J Incl Phenom Macrocycl Chem (2012) 73:467–474
DOI 10.1007/s10847-011-0034-3

SHORT COMMUNICATION

Binary and ternary inclusion complexes of dapsone in cyclodextrins and polymers: preparation, characterization and evaluation

Ivanna H. Grebogi · Ana Paula O. V. Tibola · Andersson Barison · Caroline W. P. S. Grandizoli · Humberto G. Ferraz · Letícia N. C. Rodrigues

Received: 27 April 2011 / Accepted: 12 August 2011 / Published online: 9 September 2011

Abstract Dapsone (DAP) is a synthetic sulfone drug with bacteriostatic activity, mainly against *Mycobacterium leprae*. In this study we have investigated the interactions of DAP with cyclodextrins, 2-hydroxypropyl-β-cyclodextrin (HPβCD) and β-cyclodextrin (βCD), in the presence and absence of water-soluble polymers, in order to improve its solubility and bioavailability. Solid systems DAP/HPβCD and DAP/βCD, in the presence or absence of polyvinylpyrrolidone (PVP K30) or hydroxypropyl methylcellulose (HPMC), were prepared. The binary and ternary systems were evaluated and characterized by SEM, DSC, XRD and NMR analysis as well as phase solubility assays, in order to investigate the interactions between DAP and the excipients in aqueous solution. This study revealed that inclusion complexes of DAP and cyclodextrins (HPβCD and βCD) can be produced in order to improve DAP solubility and bioavailability in the presence or absence of polymers (PVP K30 and HPMC). The more stable inclusion complex was obtained with HPβCD, and consequently HPβCD was more efficient in improving DAP solubility than βCD, and the addition of polymers had no influence on DAP solubility or on the stability of the DAP/CDs complexes.

Keywords Dapsone · Cyclodextrin · Inclusion complex · HPβCD · βCD

I. H. Grebogi · A. P. O. V. Tibola · L. N. C. Rodrigues
Departamento de Farmácia, Universidade Federal do Paraná (UFPR), Av. Lothário Meissner, 632, Curitiba, PR CEP 80210-170, Brazil

A. Barison (✉) · C. W. P. S. Grandizoli
Laboratório de Ressonância Magnética Nuclear, Departamento de Química/Centro Politécnico, Universidade Federal do Paraná, C.P. 19081, Curitiba, PR CEP 81530-000, Brazil
e-mail: andernmr@ufpr.br

H. G. Ferraz
Faculdade de Ciências Farmacêuticas, Universidade de São Paulo (USP), Avenida Prof. Lineu Prestes, 580, São Paulo, SP CEP 05508-000, Brazil

L. N. C. Rodrigues
Instituto de Ciências Ambientais, Químicas e Farmacêuticas, Universidade Federal de São Paulo (UNIFESP), Rua Arthur Riedel, 275, Diadema, SP CEP 09972-270, Brazil

Introduction

Dapsone or diaminodiphenylsulfone (DAP, Fig. 1) is a synthetic sulfone that has bacteriostatic activity, mainly against *Mycobacterium leprae*. The mechanism of action is based on the antibacterial inhibition by competitive antagonism with *p*-aminobenzoic acid, or involves inhibition of folic acid synthesis in susceptible organisms [1]. DAP is used in many compulsory-notification diseases such as leprosy and malaria, and to treat pneumonia caused by *Pneumocystis carinii* in patients with AIDS. This drug shows low solubility in water, high solubility in acetone, partially soluble in alcohols, and has a bioavailability of 70–80%. Because of its low solubility and high/low permeability, DAP is classified as a Class II or IV drug according to the Biopharmaceutics classification system (BCS) [2, 3].

Since its low solubility in water decreases the bioavailability of the drug, several approaches have been attempted in order to improve its solubility, such as nanoparticles, microemulsion and solid dispersion preparations, as well as the formation of water-soluble inclusion complexes [4]. Cyclodextrins (CDs) are cyclic torus-shaped oligosaccharides with six (αCD), seven (βCD) and eight (γCD) α-1,4-glucopyranose units. They have a

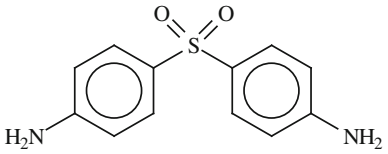

Fig. 1 Chemical structure of dapsone (DAP)

hydrophilic outer surface and a lipophilic central cavity that can accommodate a wide variety of lipophilic drugs [5]. The formation of complexes usually increases the stability, solubility, dissolution rate and bioavailability [6–12]. The efficiency of the formation of inclusion complexes with CDs can be enhanced by the addition of small amounts of polymers to the drug/CD system in order to improve the complexation and solubilization process [12, 13]. In this study, we investigated the interactions of DAP with 2-hydroxypropyl-β-cyclodextrin (HPβCD) and β-cyclodextrin (βCD) in the presence or absence of the synthetic polymer polyvinylpyrrolidone (PVP K30) and the natural polymer hydroxypropyl methylcellulose (HPMC). Nuclear magnetic resonance (NMR), Differential scanning calorimetry (DSC), powder X-ray diffractometry (XRD) and scanning electron microscopy (SEM) analyses were used to characterize the binary and ternary systems and compare them with the physical mixtures prepared in the same molar ratio. In order to evaluate the influence of CDs as well as the polymers on DAP solubility the interactions in aqueous solutions were investigated by phase solubility assays.

