Physicochemical Characterization of Febuxostat Microcomplexes with Parent and Modified Cyclodextrins

Sayee V. Aher[1] and Yogesh V. Pore[2]

[1]Department of Pharmaceutical Chemistry, Government College of Pharmacy, Karad
Maharashtra 415 124, India
[2]Department of Pharmaceutical Chemistry, Government College of Pharmacy, Ratnagiri
Maharashtra 415 612, India

ABSTRACT: Febuxostat, a BCS class II antigout drug was complexed with β-cyclodextrin (βCD), hydroxypropyl-β-cyclodextrin (HPβCD) and / or methyl-β-cyclodextrin (MβCD), to improve its physicochemical properties. Earlier phase solubility and thermodynamic investigations in acetate buffer (pH 4.5) illustrated A_L (linear) type of solubility curve and enthalpy driven complexation process, respectively. The association constant and complexation efficiency of modified cyclodextrins (CDs) were significantly higher than that of parent cyclodextrin (CD). The micro-complexes prepared by spray drying process were examined for their spectral, diffractometric, thermal, particle size, saturation solubility, Log *P* and dissolution properties. The physicochemical properties of pure drug were improved upon complexation with CDs. However, modified CDs produced amorphous micro-complexes contributing for their better performance as compared to parent CD.

Key words: Febuxostat; cyclodextrins; micro-complexes; characterization; thermodynamic; phase solubility.

INTRODUCTION

Cyclodextrins (CDs) are cyclic oligosaccharides containing internal hydrophobic central cavity and external hydrophilic surface produced from starch which contain six (α-CDs), seven (β-CDs), eight (β-CDs) glycopyranose units linked by α-1,4 glucosidic bonds. The β-form is widely accessible and mostly preferred cyclodextrin with 6-7 Å internal cavity size.[1,2] The inclusion phenomena of drug (guest) into the cyclodextrin (host) is the most extensively used and industrially applicable technique exploited to enhance the physicochemical properties of the guest.[3,4] CDs have been promisingly established to be the modifiable and flexible carriers in the pharmaceutical research. On the contrary, the natural parent β-cyclodextrin (βCD) have constrained the solubility and the complexation with the hydrophobic active moieties.[1] Further, modification in the parent CDs have widen the scope and use of modified CDs towards improving the properties of active pharmaceutical ingredients (APIs) due to their advantages such as high efficiencies, amorphous nature[5], low cost and low toxicity.[6]

Febuxostat (FBX) (Figure 1) is a thiazole derivative, non-purine-selective inhibitor of xanthine oxidase (XO) enzyme that converts oxypurines like hypoxanthine and xanthine, into uric acid.[7] It is orally used in treatment of gout. The essential structural aspect of FBX is the presence of lipophilic functionality that promotes its absorption upon oral administration. Nonethlessly, FBX exists in crystalline state and has poor water solubility and dissolution in gastrointestinal tract. Therefore, these properties of FBX are bound to limit its use resulting

Correspondence to : Yogesh V. Pore
Tel: +91-02352-221201
Email: dryogeshpore@rediffmail.com

in poor therapeutic window. Hence FBX was selected for cyclodextrin complexation. Very few experiments have been performed on FBX cyclodextrin complexation for its solubility and dissolution improvement.[8,9] However, complexation with methyl-β-cyclodextrin (MβCD) has not been reported yet.
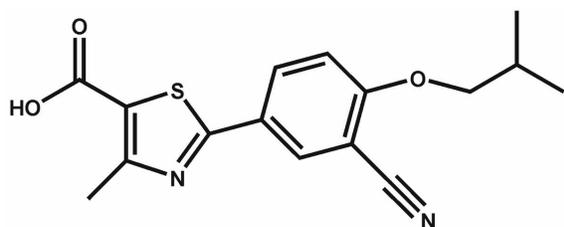

Figure 1. Chemical srtructure of febuxostat (FBX).

The objectives of the present work were to investigate the efficiencies and physicochemical properties of FBX with parent and modified cyclodextrins. Firstly, the stiochiometry of complexation along with thermodynamic parameters for the complexation phenomena was assessed by phase solubility studies. The spray dried complexes were characterized by thermal, diffractometric particle size analysis, fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), saturation solubility, partition coefficient determination (log *P*) and drug content uniformity. The dissolution profile of pure drug and complexes were further assessed in phosphate buffer pH 7.4.

MATERIAL AND METHODS

Materials. FBX was provided by INDOCO Remedies Ltd.,Waluj, India as a gift sample. βCD and hydroxypropyl-β-cyclodextrin (HPβCD) were supplied by Gangwal Chemicals, Mumbai, India. MβCD was purchased from TCI Chemicals, Mumbai, India. The reagents used were all of pharmaceutical and analytical grade. All materials were used as received without further purification.

Phase solubility studies and thermodynamic investigations. The most widely used approach to study inclusion complexation is the phase solubility

method described by Higuchi and Connors, which examines the effect of a solubilizer (CD or ligand) on the drug being solubilized (substrate).[10] For phase solubility studies, an excess amount of FBX was added to 10 mL of acetate buffer (pH 4.5) containing 0-5 mM of βCD or HPβCD or MβCD solutions and transferred to 25 mL of screw cap glass tubes. The suspensions were sealed and equilibrated in a shaking incubator at 150 rpm for 48 h at 298, 303, 310 ± 2 K temperatures. After equilibrium was achieved, aliquots of 2 ml were withdrawn and filtered immediately using 0.45μm membrane filter. The filtered samples were diluted suitably with distilled water and assayed for FBX by measuring absorbance at 313.5 nm against blank by UV-Visible spectrophotometer (Shimadzu 1800, Japan). The stability constant (*K*s) was calculated from phase solubility diagrams assuming the 1 : 1 stoichiometry, according to following equation.[5]

$$K\text{s} = \quad \text{Slope} / S_0 \, (1\text{-Slope}) \quad (1)$$

S_0 is the solubility of FBX in absence of CDs.

