EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 5
Issue: 3
542-550
Year: 2018

DISSOLUTION RATE ENHANCEMENT OF DOMPERIDONE MALEATE THROUGH FORMATION OF HYDROXYPROPYL β-CYCLODEXTRIN - HYDROPHILIC POLYMER COMPLEXES

Varalakshmi Mummidi[1]* and Ajay Babu Ch.[2]

[1]School of Pharmaceutical Sciences and Technologies, Jawaharlal Nehru Technological University, Kakinada, East Godavari District-533 003, India.
[2]Department of Pharmaceutics, MAM College of Pharmacy, Narasaraopet, Guntur District-522601, India.

***Corresponding Author: Varalakshmi Mummidi**
School of Pharmaceutical Sciences and Technologies, Jawaharlal Nehru Technological University, Kakinada, East Godavari District-533 003, India.

Article Received on 06/01/2018 **Article Revised on 26/01/2018** **Article Accepted on 16/02/2018**

ABSTRACT
Complexation of domperidone maleate with hydroxypropyl β-cyclodextrin (HPβCD) in the presence and absence of 3 hydrophilic polymers—polyvinyl pyrrolidone (PVP), and hydroxypropyl methylcellulose (HPMC), polyethylene glycol (PEG) —was investigated with an objective of evaluating the effect of hydrophilic polymers on the complexation and solubilizing efficiencies of HPβCD and on the dissolution rate of domperidone maleate from the HPβCD complexes. The phase solubility studies indicated the formation of domperidone maleate-HPβCD inclusion complexes at a 1:1M ratio in solution in both the presence and the absence of hydrophilic polymers. The complexes formed were quite stable. Addition of hydrophilic polymers markedly improved the complexation and solubilizing efficiencies of HPβCD. Solid inclusion complexes of domperidone maleate-HPβCD were prepared in 1:1 and 1:2 ratios by the kneading method, with and without the addition of hydrophilic polymers. The solubility and dissolution rate of domperidone maleate were significantly improved by complexation with HPβCD. The domperidone maleate-HPβCD (1:2) inclusion complex yielded a 11.21-fold increase in the dissolution rate of domperidone maleate. The addition of hydrophilic polymers also markedly improved the dissolution rate of domperidone maleate from HPβCD complexes: a 31.39-, 25.41-, 19.72- and fold increase was observed with PVP, HPMC and PEG respectively. X-ray diffractometry and differential scanning calorimetry indicated stronger drug amorphization and entrapment in HPβCD because of the combined action of HPβCD and the hydrophilic polymers.

KEYWORDS: Domperidone maleate, hydroxypropyl β-cyclodextrin, hydrophilic polymers, complexation, dissolution rate.

INTRODUCTION
Cyclodextrins (CDs), with their capability to form molecular inclusion complexes with drug substances, will affect many of the physicochemical properties of the drugs without affecting their essential lipophilicity or pharmacological properties.[1,2] As a result of the inclusion process, many physicochemical properties, such as solubility, dissolution rate, stability, permeability, palatability, and bioavailability, can be favorably affected.[3-5]

Cyclodextrins are cyclic (α-1,4) -linked oligosaccharides of α-D-gluco pyranose, containing a relatively hydrophobic central cavity and hydrophilic outer surface. Owing to lack of free rotation about the bonds connecting the glucopyranose units, the CDs are not perfectly cylindrical molecules but are toroidal or cone shaped.[6]

For a variety of reasons, including price, availability, approval status and cavity dimensions, the parent β-cyclodextrin (βCD) is the most widely used. However, its low aqueous solubility is a serious barrier to its wider use.[7] Therefore, derivatives such as hydroxypropyl-β-cyclodextrin (HPβCD) have been synthesized to increase the water solubility.[8] Unfortunately, the complexation efficiency of CDs is rather low and, consequently, significant amounts of CDs are needed to solubilize small amounts of water insoluble compounds. However, enhanced complexation can be obtained by formation of ternary complexes between the drug, cyclodextrin and a third component. For instance, the addition of small amounts of a water soluble polymer to an aqueous complexation medium can increase the solubility, bioavailability, palatability and stability constants of drug–CD complexes.[9]

Domperidone maleate, which is chemically designated as 5-Chloro-1-[1-[3-(2-oxo-1,3-dihydrobenzoimidazol-1-yl)propyl]-4- piperidyl]- 1,3-dihydrobenzoimidazol-2-one maleate. It is a dopamine receptor (D_2) antagonist used as anti-emetic has poor aqueous solubility (0.986mg/L) and its oral bioavailability is only 13.17%.[10] To overcome these difficulties, several approaches have been used, namely, the formation of a complex between domperidone-HPβCD in presence and absence of different hydrophilic polymers. Hence, we sought to enhance the aqueous solubility and dissolution rate of domperidone through formation of an inclusion complex with HPβCD. In the present work the effect of 3 hydrophilic polymers—Polyvinyl pyrrolidone (PVP), polyethylene glycol (PEG) and hydroxypropyl methylcellulose (HPMC)—on the complexation of domperidone maleate with HPβCD was investigated. The effect of the hydrophilic polymers on the solubilizing efficiency of HPβCD and the dissolution rate of domperidone maleate from the HPβCD complexes was also investigated.

