International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.4, No.1, pp 201-207, Jan-Mar 2012

Modification of physicochemical characteristics of Lornoxicam using cyclodextrin as modulator

Patil A. L.[1]*, Patil S. S.[2]

[1]Government College of Pharmacy, Karad, MS, India.

[2]Ashokrao Mane College of Pharmacy, Peth Vadgaon, MS, India.

*Corros. author: abhi22jan@rediffmail.com
Tel.No. +91 9822934832

Abstract: The objective of the present work was to prepare inclusion complex using HPβCD to modify the physicochemical properties of Lornoxicam (LX), a non steroidal anti-inflammatory agent for dissolution enhancement. Phase solubility study was performed according to method reported by Higuchi and Connors demonstrates formation of 1:1 inclusion complex with A_L type phase solubility profile. As the stability constant value was found to be $130M^{-1}$,a sufficiently stable one. The solid state complex were prepared by kneading method and evaluated for Differential scanning calorimetry, X-ray powder refractometry and Fourier transformation infrared spectroscopy. These studies indicated that complex prepared by kneading method showed successful inclusion of the LX into the cyclodextrin (CD) cavity. Satuation solubility performed in distilled water showed significant enhancement in solubility for kneaded product compared to pure drug while dissolution study was performed as per USP apparatus type II in phosphate buffer pH 7.4 showing marked enhancement in dissolution relase rate for kneaded product with t_{90} value < 5 min. The complexation resulted in a marked improvement in the solubility and wettability of LX.

Keywords: lornoxicam, stability constant, dissolution release rate, solid state characterization.

INTRODUCTION

Lornoxicam (LX) is a non-steroidal anti-inflammatory drug with analgesic, antipyretic and anti-inflammatory activity belongs to the class of oxicams[1]. It is widely used for the symptomatic treatment of pain and inflammation in patients with rheumatoid arthritis and osteoarthritis. Chemically LX is (3E) - 6- chloro- 3- [hydroxy(pyridin- 2- yl amino) methylene] - 2- methyl-2, 3-dihydro- 4h- thieno [2, 3-e] [1, 2] thiazin- 4- one 1, 1-dioxide (Fig 1). It showed great efficacy in various clinical trials in the management of perioperative and postoperative pain associated with gynaecological, orthopaedic, abdominal and dental surgeries[2].

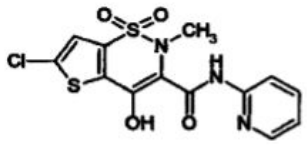


Fig. 1 Chemical structure of LX

LX is completely insoluble in water and slightly soluble in simulated gastric fluid. Its poor aqueous solubility[3] can makes its absorption dissolution rate limited and thus delay the onset of action. The dissolution of drugs is a prime determinant in the absorption of poorly water-soluble drugs and also serves as a rate-limiting step[4]. Poor aqueous solubility can cause formulation related problems. Furthermore LX showed polymorphism[5] could be one of the reasons for low aqueous solubility. The formulation of poorly water-soluble drugs is one of the most

challenging tasks to the formulation experts. An enhancement in the solubility and the dissolution rate can improve the oral bioavailability of such drugs, which further improves the therapeutic efficacy and patient compliance. Various techniques have been used to enhance the solubility of poorly water soluble drugs including the use of surfactants [6] amorphous form of drug micronisation[7] and solid dispersion [8-10] and inclusion complexation[11]. The aim of the present study was to enhance the dissolution rate of LX using cyclodetrin (CD) to form inclusion complex. Kneading method was adopted for preparation of inclusion complex which is the economic and industial applied method. Solid state characterizarion was done by using DSC, XRD and FTIR study. Furthermore inclusion complex were evaluated for saturation solubility and dissolution release rate study.

MATERIALS AND METHODS

Materials

Lornoxicam (LX) was supplied as a gift sample by Piramal Healthcare Pvt. Ltd., Mumbai. India. HPβCD was procured as a gift sample from Panacea Biotech Pvt. Ltd., Chandigad, India. All chemicals and solvents used in this study were of analytical grade. Freshly distilled water was used throughout the work.

