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Article

Amiodarone hydrochloride: enhancement of solubility and dissolution rate by solid dispersion technique

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Amiodarone HCl is an antiarrhythmic agent, which has low aqueous solubility and presents absorption problems. This study aimed to develop inclusion complexes containing hydrophilic carriers PEG 1500, 4000 and 6000 by fusion and kneading methods in order to evaluate the increase in solubility and dissolution rate of amiodarone HCl. The solid dispersion and physical mixtures were characterized by X-ray diffraction, FT-IR spectra, water solubility and dissolution profiles. Both methods and carriers increased the solubility of drug, however PEG 6000 enhanced the drug solubility in solid dispersion better than other carriers. Different media were evaluated for the solubility study, including distilled water, acid buffer pH 1.2, acetate buffer pH 4.5 and phosphate buffer pH 6.8 at 37 ºC. Based on the evaluation of the results obtained in the study phase solubility carriers PEG 4000 and PEG 6000 were selected for the preparation of the physical mixture and solid dispersion. All formulations were prepared at drug-carrier ratios of 1:1 to 1:10(w/w)**.** The results of *in vitro* release studies indicated that the solid dispersion technique by fusion method in proportion of 1:10 (w/w) increased significantly the dissolution rate of the drug. X-ray diffraction studies showed reduced drug crystallinity in the solid dispersions. FT-IR demonstrated interactions between the drug and polymers.

Uniterms: Amiodarone hydrochloride/dissolution profile. Amiodarone hydrochloride/solid dispersion. Hydrophilic polymer.

Cloridrato de amiodarona é um agente antiarrítmico que possui baixa solubilidade aquosa e apresenta problemas de absorção. Este estudo teve como objetivo desenvolver complexos de inclusão contendo carreadores hidrofílicos PEG 1500, 4000 e 6000 através dos métodos de fusão e amassamento para avaliar o aumento da solubilidade e taxa de dissolução do cloridrato de amiodarona. As dispersões sólidas e misturas físicas foram caracterizadas por difração de raios-X, espectroscopia no infravermelho com transformada de Fourier, solubilidade em água e perfis de dissolução. Ambos os métodos e carreadores aumentaram a solubilidade do fármaco, no entanto o PEG 6000 aumentou a solubilidade do fármaco na dispersão sólida mais que os outros carreadores. Diferentes meios foram avaliados para o estudo de solubilidade, incluindo água destilada, tampão ácido pH 1,2, tampão acetato pH 4,5 e tampão fosfato pH 6,8. Com base na avaliação dos resultados obtidos no estudo de solubilidade de fases, os carreadores PEG 4000 e PEG 6000 foram selecionados para a preparação das misturas físicas e dispersões sólidas. Todas as formulações foram preparadas nas razões fármaco-carreador de 1:1 a 1:10 (p/p). Os resultados de liberação *in vitro* que a técnica de dispersão sólida pelo método de fusão na proporção 1:10 (p/p) aumentou significativamente a taxa de dissolução do fármaco. Estudos de difração de raios-X mostraram redução da cristalinidade do fármaco na dispersão sólida. Análise por espectroscopia no infravermelho mostrou interações entre o fármaco e o carreador.

Unitermos: Cloridrato de amiodarona/perfil de dissolução. Cloridrato de amiodarona/dispersão sólida. Polímero hidrofílico.

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INTRODUCTION

Oral administration is the most common route for therapy of many diseases, however poorly soluble drugs have low bioavailability thereby decreasing treatment efficacy. For any active substance, aqueous solubility and intestinal permeability are key determinants that govern dissolution, absorption and oral bioavailability (Leuner, Dressman, 2000; Mutalik *et al.,* 2008; Zisiou *et al.,* 2005).

For certain drugs such as griseofulvin, indomethacin, chloramphenicol, carbamazepine, phenytoin, digoxin aqueous solubility is a challenge to researchers and the pharmaceutical industries (Badry, Fetih, Fathy, 2009; Meshal *et al.,* 1993). Hence, different studies are performed to increase the rate of dissolution of poorly water soluble drugs, to increase their effectiveness and simultaneously reduce their doses hence their toxic effects (Patel *et al.,* 2008).

