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ORIGINAL ARTICLE

Physicochemical characterization of finasteride:PEG 6000 and finasteride:Kollidon K25 solid dispersions, and finasteride: β-cyclodextrin inclusion complexes

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Abstract Finasteride is a practically insoluble in water drug that belongs to the Class II of the BCS (poor solubility and high permeability). Solid dispersions are solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. Solid dispersions are a successful strategy to improve drug release of poorly water-soluble drugs such as finasteride. Natural cyclodextrins are doughnut-shaped molecules with an internal hydrophobic cavity and a hydrophilic external surface. The lipophilic cavity enables cyclodextrins to form non-covalent inclusion complexes with a wide variety of poorly water-soluble drugs such as finasteride. The aim of this study was to investigate the formation of finasteride:PEG 6000 and finasteride:Kollidon K25 solid dispersions and finasteride:β-cyclodextrin inclusion complexes by solvent evaporation method using a mixture of water:ethanol (1:1). The formation of finasteride:PEG 6000 and finasteride:Kollidon K25 solid dispersions and finasteride:β-cyclodextrin inclusion complexes was investigated and characterized by differential scanning calorimetry (DSC), infrared (IR) spectroscopy, and dissolution studies from capsules containing a quantity equivalent to 5 mg of finasteride. The DSC thermograms revealed the transformation of finasteride into the amorphous state in solid dispersions with PEG 6000 and Kollidon K25, and in inclusion complexes with β-cyclodextrin. The IR spectra demonstrated molecular interaction in solid dispersions of finasteride with PEG 6000, and in inclusion complexes with β-cyclodextrin. Dissolution rate of solid dispersions and inclusion complexes was significantly greater than that of corresponding physical mixtures and pure drug, indicating that the formation of solid dispersions and inclusion complexes increased the solubility of the poorly soluble drug, finasteride.

Keywords Finasteride · PEG 6000 · Kollidon K25 · β-Cyclodextrin · Solid dispersion · Inclusion complex · Dissolution studies

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Introduction

Most of the new chemical entities are low water-soluble drugs and poorly absorbed after oral administration [1]. One of pharmaceutical industry major challenges is the development of strategies that improve the water solubility of drugs, and consequently their bioavailability [2]. Finasteride is practically insoluble in water and belongs to the Class II drugs of the BCS (poor solubility and high permeability) [3].

Solid dispersions [4] and β-cyclodextrins [5] strategies have been widely and successfully applied to improve the solubility, dissolution rates, and consequently, the bioavailability of poorly-water soluble drugs. Solid dispersions are solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug [6, 7]. The matrix can be either crystalline or amorphous. The drug can be molecularly dispersed, in amorphous particles (clusters) or in crystalline particles. They are characterized by the reduction of drug particle size, by solubilising or co-dissolving the drug in the water-soluble carrier, by providing better wettability and dispersibility and by forming amorphous products. Solid

