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Influence of β-Cyclodextrin Complexation on Ketoprofen Release from Matrix Formulation

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ABSTRACT
The main objective of this study was to improve the inclusion formation between Ketoprofen and β-cyclodextrin and thus enhance dissolution profile and bioavailability of the ketoprofen. Solubility studies demonstrated the formation of the ketoprofen-β-cyclodextrin inclusion complex with 1:1 stoichiometry. Equimolecular ketoprofen-β-cyclodextrin solid systems were prepared and characterized by DSC, FTIR and hot stage microscopy. Modification of the release of a ketoprofen from the hydrophilic matrices using cyclodextrin complexes was evaluated. The controlled release matrix tablets for the delivery of the ketoprofen were prepared by the direct compression using hydroypropylmethyl cellulose K100M. The tablets are further evaluated for their dissolution characteristics and swelling characteristics. *In vitro* release results demonstrated that matrix tablets containing the ketoprofen- β-cyclodextrin (KTPF-CD) solid complex displayed faster Ketoprofen release compared to those containing a mixture of physical mixture or "free" drug. Differences in the release profile of ketoprofen from the tablets could be attributed to the presence of the polymer and β-cyclodextrin complexation. The effect of polymer on ketoprofen release can affect the drug solubility (complexation) and polymer water uptake (swelling). Higher polymer water uptake may result in higher drug solubility and diffusivity in the hydrated polymeric environment.

Keywords: Ketoprofen; β-cyclodextrin; complexation; hydroypropylmethyl cellulose K100M; In vitro release; matrix tablets.

INTRODUCTION

Over recent years, cyclodextrin and their derivatives have received considerable interest in the pharmaceutical field due to their potential to form complexes with a variety of drug molecules. [1-2] Naturally occurring β-cyclodextrin (β-CD) is a cyclic oligosaccharide of seven glucose units which is the product of the enzymatic degradation of starch by *Bacillus macerans*. The physiochemical properties of the cyclodextrin are particularly well suited for utilization as carrier molecules of lipophilic drugs. Their structures are analogous to truncated cone with a hydrophilic interior and hydrophilic exterior. This allows the molecular encapsulation of hydrophilic portion of guest molecules, thus shielding them from the polar forces of aqueous solutions. Cyclodextrin interact with some hydrophilic molecules and form a non-covalent inclusion complex that lower the chemical potential of the molecule in solution and thus enhance the solubility of the molecule.

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Pharmaceutical modification of the drug molecules by inclusion complexation with cyclodextrin (CDs) has been extensively developed to improve solubility, dissolution rate, chemical stability, absorption, and bioavailability of the poorly water soluble drugs, and reduce side effect and toxicity of the drug. [3-5]

The incorporation of cyclodextrin into the polymeric drug delivery systems can influence the mechanism by which drug is released. They have potential to enhance drug release by increasing the concentration of diffusible species within the matrix. On the other hand, they may also enhance drug release by acting as channeling or wicking agent or by promoting erosion of the matrix. [6-7] Possible of in situ formation of a drug- cyclodextrin complex, and an improvement in apparent drug solubility, has been suggested by some authors. Nevertheless, it is difficult to evaluate whether both free and complexed drugs are capable of diffusing from the matrix. [8]

Apart from the complexing agent, hydrophilic matrices have attracted considerable attention as controlled drug delivery devices. Various types of polymers can be used in the hydrophilic matrix and the hydration of these polymers

results in the formation of outer layer that controls drug release. Hydroxypropyl methylcellulose, the nonionic cellulose ether, is commonly used in the formation of hydrophilic matrix systems. On the other hand other grades of hydroxypropyl methylcellulose have also attracted interest in their use in controlled drug delivery. However, formulation of poorly water-soluble drugs into matrix tablet may result in incomplete delivery of the drug because of the limited drug solubility and dissolution rate within the matrix. Drug carrier systems such as drug-cyclodextrin complexes incorporated in hydrophobic matrixes could provide controlled and complete *in vitro* drug release. [9-10]

Ketoprofen is widely used as non-steroidal anti-inflammatory, analgesic and in the treatment of rheumatoid arthritis. Previous studies showed that the dissolution properties of Ketoprofen a scarcely water soluble, can be improved by complexation with both native and chemically modified β-cyclodextrin. Moreover, an enhancement of Ketoprofen bioavailability has been reported as directly related to its higher dissolution release rate due to the presence of the cyclodextrin carrier. Since both the nature of the cyclodextrin (native or chemically modified, crystalline or amorphous) and the method of complex preparation may play a role in drug solubilization oral Ketoprofen administration is characterized by slow absorption because the drug is poorly water soluble. Molecular complexation of Ketoprofen with β-cyclodextrin improves the drug solubility, and it could be therefore expected to hasten Ketoprofen absorption, resulting in a faster onset of action. Adverse effect such as gastric intolerance associated with conventional drug administration has prompted researchers to investigate the feasibility of alternative drug delivery systems. Consequently, there is considerable interest in developing a new ketoprofen formulation with better gastrointestinal tolerability. Therefore, the aim of the present work was to study the complexation of Ketoprofen with β-cyclodextrin, and to develop a controlled release matrix formulation for the oral administration of ketoprofen. [11-15]

MATERIAL AND METHODS

Materials

Ketoprofen was received as a gift sample from BEC Chemical Ltd (Mumbai, India). B-cyclodextrin was obtained from Lupin research park (Pune, India) and Hydroxypropyl methylcellulose was supplied by Colorcon Asia Pvt Ltd. (Goa, India). All other materials and reagents used were of analytical reagent grade.

Phase solubility study (Inclusion complex of Ketoprofen)

The solubility measurements of Ketoprofen with β-cyclodextrin were performed according to Higuchi and Connors T.A., 1965. Excess amounts of drug were added to an aqueous solution containing various concentrations of cyclodextrins, and were shaken (300 rpm) at 25±0.5°C. At equilibrium after 2 days, the supernatant was filtered (0.45 µm pore size), suitably diluted with 0.1 N HCl spectrophotometrically assayed for drug content at 254.6 nm using a Shimadzu UV/Vis Spectrophotometer. Each experiment was carried out in triplicate. The apparent 1:1 binding constants of the KTPF-CD complexes were calculated from the slope and intercept of the straight lines of the phase-solubility diagrams, according to the following equation;

Kc = slope/So (1-slope)…….. (1)

Where Kc is the apparent binding / stability constant, and so (intercept) is the intrinsic solubility of the compound in absence of complexing agent.

