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Article

Inclusion complex of amiodarone hydrochloride with cyclodextrins: preparation, characterization and dissolution rate evaluation

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This study aimed to improve the water solubility of amiodarone hydrochloride (AMH) via inclusion complexes with β-cyclodextrin, methyl-β-cyclodextrin and 2-hydroxypropyl-β-cyclodextrin. Inclusion complexes were developed by physical mixture, coevaporation, spray-drying and freeze-drying. Solid state analysis was performed using X-ray powder diffraction, differential scanning calorimetry and scanning electronic microscopy. Thermodynamic studies demonstrate that the inclusion complexes of drug into different cyclodextrins were an exothermic process that occurred spontaneously. Water solubility and drug dissolution rates were significantly increased after the formation of inclusion complexes with the cyclodextrins evaluated in relation to the physical mixture and pure drug. The present study provides useful information for the potential application of complexation with amiodarone HCl. This may be a good strategy for the development of solid pharmaceutical dosage forms.

Uniterms: Amiodarone HCl/evaluation. Amiodarone HCl/solubility. Cyclodextrins/inclusion complexes. Cyclodextrins /thermodynamic studies. Dissolution rate.

INTRODUCTION

Amiodarone hydrochloride (AMH), chemically known as (2-butylbenzofuran-3-yl)[4-[2-(diethylamino) ethoxy]-3,5-diiodophenyl]methanone hydrochloride, used for the treatment of both supraventricular and ventricular arrhythmias (Lafuente-Lafuente *et al*., 2009). AMH is a white or almost white, crystalline powder and is very slightly soluble in water (0.2 – 0.5 mg mL^{-1}) (British Pharmacopoeia, 2012; Eghrary *et al*., 2012). According to the Biopharmaceutical Classification System (BCS), AMH is a class II. Class II drugs are those with low solubilities and high permeabilities (Amidon *et al.,* 1995; Benet, 2005).

For drugs with low gastrointestinal solubility and high permeability, dissolution in physiological fluids is the limiting step for oral bioavailability. These properties are a challenge for the pharmaceutical industry, since more than 70% of the new drugs have low solubility showing deficient biopharmaceutical properties (Ku, Dublin, 2012; Leuner, Dressman, 2000; Riekes *et al*., 2010; Svenson, 2009; Vasconcelos, Sarmento, Costa, 2007).

In order to improve drug solubility in physiological fluids, their effectiveness should be increased, and the doses administered and toxic effects reduced. Several strategies can be employed, such as development of solid dispersion, inclusion complexes containing cyclodextrin, chemical modification, particle micronization, pH adjustment, micellar solubilization and supercritical fluid (Adeli, 2014; Alves *et al*., 2014; Chaudhary *et al*., 2012; Frizon *et al*., 2013; Gursoy, Benita, 2004; Jagdale *et al*., 2012; Li-hong *et al*., 2013; Lu *et al*., 2012; Maulvi *et al*., 2011; Patel *et al*., 2008; Sathigari *et al*., 2009).

Cyclodextrins (CDs) are cyclic organic compounds composed of different D-glucopyranose units. CDs containing six, seven or eight natural glucose units obtained in high quantity called α-cyclodextrin (α-CD), β-cyclodextrin (β-CD) and γ-cyclodextrin (γ-CD), respectively. These structures showed different values of solubility in water and at the same time are capable of hosting hydrophobic molecules (Loftsson, Brewster, 1996; Rajewski, Stella, 1996; Uekama, 2004).

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This work aimed to develop inclusion complexes using cyclodextrins for the purpose of improving water solubility and dissolution rate of AMH. The solid state physicochemical properties were assessed using powder X-ray diffraction, differential scanning calorimetry, Fourier-transform infrared spectroscopy and scanning electron microscopy. Furthermore, in vitro dissolution profiles using different dissolution media were performed to investigate the increased solubility of this drug.

MATERIAL AND METHODS

Material

AMH (purity > 99%) was obtained from Brazilian Pharmacopeia, batch 1040. The raw material AMH batch: CAD20131006 (purity>99%) was purchased from Zhejiang Pharmaceutica® (Hong Kong, China). β-Cyclodextrin (β-CD), methyl-β-cyclodextrin, (Methyl-β-CD) and hydroxypropyl-β-cyclodextrin (HP-β-CD), with an average degree of molar substitution per anhydroglucose unit of 0.6, purchased from Sigma-Aldrich® (St. Louis, MO, USA). Ultra-pure deionized water was generated from a Millipore Milli-Q Gradient System (Billerica, MA, USA). Other reagents and solvents used were of analytical grade.

Preparation of physical mixture and inclusion complexes

Physical mixture and inclusion complexes of AMH and CDs at a 1:1 molar ratio were performed by different techniques:

Physical mixture (PM): The PM was prepared by mixing previously weighed powders in a ceramic mortar for 10 min.

