DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 12(10), 1553-1565 (1986)

THE INCORPORATION AND IN VITRO RELEASE PROFILES OF LIQUID, DELIQUESCENT OR UNSTABLE DRUGS WITH FUSIBLE EXCIPIENTS IN HARD GELATIN CAPSULES

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ABSTRACT

The *in vitro* release profiles of four liquid or deliquescent model drugs incorporated in various Gelucire[R] excipients were examined. In every case, it was possible to obtain release of the active substance as rapidly as with the equivalent commercial soft gelatine capsules tested. Gelucire[R] grades with high HLB values (despite having high melting points) were found to be the most favorable. Release patterns could be related to the behaviour of the Gelucire[R] bases in the gastric fluid.

Drug-excipient ratio played a prominent role, which differed when hydrophilic or hydrophobic Gelucire[R] types were used. Storage of the capsule formulations for more than two years did not usually change the drug release

0363-9045/86/1210-1553$3.50/0

profiles significantly, but chloral hydrate capsules could not be stocked for more than a few months.

INTRODUCTION

The manufacture of oral dosage forms containing liquid, deliquescent or unstable medicinal substances -or forms associating incompatible drugs- presents technical difficulties which are sometimes overcome by the use of soft gelatin capsules, the technology of which is possessed by only a few specialized companies.

The encapsulation of these active ingredients in oily, thixotropic vehicles, thickened by colloidal silica or wax, is a solution frequently proposed (1 - 8), but this has its drawbacks. The vegetable oils used often have a poorly defined composition and quickly become rancid. Furthermore, the thickening agents do not always prevent leakage between the two elements of the capsule. We may also note the possibility of incorporation by fusion of such active ingredients with polyethyleneglycols of high molecular weight (8). Although these excipients permit rapid release, they often have the disadvantage of presenting incompatibilities with the drugs. A new range of excipients with solid consistency, the various grades of Gelucire^{R} (Ets Gattefossé), open up new perspectives in this domain.

These products, glycerides and other esters of fatty acids with controlled hydrophilia, should make it possible to solve the problem referred to above, thanks to the variety of melting points and HLB values they offer, together with good chemical stability (9). With these excipients, encapsulation relies upon the fusion and solidification of the mixture drug-excipient.

In this work, we have tried to formulate capsules with release at least as rapid as that of products now on the market, but presented in other forms. We have studied the effect of the type of Gelucire^{R} chosen, and of drug

concentration, as well as the effect of aging on the release profile.

PRODUCTS AND METHODS

Characteristics of products

Gelucire^R: Excipients of solid consistency, more or less hard, characterized by the manufacturer by two figures, the first giving the melting point and the second the HLB value (types utilized: 50/13, 50/02, 46/07, 44/14, 42/12, 37/02, 35/10, 33/01).

BENZONATATE (Tessalon^R, Ciba) = nonaethyleneglycol monomethyl ether *p-n*-butylaminobenzoate; oily liquid, sensitive to air and light; soluble in water and most organic solvents; concentration measured by spectrophotometry at 302 nm after chloroform extraction.

Nicotinic acid (Ronicol^R, Hoffmann-La Roche) = 3-pyridinemethanol; hygroscopic liquid; highly soluble in water and some organic solvents; concentration measured by spectrophotometry at 257 nm after chloroform extraction.

Chloral hydrate : deliquescent crystals, m_p 57° C, concentration measured by colorimetry using modified Fujiwara method (10).

Paramethadione (Paradione^R, Abbott) = 3,5-dimethyl-5-ethoxazolidine-2,4-dione); liquid only slightly soluble in water, soluble in organic solvents; measurement by gas chromatography (11).

Methods

Behavior of Gelucire^R in artificial gastric fluid

Tests were made with cylinders of Gelucire^R taken with a punch from the bulk substance (diameter 10 mm, length 12 mm). Each sample was placed in 400 ml in the milieu, constantly stirred (60 rpm), by a 4-bladed paddle, halfway down, at a temperature of 37 ± 0.5° C.

Choice of Gelucire^{R} grades for manufacture of capsules

For the first active ingredient tested, paramethadione, five grades of Gelucire^{R}, differentiated by their behavior in the simulated medium were selected: 50/13, 50/02, 44/14, 35/10 and 33/01. For the other medicinal substances, we chose the masses giving the best release results. However, since chloral hydrate greatly reduces the melting points of these excipients and since associations with the grades 33/01, 44/14 and 50/13 result in leakage from the capsules, we used 37/02, 42/12, 46/04 and 50/02 which did not present these disadvantages.

