J. Pharm. Pharmacol. 1990, 42: 745–751
Received June 4, 1990

Evaluation of Methodology for Assessing Release Characteristics of Thermosoftening Vehicles

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Abstract—Methodology has been devised for the testing and evaluation of the mechanistic release of drug or markers from thermosoftening materials, as represented by the Gelucire class of excipients, which could be predictive. Release of a drug (anhydrous theophylline) and a marker (D&C yellow No. 10) was determined using a calibrated stationary disc/rotating fluid system. Of the fourteen commercially available Gelucire excipients, six were investigated in detail (G46/07, G48/09, G50/02, G50/13, G53/10, G62/05) and found to have biphasic release profiles. Lipid soluble materials demonstrated predominantly diffusion-controlled release, while water-dispersible materials absorbed water and showed signs of swelling which led to erosion as an additional component of the release characteristics.

The objective of this research was to devise methodology to test and evaluate the mechanistic release of drugs or markers from thermosoftening materials, which could be predictive and which made use of dissolution and matrix diffusion. The materials of the Gelucire class of excipients are practically inert and are derived from naturally hydrogenated food-grade oils and fats. The terminology used in their identification describes their properties: the first number is the melting point (°C) and the second number the HLB (hydrophilic-lipophilic balance) value on a scale of 1 to 14 for lipid-soluble to water dispersible material, respectively. These excipients have been used to fill oily or pasty materials into hard gelatin capsules; the physical integrity of the product is guaranteed up to the melting range of the mixture, which can be designed to meet appropriate environmental conditions. By varying the HLB of the excipients, a controlled-release-type system can be designed (Dennis et al 1987; Howard & Gould 1987).

In this study, release of drug (theophylline) or marker (D&C yellow No. 10) from thermosoftening excipients was determined using a calibrated stationary disc/rotating fluid system. All commercially available Gelucires were tested initially and those amenable to further investigation, in terms of providing adequate release and maintaining geometric integrity, were explored in detail.

Materials and Methods

Materials

All chemicals were stored over silica gel in a desiccator at 22°C: Gelucire materials (Table 1, Gattefosse Corporation, NY), benzoic acid USP (Fisher Scientific, PA), D&C yellow No. 10 (Warner Jenkinson, MO), anhydrous theophylline USP (Amend Drug and Chemical Company, NJ). The dissolution medium was a simulated gastric fluid (pH 1·2) consisting of 2 g NaCl and 7 mL conc. HCl made up to 1L with distilled water.

Release methodology

Rotating disc method. In this method, the flat-faced discs of benzoic acid were fixed to the end of a stirring shaft. Release from this system was carried out in 900 mL of degassed, distilled water at 37°C using a USP dissolution apparatus (Hanson Research, CA). Sink conditions were maintained at all speeds tested. The disc was positioned in the centre of the dissolution vessel about 6·5 cm from the bottom. Samples were collected at 10, 20, 30, 40, 50, 60 and 90 min intervals. The samples from the dissolution run were analysed by UV spectrophotometry (224 nm).

Stationary disc method. Fig. 1 shows the dissolution apparatus, which consists of a 1000 mL, USP dissolution vessel with a mount at the base to allow for easy insertion and removal of a Millipore filter holder which was used to contain the sample. The mount was fixed to the bottom of the vessel with a silicon-based adhesive (General Electric, NY) which provided a permanent attachment. The mount was the tip of a 5 mL syringe barrel cut to allow for attachment to the vessel. Once the holder was placed on the mount, a rotating paddle could be lowered to a specified distance from the top of the disc. The paddle was a USP/Method II dissolution paddle with a polyfluorocarbon coating.

Preparation of rotating or stationary discs

Benzoic acid discs were used to calibrate the test systems. Five g of benzoic acid was heated to 130°C. The molten material was poured into the female half of a 1·54 or 6·98 cm^2 Millipore filter holder. The luer-lock tip was sealed with a threaded screw to prevent leaking of the molten mass. The molten material was poured in three stages into the holder to prevent cracking on cooling. Once the mass completely congealed, the surface was levelled with a hot spatula.

