Drug Development and Industrial Pharmacy, 26(2), 167–176 (2000)

RESEARCH PAPER

Hot-Melt Coating Technology. I. Influence of Compritol 888 Ato and Granule Size on Theophylline Release

A. Faham,[1] P. Prinderre,[1] N. Farah,[2] K. D. Eichler,[3] G. Kalantzis,[4] and J. Joachim[1,*]

[1]*Laboratoire de Pharmacie Galénique, Faculty of Pharmacy, 27 bd. Jean Moulin, 13385 Marseille, France*
[2]*Gattefossé S. A., 36 chemin de Génas, BP 603, 69804 Saint-Priest, France*
[3]*Glatt Gmbh, Binzen, Germany*
[4]*Hoechst Hellas Abee, Pharma Production Plant, Tatoiou Avenue, Nea Erythrea, 10240 Athens, Greece*

ABSTRACT

The aim of this work was to study the influence of theophylline granule size and the percentage of Compritol® 888 Ato on in vitro drug release from granules and tablets. The granules were coated in a fluidized bed apparatus. The dissolution profiles of these granules differed from those of granules coated with classical agents, and there were also differences between the various sieve fractions studied. Drug release was characterized by a rapid-release phase, followed by a slow-release phase. Results indicate that theophylline release can be controlled by controlling granule size. Inspection of the appearance of the tablets at the end of the dissolution test revealed that all tablets containing Compritol 888 Ato remained intact. This indicated that the Compritol 888 Ato used in the tablet formulation created an inert matrix through which the drug diffused. It was found that the Higuchi relationship of linear square root of time was the best model to describe the release kinetics of the drug from tablets. This also confirmed that a matrix diffusion-controlled mechanism was oper-

* To whom correspondence should be addressed.

ative. Given the difference between the dissolution profiles of the granules and the tablets, it was concluded that this matrix is formed during compression.
Key Words: *Compritol 888 Ato; Fluidized bed; Granule size; Hot-melt coating; Sustained release; Tablets; Top-spray system.*

INTRODUCTION

Controlled-release dosage forms offer advantages over conventional dosage forms, particularly a steadier and more prolonged therapeutic effect (1). Coating in a fluidized bed generally requires the use of solvents or water. The recovery of these solvents causes a problem; moreover, they are expensive. Aqueous dispersions are associated with a risk of bacteriological contamination (2) and may cause hydrolysis of the drug. These problems can be avoided by the use of molten lipid agents as coating materials (3). Lipid-related research has been expanded vigorously during recent years (4). Compritol® 888 Ato (Gattefosse, Saint-Priest, France) has been used as a coating agent (5) for oral sustained-release forms.

One of the techniques employed to manufacture oral sustained-release forms involves the preparation of granules by wet granulation techniques, followed by coating with the lipid agent. This coating regulates the release of the drug from granules and tablets and is applied in a fluidized bed apparatus. The techniques of applying hot-melt coating onto a fluidized bed of particles have received no appreciable attention in the pharmaceutical literature (6).

The top-spray mode was selected for the hot-melt coating (7).

Another method without the use of an organic solvent, tumbling melt granulation (TMG) by a centrifugation granulator (CF), may be applied as a coating technique for preparing controlled-release spherical beads (8).

This article describes the study of the influence of theophylline granule size and the percentage of Compritol 888 Ato on in vitro drug release from granules and tablets.

MATERIALS AND METHODS

Materials

Theophylline monohydrate was used as a tracer for the granulation manufacture (Cooper, Melun, France). Dibasic calcium phosphate dihydrate was used as a diluent (SPCI, Lyon, France). Polyvinylpyrrolidone K30 (PVP) was used as a binder (Sigma, St. Quentin Fallavier, France). Compritol 888 Ato was used as a coating agent (Gattefosse).

Apparatus

The following equipment was used:

granular mixer (Lôdige MR 20 high-shear mixer, Marseille, France)
granular-pellicular fluidized bed (Glatt GPCG5, Binzen, Germany)
oscillating sieve (Frewit GM 263, Binzen, Germany)
flexible mixer (Turbula T2C, Geneva, Switzerland)
alternative tablet press (Frogerais OA, Paris, France)
bulk volumeter (Stav 203, Engelsmann, Germany)
friabilator (Erweka TAR, Paris, France)
hardness tester (Erweka TBT/S Vankel, Paris, Germany)
ultraviolet (UV) spectrophotometer (CAM-SPEC M330, Cambridge, UK)

The dissolution apparatus was a Dissolutest Prolabo (basket for granules and paddle for tablets) (Paris, France). The scanning electron microscope (SEM) was a JOEL JSM-35 CF (Tokyo, Japan).