Filling of capsules

Each grade of Gelucire^{R} is melted at a temperature not exceeding 10° C its fusion point. The drug is incorporated before pouring the mixture into colorless capsules (Snap-Fit^{TM}, Capsugel). The latter are kept at room temperature in closed containers sheltered from light.

Benzonatate and paramethadione are perfectly miscible with the Gelucire^{R} grades tested. Nicotinic acid is not, with the excipients 33/01 and 37/02: these two mixtures have to be poured after thickening the mass to avoid separation of the phases. On the contrary, the active ingredient forms a homogeneous and transparent gel with Gelucire^{R} 44/14.

Chloral hydrate is melted at 50° C before being incorporated with the various grades of Gelucire^{R} so as to obtain comparable mixtures, regardless of the fusion point of the excipient. The mixture of this drug with Gelucire^{R} 44/14 constitutes an oily mass which is not favorable for conservation of the capsules.

Release tests

These tests are carried out with apparatus No. 2 USP XXI/NFXVI (the paddle method) at a stirring rate of 60 rpm. One month after manufacture, the capsules are placed

in 800 ml of gastric fluid USP XXI/NF XVI without pepsin, with 0.1% of polysorbate 80 added, at a temperature of 37±0.5° C.

RESULTS AND DISCUSSION

Behavior of Gelucire^R in gastric fluid

It was observed that the nature of the surface-active agent added to artificial gastric fluid does not influence the behavior of the excipients, except for grades 42/12 and 37/02 (Table 1).

Disintegration at 37° C depends more on the fusion point than upon the HLB values of the substances.

Effect of Gelucire^R grades on drug release

Gelucire^R and benzonatate

The capsules (No. 1) contain 100 mg of the active principle, constituting 20 to 28% of the mass, depending on the density of the excipient.

The differences in availability of benzonatate incorporated in the various grades of Gelucire^R are very substantial (Figure 1).

We observe a very low release rate (less than 20% in 90 minutes) in the case of grades which do not disintegrate in the dissolution medium (35/10 and 50/02). Grade 35/10 is probably enveloped by a hydrated layer which impedes the disintegration of the mass. After 210 minutes, the differences of more than 30% between Gelucire^R grades which appear to correspond to their melting points and HLB values (33/01 and 37/02), may be explained by differences in the chemical composition of these excipients. The profiles corresponding most closely to those of soft capsules on the market (Tessalon^R) are obtained with Gelucire^R grades 50/13 and 44/14 which have high HLB values.

Gelucire^R and nicotinic alcohol

The capsules (No. 1) contain a mixture of excipient and

TABLE 1

Type of Gelucire (mp/HLB)	Medium[1]	Density[2]	Appearance of the mass[3] 5 min	30 min	60 min	Remarks
33/01	GJ	F	D+	D+	D+++	Spreads on surface, mucilaginous appearance
	GJP	F	D+	D+	D+++	
	GJS	F	D+	D+	D++	
35/10	GJ	F	D-	D-	D+	Softens
	GJP	F	D-	D-	D+	"
	GJS	F	D-	D-	D+	"
37/02	GJ	F	D+	D++	D+++	
	GJP	F	D++	S++/D+++	S++/D+++	
	GJS	F	D++	S++/D+++	S++/D+++	
42/12	GJ	U	D+	D++	D++	Transparent mass spreads at bottom of beaker
	GJP	U	D-	D+	D+	Transparent
	GJS	U	D-	D+	D+	mass deforms
44/14	GJ	U	S+	S++	S++	Remains a
	GJP	U	S+	S++	S+++	transparent
	GJS	U	S+	S+++	S+++	mass
46/07	GJ	F	D-	D-	D-	
	GJP	F	D-	D-	D-	
	GJS	F	D-	D-	D-	
48/09	GJ	F	D-	D-	D-	Remains intact, but softens
	GJP	F	D-	D-	D-	
	GJS	F	D-	D-	D-	
50/02	GJ	F	D-	D-	D-	Remains intact, but softens
	GJP	F	D-	D-	D-	
	GJS	F	D-	D-	D-	
50/13	GJ	U	D-	D-/S+	D-/S++	Entire mass sinks to bottom of beaker; softens, becomes plastic
	GJP	U	D-	D-/S++	D-/S++	
	GJS	U	D-	D-/S++	D-/S++	
53/10	GJ	U	D-	D-	D+	
	GJP	U	D-	D-	D-	
	GJS	U	D-	D-	D-	
62/05	GJ	F	D-	D-	D-	
	GJP	F	D-	D-	D-	
	GJS	F	D-	D-	D-	

