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ORIGINAL ARTICLE

Release profiles of indometacin in β-cyclodextrin complexes from HPMC capsules

P. J. Salústio · J. F. Pinto · P. C. Costa · H. M. Cabral-Marques

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Abstract Powders containing indometacin complexed with β-cyclodextrin (1:1 ratio) obtained by two complexation methods (suspension/solution [with water removed by air stream, spray– and freeze–drying] and kneading techniques) were compared between them to observe the increase on the drug solubility and yield of the complexation process. The tests used for this comparison included the determination of the moisture content, true and bulk densities, angle of repose, Carr's index and *in vitro* drug release (at pH 1.0) from HPMC capsules. In the dissolution tests the drug release was analyzed considering different parameters (similarity factor (f_2), dissolution efficiency (*DE*) and the amounts released (M_t) at certain times (30, 60 and 180 min) by statistic analysis ($\alpha = 0.05$)). The results obtained showed poor pharmaceutical properties for all mixtures and that the indometacin released from capsules containing inclusion complexes presented an increase on solubility when compared with reference formulation (lactose and microcrystalline cellulose instead of β-cyclodextrin). The release of indometacin showed no dependency on the amount of water used in the formation of the complexes being the differences observed mostly due to the characteristics of the particles, which were dependent on the complexation method. However the low yield of the complexation that occurred can be explained by the difference between the size of the drug molecule, the guest (diameter—7.5 Å, length—14.2 Å) and the size of the β-cyclodextrin cavity, the host (diameter—6.0–6.5 Å).

Keywords β-Cyclodextrin · Inclusion complex · Dissolution · Capsule · Indometacin

P. J. Salústio (✉) · J. F. Pinto · H. M. Cabral-Marques
Research Institute for Medicines and Pharmaceutical Sciences (i-Med. UL), Faculty of Pharmacy, University of Lisbon, Av. Prof Gama Pinto, 1649-003 Lisbon, Portugal
e-mail: pjsalustio@ff.ul.pt

P. C. Costa
Laboratório de Tecnologia Farmacêutica, Departamento de Ciências do Medicamento, Faculdade de Farmácia da Universidade do Porto, Rua Aníbal Cunha 164, 4050-047 Porto, Portugal

Introduction

The solubility is an important characteristic in the drugs bioavailability. All drugs with poor solubility and high permeability belonging to Class II (Biopharmaceutical Classification System, BCS [1]) need to increase their solubility when are intended to be used in the manufacture of immediately release solid dosage forms. The drug solubility, among other techniques, can be increased through the formation of inclusion complexes with cyclodextrins (CDs) characterized by a stability constant (K_s) resulting from the profile type [2, 3]. CDs comprise a family of three well known cyclic oligosaccharides, consisting of six, seven or eight glucose molecules looking a truncated cone or torus-like macro-rings built up from glucopyranose units. These substances are crystalline, homogeneous and non hygroscopic [2]. In an aqueous solution, the slightly apolar CD cavity is occupied by water molecules which are energetically unfavored (polar–apolar interaction), and therefore can be readily substituted by appropriate "guest molecules" which are less polar than water, thus producing inclusion complexes [2]. This phenomenon occurs if the guest or a fraction of this molecule has compatible size with the cavity of the β-cyclodextrin (β-CD). The literature describes several techniques for the formation of the inclusion complexes (ex: co-precipitation, complexation in

a slurry/paste [4], supercritical fluids [5]). In a previous study [6] inclusion complexes were prepared using indometacin (pK_a value of 4.5, IN) [7] as a model drug and the β-CD, through two methods of preparation (kneading and suspension/solution). In the last method the water removal was carried out by drying the materials using different techniques. All resulting powders were used in this study as raw-materials for filling the HPMC capsules without the use of other excipients.

Some studies performed by other authors, where indometacin was complexed with β-CD presented low K_s values showing low affinity of this drug for the inclusion complexes formation [6, 8–10].

The aim of this study was to obtain a more soluble form of an indomethacin HPMC capsule formulation and to evaluate the influence of the particles characteristics (depending on the different preparation and water removal methods) on the drug release from this dosage form. Moreover, the reason of the complexation process low yield was also interpreted based on the guest molecule and host cavity relative sizes, their energy conformations determined by molecular modeling and by their K_s [11].

Materials and methods

Materials

The model drug used in this study was indomethacin (1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid) a practically insoluble in water drug (supplied by Capsifar, Portugal) and the excipients were β-CD (Wacker, Germany, β-CD), lactose (Granulac 200 Meggle, Germany, LAC) and microcrystalline cellulose (Avicel PH 101, FMC Biopolymer, Ireland, MCC). Hydroxypropylmethyl cellulose capsule shells (HPMC, n°3 shells, Qualicaps Europe, Spain) were used instead of gelatine shells to prevent interferences on indometacin (IN) quantification.

