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RESEARCH PAPER

Extrusion–Spheronization Manufacture of Gelucire® Matrix Beads

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ABSTRACT

Theophylline extended-release spheres were prepared by extrusion–spheronization of matrix granulations previously obtained by incorporation of the drug in melted Gelucire® 50/02 or Gelucire 55/18. Hydrophobic Gelucire 50/02 behaved as an inert matrix and released theophylline very slowly compared with hydrodispersible Gelucire 55/18, which acted as a hydrophilic matrix. Extrusion–spheronization was more easily accomplished with Gelucire 50/02. The use of ethanol as a wetting fluid increased the rate of drug release noticeably with Gelucire 50/02 and less so with Gelucire 55/18. The use of castor oil, in conjunction with ethanol to slow down the solvent evaporation, improved extrusion and spheronization. Castor oil decreased the drug release rate with Gelucire 50/02 and increased it with Gelucire 55/18. These phenomena were explained by the different solubilities of theophylline, Gelucire 50/02, and Gelucire 55/18 in ethanol and castor oil. When microcrystalline cellulose (Avicel® CL 611) was used in the granulation matrix, extrusion was improved. The best formulation was obtained with Gelucire 55/18 and Avicel CL 611 and was wetted by a mixture of ethanol and castor oil. Regardless of the formulation, the mechanism of theophylline release appeared to be via Fickian diffusion.

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INTRODUCTION

The aim of this work was to study the extrusion–spheronization manufacture and the drug release kinetics of spheres containing theophylline as a model drug incorporated in either Gelucire® 50/02 or Gelucire® 55/18 matrix materials. Gelucires are mixtures of monoesters, diesters, and triesters of glycerol and monoesters and diesters of polyethylene glycol. The first number in the designation of a Gelucire product refers to its melting point (MP), from 33 to 64°C. The second number refers to its hydrophilic–lipophilic balance (HLB) on a scale ranging from 1 (highly fat soluble) to 18 (water dispersible).

Matrix pellets obtained by extrusion–spheronization are of great interest because a subsequent release-modifying coating is theoretically not necessary to obtain slow release of drugs. Such preparations have been recently described by several authors . The extended-release materials were chitosan (1,2), ethyl cellulose or acrylic polymers (3–6), and polyethylene glycols or glyceryl monostearate (7). Microcrystalline cellulose was often used as the spheronizing aid.

Lipidic substances such as carnauba wax or hydrogenated castor oil could also be successfully spheronized to produce sustained-release beads if the wetting fluid was ethanol instead of water (8). With Precirol® (glyceryl palmitostearate), wetting was achieved with water; however, a subsequent thermal treatment was needed to obtain extended-release spheroids (9). Beads could also be prepared with this waxy excipient or with Gelucire 50/02 if the drug was previously dispersed in the melted material (10). However, the authors have not given any results concerning drug release.

Gelucires with MPs higher than 40°C and HLBs lower than 10 are generally good materials for slow release when the drug has been included in the melted Gelucire (11). For example, Gelucire 50/02 behaves as an inert matrix with Fickian diffusion and absence of erosion (12–14). On the contrary, Gelucire 55/18 swells, forms a gel, and releases theophylline with an anomalous diffusion mechanism (15). The particular behavior of Gelucire 55/18 could be explained by its chemical composition; this product contains only esters of PEG and of fatty acids. These results were obtained with different solid dosage forms but never with spheres. The goal of this work was therefore to prepare matrix beads by extrusion–spheronization with Gelucire as carriers.

Methodology was devised to obtain a slow drug release. Theophylline was first incorporated into melted Gelucires to prepare melt granulations. Ethanol was preferred to water for wetting the granulation mass before extrusion. Microcrystalline cellulose was used if necessary to improve spheronization. The feasibility of bead manufacture was evaluated by means of the percent yields for both extrusion and spheronization and by the quality of extrudates and spheres obtained (aspect, sticking, particle size distribution). Drug-release kinetics of theophylline were investigated by fitting the dissolution data to two previously established equations by Higuchi and Ritger–Peppas.