Complexation efficiency

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

For the assessment of thermodynamic parameters from phase solubility curves, an integrated form of the Van't Hoff equation (as shown below) was employed for the calculations of the enthalpy (ΔH) and of entropy (ΔS), corresponding to the changes observed in stability constants with temperatures[5]

$$\text{In K} \quad = \quad -\Delta\text{H} /\text{RT} + \Delta\text{S} /\text{R} \quad (3)$$

ΔH and ΔS are the enthalpy and entropy of the complex respectively, R is the gas constant, and T is temperature in Kelvin.

An indication of process of transfer of FBX from pure water to buffer solution of βCD, HPβCD, MβCD was obtained from the values of Gibbs free energy of transfer (ΔG$_{tr}$°) and it was calculated using the following equation:

$$\Delta\text{Gtr}^0 = -2.303RT\log{(Sc/S_0)} \quad (4)$$

Where, Sc/S_0 is the ratio of molar solubility of FBX in buffer solution to that in buffer solution in absence of CDs.

Preparation of solid systems by spray drying. For the preparation of binary system, equimolar quantities of FBX and CDs were transferred into conical flask containing 200 ml of methanolic acetate buffer (pH 4.5) and sonicated for 10 min. The mixture was stirred for 96 h at a room temperature ($25 \pm 2°C$) on 150 rpm by using a magnetic stirrer. The solution was filtered immediately using 0.45 µm membrane filter to separate uncomplexed drug. The resultant solution was spray dried using Lab spray dryer (SPD-D-111 Techno Search Instruments, Thane, India) under following set of conditions: Inlet temp, 65°C, outlet temp 45°C, cool temp 20°C, aspirator speed 40 mbr, feed rate 8 mL/min. The spray dried powder was stored in desiccators, to prevent it from moisture absorption.

Particle size and zeta potential analysis. The micro-complexes were characterized for particle size using a Horiba nanoparticle size analyzer (HORIBA SZ-100, Japan). The particle size distribution is given by d (0.9), d (0.5) and d (0.1) which is the particle size diameters determined at the 90th, 50th, and the 10th percentile of particle undersized, respectively.

X-ray powder diffractometry (XRPD). The XRPD patterns of FBX, βCD, HPβ-CD, Mβ-CD and all complexes were recorded by using X-ray diffractometer (BRUKER-D2 PHA-SER, Germany) with tube anode Cu over the interval 10-80°/2°. The operational data were as follows: Generator tension (voltage) 40kV, Generator current 30 mA, and scanning speed 2°/ min.

Differential scanning calorimetry (DSC). Thermal analysis of all samples were performed on DSC analyzer (TA Instruments, SDT Q600,USA). A sample (5mg) was sealed in an aluminium pan and heated under a nitrogen atmosphere at a heating rate of 10°C/min over the temperature range of 30-300°C.

Fourier transform infrared spectroscopy (IR). IR (Bruker, Germany) was used in attenuated total reflectance (ATIR) model for collecting the IR spectra of the samples. The spectra of the samples were collected over the range of 4000–600 cm^{-1} in 24 scans, with a resolution of 4 cm^{-1} for each sample by using opus software.

Scanning electron microscopy (SEM). All samples were directly mounted on aluminium stub and coated with a thin gold-ion layer by sputter coated unit. The surface morphology was examined with a scanning electron microscopy (SEM-JEOL Instruments, JSM-6360, Japan.) operated at an acceleration voltage of 20kV and obtained micrographs were examined at x500, x1,000, x2,000 magnifications.

Percentage drug content study. Drug content was examined by dissolving prepared binary complexes equivalent to 5 mg drug in methanol. The volume was adjusted with distilled water. The solution was filtered through Whatmann filter paper no. 41, suitably diluted and absorbance was measured at 314.5 nm using a UV spectrophotometer (Shimadzu 1800, Japan).

Saturation solubility studies. The saturation solubility studies were carried out in triplicate manner, by adding an excess amount of FBX and / or complexes to 10 ml of distilled water in solubility tubes and shaken on rotary shaker at room temperature ($25 \pm 2°C$) on 150 rpm for 24 h. After reaching equilibrium, aliquots of the solution withdrawn and filtered with Whatman filter paper no. 41, suitably diluted and absorbance was measured at 314.5 nm by UV-spectrophotometer (Shimadzu 1800, Japan) and the results were statistically analyzed using appropriate method.

***In vitro* drug release.** The dissolution studies of FBX alone and binary systems were carried out in triplicate manner in dissolution apparatus (ELECTROLAB-TST-06L/LX, New Mumbai, India), using the paddle method, according to USP type II. Samples were added in dissolution vessel containing 900 mL of phosphate buffer (pH 7.4), maintained previously at $37 \pm 0.5°C$ at 100 rpm according to US FDA guidelines. 80 mg of pure drug or its equivalent amount of prepared binary inclusion complexes were added to 900 mL of phosphate buffer (pH 7.4). 5 ml of sample was withdrawn at time intervals of 5, 10, 15, 30, 45, 60 and 90 min. The volume of dissolution medium was adjusted to 900 ml by replacing each 5 mL aliquot withdrawn

with 5 ml of fresh phosphate buffer (pH 7.4). The solution was filtered through 0.45 µm Whatman filter paper 41, suitably diluted and concentrations of FBX in the samples were determined spectrophotometrically at 314 nm (Shimadzu 1800, Japan).

