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Influence of Formulation and Process Parameters on Pellet Production by Powder Layering Technique

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ABSTRACT The goal of the present study was to evaluate the influence of the formulation and operating conditions on pellet preparation by pan technique. To this end, a new pelletization process, typified by the application of powdered drug on sugar-based cores using the GS coating system was studied. Inert cores were intermittently treated with micronized drug powder and adhesive solution. This treatment led to the formation of multiple layers of drug particles around an inert core resulting in the production of pellets that can further be coated by different polymers to obtain modified release formulations. Different procedures have been used to evaluate a series of important parameters such as initial core weight; speed of powder application; speed, type, and position of the atomizers; atomization degree; temperature; and air cap.

Good yield of drug layering was obtained by adjusting the quantity of both the drug powder to apply and the binder solution. Pellets obtained following the optimal operating conditions (defined in a pre-formulation study) were film coated with the acrylic polymer Eudragit L30D in order to produce a model formulation consisting of enteric polymer- coated pellets containing ibuprofen. During its preparation, the formulation showed no degradation of the drug; moreover, a low percentage of residual humidity was obtained, indicating that this system is very efficient for the production of highly stable formulations. This study showed the good performance of the GS automated pan-coating system in obtaining enteric coated pellets prepared by powder layering technique using aqueous solutions.

KEYWORDS: Modified release pellets, powder layering, ibuprofen, enteric coated pellets

INTRODUCTION

Film coating is a commonly applied technique for the production of pharmaceutical products in order to achieve different requirements such as sustained- or controlled- release formulations [1,2].

Film coating techniques are characterized by the deposition of a uniform film onto the surface of a substrate. Because of the capability of depositing a variety of coating materials onto solid cores, this process has been widely used to make modified-release dosage forms starting from different formulations, such as tablets, granules, pellets, and capsules [3,4].

Nevertheless, very few cores possess the optimal physico-chemical properties needed by conventional coating processes. These properties include (1) suitable compaction, impaction, and attrition strengths to avoid ruptures during the coating process; (2) approximately spherical shape to obtain good flow and rolling

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properties in the coating equipment; and (3) suitable size, size distribution, and density as required by the coating process. Obviously, as different types of coating equipment are used, the handling of the cores and consequently the requirements of the cores for the various equipment should also be different [5].

Cores are usually prepared using one of the following processes: compaction, surface-layering, or agglomeration [2]. Among these methods, the surface-layering technique is an appealing approach. Generally, this pelletization method involves the use of inert substrates, such as sugar spheres, and their enlargement by intermittently spraying a binder solution [6] and applying the active substance powder in a rotating coating pan or in a fluidized bed [7].

In spite of interesting possibilities offered by the powder layering technique, it still presents some drawbacks as follows:

1. The powder layering process requires a great deal of repetition of wetting and powdering operations and is thus time consuming; moreover, undesired agglomeration and adhesion of the pellets to the wall of the coating equipment can occur.

2.The powder layering technique requires specialized equipment such as a rotary-tangential fluidized bed or modified rotating pans.

3. In the literature there are few or no complete studies aimed to determine whether a relationship exists between the formulation and process parameters and the physical, technological, and biopharmaceutical properties of the pellets [2–4]. Some works on the traditional method of building up cores by conventional pan coating are reported [8–10], but the layering technique used was discontinuous and without automation.

In this respect, the recent and specialized coating equipment of the GS system represents an interesting new approach allowing the use of a fully automatized aqueous-based system for powder layering on starting cores. The system is based on a rotating non-perforated pan, equipped with patented air supply (two perforated swords) and volumetric powder feeding unit. The most attractive features of this powder layering system are the uniform distribution of the powder on cores and the high drying efficiency of the binder solution, as well as the easy-to-clean pan and the possibility of applying the successive functional film coating using the same equipment. The critical aspects involved in the process of layering activated-surface powder using the aqueous binder solution are the decreased adhesiveness of the binder on cores due to the presence of a wetting agent and the high latent heat of vaporization of water used as a binder vehicle.

The aim of the present study was to evaluate the influence of the formulation and operating conditions on the pellet preparation by GS pan layering. For instance, the following parameters were considered: (1) size of the starting cores; 2) type of micronized powder with particular attention to its flowing properties and wettability; (3) binder type and concentration; (4) application rate of the sprayed binder solution and powder; (5) presence of wetting, flowing, and anti-sticking agents; (6) pan speed; (7) spray gun position and atomization degree; (8) inlet air and bed temperatures; (9) air cap type; and (10) size of the pellets.

Ibuprofen was used as poorly soluble drug model (solubility in water: 0.07 g/l), because until now, no formulation of this drug had been developed based on pellets and using only aqueous solvents.

MATERIALS AND METHODS

Materials

Ibuprofen was obtained from Resfar (Milan, Italy); colloidal silicone dioxide (Syloid 244) and talc of pharmaceutical grade were from Prodotti Gianni (Milan, Italy); hydroxypropyl cellulose (HPC LF) was from Eigenmann & Veronelli SpA (Milan, Italy); Eudragit L30D was from Röhm GmbH (Darmstadt, Germany); polyvinylpyrrolidone K30 (PVP K30) was

from Basf (Lundmingshafen, Germany); sucrose spheres (30 mesh) were from Gelfipharma International Srl (Milan, Italy). All other material and solvents of the highest purity grade were from Fluka (Buchs, Switzerland).

Physical Characterization of the Starting Materials

Carr's index determination The Carr's compressibility index was determined as an indirect method to assess the powder flow properties from bulk densities. Particularly, the compressibility index of a powder was calculated according to the following equation:

$$\text{compressibility index (\%)} = \frac{D_f - D_o}{Df} \times 100$$

where Do is the fluff or poured bulk density and Df is the tapped or consolidated bulk density. The obtained values were then interpreted according to the Carr table reporting the generalized relationship occurring between powder flow properties and compressibilty index.

