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Drug-β-Cyclodextrin Containing Pellets Prepared with a High-Shear Mixer

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ABSTRACT

This work was aimed at investigating the preparation of β-cyclodextrin-microcrystalline cellulose pellets by means of a high-shear mixer, both in the absence or in the presence of ibuprofen as model drug. Drug loading of pellets was accomplished by means of two alternative techniques: 1) solution layering or 2) powder layering. The prepared pellets were characterised in terms of size distribution, shape factor, friability and dissolution rate. The interaction between ibuprofen and β-cyclodextrin was monitored by Differential Scanning Calorimetry (DSC). Micro Fourier Transform Infrared spectroscopy (MicroFTIR) was applied to determine the distribution of components within each pellet on a micro scale. Pellets with narrow size distribution and containing up to about 90% of BCD were prepared using water as binder. The process yield resulted around 84 and 63% for drug-free and medicate pellets respectively. Drug loaded pellets with favourable technological and biopharmaceutical characteristics can be obtained both by powder or solution layering techniques. The latter proved to be more suitable for producing pellets with high drug contents, reduced friability and high drug dissolution rates.

Key Words: Pelletization; High-shear mixer; β-Cyclodextrin; Ibuprofen; Shape factor; Drug crystallinity; Dissolution; Multiparticulate drug delivery system.

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INTRODUCTION

Pellets for pharmaceutical applications are free-flowing spherical particulates of 0.2–1.5 mm average diameter size; their use offers numerous advantages, such as high flexibility, in the preparation of conventional and modified release solid dosage forms.[1–3]

The most widely used procedure for their preparation is the growth of sugar seeds mixed with powdered drug in a rotating pan. Improved powder technologies provide nowadays alternative methods for pellets preparation: extrusion-spheronisation and high-shear mixing. In particular, the pelletization by means of high-shear mixers allows the preparation of spherical particles in a single step, is very flexible and time saving (quick product changeover), thus increasing productivity and cost effectiveness.[4,5]

In a previous work,[6] the pelletization of lactose and microcrystalline cellulose using a Roto-J Zanchetta high-shear mixer and the influence of manufacturing parameters were investigated, demonstrating the possibility of obtaining pellets with optimal technological properties.

Microcrystalline cellulose was shown to be determinant for the plasticity and the binding properties, necessary for conferring strength to pellets.[7]

In addition, the possibility of preparing pellets containing a so-called ''active excipient'' like cyclodextrin, with the extrusion-spheronisation method, was preliminarly explored and tested.[8] Cyclodextrins are well known for their ability to form inclusion compounds with a variety of drugs. The improvement of drug solubility in aqueous media, physical and chemical stability, as well as the overcoming of unfavourable organoleptic properties represent the main advantages of drug-cyclodextrin interaction compounds.[9–11]

In the present work we report experimental data concerning the preparation of pellets by means of a high-shear mixer from β-cyclodextrin-microcrystalline cellulose mixtures. Drug loading of pellets was accomplished by means of two alternative strategies: 1) solution layering or 2) powder layering. Ibuprofen was chosen as the model drug, due to its low water solubility and well documented interaction ability with cyclodextrins.[12–15]

Size distribution, shape factor, friability and dissolution rates have been assessed for all products. The interaction between ibuprofen and β-cyclodextrin was monitored by Differential Scanning Calorimetry (DSC). Finally, Micro Fourier Transform Infrared spectroscopy (MicroFTIR) was applied to determine the distribution of components within each pellet on a micro scale.

MATERIALS AND METHODS

Microcrystalline cellulose (MCC) (Avicel PH101, FMC International, Cork, Ireland), and ibuprofen (IBU), (particle size range 20–180 μm) (Lisapharma, Erba, Italy) were used as supplied. β-cyclodextrin (BCD) (Roquette, Lestrem, France) was employed as such or after separating by sieving three particle size fractions, namely 355–250, 250–180 and < 180 μm.

A IBU/BCD/MCC (8.9/82/9.1) physical mixture was prepared with a Turbula® mixer (15 min) (Bachofen, Switzerland).

A high-shear mixer (ROTO Junior, Zanchetta-Romaco, Lucca, Italy) consisting of a 10 litres stainless steel vacuum-tight bowl, jacketed for temperature control and equipped with main impeller, high-speed chopper and spraying nozzle was employed for the preparation of pellets.

