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Original Article

Inclusion complexes of cefuroxime axetil with β -cyclodextrin: Physicochemical characterization, molecular modeling and effect of L-arginine on complexation[☆]Sarika Sapte, Yogesh Pore^{*}

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ABSTRACT

The inclusion complexes of poorly water-soluble cephalosporin, cefuroxime axetil (CFA), were prepared with β -cyclodextrin (β CD) with or without addition of L-arginine (ARG) to improve its physicochemical properties. We also investigated the effect of ARG on complexation efficiency (CE) of β CD towards CFA in an aqueous medium through phase solubility behaviour according to Higuchi and Connors. Although phase solubility studies showed A_L (linear) type of solubility curve in presence and absence of ARG, the CE and association constant (K_s) of β CD towards CFA were significantly promoted in presence of ARG, justifying its use as a ternary component. The solid systems of CFA with β CD were obtained by spray drying technique with or without incorporation of ARG and characterized by differential scanning calorimetry (DSC), X-ray powder diffractometry (XRPD), scanning electron microscopy (SEM), and saturation solubility and dissolution studies. The molecular modeling studies provided a better insight into geometry and inclusion mode of CFA inside β CD cavity. The solubility and dissolution rate of CFA were significantly improved upon complexation with β CD as compared to CFA alone. However, ternary system incorporated with ARG performed better than binary system in physicochemical evaluation. In conclusion, ARG could be exploited as a ternary component to improve the physicochemical properties of CFA via β CD complexation.

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1. Introduction

Cefuroxime axetil (CFA) (Fig. 1) is a β -lactamase-stable 1-acetoxyethyl ester prodrug of cefuroxime cephalosporin with high effectiveness against gram-positive and gram-negative microorganisms. It is used orally to treat respiratory tract infections, pharyngitis, tonsillitis, acute bacterial otitis, urinary tract infections and uncomplicated skin infections. The important structural feature of CFA is the presence of lipophilic 1-acetoxyethyl ester which facilitates its intestinal absorption after oral administration. However, CFA exists in crystalline and amorphous state and has poor aqueous solubility and dissolution rate in gastrointestinal tract. Consequently, these physicochemical properties of CFA are responsible for its limited and variable oral bioavailability (30%–60%) [1–5], resulting in poor therapeutic outcome.

Cyclodextrins (CDs) are cyclic oligosaccharides with hydrophobic central cavity and hydrophilic exterior, rendering them as

powerful complexing and solubilizing agents [6–8]. They are classified into α -, β - and γ -CDs consisting of (α –1, 4)-linked six, seven and eight α -D-glucopyranose units, respectively [9]. The inclusion complexation of drug (guest) molecules with CDs (host) is an industrially feasible technique used to improve the physicochemical properties of the drug, such as solubility, dissolution rate, and bioavailability [10–12]. Unfortunately, due to lower complexation efficiency (CE) of CDs, solubility enhancement via cyclodextrin (CD) complexation is limited to certain extent [13]. Several papers have reported enhancement in CE of CDs with the addition of small amounts of hydrophilic polymers [14,15], hydroxyl acids [16,17] and/or amino acids [9,18–21] as ternary components to the complexation media resulting in the formation of ternary complexes. The basic amino acid, L-arginine (ARG), was proved to be a better choice as an auxiliary substance to increase the solubilizing capacity of CDs through electrostatic interaction and salt formation during the multi-component complex formation of weakly acidic drugs [21,22]. Thus, considering the advantage of incorporation of amino acid as a ternary component during complexation of drug with CD, the proposed work was carried out to promote the physicochemical properties of poorly

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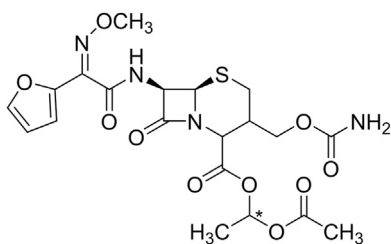


Fig. 1. Chemical structure of cefuroxime axetil.

water-soluble CFA via β -cyclodextrin (β CD) complexation using ARG as an auxiliary substance, which to our knowledge has not been reported yet.

The present study primarily focused on the investigation of the physicochemical properties of the inclusion complexes of CFA with β CD in presence of ARG as a ternary component. Initially, the possibility of complex formation was studied by molecular modeling approach and subsequently by phase solubility measurements to determine the stoichiometry of the complex formation. The binary and ternary inclusion complexes were prepared by spray drying method and characterized by differential scanning calorimetry (DSC), X-ray powder diffractometry (XRPD) and scanning electron microscopy (SEM). The saturation solubility and dissolution experiments were further conducted in distilled water and 0.07M HCl respectively to examine the physicochemical performance of the prepared complexes.

