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Evaluation of Release from Selected Thermosoftening Vehicles

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Abstract—Release of D&C Yellow No. 10 and anhydrous theophylline have been determined from a thermosoftening, hydrophilic matrix, Gelucire 50/13, incorporating a water-soluble additive, polyethylene glycol 4000. As additive level increased, release also increased. The effect of mixtures of Gelucire 50/13 (G50/13) and Gelucire 50/02 (G50/02) on release was also investigated as a function of temperature and pH. As the level of G50/02 increased, release decreased and became predominantly diffusional. As temperature was increased, release changed from diffusion to a mixed model of both diffusion and erosion. At basic pH, release from these composite systems became more erosional in character, possibly reflecting partial hydrolysis of the ester-linked matrices. Diffusion coefficients and apparent diffusion coefficients were calculated in G50/02 and G50/13 matrices, respectively, and were in agreement with published data.

Gelucires are inert materials derived from hydrogenated food-grade oils and fats, which have been developed to melt within specified ranges, as represented by the first number in their designation, and to have predetermined fat soluble or water dispersible characteristics, designated by their hydrophilic-lipophilic balance (HLB) as represented by the second number in their designation. Bowtle (1986) studied the release of four deliquescent drugs from the Gelucire class of excipients. Gelucires with high HLB values gave the most favourable release irrespective of their associated melting points. Thakkar et al (1987) studied the release of an antibiotic from G50/13, G48/09 and G46/07. Release from G50/13 and G48/09 was similar to that seen with a conventional powder-filled capsule. Release of active drug from G46/07 was not complete but the addition of hydrophilic additives enhanced overall release.

Dennis & Kellaway (1987) studied the release of ketoprofen from a slowly hydrating Gelucire matrix which had an HLB of 4·8 and a melting point of 50°C. Results suggested that even though release could be approximated by a square-root of time relationship, dissolved drug led to altered physical states of the matrix which showed deviations from the underlying assumptions surrounding strict matrix diffusion. Hence, a more appropriate model needed to be proposed to account for the observed behaviour.

To address this issue, Kopcha et al (1990) devised a series of schemes to explain drug/marker release from thermosoftening materials which included matrix hydration and erosion phenomena in addition to diffusional release. The schemes developed were used in this study to evaluate the effect of incorporating a water-soluble excipient on release of D&C Yellow No. 10 (the marker dye) and anhydrous theophylline from G50/13. They were also used to investigate the effect of mixing two thermosoftening materials, G50/02 and G50/13, which have similar melting ranges but divergent hydrophilic-lipophilic balances, on overall drug/marker dye release.

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Materials and Methods

Materials

All chemicals were stored over a desiccant of silica gel at a temperature of 22°C, and were purchased as follows: Gelucire 50/02 and 50/13 (Gattefosse' Corporation, NY), D&C Yellow No. 10 (Warner Jenkinson, MO), anhydrous theophylline USP (Amend Drug and Chemical Company, NJ), and polyethylene glycol 4000 (Amend Drug and Chemical Company, NJ). The dissolution medium was either a simulated gastric fluid (pH 1·2) consisting of 2 g NaCl and 7 mL conc HCl made up to 1 L with distilled water, or a simulated intestinal fluid (pH 8·11) consisting of 0·34 g of KH_2PO_4 and 9·12 g of Na_2HPO_4 made up to 1 L with distilled water.

Release methodology

The method and operating conditions used to monitor release from a stationary disc/rotating fluid system were as described previously (Kopcha et al 1990) for both continuous and discrete sampling.

Experiments were performed at a paddle speed of 50 rev min^{-1} with a paddle height of 1 cm and temperature maintained at 30, 37 or 42°C. Results are reported as the average of six replicates ± standard error (±s.e.).