Preparation of BCD-MCC Drug-Free Pellets

BCD (900 g) and MCC (100 g) were placed in the high-shear mixer bowl and gently mixed (impeller rotation, 100 rpm) for 5 minutes. As a binder, 200 mL of water were added, under continuous impeller rotation (250 rpm) by means of the spraying system

Table 1. Process conditions for the preparation of BCD-MCC pellets.

Time between addition (min)	Amount of water (mL)	Impeller speed (rpm)
0	20	250
3	20	250
3	20	250
3	20	300
3	20	300
3	20	300
4	10	350
4	10	350
4	10	350
4	10	400
4	10	400
4	10	400
4	5	450
4	5	450
4	5	450
4	5	450
4	5	450
4	5	450

(spraying pressure 3 bar, nozzle diameter 1.5 mm) through 18 steps, progressively decreasing from 20 to 5 mL the volume added per step with 3–4 minutes interval between each addition. The impeller rotation was gradually increased from 250 rpm up to 450 rpm providing agglomeration and spheronisation of pellets. The adopted experimental conditions are summarized in Table 1. During the process the jacketed granulation chamber was cooled with tap water to avoid excessive heating due to frictions.

Final drying was carried out by warming the jacketed bowl with hot water (40°C) for 2 hours, under mild vacuum (0.8 bar) and stirring the pellets mass (impeller rotation 100 rpm).

Preparation of Drug-Containing Pellets

Drug loading (final composition, IBU:BCD 2:3 mol:mol, IBU content 10.8% by weight) was accomplished according to the above reported layering procedures.

Powder Layering

IBU (97.2 g) was added at stage 10 of the BCD-MCC pellets preparation procedure. The process was stopped, the bowl opened and the IBU powder dispersed manually over the bowl content. The remaining eight steps were conducted as for the drug-free pellets preparation (see Table 1) (*code IBU1*).

Solution Layering

100 mL portions of an ethanolic solution of ibuprofen (1.09 g/mL) were sprayed on BCD-MCC pellets while submitted to impeller rotation (300 rpm) under vacuum (0.4 bar) (*code IBU2*).

Final drying was conducted for both procedures as reported for BCD-MCC drug-free pellets.

Sieve Analysis

Particle size distribution was determined by sieving (Endecotts Ltd., London, UK) the pellets for 20 minutes (Analysette, Fritsch, Idar-Oberstein, Germany) and collecting fractions between 300 and 1700 μm according to the ASTM progression. Fractions between 500 and 1400 μm were selected as pellets. The geometric mean diameter (d_g) and the geometric standard deviation (σ_g) were determined respectively from the particle size at 50% probability level and the slope of the regression line obtained by plotting the cumulative undersize distribution versus particles diameter in the log-probit diagram.[16]

The yield of the pelletization process was calculated as the ratio between the weight of the obtained pellets and the amount of powder introduced in the mixer.

Shape Analysis

The sphericity of pellets was determined by image analysis. Computer grabbed images (video camera CCD JVC, Tokyo, Japan) of approximately 100 pellets positioned under the lens of a stereomicroscope (Citoval2, AusJENA, Germany) were analysed using Image 1.60 NIH software (NIH, Bethesda, USA) to determine the projected area (PA) and the perimeter length (PL) for each pellet. The shape factor (SF), which provides an estimation of the regularity of the contour of the particle, was calculated according to the equation:[17,18]

$$SF = 4\pi \frac{PA}{PL^2} \quad (1)$$

An SF value of 1 indicates perfect sphericity.

Friability

Friability was measured by a Roche friabilometer (Erweka, Heuseinstamm, Germany) with a method modified from that described in EP 4th 2002[19] for uncoated tablets. Briefly, about 1 gram of pellets was placed on a sieve number 255. Loose dust was removed with pressurized air. Then, the pellets were accurately weighed, placed in the drum of the frilabilometer, and rotated 100 times. Thus, they were recovered, and reweighed after having removed any loose dust with the above-described procedure. The friability is expressed as percentage of mass loss with respect to the initial mass.

Thermal Analysis

The interaction between IBU and BCD was tested by microcalorimetry with an Indium calibrated DSC (Mettler Toledo 821e Greifensee, Switzerland) driven by STARe software.

Pellets were gently ground in a china mortar. Precisely weighed quantities (6–7 mg) were placed in 40 μL Aluminium pans and scanned, under dry

nitrogen purging (200 mL min^{-1}), from 30 to 55°C at 5 K/min, and maintained at 55°C for 30 minutes. The sample was then cooled down to 30°C (at −10K/min) and rescanned up to 100°C at 5 K/min to evaluate the drug fusion endotherm.