2. Experimental

2.1. Materials and reagents

CFA was obtained as a gift sample from Okasa Pharma Ltd. (Satara, India). β CD (Average molecular weight 1135 g/mol, purity 98%) was purchased from Himedia Laboratories Pvt., Ltd. (Mumbai, India). ARG (purity 99%) was procured from Loba Chemie Pvt., Ltd. (Mumbai, India). Analytical grade chemicals and double distilled water were used for all experimental procedures. All substances were used directly without further purification.

2.2. Molecular modeling studies

Molecular modeling simulations were performed using VLifeMDS 4.3 software Suit (VLife Sciences and Technologies, Pune, India) on Intel i3 CORE processor operated with Windows XP. The molecular structure of β CD was downloaded from Pubchem Structural Database (CID444041). The chemical structure of CFA was built on workspace of VLife Engine module. The individual structures (2D) of host and guest were converted to 3D and optimized to achieve minimum energy using Merck Molecular Force Field (MMFF) program with RMS gradient of 0.01 kcal/mol and dielectric constant of 1. Subsequently, CFA was allowed for conformational analysis using Monte Carlo simulations. One of the CFA conformers with least energy was positioned into the β CD cavity at different orientations and the structures were again minimized. The stoichiometry of the complex formation showing least energy was considered optimum from the total energies obtained after optimization of 1:1, 1:2 and 2:1 stoichiometries of CFA: β CD complexes. The stability of the complex was predicted from relative thermodynamic relationship in molecular mechanic (MM) calculations by calculating complexation energies (ΔE) [23,24].

2.3. Phase solubility studies

The solubility behaviour of CFA was examined in distilled water at room temperature (25 ± 2 °C) according to the method described by Higuchi and Connors [25]. Excess amount of CFA was added to 20 mL of aqueous solutions containing various concentrations of β CD (0–0.01 M) with or without addition of ARG (0.25%, m/v). The suspensions were mechanically shaken subsequently on a rotary shaker for 72 h at 125 rpm until equilibrium was achieved. The samples were filtered through Whatman filter paper 41, diluted if necessary and analyzed spectrophotometrically (Shimadzu UV-vis spectrophotometer 1800, Japan) at 281 nm. The association constant (K_s) of complex and CE of β CD were calculated according to the Eqs. (1) and (2), respectively [26].

$$K_s = \text{Slope}/S_0(1 - \text{Slope}) \quad (1)$$

S_0 is the solubility of CFA in absence of β CD and slope is obtained from the phase solubility diagram constructed by plotting concentration of drug on y-axis and concentration of β CD on x-axis. It gives idea about the stoichiometry of the complex formation. Linear dependence of drug concentration to β CD concentration, with slope ratio below one, usually assumes 1:1 ratio of the complex and refers to A_L (linear) type of the phase solubility curve.

$$CE = S_0 \cdot K_{1:1} = \text{Slope}/(1 - \text{Slope}) \quad (2)$$

The thermodynamic parameter, Gibbs free energy of transfer (ΔG_{tr}°), was also determined with the following equation:

$$\Delta G_{tr}^\circ = -2.303RT \log(S_c/S_0) \quad (3)$$

Where S_c/S_0 is the ratio of molar solubility of CFA in aqueous solutions of β CD with or without ARG to that in distilled water in absence of β CD. ΔG_{tr}° values demonstrate the process of transfer of CFA from pure water to aqueous solutions of β CD [5].

2.4. Preparation of binary and ternary inclusion complexes

Equimolar quantities of CFA and β CD with or without addition of ARG (0.25%, m/v) were dissolved in 100 mL of methanol and sonicated for 10 min. The mixture was stirred for 72 h at room temperature (25 ± 2 °C) on a magnetic stirrer (2MLH, Remi Laboratory Instruments, Mumbai, India) at 125 rpm. The resultant suspension was spray dried using Lab spray dryer (SPD-D-111 Techno Search Instruments, Thane, India) under the following set of conditions: Inlet temperature 65 °C, outlet temperature 45 °C, cool temperature 20 °C, aspirator speed 40 mBar and feed rate 5 mL/min. The spray dried product was collected and stored in desiccators to prevent it from moisture absorption.

2.5. DSC analysis

Thermograms of CFA, β CD, ARG and complexes were recorded on a DSC analyzer (Mettler DSC 823E Mettler Toledo Pvt. Ltd, Switzerland). A sample (5 mg) was placed in an aluminum pan and heated under a nitrogen atmosphere (flow rate 100 mL/min) at a heating rate of 10 °C/min over the temperature range of 30–300 °C. The thermal behaviour of samples was recorded and studied.

