RESEARCH ARTICLE

INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

A Path for Horizing Your Innovative Work

SOLUBILITY IMPROVEMENT OF CEFPODOXIME PROXETIL BY INCLUSION IN 2-HYDROXYPROPYL-β-CYCLODEXTRIN

***RITESH GHASADIYA, DUSHYANT SHAH, ASHOK MAHAJAN, DHAVAL PATEL, UTSAV RATHOD**

Department of Pharmaceutics, A.P.M.C. College of pharmaceutical education and research, motipura, himatnagar-383001, Gujarat state, India

Corresponding Author Email: riteshpharmacy@gmail.com

Accepted Date: 21/04/2012 **Publish Date: 27/04/2012**

Abstract: The aim of this study was to enhance the solubility and bioavailability of cefpodoxime proxetil (CFP) through complexation with 2-hydroxypropyl-β-cyclodextrin (HP- β -CD). CFP is a poorly water soluble antibiotic drug. Reportedly, it has slow, erratic, and complete absorption after oral administration. This present report describes the study of the phase solubility diagram, preparation of the inclusion complex, In-Vitro dissolution study of optimized ratio. An AL-type phase solubility diagram indicated a 1: 1 complex of CFP-HP-β-CD with the constant of complex formation of 188.35 M-1 at 37°C. The complex formation was confirmed by DSC, IR. The extent of absorption of the complex was determined in rats and was compared with that of pure drug. The pure CFP shows 9.7 % Corrected cumulative Drug release (CCDR) in hr while kneded drug complex with HP-β-CD shows 53.06 %CCDR. The solubility and dissolution rates of CFP were significantly increased by Hydroxypropyl cyclodextrin complexes.

Keywords: Cefpodoxime proxetil, Hydroxy propyl β Cyclodextrin, Phase Solubility Diagram, Inclusion Complex.

INTRODUCTION[1-3]

Hydroxypropyl beta cyclodextrin have extensively been used to increase the solubility, dissolution rate[4, 5], and bioavailability of poorly water soluble drugs[21].The ability of cyclodextrin to modify these characteristics has been at-Correspondence attributed to the formation of inclusion complex between cyclodextrin and 'guest' drug molecules. 2-Hydroxypropyl-β-cyclodextrin [HP β CD] is an amorphous mixture of modified β-cyclodextrin (βCD). It has the ability to form inclusion complexes but does not have the limitations associated with crystalline cyclodextrin such as renal toxicity. Further, the aqueous solubility of HP β CD is far greater than that of the parent β CD which results in vastly improved solubility of numerous compounds. Cefpodoxime Proxetil[22, 23] (CFP) is a major antibiotic drug for the treatment of different form of seizures. The drug is practically insoluble in water and has poor wettability properties. It is absorbed slowly and erratically after oral administration. Reportedly, it has an oral bioavailability[8] of less than 50%. These properties of CFP led to the belief that it can be a good candidate for complexation with HP β CD to increase solubility and bioavailability. The primary objective of the present study is to investigate the possibility of improving the aqueous solubility and oral bioavailability of CFP via complexation with HP β CD. The formation of such complex was confirmed by a variety of techniques such as solubility determination, Infrared spectrophotometry (IR)[9], Differential scanning calorimetry (DSC)[10]. The work also included determination of the in vitro dissolution profiles of pure drug, physical mixture and CFP : HP β CD complex system.

MATERIALS AND METHODS

Materials

Cefpodoxime proxetil was a gift from Cadilla pharmaceuticals Pvt Ltd.HPβCD were kindly supplied by Roquett Pharma. Ethanol, methanol, and water were obtained from S.D.Fine Labs, and all were of HPLC grade. All other chemicals were of analytical reagent grade.

Methods

The standard curve of CFP was prepared in distilled water dissolved by HP-β-CD.

Preparation of stock solution[19]

50 mg of CFP was accurately weighed in to 50 ml volumetric flask and dissolved in small quantity of water. The volume was made up with water to 50 ml to produce a stock solution having a concentration of 1 mg/ml. 100 mg of HP-β-CD was added to solubilize the drug with sonication.

Preparation of standard solution

An aliquot of 5 ml of the stock solution was diluted to 50 ml to get a standard solution having a concentration of 100 mcg/ml using water.