Generally the techniques of chemistry modification, micronization, micellar solubilization, pH adjustment, use of solid dispersion, and formation of the inclusion compounds such as cyclodextrin and derivatives, are utilized for enhanced solubility of drugs (Alves *et al.*, 2014; Chow *et al.,* 1995; Flego, Lovrecich, Rubessa, 1988; Habib, Attia, 1985; Jablan, Szalontai, Jug, 2012; Vemula, Lagishetty, Lingala, 2010)

The solid dispersion technique was introduced in the early 1970s. Solid dispersion is one of the most successful strategies to improve the release of poorly soluble drug. This can be defined as dispersion of poorly water soluble drugs in hydrophilic carriers (Vasconcelos, Sarmento, Costa, 2007). The basic procedures used to prepare the solid dispersion are the fusion method, solvent evaporation method and hot extrusion method (Chiou, Riegelman, 1971; Modi, Tayade, 2006; Sammour *et al.,* 2006). Drug solubility is improved based on three different mechanisms: the increased wettability of the drug, the reduction of particle size and increased surface area, and the conversion of the crystalline state to the more soluble amorphous state (Lloyd, Craig, Smith, 1999; Taylor, Zografi, 1997; Waard *et al.,* 2008).

AMH, chemically known as (2-butylbenzofuran-3-yl)[4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl] methanone hydrochloride, is a benzofuranic derivate, used for the treatment of both supraventricular and ventricular arrhythmias. AMH is a white or almost white, crystalline powder and is very slightly soluble in water (0.2–0.5 mg/mL), freely soluble in methylene chloride, soluble in methanol, sparingly soluble in ethanol (96 per cent) (British Pharmacopoeia, 2012; Eghrary *et al.,* 2012; Riekes, *et al.,* 2010; Index Merck, 2001; US Pharmacopeia, 2012). AMH is classified as a class II drug based on the Biopharmaceutical Classification System (BCS), due to its low water solubility and high permeability (Riekes, *et al.,* 2010).

Few studies were shown in the literature about the improvement of aqueous solubility and absorption of AMH including Elhasi, Astaneh, Lavasanifar(2007); Jouyban, Eghrary, Zarghami (2013); Martín-Algarra *et al.*(1995); Paduraru *et al.* (2013) and Riekes *et al.* (2010).

The present study aimed to develop inclusion complexes containing hydrophilic carriers in order to evaluate increased AMH solubility and dissolution rate. The physicochemical characteristics and dissolution were assessed using Fourier transform infrared, X-ray powder diffraction and *in vitro* dissolution profiles.

MATERIAL AND METHODS

Material

AMH with purity greater than 99.9% (standard substance) was obtained from Brazilian Pharmacopeia, batch 1040. The raw material AMH batch: 10104117A (purity > 99.0%) was purchased from Pharmanostra® (Brazil). Polyethylene glycol 1500 (PEG 1500), 4000 (PEG 4000) e 6000 (PEG 6000) was purchased from Delaware® (Brazil). Water was prepared by ultra-pure water system (Milli-Q®). Other reagents and solvents used were of analytical grade.

Methods

Determination of AMH content

The AMH was quantified using the previously validated LC-method, employing a Shimadzu® (Kyoto, Japan), equipped with an LC-20AT pump, SIL-20A ht auto sampler, CTO-20AC column oven, SPD-M20A PDA detector, CBM-20A system controller, and LC solution software. The analyses were conducted using reverse phase Phenomenex® Luna C_{18} column (150 x 4.6 mm, 5 µm). The mobile phase was composed of methanol:acetonitrile:buffer phosphate pH 2.2 (68:15:17), with a flow rate of 1.0 mL min^{-1}, at 25.0 ºC and a volume of 10 µL was injected.

Solubility studies

This study was carried out to select a suitable dissolution medium for the *in vitro* drug release. An excess amount of AMH was transferred to an erlenmeyer, containing 10 mL of different solutions (distilled water, acid buffer pH 1.2, acetate buffer pH 4.5 and phosphate

buffer pH 6.8). Flasks were covered to avoid solvent loss and then shaken at 120 rpm in an orbital shaking incubator (Novatecnica®, NT712) for 24 hours at 37 ºC ± 0.5 ºC.

Phase solubility study

The phase solubility study was performed according to the method reported by Higuchi and Connors (1965). An excess amount of AMH was transferred to an Erlenmeyer flask containing 10 mL aqueous solutions with increasing concentrations of each carrier (i.e., 0.01, 0.05, 0.1, 0.3, 0.5, 1.0, and 1.5%) (w/v). Flasks were covered to avoid solvent loss and then shaken at 120 rpm in an orbital shaking incubator (Novatecnica®, NT712) for 24 hours at 25 and 37 ºC. After equilibrium, samples were centrifuged at 4000 rpm for 15 minutes and filtered through a 0.45 µm membrane filter and analyzed for drug content using HPLC method. For determination of spontaneity of the dissolution process, the values of Gibbs free energy (ΔG_{tr}) were calculated for each carrier in different temperatures in accordance with equation 1:

$$\Delta G_{tr} = -2.303RT \log \frac{Sc}{So} \quad (1)$$

where: R is the universal gases constant (8.314472 J K^{-1} mol^{-1}), T is the temperature in Kelvin, Sc is the solubility of the drug at a certain concentration of the carrier and So is the concentration of AMH in water in the absence of carrier, both in µg/mL

Preparation of solid dispersions and physical mixture

For the preparation of the physical mixture and solid dispersions using different methods, initially the drug and carrier were sieved at 355 µm mesh to standardize particle size and for storage in a desiccator.