Preparation of stationary discs

Ten g of the appropriate Gelucire was heated to 10°C above its melting point and the additional Gelucire (27, 50, 73% w/w) or polyethylene glycol 4000 (10, 30, 50, 75, 100% w/w) was incorporated into the molten mass using a high speed, desktop homogenizer. The drug/marker dye was added lastly under continuous high shear. The molten material was poured into the female half of a 6·98 cm^2 or, for the polyethylene glycol 4000-containing system, 1·54 cm^2 Millipore filter holder. The luer-lock tip was sealed with a threaded screw to prevent leakage of the molten mass. The molten material was poured in three stages into the holder to prevent cracking on cooling. When the mass had completely congealed, the surface was levelled with a hot spatula.

Prepared discs were stored in a desiccator at ambient temperature for up to 24 h.

Differential scanning thermoanalysis

Differential scanning calorimetry (DSC) (Model DSC-7, Perkin-Elmer Corporation, CT) was carried out on 1–10 mg of Gelucire preparations. Each sample was weighed into a DSC pan to the nearest 0·1 mg and the cover crimped into place. An empty covered sample pan was used as the reference. Each sample was heated to 100°C at a rate of 20°C min^{-1}. The sample was then rapidly cooled to a final temperature of −10°C and maintained there for 5 min. Each sample was reheated to 100°C to provide a second thermogram.

Results and Discussion

Excipient effects

During early experiments it was noted that polyethylene glycol 4000 (PEG 4000) would form emulsions with molten Gelucires of low HLB, therefore, it was decided to mix this excipient with a high HLB material, G50/13.

A representative DSC thermogram for the composite system of G50/13, 30% w/w PEG 4000 and 2·5% w/w D&C Yellow No. 10 is shown in Fig. 1. Similar thermograms were noted for all comparable systems irrespective of the drug/marker dye employed. To allow for easy visualization of the endothermic peaks, the curves were not normalized to weight.

The thermograms show two distinct peaks, the lower representing the melting of G50/13, and the higher representing the melting of PEG 4000. These scans indicate that G50/13 and PEG 4000 do not form a single, homogenous phase; PEG 4000 remains as a discrete molecular entity. Therefore, the mixture can be viewed as a dispersion of one substance in the other. For PEG 4000 there was a shift in the peak maximum from 66 to 54°C. However, as the percentage of PEG 4000 increased, the melting point re-established itself closer to that of pure PEG 4000.

Figs 2 and 3 show the effect of increasing levels of PEG 4000 on the release of the marker dye and anhydrous theophylline from G50/13. A general overview shows that as the level of PEG 4000 increased, release from the matrix also increased, regardless of drug/marker dye used.

Table 1 shows the model coefficients (Kopcha et al 1990) for the release of the marker dye and anhydrous theophylline, from a stationary disc/rotating fluid system, as a function of PEG 4000 concentration. The release rate of marker dye was found to be less than that of anhydrous theophylline at any given level of PEG 4000. This is partly due to it having a molecular weight about twice that of anhydrous theophylline. Therefore, the marker dye would be expected to diffuse from the matrix more slowly than anhydrous theophylline. Also, as theophylline is partially soluble in the matrix, dissolution of the drug would not have to occur before diffusion from the matrix.

The trends are similar for anhydrous theophylline and the marker dye exhibiting a dual model of release at low levels of PEG 4000, and a diffusional process at higher levels. As the level of PEG 4000 increases within the swollen matrix, from which release occurs, the layer becomes less dense, thereby allowing drug to diffuse out easily. Thus, diffusion is enhanced and the model shifts to a diffusion-controlled process, with erosion making no significant contribution. Only when 100% PEG 4000 was used as the matrix did a complete switch to an erosional process occur.

The 100% PEG 4000 system was allowed to run for only 30 min as the material began to erode below the disc holder surface after that time thereby invalidating results.

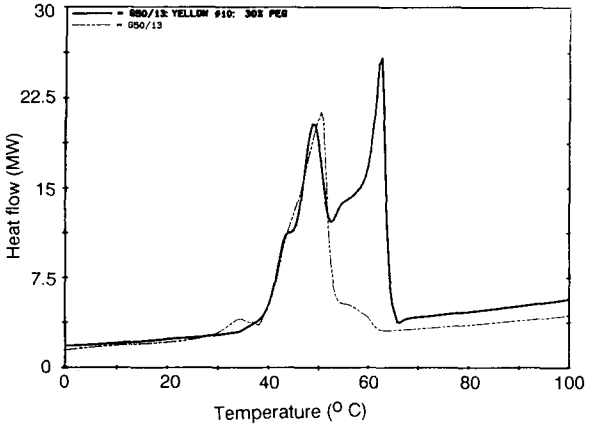

FIG. 1. Thermogram of G50/13 with a mixture of 2·5% D&C Yellow No. 10 and 30% PEG 4000.