Preparation of Ketoprofen β-cyclodextrin (β- CD) complexes

KTPF-β-CD complexes was prepared in 1:1 Ketoprofen to β-cyclodextrin molar ratio, based on the results of the solubility studies, as described by Vavia P.R. et al (1999).

Physical mixture

Ketoprofen and β-cyclodextrin (β- CD) in 1:1 molar ratio were homogeneously blended in glass mortar for 1 hour and passed through # 100, dried and finally stored in a desiccator.

Kneading Method

Weigh Ketoprofen and β-cyclodextrin (β-CD) in 1:1 Ketoprofen β-cyclodextrin molar ratio were homogeneously blended in glass mortar thoroughly and wetted with water: ethanol (1:1 v/v, 3 ml) solution, and kneaded thoroughly for 45 min, formed paste, was dried under vacuum at 45°C for two day. The dry mass was pulverized and sieved through # 100.

Co- precipitation method

Ketoprofen solution was added drop wise to aqueous β-cyclodextrin solution, with constant stirring. After complete addition, the mixture was maintained at 45°C for 2 h with stirring. The co-precipitated mixture was then evaporated on a water bath at 60°C for 8 h, and further dried under vacuum at 60°C for 24 h. The dries mass was pulverized and sieved through # 100.

Differential scanning calorimetry studies (DSC)

Perkin Elmer DSC model 7 was used for recording DSC thermograms of the ketoprofen, ketoprofen inclusion complexes and its physical mixtures. The instrument was calibrated with indium and zinc prior to analyzing the samples under nitrogen. Samples (2-4 mg) were accurately weighed and sealed hermetically in flat-bottomed open aluminum cells, at a rate of 10°C/min between a temperature range of 50°C-250°C, under a nitrogen flow of 40 ml/min,. Reproducibility was checked by running the sample in triplicate.

Fourier transforms infrared (FTIR) spectroscopy studies

FTIR spectra were recorded using FTIR spectrophotometer (Shimadzu FTIR-8700). The spectra were recorded for Ketoprofen, β-cyclodextrin, its physical mixtures, and solid inclusion complexes. Samples were prepared by the potassium bromide disc method (2 mg sample in 200 mg potassium bromide). The scanning range was 4000-370 cm^{-1}.

Hot stage microscopy studies (HSM) studies

The hot stage microscopy (HSM) study was carried out using Microtek CMI 2000. A small amount of Ketoprofen β-cyclodextrin complexes was heated 30°C-300°C in temperature range at a rate of 2°C/min, and analyzed under microscope.

Preparation of matrix formulations

Controlled release tablets were prepared by directly compressing a mixture containing either pre-complexed Ketoprofen- β-cyclodextrin complexes powder or a simple mixture of Ketoprofen and β-cyclodextrin in a similar proportion. Four formulations were fabricated with difference in their inclusion complex preparation methods. All formulations contains complexes equivalent to 75 mg Ketoprofen, free or in complex form. Formulation I contain Ketoprofen without complex and other formulation 2, 3 and 4 contains inclusion complex prepared with Physical mixture, kneading method and Co-precipitation method respectively.

All formulations have hardness value of 3-5 kg/cm^2. A single punch Royal artist (Mumbai, India) machine, equipped with flat 14 mm punches was employed. Total four formulations are prepared with Keto- β-cyclodextrin complexes and pure Ketoprofen.

Swelling studies

Water uptake of the tablets ware determined gravimetrically in distilled water. The tablets were attached to pre-weighed glass support using cyanoacrylate adhesion sealant. The supports with the tablets were immersed into the 100ml distilled water at 37°C. After 5 h time, the devices were removed from the media, blotted to remove excess water and weight. Water uptake was calculated according to following equation:

$$I = \frac{Ws - Wd}{Wd} \quad \text{…….. (2)}$$

Where *I* denotes water uptake, *Wd* and *Ws* are the weights of the dry and swollen devices, respectively. The swelling rates were determined as the slope of plots *I* verses time.

Swelling of the matrices was also characterized in terms of the tablet dimensional changes during water uptake. The formulations were immersed in distilled water in horizontal direction to observe the swelling in the redial direction at ambient temperature.

In vitro dissolution studies

In vitro dissolution studies were carried out as per USP Pharmacopoeia using USP Dissolution test apparatus (UV 1201 Shimadzu, employing the round bottom dissolution vessel and rotating paddles basket assembly at 75 rpm using 900 ml buffer at 1.2 pH for 2 h and 7.4 pH buffer for 10 hours and temperature at 37°C±1°C. to avoid the adhesion of the hydrating tablets to the bottom of the dissolution vessel the apparatus was modified by the inclusion of stainless steal ring mesh devices in each vessel. Aliquot samples were withdrawn every hour up 12 h. After each withdrawal, the withdrawn amount of dissolution was replaced with buffer. The amount of drug release was determined using UV Spectrophotometer at 254.6 nm. The dissolution characteristics of each formulation were studied. The release studies for each formulation were conducted in triplicate.

