JPP JOURNAL OF Pharmacy and Pharmacology
ROYAL PHARMACEUTICAL SOCIETY
JPP Journal of Pharmacy And Pharmacology
Research Paper

Development of carvedilol-cyclodextrin inclusion complexes using fluid-bed granulation: a novel solid-state complexation alternative with technological advantages

Ellen C. P. Alonso[a], Karina Riccomini[b], Luis Antônio D. Silva[a], Daniela Galter[b], Eliana M. Lima[a], Thomas Durig[c], Stephania F. Taveira[a], Felipe Terra Martins[d], Marcílio S. S. Cunha-Filho[e] and Ricardo N. Marreto[a]

[a]Laboratory of Pharmaceutical Technology, Federal University of Goiás, Goiânia, GO, [b]Pharmaceutical Application Laboratory, Ashland Specialty Ingredients, São Paulo, SP, Brazil, [c]Pharmaceutical and Nutrition Specialties R&D, Ashland Specialty Ingredients, Wilmington, DE, USA, [d]Chemical Institute, Federal University of Goiás, Goiânia, GO, and [e]Laboratory of Food, Drug and Cosmetics (LTMAC), School of Health Sciences, University of Brasília, Brasília, DF, Brazil

Keywords
carvedilol; hydroxypropyl-β-cyclodextrin; hydroxypropyl-γ-cyclodextrin; solid-state inclusion complex

Correspondence
Ricardo Neves Marreto, Faculdade de Farmácia UFG, Setor Leste Universitário, Rua 240, esquina com 5° Avenida, s/n, 74 605-170 Goiânia, GO, Brazil.
E-mail: ricardomarreto@ufg.br

Received April 5, 2016
Accepted June 10, 2016

doi: 10.1111/jphp.12601

Abstract

Objectives This study sought to evaluate the achievement of carvedilol (CARV) inclusion complexes with modified cyclodextrins (HPβCD and HPγCD) using fluid-bed granulation (FB).

Methods The solid complexes were produced using FB and spray drying (SD) and were characterised by differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), powder X-ray diffraction, SEM, flowability and particle size analyses and *in vitro* dissolution.

Key findings The DSC, FTIR and powder X-ray diffraction findings suggested successful CARV inclusion in the modified β- and γ-cyclodextrins, which was more evident in acidic media. The CARV dissolution rate was ~7-fold higher for complexes with both cyclodextrins prepared using SD than for raw CARV. Complexes prepared with HPβCD using FB also resulted in a significant improvement in dissolution rate (~5-fold) and presented superior flowability and larger particle size.

Conclusions The findings suggested that FB is the best alternative for large-scale production of solid dosage forms containing CARV. Additionally, the results suggest that HPγCD could be considered as another option for CARV complexation because of its excellent performance in inclusion complex formation in the solid state.

Introduction

Cyclodextrins are cyclic oligosaccharides composed of 6–8 glucopyranoside units linked by α-[1,4] bonds. The parent cyclodextrins (α, β, γ) are products of bacterial digestion of starch.[1] These substances have a central hydrophobic cavity and a hydrophilic outer surface composed of hydroxyl groups. This structure allows the inclusion of poorly soluble drugs, thus increasing their solubility and bioavailability.[2,3] The hydroxyl groups of the parent cyclodextrins can be chemically modified to improve their aqueous solubility and complexation ability.[3]

Carvedilol (CARV) is a nonselective β-blocker used in the treatment of hypertension and congestive heart failure.[4] It is a basic and lipophilic compound with pH-dependent solubility, making it a class II drug in the Biopharmaceutics Classification System.[5] These properties contribute to the poor oral bioavailability of CARV (20%).[6]

Different strategies have been studied to improve the aqueous solubility of CARV.[7–13] Inclusion complexation with cyclodextrins using different techniques has been evaluated, resulting in significant improvements in the solubility and dissolution profile of the drug.[14–19] Superior enhancement of the dissolution rate was observed when CARV was complexed with hydroxypropyl-β-cyclodextrin (HPβCD).[14,17] Nevertheless, in the major world markets, there are no commercial products containing CARV in the

form of an inclusion complex with cyclodextrin. The technological difficulties of industrial production, combined with the high costs of modified β-cyclodextrins are obstacles that still need to be overcome.

Co-precipitation, kneading, spray drying (SD) and freeze drying are methods that have been used with great results for solid-state complexation with cyclodextrins.[20] Despite their outstanding complexation performance, those methods are characterised by low yield, stability problems and difficulty of scale-up.[20,21] In contrast, fluid-bed (FB) granulation has been widely used in the development and production of solid dosage forms, because it is a fast and versatile process.[22] Solid processing by this method may allow the formation of inclusion complexes simultaneously with the granulation process. In spite of that, few studies have explored the use of this technique to produce cyclodextrin inclusion complexes. Some studies have reported the drying of drug : cyclodextrin solutions by spouted or FB apparatus.[23,24] In addition, there are reports on the preparation of solid complexes by FB coating[25,26] and, more recently, FB granulation.[27]

Accordingly, improvements in the inclusion complex formation methods of CARV : cyclodextrin, making them more suitable for industrial processing, may finally provide a commercial product of CARV : cyclodextrin in the form of inclusion complexes. This study sought to evaluate carvedilol inclusion complexes with cyclodextrins formed using FB granulation. The complexation of CARV with a modified γ-cyclodextrin, which has thus far not been tested for this drug in a solid state, was also evaluated.

Materials and Methods

Materials

Carvedilol (MW 406.5) was kindly donated by Shenyang Chengtai Fine Chemicals Factory (China) and IQUEGO (Indústria Química do Estado de Goiás, Brazil). Hydroxypropyl-β-cyclodextrin (HPβCD, degree of substitution 6.0–8.0, Cavitron W7 HP7®) and hydroxypropyl-γ-cyclodextrin (HPγCD, 4.1–5.1, Cavasol W7 HP®) were kindly donated by Ashland Inc. (São Paulo, Brazil). Lactose (Flowlac 100®) was purchased from Meggle Pharma. All solvents and reagents used in this study were of analytical grade.

Preparation of solid inclusion complexes by spray drying and fluid-bed granulation

Suspensions containing CARV and cyclodextrin (HPβCD or HPγCD) at a 1 : 1 molar ratio were prepared in a 0.1 M phosphate buffer solution (PBS), pH 6.8. In some cases, the pH of the solution was adjusted to 2.2 with phosphoric acid. The dispersions were magnetically stirred (IKA C-MAG HS 7) for 1 h at room temperature, and then they were spray-dried or used as an agglomeration liquid during FB granulation. A CARV suspension (pH 6.8) without cyclodextrin was also spray-dried under the same experimental conditions. The spray drying was carried out in an LM MSD 1.0 (Labmaq do Brasil Ltda, Ribeirão Preto, São Paulo, Brazil) laboratory-scale dryer using a double-fluid-type atomizer nozzle with an orifice of 1.2 mm. Table 1 lists the experimental conditions used in this study.