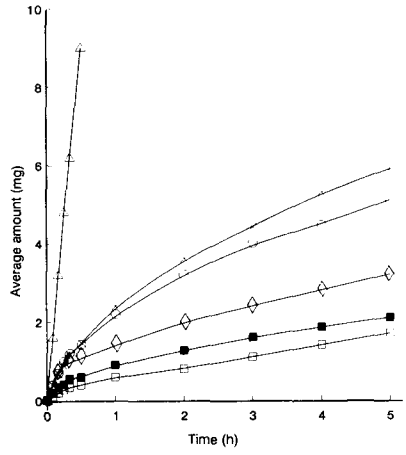

FIG. 2. Effect of increasing levels of PEG 4000 (0%, ■; 10%, □; 30%, ◇; 50%, ○; 75%, ×; 100%, △) on release of D&C Yellow No. 10 (2·5%) from G50/13.

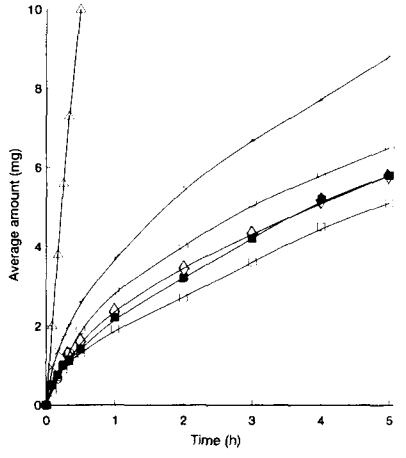

FIG. 3. Effect of increasing levels of PEG 4000 (0%, ■; 10%, □; 30%, ◇; 50%, ○; 75%, ×; 100%, △) on release of theophylline (2·5%) from G50/13.

Table 1. Model coefficients ± s.e. for Gelucire 50/13 with PEG 4000, D&C Yellow No. 10 (2·5%) or theophylline (2·5%) in simulated gastric fluid (pH 1·2) at 37°C. Paddle speed, 50 rev min^{-1}; paddle ht, 1 cm.

PEG 4000	A (mg $h^{-1/2}$)	B (mg h^{-1})	C (mg)	A/B ratio ($h^{1/2}$)
D&C Yellow No. 10				
0%	0·940 ±0·017	—	−0·034 ±0·022	—
10%	0·330 ±0·096	0·179 ±0·038	±0·073 ±0·046	1·84
30%	1·047 ±0·104	0·112 ±0·041	0·291 ±0·050	9·35
50%	2·379 ±0·016	—	−0·157 ±0·020	—
75%	2·826 ±0·020	—	−0·383 ±0·025	—
100%	—	18·19 ±0·369	0·143 ±0·112	0
Theophylline				
0%	1·616 ±0·135	0·416 ±0·053	0·019 ±0·065	3·89
10%	1·108 ±0·108	0·439 ±0·043	0·246 ±0·052	2·52
30%	1·974 ±0·065	0·201 ±0·026	0·113 ±0·031	9·82
50%	2·787 ±0·019	—	−0·022 ±0·024	—
75%	3·853 ±0·022	—	−0·283 ±0·028	—
100%	—	19·18 ±0·347	0·496 ±0·105	0

Release from the 10% PEG 4000 system, of the marker dye and anhydrous theophylline was less than release from 100% G50/13, although the difference was not significant ($P > 0·05$). Release of theophylline from 30% PEG 4000 was also similar ($P > 0·05$). This may be due to lack of significant enhancement of the diffusional or erosional characteristics to hasten the intrinsically high diffusional release of theophylline from the matrix.