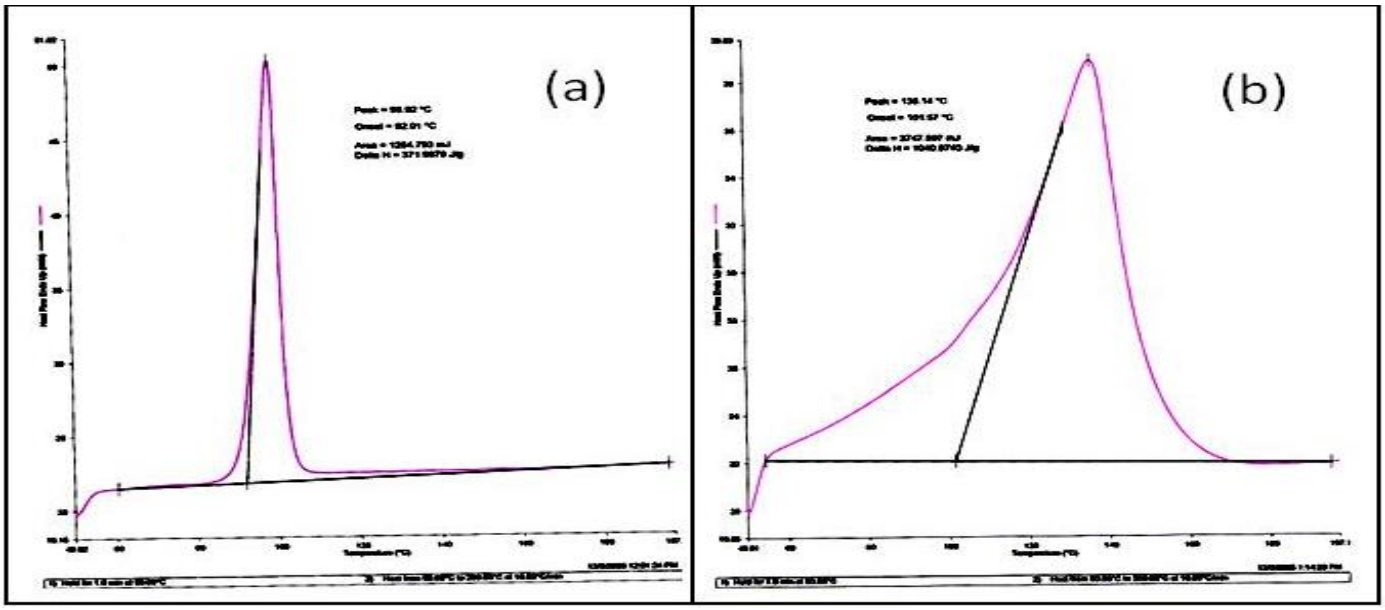


Fig. 1a: DSC Spectra of Ketoprofen (a) showing peak melting point at 98.9 °C and β-cyclodextrin (b) showing peak melting point at 136.14 °C

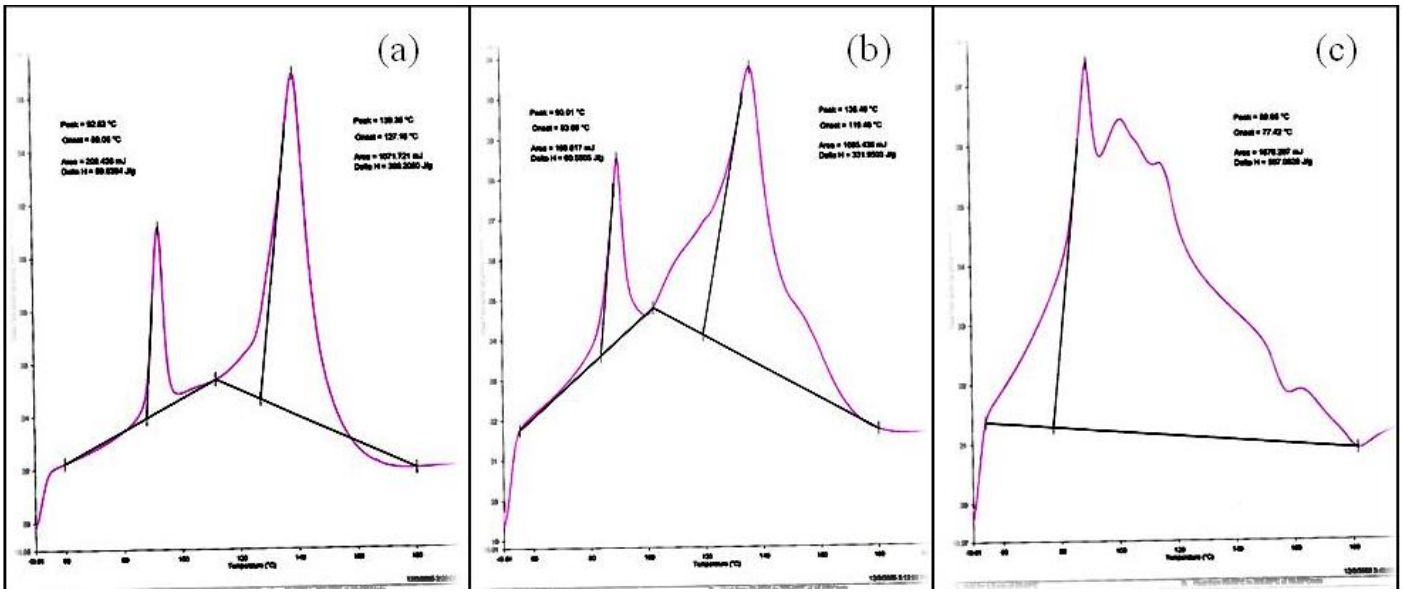


Fig. 1b: DSC Spectra of ketoprofen with β-cyclodextrin prepared by various methods: a. Physical Mixture, b. Kneaded Complex, c. Co-precipitated Complex

