Journal of PharmaSciTech
ISSN: 2231 3788 (Print)
ISSN: 2321 4376 (Online)
Research Article

Zaltoprofen- β-CD Inclusion Complex for Solubility Enhancement

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Abstract

The aim of present work was to investigate the inclusion complexation of zaltoprofen (ZPF), a water insoluble drug, with β-cyclodextrin (β-CD) in order to improve solubility and dissolution rate of the drug in an attempt to enhance its bioavailability. The complex of ZPF/ β-CD (1:1) was characterized by Differential Scanning Calorimetry (DSC), Powder X-ray Diffraction (PXRD), Fourier-transform infrared (FT-IR) spectroscopy, solubility and dissolution studies. According to the DSC/PXRD data, no endothermic and characteristic diffraction peaks corresponding to ZPF were observed for the inclusion complex, suggesting that, crystallinity of zaltoprofen was reduced. FTIR study revealed that there was no drug-polymer interaction between ZPF and β-CD. The complex ZPF/β-CD (1:1) exhibited higher dissolution rate than that of pure drug and physical mixture in both pH6.8 and pH7.4 buffer solutions. The aqueous solubility of the complex increased to about 150 and 145 folds in pH6.8 and pH7.4 buffer, respectively with that of pure ZPF. In conclusion, complexation method proved to be the better alternative for the solubility enhancement of poorly water soluble drugs.

Keywords: Zaltoprofen, β-cyclodextrin, solubility, dissolution rate, inclusion complex

Introduction

Zaltoprofen is a propionic acid derivative of non-steroidal anti-inflammatory drugs (NSAIDs). Chemically, it is 2-(10-oxo-10, 11-dihydrodibenzo [b, f] thiepin-2-yl) propionic acid,[1] (Fig. 1) an important group of NSAIDs and which has powerful inhibitory effects on acute and chronic inflammation with less adverse reactions on the gastrointestinal tract than other NSAIDs.[2-3] As zaltoprofen has a unique action to inhibit bradykinin (BK) induced nociception.[3-4]

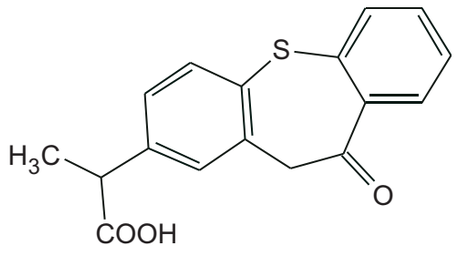


Fig. 1: Chemical structure of ZPF

ZPF exerts anti-inflammatory actions and analgesic effects by inhibiting prostaglandin synthesis and through a peripheral mechanism by inhibition of bradykinin B2 receptor-mediated bradykinin responses in primary afferent neurons.[5-6] Bawolak *et al.*[7] found that ZPF potently suppressed the relaxant response recruited by the kinin, which implied that ZPF was more potent than ibuprofen in this respect. ZPF was already used in the treatment of rheumatoid arthritis and osteoarthritis as well as to relieve inflammation and pain after surgery, injury and tooth extraction. Recently, a double-blind study[8] conducted in 170 patients indicated that the effect and safety of ZPF as a single dose to reduce inflammation in acute upper respiratory tract infection was also excellent, which provided a scientific evidence on the proper use of ZPF in the therapy of acute respiratory infections.

Cyclodextrins are crystalline, cyclic oligosaccharides with a bucket-like structure having a hydrophobic internal cavity and a hydrophilic exterior cavity that allows the configuration of inclusion complexes, in which lipophilic compounds are non-covalently bound within the cavity. Cyclodextrin have been employed in the pharmaceutical industry to increase the aqueous solubility and stability of drugs and that have been used in both parenteral and oral drug delivery systems.[9] Jadhav *et al.,* prepared oral controlled porosity osmotic pump tablet of zaltoprofen.[10] Various approaches to improve drug solubility, complexation with cyclodextrin are widely used. It was reported in 2010 that zaltoprofen was formulated into tablet to enhance the bioavailability and to achieve sustained-release using additives such as lactose monohydrate, carboxymethylcellulose and hydroxypropylmethylcellulose.[11] Cyclodextrin are powerful carriers for improving the therapeutic efficacy of drugs by means of