Phase solubility studies

Phase solubility studies were performed in distilled water in triplicate according to Higuchi and Connors method[12]. An excess amount of drug was added to 20ml of aqueous solutions containing various concentrations of HPβCD (0–0.01 M) in glass vials which were subsequently tightly closed and mechanically shaken at 25±2°C for 5days. After equilibrium was achieved, the samples were filtered through 0.45 µm membrane filter and appropriately diluted and spectrophotometrically analyzed (Shimadzu UV 1700 Japan) at 378nm. The presence of HPβCD did not interfere with the spectrophotometric assay of the drug. The apparent stability constant Ks was calculated from the slope of the linear plot of the phase solubility diagram according to Eq. 1.

$$Ks = \text{slope} / S_0 (1\text{-slope}) \quad \text{…….(1)}$$

where S_0 is the solubility of drug in absence of HPβCD.

Preparation of solid binary systems:

The following binary systems of LX and HPβCD were prepared in 1: 1 molar ratio

Physical mixture of LX with HPβCD:

For physical mixture, LX and HPβCD were weighed accurately in 1:1 molar ratio, mixed thoroughly by trituration in a mortar for 25 min and passed through sieve no. 80 (180 µm).

Kneading method:

LX and HPβCD were mixed in mortar with a pestle and the required amount of solvent (ethanol–water 1:1 mixture) just to make a smooth paste was added. The paste was then further kneaded for about 1 h. A similar method was reported by Fernandes et al.[13] where drug was kneaded with CD. During this process, an appropriate quantity of the solvent was added in order to maintain a suitable consistency. Further, the product was dried at 45°C. The dried mass was then pulverized and passed through no. 80 sieve.

Differential scanning calorimetry (DSC)

DSC measurements were performed on a TA SDT 2960 DSC (USA) differential scanning calorimeter. The accurately weighed sample was placed in an aluminium pan. An empty aluminium pan was used as reference. The experiment was carried out in nitrogen atmosphere (flow rate 10 ml/min) at scanning rate of 10^0C/min in the range of 0–350^{0}C.

X-ray powder diffractometry (XRD)

The XRD patterns of LX, HPβCD, inclusion complex and physical mixture were recorded by a Philips Analytic X-Ray – PW 3710 (Holland) diffractometer with tube anode Cu over the interval 5–70^0/2q. The operation data were as follows: Generator tension (voltage) 40 kV, Generator current 30 mA, and scanning speed 2^0/min. The scanning rate employed was 1° per min and samples were analyzed between 2θ angles of over 10– 60°.

Fourier transformation-infrared spectroscopy (FTIR)

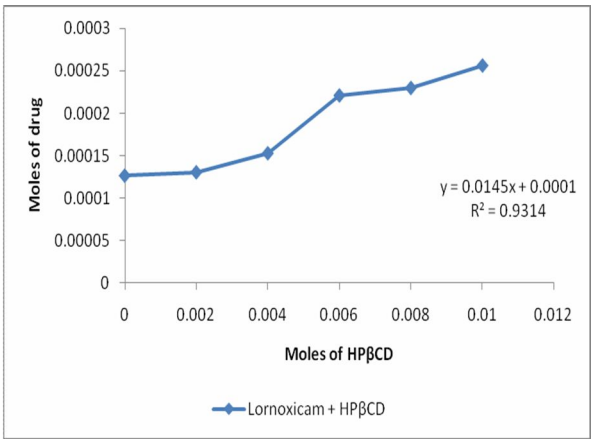
Infrared spectra were obtained using a Jasco FTIR 4100 (Japan) using KBr disk. The samples were previously ground and mixed thoroughly with KBr. The KBr disks were prepared by compressing the powder. The scanning range was kept from 4000 to 450 cm^{-1}

Saturation solubility studies

Saturation solubility studies were performed according to the method reported by Higuchi and Connors[12] to analyze the improvement in solubility in distilled water in triplicate. Excess of pure drug, physical mixture, and inclusion complex were added to 20ml of distilled water in glass vials which were subsequently tightly closed and shaken for 24 h on a mechanical shaker at room temperature to achieve the equilibrium. In preliminary studies, it was found that equilibrium solubility was achieved in 24 h and therefore, samples were shaken for 24 h. Appropriate aliquots were then withdrawn, filtered, diluted, and were analyzed spectrophotometrically at 378nm.

