Formulation and characterization of ternary complex of poorly soluble duloxetine hydrochloride

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ABSTRACT

Duloxetine hydrochloride (DXH) suffers from poor solubility and thereby poor absorption, which ultimately leads to poor bioavailability. In present study, an attempt has been made to formulate and characterize duloxetine hydrochloride (DXH) complex, using β-cyclodextrin (β-CD) and different hydrophilic polymers in order to enhance its solubility and dissolution rate. Phase solubility study was used to investigate the interaction of the drug in binary systems (DXH-β-CD) as well as ternary systems (DXH-β-CD-hydrophilic polymer). It was observed that solubilization of DXH by β-CD was further enhanced by using HPMC K4M at 0.1% w/v concentration. Several methods were used to prepare ternary complex of DXH-β-CD-HPMC K4M. Ternary complex prepared by co-evaporation method containing DXH-β-CD-HPMC K4M in the ratio of 1:1.10:0.01 has shown the fastest dissolution rate (53.65 ± 2.83% in 5 min) as compared to pure DXH (3.03 ± 1.88% in 5 min) as well as other methods used to prepare these complexes. The prepared ternary complex system was characterized by the help of X-ray powder diffraction studies, differential scanning calorimetry and scanning electron microscopy. It was observed that enhancement in solubility as well as dissolution rate of DXH was due to formation of ternary complex system.

INTRODUCTION

Duloxetine hydrochloride (DXH) is used for the treatment of major depressive disorder (MDD). It is relatively balanced and potent inhibitor of both 5-Hydroxy Tryptamine (5-HT) and Nor-epinephrine (NE) reuptake, with weak effects on dopamine reuptake (Tran *et al.*, 2003). DXH belongs to BCS class-II and thus has poor aqueous solubility. Due to its poor aqueous solubility, after oral administration it possesses lower solubility in the GI fluids. This causes its excretion from the GI tract before its complete dissolution and absorption into the systemic circulation. This causes lower absorption, decreased bioavailability (BA) and poor dose proportionality, which ultimately leads to sub-optimal dosing and poor drug performance (Elkordy *et al.*, 2013). Hence, there is a need to formulate DXH using suitable technique that could be able to enhance its poor aqueous solubility and thereby dissolution rate. The techniques like, particle size reduction to micron or, submicron level (Kubo, 1996; Singh *et al.*, 2011), amorphization

(Latinen *et al.*, 2012; Chieng *et al.*, 2008), co-amorphization (Alleso *et al.*, 2009), formulation of inclusion complexes (Ruan *et al.*, 2005; Singh *et al.*, 2012), solid dispersions (Singh et al., 2011; Barzegar-Jalali and Dastmalchi, 2007; Corrigan, 1985), generation of metastable polymorphs (Renuka *et al.*, 2014), lipid based systems (Pouton, 2000) like self – emulsifying drug delivery systems (SEDDS) have succeeded to deliver poorly soluble drugs with enhanced dissolution profile. Complexation of the API with the complexing agents like β-cyclodextrin is one of the most promising techniques used to enhance the dissolution rate of poorly water soluble drugs. Cyclodextrins have received increasing interest in the pharmaceutical field because of their ability to modify physical, chemical and biological properties of a number of hydrophobic drug molecules through the formation of inclusion complexes (Szejli, 1998; Uekama *et al.*, 1998). However, due to various reasons (such as their high molecular weight, relatively low water solubility and possible parenteral toxicity) the amount of cyclodextrins that can be used in most pharmaceutical formulations is limited (Loftsson and Brewster, 1996). Among the different approaches undertaken with this aim, recent works showed that the addition of suitable auxiliary substances can significantly increase the cyclodextrin solubilizing and complexing abilities by

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multicomponent complex formation (Loftsson and Brewster, 1996). For instance, it was shown that the addition of small amounts of a suitable water-soluble polymer to a drug–cyclodextrin system can improve the performance of the cyclodextrin (Loftsson *et al.*, 1994; Ganzerli *et al.*, 1996; Loftsson *et al.*, 1996). On the other hand, the influence of hydroxy acids in intensifying the cyclodextrin-solubilizing power toward basic drugs can be seen as a result of the combined effects of salt formation and inclusion complexation (Redenti *et al.*, 2000; Mura *et al.*, 2001). Ternary complexation involving salt formation was also reported for acidic drugs (Redenti *et al.*, 2001; Vikmon *et al.*, 1999; Piel *et al.*, 1997). In the present study, an attempt has been made to formulate different complexes of DXH using β-cyclodextrin (β-CD) as complexing agent. The effect of complexation of DXH on its solubility and dissolution rate has been studied. Furthermore, the influence of different hydrophilic polymers in form of ternary complex (i.e. DXH: β-CD: Polymer) on solubility and dissolution rate of DXH, has also been studied.

MATERIALS AND METHODS

Materials

Duloxetine Hydrochloride (DXH) was kindly provided by Intas Pharma., Gujarat, India. HPMC K4M and HPMC E5LV were procured from Colorcon Asia Ltd., Goa, India. β-cyclodextrin (β-CD) was purchased from Central Drug House, New Delhi, India. PVP K-25, PVP K-30, cross caremellose sodium were provided by Loba Chemie Ltd., Mumbai, India.