Granules were prepared in a FB granulator (FL-Multi-1; Freund-Vector Corporation, Marion, Iowa, USA) under the operational conditions described in Table 1. A suspension containing CARV and cyclodextrin was prepared in PBS, adjusted to pH 2.2 with phosphoric acid. Five hundred millilitres of the suspension was stirred for 1 h, and then it was sprayed into the processing chamber containing lactose (390 g).

Inclusion complex samples of CARV and cyclodextrins prepared by the FB or SD processes were named IC, while their physical mixtures prepared by grinding the materials in a mortar and pestle were designated PM. LAC PM is the physical mixture with lactose, mimicking the composition of FB complexes.

Thermal studies

Differential scanning calorimetry (DSC) analysis of the CARV, the physical mixtures and the different inclusion complexes was performed in a Shimadzu DSC-60 cell (Shimadzu, Kyoto, Japan) using aluminium-sealed crucibles (approximately 5.0 mg samples) under dynamic N_2 atmosphere (flow rate of 50 ml/min) and at a heating rate of 10 °C/min. The temperature ranged from 25 to 150 °C. The equipment was calibrated with indium and zinc standards.

Fourier transform infrared spectroscopy

The spectra of the CARV, the physical mixtures and the different inclusion complexes were recorded on a Spectrum 400 FT-IR/FT-NIR spectrometer (PerkinElmer, Waltham,

Table 1 Summary of experimental conditions for spray drying and fluid-bed granulation

Parameter	Spray drying	Fluid-bed granulation
T_{gi} (°C)	130	58–70
T_{go} (°C)	58–60	40–45
V_{at} (l/min)	30	45–57
P_{at} (bar)	3.0	1.0
W_e (ml/min)	3.0	5.5
Cleaning filters	–	10 s

T_{gi}, inlet temperature; T_{go}, outlet temperature; V_{at}, atomisation air volume; P_{at}, atomisation air pressure; W_e, dispersion feed outflow.

Massachusetts, USA), with wavenumbers ranging from 4000 to 400 cm^{-1}. The samples were ground and mixed thoroughly with potassium bromide in a mortar and pestle, with samples 1% (w/w) of the mixture. KBr discs were prepared by compressing the powders in a hydraulic press (Shimadzu).

Powder X-ray diffraction studies

The samples were distributed on a sample holder (grooved glass slide) and mounted on the goniometer of a Shimadzu XRD-6000 diffractometer. A graphite monochromatised X-ray beam from a copper anode (CuKα radiation, λ = 0.15418 nm) was produced into a sealed tube at generator setting of 40 kV and 30 mA. All powder X-ray diffraction profiles were measured at room temperature under continuous scan mode (θ–2θ scan axis) with a scan speed of 1.000°/min. Intensity data were recorded at each 0.020° in a 2θ range between 5° and 40°. Divergence and scattering slits were used at 1.000°, and a receiving slit (0.300 mm) and counter monochromator were used during data acquisition. The experimental setup and following data measurement were undertaken using the Search Match program (version 4.1) from Shimadzu XRD-6000. The X-ray patterns were dealt as acquired, except for the only raw data treatment of normalisation of all intensities against the most intense one of each diffraction pattern. For each sample, a file containing normalised intensity data as a function of raw 2θ positions stepped by 0.020° was generated.

Dissolution study

In vitro dissolution of CARV was studied by filling transparent capsules with pure drug or CARV : cyclodextrin physical mixtures or inclusion complexes (equivalent to 10 mg of CARV). The samples were added to cubes containing 900 ml of 0.1 M phosphate buffer solution pH 6.8, at 37 °C. Analysis was performed in a VK 7000 (VARIAN, Palo Alto, California, USA) dissolution apparatus equipped with USP apparatus II set at 50 rpm. Aliquots were withdrawn every 10 min, filtered through a 0.45-μm membrane, appropriately diluted and analyzed by UV–Vis spectrophotometry (Cary 50; Varian), at 241 nm. Data from *in vitro* dissolution were fitted to zero-order, and first-order equations (Excel®; Microsoft Corporation, Redmond, Washington, USA). Statistical analysis was performed taking into account the drug dissolved at 30 min using SPSS® version 20. All samples showed a normal distribution according to the Shapiro–Wilk test. Hence, possible differences between groups were investigated by performing ANOVA, followed by Tukey's multiple comparison test.

Scanning electron microscopy

Scanning electron microscopy (SEM) photomicrographs were taken using a JEOL JSM 6610 equipped with EDS model NSS spectral imaging (Thermo Scientific, Waltham, Massachusetts, USA). Samples were coated with gold using a sputter coater EM SCD 050 (Leica, Wetzlar, Hessen, Germany) and were examined at ×500 magnification.

Flow and particle size

The flowability of the powders was determined by pouring 100 g of the sample through a funnel (6 mm or 10 mm diameter orifice). Analyses were performed in a GTB instrument (Erweka, Heusenstamm, Germany). The average diameter and size distribution of the particles were evaluated in a laser diffraction particle size analyser (Beckman Coulter, LS 13320, Brea, California USA). Fifteen grams of inclusion complexes prepared by SD and FB were fed into the system using a dry powder sample module. Analyses were performed with an obscuration of 5% using a Fraunhofer optical model.

Results

Calorimetric and spectroscopic studies

The DSC curve of CARV (Figure 1), a crystalline compound, presents a characteristic sharp endothermic peak at 118.4 °C (ΔH 123.3 J/g), corresponding to melting, which is in accordance with other studies.[28,29] It can be observed that the endothermic peak of spray-dried CARV (CARV SD) was shifted to a lower temperature (T_{peak} 111.4 °C, ΔH 97.1 J/g). The DSC curves of the CARV : HPβCD inclusion complex, prepared at pH 6.8 by SD and its physical mixture (Figure 1a) showed only a small endothermic melting peak, which was significantly shifted to a lower temperature. In turn, the melting endotherm could not be observed in DSC curves of the complexes prepared at pH 2.2 by SD and FB techniques. Similarly, a complete absence of the endothermic melting peak could be observed in the inclusion complexes prepared with HPγCD (pH 2.2) by both methods, while its physical mixture presented only a small endothermic melting peak at a lower temperature (Figure 1b).