1 GJ = Simulated gastric juice (Ph.Helv.VI)
GJP= Simulated gastric juice with 0.1% polysorbate 80
GJS= Simulated gastric juice with 0.1% sodium laurylsulfate
2 F = Mass floats
U = Mass sinks
3 D = Degree of disintegration/deformation: none(-) to complete(+++)
S = Degree of solubilization: none(-) to complete(+++)

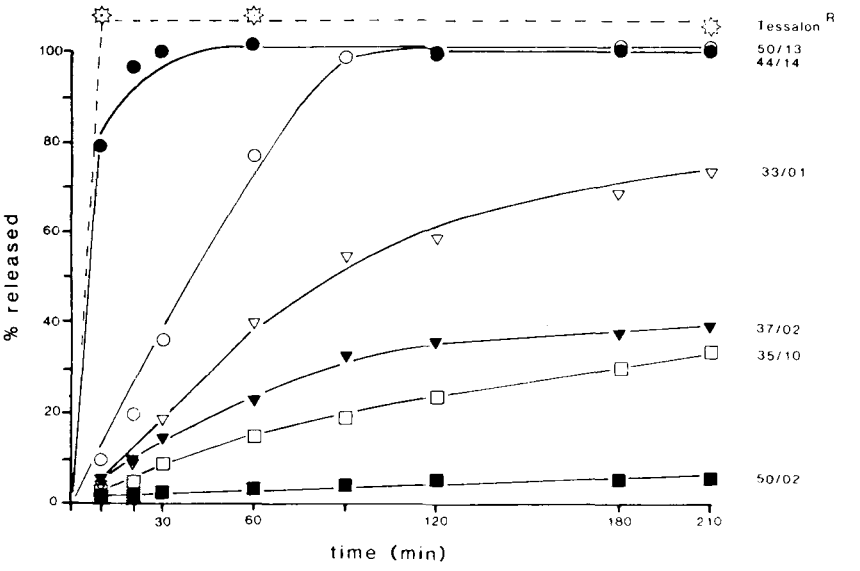

FIGURE 1
Release profiles of benzonatate

nicotinic acid, with 150 mg of the medicinal substance (about 30%, depending on the Gelucire^{R} grade used).

As in the case of benzonatate and despite poor homogenization, release of the active ingredient was more rapid with Gelucire^{R} 44/14 (Figure 2).

Gelucire^{R} and chloral hydrate

In an initial series of tests (12), the chloral hydrate and Gelucire^{R} mixtures contained 60% of the drug and its release was very rapid. In the work now reported however, the concentration was 40%, enabling us to obtain firmer masses, more suitable for the storage of capsules.

With 40% chloral hydrate, we find great differences in dissolution rates, depending on the excipient. Gelucire^{R} grades 44/14 and 42/12 release all of the active ingredient

