DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 21(8), 879-888 (1995)

RESEARCH PAPERS

AQUEOUS ACRYLIC RESIN FOR COATING AN ORIGINAL THEOPHYLLINE GRANULATE

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ABSTRACT

Spherical granules of theophylline, microcrystalline cellulose and lactose are prepared in a high speed granulator using an original method. Successively, the fraction of granules selected is coated with Eudragit RS 30D in a fluid bed coating machine using the bottom spray system and the wurster column. Finally, these granules are compressed into tablets of different hardnesses.
Dissolution studies reveal a zero order release of theophylline from the coated granules. After compression, the kinetics is modified but the tablets remain efficient to control the theophylline release during 8 hours.

INTRODUCTION

Fluid bed coating is a technique widely used nowadays because it allows, among the other applications, to coat crystals or more frequently granules with a variety of available polymers giving gastro-resistant or controlled release systems.

Eudragit RS 30D pseudolatex (as well as Eudragit NE 30D[1,2,3]) is one of the most effective polymeric preparation for controlled release systems[4] , used alone[5] or associated with other kinds of polymers[6,7,8].
In every work, undertaken to study the mechanism of film formation and the influence on it of parameters such as inert powders, quantity and type of plasticizer, different kinds of equipment, experimental parameters, adding of hydrosoluble polymers or molecules, or undertaken to realize a specific pharmaceutical formulation, the authors always present the coating of activated pellets[1,5,6,9] or loaded lactose non-pareils[2,3,7] previously purchased.
The aim of this work is to study the possibility to realize a controlled release dosage form with a theophylline granulate manufactured in the same laboratory by wet granulation in a conventional high speed granulator. The original optimized process has already been described elsewhere[10] . The obtained granulate is coated in a fluid air bed with Eudragit RS 30D at different polymer coating levels and evaluated in the present work.

MATERIALS AND METHODS

1) Wet granulation

Anhydrous theophylline (100 g), avicel PH 101 (250 g) and lactose fine crystals (150 g) are placed in the high speed granulator (Stephan UMC 5, Germany) and wetted with 200 ml of a 15% hydroalcoholic solution of hydroxypropylmethylcellulose and granulated for 12 minutes at 1100 r.p.m. per minute; then the granulate is dried under vacuum for 1 hour and finally sieved. The fraction between 200 and 1000 µm (corresponding to the 85% of the whole mass) is separated and used for the coating process[10].

2) Coating procedure

The coating dispersion is first prepared dispersing in water a quantity of plasticizer (triethyl citrate: Eudraflex, Röhm Pharma, Germany) corresponding to the 20% of the weight of the dry polymer used. This quantity is recommended because it decreases the glass transition temperature of the polymer and the minimum film formation temperature without affecting the consistence of the film. Then, an amount of talc (corresponding to the 50% of the weight of the dry polymer used) is joint and the dispersion stirred for 10 minutes. The talc is chosen in that quantity to avoid the tackiness phenomena due to the polymer characteristics without affecting the homogeneity and integrity of the film of Eudragit.

Finally, an amount of Eudragit RS 30D (Röhm Pharma, Germany) is blended with the dispersion and the final dispersed system is stirred for other 10 minutes before spraying. The formulations used are shown in table 1, where the five percentages are referred only to the amount of polymer and not to the solid totality.
The quantity of water is adjusted in order to have always a solid content of 20%; a higher quantity of solids, increasing the viscosity of the system, could modify the spraying or even plug the nozzle.
When the coating dispersion is ready, the granulate is fluidized in the air bed (Uniglatt, Glatt, Germany) and after 10 minutes of preheating at 40°C, is coated according to the parameters resumed in table 2, maintaining the coating dispersion under stirring.
The coated granulate is successively dried in the same apparatus during 20 minutes at 55°C.

3) UV analysis of the granules

The uniformity of theophylline content of the coated and uncoated granules is controlled by UV measurements in ethanol at 288 nm, after milling in a mortar an amount of granulate.

4) Hard gelatine capsules preparation

Two formulations are carried out with the 6% polymeric coating: the first one is realized filling hard gelatine capsules (size 1) with 395 mg of coated granules (corresponding to 75 mg of theophylline); the second one is realized mixing 125 mg of uncoated beads with 265 mg of coated beads (corresponding altogether to 75 mg of theophylline) and next filling hard gelatine capsules (size 1).

