Release of Chlorpheniramine Maleate from Fatty Acid Ester Matrix Disks Prepared by Melt-extrusion

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Abstract—Chlorpheniramine maleate was incorporated into disks consisting of glyceryl fatty acid esters, polyethylene glycol fatty acid esters or a combination of the two. A melt-extrusion process was used to prepare the matrix disks containing the drug. The release of the drug into distilled water, pH 1·2 buffer, and pH 7·5 buffer showed the expected square root of time dependence. An increase in the fatty acid ester hydrophilic-lipophilic balance (HLB) from 1 to 14 resulted in a 10-fold increase in the drug release rate from 0.25 ± 0.01 to 25.84 ± 1.29 mg cm^{-2} h$^{-\frac{1}{2}}$. The maximum release rate was seen from the fatty acid ester with a melting point of 44°C. The pH of the dissolution medium had a small impact on the rate of drug release, but the rate of agitation had no significant influence on the rate of drug release. By blending a fatty acid ester of a high melting point (64°C) and a low HLB value of 2 with esters of lower melting points (33 to 50°C) or higher HLB values (10 to 14), it was possible to modify the release from 10.0 ± 0.70 to 21.5 ± 0.57 mg cm^{-2} h$^{-\frac{1}{2}}$.

There are several ways by which drug release from an oral solid dosage form can be controlled to provide sustained drug release. The matrix design, in which the drug is dispersed throughout a restraining matrix, provides a simple and cost-effective method for manufacturing drug delivery systems. Traditional compression methods often involve solvent granulation of the drug with the matrix material (Onay-Basaran & Olsen 1985; Parab et al 1987). Manufacture using melt-dispersion technology offers the same advantages of simplicity and cost-efficiency, but eliminates the safety concerns associated with the use of organic solvents (Flanders et al 1987).

Melt-dispersion technology has been successfully adapted to microencapsulation techniques to prepare sustained release microspheres (Benita et al 1986; Janicki & Jedras 1987) and matrix tablets (McTaggart et al 1984). The matrix tablets were prepared by compression of either a physical mixture of the drug and the wax material (Parab et al 1986) or a granulation of the drug in the wax material prepared by melt-granulation (Ahmed & Enever 1981).

The release of drug from matrix systems has been extensively studied (Goodhart et al 1974; Fessi et al 1982; Gurny et al 1982; Droin et al 1985). The mechanism depends on the drug loading in the system (Baker 1987). At loadings below its solubility in the vehicle, the drug is dissolved in the matrix material and diffuses to the interface where it partitions into the surrounding medium. In these simple cases the release can be adequately described by the Higuchi model (1961). By applying Fick's law of diffusion to matrix systems that contain drug particles suspended in an insoluble vehicle at low loadings, Higuchi (1961) showed that the release of the drug was linearly related to the square root of time.

At higher loading levels the release mechanism becomes more complicated. Dissolution of the solid drug particles leaves behind pores within the matrix structure. At a

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sufficiently high porosity these pores could form a continuous pore structure allowing the drug an easier route of release. Therefore the release process is diffusion through channels filled with the dissolution medium. Even though the rate of release is still linear with the square root of time, the predicted rates are lower than the determined rates. This can be ascribed to the increased matrix permeability due to the formation of continuous channels. A modification of the original Higuchi equation incorporates a porosity and tortuosity factor to account for the diffusion through pores (Higuchi 1963).

Gelucires are thermosetting fatty acid esters, which are synthesized with specific melting points and HLB values. Since the different Gelucires have different characteristics, a formulator may choose a Gelucire or a combination of Gelucires which will most closely produce a desired release profile (Howard & Gould 1987; Magron et al 1987; Laghoueg et al 1989).

The purpose of this study was to determine if melt-extrusion is a viable method for preparing matrix tablets for sustained release.

