DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 13(6), 1031-1045 (1987)

DRUG RELEASE FROM THERMOSETTING FATTY VEHICLES FILLED INTO HARD GELATIN CAPSULES

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ABSTRACT

An initial in vitro study has been conducted to evaluate liquid filled hard gelatin capsules as potential sustained release products. Using the model compounds salicylic acid (a weak acid) and tioconazole (a weak base), release characteristics from a series of thermosetting fatty vehicles (Gelucires) have been investigated. Rapid and sustained release profiles were obtained by using different vehicles. Drug release obeyed the pH-partition theory, and a general relationship between the release rate of salicylic acid and vehicle HLB was found. However, a similar relationship could not be identified for the release of tioconazole. Drug release occurred by diffusion or erosion and diffusion processes, dependent on the vehicle employed. Diffusion release occurred relatively slowly (particularly with tioconazole)

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therefore for the model systems an erodible carrier would be required to achieve release rates consistent with dosing oral sustained release products.

INTRODUCTION

Recent developments in formulation and manufacturing technology have stimulated interest in liquid filled hard gelatin capsules [1-5]. A number of advantages are advanced (in favour of liquid filled hard gelatin capsules) compared to conventional capsules and include the control of dust, improved dose uniformity of high potency drugs, easier formulation of oily drugs, improved drug stability and the preparation of oral sustained release formulations [1,3]. However, few reports exist in the literature on potential sustained release systems. Therefore as an initial study to assess the feasibility of sustained release systems, drug release from a series of thermosetting fatty vehicles with controlled melting and hydrophobic/lipophilic characteristics (Gelucires, Gattefosse, France) has been investigated. A weak acid (salicylic acid; pKa = 3.00 [6]) and a weak base (tioconazole; pKa = 6.42 [7]) were employed as model compounds.

MATERIALS

Samples of Gelucires 44/14, 46/07, 48/09, 50/02, 53/10 and 62/05 were a gift from Alfa Chemicals Ltd., Wokingham, UK. The first two digits of the suffix is the nominal melting point (deg.C) and the last two digits assign the HLB (hydrophobic-lipophilic balance).

Salicylic acid, Analar grade (BDH, Dagenham, UK) and tioconazole, pharmaceutical grade (Pfizer, Sandwich, UK) were used as received.

All other chemicals were of analytical quality. Filtered distilled water of injection quality was employed in the preparation of dissolution media.

METHODS

Capsule Preparation

The bases were weighed into a glass beaker and slowly heated to 5-10 deg.C above the melting point on a hot plate and drug was added to the molten vehicle with continuous stirring. Following dissolution of the drug in the molten base, size 0 clear hard gelatin capsules were filled by weight to 400 ± 5mg using a preheated glass Pasteur pipette. Capsules were kept upright until the fill solidified, and stored at room temperature prior to testing. Capsules containing 9.1% w/w salicylic acid or 2.5% w/w tioconazole were prepared; these values were chosen so that sink conditions would be maintained in the dissolution test.

Dissolution Testing

Drug release from the capsules was assessed 24 hours post-manufacture using an adapted USP dissolution method. Capsules were placed in 40 mesh baskets and rotated at 100rpm in 900ml of either simulated gastric fluid (SGF) pH 1.2 or simulated intestinal fluid (SIF) pH 7.5 at 37 deg.C. Drug concentration in solution was determined by UV analysis (salicylic acid 296.1nm, tioconazole 245nm) using a continuously sampling automated dissolution system over a period of 5 hours. This comprised a dissolution bath (G.B. Caleva model 6ST, Ascot, UK); peristaltic pump (Watson Marlow model S01, Falmouth, UK); spectrophotometer with six cell changer (Uvikon 810, Kontron Instruments, St. Albans, UK) which was controlled by a Commodore 4032 PET computer with data capture and print facilities.

All dissolution studies were performed in duplicate.

Melting Point Determination

Melting points and the physical state (solid solution or dispersion) of the formulations were determined by hot stage microscopy.