poor aqueous solubility via inclusion complexes.[12-14] Since ZPF is a drug of potential interest, but falls in a BCS Class II, having water solubility (0.0099 mg/ml), therefore, this drug is selected for solubility enhancement for better patient compliance. The purpose of this study was to use β-cyclodextrin for inclusion complexation in order to enhance the solubility, bioavailability and dissolution rate of zaltoprofen.

Materials and Methods

Materials

Zaltoprofen (ZPF) was obtained as a gift sample from Ipca Laboratories Ltd., Kandivali, Mumbai, India. β-cyclodextrin (β-CD) was purchased from HiMedia Laboratories, Mumbai, Maharashtra, India. All other chemicals and reagents used were of analytical grade of purity.

Preparation by complexation method

The physical mixture (PM) was prepared by mixing of pulverized powder of ZPF and β-CD (1:1 molar ratio) for 15 min and then passed through US Standard Sieve Sizes (sieve # 100) ZPF was added in ethanol one third by weight to excipients and then the β-CD was added with continuous stirring until homogenous mixture is formed. The mixture is then kept for drying in an oven for 6h at 45°C. Different molar ratios (1:0.5, 1:1, and 1:2) were used for the preparation of inclusion complex.

Phase solubility studies

Measurements of solubility were performed according to Takahashr *et al.*[15] Excess ZPF was added to 30 ml of purified water (pH 6.8) containing various concentrations of β-CD (0.002–0.01 M) in a series of 100 ml volumetric flasks and the mixture was shaken for 24h at room temperature (25°C) on a shaker (150 rev/min). Then, the samples were kept aside to achieve equilibrium. The aliquots were then filtered through membrane filter (0.22μm). Samples were suitably diluted and analyzed by using UV-VIS Spectrophotometer. PharmaSpec. UV-1700 (Shimadzu Corporation, Kyoto, KYT, Japan) at λmax 242 nm. All the tests were carried out in triplicate

Differential scanning calorimetry (DSC)

DSC was performed on pure ZPF, β-Cyclodextrin, physical mixture and complex prepared by the complexation method using a differential scanning calorimeter (DSC-60, Shimadzu, Japan). Samples (2–4 mg) were sealed in aluminium pans. Next, DSC thermograms were recorded from 50 to 300°C at a heating rate of 20°C/min in an air atmosphere.

X-Ray powder diffraction (XRD)

XRD patterns of pure ZPF, β-cyclodextrin and complex were evaluated by Bruker AXS D8 Advance X-ray powder diffractometer (Bruker Biosciences Corporation Billerica, MA, USA) to assess the

FTIR spectroscopy

Fourier transform infrared (FTIR) spectra of pure ZPF, β-cyclodextrin, physical mixture and complex were obtained using an FTIR spectrometer (IR AFFINITY-1 CE, Shimadzu Corp., Japan) equipped with a pyroelectric detector. Data were acquired using IR solution software. The spectra were measured over the range 4000–400 cm^{-1} with an instrument resolution of 4 cm^{-1}. Each individual spectrum was an average of 45 scan.

Dissolution studies

The dissolution studies of pure ZPF, physical mixture and complex were performed using the USP Type II paddle method (Dissolution test TDT-08L plus, Electrolab Mumbai, Maharashtra, India) with a stirring speed of 50 rpm in a 900 ml phosphate buffer solution having pH 6.8 and 7.4 was used as a dissolution medium. Samples containing 80 mg of ZPF were spread onto the surface of dissolution medium at 37±0.5°C. At appropriate time intervals, aliquots of 5 ml were withdrawn and measured spectrophotometrically by using UV-VIS Spectrophotometer (PharmaSpec UV-1700, Shimadzu Corporation, Kyoto, Japan) at λ_{max} 242nm. Experiments were carried out in triplicate; therefore only mean values with standard deviation (SD) error bars were reported.