Coevaporation (CE): The product was prepared by dissolving a known amount of AMH and CDs in suitable volumes of water:ethanol (1:1) solution. The mixture was stirred for 2 hours and then solvent was removed in a vacuum oven at 40 ºC for 72 hours.

Freeze-drying (FD): The product was prepared by dissolving the CDs in water:ethanol (1:1) solution and adding a known amount of AMH. The mixture was agitated for 5 h at 40 ºC and organic solvent was evaporated by rotary evaporation at 40 ºC under reduced pressure (-700 mm Hg) (Fisatom®, model 802). The solution was placed in a freezer at –80 ºC for 24 hours and lyophilized in a Jouan LP3 (model 60) freeze-dryer for 24 hours.

Spray-drying (SD): The product was prepared by dissolving the CDs in water:ethanol (1:1) solution and adding a known amount of AMH. The mixture was agitated for 24 h at 25 ºC. The mixture was spray-dried using a LabMaq Brazil ® (model MSDi 1.0) spray dryer under the following conditions: sample feed rate of 4 mL/min, inlet temperature 135 ºC, outlet temperature 105 ºC and air flow rate of 45 L/min.

pH-Dependent solubility and Phase solubility studies

The pH-dependent solubility studies were determined in pH 1.2, 4.5 and 6.8 buffer solution and distilled water at 37 ºC ± 0.5 ºC. An excess quantity of AMH was placed in an erlenmeyer flask containing 10 mL of different solutions. The samples were covered to avoid solvent loss and then shaken at 140 rpm in an orbital shaking incubator (Novatecnica®, NT712) for 24 hours. After equilibrium, samples were centrifuged at 4000 rpm for 10 minutes, and then the concentration of AMH in supernatant liquid was determined by HPLC (Rubim *et al*., 2015).

The phase solubility studies were performed according to the method reported by Higuchi and Connors (1965). Briefly, an excess amount of AMH was transferred to an erlenmeyer flask containing 10 mL cyclodextrins in aqueous solutions at concentrations ranging from 0 to 10.0 mM. The flasks were covered to avoid solvent loss and then shaken at 140 rpm in an orbital shaking incubator for 24 hours at different temperatures 25 ºC and 37 ºC ± 0.5 ºC. After equilibrium, samples were centrifuged at 4000 rpm for 10 minutes, and then the concentration of AMH in supernatant liquid was determined by HPLC. All the experiments were performed in triplicate. The apparent complexation constants ($K_{1:1}$, M^{-1}) of the complexes were determined in accordance with Eq. (1) from phase solubility slope, where the intercept is the intrinsic solubility of drug absence of cyclodextrins.

$$K_{1:1} = \frac{\text{Slope}}{\text{Intercept}(1 - Slope)} \quad (1)$$

Thermodynamic parameters were obtained as a function of the temperature and complexation constant. The changes in Gibb's free energy (ΔG), enthalpy (ΔH) and entropy (ΔS) were determined using (Eq (2), (3) and (4)), respectively, where R is the gas constant (8.314 J mol^{-1} K^{-1}) and T is temperature in Kelvin.

$$\Delta G = -RT \ln K \quad (2)$$

$$\ln\left(\frac{K_2}{K_1}\right) = \Delta H \frac{T_2 - T_1}{RT_2T_1} \quad (3)$$

$$\Delta S = \frac{(\Delta H - \Delta G)}{T} \quad (4)$$

Characterization of the inclusion complex

X-ray powder diffraction analysis (XRD)

The diffraction patterns of samples were obtained with a X-ray diffractometer (Rigaku®, Miniflex 300), using Cu as an anode material, operated at a voltage of 10 mA, 30 kV, monochromatic radiation (λ = 1.54051 Å). The samples were analyzed from 5º to 50º in the range of 2θ, in increments of 0.09 º/s.

Differential Scanning Calorimetry (DSC)

The DSC studies were obtained in a DSC-60 cell (Shimadzu®) with a sensibility of 0.1 ºC, using aluminum crucibles with about 2 mg of sample. The temperature of analysis was 30 to 300 ºC, with a heating rate of 10 ºC min^{-1} in a nitrogen atmosphere with a flow rate of 100 mL min^{-1}.

Scanning Electron Microscopy (SEM)

With the help of the scanning electron microscope (Philips, Model XL 30) at an intensity of 10 kV, the samples were mounted onto a metallic base using double-sided adhesive tape vacuum-coated with gold.

Dissolution studies

The dissolution studies were performed in 500 mL dissolution medium (i.e. water, acid buffer pH 1.2, acetate buffer pH 4.5 and phosphate buffer 6.8) at 37 ºC ± 0.5 ºC using USP Apparatus 2 at 50 rpm. Briefly, AMH (50 mg), the physical mixture (PM) and inclusion complexes containing equivalent amount of AMH were separately added into vessel at a rotation speed of 50 rpm. At a pre-specified interval time, samples (10 mL) were collected and replaced with an equal volume of fresh medium to maintain a constant total volume. The percentage of drug dissolved was determined using the HPLC method.