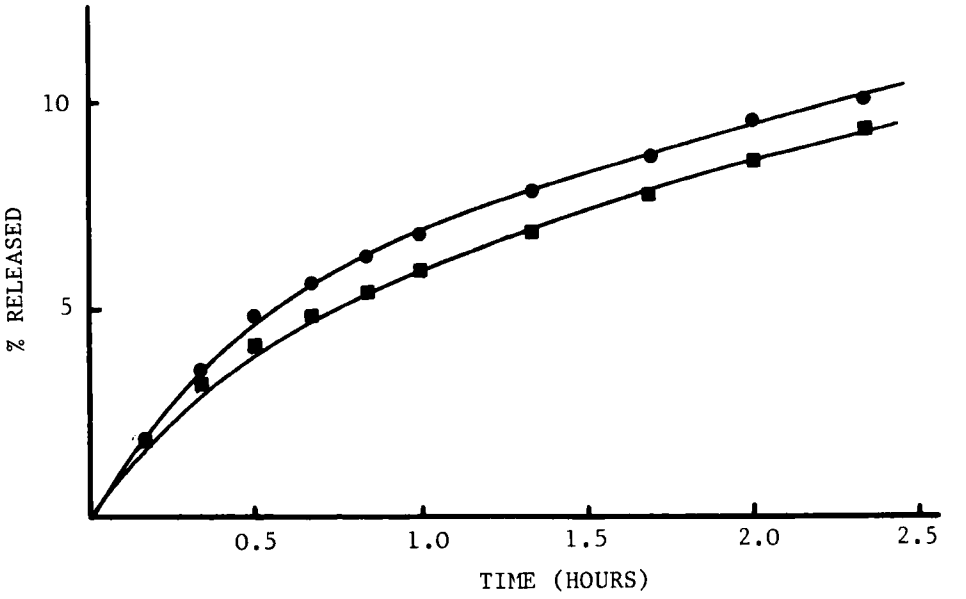

FIGURE 1

Salicylic acid release from Gelucire 50/02

(■) Batch A

(●) Batch B

RESULTS AND DISCUSSION

Assessment of the Reproducibility of Capsule Manufacture

Duplicate capsule batches (A and B) of Gelucires (G) 48/09 and 50/02 containing salicylic acid were prepared and the dissolution profile determined in SGF.

Figure 1 shows the salicylic acid release profiles from G50/02. A plot of drug release as a function of the square root time was found to be linear (Figure 2), which allowed the derivation of an apparent release rate. The results for release from G48/09 and G50/02 are shown in Table 1.