Figure 2a shows the Fourier transform infrared spectroscopy (FTIR) spectra for nonprocessed CARV, spray-dried CARV (CARV SD), and CARV : HPβCD PM, SD and FB samples. CARV spectral bands were evaluated and were found at 3343 cm^{-1} for NH and OH stretching vibrations; at 1502, 1608 and 1631 cm^{-1} for the C=C aromatic stretching vibration; at 1590 cm^{-1} for NH bending vibrations; and at 1256 cm^{-1} for CN stretching vibrations. No

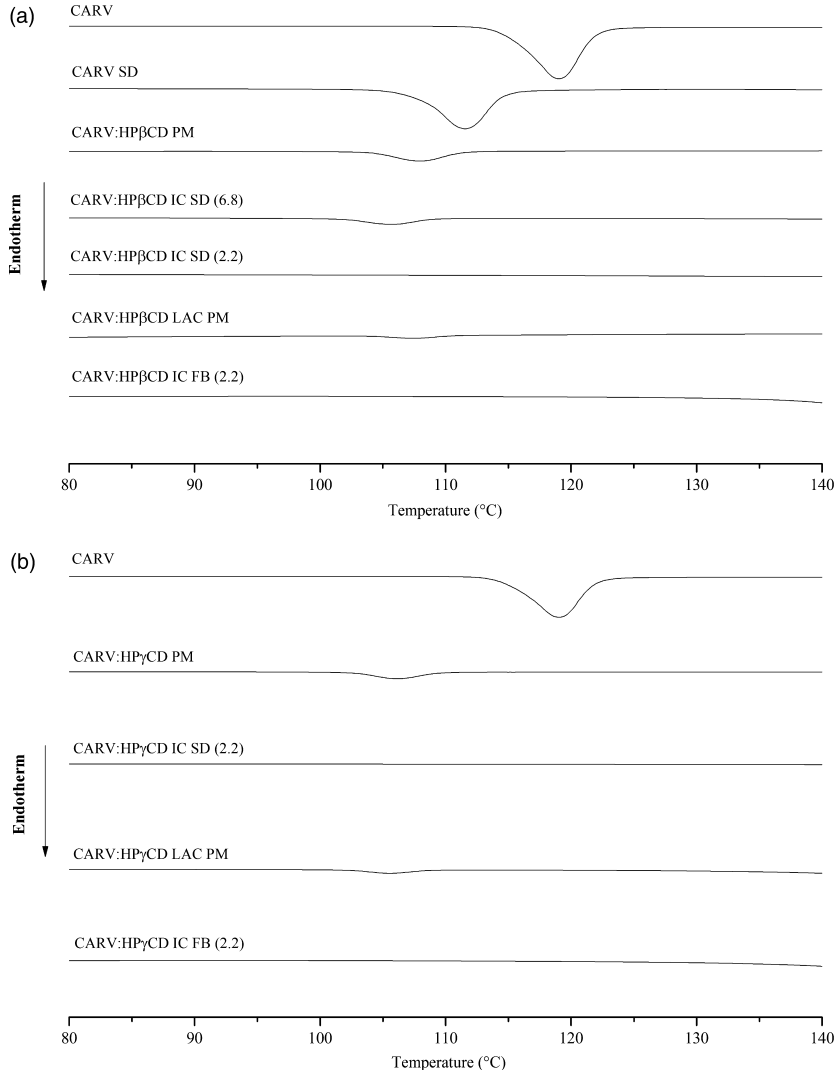

Figure 1 Differential scanning calorimetry (DSC) curves of carvedilol (CARV) inclusion complexes prepared with HPβCD (a) or HPγCD (b). CARV raw material, (IC) inclusion complexes obtained by (SD) spray drying or (FB) fluid-bed, and its physical mixture (PM and LAC PM).

significant changes were observed in the spectrum of CARV SD when compared with the spectrum of the nonprocessed CARV (Figure 2a). In contrast, differences could be observed in all binary systems at 3343 cm^{-1}, because this spectral band disappeared in complexes prepared at pH 2.2 by SD and FB or had very low intensity in complexes prepared at pH 6.8 by SD (Figure 2a). The other spectral bands of the drug are still present in the complexes with lower intensity due to a dilution effect.

Figure 2b shows the FTIR spectra of the CARV : HPγCD complexes prepared by SD and FB granulation. The findings were quite similar to that from CARV complexes with HPβCD, with a disappearance of the 3343 cm^{-1} spectral band in the processed samples, as well as its attenuation in physical mixtures.

Powder X-ray diffraction studies

In Figure 3, the experimental powder X-ray diffraction profiles of CARV, HPβCD, HPγCD and their inclusion complexes prepared at pH 2.2 or 6.8 by SD or FB techniques are shown. The theoretical powder X-ray diffractograms were simulated from single crystal structures of carvedilol Form II[30] and lactose monohydrate,[31] and are also plotted for comparison purposes. There is agreement between the simulated diffraction peaks from the crystal structure of carvedilol Form II and those observed in the experimental powder X-ray diffraction pattern of the CARV sample. The slight differences observed between the simulated and experimental patterns of CARV are due to the preferred orientation effects and overlapping of the

