

# Solubility enhancement of hydrophobic drugs using synergistically interacting cyclodextrins and cosolvent

Praveen Chaudhari<sup>1,\*</sup>, Pramodkumar Sharma<sup>2</sup>, Nilesh Barhate<sup>1</sup>, Parag Kulkarni<sup>1</sup> and Chetan Mistry<sup>1</sup>

<sup>1</sup>Padmashree Dr D.Y. Patil Institute of Pharmaceutical Sciences and Research, Pimpri, Pune 411 018, India

<sup>2</sup>University Institute of Pharmacy, Bundelkhand University, Jhansi 284 002, India

The purpose of the present study was to examine the cosolvency and cyclodextrins (CD) addition as a combined approach on the solubility of the hydrophobic drug, valdecoxib, since solubilization of nonpolar drugs constitutes one of the most important tasks in liquid orals and parenteral formulation design. An attempt has been made to improve the solubility of valdecoxib in water, using PEG-400, poloxamer-188 and 2 CDs ( $\beta$ -CD and Hp- $\beta$ -CD). The aqueous solubility of valdecoxib was 0.01 mg/ml, which was significantly improved by addition of PEG-400, CDs and poloxamer-188. In systems containing varying amounts of PEG-400 and 1, 2, 3 and 6% of  $\beta$ -CD or Hp- $\beta$ -CD in water, theoretical solubility was calculated by adding the solubilities in the individual system. The theoretical solubility values were less compared to the observed solubility values. Hp- $\beta$ -CD showed better solubility than  $\beta$ -CD. Addition of poloxamer-188 to the PEG-400/water systems containing CDs showed significant increase in the solubility of valdecoxib; hence synergism was observed. Solubility enhancement is due to affinity between the drug and interior of the CD host molecules, while the small non-polar hydrocarbon region in the cosolvent can reduce the ability of the aqueous system to squeeze out non-polar solutes. The results show that both cosolvency and CD addition are promising approaches for enhancing the solubility of valdecoxib.

**Keyword:** Cosolvency, cyclodextrin, hydrophobic drugs, solubility, synergism.

OVER the years, a variety of solubilization techniques have been studied and widely used, including pH adjustment, cosolvent addition, surfactant addition and cyclodextrin (CD) addition. Among these techniques, in this article cosolvency and CD addition are applied for non-polar solutes. Addition of cosolvent to a formulation is a commonly used method for improving the solubility of the drug, because the cosolvent reduces strong water–water interactions and thereby reduces the ability of water to squeeze out non-polar solutes. Cosolvency was often consi-

dered at early stages due to its huge solubilization potential. Because of their safety, cosolvents are employed in approximately 10% of FDA-approved parenteral products<sup>1</sup>. In intravenous (IV) preparation, the 10% ethanol–40% propylene glycol combination is most widely employed. High concentrations of cosolvent have high viscosity and high tonicity, and phlebitis can result from precipitation of the solubilized drug upon IV injection. In fact, ethanol in concentrations greater than 10% may well produce significant pain<sup>2,3</sup>.

CD complexation has been widely used to improve the physico-chemical properties of various drug molecules. CDs are able to form both inclusion and non-inclusion complexes. In addition, CDs and their complexes form water-soluble aggregates in aqueous solutions. These aggregates are able to solubilize lipophilic water-insoluble drugs through non-inclusion complexation or micelle-like structures<sup>4</sup>. Such a drug–ligand complex has a rigid structure and a definite stoichiometry, usually one-to-one at low concentration. However, use of CDs in pharmaceutical dosage forms is limited by their relatively high cost and due to problems of formulation, all principally related to the large amount necessary to obtain the desired drug-solubilizing effect<sup>5</sup>. Some CDs are reported to have significant renal toxicity<sup>6</sup>.