Methods

Formula

The formula used for granulation manufacture contained 33% theophylline, 64% dibasic calcium phosphate dihydrate, and 3% PVP K30.

Manufacture of the Granules

A total of 5 kg powder was mixed for 5 min in a 10-L high-shear mixer (Lôdige MR20) at 250 rpm. A volume of granulation liquid (900 ml) was poured on the powder mixture in 10 min. The wet mass thus obtained was passed through a 1-mm screen of an oscillating sieve (Frewit GM 263), and the resulting granules were dried in an oven at 60°C for 2 hr. Two batches of 5 kg each were prepared and mixed after drying.

Coating Process

Uncoated granules (5 kg) were fluidized with an air volume of 110 m^3/hr, which allowed good fluidization patterns, using a Glatt GPCG-5 fluidized bed with top-spray technique. The 50-μm pore size bottom mesh

screen was from Glatt International. A binary-type nozzle with a port size of 1 mm and an air dome setting of 60°C provided a good spray pattern with molten agent at an atomization pressure of 3 bar.

Atomization air was heated with an electric heater and kept at a temperature slightly higher than the wax melting point. Figure 1 illustrates the configuration of the coating process and fluidization pattern. The filter was shaken in alternative halves at 40-sec intervals for 8 sec without interruption of fluidization or spraying.

Inlet air was kept first at 60°C inlet air and increased to maintain the product temperature at 68°C, just below the melting point of Compritol 888 Ato (between 69°C and 74°C).

Molten wax was maintained at a constant temperature (120°C) using a hot plate. Using a peristaltic pump, the spray rate was 20 g/min. Coating was applied to 4% and 6% weight (200 g and 300 g, respectively). The coated granules were cooled for 15 min.

Preliminary experiments enabled us to define process conditions that achieved fast coating of granules without sealing and congealing of the coating agent.

Under these conditions, the coating material was melted, sprayed on the granules, which were cooled. The total time of these operations (warning, spraying, and cooling) was about 30 min.

Production of Sieve Fractions

A 100-g sample was sieved using sieves of 400, 200–400, and 100–200 μm to separate the sample into four sieve fractions. The sieves were placed on a Retsch sieve vibrator for 10 min at 40% of the maximal vibrational capacity. The fraction retained on each screen was weighed and expressed as a percentage of the total weight: fraction 1, <100 μm; fraction 2, 100–200 μm; fraction 3, 200–400 μm; and fraction 4, >400 μm.

Particle size analysis was performed on the uncoated granules and on the coated batches (batches 1 and 2).

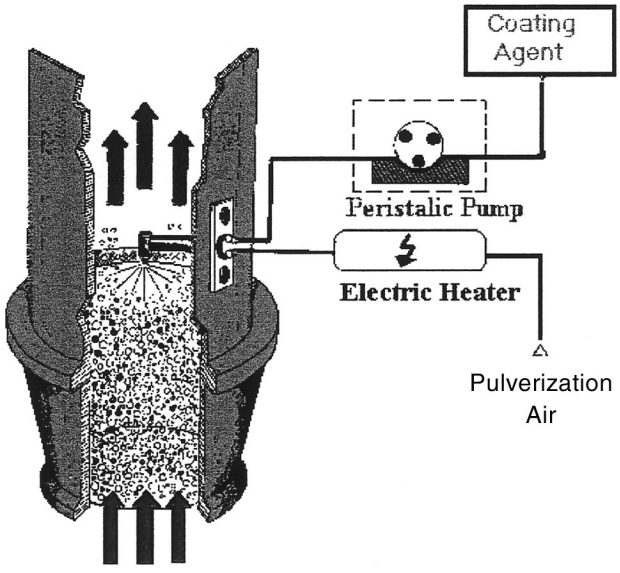

Figure 1. Configuration of experimental installation.

Rheological Properties

Flowability

The flowability test was carried out in a standardized funnel. The powder was regarded as being able to be compressed when the time taken by 100 g of powder to run out is less than 10 sec (European Pharmacopoeia, 3rd ed.). Three runs were needed.

Bulk and Tap Densities

For the bulk and tap densities, 100 g of each sieve fraction from each batch were poured into a 250-ml graduated cylinder. The volume of granules was noted after 10 and 500 taps on a tap density apparatus (Bulk Volum Stav 203) and expressed in volume.

