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RESEARCH PAPER

Evaluation of Time–Temperature Parameter Effects on the Structural Characteristics of Films Obtained by Aqueous Polymeric Dispersions

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ABSTRACT

Pellet cores, containing d-indobufen as the active principle, were prepared by the extrusion–spheronization process and coated with an aqueous polymeric dispersion using Wurster bottom-spray equipment. The present study investigated factors affecting the film properties, such as the product temperature during the coating process and the effects of the thermal postcoating treatment (curing phase), carried out in different drying conditions. The experimental results, in terms of drug release control, confirm that the properties of the film coating depend on the substrate temperature, which directly influences the coalescence process of the polymeric dispersion. Moreover, along with time and temperature of the drying phase, the type of equipment used affects the performance of the film coating dosage form. In particular, using the fluidized bed at a high temperature for a short time produced a film coating structure that seemed to remain unchanged after storage.

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INTRODUCTION

It is well known that one of the main parameters controlling the aqueous process in the use of polymeric dispersions is the temperature of the substrate product. This has to be closely related to the minimum film-forming temperature (MFT). This process temperature also influences both the particle deposition and the coalescence that leads to film formation (1). In previous works concerning the manufacturing and film coating of pellets, the importance of temperature control in defining structural characteristics of film was emphasized (2–5).

On the basis of results obtained as an extension of our recent work, it seemed worth investigating the influence of a further drying step which is generally known to contribute to the film structure definition. This thermal treatment is called the *postcoating drying* or *curing* phase.

The aims of the study were to assess (i) the influence of the inlet air and product temperatures on the coating process, and (ii) the effect of both temperature and postcoating drying duration on the final characteristics of the film. The curing phase was performed in the fluidized-bed equipment used for the coating process as well as in the tray dryer.

MATERIALS AND METHODS

Materials

- *d*-Indobufen (Farmitalia Carlo Erba)
- Microcrystalline cellulose (Avicel PH 101, FMC Corporation)
- Lactose (DMV, Veghel)
- Copolymers of methacrylic esters (Eudragit RL/RS 30 D, Rohm Pharma, Germany)
- Triethyl citrate (Citroflex 2, Pfizer, USA)
- Colloidal silicon dioxide (Syloid 244, W. R. Grace, USA)
- Simethicone emulsion (Carlo Erba, Milan, Italy)

Methods

Preparation of Pellets

Pellet cores consisting of *d*-indobufen, microcrystalline cellulose, and lactose with a mean diameter approximately of 0.900 mm were prepared by the extrusion–spheronization technique using the Nica System equipment. Pellet composition and manufacturing process are given in a previous work (4).

Coating Process

1000 g batches of pellets, were coated by Wurster bottom-spray equipment (GPGC1, Glatt, Binzen, Germany) using an acrylic water-based coating formulation (Eudragit RS and RL 30D) (5). The composition of the coating dispersions is reported in Table 1.

The following basic fluid bed operating parameters were selected: spray nozzle diameter, 1.2 mm; atomizing pressure, 1.4 atm; and air volume, 72 m^3/hr. The pellets were coated to a 6% weight gain.

Postcoating Drying (Curing Phase)

The coated pellets were cured both in the fluidized bed (air suspension system) and in a tray dryer (static system) at differing time–temperature conditions as reported in Table 2.

Physical Test

Moisture content The weight loss of pellets was determined by a thermobalance (Mettler PC 440 with IR Ray oven 100°C) at a constant weight.

"In vitro" dissolution test USP 23 method (900 ml of phosphate buffer solution at pH 7.5, 37°C, 200 rpm with Apparatus 2: Dissolutest, Prolabo). The amount of *d*-indobufen released was tested by high-performance liquid chromatography (HPLC), using an automatic system (3 MP8 Pump and M 231/401 Autosampler, GILSON).

RESULTS AND DISCUSSION

The different process parameters relevant to the coating of *d*-indobufen pellets were performed using bottom-fluidized-bed equipment and are shown in Table 2.

