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Dissolution enhancement of dronedarone hydrochloride by complexation with β-CD and HP β-CD: dissolution and physicochemical characterization

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Abstract

The study was aimed to improve solubility or dissolution characteristics of dronedarone hydrochloride by preparing its inclusion complexes (ICs) with β-cyclodextrin (β-CD) and hydroxypropyl β-cyclodextrin (HP β-CD). The phase solubility behavior of dronedarone hydrochloride in presence of various concentrations of β-CD and HP β-CD (0.5 to 4% w/v) in distilled water was obtained at 37 ± 2 ºC. The solubility increased with increasing carrier concentration. The free drug aqueous solubility was found to be 0.75 ± 0.03 mg/mL, whereas using cyclodextrins (CDs) as hydrophilic carrier the solubility is enhanced to 3.5 ± 0.03 mg/mL (five folds). Gibbs free energy (ΔG°_{tr}) values were all negative, indicating the spontaneous nature of dronedarone hydrochloride solubilization. The ICs of dronedarone hydrochloride were prepared at 1:1, 1:2 and 1:3 w/w ratio (drug:carrier) by kneading and physical mixing. Mean dissolution time (MDT) of dronedarone hydrochloride decreased significantly after preparation of ICs by physical mixing and kneading. Drug-carrier interactions were characterized in solid state FTIR and DSC analysis. Retaining of important characteristic peaks of the drug in the IR spectra of drug-CD complex indicates the drug carrier compatibility. It was found that inclusion complex by kneading with β-CD in a 1:2 and HP β-CD at 1:1 weight ratio could be used in formulation demonstrating enhanced dissolution. The study investigation suggested that HP β-CD complex of dronedarone hydrochloride may be preferred over β-CD due to its result at half of the concentration when compared. The study indicates the usefulness of cyclodextrin technology to overcome the solubility problem of dronedarone hydrochloride.

Keywords: Inclusion complexation, Dronedarone hydrochloride, Cyclodextrins, Dissolution and physicochemical characterization.

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Introduction

In modern drug development, high throughput screening techniques aid in identifying new compounds that are characterized by high lipophilicity, low aqueous solubility and poor dissolution. Thus, improving the solubility of poorly soluble drugs should increase the concentration of dissolved drug in the gastrointestinal (GI) tract and thus increase their bioavailability. Complexation with different cyclodextrin derivatives, embedding the drug in a solid dispersion or the addition of surfactants are commonly applied approaches to increase the solubility and/ or dissolution rate of a poorly soluble compound. A higher energetic state of the compound that is, the amorphous state, can increase drug solubility and improve bioavailability. Due to their simple manufacture, solid dispersions are a popular means for enhancing solubility and bioavailability of BCS class II drugs [1].

The central objective of a delivery system is the release of drugs at the desired anatomical site and the maintenance of the drug concentration within the therapeutic range for a desired duration. One approach for drug delivery is to encapsulate the drug molecule inside a macrocyclic host molecule, traditionally a cyclodextrin, thereby forming discrete host–guest complexes, in which the drug molecule is protected from the aqueous environment [2].

Cyclodextrins (CDs) are useful excipients that have enjoyed widespread attention and use, mainly as complexing and solubilizing agents. CDs are cyclic oligosaccharides with hydrophilic outer surface and a somewhat lipophilic central cavity. In aqueous solutions, CDs are able to solubilize lipophilic drugs through formation of hydrophilic inclusion complexes. These are attractive building blocks for various types of drug delivery systems due to their favorable toxicological profile and their inherent ability to partly or completely host biologically active molecules (e.g., drugs), and to protect them from the external environment. Their capacity to form inclusion complexes further gets enhanced when they self assemble to form aggregates, crosslink together or copolymerize with other compounds. The high affinity of CDs for certain drug molecules is passed on to the carrier systems which give them with a particular drug release mechanism thus helps to improve solubility in aqueous media. Dissolution rate, chemical stability and bioavailability of various drugs has been extensively investigated in recent years. Inclusion complexation of drugs with CDs may be useful to solve various pharmaceutical formulation problems such as improvement of stability, solubility and dissolution rate [3].

Studies have shown that cyclodextrins enhance oral bioavailability of FDA’s class II (Low solubility, High permeability) drugs but they can hamper bioavailability of class I (High solubility and high permeability) and class III (High solubility and low permeability) drugs. The use of complexation with cyclodextrins (α CD: α - cyclodextrin; β CD: β- cyclodextrin; HP β CD: 2-hydroxypropyl -β- cyclodextrin; RM β CD: randomly methylated β- cyclodextrin; SBE β CD: sulfobutylether β- cyclodextrins; γ CD: γ cyclodextrins; HP γ CD: 2-hydroxypropyl - γ - cyclodextrin) to improve solubility in aqueous media, dissolution rate, permeability, chemical stability and bioavailability of various drugs has been extensively investigated in recent years [4-6].