***In-Vitro* dissolution studies**

The *In-vitro* dissolution studies were performed in triplicate in dissolution apparatus (Electrolab, India) using the paddle method (USP type II). Dissolution studies were carried out using 900ml of phoshphate buffer pH 7.4 at 37± 0.5°C at 50 rpm. LX, 04 mg or its equivalent amount of LX – HPβCD complex was added to 900 ml of phoshphate buffer pH 7.4. Samples of 5 ml were withdrawn at time intervals of 5, 10, 20, 30, 45, 60 min. The volume of dissolution medium was adjusted to 900ml by replacing with 5ml of fresh phoshphate buffer pH 7.4. The solutions were immediately filtered through 0.45 µm membrane filter, suitably diluted and the concentrations of LX in samples were determined spectrophotometrically at 378nm. The dissolution profile was constructed by plotting the percent drug dissolved against time.



[a]mean ± SD n=3, linear equation is y = 0.0145x + 0.0001 (R^2= 0.931)

Fig. No. 2. Phase solubility study of LX in aqueous solution of HPβCD in distilled water.

RESULTS AND DISCUSSION

Phase solubility study

The phase solubility diagram obtained for LX-HPβCD binary system is shown in Fig. 2. The solubility of LX increased with increasing concentration of HPβCD and hence, phase solubility diagram could be classified as A_L type according to Higuchi and Connors[12]. The linear host–guest correlation coefficient R^2=0.931 and slope less than 1 indicated that a complex of 1:1 molar ratio was formed. The binding constant, $K_{(1:1)}$ obtained from the slope of linear portion of phase solubility diagram was found to be 130 M^{-1}**.** These values suggest good stability of LX– HPβCD complex at 1:1 molar ratio.

Differntial scanning calorimetry (DSC)

Fig 3 showed the DSC for pure drug, HPβCD, its physical mixture and for kneaded product. LX (fig 3A)showed exothermic peak at 223^{0}C corresponding to its melting point. The thermogram of physical mixture (fig 3C) shows the shifting of exothermic peak of drug to lower value with reduction in peak intensity while kneaded product (fig 3D) showed the disappearance of melting peak confirming the formation of inclusion complex in solid state which could be ascribed to increase in the drug–CD interaction as a consequence of the more drastic mechanical treatment during kneading. This could indicate complete drug amorphization and/or its interaction with the carrier[14]

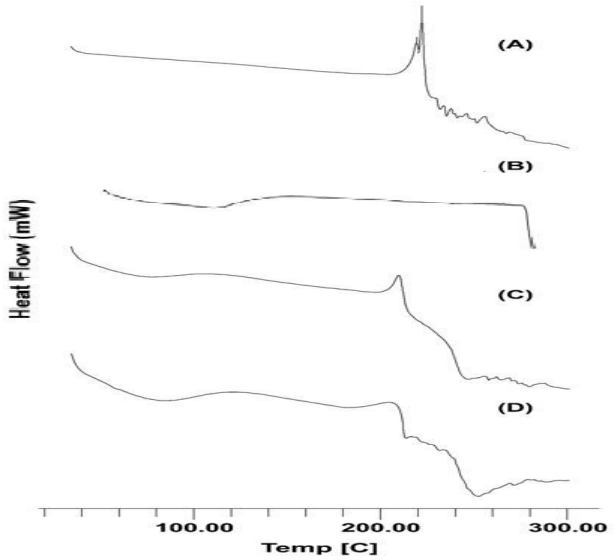


Fig. No. 3. DSC thermogram of LX with HPβCD (A) LX, (B) HPβCD (C) Physical mixture (D) Inclusion complex