Therefore, it was important to find methods to enhance the efficiency of CDs and cosolvents in terms of complexing and cosolvency, by making thus possible to considerably reduce the dose of both. Recently, the combined use of cosolvency and complexation has drawn particular interest. Loftsson *et al.*<sup>7</sup> reported that addition of polyethylene glycol or ethanol in an aqueous solution of CD reduced the solubility of ibuprofen. Pitha and Hishino<sup>8</sup> reported that the solubility of testosterone with hydroxypropyl- $\beta$ -cyclodextrin (Hp- $\beta$ -CD) is 10,000-fold lower in 80% ethanol than in water. The reason behind this was that the cosolvent may act by competing with the drug for entry into the CD cavity or by reducing solvent polarity. In other studies, it was found that the presence of cosolvents increases the formation of drug–ligand complex. Zung<sup>9</sup> hypothesized that a series of alcohols have synergistic effect on the cosolvency and complexation of pyrene. He also sug-

\*For correspondence. (e-mail: pdchaudhari\_21@yahoo.com)

gested that the cosolvent could regulate the molecule to assist the drug to fit inside the CD cavity.

Poloxamer-188 is one of the commercial grades of poloxamers, which are water-soluble, non-ionic, surface-active copolymers. The polyoxyethylene segment of poloxamer-188 is relatively hydrophilic, while the polyoxypropylene segment is relatively hydrophobic. It has been used in pharmaceutical formulations, primarily as emulsifying and solubilizing agents<sup>10</sup>. It has the ability to form a clear solution or gel in aqueous media, thus solubilizing many water-insoluble compounds by the formation of micelles<sup>11</sup>. Thus, poloxamer-188 has been selected for the study of improvement in the solubility and synergistic effect on the hydrophobic moiety.

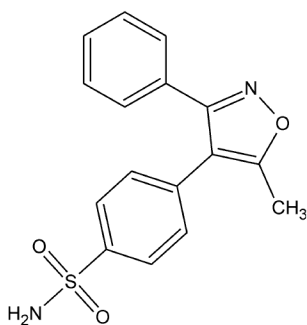
Both cosolvency and complexation have been well studied. It is of interest to explore the mechanisms of the combined effect of the two techniques on non-polar drug solubilization and to explore the dynamics among the solute, cosolvent and CD. The main objective of our study was to explain the combined effect of cosolvency and cyclodextrin addition on non-polar drug solubilization.

In the present study, valdecocix (Scheme 1) was selected as a model drug and PEG-400 was used as cosolvent for improving the aqueous solubility of hydrophobic drugs. Harada *et al.*<sup>12</sup> reported that PEGs form complexes with  $\alpha$ -CD and  $\gamma$ -CD, but not with  $\beta$ -CD. In the present study therefore,  $\beta$ -CD and Hp- $\beta$ -CD were chosen to examine the effect of CDs and PEG-400 on the solubility of valdecocix. Solubilization of valdecocix was also examined using poloxamer-188 on the synergism of PEG and CD.

## Materials and methods

Valdecocix was obtained as a gift sample from Alembic Ltd, Baroda, India.  $\beta$ -CD and Hp- $\beta$ -CD were obtained from Lupin Research Centre, Pune, India. PEG-400 was obtained from Qualigen, India and poloxamer-188 was obtained as a gift sample from BASF India Ltd, Mumbai, India.

All other chemicals were of analytical reagent grade, and freshly prepared distilled water was used throughout the study.



Scheme 1. Valdecocix.

## Solubility studies

Solubility measurements were determined in various solvents, namely water, PEG-400, aqueous solutions of poloxamer-188, and 1, 2, 3 and 6% aqueous solution of  $\beta$ -CD and Hp- $\beta$ -CD. Excess amounts of valdecocix were weighed into glass vials containing 10 ml solvents. The samples were shaken at  $25 \pm 2^\circ\text{C}$  for 24 h and passed through a  $0.45 \mu\text{m}$  filter. Next 1 ml of filtered solution was diluted to 10 ml using ethanol (which was previously used to develop the calibration curve). The concentrations of dissolved valdecocix were analysed spectrophotometrically (UV-1700, Shimadzu) at a wavelength of 246.5 nm. PEG-400–water and PEG-400–water–poloxamer-188 cosolvent systems were prepared by weight. The solution containing increasing amount of PEG-400 (1–90%) in PEG-400–water cosolvent system was prepared and solubilization capacity of the cosolvent system was investigated. In another set of experiments, the solubility of valdecocix was determined in 50% PEG–water system containing 1, 2, 3 and 6% of aqueous solution of  $\beta$ -CD and Hp- $\beta$ -CD individually, as well as in the presence of poloxamer-188 (0.5 and 1.0%).