MATERIALS AND METHODS

Materials

Domperidone maleate was a gift sample from M/s Dr Reddy's Laboratories (Hyderabad, India). HPβCD was a gift sample from M/s Alkem Laboratories (Mumbai, India). PVP (K-30), HPMC (6cps), PEG 6000, sodium lauryl sulfate (Sigma Chemical Co.) and methanol (Qualigens) were procured from commercial sources. All other materials used were of pharmacopeial grade.

Methods

Phase Solubility Studies

Phase solubility studies were performed according to the method reported by Higuchi and Connors[11]. An excess amount of domperidone maleate (25 mg) was added to 15 mL of double distilled water containing various concentrations of HPβCD (2-12 mM) taken in a series of 50-mL stoppered conical flasks and the contents were shaken at room temperature (28 ± 0.5°C) for 48 hours on a rotary flask shaker. After 48 hours of shaking to achieve equilibrium, 2mL aliquots were withdrawn at 1hour intervals and filtered immediately using 0.45µ nylon disc filter. The filtered samples were diluted suitably and assayed for domperidone maleate at 285nm against blanks prepared in the same concentration of HPβCD in water so as to cancel any absorbance that may be exhibited by the cyclodextrin molecules. Shaking was continued until three consecutive estimations were the same. Phase solubility studies were conducted in each case with and without addition of hydrophilic polymers. In the series with hydrophilic polymers, the polymer was added at a concentration of 0.5% w/v to the solution containing HPβCD. The solubility experiments were conducted in triplicate.

Preparation of Solid Inclusion Complexes

Solid inclusion complexes of domperidone maleate-HPβCD were prepared in 1:1 and 1:2 molar ratios by the kneading method, with and without the addition of hydrophilic polymers. In the series with hydrophilic polymers, the polymer was added at a concentration of 10% w/w of the solid complex. Domperidone maleate, HPβCD, and hydrophilic polymers were triturated in a mortar with a small volume of a solvent blend of water: methanol (1:1). The thick slurry formed was kneaded for 45 minutes and then dried at 55°C until it was dry. The dried mass was powdered and sieved through mesh No.100.

Estimation of Domperidone maleate

A UV spectrophotometric method based on the measurement of absorbance 285nm in 0.1N HCl and used for the estimation of domperidone maleate. The method obeyed Beer's law in the concentration range of 2 to 10 µg/mL. When a standard drug solution was assayed repeatedly (n = 6), the relative error (accuracy) and relative standard deviation (precision) were found to be 0.8% and 1.0%, respectively.

Dissolution Rate Study

The dissolution rate of domperidone maleate as such and from its cyclodextrin inclusion complexes was studied using DISSO 2000, Lab India 8-Station Dissolution Rate Test Apparatus with a paddle stirrer. The dissolution was studied in 900ml of 0.1NHCl. Domperidone maleate (50mg) or its inclusion complex equivalent to 50mg of domperidone maleate, a speed of 50rpm and a temperature of 37±1°C were used in each test. Samples of dissolution medium (5ml) were withdrawn through 0.45µ nylon disc filter at different time intervals, suitably diluted and assayed for domperidone maleate by measuring absorbance at 285nm. The dissolution experiments were conducted in triplicate.

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) thermograms of the drug, CD, polymer, and the solid binary and ternary systems were recorded on the DSC Q200 Model (TA Instruments). Samples (2-5 mg) were sealed into aluminum pans and scanned at a heating rate of 10°C/ min over a temperature range of 50 - 300°C under a nitrogen gas stream.

X-ray Diffractometry

X-ray powder diffraction patterns were recorded using a Burker axs D-8 (Advance, Germany) powder diffractometer with monochromatized Cu Kα radiation (λ = 1.540600), at a voltage of 40kV. The samples were scanned at room temperature in the continuous scan mode over the 2θ angle range of 5° to 60°, with 0.1 step size and with counting time of 1.0 seconds.

Scanning Electron Microscopy

The samples were observed under a scanning electron microscope, Philips XL-30 SEM (Basel, The Netherlands). The samples were fixed on a brass stub using double sided sticking tape and then gold coated in

vacuum by a sputter coater. The pictures were then taken at a excitation voltage of 10 kV.

Fourier Transform Infrared (FT-IR) Studies

FT-IR spectra of domperidone maleate and various HPβCD complex systems were recorded in the range of 400 to 4,000 cm^{-1} using a Jasco- FT-IR spectrophotometer (Jasco, Essex, UK) by the KBr disc method.

RESULTS AND DISCUSSION

The phase solubility diagrams for the complex formation between domperidone maleate and HPβCD in the presence and absence of hydrophilic polymers are shown in Figure 1. The aqueous solubility of domperidone maleate was increased linearly as a function of the concentration of HPβCD. The phase solubility diagrams of domperidone maleate-HPβCD complexes can be classified as type A_L according to Higuchi and Connors.[11] Because the straight line had a slope <1 in each case, the increase in solubility was due to the formation of a 1:1M complex in solution with HPβCD in the presence and absence of hydrophilic polymers. The apparent stability constant (K_c) was calculated from the slope of the linear plot of the phase solubility diagram according to the equation K_c = Slope/S_o(1 – Slope), where S_o is the solubility of the drug in the absence of CD. The estimated K_c values of various complexes are given in Table 1. The values of K_c indicated that the complexes formed between domperidone maleate and HPβCD are quite stable.

