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RESEARCH PAPERS

PREPARATION OF INDOBUFEN PELLETS BY USING CENTRIFUGAL ROTARY FLUIDIZED BED EQUIPMENT WITHOUT STARTING SEEDS

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ABSTRACT

Pellets containing Indobufen as model drug were prepared by using the centrifugal-rotary fluidized bed equipment without employing non-pareil seeds.

The influence of different amounts of spheronization enhancer (microcrystalline cellulose) and of different fillers (lactose, mannitol, calcium carbonate) on both processing and physical properties of the pellets were evaluated.

The preparation reproducibility was also investigated.

The use of 30% w/w of microcrystalline cellulose was essential to produce a good quality pellets; the

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incorporation of filler decreased the qualitative characteristics of the pellets.
The water feeding rate proved to be an important parameter for the pellet growth.
Therefore, the results showed that this technology based on the rotary fluidized bed is a promising and alternative method in producing pellets.

INTRODUCTION

The most widely used pellet preparation methods for pharmaceutical dosage forms are extrusion-spheronization and dispersion or powder layering technologies. Commonly these processes require more than one machine or need rather long processing times (1).
Centrifugal equipment, called as well rotary or tangential spray fluidized bed, is generally proposed for layering techniques. In this case the operations of blending, layering, drying and coating can be performed in the same centrifugal equipment.
The high efficiency of the rotary fluidized bed is due the combined action of air flow, centrifugal and gravitational forces, which generate a spiral material motion and a rapid turnover rate.
In alternative the centrifugal equipment has been used for producing pellets without employing non-pareil seeds, thus indicating a simple way of preparing the cores (pellets) to be coated in situ.
Using this technological approach, the preparation of Indobufen containing pellets was investigated. Indobufen, chosen as drug model, is an inhibitor of ADP-induced platelet aggregation.
The formulation of the cores was based on the drug cellulose microcrystalline and water as binding agent;

lactose, mannitol and calcium carbonate were investigated as possible less expensive fillers.

In particular the aims of this study were:

- to verify the feasibility of producing Indobufen pellets without starting seeds
- to evaluate the effect of the formula composition on the physical properties of the pellets.
- to evaluate the influence of wetting conditions (i.e. the rate of water feeding) on the growth of the pellets.

MATERIALS AND METHODS

Raw Materials

- Indobufen (Farmitalia Carlo Erba, Italy)
- Microcrystalline cellulose (Avicel PH 101, FMC Corporation, USA)
- α-Lactose monohydrate, 200 mesh (Meggle, Germany)
- Mannitol (Roquette Frérs, France)
- Calcium carbonate USP grade (Farmitalia Carlo Erba, Italy).

Equipment

A multisystem fluidized-bed MP1 (Niro-Aeromatic, Switzerland) with Roto-Processor insert was used as centrifugal equipment. It is a modified fluidized bed column containing an inner bowl that is like a simple spheronizer with rotating friction disc and straight side walls. A spray nozzle for feeding binder liquid is placed in the lower part of the side walls. When the pelletization process is complete, the side walls are pneumatically lifted to leave a gap through which the pellets are forced out by dry air at the bottom of the inner wall and recirculated along the outside of the container walls (2).

Pellet preparation

1000 g of powder mixture composition (Table I), which was previously blended in a plastic bag, was loaded into the inner bowl of the rotary fluidized bed processor.

The rotor disc was operated at specified speed, and water was sprayed at controlled rate by means of a peristaltic pump using 1.5 bar of atomization air pressure with nozzle diameter 1.2 mm. Where not indicated the water spraying rate was 20 g/min. Air flow of 50 m^3/h was used, the process temperature and disc rotation rate were adjusted each time so that the powder particles were kept in a regular spiral motion. The wet pellets were dried at 70° C with an air flow of 500 m^3/h, the disc rotation rate was maintained at 200 rpm till the exhaust air reached a temperature of 50°C.