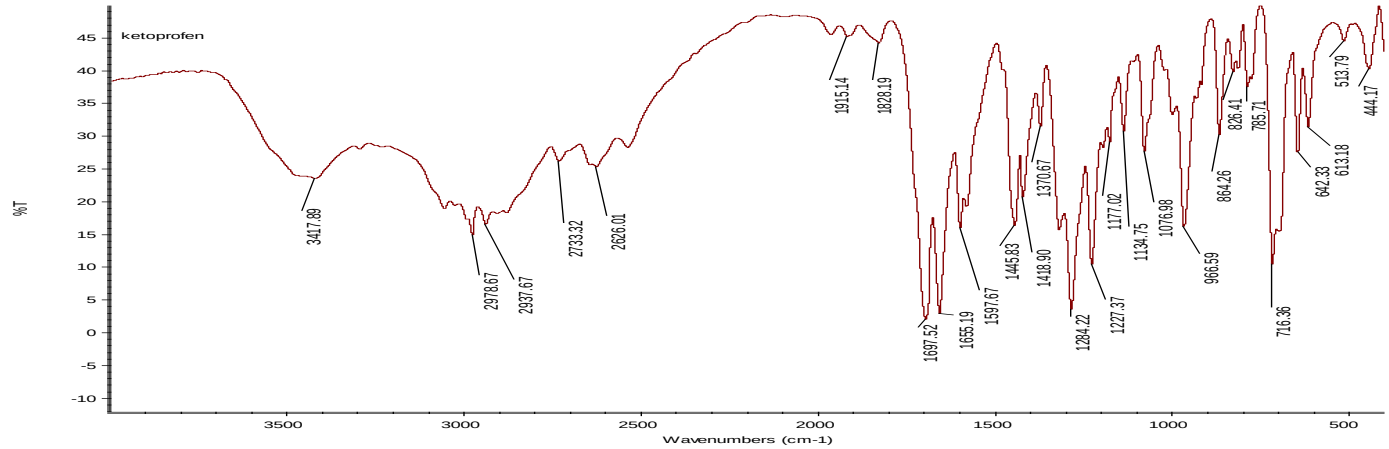


Fig. 2 (A)1: FTIR Spectra of Ketoprofen

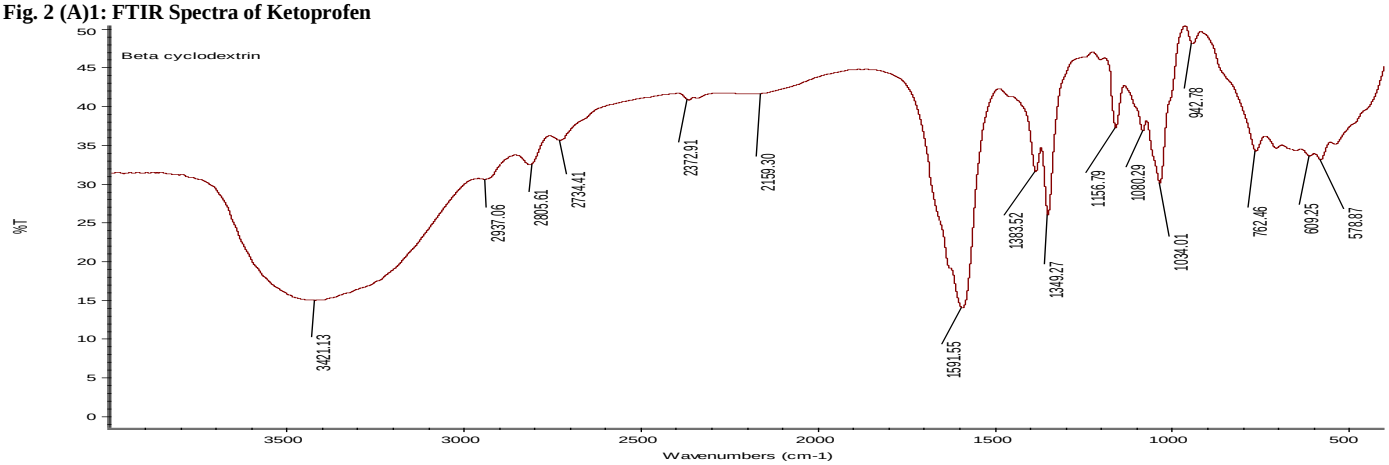


Fig. 2(A)2: FTIR Spectra of β-Cyclodextrin

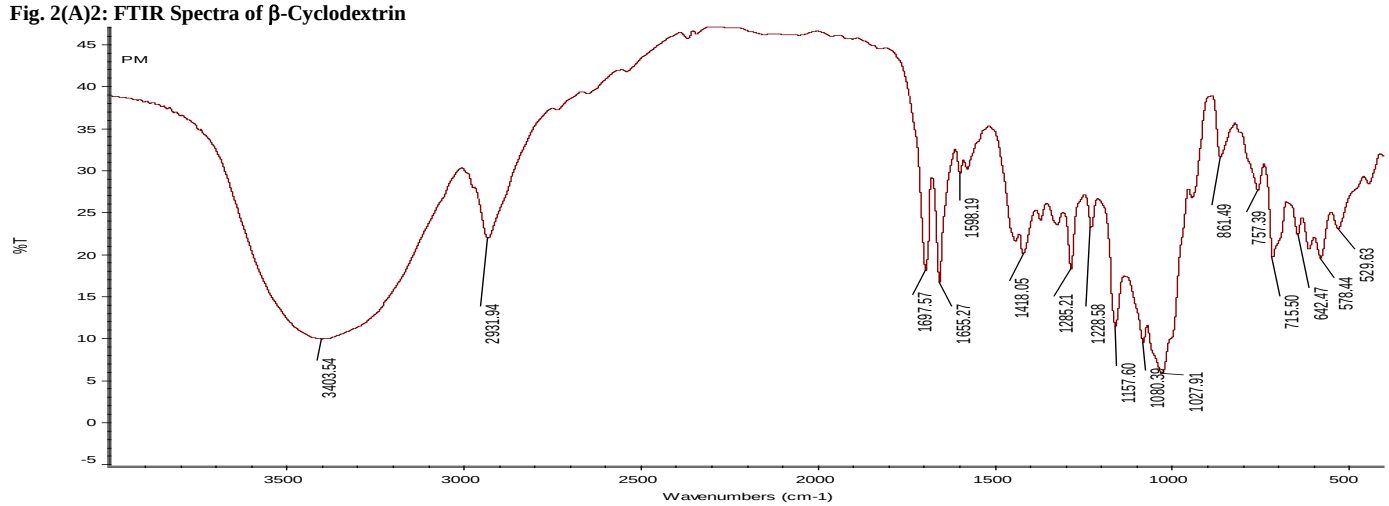


Fig. 2(B)1: FTIR Spectra of Physical Mixture