X-ray powder diffractometry (XRD)

The diffraction pattern of LX powder (fig 4 A) revealed several sharp high intensity peaks at diffraction angles 2θ of 37.08°, 32.22°, 34.46°, 38.16° suggesting that it existed as a crystalline material while HPβCD showed diffused halo pattern[15]. Crystallinity was determined by comparing some representative peak heights in the diffraction pattern of binary systems with those of reference (pure LX) (table 1). The peak height at 37.08^0 (*2θ*) was used for calculating the relative decrease in crystallinity (RDC) of binary systems. The RDC value for kneaded product was found to be 0.1476 while for physical mixture 0.2281. The diffraction pattern of physical mixture showed (fig. 4C), peaks of LX and HPβCD with little decrease in peak intensity demonstrating reduction in crystallinity while for kneaded product (fig. 4D), crystallinity of LX was reduced to a greater extent as compared to physical mixture and pure LX alone. Moreover peak at 34.46^0 and 38.16^0 were completely disappereed in kneaded product. This finding might be attributed to the reduction in the drug particle size during the kneading process.

Table 1. Peak intensities of LX in the XRD patterns of LX-HPβCD binary systems.

2θ(^{0})	**Drug**	**Drug: HPβCD binary system**	
		PM	**KN**
37.08	149	34	22
32.22	64	16	05
34.46	46	14	---
38.16	45	08	---

PM: Physical mixture, KN: Kneaded product

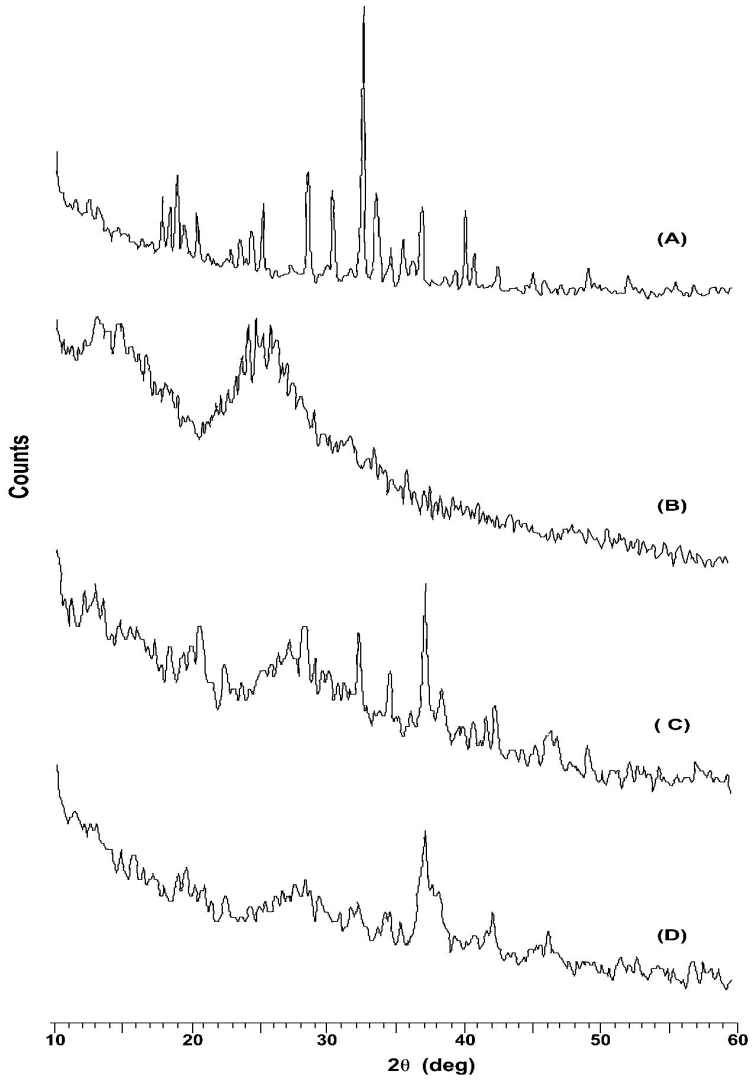


Fig. No. 4. XRD study of LX with HPβCD (A) LX, (B) HPβCD (C) Physical mixture (D) Inclusion complex