Determination of partition coefficient (log *P*). For the determination partition coefficient, 10 ml each of octanol and water were added in glass tubes and allowed to stand overnight for 24 hrs at room temperature. The excess amount (equivalent to 25 mg) of pure drug and /or complexes were added to the tubes and shaken on an incubator shaker (REMI-CIS 24 plus Incubator shaker, Mumbai, India) for 24 hrs at 25ºC. The mixtures were transferred to separating funnel and allowed to stand about 6 h for equilibration. Aqueous and organic phase was separated and concentration of drug in aqueous phase was detremined spectrophotometrically (Shimadzu 1800, Japan) at 314.3 nm. The partition coefficient was calculated by following formula,

Partition coefficient (log P) = (log$C_{octanol}$/C water)

Where C is the concentration of the drug in octanol and/or water phase.[5]

RESULTS AND DISCUSSION

Phase solubility and thermodynamic investigations. The phase solubility curve of FBX in buffer CDs solutions at 298, 303, 310 ± 2 K are shown in figure 2. All phase solubility parameters investigated are shown in table 1. The solubility of FBX increased linearly (A_L –type) as a function of CDs concentration, illustrating formation of soluble complexes in all systems.[11] The slopes of all phase solubility diagrams found to be less than unity estimating 1:1 stoichiometry in all cases.[10] The *K*s and CE of βCD were significantly upgraded in case of HPβCD and MβCD justifying positive effect of modified CDs towards solubility enhancement of FBX.

Table 1. Phase solubility data of binary complexes of FBX with βCD, HPβCD and MβCD.

Complex/ Parameter	T (K)	S_o	Slope	R^2	*K*s (M^{-1})	C.E.
FBX-βCD	298	0.00004241	0.10548	0.995	2867	0.11
	303	0.00007631	0.09189	0.997	1446	0.10
	310	0.0001607	0.11212	0.993	790	0.13
FBX-HPβCD	298	0.00004241	0.13998	0.998	3192[a]	0.16[b]
	303	0.00007631	0.15707	0.995	2662[a]	0.19[b]
	310	0.0001607	0.18705	0.996	1588[a]	0.23[b]
FBX-MβCD	298	0.00004241	0.32997	0.999	11869[a]	0.49[b]
	303	0.00007631	0.31245	0.997	9888[a]	0.45[b]
	310	0.0001607	0.49267	0.998	5019[a]	0.97[b]

Binary complexes: FBX-βCD, FBX-HPβCD, FBX-MβCD; FBX: Febuxostat; βCD: β-cyclodextrin; HPβCD: Hydroxy propyl β-cyclodextrin; MβCD: Methyl β-cyclodextrin; S_0: solubility of FBX in absence of βCD, HPβCD, MβCD; R^2: regression coefficient of phase solubility plot; *K*s (M^{-1}): association constant of complexes; CE: complexation efficiency; [a]: significant difference compared to FBX-βCD ($p < 0.001$) i.e. significant; [b]: significant difference compared to FBX-βCD ($p < 0.001$) i.e. significant.

The phase solubility data accomplished at different temperatures gave subsidiary particulars like thermodynamic specifications associated with formation of inclusion complexes as in table 2. The Van't Hoffs plot (Figure 3) exemplified the linear function between *K*s and the inverse of absolute temperatures (1/T). The values of enthalpy (ΔH) comprehending to all the systems were found to be negative, revealing the complexation process to be enthalpy driven exothermic process. The more negative values of the entropy (ΔS) indicated the high orderness of complexes in case of all the systems.

The complexation process being exothermic and decrease in the entropy of the system demonstrating the spontaneity of complex formation towards the lower temperature. An indication of process of transfer of FBX from buffer solution to aqueous buffer solution of CDs was procured from the values
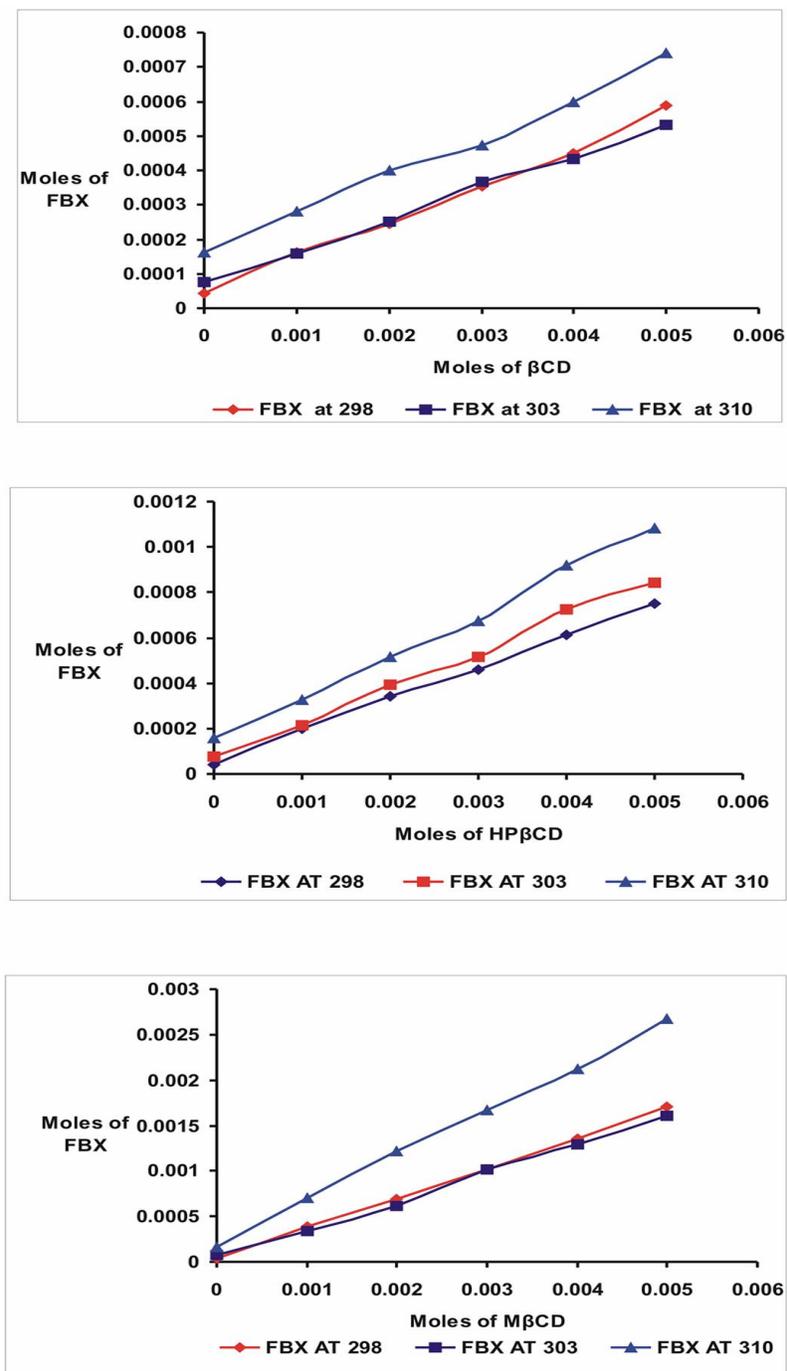