Evaluation of mixtures of Gelucire excipients

Mixture effects. The DSC thermogram for a mixture of G50/02 and G50/13 showed a minor endotherm at about 30°C with a major one at approximately 49°C. The thermogram did not show any major shifts in the endotherms to indicate an interaction between the marker dye and the mixtures of G50/02 and G50/13. Theophylline, on the other hand, showed minor shifts in the endothermic peaks which reflected a minor solubility of anhydrous theophylline in G50/13.

Since the DSC scans for both G50/02 and G50/13 overlap, it was difficult to determine whether the two materials molecularly interacted or merely formed a dispersion. Upon microscopic examination, and after a 5 h experimental test with these mixtures, discrete spots were noted within the matrix. These spots became more prevalent as the material swelled; discrete spots appeared in the swollen layer as non-hydrated regions. This indicated that G50/02 was dispersed, as discrete packets, throughout the entire matrix.

Model coefficients for release of D&C Yellow No. 10 and theophylline from mixtures of Gelucires 50/13 and 50/02 are summarized in Table 2. It is apparent that a correlation exists between release and the level of G50/02 employed. As the level increased, the overall rate of release decreased and the mechanism became more pronounced as a diffusional process. For D&C Yellow No. 10, the profiles were all linear with the square-root of time indicating matrix diffusion. Also, as the percentage of G50/02 increased, the A term decreased which further confirmed this behaviour.

A corresponding trend was also noted for theophylline mixtures. As the level of G50/02 increased, release decreased and shifted to a diffusional process. Up to the 50% mixture, both erosion and diffusion occurred but the A/B ratio indicated that diffusion was the predominant process, increasing from 7 to 20 to 100% diffusion. Release was found to be comparable between the 27% G50/02 co-mixture and 100% G50/13 ($P > 0·05$).

The decrease in release as the level of G50/02 was increased may be because the larger amount of lipophilic drug/marker dye made it harder for drug to be released. At the same time, the mechanism of release was changed from a dual one, if such was the case, to a predominately diffusional process. Increased levels of G50/02 may have also increased the internal structuring of the matrix thereby decreasing its extent of swelling. This, in turn, would decrease the ease by which drug/marker dye could elute from the matrix.

Temperature effects. Temperature effects were explored by varying the temperature of the receptor fluid on co-mixtures of G50/02 and G50/13. The general trends were the same; as the percentage of G50/13 increased, release increased regardless of the temperature studied. This was expected, since

Table 2. Model coefficients ± s.e. for Gelucires 50/13 and 50/02 with theophylline (2·5%) or D&C Yellow No. 10 (2·5%) in simulated gastric fluid (pH 1·2) at 37°C. Paddle speed, 50 rev min^{-1}; paddle ht, 1 cm.

Percent G50/02: G50/13	A (mg $h^{-1/2}$)	B (mg h^{-1})	C (mg)	A/B ratio ($h^{1/2}$)
Theophylline				
0/100	5·847 ±0·439	0·804 ±0·174	0·571 ±0·211	7·27
27/73	7·076 ±0·494	0·985 ±0·196	0·165 ±0·238	7·18
50/50	6·511 ±0·311	0·319 ±0·123	0·092 ±0·150	20·41
73/27	6·276 ±0·068	—	0·047 ±0·087	—
100/0	2·674 ±0·095	—	0·081 ±0·121	—
D&C Yellow No. 10				
0/100	4·183 ±0·253	—	−0·892 ±0·323	—
27/73	2·728 ±0·047	—	0·445 ±0·060	—
50/50	2·412 ±0·112	—	−0·029 ±0·143	—
73/27	2·208 ±0·032	—	0·010 ±0·041	—
100/0	0·668 ±0·039	—	0·026 ±0·050	—

Table 3. Model coefficients ± s.e. for anhydrous theophylline and D&C Yellow No. 10 (2·5%) in simulated gastric fluid (pH 1·2) as a function of temperature. Paddle speed, 50 rev min^{-1}; paddle ht, 1 cm.