Contact angle measurements. The contact angle of the compacted powder was measured by a wettability tester (Lorentzen-Wattre apparatus, Sweden).

Rheological studies of binder solutions. Rheological measurements have been carried out using a Rheometrics International rheometer (Rheometrics, Possum Town, NY, USA) equipped with 14w and 24 geometries coaxial cylinders according to the DIN system. Measurements were conducted at room temperature in the range of shear rate between 0 and 350 s^{-1}.

Ibuprofen size distribution determination

The size distribution of ibuprofen particles was determined by laser diffraction (Galai-cis-1, Tecnogalenica, Italy) after dispersing the powder in an aqueous 0.1% polysorbate 80 solution saturated with ibuprofen.

Powder Layering Technique

Layered pellets were prepared using GS HP/25 equipment (GS Coating System, Italy). This pilot plant is a multifunction system used to process different dosage forms such as tablets, capsules, pellets, and microgranules, using the same pan.

Sugar spheres were poured into the coating pan, then intermittently treated with a nebulized binder solution applied by spray guns and with a finely dispersed drug powder applied by a specially designed powder feeding unit. The powder feeding unit is a patented system developed by GS Coating System in which two synergic mechanical actions, the vibration applied to the powder feeding unit and the rotary movement of the helical conveyor, allow an extremely precise dosage of the powder. At the end of each cycle of wetting and powder application, the sphere bed was dried to remove the solvent completely, in this way forming the intraparticellar solid bridges between the spheres.

The powder used to obtain the pellets was prepared as follows. The drug was sieved through a 200 μm mesh sieve and then mixed with the excipients. Afterwards, the obtained mixture was passed again through the 200 μm mesh sieve. The application rate of the powder was between 200 and 300 g/min.

The weight ratio between powder and sprayed binding solution was 1–1.25:200. At the end of the layering process the obtained pellets were subjected to a screening operation using a Weston model 503 sieve (Vibrowest, Cormano, Italy).

Particle Morphology

The shape and surface characteristics of the ibuprofen-containing pellets were evaluated by scanning electron microscopy using a Stereoscan 360 microscope (Cambridge Instruments, Cambridge, UK).

Determination of Pellet Moisture Content

In order to assess the performance of the drying

process, the residual moisture present in the pellets was determined by weighing the samples before and after the drying process using a thermobalance LJ 16 Mettler Toledo (Schwerzenbach, Switzerland).

Pellet Friability Test

Resistance to abrasion was determined using a Roche TAR 10 frabilator (Erweka, Ensenstam, Germany). To this end, 10 g of pellets were mixed with 25 glass spheres (5µm in diameter) and uniformly tumbled for 10 min at 25 rpm. Weight loss from the tablet was measured afterwards.

Determination of Pellet Ibuprofen Content

Ibuprofen determination was performed as follows. One g of pellets was solubilized in 20 mL of a mixture constituted by a 1% Tween 20 aqueous solution and ethanol 90:10 (vol/vol). Afterwards, samples were centrifuged at 4000 rpm for 10 min and the supernatant was subjected to high-performance liquid chromatography (HPLC) analysis. The HPLC determination of ibuprofen was performed using a system consisting of a Bruker LC21-C chromatographic pump (Bruker, Bremen, Germany), a Rheodyne 7125 sample injection valve equipped with a 50- mL loop (Rheodyne, Cotati, USA), and a Chrom-A-Scope rapid scan ultraviolet detector (Carlo Erba Strumentazione, Milan, Italy) able to measure and store 10 spectra per minute. The elution solvent was degassed by a double-way automatic degasser Erma ERC-3311 degasser (Erma Inc., Tokio, Japan). Samples were chromatographed on a 250 x 4.6 mm reverse-phase stainless steel column packed with 5µm particles (Model BDS Hypersil C-18, Hewlett Packard, USA), eluted isocratically at room temperature using as mobile phase acetonitrile:water 60:40 vol/vol at a flow rate of 1 mL/min. Ibuprofen was monitored at 263 nm.

Enteric Coating

The enteric coating was carried out using the same HP/25 pan by means of a constant and homogeneous one-way air flow into the core bed combined with a suitable spraying system for the coating material. The composition of the enteric coating suspension was as follows: Eudragit L 30 D-55 (30% aq), 33.2%; talc, 5.0%, titanium dioxide, 3.5%; triethyl citrate, 1.0%; methylene blue, 0.5%; water, 43.2%. The process conditions employed for the enteric coating were as follows: product temperature, 37°C; spray rate, 25 mL/min; inlet air quantity, 100 cm/h; inlet air temperature, 75°C; pan speed, 17 rpm; air cap, n.1; nozzle, 1.4 mm; nebulization pressure, 0.8 bar.