Preparation of the working standard solution[20]

Standard solutions ranging in concentrations from 2 to 10 mcg/ml were prepared by appropriately diluting the stoke solution with water. The absorbance of each working standard solution was measured at 263 nm (Shimadzu UV spectrophotometer) using water having same concentration of HP-β-CD as a blank so as to nullify any absorbance that may be exhibited by the HP-β-CD molecule. Data was collected in triplicates and statistically analyzed.

Phase Solubility Study[10]

Phase-solubility studies were performed according to the method reported by Higuchi and Connors (1965). Exactly 50 mg of CFP was weighed into 20 ml scintillation vial, to which were added 10 ml of water containing different concentrations of HPβCD (5- 100 mM). Different ratios prepared were ratios are 1: 0, 1: 0.5, 1: 1, 1: 2. (CFP: HP-β-CD). The sealed vials were shaken for 2 days at a controlled temperature of 37 ± 0.5^0C. After 2 days, an aliquot was withdrawn and filtered through a 0.45micron millipore filter. The concentration of CFP in each aliquot was determined spectrophotometrically at 263 nm to have a standard plot.

Kneading Method[12]

Solid inclusion complex of Cefpodoxime proxetil (CFP) and HP-β-CD were prepared in molar ratio by following kneading method. HP-β-CD was mixed in a glass mortar along with water to obtain a homogeneous paste. The drug was slowly added to the paste and the mixture triturated for 1 hr. During the process the water

content of the paste was empirically adjusted to maintain the consistency of the paste. The paste was dried at 45 ^{0}C for 48 hrs, pulverized and passed through sieve No.100.

Physicochemical properties

IR spectroscopy of the KBr pellet was performed using a FTIR spectrophotometer (SHIMADZU). The above scans were performed on CFP, HPβCD, and the complex.

Dissolution rate

Dissolution studies were performed using the U.S.P. dissolution apparatus (paddle method) in 900 ml water as the dissolution medium. The stirring rate was 70 rpm and temperature was maintained at 37 ±0.5 ^{0}C. Dissolution samples were passed through 30 meshe and retained on 80 mesh USP standard and contained the equivalent of 100 mg cefpodoxime proxetil.

RESULTS AND DISCUSSION

The absorbance data for standard calibration curves are given in table-1. The standard calibration curve yields a straight line, which shows that the drug follows Beer's law in the concentration range at 2 to 10 mcg/ ml.

Table1.

Absorbance Data

Concentration (mcg/ml)	Absorbance
0	0
2	0.055±0.25
4	0.117±1.08
6	0.164±1.22
8	0.221±1.36
10	0.273±1.05