Figure 2. Phase solubility diagram of FBX:βCD, FBX:HPβCD, FBX:MβCD inclusion complexes at 298, 303, 310 ± 2 K in acetate buffer pH 4.5. FBX: Febuxostat; βCD: β-cyclodextrin; HPβCD: Hydroxy propyl β-cyclodextrin; MβCD: Methyl β-cyclodextrin.

Table 2. Thermodynamic specifications involved in inclusion phenomena of FBX with cyclodextrins.

Complex /Thermodynamic Parameter	ΔH (kJ/mol)	ΔS (J/mol/K)	ΔG (kJ/mol)
FBX-βCD	-81.60	-208.01	-19.62
FBX-HPβCD	-45.39	-84.81	-20.11
FBX-MβCD	-57.13	-113.06	-23.42

Binary complexes: FBX-βCD, FBX-HPβCD, FBX-MβCD; FBX: Febuxostat; βCD: β-cyclodextrin; HPβCD: Hydroxy propyl β-cyclodextrin; MβCD: Methyl β-cyclodextrin; ΔH: enthalpy; ΔS: entropy; ΔG: Gibb's free energy

Table 3. Particle size, zeta potential and polydispersity index of microcomplexes of FBX with cyclodextrins.

Complex/ Parameter	Particle size (μm)	Zeta potential (± mV)	Polydispersity index (PI)
FBX	2.7333	-41.3	3.424
FBX-βCD	1.0889	-25.6	0.449
FBX-HPβCD	0.1901	-41.7	2.716
FBX-MβCD	0.8227	-28.8	0.528

Binary complexes: FBX-βCD, FBX-HPβD, FBX-MβCD; FBX: Febuxostat; βCD: β-cyclodextrin; HPβCD: Hydroxy propyl β-cyclodextrin; MβCD: Methyl β-cyclodextrin

of gibbs free energy change. For the concentration of βCD, HPβCD, MβCD, 0.001, 0.002, 0.003, 0.004, 0.005 M, the values of ΔGtr° (kJ/mol) in buffer solution of βCD were found to be, -279.84, -365.41, -441.27, -476.45, -546.14, HPβCD were found to be,-340.77,-440.51,-494.69,-554.7,-597.59 and in case of MβCD,-461.65,-582.47,-661.28,-721.97,-770.41. The ΔGtr° values were all negative for CDs at various concentration, giving idea about the spontaneous nature of FBX solubilisation, and it decreased with an increase in its concentration, indicating that the reaction became more favourable as the concentration of CDs increased.[12] These values indicated that the system was releasing the energy upon complexation forming a ordered complexes respectively, implying highly stable physical state of all the complexes.

Particle size and zeta potential analysis. The particle size analysis found out of all complexes to be in micron range. The particle size of pure FBX was found to be 2.7333μm. The particle size of the binary systems was, 1.0889 μm 0.1901μm, 0.8227 μm of βCD, HPβCD and MβCD complexes respectively. Using spray drying technology, the size of pure drug was significantly reduced in formulations.[13] This has increased the specific surface area thereof enhancement of dissolution of FBX particles.[14] The uniformity of the particle size can be examined by the determination of the polydispersity index (PI) which was found to be less than 1 in case of HPβCD and MβCD systems whereas βCD system showed the PI approaching the value 1 as shown in table 3. All the systems were subjected to zeta potential analysis and values were found to be as shown in table 3. The values of zeta potential for βCD and MβCD systems were found to be approaching towards the stability values whereas the HPβCD system showed slight increase in the stability than that of the FBX.[15]

X-ray powder diffractometry (XRPD). The physical state of pure drug and all binary systems can be determined by evaluating the XRPD patterns as shown in the figure 4. The diffractogram of FBX (Figure 4A) exhibited 2θ values at 11.30 (1020), 15.48 (522), 17.04 (466), 24.60 (819), 25.33 (839) indicative of its crystalline nature. In case of HPβCD and MβCD (Figure 4B, 4F respectively) a typical halo-pattern unveiling its amorphous character appeared whereas βCD (Figure 4D) showed the 2θ values at 10.67 (1750), 12.39 (1554), 15.38 (734),18.71 (1027), 22.65 (1051) indicating its crystalline nature. The intense peaks in the diffraction pattern of FBX and CDs (Figure 4C, 4E, 4G) were

completely diffused in the binary complexes providing the information of significant reduction in

