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A new approach to the granulation of β-cyclodextrin inclusion complexes

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ABSTRACT

Cyclodextrins (CDs) are annular oligosaccharides containing 6–12 glucose unities joined together by α-1,4 bonds. They have a conical-truncated shape with a lipophilic cavity in which different molecules can be included resulting in a stable inclusion complex. The cyclodextrins have been widely applied in pharmaceutical technology with the objective of increasing the solubility, stability and bioavailability of drugs in different pharmaceutical dosage forms, such as tablets. In order to obtain β-CD tablets, liquid dispersions of drug/β-CD are usually submitted to different drying processes, like spray-drying, freeze-drying or slow evaporation, being this dry material added to a number of excipients. However, such drying processes can generate particulate materials showing problems of flow and compressibility, needing their conversion into granulates by means of wetting with granulation liquid followed by additional drying. In this work, the main objective was to evaluate the preparation of tablets without the need of this additional drying step. For this purpose an aqueous dispersion containing acetaminophen/β-CD complex and cornstarch was dried using a spouted bed and the obtained granules were compressed in tablets. Acetaminophen was used as model drug due to its low water solubility and the inexpensive and widely available cornstarch was chosen as excipient. Acetaminophen powder was added into a β-cyclodextrin solution prepared in distilled water at 70 °C. Stirring was kept until this dispersion cooled to room temperature. Then cornstarch was added and the resulting dispersion was dried in spouted bed equipment. This material was compressed into tablets using an Erweka Korsh EKO tablet machine. This innovative approach allowed the tablets preparation process to be carried out with fewer steps and represents a technological reliable strategy to produce β-cyclodextrin inclusion complexes tablets.

1. Introduction

Cyclodextrin complexes represent very important systems in pharmaceutical technology. The cyclodextrins (CDs) are products of enzymatic hydrolysis of starch, showing primary and secondary hydroxyl groups in the smaller and larger openings, respectively, of its three-dimensional toroidal structure. Due to this spatial arrangement, the exterior of the toroid is much more hydrophilic than its interior, resulting in a capacity to host hydrophobic substances in a system known as inclusion complex, while imparting water solubility to the whole system (Fig. 1). This property allows CDs to be applied in several pharmaceutical dosage forms aiming to improve the drug solubility in water and thus its bioavailability. These CD inclusion complexes have been prepared as solutions or particulate solid forms [1,2]. After preparation of inclusion complexes in solution, a drying step is carried out by freeze-drying or spray-drying [3].

Acetaminophen (ACP) is an analgesic and antipyretic drug largely used to relieve mild to moderate pain and may also be used to relieve the pain of osteoarthritis. ACP comes as tablet, chewable tablet, capsule, suspension or solution, extended-release tablet, and orally disintegrating tablet [4]. This drug has been previously used as a model for CD inclusion complex studies performed by several methods, including spray-drying and freeze-drying [5–7] with good inclusion results. However, Lin and Kao [5] reported poor flow properties of ACP/CD complexes prepared by spray-drying and freeze-drying, which was attributed to the small particles sizes obtained with these drying methods. Besides, the conventional CD inclusion complex preparation methods require further steps to obtain a solid dosage form, like grinding, mixing with excipients, agglomeration and sieving. In pharmaceutical technology it is essential to control powder characteristics during manufacturing [8].

Drying is a key unit operation in the pharmaceutical technology, as well as for the preparation of API/CD complexes. The drying of

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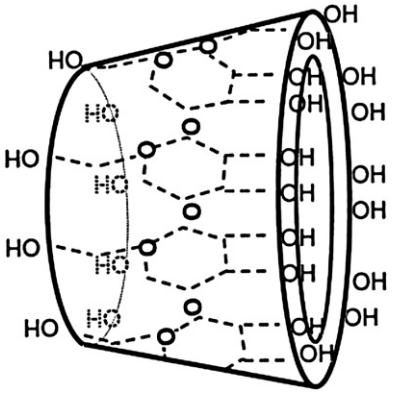

Fig. 1. Toroid of β-cyclodextrin.