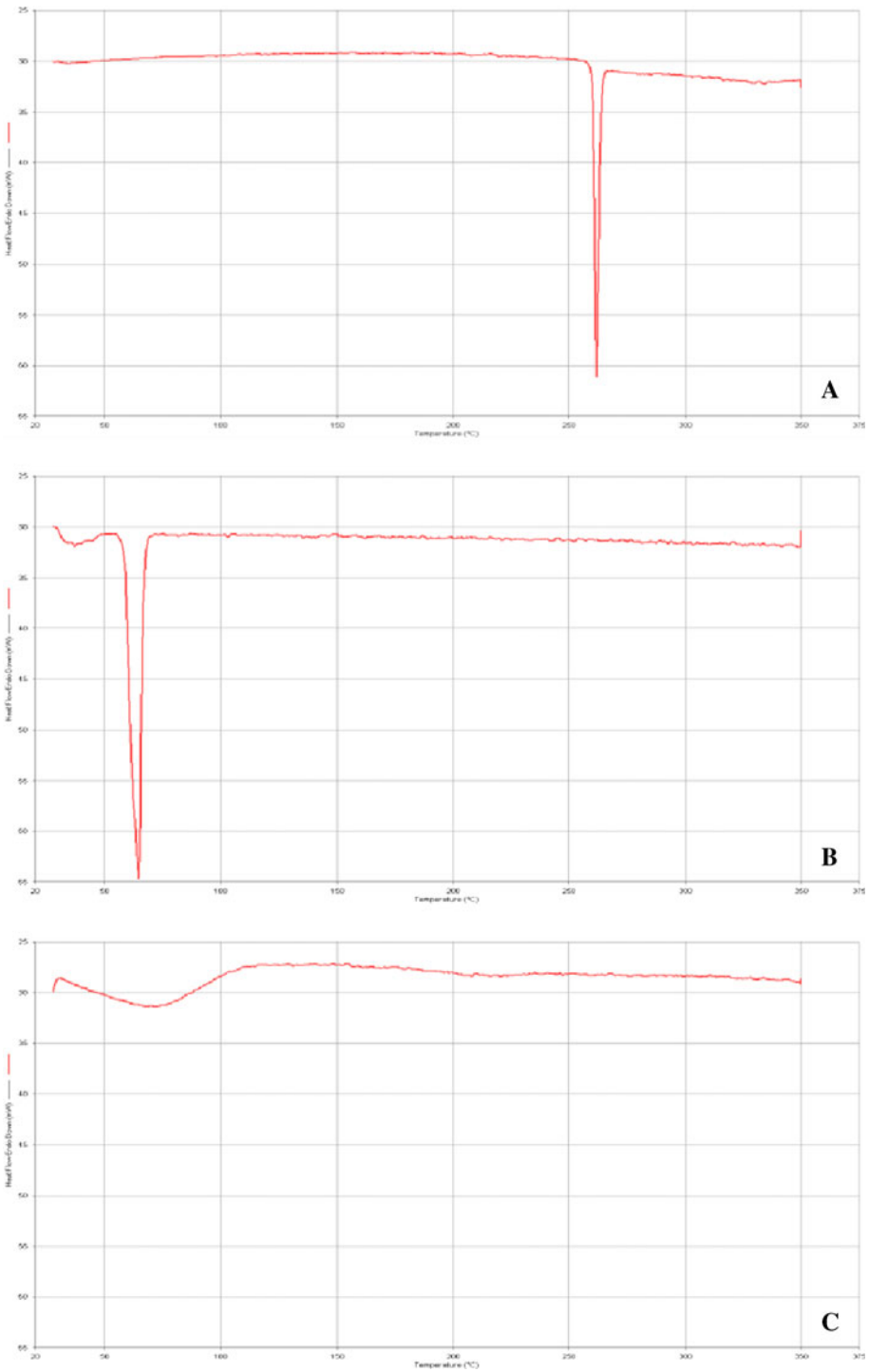

Fig. 1 DSC thermograms of **a** finasteride, **b** PEG 6000 and **c** Kollidon K25. Heat flow endothermic down (mV) vs. temperature (°C)

dispersions can be prepared by melting method or solvent evaporation method [8, 9].

β-Cyclodextrins are cyclic oligosaccharides, formed of 7 glucopyranose units, linked by α-1,4-glycosidic bounds [10]. They are doughnut-shaped molecules with an internal hydrophobic cavity and a hydrophilic external surface [11, 12]. The lipophilic cavity enables β-cyclodextrins to form non-covalent inclusion complexes with a wide variety of poorly water-soluble drugs such as finasteride. Such molecular encapsulation has been shown to improve a variety of drug properties, such as chemical stability, solubility, dissolution rate, bioavailability and clinical activity.

The aim of this study was to investigate the formation of finasteride:PEG 6000 and finasteride:Kollidon K25 solid dispersions and finasteride:β-cyclodextrin inclusion complexes by solvent evaporation method using a mixture of

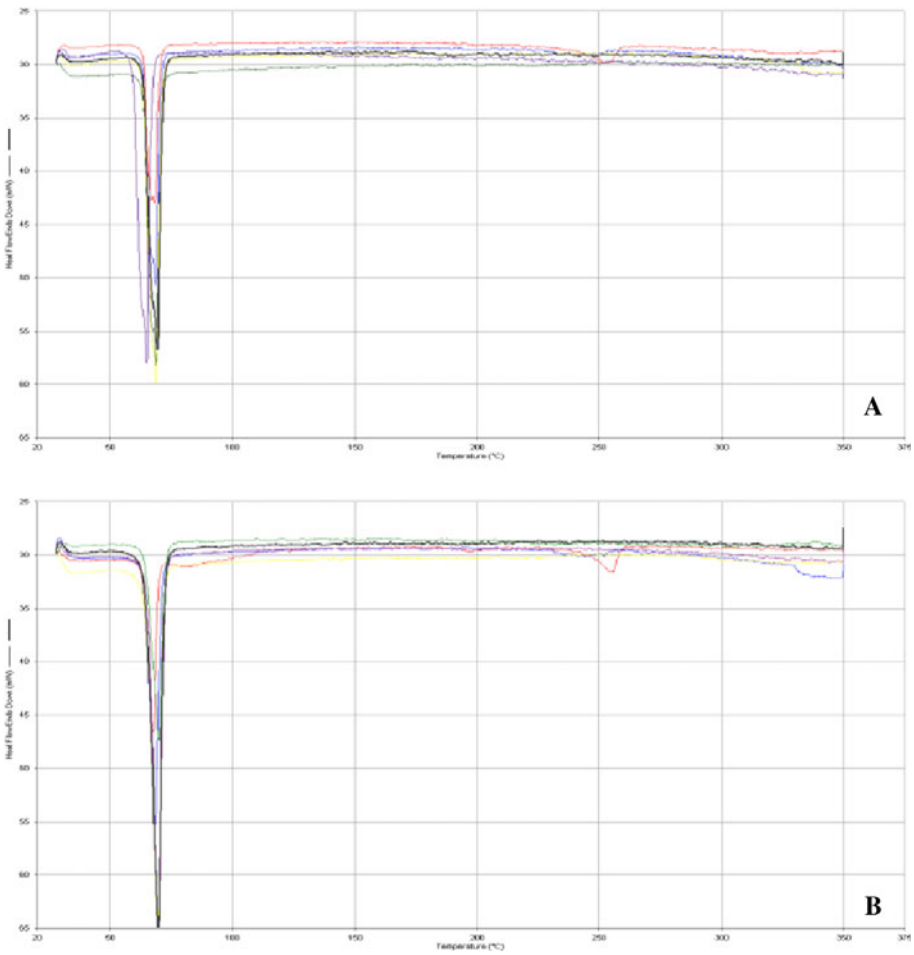

Fig. 2 DSC thermograms of **a** finasteride:PEG 6000 physical mixtures and **b** finasteride:PEG 6000 solid dispersions. Drug:carrier mass ratios of *red line* (1:1), *blue line* (1:2), *green line* (1:4), *yellow line* (1:6), *violet line* (1:8), *black line* (1:10). Heat flow endothermic down (mV) vs. temperature (°C). (Color figure online)

water:ethanol (1:1). These binary systems formation was investigated and characterized by differential scanning calorimetry (DSC), infrared (IR) spectroscopy, and dissolution studies from capsules containing a quantity equivalent to 5 mg of finasteride.