2.6. XRPD analysis

The XRPD analysis of all samples including pure CFA was performed using X-ray diffractometer (PW 1729, Philips, the Netherland) with copper (Cu) anode, generator tension 40 kV, generator current 30 mA, and scanning speed 2°/min over the interval of 10–90°/2 θ .

2.7. SEM analysis

The surface morphological features of all samples were investigated using a scanning electron microscope (SEM-JOEL Instruments, JSM-6360, Japan) operated at an acceleration voltage of 20 kV and the obtained microphotographs were examined at $\times 500$ and $\times 2000$ magnifications.

2.8. Saturation solubility studies

Saturation solubility studies of CFA and inclusion complexes were conducted in triplicate as follows: an excess amount of CFA and/or complexes were added to 20 mL of distilled water in vials sealed with stoppers and shaken in a rotary flask shaker at room temperature (25 ± 0.5 °C) for 24 h. A portion of solution was withdrawn, filtered through Whatman filter paper 41 and analyzed spectrophotometrically (Shimadzu UV–vis spectrophotometer 1800, Japan) at 280 nm. The data of saturation solubility were analyzed statistically using ANOVA (Instat[®], GraphPad software Inc. Version 3.05).

2.9. Dissolution studies

The dissolution studies of CFA and complexes were carried out in eight station dissolution test apparatus (Disso 2000 Tablet dissolution test apparatus, Lab India, Mumbai, India) according to USP type II. A total of 125 mg of pure CFA or complexes were added into a dissolution vessel containing 900 mL of 0.07 M HCl, maintained at 37 ± 0.5 °C at 55 rpm. A total of 6 mL of samples were withdrawn at appropriate time intervals. The volume of dissolution medium was adjusted to 900 mL by replacing each 6 mL of aliquot withdrawn with 6 mL of fresh 0.07 M HCl. The solution was immediately filtered through Whatman filter paper 41, suitably diluted and analyzed spectrophotometrically (Shimadzu UV–vis spectrophotometer 1800, Japan) at 281 nm. The data of dissolution studies were analyzed statistically using ANOVA (Instat[®], GraphPad software Inc. Version 3.05).

3. Results and discussion

3.1. Molecular modeling studies

The possibility of complex formation was assessed with the molecular mechanic calculations. The total energies of complex formation for 1:1, 1:2, 2:1 stoichiometries were found to be 422.5, 9072, and 4235 kcal/mol, respectively. As the lowest total energy was shown by 1:1 stoichiometry of CFA: β CD inclusion complex, it was considered to be the most stable inclusion complex among all the stoichiometries examined (Fig. 2).

As shown in Fig. 2, insertion of furan ring from narrow rim of β CD (Fig. 2A) and insertion of dihydrothiazine ring from wider rim of β CD (Fig. 2B) were the most appropriately predicted inclusion geometries for binary and ternary complexes, respectively, corresponding to the greatest absolute value of heat of formation and the lowest complexation energies (ΔE) (Table 1) [23].

Thus, it could be concluded that β CD could accommodate furan ring from narrow rim inside the β CD cavity in absence of ARG while insertion of dihydrothiazine moiety in β CD cavity was favored through wider rim in presence of ARG, indicating ARG involvement in the hydrogen bonding interactions with β CD and CFA outside the β CD cavity.

3.2. Phase solubility studies

The phase solubility diagrams of CFA in aqueous β CD solution in presence and absence of 0.25% ARG exhibited A_L type of

solubility curve with linear increase in solubility of CFA upon increasing the concentration of β CD (Fig. 3).

The slopes of phase solubility curves were less than 1, indicating the formation of water soluble complexes with 1:1 stoichiometry [13,25]. As shown in Table 2, the values of S_0 , slopes, K_s , and CE of complex increased with the addition of ARG to the complexation media, indicating greater effectiveness of ternary systems over binary one.

This enhancement in phase solubility parameters of CFA upon complexation with β CD in presence of ARG might be attributed to its electrostatic/hydrogen bonding interaction and salt formation with β CD and CFA [11,19]. In addition to that, molecular interactions based on solubilization of the drug such as hydrophobic bonding, Van der Waals dispersion forces and/or promoting the release of high-energy water molecules present in the cavity might have also contributed to beneficial effects of ARG as a ternary component [20–22,26].

Table 3 shows Gibbs free energy change (ΔG_{tr}°) values to predict the thermodynamics of process of transfer of CFA from pure water to aqueous solution of β CD. ΔG_{tr}° values were found to be negative at various concentrations of β CD in all cases, indicating the spontaneous nature of CFA solubilization. The values were decreased upon increasing concentration of β CD, indicative of more favorable solubilization reaction as the concentration of β CD increased [5,11,27].

These values indicated that the system was releasing energy upon complexation undergoing Vander Waals and electrostatic interactions and became more favorable in presence of ARG, suggesting its effectiveness as ternary component to prepare ternary systems.