The Gelucire discs were prepared similarly; 10 g of each Gelucire was heated to 10°C above its melting point, and the drug or marker was incorporated into the molten mass (2·5% w/w), using a high speed, desk-top homogenizer (Tissumizer, Model SDT-1810, Tekmar, OH). This produced marker particles with sizes ranging from 5–82 μm as compared to the unprocessed marker particle sizes of 80–570 μm. The particle size ranges were determined microscopically.

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Table 1. Gelucire specifications.

Type of Gelucire (MP/HLB)	Acid value[a] (mg)	Saponification value[b] (mg)	Hydroxyl value[c] (mg)	Iodine value[d] (%)	Melting point (°C)
33/01	<2	240–260	<10	<3	31–36
35/10	<2	120–140	<110	<3	37–38
37/02	<2	200–220	<60	<3	35–38
42/12	<2	95–125	<70	<3	41–44
44/14	<2	70–1005	<70	<3	42–46
46/07	<2	130–150	<100	<3	43–49
48/09	<2	105–130	<85	<3	45–50
50/02	<2	180–200	<60	<3	48–52
50/13	<2	65–85	<60	<3	47–51
53/10	<2	100–120	<40	<3	51–55
55/18	<6	8–20	—	<3	55–59
62/05	<5	70–90	<60	<10	60–65
64/02	<2	170–190	<120	<3	62–66
70/02	<4	145–165	—	<3	70

[a] Amount of potassium hydroxide required to neutralize the free fatty acids. [b] Amount of potassium hydroxide required to neutralize free acids and saponify the esters. [c] Amount of potassium hydroxide required to neutralize the volatile water-soluble acids. [d] Indicates the degree of unsaturation; numerically the percentage of iodine absorbed by the sample.

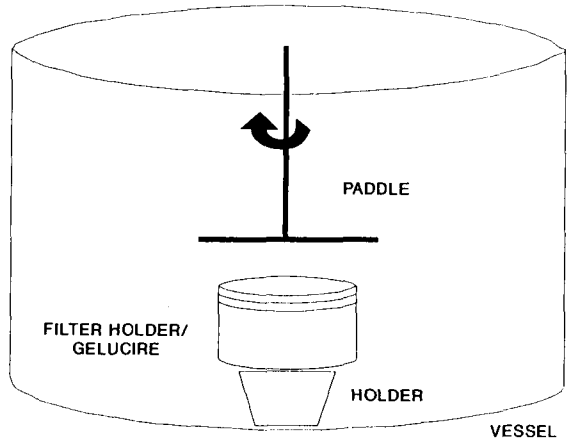

FIG. 1. Scheme of stationary disc/rotating fluid method.

Prepared discs were stored in a desiccator at ambient temperature for no longer than 24 h.

Disc content uniformity

Approximately 60 g of a 2·5% w/w dispersion of anhydrous theophylline with molten Gelucire 50/13 was prepared. The mixture was allowed to congeal to room temperature (20–23°C) without further processing.

Samples were drawn from the cooled mixture from the top left, top centre, top right, middle left and bottom left sides of the container. Each sample was weighed and placed into a 10 mL volumetric flask with the addition of 8 mL of distilled water. The samples were sonicated for 10 min and allowed to cool for 1·5 h. The solutions were brought to volume and theophylline concentrations determined by spectrophotometry.

Mixing efficiency

A study was performed to determine that the stationary disc/rotating fluid system maintained a homogeneous concentration of drug or marker during the course of experimentation. A stationary 1·54 cm^2 disc with benzoic acid was used and the paddle height set at 3 cm in an aqueous system at 37°C. Paddle speed was initiated at 30 rev min^{-1} and changed to 40 rev min^{-1} after 40 min. Samples were taken in an alternating fashion from the top, middle and bottom of the dissolution vessel.

Release studies

Continuous sampling. A continuous profile of the release of drug or marker from the system was obtained, using a flow-through system. The dissolution medium was allowed to circulate through a 1·0 cm, quartz micro-flow cell in a UV spectrophotometer. The absorbance was continuously recorded and the medium was returned to the dissolution vessel. There was no absorption of drug or marker to the sampling system.