Drug Release Test

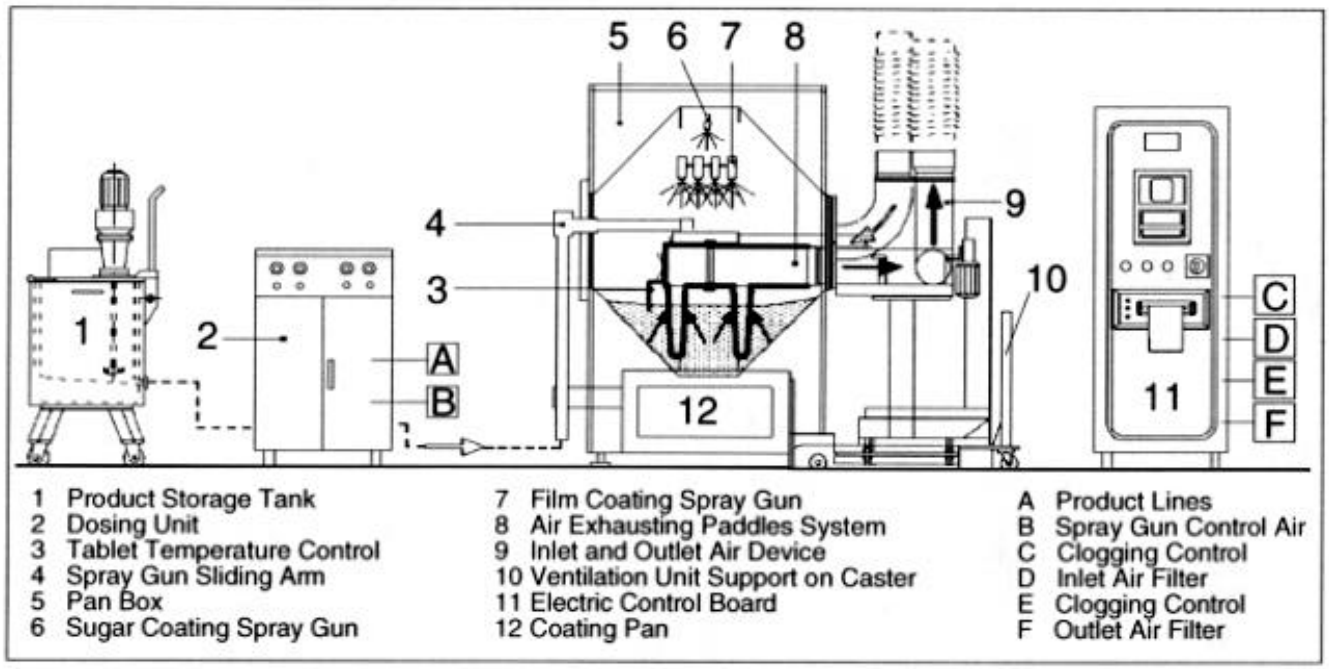
The disintegration time and the drug release rate from enteric coated and uncoated pellets were determined according to the procedures reported in the USP XXIII [11], method A, page 1795 (apparatus 2, 100 rpm, 37°C, acid stage: 750 mL of 0.1 N hydrochloric acid for 2 hours and buffer stage: add 250 mL of 0.2 M tribasic sodium phosphate and adjust to a pH of 6.8).

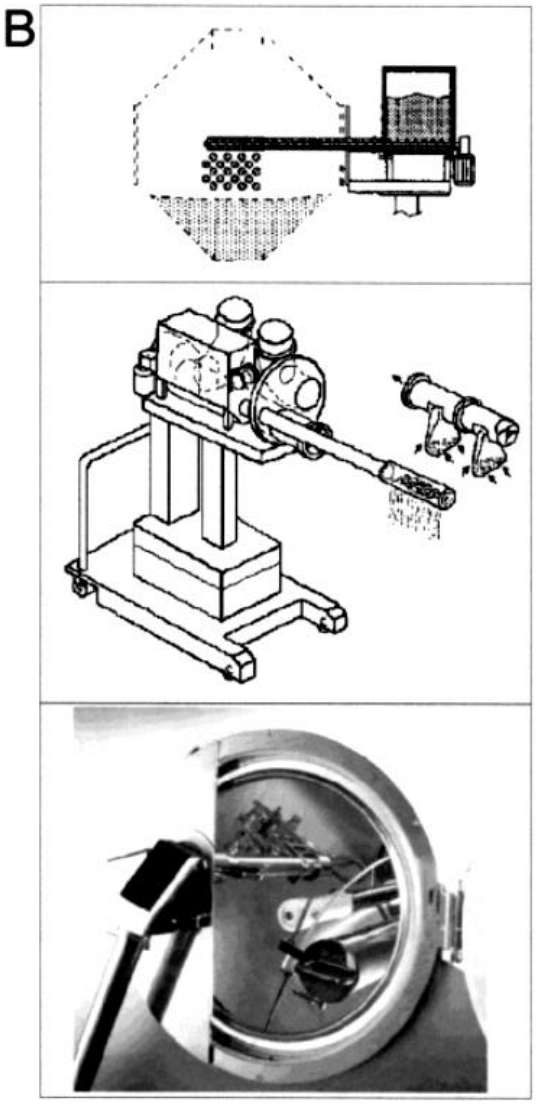
RESULTS AND DISCUSSION

Powder Layering Process

Pellets containing ibuprofen (chosen as the model drug) were prepared using the multifunction GS Coating System HP/25 plant (see Figure 1A), which is able to process pellets, microgranules, and tablets using the same pan. The plant was equipped with a special powder feeding system designed by GS Coating System for drug powder application (see Figure 1B). The equipment is driven by a digital control panel constantly reporting to the operator all the operative conditions of the pelletization process.

The entire powder layering process was conducted as follows: sugar spheres, used as inert seeds, were poured into the pan, then intermittently treated with (1) a nebulized binder solution applied using spray guns (see Figure 1C) until the bed was wet and tacky and (2) a finely dispersed drug powder until the bed was dry (see Scheme 1).