MATERIALS AND METHODS

Materials

Theophylline monohydrate (Boehringer, Ingelheim, Germany) of 50 μm mean particle size was the drug used in this study. Gelucire 50/02 and Gelucire 55/18 (Gattefossé, Saint-Priest, France) were the lipid matrix excipients with a MP of 50 and 55°C and an HLB value of 2 and 18, respectively. Other auxiliary substances were denatured ethanol 95% (Prolabo, Paris, France), Avicel® CL 611(FMC, Philadelphia, PA), and castor oil (Prolabo).

Bead Manufacturing

Table 1 describes the different formulations used in this study. Theophylline was incorporated into the melted Gelucire at MP + 10°C using a water bath and an Ultra-Turrax stirrer (Ikawerk, Staufen i. Breisgau, Germany). The resulting mixtures were cast in a layer of 1-cm thickness on previously cooled plates and stored overnight at between 0 and +4°C. The congealed mixtures were milled using a 2-mm screen (Alexanderwek, Remscheid, Germany) to obtain granulations that were not sized afterward. Avicel CL 611 was added depending on the formula (Table 1), and the wetting was done in a planetary mixer (Kenwood, Havant, UK) with ethanol or a mixture of ethanol–castor oil (57:43%). Mixing time was always 5 min.

Extrusion was performed on a Pelleter EXDCS 100 (Fuji Denki Kogyo, Osaka, Japan) equipped with a 1-mm screen and operated at 25 rpm. Spheronization was carried out on a Marumerizer Q 400 (Fuji Denki Kogyo) equipped with a 1-mm serrated plate of 39.5-cm diameter and operated at 875 rpm. The residence time varied from 15 sec to 3 min, depending on the formula. Although the residence time in the spheronization process is one of the most important factors affecting particle size, density, porosity, and roughness of beads (16) and the drug re-

Table 1

Influence of Formulation on the Feasibility of Beads

	Formula (%)							
	1	2	3	4	5	6	7	8
Theophylline	30	30	30	30	30	30	30	30
Gelucire® 50/02	70	70	50	50	—	—	—	—
Gelucire® 55/18	—	—	—	—	70	70	50	50
Avicel® CL 611	—	—	20	20	—	—	20	20
Ethanol	—	20	20	8	—	11	11	8
Castor oil	—	—	—	6	—	—	—	6
Extrusion								
Yield (%)		81	87	93		46	70	86
Quality		+	+	+		Sticking	±	±
Spheronization								
Yield (%)		90	91	94		0	10	95
Time (sec)		35	150	15		30	150	180
Quality		+	±	+		0	±	±

0, poor; ±, average; +, suitable.

lease, varied residence times were used to obtain spheres for each formulation. All pellet formulations were dried for 24 hr in a conventional hot-air oven (Memmert UL 30, Schwabach, Germany) at a temperature of 38°C. The batch size for these experiments was 1000 g.

Testing

The particle size characterization was performed by applying vibrations (Tamisor, Paris, France) with an intensity of 70 for 15 min to a set of sieves with 0.315-, 0.63-, 0.8-, 1-, 1.25-, and 1.6-mm apertures. One hundred grams of beads were used. Because the particle size distributions were clearly not normal, median and interquartile range were used to characterize the distributions. These two parameters were determined by plotting the cumulative retained sieve fractions in percentages on a semilogarithmic paper. Additionally, the sieve fraction less than 0.8 mm was used to characterize the efficacy of the process with the criteria of obtaining the least possible in this fraction.

The percent yields of extrusion and spheronization were calculated by weighing the amounts of products before and after each operation. The roundness of beads was assessed by observation with an optical microscope (Bioblock Scientific, Illkirch, France).