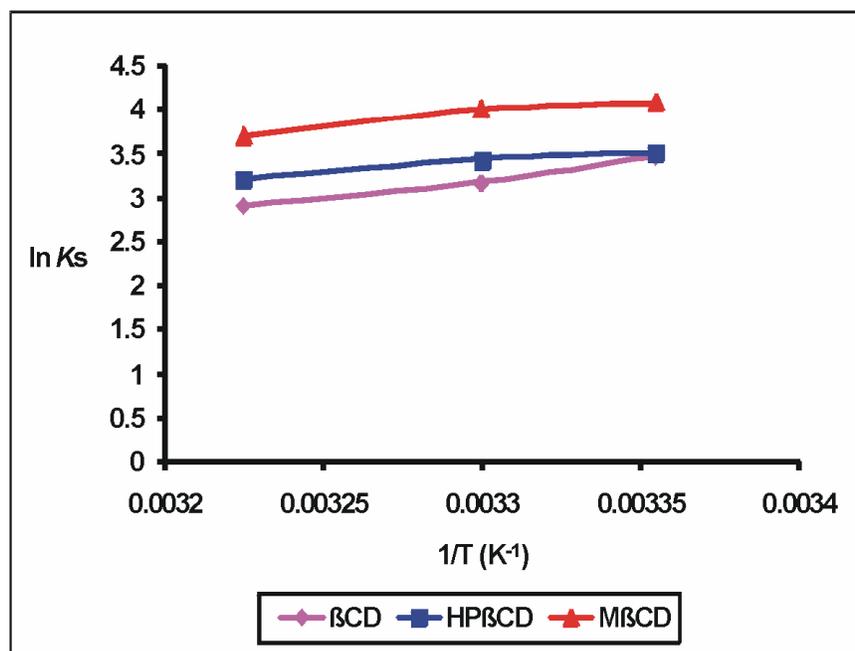the crystallinity contributing to its solubility and dissolution enhancement.[14]

Figure 3. Van't Hoff plots (ln *K* vs 1/*T*) for FBX:βCD, FBX:HPβCD, FBX:MβCD inclusion complexes, determined by solubility diagrams experiments. FBX:Febuxostat; βCD: β-cyclodextrin; HPβCD: Hydroxy propyl β-cyclodextrin; MβCD:Methyl β-cyclodextrin.

Differential scanning calorimetry (DSC). DSC technique has been widely used to study the interaction between host and guest molecules. When the drug is complexed in CD cavity, its melting points usually shift to different temperatures or disappears.[16-18]

DSC pattern of FBX and all systems are shown in Figure 5. DSC thermogram of FBX showed sharp melting point endotherm at 195.36ºC (Figure 5A), while thermogram of HPβCD did not exhibit any melting endotherm (Figure 5B) indicating its amorphous nature. The broad endothermic peaks shown by βCD at 96.41ºC (Figure 5D), indicated the crystalline phase that was diffused in its binary complex. MβCD exhibited the endothermic peak at 73.67 ºC (Figure 5F), indicative of water loss due to dehydration process.[19,20] The binary complexes

(Figure 5C, 5E, 5G) showed the disappearance of the broad endotherms of pure FBX confirming its entrapment in CD cavities replacing the water molecules. These results theorize the presence of physical interaction between the FBX and CDs forming stable inclusion complex.

Fourier transformation infrared spectroscopy (FTIR). The various possible interactions between the drug and the CDs were studied by ATR-IR spectroscopy. The IR spectras of all the systems are shown in Figure 6.