Hydrochloric acid (pH 1.0) and phosphate buffer (pH 7.2) solutions were used as dissolution media [12].

Methods

Molecular modeling

IN and CD geometry molecules were optimized based in Density Functional Theory [13] with B3LYP hybrid functional [14] and with a 3-21G(d) [15] and using Gaussian 03 programme [www.gaussian.com]. Minimized energy was estimated using available protocol in same MOE software [http://www.chemcomp.com/].

Preparation of inclusion complexes

Inclusion complexes powders (Table 1) were obtained by two methods of complexes preparation: a) suspension/solution with different processes of drying (air stream [AS], spray–drying [SD], freeze–drying [FD]) and b) kneading [K] that were described in previous study [6]. Briefly, in K method the water was added either 50 or 70 % (w/w) (K50, K70) and in suspension/solution the water was added according to β-CD solubility (1.63×10^{-2} M at 25 °C). The knead mass was dried in the preparation mortar whereas the water in suspension/solution was dried by SD (Büchi MiniSpray Dryer B-191, Switzerland: inlet air temperature 125 °C, outlet air temperature 98 °C, aspirator set at 100 % and flow rate set at 2.3 ml/min), by FD (Christ Alpha 1–4, B. Braun Biotech International, Germany: samples were previously frozen at −20 °C and then dried at 4.5–7.0 μbar for 48 h) and drying by stream of air (room temperature, 21 °C, for 7 days) [6].

Preparation of references mixtures

Physical mixtures (PM) containing IN and β-CD and mixtures with diluents (LAC or MCC instead of β-CD) were produced in tumble mixer for 10 min (Fisher–Kendall Scientific Co., USA).

All raw-materials and mixtures were sieved (250 µm, Retsch, Germany) and, if necessary, ground in a mortar with a pestle for the production of particles with less than 250 µm in diameter.

Characterization of the mixtures of powders

The formation of complexes (INβCD) was proved by optical microscopy (OM), ultra-violet and infra-red spectroscopy (UV, IR), differential scanning calorimetry (DSC), nuclear magnetic resonance (NMR) and X-ray diffraction (XRPD) in a previous study [6].

In this study the raw-materials (IN, β-CD and LAC) and all powder mixtures (Table 1) were observed by electron microscope (JEOL-JSM-S200LV Scanning Microscope, JOEL-JFC-1200 Fine Coater, USA) on a magnification 100, 350 and 1,500 times and their moisture contents also was performed in a moisture analyzer (Sartorius GmbH, Germany, at 100 °C). A measuring cylinder (50 cm^3) was used for the assessment of the bulk and tap densities (Stampfvolumeter, Germany) [12, 16]. The Carr index (IC_r) [17] was determined using the following equation:

$$IC_r = \frac{D_f - D_0}{D_f} \times 100 \quad (1)$$

where, D_0 is the initial bulk density and D_f is the tap bulk density. The true density was determined by helium pycnometry (AccuPyc 1330, Micromeritics, USA). The flow

Table 1 Mixtures of powders containing indometacin

Indometacin	Preparation method	Drying technique
INLAC	Powder mix	Not applicable
INMCC	Powder mix	Not applicable
INβCD PM	Powder mix	Not applicable
INβCD AS	Suspension/solution	Air stream
INβCD K50	Kneading (50 % of water)	Stirring evaporation
INβCD K70	Kneading (70 % of water)	Stirring evaporation
INβCD SD	Suspension/solution	Spray–drying
INβCD FD	Suspension/solution	Freeze–drying

properties of the powders were examined with an Erweka GT Granule tester (Erweka, Germany): powders were poured into a funnel and then allowed to pass through a nozzle of 15 mm diameter onto a plate for 10 s. The angle of repose was found as the angle of the powder's cone to the plate.

Preparation and characterization of HPMC capsules

An accurate amount of each powder mixture (50 mg, *i.e.,* 11.98 mg IN—Table 1) was manually filled into the capsule body. The filled capsules were submitted to the disintegration and dissolution test.

Disintegration and dissolution studies

Disintegration test was performed in disintegration apparatus (Erweka ZT3, Germany) using hydrochloric acid pH 1.0 and phosphate buffer pH 7.2 solutions at 37 ± 1 °C.