Solubility studies of DXH using cyclodextrin and different polymers

Phase solubility studies

Phase solubility studies were carried out according to Higuchi and Connors method (Higuchi and Connors, 1965). An excess amount of DXH was added to 10 ml of phosphate buffer (pH 6.8) containing various concentrations of β-CD (0-10 mM) in 10 ml volumetric flasks. Dispersions were shaken for 24 h at room temperature (25 ± 2°C) on a mechanical shaker at 150 rpm. Further, suitable aliquots were withdrawn and filtered through nylon filter paper 0.45 μm (Nylon Acrodisc, Gelman, USA). The filtered solutions were analysed UV-Spectrophotometrically (UV 1800, Shimadzu, Japan) at 289 nm. The apparent solubility constant (K_S) and complexation efficiency (CE) were calculated as follow:

$$K_S = \text{Slope} / S_o (1 - \text{Slope})$$

Complexation efficiency (CE) = Slope / (1 – Slope)
Where, S_o is the solubility of drug in absence of β-CD

Effect of preheating and type of polymer on complexation efficacy of cyclodextrin

In this study an attempt has been made to evaluate the influence of different type of polymers on the complexation efficiency of β-CD. In view of this, four 10 ml standard volumetric flasks were taken, and 6 mM of β-CD was transferred to each of the flasks. Further, to the first volumetric flask HPMC K4M, to second volumetric flask HPMC E5LV, to third volumetric flask PVP K-30 and to the fourth volumetric flask PVP K-25 were added in a concentration of 0.25 % w/v. To all these flasks a known excess of DXH was added and the solutions were kept on a mechanical shaker at 150 rpm at 25 ± 2°C for 24 h. Afterwards, suitable aliquots of samples were withdrawn, filtered through 0.45 μm membrane filter and analysed spectrophotometrically at 289 nm. Further, this study was explored to check combined effect of preheating and type of polymers on complexation efficiency of β-CD. In this the solutions containing DXH were prepared in the same way, but prior to subject the solutions for mechanical shaking for 24 h, they were kept in hot air oven at 60-70°C for 1h. Further, the samples were kept on mechanical shaker and the study was carried out as described in the above paragraph.

Optimization of suitable concentration of hydrophilic polymer

In order to achieve the optimum concentration of selected polymer (i.e. HPMC K4M and PVP K-25), a series of solutions were prepared for both polymers, in the range of 0 to 0.4 % w/v. To all these solutions, 6 mM of β-CD and a known excess of DXH were added. Samples were heated in hot air oven at 70°C for 1 h prior to put on mechanical shaker at 25 ± 2°C for 24 h. After equilibration at room temperature, the suspension was filtered through 0.45μm nylon filter and analysed spectrophometrically at 289 nm after necessary dilution using 0.2M phosphate buffer (pH 6.8).

Preparation of solid complex

Solid complex for ternary complex system (DXH: β-CD: HPMC K4M = 1:1.10:0.01) was formulated by various methods such as physical mixing, kneading, co-precipitation and co-evaporation method. Description of methods is discussed in following sections:

Physical mixing

Physical mixture was prepared by taking DXH, β-CD and HPMC K4M in required ratio. The individual components were sieved (60#) prior to mixing. Mixing was done for 30 and 60 min to investigate effect of mixing time on complexation. These powdered mixtures were stored in desiccator at 25 ± 2°C.

Kneading method

For preparation of ternary complex, DXH, β-CD and HPMC K4M in required quantity, were wetted with minimum quantity of water in order to obtain pasty mass. To evaluate the effect of trituration time, kneading was carried out for 30 and 60 min, respectively. Afterwards, obtained powders were kept for drying at 50°C for one day, further they were crushed, sieved (60#) and stored in desiccator at 25 ± 2°C.

Co-precipitation method

HPMC K4M and β-CD were dissolved in 50 ml of water maintained at 75°C on a magnetic stirrer. DXH (100 mg) was

dissolved in 10 ml of methanol. This was added drop wise into the aqueous solution of HPMC K4M and β-CD. Stirring was continued up to 1 h at 75°C. The solution was gradually cooled to room temperature. The obtained precipitates were filtered, dried, sieved (60#) and stored in desiccator at 25 ± 2°C.

Co-evaporation method

Known amount of DXH, β-CD and HPMC K4M were added in 50 ml of 50% aqueous ethanol to obtain suspension. The suspension was kept for sonication to get clear solution. This solution was subjected to evaporate on magnetic stirrer at 70°C. The obtained complex was dried, sieved (60#) and stored in desiccator at 25 ± 2°C.

In vitro dissolution study

Powders containing DXH equivalent to 22 mg were taken from each batch of prepared complexes and filled into transparent capsule shell. The capsules were subjected for in vitro dissolution study. Dissolution study was performed by using USP I (basket type) dissolution test apparatus (DS 8000, Lab India, Mumbai, India).

Experiment was conducted in 900 ml dissolution medium (0.2 M phosphate buffer pH 6.8) using 75 rpm at 37 ± 0.5°C. Samples (5 ml) were withdrawn at predetermined time intervals from the dissolution medium and equal volume was replaced immediately by fresh medium. The withdrawn samples were filtered through 0.45µm membrane filter and analysed spectrophotometricaly at 289 nm.

Characterization of complex and physical mixture

The thermal behavior of different components (DXH, β-CD, HPMCK4M), physical mixture as well as formulated complex powder (selected batch) were investigated using a differential scanning calorimeter (DSC). Sample (2.5 mg) was heated in hermetically sealed standard aluminum pan. The thermograms were obtained over the temperature range of 50-250°C with heating rate of 10°C/min under nitrogen atmosphere maintained at flow rate of 50 ml/min.