Solubility determination

An excess amount of pure ZPF and the complex was placed in contact with pH6.8 and 7.4 phosphate buffers. The samples were shaken for 48h at 37°C in an orbital shaker. The supernatant was filtered through a membrane filter paper (0.22μn) and the filtrate was suitable diluted and measured spectrophotometrically at 242 nm. All experiments were conducted in duplicate.

Results and Discussion

Phase-solubility study

The phase solubility diagram for the complex formation between zaltoprofen and β-CD is shown in Fig. 2. The aqueous solubility of ZPF increased linearly as a function of β-CD concentration. The phase solubility diagram of ZPF/β-CD complex can be classified as type (BCS) according to Takahashr *et al*.[15] It is assumed that the increase in solubility observed was due to the formation of a 1:1 M inclusion complex. It has been reported that the driving force for inclusion complexation between β-cyclodextrin and a guest (zaltoprofen) may include vander Waals interaction, hydrogen bonding, and hydrophobic interaction, resulting in release of high energy water molecules from the cavity of β-cyclodextrin and release of strain energy in the ring of cyclodextrin. Therefore, it may be concluded that the binary complex are capable of improving the solubility and stability of zaltoprofen.[15]

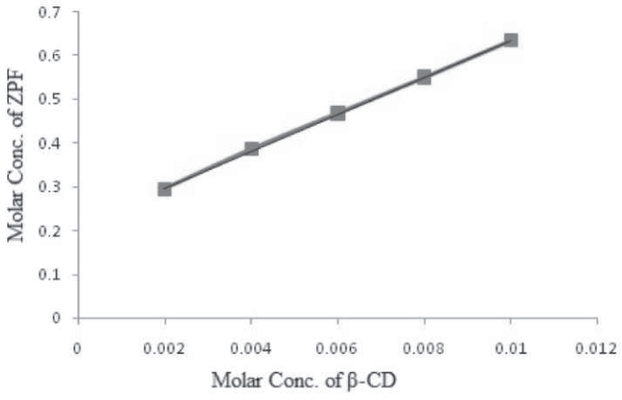
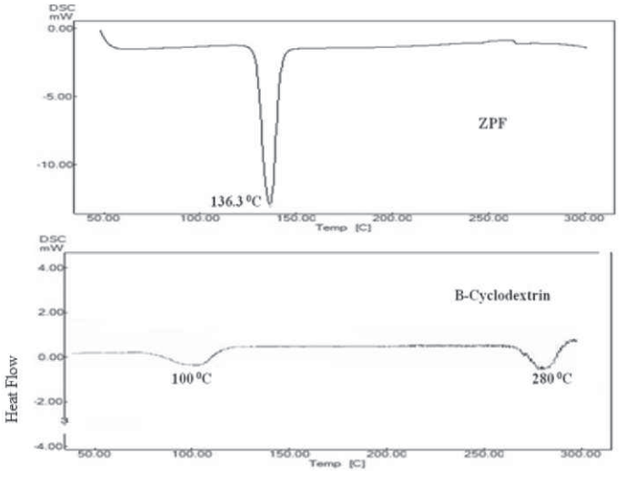


Fig. 2: Phase-solubility profile of ZPF/β-CD complex (1:1)

DSC study

It has been reported that DSC is a very useful tool in the investigation of thermal properties of CD complexes and can supply both qualitative and quantitative information about the physicochemical state of the drug inside the CD complexes. In general, complexation results in the absence of endothermic peak or shifting to different temperature, indicating a change in the crystal lattice, melting, boiling, or sublimation points.[16] DSC thermograms of pure ZPF, β-cyclodextrin, physical mixture and complex are depicted in Fig. 3. Pure ZPF displayed endothermic peak at 136.3°C corresponding to its melting point. In the thermogram of β-CD, two endothermic peaks were at 100°C due to the loss of water and near to about 280°C, which corresponds to the β-CD fusion.[17] The endothermic peak of physical mixture and complex is slightly shifted to 135.7°C and 134.4°C, respectively with that of pure drug but the intensity of peak is greatly reduced, while the endothermic peak deviates from 280°C to 288.7°C and 290.25°C, respectively. This can be considered as indicative of drug amorphization and/or inclusion complex formation between ZPF and β-CD, resulting in improved aqueous solubility and chemical stability.