Discrete sampling. Samples were taken at times previously determined from the continuous-flow recordings (5, 10, 15, 20, 30, 60, 120, 180, 240 and 360 min). Each sampling probe had a 35 μm full-flow filter attached to remove any particulates from the drawn sample. The tubing was connected to a 12 channel peristaltic pump (Model 10450, VanKel, NJ) which allowed for transfer of the sample to a 6-vessel fraction collector (VanKel, NJ) where samples were stored. The samples were then read on a DU-40 spectrophotometer (Beckman, CA).

Operating conditions

Determination of paddle height. Paddle height was determined by attaching a 6·98 cm^2 filter holder, filled with benzoic acid, to the base of a USP dissolution vessel and monitoring flux (mg cm^{-2} s^{-1}) as a function of paddle height and speed. Paddle height was set at 1 and 3 cm, while paddle speeds were selected at 30, 45, 60 and 75 rev min^{-1} (angular velocity: 3·142, 4·712, 6·283 and 7·854 rad s^{-1}, respectively).

Determination of paddle speed and pumping rate. An optimum paddle speed was determined to allow for adequate mixing within the dissolution vessel while maintaining the integrity of the compact. For the continuous flow system, paddle speed was set to ensure efficient mixing of the returned medium.

To adequately determine paddle speed, an optimum pumping rate of medium to and from the spectrophotometer had to be determined which would allow for accurate recording of changes in drug concentration as a function of time. A set of experiments was performed in which three lag parameters were monitored: 1) time lag before solution reached the detector; 2) time for the mixing phase; and 3) total system lag time as described by Cartwright (1979); paddle speed was set at 50 rev min^{-1} and the pumping rate allowed to vary.

Results and Discussion

Evaluation of stationary disc/rotating fluid methodology

The system design used in this study was that of a stationary disc/rotating fluid system. This system was characterized by relating release to that of a rotating disc design. Therefore, the cell was first evaluated for its conformity to the equations

derived by Levich (1962) using a rotating, fused benzoic acid disc and comparing this with the stationary disc/rotating fluid design.

The exact solution to this problem gives the velocity distribution throughout the body of a viscous fluid and takes the following forms for the mass flux to the disc surface as derived by Levich (1962):

$$J = 0{\cdot}62\, D^{2/3}\, v^{-1/6}\, w^{1/2}\, Co \quad (1)$$

$$Sh = 1{\cdot}554\, (Sc)^{1/3}\, (Re)^{1/2} \quad (2)$$

$$\log [Sh/(Sc)^{1/3}] = \log 1{\cdot}554 + 0{\cdot}5 \log (Re) \quad (3)$$

where: J = mass flux, D = diffusivity of solute in solvent, v = kinematic viscosity, w = angular velocity, Co = saturated solution concentration, Re = Reynold's Number, Sc = Schmidt Number, Sh = Shawn Number.

The cumulative amount of benzoic acid dissolved from the fused disc, for a 1·54 cm^2 disc and 6·98 cm^2 disc, as a function of time, showed a linear increase in the amount of benzoic acid dissolved over 90 min. An increase in the rate of benzoic acid dissolution with an increase in rotational speed was also noted. At a given speed, the dissolution rate increased as the surface area increased. The net flux and other calculated parameters, as a function of rotational speed (10, 30, 50, 75 and 100 rev min^{-1}) or angular velocity (1·049, 3·142, 5·234, 7·854 and 10·474 rad s^{-1}, respectively), (eqns 1, 2) are summarized in Table 2.

A plot of flux as a function of the square-root of angular velocity demonstrated a linear relationship. Positive deviations from linearity were observed at 100 rev min^{-1}, for the 6·98 cm^2 disc, as a result of changes in flow pattern from laminar to turbulent flow at high rotational speeds. The distribution of streamlines or swirls was noted at the surface of the rotating discs. It was also noted that as the size of the rotating disc increased, the flux decreased. This may be due to increased energy dissipation at the wall surface of the dissolution vessel. The underlying theory assumes that an infinitely large vessel is used to avoid turbulence in flow pattern. Since a 1000 mL USP dissolution vessel is finite in volume, the flow patterns may deviate from theory and this may account for the deviation in plots of flux as a function of the square-root of angular velocity with different size filter holders.