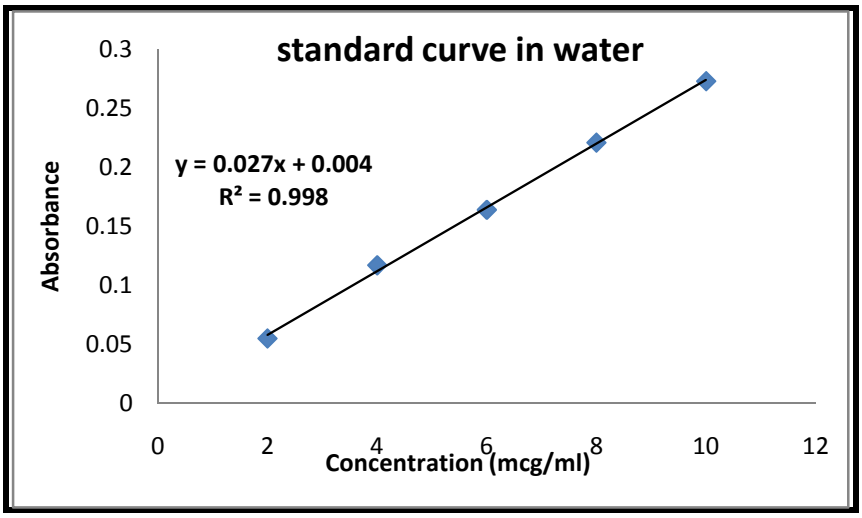

Figure 1: Standard Calibration Curve in Water

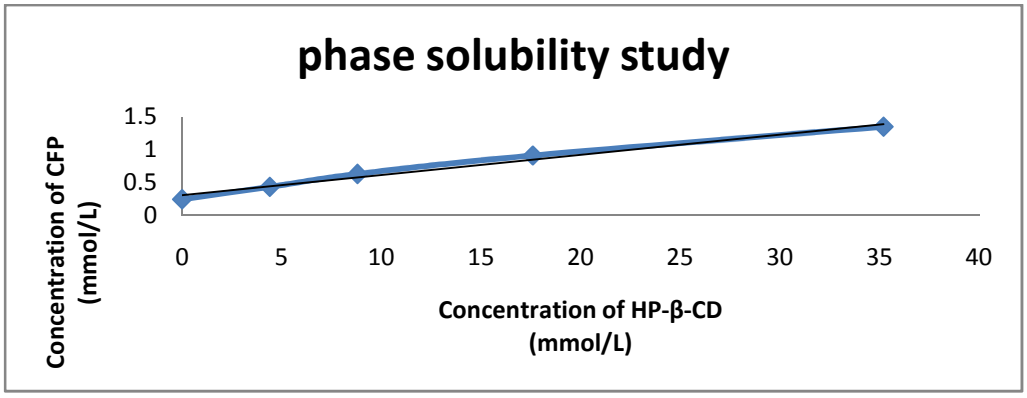

Figure 2. Phase solubility diagram

The phase solubility diagrams shown in Fig. 1 can be classified as type A_L according to Higuchi Connors Phase solubility diagram of CFP and HP-β-CD systems in distilled water at 37°C.

Because the straight line had a slope less than unity, it was assumed that the increase in solubility observed was due to the formation of a 1 : 1 complex. The observed rate constants for the formation of the complex (K_F) were calculated for HPβCD Equation 1[13-15] and were found to be 188 M^{-1}.

$$K_{a:b} = \frac{\text{slope}}{S0(1-\text{slope})} \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (1)$$

As observed from Fig. 2 a considerable increase in solubility of CBZ was obtained with HPβCD.

The IR spectra of the inclusion complex (Fig. 5) did not show any significant differences from the respective spectra of the pure compounds. The absorption peaks characteristic of the carbonyl group[16] of CFP in the range 1735-1760 cm^{-1} and the amino groups[17,18] in the range 3200-3600cm^{-1} have disappeared from the spectrum of the inclusion complex. These spectral changes may have resulted from the inclusion of CFP within the cavity of HPβCD.