RESULTS AND DISCUSSION

pH-Dependent solubility and Phase solubility studies

The solubility of AMH as a function of pH was determined in various aqueous media (water, acid buffer pH 1.2, acetate buffer pH 4.5 and phosphate buffer pH 6.8). The solubility values found were: in water, 21.86 ± 1.6011 µg mL^{-1}; in acid buffer pH 1.2, 8.33 ± 0.1162 µg mL^{-1}; in acetate buffer pH 4.5, 26.93 ± 0.2944 µg mL^{-1}; in phosphate buffer pH 6.8, 1.18 ± 0.0877 µg mL^{-1}. In solutions with low pH the AMH has appreciable solubility due to its basic nature and ionization (6.56 ± 0.06). On the other hand it is obvious that AMH shows low solubility in a higher pH solution in which it remains in a unionized form (Lamprecht, Bouligand, Benoit, 2002; Paduraru *et al.,* 2013).

The solubility behaviors found are according to the low solubility obtained with acid buffer pH 1.2. This can be explained as due to the formation of insoluble complex between drug and anions dissolved in buffer solution (Avdeef, 2007; Boury *et al.,* 2001; Ravin, Shami, Rattie, 1975).

Phase solubility studies were used for the evaluation of AMH behavior in an aqueous solution of β-CD, methyl-β-CD and HP-β-CD at 25 and 37 ºC. The results are shown in Figure 1. AMH solubility linearly increased with increasing concentrations of cyclodextrins over the concentration range evaluated.

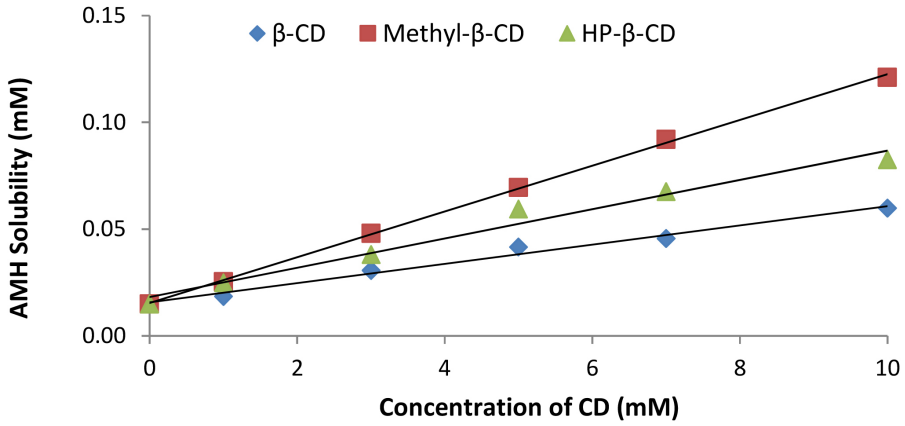

FIGURE 1 - Phase solubility diagrams of AMH in the presence of cyclodextrins in (A) 25 ºC and (B) 37 ºC ± 0.5 ºC (n = 3).

The diagrams obtained were classified as A_L type, according to Higuchi and Connors (1965). This classification is observed when the guest solubility increases linearly with the cyclodextrin concentration, over the concentration range evaluated, indicating a 1:1 molecular complex formation between AMH and different cyclodextrins. The solubility of AMH in water increased significantly (more than 7, 14 and 9-fold at 25 ºC) for β-CD, Methyl-β-CD and HP-β-CD at 10 mM, respectively and (more than 4, 8 and 5-fold at 37 ºC) for β-CD, Methyl-β-CD and HP-β-CD at 10 mM, respectively. This increased solubility can be explained by the formation of an inclusion complex with cyclodextrins. The thermodynamics parameters ($K_{1:1}$, ΔG, Δ*H,* Δ*S*) were calculated from the slopes of the linear phase-solubility plots, and are summarized in Table I.

The high ($K_{1:1}$) values were observed for all cyclodextrins evaluated in this study, indicating the formation of a stable complex. The stability constants were highest for the complex formed with Methyl-β-CD, followed by HP-β-CD and β-CD. It has been suggested that the steric effect, which depends on the size of cyclodextrins, is one of the main factors of inclusion complex formation (Del Valle, 2004).

Furthermore the ΔG values were negative for all complexes, indicating that the inclusion of AMH in the different cyclodextrins is a spontaneous process and thermodynamically favorable. This increase in solubility is directly associated with values of $\Delta G_{tr}<0$ being proportional to the increased carrier concentration (Patel *et al*., 2008). The values of the enthalpy change (ΔH) were negative, indicating that the interaction between AMH and cyclodextrins is an exothermic process, nonetheless the magnitude of the change suggests that the interactions were of the low energy type.