pharmaceutical solutions, suspensions and pastes is still a challenge due to the considerably large diversity of products and properties and their usual thermal lability [9]. As a consequence, there is not a universal dryer for pharmaceuticals, although the freeze and spray dryers are the mostly used by far [10]. However, other dryers have been demonstrated as convenient options when specific characteristics are desired to solid forms [11]. The application of spouted beds (SB) with inert bodies for drying of microcapsules and pharmaceuticals [11,12] proved to be feasible to design pharmaceutical powders. Although this technique was proposed in the 1980s, only recently the possibility of employing for drying pharmaceuticals has been studied [11,13–15]. Furthermore, SBs have been also proposed for granulation of pharmaceutical coarse particles [16] and one of the features observed during the drying of microcapsules in SBs is their agglomeration [11,12]. The application of SB for the drying of pharmaceutical materials has been the object of many researches. The results showed that SB is promising for the drying of medicinal plant extracts [13] and microcapsules [12]. In some cases the SB process for product drying is competitive when compared to others methods [11].

The aim of the study reported here was to propose and evaluate the spouted bed as a method for direct drying of a liquid mixture containing ACP/CD complex and starch. The characteristics of the ACP/CD/starch particulate solids obtained were determined by particle size analysis, flowability, compactability, X-ray powder diffraction and differential scanning calorimetry. The particles were compressed and the resulted tablets were analyzed for physical properties.

2. Experimental

The acetaminophen and cornstarch were purchased from Henrifarma Ltd. (São Paulo, Brazil) and the β-cyclodextrin (Kleptose™) was supplied by Roquette (Lestrem, France).

2.1. Method of ACP/CD inclusion complex and starch preparation

ACP and β-CD were weighed and added to distilled water in a stirred glass jacketed vessel. Temperature was kept constant at 70 °C with a heating fluid circulating from a thermostatic bath. After complete β-CD dissolution, the mixture was kept under stirring until it reached room temperature. Then, the aqueous β-CD/ACP dispersion (250 mL) was added to 200 g of cornstarch and the resulted mass was dried using the spouted bed technique.

A schematic diagram of the procedure to prepare ACP/CD/starch dispersion is shown in Fig. 2.

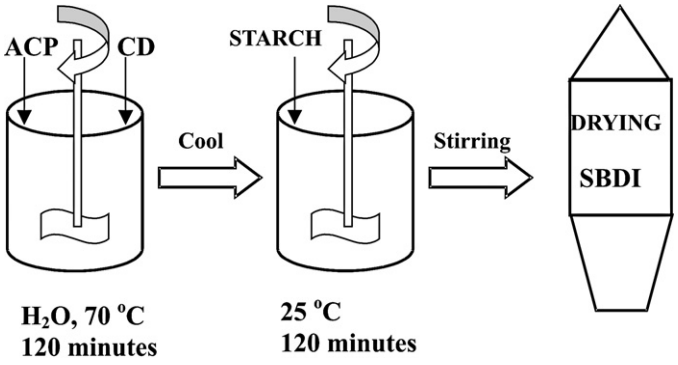

Fig. 2. Schematics showing the procedure to prepare ACP/CD/starch dispersions.

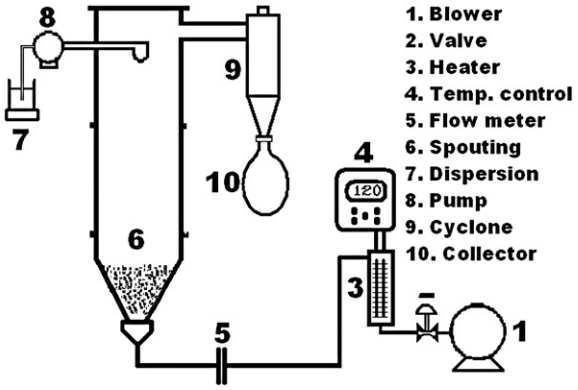

Fig. 3. Experimental spouted bed apparatus.

2.2. Granulation of inclusion complex β-CD/ACP and starch

The experimental setup was made in stainless steel and borosilicate glass, with a cylindrical column 14.0 cm in diameter, 83.0 cm height and a conical base with 60° included angle and 9.5 cm height. The air inlet had an orifice diameter of 2.2 cm. Spouting air was supplied by a compressor (Wayne, 120 scfm) and its mass flow rate measured by a calibrated orifice meter. A PID controller HW 2000 (Coel Ltd., Brazil) and an electrical heater were used to set process temperature. The ACP/CD/starch dispersion was fed into the chamber by a tube centralized at the top of the cylindrical column with a Masterflex Digital peristaltic pump, set to 10 mL min^{-1}. Also a cyclone was installed at the air exit of the cylindrical column to retain dried particles. Fig. 3 presents a schematic diagram of the experimental apparatus.