## UV method for analysis

Valdecocix is freely soluble in ethanol. Hence ethanol was used as a solvent to develop the calibration curve of valdecocix using the UV method. The concentration range of  $2\text{--}16 \mu\text{g/ml}$  was found to obey Beer–Lambert's law. The working curve equation for valdecocix was

$$Y = 0.0595X + 0.0125,$$

with correlation coefficient  $r^2 = 0.999$ .

Once the equilibrium solubility was achieved after shaking the drug with the PEG-400–water system for 24 h, the solution was filtered and 1 ml of it was diluted to 10 ml with ethanol (which was previously used to develop the calibration curve). Absorbances were measured at 246.5 nm using a UV spectrophotometer.

The UV spectrometer was previously calibrated according to the method mentioned in Indian Pharmacopoeia (I.P.) 1996, i.e. control on absorbances test, in which absorbance of potassium dichromate solution was checked at the wavelengths indicated in I.P. 1996. The A (1%, 1 cm) for each wavelength was measured and found in the permitted limits according to I.P. 1996.

## Results and discussion

The solubility enhancement of valdecocix by use of PEG 4000 (ref. 13) and CD<sup>14</sup> has been extensively studied. In the present investigation, solubility enhancement caused by complexation with different concentrations in  $\beta$ -CD

compared to that of Hp- $\beta$ -CD was determined under the influence of PEG-400 as cosolvent. The solubility enhancement of valdecoxib at 25°C in the presence of PEG-400, poloxamer-188 and with different concentrations of  $\beta$ -CD and Hp- $\beta$ -CD is given in Table 1. The solubility of valdecoxib increases with increasing amounts of both CDs, due to the increasing concentration of valdecoxib in complexed form. The solubility increased in both systems with further addition of CDs, but it was found that Hp- $\beta$ -CD dissolves valdecoxib slightly better.

The solubility of low-soluble compounds and their association equilibria with CD were strongly influenced by the cosolvent. Therefore, addition of cosolvents only changes the solubilities of compounds to higher extent. Seedher and Bhatia<sup>15</sup> reported that improvement in solubility using cosolvent may be due to physico-chemical properties of the solvent, such as polarity, intermolecular interactions, and the ability of the solvent to form a hydrogen bond with the drug molecules. In a 50% PEG-400–water system, solubility of valdecoxib decreases. The theoretical and observed solubility values of valdecoxib in the PEG-400–water system containing 1%  $\beta$ -CD and 1% Hp- $\beta$ -CD at 25  $\pm$  2°C are listed in Table 2. In solutions containing Hp- $\beta$ -CD, at lower PEG-400 concentrations (less than 50%), the observed solubility was significantly greater than the expected solubility. For example, the theoretical value in 30% PEG-400–water system containing 1% Hp- $\beta$ -CD was 1.60 mg/ml. The observed solubility of valdecoxib in the same system was 2.57 mg/ml, showing approximately a 60.62% increase in comparison to the theoretical value. The influence of PEG-400 on valdecoxib solubility in 2%  $\beta$ -CD and 2% Hp- $\beta$ -CD is given in Table 3. While the PEG–CD system shows profound increase in solubility,

the solubility in PEG-400–water + 2%  $\beta$ -CD system was much less compared to PEG-400–water + 2% Hp- $\beta$ -CD system. Solubility values achieved in the PEG-400–water system containing 3 and 6% of both  $\beta$ -CD and Hp- $\beta$ -CD are given in Tables 4 and 5 respectively. Increase in solubility of valdecoxib was observed in 3 and 6% of Hp- $\beta$ -CD than in 3 and 6% of  $\beta$ -CD. Improvement in solubility due to synergism was observed in all systems. Synergism was higher in case of Hp- $\beta$ -CD than in  $\beta$ -CD. Overall, PEG-400,  $\beta$ -CD and Hp- $\beta$ -CD showed a synergistic effect, described by an increase in solubility produced by cosolvent as well as increase in solubility produced by the CDs, in improving valdecoxib solubility in water.