Dissolution profiles for the various formulations were determined in a dissolution apparatus (Prolabo) by using the USP/NF method I at a basket rotation speed of 60 rpm, with 1000 ml of purified water at 37°C as test medium. The rotating basket was preferred to the rotating paddle because it prevents pellets from floating at the medium surface. The amount of spheroids used for the dissolution tests corresponded to a quantity of 300 mg of theophylline. Particles of 1.25–1.6 mm in diameter were selected for dissolution studies because they typically corresponded to the main sieve fraction. Samples were analyzed by UV spectrophotometry (Beckman, Gagny, France) at 272 nm. Mean results of three trials were used.

The release kinetics were investigated with the square root of time relationship (17) according to Eq. 1 and with the power relationship (18) according to Eq. 2:

$$Q = at^{1/2} + b \quad (1)$$

$$M = Kt_n \quad (2)$$

where Q (=90%) and M (=70%) are the percentage of drug released at time t, n is the release exponent indicative of the release mechanism, and a, b, and K are regression constants. The value of ''a'' represents the drug release rate and allows comparison of the different formulas.

RESULTS AND DISCUSSION

Table 1 shows the influence of formulation on the feasibility of bead formation, illustrated by the percent yield and quality of extrusion and spheronization. Table 2 indi-

Table 2

Influence of Formulation on the Particle Size

	Formula						
	1	2	3	4	5	7	8
<0.315 mm	5.1	0	0.3	0	10.3	6.3	0
0.315–0.63	11.5	0	0.6	0	13.0	2.3	0
0.63–0.8	10.5	0.3	0.6	0	2.5	0.1	0
0.8–1	12.1	6.6	22.9	6.2	6.8	30.9	12.0
1–1.25	7.8	15.1	10.5	6.1	3.0	31.3	15.9
1.25–1.6	53.0	27.5	65.1	46.0	64.4	29.1	33.0
>1.6 mm	0	50.5	0	41.7	0	0	39.1
% < 0.8 mm	27.1	0.3	1.5	0	25.8	8.7	0
Median (mm)	1.28	1.61	1.35	1.54	1.34	1.08	1.48
Interquartile	0.68	0.49	0.45	0.41	0.73	0.42	0.52

cates the results of sieve analyses. Table 3 and Figs. 1 and 2 concern theophylline release. The quality of fitting of the dissolution data is estimated by the correlation coefficient *r*. The degree of significance of the correlation is always less than 0.001.

Melt Granulations

Formulas 1 and 5 correspond to the granulations obtained before extrusion with Gelucire 50/02 and Gelucire 55/18, respectively. The interquartile ranges of the particle size distributions and the sieve fractions less than 0.8 mm were high in both cases because the milling of congealed mixtures generated a significant amount of fine particles.

Concerning drug release, hydrophobic Gelucire 50/02 released theophylline very slowly compared with hydrodispersible Gelucire 55/18 of high HLB value (formulas 1 and 5). During the dissolution test, particles made from Gelucire 50/02 kept their initial shape, whereas particles made from Gelucire 55/18 became a gelatinous heap after swelling in the dissolution basket.

Hydrophobic Gelucire 50/02 behaved as an inert matrix, whereas hydrodispersible Gelucire 55/18 acted as a hydrophilic matrix. In both cases, a good linearization of the percentage released according to the square root of time was obtained. Likewise, the *n* values of Ritger and Peppas (18) were close to the theoretical value of 0.43 and confirmed the release mechanism of Fickian diffusion (Table 3).