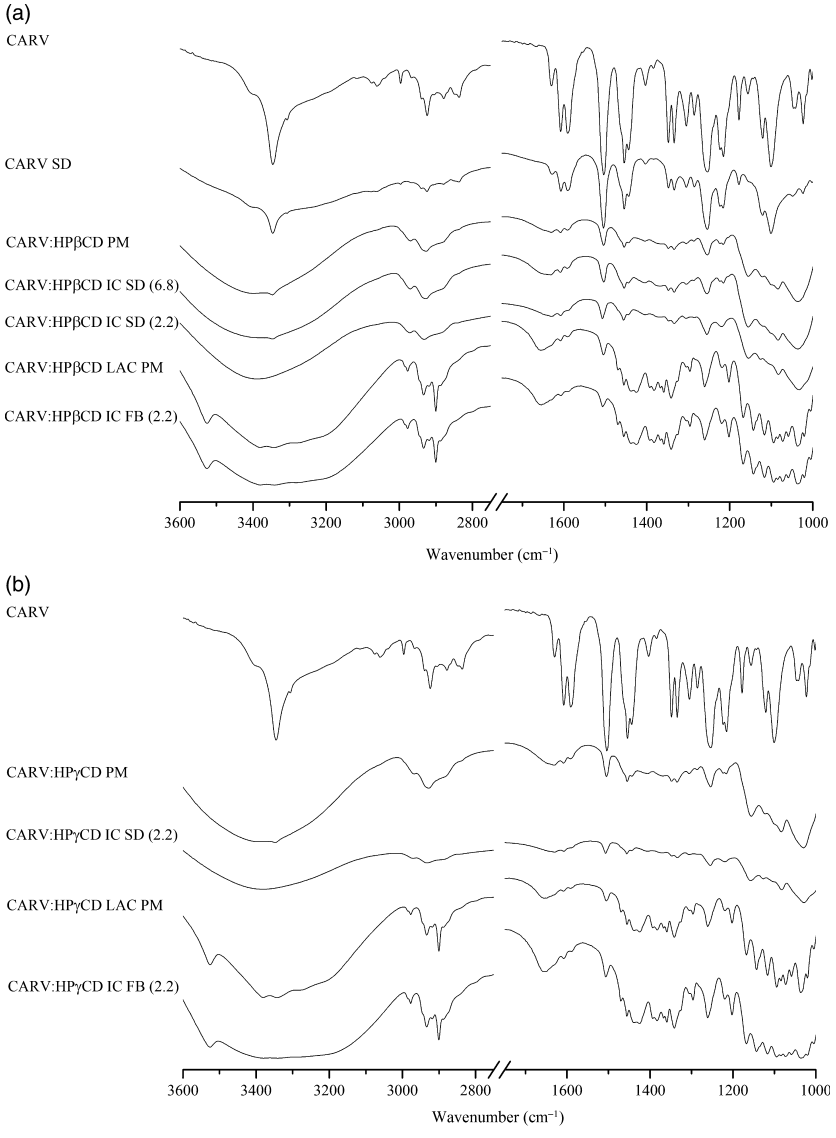

Figure 2 Fourier transform infrared spectroscopy (FTIR) spectra of carvedilol (CARV) complexes prepared with HPβCD (a) or HPγCD (b). CARV raw material, (IC) inclusion complexes obtained by (SD) spray drying or (FB) fluid-bed, and its physical mixture (PM and LAC PM).

diffraction peaks. Therefore, based on the matching of the crystal structure and experimental powder X-ray diffraction peaks, the CARV sample could undoubtedly be identified as being Form II of the drug, which is an anhydrous polymorph composed of the free base only. That both HPβCD and HPγCD samples are amorphous can be concluded from the fact that there are no diffraction peaks in their X-ray diffractograms. Only broad humps are seen. The X-ray diffractogram of the CARV : HPβCD inclusion complex sample, prepared at pH 6.8 by SD, contains both the broad hump from HPβCD phase and the Bragg peaks from CARV. Therefore, it is concluded that this sample has a mixture of these two phases, which, however, does not rule out the possibility that an amount of the drug is included in the HPβCD. In case of the CARV : HPβCD and CARV : HPγCD inclusion complex samples, prepared at pH 2.2 by SD, only the amorphous humps from either HPβCD or HPγCD were identified in their X-ray diffraction patterns. No Bragg peaks from CARV were observed, which suggests that the occurrence of the drug inclusion phenomenon resulting in a single amorphous phase comprised of either CARV : HPβCD IC or CARV : HPγCD IC. In the two corresponding samples prepared by the FB rather than the SD technique, however, only lactose monohydrate could be identified. All the peaks in the experimental X-ray diffractograms of CARV : HPβCD and

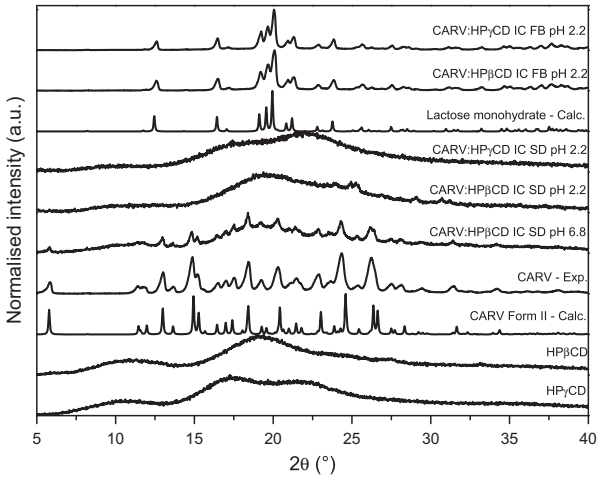

Figure 3 Experimental powder X-ray diffractograms of carvedilol (CARV), HPβCD, HPγCD and their inclusion complexes prepared at pH 2.2 or 6.8 by SD or fluid-bed (FB) techniques. Predicted powder X-ray diffractograms simulated from the single crystal structures of carvedilol Form II[30] and lactose monohydrate[31] are also given.

CARV : HPγCD samples obtained at pH 2.2 by FB were superimposed on those observed in the simulated X-ray diffractogram from the single crystal structure of lactose monohydrate.

Dissolution study

The CARV dissolution profiles determined from the different systems studied are shown in Figures 4a and 4b, along with the statistical analysis performed with the percentage of CARV dissolved in 30 min. Other dissolution parameters are summarised in Table 2. It is important to note that the dissolution of CARV, alone or complexed, followed zero-order kinetics. CARV alone showed well-defined zero-order dissolution kinetics ($r > 0.9630$). On the other hand, CARV IC samples, although still fitting a zero-order kinetic ($r = 0.8413$–0.8467), also show a good fit for first-order kinetics ($r = 0.6154$–0.7014), which suggests a change on the drug release profile and could be considered additional evidence of inclusion complex formation.

Figure 4a shows the dissolution curves of CARV : HPβCD IC. It can be noted CARV SD (prepared without the addition of cyclodextrin) increased the drug dissolution rate; however, after 30 min, CARV dissolution was only ~40%, and it had not reached completion by the end of the experiment. The CARV dissolution rate from physical mixtures was lower than that calculated from IC prepared by both techniques, but it was higher than that observed for CARV SD. The CARV : HPβCD IC prepared by SD showed a significant increase in drug dissolution