Table 2. Hydrodynamic results for the 1·54 cm^2 and 6·98 cm^2 rotating disc.

Angular velocity (rad s^{-1})	Amount released (mg L^{-1} s^{-1})	Flux (mg cm^{-2} s^{-1})	Diffusion layer thickness (cm)
	1·54 cm^2 rotating disc		
1·049	0·00578	0·00370	0·01675
3·142	0·01207	0·00768	0·00967
5·234	0·01463	0·00937	0·00749
7·854	0·01958	0·01253	0·00611
10·474	0·02232	0·01429	0·00530
	6·98 cm^2 rotating disc		
1·049	0·02699	0·00336	0·01675
3·142	0·04788	0·00593	0·00967
5·234	0·05901	0·00762	0·00749
7·854	0·07717	0·00956	0·00611
10·474	0·11208	0·01445	0·00530

Values for benzoic acid and water system at 37°C. Cs = Saturation solubility = 4·39 mg cm^{-3}. D = Diffusivity in water = 1·45 × 10^{-5} cm^2 s^{-1}. Density of water = 0·99336 g cm^{-3}. Kinematic viscosity = 6·915 × 10^{-3} g cm^{-1} s^{-1}. d_1 = Diameter of 1·54 cm^2 disc = 1·40 cm. A_1 = Area of disc = 1·54 cm^2. d_2 = Diameter of 6·98 cm^2 disc = 2·98 cm. A_2 = Area of disc = 6·98 cm^2.

Table 3. Experimental parameters for evaluating hydrodynamics of the 1·54 cm^2 and 6·98 cm^2 stationary disc/rotating fluid system.

Angular velocity (rad s^{-1})	Amount released (mg L^{-1} s^{-1}) 1 cm paddle ht {3 cm paddle ht}	Flux (mg cm^{-2} s^{-1}) 1 cm paddle ht {3 cm paddle ht}	Diffusion layer thickness (cm) 1 cm paddle ht {3 cm paddle ht}
	1·54 cm^2 stationary disc		
3·142	0·01143 {0·01273}	0·007315 {0·008146}	0·00953 {0·00856}
4·712	0·01527 {0·01512}	0·009769 {0·009675}	0·00713 {0·00720}
6·283	0·01828 {0·01845}	0·011697 {0·011803}	0·00596 {0·00591}
7·854	0·02025 {0·02165}	0·012960 {0·013854}	0·00538 {0·00503}
	6·98 cm^2 stationary disc		
3·142	0·050 {0·04814}	0·00615 {0·00596}	0·0113 {0·0117}
4·712	0·06786 {0·06708}	0·00878 {0·00867}	0·00794 {0·00804}
6·283	0·08414 {0·08342}	0·01042 {0·01034}	0·00669 {0·00674}
7·854	0·10576 {0·09338}	0·01182 {0·01157}	0·00590 {0·00603}

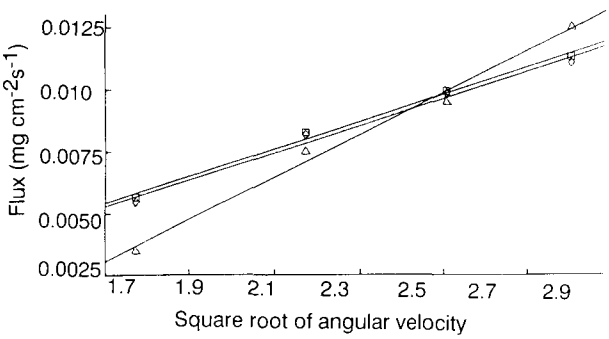

FIG. 2. Plots of flux (mg cm^{-2} s^{-1}) against the square-root of the angular velocity for a rotating disc (△) and stationary discs (paddle ht 1 cm, □; paddle ht 3 cm, ◇).

The next step was to use the stationary disc/rotating fluid system and monitor the change in flux as a function of angular velocity and paddle height. The results (Table 3, Figs 2, 3) demonstrate that flux is a linear function of the square-root of angular velocity and that it is also independent of paddle height between 1 and 3 cm. This suggested that the thickness of the hydrodynamic diffusion layer was independent of paddle height. In all subsequent experiments, a paddle height of 1 cm was chosen. The boundary layer thickness was calculated by use of the equation derived by Khoury et al (1988).