3.3. DSC analysis

DSC technique has attracted attention to examining the interaction between host and guest molecules during the complex formation. When guest molecules are embedded in the β CD cavity, their melting points usually shift to a different temperature or disappear [22,28]. The thermograms of CFA, β CD, ARG and their complexes are shown in Fig. 4.

The DSC curve of CFA (Fig. 4a) exhibited glass transition temperature (T_g) at 86.52 °C, indicating its amorphous nature. The appearance of a broad endotherm at 134.02 °C in DSC curve of β CD was attributed to loss of water from β CD cavity (Fig. 4b). ARG exhibited broad peaks (Fig. 4c) at 93.45 and 99.55 °C due to loss of water of crystallization from small portions of L-arginine $2H_2O$ and two melting endotherms at 225.83 and 232.96 °C with different intensities, indicating melting with decomposition of anhydrous ARG and total decomposition of the melt, respectively [20,22].

The binary and ternary complexes showed appearance of broad peaks at 110.76 °C and 120.84 °C, respectively (Fig. 4d and e), as-signable to water loss and disappearance of T_g of CFA ensuring entrapment of CFA inside β CD cavity with replacement of water molecules. The peaks of ARG also disappeared in ternary systems, indicating ARG involvement in the complexation process. These results strongly suggested an existence of strongly physical interaction between CFA and β CD and formation of stable inclusion complex in solid state.

3.4. XRPD analysis

The physical state of pure drug and its complexes could be assessed by examining their XRPD patterns as shown in Fig. 5. The diffractogram of CFA (Fig. 5a) exhibited diffused peaks, indicating its amorphousness. However, there were certain peaks still detectable at $2\theta^\circ$ values of 11.17 (515), 13.95 (642), 16.42 (715), 19.28 (979), 20.23 (949), 21.49 (1026), 22.18 (982), 22.93 (977), 23.56

