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Research Article

Physicochemical Characterization of Efavirenz–Cyclodextrin Inclusion Complexes

Sateeshkumar Sathigari,[1] Gurkishan Chadha,[1] Y-H. Phillip Lee,[1] Nydeia Wright,[2] Daniel L. Parsons,[1] Vijay K. Rangari,[2] Oladiran Fasina,[3] and R. Jayachandra Babu[1,4]

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Abstract. Efavirenz (EFV) is an oral antihuman immunodeficiency virus type 1 drug with extremely poor aqueous solubility. Thus, its gastrointestinal absorption is limited by the dissolution rate of the drug. The objective of this study was to characterize the inclusion complexes of EFV with β-cyclodextrin (β-CD), hydroxypropyl β-CD (HPβCD), and randomly methylated β-CD (RMβCD) to improve the solubility and dissolution of EFV. The inclusion complexation of EFV with cyclodextrins in the liquid state was characterized by phase solubility studies. The solid-state characterization of various EFV and CD systems was performed by X-ray diffraction, differential scanning calorimetry, and scanning electron microscopy analyses. Dissolution studies were carried out in distilled water using US Pharmacopeia dissolution rate testing equipment. Phase solubility studies provided an A_L-type solubility diagram for β-CD and A_P-type solubility diagram for HPβCD and RMβCD. The phase solubility data enabled calculating stability constants (K_s) for EFV-βCD, EFV-HPβCD, and EFV-RMβCD systems which were 288, 469, and 1,073 M^{-1}, respectively. The physical and kneaded mixtures of EFV with CDs generally provided higher dissolution of EFV as expected. The dissolution of EFV was substantially higher with HPβCD and RMβCD inclusion complexes prepared by the freeze drying method. Thus, complexation with HPβCD and RMβCD could possibly improve the dissolution rate-limited absorption of EFV.

KEY WORDS: cyclodextrins; dissolution rate; efavirenz; inclusion complexes; solubility.

INTRODUCTION

Efavirenz (EFV) [(S)-6-chloro-4-(cyclopropylethynyl)-1, 4-dihydro-4-(trifluoromethyl)-2H-3, 1-benzoxazin-2-one] is a non-nucleoside reverse transcriptase inhibitor approved for the treatment of human immunodeficiency virus type 1 infection (Fig. 1). It is a crystalline lipophilic solid (log octanol water partition coefficient of 5.4) with a molecular mass of 315.68 and an aqueous solubility of 9.0 μg/ml (1,2). This is a class II drug (low solubility, high permeability) according to the biopharmaceutical classification system guidance by the Food and Drug Administration (3,4). Highly permeable, poorly soluble drugs often demonstrate poor gastrointestinal (GI) absorption due to inadequate drug solubility in GI fluids (5). Furthermore, efavirenz has a considerably low intrinsic dissolution rate of 0.037 mg/cm^2/min (unpublished findings), which suggests dissolution rate-limited absorption problems for this drug. The intrinsic dissolution rate less than 0.1 mg/min/cm^2 could be a rate-limiting factor for oral absorption of the given drug (6). EFV is currently marketed as tablets and capsules containing the drug in the crystalline form with controlled particle size. For poorly water soluble drugs, the solid state properties of the drug such as particle size, crystal structure, and physical form greatly influence their dissolution properties and also directly influence their bulk powder properties such as density and flowability (7,8). EFV is a hydrophobic drug with low density and high flow resistance (9). Since the particle size and morphology are the critical parameters in the development of formulations for effective GI drug delivery, there is a need to develop the amorphous state of EFV with enhanced solubility related oral bioavailability (10).

Cyclodextrins (CDs) are cyclic (α-1, 4)-linked oligosaccharides of α-D-glucopyranose containing a relatively hydrophobic central cavity and hydrophilic outer surface. Complexation with CDs enhances the solubility, dissolution rate, and bioavailability of poorly soluble drugs (11). In addition to solid dosage forms, the pharmaceutical development of oral liquid dosage forms of EFV for use in pediatrics or in adults with difficulty in swallowing is challenging. Not only is the solubility of EFV very low, but it imparts a strong and prolonged burning sensation to the mouth and throat when incorporated in water containing liquid formulations (2). CDs can be used to reduce the GI irritation and unpleasant taste of drugs (12). CDs possess a special ability to complex drugs to increase solubility, reduce bitterness, enhance stability, and