The order of magnitude for the hydrodynamic diffusion layer was found to be 10^{-3} cm, suggesting that a correlation may exist between the rotating disc system and the stationary disc/rotating fluid system. Figs 2, 3 show benzoic acid flux as a function of the square-root of angular velocity for both system designs, demonstrating that the two systems are only coincidental at one point. However, a correlation can be

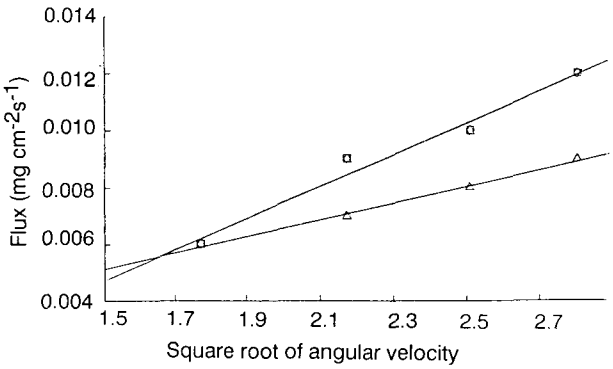

FIG. 3. Plots of flux (mg cm^{-2} s^{-1}) against the square-root of the angular velocity for a 6·98 cm^2 rotating disc (△) and stationary discs (paddle ht 1 cm, □; paddle ht 3 cm, ◇).

made between the two different testing arrangements in terms of flux at a given rotational speed. It should also be noted that flux, as a function of the square-root of angular velocity, is the same for both the 1·54 and 6·98 cm^2 stationary discs (calculated slopes of 0·0055 and 0·0056, respectively).

Disc content uniformity

Marker, drug and excipients were found to be uniformly mixed and the method of preparation was adequate to maintain the homogeneity of the final mixture.

Mixing efficiency

For both 30 and 40 rev min^{-1}, the amount released was linear with time; when the paddle speed was increased by 33·3%, the slope or release rate increased by 27%, showing that the system was well mixed and was sensitive to changes in paddle speed.

Feasibility testing

The release profile generated using the flow-through system was biphasic with a high release rate for approximately the first hour. This may be due, in part, to surface release of drug giving an initial sharp increase in concentration. Similar profiles were observed for all the Gelucire bases.

From the 14 available Gelucires, 8 were selected for detailed study. (The melting points of five were too low to be tested adequately at 37°C, the high HLB value of G55/18 allowed it to swell rapidly and be pulled out of the holder into the rotating paddle.)

Paddle speed and pumping rate effects

At speeds above 75 rev min^{-1} the integrity of the disc, in terms of its planar geometry, was not maintained; the softened material was pulled out of the holder, distorting its initial geometry.

Paddle speeds of both 75 and 50 rev min^{-1} produced a lag time of 13·75 s to reach the detector. However, the 75 rev min^{-1} speed allowed for a shorter total lag time by approximately 8 s. It has been shown by Poole (1969) that lag times observed at paddle speeds of 50 and 100 rev min^{-1} are of minor consequence in the final results obtained for a continuous dissolution profile. Therefore, maintenance of the planar geometry was the deciding factor in determining a final paddle speed of 50 rev min^{-1}.

A flow rate of 30 mL min^{-1} was chosen for subsequent experiments, providing an adequate pumping rate with acceptable lag times. It has been shown (Wahlich 1980) that flow rates of up to 35 mL min^{-1} through an automated dissolution system do not contribute to the dissolution process.

Evaluation of release mechanisms

Release rates from the selected Gelucires were investigated in terms of diffusional and/or erosional release. Matrix-diffusion has been extensively studied and modelled (Higuchi 1963) and is found to follow a square-root of time dependency:

$$M = At^{1/2} + C \tag{4}$$

where: M = amount of solute released, A = diffusional term, C = constant.