Physical mixtures (PM)

The PM of drug with carrier was prepared by mixing proportions 1:1 and 1:10 (w/w), respectively in a mortar for 10 min.

Solid dispersion by kneading method (SDKN)

The SDKN of drug with carrier was started from the PM, with subsequent kneading using water in a sufficient quantity to maintain a slightly moist consistency. After 20 min of kneading, the mixture was left at room temperature for 24 hours and the product obtained was powdered in a mortar and passed through a 335 µm mesh.

Solid dispersion by fusion method (SDFM)

The SDFM of drug in carrier was prepared as follows. The drug was added to the molten carrier at 80 ºC with continuous stirring until the formation of a homogeneous dispersion. The dispersion was placed in a freezer at –80 ºC for 24 hours. After this period the product was ground using a mortar and passed through a 355 µm mesh.

Characterization of the solid dispersions

Fourier transform infrared spectroscopy (FT-IR)

The samples were weighed about 5 mg and they were homogenized with 300 mg of potassium bromide using a mortar. The samples were then compressed using a hydraulic press to obtain a translucent tablet. The samples were scanned from (4000 to 450 cm^{-1}) using a Perkin Elmer® spectrometer.

X-ray powder diffraction analysis (XRD)

The diffraction patterns of samples were obtained using an X-ray diffractometer (Rigaku®, Miniflex300), 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 60º in the range of 2θ, in increments of 0.03 º/s.

In vitro dissolution profiles

Studies of dissolution of pure AMH, PMs and SDs with different carriers were performed in triplicate using dissolution test equipment, USP Apparatus 2 at 50 rpm with 900 mL dissolution medium (i.e. water, hydrochloric acid pH 1.2, buffer acetate pH 4.5 and buffer phosphate 6.8) at 37 ºC ± 0.5 ºC. Samples of pure drug, PMs and SDs equivalent to 100 mg of the drug were utilized in evaluation. Dissolution studies were conducted for 90 minutes, and 10 mL were collected at 5, 10, 15, 30, 60 and 90 min intervals 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

Solubility studies

The effect of pH on AMH solubility was observed. This drug presented poorly solubility in pH similar to the intestine, whereas in more acidic pH the values were higher. The results found are shown in Table I.

After evaluation of this study it became clear that in media with a pH equal to or greater than pKa the drug (6.56 ± 0.06) the molecule remains in a unionized form reducing the solubility (Boury *et al.,* 2001; The Index Merck, 2001).

TABLE I - Solubility values of AMH in different dissolution media at 37 ºC ± 0.5 ºC

Dissolution media	% drug solubility[a]
Water distilled pH 5.5	14.20 ± 0.5330
Acid buffer pH 1.2	0.1395 ± 0.018
Acetate buffer pH 4.5	1.154 ± 0.2152
Phosphate buffer pH 6.8	0.0409 ± 0.0167

[a] values are expressed as mean ± SD, *n = 4*.

According to results, an increase of drug solubility in media with pH between 4.5 and 5.5 became clear. For this reason, these media were selected for evaluation of AMH solubility in solid dispersion. The high solubility of the drug in water when compared with the other media may be due to the presence of anions dissolved in buffer solutions, insoluble complexes being formed with molecules of the drug. (Avdeef, 2007; Boury *et al.,* 2001; Ravin, Shami, Rattie, 1975).