Materials

Finasteride was obtained from Dr. Reddy's. PEG 6000 was purchased from Clariant. Kollidon K25 was supplied by BASF. β-cyclodextrin was obtained from Sigma Chemie GMBH. Capsules no. 4 were obtained from Capsulgel. All other reagents were of analytical reagent grade.

Methods

Physical mixtures

The physical mixtures were prepared by mixing finasteride and the carriers (PEG 6000, Kollidon K25) at drug:carrier mass ratios of 1:1, 1:2, 1:4, 1:6, 1:8 and 1:10 using a glass mortar and pestle. The physical mixtures of the drug with β-cyclodextrin at mass ratios of 1:1 and 1:2 were prepared by the same method.

Solid dispersions

Solid dispersions containing finasteride and carriers (PEG 6000, Kollidon K25) in the mass proportions of 1:1, 1:2, 1:4, 1:6, 1:8 and 1:10, were prepared by solvent evaporation method. In this method both finasteride and each carrier were dissolved in 1,000 mL of water/ethanol (1:1), by stirring at 70 rpm during 1 h. The solvent was removed by vacuum in a rotary evaporator at about 70 °C. All the samples were dried in an oven at 40 °C for 8 h.

Inclusion complexes

Finasteride:β-cyclodextrin inclusion complexes were prepared at the mass proportions of 1:1, 1:2, 1:4 and 1:6, by the same method used for solid dispersions preparation.

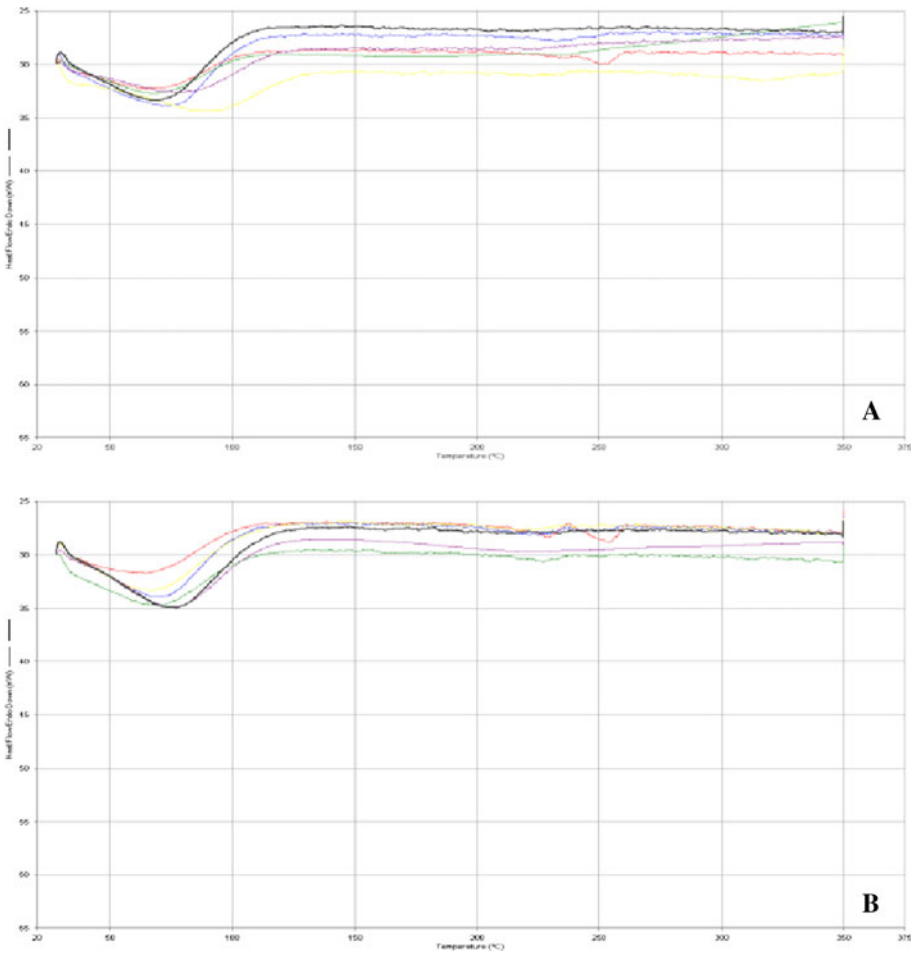

Fig. 3 DSC thermograms of **a** finasteride:Kollidon K25 physical mixtures and **b** finasteride:Kollidon K25 solid dispersions. Drug:carrier mass ratios of *red line* (1:1), *blue line* (1:2), *green line* (1:4), *yellow line* (1:6), *violet line* (1:8), *black line* (1:10). Heat flow endothermic down (mV) vs. temperature (°C). (Color figure online)

DSC

The DSC thermograms were investigated on a Perkin-Elmer 6 DSC calorimeter, using 4 mg samples in closed aluminium pans at a heating rate of 10 °C/min from 30 to 300 °C, under a nitrogen gas flow of 20 mL/min.