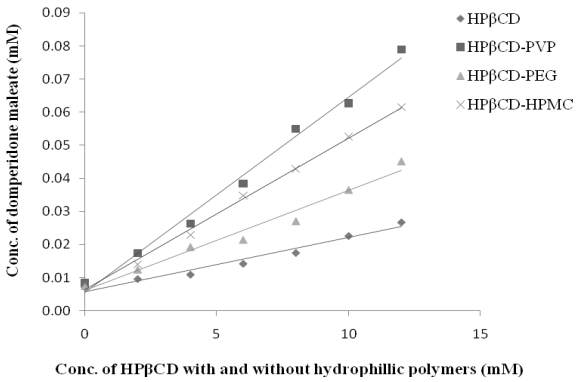

Figure 1. Phase solubility diagrams of domperidone maleate - HPβCD complexation in the presence and absence of hydrophilic polymers.

To evaluate the effect of hydrophilic polymers, the solubilizing efficiency of HPβCD was calculated in each case as the ratio of the drug solubility in aqueous solution (12 mM) of HPβCD (with and without hydrophilic polymers) to the drug solubility in water. The solubilizing efficiency values are given in Table 1. HPβCD alone yielded a 3.88 fold increase in the solubility of domperidone maleate, whereas in the presence of hydrophilic polymers it gave a 11.43, 8.91 and 6.55 fold increase with PVP, HPMC and PEG respectively. Thus the addition of hydrophilic polymers markedly enhanced the solubilizing efficiency of HPβCD. The values of the stability constant (K_c) were found to be higher in the presence of hydrophilic polymers, indicating higher complexation efficiency. A 3.76, 2.88 and 1.87 fold increase in the K_c value was observed in the presence of PVP, HPMC and PEG respectively. In this case, PVP has given higher enhancement in complexation efficiency. The order of polymers in enhancing the complexation efficiency was PVP>HPMC>PEG with HPβCD.

Table 1. Effect of PVP, PEG, and HPMC on the Apparent Stability Constant (K_c) and Solubilizing Efficiency of Domperidone maleate-HPβCD Complexes*

Sample	K_c (M^{-1})	Solublizing efficiency†
D-HPβCD	228.93	3.88
D-HPβCD-PVP	862.31	11.43
D-HPβCD-PEG	429.86	6.35
D-HPβCD-HPMC	660.17	8.91

*PVP indicates polyvinyl pyrrolidone; PEG, polyethylene glycol; HPMC, hydroxypropyl methylcellulose; HPβCD, hydroxypropyl β-cyclodextrin; and D, domperidone maleate.

†Ratio of drug solubility in aqueous solution (12mM) of cyclodextrin (with or without hydrophilic polymers) to drug solubility in water.

All the solid complexes prepared were found to be fine and free-flowing powders. The angle of repose (θ) was below 20°. The free flow may be due to the inclusion of the drug in HPβCD. Low coefficient of variation (CV) (<1.0%) values in the percentage of drug content indicated uniformity of drug content in each batch of solid inclusion complex prepared. The dissolution rate of domperidone maleate alone and from various solid inclusion complexes was studied in 0.1N HCl as the dissolution fluid. The dissolution profiles of various complexes are shown in Figure 2. The dissolution of domperidone maleate was rapid and higher from all the solid inclusion complexes when compared with domperidone maleate pure drug. The dissolution of domperidone maleate alone and from various complexes followed first-order kinetics (r > 0.910). Dissolution rate constants (K_1) were calculated from the slopes of the first-order linear plots of the dissolution data. Dissolution efficiency (DE_{30}) values based on the dissolution data were calculated as per Khan.[12] $T_{50\%}$ (time taken for 50% dissolution) values were recorded from the dissolution profiles. The dissolution parameters are summarized in Table 2.

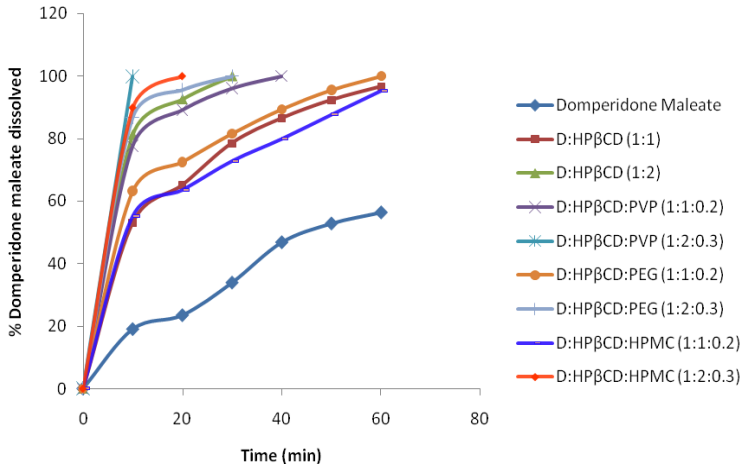

Figure 2. Dissolution profiles of domperidone maleate and its hydroxypropyl-β-cyclodextrin complexes.

