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Research paper

Compritol® 888 ATO: an innovative hot-melt coating agent for prolonged-release drug formulations

Philippe Barthelemy[a,*], J.P. Laforêt[a], N. Farah[a], J. Joachim[b]

[a]*Gattefossé s.a., Saint Priest, France*
[b]*Université d'Aix, Marseilles II, Marseilles, France*

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Abstract

The aim of the present study was to assess the coating of drug-loaded sugar beads and lactose granules with Compritol® 888 (National Formulary (NF) – Glyceryl Behenate). Theophylline was used as tracer and layered onto the beads, or granulated with lactose and sugar. Coating conditions (temperature, spray-rate, air pressure, etc.) were investigated for the production of prolonged release beads or granules, and dissolution kinetic curves were discussed. The study confirms the satisfactory coating potential of the hot-melt fluid-bed coating process on large spherules or granules. The optimized conditions confirm previous work, underscoring the considerable importance of the temperature of molten coating materials and the atomization air pressures. More sophisticated equipment would undoubtedly produce more efficient coating but the technique nevertheless seems promising. Practical data is now available for standard top spray equipment for fine and coarse granules. (1) Granule and spherule surface adhesion is controlled and consistent; (2) the coating is homogeneous, with continuous atomization and spraying onto the support; and (3) the release profile is directly related to the quantity of wax applied. Several competing mechanisms are also involved, including a diffusion-controlled process and a dissolution mechanism. Dissolution profiles appear to be consistent from one batch to another.

Keywords: Hot-melt coating; Prolonged release; Wax coating; Compritol® 888 ATO; Glyceryl behenate; Fluid-bed coating

1. Introduction

The use of fluid-bed processing in the development and production of solid dosage forms is on the increase. Fluid-beds are traditionally used for granulation and the drying and coating of powders, granules, tablets, beads and spherules using spraying techniques. Generally speaking, the coating material is dissolved in a solvent (water or organic) prior to spraying. During and after coating the solvent must be evaporated. The use of solvents nowadays is under constraint due to the problems of trace levels, while recovering a solvent often proves expensive. Due to its long evaporation time water could also be a problem. In order to avoid such problems and to reduce costs, it is appealing to use a meltable product – a wax or derivative – as coating materials. However, few authors have published on this subject and little attention has been given to this technique in the pharmaceutical literature.

An excellent review of the process conditions and equipment for hot-melt coating has been published by Jones and Percel [1]. Wax formulations for coating drug-loaded sugar beads have been investigated by Bhagwatwar and Bodmeier [2], while Achanta et al. [3] have written a general overview of the development of pharmaceutical coating technologies, including hot-melt coating methods.

Optimization of the coating process has been investigated by Jozwiakowski et al. [4]. Hot-melt coating requires a longer expansion chamber and an alternate filter agitating system. The most interesting part of this investigation is the study of the influence of process variables on the character-

* Corresponding author. Gattefossé s.a., 36 Chemin de Genas, BP 603, 69804 Saint Priest cedex, France. Tel.: +33-4-72229800.

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Table 1

Parameters for top spray hot-melt coating

Parameters	Spherules	Granules
Nozzle port size (mm)	1	1
Fluidization value (%)	40	30
Atomization air pressure bar)	3.5	1.5
Atomization air temperature (°C)	90	120
Flow rate of coating (g/min)	7–8	8–9
Intermediate shaking time (s)	30	30
Shaking time (s)	3	3
Bed temperature (°C)	63–64	66–68
Spraying angle (turn)	1	4/6

istics of coated beads through a modified central composite design.

In this study of state-of-the-art hot-melt coating, the major variables were: product bed temperature, molten wax temperature, spray rate, and atomization air pressure. Batch size, fluidization velocity, nozzle port size and coating percentage were fixed, as was the product bed temperature (54°C).

The experimental design was a modified central composite design and leads to a second-order regression model. The regression model equation shows interaction between the process variables and a significant influence of the atomization air pressure which varies to power 2.