Dronedarone is N-[2-butyl-3-({4-[3-(dibutyl amino) propoxy] phenyl} carbonyl)-1 benzofuran-5-yl] methanesulfonamide. A pharmaceutically acceptable salt for dronedarone is preferably its hydrochloride. Dronedarone hydrochloride has been shown to be particularly advantageous in the cardiovascular field, in particular as antiarrhythmic agent. Dronedarone in form of its hydrochloride exhibits a limited solubility in an aqueous medium. The solubility is 0.5 mg/mL at pH = 4.85 at ambient temperature. In the pH range from 1.5 to 5, this solubility is virtually constant and then becomes virtually negligible at pH values of greater than 5.5. It has been reported that aqueous solutions of cyclodextrin derivatives, in particular β-CD or HP β-CD, are capable of increasing solubility of dronedarone hydrochloride and do not cause local irritation [7]. The structure of dronedarone hydrochloride is shown under Figure 1. So far, work on dronedarone hydrochloride for its solubility, dissolution rate, the solid state or solution state characterization with CDs is limited. The primary objective of the present work is to investigate the effect of β-CD or HP β-CD on the solubility and dissolution properties of dronedarone hydrochloride, to investigate the interaction between dronedarone hydrochloride and β-CD or HP β-CD. Solid state interaction was investigated by FT-IR and DSC analysis. Interaction in solution state was studied from spectral analysis, phase solubility analysis and dissolution experiments.

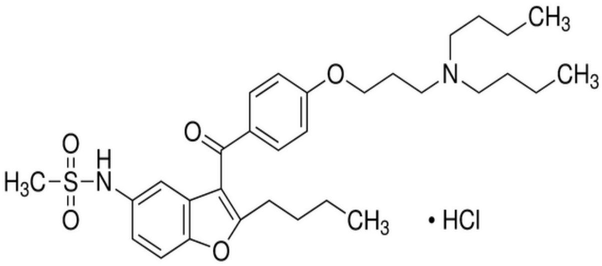

Figure 1 Structure of Dronedarone HCl

Materials and Methods

Gift sample of dronedarone hydrochloride was received from Glenmark pharmaceuticals (Mumbai), β-CD and HP β-CD received from Yarrow Chem Products, double distilled water was used throughout the study and all the other chemicals used were of analytical grade.

Preparation of inclusion complexes. Inclusion complexes of dronedarone hydrochloride with β-CD and HP β-CD were prepared by kneading and physical mixing technique. Kneading is a hand mixing process by which, you press and squeeze a wet mass or dough with your hands or with your fingers. A mixture of β-CD or HP β-CD and dronedarone hydrochloride (1:1, 1:2 and 1:3 by weight) was wetted with aqueous alcohol i.e., water- methanol (8:2 by volume) and kneaded thoroughly for 30 minutes in a glass mortar. The wet mass (thick paste) formed was dried at 45 to 50 ºC for 24 h. All the dispersions were prepared in triplicate and were sieved through 60 mesh sieve and stored in a desiccator until further evaluation. Physical mixtures (PM) were obtained by pulverizing in a glass mortar and carefully mixing accurately weighed (1:1, 1:2 and 1:3 by weight) amounts of dronedarone hydrochloride with β-CD and HP β-CD [8].

Solubility determinations. Solubility determinations were performed in triplicate (n=3) according to the method of Higuchi and Connors [9]. An excess amount of dronedarone hydrochloride was added to screw capped glass vials containing different concentrations of β-CD or HP β-CD in 25 mL of water (0.5 to 4 % w/v). The vials were shaken for 48 h using a water bath shaker (Remi Pvt Ltd, Mumbai) maintained at 37 ± 2 ºC. After 48 h, samples were filtered through 0.45 µm pore size filter. Samples were then analyzed by UV (at 290 nm) with suitable dilutions using Agilent Cary 60 spectrophotometer. Experiments were completed in triplicate (n=3) [10].

The saturation solubility of drug in pure water without taking hydrophilic carrier was also determined. An indication of the process of transfer of dronedarone hydrochloride from pure water to the aqueous solutions of β-CD and HP β-CD was obtained from the values of Gibbs free energy change. The Gibbs free energy of transfer (ΔG_{tr}°) of dronedarone hydrochloride from pure water to the aqueous solution of carriers was calculated using following Equation 1.

$$\Delta G_{tr}{}^{\circ} = -2.303\, RT\, log\, S_0/S_s \qquad \text{Eq---------- (1)}$$

Where S_o/S_s = the ratio of molar solubility of drug in aqueous solutions of carriers to that of the pure water [11].

Dissolution studies Dissolution studies of the dronedarone hydrochloride, in powder form and ICs were performed by using the U.S. Pharmacopoeia (USP) model digital dissolution test apparatus type-2 (Lab India, Mumbai) at the paddle rotation speed of 75 rpm using 900 mL of phosphate buffer of pH 4.5 as dissolution media at 37 ± 0.5 ˚C. The ICs equivalent to 200 mg of the dronedarone hydrochloride was weighed using a digital balance (Infra Instruments Ltd) and added to the dissolution medium. At the specified times, 5 mL samples were withdrawn by using syringe filter, pore size 0.45 µm (Sepyrane, Mumbai) and then assayed for the dronedarone hydrochloride content by measuring the absorbance at 290 nm using the UV-Visible spectrophotometer and volume is adjusted by fresh medium maintained at 37 ˚C after each sampling to maintain its constant volume throughout the test. Dissolution studies were performed in triplicate (n=3), calculated mean values of cumulative drug release and data were used while plotting the release curves.

Fourier-Transform Infrared Spectroscopy The FTIR spectra were obtained by using an FTIR spectrometer (Shimazdu, Japan). The samples were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:100 (Sample: KBr) ratio respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Scans were obtained at a resolution of 2 cm^{-1}, from 4000 to 400 cm^{-1}.