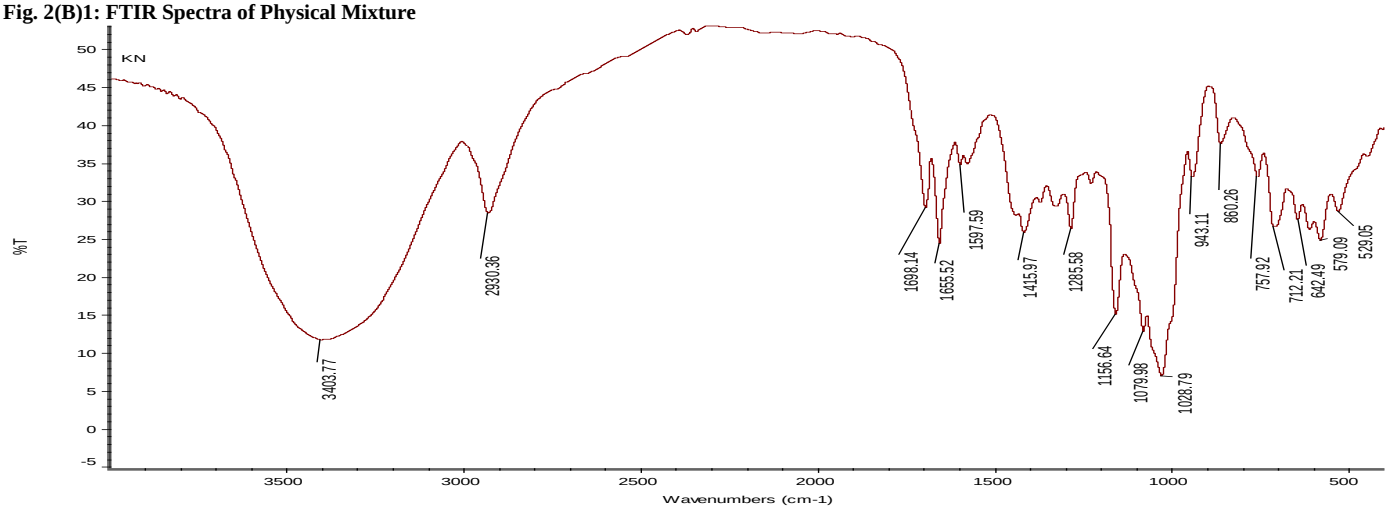


Fig. 2(B)2: FTIR Spectra of Kneaded Complex

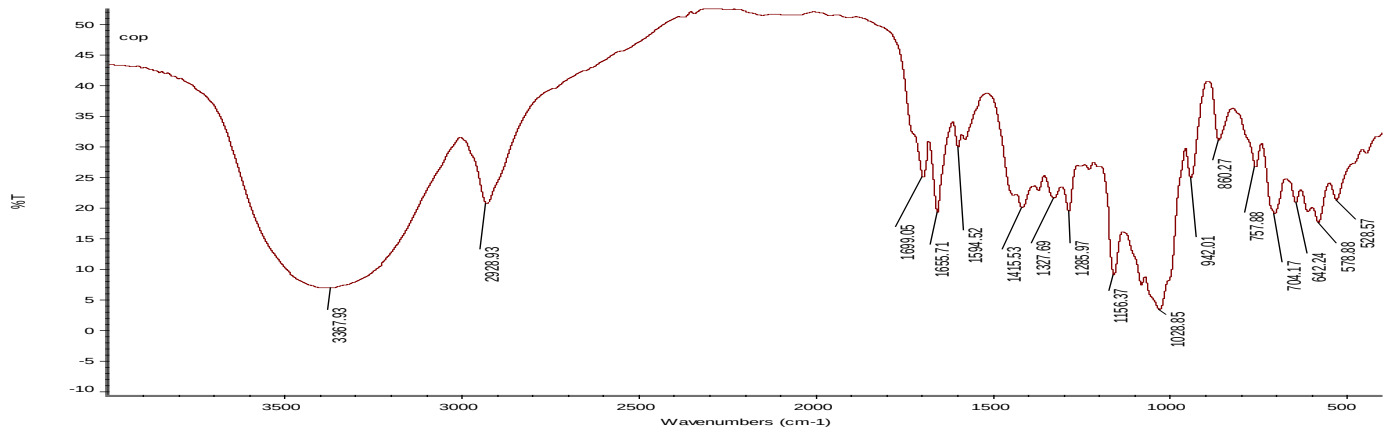
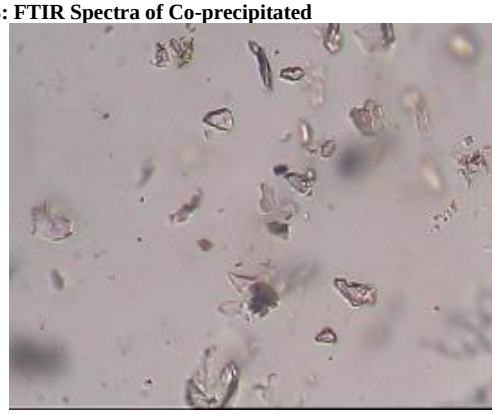
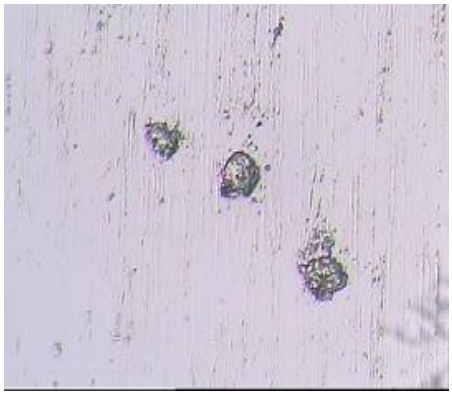


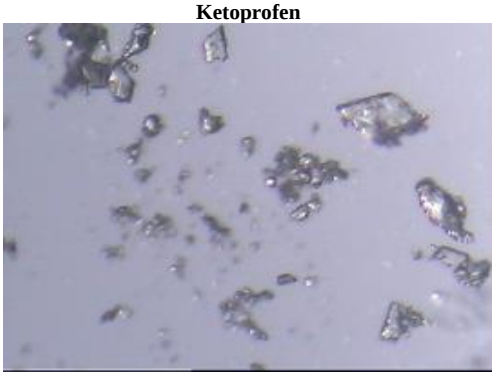
Fig. 2(B)3: FTIR Spectra of Co-precipitated