2. Materials and methods

2.1. Materials

The USP/NF Glycerol behenate (Compritol® 888 ATO, a Gattefossé, registered name product in France) was chosen because of its chemical characteristics, which give little polymorphic potential variation.

Coated lactose spherules ranging from 0.71 to 0.85 mm, made by Werher, Germany were used. Theophylline monohydrate produced by Cooper in Melun, France was used as tracer. Polyvinyl pyrrolidone (PVP K30) was supplied by BASF, Germany. Cooper, in Melun, France also supplied lactose, corn starch and sucrose. The hydroxypropyl cellulose (HPMC) came from Seppic, France.

The equipment used was: (1) GPCG3 fluid-bed granulator, Glatt Brinzen, Germany, fitted with a binary nozzle and a heating device for atomization air; and (2) High shear mixer, Lödige, Germany.

2.2. Methods

Theophylline was coated onto the spherules using the bottom-spray technique in a GPCG3 fluid-bed granulator fitted with a Wurster column. A solution of PVP K30 in alcohol and water was used as binder and vehicle. For the production of granules, lactose and theophylline were mixed together in the Lödige with corn starch and HPMC. A sucrose solution was used for granulation, with oven-drying at 50°C; the granules were then sieved with a 0.80 mm screen.

The USP basket method was chosen for the dissolution study. The temperature was 37°C, the dissolution medium was gastric USP type of pH 1.2 with 100 rpm stirring and the sample was 1 g. The optical density was measured at 268 nm to determine the theophylline concentration (n = 3).

The hot-melt coating process was conducted in line with the process variables described by Mehta [5]. The air spray technique was used for the atomization of the liquid. The coaxial wand was located at the low level of the equipment.

The spraying angle was adjusted to correspond to the volume of the powder in the basket. The fluid bed was not equipped with a continuous agitation system and spraying had to be stopped during filter agitation. The nozzle diameter was 1 mm.

3. Results and discussion

The optimized process conditions are shown in Table 1.

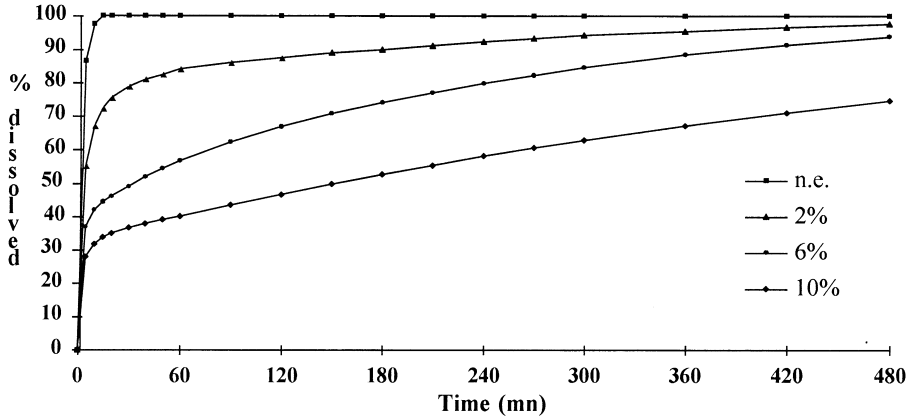

Fig. 1. Release of theophylline from loaded spherules coated with Compritol® 888 ATO.

As far as atomization air pressure is concerned there are considerable partial differences in coating parameters for spherules and granules. This is certainly due to the higher fluidization air value for spherules. The more cohesive material and the smoother surface of spherules could also explain their lower atomization air temperature.