Preliminary, since the evaporation rate of coating liquids can significantly affect film formation in aque-

Table 1

Formulation of Aqueous Polymeric Dispersion

Ingredients	Amount (g)
Eudragit RL 30D	240.00
Eudragit RS 30D	60.00
Citroflex 2	18.00
Syloid 244	27.00
Simethicone emulsion	0.45
Purified water	554.55

Table 2

Mean Parameters of Coating Process (Weight Gain 6%)[a]

Parameter	Preparation Code				
	A	B	C	D	E
Air inlet temperature, °C	40	55	70	40	70
Air outlet temperature, °C	22	33	51	32	34
Product temperature, °C	21	32	52	32	32
Spray rate, g/min	20	20	20	6	30[b]
Coating time, min	37	37	37	123	25

[a]The drying phase was conducted for 30 min with an air inlet temperature of 55°C and an air volume of 60 m^3/hr.
[b]Average value during the spray process.

ous systems, differing inlet air temperature conditions, which are mainly responsible for the overall drying process, were applied by keeping the pumping rate constant (A, B, and C preparations). As expected, the product temperature which represents the drying condition at the substrate surface varied dramatically.

When the air inlet temperature was set at 70°C, some technical problems were encountered, mainly due to the incipient coalescence of polymeric particles in the spray gun, particularly in the nozzle. This can be reasonably associated with the relatively high environmental temperature conditions that are reached inside the fluidized-bed coating chamber.

When the air temperature was kept at 40°C the product temperature dropped to about 20°C. This temperature is very close to the minimum film formation temperature (MFT) and, according to the literature data (4), should not be capable of promoting the coalescence of the polymer particles.

Operating at 55°C, the product temperature stabilized at 32°C, about 10°C above the MFT. No spraying difficulties occurred, so these test conditions seemed to be the most favourable among those investigated.

With the purpose of operating with the product temperature at 32°C, the influence of differing inlet air conditions were assessed. As a consequence, it was necessary to set up an adequate pumping rate of spraying (preparations D and E). The use of a 40°C inlet air temperature involved a lower liquid spray rate and caused a dramatic increase of the coating time. Obviously a significant reduction of coating time was obtained when the inlet air was at 70°C. However, in this case serious technical problems in equilibrating the product temperature must be faced, rendering the whole process not easy reproducible.

Despite the various technological settings of the different manufacturing conditions, in all cases the pellets obtained from preparations A to C showed satisfactory morphological aspects of the film in terms of appearance and homogeneity. Moreover, the films obtained showed an analogous capability in controlling the drug release; however, the 32°C temperature of the substrate seems to guarantee an improved uniformity of the release rates (Figs. 1 and 2).

On the basis of these results and taking into account the technological-manufacturing aspects which emerged, we selected the B preparation as a model product to evaluate the effects of the thermal postcoating temperature (curing phase). So a new B batch of pellets was prepared having a practical superimposable release profile. This batch was immediately divided after the end of the coating into 12 parts which were treated accord-

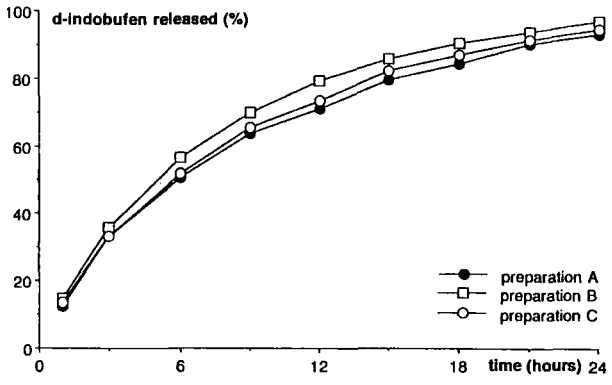

Figure 1. Release profiles of *d*-indobufen from pellets coated with acrylic aqueous dispersions operating at differing inlet air temperatures with a constant spray rate (20 g/min).