Percent G50/02: G50/13	30°C A ($mg\ h^{-1/2}$)	30°C B ($mg\ h^{-1}$)	30°C C (mg)	42°C A ($mg\ h^{-1/2}$)	42°C B ($mg\ h^{-1}$)	42°C C (mg)
Theophylline						
0/100	8·352 ±0·044	—	−0·643 ±0·056	11·51 ±0·088	—	−1·228 ±0·11
27/73	4·242 ±0·407	1·219 ±0·161	0·670 ±0·196	7·003 ±0·954	1·850 ±0·379	0·054 ±0·45
50/50	5·236 ±0·224	0·348 ±0·089	0·262 ±0·108	5·112 ±0·583	1·669 ±0·231	1·082 ±0·28
73/27	4·215 ±0·213	0·228 ±0·084	0·210 ±0·102	5·124 ±0·493	1·452 ±0·196	0·742 ±0·23
100/0	0·529 ±0·014	—	0·039 ±0·018	1·562 ±0·208	0·705 ±0·083	−0·249 ±0·10
D&C Yellow No. 10						
0/100	4·415 ±0·145	—	−0·565 ±0·185	2·268 ±0·348	0·900 ±0·138	0·115 ±0·170
27/73	1·705 ±0·023	—	0·327 ±0·030	3·199* ±0·074	—	0·211 ±0·060
50/50	1·487 ±0·017	—	0·278 ±0·022	3·104* ±0·272	—	−0·350 ±0·210
73/27	1·073 ±0·085	0·266 ±0·034	0·335 ±0·041	1·640 ±0·196	0·786 ±0·078	0·335 ±0·010
100/0	0·314 ±0·015	—	0·306 ±0·019	1·362 ±0·345	0·645 ±0·137	−0·223 ±0·170

*Calculated for the first 2 h. See text for explanation.

temperature was approaching the softening range of the mixtures. At about 30°C, the first softening peak of G50/02 and G50/13 is reached. At 37°C, the peak is overcome and the major melting endotherm is approached. Thus, the bases continued to soften and became less rigid, allowing water to penetrate and drug/marker dye to diffuse outward. At 42°C, the ascending part of the major melting endotherm is approached; further softening occurred and the rigidity of the matrix continued to decrease.

From Tables 2 and 3, it is apparent that the mechanism of release changes as temperature increases. At 30°C the release of anhydrous theophylline from G50/02 is diffusion controlled. At 37°C, the mechanism is still diffusional but the A coefficient has increased five-fold. At 42°C, which is close to the onset of melting of the matrix, the release mechanism has converted to a mixed one of both diffusion and erosion. This was expected for several reasons: (1) as temperature increases, the diffusion coefficient of theophylline would also increase, reflecting the dependency of diffusion on temperature; (2) as temperature increases, the matrix softens and poses a weaker resistance to drug diffusion; and (3) as temperature approaches the onset of melting, the matrix becomes more susceptible to erosion as an additive process for release.

For the 27% G50/02 co-mixture, with theophylline, as temperature was increased from 30 to 37°C, release became more diffusional; the A/B ratio increased. As temperature was further increased to 42°C, release became more dependant on erosion; the A/B ratio decreased. Similar trends were noted for the 50 and 73% G50/02 co-mixtures supporting the hypothesis that from 30 to 37°C it is the diffusional release mechanism which is enhanced. When temperature is increased to 42°C, the shift is to a combined model with the emphasis on erosion.

At 30°C, the release of theophylline from G50/13 was diffusional. Going from 30 to 37°C, the matrix softened and erosion became a minor component of release; the A/B ratio decreased. However, as temperature increased to 42°C, only diffusion was seen. This may be due to the absence of G50/02 from the matrix, which would have contributed to erosion of the matrix at this temperature. G50/02 does not swell but, as temperature increases, it does soften. Also, since it lacks the gelling ability of G50/13, it cannot maintain the integrity of the disc at elevated temperatures. As temperature increased, G50/13 remained pliable and retained disc integrity affording drug release by a diffusional process without a significant contribution from erosion.