[1] Department of Pharmacal Sciences, Harrison School of Pharmacy, Auburn University, Auburn, Alabama 36849, USA.
[2] Center for Advanced Materials (T-COM), Tuskegee University, Tuskegee, Alabama 36088, USA.
[3] Biosystems Engineering, Auburn University, Auburn, Alabama 36849, USA.
[4] To whom correspondence should be addressed. (e-mail: rjbabu68@gmail.com)

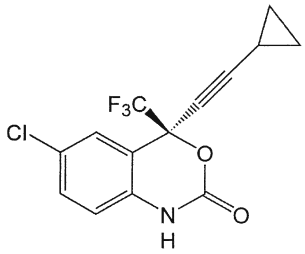

Fig. 1. Structure of efavirenz

decrease tissue irritation upon dosing (13). The objective of this study was to characterize the inclusion complexes of EFV with β-cyclodextrin (β-CD), hydroxypropyl-β-CD (HPβCD), and randomly methylated-β-CD (RMβCD) to improve solubility and dissolution. It is also expected that the burning sensation of oral liquid-based EFV formulations could be minimized by inclusion complexation with CDs.

MATERIALS AND METHODS

Materials

Efavirenz was a generous gift from Aurobindo Pharma Co. (Hyderabad, India). β-Cyclodextrin was kindly provided by ISP Technologies (Wayne, NJ, USA). Hydroxypropyl-βCD and randomly methylated-βCD were procured from Cyclodex Technologies Inc. (High Springs, FL, USA). All reagents and solvents used were of analytical grade.

Phase Solubility Studies

Phase solubility diagrams of EFV with various CDs in water at 25°C were obtained according to Higuchi and Connors (14). An excess of drug was added to 5 ml of water or CD aqueous solutions (0.002–0.3 M) in 20-ml glass vials and sonicated for 30 min five times a day for 2 days. After equilibration for 24 h, aliquots of the supernatant were withdrawn, filtered through 0.22 μm nylon membranes, and the EFV content, after suitable dilution, was determined spectrophotometrically at 246 nm (Shimadzu UV–VIS spectrophotometer, Norcross, GA, USA). Each experiment was conducted in triplicate. The apparent 1:1 stability constants of the EFV–CD complexes were calculated from the linear portion of the phase solubility diagrams (15).

Preparation of CD Formulations

Various EFV–CD formulations were prepared in a 1:1 molar ratio by the following methods:

(a) *Physical mixing*: Efavirenz and CD were mixed intimately in a screw-cap glass vial. To ensure uniform mixing, the vial was subjected to vortex mixing for 5 min.
(b) *Kneading*: CD and EFV were blended together in a mortar with 1 ml of 50% ethanol, kneaded for 15 min, and dried at 50°C for 24 h. The resultant dry solid mass was powdered well, passed through a 60-mesh sieve and stored in a sealed glass vial.
(c) *Freeze-drying*: The required 1:1 stoichiometric quantity of EFV (1 M) was dissolved in 50% ethanol and added to an aqueous solution of HPβCD or RMβCD (1 M). In the case of βCD, an isopropyl alcohol/water (3:4) mixture was used. The resulting solutions were frozen at −70°C and lyophilized in a freeze dryer (Labconco, FreezeZone, Kansas City, MO, USA). The lyophilized powder was passed through a 60-mesh sieve and stored in a sealed glass vial.

Differential Scanning Calorimetry Studies

Differential scanning calorimetry (DSC) analysis was performed using a Q200 DSC apparatus (New Castle, DE, USA). The samples were sealed in aluminum pans and the DSC thermograms were recorded at a heating rate of 10°C/min from 30°C to 180°C.

X-ray Diffraction Studies

X-ray powder diffraction patterns were obtained at room temperature with a Rigaku X-ray diffraction (XRD) analyzer (Rigaku Americas, The Woodlands, TX, USA) using Cu Kα radiation. The scanning speed employed was 2°/min.

Scanning Electron Microscopy Studies

The surface morphology of EFV and its binary systems with various CDs was analyzed by a scanning electron microscope (SEM; JEOL-JSM-5800, Tokyo, Japan). The powdered samples were uniformly spread on double-sided carbon tape, fixed on a stainless steel stub, and coated with gold/palladium to prevent charge buildup by the electrons absorbed by the specimen. The micrographs were obtained at an excitation voltage of 12 kV and magnification factors of ×1,000.

