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Solid state characterization of multicomponent inclusion complex of domperidone with β-cyclodextrin, polyvinyl pyrrolidone and citric acid

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ABSTRACT

The purpose of this study was to improve the solubility and dissolution rate of domperidone (DOM) by preparing its multicomponent inclusion complex. Inclusion complexes of DOM were prepared by kneading method along with β-cyclodextrin (β-CD) using polyvinyl pyrrolidone (PVP K40) and citric acid. Phase solubility studies were conducted to monitor the formation of complex and effect of water soluble polymers and citric acid on solubility of DOM. The prepared complexes were characterized by differential scanning calorimetry, fourier transform infrared spectroscopy, scanning electron microscopy, optical microscopy, X-ray diffractometry and nuclear magnetic resonance spectroscopy. Water soluble polymers synergistically enhanced solubilizing efficiency of β-CD and solubility of DOM in presence of citric acid.

Keywords: Domperidone, β-cyclodextrin, Multicomponent inclusion complex, Solubility.

INTRODUCTION

Poorly water-soluble drugs provide challenges for the oral formulation since their water-solubility and rate of dissolution are a limiting factors for their absorption and biological availability.[1] Thus there is a need to improve their solubility so as to increase their oral bioavailability. Cyclodextrins (CDs) are powerful carriers for improving aqueous solubility through inclusion complexes.[2] However the complexation efficiency of CDs is low and consequently a significant amount of CD is needed to solubilize small amount of a water insoluble drug. The drug solubility in the presence of CD can be dramatically improved by addition of suitable components such as hydroxy acids and water soluble polymers. Multicomponent inclusion complex of a poorly soluble basic drug, CD, water soluble polymer and hydroxy acid can enhance the solubility of drug multifold.[3, 4]

Domperidone (DOM) is a poorly water soluble dopamine D2 antagonist and widely used as an antiemetic. It is a basic, lipophilic BCS Class II drug with poor oral bioavailability and significant first pass metabolism. An intravenous administration of domperidone causes cardiac arrest.[5] Thus, there is need to improve bioavailability of DOM by increasing its aqueous solubility and overcoming the first pass metabolism if it is to be delivered by oral route.[6] This

encouraged the authors to study the improvement of solubility of DOM by preparing multicomponent inclusion complex with β-CD, water soluble polymer and hydroxy acid.

MATERIALS AND METHODS

Materials

Domperidone was kindly gifted by FDC, Mumbai, Maharashtra, India. β -cyclodextrin was available from commercial source. All other chemicals used in the study were of analytical grade.

Phase solubility studies

Phase solubility studies for DOM were performed as described by Higuchi and Connors (1965)[7]. An excess amount of drug was added to distilled water containing increasing concentration of β-CD (0-5 mM). Each molar solution was filled in vial. The vials were kept for shaking at ambient temperature for 48 hrs using lab shaker to attain equilibrium. Supernatant solution was filtered with 0.45 μm Millipore filter, and spectrophotometrically assayed at 284 nm. The stability constant and solubilizing efficiency were calculated from the slope of phase solubility diagram and the solubility of DOM in water. Phase solubility studies for ternary systems(DOM/ β-CD/ polyvinyl pyrrolidone (PVP) K40, DOM/ β-CD/ hydroxypropyl methylcellulose (HPMC) E5 , DOM/ β-CD/ polyethylene glycol (PEG) 4000, DOM/ β-CD/ citric acid) were performed analogously to those for binary system (DOM/ β-CD), but in presence of fixed amount of water soluble polymers (0.5%w/w) or citric acid (10mM). The polymer which showed good result in the phase solubility study of ternary system was used further for the phase solubility study of quaternary system (DOM/β-CD/optimized polymer/citric acid) which was carried out in 0.5%w/w optimized polymer and 10 mM citric acid solution containing increasing concentration of β-CD (0-5 mM).