Materials and Methods

Gelucires and drugs
The following materials were used as received: Gelucire 33/01, 35/10, 44/14, 50/13, and 64/02 (Gattefosse, France); chlorpheniramine maleate (Sigma Chemical Co). The first number in the Gelucire suffix refers to the melting point of the Gelucire and the second number in the suffix refers to the hydrophile-lipophile balance (HLB) value of the Gelucire. The characteristics of these esters are listed in Table 1.

Determination of Gelucire properties
The Gelucire melting points were determined in triplicate using a Fisher-Johns melting point apparatus. The swelling of the Gelucires in distilled water was determined by volume (n = 3). Approximately 2 g of each ester was placed in a 10 mL graduated cylinder, melted and allowed to congeal. The

Table 1. Properties of the Gelucires used (from the manufacturer's data sheets).

Gelucire	33/01	35/10	44/14	50/13	64/02
Melting point (°C)	31.7 ± 0.58	34.3 ± 0.58	40.7 ± 0.58	46.7 ± 0.58	65.8 ± 0.84
HLB[a]	1	10	14	13	2
Acid value[b]	<2	<2	<2	<2	<2
Hydroxyl value[c]	<10	<110	<70	<60	<120
Saponification value[d]	240–260	120–140	70–105	65–85	170–190
Expanded volume (mL g^{-1})	–	0.14 ± 0.02	0.25 ± 0.02	0.27 ± 0.03	–
Expansion (% g^{-1})	–	6.02 ± 1.26	11.14 ± 0.94	13.13 ± 1.64	–
Release rate (mg cm^{-2} h$^{-\frac{1}{2}}$) constant	0.20 ± 0.02	6.12 ± 1.90	41.54 ± 3.36	4.83 ± 0.40	0.70 ± 0.27

[a] Hydrophile-lipophile balance. [b] mg of KOH required to neutralize the free acids in 1 g of Gelucire. [c] mg of KOH required to neutralize the acetic acid which combines on acetylation of 1 g of Gelucire. [d] mg of KOH required to saponify 1 g of Gelucire.

volume occupied by the congealed Gelucire was measured after 24 h. Five mL of distilled water was placed on top of the Gelucire and the system was maintained at $37 \pm 0.5°C$. The volume of the Gelucire was measured again after 24 h. The increase in volume was normalized for the weight of Gelucire used. The percent increases in volume are shown in Table 1.

Effect of Gelucire properties

To study the release of chlorpheniramine maleate from individual Gelucires while minimizing the effects due to disintegration, copper cups with a single exposed surface (7.92 ± 0.08 cm^2) were used. Each Gelucire was melted in six cups, each containing a magnetic microbar, at the required temperatures (33–64°C). Chlorpheniramine maleate (10%) was dispersed in the melt in five cups, leaving one cup as a control. The dispersion was rapidly cooled with continuous agitation.

Melt extrusion

A disk mould (16.2×0.21 mm) was used for the melt-extrusion. The required amount of Gelucire(s) was placed in the melt-extruder cup and equilibrated at 69°C. After 10 min, the chlorpheniramine maleate (45 or 65%) was added, mixed for one min, and extruded into the disk mould. When the mould had cooled, the Gelucire disk containing the dispersed drug was removed and inspected for any apparent defects.

Drug release studies

Drug release studies were conducted at 37°C with stirring rates of 50 and 100 rev min^{-1} using distilled water, an HCl/NaCl buffer (pH 1.2), and a NaOH/KHP$_2$O$_4$ buffer (pH 7.5) as media. The cups were placed at the bottom of the dissolution vessel. A coarse wire screen (3 mm opening) was used to prevent the Gelucire disks from rising to the surface during dissolution. Samples (3 mL) were removed at specified times and the drug content was determined by spectroscopy (260 nm). After 8 h the disks were thoroughly crushed and exposed to the dissolution medium for 16 h to obtain the drug contents. A blank Gelucire cup or disk was used as a control. The absorbance of the Gelucire was negligible compared with that of the drug.