Uniformity of Drug Distribution

Drug content was determined on the global (unsieved) sample and on each sieve fraction. A 400-mg sample was dissolved in 1000 ml of buffer solution (pH 1.2) and was mixed until the drug was completely released. Absorbances measured by UV spectrophotometry at 271 nm were used to calculate the concentration of the drug in the global sample and in each sieve fraction.

Percentage of Coating Material Deposited

The efficacy of the coating process was evaluated by calculating the percentage of Compritol 888 Ato actually deposited on the theophylline granules. A 400-mg sample of each batch of granules was dissolved in 1000 ml of buffer (pH 1.2) until complete release of the drug. The theophylline content of the granules before and after the coating process was used to calculate the actual percentage of Compritol 888 Ato deposited per total batch.

According to this method, we calculated 4.1% for the first batch and 6.1% for the second batch. The experimental percentages of the coating agent are close to the theoretical percentages, thus demonstrating the efficacy of the coating operation and the feasibility of the process.

Tablet Manufacture

The granules were lubricated directly after coating by the addition of 1% of talc and 1% of magnesium stearate and were mixed for 10 min at 40 rpm in a Turbula T2C to improve density, flowability, and compressibility.

The tablets were made with an alternative Frogerais single-punch machine (D10R10) at 54 tablets per mine. The tablets contained 100 mg of theophylline.

Tablets thus prepared were subjected to the tests for uniformity of mass, hardness, friability, drug content, and drug content uniformity (European Pharmacopoeia, 3rd ed.). Tests for hardness, friability, and weight conformity were performed on the tablets manufactured starting from batch 2 and from its fractions. Hardness was measured with a Durometer Erweka TBT/S ; an average hardness for 10 tablets was calculated.

The friability was measured with an Erweka TA3R (100 turns at 25 turns per min). The in vitro dissolution test was then performed as for the granules.

Dissolution Study

After coating, the different fractions were tested for in vitro theophylline release using a USP apparatus (basket for granules and paddle for tablets) with 1000 ml of pH 1.2 $\pm$ 0.5 buffer solution (artificial gastric juice) as the dissolution medium at 37°C and at 100 rpm.

Scanning Electron Microscopy Experiments

Granules were gold coated and photographed using a JOEL JSM-35 CF SEM.

RESULTS AND DISCUSSION

Table 1 shows populations of the different sieve fractions. The increase in the coating percentage was characterized by a decrease of fractions 1 and 2 and an increase of fractions 3 and 4.

Table 1

Particle Size Distribution (%)

Sieve Fractions	Uncoated Batch	Batch 1	Batch 2
Fraction 1	10.02	8.33	5.28
Fraction 2	30.80	20.65	17.53
Fraction 3	19.21	25.40	27.45
Fraction 4	39.96	45.62	49.74

All sieve fractions from the various batches exhibited good flow properties. Furthermore, tablets obtained, without any signs of capping or sticking, were found to satisfy the European Pharmacopoeia, 3rd edition, requirements for weight uniformity and hardness (69 to 78 newton), as well as the friability test ($<$1%).

The results obtained for theophylline content for the global sample and for the various sieve fractions showed that the drug was uniformly distributed (Table 2).

Influence of the Percentage of Compritol 888 Ato on Theophylline Release from Granules

Drug release from uncoated granules was about 90% in 15 min. The coated granules exhibited sustained-release characteristics, with the two batches presenting similar dissolution profiles.

An increase in the percentage of coating material (from 4% to 6%) did not greatly affect drug release; the release profiles of the two batches were virtually identical (Fig. 2).

The dissolution profiles can be divided into two distinct phases. The first phase (0–45 min) is related to the distribution of the droplets deposited around the drug particles. It is principally in this field that we can observe the coating efficacy. In the second phase ($>$45 min), the main mechanism of release is diffusion through the lipid matrix. Note that any uncoated theophylline will have dissolved before this time.

In the hot-melt coating technique, the lipid agent does not form a continuous film; rather, the solid droplets that hit the core may form a film composed of several layers, depending on the quantity of Compritol deposited. This leads to dissolution profiles that are quite different from those obtained with classical polymers (9,10).

These results are in agreement with the photographs, which show significant differences on the surface of the granules. Figure 3 shows an SEM of an average granule prior to coating, and Fig. 4 shows a lipid-coated granule (6% coating by weight). In Fig. 4, one can see droplets of Compritol deposited; this coating did not form a homogeneous film around the granules.