Preparation of solid inclusion complexes

The DOM/ β-CD binary complex (1:1), DOM/ β-CD/ citric acid ternary complex (1:1:0.5), DOM/ β-CD/ PVP K40 ternary complex (1:1:14%w/w) and DOM/ β-CD/ citric acid/PVP K40 quaternary complex (1:1:0.5:14%w/w) were prepared by kneading method. Accurately weighed quantity of β-CD was mixed with sufficient quantity of water to obtain a smooth and homogenous paste. Weighed quantity of DOM alone (for binary complex) or along with citric acid and/or PVP K40 (for ternary and quaternary complex) was added slowly by grinding. The mixture was ground for one hour. Finally the paste was dried in hot air oven at 40^{o}C for 48 hrs. The dried complex was powdered and passed through sieve no. 100 and stored in air tight container till further use. The physical mixtures containing same composition as that of respective complexes were also prepared for comparative study.

Characterization of inclusion complexes

Drug content estimation

Complexes equivalent to 10 mg of DOM was accurately weighed and added into 100 ml volumetric flask and 50 ml of 0.1 M HCl (methanolic) was added to it. The resultant solution was stirred for 60 minutes, till the entire drug leached out. The solution was filtered and suitably diluted with distilled water. Drug content was estimated UV spectrophotometrically at 284 nm.

In-vitro dissolution studies

Dissolution studies for DOM inclusion complexes and physical mixtures were performed in 900 ml phosphate buffer pH 6.8 at stirring speed 50 rpm and temperature 37^{o}c ± 0.5 ^{o}c. Powder sample equivalent to 10 mg DOM was tested in phosphate buffer pH 6.8. At fixed time intervals,

samples were collected, filtered by using a 0.45 μm Millipore filter and spectrophotometrically analyzed at 284 nm.

Fourier transform infrared spectroscopy (FT-IR)

Infrared spectra of DOM, β-CD, citric acid, PVP K40, inclusion complexes and physical mixture of quaternary system were recorded by KBr method using Fourier Tranform Infrared Spectrophotometer (Perkin Elmer spectrum100 FIIR Spectrophotometer). Scanning was done from 4000 to 500 cm^{-1}.

Differential scanning calorimetry (DSC)

The thermograms of DOM, β-CD, inclusion complexes and physical mixture of quaternary system were recorded on Perkin Elmer DSC 7 differential scanning calorimeter. The thermal behavior was studied by heating all samples (5-10 mg of drug or its equivalent complexes) in sealed aluminum pans, using an empty sealed pan as reference, over a temperature range of 30 – 300 ^{0}C and at heating rate of 10° C/min.

X-ray diffractometry (XRD)

X-ray diffraction patterns of DOM, β-CD and inclusion complexes were recorded on X-ray diffractometer (Rigaku miniflex) with CuKα target tube, NaI detector, operated at voltage of 30 kV, 15 mA current, at 2^{o}C/min scanning speed and scanning angle ranging from 0-50^o (2θ).

Proton nuclear magnetic resonance (^{1}H NMR) spectroscopy

^{1}H NMR spectra of DOM, β-CD and complexes in dimethyl sulfoxide (DMSO) were recorded on a Bruker spectrophotometer. ^{1}H NMR chemical shifts ($\Delta\delta$) were used to confirm the inclusion of DOM in βCD and calculated according to the formula $\Delta\delta = \delta$ (complex) - δ (free).

Scanning electron microscopy (SEM)

The surface morphology of DOM and complexes were studied using scanning electron microscopy (SEM), JEOL 6386 ®, Japan. Samples were sprinkled on to double side tape, sputter coated with platinum and examined in the microscope at 10 kV.

RESULTS AND DISCUSSION

Phase solubility studies

Phase solubility diagram of DOM/β-CD binary system is as shown in Figure 1a. The diagram could be classified as A_L type according to Higuchi and Connors.[7] A linear increase in DOM solubility with increasing β-CD concentration (0-5 mM) was found. The stability constant (K_c) for DOM/β-CD system was found to be 217.07 M^{-1}. The intrinsic solubility (S_0) of DOM in water was very low 0.01218 mM (0.005187 mg/ml). The solubility was found to be increased as function of the cyclodextrin concentration.