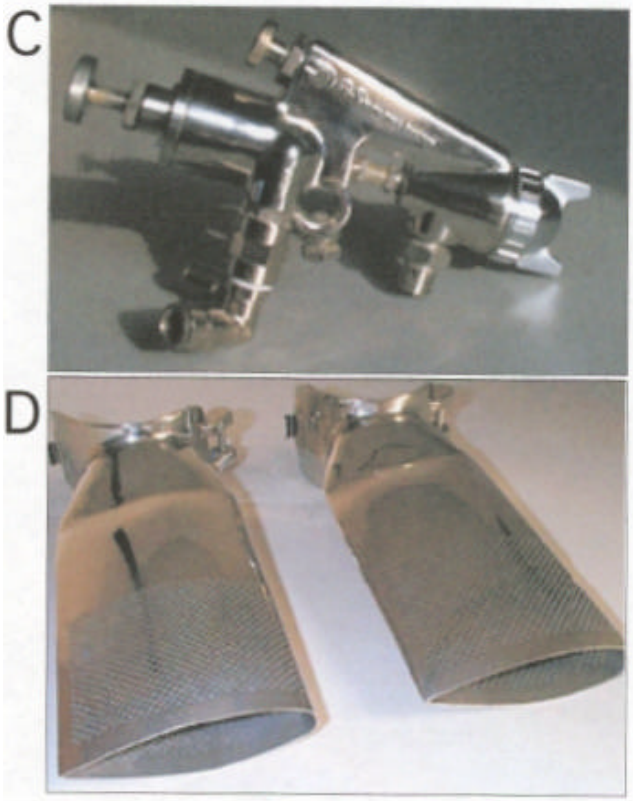
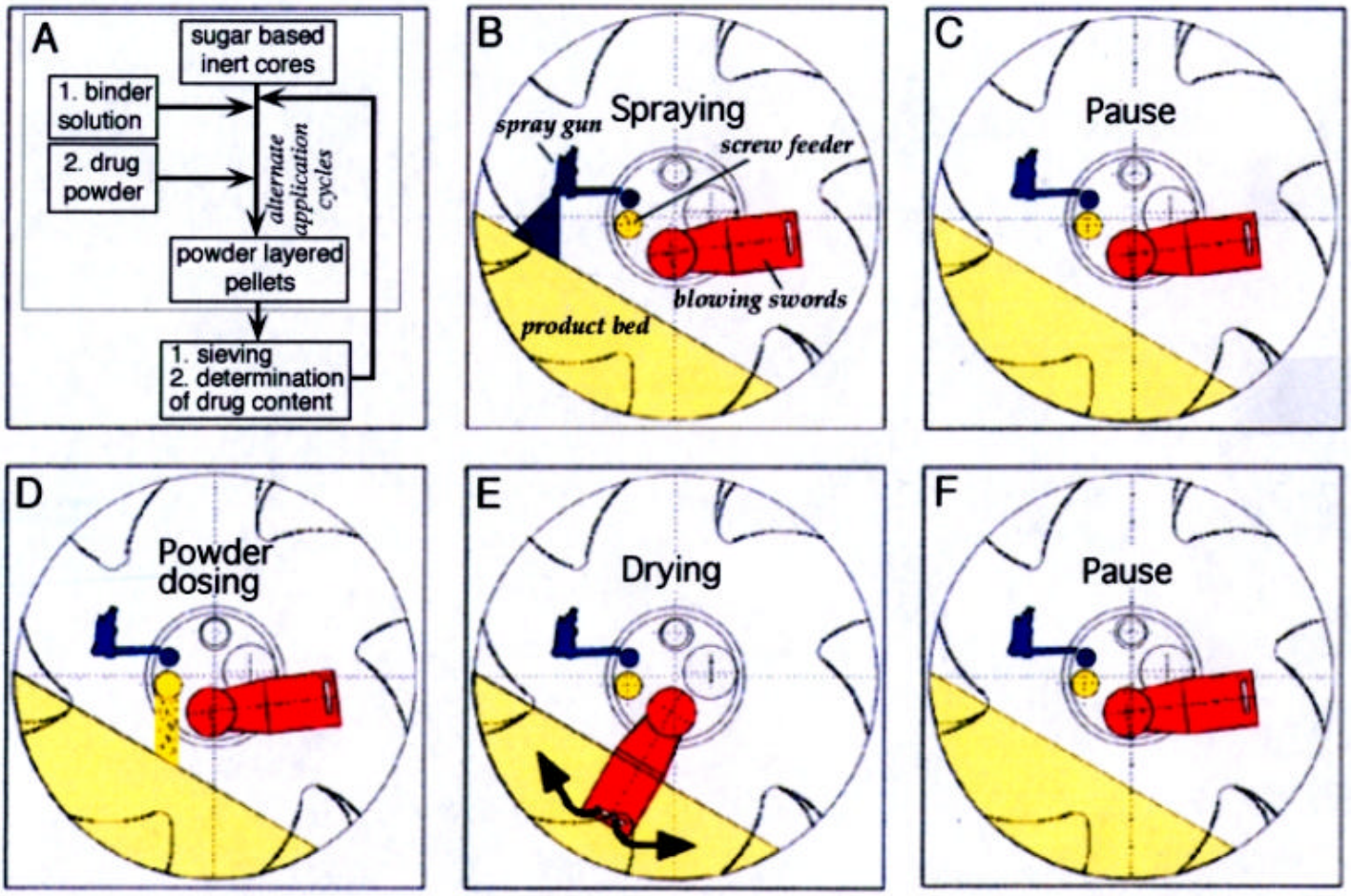


Figure 1. Panel A: Schematic representation of the GS Coating System HP/25 plant. Panel B, Upper frame: Schematic representation of the powder system option; Central frame: Schematic representation of the powder dosing unit; Lower frame: Photographic representation of the GS coating pan. Panel C: Spray guns. Panel D: Air sword system.



Scheme 1. Schematic representation of the powder layering process in the GS coating pan.

This process led to the formation of multiple layers of drug particles that adhere to one another due to capillary pressure and interfacial forces originating from the liquid phase, allowing the enlargement of the initial cores. It should be noted that, in principle, the process of powder layering can be continued until reaching the desired particle size. Intraparticellar solid bridges were formed after each wetting-powder cycle by the complete removal of water by a stream of warm air blown through the perforated sword system present in the GS coating equipment (**Figure 1D**). The resulting final pellets can further be filmed by different polymers in order to obtain multiparticulate dosage forms with enteric or modified release properties [12, 13].

Preformulatory Study

Sugar spheres consisting of sugar and starch, with a mean diameter of 600 μm, were chosen as inert seeds in order to obtain final pellets having dimensions compatible with the filling of hard gelatin capsules of intermediate size such as size n. 1. In order to maximize the interactions between drug and inert cores, a micronized ibuprofen powder with a mean diameter (by number) of 6 μm was chosen, resulting in a size-ratio of 1:100 between the drug particles and the inert cores. **Figure 2** reports the size distribution by cumulative frequency of the used ibuprofen powder.