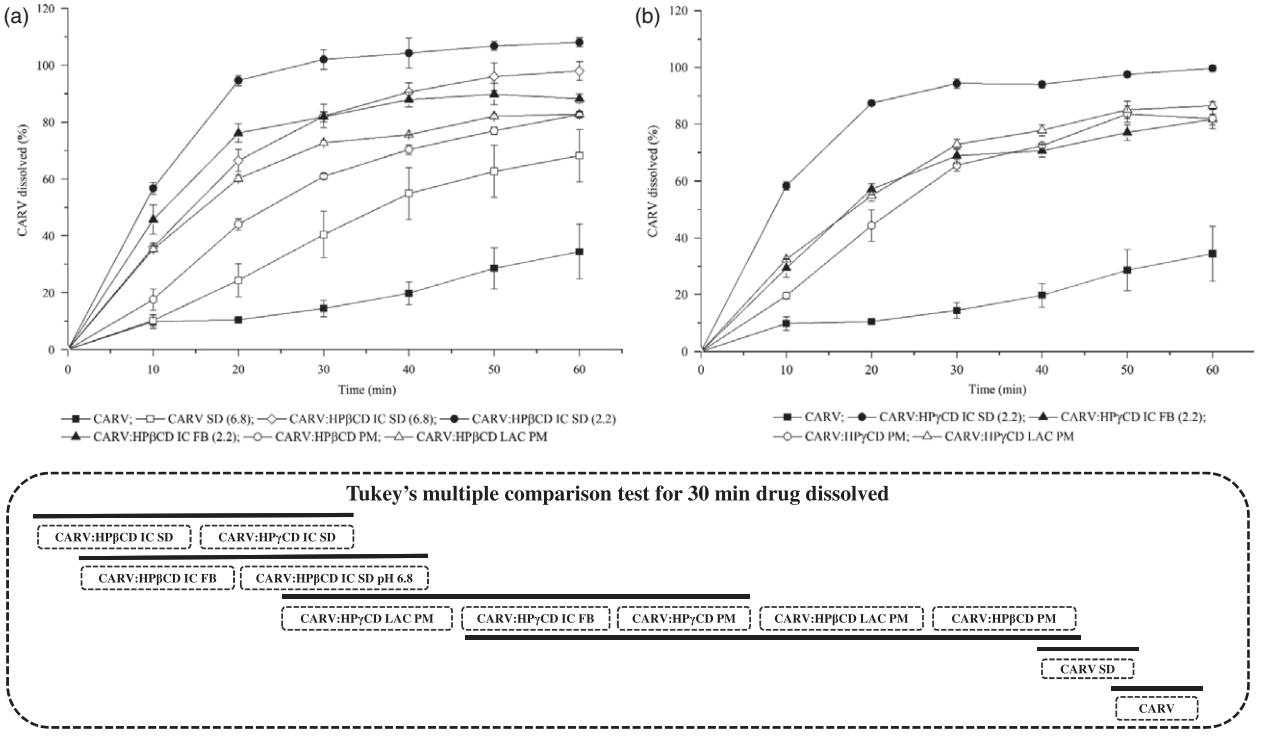

Figure 4 Dissolution profiles of carvedilol (CARV) complexes prepared with HPβCD (a) or HPγCD (b). CARV raw material, (IC) inclusion complexes obtained by (SD) spray drying or (FB) fluid-bed, and its physical mixtures (PM and LAC PM).

Table 2 Dissolution parameters of carvedilol raw material (CARV), CARV : cyclodextrin physical mixtures (PM) and inclusion complexes (IC) obtained using spray drying (SD) and fluid-bed (FB)

Product	% Dissolved in 10 min	% Dissolved in 30 min	*K* (/min)	Increase in *K* (folds)
CARV	9.8 ± 2.45	13.9 ± 2.79	0.46	–
CARV SD	10.3 ± 2.04	40.4 ± 8.18	1.56	2.55
CARV : HPβCD PM	17.6 ± 3.73	61.0 ± 0.96	1.40	3.01
CARV : HPβCD IC SD pH 6.8	36.1 ± 1.48	82.1 ± 4.14	1.56	3.36
CARV : HPβCD IC SD	56.8 ± 2.14	102.0 ± 3.43	3.44	7.39
CARV : HPβCD LAC PM	35.3 ± 1.05	72.7 ± 0.90	1.27	2.74
CARV : HPβCD IC FB	45.7 ± 5.22	81.8 ± 1.78	2.12	4.55
CARV : HPγCD PM	19.6 ± 1.08	65.6 ± 2.08	1.70	3.67
CARV : HPγCD IC SD	58.3 ± 1.49	94.3 ± 1.62	3.12	6.70
CARV : HPγCD LAC PM	32.5 ± 0.16	72.9 ± 1.79	1.65	3.56
CARV : HPγCD IC FB	29.3 ± 3.10	68.9 ± 2.68	1.49	3.26

rate, notably for the complex prepared in acidic pH (Table 2, Figure 4), which shows a complete dissolution of CARV in 30 min with $k = 3.44$. Likewise, the CARV : HPβCD IC produced using FB granulation showed a fast dissolution profile, with 82% of CARV dissolved in 30 min and $k = 2.12$ (Table 2).

Figure 4b shows the differences in the dissolution profiles of the inclusion complexes prepared with HPγCD. The IC obtained using SD showed a fast CARV dissolution profile, with 94% of the drug dissolved in 30 min and $k = 3.12$ (Table 2). In case of this cyclodextrin, in contrast to what happened with HPβCD, FB granulation presented an inferior ability in accelerate CARV dissolution, showing a drug dissolution of 69% in 30 min and $k = 1.26$ (Figure 4b, Table 2).

Complexation using SD showed that there were no differences in dissolution profile between the two selected cyclodextrins (Figure 4). In contrast, there are marked differences between the two cyclodextrins in inclusion complexes obtained by FB. While HPβCD promote significant improvements in dissolution of CARV, complexes obtained with HPγCD showed an inferior performance, presenting a dissolution profile statistically equal to the PM.

Scanning electron microscopy

The SEM photomicrographs of pure CARV, CARV SD and its complexes with HPβCD or HPγCD produced by the SD and FB techniques are shown in Figure 5. Figure 5a shows CARV raw material that is characterised by the presence of irregular crystals. These CARV crystals still could be observed, embedded in an amorphous material, in spray-dried CARV (Figure 5b). In contrast, inclusion complexes prepared by SD in acidic pH showed significant changes in particle shape and size. These complexes appeared as small and spherical particles, without any significant differences between HPβCD and HPγCD complexes (Figures 5c and 5d). Figures 5e and 5f show solid complexes obtained by FB granulation. In these cases, it could be observed the presence of round shape larger agglomerates.

Particle size and flow

Solid complexes that showed the highest improvement in dissolution rate were selected for size analysis and flow measurement. Table 3 shows size parameters of the selected formulations. It can be seen that complexes obtained by the FB technique showed a more uniform size distribution and bigger particle size than SD complexes. The type of cyclodextrin used had no effect on the particle size. In contrast, the differences in particle size between SD and FB complexes resulted in a drastic effect on flow measurements. Spray-dried complexes did not flow through a 6- or 10-mm diameter orifice of the GTB flow tester. Solid complexes prepared by FB granulation exhibited a marked improvement in flowability (Table 3).