Dissolution Rate Studies

The dissolution rate studies of the formulations were performed in 500 ml distilled water using US Pharmacopeia II dissolution apparatus (Hansen Research, Chatsworth, CA, USA) at a temperature of 37°C and a stirring rate of 50 rpm. The sink conditions were maintained throughout the period of dissolution study. Efavirenz and binary mixtures of EFV with various CDs, each containing 10 mg of EFV, were subjected to dissolution testing. The drug and various drug–CD mixtures (physical, kneaded, and freeze dried) were passed through an 80-mesh sieve prior to conducting the dissolution studies. At fixed time intervals, 10 ml samples were withdrawn through a filter and the drug content was assayed spectrophotometrically at 246 nm. The dissolution profiles were evaluated on the basis of the dissolution efficiency parameter at 30 min (DE_{30}, %) and at 180 min (DE_{180}, %). The dissolution efficiency parameters were calculated from the area under the dissolution curves and expressed as a percent of the area of the rectangle described by 100% dissolution in the same time period (15).

Statistical Analysis

The differences between multiple groups of dissolution efficiency data (DE_{30min} and DE_{180min}) were assessed by analysis of variance followed by Turkey's posttest to determine the level of significance between different groups. Mean differences with $P<0.05$ were considered to be significant.

RESULTS AND DISCUSSION

Phase Solubility Studies

Traditional phase solubility analysis of the effect of complexing agent on the drug compound can provide not only the stability constant of the complex but also to give insight into the stoichiometry of the complex at equilibrium (10). The phase solubility diagrams were obtained by plotting the apparent equilibrium concentration of the drug against CD concentrations and are shown in Fig. 2. For βCD, the apparent solubility of EFV increased linearly as a function of βCD concentration over the entire concentration range studied. This linearity was characteristic of an A_L-type system (10) and suggested the formation of inclusion complexes in a 1:1 EFV/CD molar ratio. For HPβCD and RMβCD, the apparent solubility of EFV increased linearly as a function of the corresponding CD to approximately 80 mM indicating the formation of inclusion complexes in a 1:1 molar ratio. At higher CD concentrations, the slope of the plot increased rapidly indicating the formation of 1:2 or higher complexes. The apparent stability constants (K_s) of the 1:1 complexes were calculated from the initial linear slopes of the phase solubility diagrams and the intrinsic solubility (S_o) of EFV (14). The K_s values of the EFV-βCD, EFV-HPβCD, and EFV-RMβCD complexes were 288, 469, and 1,073 M^{-1}, respectively.

X-ray Diffraction Studies

Figure 3 shows the X-ray diffraction patterns of EFV, βCD, HPβCD, and RMβCD and the binary systems of EFV with various CDs. The XRD pattern of EFV presented multiple peaks indicating the crystalline nature of the drug. Among the CDs, the βCD exhibited a typical crystalline diffraction pattern and diffraction peaks relevant to crystalline EFV were detectable in all the binary systems with βCD. Both HPβCD and RMβCD exhibited an amorphous diffraction pattern (Fig. 3). The diffraction patterns of physical mixtures of EFV with HPβCD and RMβCD revealed the presence of free crystalline drug. The diffraction peak intensity in the kneaded mixture of HPβCD was similar to the physical mixture. However, an amorphous structure was observed for the kneaded mixture with RMβCD, indicating complex formation. Complete drug amorphization was observed in the freeze-dried products of EFV with each amorphous βCD derivative (HPβCD and RMβCD). Similar results were reported for other drugs with amorphous βCD derivatives (16,17).

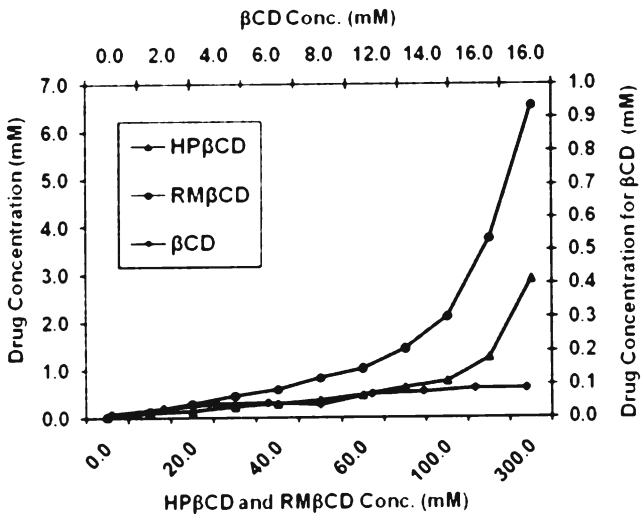

Fig. 2. Phase solubility diagram of efavirenz with βCD, HPβCD, and RMβCD in water at room temperature (~25°C)