Influence of Granule Size on Drug Release

Theophylline Release from the Granules

The dissolution tests performed on the various fractions (Figs. 5 and 6) showed differences in the release kinetics. The dissolution profiles from the sieve fractions of batch 1 showed that theophylline release decreased

Table 2

Theophylline Content in Each Sieve Fraction

	Batch 1 (4%)					Batch 2 (6%)				
Fractions	1	2	3	4	Total Batch	1	2	3	4	Total Batch
Drug content (%)	30.70	31.20	31.70	30.40	31.63	30.30	30.60	31.30	31.70	30.96

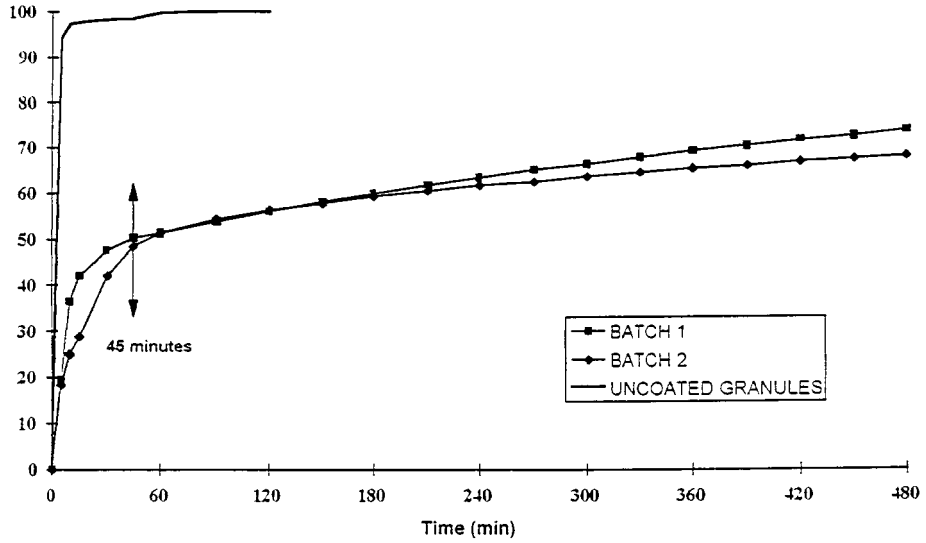

Figure 2. In vitro dissolution profiles from the coated granules (batches 1 and 2).

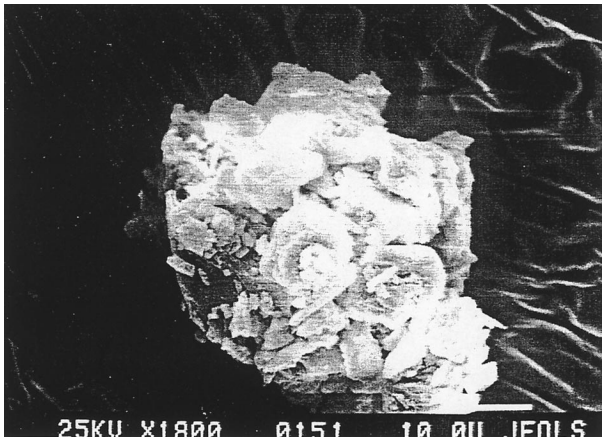

Figure 3. Scanning electron micrograph of uncoated granule at 1800× magnification.

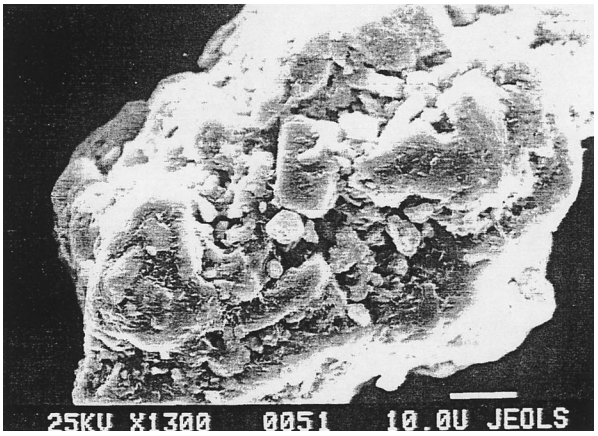

Figure 4. Scanning electron micrograph of wax-coated granule. Total batch 2 (6%) at 1300× magnification.