Differential scanning calorimetry Measurements were performed on a DSC- 6100 (Seiko Instruments, Japan) with a thermal analyzer. All accurately weighed samples (about 2 mg of dronedarone hydrochloride or its equivalent) were placed in sealed aluminum pans, before heating under nitrogen flow (20 mL/min) at a scanning rate of 10 ˚C min^{-1} from 50 to 300 ˚C. An empty aluminum pan was used as reference.

Results and Discussion

Solubility Studies. The phase solubility study was conducted for solubility determination of dronedarone hydrochloride using different concentrations of cyclodextrins at 0.5, 1, 2 and 4 % w/v respectively. From the study saturation solubility and Gibb's free energy values can be obtained. An increase in values of Gibb's free energy in negative shown under (Table 1) indicates spontaneous nature of drug solubilization and increase in solubility due to increase in the carrier concentration. Phase solubility diagram was plotted to obtain correlation coefficient (r^2) and slope (m) as important parameters under the study. Phase solubility diagram could be classified as A_L type according to Higuchi and Connors. The linear host guest correlation coefficient r^2 for β CD was found to be 0.933 with slope value of 0.218 and the same for HP β CD was found to be 0.931 with slope value of 0.249 shown under Figure 2. Slope less than one indicates formation of 1:1 stoichiometric inclusion complex.

It has been found that hydrophilic carriers mainly interact with drug molecules by electrostatic bonds (ion-to-ion, ion-to-dipole, and dipole-to-dipole bonds), even though other types of forces, such as Van der Waals forces and hydrogen bonds, can frequently play a role in the drug-carrier interaction [12].

In vitro dissolution studies. All the formulations of dronedarone hydrochloride were subjected to *in vitro* dissolution studies using phosphate buffer of pH 4.5 as dissolution media at 37 ± 0.5 ˚C to access various dissolution properties. To compare dissolution profiles, several approaches can be followed such as model-

Table 1 Effect of various concentrations of β-CD and HP β-CD on dronedarone hydrochloride solubility and thermodynamic parameters of the solubility process in different carrier-water solutions at 37 ± 2 ºC (n=3)

Concentration of Carrier in water (% w/v)	Solubility (mg/mL)		Gibb's free Energy ΔG^0_{tr} (J/mol)	
	Solubility with β-CD (mg/mL)	Solubility with HP β-CD (mg/mL)	β-CD	HP β-CD
0.5	2.53 ± 0.02	2.63 ± 0.02	-3143	-3235
1	2.63 ± 0.01	2.78 ± 0.01	-3238	-3382
2	3.03 ± 0.04	3.22 ± 0.04	-3605	-3767
4	3.28 ± 0.01	3.50 ± 0.03	-3812	-3982

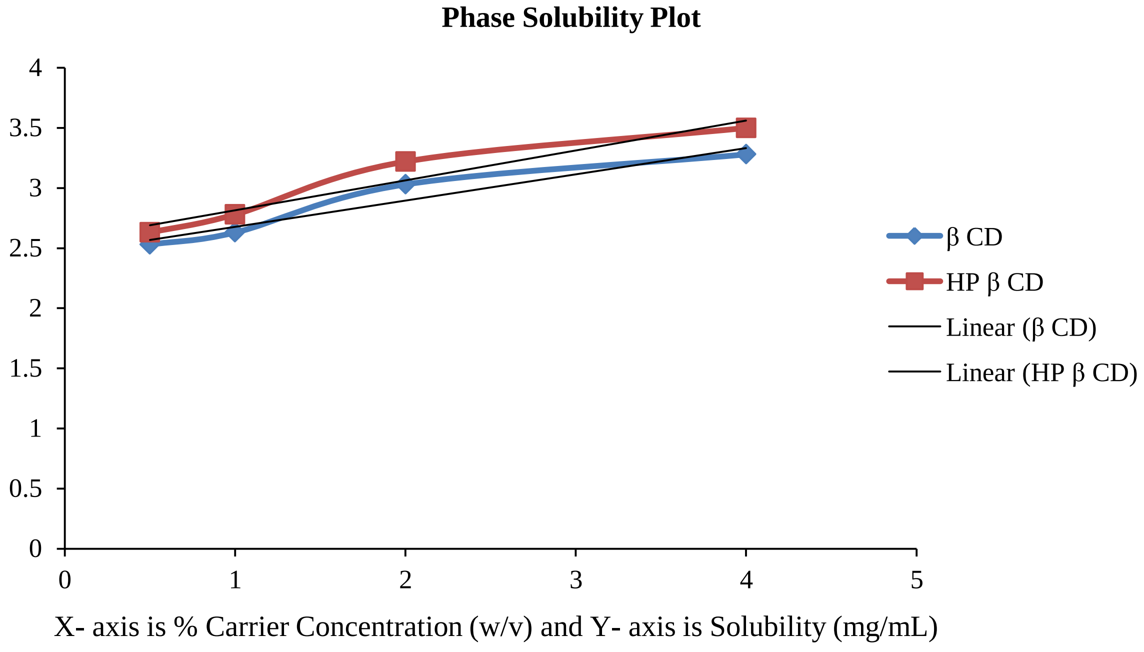

Figure 2 Phase Solubility diagram of Dronedarone HCl with β-CD and HP β-CD

independent and model- dependent approaches.