Discussion

Fluid-bed technology has been frequently used in the pharmaceutical industry to manufacture solid dosage forms. This granulation method is a 'one-step' process capable of removing solvents with high efficiency at relatively low temperatures.[32] Recently, FB coating was used for complexation of piroxicam with modified cyclodextrins.[26] The authors showed a significant improvement in drug dissolution from pellets based on complexes of the drug with cyclodextrins. However, there have been few reports in the literature of the complexation of drugs with cyclodextrins using FB granulation.[27] In this study, we explored FB granulation as a possible method of producing inclusion complexes and compared it with SD, one of the most efficient methods of obtaining inclusion complex in the solid state.

Carvedilol is a basic lipophilic drug that has been tested with different cyclodextrins (parent and

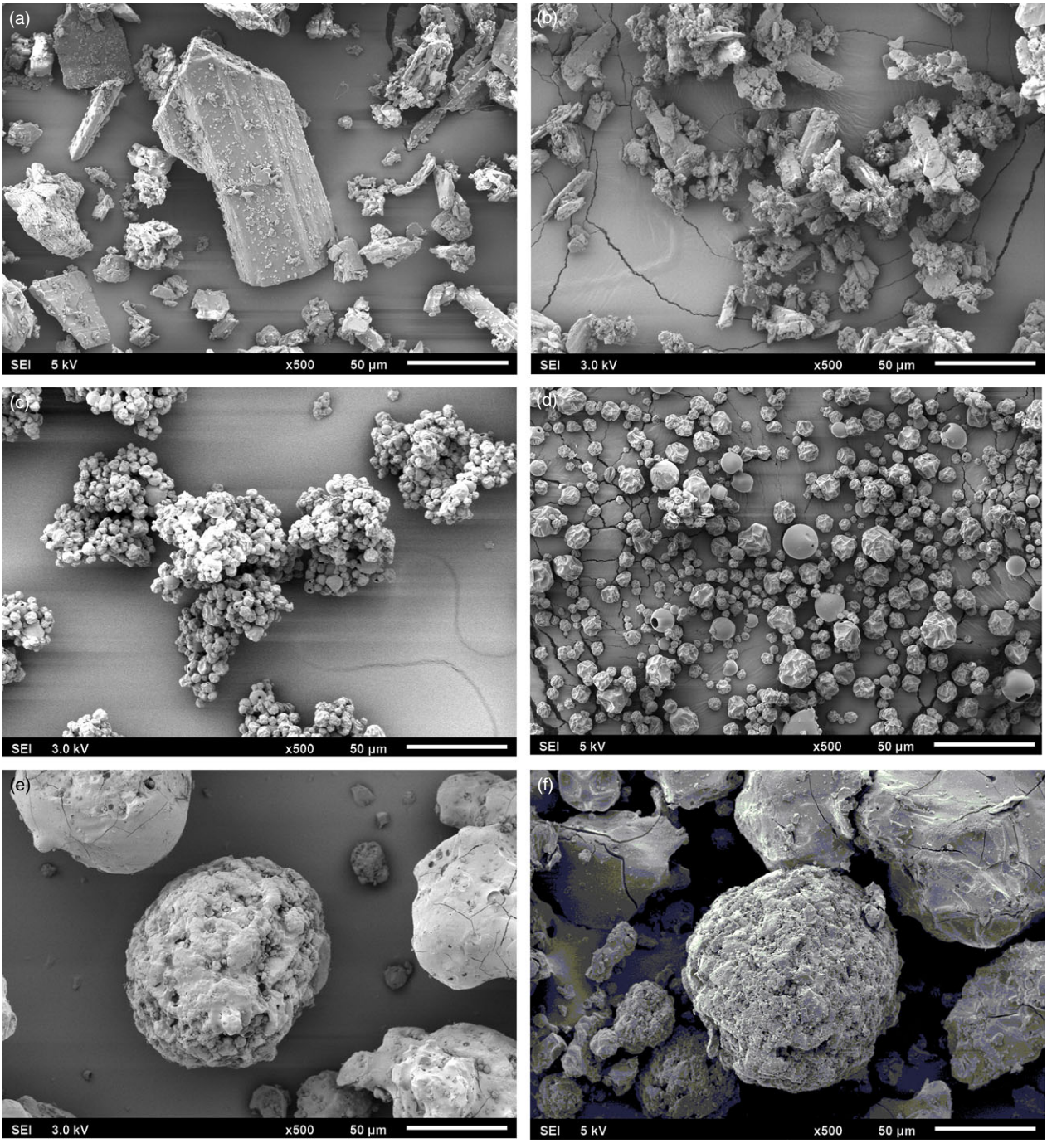

Figure 5 Scanning electron microscopy images of nonprocessed and spray-dried carvedilol (CARV) and its inclusion complexes (IC) at 500× magnification. (a) CARV (pure carvedilol); (b) CARV SD (spray-dried carvedilol); (c) CARV : HPβCD IC SD; (d) CARV : HPγCD IC SD; (e) CARV : HPβCD IC FB; (f) CARV : HPγCD IC FB.

modified).[14–19] Loftsson *et al.*[5] showed that HPβCD had the highest overall complexation efficiency for CARV in an aqueous, acidic solution. Yuvaraja and Khanan[19] also showed that HPβCD is a better carrier for CARV than βCD. These authors showed that complexation under acidic conditions could further improve the aqueous solubility of CARV by a combination of drug ionisation and drug complexation. Thus, we decided to test two media at different pH (2.2 and 6.8) for the complexation of CARV using SD. Additionally, γ-cyclodextrins

Table 3 Size parameters and flowability of carvedilol (CARV) inclusion complexes (IC) with HPβCD or HPγCD using spray drying (SD) or fluid-bed (FB)

	Particle size				Flowability	
Inclusion complex	d_{10} (μm)	d_{50} (μm)	d_{90} (μm)	Span	6 mm (s/100 g)	10 mm (s/100 g)
CARV : HPβCD IC SD	3.99	10.31	20.99	1.64	–	–
CARV : HPβCD IC FB	83.87	159.4	241.4	0.99	42.4 ± 0.24	10.4 ± 1.11
CARV : HPγCD IC SD	3.99	10.73	22.58	1.73	–	–
CARV : HPγCD IC FB	85.17	166.2	295.7	1.26	44.8 ± 1.06	32.1 ± 1.47

have not yet been exploited for inclusion complexation with CARV in the solid state. Considering the volume of the carvedilol molecule, with its bulky cyclic groups on both sides, the larger cavity available in γ-cyclodextrin, approximately 15% larger than that of β-cyclodextrin, can favour the formation of inclusion complexes with this drug. Based on this, HPγCD, a gamma derivative with high aqueous solubility was selected for this work, along with HPβCD.