Experimental

Materials

Dapsone (diaminodiphenylsulfone) was obtained from Farmos® Distribuidora de Produtos Químicos e Farmacêuticos LTDA, part number 20051104, 99.15% purity. β-Cyclodextrin (Glycosan®) with average molecular weight of 1,135 Da and 2-hydroxypropyl-β-cyclodextrin (Glycosan® HPβCD) with average molecular weight of 1,400 Da and average degree of molar substitution of 0.58–0.73 were purchased from Chemyunion. Polyvinylpyrrolidone (PVP K30) was purchased from Basf, and hydroxypropyl methylcellulose (HPMC) was obtained from Galena. All other chemicals were of analytical grade.

Phase solubility assays

The phase solubility assays were performed according to the Higuchi and Connors method [14]. The binary systems were carried out with an excess amount of DAP ($\sim$1 g) added to aqueous solutions containing increasing concentrations of PVP K30 or HPMC (0.00–0.30%, w/w) or HPβCD or βCD (0–40 mmol L^{-1}). Subsequently, the ternary systems of DAP/HPβCD and DAP/βCD were generated with the addition of 0.25% (w/w) of PVP K30 or 0.15% (w/w) of HPMC. The suspensions were equilibrated at room temperature under mechanical stirring for 72 h. Follow, they were filtered (0.45 μm pore size) and the absorbance was measured on a Shimadzu UV-1601 UV–Vis spectrophotometer at 290 nm. The apparent stability constants (K_c) of the inclusion complexes were determined from the slope of the phase solubility diagrams and the solubility of the drug in water (S_0).

$$K_c = \text{slope}/S_0(1 - \text{slope})$$

Solid systems preparation

Binary and ternary physical mixtures

Equimolar amounts of DAP and HPβCD or βCD were prepared by blending in a mortar until a homogeneous mixture was obtained. For ternary physical mixtures, PVP K30 or HPMC was added to the binary systems to obtain a final concentration of 0.25 and 0.15% (w/w), respectively.

Binary and ternary systems

Equimolar amounts of DAP and HPβCD or βCD were dissolved in methanol and water, respectively. The two solutions were mixed and stirred magnetically for 24 h at room temperature. The resulting suspension was evaporated in an oven at 40 °C for 56 h. The ternary systems were prepared in the same way, but PVP K30 or HPMC was added to the CDs aqueous solution, to reach the same final concentrations as for the physical mixtures.

NMR analysis

The formation of inclusion complexes between DAP and HPβCD or βCD was investigated stepwise by means of NMR spectroscopy analysis. For this, ^{1}H and 1D ROESY NMR experiments were performed at 293 K on a Bruker AVANCE 400 NMR spectrometer operating at 9.4 Tesla, observing ^{1}H at 400.13 MHz, equipped with a 5 mm multinuclear direct detection probe with z-gradient. The DAP, HPβCD and DAP/HPβCD NMR investigations were performed in MeOD-d_4 and the βCD and DAP/βCD spectra were obtained in D_2O. The ^{1}H NMR spectra were acquired with a spectral width of 3,306.88 Hz ($\cong$8.3 ppm) and 64 K data points, providing a digital resolution of 0.05 Hz. The 1D ROESY experiments were obtained with the same conditions as in ^{1}H NMR spectra, although using selective 180° pulse excitation and selective refocusing

with shaped pulse through the gradient *selrogp* pulse sequence, using a mixing time of 200 or 300 ms for ROESY spin-lock, a recycle delay of 1.0 s and 512 transients. The ^{1}H and 1D ROESY NMR spectra were processed by applying Fourier transform with zero-filling to 128 K data points and by an exponential multiplication of the FIDs by a factor of 0.3 and 1 Hz for ^{1}H and 1D ROESY NMR, respectively. All ^{1}H NMR chemical shifts are given in ppm related to the TMS or TMSP-d_4 signal at 0.00 ppm as internal references, and all pulse programs were supplied by Bruker BioSpin.

DSC analysis

Samples of DAP, CDs, polymers, DAP/CDs and DAP/CDs/polymers physical mixtures, and inclusion complexes in powdered form were examined by DSC on a TA Instruments DSC-910, using aluminum crucibles with approximately 2 mg of sample in a dynamic nitrogen atmosphere (100 mL min^{-1}) and a heating rate of 10 °C min^{-1} in the temperature range of 40–300 °C. The DSC cell was calibrated with indium (mp 156.4 °C; $\Delta H_{fus} = 28.5$ J g^{-1}) and zinc (mp 419.6 °C).

XRD analysis

X-ray powder diffraction patterns of the samples described above were collected on a Shimadzu XRD-6000 powder diffractometer at room temperature. The diffractograms were recorded in the 2θ angle range, using a scan step size of 2° min^{-1}, operating with 40 kV and 40 mA using polycrystalline silicon (Si) as standard.