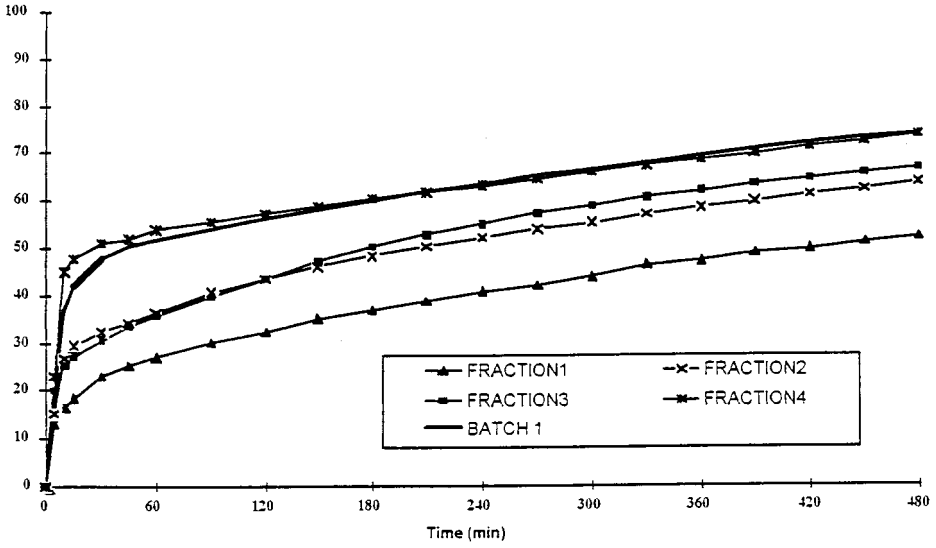

Figure 5. In vitro dissolution profiles of the different granule size fractions (batch 1).

with decreasing granule size (fraction 1). Only 52% of the drug from sieve fraction 1 was released in 8 hr. Release kinetics of sieve fractions 2 and 3 were similar. An increase in drug release was observed with fraction 4 (granule size $>$ 0.4 mm). These profiles suggest the following hypothesis: In the case of batch 2, lower profiles (that is, better sustained-release characteristics) were related to a decrease in granule size.

Figures 7 and 8 show the difference of coating between two granule sizes, fractions 1 and 4. Indeed, from Fig. 7, one can see that the Compritol 888 Ato is spread out well on the surface of the granule. There are enough droplets to form a multilayer film. This film is not continuous, but covers the main surface of the granules. On fraction 4, one can see that the greasy substance is in the form of droplets that are solidified on the surface of the grain. According to granule size, additional droplets are needed to form a multilayer film.

In the two batches, the lowest profiles were obtained with the smallest granules due to the fact that the droplet diameter of Compritol 888 Ato is constant (fixed by nozzle port size, spraying dome, and atomization air pres-

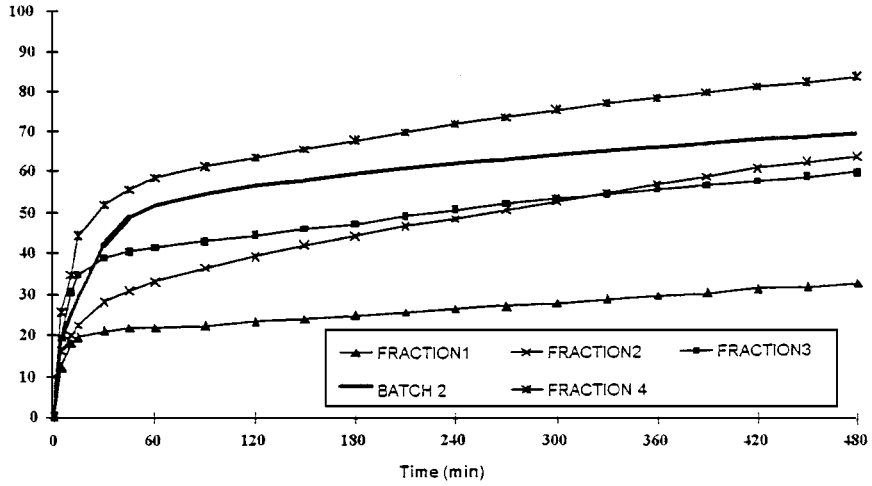

Figure 6. In vitro dissolution profiles of the different granule size fractions (batch 2).