The principle absorption peaks of FBX (Figure 6A) were observed at 2227cm⁻¹ (C≡N stretch), 2964 cm⁻¹ (C-H stretch, aliphatic/ asymmetric), 2876.91cm⁻¹ (C-H stretch, aliphatic symmetric), 1424.72 cm⁻¹ (C=N), 1513.45 cm⁻¹ (C=C stretch, aromatic), 725.12cm⁻¹ (CH$_2$-stretch), 1288.46 cm⁻¹ (C-N stretch)
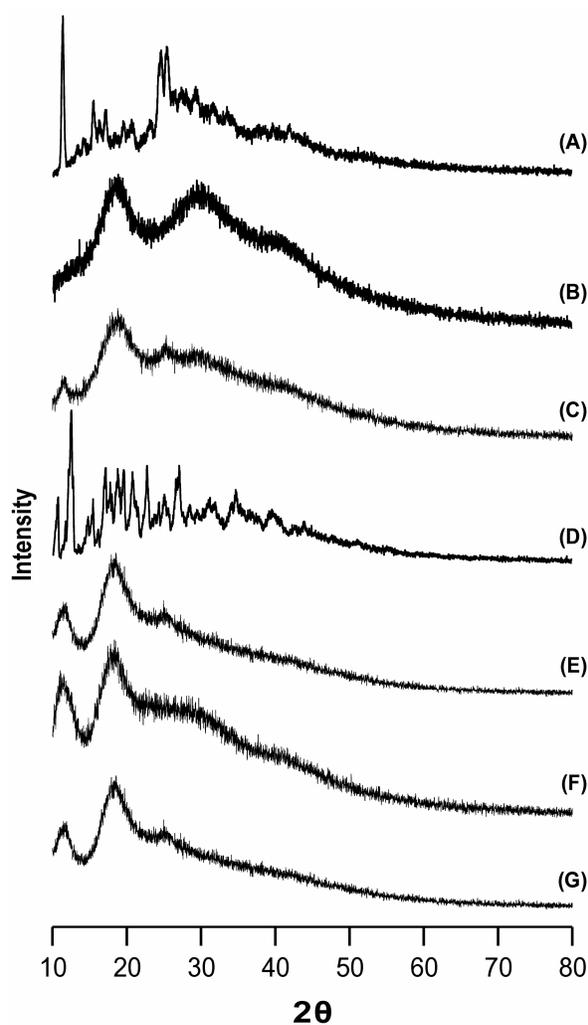
Figure 4. XRPD patterns of FBX (A), HPβCD (B), HPβCD complex (C), βCD (D), βCD complex (E), MβCD (F), MβCD complex (G). FBX: Febuxostat; βCD: β-cyclodextrin; HPβCD: Hydroxy propyl β-cyclodextrin; MβCD: Methyl β-cyclodextrin.
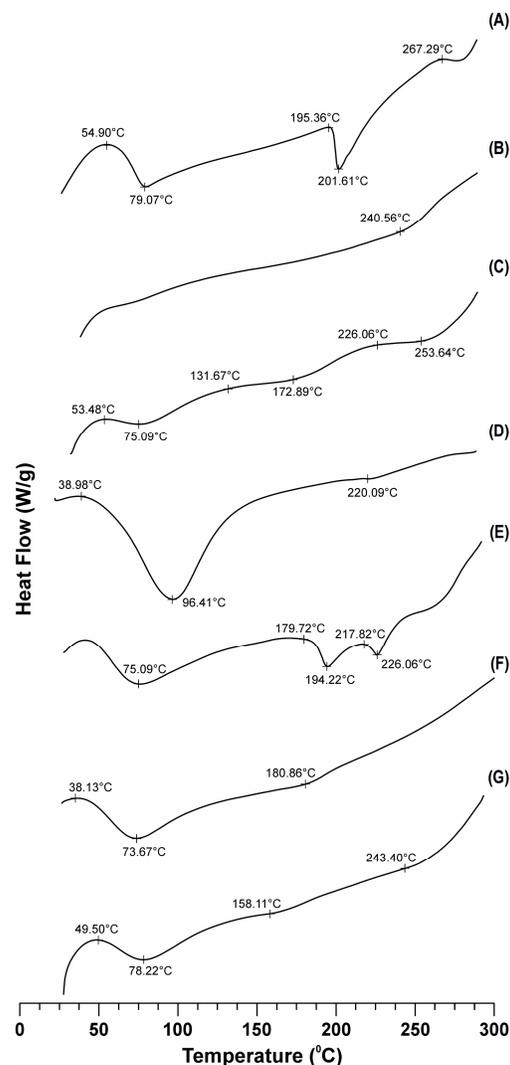
Figure 5. DSC thermograms of FBX (A), HPβCD (B), HPβCD complex (C), βCD (D), βCD complex (E), MβCD (F), MβCD complex (G). FBX: Febuxostat; βCD: β-cyclodextrin; HPβCD: Hydroxy propyl β-cyclodextrin; MβCD: Methyl β-cyclodextrin.

and 3534.29 cm^{-1}(O-H stretch). Figure 6B shows absorption bands of HPβCD at 3379.88 cm^{-1} (O-H stretch), 1022.17 cm^{-1} (C-O-C stretch), 1655.32 cm^{-1} (H-OH bending). Figure 6D displays spectra of βCD at 3405.10 cm^{-1} (O-H stretch), 2945.01 cm^{-1} (C-H stretch, symmetric), 1645.63 cm^{-1} (H-OH bending), 1030.45 cm^{-1} (C-O-C stretch). In the spectra of MβCD (Figure 6F), absorption peaks appered at 3362.41cm^{-1} (O-H stretch), 1010.32 cm^{-1} (C-O-C), 2943.88 cm^{-1} (C-H stretch), 1637.28 cm^{-1} (H-O-H),

2943.88 cm^{-1} (C-H aliphatic). In case of all the binary systems (Figure 6C, 6E, 6G) the prominent peaks of FBX and the CDs were modified (frequency shift / attenuation/ broadening). The peaks observed in the formulation were found to be smooth and showed no appearance of any new peak suggesting existence of only physical interaction between host and guest.[21]

Scanning electron microscopy (SEM). SEM was used to investigate the microscopic surface and morphological characteristics of pure drug and