Phase solubility study

The phase solubility curves of pure AMH in the presence of PEG 1500, 4000 and 6000 at 25 and 37 ºC are shown in Figure 1. The apparent solubility of AMH increased with increasing temperature and carrier concentrations. Using the highest carrier concentration, the aqueous solubility increased approximately 1.07, 1.31 and 5.72-fold for PEG 1500, 4000 and 6000, respectively at 25 ºC and 1.25, 1.58 and 3.51-fold, respectively at 37 ºC compared to pure drug. The solubility found this study for AMH in water at 25 and 37 ºC was 0.2815 and 0.4808 mg/mL, respectively, very similar to that reported in the

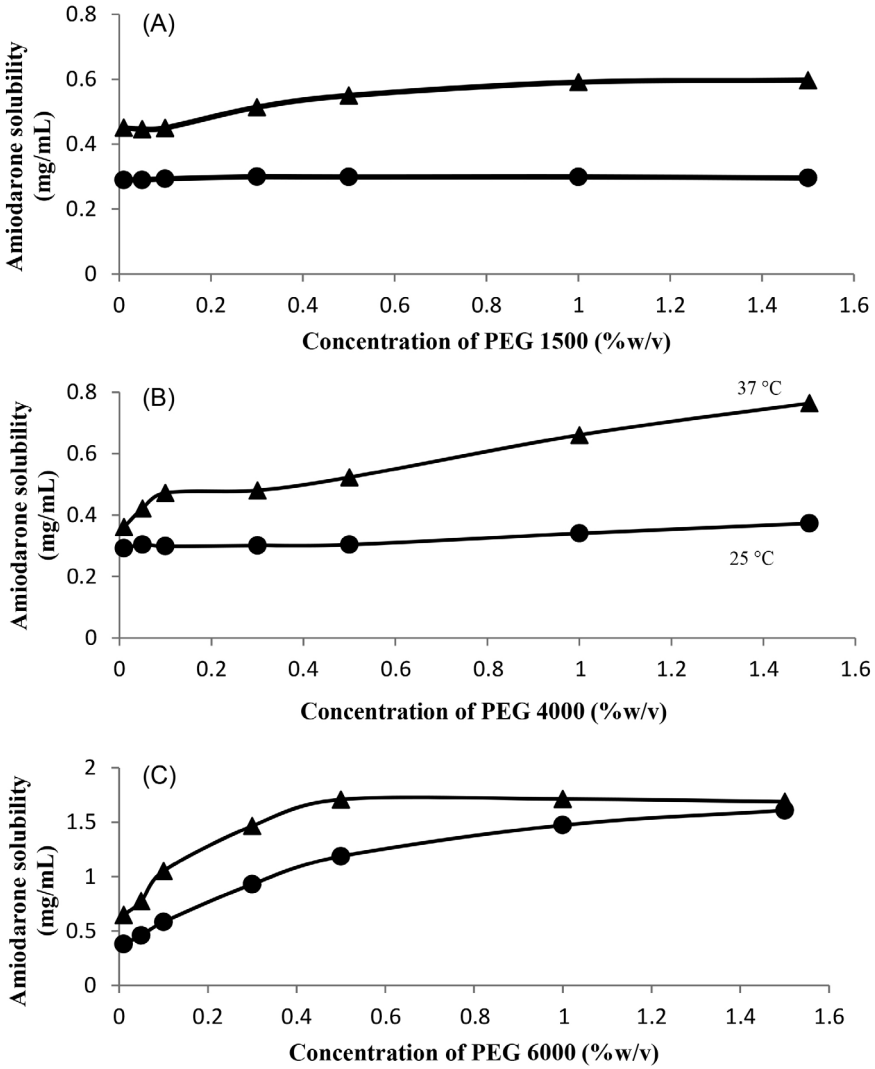

FIGURE 1 - Phase solubility curves of AMH in aqueous solutions of (A) PEG 1500, (B) PEG 4000 and (C) PEG 6000 at 25 and 37 ºC ± 0.5 ºC (n = 3).

literature (Amidon *et al*., 1995; Eghrary *et al.,* 2012).

Table II shows the slopes of the curves. The higher slope value is associated with enhancement of the solubility. The Gibbs free energy (ΔG_{tr}) relating to the spontaneity of the process of drug dissolution in aqueous solutions containing different carriers is shown in Table II. Generally, the increase in solubility is directly associated with values of $\Delta G_{tr} < 0$ being proportional to the increased carrier concentration (Patel *et al.,* 2008).

In accordance with the results, the most negative values of ΔG_{tr} were found for carrier PEG 4000 and PEG 6000 in higher concentrations. After evaluation of the results obtained carriers PEG 4000 and PEG 6000 were selected for the preparation of the PMs and SDs. All formulations were prepared in the drug-carrier proportion of 1:1 and 1:10 (w/w).