Thermogravimetric analysis (TG 50, Mettler Toledo) was carried out in 70 μL alumina pans in the same experimental conditions adopted for DSC runs.

MicroFTIR Spectroscopy

MicroFTIR spectra were recorded by means of a 200 MicroSampling FT-IR (Jasco, Tokyo, Japan) in the 4000–400 cm^{-1} wavenumber interval. Intact pellets or the radial sections (obtained by fracturing with a lancet) were analyzed on a KBr disc without any further handling.

SEM Analysis

Morphological characterization of cross sectioned pellets was performed by Scanning Electron Microscopy (SEM) (JEOL 6400, Japan) at 10 kV on samples sputtered with gold (thickness 200–400 Å).

Drug Loading

About 20 mg (accurately weighed) of thoroughly ground IBU1 or IBU2 pellets were suspended in 100 mL of a 50:50 ethanol-water mixture and submitted to magnetic stirring for 60 minutes. After filtration, an aliquot of the solution was made up to volume with the same solvent mixture. IBU concentration was determined spectrophotometrically (Spectracomp 602, A.P., Milan, Italy) at 222 nm in comparison with a standard solution.

Drug Dissolution

Dissolution experiments were performed at 37°C in distilled water (1 L) using a USP 27 Dissolution Apparatus II (DTR6 Erweka, Heuseinstamm, Germany) with the paddle rotating at 100 rpm. In order to comply with sink conditions requirements, 10 mg of IBU or the equivalent containing-dose of IBU1, IBU2 or IBU/BCD/MCC physical mixture were assayed using the dispersed amount technique. IBU concentration in water was determined spectrophotometrically (continuous flow-through cell, Spectracomp 602, A.P., Milan, Italy) at 222 nm and plotted, as IBU dissolved fraction, vs. time. Each dissolution experiment was performed in triplicate.

RESULTS AND DISCUSSION

Drug-Free Pellets

The particle size distribution of the obtained drug-free pellets is reported in Fig. 1. It can be observed that

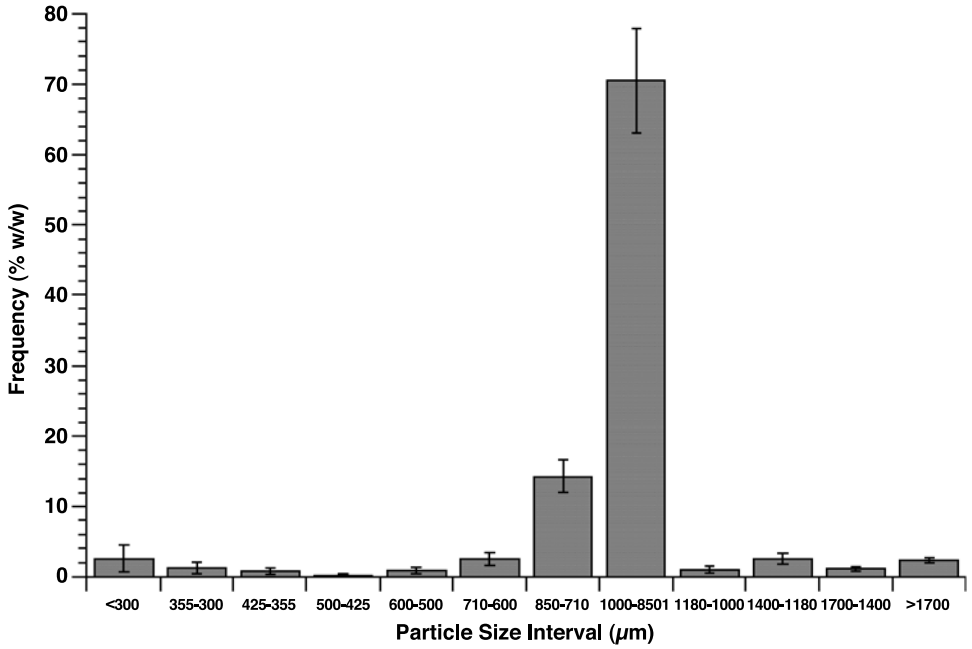

Figure 1. Particle size distribution (% w/w) of BCD-MCC (drug-free) pellets.