SEM analysis

Samples of DAP, CDs, polymers, DAP/CDs and DAP/CDs/polymers physical mixtures, and inclusion complexes in powdered form were examined by conventional scanning electron microscopy on a JEOL JSM-6360 LV microscope. For this, the samples were fixed on a metallic support using double-face tape and copper-coated under vacuum, to make them electrically conductive. The observation was performed in increments from 300 to 1,000 times with an excitation voltage of 10 kV A15.

Results and discussion

Phase solubility assays

The phase solubility assays were performed with the binary systems DAP/HPβCD and DAP/βCD as well as with the ternary systems DAP/HPβCD/PVP, DAP/βCD/PVP, DAP/HPβCD/HPMC and DAP/βCD/HPMC. All phase solubility diagrams were Higuchi & Connors A_L type, showing linear increases in drug solubility as a function of the CDs concentrations, indicating the formation of a first-order complex with HPβCD and βCD (Fig. 2). As the slopes of all phase solubility diagrams were lower than 1 (Table 1), a 1:1 stoichiometry can be assumed [4]. Many authors have demonstrated that polymers can improve the complexation efficiency with different drugs by increasing their solubility [15–17]. They can interact with the outer surface of CDs torus as well as with the drug/CD systems, forming co-complexes or aggregates that can show higher stability constants (K_c). The DAP intrinsic solubility was 0.0233 mM (Table 2). In the study of the effect of polymers PVP or HPMC on the solubility of DAP, the highest solubility of DAP was observed when 0.15% of HPMC (0.1060 mM) was used, and this value was used to obtain the ternary system containing HPMC, however, the

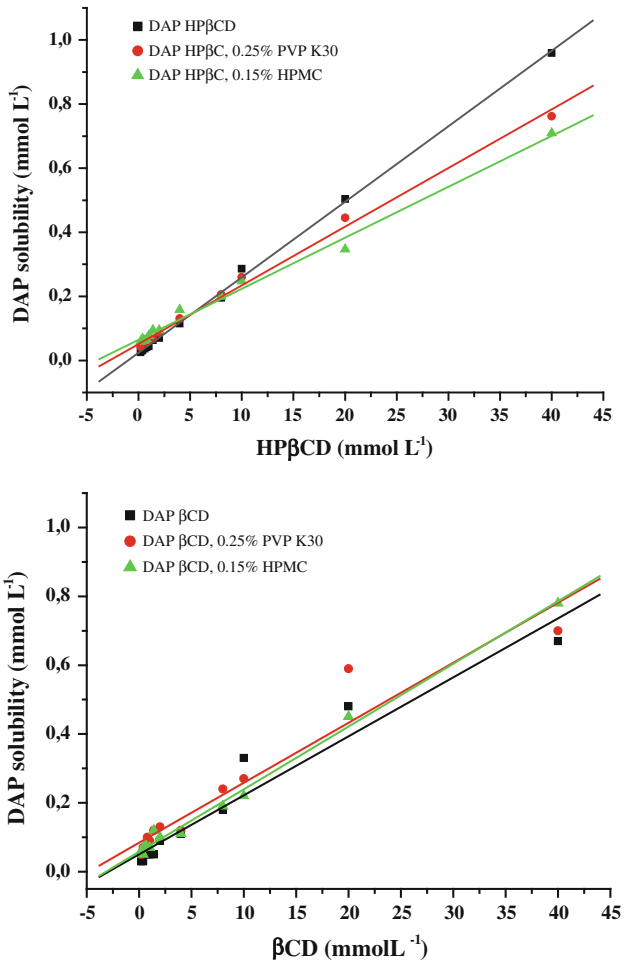

Fig. 2 Phase solubility diagrams for the binary systems DAP/HPβCD and DAP/βCD in the presence or absence of polymers (PVP K30 or HPMC).The *lines* represent the best-fit linear regression of data points

Table 1 Dapsone intrinsic solubility (S_0), slope and correlation coefficient (R) from phase solubility diagrams

System	S_0 (mmol L^{-1})	Slope	R
DAP/PVP K30	0.0170		
DAP/HPMC	0.1060		
DAP	0.0233		
DAP/HPβCD	0.9751	0.0235	0.9993
DAP/HPβCD/PVP K30	0.3574	0.0183	0.9953
DAP/HPβCD/HPMC	0.2469	0.0159	0.9915
DAP/βCD	0.3546	0.0171	0.9444
DAP/βCD/PVP K30	0.2094	0.0174	0.9310
DAP/βCD/HPMC	0.3137	0.0181	0.9935

Table 2 Solubility values and solubility increment for the DAP from the binary and ternary systems obtained by coevaporation using βCD or HPβCD