Ketoprofen



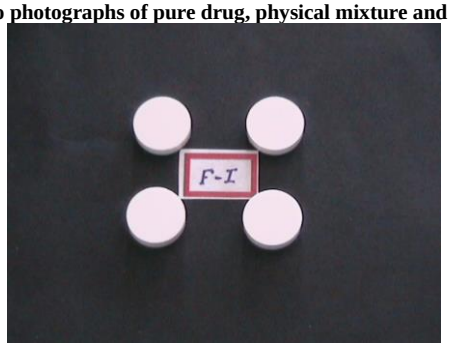
Physical Mixture

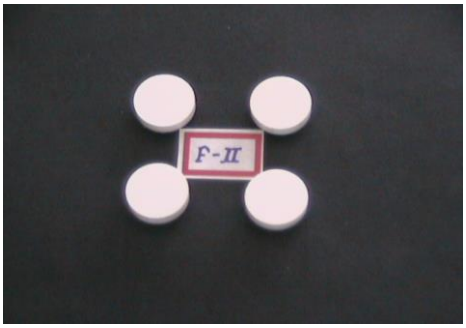


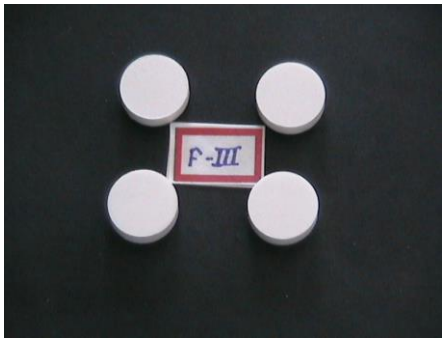
Kneaded Complex

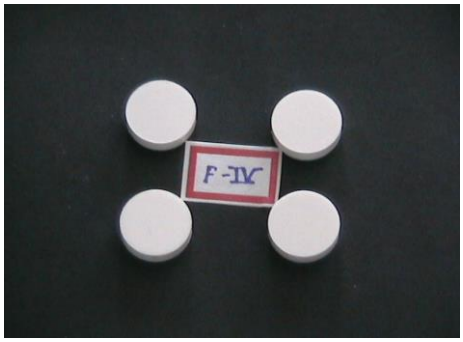
Co-precipitated Complex

Fig. 3: Micro photographs of pure drug, physical mixture and complexes









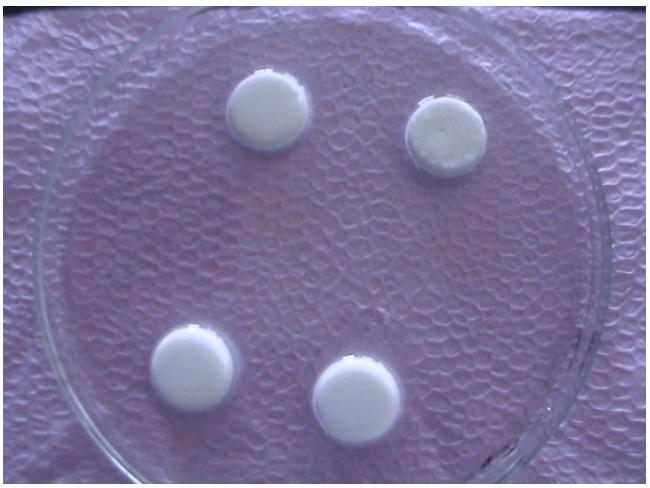


Fig. 4: Tablets of Different Formulations and Swelling of Tablet

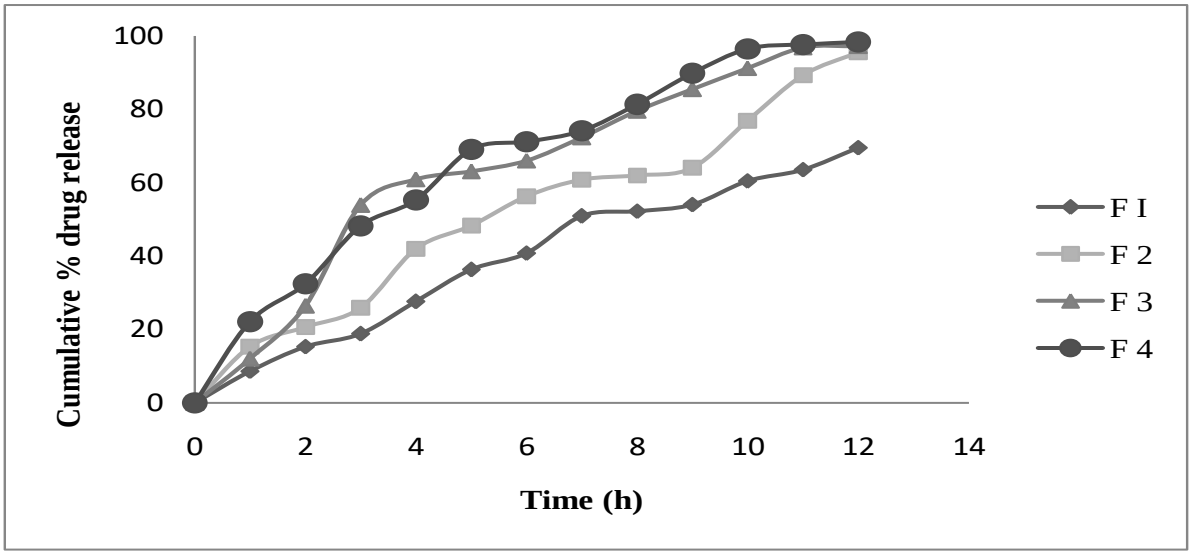


Fig. 5:Cumulative % release v/s Time curve for Formulation F1 to F4.

RESULTS AND DISCUSSION

Ketoprofen - β-cyclodextrin complexation characterization

Phase solubility Diagramme

Phase solubility diagrams obtained with β-cyclodextrin, showed a linear relationship between the amounts of Ketoprofen solubilized, and the concentration of cyclodextrin in solution (AL type diagram). According to Higuchi and Connors (1965), this may be attributed to the formation of soluble 1:1 KTPF-β-CD inclusion complexes. The interaction in solution between Ketoprofen and β-cyclodextrin has been already been investigated in depth by phase-solubility and C-NMR studies. [2] Therefore, in the present work, we devoted our research work to the solid state characterization of the different KTPF-β-CD inclusion complexes prepared.

Differential Scanning Colourimetry (DSC)

The thermal curve of the pure Ketoprofen, β-cyclodextrin (β CD) and their respective equimolar physical mixture, Kneading Product and Co- precipitation product are reported in Fig. 1. The thermal curve of the Ketoprofen obtained indicated its crystalline anhydrous state, exhibiting a sharp endothermal peak at 94.5°C, while β-CD showed a broad endothermal effect at 136°C, associated with water loss. Endothermic peaks of Ketoprofen and β-cyclodextrin is detectable at their corresponding endothermic points in case of physical mixture and Ketoprofen formulations. However, inclusion complex prepared with kneading method and co-precipitation method demonstrate disappearance of β-cyclodextrin peak and shifting of Ketoprofen peak indicating drug complexation.