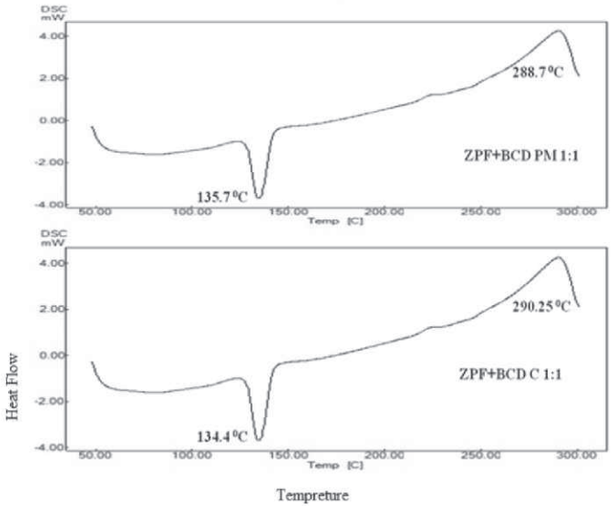


Fig. 3: DSC thermogram of pure ZPF, β-CD, physical mixture and complex

XRD study

In order to clarify the physicochemical characteristics of pure ZPF, β-CD and complex, X-ray diffraction measurements were conducted as shown in Fig. 4. The XRD of pure ZPF exhibited sharp, highly intense and less diffused peaks indicating the crystalline nature of drug. It showed sharp diffraction peaks at *2θ* values of 10.33°, 15.36°, 19.22°, 22.98°, 24.97°, 27.67°, and 31.83°. β-CD in its crystalline form exhibits diffraction peaks at *2θ* values of 4.75°, 12.7°, 19.7°, 21.1°, 22.8°, 24.3° and 35.9°. The XRD of complex (1:1) showed undefined, broad, diffuse peaks of low intensities at *2θ* values of 10.55°, 15.72°, 18.14°, 19.66°, 23.28°, 25.41°, 28.14°, and 32.26°. At diffraction angle of *2θ*, new peaks at 5.98°, 6.93° characteristic to β-CD are observed in diffractogram of complex, suggesting the formation of inclusion complex.