Hydroxypropyl substitution in  $\beta$ -CD may have resulted in higher binding constants than those observed with  $\beta$ -CD apparently due to the extension of the hydrophobic cavity<sup>16</sup>. Hence the solubility of valdecoxib may be higher in Hp- $\beta$ -CD than in  $\beta$ -CD. The percentage increase in solubility of valdecoxib was found to be higher at 10% PEG-400 in the PEG-400–water system in all cases. The percentage increase in solubility increases with the addition of  $\beta$ -CD, i.e. 6 > 3 > 2 > 1%. Similar results were obtained in case of Hp- $\beta$ -CD.

Results from the present study shows that poloxamer-188 has significant solubilization effect on valdecoxib at 25  $\pm$  2°C (Figure 1 a–d). Solubility of valdecoxib increased as the concentration of poloxamer-188 in the PEG–CDs solution was increased from 0.5 to 1%. Poloxamer-188 may enhance the solubility of valdecoxib either by micellar solubilization or reducing the activity coefficient of the drug by reducing the hydrophobic interaction or both processes. In addition, improvement in the wetting of the hydrophobic valdecoxib crystals may occur, which is needed for solubilization, contributing to increase in the synergistic effect. At low concentrations, the poloxamer monomers are thought to form monomolecular micelles by a change in configuration in solution. At higher concentration, these monomolecular micelles associate to form aggregates of varying sizes, which have the ability to solubilize drugs and to increase the stability of solubilizing agents.

The binding affinity between the CD molecule and the inclusion compound is influenced by the molecular properties of the guest molecule as well as the CD used. Its internal cavity has the ability to incorporate hydrophobic aromatic guest molecules in aqueous solution, provided that the host internal cavity and the entry point of the guest molecule are suitable for complexation. Steric as well as electrostatic parameters influence inclusion complexation, as the molecular surface of the guest molecule should fit as accurately as possible into the interior of the CD<sup>17</sup>. Moreover, electrostatic potential and hydrophobicity affect the binding affinity to a great extent. A variety of factors, such as van der Waals, hydrogen bonding and hydrophobic forces, play an important role in forming a stable complex<sup>18</sup>. The flexibility of the host molecule is an additional parameter which is responsible for the

**Table 1.** Solubility of valdecoxib in selected vehicles at 25  $\pm$  2°C

Vehicle	Solubility of valdecoxib (mg/ml)*
PEG-400	36.65 $\pm$ 0.05
PEG-400/water (90 : 10)*	3.07 $\pm$ 0.07
PEG-400/water (70 : 30)*	2.59 $\pm$ 0.06
PEG-400/water (50 : 50)*	1.76 $\pm$ 0.04
PEG-400/water (30 : 70)*	1.46 $\pm$ 0.06
PEG-400/water (10 : 90)*	1.14 $\pm$ 0.02
PEG-400/water (05 : 95)*	1.11 $\pm$ 0.03
PEG-400/water (01 : 99)*	0.92 $\pm$ 0.2
0.5% Poloxamer-188	1.99 $\pm$ 0.03
1% Poloxamer-188	3.45 $\pm$ 0.05
1% $\beta$ -CD	0.1 $\pm$ 0.02
2% $\beta$ -CD	0.12 $\pm$ 0.04
3% $\beta$ -CD	0.13 $\pm$ 0.05
6% $\beta$ -CD	0.184 $\pm$ 0.03
1% Hp- $\beta$ -CD	0.119 $\pm$ 0.08
2% Hp- $\beta$ -CD	0.158 $\pm$ 0.06
3% Hp- $\beta$ -CD	0.226 $\pm$ 0.02
6% Hp- $\beta$ -CD	0.383 $\pm$ 0.05
Water	0.01 $\pm$ 0.0004

Expressed as mean  $\pm$  SD ( $n = 3$ ).

\*Solubility measurement in 50% PEG-400–water system.