In the present work model-independent approaches are based on the ratio of area under the dissolution curve (dissolution efficiency). Percent dissolution efficiency (% DE) was computed to compare the relative performance of various concentrations of carrier in ICs by kneading and physical mixing. The magnitude of % DE at 45 min time point (% $DE_{45\ min}$) for each formulation was computed as the percent ratio of area under the dissolution curve up to the time, *t*, to that of the area of the rectangle described by 100% dissolution at the same time as Equation 2 using PCP Disso V3 software (Pune, India).

$$\% DE = \frac{\int_0^t Y\,dt}{Y_{100}\,t} \qquad \text{Eq------- (2)}$$

In the model-dependent approaches, release data were fitted to five kinetic models including the zero order (Equation 3), first order (Equation 4), Higuchi matrix (Equation 5), Peppas–Korsmeyer (Equation 6) and Hixson–Crowell (Equation 7) release equations to find the equation with the best fit.

$$R = k_1 \qquad \text{Eq--- (3)}$$

$$\log UR = \frac{k_2\ t}{2.303} \qquad \text{Eq--- (4)}$$

$$R = k_3 \sqrt{t} \qquad \text{Eq--- (5)}$$

$$\log R = \log k_4 + n \log t \qquad \text{Eq----(6)}$$

$$(UR)^{\frac{1}{3}} = k_5 \qquad \text{Eq--- (7)}$$

Where *R* and UR are the released and unreleased percentages, respectively at time (*t*); k_1, k_2, k_3, k_4, and k_5 are the rate constants of zero-order (plot of cumulative % drug released Vs square root of time), Peppas–Korsmeyer (plot of log % drug released Vs log time), and Hixson–Crowell model (plot of cubic root of drug unreleased Vs time), respectively [13].

The results of the dissolution studies for individual samples (Dronedarone hydrochloride, ICs by physical mixing and kneading) over the period of 45 min are shown in Table 2. Q10, Q15, Q20, Q30, and Q45 values along with dissolution efficiency at 45 min (% DE45 min) are reported in Table 2.

From table it is evident that onset of dissolution of pure dronedarone hydrochloride is very low, about 27.69 % of drug being dissolved within 45 min. ICs of dronedarone hydrochloride by kneading with β-CD and HP β-CD considerably enhanced dissolution rates within 45 min compared to pure dronedarone hydrochloride and its ICs by simple mixing. The value of % DE for pure dronedarone hydrochloride was enhanced in ICs by simple physical mixing as well as in ICs prepared by kneading.

The fit for various models [14] are investigated for drug and ICs prepared by simple mixing or kneading with β-CD and HP β-CD. Pure drug indicate that its release is concentration dependent and occurs by dissolution or erosion controlled with n value 0.374 (K-P model) hence exhibits non Fickian diffusion i.e., anomalous type. β - CD ranked in order of Korsemeyer–Peppas > Higuchi >First order >Hixson –Crowell cube root law> Zero order and HP β-CD in Korsemeyer–Peppas > First order >Hixson –Crowell cube root law> Higuchi > Zero order. Table 3 shows the regression parameters obtained after fitting various release kinetic models to the in vitro dissolution data. This enhancement of dissolution of dronedarone hydrochloride from drug carrier systems can beattributed to several factors. Lack of crystallinity, i.e., amorphization, increased wettability and dispersibility and particle size reduction are considered to be important factors for dissolution rate enhancement. Physical mixing of drug with a hydrophilic carrier results in greater wetting and increases surface available for dissolution by reducing interfacial tension between hydrophobic drug and the dissolution media. Furthermore, the drug micro crystals are embedded in the water-soluble matrix. Thus the hydrophilic carrier which presents the ability of rapidly dissolving in the dissolution medium causes rapid wetting of dronedarone hydrochloride, leading to an improvement in its dissolution rate. Moreover, hydrophilic carrier encircling the hydrophobic drug decreases aggregation and agglomeration of drug particles, allowing a faster dissolution process [15].

The pure drug showed up to 27.69 % dissolution over a period of 45 min, but its ICs prepared by kneading with β-CD at 1:1 showed up to dissolution of 75 % whereas HP β-CD at 1:1 w/w ratio showed more than 85 % over a period of 45 min, shown under Figure 3.

Comparing β-CD and HP β-CD inclusion complexes prepared by kneading and physical mixing, kneading method showed better profile for dissolution rate. Comparing β-CD and HP β-CD, HP β-CD showed better result at low drug:carrier weight ratio.

In vitro release data of drug best fitted to Korsemeyer-Peppas model with n value of 0.207 and hence exhibits Fickian diffusion.

The United State Food and Drug Administration (USFDA) dissolution methods database has mentioned dissolution medias containing sodium lauryl sulphate (SLS) at different concentrations for the dissolution study of many poorly soluble drugs e.g., fenofibrate, carbamazepine, efavirenz, griseofulvin, nisoldipine, mebendazole, tadalafil etc. Dissolution media containing surfactants like SLS if promising is used for the dissolution study of poorly soluble drugs. The use of surfactants in the dissolution systems may be physiologically more meaningful, due to the presence of natural surfactants like bile salts in the gastrointestinal tract. The ability of surfactants to accelerate the *in vitro* dissolution of poorly water-soluble drugs has been attributed to wetting, micellar solubilization, and/or deflocculation [16].