complexes as shown in figure 7. FBX was characterized by the presence of uneven and elongated particles. The microphotographs of spray dried inclusion complexes showed the characteristic morphology as spherical pieces of amorphous aggregates and the original morphologies of pure FBX diminished. These microphotographs suggested
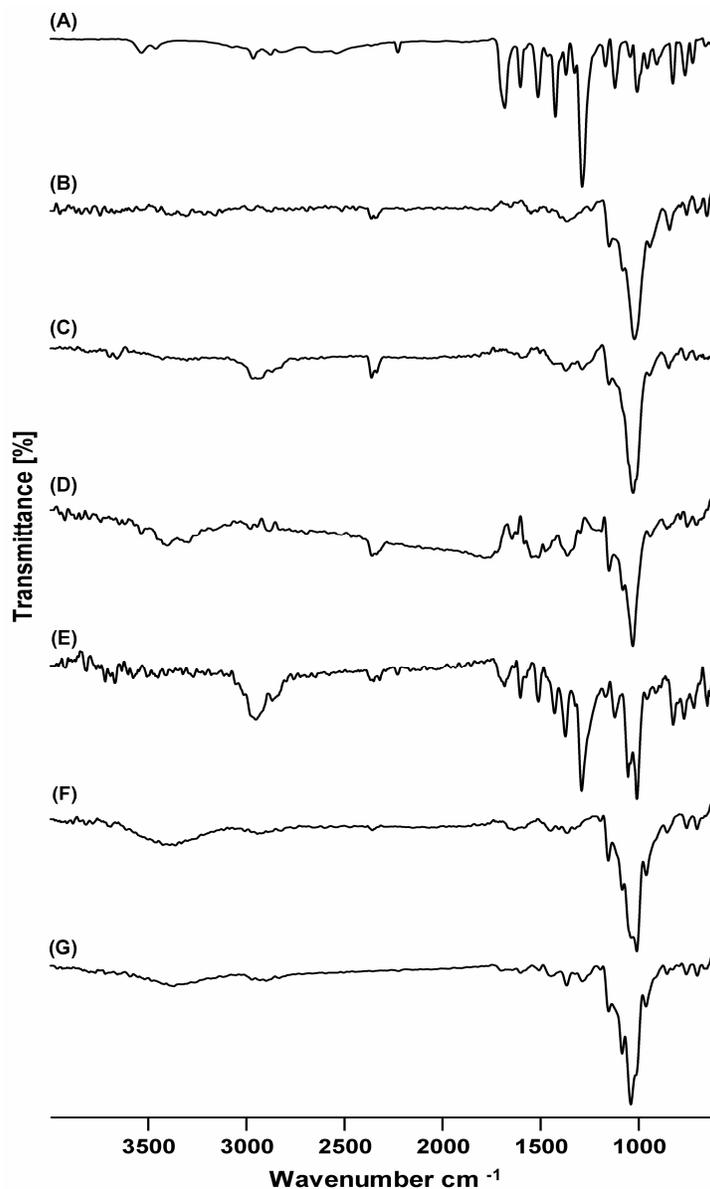

Figure 6. IR spectra FBX (A), HPβCD (B), HPβCD complex (C), βCD (D), βCD complex (E), MβCD (F), MβCD complex (G). FBX: Febuxostat; βCD: β-cyclodextrin; HPβCD: Hydroxy propyl β-cyclodextrin; MβCD: Methyl β-cyclodextrin.

the formation of complexes of FBX with hydrophilic βCD, HPβCD and MβCD in the solid state. Thus, altered particle shape, amorphous aggregates and close contact between hydrophilic CD in complexes might be responsible for improved physicochemical properties of FBX. Further spray drying technology had contributed for amorphous natured complexes resulting improved drug release from the complexes.[14]

Percentage drug content and saturation solubility studies. The percentage drug content of FBX-βCD, FBX-HPβCD and FBX-MβCD microcomplexes were found to be 71.35 ± 0.65, 99.03 ± 0.24 and 99.99 ± 1.01 w/w respectively.

The saturation solubility of pure FBX, FBX-βCD, FBX-HPβCD and FBX-MβCD complexes observed to be 14.9 ± 0.0200 µg/ml, 21.693 ± 0.03512 µg/ml, 304.7 ± 0.04163 µg/ml and 1200.3 ±

0.25 µg/ml, respectively. The spray dried βCD, HPβCD, MβCD systems showed 1.451, 20.424 and 80.449 fold increase in solubility as compared to pure FBX alone. The enhancement in solubility of FBX from complexes was associated to amorphisation, wetting property and hydrophilicity of CDs, improved complexation efficiency and formation of stable inclusion complexes.[14]
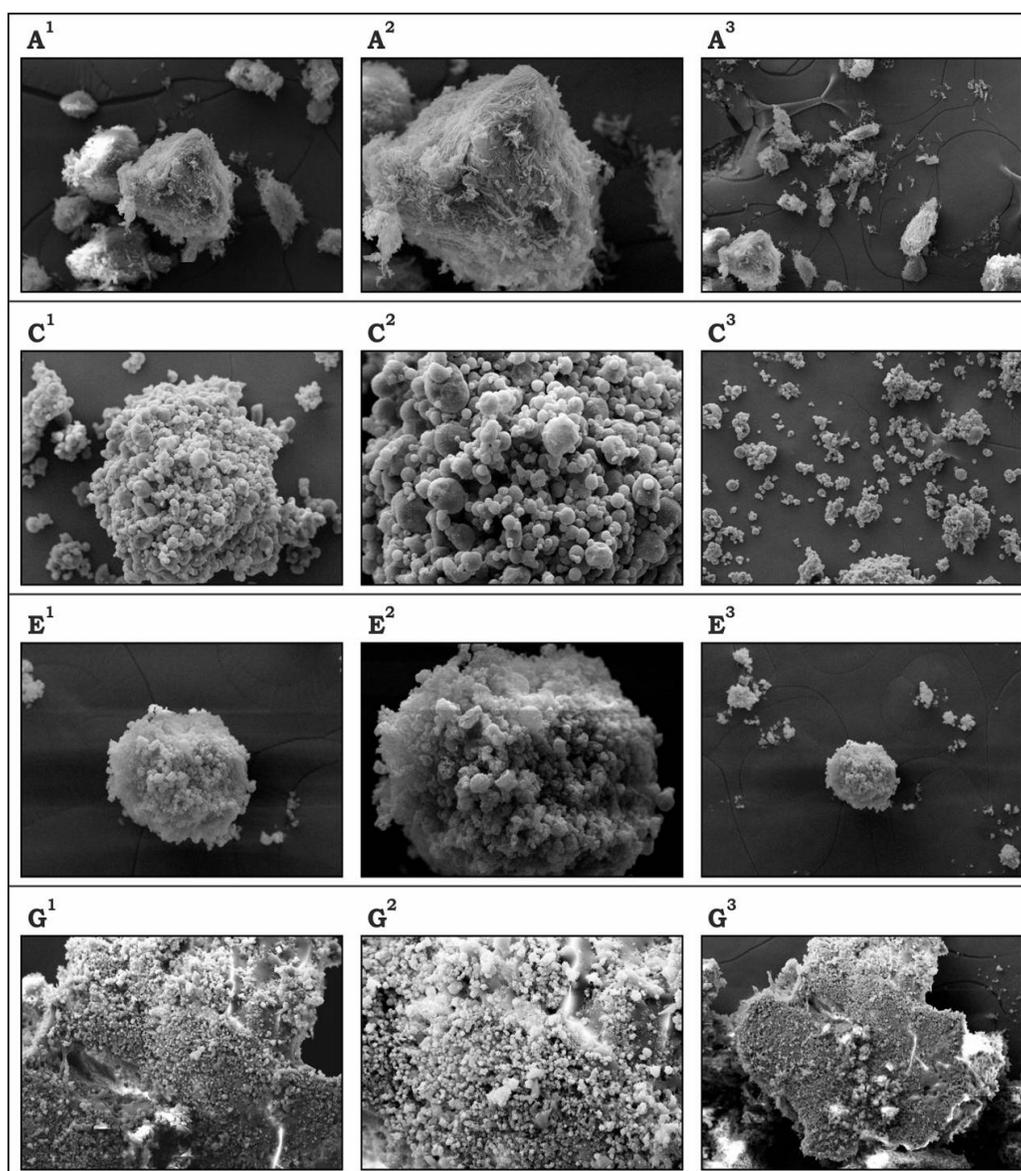

