. The release, water-uptake and the erosion profiles of Gelucire 50/02 containing 30% theophylline. Solid line graph, the release profile; solid bar, matrix weight loss at 20 h after dissolution test; open bar, weight of water (in % w/w of dry base) taken up by the matrices after 20 h of dissolution test.

Gelucire 50/13 matrices was due to surface disintegration of matrix materials caused by the inability of the matrices to accommodate the swelling due to water. This is in contrast to the erosion of Gelucire 55/18, which was due largely to the formulation of a gel layer and subsequent dissolution of this gel.

Examination of the drug release and erosion profiles of Gelucire 50/13 matrices (Figs 5, 6) indicates that the erosion of the matrix was a linear process and that the drug release followed the matrix erosion. However, examination of the kinetics of drug release indicates that the drug dissolution was more adequately modelled by $t^{\frac{1}{2}}$ kinetics ($r > 0.999$). This discrepancy may be due to diffusion of theophylline through the swollen matrices; thus will be a diffusion component to the drug release which causes a deviation from the zero-order kinetics which may be expected if the dissolution process was due only to erosion of the matrix.

Release from Gelucire 50/02 matrices. Gelucire 50/02 consists mainly of hydrophobic glycerides (80%) with only 20% of hydrophilic PEG esters. Fig. 8 shows the release, erosion and the swelling profiles of 50/02 matrices containing 30% drug. At 20 h of dissolution, $\approx 10\%$ of drug was released, while only 2·5% of the matrix material had eroded and the water uptake corresponded to 5·6% of the dry weight. The release of drug probably occurred predominantly by diffusion through the water-filled pores or channels created by the eroding matrices and the released drug. The presence of PEG esters resulted in the matrices with higher hydrophilicity than pure glyceride matrices (43/01, 54/02), as the esters may take up water, dissolve or swell, as seen in 50/13 and 55/18, thus creating channels for drug release. The inclusion of PEG esters in Gelucire 50/02, therefore, resulted in swelling and water uptake which was not observed in Gelucires containing only glycerides, despite the similarity of the HLB values for the three bases.

Conclusions

The study has investigated the mechanisms of drug release from a range of Gelucire bases and has indicated that for Gelucires containing only glycerides or, in the case of Gelucire 50/02, only small levels of PEG esters, release occurs principally by diffusion through pores in the matrix. Gelucire 55/18, however, shows both erosion and diffusional release, with a dependence on the mechanism seen on the level of incorporated drug. Gelucire 50/13 matrices exhibited erosion kinetics, although the drug may be released by a diffusion mechanism.

This investigation has highlighted the necessity of measuring not only the release kinetics but also the erosion, swelling and water-uptake profile of the bases in order to gain a more thorough understanding of the mechanisms of drug release. Furthermore, while the HLB value of the Gelucire base is a useful measure of the hydrophobicity of the base, it may be more useful to consider the Gelucires in terms of their chemical composition, as this study has shown that it is possible to correlate the behaviour of the bases with the composition more easily than with the HLB value.

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