Statistical analysis

The influence of drug content, dissolution medium pH and stirring rate (rev min^{-1}) on drug release was analysed using one-way analysis of variance. The effects of Gelucire blends

on drug release from, and drug content of, the disks were analysed by a one-way analysis of variance using Tukey's multiple range criterion ($P = 0.05$).

Results and Discussion

Release mechanism

The release of chlorpheniramine maleate was analysed by zero-order, first-order and square root of time (Higuchi) models. The zero-order and the first-order plots were non-linear. The square root of time plots were linear with correlation coefficients ranging from 0.966 to 0.999.

The dependence of the chlorpheniramine maleate release from the matrix systems on the square root of time suggests that the release of the drug is controlled by diffusion through the Gelucire. Higuchi (1963) proposed two equations to describe the release of drugs from matrices. If the release of drug is by dissolution in the matrix material followed by diffusion to the interface with the surrounding fluid, then the release could be described by the following equation:

$$Q = [D(2A - C_s)C_s t]^{\frac{1}{2}} \tag{1}$$

However, if the diffusion is not through the matrix material, but through water-filled channels, the equation was modified by incorporating a porosity term and a tortuosity term:

$$Q = \left[\frac{D\varepsilon}{\tau} (2A - \varepsilon C_s) C_s t \right]^{\frac{1}{2}} \tag{2}$$

In equations 1 and 2, Q is the amount of drug released per unit exposed surface area, D is the diffusion coefficient, τ is the porosity of the matrix, ε is the tortuosity of the matrix, A is the initial drug concentration, C_s is the drug solubility, and t is the time. These equations could be simplified to:

$$Q = K t^{\frac{1}{2}} \tag{3}$$

The release rate constant, K, is calculated from the slope.

Effect of Gelucire properties

The copper cups used during the initial drug release studies prevented the drug-dispersions from disintegrating, and, thereby minimized possible surface area changes due to disintegration. Therefore the Gelucire HLB and melting point were the dominant factors in determining the rate at which chlorpheniramine maleate was released from the drug-dispersions. The release of chlorpheniramine maleate was linear with the square root of time. After release of

Table 2. Formulation compositions (%).

Formulation number	Theoretical drug content	Actual drug content	Gelucires content				
			64/02	50/13	44/14	35/10	33/01
1	65	65 ± 2·56	35				
2	45	44 ± 5·01	55				
3	45	45 ± 4·32	45	10			
4	45	47 ± 3·88	45		10		
5	45	45 ± 3·83	45			10	
6	45	46 ± 2·30	45				10
7	45	45 ± 2·23	50	5			
8	45	47 ± 2·38	52·5	2·5			
9	45	45 ± 3·76	50		5		
10	45	43 ± 1·98	52·5		2·5		

approximately 90% of the drug content, the drug release showed a negative deviation from the predicted behaviour.

An analysis of variance on the release rates of chlorpheniramine from the Gelucires revealed that the rates could be separated into three distinct categories based on Tukey's multiple range criterion ($W = 3·80$). The three categories can be rank ordered in terms of increasing release rates as follows: $33/01 = 64/02 < 35/10 = 50/13 < 44/14$ (see Table 1). As expected, Gelucires with higher HLB values released chlorpheniramine maleate significantly faster compared with Gelucires with lower HLB values. Gelucires with higher HLB values are more hydrophilic and may have a higher affinity for water. Because of this potential increased affinity, water may penetrate matrices prepared with Gelucires of higher HLB values more easily. This may lead to a faster release of chlorpheniramine maleate from such matrices.

The influence of the Gelucire melting point on drug release was less obvious. Maximum drug release was obtained with Gelucire 44/14. Slower release was observed from Gelucires with melting points above and below this maximum. Since the release studies were run at 37°C, Gelucires 33/01 and 35/10 existed in the melted state. One effect melting of the Gelucires could have, is to cause collapse of the pores created by dissolution of the dispersed drug particles. This would reduce the porosity of the matrix system and may prevent an increase in the matrix permeability. The effect of melting on the release of drug seems to be negligible, since the release from 64/02 and 33/01 or 50/13 and 35/10 are not significantly different.