Fourier transformation-infrared spectroscopy (FTIR)

Fig. 5 demonstrates the FTIR spectra of LX with HPβCD in 1:1 molar ratio. LX (fig 5A) showed peaks at 1546 and at 1594 cm^{-1} due to bending vibration (N-H) of secondary amide, peak at 3067 cm^{-1} (N-H stretching vibration), strong absorption peak at 1646 cm^{-1}(c-o stretching vibration) of primary amide. Some peaks appeared at 1146, 1382 cm^{-1} due to stretching vibrations of the 0=S=0. Peaks appeared at 830cm^{-1} showed bending vibration (CH aromatic ring). The FTIR spectra of the CD (fig 5B) illustrated intense broad absorption bands at 3,800–3,100 cm−1 corresponding to the free –OH stretching vibration. The vibration of the –CH and $–CH_2$ groups appeared in the region 2,950–2,600 cm^{-1}. A shorter band appeared in the region 1,500–1,200 cm^{-1} that could be ascribed to the hydrated bonds within CD molecules. Another large band assigned to the C–O–C stretching vibration occurred between 1,200 and 1,030 cm^{-1}. The FTIR spectra of the investigated physical mixtures (fig 5C) did not show any significant shifts with respect to the FTIR spectra of the components and, in particular, the characteristic carbonyl stretching and the N–H bending of LX However, the same band was diminished in the case of the LX–HPβCD kneaded product (fig 5D) when compared to the corresponding physical mixture, suggesting interaction of the drug with the HPβCD molecule.