Differential Scanning Calorimetry

For drugs that form inclusion complexes with CDs, DSC is a fast and relatively inexpensive technique to examine the absence of the drug-melting endotherm in order to verify that the drug was successfully complexed (18). The DSC thermograms of EFV, βCD, HPβCD, RMβCD, and the binary systems of CDs with EFV are shown in Fig. 4. Efavirenz showed the typical behavior of an anhydrous crystalline drug with a well-defined melting peak at 137.2°C (ΔH=49.10 J/g). The DSC curve of βCD exhibited a very broad endothermal phenomenon between 60°C and 120°C due to the loss of water (19). The DSC thermograms for EFV–βCD complexes have a small endothermic peak for the physical and kneaded mixtures and the freeze-dried formulation, suggesting that each had a free EFV component. It appears that the freeze drying method did not produce a complete inclusion complex. In the case of EFV–HPβCD formulations, the DSC thermograms have a small endothermic peak for the physical and kneaded mixtures corresponding to the melting point of EFV. However, in the freeze-dried mixture, the endothermic peak was absent suggesting the formation of an inclusion complex without any free EFV. Similar results were observed for EFV–RMβCD complexes, but in contrast to HPβCD, the endothermic peak was also completely absent for the kneaded mixture. This suggested a solid-state interaction of RMβCD and EFV by the kneading method as well as the freeze-dried method. All of the DSC results were in good agreement with those obtained by XRD to prove the complexation of EFV with CDs in the solid state.

Scanning Electron Microscopy

The scanning electron microphotographs of EFV and its binary systems with various CDs are presented in Fig. 5. Efavirenz was in the form of distinct regularly sized crystals. In the physical mixtures, the typical EFV crystals, which were mixed between the CD particles or coated to their surface, were clearly detectable, thus confirming the presence of crystalline drug. It was also evident that βCD is a crystalline solid while HPβCD and RMβCD are homogeneous spherical-shaped spray-dried particles in the micron-size range (20). In the kneaded mixtures of CD and EFV, it is still possible to distinguish