In ternary phase solubility (Figure 1a), after addition of hydrophilic polymers (0.5% w/w) such as hydroxypropyl methylcellulose (HPMC) E5, polyethylene glycol (PEG) 4000 and polyvinyl pyrrolidone (PVP) K40, solubility of DOM was found to be increased as compared to the binary system, however PVP K40 showed the maximum increase in the solubility of DOM. The slope values in all phase solubility profiles were less than one suggesting the formation of 1:1 stoichiometry complexes in solution**.** In presence of hydrophilic polymers the solubility isotherm showed negative deviation from linearity. The phase solubility curves of DOM/β-CD in presence of hydrophilic polymers were of A_N type, which can be due to change in solute solvent interaction. The value of K_c cannot be calculated from this solubility profile.[8, 9]

The phase solubility profile of DOM/β-CD in presence of 10 mM citric acid is shown in Figure 1b. Citric acid was found to increase the solubility of DOM to large extent as compared to other hydroxy acids (tartaric acid, malic acid).[10] The phase solubility profile in presence of citric acid was also found to be of A_N type, however the solubilizing efficiency (Table 1) was found to be significantly increased ($p<0.05$) as compared to the ternary systems containing the water soluble polymers. This may be due to combined effect of drug ionization in the acidic environment and complexation. When PVP K40 (0.5% w/w) was added to the DOM/β-CD/citric acid system, the solubility of DOM was found to be surprisingly increased by 204 folds. This may be due to simultaneous presence of citric acid and PVP K40, both known to increase the solubilizing efficiency, which showed the positive effect on DOM solubility.[3]

Figure 1a. Phase solubility profiles of DOM and complexes.

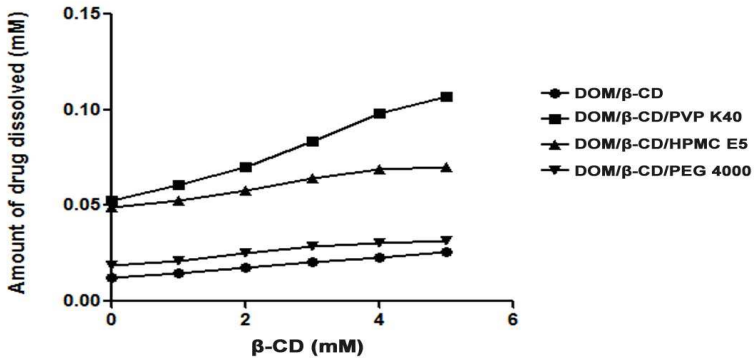


Figure 1b Phase solubility profiles of DOM and complexes

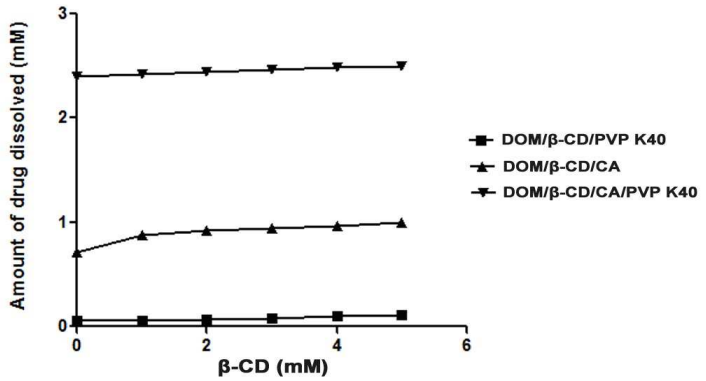


Table 1 Solubilizing efficiencies of binary system, ternary systems and quaternary system