The X-ray powder diffraction (XRPD) studies were carried out to determine crystallinity of drug in the complex and physical mixture. XRPD pattern of individual components (DXH, β-CD, HPMC K4M), physical mixtures and inclusion complex were recorded on scanning powder X-ray diffractometer using an X'Pert PRO instrument, equipped with an X'Pert PRO Data Collector software. The radiation used was generated by a Cu/Kα source fitted with a Ni filter at 0.154 nm wavelengths at 40 mA and 45 kV. Samples were scanned for 2θ values over a range from 5-45°C, at scan rate of 10°C/min.

The surface morphology of the DXH, β-CD, physical mixture and inclusion complex (selected batch) were examined by scanning electron microscopy (SEM). Samples were fixed on brass stub using double-sided tape and made electrically conductive by coating with a thin layer of gold by sputter coater (Ion sputter E-1010). Photographs were taken at an electric voltage of 15 kV.

RESULTS AND DISCUSSION

Solubility studies using cyclodextrin and different polymers
Phase solubility studies

According to Higuchi and Connors (1965), phase solubility diagram (Fig. 1) can be categorized as type Bs. Such phase solubility diagram is typically obtained while β-CD is used as a complexing agent because of its low solubility (1.8 g/100 ml) (Martin Del Valle, 2004). Fig. 1 showed that at higher concentration of β-CD, there was formation of insoluble complex that led to decrease in drug solubility. In order to find out the amount of drug that can fit into β-CD cavity, binding constant was determined by taking slope of initial inclined portion of phase solubility diagram. The slope of phase solubility diagram was found to be 0.2883, which was less than 1 (Table 1). This indicated that 1:1 inclusion complex formation has been achieved. Binding constant (Ks) and complexation efficiency (CE) were found to be 151.15 and 0.4 (Table 1). Lower complexation efficiency (0.4) indicated that free β-CD was more available in aqueous media (Loftsson *et al.*, 2005).
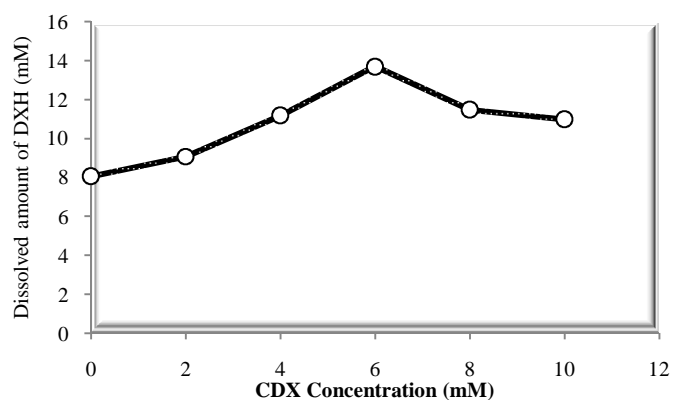

Fig. 1: Phase solubility diagram of DXH in β-CD (0-10 mM).

Effect of preheating and type of polymer on complexation efficacy of cyclodextrin

Results obtained for DXH solubility in presence of polymer are shown in Fig. 2. Among all the polymers tested for complexation, the solubility of DXH was found to be higher in case of PVP K-25 and HPMC K4M (Fig. 2). Moreover, when this phenomenon was tested with the effect of preheating, it was observed that preheating of DXH-β-CD-polymer has increased the drug solubility as compared to non-heated solutions. This indicated that at elevated temperature, complexation efficiency of β-CD has increased (Loftsson and Sigurdardottir, 1996; Maragos *et al.*, 2009). It has been reported in literature that addition of polymer to the complex further enhances the solubility of drug due to molecular interactions such as formation of hydrophobic bonds, Van der Waals dispersion forces, or hydrogen bond and/or promoting the release of high-energy water molecules present in their cavity (Rekharshy and Inoue, 1998; Fridriksdottir *et al.*, 1994). An enhancement in drug solubility was observed with HPMC K4M (8.523 mg/ml) and PVP K-25 (7.309 mg/ml) (S$_1$) which was about 3.180 and 2.727 fold more as compared to

intrinsic solubility (S_0) of DXH (Table 2). The ratio of solubility enhancement in between ternary system to binary system with cyclodextrin ($S_{TS}/S_{BS}{}^g$) was also found to be greater in HPMC K4M and PVP K-25 i.e. 1.804 and 1.547 as compared to those obtained in case of HPMC E5LV and PVP K-30. This might be due to effect of structure and polymer viscosity on weak hydrogen bonding interaction, which is normally observed in ternary complex system of polymer, cyclodextrin and drug molecule (Faucci and Mura, 2001; Ribeiro *et al.*, 2003).
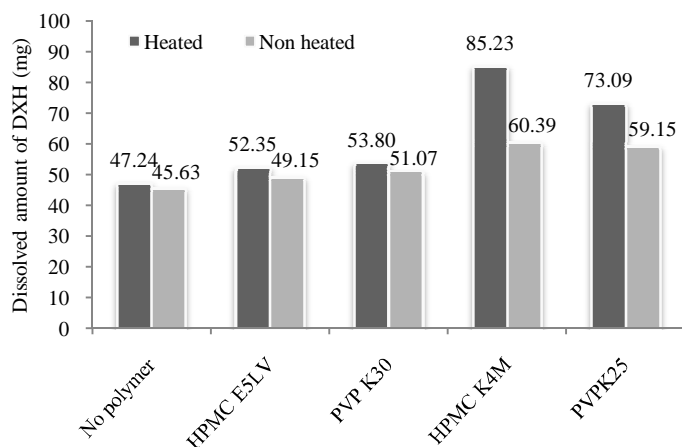

Fig. 2: Comparative evaluation of preheated and non-heated samples of ternary complex solution [i.e. β-CD (6mM) and hydrophilic polymer (0.25 % w/v)].