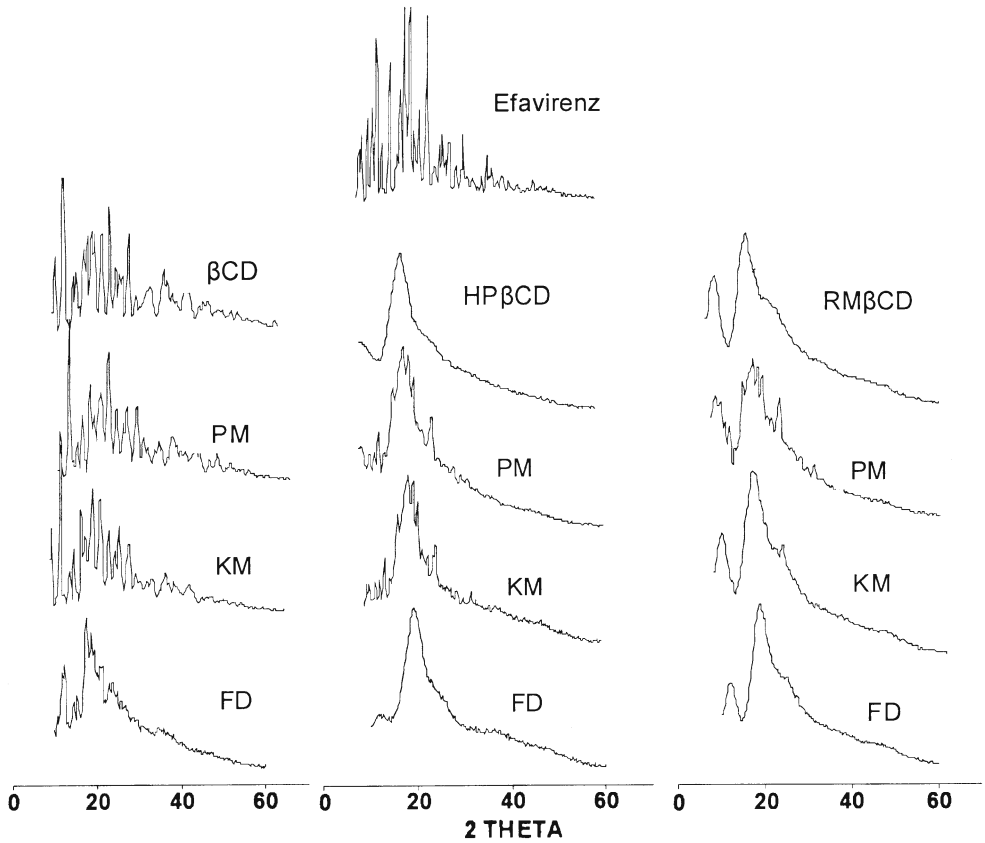

Fig. 3. X-ray diffraction analysis of efavirenz, βCD, HPβCD, RMβCD, and their physical mixtures (*PM*), kneaded mixtures (*KM*), and freeze-dried complexes (*FD*)

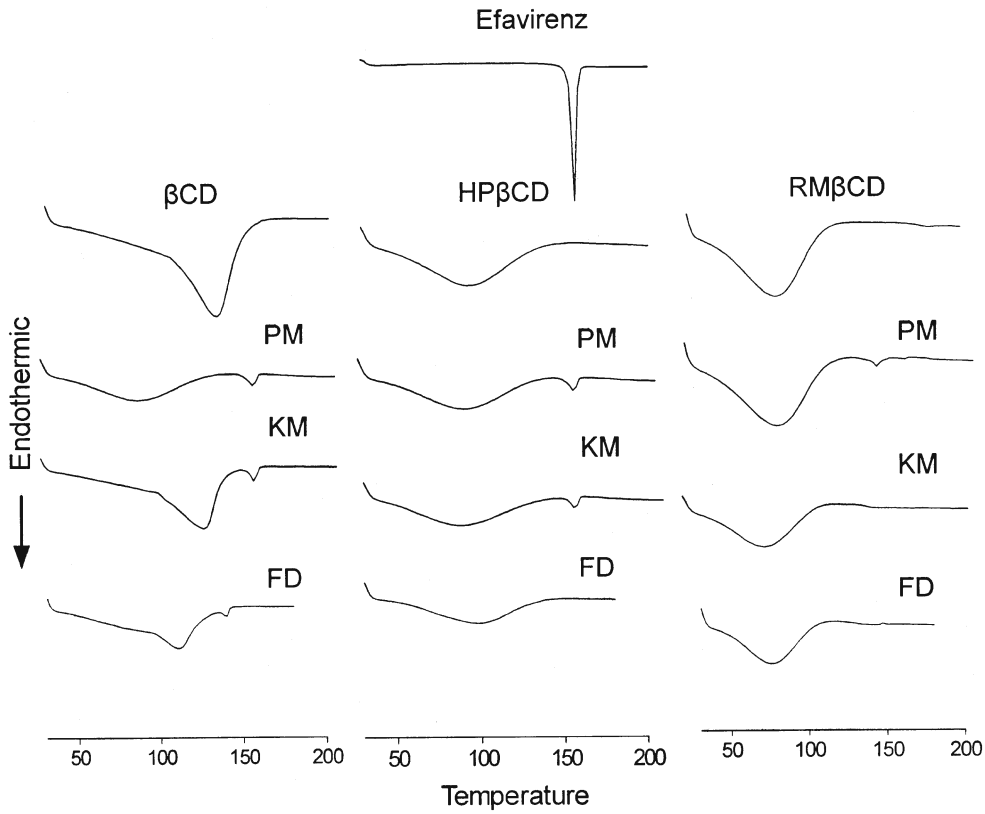

Fig. 4. Differential scanning calorimetry thermograms of efavirenz, βCD, HPβCD, RMβCD, and their physical mixtures (*PM*), kneaded mixtures (*KM*) and freeze-dried complexes (*FD*)