Differential scanning calorimetry was used to characterise the solid systems. The DSC curve of the CARV SD (prepared without addition of cyclodextrin) suggested its partial amorphisation, which is probably related to the drying process. In turn, the CARV melting endotherm was markedly reduced after SD of CARV : HPβCD dispersions (prepared in PBS pH 6.8). The reduction in expected melting enthalpy seen in physical mixtures could be attributed to an *in situ* complexation that occurs during thermal analysis.[33] No melting peak could be detected in IC containing HPβCD or HPγCD prepared in an acidic medium, which can be attributed to a combined effect of drug ionisation and drug complexation, as discussed before.[16] Drug amorphisation is an evidence of inclusion complex formation.[34] FTIR analysis of the solid complexes showed consistent changes in the drug's spectral band at 3343 cm^{-1}, which was reduced (for complexes prepared at pH 6.8) or absent (for complexes prepared at pH 2.2) in the spectra of the binary systems containing HPβCD or HPγCD, prepared by SD or FB. This finding suggests the formation of hydrogen bonds between CARV and cyclodextrin[19] and corroborated the thermal results as an additional sign of complexation. No chemical differences were observed between SD and FB samples. IC prepared from a dispersion in a pH 6.8 medium demonstrated an inferior level of interaction compared with IC prepared from a dispersion in a pH 2.2 medium. As discussed by Loftsson and Brewster[1], in an acidic medium there is a higher level of CARV ionisation which increases its aqueous solubility and can improve complexation efficiency. This effect could explain the higher drug : cyclodextrin interaction observed in complexes prepared at pH 2.2.

Powder X-ray diffraction analyses showed complete amorphisation of CARV : HPβCD and CARV : HPγCD when prepared at pH 2.2 by SD technique. This indicates that the drug, in its protonated form acquired at such low pH,[35] could have been included in the cyclodextrins. Nevertheless, the sorption phenomenon on the cyclodextrin surface cannot be ruled out. By contrast, the samples prepared at pH 6.8 by the same technique presented a phase mixture of crystalline CARV and amorphous β-cyclodextrin. In this case, the inclusion complex could have been formed, but, undoubtedly to a lesser extent, as most of the drug content crystallised at this pH. This can be stated on the basis that the diffraction peaks from crystalline CARV are relatively intense. Using another technique (FB) but at the same pH 2.2, however, no broad humps from cyclodextrin or diffraction peaks from CARV could be detected. Only Bragg reflections typical of lactose monohydrate were seen, which is in accordance with the high content of this excipient.

The dissolution study showed very low dissolution of raw CARV at 30 min (13.9%). Spray drying of a CARV suspension resulted in a 2.61-fold increase of the dissolution rate constant. This can be attributed to a partial conversion from the crystalline to the amorphous state during the drying process. CARV : HPβCD and CARV : HPγCD physical mixtures also showed an improvement in dissolution rate, which is related to CARV : cyclodextrin surface interactions in the solid state, formation of inclusion complexes during the dissolution process, or improvement in powder wettability.[18] A higher improvement was seen when CARV was complexed through SD or FB. The highest increase was observed for HPβCD complex prepared in acidic conditions by SD, probably due to combined effect of salt formation and complexation. The same behaviour was reported by Yuvaraja and Khanan[19] for solid dispersions prepared by a kneading method, which resulted in rapid dissolution for the tertiary and quaternary complexes containing CARV, HPβCD, PVP-K30 and tartaric acid, prepared with a 1 : 3 molar ratio of drug : cyclodextrin. CARV dissolution from these formulations was ≥95% after ≤30 min at pH 6.8.[19] In the present work, CARV : HPβCD complexes were prepared at a 1 : 1 molar

ratio and showed complete drug dissolution (102%) at 30 min. The complexes prepared with HPγCD by spray drying showed ~95% dissolution at 30 min. It is important to note that the formulations reported here showed comparable CARV dissolution even when using a significantly lower amount of cyclodextrin. The IC produced by SD of a dispersion in a pH 2.2 medium dispersion showed better dissolution results, than the IC from SD of a pH 6.8 dispersion, probably due to ionisation of the drug.

Both complexation methods evaluated showed superior dissolution results to the raw CARV or CARV in physical mixtures. The complexes obtained from SD showed faster drug dissolution than ones obtained from FB. Those differences in dissolution profile can be attributed to the differences in particle size, the changes in drug crystallinity,[7] or even the complexation efficiency. Despite these differences, all inclusion complexes obtained meet the requirements of the FDA for immediate release of drugs, with 85% of the dose having dissolved within 60 min.[36]

To elucidate the effects of particle size on dissolution performance, the CARV : HPβCD complex prepared by FB granulation was ground, and the dissolution profile of the resulting product was compared with that of the corresponding unground sample. The dissolution curves overlapped (data not shown), and k values were comparable (2.10 vs 2.12, for ground and unground samples). These findings suggested that the differences between spray-dried and FB dried samples were not related to the differences in particle size. This result reinforce that the treatment plays a significant role in complex efficiency and consequently in drug dissolution profile.

With regard to the cyclodextrins, the dissolution results obtained to date with HPβCD or HPγCD using SD statistically present the same performance when considering the percentile dissolved at 30 min. In this context, HPγCD appears to be one more option for CARV complexation, with great inclusion complex formation in the solid state, although HPβCD remains the most potent material for augmentation of the CARV dissolution profile considering the results of complexation by FB. In spite of the improvement in dissolution, technological aspects should be taken into account when considering large-scale pharmaceutical production. Good flow properties are critical for capsule filling and tableting.[20] SD complexes showed d_{50} values approximately 15 times lower than the corresponding FB solid complexes (Table 3). In addition, SD complexes were shown to be agglomerated and cohesive (Figure 5). These properties resulted in very poor flow behaviour. On the other hand, FB complexes showed good flowability, indicating its adequate technological properties for the development of solid dosage forms.

Among all of the studied systems, the complex obtained using HPβCD by the FB process produced the best results, showing a high degree of drug-cyclodextrin interaction, rapid dissolution and excellent flow characteristics, presenting better prospects for industrial production.

Conclusions

This study demonstrates that the method, the production conditions and the cyclodextrin variety dramatically influence the performance of a solid system obtained with CARV. SD and FB techniques were able to produce CARV : cyclodextrin inclusion complexes, which met the requirements of the FDA for immediate release of drugs. However, only FB complexes showed good flowability, indicating that this technique seems to be the best alternative for large-scale production of solid dosage forms containing CARV. In terms of the cyclodextrins, there is no difference in dissolution performance between the cyclodextrins studied using SD. However, dissolution results with HPβCD are better than those with HPγCD considering FB technique. In this context, HPγCD appears to be one more option for CARV complexation with great inclusion complex formation in the solid state.