Systems	Solubilizing efficiency		
	S_1 mM/ml	S_2 mM/ml	S_2/S_0
DOM/ β-CD	-	0.02549	2.0928
DOM/ β-CD/PEG 4000	0.01845	0.03176	2.6076
DOM/ β-CD /HPMC E5	0.04910	0.07023	5.7660
DOM/ β-CD /PVP K40	0.05145	0.10673	8.7619
DOM/ β-CD/citric acid	0.7111	1.2356	82.08
DOM/ β-CD/citric acid/PVP K40	2.3994	2.4959	204.91

S_1- Solubility of DOM with hydrophilic polymers, citric acid and both (absence of β-CD).
S_2 - Solubility of DOM after addition of 0.005M β-CD.
S_0 - Solubility of pure DOM in water (S_0 = 0.01218 mM).

Preparation of multicomponent inclusion complexes

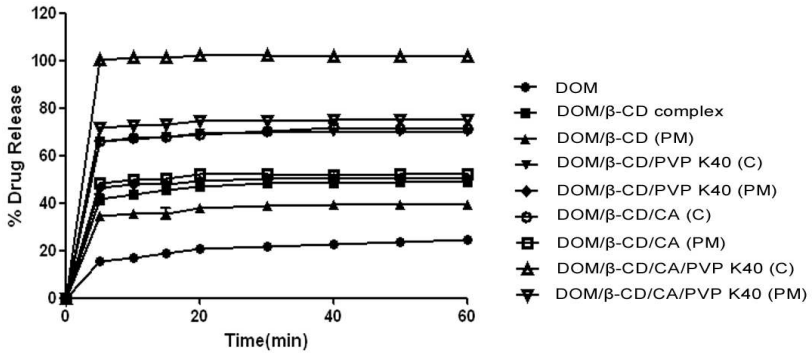
Inclusion complexes were prepared by kneading method. The physical mixtures containing same composition as that of respective complexes were prepared for comparing their dissolution with the complexes.[11]

Characterization of inclusion complexes

Drug content estimation

The drug content in all complexes was found to be in the range of 99 to 101.9 %.

Figure2. Dissolution profile of DOM, inclusion complexes and physical mixtures



[(C): Inclusion complex; (PM): Physical mixture; (CA): Citric acid]

In-vitro dissolution Studies

Comparisons of dissolution patterns of pure DOM with various inclusion complexes and physical mixtures are shown in Figure 2. The release rate profiles were expressed in percentage of drug released versus time. The quaternary inclusion complex showed higher dissolution rate as compared to ternary complex with PVP K40, ternary complex with citric acid, binary complex and pure drug. Pure drug showed 18.88 % release whereas binary complex showed 47.71 % release within 5 min (DP_5). The ternary inclusion complex containing PVP K40 (14%) showed 66.28% drug release within 5 min. The preliminary studies revealed that dissolution of DOM

decreased after increasing polymer concentration above 14%. This may be due to formation of water insoluble inclusion complexes between polymer and several β-CD molecules[5]. The ternary inclusion complex with citric acid showed 66.36% release. The quaternary inclusion complex showed 100.66% release within 5 min which was significantly higher ($p<0.05$) than physical mixtures and binary complex. The enhancement in the dissolution was due to formation of inclusion complexes in the solid state with reduction in the crystallinity of DOM, as confirmed by XRD studies, leading to increased hydrophilicity, higher wetting effect and increased contact between drug and the carrier.

Fourier transform infrared spectroscopy (FT-IR)

The FTIR spectra of DOM, β-CD, citric acid, PVP K40 and inclusion complexes are shown in Figure 3. The FTIR spectra of DOM showed N-H stretching at 3129.90 cm^{-1}, N-H bending at 1620.6 cm^{-1} and C = O stretching at 1711.80 cm^{-1}, indicating the presence of –CONH group, asymmetric C-H stretching at 2943.10 cm^{-1}, symmetric C-H stretching at 2816.60 cm^{-1}, aromatic C-H stretching at 3015.70 cm^{-1}. The characteristic absorption band at 759.30 $cm^{-1}$with strong stretching intensities may be attributed to presence of C-Cl bond.