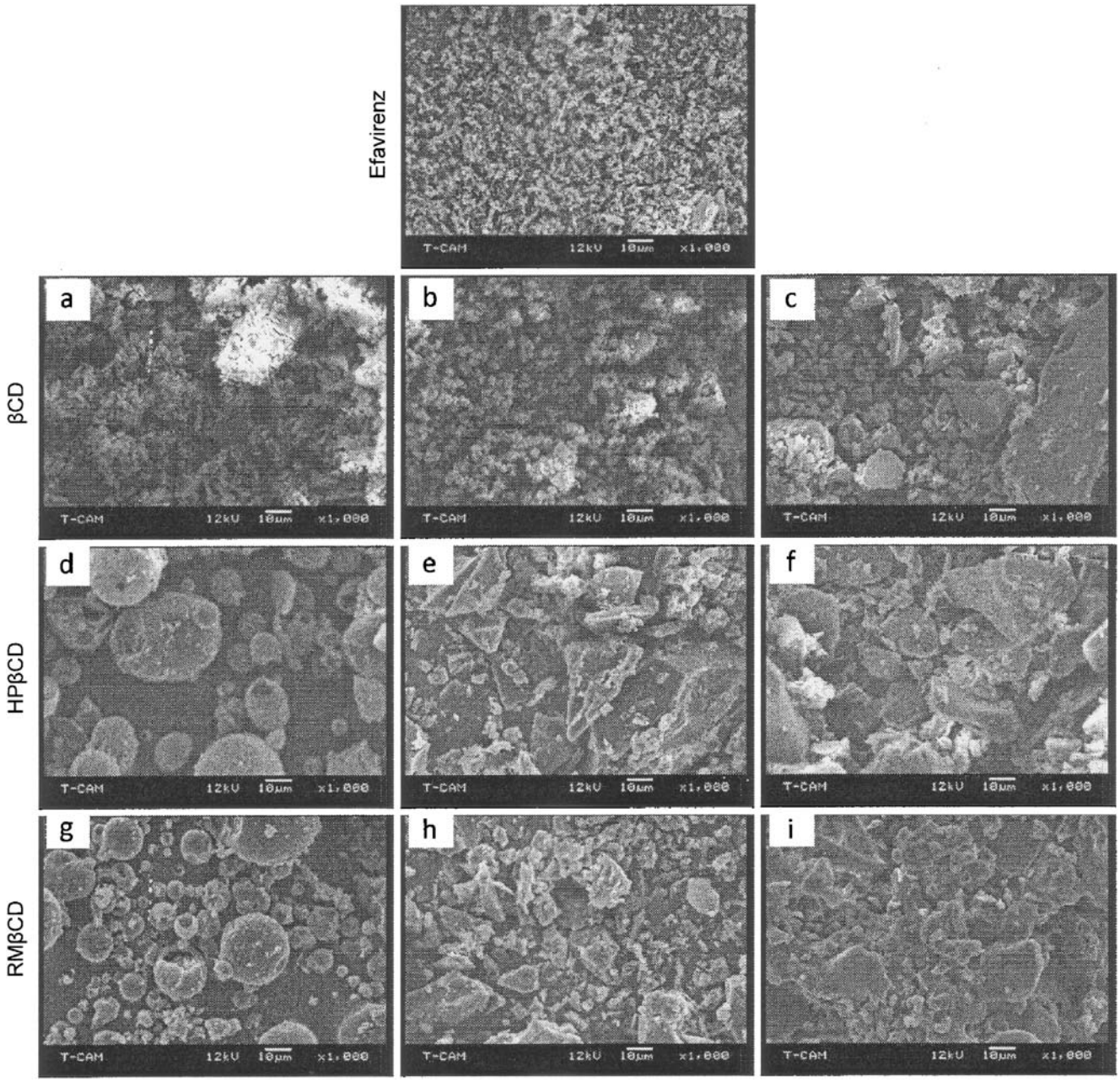

Fig. 5. Scanning electron microphotographs of efavirenz, physical mixture of EFV with βCD (**a**), kneaded mixture of EFV with βCD (**b**), inclusion complex of EFV with βCD (**c**), physical mixture of EFV with HPβCD (**d**), kneaded mixture of EFV with HPβCD (**e**), inclusion complex of EFV with HPβCD (**f**), physical mixture of EFV with RMβCD (**g**), kneaded mixture of EFV with RMβCD (**h**), and inclusion complex of EFV with RMβCD (**i**)

EFV crystals associated with the CDs which had lost their original shape due to the kneading process. In the freeze-dried products, the original morphology of EFV and CD had disappeared and it was not possible to differentiate the two components. Generally, all freeze-dried products appeared to have less crystalline structure with a uniform appearance. Again, crystals of EFV were not distinguishable, indicative of the presence of a new solid phase. While the SEM technique is inadequate to conclude in the formation of a genuine complex, the microphotographs support the consecution of a new single component (20,21).