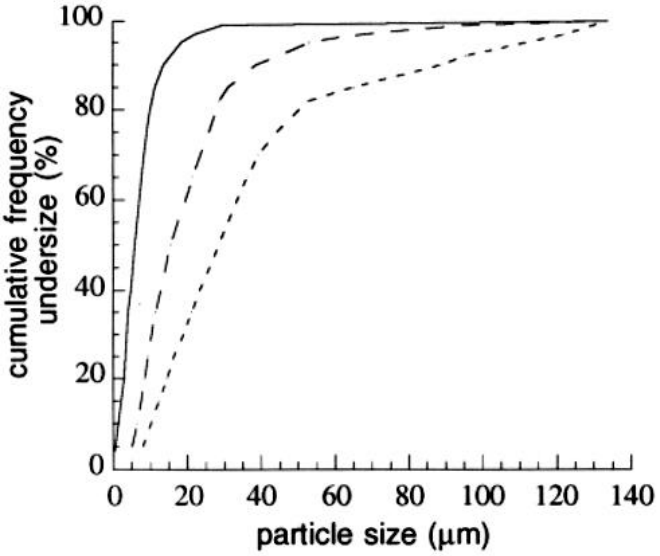


Figure 2. Size distribution by cumulative frequency of the used ibuprofen powder. Plain line: number distribution; dashed line: area distribution; dotted line: volume distribution.

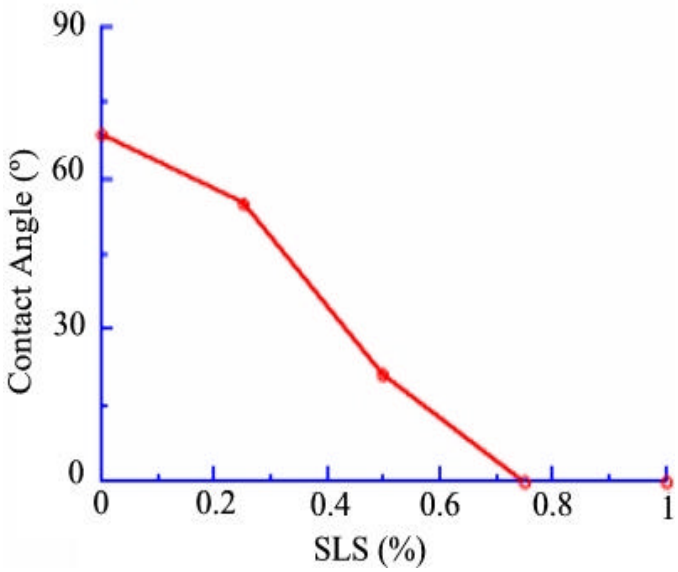


Figure 3. Effect of sodium lauryl sulfate (SLS) on the contact angle of ibuprofen powder.

The wettability of the drug powder was also considered. In fact, it is well known that successful interaction between the drug and the binder solution is greatly influenced by the wettability of the drug (as measured by the contact angle, which should be kept as low as possible). For instance, ibuprofen, being a hydrophobic compound, is characterized by an unfavorable wettability expressed by a contact angle of 70°. In order to reduce this value, a surface agent (sodium lauryl sulfate, SLS) was included in the formulation to aid the wetting of the drug. **Figure 3** reports the effect of SLS on the contact angle of ibuprofen. The results clearly indicate that a formulation including 0.75% (wt/wt) SLS was able to sharply reduce the contact angle to 0°, representing complete wetting of a solid surface.

The micronized ibuprofen powder was also characterized by a scarce flowability. To overcome this problem, colloidal silicone dioxide (CSD) was employed as a flow activator. CSD was found effective in improving the powder flow properties; in fact, the addition of 2% CSD resulted in a significant reduction of the Carr's index from 52% to 29.2%. Drug and other excipients were mixed in a twin-shell mixer for 15 minutes. With respect to these values, it should be remembered that the Carr's index is usually used to obtain information on the behavior of powders for tablet production, where the feeding of the die is accomplished by gravity and thus a very free-flowing powder is required. In the GS system, however, the powder is dosed by two synergic mechanical actions, the vibration applied to the powder feeding unit and the rotary movement of the helical conveyor. Under these conditions, powders with a Carr's index up to 35%–40% also can be dosed very accurately, as proved by a preliminary set of experiments demonstrating that the powder dosing was always within 3% of the correct value.

Other important parameters to be considered in order to obtain optimal powder layering are the type and quantity of binder. The binder has to possess high adhesivity and an appropriate viscosity, to guarantee a good adhesion between sugar cores and drug particles, resulting in a high concentration of drug in the pellets. In the present study two different binders were assayed, namely hydroxypropyl cellulose (HPC) and polyvinylpyrrolidone (PVP K30). PVP is a water-soluble binder that allows a rapid dissolution of the final pellet. HPC, being a less water-soluble polymer, gave rise to slower dissolution rates.

Preliminary Experiments of Layered Pellet Production

On the basis of the data from the preformulatory study, an easily-wettable and sufficiently flowable powder was formulated, as well as a binding solution thatg was not too viscous (see **Table 1**).