In vitro drug release was monitored taking into consideration the dissolution test described in the European Pharmacopoeia [12], paddle method (75 rpm) using a dissolution apparatus (Sotax model AT7, Switzerland) containing 1,000 ml of hydrochloric acid pH 1.0 or phosphate buffer pH 7.2 solutions. IN is characterized by a pH dependent solubility. If the dissolution medium has a low pH (gastric conditions), which is the worst-case scenario for IN immediate release dosage forms, the *in vitro* release test results could be explained by the low drug release rate or by the low drug solubility in that medium. In this case, the increase of the drug solubility will result from the existence of the inclusion complex in the medium. In case of IN be tested in optimal pH conditions (alkaline medium, pH 7.2), the higher dissolution during the *in vitro* test will be attributed to the high solubility of the IN in these pH conditions and not to the solubility increase due to inclusion complexes (INβCD). The IN released was quantified in a UV–Vis spectrophotometer (U-200, Hitachi, Japan) set at 265 nm, at predetermined times (10, 20, 30, 40, 60, 90, 120, 180 and 1,440 min). The cumulative fraction of the drug released was calculated from the total amount of indometacin and plotted as a function of time ($n = 3$). HPMC capsules produced as described were placed in each dissolution vessel (no sink conditions).

The data from the release of indometacin was analyzed using different dissolution parameters, namely, comparison of the amounts released at determined times (M_{tmin}), the efficiency of dissolution (*DE*) and the similarity factor (f_2) using the following equations [18, 19]:

$$ED = \frac{\int_0^t y \times dt}{y_{100} \times t} \times 100\,\% \quad (2)$$

$$f_2 = 50 \times \log\left\{\left[1 \Big/ \sqrt{1 + \frac{1}{n}\sum_{j=1}^{n}\left(R_j - T_j\right)^2}\right] \times 100\right\} \quad (3)$$

where T_j and R_j mean test and reference products over all time points (n).

Dissolution data, at some time points (M_t) (30, 60 and 180 min) was compared statistically by ANOVA and by post hoc HSD Tukey test (SPSS Statistics 17.0, SPSS Inc., Chicago, USA), at $\alpha = 0.05$ significance level.

Results and discussion

Predicting complexation

The results obtained through the molecular modelling showed the following values for energy conformations ($E_{interaction} = -106.6$ and -84.3 kcal/mol) for the inclusion complex (INβCD) which were similar to those described in the literature [8, 11]. These values correspond to the interaction energy of the two more stable conformations that were found to inclusion complex INβCD. The K_s value was determined in a previous study ($K_{1:1} = 366\ M^{-1}$) [6, 20]. These results together with the size of the drug molecule, the guest (diameter—7.5 Å, length—14.2 Å) [21] and the size of the CD cavity, the host

(diameter—6.0–6.5 Å, host) [2] allow to predict a low yield inclusion complexation. The assay carried out in previous study [6] and the dissolution tests described below corroborated this interpretation. A parallel study performed in the same conditions using Ibuprofen (IB) as drug model showed a higher yield inclusion than obtained for IN [6]. This difference in yield complexation process can be explained because the IB molecular size, the guest (diameter—5 Å, length—10.0 Å) [22] is lesser than that of the IN thus being compatible with the diameter size of the β-CD cavity. This interpretation was corroborated with the results obtained for IB energy conformations ($E_{interaction} = -127.9$ kcal/mol e -153.7 kcal/mol) and K_s ($K_{1:1} = 2{,}016\ M^{-1}$), which justify its higher inclusion [6, 23].

Properties of the powders (inclusion complexes and reference mixtures)

The PM (references) produced particles with sizes and shapes identical to those observed for the raw-materials (Fig. 1a). The particles of β-CD present a rectangular shape, while IN particles presented an irregular shape. As an example, the PM (INβCD PM) was composed of irregular particles (IN) and rectangular shaped (β-CD) particles [24]. For the other PM containing LAC or MCC, instead of β-CD, the powders were composed of irregular particles (IN), rough irregular particles (LAC) and irregular shaped particles (MCC) (Fig. 1b). On the other hand, the shape of the powders particles produced in the presence of water became more spherical by opposition to the rod shaped original particles, suggesting that new particles, such as complexes, were produced. In the powders (Fig. 1c) containing inclusion complexes (INβCD) the presence of the free IN and β-CD particles was observed. Due to the fact that the complexation yield was very low (0.82–0.95 %) as cited in a previous study [6], the number of particles produced corresponding to the inclusion complex was not sufficient to provide evidence related to the changes of particles of INβCD in comparison with the raw-materials. Particles from powders obtained by K or suspension/solution with SD presented smaller sizes but identical shapes to the PM powder. However powders produced by FD showed particles with different shapes. The FD method was the possible explanation to this phenomenon due to the fact that the complex was not present in enough amounts for its effect to be significant. Again, the size of the particles was very low and this can be related to the method of drying [5].

