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MODELLING OF THEOPHYLLINE COMPOUND RELEASE FROM HARD GELATIN CAPSULES CONTAINING GELUCIRE MATRIX GRANULES

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ABSTRACT

Hard shell capsules containing four theophylline compounds of different solubilities (theophylline , etofylline, diprophylline and proxyphylline) were prepared with saturated polyglycolysed glycerides (Gelucires) of melting point above 45°C and HLB value below 10. A polyvalent formulation was obtained after granulation by melting and congealing and use of glyceryl behenate (Compritol) as a lubricant of the solidified suspensions. The best yields of granulation were obtained with Gelucires 64/02, 54/02 and 50/02. The influence of three parameters was studied: melting point and HLB of the Gelucires, as well as drug solubility. Drug release was found to increase as the melting point decreased and as HLB and drug solubility rose. Theophylline showed abnormal behaviour because

the length of its needle-like crystals reduced its capacity for inclusion in the fatty matrix. Multiple linear regression was used to evaluate the influence of the three formulation parameters and thus confirmed the validity of the mathematical model initially formulated for tablets made with the same granules.

INTRODUCTION

In previous studies[1,2], optimization of sustained release solid dosage forms was successfully made with fatty matrix excipients such as carnauba wax or hydrogenated castor oil. Following these ideas, amphiphilic vehicles such as Gelucires are promising substances for modulating release of drugs of different solubilities e.g.theophylline compounds already used in a former research project[3]. Melted blends of Gelucires are generally employed to fill hard gelatin capsules[4,5]. Their use for the manufacture of granules enables large amounts of drug to be included because viscosity of the molten mixture can be raised to reach a hard paste consistency.

Thus, the aim of this work is to prepare and fill hard shell capsules with matrix granules made from six different Gelucires containing four theophylline derivatives. The influence of three formulation parameters (melting point and HLB of Gelucires, drug solubility) was investigated using multiple linear regression analysis, in the hope of improving existing release characteristics.

MATERIALS AND METHODS

Drugs, used as received from the manufacturer, were monohydrated theophylline (Cooper), etofylline (Sigma),

dyphylline (Cooper) and proxyphylline (Sigma) whose solubilities at 25°C are respectively 0.006, 0.049, 0.140 and 0.601 g/cm^3. These active ingredients were measured spectrophotometrically at 271 nm for theophylline and at 273 nm in the case of the three other products.

The Gelucires (Gattefossé) studied were saturated polyglycolysed glycerides with different melting points and HLB values[6]. The choice of Gelucires was based on the following criteria: M.P. above 45°C in order to avoid blocking during granulation and HLB below 10 to prevent a too rapid release of the drug. Gelucires selected were therefore types 64/02, 54/02, 50/02, 62/05, 46/07 and 48/09. These Gelucires had previously been shown to release less than 70% of the same drugs in 8 hours when they were used to make tablets[7].

Two other excipients were employed: (i) Compritol 888 (Gattefossé), a glyceryl behenate which acts as a miscible wax and lubricant of solidified suspensions, (ii) Emcompress (Ed. Mendell Co), as an insoluble filler to complete granule volume level in the capsules.

Drugs were incorporated into Gelucires by a process of melting (at 80°C) and congealing (at 4°C) followed by granulation[7]. After milling, granules were calibrated on an oscillating granulator with a 0.630 mm screen.

The formulation of a typical capsule was:

Granules	Gelucire	117	367mg
	Compritol	50	
	drug	200	
Emcompress to			0.95cm^3

Therefore, 200mg of drug were contained in 00 size capsules. 100 capsules were prepared with semi-automatic capsule-filling apparatus.

TABLE 1

Characteristics of Granules and Capsules

Drug	Gelucire	Yield (%)	Bulk Density	Emcompress Volume(cm^3)
theophylline	64/02	93	0.50	23
	54/02	94	0.47	16
	50/02	80	0.45	9
	62/05	44	0.37	0
etofylline	64/02	92	0.47	33
	54/02	92	0.48	30
	50/02	82	0.48	20
dyphylline	64/02	90	0.58	32
	54/02	90	0.55	30
	50/02	96	0.48	20
	46/07	87	0.48	18
	48/09	79	0.49	22
proxyphylline	64/02	90	0.51	28
	54/02	93	0.53	29
	50/02	85	0.46	15

Study of drug release was carried out in a rotating paddle apparatus with 1000cm^3 of distilled water at 37°C and a rotation speed of 100 rpm. Released active ingredients were measured by UV spectrophotometry. Mean results of six trials enabled dissolution efficiencies to be calculated[3,7].