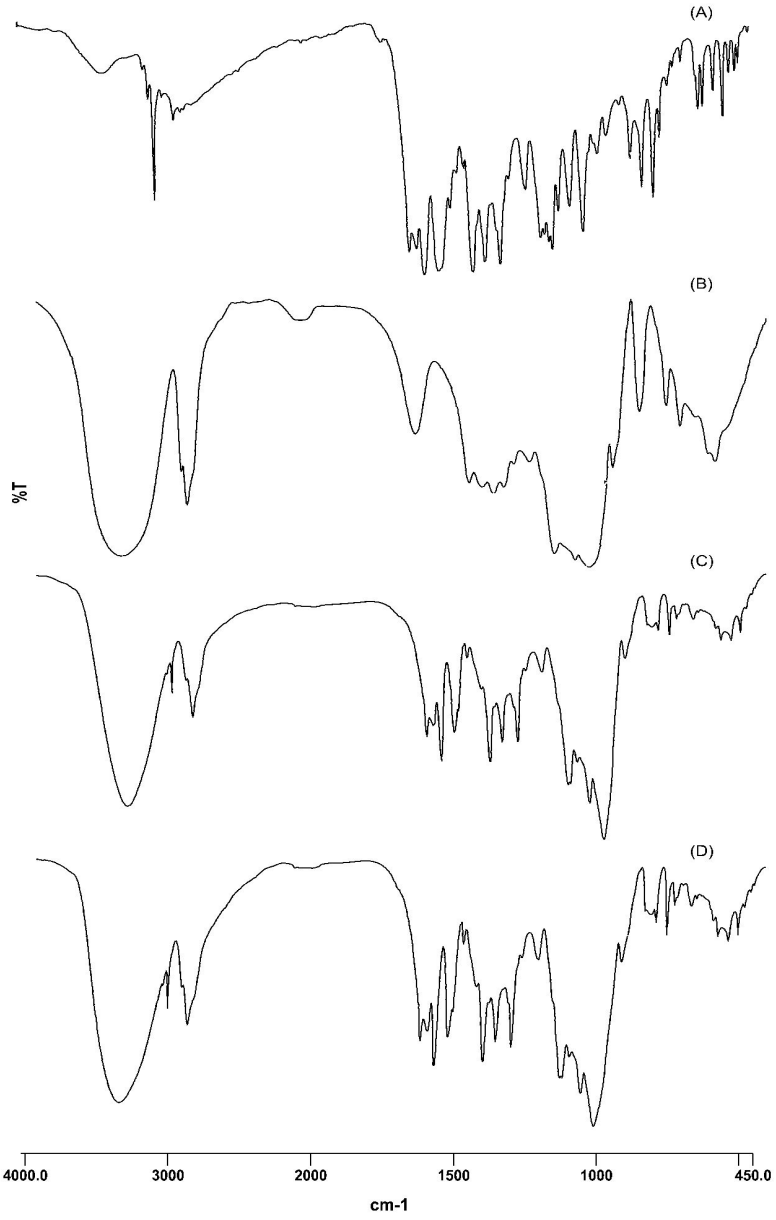


Fig. No. 5. FTIR spectra of LX-HPβCD systems (A) LX, (B) HPβCD, (C) physical mixture, (D) inclusion complex

Saturation solubility studies

All prepared binary systems showed enhancement in the solubility (table 2) compared to pure drug alone especially kneaded product showed 7994% enhancement in solubility compared to pure drug. The reason behind this significant improvement in solubility could be due to greater hydrophilicity provided by the HPβCD improving wettability of the drug, simultaneous reduction in crystallinity of drug due to kneading process and formation of stable inclusion complex with HPβCD.

Table 2. Solubility study of LX with HPβCD in distilled water

System	Solubility in water at 25°C (mg/ml)
LX	0.000861
Physical mixture	0.0438
Kneaded product	0.0689

***In-vitro* dissolution study:**

The *in-vitro* dissolution curves of the LX, physical mixture and Kneaded product are shown in Fig. 6. The release rate profiles were expressed as % drug released (Vs) time (min). The dissolution time of LX from physical mixture and inclusion complex were determined and $t_{90\%}$ values are reported in table 3 compared to pure LX alone.

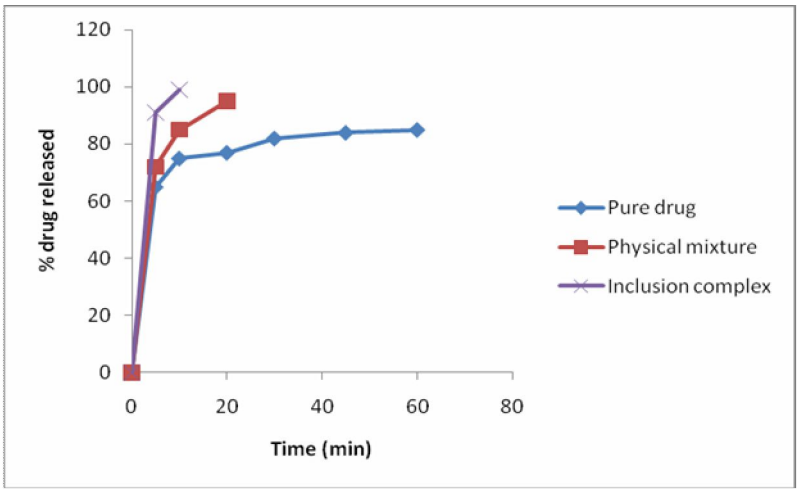
Table 3. The dissolution time of LX-HPβCD binary systems in phoshphate buffer pH 7.4 at 37± 0.5°C

Sample source	Dissolution time (min) $t_{90\%}$
LX	>60
Physical mixture	15
Kneaded product	<5

The dissolution rate of kneaded product was higher compared to its physical mixture and the pure drug alone. The dissolution profile of the kneaded complex showed 90% drug released in less than 05 min while that of the physical mixture and pure drug showed in 15 min and >1h respectively. This enhanced dissolution rate could be due to higher wetting property and hydrophilicity provided by HPβCD.