System	Solubility		Increment solubility
	mg mL^{-1}	mM	
DAP	5.77	0.0233	
DAP/HPβCD	242.12	0.9751	×42
DAP/HPβCD/PVP K30	88.75	0.3574	×15
DAP/HPβCD/HPMC	61.30	0.2469	×11
DAP/βCD	88.06	0.3546	×15
DAP/βCD/PVP K30	51.99	0.2094	×9
DAP/βCD/HPMC	77.89	0.3137	×13

solubility of DAP remained unchanged throughout the concentration range of PVP evaluated (0.05–0.30%) and the amount of 0.25% PVP was selected for the preparation of the ternary system containing PVP K30. For the systems with HPβCD, DAP solubility increased 42-fold in the binary complex and 15- and 11-fold in the ternary systems with PVP K30 and HPMC, respectively, while the systems with βCD, DAP solubility increased 15-fold in the binary system and 9- and 13-fold in the ternary systems with PVP K30 and HPMC, respectively (Table 2). A reduction in the solubility of DAP was observed by the addition of polymers (HPMC or PVP K30), compared the solubility obtained for the binary system (Table 2). Several authors have shown an increase in solubility of drugs by means of addition to complexation of a small amount of water-soluble polymers, followed by heating in an autoclave. In this case, the heating and consequent reduction of medium viscosity was not performed, and thus, the high viscosity of medium complexation resulted in a reduction in mobility of hindering the formation of DAP/CDs systems due to the presence of polymers.

According to Rama et al. [18], only complexes with K_c between 100 and 1,000 mol L^{-1} have biological applications, because complexes with K_c lower than 100 mol L^{-1} constitute unstable drug/CD systems, whereas complexes with a K_c higher than 1,000 mol L^{-1} could adversely affect the absorption of the drug. The K_c values found in all the systems investigated (Table 3) indicate the formation of inclusion complexes with a suitable stability. Loftsson et al. [4] proposed another method to evaluate the solubilizing effects of CDs, which consists of determining the complexation efficiency (CE) by either the slope of the phase solubility profile or the complex to free cyclodextrin concentration ratio:

$$CE = S_0 K_{1:1} = [D/CD]/[CD] = Slope/1 - Slope$$

where [D/CD] is the concentration of dissolved complex, [CD] the concentration of dissolved free cyclodextrin and Slope is the slope of the phase solubility diagrams.

From the value of CE is possible to determine the molar ratio (MR) drug/CD complexation obtained by the relationship:

$$MR = 1 : (1 + 1/CE)$$

Since the numerical value of CE is only dependent of the slope of the phase solubility profile less variation is usually observed in the CE values compared to the $K_{1:1}$ values. If CE is 0.1 then 1 out of every 11 cyclodextrin molecules forms a complex with the drug and if CE is 0.01 then only 1 out of every 100 cyclodextrin molecules forms a complex. Based on this approach, the DAP/CD ratio was determined (Table 3). The addition of PVP K30 or HPMC did not greatly affect the K_c or CE values or the molar ratio for the both systems. Higher values for K_c and CE as well as lower molar ratio were observed for the binary system DAP/HPBCD (Table 3).

Table 3 Stability constant (K_c), complexation efficiency (CE) and molar ratio (MR) for binary and ternary systems

System	K_c (mol L^{-1})	CE	MR (DAP/CD)
DAP/HPβCD	1,035	0.0241	1:43
DAP/HPβCD/PVP K30	802	0.0186	1:55
DAP/HPβCD/HPMC	695	0.0162	1:63
DAP/βCD	753	0.0174	1:58
DAP/βCD/PVP K30	761	0.0177	1:58
DAP/βCD/HPMC	793	0.0185	1:55

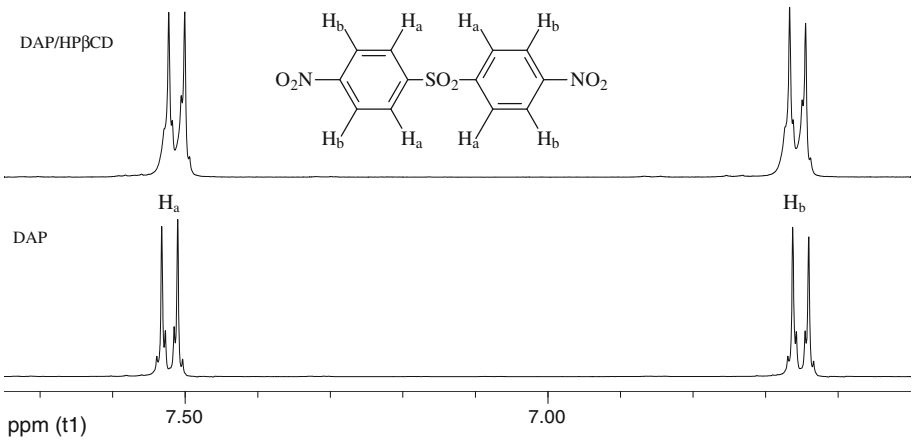

Fig. 3 ^{1}H NMR spectra for DAP (*bottom*) and DAP/HPβCD inclusion complex (*top*), showing the changes in the chemical shifts