IR Spectroscopy

IR spectra were performed on a Nicolet 380 Fourier transform infrared (FTIR) spectrophotometer, by the KBr disk method from 4000 to 400 cm^{-1}.

Dissolution studies

Finasteride, physical mixtures, solid dispersions and inclusion complexes were sieved through 250 μm, and the quantity equivalent to 5 mg of finasteride, was manually filled into hard gelatin capsules. Dissolution studies of the capsules were conducted using USP dissolution apparatus I, in 900 ml of H_2O, at 37 ± 0.5 °C at a speed of 75 rpm. 10 mL of samples were withdrawn at pre- established time intervals of 5, 10, 15, 30, 45 and 60 min. The concentration of finasteride in each sample was determined by HPLC method, with UV/VIS detector at 220 nm, using a mixture of acetonitrile:water (58:42) as mobile phase.

Results and discussion

DSC

The DSC finasteride thermogram shows one characteristic sharp endothermic peak at around 262 °C, indicating the melting point of the drug (Fig. 1a). The DSC PEG 6000 thermogram shows one endothermic peak at around 64.6 °C indicating its melting point (Fig. 1b). But the Kollidon K25 thermogram didnot presents any endothermic peak revealing its amorphous structure (Fig. 1c).

The absence of the characteristic endothermic peak of finasteride on the physical mixtures with PEG 6000 and Kollidon K25 was due to the solubilisation of the drug in both carriers (Figs. 2a, 3a). The thermograms of solid dispersions with PEG 6000 show one endothermic peak