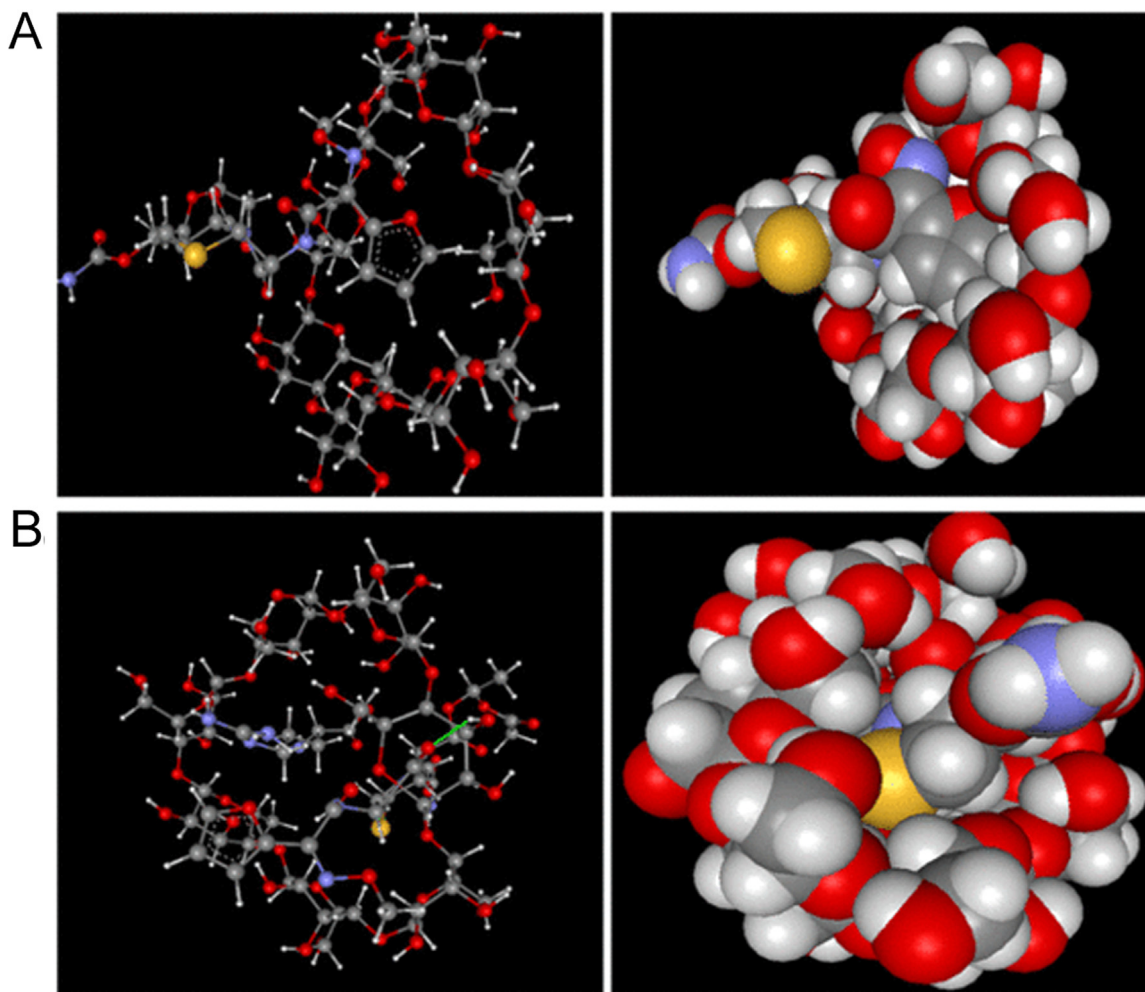


Fig. 2. Optimized geometric models of (A) CFA:βCD binary system (B) CFA:ARG:βCD ternary system.

Table 1

Enthalpies (ΔH) and complexation energies (ΔE) of optimized CFA:βCD binary and CFA:ARG:βCD ternary complexes (kcal/mol).

Possible geometries of CFA inside βCD cavity	CFA:βCD		CFA:ARG:βCD	
	ΔH	ΔE	ΔH	ΔE
Furan ring in narrow rim	−63,552	−157.5	−708,902	305.63
Furan ring in wider rim	−13,207	−30.5	−746,427	663.34
Dihydrothiazine ring in narrow rim	−98,571	−30.5	−352,425	−21.5
Dihydrothiazine ring in wider rim	−2,099,959	655.41	−132073.03	−27.5

Enthalpy (ΔH): Enthalpy of formation of complex – sum of enthalpies of formation of guest and host; Complexation energy (ΔE): Energy of the complex – sum of the energies of guest and host in their respective equilibrium geometry; CFA: cefuroxime axetil; βCD: β-cyclodextrin; ARG: L-arginine.

(956) 26.84 (727), and 29.62 (599), revealing the presence of some crystalline traces in the diffractogram of CFA. The crystalline nature of βCD was clearly shown by the appearance of sharp peaks at 10.60 (807), 10.71 (539), 11.94 (639), 12.57 (786), 12.49 (1111), 12.37 (1404), 12.41 (1349), 15.29 (700), 17.07 (982), 19.50 (1128), 20.74 (1070), and 22.56 (902) in its diffractogram (Fig. 5b). ARG displayed major peaks at 11.19 (519), 14.88 (1004), 16.63 (850), 19.26 (2111), 23.09 (3126), and 27.55 (3560) in crystalline state (Fig. 5c).

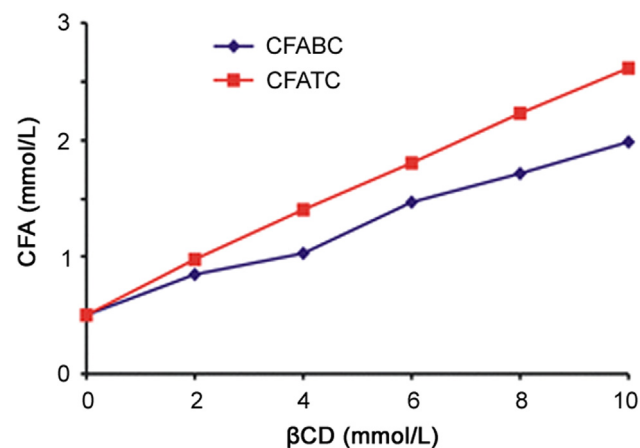


Fig. 3. Phase solubility diagram of CFA:βCD inclusion complexes in water at 25 ± 2 °C. CFABC: binary system; CFATC: ternary system with ARG.

The examination of XRPD patterns of binary (Fig. 5d) and ternary (Fig. 5e) complexes showed maximum appearance of peaks of βCD and an absence of crystalline traces of CFA, confirming spatial entrapment of CFA inside βCD cavity. In ternary systems, the overlapping of βCD and ARG crystalline peaks was noticed. However, the peaks of ARG were diffused to certain extent due to solid state interaction during complex formation [9].

Table 2
Phase solubility data of binary and ternary inclusion complexes of CFA with β CD.

Complexes	S_0	Slope	r^2	K_s (M^{-1}) ^a	K_{TS}/K_{BS}	CE
CFA: β CD	0.00051	0.1485	0.9922	339.74 ± 1.5	–	0.17
CFA:ARG: β CD	0.00054	0.2096	0.9989	490.98 ± 2.7^b	1.44	0.27

CFA: cefuroxime axetil; β CD: β -cyclodextrin; ARG: L-arginine; S_0 : solubility of CFA in absence of β CD; r^2 : regression coefficient of phase solubility plot; K_s (M^{-1}): association constant of complexes; K_{TS}/K_{BS} : the ratio of K_s for ternary and binary systems; CE: complexation efficiency.