It therefore appears that the HLB of the Gelucire is more important than the melting point in determining the rate of chlorpheniramine maleate release from these matrices.

Table 1 lists the extent of swelling of the different Gelucires. Gelucires 33/01 and 64/02 showed no significant swelling in 24 h. The rest of the Gelucires can be ranked in terms of increasing swelling as follows: $35/10 < 44/14 = 50/13$. The expansion seen with Gelucire 50/13 was approximately twice that seen with Gelucire 35/10. However, their release rates were not significantly different. The increase in volume for Gelucires 44/14 and 50/13 were similar, but the release rate from Gelucire 44/14 was approximately 10 times larger than that from Gelucire 50/13. The increase in volume did not seem to influence the release of chlorpheniramine maleate. This apparent paradox may be due to the limited expansion of the Gelucires.

Effect of drug loading

The formulations studied are listed in Table 2. All the formulations comprise Gelucire 64/02 alone or in combination with a second Gelucire and chlorpheniramine maleate. Except for the drug content of formulation 1, the actual drug contents for all the other formulations were not significantly different.

The effect of drug loading on the release of chlorpheniramine maleate is depicted in Fig. 1. The initial drug release was not linear with the square root of time. Therefore, the release rates were calculated from the terminal linear segment by least squares regression. Incorporation of larger quantities of drug into the matrix resulted in a significantly faster drug release rate (see Table 3). The x intercept was taken as the lag time (t_{lag}) required to establish a quasi-stationary state (Higuchi 1961). The increased drug loading had no significant effect on the time required to attain steady state for release ($P = 0·410$). However, this method of modifying drug release had a limitation. Drug loading in excess of 65% was not feasible due to the increase in viscosity of the melted Gelucire-drug dispersion, which prevented extrusion of the mass. Even at 65% drug loading only 64% of the drug was released in 8 h from Gelucire 64/02. To increase the rate of drug release further and to enhance the ease of manufacture of the disks, Gelucire blends were substituted for Gelucire 64/02.

Effect of Gelucire blends

Each of the Gelucires was blended with Gelucire 64/02 (1:9, w/w) (Fig. 2). The melting points of the 10% Gelucire blends
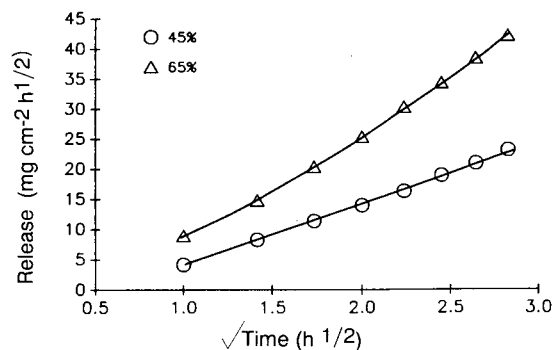

Fig. 1. Effect of drug loading on the rate of drug release from Gelucire 64/02 disks (formulations 1 △ and 2 ○).

Table 3. The influence of several variables on the release of chlorpheniramine maleate from Gelucire disks.