Ternary complex system (TS) was also found to be superior as compared to binary system (BS) prepared by using water soluble polymers (HPMC K4M and PVP K-25). It was computed by determining the solubility enhancement ratio ($S_{TS}/S_{BS}{}^h$) in between binary system (DXH – HPMC K4M and DXH-PVP K-25) and ternary complex system (DXH-β-CD-HPMC K4M and DXH- β-CD –PVP K-25). The value was found to be 1.736 and 1.606 for HPMC K4M and PVP K-25, respectively (Table 2). The ratio of pre-heated system and non-heated system (S_{HS}/S_{NHS}) was found to be 1.411 and 1.236 for HPMC K4M and PVP K-25, which has further confirmed importance of preheating before samples were kept on equilibration. This ratio was lower in case of HPMC E5LV and PVP K-30, which might be due to the effect of viscosity of polymer.

Optimization of suitable concentration of hydrophilic polymer

Phase solubility diagram of DXH in ternary system (DXH- β-CD- HPMC K4M and DXH- β-CD- PVP K-25) in the range of (0-0.3%w/v) is represented in Fig.3. Complexation constant of DXH- β-CD- HPMC K4M and DXH- β-CD- PVP K-25 was computed from the slopes of the corresponding regression lines obtained from initial straight line portion. The slope value was found to be less than 1 that reflected that there was formation of 1:1 complex (Table 3). It was observed that solubility of complex decreased at higher polymer concentrations. This could be due to formation of water-insoluble inclusion complexes between the polymer and β-CD. Such precipitates are commonly

formed when polyrotaxanes of β-CD are formed in aqueous solutions (Fujita *et al.*, 1996). Addition of polymer further enhanced the solubility constant, which could be attributed to the increase in cyclodextrin complexation efficiency towards DXH. The ratio of binding constant in ternary system and binary system (K_{TS}/K_{BS}) was found higher in HPMC K4M than PVP K-25 (4.87 > 2.07) (Table 3).

Moreover, the solubility ratio in ternary system and binary system (S_{TS}/S_{BS}) was greater for HPMC K4M than PVP K-25 (2.64 > 2.21). The results revealed that solubility enhancement effect of HPMC K4M was found higher as compared to PVP K-25. Hence, DXH:β-CD:HPMC K4M complex system was selected for preparation of solid complexes using physical mixing, kneading, co-precipitation and co-evaporation methods. Binary complex system (DXH:β-CD) has been excluded for preparation of solid complex system.
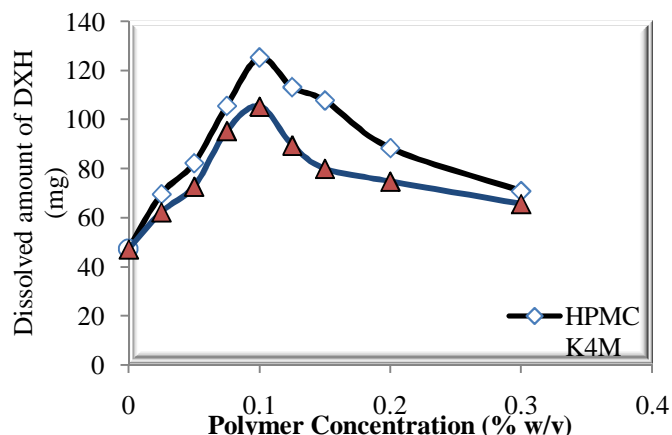

Fig. 3: Phase solubility diagram of DXH in ternary complex system [i.e. polymer in HPMC and PVP K-25 (0-0.3% w/v) with constant β-CD (6mM)].

Evaluation of formulated complexes
In vitro dissolution study

Mean dissolution profile for pure drug (DXH) and ternary complex system (DXH:β-CD: HPMCK4M) prepared by physical mixing (P.M.), kneading (K.M.), co-precipitation (Co-ppt.) and co-evaporation (Co-evap.) is shown in Table 4 and Fig.4. The release of pure DXH was found to be only 75.68 % in 30 min. However the release of pure DXH within 15 min was just 38.39 %. This is due to poor aqueous solubility of DXH and hence, this gave significance for formulation of complexation of DXH with β-CD and other solubilizing agent. In case of ternary complex systems, a drastic difference in release of DXH was found as compared to pure drug. Among all the methods for preparation of complex, co-evaporation method was found to be best method in terms of DXH release. DXH release was found to be 53.65 ± 2.83 % in 5 min for DXH-β-CD-HPMC K4M complex prepared by co-evaporation method, which was 17 folds more than the pure API (3.03 ± 1.88%). More than 85 % of drug got released in 15 min for inclusion complex powder prepared by co-evaporation method, whereas release of pure drug was found to be only 75% in 30 min.