The moisture content of the raw-materials varied between them (Table 2). The results for binary mixtures highlight these differences, but without any proportionality showing that in the product end-point this parameter was more related to the drying processes than to the remaining water content of the raw-materials. The moisture content in the PM should be taken into account because the residual water may promote the formation of the complex as shown by Frömming and Szejtli [4]. Discussed below the FD and SD techniques were more efficient on the drying step than the others, but the residual water seemed to be useful to improve the powders flow ability and compressibility (Table 2, IC_r and angle of repose). The results obtained for bulk (D_0) and tap (D_f) densities (Table 2) showed that the raw-materials IN and LAC exhibited higher inter-particle porosity than the other raw-materials. The values of β-CD are largely in line with those presented in the literature (0.42–0.59 and 0.74–0.76 g/cm^3 for the bulk and tapped densities, respectively) [4]. The processed formulations showed a high inter-particle porosity for powders prepared by FD and SD while for the others this parameter was similar between them (AS, K50, K70). These values reflected a greater influence of the drying techniques than due to the production of the complexes themselves. As a consequence, the analysis of the results for the Carr's index showed that low moisture contents produced the materials with higher compressibility and higher angles of repose [17]. This suggested that the water had a binding effect by approaching the particles (higher bulk and tap densities) and could provide some lubrication (lower Carr's index and angle of repose) to the particles, as their size was kept constant [25]. Nevertheless, all materials showed poor flow properties (Table 2). The Carr's index and angle of repose observations were confirmed on the preparation of the capsules. The manual filling of the capsules showed that the poor flowability of the powders was more noticed in the INβCD SD and INβCD FD cases (amorphous material with small and porous particles) [4, 26]. This operation could be improved with the addition of a glidant. The true densities values for the raw-materials were in agreement with the literature [4, 27]. For the processed materials this parameter (expected and measured) didn't show relevant differences confirming the low formation of new entities [6]. The expected densities (Table 2) for the mixtures with IN (1:1) were calculated using the following expression:

$$(\%\ \text{drug} \times \text{true density of drug}) + (\%\ \beta\text{CD or excipient} \times \text{true density of } \beta\text{CD or excipient}) . \quad (4)$$

Disintegration tests

All HPMC capsules filled with the tested mixtures disintegrated in a short period of time (between 3–12 min).

Dissolution tests

At pH = 1.0, the IN release profiles showed differences between capsules containing reference mixtures (INLAC,