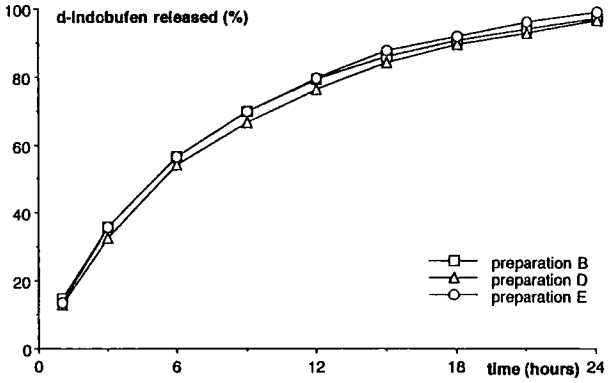

Figure 2. Release profiles of *d*-indobufen from pellets coated with acrylic aqueous dispersions operating at differing inlet air temperatures and keeping a constant product temperature (32°C).

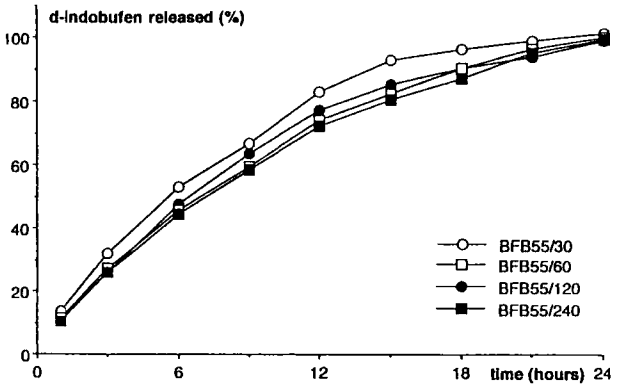

Figure 3. Release profiles of *d*-indobufen from coated pellets cured in a fluidized bed at 55°C for differing times.

ing to different curing conditions as reported in Table 3.

The release profiles of pellets subjected to different curing conditions are shown in Figs. 3 and 4. As far as the FB 70 and TD 40 products are concerned, the release curves reported in Fig. 4 are relevant only to the two extreme values of curing conditions.

When the curing was carried out in the fluidized bed at 55°C, the prolongation of the drying phase seemed to cause a slight decrease in the release rate depending on the thermal treatment duration.

Generally speaking, the postcoating drying carried out at 70°C on the same apparatus determined an apparent reduction of the release rate; however, no significant differences could be found when different durations of thermal treatment were applied. When the tray dryer was used the behavior was similar to that obtained with the fluidized bed operating at 55°C.

These results were confirmed on the basis of the drug dissolution rate data obtained from pellets treated thermally and stored at accelerated stability conditions. The release profile obtained after storage for 1 month at 40°C showed a further decrease in the release rate. The decrease was more evident when the curing was based on lower temperatures (Figs. 5, 6, and 7).

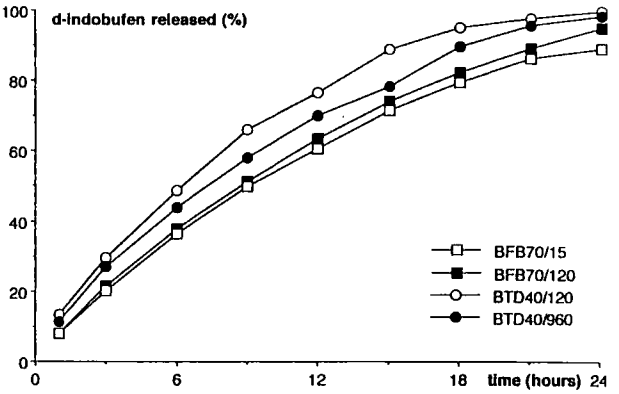

Figure 4. Release profiles of *d*-indobufen from coated pellets cured in a fluidized bed at 70°C and in a tray dryer at 40°C for differing times (extreme values of curing conditions).

Table 3

Curing Conditions After Film Coating[a]

Apparatus	Temperature, °C	Curing Time, min			
Fluidized bed (FB)	55	30	60	120	240
Fluidized bed (FB)	70	15	30	60	120
Tray dryer (TD)	40	120	240	480	960

[a]According to the process parameters reported, the product code used for the test, and including the curing conditions, must be read as illustrated in the following examples: BFB 55/30 and BTD 40/120, where B is the preparation, FB and TD indicate the fluidized bed and the tray dryer, 55 and 40 are the inlet temperatures, and 30 and 120 are the curing time duration, respectively.