Table 1: Analytical parameter of phase solubility diagram and estimated value of binding constant (Ks) and complexation efficiency (CE).

Parameter	S0*	Slope	Regression coefficient (r2)	Value
Binding Constant (Ks)	0.00268	0.2883	0.9882	151.15
Complexation efficiency (CE)				0.4

*indicates solubility in g/ml

Table 2: Evaluation of intrinsic solubility of drug (S_0) and solubility enhancement factor.

Component	Treatment	Solubility of Drug (n=3)					
		S_0 [d]	S_1 [e]	S_1 / S_0 [f]	S_{TS} / S_{BS} [g]	S_{TS} / S_{BS} [h]	S_{HS} / S_{NHS} [i]
Drug		2.680					
Binary complex system							
β-CD [a]			4.724	1.763			1.044
HPMC K4M [b]	Preheated		4.910	1.832			
PVP K-25 [b]			4.550	1.698			
β-CD [a]	Non- heated		4.524	1.688			
Ternary complex system [c]							
HPMC E5LV			5.235	1.953	1.108		1.065
HPMC K4M	Preheated		8.523	3.180	1.804	1.736	1.411
PVP K-25			7.309	2.727	1.547	1.606	1.236
PVP K-30			5.380	2.007	1.139		1.053
HPMC E5LV			4.915	1.834	1.040		
HPMC K4M	Non- heated		6.039	2.253	1.278	1.230	
PVP K-25			5.915	2.207	1.252	1.300	
PVP K-30			5.107	1.906	1.081		

a = Drug is added into 6mM β-CD solution; b = Drug is added into the polymer solution (0.25 %w/v); c = Drug is added in 6mM β-CD and 0.25% w/v with respect to polymer in 10 ml medium; n = number of replicates; d = intrinsic solubility of drug in 0.2M phosphate buffer (pH 6.8) in mg/ml; e = solubility of drug in complexation media (i.e.) binary system (BS) and ternary system (TS)) in mg/ml; f = solubility enhancement factor calculated by the ratio of solubility of drug in complexation media (S1) -i.e. either binary or ternary complex system and intrinsic solubility of drug (S0); g = solubility enhancement factor computed by the ratio of solubility of drug in ternary system (TS) (i.e. β-CD 6mM and 0.25% w/v polymer) and solubility of drug in binary system (BS) (i.e. β-CD in 6mM); h = solubility enhancement factor computed by the ratio of solubility of drug in ternary system (TS) (i.e. β-CD 6mM and 0.25% w/v polymer solution) and solubility of drug in binary system(BS) (i.e. 0.25% w/v polymer solution)
 i = solubility enhancement factor calculated by the ratio of solubility of drug in ternary system in preheated samples (HS) and solubility of drug in ternary system in no heated samples (NHS)

Table 3: Analytical parameter evaluation in ternary complex system and determination of solubility enhancement factor.

Complexation media	Slope	Regression co-efficient (r)	Ks	STS/SBS c	KTS/KBS d
β-CD a	0.2883	0.9882	151.15		
HPMC K4Mb	0.7693	0.9938	736.72	2.64	4.87
PVP K-25b	0.5974	0.9862	314.11	2.21	2.07

a = 6mM β-CD solution; b = ternary complexation medium consisted of 6mM β-CD and 0.1 %w/v hydrophilic polymers. c = is the solubility ratio in between ternary system (TS) and binary system (BS); d = Kc is the ratio of binding constant in between ternary system and binary system.

Table 4: Mean dissolution profile of pure drug (DXH) and its ternary complex system (DXH:β-CD:HPMC K4M) prepared by various methods.

Time (min)	Mean cumulative drug release ± S.D. (%) (n=3)						
	D	P.M. a	P.M. b	K.M. c	K.M. d	C.P.	C.E.
5	3.02 ± 1.88	6.71 ± 2.38	10.08 ± 3.07	15.76 ± 5.49	17.76 ± 6.56	30.87 ± 2.48	53.65 ± 2.83
10	15.52 ± 3.67	20.20 ±4.63	23.28 ± 2.79	34.62 ± 4.62	31.07 ± 7.17	48.49 ± 3.46	78.11 ± 6.49
15	38.39 ± 4.20	47.51 ±6.63	51.58 ± 6.40	62.47 ± 5.32	66.82 ± 7.74	73.00 ± 2.85	89.55 ± 7.83
20	55.27 ± 6.67	70.92 ±2.89	77.03 ±5.79	84.29 ± 6.08	89.51 ± 2.43	87.82 ± 7.84	91.47 ± 1.92
30	75.68 ± 3.48	86.84 ±5.41	89.55 ± 8.08	90.40 ± 4.26	93.91 ± 4.33	92.49 ± 7.06	95.51 ± 7.56

D = Duloxetine hydrochloride; a = Physical mixing for 30 min; b = physical mixing for 60 min; c = kneading of materials for 30 min; d = kneading of materials for 60 min; C.P. = complex prepared by co-precipitation method; C.E. = complex prepared by co-evaporation method.