Table 2. Technological, physico-chemical and pharmaceutical parameters of prepared pellets (standard error of the mean) (n=3).

	Drug-free pellets	IBU1	IBU2
Yield %	83.7 (2.5)	63.6 (4.2)	62.5 (4.8)
Friability %	4 (1.1)	12 (4.2)	7 (3.1)
Shape factor	0.92 (0.05)	0.85 (0.08)	0.88 (0.06)
d_g, μm (σ_g)	818 (2.12)	749 (1.57)	1126 (2.46)
Crystalline ibuprofen %	/	33 (2.6)	14 (0.99)
Drug content %	/	8.79 (0.50)	9.24 (0.49)

nearly 70 % lie in the 850–1000 μm range. The yield value related to the 500–1400 μm interval was 83.7 %.

When pellets were prepared with BCD as supplied, optical microscopy evidenced the presence of large BCD crystals on the surface of pellets, negatively affecting the regularity of the particles (SF=0.69). On the other hand, when BCD selected fractions were used the shape factors significantly increased as a consequence of particle size reduction (0.80, 0.85 and 0.92 respectively, for 355–250, 250–180 and <180 μm BCD fractions). Therefore, the <180 μm fraction was selected for further studies.

Drug-Loaded Pellets

With respect to the production of medicated pellets, the simultaneous addition of IBU and BCD at the beginning of the kneading process in the bowl of the ROTO-J granulator caused, just after the first addition of the binder, a dramatic increase of the viscosity of the slurry with formation of a hard paste, and eventually blockage of the main impeller. This effect could be reasonably ascribed to the formation of the IBU-BCD interaction compound.

For this reason, drug-containing pellets were prepared with the two layering techniques.

In Table 2, some technological and pharmaceutical parameters relevant to loaded pellets, obtained with the two layering procedures, are presented in comparison with those of drug-free pellets.

Both the yield of the process and the shape factor were practically the same for IBU1 and IBU2 and lower than those of drug-free pellets. In particular, a significant decrease (approximately, from 84 down to 63 %) was observed in the process yield.

As expected, IBU2 preparation consisted of significantly larger pellets; this can be justified considering that the solution layering was carried out on already formed drug-free pellets.

Drug-loaded pellets (IBU1 and IBU2) were more friable than drug-free ones: furthermore, IBU1 (pow-

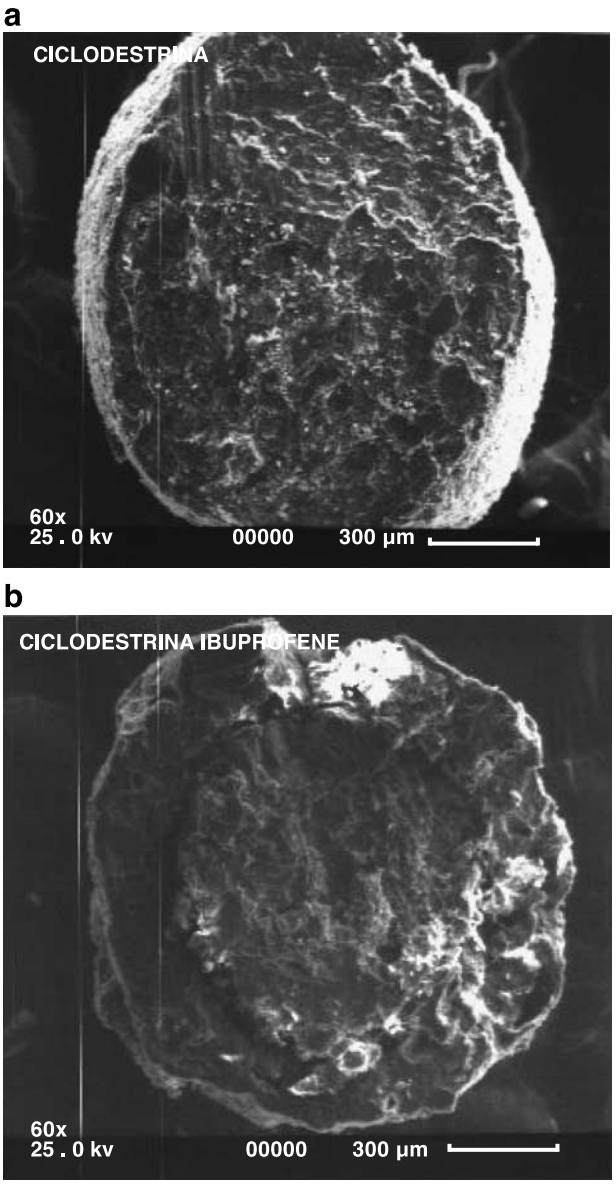

Figure 2. SEM pictures (×100) of cross-sectioned pellets: drug-free pellet (a) IBU 1 (b).

der layering) resulted more friable than IBU2 (solution layering).