CONCLUSION

Prepared solid state inclusion complex of LX with CD which was confirmed by using DSC, XRD and FTIR studies revealed the formation of 1:1 stable inclusion complex which helps to enhance the dissolution rate of LX, a rate limiting step for absorption of poorly water soluble drug. Such signicant enhance in dissolution rate further causes faster onset of action which will helpful in case of reliving the pain.



[a]mean ± SD, n=3

Fig. No. 6. Dissolution rate study for LX-HPβCD binary systems at 37 ± 0.5 °C

ACKNOWLEDGEMENT

The authors are thankful to Principal, Govt. College of Pharmacy, Karad for providing necessary facilities and constant encouragement. The authors are thankful to Shivaji University, Kolhapur, Maharashtra, India for providing FTIR and XRD facilities. The authors are also thankful to Principal, SGVM'S College of Pharmacy, Panchavati, Nashik, for providing DSC facilities.

REFERENCES

1. Homdrum E.M., Likar R., Nell G. X., Rapid: a novel effective tool for pain treatment, Eur. Surg., 2006, 38, 342-52
2. Kidd b., Frenzel W., A multicenter, randomized, double blind study comparing lornoxicam with diclofenac in osteoarthritis, J Rheumatoid, 1996, 23, 1605-11
3. http://www.rxlist.com
4. Horter D., and Dressman J. B., Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract, Adv. Drug Deliv. Rev., 1997, 25, 3–14.
5. Hong-Hao Zhou, Effect of the CYP2C9*3 allele on lornoxicam metabolism, Clinica Chimica Acta**,** 2006, 364, 287 – 291.
6. Schott H., Kwan C. L., and Feldman S., The role of surfactant in the release of very slightly soluble drugs from tablets, J. Pharm. Sci., 1982, 71, 1038–1045.
7. Hancock B. C, and Zografi G.. Characteristics and significance of the amorphous state in pharmaceutical systems, J. Pharm. Sci., 1997, 86, 1–12.
8. Chiou W. L., and Riegelman S., Pharmaceutical applications of solid dispersion systems, J. Pharm. Sci. 1971, 60, 1281–1302.
9. Christian L., and Dressman J., Improving drug solubility for oral delivery using solid dispersions, Eur. J. Pharm. Biopharm., 2000, 50, 47– 60.
10. Serajuddin A. T. M., Solid dispersion of poorly water-soluble drugs: Early promises, subsequent problems, and recent breakthroughs, J. Pharm. Sci. 1999, 88, 1058–1066.
11. Veiga F., Teixeria-Dias J. J. C., Kedzeierewicz F., Sousa A., and Maincent. P., Inclusion complexation of tolbutamide with β- cyclodextrin and hydroxypropyl-β-cyclodextrin., Int. J. Pharm., 1996, 129, 63–71.
12. Higuchi T, Connors K.A., Phase-solubility techniques. Adv AnalChem Instr., 1965, 4, 117–212.
13. Fernandes C. M., Vieira M. T., and Veiga F. J. B., Physicochemical characterization and in vitro dissolution behavior of nicardipine– β-cyclodextrins inclusion compounds, Eur. J. Pharm. Sci., 2002, 15, 79–88.
14. Fernandes C. M., Teresa V.M., Veiga F.J., Physicochemical characterization and in vitro dissolution behavior of nicardipine–cyclodextrins inclusion compounds, Eur J Pharm Sci., 2002, 15, 79–88.
15. Badr-Eldin S.M., Elkheshen S.A., Ghorab M.M., Inclusion complexes of tadalafil with natural and chemically modified β cyclodextrins. I: preparation and in-vitro evaluation, Eur J Pharm Biopharm., 2008, 70, 819–27.

*****