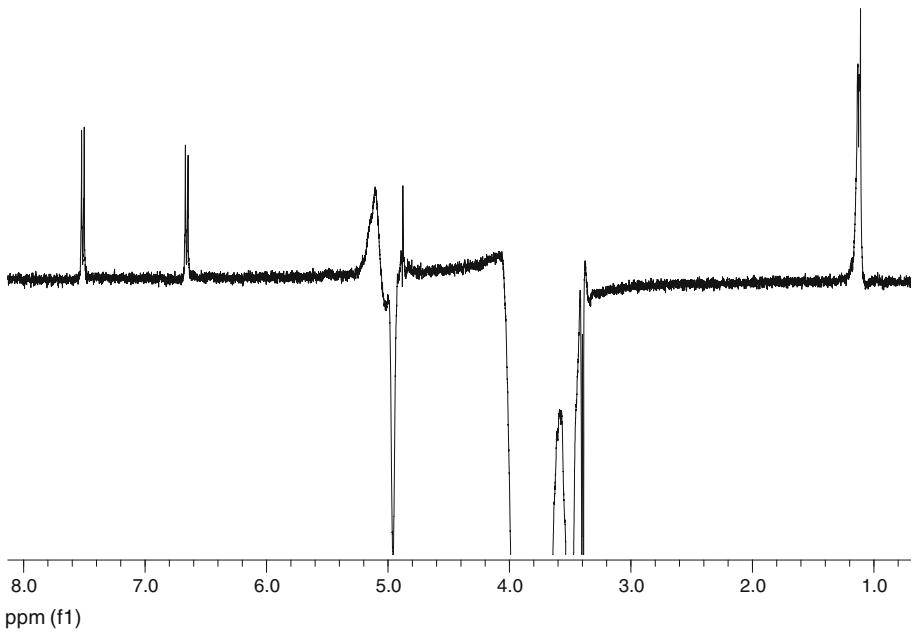

Fig. 4 1D ROESY NMR spectrum for the DAP/HPβCD inclusion complex obtained by selective irradiation of the signal at 3.88 ppm corresponding to the H-3 and H-5 hydrogens of HPβCD, showing nOe enhancements of DAP hydrogen signals

NMR analysis

The formation of DAP/CDs complexes was first evidenced by comparing DAP, and DAP/HPβCD and DAP/βCD ^{1}H NMR spectra, recorded under the same experimental conditions, which revealed a significant interaction between DAP and both CDs. Variations as well as broadening of the ^{1}H NMR signals from aromatic hydrogens of DAP [doublets at 6.65 (8.9 Hz, H_a) and 7.52 ppm (8.9 Hz, H_b)] were observed (Figs. 3 and 5). This specific interaction was supported by one-dimensional rotating frame nuclear Overhauser effect (1D ROESY) NMR experiments, which are usually suitable to measure nOe in complexes. The 1D ROESY NMR experiment obtained by selective excitation

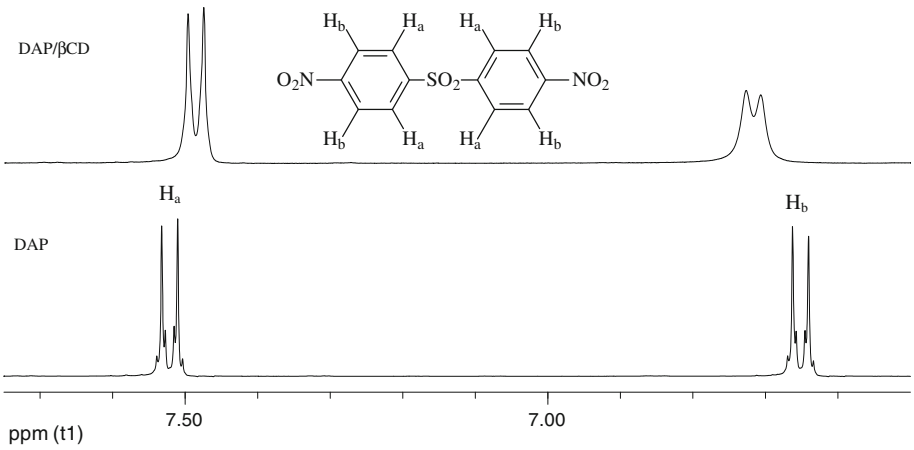

Fig. 5 ^{1}H NMR spectra for DAP (*bottom*) and DAP/*β*CD inclusion complex (*top*), showing the changes in the chemical shifts