The FTIR spectra of ternary inclusion complex containing PVP K40 (1:1:14%w/w) showed, C = O stretching at 1717.43 cm^{-1}. It confirmed the intactness of the amide group in the drug after complexation. The asymmetric C-H stretching was found at 2928.57 cm^{-1}. The characteristic absorption band at 754.51 cm^{-1} attributed to presence of –C-Cl bond, which confirmed that no chemical bonding occurred at –C-Cl bond position during complexation. The complex of 1:1:0.5 (DOM: β-CD: citric acid) showed N-H bending at 1624.15cm^{-1} and C = O stretching at 1714.69 cm^{-1} (indicative of –CONH group) and asymmetric C-H stretching at 2923.07cm^{-1}.

On comparing the FTIR spectra of physical mixture and complex of quaternary system, it was found that the spectra of physical mixture of quaternary system (1:1:0.5:14%w/w) showed N-H bending at 1621.41cm^{-1}, which disappeared in the quaternary complex. The C = O stretching at 1714.69 cm^{-1} and asymmetric C-H stretching at 2928.57 cm^{-1} in physical mixture shifted to 1704.55 cm^{-1} and 2923.07 cm^{-1} respectively after complexation. The absorption band at frequency of 756.75 cm^{-1} for physical mixture shifted to 757.25 cm^{-1} after complexation. Since all these shifts were within the minute range of 1700-1725 cm^{-1}, 1550-1640 cm^{-1} and 600-800 cm^{-1} respectively, it indicated that there were no any chemical changes involved. This peak shifting towards lower frequency with change in intensity suggested change in the environment of the C = O, amide N-H and –C-Cl groups of drug. The slight shift of absorption bands to a lower frequency may be attributed to the breakdown of the intermolecular hydrogen bonds associated with crystalline drug molecule by formation of hydrogen bonds with external OH groups of β-CD and citric acid.[10, 12]

Differential scanning calorimetry (DSC)

DSC thermograms of DOM, β-CD, inclusion complexes and physical mixture of quaternary inclusion complex are shown in Figure 4. Thermal curve of pure DOM showed sharp endothermic peak at 247.13 ^{0}C corresponding to the melting point of DOM (242.5 ^{0}C). In binary complex and ternary complex with citric acid characteristic thermal profile of DOM was shifted to lower temperatures, but in ternary complex with PVP K40 and quaternary inclusion complex, endothermic peaks were totally absent, indicating formation of amorphous entities or inclusion complex. [13]

Figure 3. IR analysis of DOM (a), β-CD (b), Citric acid (c), PVP K40 (d), DOM/ β-CD complex (e), DOM/β-CD/citric acid complex (f), DOM/β-CD/PVP K40 complex (g), DOM/β-CD/citric acid/PVP K40 physical mixture (h), DOM/β-CD/citric acid/PVP K40 complex (i)