Characterization of the complexes

X-ray powder diffraction analysis

X-ray analysis is a tool utilized to characterize the crystalline state, to evaluate the different crystalline forms and also to confirm the formation of host-guest inclusion complexes. The solid state form of the particles as amorphous, crystalline or polymorphic is a parameter that determines the solubility and dissolution rate of drugs (Markovich *et al*., 1997). Figure 2 shows the diffractogram pattern of AMH and corresponding inclusion complexes with CDs prepared by different methods.

Figure 2 shows the intense peaks of crystalline state of the drug structure and the influence that each CD and preparation method can have on the crystalline state of the drug. The PM product using the three carriers showed a diffractogram pattern similar to that of the pure drug. The CE method using β-CD showed a similar diffractogram to that of PM, while those obtained by SD and FD methods showed the absence of any peaks indicating a transition from crystalline to an amorphous state. Similar results were observed with Methyl-β-CD and HP-β-CD by spray-drying and freeze-drying methods. This solid state form transition was also observed by Bankar and Mahatma (2012), Paduraru *et al*. (2013) and Riekes *et al*. (2010), when the amorphization of the compounds after complexation with cyclodextrins was demonstrated.

Thermal analysis

DSC is a tool utilized in the pharmaceutical industry for the purpose of evaluating the physicochemical properties of drugs and excipients, evaluation of degradation kinetics and stability. Furthermore, these analyses are commonly used to characterize the solid state inclusion complexes (Vecchio *et al*., 2001;

TABLE I - Thermodynamic parameters obtained from phase solubility studies with AMH and cyclodextrins at different temperatures (values are the mean ± SD of triplicate experiments)

Systems	T[A]	S_o[B]	$K_{1:1}$[C]	ΔG[D]	Δ*S*[E]	Δ*H*[F]
AMH:β-CD	25	0.009 ± 0.001	446.23 ± 2.1985	-15.12 ± 0.8952	-58.46 ± 0.9211	32.55 ± 0.3911
	37	0.015 ± 0.002	268.46 ± 1.6874	-14.42 ± 1.0283	-58.46 ± 0.0391	
AMH:Methyl-β-CD	25	0.008 ± 0.004	1135.22 ± 2.2021	-17.44 ± 1.2418	-23.51 ± 0.7769	24.45 ± 1.5885
	37	0.013 ± 0.004	775.19 ± 1.5733	-17.16 ± 0.8496	-23.50 ± 1.2059	
AMH:HP-β-CD	25	0.011 ± 0.003	458.72 ± 2.9982	-15.19 ± 1.8541	-38.16 ± 1.3361	20.10 ± 1.0211
	37	0.018 ± 0.011	335.19 ± 3.5874	-14.99 ± 0.1774	-16.48 ± 0.5587	

[A] Temperatures evaluated in (ºC); [B] Solubility of AMH in the absence of cyclodextrins (mM); [C] Apparent complexation constant (M^{-1}); [D] Change in Gibbs-free energy (KJ mol^{-1}); [E] Change in entropy (J mol^{-1} K^{-1}); [F] Change in enthalpy (KJ mol^{-1}).