Table 2. Dissolution Parameters of Various Domperidone maleate-HPβCD Solid Inclusion Complexes*

Complex System	Percent Dissolved in 10 Minutes	DE_{30} (%)	K_1 (min^{-1})	T_{50} (min)	Increase in K_1 (folds)†
Domperidone maleate	19.01±1.02	19.93	0.0115	>60	-
D-HPβCD (1:1)	53.05±0.63	56.21	0.0474	14.60	4.12
D-HPβCD (1:2)	81.29±0.68	80.29	0.1404	4.93	12.21
D-HPβCD-PVP (1:1:0.2)	77.72±0.56	76.68	0.1289	5.37	11.20
D-HPβCD-PVP (1:2:0.3)	100.00±0.02	91.42	0.3670	0.81	31.39
D-HPβCD-PEG (1:1:0.2)	63.23±0.54	62.70	0.0506	13.67	4.40
D-HPβCD-PEG (1:2:0.3)	89.67±0.65	85.51	0.2270	3.05	19.72
D-HPβCD-HPMC(1:1:0.2)	67.27±0.85	64.78	0.0534	12.97	4.64
D-HPβCD-HPMC(1:2:0.3)	94.63±0.96	88.19	0.2924	2.36	25.41

*HPβCD indicates hydroxypropyl β-cyclodextrin; DE, dissolution efficiency; D, domperidone maleate; PVP, polyvinyl pyrrolidone; PEG, polyethylene glycol and HPMC, hydroxypropyl methylcellulose.
†Ratio of K_1 of CD complexes to K_1 of domperidone maleate.

All CD complexes exhibited higher rates of dissolution and dissolution efficiency values than domperidone maleate, indicating rapid and higher dissolution of domperidone maleate from its HPβCD complexes. The K_1 and DE_{30} values were increased as the proportion of HPβCD in the complex was increased. The increase in K_1 (folds) with various CD systems is shown in Table 2. The addition of hydrophilic polymers markedly enhanced the dissolution rate and efficiency of domperidone maleate from CD complexes. The domperidone maleate-HPβCD (1:2) complex yielded a 11.20 -fold increase in the dissolution rate of domperidone maleate, whereas in the presence of hydrophilic polymers, it yielded a 31.91, 19.72 and 25.4 -fold increase with PVP, PEG, and HPMC respectively. The order of hydrophilic polymers in enhancing the solubilizing efficiency and dissolution rate of HPβCD complexes was PVP>HPMC>PEG. Thus, inclusion of hydrophilic polymers in the CD complexes markedly enhanced both the complexation and solubilizing efficiencies of the HPβCD, and the solid inclusion complexes of HPβCD with hydrophilic polymers yielded rates of dissolution several times higher than those of domperidone maleate and its complexes with HPβCD alone.

DSC was used to characterize the domperidone maleate-HPβCD solid complexes prepared with and without hydrophilic polymers. The DSC thermograms of various products are shown in Figure 3 and fractional crystallinity [(ΔH_f) sample / (ΔH_f) crystal] values are given in Table 3. The DSC curve of domperidone maleate showed a single sharp endothermic peak at 171.0°C corresponding to its melting point. HPβCD, PVP, PEG and HPMC showed (B, C, D, E) broad endothermic peaks associated with loss of water. In the thermograms of domperidone maleate-HPβCD (F,G), the intensity (or height) of the endothermic peak at 227.49°C was reduced indicating interaction of domperidone maleate with HPβCD. With the domperidone maleate-HPβCD-PVP (H,I) domperidone maleate-HPβCD-PEG (J,K), and domperidone maleate-HPβCD-HPMC (L,M) systems, the endothermic peak at 227.49°C was markedly reduced in 1:2:0.3 systems indicating the absence of crystalline drug and its complete complexation with HPβCD. The crystallinity level is obtained by measuring the enthalpy of fusion for a sample (ΔH_f) and comparing it to the enthalpy of fusion for the fully crystalline material (ΔH_f) crystal.[13]