For a powdered drug homogeneously dispersed in an insoluble matrix, the drug is assumed to dissolve within the matrix and to diffuse out via the surface of the device (Scheme 1). For drug eluted from a homogeneous polymer matrix, the equation describing drug release from the planar surface of an insoluble matrix is:

$$\frac{M}{S} = [D(2Wo - Cs)Cst]^{1/2} \tag{5}$$

where D is the diffusion coefficient of the drug in the matrix, Wo is the initial loading dose of drug in the matrix, Cs is the solubility or saturation concentration of drug in the matrix, t is time, and S is the surface area of the matrix.

In most circumstances, $Wo \gg Cs$, and equation 5 reduces to:

$$\frac{M}{S} = (2WoDCst)^{1/2} \tag{6}$$

The "A" term in equation 4 then represents the following for release from a homogeneous insoluble matrix:

$$A = [D(2Wo - Cs)Cs]^{1/2} \text{ or}$$
$$A = (2WoDCs)^{1/2} \text{ for } Wo \gg Cs$$

Applying this scheme to the release of a solid drug from a granular matrix, we have the simultaneous penetration of the surrounding liquid, dissolution of drug, and leaching out of the drug through interconnecting channels or pores. The volume and length of the pores in the matrix can be included in the diffusional equation leading to another form of equation 4:

$$\frac{M}{S} = \left[\frac{D\varepsilon}{\tau}(2Wo - \varepsilon Cs)Cst\right]^{1/2} \tag{7}$$

in which ε is the porosity of the matrix and τ is the tortuosity of the capillary system, both parameters being dimensionless quantities.

If $Wo \gg Cs$, such that the dissolution rate is a rate-determining step, the following equation describes release from a granular matrix:

$$\frac{M}{S} = 2Wo(Dt/\pi)^{1/2} \tag{8}$$

Release is directly proportional to the amount of dispersed drug.

For a granular matrix, the "A" term in equation 4 then becomes a function of both porosity and tortuosity as seen in the following equations:

$$A = [\frac{D\varepsilon}{\tau}(2Wo - \varepsilon Cs)Cs]^{1/2} \text{ or}$$

$$A = 2Wo(D/\pi)^{1/2} \text{ if } Wo \gg Cs$$

The assumptions surrounding equations 5-8 are: a pseudo-steady state is maintained during release; the amount of drug in the matrix is much greater than its solubility within the matrix; no diffusional boundary layer exists; sink conditions are maintained; and the apparent diffusion coefficient remains constant.

Equation 4 also describes a solid drug dispersed in a matrix which swells over time (Scheme 2). In this model, water penetration is characterized as a front moving into the matrix, hydrating this matrix, and dissolving the active material which then diffuses out through the swollen region. If the drug has limited water solubility such that it has not completely dissolved when the matrix is hydrated, then diffusion commences from a saturated solution. The expression describing drug release from a single planar surface is:

$$\frac{M}{t^{1/2}} = S[D'Cs(\frac{2Wo}{V} - Cs)]^{1/2} \quad (9)$$

where Wo is the dose of the drug, S is the effective diffusional area, V is the effective volume of the hydrated matrix, Cs is the solubility of the drug in the matrix and D′ is the apparent diffusion coefficient of drug in the hydrated matrix which takes into account both tortuosity and porosity of the hydrated matrix. Therefore, the "A" term is a function of these parameters. It is assumed that even though the surface to volume ratio may vary with time, its ratio remains relatively constant after the initial hydration period. Also, the apparent diffusion coefficient is assumed to remain constant.

If drug has completely dissolved when the matrix is hydrated, then the following equation would apply:

$$\frac{M}{t^{1/2}} = 2Wo\ (S/V)\ (D'/\pi)^{1/2} \quad (10)$$

An erosional process coupled with a diffusional one may account for some of the profiles obtained. The equation, in its simplest form, can be expressed as follows:

$$M = At^{1/2} + Bt + C \quad (11)$$

where: B = dissolution or erosional term and the other terms are as defined above.