The release of the marker dye as a function of temperature (Tables 2, 3), followed in an expected fashion. As the level of G50/13 increased, the amount of marker dye released also increased. Release from the 27, 50 and 73% G50/13 matrices was similar demonstrating that these levels of G50/13 are not sufficient to enhance overall release. Since D&C Yellow No. 10 is a charged molecule, it may have difficulty diffusing through a matrix which has become more lipophilic by addition of G50/02. It should be kept in mind, however, that as the level of G50/02 increased, release did decrease but not as dramatically as expected. Thus, release was predominately diffusional at both 30 and 37°C with an increase in rate as temperature was increased. Erosion only became significant when temperature was increased to 42°C. The effect of temperature was seen noticeably for the 27 and 50% G50/02-containing systems. Their profiles were best represented by an initial square-root of time relationship which became

Table 4. Model coefficients ± s.e. for theophylline (2·5%) and D&C Yellow No. 10 (2·5%) in simulated intestinal fluid (pH 8·11) as a function of G50/02 and G50/13 composition at 37°C. Paddle speed, 50 rev min^{-1}; paddle ht, 1 cm.

Percent G50/02: G50/13	Theophylline A ($mg\ h^{-1/2}$)	Theophylline B ($mg\ h^{-1}$)	Theophylline C (mg)	D&C Yellow No. 10 A ($mg\ h^{-1/2}$)	D&C Yellow No. 10 B ($mg\ h^{-1}$)	D&C Yellow No. 10 C (mg)
0/100	7·964 ±0·042	—	−0·167 ±0·054	1·605 ±0·356	0·991 ±0·141	0·498 ±0·17
27/73	5·568 ±0·230	0·705 ±0·091	0·361 ±0·111	2·115 ±0·280	0·045 ±0·111	0·386 ±0·14
50/50	4·846 ±0·284	1·040 ±0·113	0·653 ±0·137	1·922 ±0·150	0·231 ±0·060	0·301 ±0·07
73/27	4·794 ±0·119	0·393 ±0·047	−0·076 ±0·057	1·535 ±0·050	0·437 ±0·020	0·199 ±0·02
100/0	2·966 ±0·061	—	0·552 ±0·078	0·145 ±0·074	0·244 ±0·029	0·288 ±0·04

linear with time. This reflected a predominately erosional mechanism after 2 h. These observations support the hypothesis that G50/02 is the excipient which contributes mostly to matrix erosion.

pH effects. In simulated intestinal fluid (pH 8·11) release of theophylline and the marker dye correlates with increasing levels of G50/13 (Table 4).

For the theophylline-containing system, release from the 50 and 27% G50/02 preparations was similar. Similar behaviour was seen for the marker dye and theophylline-containing systems in simulated gastric fluid (pH 1·2). We suggest that two opposing factors prevent any noticeable change in release at these levels of G50/02. As the level of G50/02 increased, the extent of swelling of the hydrated layer decreased. This would be expected to enhance diffusion of the drug marker dye from the system because the diffusional pathlength decreased. However, as the level of G50/02 increased, the system became more lipophilic which thwarted drug/marker dye release by preventing water from easily permeating the matrix.

The following discussion will make comparisons between the various mixtures of G50/02 and G50/13 in both simulated gastric (Table 2) and intestinal fluid (Table 4) for the theophylline-containing systems. For the G50/02 system, the two curves were essentially the same ($P > 0.05$); release into either medium was diffusion-controlled.

For G50/13, although the two profiles were found to be coincidental over the test period, the mechanisms of release were not identical. In gastric fluid, a dual mechanism of erosion and diffusion was noted, whereas in the basic intestinal fluid only diffusion was seen. This may be due to a pH partitioning effect of theophylline into the basic medium; pH was close to the pK_a.

For the 73% G50/02 system, the profiles were found to be the same ($P > 0.05$). In the acidic media, a diffusional model was noted while in the basic solution, a mixed model was fitted. Erosion became more noticeable in the basic medium.

For 27% G50/02, A/B ratios of 7·90 and 7·18 were noted for the basic and acidic mediums, respectively, which are not statistically different ($P > 0.05$). Hence, erosion and diffusion are seen to effect release from this system.