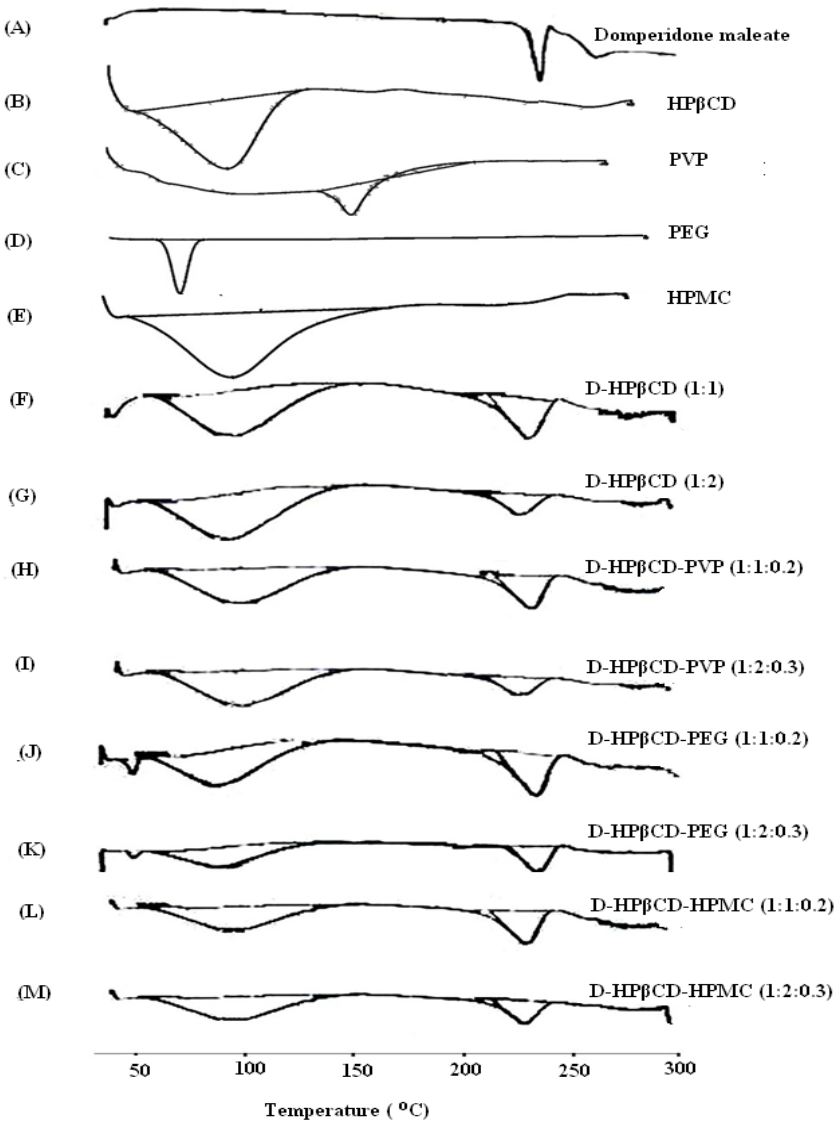

Figure 3. Differential scanning calorimetry thermograms of domperidone maleate and its cyclodextrin complex systems with and without hydrophilic polymers.

Table 3. DSC Studies of Domperidone maleate - Binary and Ternary Complex Systems*

Product	DSC (°C)		Fractional Crystallinity (%)
	T_{peak} (°C)	ΔH_{fusion} (J/g)	
Domperidone maleate	227.49	63.48	-
D-HPβCD (1:1)	230.76	34.34	54.74
D-HPβCD-PVP (1:1:0.2)	225.59	21.95	34.57
D-HPβCD-PEG (1:1:0.2)	227.25	24.89	39.20
D-HPβCD-HPMC (1:1:0.2)	225.77	23.20	36.54
D-HPβCD (1:2)	226.39	21.44	33.78
D-HPβCD-PVP (1:2:0.3)	225.31	11.02	17.30
D-HPβCD-PEG (1:2:0.3)	226.03	20.02	31.82
D-HPβCD-HPMC (1:2:0.3)	225.62	18.88	29.74

*HPβCD indicates hydroxypropyl β-cyclodextrin; D, domperidone maleate; PVP, polyvinyl pyrrolidone; PEG, polyethylene glycol and HPMC, hydroxypropyl methylcellulose.

Powdered X-ray diffraction patterns of domperidone maleate and its various complexes with HPβCD are shown in Figure 4. XRD of domperidone maleate exhibited characteristic diffraction peaks at 10.2°, 15.2°,

16.3°, 17.8°, 23.4°, 23.8°, 24.2°, 27.6°, and 32.3° indicating its crystalline nature. Where as a hollow pattern was recorded for HPβCD, PVP, PEG and HPMC indicating their amorphous state. Crystallinity can be determined by comparing a few representative peak heights in the diffraction patterns of the binary and ternary systems with those of a reference. The relationship used for the calculation of crystallinity was relative degree of crystallinity (RDC).

RDC= I_{sam} / I_{ref},

Where I_{sam} is the peak height of the sample under investigation and I_{ref} is the peak height at the same angle for the reference with the highest intensity.[14]