^a indicates mean \pm SD ($n=3$); SD: Standard deviation.

^b Significant difference compared to K_s of β CD binary system ($p < 0.001$).

Table 3
Gibbs free energy of transfer (ΔG_{tr}°) of CFA from pure water to aqueous solutions of β CD in presence and absence of auxiliary substance ARG (0.25%, m/v).

Concentration of β CD (mmol/L)	ΔG_{tr}° (J/mol)	
	CFA: β CD	CFA:ARG: β CD
0.002	–108.82	–139.67
0.004	–146.97	–212.80
0.006	–221.53	–265.05
0.008	–254.39	–309.59
0.010	–284.66	–342.30

CFA: cefuroxime axetil; β CD: β -cyclodextrin; ARG: L-arginine.

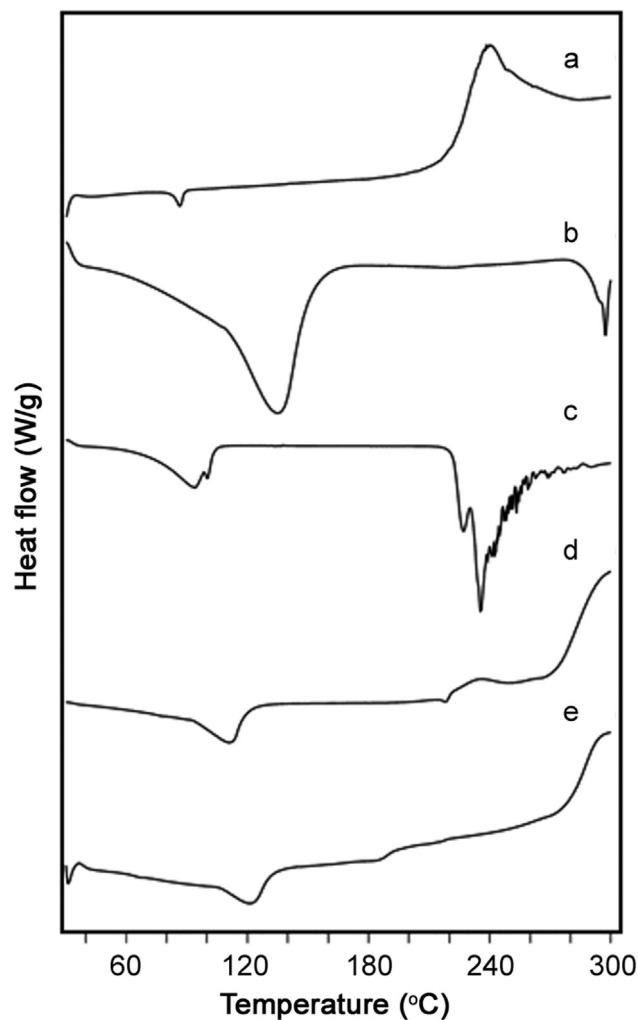


Fig. 4. DSC thermograms of CFA (a), β CD (b), ARG (c), CFA: β CD binary system (d) and CFA:ARG: β CD ternary system (e).