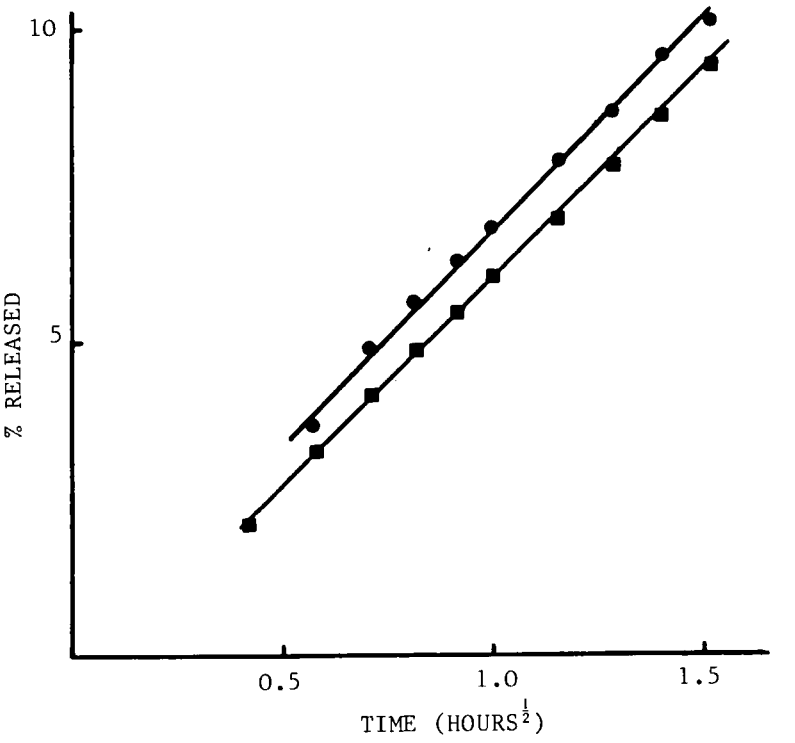

FIGURE 2

Salicylic acid release from Gelucire 50/02 as a function of the square root of time

(■) Batch A

(●) Batch B

In the following presentation drug release root time plots were employed in the analysis of release profiles; linear regression coefficients >0.99 were observed unless otherwise indicated.

Salicylic Acid Release From Gelucire Vehicles

The melting points and physical state of the salicylic acid/Gelucire compositions are shown in Table 2.

TABLE I

Salicylic Acid Release From G48/09 and G50/02 Reproducibility of Capsule Manufacture

Gelucire Vehicle	Batch	Release Rate (% hr-1/2) (Standard Error) SGF
48/09	A	13.8 (0.27)
	B	13.4 (0.74)
50/02	A	6.6 (0.10)
	B	7.0 (0.28)

Satisfactory agreement was observed between the drug release rates from batches A and B for both vehicles, validating the reproducibility of the method of manufacture.

TABLE 2

Salicylic Acid/Gelucire Formulations, Melting Points, Physical State and Drug Release Rates

Gelucire Vehicle	Melting Point Range deg.C	Physical State	Release Rate (% hr-1/2) SGF	SIF
44/14	36.5 - 37.8	SS	100% release in 20 minutes	
46/07	43.3 - 47.2	SS	7.2 (>24)	16 (10)
48/09	44.5 - 47.2	SS	13 (15)	19 (7)
50/02	45.3 - 48.4	SD	7.0 (>24)	9.1 (>24)
53/10	50.5 - 51.0	SS	19 (7)	23 (5)
62/05	61.9 - 63.9	SD	3.5 (>24)	6.7 (>24)