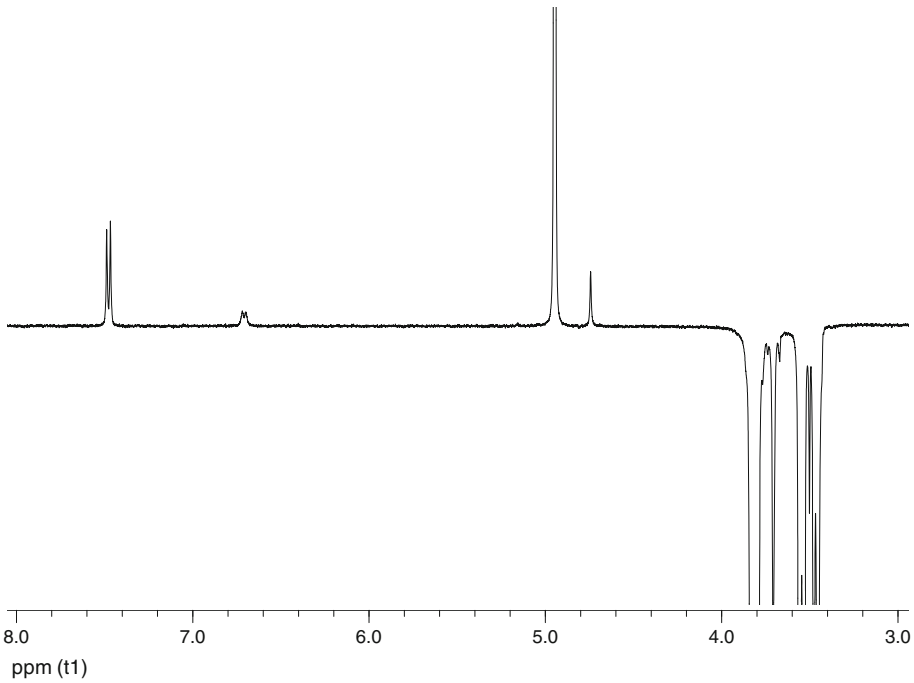

Fig. 6 1D ROESY spectrum for DAP/*β*CD inclusion complex obtained by selective irradiation of the signal at 3.84 ppm corresponding to the H-3 hydrogens of *β*CD, showing nOe enhancements of the DAP hydrogen signals

of the hydrogens H-3 and H-5 at 3.88 ppm in HP*β*CD and hydrogen H-3 at 3.84 ppm in *β*CD has caused nOe enhancement in the aromatic hydrogen signals of DAP (Figs. 4 and 6). The higher nOe intensification observed for the signal of the hydrogens H_a (doublet at 7.52 ppm, Fig. 6) in the DAP/*β*CD system is due to the selective excitation of only H-3 in the *β*CD structure.

The intensification of DAP signals in the 1D ROESY NMR spectra, after selective excitation of the resonance frequency of H-3 and/or H-5 CDs hydrogens, as well as the variations and broadening on the ^{1}H NMR chemical shifts of DAP, revealed that DAP/CDs inclusion complexes were formed, with DAP structure inserted in the cavity of HP*β*CD or *β*CD (Fig. 7). This means that the drug hydrogens (termed H_a and H_b) are interacting with the CDs hydrogens H-3 and/or H-5 (Fig. 7).

The NMR results indicate that the drug DAP is fully enclosed within the HP*β*CD and *β*CD cavities, as represented in Fig. 7. The intensity of signals in the ROESY 1D NMR spectra of the DAP/HP*β*CD system was higher than in the DAP/*β*CD system, indicating that the inclusion complex formed with HP*β*CD was more effective or stable than those formed with *β*CD. These observations are in accordance with the K_c and CE values from the phase solubility assays.

DSC analysis

In a previous study we demonstrated that DSC can be used to characterize drug/CDs inclusion complexes [12]. Therefore, DSC was used to characterize the DAP/HP*β*CD and DAP/*β*CD complexes in the solid state, and to obtain further supporting evidence of complex formation. The

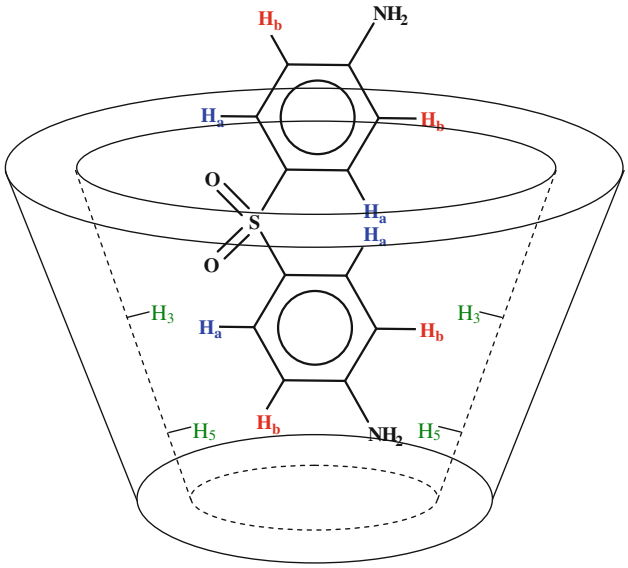

Fig. 7 Representation of DAP/CD inclusion complex, showing DAP structure inserted in the CD cavity