In these conditions spherules were coated with 2%, 6% and 10% of NF Glyceryl behenate (Compritol® 888 ATO). Fig. 1 shows the release of theophylline from the loaded spherules coated with NF Glyceryl behenate at different concentrations. Increasing the percentage of coating material led to prolonged drug release. The spherules maintained the same appearance throughout the dissolution test. Four types of dissolution profiles were observed. (1) n.c. – this corresponds to the uncoated spherules with a complete theophylline release within 10 min; (2) with 2% of Compritol® 888, a slight reduction of the release is observed. Theophylline (85%) is released within 1 h; (3) with 6% of Compritol® 888, the barrier effect of Compritol® 888 becomes efficient and only 55% of the theophylline is released within 1 h (35% in 5 min); (4) with 10% of Compritol® 888, the barrier effect is more evident as 38% of the theophylline is released within 1 h, the initial release remains high (28% in 5 min).

The three curves (2%, 6% and 10%) show two release phenomena (Fig. 1): (1) during the first few minutes, the uncoated or uncompletely coated spherules immediately release the theophylline by dissolution; (2) the coated spherules – depending on the quantity of coating material – show a diffusion of theophylline through the wax barrier [6].

After the rapid release phase, the theophylline release from coated spherules could be described as zero order [7], showing that the system is diffusional.

Since the distribution profile of spherules coated with 6% of Compritol® 888 gave a good prolongation-release profile over 8 h, this was the percentage chosen for the coating of the granules. The 2% concentration and the non-coated granules were maintained so as to compare the different coating material concentrations and the spherules. Modification of the coating conditions was applied as shown in Table 1.

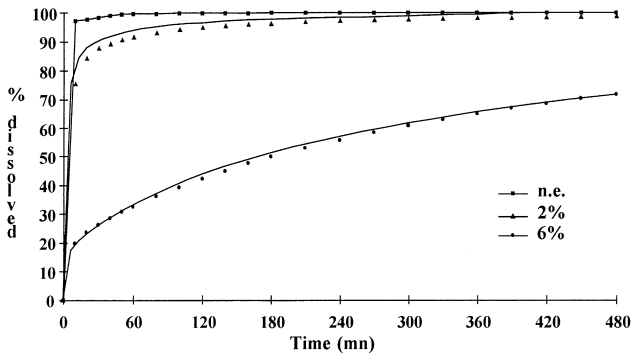

Fig. 2. Release of theophylline from granules coated with Compritol® 888 ATO.

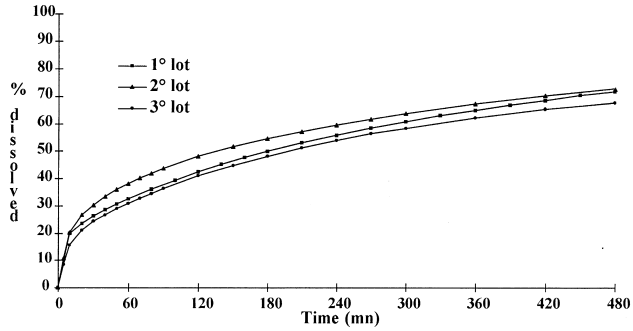

Fig. 3. Dissolution curves of theophylline granulates coated with 6% Compritol® 888.

In these conditions the coating on the granules appears to be as efficient as on the spherules. Nevertheless, only 20% of the active is released through dissolution versus 35% for the spherules. After 8 h, 70% of the active is released. When 90% of the active is released from the spherules, this difference seems to be due to the coating conditions and the granules' characteristics (Fig. 2).

In the case of spherules, all the active is located on the surface, and the membrane is saturated as soon as the active is solubilized. In the case of granules, the active is trapped within the granules. The coating conditions, especially the temperature of the coating material, are of highest importance for the spreadability and consistence of the coating. Higher temperatures lead to better covering of the granules, in spite of their irregular surfaces. This process was repeated on granules (Fig. 3) and seems to be consistent enough to give reproducible release profiles.

4. Conclusion

This study shows that hot-melt coating techniques can be carried out in standard-sized laboratory fluid bed granulators using top spray techniques. Both spheroidal particles and granules can be coated using this technique in spite of their differences in density, porosity and surface roughness. Spraying conditions appear to be of the highest importance, especially the molten wax temperature and the atomization air pressure.

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