Declaration

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Loftsson T, Brewster ME. Cyclodextrins as functional excipients: methods to enhance complexation efficiency. *J Pharm Sci* 2012; 101: 3019–3032.
2. Kurkov SV, Loftsson T. Cyclodextrins. *Int J Pharm* 2013; 453: 167–180.
3. Loftsson T, Duchêne D. Cyclodextrins and their pharmaceutical applications. *Int J Pharm* 2007; 329: 1–11.
4. Chakraborty S *et al.* Assessment of solubilization characteristics of different surfactants for carvedilol phosphate as a function of pH. *J Colloid Interface Sci* 2009; 335: 242–249.
5. Loftsson T *et al.* Carvedilol: solubilization and cyclodextrin complexation: a technical note. *AAPS PharmSciTech* 2008; 9: 425–430.
6. Singh B *et al.* Optimized nanoemulsifying systems with enhanced bioavailability of carvedilol. *Colloids Surf B Biointerfaces* 2013; 101: 465–474.

7. Sharma A, Jain CP. Preparation and characterization of solid dispersions of carvedilol with PVP K30. *Res Pharm Sci* 2010; 5: 49–56.
8. Planinšek O *et al.* Carvedilol dissolution improvement by preparation of solid dispersions with porous silica. *Int J Pharm* 2011; 406: 41–48.
9. Shete AS *et al.* Chitosan and chitosan chlorhydrate based various approaches for enhancement of dissolution rate of carvedilol. *DARU* 2012; 20: 93.
10. Tapas A *et al.* An improvement in physicochemical properties of carvedilol through spherically agglomerated solid dispersions with PVP K30. *Acta Pol Pharm* 2012; 69: 299–308.
11. Kukec S *et al.* Characterization of agglomerated carvedilol by hot-melt processes in a fluid bed and high shear granulator. *Int J Pharm* 2012; 430: 74–85.
12. Shamma RN, Basha M. Soluplus: a novel polymeric solubilizer for optimization of carvedilol solid dispersions: formulation design and effect of method of preparation. *Powder Technol* 2013; 237: 406–414.
13. Lee SN *et al.* A novel surface-attached carvedilol solid dispersion with enhanced solubility and dissolution. *Arch Pharm Res* 2013; 36: 79–85.
14. Bhutani S *et al.* Preparation and evaluation of inclusion complexes of carvedilol. *J Sci Ind Res* 2007; 66: 830–834.
15. Hirlekar R, Kadam V. Preparation and characterization of inclusion complexes of carvedilol with methyl-*b*-cyclodextrin. *J Incl Phenom Macrocycl Chem* 2009; 63: 219–224.
16. Pokharkar V *et al.* Ternary complexation of carvedilol, beta-cyclodextrin and citric acid for mouth-dissolving tablet formulation. *Acta Pharm* 2009; 2: 121–132.
17. Murthy TGEK, Sowjanya G. Evaluation of some methods for preparing carvedilol-hydroxypropyl-β-cyclodextrin inclusion complexes. *Asian J Biochem Pharm Res* 2011; 1: 676–683.
18. Pamudji JS *et al.* Improvement of carvedilol dissolution rate through formation of inclusion complex with β-cyclodextrin. *Int J Pharm Sci* 2014; 6: 228–233.
19. Yuvaraja K, Khanam J. Enhancement of carvedilol solubility by solid dispersion technique using cyclodextrins, water soluble polymers and hydroxyl acid. *J Pharm Biomed Anal* 2014; 96: 10–20.
20. Miller LA *et al.* Practical considerations in development of solid dosage forms that contain cyclodextrin. *J Pharm Sci* 2007; 96: 1691–1707.
21. Patyi G *et al.* Thermal and spectroscopic analysis of inclusion complex of spironolactone prepared by evaporation and hot melt methods. *J Therm Anal Calorim* 2010; 102: 349–355.
22. Nagane K *et al.* Practical approach to prepare solid dispersion drug product using spherical silicate. *Int J Pharm* 2014; 475: 364–371.
23. Fini A *et al.* ATR/Raman and fractal characterization of HPBCD/progesterone complex solid particles. *Pharm Res* 2008; 25: 2030–2040.
24. Castro *et al.* A new approach to the granulation of β-cyclodextrin inclusion complexes. *Chem Eng J* 2010; 164: 316–321.
25. Lu Y *et al.* Enhanced dissolution and stability of lansoprazole by cyclodextrin inclusion complexation: preparation, characterization, and molecular modeling. *AAPS PharmSciTech* 2012; 13: 1222–1229.
26. Zhang X *et al.* Piroxicam2-hydroxypropyl-beta-cyclodextrin inclusion complex prepared by a new fluid-bed coating technique. *J Pharm Sci* 2009; 98: 665–675.
27. Gyanani V *et al.* Evaluation of various processes for simultaneous complexation and granulation to incorporate drug–cyclodextrin complexes into solid dosage forms. *Drug Dev Ind Pharm* 2015; 41: 1856–1863.
28. Borba P *et al.* Pharmaceutical approaches involving carvedilol characterization, compatibility with different excipients and kinetic studies. *J Therm Anal Calorim* 2014; 115: 2507–2515.
29. Talvani A *et al.* Carvedilol: decomposition kinetics and compatibility with pharmaceutical excipients. *J Therm Anal Calorim* 2014; 115: 2501–2506.
30. Yathirajan HS *et al.* A second polymorph of carvedilol. *Acta Crystallogr Sect E* 2007; 63: o542–o544.
31. Fries DC *et al.* Structural chemistry of carbohydrates. III. Crystal and molecular structure of 4-O-β-D-galactopyranosyl-a-D-glucopyranose monohydrate (a-lactose monohydrate). *Acta Crystallogr Sect B* 1971; 27: 994–1005.
32. Qi J *et al.* Manufacturing solid dosage forms from bulk liquids using the fluid-bed drying technology. *Curr Pharm Des* 2015; 21: 2668–2676.
33. Silva-Alves L *et al.* Preformulation studies of itraconazole associated with benznidazole and pharmaceutical excipients. *Termochim Acta* 2014; 575: 29–33.
34. Cunha-Filho MSS *et al.* Characterization of β-lapachone and methylated β-cyclodextrin solid-state systems. *AAPS PharmSciTech* 2007; 8: E68–E77.
35. Prado LD *et al.* An insight into carvedilol solid forms: effect of supramolecular interactions on the dissolution profiles. *CrystEngComm* 2014; 16: 3168–3179.
36. FDA guidance for industry. Dissolution Testing of Immediate Release Solid Oral Dosage Forms, 1997.