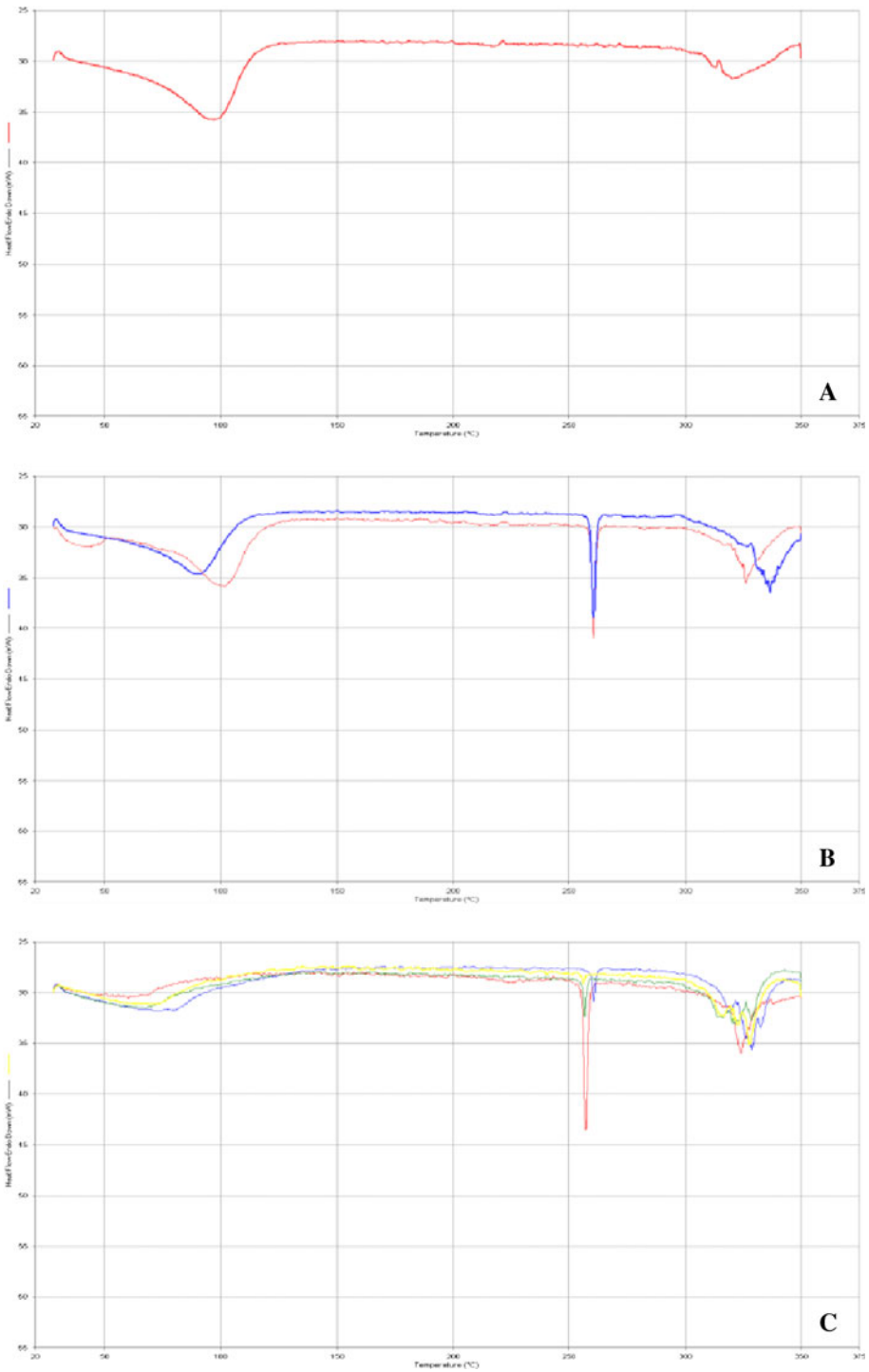

Fig. 4 DSC thermograms of **a** β-cyclodextrin, **b** finasteride:β-cyclodextrin physical mixtures and **c** finasteride:β-cyclodextrin inclusion complexes. Drug:carrier mass ratios of *red line* (1:1), *blue line* (1:2), *green line* (1:4), *yellow line* (1:6), *violet line* (1:8), *black line* (1:10). Heat flow endothermic down (mV) vs. temperature (°C). (Color figure online)

corresponding to the melting of the solid dispersion formed (Fig. 2b). The disappearance of finasteride melting endothermic was attributed to the conversion of finasteride to an amorphous state in crystalline PEG 6000. The solid dispersions with Kollidon K25 didn′t show any endothermic peak on their thermograms, suggesting the formation of one truly amorphous structure between drug and carrier (Fig. 3b) [13–16].

The DSC thermogram of β-cyclodextrin shows a large endothermic peak between 30 and 126.5 °C, due to the release of water from the molecule (Fig. 4a). The endothermic peak of finasteride was present in the thermograms of physical mixtures (Fig. 4b). However, in inclusion complexes this peak became smaller with the increase of β-cyclodextrin proportion, due to the inclusion complexation with β-cyclodextrin, suggesting that the drug is

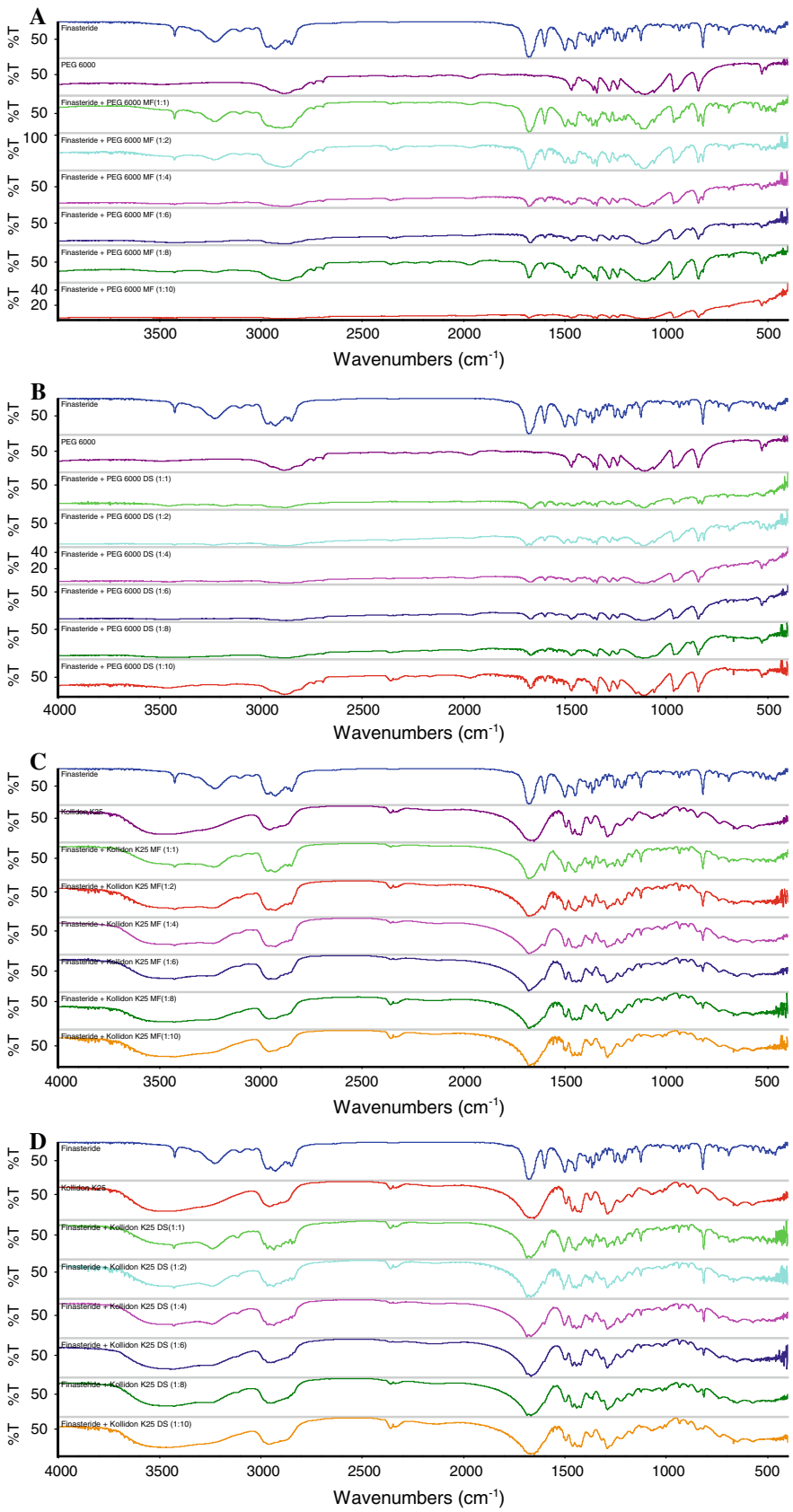

Fig. 5 IR spectra of **a** finasteride:PEG 6000 physical mixtures, **b** finasteride:PEG 6000 solid dispersions, **c** finasteride:Kollidon K25 physical mixtures and **d** finasteride:Kollidon K25 solid dispersions