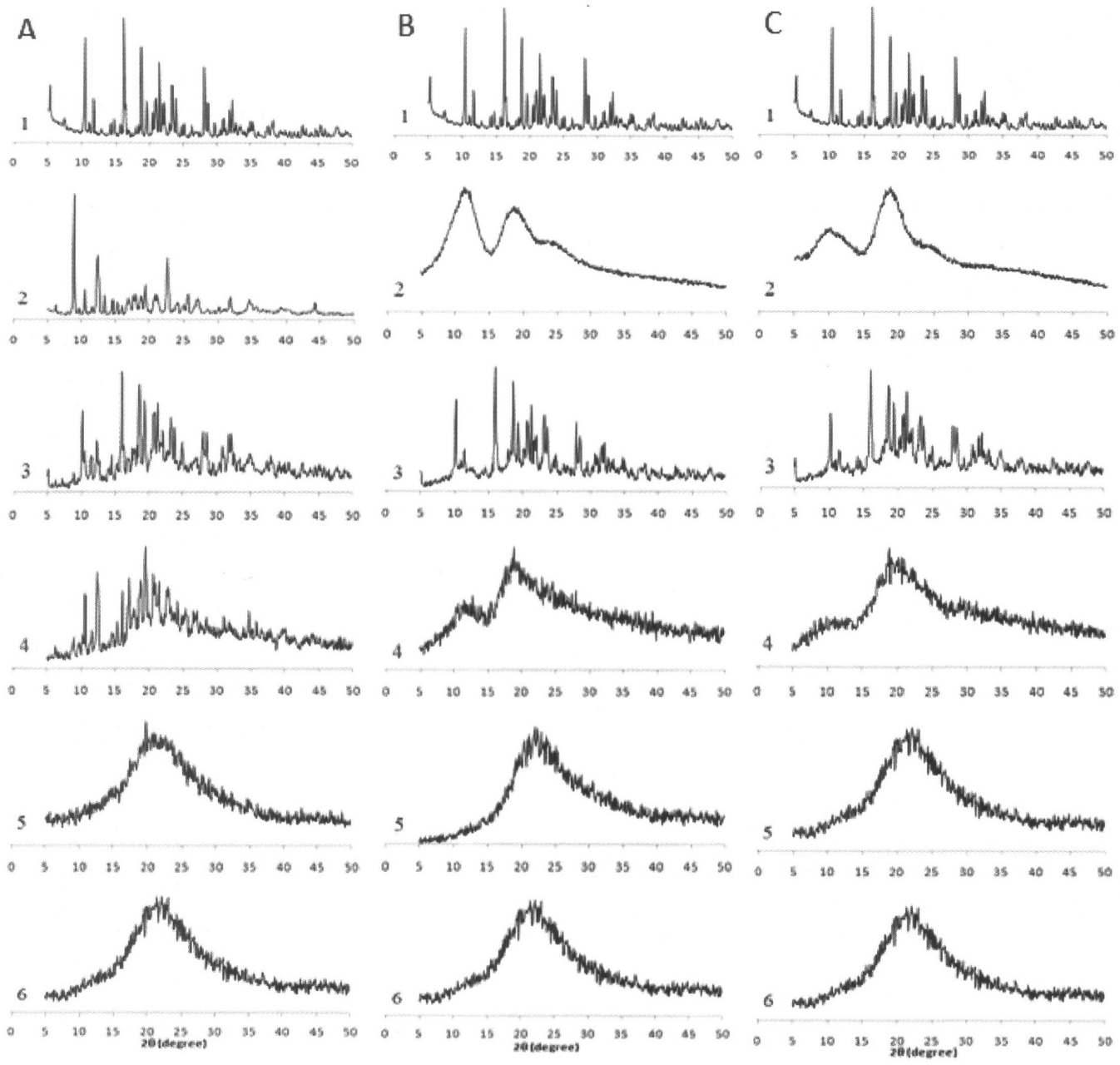

FIGURE 2 - X-ray diffractograms corresponding to: (A): 1 – AMH, 2 - β-CD, 3 – AMH/β-CD/PM, 4 – AMH/β-CD/CE, 5 – AMH/β-CD/SD, 6 – AMH/β-CD/FD, (B): 1 – AMH, 2 - Methyl-β-CD, 3 – AMH/Methyl-β-CD/PM, 4 – AMH/Methyl-β-CD/CE, 5 – AMH/Methyl-β-CD/SD, 6 – AMH/Methyl-β-CD/FD and (C): 1 - AMH, 2 - HP-β-CD, 3 – AMH/HP-β-CD/PM, 4 – AMH/HP-β-CD/CE, 5 – AMH/HP-β-CD/SD, 6 - AMH/HP-β-CD/FD.

Yoshida *et al*., 2011). The thermal behavior of the drug, cyclodextrins and inclusion complexes are presented in Figure 3.

The DSC curve shows that AMH has a sharp melting endothermic peak at about 163.47 ºC, indicating a typical behavior of the anhydrous crystalline state. This DSC curve was similar to those in other studies (Paduraru *et al*., 2013, Riekes *et al*., 2010). During the DSC analysis the thermogram of HP-β-CD showed a very broad endothermic peak between 60 ºC and 110 ºC. The formulations produced by different methods containing the three cyclodextrins showed a reduction of intensity and an alteration in position of the endothermic peak of the drug. When the spray-drying method was utilized, the complete disappearance of the endothermic peak corresponding to AMH was evident, indicating the formation of an amorphous inclusion complex that was confirmed by the results obtained after XRD analysis.