Physical testing on the pellets

- Sieve analysis - 100 g of pellets were sieved into a Jel 200 vibratory shaker for 5 minutes
- Poured bulk density - 100 g pellets were poured gently through a glass funnel into a graduated cylinder
- Friability - 10 g of the pellets together with 25 glass spheres (7 mm diameter) were rotated in a Roche friabilator for 10 min; the resulting material were placed on a 250 μm sieve and shaken for 5 min on a Jel 200 vibratory shaker, the amount of material passed through the sieve was weighted and expressed as a percentage
- Moisture content - the weight loss was determined by thermobalance at 100° C for 20 minutes (Mettler PC 440 with IR ray oven)
- Dissolution testing - USP XXII apparatus, Method I, 200 rpm, 37°C, in 900 mL of phosphate buffer solution. The drug concentration was assayed by UV at 280 nm (Perkin Elmer, Lambde 15)

Table I - Composition of pellets and relevant processing conditions

FORMULAE	I	II	III	IV	V	VI
Indobufen	8.5	7.0	5.5	7.0	7.0	7.0
Cellulose MC	1.5	3.0	4.5	2.0	2.0	2.0
Lactose				1.0		
Mannitol					1.0	
Calcium carbonate						1.0
PROCESS CONDITIONS						
Disc rotation, rpm	500	500	700	600	600	700
Inlet air, °C	45	41	41	26	33	17
Exhaust air, °C	18	34	27	24	25	16
Spray water, g	500	700	960	600	470	650
Granulation time, min	25	35	48	30	24	33
Drying time, min	33	35	29	36	22	43

RESULTS AND DISCUSSION

The use of relatively large amounts (35-45%) of microcrystalline cellulose brought about the satisfactory results of processing when the one-step pelletization with rotary centrifugal technique in fluidized bed is applied. As expected a decrease of cellulose led to an increased stickiness of the material and produced irregular large granules; also the electrostatic charges tended to become stronger.

For the drug formulations I-III, that contain only microcrystalline cellulose as spheronization enhancer, the amount of water required for wetting the powder mass was

found to be proportional to the amount of microcrystalline cellulose (Fig.1A). The cellulose acts by controlling the movement of the water through the wet powder mixture during the various stages of processing (3).

When a part of the cellulose was substituted with a filler (formulae II,IV-VI), the amount of the water required can vary depending on the physical properties of the specific employed material (Fig.1B).

Calcium carbonate and mannitol proved to be less suitable than lactose for processing by rotary fluidized bed technique. The incorporation of calcium carbonate led to the sticking wetted mass, while the mannitol caused the formation of larger granules along with a more evident development of electrostatic charges.

The physical and technological properties of Indobufen pellets prepared by centrifugal equipment without employing starting seeds are shown in Table II and in Figure 2.

The pellets prepared by this technique were substantially spherical, with sufficient heaviness and acceptable mechanical resistance, except for calcium carbonate containing pellets.

When the amount of microcrystalline cellulose was above 30% w/w (Formulae II,III), the pellets showed an homogeneous size distribution, approximately 95% of the pellets were in the 500-1000 μm range. On the contrary, when the microcrystalline cellulose was of 15% w/w (Formula I), the pellets showed a bimodal size distribution, characterized by a large portion in the oversized (> 1800 μm) range.

This suggests the ineffectiveness of the rotary fluid bed process for preparing Indobufen pellets at high dosage (85% w/w).

The property of the microcrystalline cellulose, described as a "molecular sponge" to physically retain water, proved to be of great importance in controlling the movement or distribution of the water in wet powder masses to be