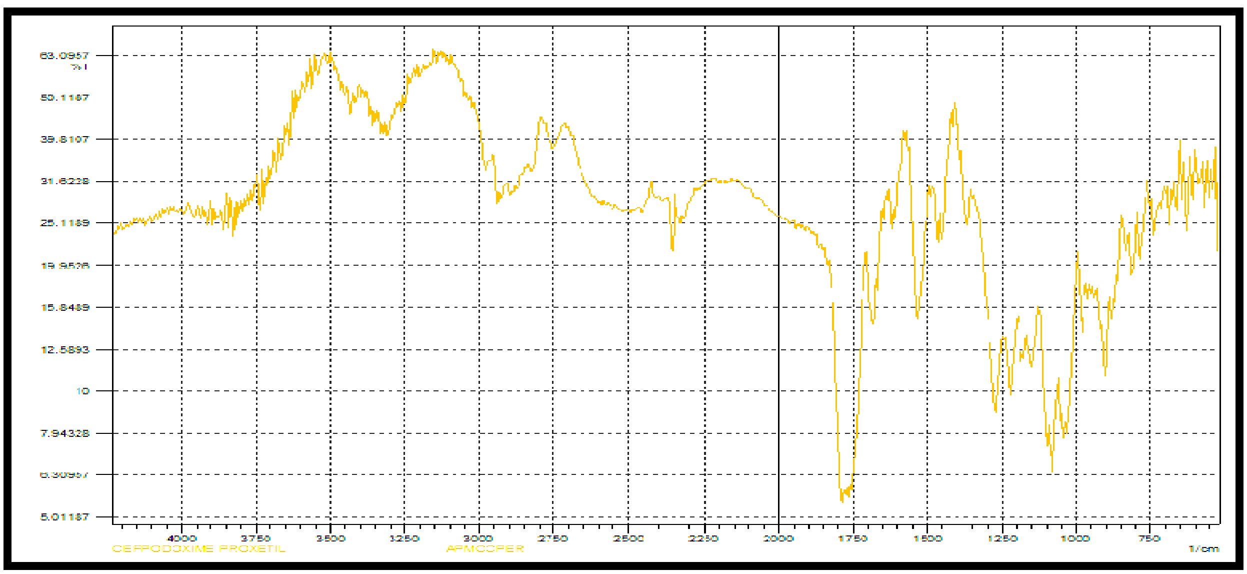

Figure 3. FTIR of Cefpodoxime Proxetil

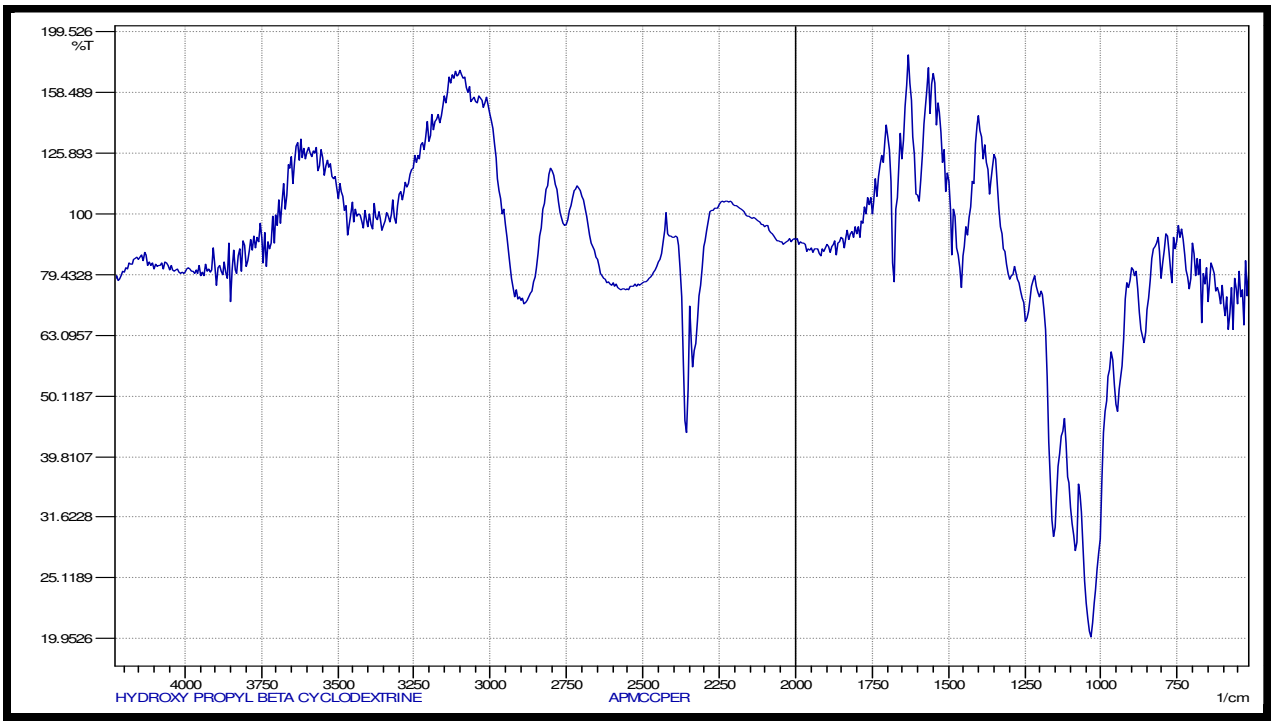

Figure 4. FTIR of HP-β-CD

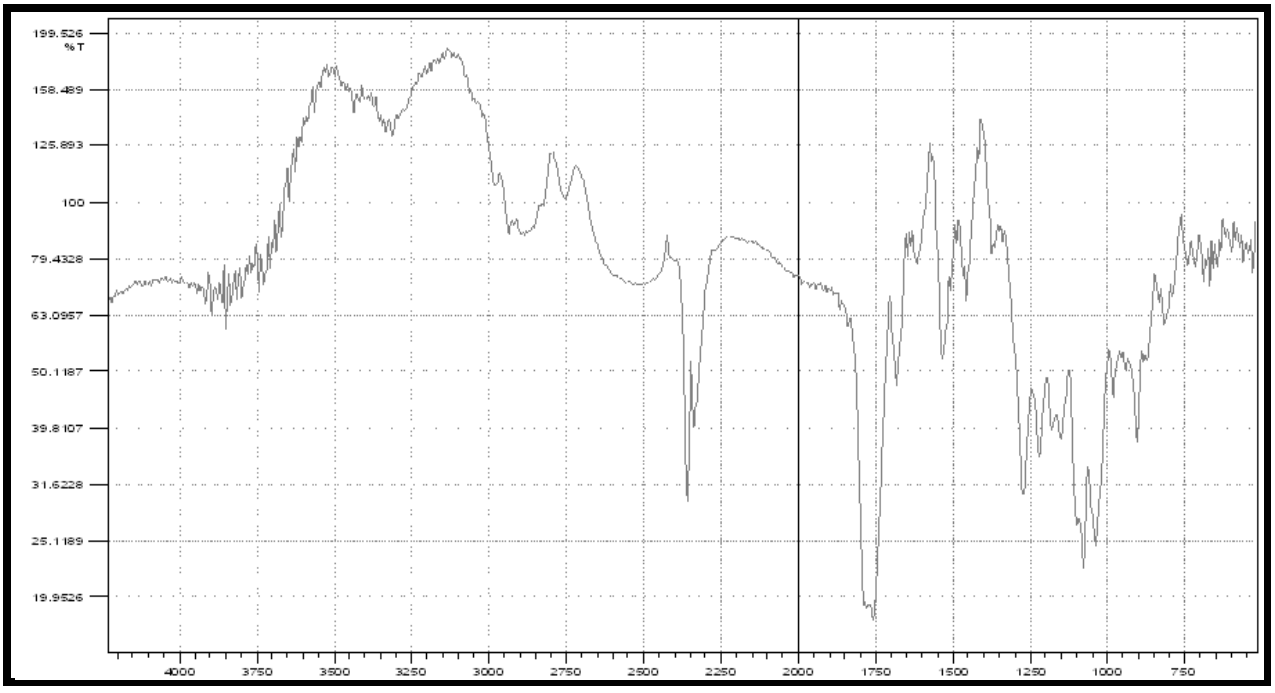

Figure 5. FTIR of Inclusion complex

Figure 6 shows the dissolution profiles[6, 7] of CFP from complex, physical mixture, and powders. It is evident that the release of CFP was significantly enhanced by complexation. Within 1 hr, the percentage of drug released was approx 10 and 50 % for the powdered drug and the complex samples, respectively. Additionally, in this study, improved wettability of CFP in the samples of