Glass spheres with diameter 2.6 mm were used as inert bodies and the main hydrodynamic characteristics of their spouting, like minimum spouting velocity, pressure drops and maximum stable spouting bed height were determined [17]. The spouting conditions employed in the drying experiments are detailed in Table 1.

The dry granules collected by the cyclone were stored in amber flasks until sampling for further characterization or tabletting.

Table 1
Operational conditions for ACP/CD/starch drying in SBDI.

Hmax (m)	*H*/Hmax	VMS (m^3 min^{-1})	*V*/VMS	Ti (°C)	To (°C)
SBDI					
0.28	0.33	0.0252	1.2	80	61

Hmax: maximum height of spouting, H/Hmax: relation between the height used (14 cm) and maximum height of stable spouting determined (28 cm), VMS: minimum velocity of spouting, V/VMS: relationship between velocity used and minimum velocity of spouting, Ti: temperature inlet, To: temperature of outlet.

2.3. Granulates evaluation

2.3.1. Moisture

Loss on drying of granules was assessed with an analytical infrared moisture balance (Mettler™, PL 200/LP 11) [18]. For this, approximately 1 g accurately weighed was placed on the holder and dried at 120 °C until constant weight. The results are expressed as water loss in relation to the initial mass.

2.3.2. Morphological analysis

Morphological analysis of β-CD, ACP and granules was carried out by means of photomicrographs obtained by scanning electron microscopy (Jeol—JSM T330A). Samples were distributed on adhesive double face tape fixed on metal supports and covered with colloidal gold under argon atmosphere.

2.3.3. Granulometric distribution

Assessment of granules particle size distribution was performed on an optical microscope DMRXA (Leica™), using Leica™ Qwin Image Systems software for image capture and measuring. Feret's diameter at 0° of at least 200 particles was measured [19,20].

For constructing the graph of particles size distribution, the number of classes was calculated using the following equation [21]:

$$k = 1 + 3.22 \ \log n \tag{1}$$

where k is the number of classes and n the number of data.

2.3.4. Apparent bulk and tapped densities

Apparent densities of granules were determined, indirectly, by their apparent volumes. For the apparent bulk density assay, the material was put in a 250 mL graduated cylinder (Tapped Volumeter Erweka™ SVM 12) and the mass was registered on a semi-analytical balance (Ohaus™ PL 400) [22]. The apparent bulk density was calculated by means of the equation:

$$d_b = \frac{m}{V_b} \tag{2}$$

where d_b = apparent bulk density (g/mL); m = mass (g) and V_b = apparent bulk volume (mL).

For the determination of apparent tapped density, the graduated cylinder containing the sample was submitted to 1250 vertical motions (Tapped Volumeter Erweka™ SVM 12). At the end of each series of compaction, the volume occupied by the material was read and the procedure was repeated until the decreasing of apparent volume was about 2% and the tapped volume was considered to be the penultimate determination [22]. Apparent tapped density was calculated by means of the following equation:

$$d_t = \frac{m}{V_t} \tag{3}$$

where d_t = apparent tapped density (g/mL); m = mass (g) and V_t = apparent tapped volume (mL).

2.3.5. Carr index

From the values of apparent bulk and tapped densities, it was possible to calculate the Carr index, *CI%*, with the equation: [23]

$$CI\% = \frac{d_t - d_b}{d_t} \times 100 \tag{4}$$

where *CI%* is the Carr index, d_t is the apparent tapped density (g/mL) and d_b is the apparent bulk density (g/mL).

2.3.6. Hausner ratio

According to the methodology referred by [24], the Hausner ratio (*HR*) was determined by the ratio between tapped and bulk densities, as follows:

$$HR = \frac{d_t}{d_b} \tag{5}$$

where *HR* is the Hausner ratio, d_t is the apparent tapped density (g/mL) and d_b is the apparent bulk density (g/mL).

2.3.7. X-ray powder diffraction

The identification of the crystalline structure of ACP, β-CD, granules and of the physical mixture prepared with 1:1 ACP and β-CD was assessed by X-ray diffractometry. The mixture of ACP/β-CD (1:1) was gently carried out by mortar and pestle. X-ray powder of the samples were collected on a Siemens D-500 diffractometer (CuKα radiation, λ = 1.541 Å) with a curved graphite monochromator. Data were treated by Winmetric software and the refining of crystallographic parameters was done from the diffraction data (2θ and intensity). The scanning rate was 0.3 s at each 0.02° in the range from 20° to 120°.