Both preparation procedures gave rise to similar drug loading, fairly close to the theoretical value (8.9% by weight).

Thermal Analysis

The disappearance, or reduction, of the endotherm relative to the melting of the crystalline drug in the DSC profile of the processed drug/BCD binary is generally taken as an indication of the interaction between the components.

Since IBU fusion occurs at 78°C, within the same temperature interval of BCD dehydration (approximately, 50–110°C),[20] a preliminary isothermal treatment at 55°C was necessary to eliminate water from the binary and allow the determination of the endotherm relevant to IBU fusion.

TGA runs, at the same temperature and scanning conditions, confirmed that no further weight loss was detectable after the isothermal treatment.

From the ratio between the fusion enthalpy (ΔH_f in the 74–82°C interval) measured for samples obtained from the different pellets and that of unprocessed IBU/BCD/MCC physical mixture, the crystallinity percentage of IBU was calculated (Table 2).

Loaded pellets were significantly different in terms of percentage of amorphous (non crystalline) ibuprofen. This is not surprising considering that, in the case of the powder layering process, the interaction between IBU and BCD could occur only to a limited extent due to the partial dissolution of ingredients in the binding liquid. In the case of the solution layering process (IBU2), the interaction between drug and BCD substantially improved.

Figure 2 shows, as an example, SEM pictures of a cross section of drug free (panel a) and IBU1 (panel b) pellets. While drug free and IBU2 pellets (not shown), similar to each other, are apparently rather homogeneous, an external layer of different morphology was observed in the case of IBU1 pellets, likely ascribable to the IBU/β-CD binary.

The chemical composition of the external layer, in comparison with the core, was investigated by micro-FTIR analysis.

Figure 3 reports the spectra limited to the 1800–1550 cm^{-1} wavenumber interval. Due to the large excess of BCD present in the mixture with respect to IBU and MCC, only this ir region was found to show distinctive bands for BCD and IBU.

As expected, the ir spectrum of the core (both for IBU1 and IBU2) was practically superimposable to that of pure BCD (Fig. 3a). The IR spectrum of the external layer largely overlapped that of BCD, in the case of IBU1, except for the presence of a band at 1720 cm^{-1} corresponding to the C=O stretching of the carboxyl group of IBU (see traces c and e of Fig. 3). This confirms that the drug was not uniformly distributed within the pellet.

Partial interaction of IBU with BCD during the IBU1 process is further demonstrated by the shift

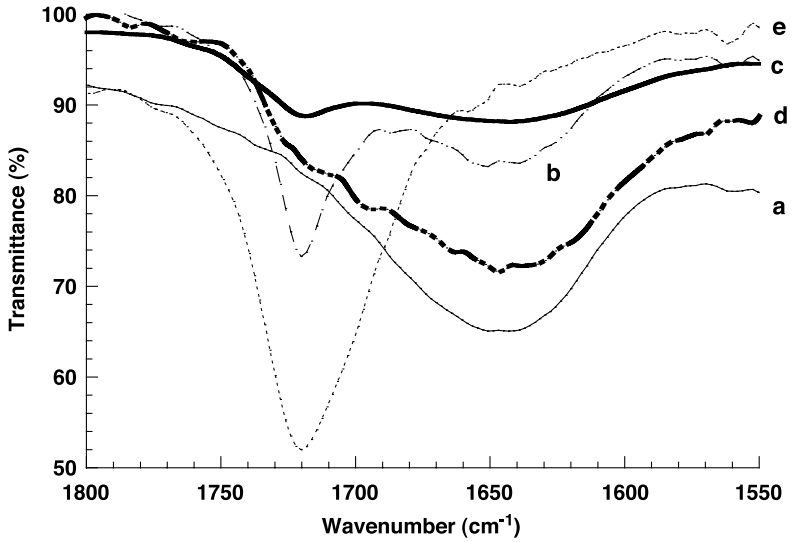

Figure 3. MicroFTIR spectra in the wavenumber interval 1800–1550 cm^{-1}: a) cores of IBU1, IBU2 and drug free pellets; b) IBU/BCD/MCC physical mixture; c) IBU1 external layer; d) IBU2 external layer; e) IBU.