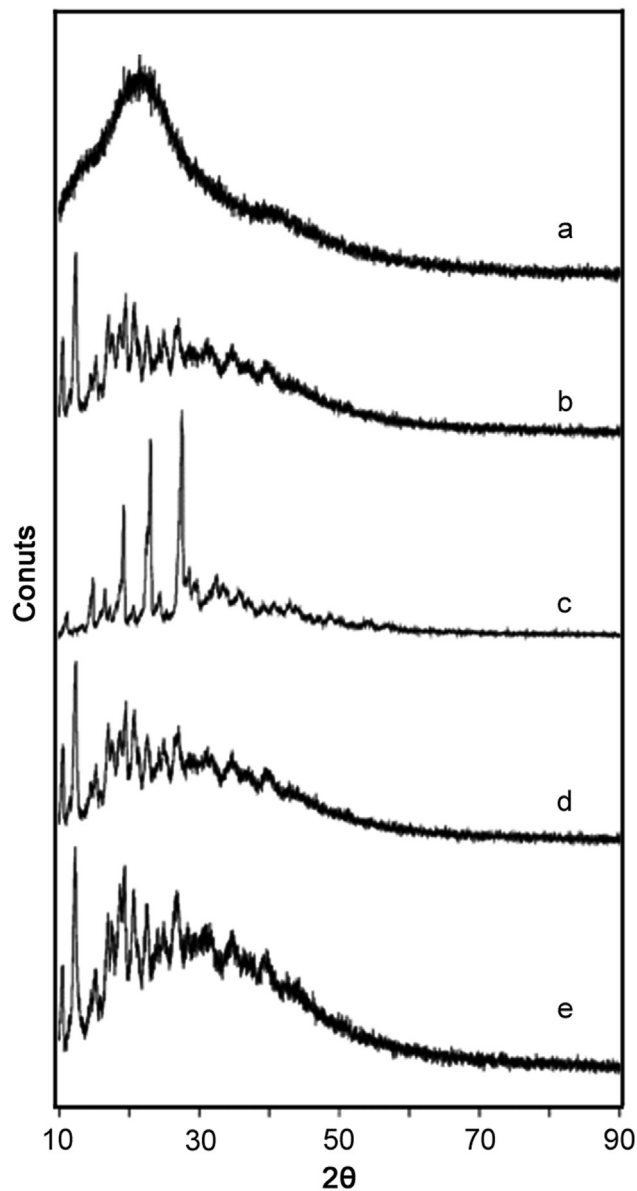


Fig. 5. XRPD patterns of CFA (a), β CD (b), ARG (c), CFA: β CD binary system (d), and CFA:ARG: β CD ternary system (e).

3.5. SEM analysis

The surface morphological features of pure CFA and complexes are shown in Fig. 6. Pure CFA appeared as amorphous broken spherical particles as separate entities (Fig. 6A). There were distinct changes observed in morphology of spray dried complexes. The particles of binary complexes exhibited altered shape and showed bulky spherical agglomerate type morphology (Fig. 6B) due to crystalline nature of β CD. The crystalline nature of β CD and ARG also further contributed to change in morphology of ternary complexes (Fig. 6C) showing characteristic bulky agglomerated crystalline structure images. The alteration in the morphology of particles in spray dried complexes confirmed the presence of a new solid phase in the complex achieving maximum complexation [29].

3.6. Saturation solubility studies

The saturation solubility studies of binary and ternary systems showed remarkable enhancement in the solubility as compared to pure CFA ($p < 0.001$). Pure CFA exhibited a solubility of