Solid state characterization study

FT-IR spectroscopy studies

Spectroscopy analysis was utilized for verification of nature of interactions between AMH and carrier PEG 6000. According to Verheyen *et al.* (2002), hydrogen bonding could be expected from the hydroxyl groups of PEG 6000. In the case of the AMH spectrum, the peaks in the region between 2960 and 2800 cm^{-1} are assigned to aliphatic C-H, the absorption bands characteristic to tert-amine NH^{+} stretching are located in the 2700-2200 cm^{-1} range, at 1558 cm^{-1} and 1529 cm^{-1} related to aromatic C=C ring stretching. The spectrum of pure AMH, PEG 6000 and solid dispersions by fusion method are shown in Figure 2.

The intensity of peaks in 1477 and 1454 cm^{-1} for the aromatic C=C ring semi-circle, at 1284 cm^{-1} specific to the ketonic C=O binding, had a significant reduction in the spectrum of the solid dispersion by fusion method 1:10 (w/w), moreover the bands between 2700-2200 cm^{-1} disappear from spectrum of solid dispersion. The FT-IR spectrum indicates that there is interaction between solid dispersion compounds and that it is likely that the complexation process was performed at the tert-amine of the AMH molecule.

TABLE II - Parameters for phase solubility studies of AMH obtained with different carriers at 25 and 37 ºC ± 0.5 ºC

	Temperatures					
	25 ºC			37 ºC		
Carrier	Slope	Solubility[a]	ΔG^{b}_{tr}	Slope	Solubility[a]	ΔG^{b}_{tr}
PEG 1500	0.0041	0.3 ± 0.006	- 171.27	0.1102	0.6 ± 0.006	- 575.47
PEG 4000	0.051	0.37 ± 0.004	- 691.36	0.2449	0.76 ± 0.004	- 245.56
PEG 6000	0.8308	1.61 ± 0.006	- 4336.58	0.6434	1.69 ± 0.021	-1185.38

[a]Values of solubility in 1.5% (w/v) of carrier concentration, in mg/mL ± SD, *n = 2*; [b]Gibbs energy free in J/mol.

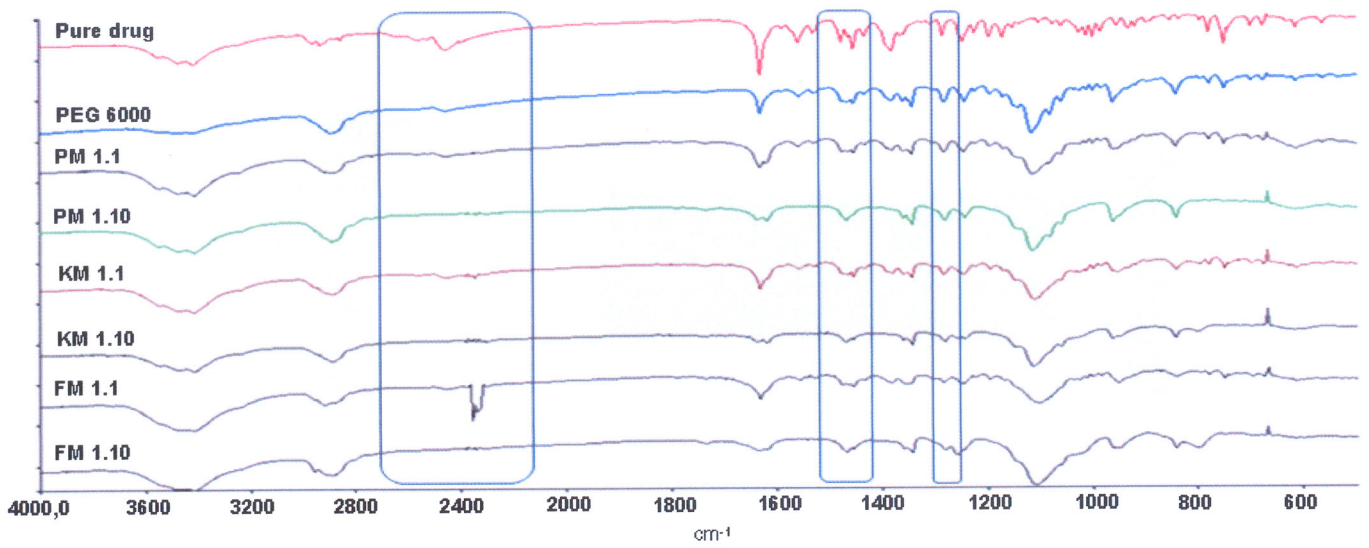

FIGURE 2 - FT-IR of the AMH pure (A), PEG 6000 (B), physical mixture, kneading method and fusion method.

XRD analysis

The solubility, dissolution rate and bioavailability of some drugs can be parameters that depend on the solid-state form of the particles as amorphous, crystalline or polymorphic. The crystal is an organized structure in relation to molecules and atoms; on the other hand, the amorphous form is characterized by a random, generally more soluble state (Markovich *et al*., 1997).