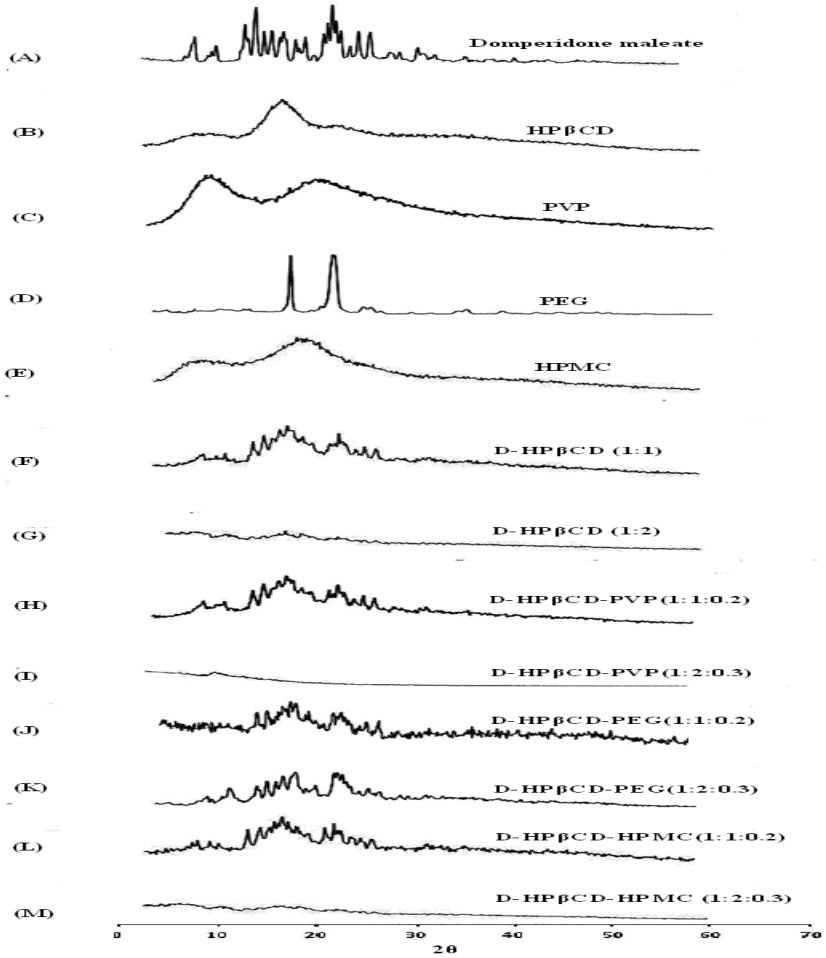

Figure 4. **X-ray diffractograms of powder samples of domperidone maleate and its cyclodextrin complex systems with and without hydrophilic polymers.**

The diffraction peaks were much reduced in the case of binary (domperidone maleate-HPβCD) systems and were absent in the case of ternary (domperidone maleate-HPβCD-PVP/PEG/ HPMC) systems respectively. The disappearance of domperidone maleate crystalline peaks confirmed the stronger drug amorphization and entrapment in HPβCD due to the combined action of HPβCD and hydrophilic polymers. Pure drug peak at 23.8° (2θ) was used for calculating RDC of binary and ternary systems and these values are shown in Table 4. The RDC values of the complexes were less than those of the drug and can be arranged in the following order: D-HPβCD > D-HPβCD-PEG > D-HPβCD-HPMC > D-HPβCD-PVP. Furthermore, a reduced number of signals were noticeable in the complexes, of remarkably lowered intensity, indicating a greater amorphousness of the inclusion compounds, compared to the free molecules.[15]

Table 4: % RDC values from X-Ray Diffractograms of Domperidone maleate and its Binary and ternary complex systems.

Product	2θ	% RDC
Domperidone maleate	1648	-
D-HPβCD (1:1)	450	27.31
D-HPβCD-PVP (1:1:0.2)	801	48.60
D-HPβCD-PEG (1:1:0.2)	706	42.84
D-HPβCD-HPMC (1:1:0.2)	773	46.91
D-HPβCD (1:2)	1089	66.08
D-HPβCD-PVP (1:2:0.3)	1296	78.64
D-HPβCD-PEG (1:2:0.3)	1139	69.11
D-HPβCD-HPMC (1:2:0.3)	11.83	71.78

*RDC indicates relative degree of crystallinity; HPβCD, hydroxypropyl β-cyclodextrin; D, domperidone maleate; PVP, polyvinyl pyrrolidone; PEG, polyethylene glycol and HPMC, hydroxypropyl methylcellulose.

Scanning electron microscopy was used to study the microscopic crystal characters for domperidone maleate, HPβCD and their CD complex systems with and without hydrophilic polymers. The SEM photographs of various products are shown in Figure.5. SEM of domperidone maleate powder showed crystals of different sizes with smooth surfaces. The smaller crystals were seen to have adhered to the surfaces of larger ones. In the SEM of HPβCD, the particles are having rounded shape, smooth surfaces and are in different sizes. The particles are also having big concave depressions on the surface. Smaller particles were seen to have adhered to the larger particles. Figure (C, D, E and F) shows the SEM of kneaded systems of domperidone maleate-CDs with and without hydrophilic polymers. In the SEM of all these systems, the crystalline characters of domperidone maleate were absent and the crystals of the components i.e, domperidone maleate and CDs could not be differentiated. The samples were more homogenous and the particles in all the systems were all irregular in shape. These microscopic observations indicated a good physical interaction of drug particles with CDs and the hydrophilic polymers added. Although SEM technique is inadequate to conclude complex formation, the SEM micrographs support the formation of CD complexes entrapping the drug particles.