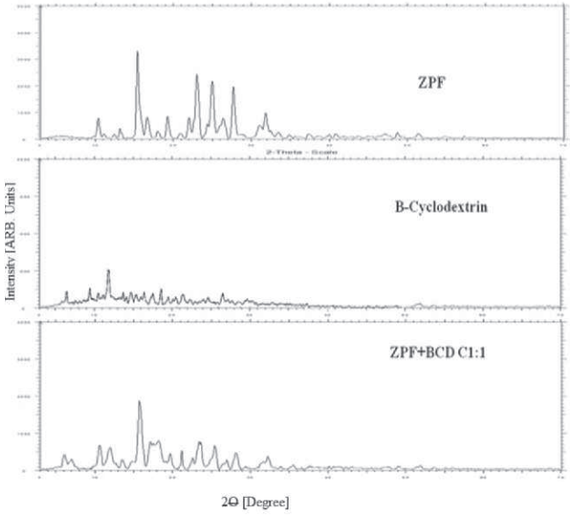


Fig.4: XRD diffractograms of pure ZPF, β-cyclodextrin and ZPF/β-CD complex

FTIR study

In order to further study whether zaltoprofen undergoes a polymorphic change during the preparation of the complex and to test for possible intermolecular interactions between ZPF and β-CD, FTIR was used. The FTIR spectra of pure ZPF, β-CD, Physical mixture and complex are depicted in figure below. Pure ZPF presents characteristic infrared spectra in the region of 3400-2400cm^{-1} explains carboxylic acid (COOH) functional group, while 1280 cm^{-1} suggests C-O group. It also exhibits characteristic infrared spectra in the C=O stretching region of functional carbonyl group band at 1700 cm^{-1}, showing its crystalline nature. The characteristic acid carbonyl stretching band at 1700 cm^{-1} (Fig. 5) of pure ZPF appeared unchanged in physical mixture and complex. The superimposition of spectra at 2975 cm^{-1} of ZPF, PM and complex, suggests no ZPF/β-CD interaction between ZPF and β-CD. As a result, there is no polymorphic changes in the physical mixture and complex, it was then concluded there were no intermolecular interactions between the ZPF and the β-CD.

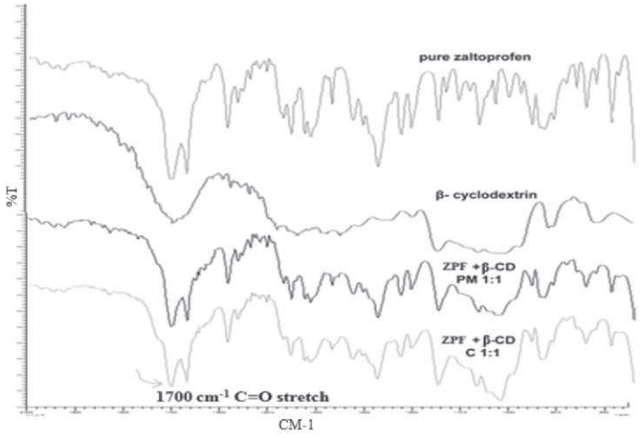


Fig. 5: IR spectra of pure ZPF, β-CD, physical mixture and complex

Dissolution rate study

Fig. 6-7 showed the dissolution behavior of pure ZPF, physical mixture and complex both in pH 6.8 and 7.4 buffers, respectively. The release rate profiles were drawn as the percentage ZPF dissolved from the inclusion complex, physical mixture and pure ZPF versus time. It is evident that both the complex and physical mixture exhibit a faster dissolution rate than the free drug.[12] Pure ZPF showed release upto 90.12% and 88.49% in pH6.8 and pH7.4 buffers, respectively. The dissolution rate was markedly increased in case of physical mixture while tremendous increase was observed in case of complex (1:1). This might be due to improvement of the wettability and solubility of the ZPF resulting from the coexistence of the β-CD in the dissolution medium. The enhancement in dissolution profile has been attributed due to the formation of inclusion complex in the solid state and reduction in the crystallinity of the product, as confirmed by powder XRD study. The Dissolution Efficiency (DE_{60min}) of pure ZPF, physical mixture and complex are given in Table 1.

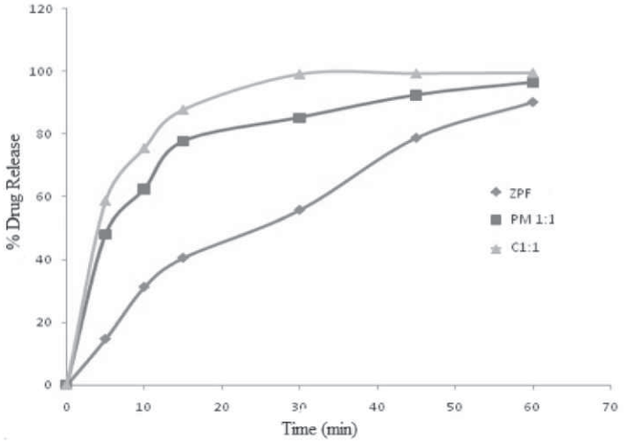


Fig. 6: Dissolution profiles of pure ZPF, physical mixture and complex in pH6.8 phosphate buffer solution