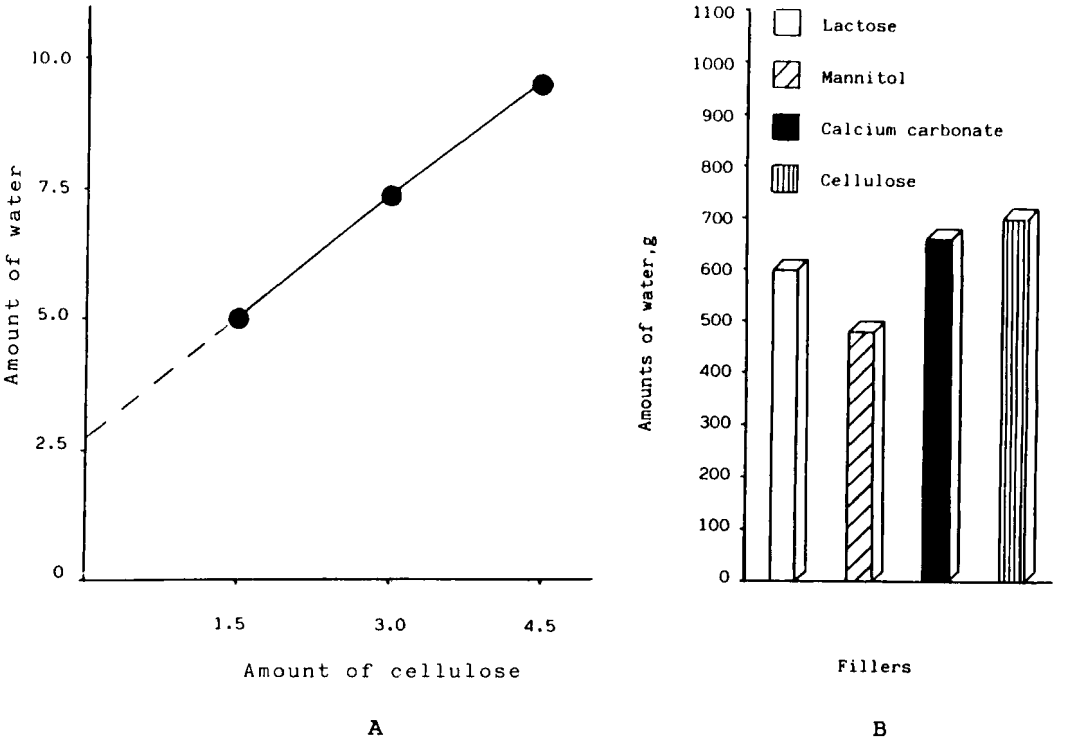


Fig.1 Amounts of water used with MP1 centrifugal equipment:
A) Relation between water and microcrystalline cellulose (Formulae I-III)
B) Amount of water used with different fillers (Formulae II,IV-VI)

Table II. Physical properties of pellets of different compositions

Tests	I	II	III	IV	V	VI
Average size, μm	1163	742	652	1254	956	636
Poured density, g/L	629	559	636	661	649	681
Friability, %	2.6	3.4	3.0	2.8	1.4	9.0
Moisture content, %	1.4	1.6	2.4	1.3	0.9	1.1