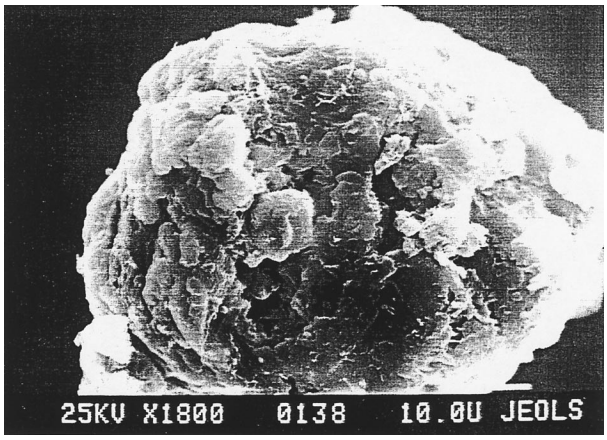

Figure 7. Scanning electron micrograph of wax-coated granule. Fraction 1 (8.2%) of batch 2 at 1800× magnification.

sure), resulting in greater coverage of the smallest granules.

The difference in the dissolution profiles obtained with each of the four fractions leads us to the suggestion that a large quantity of Compritol 888 Ato was deposited on the fractions with a small particle size.

To verify this hypothesis, we determined the actual percentage deposited on each sieve fraction (Table 3). As the two batches were coated under the same operating conditions except for percentage deposited, from Table 4 we suggest that the percentage of Compritol 888 Ato was mainly responsible for the dissolution kinetic differences between the different sieve fractions. The influence of the granule size on the theophylline release was studied by plotting on the same graph (Fig. 9) the different granule sizes with the same amount of Compritol 888 Ato: B1F1, batch 1 and fraction 1; B1F2, batch 1 and fraction 2; B1F3, batch 1 and fraction 3; B2F2, batch 2 and fraction 2; B2F3, batch 2 and fraction 3; and B2F4, batch 2 and fraction 4.

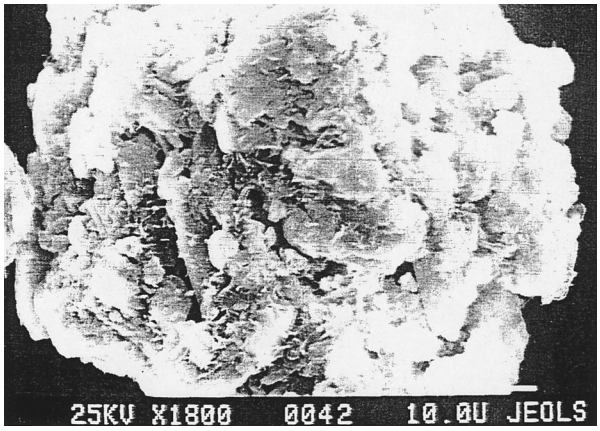

Figure 8. Scanning electron micrograph of wax-coated granule. Fraction 4 (3.8%) of batch 2 at 1800× magnification.

One can see that granule size mainly controls the theophylline release, especially for the smallest and the largest granules. Indeed, only a few differences were shown between B1F2 and B2F3, so theophylline release does not really depend on the size difference between 100–200 μm and 200–400 μm.

Last, we compared, on one hand, B1F1 and B2F2, and on the other hand, B1F3 and B2F4; in each group, the granules contain approximately the same amount of coating agent. Accordingly, the surface influence on theophylline release is particularly important for granules smaller than 100 μm and for granules larger than 400 μm.

Figures 8 and 10 show that, for the same percentages of Compritol 888 Ato deposited on granules (3.8% and 4%), when granule size decreases, the uniformity of the film improves. So, the uniformity of the film depends on the percentage of Compritol deposited and on the particle size.

Batch 2 granules exhibited the greatest differences in dissolution profiles, depending on granule size. Values for granules from this batch were then tabulated.

Theophylline release from the tablets

The dissolution profiles of the tablets prepared with the coated granules are shown in Fig. 11. These dissolution profiles were very different from those of the granules. The linearity of the curves prevented division of the profiles into two phases. These data were modeled and were fit the Higuchi model well (Table 5).

The different fractions exhibited the same dissolution profiles, except for fraction 1 (0–100 μm), because of the matrix effect Compritol 888 Ato created during compression. Only the fraction with the smallest particle size exhibited the lowest quantity released (60% for this fraction and 80% for the others after 8 hr).