Characterization of complex and physical mixture

The optimized ternary complex powder prepared by co-evaporation method was characterized by DSC, XRD and SEM analysis.
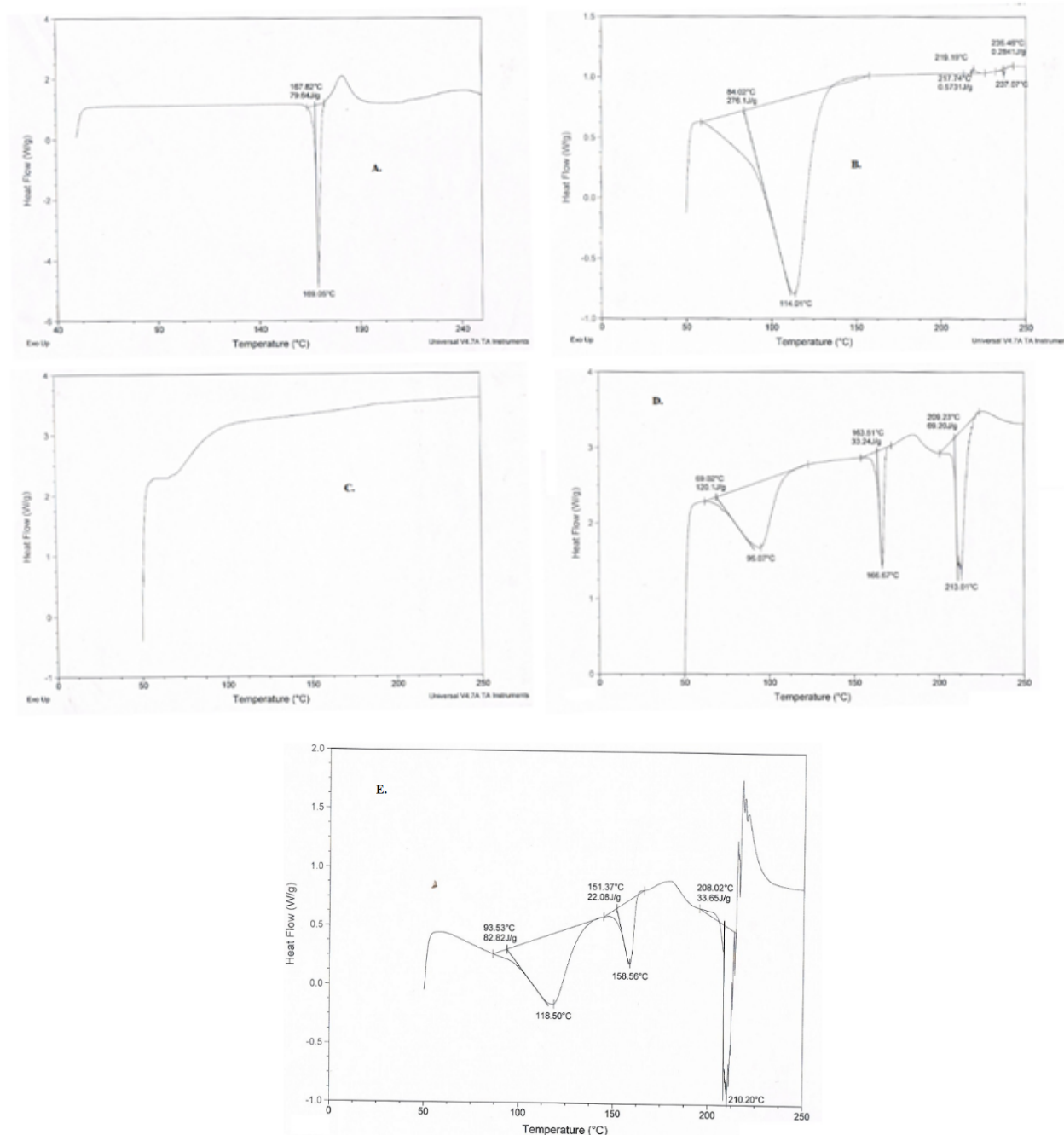
Differential scanning calorimetry studies

DSC can be used for the recognition of inclusion complexes. When guest molecules were enclosed in cyclodextrin cavities or in the crystal lattices, their melting, boiling, or sublimation point generally shifted to a different temperature or disappeared (Cabral *et al.*, 1990). The thermogram of DXH, β-CD, ternary physical mixture and ternary inclusion complex   prepared

by co-evaporation method are presented in Fig. 5. The DSC thermogram of DXH (Fig. 5-A) exhibited a sharp crystalline endothermic peak at 169°C, indicating the melting point of DXH. The thermogram of β-CD (Fig. 5-B) showed a very broad endothermic peak in between 60 and 110° C, which corresponded to dehydration process followed by solid-solid phase transition at 214°C (Giordano *et al.*, 2001; Liu and Zhu, 2006). Thermogram of HPMC K4M revealed its amorphous behavior as it has no any endothermic peak (Fig. 5-C). For ternary physical mixture of β-CD: DXH : HPMC K4M (Fig. 5-D), the drug endothermic peak was slightly shifted from 169.05°C to 165.67°C, but the height of the peak was not much affected. However, the enthalpy of fusion

required to melt DXH physical mixture was decreased (33.24 J/g) as compared to that of pure DXH (79.64 J/g). It showed that there was an interaction between β-CD, DXH and HPMC K4M. Whereas, in case of ternary complex prepared by co-evaporation method, peak was shifted to lower temperature (169.05°C to 158.56°C) with significant reduction of height of peak (Fig. 5-E). The DSC thermogram showed that the energy required for melting of β-CD: DXH: HPMC K4M complex was lesser around (3.6 fold) than the energy required for pure DXH. This revealed that   DXH

was completely included in the cavity of β-CD which confirmed the observations obtained from complexation efficiency and binding constant studies. The amorphous HPMC K4M provided a larger surface area to the dissolution medium which allowed the dissolution medium to completely wet the DXH. This might be the reason behind the enhanced solubility and dissolution of DXH: β-CD: HPMC K4M complex. The observations of DSC were further confirmed by PXRD studies which are discussed in the subsequent section.