Scheme 3 described by equation 11, is a combination of Schemes 1 or 2 and an erosional process. The erosional or "B" term, as defined by Harland et al (1988), is a function of the mass transfer coefficient, k, of the dissolved drug at the dissolution medium/swollen matrix interface, and the polymer volume fraction, cd, at the swollen matrix/dissolution medium interface so that:

$$B = k(cd) \quad (12)$$

Whether the system swells, and whether the drug is completely dissolved in the hydrated matrix, will determine which scheme the "A" coefficient is related to. Thus, there are six physical models which may describe release from the Gelucire excipients. All six models would demonstrate matrix diffusion whether it be from a swollen matrix or not, coupled with erosion as an additional process for drug or marker release.

The "C" term associated with each of these models is related to physical parameters. If "C" is small in relation to the "A" and "B" coefficients, it would represent the error associated with curve fitting as well as error incurred during experimentation. If it is a large positive number, it would be indicative of an initially high release of surface material (i.e. burst release). If the number is a large negative number, it would indicate a lag time before release from the matrix occurred.

All experiments were performed in replicates of six and results are expressed as means ± standard errors.

Each set of profiles, replicates included, was analysed in terms of all models. The model which showed the best fit was used. Error between the observed amount released and the predicted amount were also plotted to monitor the goodness of fit. Decisions were not solely based on high correlation coefficients but, instead, on the standard error and a 95% confidence limit on each of the coefficients generated for the given model. If the standard error was large and/or the confidence level associated with the coefficients was low, the model was rejected.

From Table 4 it is apparent that for the bases with an HLB of 7 or less, and a disc size of 1·54 cm^2, with anhydrous theophylline as the marker, the best model is that of Scheme 1 for a granular matrix. This was expected since no erosion or swelling was noted. As drug is eluted from the matrix, it leaves pores which are accessible to the eluting medium to aid in further release of drug. The one exception to this generalization was Gelucire 46/07 which demonstrated a fit to Scheme 3. This could be attributed to its intermediate HLB and low melting range (43–49 C) (Gattefosse' Corp., 1982, 1985) causing it to soften and erode at 37 C.

The material with HLB values of 9 or greater were better fit by Scheme 3 for a swellable/erodible matrix. The high HLB permits the imbibition of water and consequently allows for swelling of the matrix, and subsequently it can be eroded more easily because the matrix is more pliable and easily broken.

An interesting phenomenon exists as surface area is increased from 1·54 to 6·98 cm^2. Both G53/10 and G46/07 showed a switch from a combined model of Scheme 3, to a diffusional one. This reflects the possibility that erosion is a small component of their release as compared with a diffusional process over the predetermined time of experimentation.

For the theophylline-containing systems, as surface area was increased for a particular Gelucire, the "A" coefficient, when normalized to surface area, remained constant as theory would predict. The deviations for some of the above systems may be related to additional erosional processes.

We also monitored the diffusion to erosion ratio, A/B, ($h^{1/2}$). Going from 1·54 to 6·98 cm^2, the ratio was as follows for Gelucires 46/07, 48/09, 50/13 and 53/10; 1·7 to infinity, 7·18 to 33·6, 3·86 to 7·29, and 8·69 to infinity, demonstrating that diffusion was the predominate process as surface area was increased.

Table 4. Model coefficients ± s.e. for survey of Gelucires with anhydrous theophylline (2·5%) in simulated gastric fluid at 37°C. Paddle speed, 50 rev min^{-1}; paddle ht, 1 cm.

	1·54 cm^2 Disc			6·98 cm^2 Disc		
Gelucire	A ($mg\ h^{-1/2}\ cm^{-2}$)	B ($mg\ h^{-1}$)	C (mg)	A ($mg\ h^{-1/2}\ cm^{-2}$)	B ($mg\ h^{-1}$)	C (mg)
46/07	0·161 ±0·01	0·148 ±0·01	0·048 ±0·01	0·514 ±0·00	—	−0·310 ±0·02
48/09	0·504 ±0·04	0·108 ±0·02	−0·045 ±0·03	0·410 ±0·01	0·085 ±0·03	−0·038 ±0·04
50/02	0·299 ±0·05	—	0·020 ±0·04	0·383 ±0·01	—	0·081 ±0·12
50/13	1·050 ±0·09	0·416 ±0·05	0·019 ±0·044	0·838 ±0·06	0·804 ±0·17	0·517 ±0·21
53/10	0·734 ±0·06	0·133 ±0·04	0·122 ±0·04	0·983 ±0·00	—	0·388 ±0·03
62/05	0·198 ±0·00	—	0·090 ±0·01	0·135 ±0·00	—	0·102 ±0·05
64/02	0·149 ±0·02	—	0·195 ±0·03	0·032 ±0·00	—	0·149 ±0·02
70/02	0·088 ±0·01	—	0·097 ±0·02	0·019 ±0·00	—	0·284 ±0·02

All systems were initially fitted to eqn 11 which is the combined model of diffusion and erosional release. See text for explanation of final model assigned to individual systems.