2.3.8. DSC curves

About 2.6 mg of each ACP, β-CD, starch, granules, and of the physical mixture of the three components (ACP, β-CD and starch) were placed in sealed aluminum pans (DSC 50-Shimadzu™). Curves were obtained under nitrogen atmosphere and the heating rate was set at 10 °C/min.

2.4. Compression and tablets evaluation

The granules were compressed into tablets with a single punch tablet machine (Erweka EKO™) fitted with a 12 mm flat faced punch at a constant compression force. The following physical properties of the tablets were evaluated.

2.4.1. Aspect

Properties of the pharmaceutical dosage form, like geometrical shape, surface, color and presence of foreign material were visually observed.

2.4.2. Weight variation

Twenty tablets were individually weighed on an analytical balance (Ohaus™, model AS 200) and the mean and standard deviation were calculated.

2.4.3. Mechanical resistance

In order to evaluate the mechanical resistance of the tablets against radial pressure, the hardness of 20 tablets was measured (Schleuniger Pharmatron™, model 6D). For the assessment of friability, a type Roche friabilometer (Erweka™, model TA20) was used. The test was carried out by weighing 20 dust free tablets, which were submitted to 100 free falls from a height of about 13 cm inside the rotating drum of the equipment. After the rolling, the dust free tablets were weighed again and the friability was expressed as function of the percentage of powder loss [18].

2.4.4. Disintegration time

Eighteen tablets were analyzed on an apparatus for measuring disintegration time (Erweka™, model ZT-502), according to criteria established by the United States Pharmacopeia [18]. This apparatus is constituted by 6 glass opened tubes with 7.5 cm length and attached to 10-mesh sieve. For the determination of the disintegration time, one tablet was placed into each tube and the basket holder was immersed into a recipient containing 1 L water maintained at 37 ± 1 °C, in such a way that the tablets could stay at 2.5 cm under the liquid surface during the ascending motion and 2.5 cm over the recipient bottom during the descending movement.

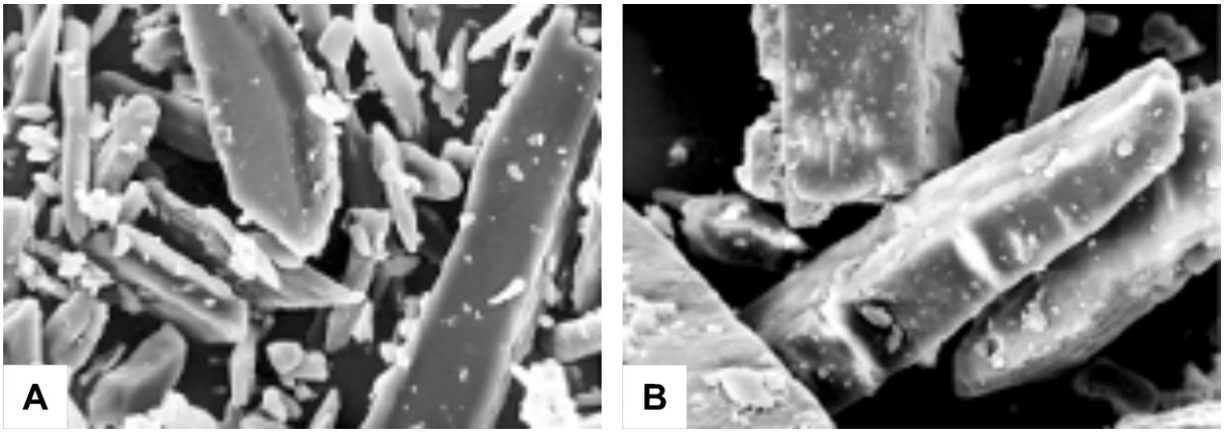

Fig. 4. Photomicrographs of ACP and β-CD (magnification 750×).