The DSC curve of the physical mixture with β-CD (Formulation 2) was consisting of thermal profiles of Ketoprofen and β-cyclodextrin with no significant change in the peak, indicative of no drug- cyclodextrin interactions. A similar effect was also observed in mixture of β-CD with naproxen and attributed to reversible transformation of β-CD. DSC curve for the product obtained by Co-precipitation method showed a slight boarding of the endothermal peak for Keto at 89.86°C, indicative of Ketoprofen-β-CD interaction.

Fourier transform infrared (FTIR) spectroscopy studies

Infrared spectra of Ketoprofen, as well as those of its different complexes with β-CD, are presented in Fig. 2. Ketoprofen crystals show two carbonyl absorption bands at 1696 cm^{-1} and 1652 cm^{-1}, assigned to carboxyl carbonyl and ketonic carbonyl stretching, respectively. The characteristic acid carbonyl stretching band of the pure Ketoprofen appeared unchanged in formulations with β-CD, except co-evaporation ones where they were markedly decreased, probably as a consequence of inclusion complex formation. On the contrary, this band appeared shifted to higher frequency in the case of the products obtained by kneading. This effect can be attributed to the breakdown of the intermolecular hydrogen bonds associated with the crystalline drug molecules and the formation of hydrogen bonding of monomeric drug with β-CD. Taken together FTIR

and DSC analysis suggest strong interaction between Ketoprofen and β-CD in the solid complexes rather then in simple Physical mixture, probably as a consequence of KTPF-β-CD inclusion complexes.

Hot Stage Microscopy (HSM)

HSM analysis (Fig. 3) was carried out to confirm the formation and stability of the solid complexes and to supported the interpretation of DSC results, making it possible to detect in both simple blends, at around 94-99°C, the melting process of the characteristic drug polyhydric crystal; on the contrary, no fusion phenomena were observed at this same temperature in either kneading or co-precipitation formulations.

Evaluation of KTPF-β-CD inclusion complexes formulations

KTPF-β-CD inclusion complexed matrix tablets were prepared using HPMC K100M polymer. All the formulations contained the same amount of drug and soluble excipients (Table 1).

Swelling characteristics of matrix tablet

Swelling of the matrices was also characterized in terms of the tablet dimensional changes in the gel layer growth during water uptake. After 5 h of incubation in the distilled water the matrices displayed their original, although swollen, shape with slightly eroded surface. The initial surface area of all the formulation was varying from 1.2245 cm^{-1} to 1287 cm^{-1}. Swelling characteristics of HPMC based formulations indicate the tablet surface area increases with time (Table 2). The tablets formulated with HPMC rapidly absorb water and showed higher degree of swelling. This is because of polymer content and β-CD complexes, and the formation of strong gel is prerequisite for retarding drug release from gel matrix. Cyclodextrins have been suggested to act as penetration enhancers. They enhance the penetration of drug by carrying the drug through the aqueous barrier towards the surface of the membrane, where the drug passes from the complex in to membrane, addition of β-CD to the matrix increased flux by increasing the solubility of Ketoprofen, thus improving the diffusible form of the drug species at the tablet membrane interface. Through the complex did not penetrate the membrane, the drug in the complex was in rapid dynamic equilibrium with the free drug, thus continuously supplying the drug molecule to the membrane surface in the diffusible form (Fig. 4).

Dissolution Studies

Tablets were produced with 75 mg of Ketoprofen in order to assure sink condition in the dissolution testing. The hardness of all the tablets was quite similar (3-5 kg/cm^2). Figure 5 shows Ketoprofen and β-CD release for each of four formulations. Differences in the Ketoprofen release rate from the tablets can be attributed to the presence of polymers and cyclodextrin. In the formulation prepared, a zero order equation showed a significantly better fit then Higuchi's squire root of time equation (Table 3). The dissolution data were analyzed using the equation proposed by Korsmeyer [13]

$$Mt / M\infty = kt^n \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (3)$$

Where $Mt/M\infty$ is the fractional amount of drug release, at time t, k the release constant, and *n* is the diffusion exponent that characterized the type of release mechanism during the dissolution process. The values of *n* and k estimated by linear regression of log ($Mt / M\infty$) verses log time.

For non- Fickian release, the n values falls between 0.5 and 1.0, while in the case of Fickian diffusion n= 0.5, for zero-order release (case II transport), n= 1, and for supercase II transport n >1. The values of the release exponent, however, indicated that the release mechanism changed with the type of the method and presence of HPMC K100M, the values of n were nearly 0.5, which was indicative of Fickian release i.e. the drug release proceeded may be by diffusion-controlled mechanism and erosion of the polymer. [8]

In vitro dissolution profile of formulations showed faster Ketoprofen release rate in the case of kneading (formulation #3, F3) and the co-precipitation method (formulation #4. F4) as compared to the physical mixture (formulation#2, F2). This increase on Ketoprofen release is related to an improvement in its solubility, caused by KTPF-β-CD inclusion complexes. The hydroxypropyl methyl cellulose based formulations undergoes swelling and very slow erosion. The drug release was found to be 69.5, 95.5, 97.1, and 98.3 % in 12 hours for F1, F2, F3 and F4, respectively. It was found that drug release was complete and prolonged to desired level with KTPF-β-CD inclusion complexes; this may be due to different method used in complexation of drugs with β-CD, high concentration of polymer with buffering agent like Sodium carbonate and Sodium bicarbonate employed. When the dissolution media penetrate into swellable matrices, the particles of the polymer swell, modifying the matrix volume and behave according to the solubility of the loaded drug the characteristics of excipients. Buffering agents altered the formulation pH and made the drug more soluble in dissolution media. One can clearly observe the matrix tablets displayed dissolution profiles compatible with nearly zero-order kinetics in the interval 0-12 h, which is suitable for controlled release formulation.

The release of Ketoprofen from the tablets formulated with HPMC K100M (with β-CD complex) reached almost 60 % within 5hours. Release of the drug from the tablet formulated with Ketoprofen (without β-CD complex) was slower, with about 37 % of the drug release in 5 h. But, the drug was released from all the formulations in a constant mode. According to the Ketoprofen solubility determined by β-CD complexation and based on Higuchi and Connors finding [7], we may not rule out the in situ complexation occurs in the tablet containing simple physical mixture (formulation # 2) of Ketoprofen and β-CD. Physical mixture presented slower Keto release profile then the corresponding Kneading and Co-evaporation method formulations, but faster then pure Ketoprofen in absence of β-CD, which could denoted that the increase solubility on Keto solubility would related to the amount of complex formed in situ.