Table 5. Model coefficients ± s.e. for survey of Gelucires with yellow No. 10 (2·5%) in simulated gastric fluid at 37°C. Paddle speed, 50 rev min^{-1}; paddle ht, 1 cm.

	1·54 cm^2 Disc			6·98 cm^2 Disc		
Gelucire	A ($mg\ h^{-1/2}\ cm^{-2}$)	B ($mg\ h^{-1}$)	C (mg)	A ($mg\ h^{-1/2}\ cm^{-2}$)	B ($mg\ h^{-1}$)	C (mg)
46/07	0·178 ±0·01	0·065 ±0·01	−0·010 ±0·01	0·169 ±0·00	0·238 ±0·02	−0·100 ±0·02
48/09	0·313 ±0·00	—	−0·056 ±0·01	0·284 ±0·00	—	−0·038 ±0·01
50/02	0·292 ±0·01	—	0·168 ±0·02	0·096 ±0·00	—	0·026 ±0·05
50/13	0·610 ±0·00	—	0·034 ±0·02	0·599 ±0·04	—	0·892 ±0·32
53/10	0·218 ±0·01	0·057 ±0·01	0·037 ±0·01	0·252 ±0·00	—	0·138 ±0·03
62/05	0·151 ±0·00	—	0·036 ±0·01	0·133 ±0·00	—	0·146 ±0·01
64/02	0·018 ±0·00	—	0·034 ±0·002	0·013 ±0·00	—	0·142 ±0·01
70/02	0·049 ±0·00	—	0·072 ±0·006	0·031 ±0·00	—	0·119 ±0·01

All systems were fitted to eqn 11 which is the combined model of diffusion and erosional release. See text for explanation of final model assigned to individual systems.

For the fitted coefficients, some of the constants are negative, implying a lag time before drug was released from the matrix or, more probably, an error associated with the preparation and monitoring of release from the discs, or an error associated with curve fitting.

For Gelucire 64/02 and 70/02, there appears to be a small difference in the square-root of time equation fitted for the data for both size discs. This suggested that release was predominately from the surface without much release from the inner matrix. If a cylindrical disc is assumed, the depth of a penetration over a 5 h period for both G64/02 and G70/02 would be 0·40 and 0·22 mm, respectively. Therefore, the high melting range coupled with the low HLB combined to inhibit drug release over the 5 h test. This would limit the use of these bases.

For the low HLB Gelucires (i.e. below 7) release is strictly diffusional (Scheme 1). Therefore, the release of both anhydrous theophylline and yellow No. 10 from the highly lipophilic matrices is controlled predominantly by diffusion of drug or marker from the matrix (Table 5).

Looking at the hydrophilic bases and reviewing the 1·54 cm^2 filter holder for both anhydrous theophylline and yellow No. 10, it is apparent that anhydrous theophylline shows a dual model for release while yellow No. 10 is predominantly diffusional. However, if the A/B ratios for anhydrous theophylline and yellow No. 10 are observed, diffusion

outweighs erosion by a factor of at least 4, suggesting the mechanisms of release are similar for the two test compounds. Also, in some cases, as surface area increased, the mechanism went from a dual model to a diffusional one. Hence, if erosion was such a large factor, erosion would be expected to become more predominant at larger surface areas. Since this was not observed, erosion appears to be a minor component of drug release.

The "A" coefficient, normalized to surface area is constant for a given Gelucire (Table 5), indicating diffusion is the predominant mechanism for release of yellow No. 10 and these systems are adequately described by equation 4.

Acknowledgements

The author wishes to thank the Gattefosse' Corporation for providing samples used in this study as well as for their product related technical support.

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