For the 50% G50/02 mixture, even though overall release from this system was similar at both pH values, the mechanisms were different. The A/B ratio for the basic system was 4·66 while that for simulated gastric fluid was 20·41. Hence, the basic environment allowed for a more erosional process to occur while the acidic solution allowed for a more diffusional process to occur.

The release of the marker dye in simulated gastric fluid, is by diffusion, whereas in simulated intestinal fluid, release is by a dual mechanism; erosion appears to occur more noticeably in a basic environment, which may be attributed to the partial hydrolysis of the ester-linked matrices.

Predictive ability

To evaluate the predictive nature of the models described previously (Kopcha et al 1990), the diffusion coefficient for the drug/marker dye in G50/02 and apparent diffusion coefficient in G50/13 were determined as follows: for D&C Yellow No. 10 in G50/02, $2{\cdot}66 \times 10^{-7}$ and in G50/13, $8{\cdot}82 \times 10^{-6}$; and for theophylline in G50/02, $1{\cdot}98 \times 10^{-5}$ and in G50/13, $1{\cdot}72 \times 10^{-5}$.

For G50/02, the A term was evaluated for a rigid matrix as described by Paul & McSpadden (1976).

$$M = \frac{1+H}{(3H)^{1/2}}[C_s(Dt)]^{1/2} \quad (1)$$

where:

$$H = 5\frac{(W_o)}{C_s} - 4 + [\frac{(W_o)^2}{C_s} - 1]^{1/2} \quad (2)$$

M = amount of solute released per unit area, W_o = initial drug loading per unit volume, C_s = equilibrium drug solubility, D = drug diffusion coefficient, and t = time. This approximate analytical solution is valid for all W_0/C_s values.

Note that strict matrix diffusion was assumed. No hydrodynamic diffusion boundary layer was considered in this calculation, as a first approximation. Ignoring this effect, the results were still in agreement with published data. This reflects the hypothesis that the matrix, and not drug/marker dye dissolution, was the predominate resistance to drug release. Thus, the effect of a boundary layer can be considered insignificant (i.e. 10^{-3} cm).

The apparent diffusion coefficient for drug/marker dispersed in G50/13 was calculated from:

$$\frac{M}{t^{1/2}} = 2W_o\left(\frac{S}{V}\right)\frac{(D')^{1/2}}{\pi} \quad (3)$$

where S is the effective diffusional area, V is the effective volume of the hydrated matrix, D′ is the apparent diffusion coefficient of drug in the hydrated matrix which takes into account both tortuosity and porosity of the hydrated matrix, and the other terms are as defined previously.

Results were compared with those calculated by Harland et al (1988). The order of magnitude for these coefficients is in agreement with the published data. The calculated coefficients for G50/13 are somewhat larger than those seen with G50/02; the system is less lipophilic which allows drug to diffuse more easily through the matrix. Thus, it appears that the models used to quantitate release from these excipients are adequate and can realistically predict the processes associated with release.

References

Bowtle, W. (1986) The application of semi-solid capsule technology to antibiotic formulation. Boll. Chim. Farm. 125: 72–74

Dennis, A. B., Kellaway, I. W. (1987) Drug release from a slowly hydrating semi-solid matrix. J. Pharm. Pharmacol. 39 (Suppl.): 40P

Harland, R. S., Gazzaniga, A. M., Sangalli, M. E., Colombo, P., Peppas, H. A. (1988) Drug/polymer matrix swelling and dissolution. Pharm. Research 5: 488–494

Kopcha, M., Tojo, K. J., Lordi, N. G. (1990) Evaluation of methodology for assessing release characteristics of thermosoftening vehicles. J. Pharm. Pharmacol. 42: 745–751

Paul, D. R., McSpadden, S. K. (1976) Diffusional release of a solute from a polymer matrix. J. Membr. Sci. 1: 33–48

Thakkar, A. L., Gibson, L. L., Quay, J. F. (1987) Semi-solid matrix capsule in formulations of cephalexin: comparative bioavailability in the dog. J. Pharm. Sci. 76: S301