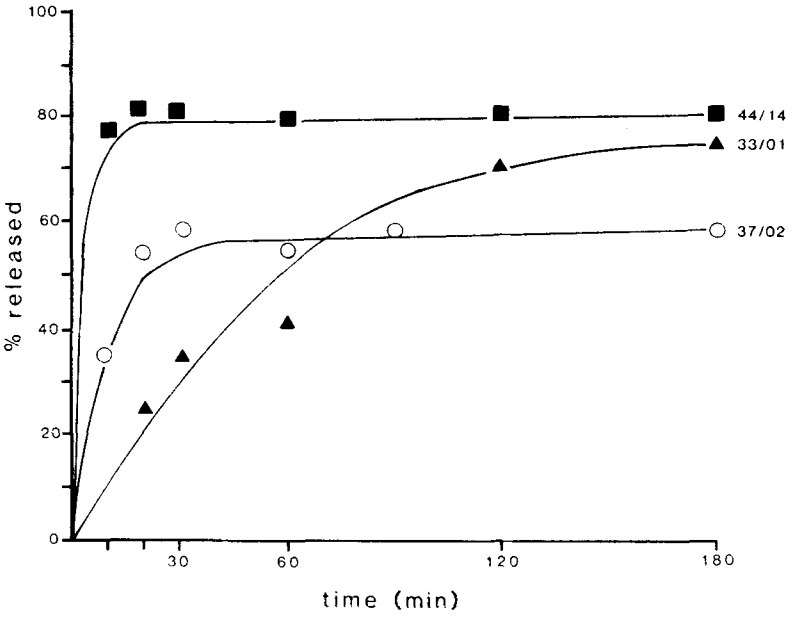

FIGURE 2
Release profiles of nicotinic acid

in 30 minutes. Other mixtures, even though they have a pasty consistency, those with grades 33/01 and 37/02, for example, have release rates which are two or three times lower. Two Gelucire^{R} grades, 50/13 and 50/02, form compact and hard mixtures which do not disintegrate and which release barely 30% of the chloral hydrate in 5 hours (Figure 3).

Gelucire^{R} and paramethadione

With Gelucire^{R} 35/10, 37/02 and 50/02, the capsules contained 40% paramethadione. Grade 44/14 had only 20% of the drug since any higher percentage resulted in liquefaction of the mass as soon as the temperature reached 25° C. Despite its great liposolubility, paramethadione shows dissolution profiles comparable to

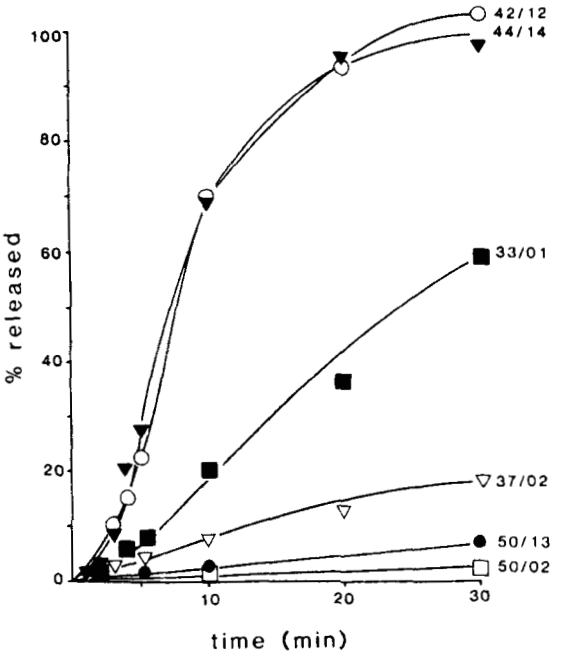

FIGURE 3
Release profiles of chloral hydrate

the hydrosoluble substances previously tested (Figure 4). Thus, Gelucire^{R} 44/14 permits rapid and complete release of the active ingredient. Availability is better with 37/02 than with 35/10, whereas 50/02 releases paramethadione slowly and incompletely. We may also note that Gelucire^{R} 37/02, which is not favorable for hydrosoluble substances, in this case, provides complete release in less than one hour. With soft gelatin capsules now on the market (Paradione^{R}, 500 and 300 mg), dissolution is less rapid than with capsules containing grades 37/02 and 44/14.

Effect of drug concentration on the rate of release

Since the concentration of the drugs in Gelucire^{R} depends upon the doses to be incorporated in the form,

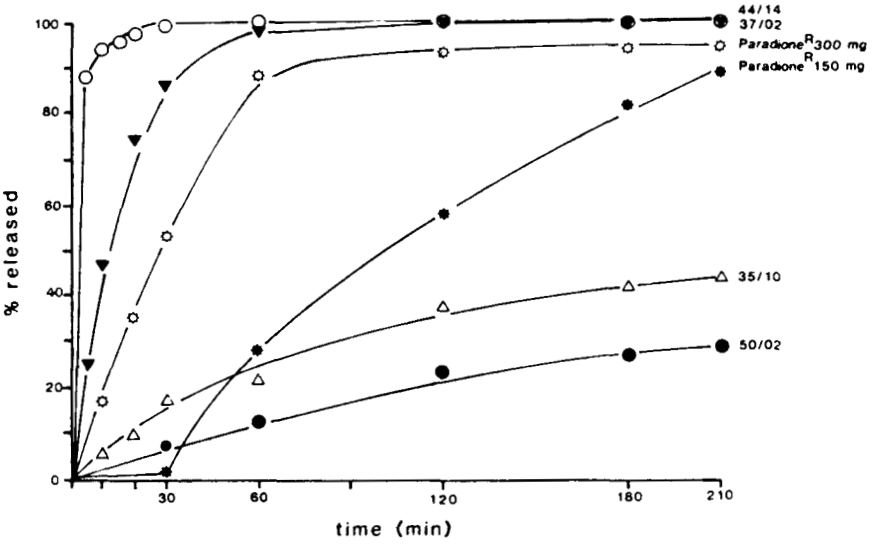

FIGURE 4
Release profile of paramethadione

the percentages vary from one product to another. We therefore found it interesting to determine the influence of different percentages on the release of the drug. Tests were made with paramethadione at concentrations of 10%, 14%, 17% and 25% in Gelucire^{R} 50/13, which gave an average release profile in the initial test.