**Table 2.** Solubility of valdecoxib in PEG-400–water systems with 1%  $\beta$ -CD and 1% Hp- $\beta$ -CD at  $25 \pm 2^\circ\text{C}$ 

Percentage of PEG-400 in PEG-400–water system	Solubility of valdecoxib (mg/ml)			
	Theoretical value* with 1% $\beta$ -CD	Observed value with 1% $\beta$ -CD	Theoretical value* with 1% Hp- $\beta$ -CD	Observed value with 1% Hp- $\beta$ -CD
90	3.17	3.29 (3.78%)	3.19	3.29 (3.13%)
70	2.69	2.90 (7.8%)	2.70	3.01 (11.48%)
50	1.86	2.35 (26.34%)	1.88	2.94 (56.38%)
30	1.59	1.98 (24.52%)	1.60	2.57 (60.62%)
10	1.24	1.57 (26.62%)	1.30	2.08 (60.00%)
5	1.21	1.33 (9.91%)	1.24	1.72 (38.70%)
1	1.02	1.10 (7.84%)	1.05	1.31 (24.76%)

\*For Tables 2–5, theoretical solubility value is the summation of solubility of valdecoxib in 1, 2, 3 and 6% aqueous solution respectively as well as in a PEG-400–water system.

Values in brackets indicate percentage increase in solubility, which is calculated using the following equation.

Per cent increase in solubility =  $(\text{Observed solubility} - \text{Theoretical solubility}) \times 100 / \text{Theoretical solubility}$ .

**Table 3.** Solubility of valdecoxib in PEG-400–water systems with 2%  $\beta$ -CD and 2% Hp- $\beta$ -CD at  $25 \pm 2^\circ\text{C}$ 

Percentage of PEG-400 in PEG-400–water system	Solubility of valdecoxib (mg/ml)			
	Theoretical value* with 2% $\beta$ -CD	Observed value with 2% $\beta$ -CD	Theoretical value* with 2% Hp- $\beta$ -CD	Observed value with 2% Hp- $\beta$ -CD
90	3.19	3.56 (11.59%)	3.22	4.20 (30.43%)
70	2.70	3.09 (14.44%)	2.74	4.01 (46.35%)
50	1.88	2.67 (42.02%)	1.92	3.86 (101.04%)
30	1.59	2.31 (45.28%)	1.64	3.44 (109.7%)
10	1.29	1.95 (51.16%)	1.33	3.10 (133.0%)
5	1.23	1.78 (44.71%)	1.28	2.72 (112.5%)
1	1.05	1.21 (15.23%)	1.09	2.21 (102.7%)

**Table 4.** Solubility of valdecoxib in PEG-400–water systems with 3%  $\beta$ -CD and 3% Hp- $\beta$ -CD at  $25 \pm 2^\circ\text{C}$ 

Percentage of PEG-400 in PEG-400–water system	Solubility of valdecoxib (mg/ml)			
	Theoretical value* with 3% $\beta$ -CD	Observed value with 3% $\beta$ -CD	Theoretical value* with 3% Hp- $\beta$ -CD	Observed value with 3% Hp- $\beta$ -CD
90	3.20	3.78 (18.12%)	3.27	6.88 (110.3%)
70	2.72	3.37 (23.89%)	2.81	5.91 (110.32%)
50	1.91	3.04 (59.16%)	1.98	5.37 (171.2%)
30	1.61	2.82 (75.15%)	1.71	4.89 (185.9%)
10	1.31	2.43 (85.49%)	1.40	4.02 (200.0%)
5	1.25	1.90 (52.0%)	1.35	3.76 (178.5%)
1	1.06	1.41 (33.01%)	1.16	2.99 (157.7%)

geometry and consequently for the stability of the complex. The type, length and degree of substitution also affect the solubilization effect of the CDs.