* SS = Solid solution SD = Solid dispersion
Calculated t50% values ( ) hours

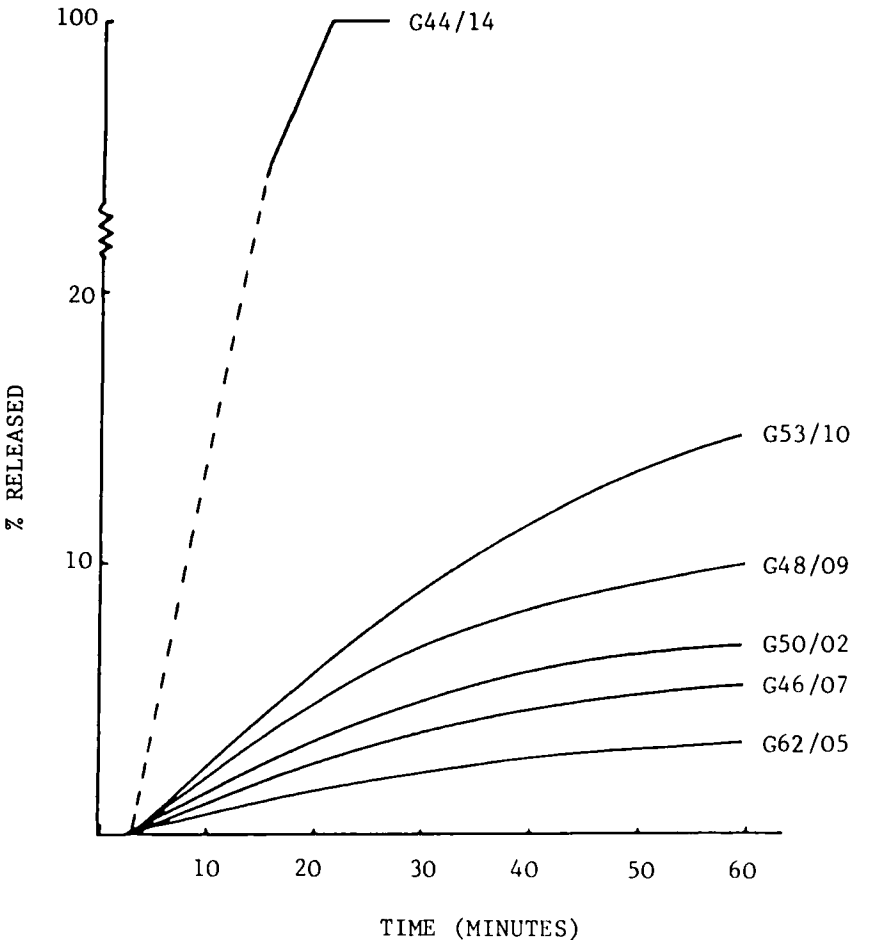

FIGURE 3

Salicylic acid release from different Gelucire vehicles into SGF

The formulations exhibited relatively broad melting point ranges which were generally a few degrees below the nominal vehicle melting points. Solid solutions were formed in all the bases except G50/02 and G62/05. Crystalline material was observed in melting the latter compositions. The drug subsequently dissolved on raising the temperature above the vehicle melting point.

Figure 3 illustrates drug release profiles over the first hour into SGF. A similar pattern of profiles were observed on

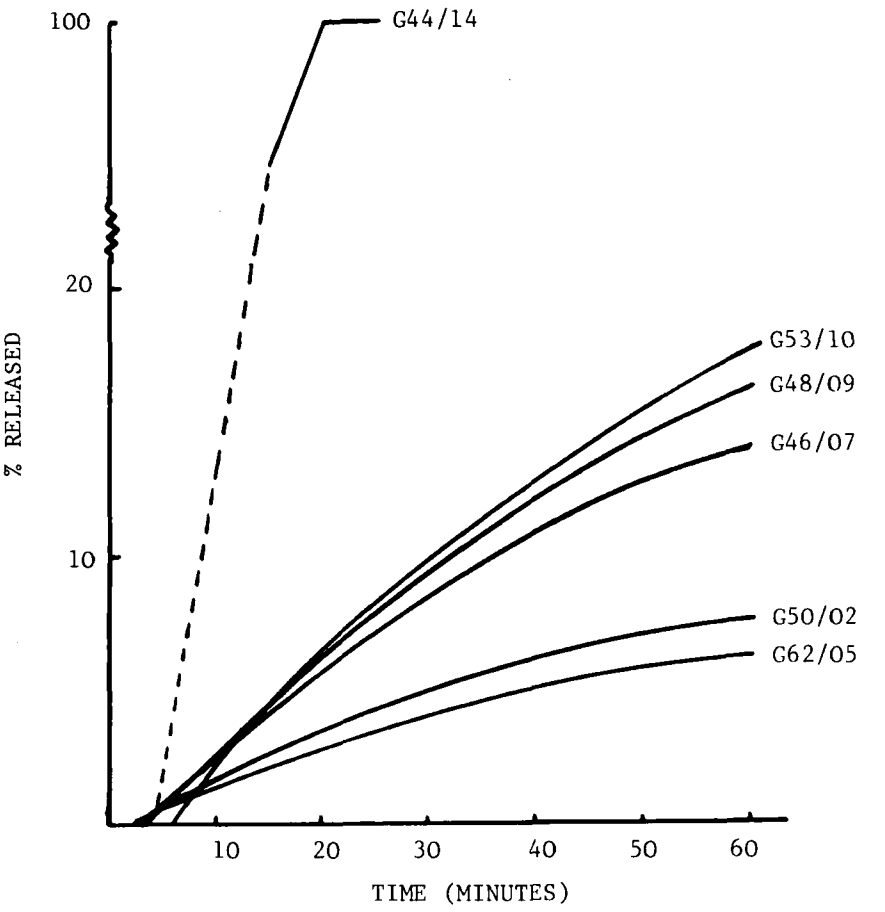

FIGURE 4

Salicylic acid release from different Gelucire vehicles into SIF

dissolution into SIF (Figure 4) the calculated release rates are given below. Typical release/root time plots are shown in Figure 5.