Fig. 5: DSC thermograms of DXH (A); β-cyclodextrin (B); HPMC K4M (C); ternary physical mixture (D) and inclusion complex powder prepared by co-evaporation method (E).
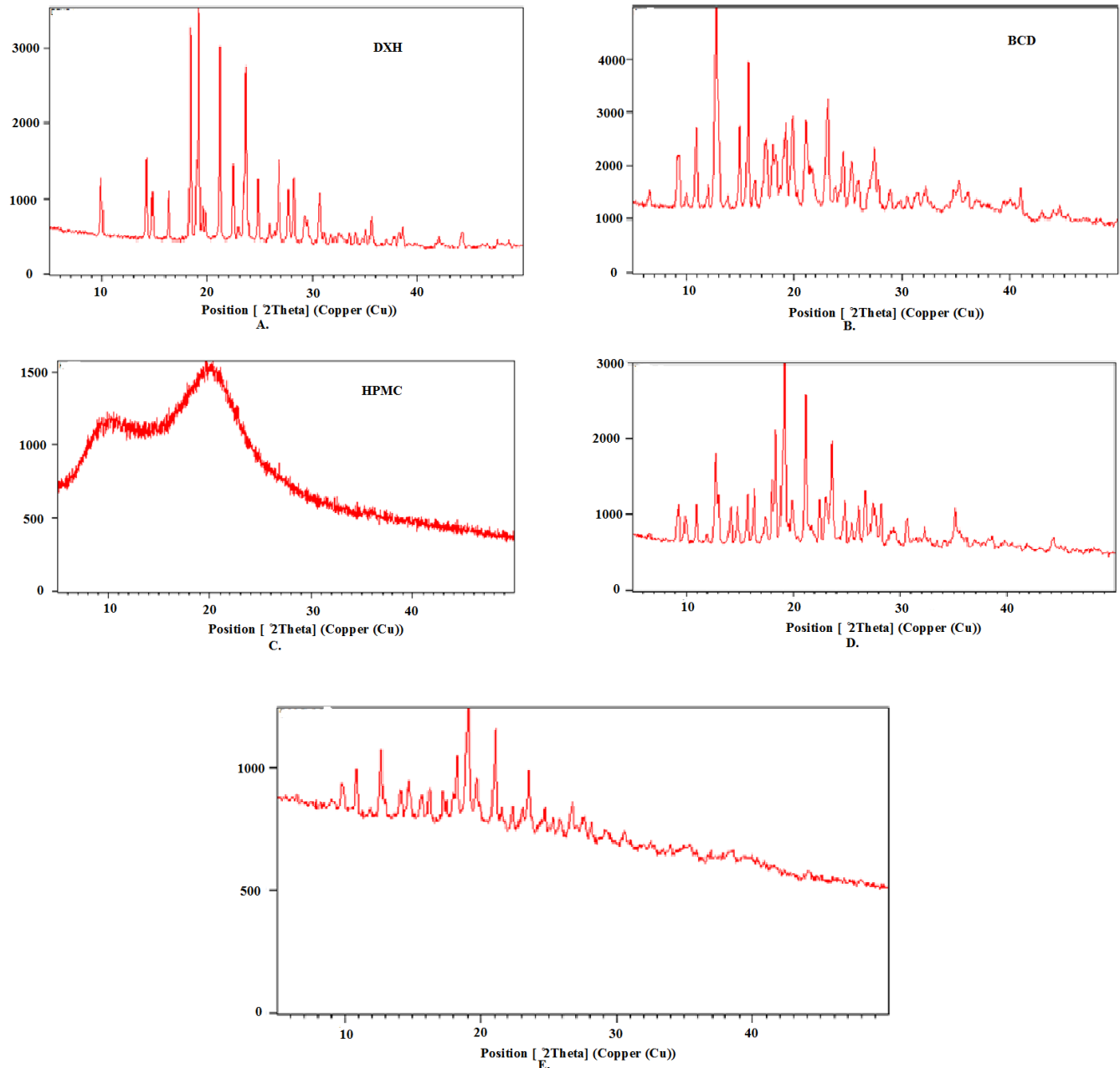
Fig. 6: PXRD spectra of DXH (A); β-CD (B); HPMC K4M (C); ternary physical mixture (D) and ternary inclusion complex prepared by co-evaporation method (E).
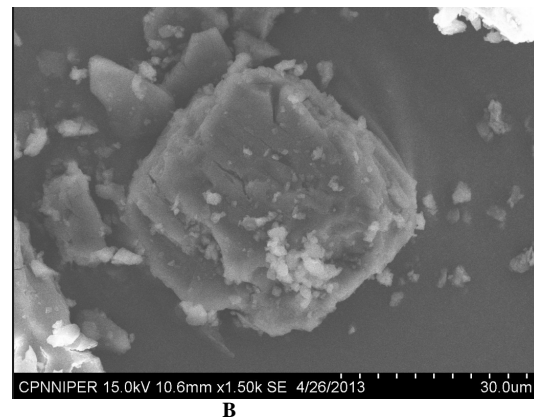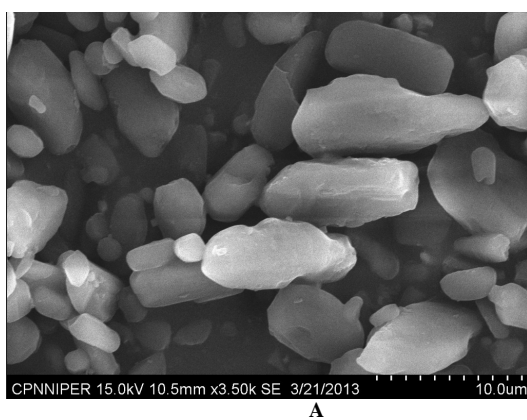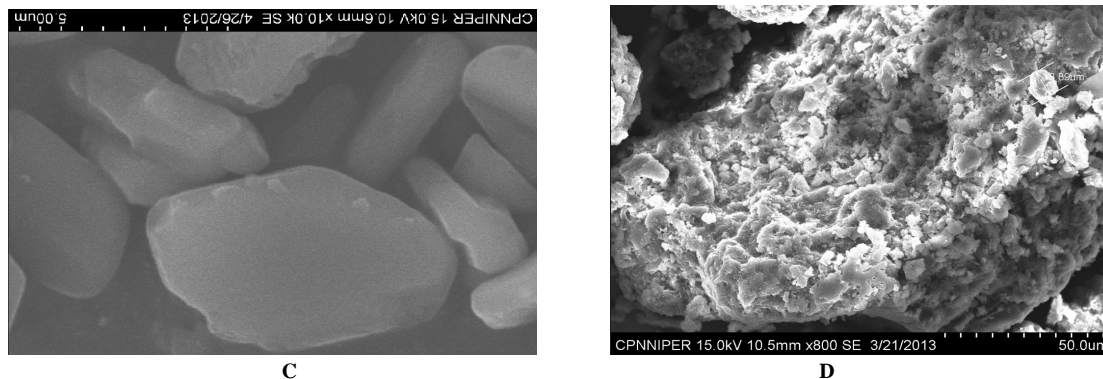