To identify the effect of SLS (anionic surfactant) on the dissolution rate of dronedarone hydrochloride, dissolution study was conducted using 0.5 % SLS as a medium as a trial apart from its dissolution study using phosphate buffer of pH 4.5 as dissolution media and observed not suitable. Use of SLS media showed the drug or the drug-inclusion complexes remained as a sticky mass at the bottom of the dissolution basket under the hydrodynamic conditions of the study, limiting the drug release. This may be due to; dronedarone has powerful ionic surfactant properties. This surfactant nature moreover proves to be as powerful in the presence as in the absence of a phosphate buffer and can be held as being partially

Table 2 *In vitro* dissolution parameters of dronedarone HCl inclusion complexes by physical mixing and kneading in pH 4.5 Phosphate buffer.

Samples	Drug: Carrier Ratio (w/w)	Dissolution parameters						
		$Q_{10\ min}$	$Q_{15\ min}$	$Q_{20\ min}$	$Q_{30\ min}$	$Q_{45\ min}$	%DE 45min	MDT 45min
Dronedarone HCl (Drug)		14.89	17.94	22.08	24.25	27.69	19.71	13.54
ICs with β-CD by Physical Mixing	1:1	18.24	25.31	32.10	40.73	45.66	30.51	15.45
	1:2	21.41	27.54	34.15	43.31	47.15	32.64	14.52
	1:3	22.66	29.54	37.18	45.21	50.62	34.81	14.73
ICs with β-CD by Kneading	1:1	57.61	63.21	66.43	71.63	75.09	60.92	9.31
	1:2	61.38	64.12	73.44	80.89	86.25	67.39	10.60
	1:3	67.39	70.23	75.32	84.75	87.43	70.74	9.40
ICs with HP β-CD by Physical Mixing	1:1	23.10	27.35	34.23	46.62	51.48	34.54	15.34
	1:2	24.15	29.53	36.73	47.41	52.51	35.79	14.88
	1:3	23.48	31.33	38.25	47.61	53.74	36.39	15.07
ICs with HP β-CD by Kneading	1:1	61.05	68.23	77.59	81.48	83.79	68.23	9.15
	1:2	63.80	70.70	76.59	82.94	85.15	69.43	9.09
	1:3	62.34	71.74	79.23	83.61	85.44	69.97	8.94

PMs: Physical Mixtures
ICs: Inclusion complexes
% DE 45min: % dissolution efficiency at 45 minutes
MDT: Mean dissolution time

responsible for a self-aggregation of dronedarone molecules with formation of dimers in aqueous solution as reported [7].

Fourier-Transform Infrared Spectroscopy. The interaction between drug and the excipients often leads to identifiable changes in the IR spectra of the drug excipient mixture. IR spectrum of Dronedarone hydrochloride was characterized by the absorption peak at 1715 cm^{-1} due to the (C=O) stretching vibration. Identification of amide functional group is confirmed by the presence of doublet at 3093 and 3063 cm^{-1} due to the –NH stretch peaks at 2958 and 2879 cm^{-1} are due to –CH and $–CH_2$ stretching vibration. Strong absorption peak at 1257 cm^{-1} is due to the symmetrical vibration peak of S=O bond. Peaks in the range of 900 – 600 cm^{-1} indicates the presence of aromatic ring.

The IR spectrum of cyclodextrins (β-CD and HP β-CD) is characterized by intense bands at 3528 to 3373 cm^{-1} associated with the absorption of hydrogen bonded –OH groups of cyclodextrins. Thus as spectral changes always concern C–OH, $–CH_2$, and –CH groups of the cyclodextrins it should be suggested that the host guest interactions are dominated by the hydrogen bonds among the above mentioned groups. The IR spectrum for the inclusion complexes of the drug with cyclodextrins (β-CD or HP β-CD) indicates a broad peak overlapping the doublet peak for $–NH_2$ at (3093 and 3063 cm^{-1}). Peak at 2958 cm^{-1} may be due to –CH bond. Peak at 1715 cm^{-1} is for carbonyl C=O stretching of the amide functional group shifted to lower frequency 1700 cm^{-1} suggesting the formation of the hydrogen bonds between the –CO group of the drug and cyclodextrins during the inclusion complexation. Peak at 1257 cm^{-1} (one characteristic peak for drug S=O) was shifted to a higher frequency of 1460 cm^{-1}, indicating an interaction between dronedarone hydrochloride and cyclodextrins. However, few