Improvement was noted in the availability of the drug as concentrations of the active ingredient were increased, in view of the more rapid disintegration of the mass (Figure 5).

Aging of capsules

The evolution of different batches of capsules was observed for three years of storage at room temperature, sheltered from light. All capsules containing benzonatate maintained a perfect appearance. However, some dissolution tests made after one year yielded

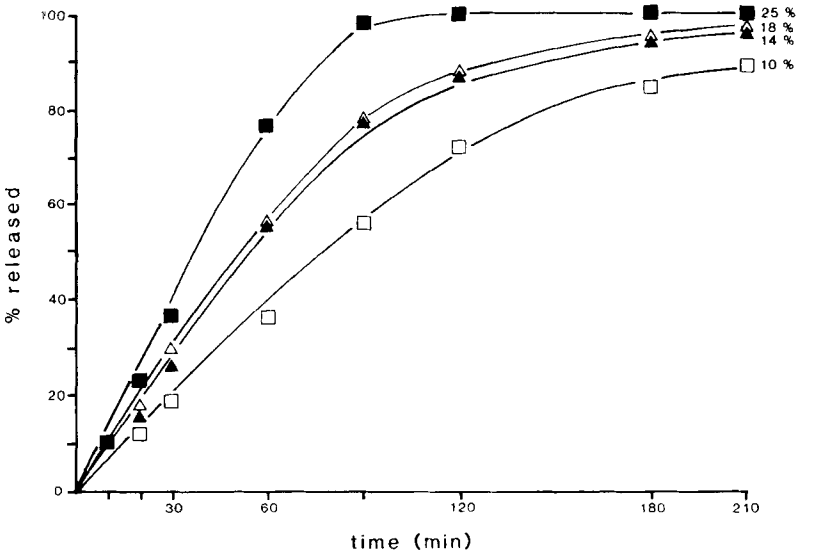

FIGURE 5
Release of benzonatate, incorporated in Gelucire^{R} 50/13 at different concentrations

values slightly higher than those obtained in recently manufactured capsules, but the differences remained within accepted limits. This phenomenon doubtless depends upon the progressive transformation of the crystalline state of the waxy excipient, producing an expulsion of the drug from the crystallites and hence increase in the rapidity of release.

Capsules containing 40% paramethadione (20% for 44/14) remained intact after two years. During the same length of time, capsules containing nicotinic alcohol did not all evolve in the same manner. Mixtures based on Gelucire^{R} 37/02 remained intact, but the walls of capsules containing 44/14 and 33/01 were yellowed and softened; in addition, in the case of 44/14, there was a leakage of the contents.

In the case of chloral hydrate, no excipient permitted storage for more than a few months. The gelatin hardened and became yellow with 33/01 and 37/02; even though the mass remained solid, the capsules became sticky due to cracks in the envelopes. The shells containing Gelucire^{R} 50/13, 44/14 and 42/12 remained flexible and transparent, although the semi-liquid mass made the capsules sticky.

To summarize, capsules based on Gelucire^{R} withstood the passage of time perfectly in the case of some active ingredients whereas prolonged storage for others was not possible with the types of Gelucire^{R} tested without a modification of the formulation.

CONCLUSIONS

This work as a whole demonstrates the importance of the grade of Gelucire^{R} chosen upon the release of the active ingredients. Whether the latter are hydro- or liposoluble has little influence on their availability.

In the present case, the grades with high HLB (44/14 and 50/13), despite their melting points above 37° C, offered the most favorable release characteristics.

The content of the mixtures of active ingredients also had an effect; release was accelerated with higher concentrations of the drugs. This phenomenon is readily explainable for the hydrophilic substances due to better dispersion of the mass in the liquid medium. The hydrodispersible adjuvants form pores which result in reduced cohesion of the excipient, making possible a more rapid release of the active ingredient.

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