CONCLUSION

We coated the immediate-release theophylline granules with two different proportions of lipid agent and studied the influence of particle size and concentration of Compritol 888 Ato deposited on the in vitro theophylline release from granules and tablets. The dissolution profiles

Table 3

Real Percentage of Compritol 888 Ato Deposited on Each Fraction

	Batch 1 (4%)					Batch 2 (6%)				
Fractions	1	2	3	4	Total Batch	1	2	3	4	Total Batch
Compritol 888 Ato (%)	6.80	5.30	3.80	1.70	4.10	8.20	7.20	5.30	4.00	6.10

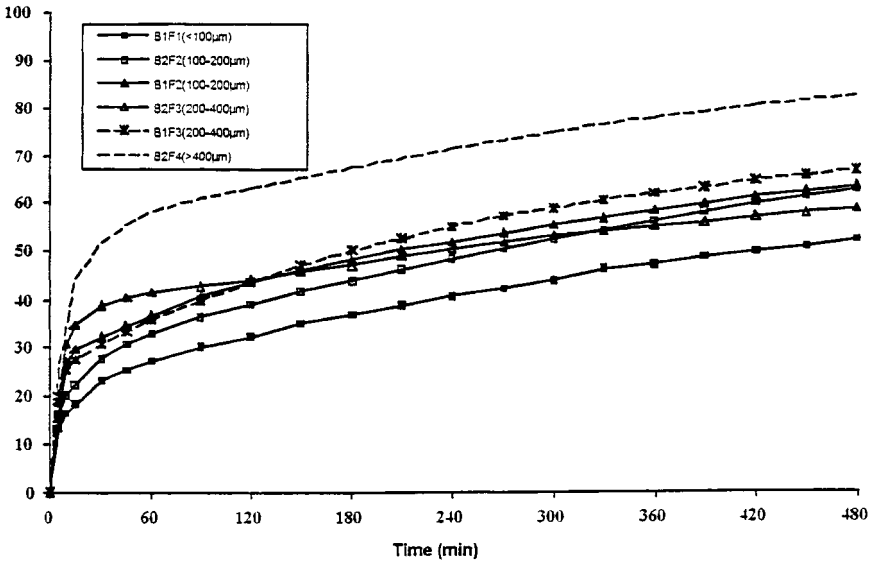

Figure 9. Influence of granule size and amount of Compritol 888 Ato deposited on dissolution profiles.

Table 4

Influence of Granules Size and Amount of Compritol 888 Ato Deposited on Theophylline Release

	Compritol 888 Ato (%)	Theophylline Dissolved (%)	
		1 hr	8 hr
B1F1 (<100 µm)	6.8	27	52
B1F2 (100–200 µm)	5.3	37	64
B1F3 (200–400 µm)	3.8	36	67
B2F2 (100–200 µm)	7.2	33	63
B2F3 (200–400 µm)	5.3	41	59
B2F4 (>400 µm)	4.0	58	82

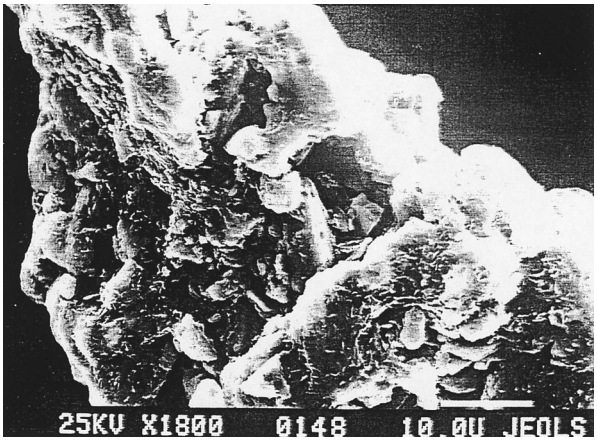

Figure 10. Scanning electron micrograph of wax-coated granule. Fraction 3 (3.8%) of batch 1 at 1800× magnification.