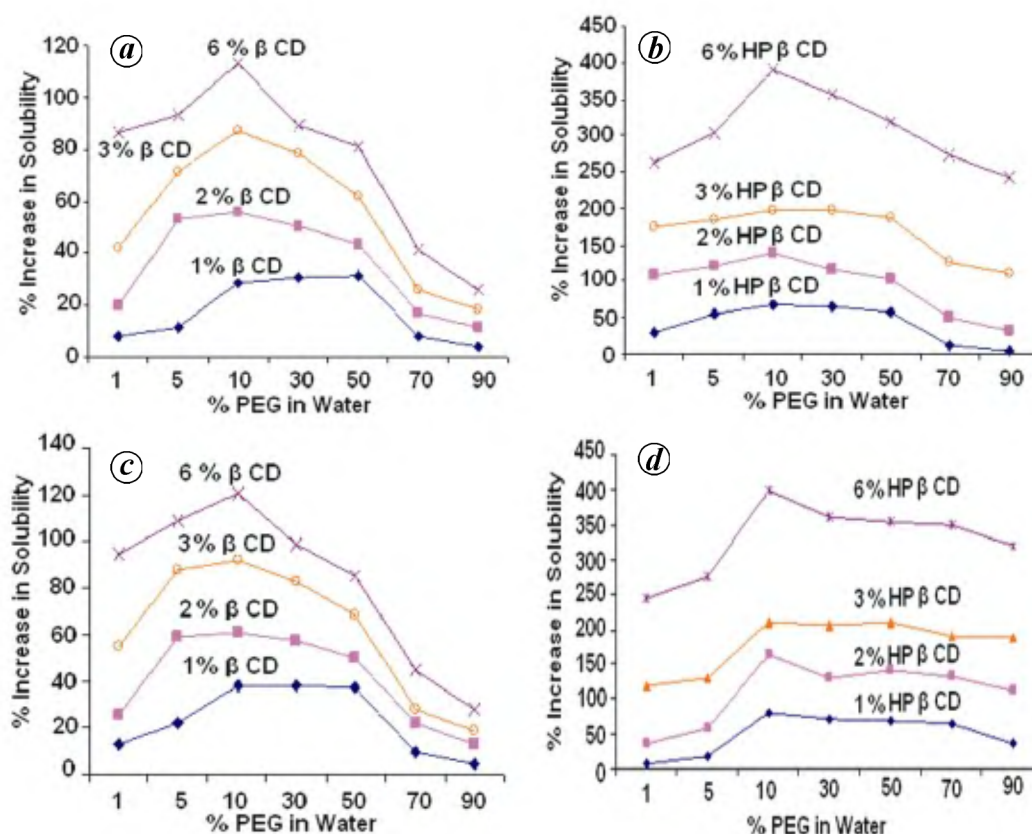
Water as a solvent has some unique properties: large surface tension (71.8 dynes/cm), a high level of hydrogen bonding and a sizable dielectric constant (80 at  $20^\circ\text{C}$ ). The structure of PEG-400 is  $\text{H}-(\text{O}-\text{CH}_2-\text{CH}_2)_n-\text{OH}$ , where  $n$  is approximately 8 to 9. Hydrogen bonding makes this peculiar structure of PEG miscible with water. Hydrogen bonding between water molecules is broken with the help of hydrophobic hydrocarbon regions of insoluble drugs, thus reducing intermolecular interactions<sup>19</sup>. Also it can be

stated that PEG may assist to reduce the dipole moment of water and allow hydrophobic compounds to fit in.

In the early 1990s, the solubilization capacity of CDs was believed to be reduced by the use of cosolvent. The solubility of testosterone with Hp- $\beta$ -CD was 10,000-fold lower in 80% ethanol than in water<sup>8</sup>. However, in recent years polymers have been reported to improve the solubilization capacity of CDs. Li *et al.*<sup>20</sup> developed a mathematical model to explain the decrease in drug solubility produced by low cosolvent concentrations as well as the increase in solubility produced by high cosolvent concentrations that are observed at all CD concentrations. The

**Table 5.** Solubility of valdecoxib in PEG-400–water systems with 6%  $\beta$ -CD and 6% Hp- $\beta$ -CD at  $25 \pm 2^\circ\text{C}$ 