Dissolution Rate Studies

Dissolution profiles for the drug, physical mixture of the drug and CD, and/or complex of drug and CD are often presented to demonstrate the influence of a CD on dissolution kinetics and the total amount of drug in solution (22). Rapid dissolution as compared with the pure drug is the characteristic behavior of inclusion complexes (23). The dissolution profiles of EFV and various binary systems are presented in Fig. 6. It was observed during these studies that the hydrophobic property of the drug prevented its contact with the dissolution medium causing it to float on the surface.

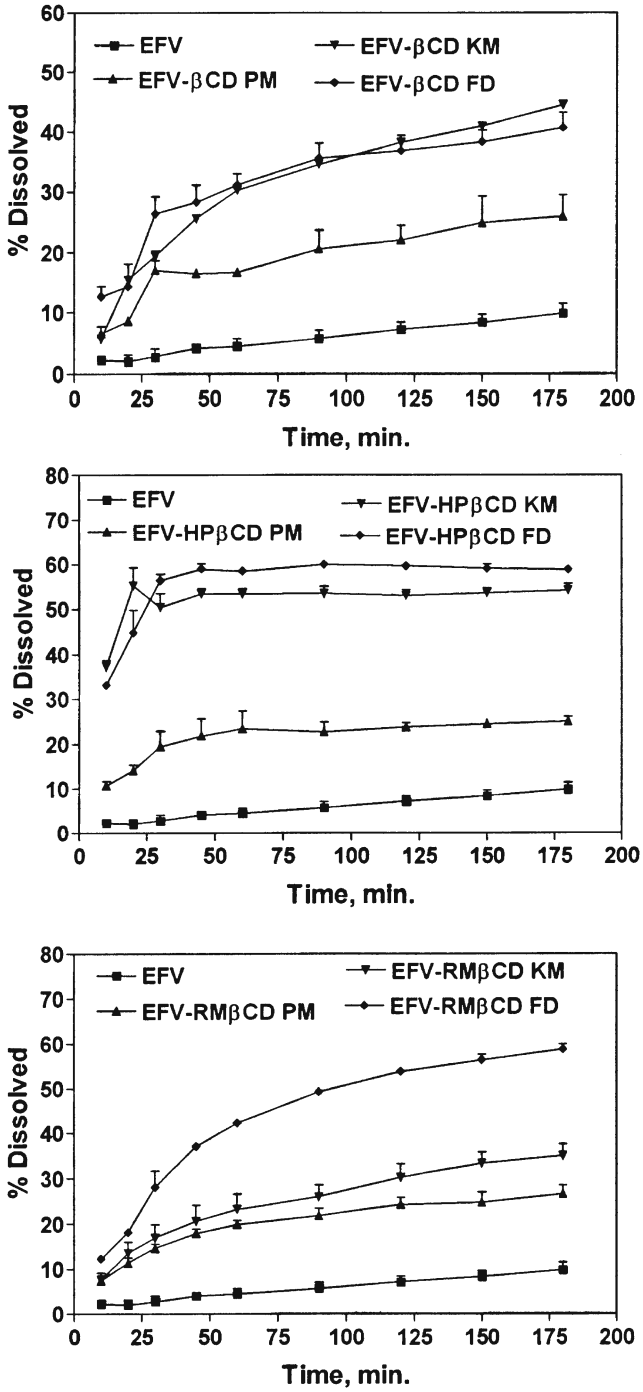

Fig. 6. Dissolution profiles of various efavirenz–CD formulations. *PM* physical mixture, *KM* kneaded mixture, *FD* freeze-dried complex

Thus, only ~10% (1 mg) of the EFV dissolved even after 180 min. Physical mixtures prepared with various CDs yielded a dissolution profile that was slightly higher than that of EFV. The improvement in dissolution rate with the physical mixtures can be attributed to both improved drug wettability due to the presence of the hydrophilic CD which can reduce the interfacial tension between poorly soluble drug and dissolution medium and the formation of readily soluble complexes in the dissolution medium (24). The kneaded mixture and freeze-dried mixture of βCD, HPβCD, and RMβCD showed a significant increase in EFV dissolution compared to their corresponding physical mixture. This suggested a better interaction of the drug with CD by these processes, as expected from the physicochemical characterization.