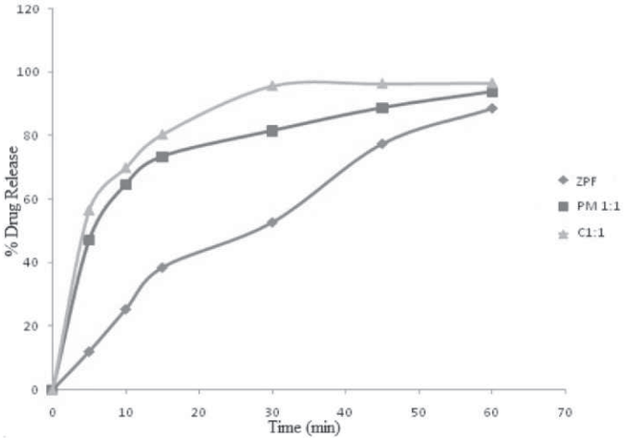


Fig. 7: Dissolution profiles of pure ZPF, physical mixture and complex in pH7.4 phosphate buffer solution

Table 1. Dissolution Efficiency (60 min) of pure ZPF, physical mixture and complex in pH 6.8 and 7.4 phosphate buffers at 37°C

Sample	DE_{60min} (pH6.8) Mean ± S.D (n=3)	DE_{60min} (pH7.4) Mean ± S.D (n=3)
Pure ZPF	90.12 ±1.2	88.49 ± 1.8
Physical mixture (1:1)	96.45 ± 1.5	93.73 ± 1.2
ZPF/ β-CD complex (1:1)	99.62 ± 1.0	96.57 ± 1.1

S.D indicates standard deviation

Solubility study

The effect of inclusion complexation with β-cyclodextrin on the solubility of ZPF can be explained in terms of the reduction in the crystallinity of the drug caused by the complexation method and the inclusion into the hydrophobic cavity of the β-cyclodextrin. The aqueous solubility of ZPF was found to be 0.0099 mg/ml. The maximum aqueous solubility was observed in pH6.8 (150-fold) and in pH7.4 (145-fold) buffer solution as shown in Table 2. The improvement of aqueous solubility was perhaps due to the formation of non-covalent inclusion complex[18] between ZPF and β-CD.

Table 2. Solubility of ZPF in phosphate buffer solution (pH6.8, 7.4) at 37±0.5°C after 48h

Sample	Solubility in pH6.8 buffer solution (mg/ml) ± SD, *n*=3	Solubility in pH7.4 buffer solution (mg/ml)± SD, *n*=3
Pure ZPF	0.0099 ± 0.8	0.0099 ± 0.8
Physical mixture	0.9570 ± 0.6	0.9354 ± 0.7
Complex	1.4969 ± 0.6	1.4583 ± 0.6

Conclusion

In this study, complexation method has been applied to prepare inclusion complex of ZPF with β-CD. The phase solubility diagram of ZPF/β-CD complex was classified as AL-type, indicating the formation of 1:1 stoichiometric inclusion complex. No endothermic and characteristic diffraction peaks corresponding to ZPF was observed for the inclusion complex in DSC and PXRD, suggesting in the formation of amorphous form. FT-IR study revealed no drug-polymer interaction occurred between ZPF with β-CD. Dissolution study indicated that the dissolution rates were remarkably increased in ZPF/β-CD (1:1) complex, compared with the physical mixture and ZPF alone. Through complexation with the β-cyclodextrin, the aqueous solubility of ZPF has been improved substantially (up to 150-fold) in pH6.8 and (up to 145-fold) in pH7.4. In conclusion, complexation method proved to be the better technique for the maximum solubility, dissolution rate and bioavailability of ZPF.

Acknowledgements

The authors are grateful to Ipca Laboratories Ltd., Kandivali, Mumbai, India for providing gift sample of Zaltoprofen and H. R. Patel Institute of Pharmaceutical Education and research, Shirpur, India for their necessary facility and support.

Conflict of Interest

The authors report no conflicts of interest.