Table 1. Drug and excipients used for the preparation of ibuprofen pellets by powder layering technique

	POWDER				BINDER		SOLUTION	
Batch	Sugar spheres inert cores (kg)	Ibu-profen drug (kg)	Syloid 244 flowing agent (kg)	SLS wetting agent (g)	Talc antisticking agent (g)	HPC-LV binder (g)	PVP-30K binder (g)	Water (kg)
#1	8.0	4.0	20.0	30.0	—	150.0	—	2.8
#2	8.0	2.0	10.0	15.0	—	150.0	—	2.8
#3	8.0	2.0	10.0	15.0	—	150.0	—	2.8
#4	8.0	2.0	40.0	15.0	300.0	150.0	—	2.8
#5	8.0	2.0	40.0	15.0	300.0	90.0	—	2.8
#6	8.0	4.0	20.0	30.0	—	—	315.0	4.2
#6.1	8.0	2.0	40.0	15.0	300.0	—	210.0	2.8
#6.2	9.6	2.0	40.0	15.0	300.0	—	273.0	3.6
#6.3	11.5	2.0	40.0	15.0	300.0	—	280.0	3.7

In order to obtain pellets with optimal characteristics, a series of parameters were considered, such as (1) initial core load, (2) pan speed, (3) powder application rate, (4) type and position of the atomizers (spray guns), (5) atomization pressure, (6) air cap type, and (7) temperature of the bed..

Good drug layering yields were obtained by carefully adjusting the quantity of both the applied drug powder and the binder solution. Particularly, an excess of drug powder resulted in a high loss of drug through the exhaust system, powder caking on the pan walls, and formation of seedless drug agglomerates of various size. On the other hand, an excess of binder solution led to an overwetted bed, causing the formation of sticky agglomerates between pellets and the wall of the pan.

Pan speed was also found to heavily influence the powder layering process. In fact, low pan rate rotation (such as 10 rpm) caused the agglomeration of the cores, while higher rotation rates such as 20 rpm allowed a good application of the powder on the core surface without aggregation problems.

Other operating parameters such as type of air cap, atomization pressure, and position of the spray guns were also considered. For instance, air cap was found to heavily influence both the diameter of the sprayed binder droplets and the spray angle. In the case of core pellets with sizes between 400 and 600 μm, optimal results were obtained using the size #4 air cap, which strongly reduced sticking and adhesion problems.

Finally, by modulating the temperature of the inlet air, it was possible to maintain a constant bed temperature during the application of both the binder solution and the powder, overcoming in this way the cooling effect due to evaporation of the binder solution solvent. When inlet air temperature was too high, an extreme drying process resulted, causing an elevated particle friction phenomenon that increased the percentage of product loss.

On the basis of the considerations above, the initial pelletization process was performed by preheating the cores to 34°C; afterwards, the powder containing the drug and the excipients were applied at a bed temperature between 34 and 35°C. At the end of the process, each batch was subjected to further drying for 5 minutes to remove the residual water . Initially, the binder of choice was HPC. The photomicrographs of the pellets prepared using HPC (batch #1) are reported in **Figure 4A** . They show a quite uniform rough surface, but are not completely free of imperfections.

The resulting pellets were sticky to a certain degree, probably because of the low initial temperature of the cores and the high powder dosing rate. In an attempt to solve the problem, pellets were prepared with an increase in initial temperature of the cores from 35 to 38°C, but these pellets did not change substantially with respect to the previous samples (see **Figure 4B** , batch #2).

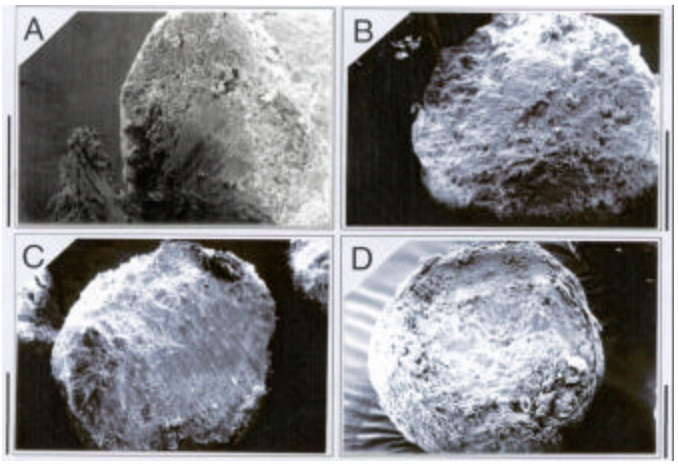


Figure 4. Scanning electron micrographs showing the external and internal morphology prepared using HPC, batch #1 (Panel A); batch #2 (Panel B); batch #3 (Panel C), and batch #5 (Panel D).

As further improvement, the rate of powder application was reduced from 331 to 180 g/min to obtain a more gradual and homogeneous distribution of the powder. Notwithstanding this change, a marked stickiness of the pellets was again evident, together with a high degree of free drug particles in the pan. Nevertheless, the size and morphological characteristics of the isolated pellets were almost comparable with those of the previous preparations (see **Figure 4C** , batch #3).

Finally, in order to promote the pellet separation into distinct units, 15% (wt/wt, with respect to the drug) talc was added to the drug powder as an antisticking agent (batch #4). Although talc is recognized as a hydrophobic excipient possibly resulting in reduced powder flowability and in delayed disintegration (not optimal for a rapid release formulation), it was maintained in the formulation to guarantee a high separation of the pellets. Obviously talc was used in association with SLS and CDS respectively representing efficient wetting and glidant agents that are able to guarantee sufficient flow of the powder (see **Figure 5**). Unfortunately, the addition of talc did not completely solve the stickiness problem; in fact at the end of the process out of 100 units, 95 were single pellets and 5 were pellet agglomerations (5% of the pellets were part of pellet agglomerations).