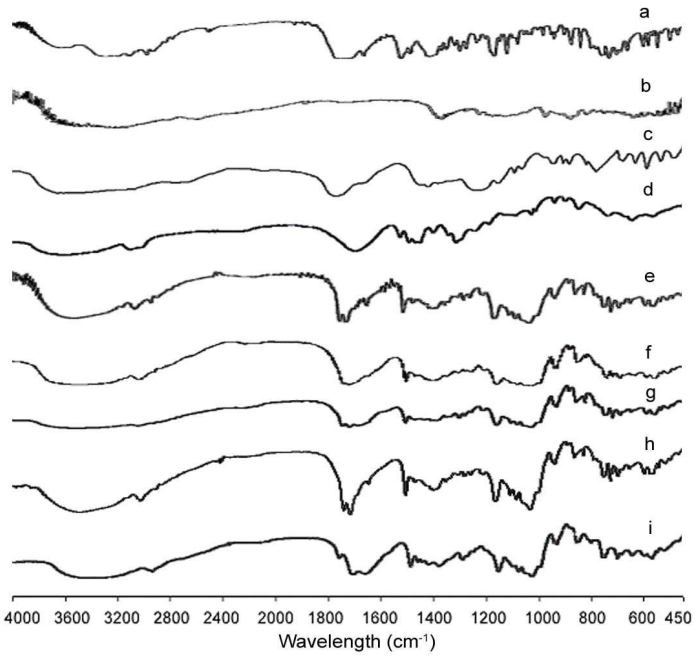
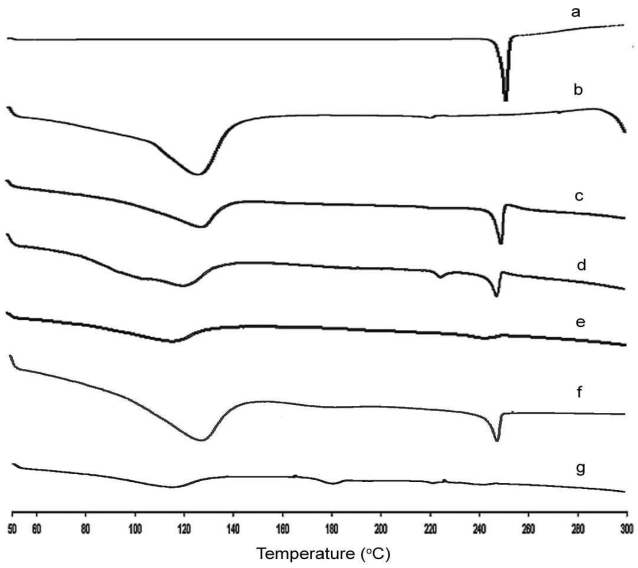


Figure 4. DSC analysis of DOM (a), β-CD (b), DOM/β-CD complex (c) and DOM/β-CD/citric acid complex (d), DOM/β-CD/PVP K40 (e), DOM/β-CD/citric acid/PVP K40 physical mixture (f), DOM/β-CD/citric acid/ PVP K40 complex (g)



Proton nuclear magnetic resonance (^{1}H NMR) spectroscopy

Chemical shift changes in the ^{1}H NMR spectra were used to monitor the complex formation process. If a guest is incorporated into the CD cavity, the hydrogen atoms located in the interior of the cavity (H-3 and H-5) get considerably shielded by the guest molecule, whereas the hydrogen atoms on the outer surface (H-1, H-2, H-4 and H-6) remain unaffected or experience a marginal shift. When any guest molecule gets incorporated in the CD cavity, the hydrogen atoms located inside the cavity experience significant changes in the δ ppm values. But in case of association of guest molecule with CD the hydrogen's on the exterior surface shows shifts in δ

ppm values. In this convection, a positive sign of Δ δ ppm shows a downfield displacement and a negative sign show an up field displacement. Table 2 shows chemical shifts corresponding to β-CD in free and complexed state. For binary complex, Δ δ ppm values for H_3 and H_5 were changed indicating formation of complex. It was found that there were changes in the δ ppm values for interior as well as exterior hydrogen's of β-CD for ternary and quaternary inclusion complexes. This suggested that there was association as well as complexation of drug with β-CD. [3, 14]

Table 2 1H Chemical shifts corresponding to β-CD in free and complexed state.