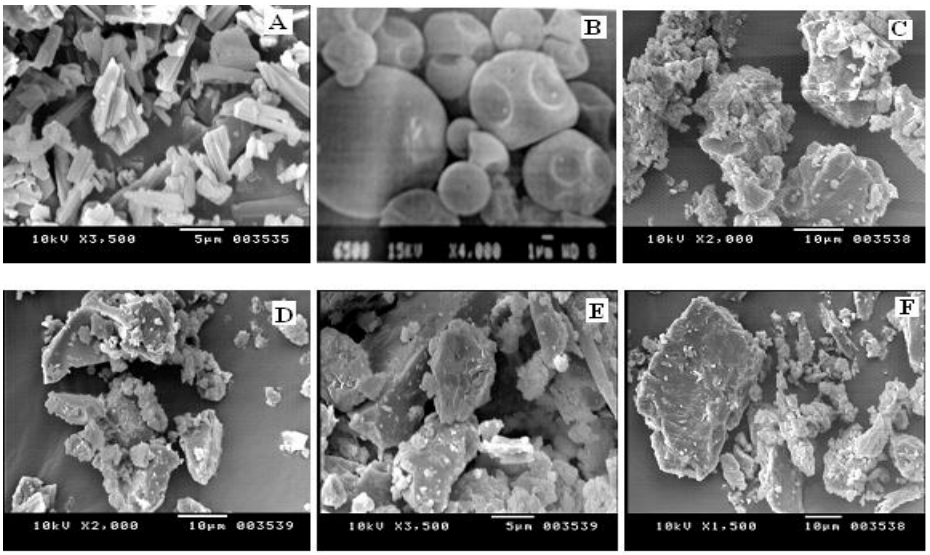

Figure 5. SEM Photographs of (A) Domperidone maleate, (B) HPβCD, (C) D-HPβCD D) D-HPβCD-PVP (E) D-HPβCD-PEG and (F) D-HPβCD-HPMC.

The FT-IR spectra of domperidone maleate and its binary system with HPβCD and ternary systems with hydrophilic polymers such as PVP, PEG and HPMC are shown in Figure.6. The main absorption bands of domperidone maleate at 3376.12 cm^{-1} (N-H, stretching), 1696.74 cm^{-1} (C=O, stretching) indicating the presence of –CONH group, 3023.28 cm^{-1} (Ar-C-H stretching), 2933.08 cm^{-1}(C-H stretching), 1580.16 cm^{-1}(Ar-C=H stretching), 1299.43cm^{-1} (C-N stretching) and 655.48 cm^{-1}(C-Cl) were all observed in the spectra of domperidone maleate as well as in its complex systems. The spectra of pure HPβCD showed the vibration of free -OH groups between 3300 and 3500 cm^{-1} and bound -OH groups at 2910 cm^{-1}. These spectral observations of the spectra thus corroborate the absence of solid-state interactions between domperidone maleate, HPβCD and hydrophilic polymers.

The spectra of binary/ternary complex of domperidone maleate shows a broad peak at around 3400 cm^{-1} and less

intense absorption at around 2933, 1696, 1580, 1299 and 655 $cm^{-1.}$ The sharp absorptions at 3400 and 3023 cm^{-1}, which were observed in the spectrum of domperidone maleate have disappeared in these spectra. These indicated the conclusion that some groups of domperidone maleate molecules might be included in the cavities of CD molecules to form the inclusion complex.

The much-enhanced dissolution rate observed with domperidone maleate-HPβCD systems containing hydrophilic polymers was due to (1) the enhancement of the complexation and solubilization efficiencies of HPβCD by the added hydrophilic polymers, and (2) the stronger drug amorphization and better inclusion caused by the combined action of HPβCD and the hydrophilic polymers.

Because of the enhancement in the HPβCD complexation and solubilizing efficiencies caused by the presence of hydrophilic polymers, a low amount of CD can be used to obtain the desired dissolution rate and efficiency. Thus, addition of hydrophilic polymers could be a strategy for improving the usefulness of CDs.