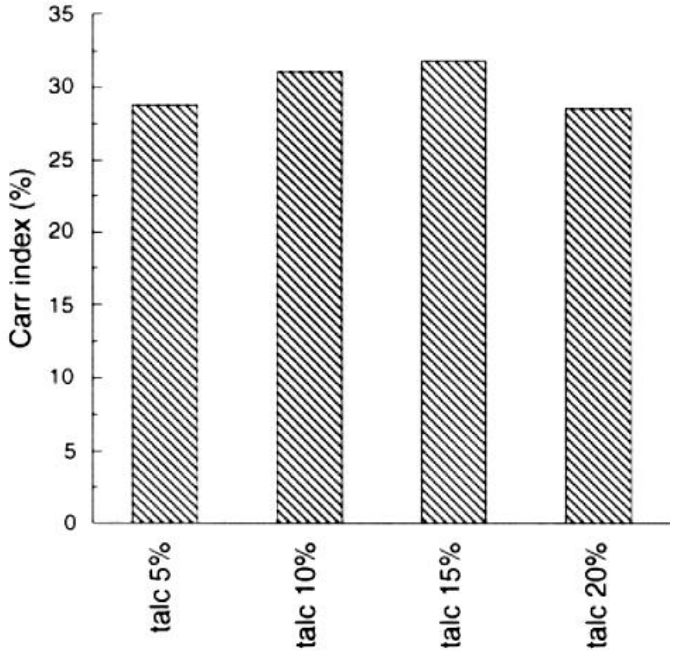


Figure 5. Effect of talc on ibuprofen flowability measured by means of the Carr's index.

As further modification of the formulation, the viscosity of the binder solution was decreased by reducing HPC in the binder solution from 5% to 3% (batch #5). The pellets produced indeed presented a strong reduction of the surface defects (see **Figure 5D**); in addition, an increase in recovery of up to 98% was obtained. The use of a more dilute binder solution and the presence of talc as an antisticking agent resulted in the separation of each pellet into individual units during the layering process.

In light of these results, the preparation of pellets was tentatively conducted employing an alternative, less viscous and sticky binder, an aqueous 7% (wt/wt) PVP K30 solution. The formulation of the first batch of pellets produced with PVP (batch #6) is reported in **Table 1.** The scanning electron photomicrograph of both the surface and the section of the pellets (see **Figure 6A**), clearly shows that the particles present a relatively smooth surface and homogeneous morphological characteristics. The percentage of pellet recovery was satisfactory, namely 96.8%, but the obtained pellets contained some seedless drug particles. This problem was tentatively attributed to the too-low adhesion capacity of PVP (with respect to HPC), leading to the formation of small dispersed particles that induced the formation of seedless drug aggregates.

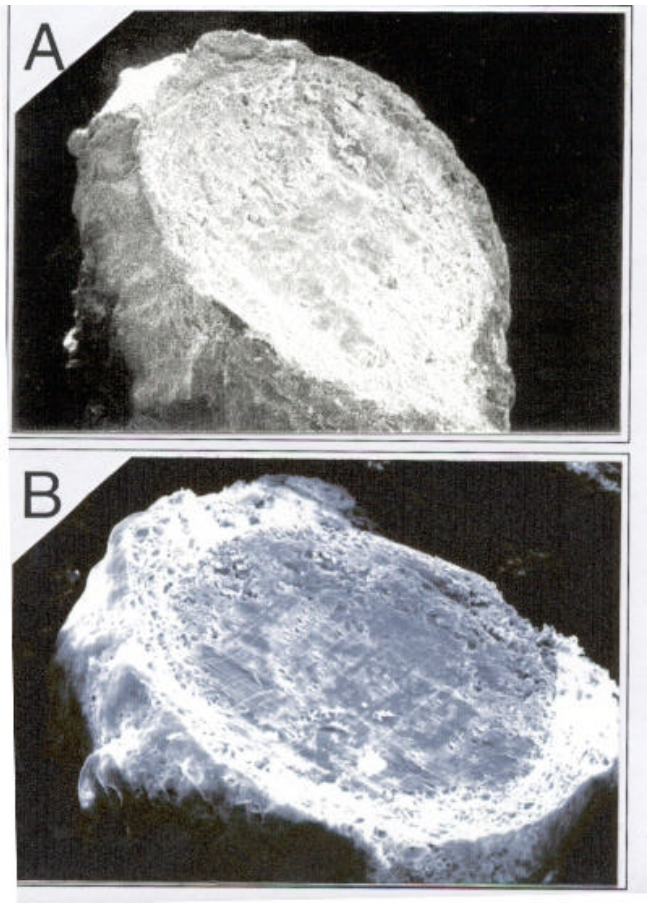


Figure 6. Scanning electron micrographs showing the external and internal morphology of the optimized pellets before (batch #6, Panel A) and after (batch #6.3, Panel B) the application of three successive layers of powder.

Pellet Preparation by Powder Layering Technique

At the end of the preliminary experiments, the formulation used for the preparation of batch #6 (reported in **Table 1**) was tentatively chosen as standard for the successive layering cycles. The parameters and the technical data characterizing this powder layering process are reported in **Table 2** . These operating conditions arose from the preparation of pellets containing 18.4% (wt/wt) of drug; however, because our final goal was to obtain pellets containing at least 600 mg of ibuprofen per gram of product, further analyses were performed, based on the application of successive layers of powder to the batch #6 pellets.

Table 2. Parameters and technical data characterizing the powder layering process

		Batch				
Parameter	**Units**	**#6**	**#6.1**	**#6.2**	**#6.3**	**#7**
Initial loading	kg	8	9.56	11.36	12.79	8
Core temperature	°C	35.5	36	36.5	35.5	35.5
Powder dosing rate	g/min	182	184	182	182	182
Applied powder	kg	2.3	2.32	2.33	2.04	14
Applied binder	kg	0.2	0.25	0.27	0.32	0.5
% of ibuprofen in the applied powder	%	84.9	84.9	84.9	84.9	84.9
Effective amount of applied ibuprofen	kg	2.0	2.0	2.0	1.7	11.9
Loss of product (> 800 micron)	%	0.9	1.2	0.8	6.0	0.3
Recovery of pellets	%	96.8	94.8	95.9	92.4	95.6
Powder/binder ratio	p/p	0.8	0.6	0.6	0.5	0.8
Residual moisture	%	1.9	1.6	2	1.8	1.9
Friability index	%	0.98	2.7	1.2	1.3	3.0
Final ibuprofen content°	%	18.4	29.6	36.7	41.7	54.5

°Determined by HPLC analysis

Three successive amounts of ibuprofen, consisting of 2 kg each, were applied to batch #6 pellets, using the powder layering technique described above (see **Scheme 1**). After each application step, the pellets were sieved to eliminate the small seedless aggregates and successively poured into the coating pan for the application of a further batch of drug. Three loads of ibuprofen were applied to batch #6, resulting in batch #6.1, batch #6.2 and batch #6.3. By the successive application of drug layers, the content of ibuprofen in the pellets gradually augmented up to 41.7% (wt/wt) (see **Figure 7**).