Fig. 7:...

Fig.7: SEM of DXH (A); β-CD (B); ternary physical mixture (C) and ternary inclusion complex prepared by co-evaporation method (D).

Powder X-Ray Diffraction studies

The powder diffraction patterns of DXH, β-CD, HPMC K4M, ternary physical mixture (DXH: β-CD: HPMC K4M) and ternary inclusion complex (DXH: β-CD: HPMC K4M) prepared by co-evaporation method are shown in (Fig. 6). The PXRD pattern of drug (Fig. 6-A) was characterised by presence of sharp peaks at 14.21°, 14.79°, 18.37°, 19.18°, 21.17°, 23.54° indicative its crystalline behaviour. The crystalline nature of β-CD (Fig. 6-B) was evidenced from presence of sharp peaks at 7.31°, 10.38°, 12.38 °, 14.48° and 22.38. The hallo pattern X-ray diffractograms obtained from HPMC K4M (Fig. 6-C) confirmed that it is amorphous in nature. The ternary physical mixture was characterized by presence of combined peaks of drug as well as β-CD, however, with slightly reduced intensities (Fig. 6-D). In case of ternary complex prepared by co-evaporation method, the sharpness of peaks was found to decrease indicating loss of its crystalline behavior (Fig. 6-E). The sharpness as well as the number of sharp peaks existing with plain drug was found to be significantly diminished in case of ternary complex (DXH: β-CD: HPMC K4M). Lower intensities of the diffraction peaks were observed for the ternary complex of DXH: β-CD: HPMC K4M due to particle size reduction during mixing (Riberio *et al.*, 2003). According to Williams et al., (1998), decrease of crystallinity is an added evidence for the formation of inclusion complex.

Scanning electron microscopy (SEM) studies

From SEM scans as seen in Fig. 7-A, pure DXH particle appeared as crystalline, β-CD particles (Fig. 7-B) appeared like cluster structure. Microscopic examination of ternary physical mixture (DXH: β-CD: HPMC K4M) (Fig. 7-C) showed the presence of DXH crystals mixed and adhered on the surface of CD particle revealing no apparent interaction between both species in the solid state. Ternary complex prepared by co-evaporation method, as seen in (Fig. 7-D) showed small and irregular piece and like engulfment of material in cavity. Fernandes et al., (2002), have reported that a modification in the shape of drug particles was indicative of a new solid state. Thus, change in the morphology of complex as compared to drug showed interaction between DXH and complexing agent. The result revealed that there might be increase the surface area of DXH due to complexation. Due to increased surface area, porosity of material was also increased. The improvement of porosity of material had further enhanced the wettability of material. The wettability (water uptake capacity) might have accelerated the solubility as well as dissolution rate of DXH.

CONCLUSION

The present study revealed that the solubility of DXH was found to be higher in ternary complex system (DXH: β-CD: HPMC K4M) as compared to binary complex systems (DXH: β-CD and DXH: HPMC K4M) and other ternary complex systems prepared by PVP K-25, HPMC E5LV and PVP K-30. Physical characterization techniques showed that crystallinity behaviour of DXH was found to be decreased due to formation of ternary complex system. This led to enhancement in solubility as well as dissolution rate of DXH. Ternary complex system was also found to give faster drug release as compared to pure API.

Conflict of interest

The authors report no declaration of interest.

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