Percentage of PEG-400 in PEG-400–water system	Solubility of valdecoxib (mg/ml)			
	Theoretical value* with 6% $\beta$ -CD	Observed value with 6% $\beta$ -CD	Theoretical value* with 6% Hp- $\beta$ -CD	Observed value with 6% Hp- $\beta$ -CD
90	3.27	4.02 (22.93%)	3.45	11.59 (235.9%)
70	2.75	3.81 (38.54%)	2.97	10.87 (265.9%)
50	1.96	3.39 (72.95%)	2.15	8.80 (309.3%)
30	1.67	2.99 (79.04%)	1.87	8.35 (346.5%)
10	1.37	2.72 (98.54%)	1.56	7.50 (380.7%)
5	1.31	2.36 (80.15%)	1.51	5.95 (294.03%)
1	1.12	1.99 (77.67%)	1.32	3.86 (192.4%)

**Figure 1.** Effect of 0.5% poloxamer-188 and  $\beta$ -CDs (a); 0.5% poloxamer-188 and Hp- $\beta$ -CDs (b); 1% poloxamer-188 and  $\beta$ -CDs (c), and 1% poloxamer-188 and Hp- $\beta$ -CDs (d) on solubility of valdecoxib.

results obtained by us were similar to those reported by Li *et al.*<sup>20</sup>. Faucci and Mura<sup>21</sup> studied synergism between CD and water-soluble polymers on naproxen solubility. The water-soluble polymers increased the complexation efficacy of CDs toward naproxen. Viernstein *et al.*<sup>22</sup> reported the influence of ethanol as cosolvent on the solubility enhancement of triflumizole by complexation with  $\beta$ -CD and with dimethyl- $\beta$ -CD. They reported the linear dependence of non-polar solute solubility upon CD concentration that is observed at all ethanol concentrations. Liberation of a solute molecule, creation of a hole in the solvent, and accommodation of the solute molecule in the

solvent cavity are the most fundamental models involved in the solubilization of a solute in a solvent. The intermolecular forces of attraction in dissolving a solute should be reduced in order to improve the solubility of the drug<sup>23</sup>. Four types of interactions, namely solute–solvent, ion–dipole, dipole–dipole and hydrogen bonding–hydrophobic moiety have been reported. If the system consists of polymers, conformation of the polymer chains also plays a role in solute–solvent interaction. In the present study, the system examines the potential of  $\beta$ -CD, Hp- $\beta$ -CD, PEG-400 and poloxamer-188 as solubilizing agents for valdecoxib. The synergistic effect of CD and PEG-400 in

the present study could be attributed to additional breaking of hydrogen bonds in the structure of water and a decrease in the dipole moment.

## Conclusion

Our results suggest that the increase in valdecoxib solubility was due to synergistic effect in the presence of CDs and PEG-400, as well as increase in CD complexation efficiency. Addition of PEG-400, poloxamer-188 and CDs increased the solubility of the model drug from 0.01 mg/ml in distilled water. However, addition of poloxamer-188 made the system more complex and hampered the synergistic effect at higher concentrations. The present study describes the increase in solubility produced by cosolvents as well as the increase in solubility produced at all CD concentrations. Thus it provides the dynamics of the combined cosolvent-CD technique in solubilization of non-polar drugs.