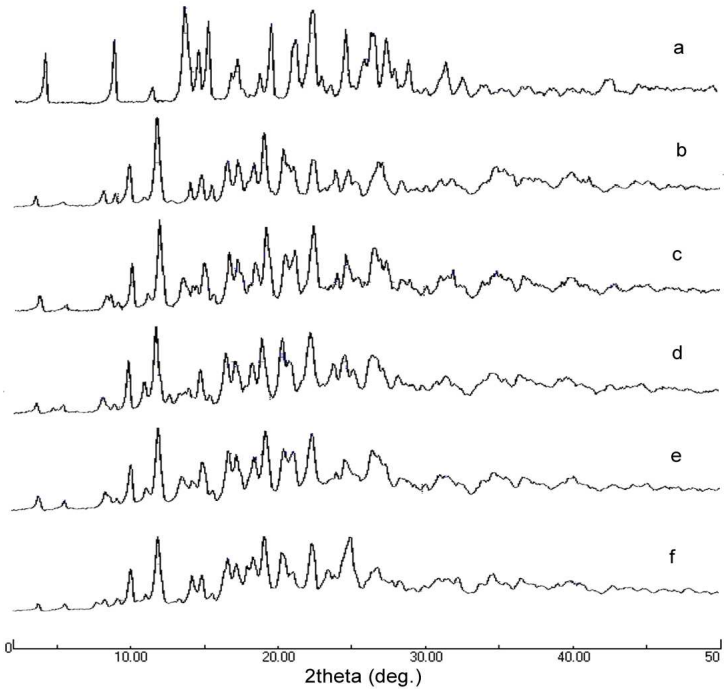
DOM/β-CD (1:1 complex)			
β-CD protons	δ (*free*)	δ (*complex*)	Δδ
H-1	4.809	4.813	0.004
H-2	3.346	3.338	-0.008
H-3	3.613	3.649	0.036
H-4	3.297	3.293	-0.004
H-5	3.523	3.534	0.011
H-6	3.558	3.568	0.010
DOM/β-CD/PVP K40 (1:1:14%w/w complex)			
β-CD protons	δ (*free*)	δ (*complex*)	Δδ
H-1	4.809	4.810	0.001
H-2	3.346	3.337	-0.009
H-3	3.613	3.647	0.034
H-4	3.297	3.288	-0.009
H-5	3.523	3.531	0.008
H-6	3.558	3.564	0.006
DOM/β-CD/citric acid/PVP K40 (1:1:0.5:14%w/w complex)			
β-CD protons	δ (*free*)	δ (*complex*)	Δδ
H-1	4.809	4.810	0.001
H-2	3.346	3.338	-0.008
H-3	3.613	3.647	0.034
H-4	3.297	3.289	-0.008
H-5	3.523	3.531	0.008
H-6	3.558	3.564	0.006

$$\Delta\delta = \delta \text{ (complexed)} - \delta \text{ (free)}$$

X-ray diffractometry (XRD)

The powder x-ray diffraction patterns of DOM, βCD, and various inclusion complexes are shown in Figure 5. The X-ray diffractogram of the drug powder was characterized by the presence of sharp peaks indicative of the crystalline nature of drug. The diffraction of βCD was also characterized by presence of sharp peaks indicative of its crystalline nature. The diffractograms of all inclusion complexes were studied for presence of the characteristic peaks of the drug. The sharpness of peaks as well as the number of sharp peaks existing with pure drug were found to be significantly diminished in case of all complexes which may be due to the existence of drug in a amorphous form as a result of processing during the formulation of inclusion complexes.[13]

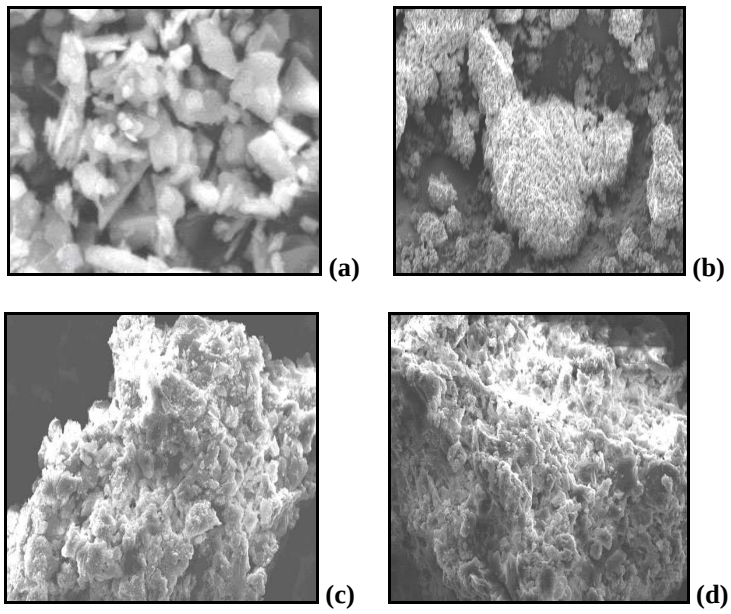
Figure5. XRD analysis of DOM (a), β-CD (b), DOM/β-CD complex (c) and DOM/β-CD/citric acid complex (d), DOM/β-CD/PVP K40 (e) and DOM/β-CD/citric acid/ PVP K40 complex (f)