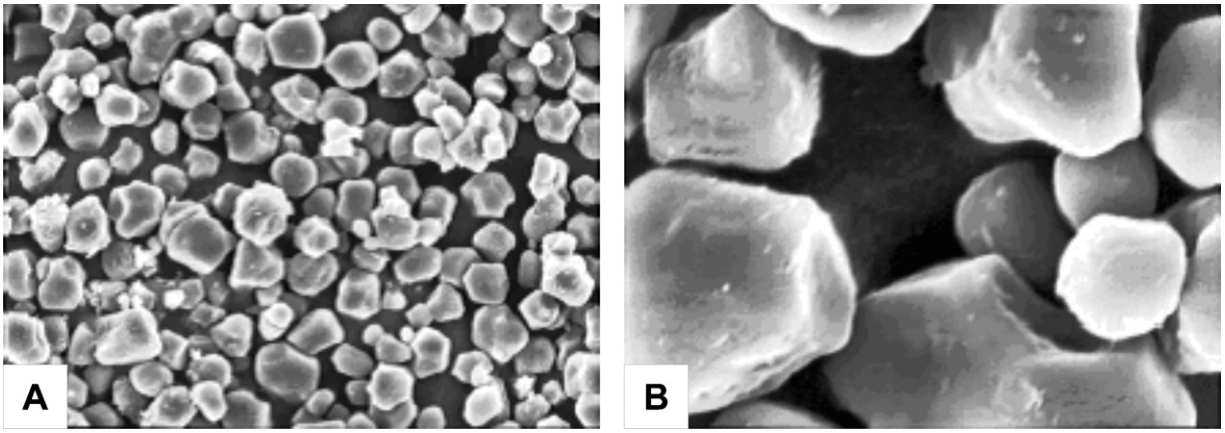

Fig. 5. Photomicrographs of granules (magnification 750 and 3500×).

3. Results and discussion

3.1. Preparation of granules

By means of preliminary studies, it was ascertained that a system constituted by 150 g of starch and 90 mL of β-CD/ACP dispersions is ideal for sieve granulation. For spouted bed granulation, 200 mL of the β-CD/ACP liquid dispersion was used to moisten 200 g of cornstarch. Such amounts were required in order to allow the peristaltic pump attached to the equipment to introduce, by uniform dropping, the dispersion into the spouted bed. After drying, the granules presented residual moisture of 3.6%.

3.2. Morphological analysis of CD, ACP and granules

Fig. 4 depicts the crystalline form of ACP as monoclinic and prismatic system [25] and of typical β-CD crystals. Such crystals have dimension about some tens of micron, smooth surface and well-defined contours [26].

Summers and Aulton [27] reported that granules produced on fluid beds are similar to those produced by sieving, these latter being more porous. Fig. 5 shows very uniform granules particles.

3.3. Size distribution

Fig. 6 depicts the size distribution and cumulative frequency for granules. Above 80% of the material presented Feret's diameter between 3.0 and 11.0 μm, resulting in a uniform particle size distribution. Considering the average point in the classes of particle size frequency, it can be observed that both mode and median are 9. The arithmetic mean considered as a summary of values distribution as a whole was 8.7. The proximity of values observed for mode, median and arithmetic mean ratify a very uniform particles size distribution.

3.4. Flow properties

Granules show bulk density of 0.454 g/mL, tapped density of 0.520 g/mL, *CI%* of 11.92 and 1.14 for *HR*. These results indicate that

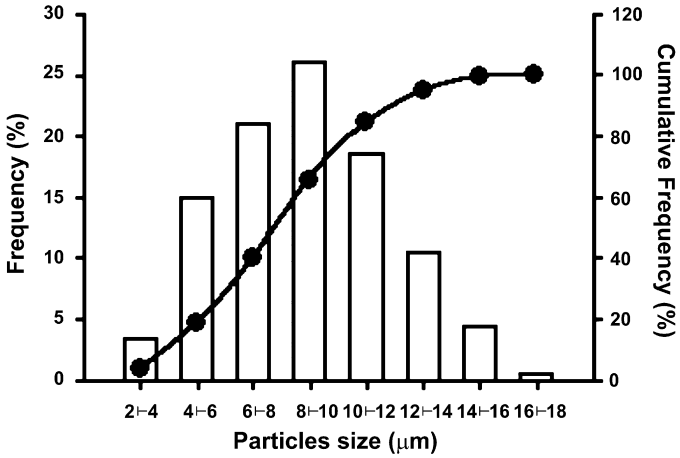

Fig. 6. Granules particle size distribution.