The dissolution efficiency data calculated based on 30 (DE_{30}) and 180 min (DE_{180}) are presented in Table I. The DE_{30min} of the HPβCD-kneaded mixtures and freeze-dried complexes were both about 20-fold higher than EFV ($P<0.001$). The DE_{180min} of the HPβCD-kneaded mixtures and freeze-dried complexes were about tenfold higher than EFV ($P<0.001$). The DE_{30min} of the RMβCD-kneaded mixtures and freeze-dried complexes were about six- and eightfold, respectively, higher than EFV ($P<0.001$). The DE_{180min} of the RMβCD-kneaded mixtures and inclusion complexes were about four- and eightfold higher, respectively, than EFV ($P<0.001$). The freeze-dried product showed much better dissolution than the kneaded product with RMβCD. This suggested better complexation by the freeze-drying technique, as might be expected. However, the dissolution profiles for the kneaded and freeze-dried mixtures were very similar for βCD as well as for HPβCD. This suggests that complex formation can occur efficiently through simple kneading for these compounds, though not for RMβCD.

Among all the complexes, the EFV–HPβCD-kneaded and freeze-dried mixtures exhibited the best dissolution by far based on DE_{30min} values. Based on the physicochemical data presented, one would not expect such a large difference in the dissolution rates of the HPβCD and RMβCD freeze-dried formulations. Based on the phase solubility diagram (Fig. 2) and resulting K_s values, one would actually predict better dissolution with RMβCD. It is clear from the dissolution profiles (Fig. 6) for HPβCD that there is rapid dissolution of the EFV as a complex, reaching the maximum concentration (~55%) within approximately 30 min. In contrast, the dissolution profile for freeze-dried RMβCD shows a relatively slow and continuous increase in the % EFV dissolved that reaches ~55% dissolved after 180 min. There is no clear explanation for this phenomenon. Dollo *et al.* (25) studied the effect of HPβCD and sulfobutyl ether-7-βCD (SBE7βCD) on the solubility and dissolution rate improvement of anethole-

Table I. Effect of CDs on the Dissolution Efficiency of Efavirenz

Product	Dissolution efficiency 0–30 min	Dissolution efficiency 0–180 min
Efavirenz	1.51±0.645	5.64±1.149
Effect of βCD efavirenz		
Physical mixture	6.78±0.170*	18.74±2.100**
Kneaded mixture	9.34±1.364**	30.95±0.058***
Freeze-dried mixture	11.26±1.304***	31.16±2.189***
Effect of HPβCD efavirenz		
Physical mixture	9.74±1.177**	21.08±1.900***
Kneaded mixture	33.04±0.625***	49.98±1.053***
Freeze-dried mixture	29.87±1.805***	54.25±1.031***
Effect of RMβCD efavirenz		
Physical mixture	7.47±0.573**	19.84±1.425**
Kneaded mixture	8.60±1.552**	24.58±2.684***
Freeze-dried mixture	12.78±0.317***	43.13±0.331***

*$P<0.05$; **$P<0.01$; ***$P<0.001$ *versus* efavirenz

trithione. The K_s values of HPβCD and SBE7βCD complexes were 6,227 and 12,834, respectively, indicating much better solubility by the SBEβCD complex. The dissolution studies in contrast demonstrated initial slow dissolution by the SBEβCD complex as compared to HPβCD. In an earlier study (26), we found an initial slow dissolution by the RMβCD complex of gefitinib as compared to HPβCD, though the former complex had a much higher solubility and K_s value.

Conclusions

Phase solubility studies demonstrated an A_L-type solubility diagram for β-CD indicating the formation of inclusion complexes in a EFV/CD 1:1 stoichiometric ratio. An A_P-type solubility diagram for HPβCD and RMβCD indicated a 1:1 stoichiometry complex in the initial linear portion and 1:2 or greater stoichiometry complexes at higher CD concentrations. The inclusion complex formation of EFV with different CDs in the solid state was confirmed by DSC, XRD, and SEM studies. The dissolution of EFV was substantially higher for HPβCD and RMβCD inclusion complexes prepared by the freeze-drying method. Thus, complexation with HPβCD and RMβCD could possibly help improve the dissolution rate-limited absorption problems for EFV.

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