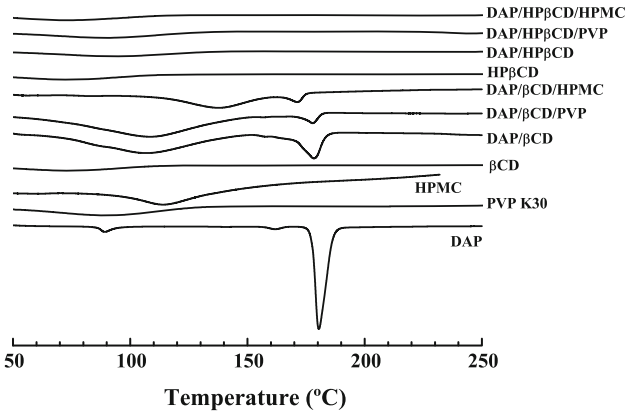

Fig. 8 DSC curves of DAP, CDs (βCD and HPβCD), polymers (PVP K30 and HPMC), and inclusion complexes (DAP/βCD, DAP/βCD/PVP, DAP/βCD/HPMC, DAP/HPβCD, DAP/HPβCD/PVP and DAP/HPβCD/HPMC) obtained in dynamic nitrogen atmosphere (100 mL min^{-1}) and a heating rate of 10 °C min^{-1}

thermal curve of DAP was typical of a crystalline anhydrous substance (Fig. 8), with a sharp endothermic event at 180.4 °C corresponding to DAP melting point, and an endothermic event at 83–84 °C corresponding to the polymorphic forms of DAP. For HPβCD as well as for βCD broader endothermal events associated with starch gelatinization were observed (Fig. 8). For DAP/HPβCD physical mixtures, the characteristic thermal profile of DAP was still present at around 180 °C. On the other hand, in binary and ternary systems containing HPβCD, the endothermic event associated with DAP melting was totally absent, indicating the formation of amorphous entities or inclusion complexes (Fig. 8). When HPβCD was replaced

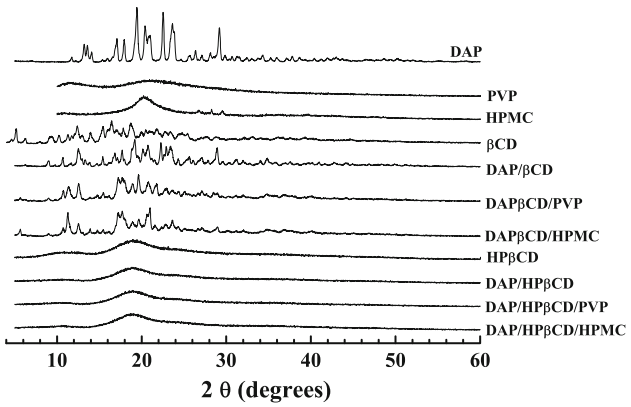

Fig. 9 Powder XRD patterns of DAP, CDs (βCD and HPβCD), polymers (PVP and HPMC), and inclusion complexes (DAP/βCD, DAP/βCD/PVP, DAP/βCD/HPMC, DAP/HPβCD, DAP/HPβCD/PVP and DAP/HPβCD/HPMC)

by βCD in the binary and ternary systems in both the physical mixtures and complexes, the characteristic thermal profile of DAP was still present, indicating the presence of free DAP without interaction with βCD (Fig. 8) and therefore in accordance with the NMR analysis and phase solubility assays.

XRD analysis

Powder XRD was also used to characterize the DAP/HPβCD and DAP/βCD complexes in the solid state, because it is a useful method for detecting complexation in powder or microcrystalline states. If a true inclusion complex is formed, the diffraction pattern of the complex should be clearly distinct from those of the pure forms. The XRD pattern of DAP revealed high-intensity reflections corresponding to the diffraction peaks at 19.5°, 20.7°, 22.5°, 23.8° and 29.2° (2θ), which indicated its crystalline character (Fig. 9). On the other hand, a hollow pattern was recorded for HPβCD, PVP K30 and HPMC, indicating their amorphous state (Fig. 9). For DAP/HPβCD, some diffraction peaks assigned to DAP crystals were still detectable in the physical mixtures, whereas they were totally absent in the respective binary and ternary systems, indicating the formation of complexes (Fig. 9). For the DAP/βCD physical mixtures, as well as in the binary and ternary systems, some DAP crystal diffraction peaks were still detectable (Fig. 9), which is in full accordance with the DSC and NMR analyses as well as the phase solubility assays, indicating the presence of free DAP without interaction with βCD.

SEM analysis

Scanning electron microscopy photomicrograph shows that the drug (DAP) is composed of irregular orthorhombic

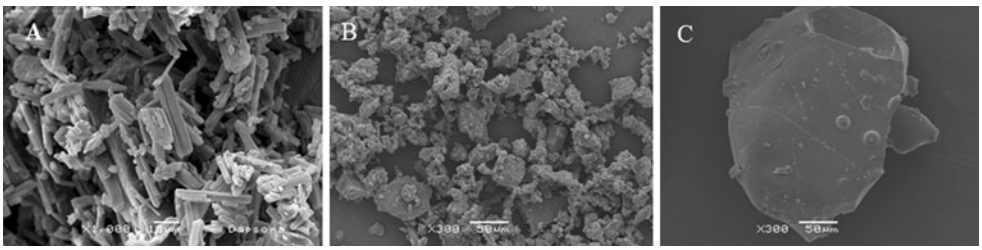

Fig. 10 Scanning electron microscopy (SEM) of DAP (**a**) and the binary systems [DAP/βCD (**b**) and DAP/HPβCD (**c**)]

crystals (Fig. 10a), while HPβCD is composed by regular spherical particles. On the other hand, SEM analysis shown that βCD is consisted of irregular crystals, and the photomicrograph of DAP/βCD system was not conclusive due to the characteristic crystalline structure of βCD (Fig. 10b). However, for the binary system DAP/HPβCD, the photomicrograph demonstrate the formation of well-defined spherical particles, suggesting an interaction between the drug and HPβCD (Fig. 10c).