The XRD pattern of pure drug, physical mixture and their solid dispersion using PEG 6000 as carrier are shown in Figure 3. The XRD pattern of pure AMH showed intense peaks of crystallinity and PEG 6000 exhibited distinct patterns with diffraction peaks. This characteristic was also observed in studies by Mandal *et* al. (2010) and Riekes *et al*. (2010), when the interaction between simvastatin and PEG 6000 and AMH and β-cyclodextrin, respectively, was evaluated.

PM and SDKM showed characteristic peaks of both drug and polymer indicating the presence of drug crystallinity in these samples. In solid dispersion by fusion method in a proportion of 1:10 (SDFM 1:10), the intensity of characteristic drug peaks decreased and some peaks were suppressed, thus indicating reduction of drug crystallinity.

In vitro dissolution profiles

For drugs with low gastrointestinal solubility and high permeability, in this case the AMH, oral drug release is a limiting step for bioavailability. According to some authors, by improving drug solubility it is possible to

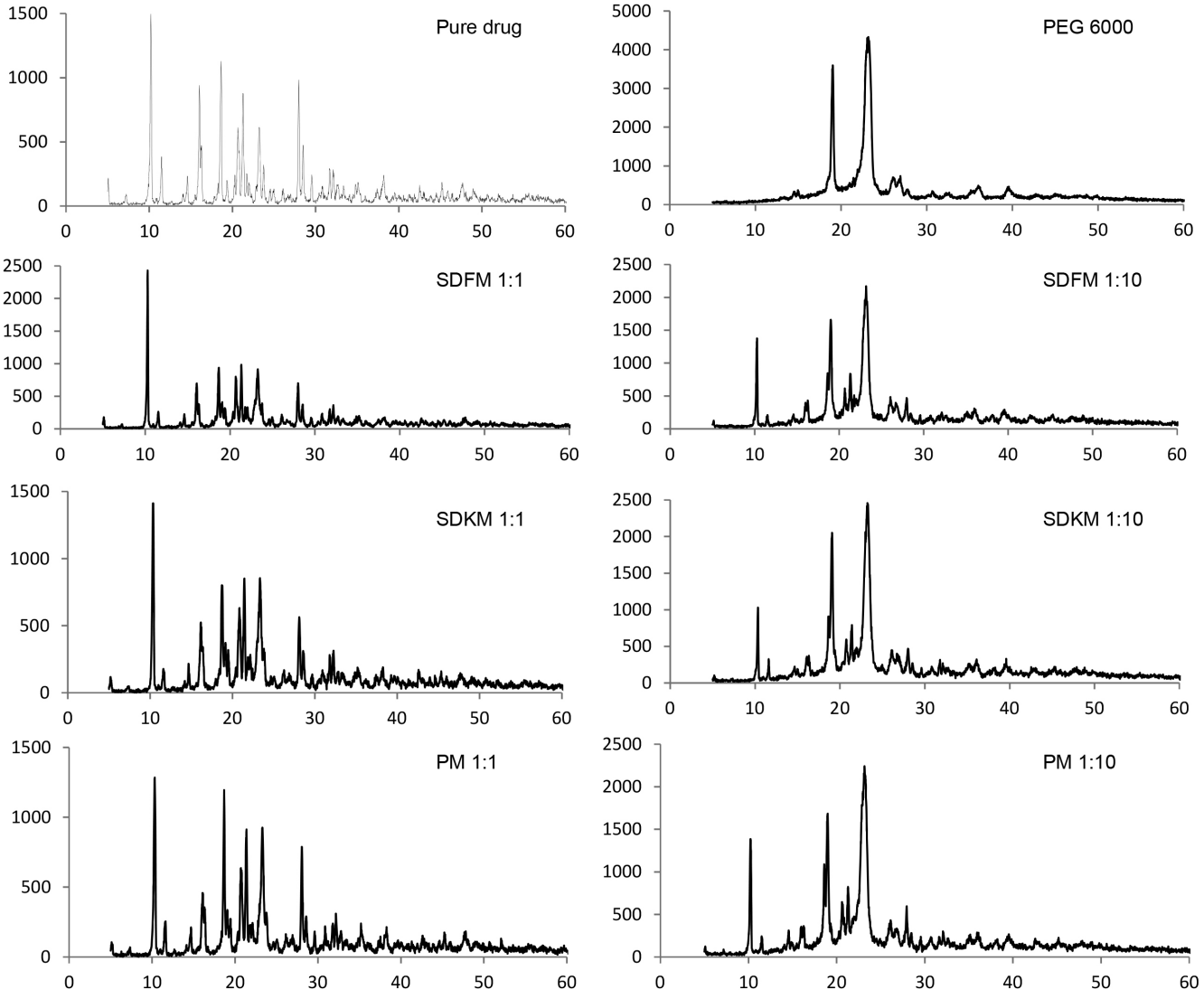

FIGURE 3 - X-ray diffraction patterns of AMH, physical mixture and solid dispersions.