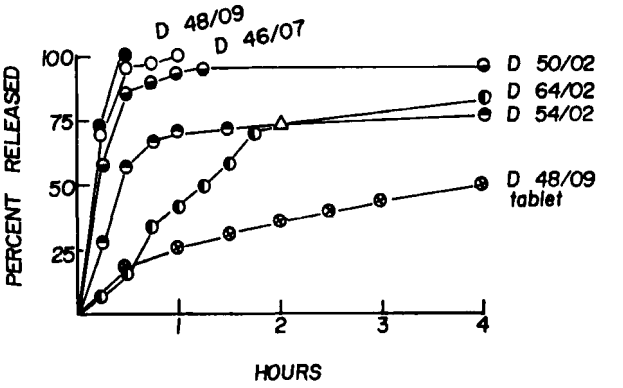

FIGURE 1

Influence of Gelucire type on dyphylline release from capsules containing matrix granules

RESULTS AND DISCUSSION

Influence of the Formulation Parameters

Table 1 shows the results obtained with the different Gelucires, particularly the yield after calibrating at 0.630mm which is a reflection of the importance of blocking during granulation. From this point of view, Gelucires 64/02, 54/02 and also 50/02 gave the best yields.

Figure 1 shows that dyphylline release increased in response to Gelucire HLB values as many previous researchers have already observed[7-11].

Drug release was much quicker from capsules than from tablets made with the same granules[7]. The main quantity of the drug was essentially released in the first two hours. This result agrees with those obtained by other workers who compared release from granules and tablets[12-15]. In the case of tablets, the added compression force

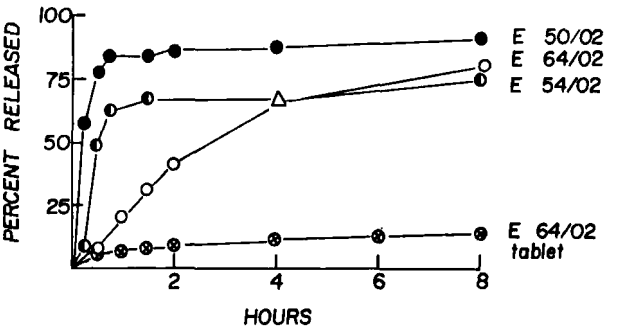

FIGURE 2

Influence of Gelucire melting point on etofylline release from capsules containing matrix granules

constituted an effective sustained-release matrix which leached drugs very slowly. In the case of hard shell capsules containing matrix granules, the available dissolution area was much increased because of the great number of individual particles exposed to the dissolution fluid, this being a logical explanation for the fast release observed.

Figure 2, in the case of etofylline, shows that drug release decreased as Gelucire melting points rose, as previously noted by other authors[10,16,17].

The influence of drug solubility is illustrated in Figure 3. Except for the case of theophylline, release increased with greater solubility of the active ingredient. The abnormal behaviour of theophylline was certainly caused by the excessive size of the crystals whose needle forms were 40 times longer than the mean diameter of the three other product particles (10μm) and consequently were not well included in the Gelucire granules.

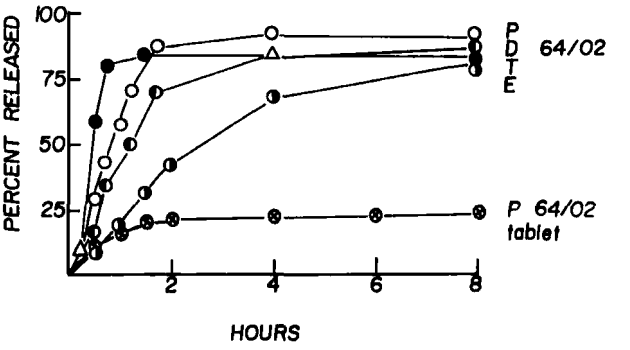

FIGURE 3

Influence of drug solubility on release from capsules containing matrix granules made of Gelucire 64/02

Modelling of Drug Release

It was shown above that drug release increased directly in relation to the Gelucire HLB and the drug's solubility (except for theophylline). There was also increased release as the melting point of the fatty excipient decreased. It seemed therefore that these three factors simultaneously influenced drug release in the same manner as previously reported for tablets made with these granules[7]. The same mathematical model was tested with the following equation:

$$Y = a\ln X_1 + bX_2 + cX_3 + d$$

where: Y is the dissolution efficiency at time t

X_1 the melting point of the Gelucire

X_2 the HLB of the Gelucire

X_3 the drug solubility

a,b,c and d are the multiple linear regression constants.