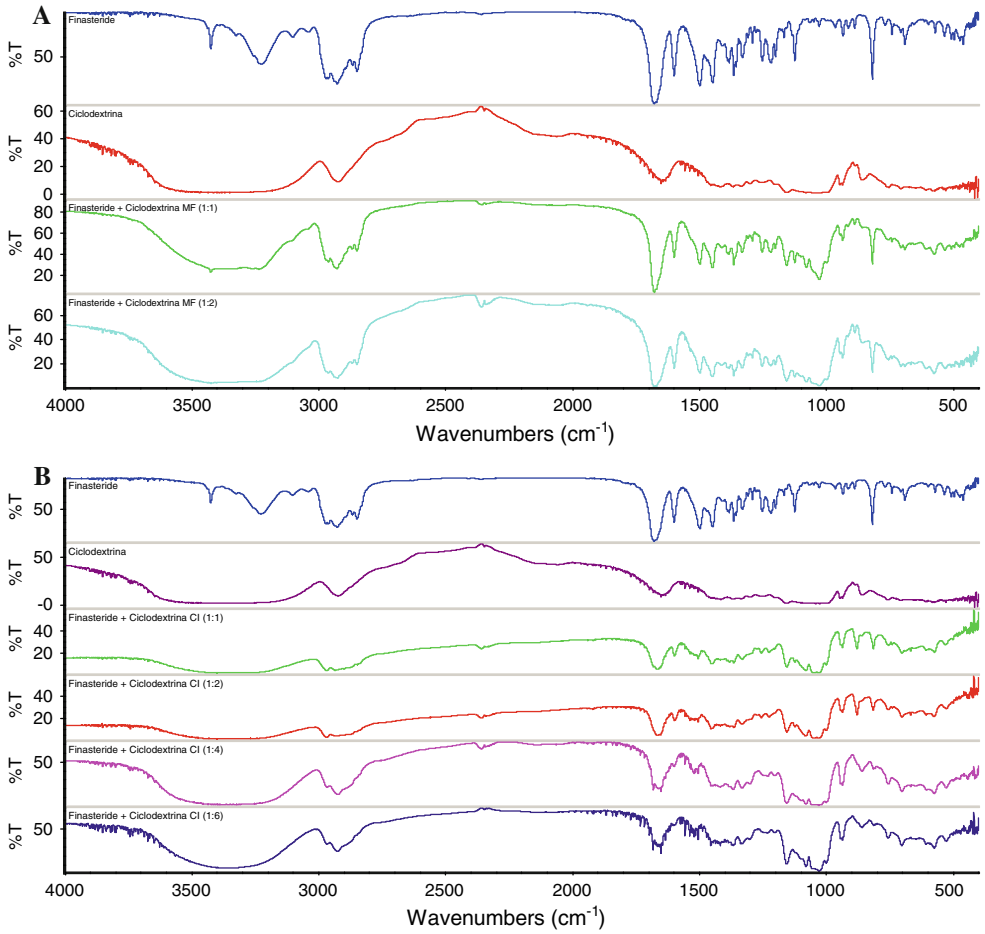

Fig. 6 IR spectra of **a** finasteride:β-cyclodextrin physical mixtures and **b** finasteride:β-cyclodextrin inclusion complexes

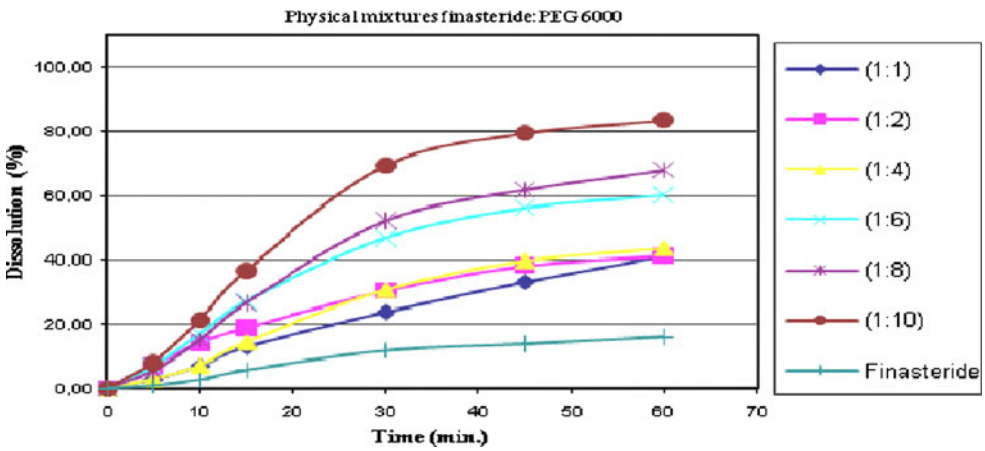

Fig. 7 Dissolution profiles of finasteride and physical mixtures finasteride:PEG 6000 capsules

monomolecularly dispersed into the β-cyclodextrin cavity (Fig. 4c) [13–16].