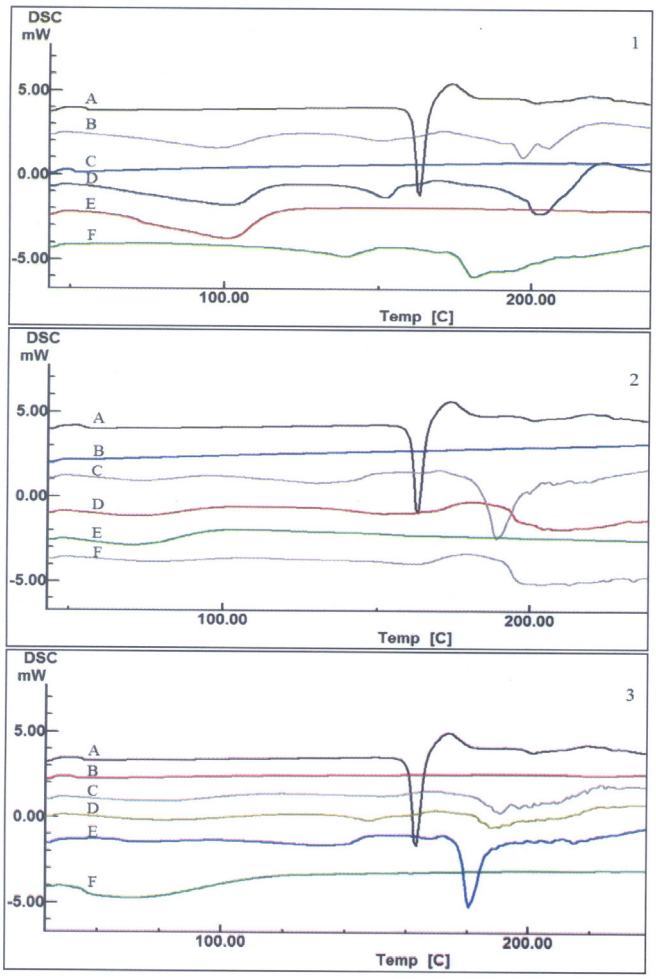

FIGURE 3 - DSC thermograms: 1: (A) AMH powder, (B) physical mixture, (C) spray-dried, (D) coevaporated, (E) β-CD and (F) freeze-dried; 2: (A) AMH powder, (B) spray-dried, (C) coevaporated, (D) physical mixture, (E) freeze-dried and (F) Methyl-β-CD; and 3: (A) AMH powder, (B) spray-dried, (C) coevaporated, (D) physical mixture, (E) freeze-dried and (F) HP-β-CD.

Scanning electron microscopy

The images obtained for the formulations are presented in Figure 4. The micrographs are used to evaluate the morphological aspects of polymers, solid dispersions, drugs, cyclodextrins and inclusion complexes (Naidu *et al*., 2004).

AMH showed the irregular size and characteristic morphology of drug crystals, which is in accordance with the X-ray analysis that showed the crystalline nature of AMH. It was also evident that β-CD is a crystalline solid while Methyl-β-CD and HP-β-CD are regular and spherical particles.

In the physical mixtures and coevaporation method the AMH crystals were clearly detectable on the surface of cyclodextrins indicating little complexation between compounds. All spray dried powders showed an interaction between drug and cyclodextrins, indicated by the complete disappearance of the crystalline morphology of AMH. This drastic change of morphology and particle shape was indicative of the formation of the new solid phase. Results obtained by others evaluations, DSC and X-ray powder corroborated the formation of an amorphous system.

Dissolution rate studies

In drugs that present low gastrointestinal solubility and high permeability, in this case AMH, the oral drug release is a limiting step for bioavailability. The bioavailability depends on a series of factors, including the physicochemical properties of its formulation, and the physiological state of the patients (Fernandes, Vieira, Veiga, 2002).

To evaluate whether the inclusion complexes affected the dissolution rates of AMH, dissolution profiles were performed on pure drug, physical mixtures and inclusion complexes with cyclodextrins, with three pH values and water. Rapid dissolution rate as compared with the pure drug is the characteristic behavior of inclusion complexes (Baboota, Dhaliwal, Kohli, 2005). Dissolution profiles for the pure AMH, physical mixture of the drug and inclusion complexes obtained by different methods are presented in Figure 5.

Pure AMH shows about 22.20% dissolution in water, 7.83%, 18.31% and 4.82% dissolution in acid buffer pH 1.2, acetate buffer pH 4.5 and phosphate buffer pH 6.8, respectively after 60 minutes of study. As expected, AMH is a drug that depends on the pH value due to the presence of a tert-amine ionizable in different fluids (Paduraru *et al*., 2013).

The physical mixtures containing the three cyclodextrins show a similar dissolution rate of about 30% at 60 minutes in water and acetate buffer pH 4.5. The increment in the dissolution rate of AMH with the physical mixture can be explained by improved drug wettability due to the presence of the cyclodextrins, which can reduce the interfacial tension between particle and dissolution medium. The coevaporation, spray-drying and freeze-drying methods of β-CD, Methyl-β-CD and HP-β-CD showed a significant increase in drug dissolution compared to physical mixture. This can be attributed to the better interaction between drug and CDs, as confirmed by physicochemical characterization.