Complex was observed. The enhanced dissolution rate is probably due to increased solubility, decreased crystallinity and improved wettability.

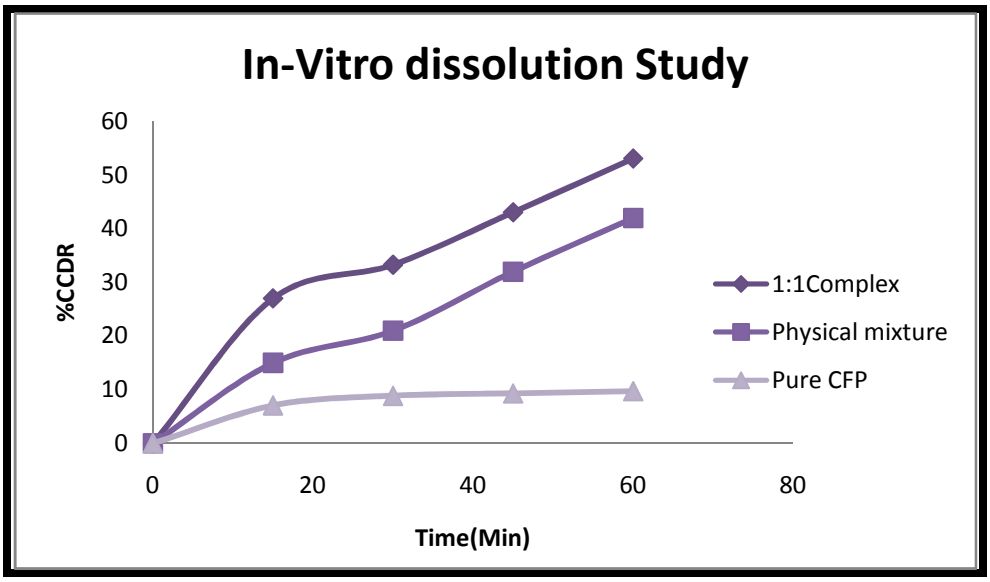

Figure 6. *In Vitro* dissolution Study of Inclusion complex, physical mixture and pure drug

CONCLUSION

The above data clearly indicate that the inclusion complex makes the drug more soluble. This enhancement in drug solubility is due to fast dissolution rate of the complex. Thus, HPβCD could be a useful additive to solid Cefpodoxime proxetil. Formulations having Inclusion Comlexation with HP-β-CD result in a more rapid absorption and improved bioavailability of the drug.