Influence of Extrusion–Spheronization

Extrusion and spheronization decreased the interquartile range of the particle size distribution and the sieve fraction less than 0.8 mm, because the wetting with

Table 3

Influence of Formulation on the Release Kinetics

	Higuchi			Ritger–Peppas		
Formula	*r*	a ($\% \cdot hr^{-1/2}$)	b	*r*	K ($\% \cdot hr^{-n}$)	*n*
1	0.978	7.35	1.19	0.973	8.62	0.44
2	0.996	42.9	−3.15	0.994	39.2	0.60
3	0.996	53.9	−2.37	0.990	53.0	0.61
4	0.995	42.2	4.60	0.999	46.6	0.41
5	0.998	25.8	1.55	0.999	27.5	0.48
6	0.995	28.7	12.1	0.990	41.7	0.35
7	0.991	34.5	12.4	0.972	47.6	0.41
8	0.994	39.7	−1.88	0.993	37.6	0.49

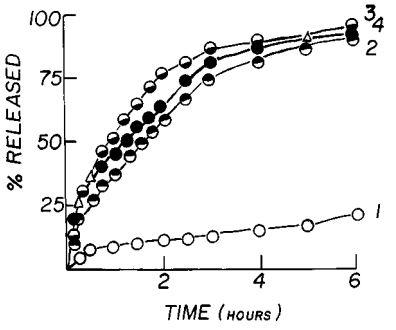

Figure 1. Influence of formulation on theophylline release kinetics from Gelucire® 50/02 (1: ○, melt granulation; 2: ○ particles; 3: ○, Avicel® beads; 4: ●, Avicel–castor oil beads).

ethanol and the extrusion process both agglomerated fine particles (Table 2). In the case of formula 2 with Gelucire 50/02, the wet mass had a good consistency and extrusion unrolled well. The loss of product, as noted by the yield value, indicates that the wetting was too much. During spheronization, there was neither sticking to the plate and the wall nor the presence of dust. Well-rounded pellets were obtained. In the case of formula 6 with Gelucire 55/18, the surface of the wetted mass displayed a rough texture and indications of overwetting. This triggered pronounced sticking and resulted in the low extrusion yield (Table 1). No beads could be obtained. After a spheronization time of 30 sec, a significant amount of dust was generated after the evaporation of ethanol. For dissolution studies, extrudate was screened to obtain particles of 1.25–1.6 mm in diameter.

Extrusion–spheronization strongly increased the rate of drug release in the case of Gelucire 50/02 (formula 2, Table 3). The release rate ''a'' was sixfold that of melt granulation. This phenomenon is due to the use of ethanol

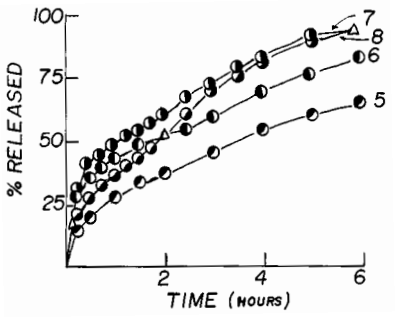

Figure 2. Influence of formulation on theophylline release kinetics from Gelucire® 55/18 (5: ○, melt granulation; 6: ○, beads; 7: ○, Avicel® beads; 8: ○, Avicel–castor oil beads).

during extrusion. Theophylline is more soluble in ethanol than Gelucire 50/02. The drug dissolves in the solvent during the kneading process and migrates to the surface of the granulates before the extrusion process. Because ethanol evaporates during the extrusion–spheronization process or the drying phase, theophylline crystallizes at the surface of the extrudate and of the beads. Hence, drug release is high during the first hours of dissolution of the final spheroid.

With Gelucire 55/18 (formula 6), drug release is slower than with Gelucire 50/02 (formula 2) because Gelucire 55/18 is slightly more soluble in ethanol than theophylline. As a result, the waxy material partially coats drug particles after solvent evaporation. Hence, there is only a minor increase in the drug release rate (formulas 5 and 6) when ethanol is added. This can be attributed to the increase in particle porosity when theophylline located at the particle surface dissolves, thereby allowing better penetration of the dissolution solvent.