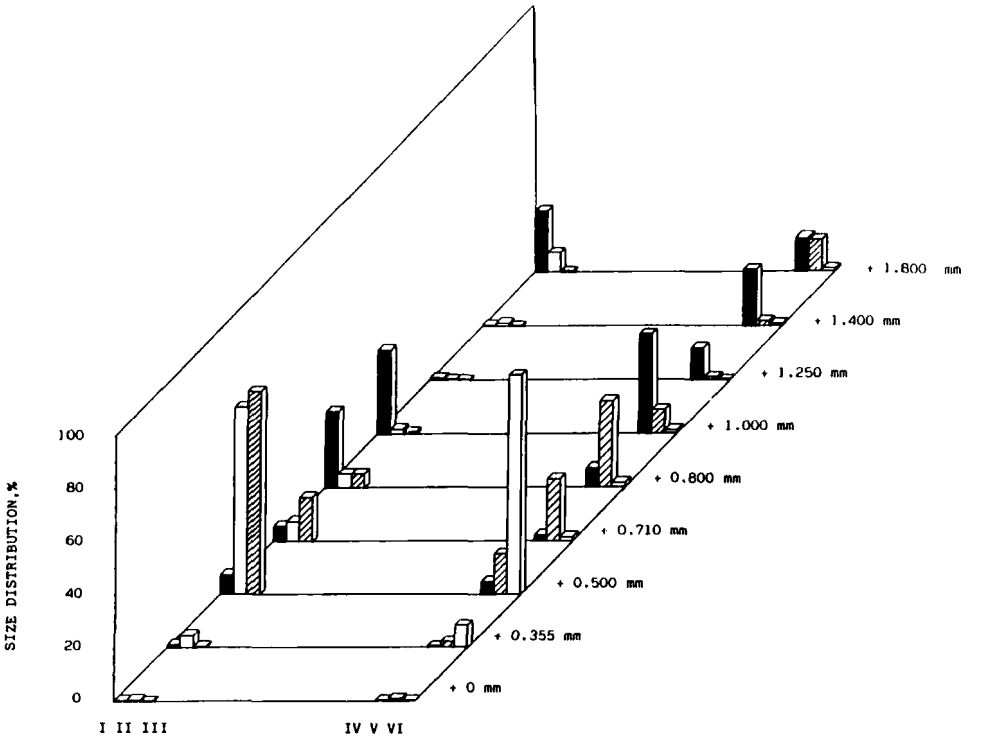


Fig.2 Size distribution of different formulation pellets prepared by MP1 centrifugal equipment:
I: Drug/Cellulose, 8.5:1.5
II: Drug/Cellulose, 7.0:3.0
III: Drug/ Cellulose, 5.5:4.5
IV: Drug/Cellulose/Lactose,7:2:1
V: Drug/ Cellulose/Mannitol, 7:2:1
VI: Drug/Cellulose/Ca Carbonate, 7:2:1

processed (3). When the nuclei of pellets have a slight excess surface moisture, they can deform and coalesce easily without subjecting to significant mechanical pressure. Microcrystalline cellulose not only confers plasticity to the wetted mass, but also imparts binding properties that are essential to obtain pellet strength and integrity.

The substitution of a part of cellulose with a corresponding amount of lactose or mannitol led to pellets

Table III - Physical properties of the pellets of formula II obtained by different wetting conditions

Water amount, g	770	800	950	600	770	950
Spraying rate, g/min	20	20	20	40	40	40
Average size, μm	638	603	778	693	826	1988
Poured density, g/L	654	670	768	678	633	718
Friability, %	2.2	2.1	1.9	2.3	2.0	1.8
Moisture content, %	1.7	1.8	1.5	1.9	1.7	2.2