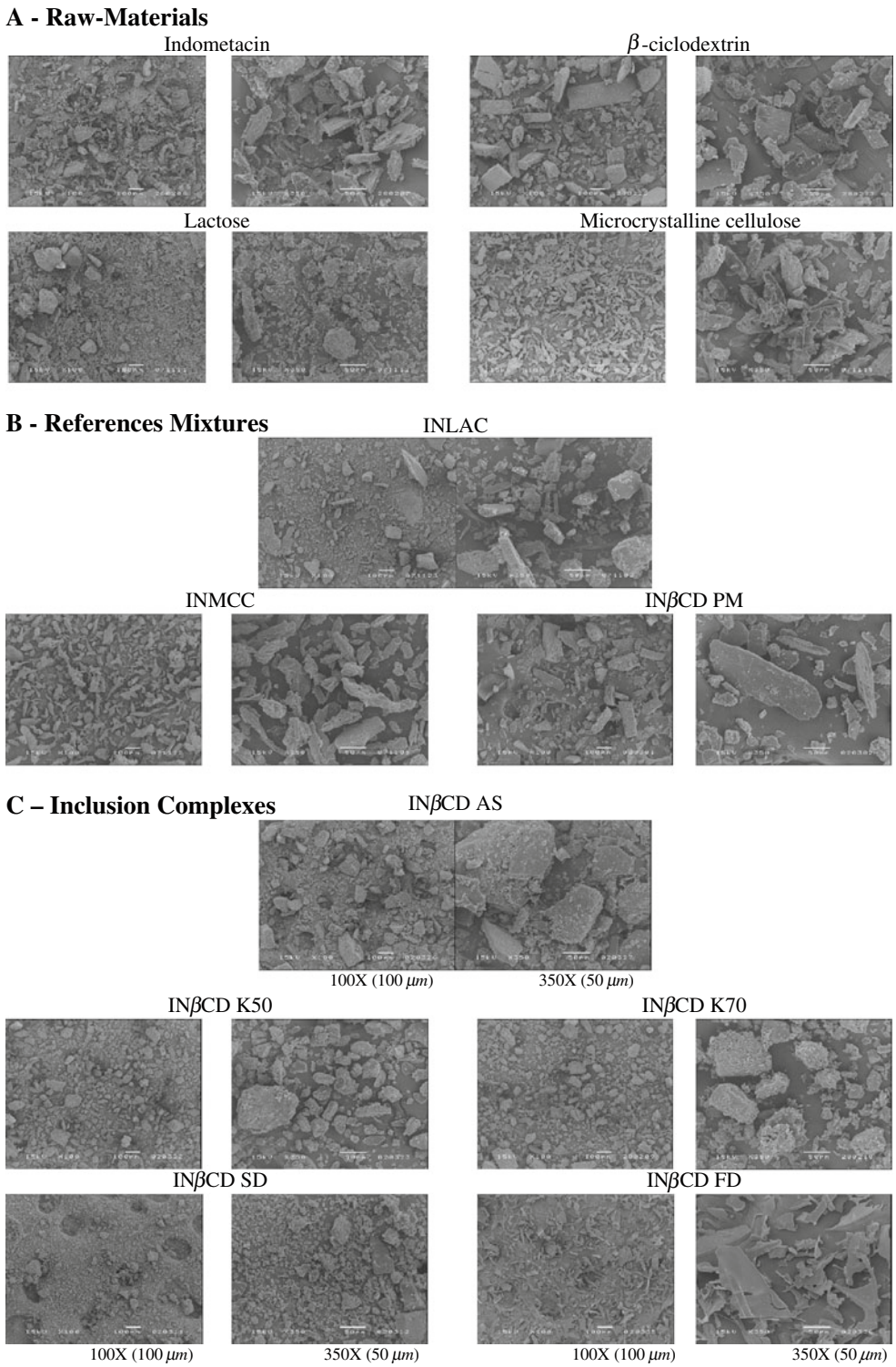

Fig. 1 Scanning electron micrographs: **a** raw-material (IN, β-CD, LAC, MCC); **b** reference mixtures (INLAC, INMCC, INβCD PM); **c** inclusion complexes mixtures (INβCD AS, INβCD K50, INβCD K70, INβCD SD, IBβCD FD)

INMCC, INβCD PM) and those produced from INβCD complexes (Fig. 2a). The faster release for the processed formulations was due to the presence of INβCD complexes and to the structure of the particles, namely, specific surface area, porosity or balance between amorphous and crystalline fractions of materials [26, 28, 29]. The Fig. 2b shows that the IN released didn't achieve 100 % due to be practically insoluble in this pH, thus proving a low yield

Table 2 Moisture content, bulk and tap densities, compressibility index, porosity, angle of repose and true density (expected and experimental) for all mixtures[a]

	Moisture (%)	D_0 (g/cm^3)	D_f (g/cm^3)	IC_r (%)	Angle of repose (°)	ρ (g/cm^3) expected	ρ (g/cm^3) measured
Raw-materials							
IN	1.53	0.45	0.73	38.0	53.77	–	1.39
β-CD	16.46	0.54	0.75	28.0	47.80	–	1.48
LAC	2.95	0.53	0.89	41.0	51.53	–	1.55
MCC	10.07	0.33	0.47	31.0	47.43	–	1.56
Mixtures with IN							
INLAC	3.01	0.53	0.86	38.0	55.30	1.51	1.51
INMCC	8.37	0.35	0.53	34.0	46.37	1.53	1.52
INβCD PM	12.12	0.52	0.75	30.0	48.20	1.46	1.45
INβCD AS	12.28	0.56	0.79	29.0	47.90	1.46	1.46
INβCD K50	19.63	0.54	0.76	29.0	44.77	1.46	1.46
INβCD K70	17.36	0.56	0.79	29.0	45.67	1.46	1.46
INβCD SD	11.51	0.44	0.65	32.0	56.70	1.46	1.45
INβCD FD	10.79	0.17	0.30	42.0	58.43	1.46	1.47

[a] Results are the mean of three measurements

The coefficient of variation was below 1 % for all cases

D_0 = bulk density, D_f = tap density, IC_r = compressibility index, ρ = true density

inclusion previously explained [30]. Due to low inclusion the saturation of the solvent (no sink conditions) occurs rapidly not allowing the total IN release. The processed powders showed practically the same release profiles, which corroborates that the amount of the water used in complexes formation [6] didn't influence the yield of inclusion. The low differences between dissolution profiles occurred mostly due to the characteristics of the particles which were dependent on both complexation methods and on the different processes of drying [6].

Table 3 summarizes the data parameters (M_{tmin}, DE and f_2) resulting from the dissolution tests for all capsules formulations. Amounts released (%) at 30, 60 and 180 min from the various formulations processed confirms the existence in theses mixtures of IN under inclusion complex form although this amount seemed to be low [6]. At time 30 min MCC, LAC, PM and LAC, PM, AS groups presented results statistically different of the AS, FD and K50, K70, SD groups. At time 60 min MCC, LAC, PM group was statistically different of the AS, SD, FD and K50, K70, SD, FD groups. For the time 180 min MCC, LAC, PM and LAC, PM, FD groups showed results statistically different from the PM, AS, K50, SD, FD and AS, K50, K70, SD, FD groups. Through the results expressed in Table 3 was possible to observe that formulations with inclusion complexes were not significantly different between them above 60 min. The increase of the PM mixture solubility compared to reference mixture (absence of the β-CD) was due to the occurrence of inclusion during the dissolution test [23, 31]. The interpretation of DE values is the same for M_t. The slight differences for the M_t, DE values observed at time 30, 60 and 180 min for mixtures containing inclusion complexes resulted from the different characteristics of particles as previously cited and the disintegration period of the HPMC