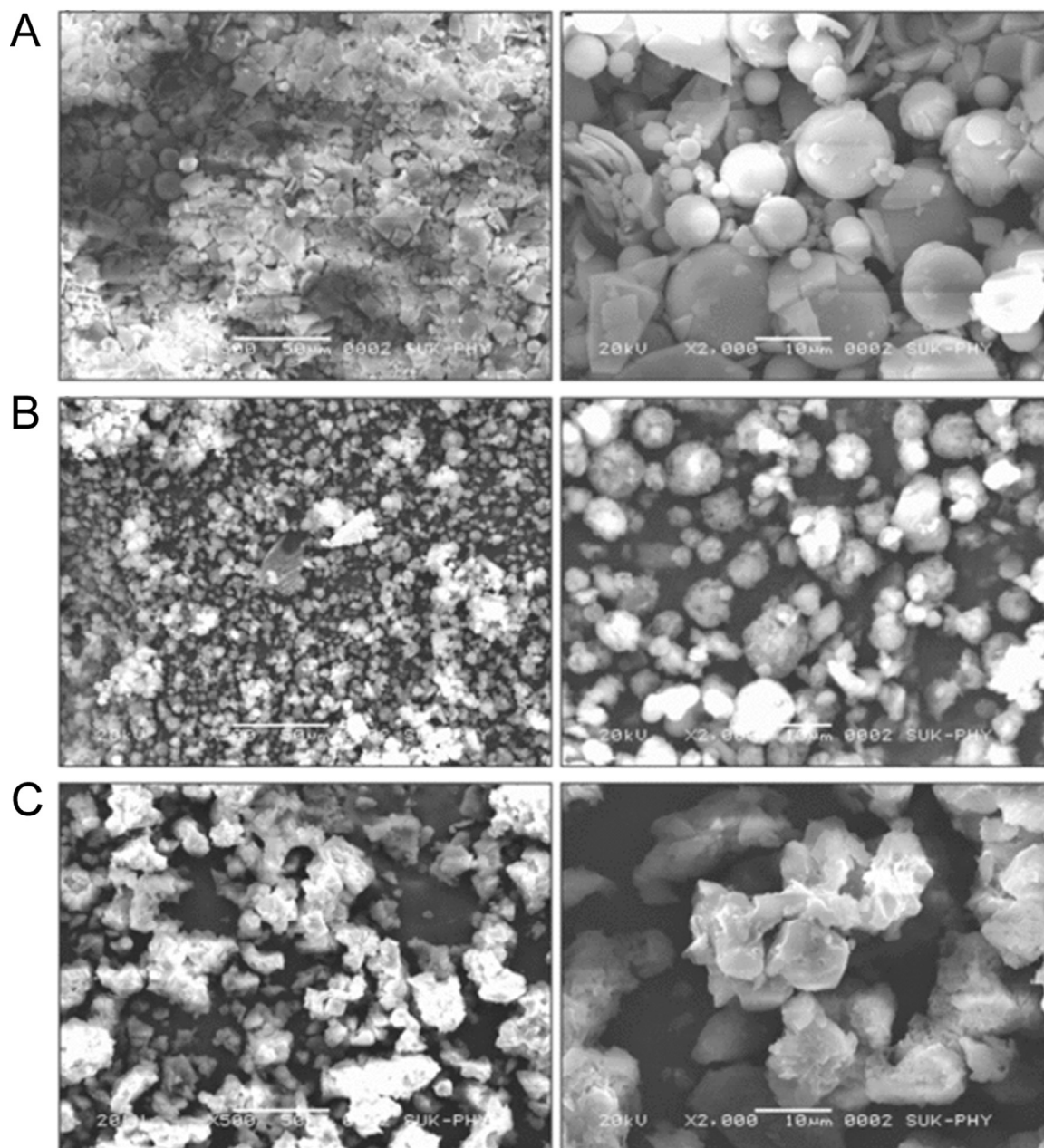


Fig. 6. SEM of (A) CFA, (B) CFA:βCD binary system and (C) CFA:ARG:βCD ternary system.

0.355 ± 0.04 mg/mL in distilled water. The binary and ternary complexes showed solubility of 8.66 ± 0.30 and 16.87 ± 0.72 mg/mL, respectively. There was 24.39 fold increment in the solubility of binary complex observed, whereas 47.50 fold increment in the solubility of ternary complex was noted, which was almost double than that of binary complex. The enhancement in solubility of complex was attributed to the formation of stable inclusion complex of CFA with βCD. In ternary systems, ARG played a significant role as a ternary component resulting in better performance than binary system.

The improvement in water solubility of CFA from the complexes could be explained in terms of wetting property and hydrophilicity of βCD, altered surface morphological features of the complexes due to spray drying technique and inclusion into the hydrophobic βCD cavity [30].

3.7. Dissolution studies

The dissolution curves of CFA and spray dried complexes are

shown in Fig. 7. According to the results, an increment in dissolution profile was noted for solid complexes as compared to pure CFA ($p < 0.001$). The binary systems showed almost complete drug release in 60 min. Indeed, ternary complexes demonstrated faster dissolution profile than binary complexes with 99.87% drug release within 25 min in dissolution media. However, the release of pure drug was incomplete even in 90 min.

The significant improvement in dissolution rate of CFA from inclusion complexes could be ascribed to greater hydrophilicity, wetting property, increased contact between the drug and βCD due to spray drying technology and ability to form stable inclusion complex with βCD [30]. The greater effectiveness of ternary complex for higher release rate was due to positive effect of addition of basic amino acid ARG which drastically promoted phase solubility parameters such as K_s and CE, interacting simultaneously both with βCD (via hydrogen bonding) and CFA (via electrostatic interactions and salt formation) [11,22,31]. Thus, it

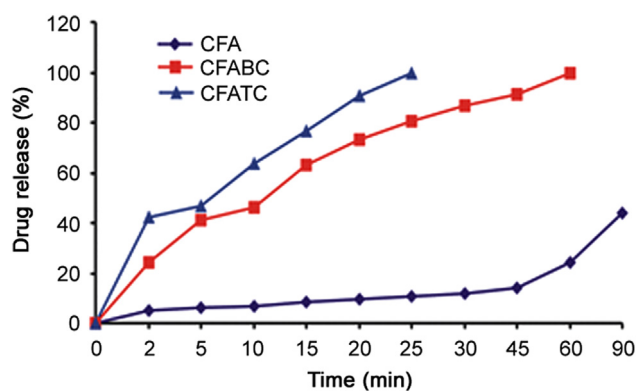


Fig. 7. The dissolution profile of CFA, binary and ternary inclusion complexes at 37 ± 0.5 °C. CFA: cefuroxime axetil; CFABC: binary system; CFATC: ternary system with ARG.

can be concluded that ternary systems of CFA with β CD and ARG could be a reliable approach for improved dissolution properties.

4. Conclusions

The present study demonstrated a successful application of basic amino acid ARG as a ternary component to improve the physicochemical properties of CFA via ternary complexation with β CD. The significant enhancement in association constant and complexation efficiency of β CD towards CFA in presence of ARG could be possibly helpful in reducing the workable amount of β CD during formulation of complexes. In conclusion, CFA can form stable inclusion complexes with β CD in presence of ARG as an auxiliary substance to offer ternary systems with better performances.

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