| Variable	Formulation number	Dissolution rev min^{-1}	Dissolution medium	K (mg cm^{-2} h$^{-\frac{1}{2}}$)	t_{lag} (h)	r^2
Drug content	1	100	DW[a]	18·44 ± 1·40	0·58 ± 0·08	0·996
	2	100	DW	10·32 ± 1·64	0·63 ± 0·10	0·994
Gelucire blend	3	100	DW	28·13 ± 2·01	0·57 ± 0·08	0·990
	4	100	DW	27·79 ± 1·80	0·77 ± 0·05	0·983
	5	100	DW	19·33 ± 1·88	0·39 ± 0·06	0·996
	6	100	DW	13·64 ± 3·48	0·88 ± 0·08	0·983
50/13 content	2	100	DW	10·32 ± 1·64	0·63 ± 0·10	0·994
	3	100	DW	28·13 ± 2·01	0·57 ± 0·08	0·990
	7	100	DW	24·84 ± 2·11	0·60 ± 0·02	0·989
	8	100	DW	15·65 ± 1·14	0·49 ± 0·02	0·991
44/14 content	2	100	DW	10·32 ± 1·64	0·63 ± 0·10	0·994
	4	100	DW	27·79 ± 1·80	0·77 ± 0·05	0·983
	9	100	DW	18·74 ± 2·10	0·73 ± 0·12	0·968
	10	100	DW	10·38 ± 0·61	0·47 ± 0·05	0·995
Effect of pH	4	100	pH 1·2	30·03 ± 1·36	0·44 ± 0·12	0·981
	4	100	pH 7·5	24·18 ± 1·93	0·68 ± 0·09	0·988
Effect of agitation	4	50	DW	27·26 ± 2·25	0·68 ± 0·04	0·996
	4	100	DW	27·79 ± 1·80	0·77 ± 0·05	0·983

[a] DW = distilled water.
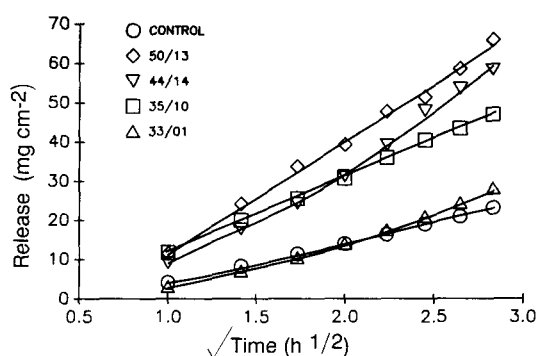
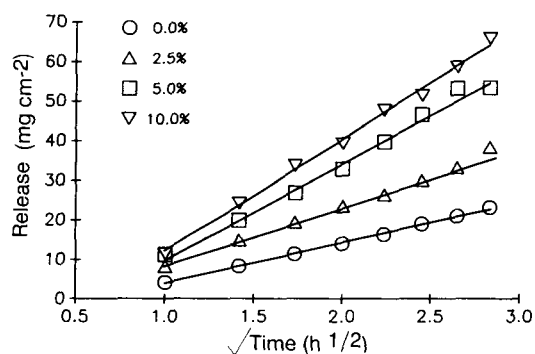FIG. 2. Effect of Gelucire blends on drug release (formulations 2, 3, 4, 5 and 6).

FIG. 4. Effect of Gelucire 50/13 on the drug release from Gelucire 64/ 02–50/13 blends (formulations 2, 3, 7 and 8).

were not significantly different from that of Gelucire 64/02. The release rate constants, with their corresponding correlation coefficients, and the t_{lag} values are listed in Table 3. To confirm that the observed differences in drug release were due to the Gelucire blend and not due to fluctuations in drug content between the different formulations, a one-way

analysis of variance on drug content of the various disks was performed. No significant differences in drug content were detected ($P = 0·45$). The release rates from the blends were significantly higher ($P < 0·001$) than those from Gelucire 64/02, except that from the blend with Gelucire 33/01. The release rates from the blends containing Gelucire 44/14 or 50/
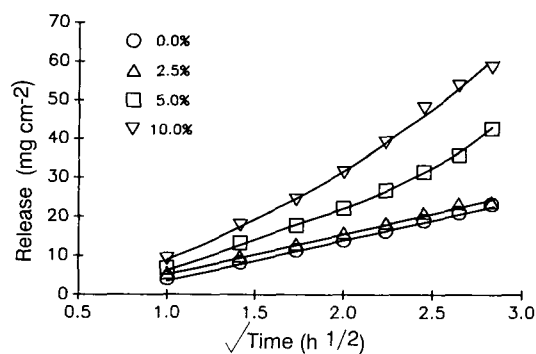