References

1. Japanese Pharmacopoeia XV, Society of Japanese Pharmac 2006; 15 Ed: 1242-1244.
2. Tsurumi K, Kyuki K, Niwa M. Pharmacological investigations of the new anti-inflammatory agent 2-(10,11-dihydro-10 oxodibenzo[b,f]thiepin-2-yl) propionic acid. 1st communication: inhibitory effects of rat paw edema. Arzneimittelforschung 1986; 36:1796-1800.
3. Azuma A, Kudoh S, Nakashima M, Nagatake T. Antipyretic and analgesic effects of zaltoprofen for the treatment of acute upper respiratory tract infection: verification of a noninferiority hypothesis using loxoprofen sodium. Pharmacol 1986; 87:204-213.
4. Hiroshi U, Misaki M, Makoto I. NSAID zaltoprofen possesses novel anti-nociceptive mechanism through blockage of B2-type bradykinin receptor in nerve endings. Neurosci Lett 2006; 397:249-253.
5. Tang HB, Inoue A, Oshita K, Hirate K, Nakata Y. Zaltoprofen inhibits bradykinin-induced responses by blocking the activation of second messenger signaling cascades in rat dorsal root ganglion cells. Neuropharmacology 2005; 48:1035-1042.
6. Hirate K, Uchida A, Ogawa Y, Arai T, Yoda K. Zaltoprofen, a non-steroidal anti-inflammatory drug, inhibits bradykinin-induced pain responses without blocking bradykinin receptors. Neurosci Res 2006; 54:288-294.
7. Bawolak MT, Marceau F. Does zaltoprofen antagonize the bradykinin receptors. Regul Pept 2007; 140:125-130.
8. Azuma A, Kudoh S, Nakashima M, Nagatake T. A double-blind study of zaltoprofen for the treatment of upper respiratory tract infection. Pharmacol 2010; 85:41-47.
9. Loftsson T, Brewster ME. Pharmaceutical applications of cyclodextrins. Part 1. Drug solubilization and stabilization. J Pharm Sci 1996; 85:1017-1025.
10. Jadav M.M., Teraiya S.R., Patel K.N., Patel B.A., Patel P.A. Formulation and evaluation of oral controlled porosity osmotic pump tablet of zaltoprofen. Int J Pharm Res Schol 2012; 1:254-267.
11. Park H, hong H, Song S, Hong M. Improvement of dissolution rate of zaltoprofen tablets using CMC & HPMC. Polymer Korea 2010; 34:300-305.

12. Loftsson T, Hreinsdottir D, Masson M. Evaluation of cyclodextrin solubilization of drugs. Int J Pharm 2005; 302:18-28.
13. Loftsson T, Jarho P, Masson M, Jarvinen T. Cyclodextrin in drug delivery. Expert Opin Drug Del 2005; 2:335-351.
14. Yalcin OZ, Tamer A, Necati D, Askin I, Hassan Y, Aboul E. Improvement of water solubility and in vitro dissolution rate of gliclazide by complexation with β-cyclodextrin. Pharm Acta Helv 2000; 74:365-370.
15. Takahashi T, Kagami I, Kitamura K, Nakanishi Y, Imasato Y. Stabilization of AD-1590, a non-steroidal anti-inflammatory agent, in suppository bases by β-cyclodextrin complexation. Chem Pharm 1986; 34:1770-1774.
16. Yadav VR, Suresh S, Kshama D, Yadav S. Effect of cyclodextrin complexation of curcumin on its solubility and antiangiogenic and anti-inflammatory activity in rat colitis model. AAPS PharmSciTech 2009;10:752-762.
17. Farcas A, Jarroux N, Farcas AM, Harabagiu V, Guegan P. Synthesis and Characterization of Furosemide Complex in β-Cyclodextrin. Digest J Nanomaterials and Biostructures 2006; 1: 55-60.
18. Marcus E. Brewster, Thorsteinn Loftsson. Cyclodextrins as pharmaceutical solubilizers. Adv Drug Deliv Rev 2007; 59: 645-666.