A 2 to 3 minute lag time was observed between the immersion of the capsules and the appearance of drug in the receptor phase. This represents the time taken for the capsule shell itself to dissolve, before exposing the inner core.

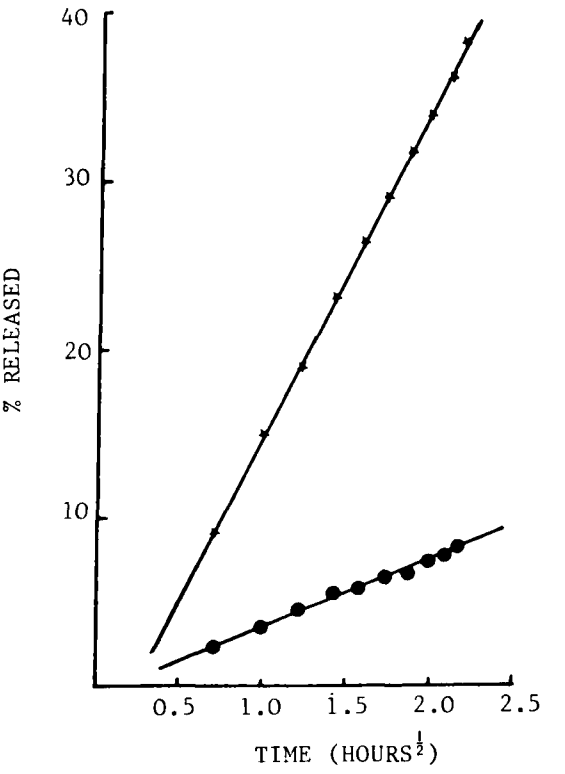

FIGURE 5

Typical drug release vs. root time plots

(✦) Salicylic acid release into SGF from Gelucire 53/10
(●) Salicylic acid release into SGF from Gelucire 62/05

Drug release occurred significantly faster from G44/14 than from the other vehicles, and occurred because of the low melting point and ability of G44/14 to rapidly disperse and dissolve in aqueous dissolution media. As might be expected, root time kinetics did not apply to drug release from this base.

In the other formulations, where the vehicle remained as a complete, hydrated or partially eroded solid 'core' in the

dissolution media, slower drug release occurred. Release from G53/10, which hydrates and partially erodes in SGF and SIF, occurred at a faster rate than the other systems which showed diffusion rate controlled release with no significant erosion. Therefore, to achieve a release profile intermediate between that of G44/14 and G53/10 it is likely that a vehicle which releases drug in part by an erosion process would be necessary.

A hydrated sheath appeared to form around the G48/09 core which probably promoted drug release. The G46/07 composition softened on contact with both dissolution media. The G50/02 and G62/05 formulations did not undergo visual changes in either dissolution media. Drug release from non-eroding systems was generally found to be quite slow. Therefore, for this model system these vehicles would be of limited use for oral sustained release drug delivery due to the extended t50% values (Table 2).

The calculated drug release rates from G46/07 and G50/02 into SGF are similar. However drug was initially released faster from G50/02 (Figure 3), which may reflect an initial difference in the surface availability of drug. This observation was not repeated on dissolution into SIF (Figure 4) where release from G46/07 was significantly faster than from G50/02. However, G46/07 appeared to undergo greater softening in SIF than SGF which may account for the rapidity of release.