5) Granules compression

Two formulations are carried out with the 6% polymeric coating: the first one is realized compressing (Korsch EKO press, Germany) at different hardnesses (4,6,8,10,12 kg/cm^2) a mixture of coated granules (60,5%), avicel PH 101 (38,5%) and magnesium stearate (1%), in order to obtain tablets of 650 mg (corresponding to 75 mg of theophylline); the second one is realized compressing, at the same described hardnesses, a mixture of coated granules (40,5%), theophylline for direct compression (4%), avicel PH 101 (54,5%) and magnesium stearate (1%), in order to obtain tablets of 650 mg (corresponding to 75 mg of theophylline).

TABLE 1
Composition of the coating dispersions.

	4% COAT g	5% COAT g	6% COAT g	8% COAT g	10% COAT g
EUDRAGIT RS 30D	40	50	60	80	100
EUDRAFLE	2,4	3	3,6	4,8	6
TALC	6	7,5	9	12	15
WATER	50	62,5	75	100	125

TABLE 2
Processing condition of coating

PARAMETERS	SETTING
GRANULATE LOAD	300 g
INLET TEMPERATURE	40°C
OUTLET TEMPERATURE	34°C
FLUIDIZATION AIR VOLUME	40-60 m^3/hour
FLOW RATE	4 ml/min.
ATOMIZATION AIR PRESSURE	1,2 kg/cm^2
NOZZLE WIDTH	1 mm

6) In vitro dissolution studies

Dissolution studies are carried out in distilled water at 37°C with a Prolabo Dissolutest and UV-2101 PC Scanning Spectrophotometer (Shimadzu, Japan) connected to a 486 DX 60 mhz computer, assaying the samples spectrophotometrically at 288 nm, at preselected time intervals, for 8 hours.

RESULTS AND DISCUSSION

All the experiments are repeated 3 times without giving significant differences, and this confirms the high reproducibility of the results.
Figure 1 shows that, as expected, the theophylline release from the coated granules depends on the thickness of the film applied all around and that it gradually decreases with the increasing of the quantity of polymer.
Only the formulation with the 4% of coating delivers the 100% of theophylline after 8 hours; the percentages of drug release of the other formulations are 97,6 for the 5%, 86,4 for the 6%, 63,2 for the 8% and 31,2 for the 10% of coating.
As the thickness of the coating increases, the linearity of the release curves increases too, and (excluding the very first minutes) the kinetics of the system approaches the 0 order; in fact there is a sharp difference between the two first formulations (4 and 5%) and the others.
The 6% of coating is the minimum absolutely necessary to obtain the linearity; a lower quantity of polymer is not able to coat uniformly the granulate, probably because of the use, for the coating process, of a large diameter range of particles. So, if a release faster than 86% is needed, the Eudragit RS 30D should be mixed with Eudragit RL 30D in order to have a complexive quantity of polymer not inferior to the 6%; in this way, the theophylline release will increase (Eudragit RL is a more water permeable methacrylic copolymer) but the linearity of the curve might be conserved.
As the transit through the gastro-intestinal apparatus is estimated about 8-10 hours, the formulation with the 6% of coating is better suitable for an oral controlled delivery system, because it releases all the theophylline after 10 hours; so, this formulation is used for any successive studies.
The scanning electron microscope analysis (Jeol, Japan) of the coated beads reveals a quite smooth and continuous surface, without presence of pores (figure 2).
The dissolution curves of the hard gelatine capsules, first realized, are shown in figure 3, where the two dosage forms are compared with the free coated granulate. While the capsule filled with all coated granules has

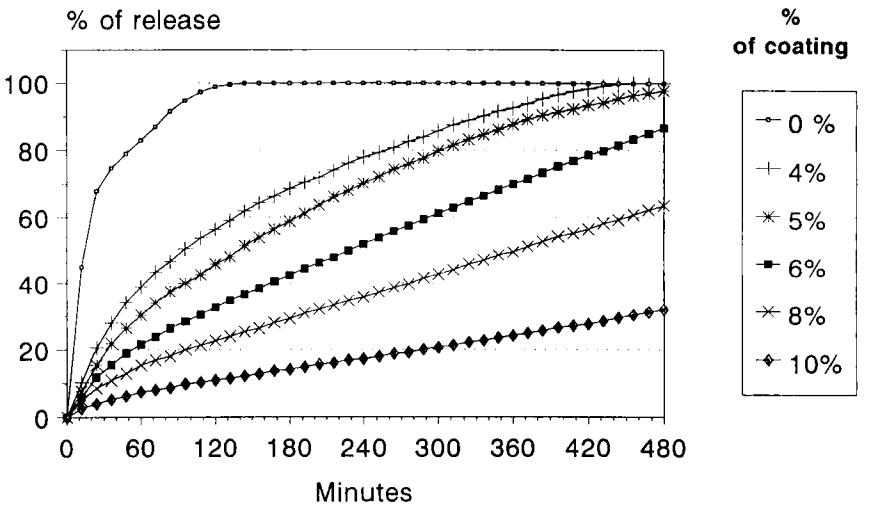

FIGURE 1
Theophylline release from the coated granules.