The mechanism of drug release is, for the most part, Fickian diffusion, and good regression coefficients are obtained following the models of Higuchi and of Ritger–Peppas. The *n* value for Gelucire 50/02 is a bit high (0.60) and corresponds more to an anomalous diffusion.

Influence of Microcrystalline Cellulose

In the case of Gelucire 55/18 (formula 6), the wet mass showed asperities, the extrudate was indented, and no beads were obtained. To improve extrusion–spheronization, microcrystalline cellulose was added to the granulations just before wetting with ethanol (formulas 3 and 7). In the formulation, 20% of Avicel CL 611 was used in place of the same amount of waxy material. Avicel CL 611 was chosen instead of Avicel® PH 101 or Avicel® RC 581 because it better retards drug release (19). This microcrystalline cellulose contains 15% of carboxymethyl cellulose sodium and gives a water-swellable hydrogel matrix.

With both Gelucires, the extrusion yield increased and the extrudate was not indented. The interquartile range of the particle size decreased and the material weight of sieve fraction less than 0.8 mm was low. With Gelucire 50/02 (formula 3), beads of average sphericity were obtained, whereas very few spheres were produced with Gelucire 55/18 (formula 7). The addition of Avicel CL 611 improved extrusion but did not significantly improve spheronization. Concerning drug release, Avicel CL 611 increased the release rate because contained carboxymethyl cellulose sodium enhanced the hydrophilicity of the wax beads, water penetration rate, and bead

porosity. No changes in the release mechanism were observed.

Influence of Castor Oil

To reduce ethanol evaporation, a mixture of ethanol and castor oil was used as a wetting fluid (formulas 4 and 8). With both Gelucires, extrusion was easily accomplished and spheres were obtained. The Gelucire 55/18 formula was slightly more sticky during the granulation and spheronization stages. The interquartile ranges of the particle size were narrow and no sieve fraction less than 0.8 mm was obtained. In both cases, the median diameter of the spheres was close to 1.5 mm.

Concerning drug release, the presence of castor oil decreased the theophylline release rate with Gelucire 50/02 and increased the release rate with Gelucire 55/18. This phenomenon can be explained as follows. Gelucire 50/02 is more soluble in castor oil than in ethanol. It preferably dissolves in castor oil and forms a hydrophobic coating on the granulate surface. Therefore, the release of theophylline in aqueous media decreases (formulas 3 and 4). Contrarily, Gelucire 55/18 is more soluble in ethanol than in castor oil. As the amount of ethanol decreases (formulas 7 and 8), the amount of Gelucire 55/18 dissolved in ethanol is smaller, which incompletely coats drug particles. Therefore, the release rate of theophylline increases. No changes in the release mechanism were observed; good regression coefficients were obtained following the models of Higuchi and of Ritger–Peppas, with n values near the theoretical value of 0.43 for spheres. The release mechanism by Fickian diffusion was confirmed.

CONCLUSION

The formulation of extended-release matrix beads by extrusion–spheronization calls for two requirements: spheres must be easily manufactured and a sufficient sustained release of the incorporated drug must be obtained, despite the large dissolution surface. In this work, the best spheres were obtained with Gelucire 50/02. However, theophylline was released quickly (more than 50% in 2 hr) as is frequently described for other drugs and polymers (3,6,7,9). On the other hand, Gelucire 55/18 provided the best drug release rate but was more sticky and less easily extruded and spheronized. Nevertheless, the best compromise was represented by formula 8, which was deemed acceptable for its release control and for its ease of manufacture. This formulation contained Gelucire 55/18 and Avicel CL 611 and was wetted by a mixture of ethanol and castor oil. Extended-release beads can therefore be manufactured with Gelucires. Because the two products tested in this work were selected from opposite ends of the product spectrum, it is likely that other drug-release profiles could be obtained with Gelucires of differing MPs and HLB values. Because it is well known that release profiles from Gelucire matrices can be sensitive to aging, it would be important to verify there are no changes in release rate according to storage conditions.

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