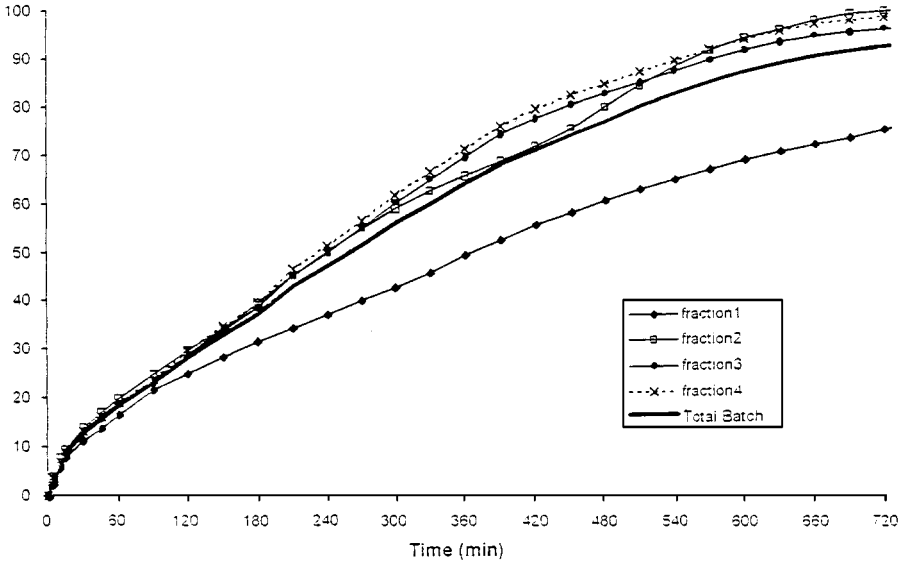

Figure 11. In vitro dissolution profiles of tablets prepared from different sieve fractions (batch 2).

of the theophylline starting from the total batch show a fast-release phase of the active drug, followed by a diffusion phase that was spread out over several hours. The dissolution results obtained by the sieve fractions according to percentage of Compritol 888 Ato deposited on each fraction show that the size fraction greater than 200 μm was responsible for the fast release of theophylline during the first 60 min. The release rate of theophylline can be modulated according to the size of the granules and the quantity of the greasy substance deposited. As a matter of fact, the smaller the granule size was, the better the covering of lipidic agent was. The photographs under the electron microscope show clearly that Compritol 888 Ato does not settle in a continuous film, but in several layers, with a recovery that depends on the quantity of the greasy substance deposited and on the size granules.

The dissolution test results were very different whether in the form of granules or tablets.

Stability and aging studies designed to complement this research are ongoing and will be the subject of a subsequent article.

The experimental results given here lead to the following conclusions:

Hot-melt coating on granules was successful using a top-spray technique with Compritol 888 Ato.

An increase in the percentage of coating material prolonged drug release.

There was a relationship among granule size, percentage of Compritol 888 Ato, and theophylline release rate. The quantity of greasy substance deposited decreased with the increase of granule size, resulting in an acceleration of theophylline dissolution.

Theophylline release can be controlled by granule size and percentage of Compritol 888 Ato deposited.

In hot-melt coating technology with a top-spray technique, in our experimental conditions, the lipid agent did not form a continuous film, but formed a multilayer discontinuous film. This sort of film is responsible for the typical theophylline dissolution profiles from granules. In the case of the smallest and the largest fractions, granule size had the main

Table 5

K *and* R^2 *Values from Higuchi Model from Batch 2*

$Q = K\,t^{1/2}$	Fraction 1	Fraction 2	Fraction 3	Fraction 4	Total Batch
K	2.92	4.00	4.01	4.11	3.76
R^2	.992	.988	.986	.986	.990

influence on the dissolution release rate. Because of the matrix effect during compression, theophylline dissolution profiles from tablets are quite different from those for granules.

The dissolution rate can be varied with percentage deposited, granule size, and with the form (granules or tablets).

REFERENCES

1. E. M. Ouriemchi, J. Bouzon, and J. M. Vergnaud, Int. J. Pharm., 113, 231–240 (1995).
2. G. S. Banker and G. E. Peck., Pharm. Technol., 5, 55–61 (1981).
3. J. Joachim, E. Cauture, P. Prinderre, N. Farah, J. P. Laforet, and P. Barthelemy, Pharm. Man. Rev., 8, 24–28 (1996).
4. T. Fuchizawa, J. dispersion Science and Technology., 10, 667–691 (1989).
5. A. Faham, P. Prinderre, E. Cauture, G. Kalantzis, N. Farah, and J. Joachim., First Pharmaceutical Sciences Conference, Faculty of Pharmacy Assiut, March 4–5, 1998.
6. M. J. Jozwiakowski, D. M. Jones, and R. M. Franz, Pharm. Res., 7, 1119–1126 (1990).
7. M. A. Mehta, Pharm. Technol., 12, 46–52 (1988).
8. T. Maejima, O. Takashi, K. Nakajima, and M. Kobayashi, Chem. Pharm. Bull, 45, 904–910 (1997).
9. G. F. Palmieri, P. Wehrlë, and A. Stamm., Drug Dev. Ind. Pharm., 21, 879–888 (1995).
10. P. Prinderre, E. Cauture, Ph. Piccerelle, G. Kalantsis, J. Kaloustian, and J. Joachim., Drug Dev. Ind. Pharm., 23, 817–826 (1997).