The spray-drying products with methyl-β-CD showed about 55%, 56%, 65% and 38% dissolution in water, acid buffer pH 1.2, acetate buffer pH 4.5 and phosphate buffer pH 6.8, respectively. The great influence of methyl-β-CD can be explained based on its good

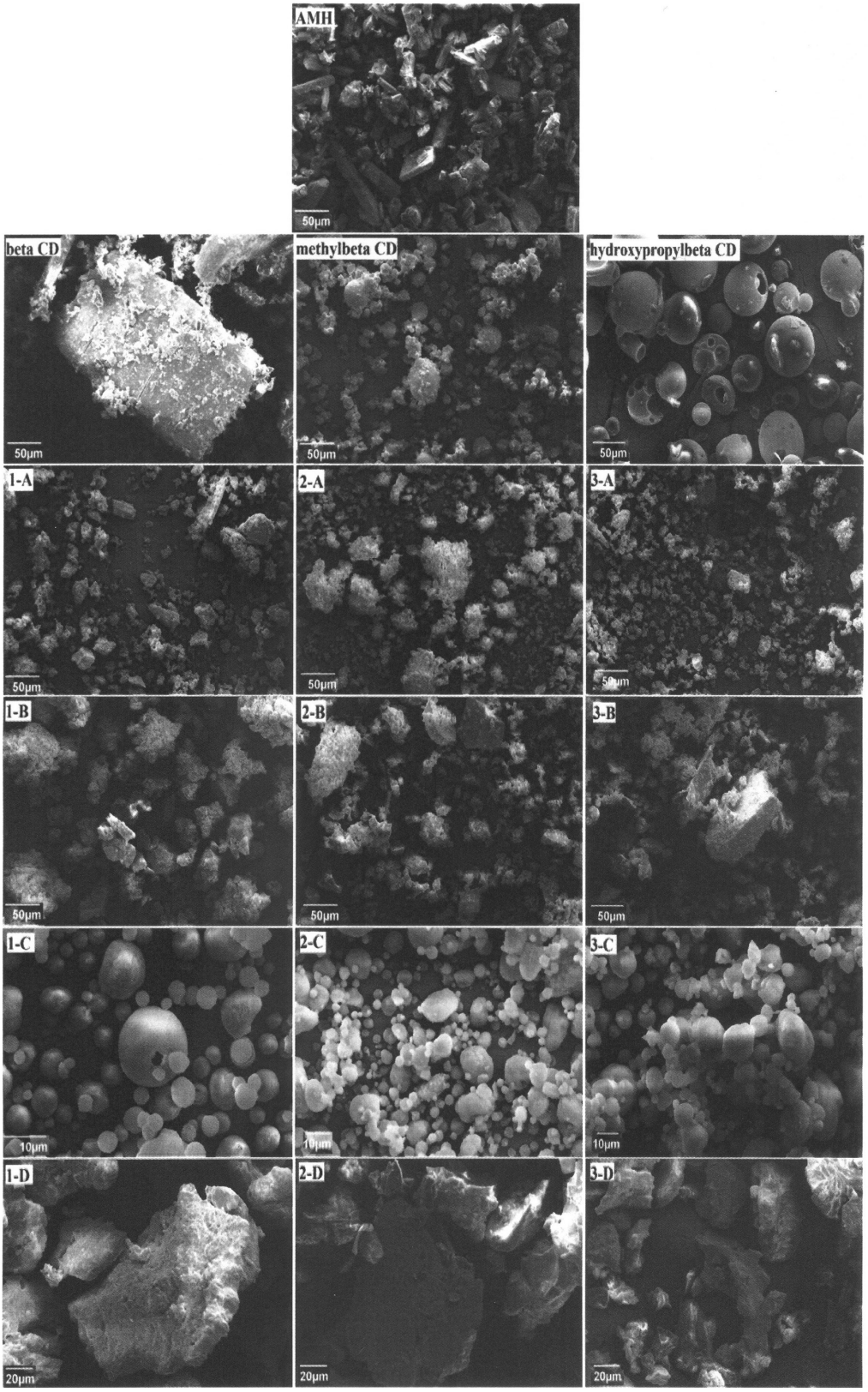

FIGURE 4 - Scanning Electronic Microscopy of AMH, beta-CD, methylbeta-CD, hydroxypropylbeta-CD, AMH/beta-CD/PM (1A), AMH/beta-CD/CE (1B), AMH/beta-CD/SD (1C), AMH/beta-CD/FD (1D), AMH/methylbeta-CD/PM (2A), AMH/methylbeta-CD/CE (2B), AMH/methylbeta-CD/SD (2C), AMH/methylbeta-CD/FD (2D), AMH/hydroxypropylbeta-CD/PM (3A), AMH/hydroxypropylbeta-CD/CE (3B), AMH/hydroxypropylbeta-CD/SD (3C) and AMH/hydroxypropylbeta-CD/FD (3D).