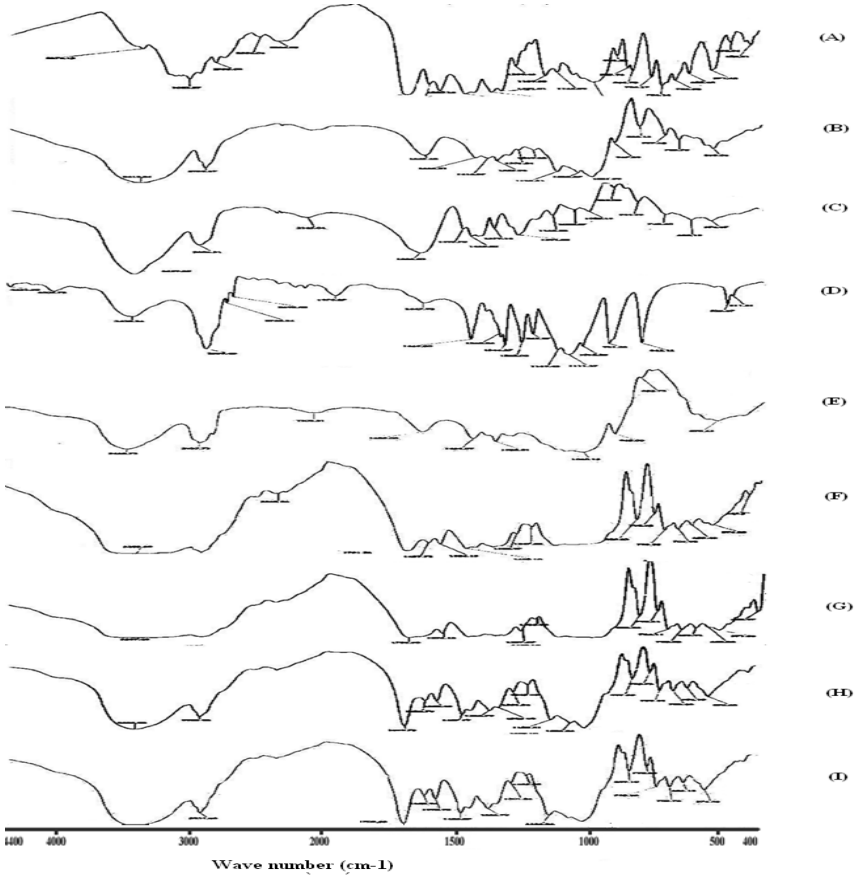

Figure 6. FT-IR Spectra of (A) Domperidone maleate, (B) HPβCD, (C) PVP (D) PEG (E) HPMC (F) D-HPβCD (G) D-HPβCD-PVP (H) D-HPβCD-PEG and (I) D-HPβCD-HPMC.

CONCLUSIONS

Domperidone maleate formed inclusion complexes with HPβCD at a 1:1M ratio in solution in the presence and absence of hydrophilic polymers. The addition of hydrophilic polymers resulted in a higher complexation efficiency and markedly enhanced the solubilizing efficiency of HPβCD. Solid inclusion complexes of HPβCD with hydrophilic polymers yielded rates of dissolution several times higher than those of domperidone maleate and its complexes with HPβCD alone.

DECLARATION OF INTERST

None.

REFERENCES

1. Fromming KH, Szejtli J. CDs in Pharmacy. Dordrecht, The Netherlands: Kluwer Academic Publishers, 1994: 1-81.
2. Duchene D, Wouessidjewe D. Pharmaceutical and medicinal applications of cyclodextrins. In: Dumitriu S, editors. Polysaccharides in Medical Applications. New York: Marcel Dekker, 1996: 575-602.
3. Uekama K, Hirayama F, Irie T. Cyclodextrin drug carrier systems. Chem Rev, 1998; 98: 2045-76.
4. Loftsson T, Brewster ME. Pharmaceutical applications of cyclodextrins, I: drug solubilization and stabilization. J Pharm Sci, 1996; 85: 1017-25.

5. Rajewski RA, Stella VJ. Pharmaceutical applications of cyclodextrins II: in vivo drug delivery. J Pharm Sci, 1996; 85: 1142-69.
6. Narender Reddy M, Tasneem Rehana, Ramakrishna S, Chowdary KPR, Prakash V Diwan. Cyclodextrin Complexes of Celecoxib: Molecular Modeling, Characterization and Dissolution Studies. AAPS Pharm Sci, 2004; 6(1)Article7: 1-9.
7. Szejtli J. Medicinal applications of cyclodextrins. Med Res Rev, 1994; 14: 353-86.
8. Pitha J. Cyclodextrin derivatives with enhanced solubility power and lower toxicity. Proc. of 9th Int. Symposium on Cyclodextrins, Santiago de Compostela, 1998: 210-15.
9. Loftsson T, Brewster ME. Pharmaceutical applications of cyclodextrins. 1. Drug solubilization and stabilization. J Pharm Sci, 1996; 85: 1017-25.
10. Barone JA. Domperidone – A peripherally acting dopamine 2 receptor antagonist. Ann. Pharmacother., 1993; 33: 429-440.
11. Higuchi T, Connors KA. Phase-solubility techniques. In: Reilly CN, ed. Advances in Analytical Chemistry and Instrumentation. New York, NY: Wiley-Interscience, 1965; 117-212.
12. Khan KA. The concept of dissolution efficiency. J Pharm Pharmacol, 1975; 27: 48-49.
13. Douglas AS, James HF, Stanley RC. Principles of Instrumental analysis. Australia: Thomson Brooks/Cole Publisher, 2007: 894-906.
14. Ryan JA. Compressed pellet X-ray diffraction monitoring for optimization of crystallinity in lyophlilized solids: imipenem: cilastatin sodium case. J Pharm Sci, 1986; 75: 805–7.
15. Calabro ML, Tommasini S, Donato P, Raneri D, Stancanelli R, Ficarra P, Ficarra R, Costa C, Catania S, Rustichelli C, Gamberini G. Effects of α- and β-cyclodextrin complexation on the physico-chemical properties and antioxidant activity of some 3-hydroxyflavones**.** J Pharm Biomed Anal, 2004; 35(2): 365-77.