Table 2 shows the multiple correlation coefficient obtained when regressions were made with dissolution efficiencies at times 2,4 or 8 hours (theophylline capsules were not included).

TABLE 2

Dissolution Efficiencies Y and Multiple Correlation Coefficients r at time t = 2,4,8 hours

Drug	Gelucire	Y_2	Y_4	Y_8
etofylline	64/02	19.421	37.001	55.270
	54/02	52.124	59.287	65.036
	50/02	74.180	80.270	84.457
dyphylline	64/02	38.854	58.435	71.707
	54/02	58.830	66.718	74.486
	50/02	82.296	88.648	93.074
	46/07	89.134	94.567	97.283
	48/09	90.300	95.150	97.575
proxyphylline	64/02	52.492	71.463	81.877
	54/02	89.175	94.587	97.294
	50/02	87.470	93.735	96.867
r		0.938	0.900	0.861

Because of the generally quick release of the drugs, the best correlation was obtained with dissolution efficiencies at 2 hours.

The least-squares values of the multiple linear regression calculated with these dissolution efficiencies are the following:

$a = -175.385$ $b = 0.770$

$c = 45.831$ $d = 752.960$

The equation of the line shown in Figure 4 with a correlation coefficient $r = 0.97$ was $y = x - 0.0008$,

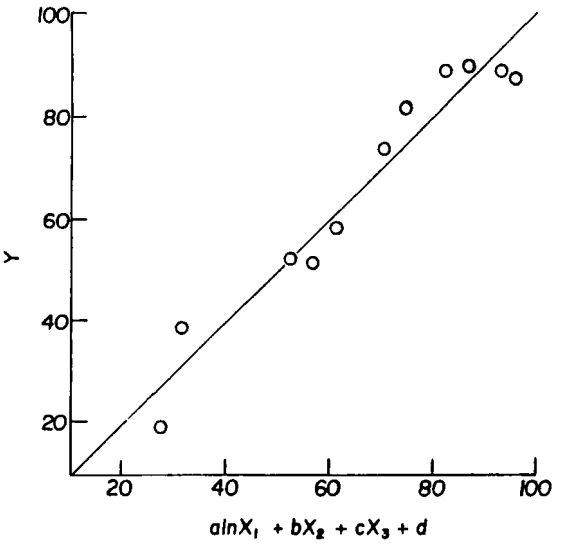

FIGURE 4

Influence of melting point X_1 and HLB X_2 of Gelucires and of drug solubility X_3 on the dissolution efficiency Y, according to the equation $Y = a\ln X_1 + bX_2 + cX_3 + d$

therefore close to the equation for the bisecting line of the co-ordinate axes[18].

CONCLUSIONS

Our study allowed us to define a polyvalent formulation consistent with the four theophylline derivatives and the lipidic Gelucire excipients used.

Drug release from the hard shell capsules containing matrix granules was very fast in comparison with release from tablets made with the same granules. This was due to a greater dissolution area resulting from a larger number of particles being exposed to the dissolution fluid. Drug release was also increased when the HLB value and the solubility of the drug rose but was decreased with higher Gelucire melting points. In the

case of theophylline, the size of the crystals prevented effective inclusion of the drug in Gelucires and release was always faster than expected.

The mathematical model governing the influence of the three formulation parameters (melting point and HLB of Gelucires, drug solubility) previously defined for the tablets was equally valid for the capsules filled with the same granules. The use of this model to optimize the release of each of the active ingredients from waxy formulations made from mixtures of Gelucires will be described in a further publication. However, discussion will be restricted to the use of the tablets because drug release from the hard gelatin capsules filled with granules seemed to be too quick to obtain a true sustained-release formulation.

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