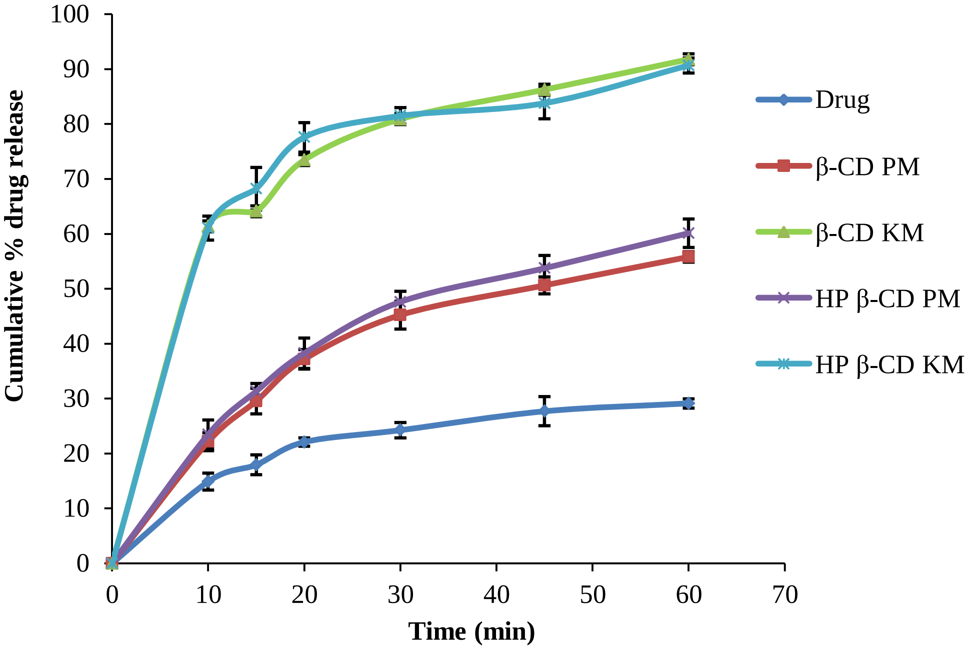

Figure 3 Dissolution profiles of β-CD and HP β-CD by physical mixing and kneading techniques.

Table 3 Statistical parameter of various formulations after fitting drug release data to various release kinetic models.

Formulations	Zero order		First order		Higuchi-Matrix		Korsemeyer-Peppas			Hixson-Crowell	
	R^2	K_1	R^2	K_2	R^2	K_3	R^2	K_4	n	R^2	K_5
DRUG	0.890	0.271	0.905	-0.003	0.948	3.07	0.960	6.609	0.374	0.900	-0.005
β CD PM (1:1)	0.919	0.634	0.953	-0.010	0.968	7.167	0.964	5.345	0.570	0.943	-0.013
β CD PM (1:2)	0.919	0.614	0.848	-0.016	0.966	6.936	0.970	7.014	0.509	0.941	-0.013
β CD PM (1:3)	0.904	0.653	0.944	-0.010	0.959	7.20	0.960	7.464	0.507	0.932	-0.014
β CD KM (1:1)	0.900	0.387	0.950	-0.012	0.975	4.392	0.982	39.35	0.170	0.935	-0.013
β CD KM (1:2)	0.923	0.607	0.988	-0.030	0.965	6.834	0.974	35.318	0.235	0.975	-0.027
β CD KM (1:3)	0.910	0.490	0.970	-0.027	0.955	5.530	0.971	43.85	0.182	0.955	-0.023
HPβCD PM (1:1)	0.926	0.695	0.956	-0.011	0.967	7.820	0.973	6.79	0.534	0.947	-0.015
HPβCD PM (1:2)	0.923	0.672	0.956	-0.012	0.969	7.584	0.975	7.798	0.504	0.946	-0.015
HPβCD PM (1:3)	0.926	0.696	0.965	-0.012	0.973	7.854	0.973	7.655	0.516	0.954	-0.016
HPβCD KM (1:1)	0.846	0.517	0.938	-0.025	0.906	5.852	0.966	39.174	0.207	0.917	-0.022
HPβCD KM (1:2)	0.886	0.491	0.963	-0.026	0.942	5.581	0.968	42.072	0.190	0.946	-0.022
HPβCD KM (1:3)	0.832	0.508	0.936	-0.028	0.896	5.809	0.927	41.411	0.200	0.915	-0.024