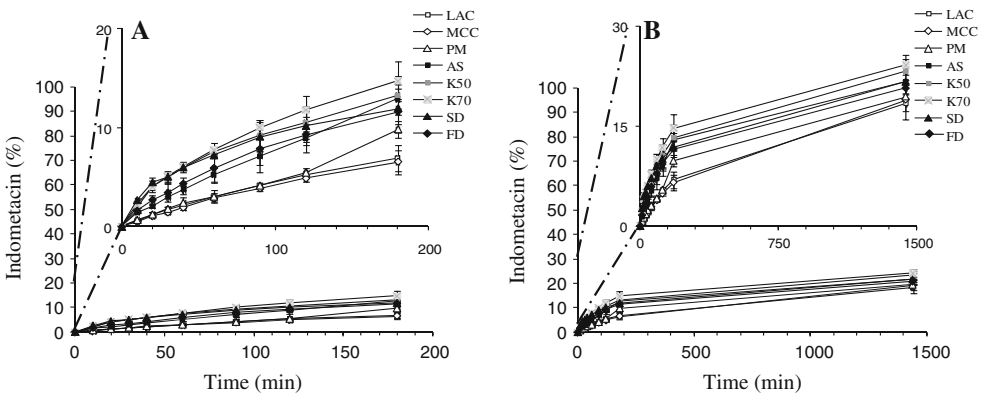

Fig. 2 Dissolution profiles of the capsules formulation at 180 (**a**) and 1440 min (**b**) at pH 1.0

Table 3 Dissolution parameters for IN released from capsules (pH 1.0)

	M_t (%)[a]			*DE* (%)			f_2 (%)
	30	60	180	30	60	180	
INLAC	1.77 ± 0.29	2.98 ± 0.44	6.92 ± 1.30	0.91	1.65	3.96	(*100.00*)
INMCC	1.44 ± 0.21	2.87 ± 0.12	6.54 ± 1.22	0.77	1.47	3.68	99.20
INβCD PM	1.80 ± 0.21	3.04 ± 0.65	9.81 ± 0.83	0.95	1.73	4.52	92.20
INβCD AS	2.97 ± 0.14	5.25 ± 0.74	12.92 ± 0.98	1.67	2.89	6.99	75.40
INβCD K50	4.99 ± 0.55	7.57 ± 0.44	13.28 ± 1.96	2.85	4.60	8.54	67.64
INβCD K70	5.13 ± 0.09	7.75 ± 0.74	14.71 ± 2.04	2.94	4.70	9.29	64.76
INβCD SD	5.06 ± 0.53	7.19 ± 0.14	11.93 ± 2.44	3.23	4.74	8.22	68.98
INβCD FD	3.44 ± 0.94	5.91 ± 1.50	11.59 ± 1.25	2.02	3.37	7.18	75.14

[a] Mean ± SD ($n = 3$)

Table 4 Dissolution parameters for IN released from capsules (pH 7.2)

	M_t (%)[a]			*DE* (%)			f_2 (%)
	30	60	180	30	60	180	
INLAC	49.90 ± 3.41	78.88 ± 1.18	94.57 ± 1.42	18.88	42.63	74.10	(100.00)
INMCC	50.62 ± 6.28	81.36 ± 1.42	99.45 ± 3.23	19.61	43.92	77.22	75.61
INβCD PM	48.89 ± 4.94	77.28 ± 3.23	94.82 ± 1.36	22.85	43.95	74.96	72.17
INβCD AS	62.03 ± 1.53	85.05 ± 1.36	97.71 ± 0.90	32.35	53.90	80.74	48.29
INβCD K50	72.22 ± 0.20	89.68 ± 0.90	99.34 ± 2.00	34.55	58.61	83.78	41.32
INβCD K70	70.65 ± 5.65	89.19 ± 2.00	97.19 ± 2.11	34.20	57.98	82.63	42.78
INβCD SD	67.03 ± 1.47	87.32 ± 2.11	98.49 ± 2.03	35.72	57.14	82.61	43.14
INβCD FD	60.47 ± 1.45	87.86 ± 2.03	100.53 ± 0.00	28.67	52.30	82.64	50.41

[a] Mean ± SD ($n = 3$)

capsule. The similarity factor (f_2) (MCC, PM, AS, K50, K70, SD, FD) did show equivalence for all mixtures (LAC used as reference for the calculation of this parameter) thus confirming low inclusion.

The analysis of all values showed a similar increase on the IN dissolution from processed powders due to the existence of the IN under inclusion complex form. For all cases, the complete release of IN was not reached before 1,440 min which corroborated the aforementioned low inclusion yield [6] and the presence of the higher amounts of the free IN in the processed mixtures.