REFERNCES

1. Hamada Y, Nambun N and Nagai T: Interactions of and P-cyclodextrins with several non-steroidal anti inflammatory drugs in aqueous solution. Chem. Pharm. Bull.1975; 23: 1205-1211.

2. Glomot F, Benkerrour L, Duchene D and Poelman MC: Improvement in availability and stability of a dermocorticoid by inclusion in P-cyclodextrin. In. J. Pharm. 1988; 46: 49-55.

3. Yousef Javadzadeh: Liquid solid technique for dissolution rate enhancement of a high dose water-insoluble drug (carbamazepine), International Journal of Pharmaceutics-2007.

4. Uekama K, Narisawa S, Hiryama, F. and Otagiri M, Improvement of dissolution and absorption characteristics of benzodiazepines by cyclodextrin complexation. Int. J. Pharm. 1983; 16: 327-338.

5. Nambu N, Shimoda M, Takahashi Y, Ueda H and Nagai T: Bioavailability of powdered inclusion compounds of non steroidal anti inflammatory drugs with P-cyclodextrin in rabbits and dogs. Chem. Pharm. Bull. 1978; 26: 2992- 2996

6. Indian Pharmacopoeia, Volume -III, the Indian Pharmacopoeia Commission, Ghaziabad, Govt. of India, Ministry of Health and Family Welfare. **2007**: 232-233

7. United state pharmacopoeia 30- National formulary 25, United state pharmacopoeial convention.

8. Li-Ping Ruan: Improving the solubility of ampelopsis by solid dispersions and inclusion complexes, Journal of Pharmaceutical and Biomedical Analysis-2005.

9. R. Nair: Influence of polyethylene glycol and povidone on the polymorphic transformation and solubility of carbamazepine, International Journal of Pharmaceutics-2002.

10. Higuchi, T. and Connors, K.A., Phase solubility techniques. In Reilley, C.N. (Ed.), Advances in Analytical Chemistry and Instrumentation, Interscience, New York, 1965:132.

11. KPR Chowdary: Effect of polyvinyl pyrrolidone on complexation and dissolution rate of beta and hydroxy propyl beta cyclodextrin of celecoxib. IJPS 2010.

12. Tarun K. Patel et al. Comparative study on effect of Natural and Synthetic super Disintegrates in the formulation of Carbamazepine Fast Dissolving Tablets, JPSBR-2011.

13. Sarasija Suresh: Effect of beta cyclodextrin complexation on the solubility and dissolution rate of carbamazepine tablet, ,International Journal of Pharmaceutical science 2010.

14. Rawat S and Jain SK: Rofecoxib—cyclodextrin inclusion complex for solubility enhancement. Pharmazie.

15. Rajeswari Challa: Cyclodextrins in Drug Delivery: An Updated Review Submitted: June 11, 2004; Accepted: January 26, 2005; Published: October 14, 2005.

16. CR Palem, S Patel and VB Pokharkar Solubility and Stability Enhancement of Atorvastatin by Cyclodextrin Complexation PDA J Pharm Sci and Tech 2009; 63: 17-225.

17. Rajewski RA, Stella VJ. Pharmaceutical applications of cyclodextrins. 2. In vivo drug delivery. J Pharm Sci. 1996; 85: 1142-1168.

18. Castillo JA, Canales JP, Garcia JJ, Lastres JL, Bolas F, Torrado JJ. Preparation and characterization of albendazole beta-cyclodextrin complexes. Drug Dev Ind Pharm. 1999; 25: 1241-1248.

19. Diaz D, Escobar Llanos CM, Bernad MJB. Study of the binding in an aqueous medium of inclusion complexes of several cyclodextrins involving fenoprofen calcium. Drug Dev Ind Pharm. 1999; 25: 107-110.

20. Arias-Blanco MJA, Moyano JR, Martinez JIP, Gines JM. Study of inclusion complex of gliclazide in α-cyclodextrin. J Pharm Biomed Anal. 1998; 18: 275-279.

21. K D Tripathi ”Essentials of Medical Pharmacology” Edition 6th, Published by Jaypee Brothers Medical Publishers.

22. HP Rang, M. Maureen Dale, Rang and Dale's pharmacology, Edition 6, illustrated, Published by Churchill Livingstone, **2007**.

23. “Drug information handbook” by LEXI-COMP’S Clinical Reference library, 8th Edition 2000-2001.