Scanning electron microscopy (SEM)

The microphotographs of DOM, binary complex, ternary complex with PVP K40 and quaternary complex are shown in Figure 6. The pure drug appeared to be in crystalline form. In case of ternary and quaternary complexes particles appeared as irregularly shaped agglomerates with surface smoothness indicating an amorphous nature. These results support the XRD and DSC studies.[15]

Figure 6. SEM analysis of DOM (a), DOM/β-CD complex (b), DOM/β-CD/PVP K40 complex (c) and DOM/β-CD/citric acid/ PVP K40 complex (d)



CONCLUSION

As a result of this study, the enhancement in solubility of DOM without increasing the amount of β-CD, the quaternary inclusion complex of DOM showed good solubility and dissolution rate as compared to ternary inclusion complex with citric acid, ternary inclusion complex with PVP K40, binary complex and physical mixtures. The quaternary inclusion complex of DOM may have greater utility in the fast dissolving dosage forms, with possible enhancement of oral bioavailability.

REFERENCES

[1] PJ Salustio; G Feio; JL Figuirinhas; JF Pinto; HM Cabral Marques. *Eur. J. Pharm. Biopharm.,* **2008,** 71, 377-86.
[2] EM Martine Del Valle. *Process Biochem.,* **2004**, 39,1033-46.
[3] L Ribeiro; RA Carvalho; DC Ferreira; JB Veiga Francisco. *Eur. J. Pharm. Sic.*, **2005**, 24, 1-13.
[4] T Loftsson; H Frioriksdottir. *Int. J. Pharm.*, **1998**, 163,115-121.
[5] RJ Osborne; ML Slevin; RW Hunter; J Hamer. *Lancet*, **1985,** 2, 385.
[6] SC Reddymasu; RW Mccallum. *Am. J. Gastroenterol.,* **2007**, 102, 2036-45.
[7] T Higuchi; KA Connors. *Adv. Anal. Chem. Instrum.*, **1965**, 4,117-150.
[8] V Pokharkar; A Khanna. *Acta Pharma.*, **2009**, 59, 121-132.
[9] R Kalaiselvan; GP Mohanta; PK Manna; R Manavalan. *Acta Pharm. Sci.,* **2006**, 48,19-33.
[10] KK Mali; RJ Dias; VS Ghorpade; VD Havaldar. *Latin Am. J. Pharm***., 2010**. (Article in Press).
[11] K Dua; MV Ramana; UV Sing-Sara; M Himaja; A Agrawal; V Garg; K Pabreja. *Curr. Drug. Deliv.,* **2007**,4, 21-25.
[12] T Loftsson; M Masson. *Int. J. Pharm.*, **2001**, 225, 15-30.
[13] ACC Asbahr; L Franco. *Bioorganic Med. Chem*., **2009**, 17, 2718-23.
[14] S Anguiano-Igea; FJ Otero-Espinar; JL Vila-Jato; J Blanco-Mendez. *Eur. J. Pharm. Sic.*, **1997**, 5, 215-221.
[15] AR Patel; PR Vavia. *AAPS PharmSciTech*., **2008**, 9, 554-550.