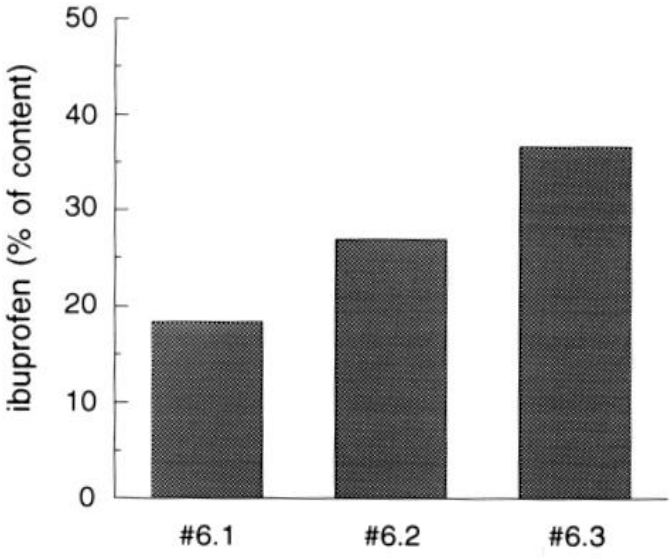


Figure 7. Increase of the content of ibuprofen in the pellets after the application of three successive layers of powder.

The scanning electron microscope analysis of batch #6.3 (reported in **Figure 6B**) showed that the last applied powder layer possesses a higher porosity with respect to the previous layers. This phenomenon could take place for the following reasons: (1) low adhesion capacity of the binder solution; (2) unfavorable ratio between powder and binder; (3) inadequate drying time; and finally (4) possible interaction between water present in the binder solution and the underlying ibuprofen layer, which could lead to the reduction of the adhesion between drug particles.

In order to possibly solve this problem, the ratio between powder and binder, core temperature, and binder solution were modified. With respect to this latest parameter, the optimal composition of the binder for ibuprofen powder application was determined to be a mixture 1:1 (wt/wt) of aqueous 7% PVP and 3% HPC solutions, associating in this way the binding capacity of both the excipients. These experimental parameters were employed for the production of batch #7 pellets, to which (as previously described for batch #6) were successively applied three further loads of ibuprofen resulting in batch #7.1, #7.2, and #7.3. Using the parameters reported in **Table 2** , the final concentration of ibuprofen in the #7.3 pellets was 54.5%. As previously stated, these pellets can be conveniently metered into hard gelatin capsules, size number 00, resulting in a final 200 mg of active/capsule.

Enteric Coating

Pellets obtained following the operating conditions determined above, namely batch #7.3, were subjected to a film coating process using the acrylic polymer Eudragit L30D-55 in order to produce a gastro-resistant formulation. The final enteric coating has been also applied in a GS pan coating plant, by means of an air-spraying system and continuous drying. The drying air was flowed through immersed swords (see **Figure 1D**) that force the drying air to flow across and within the core bed, ensuring a constant and effective heat exchange and a considerable reduction of time process. The increase of pellet weight after coating was 6%, while the pellet recovery was 96%. A photomicrograph of enteric coated pellets is reported in **Figure 8** . In order to test the enteric properties of the pellets, they were placed in a 0.1 N hydrochloride acidic solution at pH 1. In these conditions the pellets showed a disintegration time of more than 3 hours; conversely, when placed in a 0.05 M phosphate buffered solution at pH 6.8 (as suggested by USP XXIII) the pellets disintegrated within 20 minutes.

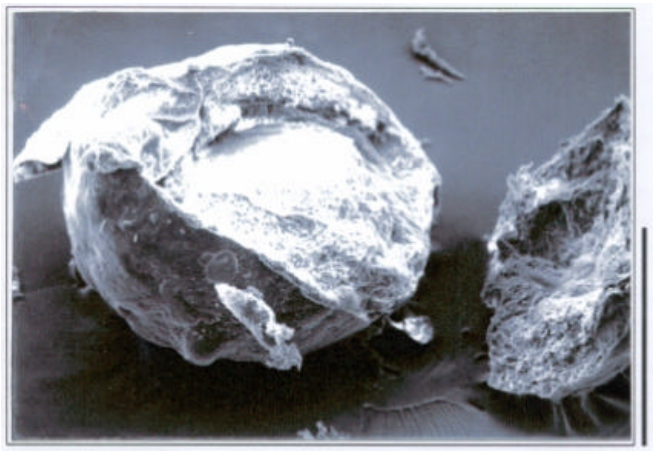


Figure 8. Scanning electron micrographs showing the external and internal morphology of the enteric coated pellets.

Finally, it has to be emphasized that during all the preparation steps, no sign of drug degradation was

detectable. Moreover, the small percentage of residual moisture indicates that the system here described allows the production of highly stable formulations.

CONCLUSIONS

The present study confirmed the good performance of the GS automated pan coating system in obtaining enteric coated pellets by a powder layering technique using aqueous solutions. It demonstrated the importance of an accurate selection of both the layering powder and the aqueous binder formulations, in particular when the drug must be treated with surfactant in order to increase the wettability. Moreover, during the initial formulation trials, the careful evaluation of the process variables was essential to optimize the powder layering process.

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