enhance their bioavailability and reduce side effects. This effect of increasing bioavailability is so great that the dose administered could be lowered (Leuner, Dressman, 2000; Streubel, Siepmann, Bodmeier, 2006; Vasconcelos, Sarmento, Costa, 2007). Poorly water-soluble drugs exhibit an insufficient dissolution rate and potential bioavailability problems due to erratic and incomplete absorption from the gastrointestinal tract (Bankar, Mahatma, 2012; Chiou, Riegelman, 1971).

The dissolution profiles of pure drug, physical mixture and solid dispersions in 1:1 and 1:10 ratios (w/w) using PEG 4000 and PEG 6000 in dissolution media such as water and acetate buffer pH 4.5 are shown in Figure 4 and Figure 5, respectively.

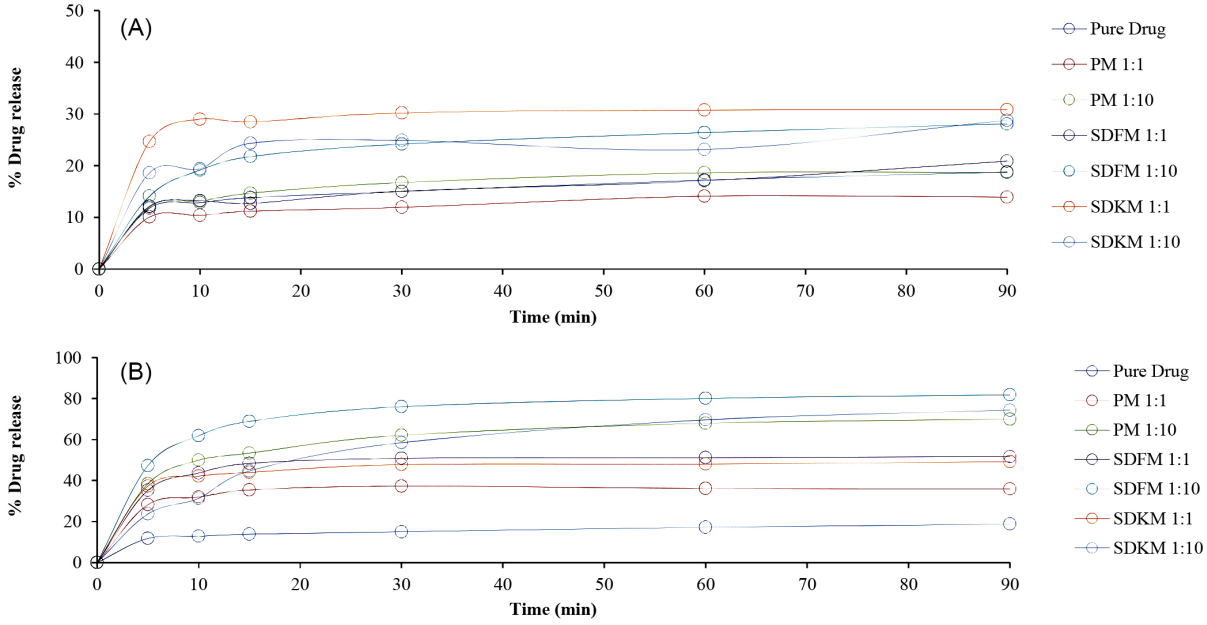

FIGURE 5 - Drug release profiles of pure AMH, physical mixture and solid dispersions obtained from fusion and kneading methods using acetate buffer pH 4.5 as dissolution medium at 37 ºC ± 0.5 ºC and carrier PEG 4000 (A) and carrier PEG 6000 (B).