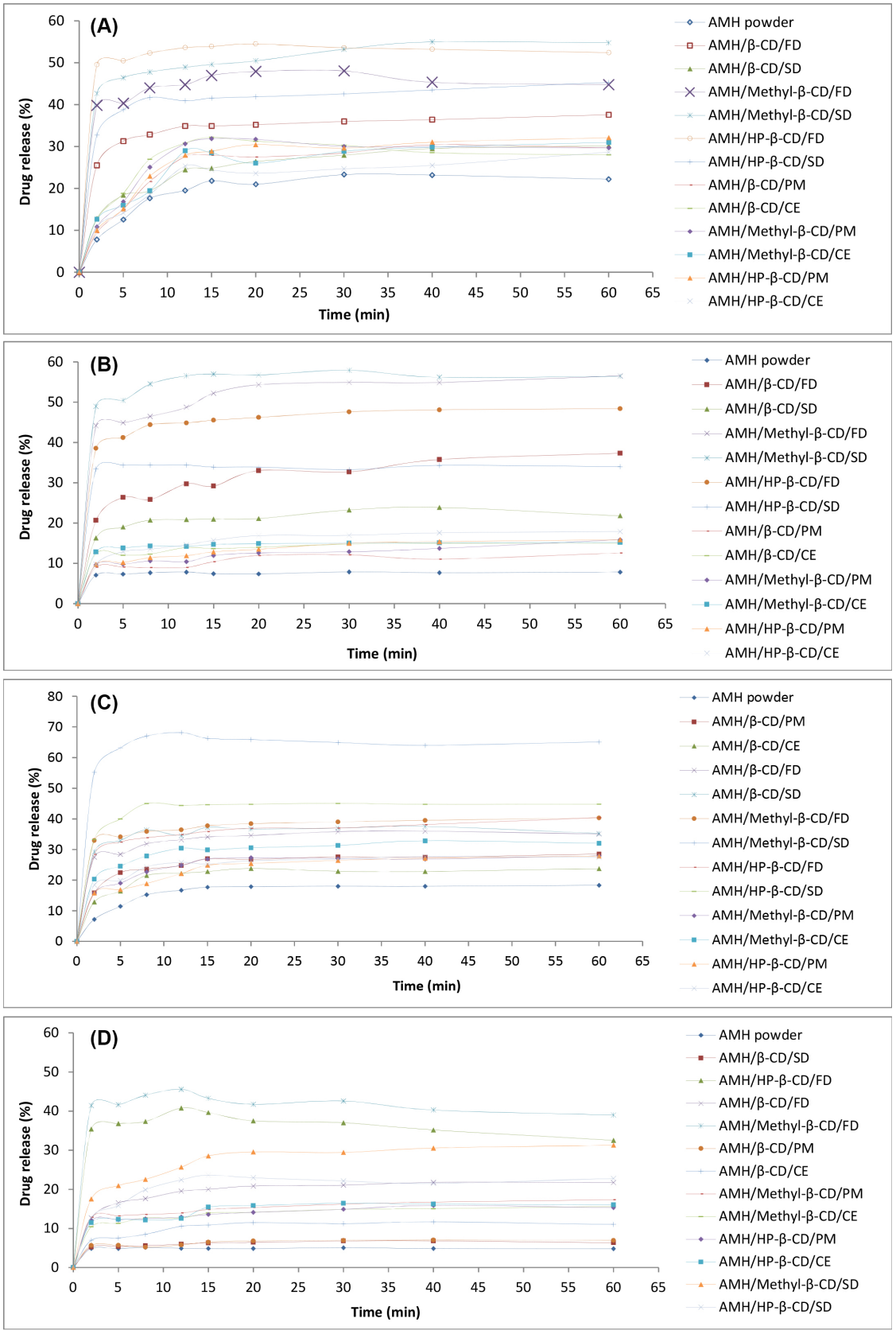

FIGURE 5 - Dissolution curves of AMH powder and different formulations using: (A) water, (B) acid buffer pH 1.2, (C) acetate buffer pH 4.5 and (D) phosphate buffer pH 6.8 as dissolution medium at 37 ºC ± 0.5 ºC.

solubility, higher amorphization, wettability and capacity of complexation in solid state (Fernandes, Vieira, Veiga, 2002).

CONCLUSIONS

In the present work, the complex formed between AMH and CDs presented an enhanced solubility and dissolution rate for all complexes formed other than either physical mixture or pure drug. AMH solubility linearly increases with increasing concentrations of CDs of both temperatures indicating an A_L-type diagram over the entire concentration range evaluated. The ΔG_{tr} values were negative for all formulations indicating a spontaneous process which was thermodynamically favorable to drug solubility. The Kc result suggests good stability for both temperatures evaluated of the inclusion complex formed by AMH-Methyl-β-CD. The characterization of physicochemical results confirmed the formation of complexes with different cyclodextrins. The dissolution profiles of formulations demonstrated the great influence on drug solubility especially when prepared by the spray-drying method with methyl-β-CD for all dissolution mediums evaluated. After studies using different CDs and complexation process, the results obtained demonstrated that the CDs are good excipients to increase molecule solubility.

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