Figure 7. SEM of FBX (A), HPβCD complex (C), βCD complex (E), MβCD complex (G) [1]1kx magnification; [2]2kx magnification; [3]500x magnification. FBX: Febuxostat; βCD: β-cyclodextrin; HPβCD: Hydroxy propyl β-cyclodextrin; MβCD: Methyl β-cyclodextrin.
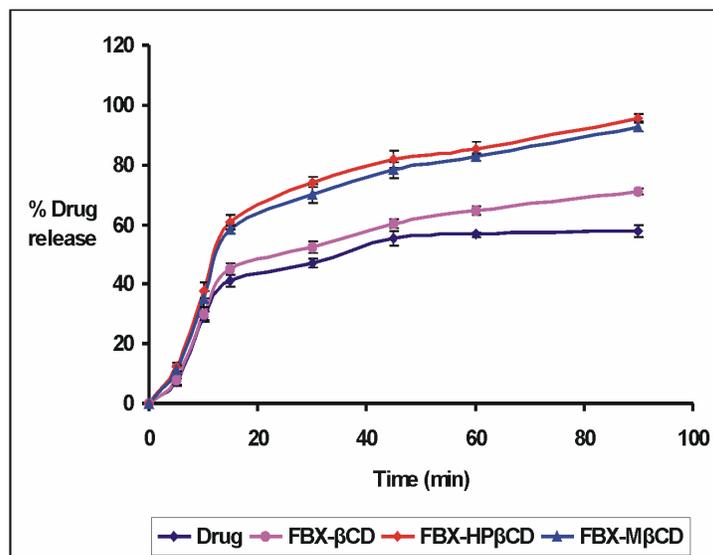
Figure 8. The dissolution Profile of FBX, FBX-βCD, FBX-HPβCD, FBX-MβCD complexes at 37 ± 0.5ºC in phosphate buffer (pH 7.4). FBX: Febuxostat; βCD: β-cyclodextrin; HPβCD: Hydroxy propyl β-cyclodextrin; MβCD: Methyl β-cyclodextrin.

***In vitro* drug release.** The FBX release profile from respective complexes is presented in figure 8. The release rate profiles were given as the percentage of drug dissolved (vs.) time. The values of % drug dissolved in 90 mins (DP$_{90}$) were statistically evaluated. From the results obtained, an improvement in dissolution profile was seen for the binary complexes in comparison to the pure drug. Within the complexes, HPβCD and MβCD systems demonstrated the highest drug dissolution in 90 min than that of βCD which might be attributed to amorphous natute of HPβCD and MβCD over crystallinity of βCD. However, no significant difference was observed between dissolution profiles of the HPβCD and MβCD complexes. The improvement in dissolution of the complexes was attributed to greater hydrophilicity, wetting property, increased contact amoung the drug and the CDs due to use of spray drying technology and ability to form stable inclusion complexes.[22-25]

Determination of partition coefficient (log *P*). The log *P* values of FBX, FBX-βCD, FBX-HPβCD and FBX-MβCD complexes were found to be 3.953 ± 0.056, 2.03 ± 0.020, 1.533 ± 0.025, 1.666 ± 0.025, respectively at 25 ± 2ºC. The reduced log *P* values indicated enhancement in hydrophilicity of binary complexes in correlation to that of the FBX.[5] The use of modified CDs and amorphisation by spray drying resulted in more promising physiochemical properties of FBX.

CONCLUSION

The present studies revealed that FBX microcomplexes with parent and modified CDs were successfully formulated using spray drying technology that aided in an improvement of physicochemical properties in comparison to the drug alone. The thermodynamic specifications accomplished from solubility data at different temperatures was contributive in revealing complex formation between the CDs and FBX which was enthalpy driven exothermic process and spontaneous in nature. It could be concluded that the use of modified CDs over parent CD has offered remarkable advantage towards higher complexation efficiencies as well as dissolution profile due to formation of amorphous of complexes. The enhancement in solubility and dissolution profile of FBX was comprehensively attributed to inclusion complexation, amorphization and reduction in particle size attained using the spray drying technology.

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