The results obtained for dissolution medium at pH 7.2 (Table 4) showed the release for all formulations reaching approximately 100 % at 180 min (Fig. 3). However the similarity factor (f_2) showed no similar release profiles between reference and processed mixtures. These differences can be explained by the dissolution behavior of IN inclusion complex when compared with free IN. At this pH the pure IN presents lower solubility than the INβCD inclusion complex. In the first dissolution times this phenomenon is observed by the different amounts released from reference and processed mixtures.

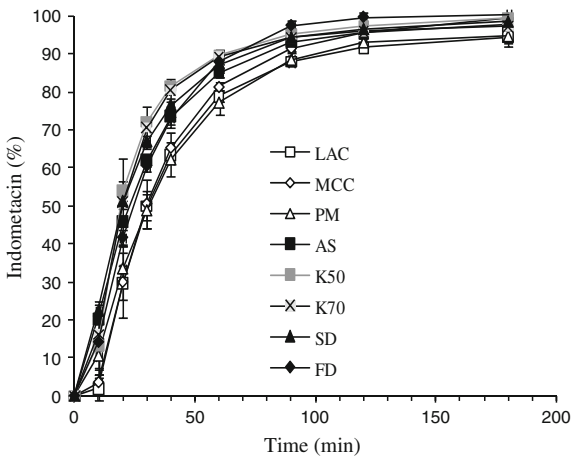

Fig. 3 Dissolution profiles of the capsules formulation at 180 min at pH 7.2

Comparing all the results cited it is possible to observe the slight increase in IN solubility (acidic pH, Fig. 2) from processed powders that corroborate the existence of inclusion complexes in this material.

Conclusion

In this study the formation of inclusion complexes between indomethacin and β-CD was confirmed. Such complexes presented differences namely on characteristics particles (morphology and crystalline or amorphous state). Moreover in the dissolution test was possible to confirm that inclusion complex could be prepared with different amounts of water described in a previous study [6]. Dissolution tests confirmed the increase on the IN dissolution rate from mixtures containing inclusion complexes and showed the occurrence of complexation in the physical mixture as cited by other authors [31]. Comparison of the dissolution profiles and dissolution parameters (M_t, DE and f_2) has shown the effect of the complex on the release of indomethacin.

The pharmaceutical tests showed that alls mixtures used in this work have poor flow abilities (Carr's index and angle of repose), which difficult their processability. The method of complexation and the final drying process affected the characteristics of the complex's particles, but not the complex itself. The low yield of the indomethacin molecule entrapment inside of the β-CD cavity could be related with their structural relative sizes.