Conclusions

All our investigations revealed that inclusion complexes of dapsone (DAP) and cyclodextrins (HPβCD and βCD) can be produced in order to improve DAP solubility and bioavailability in the presence or absence of polymers (PVP K30 and HPMC). However, the addition of polymers had no influence on DAP solubility or on the stability of the DAP/CDs complexes. The more efficient or stable inclusion complex was obtained with HPβCD, and consequently HPβCD was more efficient in improving DAP solubility than was βCD.

References

1. Grunwald, M.H., Amichai, B.: Dapsone—the treatment of infectious and inflammatory diseases in dermatology. Int. J. Antimicr. Agents **7**, 187–192 (1996)
2. Lindenberg, M., Kopp, S.E., Dressman, J.B.: Classification of orally administered drugs on the World Health Organization Model list of essential medicines according to the biopharmaceutics classification system. Eur. J. Pharm. Biopharm. **58**, 265–278 (2004)
3. Cao, X., Gibbs, S., Fang, L., Miller, H., Landowski, C.P., Shin, H., Lennernas, H., Zhong, Y., Amidon, G.L., Yu, L.X., Sun, D.: Why is it challenging to predict intestinal drug absorption and oral bioavailability in human using rat model. Pharm. Res. **23**, 1675–1686 (2006)
4. Loftsson, T., Hreinsdóttir, D., Másson, M.: Evaluation of cyclodextrin solubilization of drugs. Int. J. Pharm. **302**, 18–28 (2005)
5. Veiga, F., Teixeira-Dias, J.J.C., Kedzierewicz, F., Sousa, A., Maincent, P.: Inclusion complexation of tolbutamide with β-cyclodextrin and hydroxypropyl-β-cyclodextrin. Int. J. Pharm. **129**, 63–71 (1996)
6. Andersen, F.M., Bundgaard, H.: Inclusion complexation of metronidazole benzoate with β-cyclodextrin and its depression of anhydrate-hydrate transition in aqueous suspensions. Int. J. Pharm. **19**, 189–197 (1984)
7. Loftsson, T., Hreinsdóttir, D., Másson, M.J.: The complexation efficiency. Incl. Phen. Macr. Chem. **57**, 545–552 (2007)
8. Brewster, M.E., Loftsson, T.: Cyclodextrins as pharmaceutical solubilizers. Adv. Drug Deliv. Rev. **59**, 645–666 (2007)
9. Blanco, J., Vila-Jato, J.L., Otero, F., Anguiano, S.: Influence of method of preparation on inclusion complexes of naproxen with different cyclodextrins. Drug Dev. Ind. Pharm. **17**(7), 943–957 (1991)
10. Loftsson, T.J.: Cyclodextrins and the biopharmaceutics classification system of drugs. Incl. Phen. Macr. Chem. **44**, 63–67 (2002)
11. Lobenberg, R., Amidon, G.L.: Modern bioavailability, bioequivalence and biopharmaceutics classification system. New scientific approaches to international regulatory standards. Eur. J. Pharm. Biopharm. **50**, 3–12 (2000)
12. Asbahr, A.C.C., Veiga, F., Franco, L., Barison, A., Silva, C.W.P., Ferraz, H.G., Rodrigues, L.N.: Binary and ternary inclusion complexes of finasteride in HPβCD and polymers: preparation and characterization. Bioorg. Med. Chem. **17**, 2718–2723 (2009)
13. Loftsson, T., Fridriksdóttir, H., Sigurdardóttir, A.M., Ueda, H.: The effect of water-soluble polymers on drug-cyclodextrin complexation. Int. J. Pharm. **110**, 169–177 (1994)
14. Higuchi, T., Connors, K.A.: Phase-Solubility Techniques. In: Nurnberg, H.W. (ed.) Advances in analytical chemistry instrumentation, vol. 4, pp. 117–212. Wiley, New York (1965)
15. Bettinetti, G.P., Mura, P.: Dissolution properties of naproxen in combinations with polyvinylpirrolidone. Drug Dev. Ind. Pharm. **20**, 1353–1366 (1994)
16. Loftsson, T., Fridriksdóttir, H., Gumundsdóttir, T.K.: The effect of water-soluble polymers on aqueous solubility of drugs. Int. J. Pharm. **127**, 293–296 (1996)
17. Loftsson, T., Másson, M., Sigurjonsdóttir, J.F.: Methods to enhance the complexation efficiency of cyclodextrins. Pharma. Sci. **9**(3), 237–242 (1999)
18. Rama, A.C.R., Veiga, F., Figueiredo, I.V., Souza, A., Caramona, M.: Aspectos biofarmacêuticos da formulação de medicamentos para neonatos. Fundamentos da complexação de indometacina com hidroxipropil-β-ciclodextrina para tratamento oral do fechamento do canal arterial. Braz. J. Pharm. **41**, 281–299 (2005)