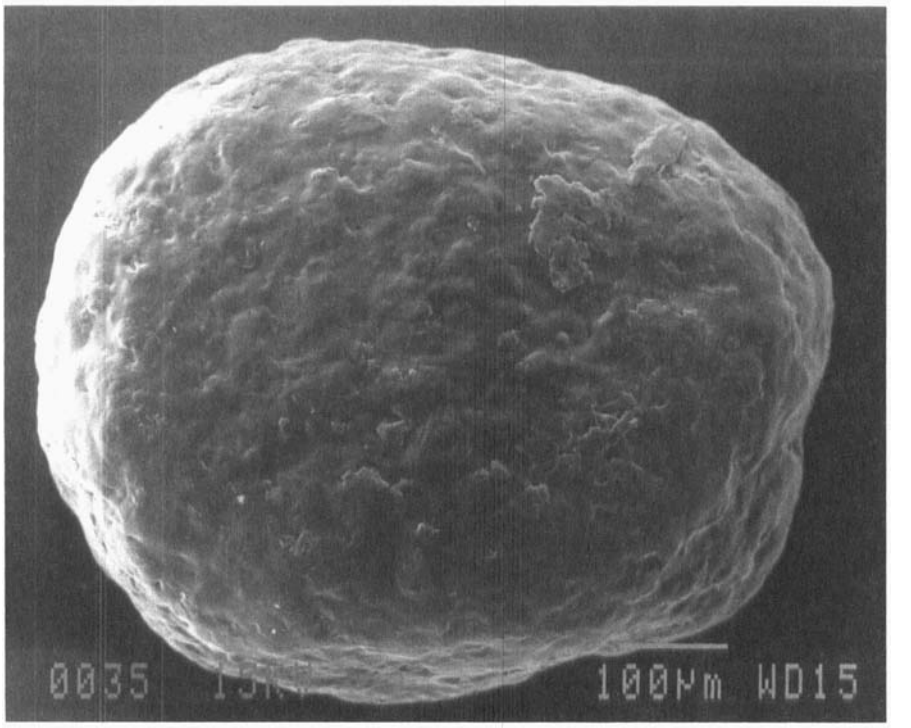

FIGURE 2
S.E.M. (x 130) of a coated granule.

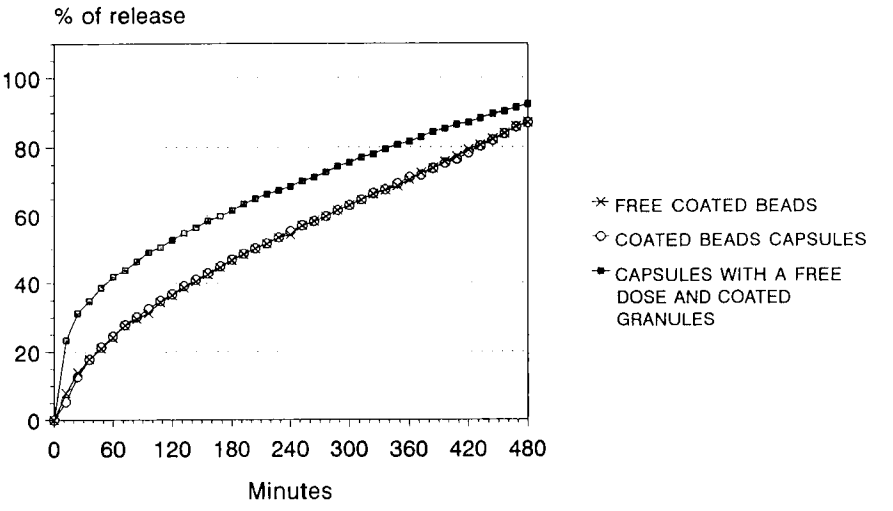

FIGURE 3
Theophylline release from hard gelatine capsules.

practically the same release of the free granules, the other one clearly shows the immediate release of the free dose and then the slow release of the remaining drug with a kinetics very close to the 0 order.

Successively, the tablets are made in an attempt to realize an alternative pharmaceutical form. Figure 4 represents the dissolution of the tablets obtained by compression of the coated granulate, at different hardnesses.

The compression force has a marked effect on the drug release: whilst the capsule maintains the same kinetics of the free coated granules, the tablets have a 1 order kinetics, even if they conserve a good power to slow down the theophylline release. Besides, unexpectedly, there is not a great difference between the tablets of hardness 4 kg/cm^2 and the tablets of hardness 12 kg/cm^2.