FIG. 3. Effect of Gelucire 44/14 on the drug release from Gelucire 64/ 02–44/14 blends (formulations 2, 4, 9 and 10).
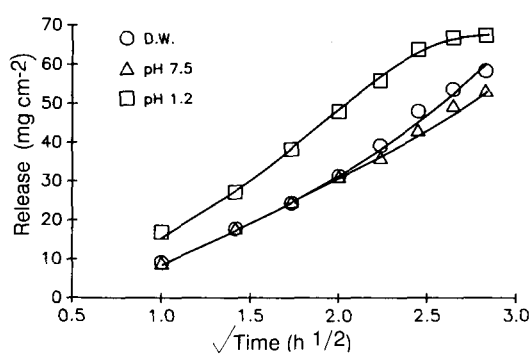

FIG. 5. Effect of the pH of the dissolution media on the release of drug from a 10% Gelucire 64/02–44/14 blend. D.W., distilled water.
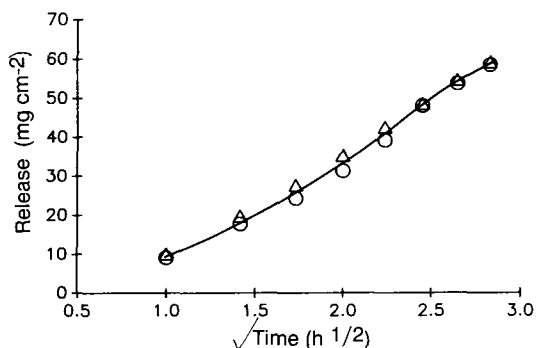
FIG. 6. Effect of the agitation of the dissolution media on the release of drug from a 10% Gelucire 64/02–44/14 blend. △ 50 rev min^{-1}, ○ 100 rev min^{-1}.

13 were not significantly different. The observed lag times for the blended formulations were generally longer compared with that of the Gelucire 64/02.

Since Gelucires 44/14 and 50/13 showed the most rapid release of chlorpheniramine maleate (Table 1), these were blended with Gelucire 64/02 at three different levels (Figs 3, 4). Addition of 2·5% of Gelucire 50/13 or 44/14 did not significantly increase the release rate. At the higher concentrations of Gelucire 50/13 or 44/14 a significantly faster release rate was obtained. The t_{lag} values for the blends with Gelucire 4/14 or 50/13 were not significantly different from the t_{lag} value for Gelucire 64/02.

Effect of pH of the medium

The dissolution medium had a small impact on the rate of drug release from formulation 4 (Table 3, Fig. 5). Faster drug release from the disks was obtained at pH 1·2 compared with pH 7·5. This difference in drug release may be due to ionization of the drug. Chlorpheniramine is a base with a pK$_a$ of 9·16 and at pH 1·2 chlorpheniramine is 99% ionized compared with 97% at pH 7·5. The un-ionized species may have a higher affinity for the waxy Gelucire compared with the ionized species.

Effect of stirring rate

There was no significant difference in release of chlorpheniramine maleate from formulation 4 at different rates of agitation (Table 3 and Fig. 6). This indicates that the release of drug from the matrix disk was controlled by the Gelucire blend and not by external agitation.

Conclusion

Melt-extrusion is a viable method for preparing sustained release matrix systems. The release of chlorpheniramine maleate from the disks was diffusion controlled and could be modified by the selection of an appropriate matrix material, such as a fatty acid ester with the proper hydrophile-lipophile balance. This method is limited by the fluidity of the extruded mass, which controls the amount of drug which can be incorporated and necessitates careful selection of matrix materials exhibiting low viscosity in the melted state.

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