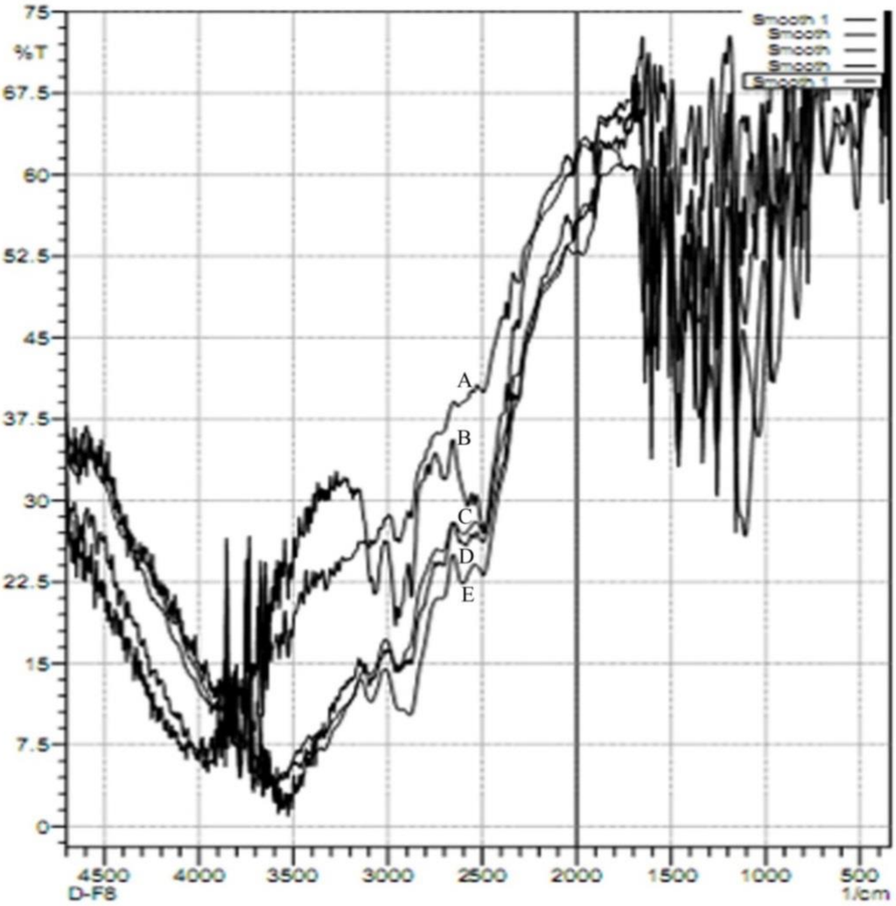

Figure 4 FTIR overlay spectrogram (A) Dronedarone hydrochloride (B) β-CD (C) HP β-CD (D) Drug Inclusion complexes with β-CD (E) Drug Inclusion complexes with HP β-CD.

characteristic peaks for the drugs appear in the spectra of binary systems of the drug and cyclodextrin at the same wave number.

The FTIR spectrogram of (A) Dronedarone hydrochloride (B) β-CD (C) HP β-CD (D) Drug inclusion complexes with β-CD (E) Drug inclusion complexes with HP β-CD are overlaid and shown in Figure 4.

Differential scanning calorimetry. Thermal behaviour of pure drug and corresponding drug carrier system are depicted in the Figure 5. The DSC curve of dronedarone hydrochloride profiles a sharp endothermic peak at 150.2^{o} corresponding to its melting point, indicating its crystalline nature. The DSC curve for β-CD and HP β-CD is observed at 143.23^{o} and 110.96^{o} corresponding to their melting point. However the characteristic endothermic peak, corresponding to drug melting was shifted towards lower temperature with same peak intensity for both inclusion complex of drug with β-CD and HP β-CD indicating the drug in crystalline state. Moreover, for the dronedarone hydrochloride and β-CD or HP β-CD binary systems, it seems to be no interaction between the components of the binary system as in the DSC profile peak is also observed for β-CD or HP β-CD corresponding to their melting point in their thermogram.

The DSC thermogram of (A) Dronedarone hydrochloride (B) β-CD (C) HP β-CD (D) Drug inclusion complexes with β-CD (E) Drug inclusion complexes with HP β-CD are overlaid and shown in Figure 5.

Conclusion

The solubility and dissolution rate of dronedarone hydrochloride can be enhanced by formulating ICs of dronedarone hydrochloride with β-CD or HP β-CD. The solubilization effect of β-CD or HP β-CD may be due to the structure of the drug with the phenyl ring that fit into the cyclodextrin cavity and the complex association, strengthened by hydrogen bonding between the amino group of the drug and the OH–groups of

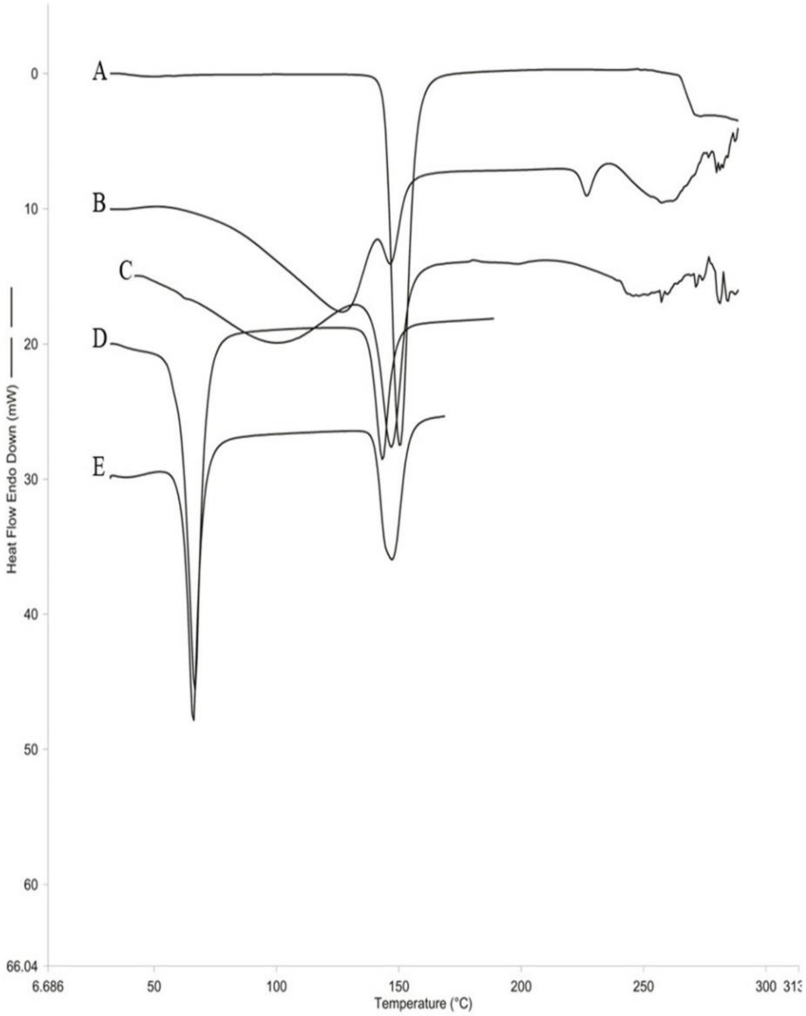

Figure 5 DSC thermogram overlay of (A) Dronedarone hydrochloride (B) β-CD (C) HP β-CD (D) Drug Inclusion complexes with β-CD (E) Drug Inclusion complexes with HP β-CD