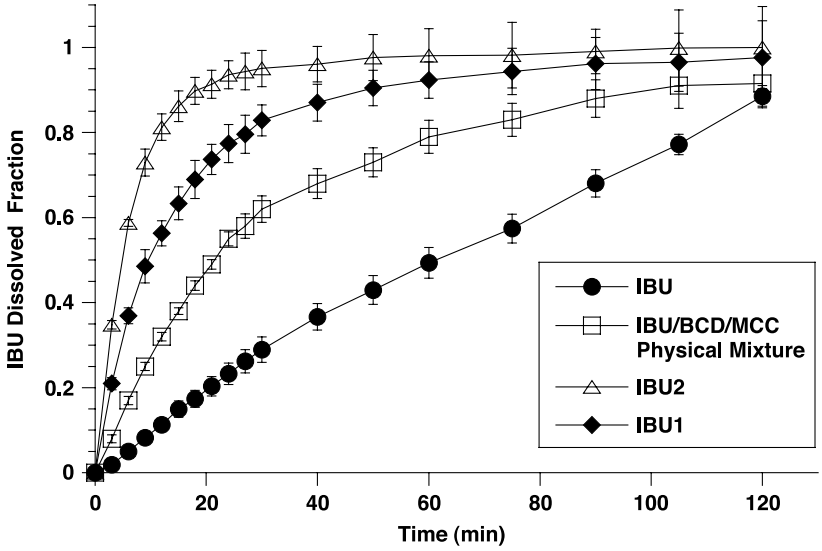

Figure 4. Fraction of ibuprofen dissolved versus time from ibuprofen alone (IBU), IBU/BCD/MCC physical mixture and IBU1 or IBU2 pellets. The bars represent the standard error of the mean (n=3).

of the relative intensities of the bands at 1720 and 1650 cm^{-1}, the latter relevant to BCD, with respect to the physical mixture (Fig. 3b).

The micro-FTIR analysis of the surface of IBU2 pellets (Fig. 3d) shows only a barely perceptible shoulder at 1720 cm^{-1} of the main band at 1650 cm^{-1}, thus indicating that the interaction between IBU and BCD is almost complete, in agreement with the results of thermal analyses, previously reported in Table 2.

Dissolution Measurements

It is worthy to mention that pellets did not disintegrate during the dissolution test.

Dissolution profiles of ibuprofen from IBU1 and IBU2 preparations are reported in Fig. 4, together with the results obtained with ibuprofen alone and the IBU/BCD/MCC physical mixture.

While IBU alone dissolves almost linearly and slowly (nearly 85% in 2 hours), the presence of BCD remarkably increases IBU dissolution rate from the physical mixture, probably owing to the formation of water-soluble complexes.[12,13]

On the other hand and quite unexpectedly, even higher dissolution rates were measured for IBU1 and IBU2. In principle, the large particle size of pellets should be considered an unfavourable factor in terms of surface area exposed to the dissolution medium in comparison to that of the pure drug and the physical mixture. Evidently, the solid state characteristics of the drug within the pellet play a prominent role on drug dissolution. In this case, the significant increase in drug dissolution rate should rather be ascribed to the large fraction of non crystalline IBU (see Table 2). The difference between IBU1 and IBU2, concerning the contents of amorphous IBU, is further reflected by the significant difference between the respective dissolution rates.

CONCLUSIONS

The high-shear mixer proved to be suitable for the preparation of pellets containing up to about 90% of BCD using water as binder.

The possibility of preparing pellets having a content of BCD up to 90% by weight is particularly important when the formulation of multiple unit dosage forms, containing suitable quantities of the drug as an inclusion compound with cyclodextrins, is needed. It is worth to remind that this generally requires a large amount of cyclodextrin, with respect to the active principle, due to the molecular weights ratio (∼4:1, CD:DRUG).

Drug loaded pellets with favourable technological and biopharmaceutical characteristics can be obtained both by powder or solution layering procedures. In particular, the latter seems more suitable for producing pellets with high drug contents, reduced friability and high drug dissolution rates.

In general, BCD containing pellets can be envisaged as suitable carriers for controlled drug release,

in particular in the case when drug dissolution enhancement is required.

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