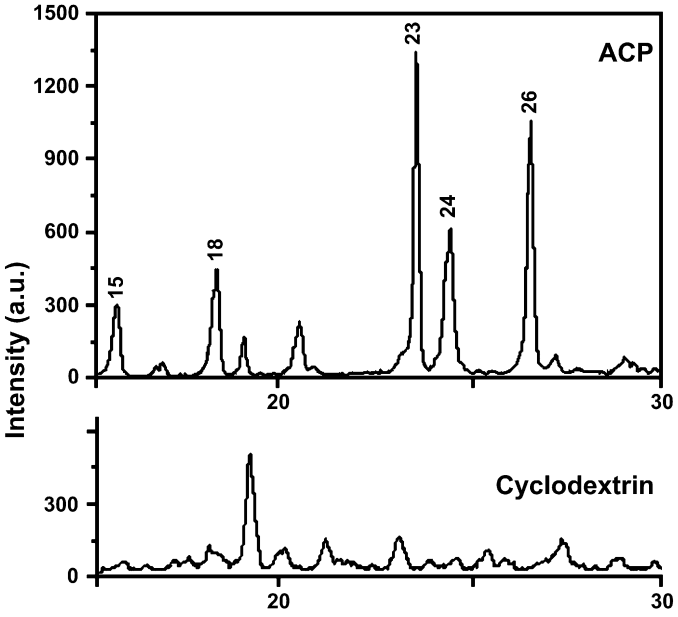

Fig. 7. X-RPD of ACP and β-CD.

the granulate presents good flow characteristics, since *CI* values below 15% and *HR* < 1.25 generally reflect easiness of particles flow [28].

3.5. X-ray diffraction

ACP is in crystalline form and its diffractogram presents narrow and very intense peaks at $2\theta = 23^\circ$, $2\theta = 24^\circ$ e $2\theta = 26^\circ$, as well as β-CD, which presents a very intense peak of preferential increasing of crystalline structure at $2\theta = 19^\circ$. On the other hand, the X-rays diffractogram of sample of granules does not present fine peaks, an indication of its amorphous nature (Figs. 7 and 8).

The results expressed in Table 2 demonstrated that the width at peak half height of some peaks on granules diffractogram is greater than those widths for the ACD and β-CD (1:1) mixture.

According to Scherrer's equation [29], the width at peak half height and the crystal size are inversely proportional quantities. Since the crystal size is related to the extension of crystallinity degree, as greater the crystal size is, bigger is the number of crystallographic plans into *hkl* directions and, therefore, bigger is the crystallinity degree [29]. As suggested by El-Said and Garekani the differences in the relative intensities of the peaks may be attributed to differences in the crystal sizes of the samples [30,31].

Table 2
Peak width at some angles of diffractogram for physical mixture and granules.

2θ	Width (Å)
Physical mixture	
15.536	0.2165
18.050	0.5944
23.487	1.0974
Granules	
15.208	1.4276
18.013	1.1837
23.296	1.5441

3.6. DSC data

The thermogram of β-CD, between 50 °C and 250 °C is represented in Fig. 9. It is possible to observe a peak at 88.60 °C, probably relative to loss of molecules of solvation water of the cavity. DSC curve for ACP shows an endothermic peak at 169.45 °C, corresponding to melting point of the drug [25]. DSC curve of starch shows a broad endothermic peak between 40 °C and 150 °C, concerning to dehydration [32].

The peak corresponding to melting point of ACP is visible on the DSC curve for the physical mixture. Disappearance of ACP endothermic can be attributed to changing of ACP from the crystalline to the amorphous state, such data being in accordance with the X-ray diffraction results.

3.7. Tablets evaluation

The tablets (Fig. 10) presented the following characteristics: they are plan with circular shape, smooth surface, white color and free of foreign material. During the compression no capping or breakage was observed.