CDs. The mechanism of solubility enhancement involves, cyclodextrins prevent the self- aggregation or association of molecules of dronedarone or of its pharmaceutically acceptable salts by forming of an encapsulation complex. In addition, reduction of particle aggregation of the drug, formation of microcrystalline or amorphous drug, increased wettability and dispersibility, and altered surface properties of the drug particles also contribute to the enhanced solubility and dissolution rates. The DSC profile of inclusion complexes indicates the drug in crystalline state; hence the enhancement of solubility and dissolution rate of drug may be due to hydrogen bonding or other mechanisms but not due to change in crystalline nature of the drug. The study indicates HP β-CD is better carrier for solubility and dissolution enhancement of dronedarone hydrochloride than β-CD as similar result is observed for HP β-CD at half of the carrier concentration compared to β-CD.

Conflict of Interests

Herewith the author(s) declare(s) that there is no conflict of interests regarding the publication of this article.

References

[1]T. Taupitz, J. B. Dressman, C. M. N Buchana, and S. Klein. Cyclodextrin-water soluble polymer ternary complexes enhance the solubility and dissolution behavior of poorly soluble drugs. Case example: Itraconazole, *Eur. J. Pharm. Biopharm.* 83: 378–387 (2013).

[2]C. O. Mellet, J. M. G. Fernandez, and J. M. Benito. Cyclodextrin-based gene delivery systems, *Chem. Soc. Rev*. 40: 1586–1608 (2011).

[3]M. D. Moya-Ortega, C. Alvarez-Lorenzo, A. Concheiro, and T. Loftsson. Cyclodextrin-based nanogels for pharmaceutical and biomedical applications, *Int. J. Pharm*. 428: 152– 163 (2012).

[4]M. E. Brewster, and T. Loftsson. Cyclodextrins as pharmaceutical solubilizers, *Advanced Drug Delivery Reviews*. 59: 645–666 (2007).

[5]M.Shaimaa, B. Eldin, S. A. Elkheshen, and M. M. Ghorab. Inclusion complexes of tadalafil with natural and chemically modified β-cyclodextrins I: Preparation and *in vitro* evaluation, *Eur. J. Pharm. Biopharm.* 70: 819–827 (2008).

[6]M. S. Nagarsenker, and M. S. Joshi. Celecoxib-cyclodextrin systems: characterization and evaluation of *in vitro* and in vivo advantage, *Drug Dev. Ind. Pharm.*, 31: 169–178 (2005).

[7]http://patents.justia.com/patent/20040044070

[8] A. K. Mahapatra, P. N. Murthy, S. Biswal, A. P. K. Mahapatra, and S. P. Pradhan. Dissolution Enhancement and Physicochemical Characterization of Valsartan in Solid Dispersions with β- CD, HP β-CD, and PVP K-30, *Dissolution Technologies*. 39 - 45 February (2011).

[9]T. Higuchi, and K. Connors. Phase solubility techniques, *Adv. Anal. Chem. Instrum.* 4: 17-123 (1965).

[10]N. Ahuja, O. P. Katare, and B. Singh. Studies on dissolution enhancement and mathematical modeling of drug release of a poorly water-soluble drug using water- soluble carriers, *Eur. J. Pharm. Biopharm.* 65: 26–38 (2007).

[11]M.Cirri, P. Mura, A. M Rabasco, J. M.Gine´s, J. R. Moyano, and M. L. Gonzalez- Rodriguez. Characterization of ibuproxam binary and ternary dispersions with hydrophilic carriers, *Drug Dev. Ind. Pharm.* 30(1): 65–74 (2004).

[12]C.Liu, and K.G.H Desai. Enhancement of Dissolution Rate of Valdecoxib Using Solid Dispersions with Polyethylene Glycol 4000, *Drug Dev. Ind. Pharm.* 31: 1–10 (2005).

[13]A.K. Mahapatra, P.N. Murthy, R. K. Patra, and S. Pattnaik. Solubility enhancement of Modafinil by Complexation with β-cyclodextrin and hydroxypropyl β-cyclodextrin: A Response Surface modeling Approach, *Drug Delivery Letters*. 3: 1-10 (2013).

[14]S. A. Kustrin, D. Morton, M. Worthington, and B. Glass. Modeling the effect of selected cyclodextrins on nifedipine solubility, *Current Drug Discovery Technologies*. 8: 146–154 (2011).

[15]M. M. Varma, and J. K. Pandi. Dissolution, solubility, XRD and DSC studies on Flurbiprofen- Nicotinamide solid dispersions. *Drug Dev. Ind. Pharm.* 31: 417–423 (2005).

[16]M. A. B. Jonathan, M. A. Dahan. The interaction of nifedipine with selected cyclodextrins and the subsequent solubility–permeability trade-off. *Eur. J. Pharm. Biopharm.* 85: 1293–1299 (2013).