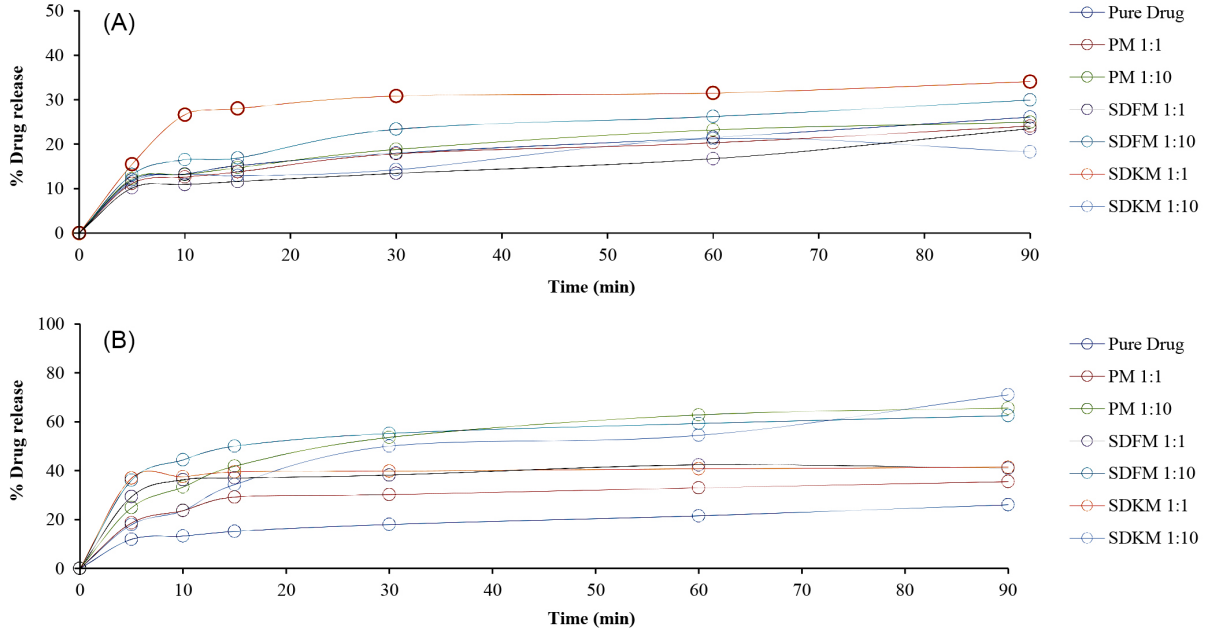

FIGURE 4 - Drug release profiles of pure AMH, physical mixture and solid dispersions obtained from fusion and kneading methods using water as dissolution medium at 37 ºC ± 0.5 ºC and carrier PEG 4000 (A) and carrier PEG 6000 (B).

Using PEG 4000 for preparation of formulations by the kneading method in the drug carrier proportion of 1:1 (w/w), the highest values of dissolution rate of AMH were 0.038 mg/mL and 0.034 mg/mL in water and acetate buffer pH 4.5, respectively. For preparation methods by fusion and physical mixture, the drug dissolution was similar for both media and proportions of drug-carrier evaluated.

On the other hand, using PEG 6000 as carrier, the dissolution rate of AMH was greater and faster for formulation prepared by the fusion method in a 1:10 (w/w) proportion of drug:carrier in both dissolution media. After evaluation of the dissolution rate between the media, the drug solubility was more relevant when acetate buffer pH 4.5 was utilized as a dissolution medium. The product prepared by the fusion method at a proportion of 1:10 (w/w) presented approximately a 4.4 fold increased solubility in acetate buffer 4.5 when compared with pure drug, demonstrating that it is an important tool for increasing the solubility of many molecules in biological fluids. With solid dispersion it became clear that drug solubility was increased compared with pure drug. This is explained by the formation of amorphous particles (as indicated by XRD analysis results), reduction of particle size and consequently larger surface area in contact with medium (Leuner, Dressman, 2000). Solid dispersions are one of the most successful strategies to improve solubility of drugs with low gastrointestinal solubility, where this promotes a greater quantity of drug molecules dissolved and free to be absorbed in the intestinal mucosa as in the case of AMH.

CONCLUSION

In this work, solid dispersions were prepared with AMH and PEG 1500, 4000 and 6000 with different weight rates and methods. In the solubility study, the AMH shows a good result in water and acetate buffer pH 4.5 when compared with other media tested. The apparent solubility of AMH increased with increasing temperature and carrier concentrations and a more negative value of Gibbs free energy was obtained with carrier PEG 6000. FTIR and XDR studies showed evidence of interaction between the drug and PEG 6000 carrier for formulation SDFM 1:10 (w/w). Furthermore, this formulation showed significantly higher drug solubility compared with pure drug after *in vitro* dissolution studies. In conclusion, these results could be an indication that solid dispersion by the fusion method could be useful for the development of pharmaceutical products containing AMH.

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