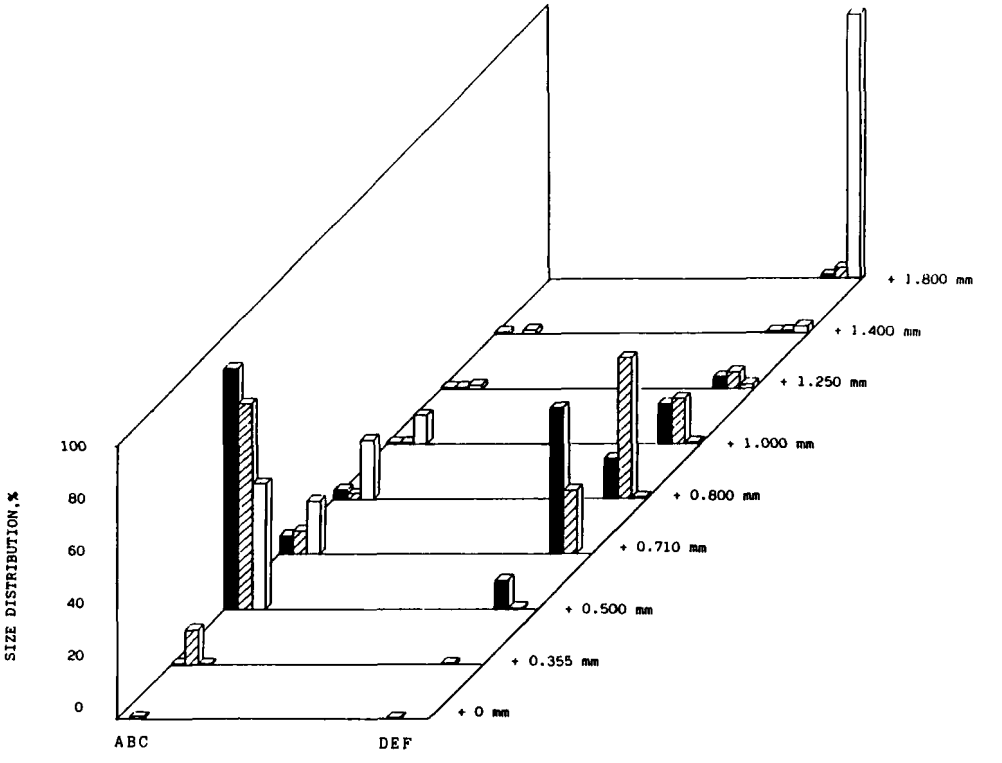
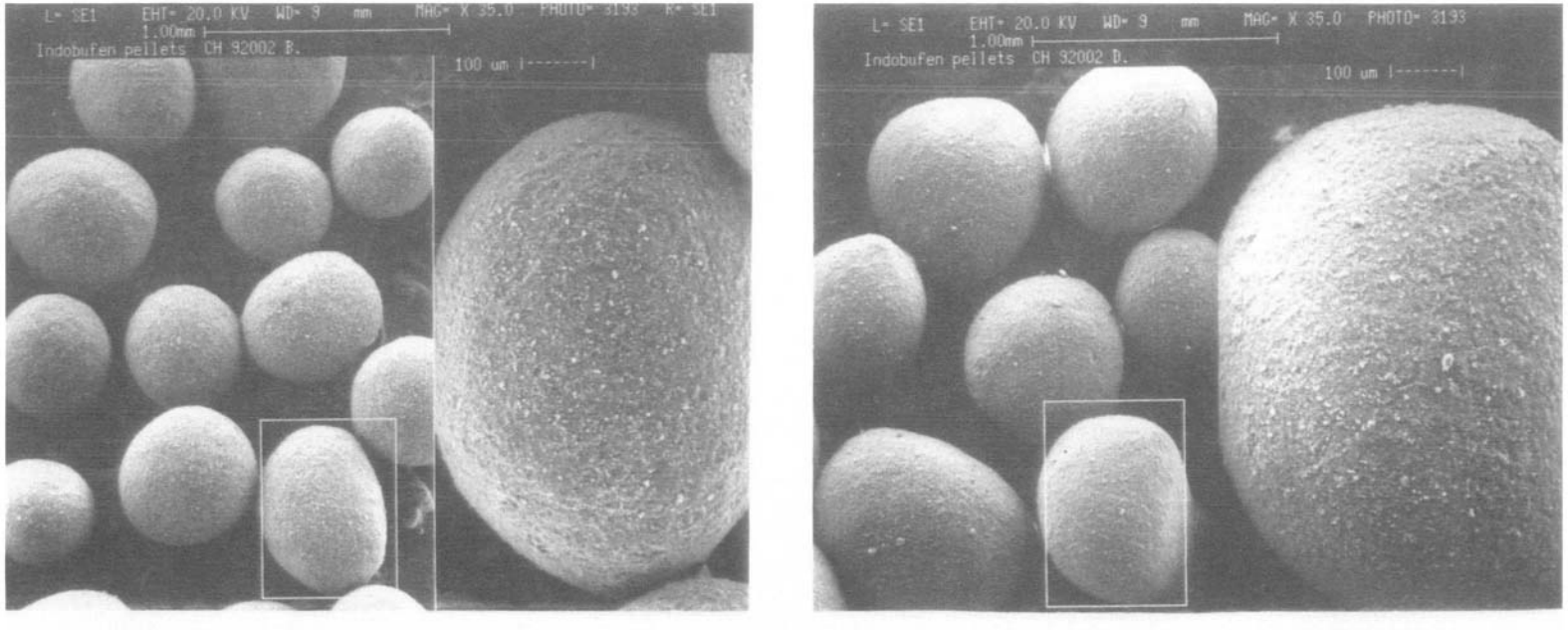


Fig.3 Size distribution of pellets (formulation II) prepared by MP1 centrifugal equipment applying different wetting conditions.
Spray rate of 20 g/min:
A) 770 g, B) 800 g and C) 950 g of water.
Spray rate of 40 g/min:
D) 600 g, E) 770 g and F) 950 g of water



A B

Fig.4 Scanning electron microscope of pellets (formulation II) obtained by MP1 centrifugal equipment:
A) 20 g/min spray rate and 700 g of water
B) 40 g/min spray rate and 600g of water