- Sweetana, S. and Aker, M. J., Solubility principles and practices for parenteral drugs dosage forms development. *PDA J. Pharm. Sci. Technol.*, 1996, **50**, 330–342.
- Yalkowsky, S. H., Formulation related problems associated with intravenous drug delivery. *J. Pharm. Sci.*, 1998, **87**, 787–795.
- Rubino, J. T., Solubilization of some poorly soluble drugs by cosolvents. PhD dissertation, The University of Arizona, USA, 1984.
- Loftsson, T., Masson, M. and Brewster, M. E., Self-association of cyclodextrins and cyclodextrin complexes. *J. Pharm. Sci.*, 2004, **93**, 1091–1099.
- Loftsson, T. and Brewster, M. E., Pharmaceutical applications of cyclodextrins 1. Solubilization and stabilization. *J. Pharm. Sci.*, 1996, **85**, 1017–1025.
- Rajewski, R. A. and Stella, A. J., Pharmaceutical applications of cyclodextrins 2. *In vivo* drug delivery. *J. Pharm. Sci.*, 1996, **85**, 1142–1168.
- Loftsson, T., Olafsdottir, B. J., Fridriksdottir, H. and Jonsdottir, S., Cyclodextrins complexation of Nonsteroidal Antiinflammatory Drugs (NSAID'S): Physico-chemical characteristics. *Eur. J. Pharm. Sci.*, 1993, **1**, 95–101.
- Pitha, J. and Hishino, T., Effect of ethanol on formation of inclusion complexes of hydroxypropyl cyclodextrins with testosterone or with methyl orange. *Int. J. Pharm.*, 1992, **80**, 243–251.
- Zung, J. B., Influence of alcohol addition on the  $\gamma$ -CD:pyrene complex. *J. Phys. Chem.*, 1991, **95**, 6701–6709.
- Rowe, R. C., Sheskey, P. J. and Weller, P. J., Poloxamer. In *Handbook of Pharmaceutical Excipients*, American Pharmaceutical Association, Pharmaceutical Press, London, 2003, 4th edn, pp. 447–450.
- Lin, S. L. and Kawashima, Y., The influence of three poly (-oxtetethylene) poly (oxypropylene), surface-active block copolymers on the solubility behavior of indomethacin. *Pharm. Acta Helv.*, 1985, **60**, 339–344.
- Harada, A., Preparation and structures of supramolecular between cyclodextrins and polymers. *Coord. Chem. Rev.*, 1996, **148**, 115–133.
- Liu, Chengsheng, Liu, Chenguang, Goud, K. and Desai, H., Enhancement of dissolution rate of valdecoxib using solid dispersion with PEG 4000. *Drug Dev. Ind. Pharm.*, 2005, **1**, 1–10.
- Kale, R., Saraf, M. and Tayade, P., Cyclodextrin complexes of valdecoxib: Properties and anti-inflammatory activity in rats. *Eur. J. Pharm. Biopharm.*, 2005, **60**, 39–46.
- Seedher, N. and Bhatia, S., Solubility enhancement of Cox-2 inhibitors using various solvent systems. *AAPS Pharm. Sci. Technol.*, 2003, **4**, article 33.
- Yoshida, A., Yamamoto, M., Irie, T., Hirayama, F. and Uekama, K., Some pharmaceutical properties of 3-hydroxypropyl and 2,3-dihydroxypropyl  $\beta$ -CD, and their solubilizing and stabilizing abilities. *Chem. Pharm. Bull.*, 1989, **37**, 1059–1063.
- Saenger, W., Cyclodextrin inclusion compounds in research and industry. *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 344–362.
- Nandi, I., Bateson, M., Bari, M. and Joshi, H. N., Synergistic effect of PEG-400 and cyclodextrin to enhance solubility of progesterone. *AAPS Pharm. Sci. Technol.*, 2003, **4**, 1–5.
- Millard, J. W., Alvarez-Nunez, F. A. and Yalkowsky, S. H., Solubilization by cosolvent – Establishing useful constants for the log-linear model. *Int. J. Pharm.*, 2002, **245**, 153–166.
- Li, P., Zhao, L. and Yalkowsky, S. H., Combined effect of cosolvent and cyclodextrin on solubilization of non-polar drugs. *J. Pharm. Sci.*, 1999, **88**, 1107–1111.
- Fauci, M. T. and Mura, P., Effect of water soluble polymers on naproxen complexation with natural and chemically modified  $\beta$ -cyclodextrins. *Drug Dev. Ind. Pharm.*, 2001, **27**, 909–917.
- Viernstein, H., Weiss-Greiler, P. and Wolschann, P., Solubility enhancement of low soluble biologically active compounds by  $\beta$ -cyclodextrins and dimethyl- $\beta$ -cyclodextrins. *J. Incl. Phenom.*, 2002, **44**, 235–239.
- Martin, A., Physico-chemical principles in pharmaceutical sciences. In *Physical Pharmacy*, Lippincott Williams & Wilkins, Maryland, USA, 2001, 4th edn, pp. 223–225.

Received 5 July 2006; revised accepted 22 January 2007