References

1. Amidon, G.L., Lennernas, H., Shah, V.P., Crison, J.R.: A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm. Res. **12**, 413–420 (1995)
2. Szejtli, J.: Introduction and general overview of cyclodextrin chemistry. Chem. Rev. **98**, 1743–1753 (1998)
3. Loftsson, T., Duchêne, D.: Cyclodextrins and their pharmaceutical applications. Int. J. Pharm. **329**, 1–11 (2007)
4. Frömming, K.H., Szejtli, J.: Cyclodextrins in Pharmacy. Kluwer Academic Publishers, Dordrecht (1994)
5. Junco, S., Casimiro, T., Ribeiro, N., Nunes Da Ponte, M., Cabral-Marques, H.: A comparative study of naproxen–beta cyclodextrin complexes prepared by conventional methods and using supercritical carbon dioxide. J. Incl. Phenom. Macrocycl. Chem. **44**, 117–121 (2002)
6. Salústio, P.J., Feio, G., Figueirinhas, J.L., Pinto, J.F., Cabral-Marques, H.M.: The influence of the preparation methods on the inclusion of model drugs in a β-cyclodextrin cavity. Eur. J. Pharm. Biopharm. **71**, 377–386 (2009)
7. O'Brien, M., McCauley, J., Cohen, E.: Indomethacin. In: Florey, K. (ed.) Analytical Profiles of Drug Substances, vol. 13, pp. 211–238. Academic Inc., San Diego (1984)
8. Jambhekar, S., Casella, R., Maher, T.: The physicochemical characteristics and bioavailability of indomethacin from β-cyclodextrin, hydroxyethyl-β-cyclodextrin, and hydroxypropyl-β-cyclodextrin complexes. Int. J. Pharm. **270**, 149–166 (2004)
9. Acosta, G., Linares, D., Olsina, R., Martinez, L.D., Gomez, M.R.: Determination of the binding constant of indomethacin-beta cyclodextrin complex by capillary electrophoresis: experimental optimization and temperature study. Pharmazie. **62**, 847–852 (2007)
10. Alsarra, I.A., Ahmed, M.O., Alanazi, F.K., ElTahir, K.E.H., Alsheikh, A.M., Neau, S.H.: Influence of cyclodextrin complexation with NSAIDs on NSAID/cold stress-induced gastric ulceration in rats. Int. J. Med. Sci. **7**, 232–239 (2010)
11. Fronza, G., Mele, A., Redenti, E., Ventura, P.: ^{1}H NMR and molecular modeling study on the inclusion complex β-cyclodextrin–indomethacin. J. Org. Chem. **61**, 909–914 (1996)
12. European Pharmacopoeia, Council of Europe, Strasbourg (2008)
13. Hohenberg, P., Kohn, W.: Inhomogeneous electron gas. Phys. Rev. **136**, B864–B871 (1964)
14. Lee, S.J., Fink, J., Balantekin, A.B., Strayer, M.R., Umar, A.S., Reinhard, P.G., Maruhn, J.A., Greiner, W.: Relativistic hartree calculations for axially deformed nuclei. Phys. Rev. Lett. **57**, 2916 (1986)
15. Binkley, S., Reilly, K., Hernandez, T.: *N*-acetyltransferase in the chick retina. J. Comp. Physiol. **140**, 181–183 (1980)
16. Holman, L.E., Leuenberger, H.: The effect of varying the composition of binary powder mixtures and compacts on their properties: a percolation phenomenon. Powder Technol. **60**, 249–258 (1990)
17. Carr, R.L.: Evaluating flow properties of solids. Chem. Eng. **18**, 163–168 (1965)
18. Guidance for Industry, Dissolution testing of immediate release solid oral dosage forms. U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). http://www.fda.gov/cder/guidance/index.htm (1997). Accessed on 18 June 2011
19. Khan, K.A.: The concept of dissolution efficiency. J. Pharm. Pharmacol. **27**, 48–49 (1975)
20. Xin, J., Guo, Z., Chen, X., Jiang, W., Li, J., Li, M.: Study of branched cationic β-cyclodextrin polymer/indomethacin complex and its release profile from alginate hydrogel. Int. J. Pharm. **386**, 221–228 (2010)
21. Del Arco, M., Cebadera, E., Gutiérrez, S., Martín, C., Montero, M.J., Rives, V., Rocha, J., Sevilla, M.A.: Mg, Al layered double hydroxides with intercalated indomethacin: synthesis, characterization, and pharmacological study. J. Pharm. Sci. **93**, 1649–1658 (2004)
22. Zhu, Y., Shi, J., Chen, H., Shen, W., Dong, X.: A facile method to synthesize novel hollow mesoporous silica spheres and advanced storage property. Micropor. Mesopor. Mat. **84**, 218–222 (2005)
23. Salústio, P.J., Cabral-Marques, H.M., Costa, P.C., Pinto, J.F.: Comparison of ibuprofen release from mini tablets and capsules containing ibuprofen: β-cyclodextrin complex. Eur. J. Pharm. Biopharm. **78**, 58–66 (2011)
24. Fini, A., Fernàndez-Hervàs, M.J., Holgado, M.A., Rodriguez, L., Cavallari, C., Passerini, N., Caputo, O.: Fractal analysis of β-cyclodextrin–indometacin particles compacted by ultrasound. J. Pharm. Sci. **86**, 1303–1309 (1997)
25. Faqih, A.M., Mehrotra, A., Hammond, S.V., Muzzio, F.J.: Effect of moisture and magnesium stearate concentration on flow properties of cohesive granular materials. Int. J. Pharm. **336**, 338–345 (2007)
26. Berggren, J., Frenning, G., Alderborn, G.: Compression behaviour and tablet-forming ability of spray–dried amorphous composite particles. Eur. J. Pharm. Sci. **22**, 191–200 (2004)
27. Sun, C.: True density of microcrystalline cellulose. J. Pharm. Sci. **94**, 2132–2134 (2005)
28. Husseina, K., Türkb, M., Wahl, M.A.: Drug loading into β-cyclodextrin granules using a supercritical fluid process for improved drug dissolution. Eur. J. Pharm. Sci. **33**, 306–312 (2008)
29. Doile, M.M., Fortunato, K.A., Schmücker, I.C., Schucko, S.K., Silva, M.A., Rodrigues, P.O.: Physicochemical properties and dissolution studies of dexamethasone acetate-beta-cyclodextrin inclusion complexes produced by different methods. AAPS Pharmscitech. **9**, 314–321 (2008)

30. Backensfeld, T., Müller, B.W., Wiese, M., Seydel, J.K.: Effect of cyclodextrin derivatives on indomethacin stability in aqueous solution. Pharm. Res. **7**, 484–490 (1990)

31. Cirri, M., Rangoni, C., Maestrelli, F., Corti, G., Mura, P.: Development of fast-dissolving tablets of flurbiprofen-cyclodextrin complexes. Drug Dev. Ind. Pharm. **31**, 697–707 (2005)