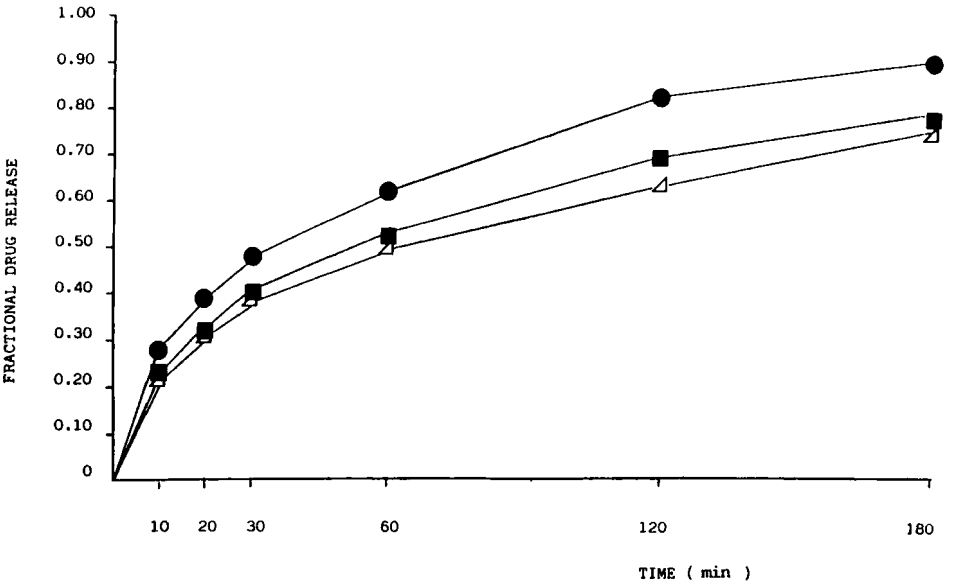


Fig.5 Release curves of pellets with different drug/microcrystalline cellulose ratio:

■ : 8.5/1.5; ● : 7.0/3.0 and ◿ : 5.5/4.5

more irregular in shape, larger in size, with a wider size distribution; calcium carbonate produced an almost monosize product.

The presence of lactose as well as mannitol implied that some of the filler could be dissolved in the "free" water and consequently increases the effect of wetting thus anticipating the end point of granulation.

The influence of both water amount and spraying rate has been evaluated on formula II.

The use of relatively high amounts of water and its addition to the powders in a short time led to fast growth of the granules (Tab. III and Fig.3).

The pellets obtained by employing 700 and 800 g of water at lower spraying rate had a sufficiently homogeneous and very narrow size distribution; the 80% of the pellets were in

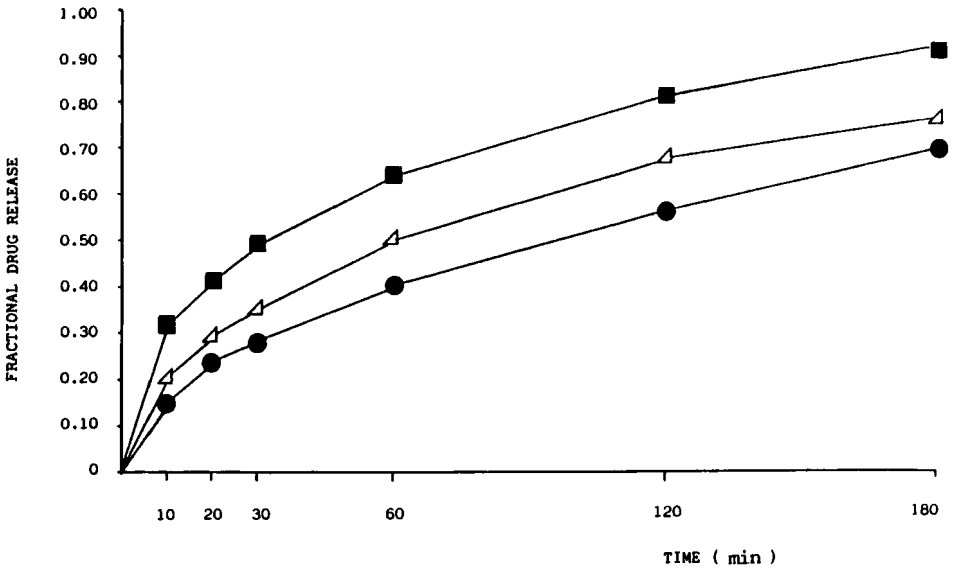


Fig.6 Release curves of pellets containing of different fillers:
● : formulation IV (lactose),
-◿- : formulation V (mannitol) and
■ : formulation VI (calcium carbonate)