IR Spectroscopy

Pure finasteride showed IR absorption at 1680 cm^{-1} for the (amide) C=O stretching band, and at 3229 and 3426 cm^{-1} for the (amide) N–H stretching band. PEG 6000 showed a characteristic broad peak of O–H stretching vibration from 3300 to 3600 cm^{-1}, and C–H stretching of OC_2H_5 groups from 2800 to 2900 cm^{-1}. Kollidon K25 showed a characteristic peak at 1653 cm^{-1} due to the C=O stretching.

In the physical mixtures with PEG 6000 and Kollidon K25, the spectra are the superposition of those of the pure products with attenuation of the finasteride peaks, showing no significant differences from the respective spectra of the pure components (Fig. 5a, c). In the solid dispersions with PEG 6000 the absorption intensities of some finasteride

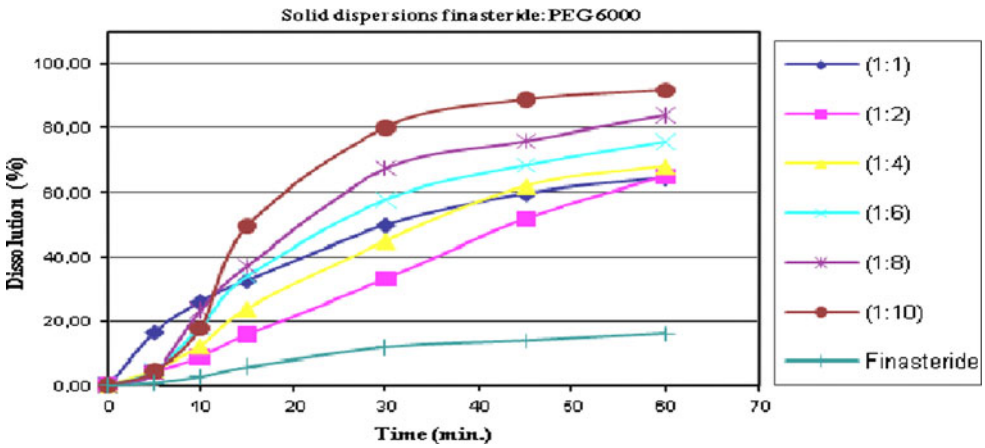

Fig. 8 Dissolution profiles of finasteride and solid dispersions finasteride:PEG 6000 capsules

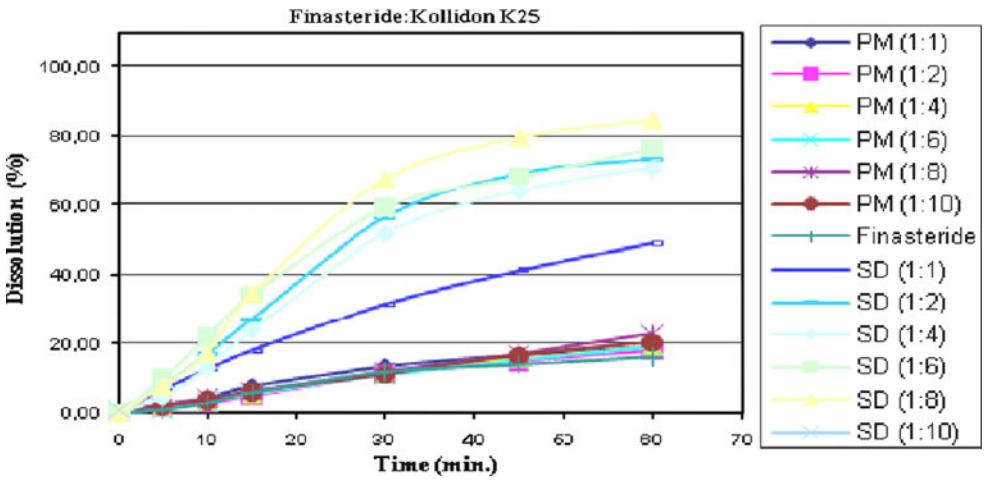

Fig. 9 Dissolution profiles of finasteride, physical mixtures (PM) and solid dispersions (SD) finasteride:Kollidon K25 capsules

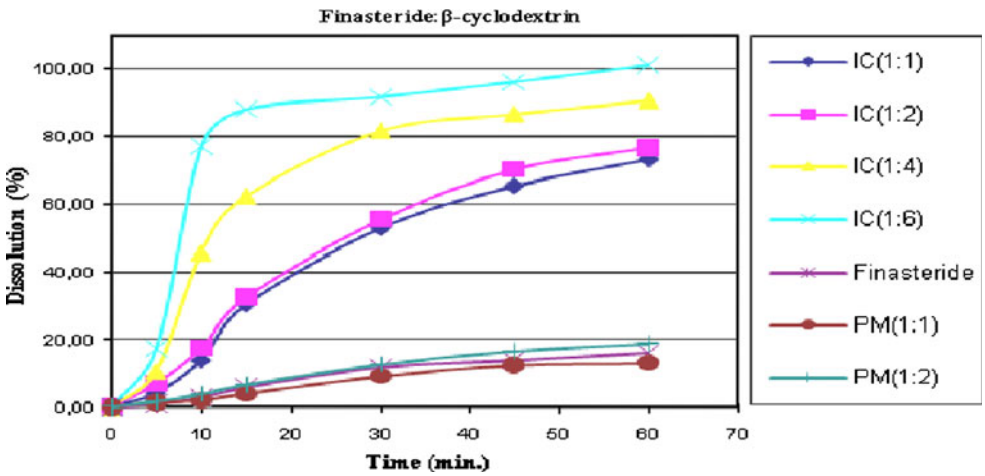

Fig. 10 Dissolution profiles of finasteride, physical mixtures (PM) and inclusion complexes (IC) finasteride:β-cyclodextrin capsules