More rapid drug release occurred into SIF than into SGF. This can be explained on the basis of the pH-partition theory as salicylic acid, (pKa of 3.00[6]) would be expected to distribute preferentially into SIF (pH 7.5) compared to SGF (pH 1.2). Generally, as the HLB of the vehicle decreases (increasing lipophilicity), drug release decreased in both dissolution media. A relationship between log drug release into SGF and vehicle HLB was observed and a similar trend was observed into SIF (Figure 6), with the exception of release from G50/02. Drug release from G50/02 occurred significantly faster than would be expected from

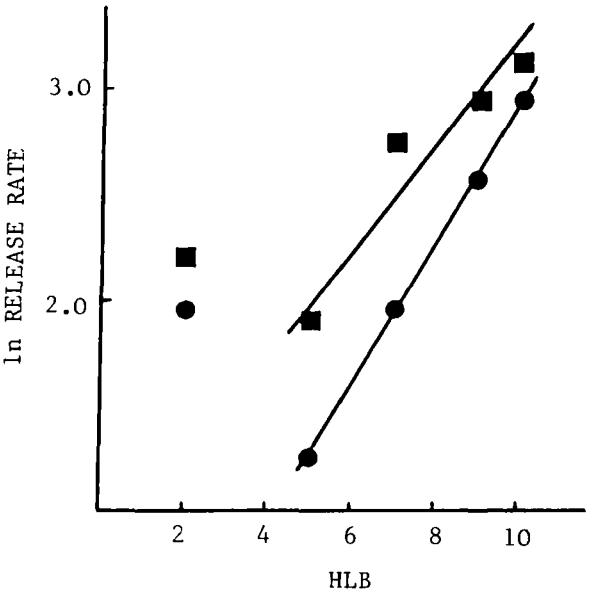

FIGURE 6

The relationship between salicylic acid release rate and Gelucire HLB value, showing the anomalous behaviour of Gelucire 50/02

(■) Release into SIF

(●) Release into SGF

vehicle HLB, which suggests that factors other than partition may influence drug release from gelucire vehicles. In particular the effects of the drug or dissolution media on the vehicle may be significant. Indeed drug release from G46/07 into SIF was faster than expectd from vehicle HLB, and probably results from the vehicle softening which occurred in SIF.

To further examine the potentially predictive relationship between vehicle HLB and release rates, salicylic acid release rates into SGF from mixed G48/09 and G62/05 vehicles were evaluated. The results are given in Table 3.

TABLE 3

Salicylic Acid Release From G48/09-G62/05 Binary Systems

% Gelucire 48/09	% Gelucire 62/05	Vehicle HLB	Release Rate (% hr-1/2)	Predicted Release Rate (% hr-1/2)
80	20	8.2	10	10
50	50	7.0	5.9	6.9
20	80	5.8	4.1	4.6

Salicylic acid formed solid solutions in the binary vehicles. Vehicle HLB values were calculated as a linear function of vehicle composition and predicted release rates were calculated from the linear relationship between vehicle HLB and log release rates for mono-component vehicles.

The observed release rates shown in Table 3 are in broad agreement with the predicted values. The data is presented graphically in Figure 7, which confirms the log linear relationship between release rates and vehicle HLB.

Therefore, for this system the relationship between vehicle HLB and drug release would allow prediction of drug release profiles. The use of mixed vehicle systems appears to be of particular utility as vehicles with a wide range of vehicles HLB's can be prepared.

Tioconazole Release From Gelucire Vehicles

Tioconazole formed solid solutions in the Gelucire vehicles under study. The melting points of the compositions were broad and in general higher than those observed with salicylic acid (Table 4). This may simply be a reflection of the difference in the drug loading.