The explanation of these phenomena may be the quantity of coated granules contained in the tablets: of course, granules alone cannot be compressed without breaking the film and compromising the controlled release system, but to avoid this, they must be mixed with a good excipient for direct compression, able to deaden the force developing during the compression.

Avicel PH 101 possesses this characteristic, but there is a limit to the quantity of coated granules that a certain amount of avicel can bear; probably the 60,5% of granules contained in the formulation is a too high percentage and a part of the polymeric films is damaged by the compression

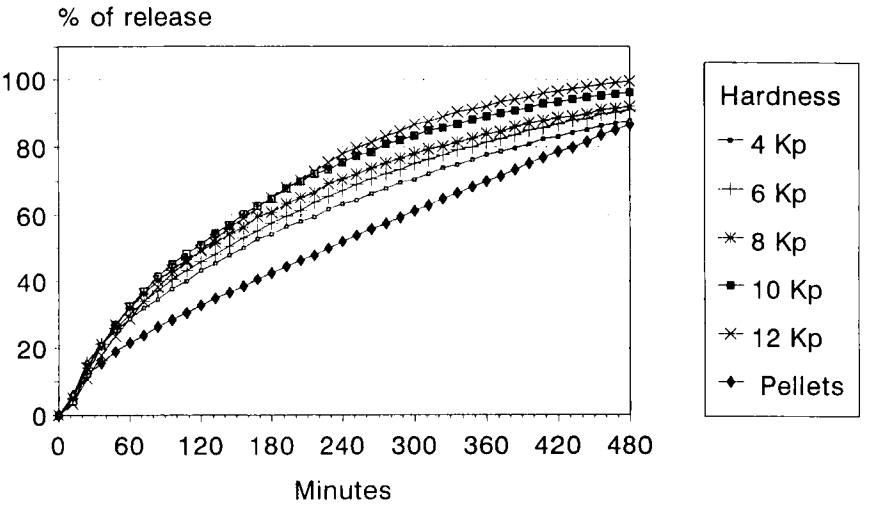

FIGURE 4
Theophylline release from tablets containing coated granules.

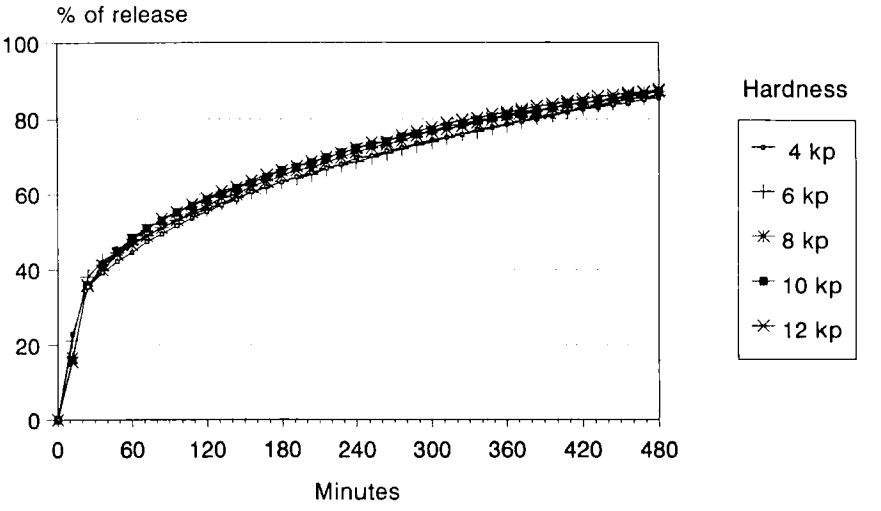

FIGURE 5
Theophylline release from tablets with a free dose and coated granules.

force giving a kinetics variation, which is more remarkable with the increasing of the compression force.
The confirmation of this theory can be found in figure 5 representing the theophylline release from the formulation containing a free dose of drug. In fact, as there is only the 40,5% of coated granules and the stress on the polymeric coating is reduced, the difference between the five formulations is very low.
Very sharp is the change of drug release after the dissolution of the free dose.

CONCLUSION

The optimized granulate[10], for its characteristics, can be easily coated in order to realize a "reservoir" system. Compared with the quantities of Eudragit RS normally necessary to obtain a good release kinetics, this granulate needs only a little amount (6%).
Eudragit RS is confirmed to be a very useful polymer for controlled release delivery systems.
Between the two oral solid dosage forms which are tested, the capsules are the best because they conserve the same properties of the free coated granules; on the contrary, the tablets change the kinetics toward a 1 order release system.
So, the compression of coated particles represent a valid alternative to the capsules if the tablet contain a low amount of these particles.

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