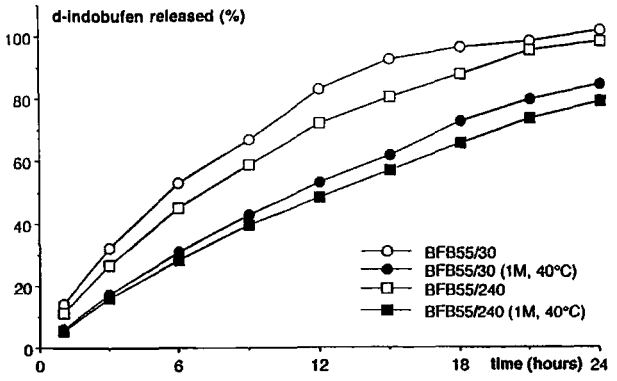

Figure 5. Release profiles of *d*-indobufen from coated pellets cured in a fluidized bed at 55°C for differing times after storage for 1 month at 40°C.

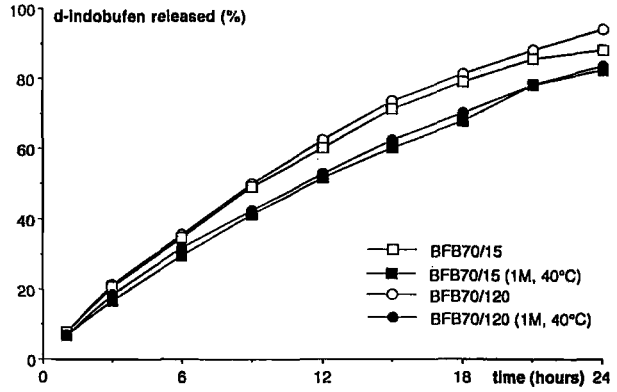

Figure 6. Release profiles of *d*-indobufen from coated pellets cured in a fluidized bed at 70°C for differing times after storage for 1 month at 40°C.

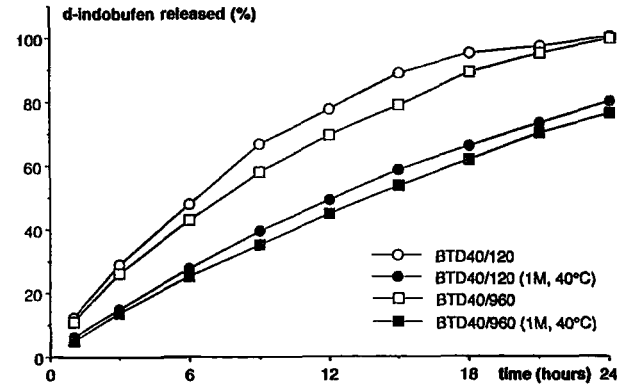

Figure 7. Release profiles of *d*-indobufen from coated pellets cured in a tray dryer at 40°C for differing times after storage for 1 month at 40°C.

Following these results, in the case of postcoating drying carried out at 70°C the film seems to work as a control barrier to the drug diffusion in a more uniform manner, thus indicating that a nearly definite structure was obtained. In other words, the permeability does not seem to change significantly after storage as the drying process lasted for a short time at a high temperature.

CONCLUSIONS

Temperature proved to be of great importance in the definition of the membrane structure and therefore determines the stability in terms of release rate reproducibility in time. It was confirmed that during a coating process involving an aqueous polymeric dispersion, the fundamental parameter is represented by the product temperature, closely linked to MFT of the polymer, and then to the coalescence process of the polymeric particles that lead to the formation of the film. As far as the postcoating drying phase (curing) is concerned, the temperature, duration of thermal treatment, and equipment used played an important role. Data from *d*-indobufen-containing pellets, coated with acrylic resins dispersions, suggest that the most promising results in terms of the stabilization of the film were obtained using the fluidized bed at a high temperature for a short time, as indicated by the accelerated stability testing.

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