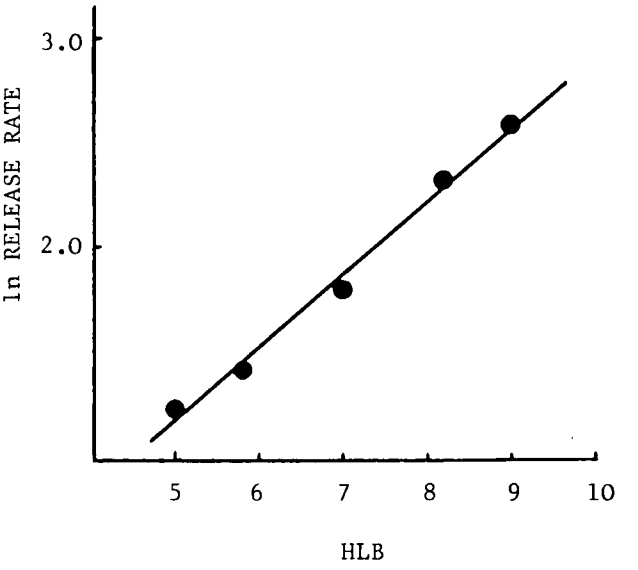

FIGURE 7

The relationship between salicylic acid release and vehicle HLB value, for G48/09-G62/05 binary systems

TABLE 4

Tioconazole/Gelucire Formulations, Melting Points and Drug Release Rates

Gelucire Vehicle	Melting Point Range deg.C	Release Rate % hr-1/2 SGF	SIF
44/14	41.5 - 43.2	100% release in 25 minutes	
46/07	44.9 - 46.5	11 (21)	2.8* (>24)
48/09	47.4 - 48.6	12 (17)	9.7 (>24)
50/02	46.1 - 48.1	10 (>24)	2.5* (>24)
53/10	50.1 - 51.7	16 (10)	4.8* (>24)
62/05	60.1 - 63.5	11 (21)	2.5* (>24)

* Linear regression coefficient >0.95
Calculated t50% values ( ) hours

Tioconazole, similarly to salicylic acid, was released rapidly from the G44/14 vehicle (Table 4). However, unlike salicylic acid, tioconazole release rates do not appear to be a simple function of vehicle HLB. The long t50% values (Table 4), even with eroding vehicles (G53/10) suggests that for a lipophilic drug such as tioconazole a rapidly eroding vehicle would be required to enhance release to levels suitable for oral sustained release dosing. Interestingly, tioconazole was released at similar rates (10-12% hr-1/2) into SGF from G46/07, 48/09, 50/02 and 62/05 vehicles. Tioconazole (log P 4.5[9]) is considerably more hydrophobic than salicylic acid (log P ~2[7]), suggesting that the hydrophobic nature of tioconazole rather than vehicle HLB dominates drug release. Factors such as drug solvation phenomena at the interface may also be important. As expected from pH-partition considerations tioconazole (pKa 6.42[7]) was released more quickly into SGF (pH 1.2) than SIF (pH 7.5). However, the rate of release into SIF from the various vehicles assumed a different rank order compared to release into SGF, although it should be noted that at the slowest release rates the limit of detector sensitivity is approached.

CONCLUSIONS

The data shows that in vitro it is possible to demonstrate sustained release drug dissolution profiles using thermosetting fatty vehicles filled as liquids into hard gelatin capsules. Moreover, a predictive relationship between vehicle HLB and salicylic acid release rates was defined. However, the relationship was found to be drug dependent, and some vehicles exhibited anomalous drug release properties. The model drugs were released by diffusion or an erosion and diffusion process. However, release from diffusion controlled non-eroding systems was relatively slow, long t50% values being apparent. The data suggests that for these model systems it would be necessary to adopt vehicles which release drug in part by an erosion process to achieve appropriate drug release for sustained release oral drug delivery. This could ultimately prove problematical in vivo as the

performance of an erodible device may be dependent on the contents and action of the gut. In addition drug release was found to be pH-dependent and ideally this should be overcome in order to produce a robust oral sustained release dosage form.

In conclusion it is evident that sustained release formulations can be prepared, although a number of potential problems have been identified. Further drugs need to be evaluated in these systems and factors such as drug loading and dosage form stability remain to be investigated. Ultimately, in vivo studies would be required to qualify the in vitro findings.

ACKNOWLEDGEMENTS

Our thanks are due to Miss S. Craker for her technical assistance and to Mrs. K. Mills for typing the manuscript.

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