Tablets made of granules presented mean weight of 0.514 mg. This value does not exceed 5% of the theoretical weight (0.500 g), corresponding to the specifications of USP [18]. The hardness of a tablet is function of both the dye filling and the compression force applied [33]. The force used was set at level 8 of the equipment scale (maximal value is 10). The tablets showed adequate values for hardness, above 30N, which are in accordance with those recommended

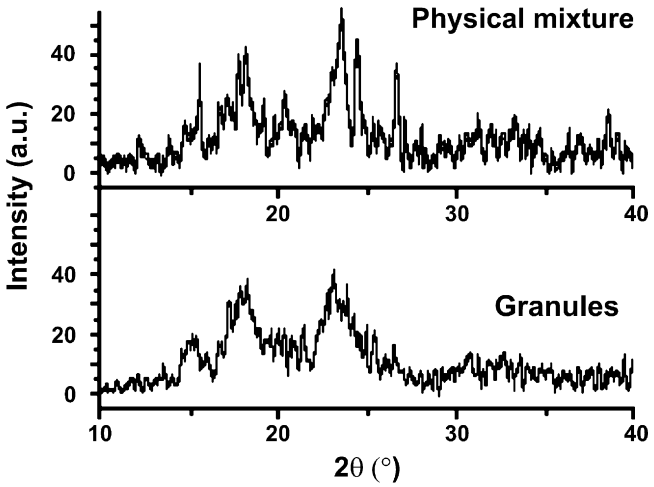

Fig. 8. X-RPD of physical mixture and granules.

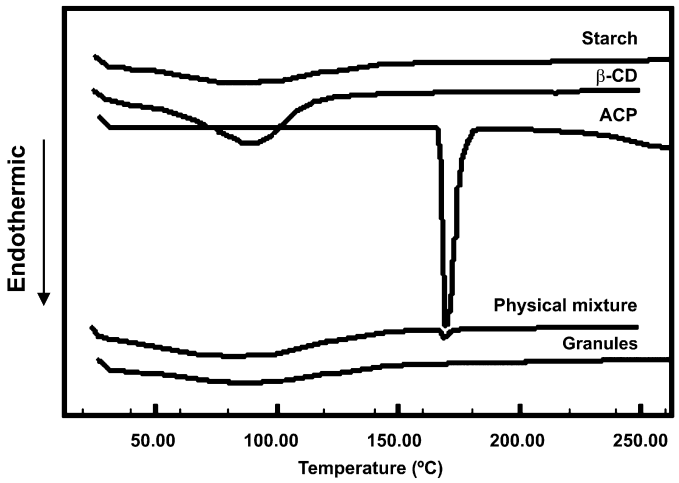

Fig. 9. DSC of starch, β-CD, ACP, physical mixture and granules.

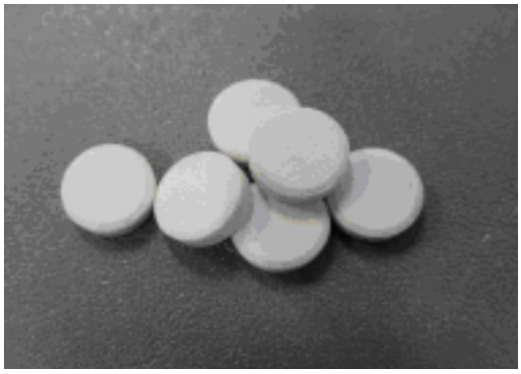

Fig. 10. Tablets obtained with granules.

by Farmacopéia Brasileira [34] and indicating that cohesive compacts were built. The friability test denotes the resistance against impact, rolling and friction the tablets present when submitted to processes of agitation, rolling or falling. According to the USP [18], are considered adequate those tablets that loss less than 1.0% of their initial weight. The value of 1.67% found suggests that β-CD does not show agglutinant features. The tablets disaggregated quickly (less than 100 s). This fast disintegration may be attributed to starch, which favors water penetration into the tablet, probably as a result of hydration of hydroxyl groups of starch molecule, being, therefore, efficient as disintegrant agent.

4. Conclusion

In the usual process for preparing β-CD containing tablets, liquid drug/β-CD dispersions are submitted to drying processes based on freeze-drying, evaporation or spray-drying and the dry material is incorporated into various excipients. However, these processes are time consuming due to the several steps involved: initial reaction, recrystallizing, filtration and drying. Furthermore, the material prepared by the process usually conducts to highly porous materials and inadequate flow properties. This study showed that the process involving the incorporation of β-CD/ACP liquid dispersion in an excipient and subsequent drying in spouted bed produced tablets with good tabletting properties, except for friability, which can be easily adjusted by few changes in formulation. The process studied is technologically feasible to prepare β-CD containing tablets and opens a new and interesting perspective to the development of tablets of drugs with low solubility, using a less time consuming and less expensive process, which may have great potential for use in the pharmaceutical industry.

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