In the present work an enhancement of Ketoprofen solubility was obtained by its complexation with β-cyclodextrin. The incorporation of previously complexed with β-cyclodextrin influenced its dissolution profile. Formulations containing Co-precipitation or Kneaded Ketoprofen-β-cyclodextrin inclusion complexes presented faster dissolution rates compared to those containing simple physical mixtures. The analysis of Ketoprofen and β-cyclodextrin release in matrix tablets containing HPMC K100M demonstrates that diffusion throughout the matrix is the limiting step of Ketoprofen / β-cyclodextrin release. In this way, we demonstrated that β-cyclodextrin from the matrices was almost simultaneous to Ketoprofen release. This is the important finding once its points to the outlook for modulation of drug release and improvement on the bioavailability.

Table 1: Composition of Controlled Release Matrix formulation of Ketoprofen (in mg)

Ingredients (mg/tablet)	Composition of different formulations			
	F#1* (Ketoprofen only)	F#2** (Physical mixture)	F#3** (Kneading method)	F#4** (Co-precipitation method)
Ketoprofen (complex equivalent to 75mg)	-	322.5	322.5	322.5
Ketoprofen	75	-	-	-
HPMC K100M	150	150	150	150
Mannitol	-	97.5	-	97.5
Magnesium stearate	2	2	2	2
Sodium carbonate	20	20	20	20
Sodium bicarbonate	4	4	4	4
Talc	1	1	1	1

* weight of tablet – 350mg
** weight of tablet- 600mg

Table 2: Swelling Characteristics of Tablet Formulations.

S. No.	Formulation	Radius (cm)		Thickness (cm)		Surface Area (cm^2)	
		Before hydration	*After hydration*	*Before hydration*	*After hydration*	*Before hydration*	*After hydration*
1	F1	0.65	0.70	0.30	0.50	1.2246	2.198
2	F2	0.65	0.75	0.35	0.55	1.4287	2.5905
3	F3	0.65	0.80	0.35	0.70	1.4287	3.5168
4	F4	0.65	0.85	0.35	0.75	1.4287	4.0035

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REFERENCES

1. Mura P, Faucci MT, Parrini PL, Furlanetto S, Pinzauti S. Influence of the preparation method on the physicochemical properties of ketoprofen–cyclodextrin binary systems. International journal of Pharmamaceutics 1993; 179: 117–128.
2. Mura P, Bettinetti GP, Manderioli A, Faucci MT, Bramanti G, Sorrenti M. Interactions of ketoprofen and ibuprofen with b-cyclodextrins in solution and in the solid state. International journal of Pharmamaceutics 1998; 166: 89–203.
3. Koster LS, Juliana BB, Katia RG, Rosli M, Paulo M, Teresa DS, Valquiria LB. Bioavailability of carbamazepine:b-cyclodextrin complex in Beagle dog from hydroxypropyl methylcellulose matrix tablets. European journal of Pharmaceutics and Biopharmaceutics 2004; 22: 201-07.
4. Bibby DC, Devis NM, Tucker IG. Mechanisms by which Cyclodextrins modify drug release from polymeric drug delivery systems. International journal of Pharmamaceutics 2000; 197: 1-11.
5. Rao VM, Hasam JL, Stella VJ, Controlled and complete release of model poorly water- soluble drug, prednisolone, from hydroxypropyl methylcellulose metrix tablet using (SEB)7m - with β-cyclodextrin as solubilizing agent. Journal of Pharmaceutical Sciences; 90: 807-816.
6. Sangalli ME, Zema L, Maroni A, Foppoli A, Giordano F, Gazzaniga A. Influence of beta-cyclodextrin on the release of poorly soluble drugs from inhert and hydrophilic heterogeneous polymeric matrices. Biomaterials 2001; 22: 2647-2651.
7. Leticia SK, Clarissa RX, Paulo M, Valquiria LB. Influence of β-cyclodextrin complexation on carbamazepine release from hydroxypropyl methylcellulose matrix tablets. European journal of Pharmaceutics and Biophamaceutics 2003; 55: 85–91.
8. Mario J, Mira B. Influence of hydroxypropyl- β-cyclodextrin complexation on piroxicam release from buccoadhesive tablets. European journal of Pharmaceutical Sciences 2004; 21: 251–260.
9. Brunella C, Giuseppe DR, Lucia G, Maria I, Rotonda L, Giuseppe M, Agnes. M, Fabiana Q, Roberto R. Cyclodextrin-containing poly (ethyleneoxide) tablets for the delivery of poorly soluble drugs: potential as buccal delivery systems. International journal of Pharmamaceutics 2006; 319: 63-70.
10. Bettinetti GP, Mura P, Liguori A, Bramanti G, Giordano F. Solubilization and interaction of naproxen with cyclodextrins in aqueous solution and in the solid state. IL Farmaco 1989; 44: 195–213.
11. Vavia PR, Tayade PT. Inclusion complexes of Ketoprofen with β-cyclodextrins: Oral pharmacokinetics in human, Indian journal Pharmaceutical Sciences, March - April, 2006; 164-70.
12. Maestrelli F, Mari A, Mura P. Preparation and characterization of liposomes encapsulating ketoprofen-cyclodextrin complexes for transdermal drug delivery. International journal of Pharmamaceutics 2005; 298: 55-67.
13. Karsemeyer W, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of potassium chloride release from compressed, hydrophilic, polymeric matrices: Effect of entrapped air, Journal of Pharmceutical Sciences 1983; 72(10): 1189-1191.
14. Seoung W, Kim JM, Hee JP, Sibeum L, Jong-Soo W. Sung-Joo H. Preparation and characterization of simvastatin/hydroxypropyl-β-cyclodextrin inclusion complex using supercritical antisolvent (SAS) process. European journal of Pharmaceutics and Biophamceutics 2007; 66: 413–421.
15. Fangjing W, Gerald MS, Jinming G. A mechanistic model of controlled drug release from polymer millirods: Effects of excipients and complex binding. Journal of control release 2007; 119: 111–120.