bands were markedly reduced at the higher proportions of PEG (Fig. 5b). The (amide) C=O stretching band of finasteride slightly shifted to a lower frequency (1669 cm^{-1}), suggesting intermolecular interaction between finasteride and PEG molecules. In the solid dispersions with Kollidon K25, the spectra are the superposition of those of the pure products with attenuation of the finasteride peaks (Fig. 5d) [17–19].

The spectrum of pure β-cyclodextrin showed the very intense O–H stretching band at 3000–3600 cm^{-1}. In the

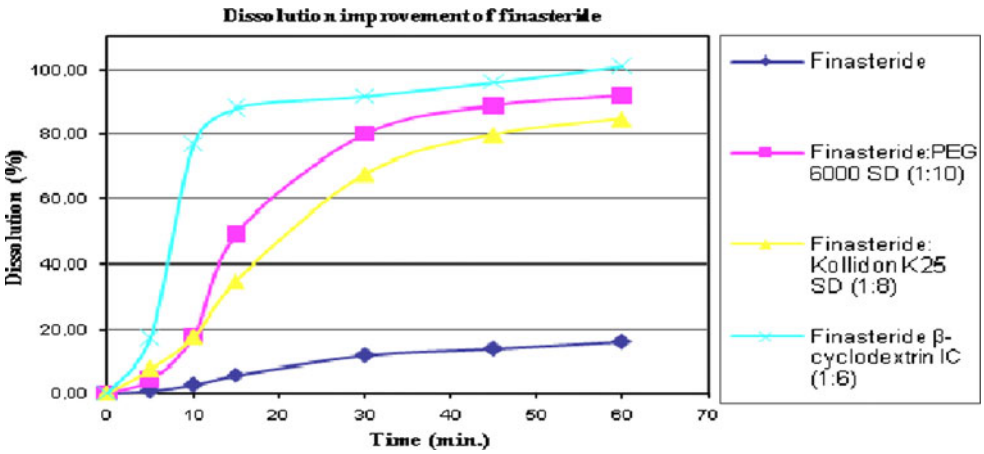

Fig. 11 Dissolution profiles of finasteride, finasteride:PEG 6000 solid dispersion (1:10), finasteride: Kollidon K25 solid dispersion (1:8) and finasteride:β-cyclodextrin inclusion complex (1:6)

physical mixtures, the spectra are the superposition of those of the pure products with attenuation of the finasteride peaks (Fig. 6a). However, the IR spectrum of the inclusion complex exhibited some significant differences. The (amide) C=O stretching band of finasteride slightly shifted to a lower frequency (1668 cm^{-1}), suggesting intermolecular interaction between finasteride and β-cyclodextrin in the inclusion complex (Fig. 6b) [17–19].

Dissolution studies

Dissolution of finasteride increased with the amount of PEG 6000. The increase in the dissolution rate might be due to improved wettability by the carrier in physical mixtures (Fig. 7), and amorphization of the drug by the carrier on solid dispersions (Fig. 8) [2, 4].

Physical mixtures of finasteride with Kollidon K25 didnot increase the finasteride dissolution rate. Solid dispersions increased significantly the drug dissolution rate due to amorphization of the drug by the carrier (Fig. 9) [2, 4].

The dissolution rate of inclusion complexes was significantly higher than that of finasteride and physical mixtures (Fig. 10), and could be explained from an increase in solubility, a reduction in cristallinity and an improved wettability of the drug by the inclusion complex formation. The inclusion complex finasteride:β-cyclodextrin (1:6) has shown the best dissolution rate of all, with 100% of finasteride dissolved after 60 min [10, 11].

As demonstrated in Fig. 11, solid dispersions with PEG 6000 and Kollidon K25, 1:10 and 1:8 ratios, respectively, exhibited the best dissolution rate, with 91.81 and 84.75% of finasteride dissolved after 60 min, i.e., 5.7 and 5.3 times higher than finasteride alone. In inclusion complexes with β-cyclodextrin the ratio 1–6 achieved the best result with 100% of finasteride dissolved after 60 min (6.3 times higher than finasteride alone).

Conclusion

The DSC thermograms revealed the transformation of finasteride into the amorphous state in solid dispersions with PEG 6000 and Kollidon K25, and in the inclusion complexes with β-cyclodextrin. The IR spectra demonstrated molecular interaction in solid dispersions of finasteride with PEG 6000, and in the inclusion complexes with β-cyclodextrin. Solid dispersions with PEG 6000 and Kollidon K25 and inclusion complexes with β-cyclodextrin prepared by solvent evaporation method were successful approaches in increasing finasteride dissolution rate. The inclusion complex finasteride:β-cyclodextrin (1:6) was the best association investigated, with the total amount of finasteride dissolved after 60 min.

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