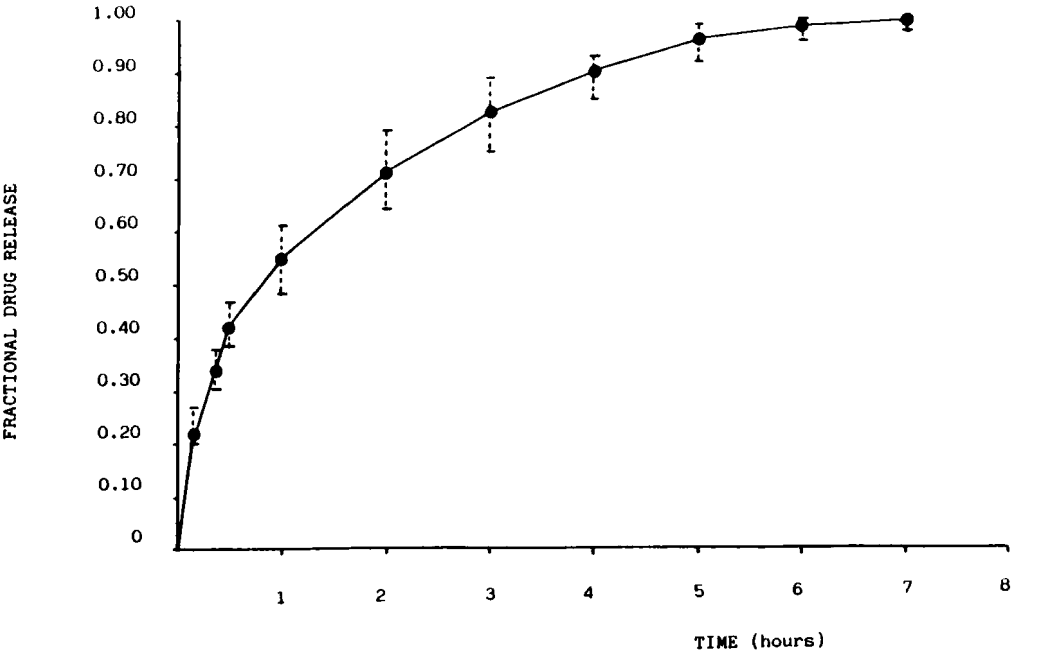


Fig.7 Release curves of pellets (formulation II) prepared by MP1 centrifugal equipment using 700 to 800 g of water, spraying rate 20 g/min. The values are the mean of three batches (the bars represent the range)

the 500-710 μm range. These results proved an acceptable reliability of the process.

When a spraying rate of 40 ml/min and/or 950 ml of water were used, both higher mean diameter and larger distribution sizes of pellets were obtained except in the case where the amount of water used was of 600 ml. The quality of the pellets is confirmed by SEM photomicrographs in Fig.4.

The dissolution characteristics of the prepared pellets were also evaluated. The release profiles of Indobufen pellets containing only microcrystalline cellulose, are reported in Fig.5 and were found to be substantially dependent on the drug contents.

Differences of drug release profiles were observed for pellets containing soluble or insoluble filler; the particle size and the consistency of the pellets seem to be the parameters more effective in influencing drug release (Fig.6).

Moreover, the drug release profiles of three batches of formula II differently wetted (700 to 800 g of water, spraying rate 20 ml/min) are sufficiently closed thus indicating the reproducible performance of the process (Fig.7).

CONCLUSION

The feasibility of producing pellets without seeds using centrifugal-rotary fluidized bed equipment was confirmed. Good viscoelastic properties of the wetted components mass as well as a careful processing made it possible to minimize the limitations of this equipment and to achieve good quality pellets. The plastic and binding properties of microcrystalline cellulose are fundamental for pellet formation, as well as for mechanical properties.

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