Dissolution profile of ketoprofen cyclodextrin complex

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Abstract

Ketoprofen, 3-benzoyl-α-methylbenzeneacetic acid, is one type of non-steroidal anti-nflammatory drug and a weak acid poorly soluble in water. The effect of complexation Ketoprofen, a poorly water soluble non-steroidal anti-inflammatory drug (NSAID) with Cyclodextrins showed significant increase in dissolution profile with comparison a pure drug. Inclusion complexes were prepared by various methodologies i.e. co-precipitation, kneading etc, in molar ratio 1:1, 1:2, 1:3.

Key words: Ketoprofen, β-Cyclodextrins, HP-β-Cyclodextrins

Introduction

Cyclodextrins have been recognized as a group of useful pharmaceutical excipient [1-4]. They are cyclic oligosaccharides composed of dextrose units joined through 1-4 bonds. They and their derivatives have been widely used in drug delivery application due to their capability of forming inclusion complexes with drug molecules. The special confirmation of Cyclodextrin gives them the ability to include various guest molecules on the condition that their stearic hindrance is compatible with the cavity size of the host molecule. Their complexes are capable of altering the release pattern, changing the solubility and increasing the solubility of the drugs [5-7]. Cyclodextrins promote dissolution of sparingly soluble drugs. The uncharged cyclodextrins have larger solubilizing effect than charged cyclodextrins [8, 9].

Cyclodextrins have the capability to enhance the absorption of the complexed drug in the *in- vivo* system [10]. The mechanism of absorption enhancing effect of cyclodextrins and their derivatives have been suggested by Vekama *et.al.* Due to the possibility of cyclodextrins to affect drug absorption through modification of the mucosal membrane. β- Cyclodextrins (β-CD) are toroidally cyclic oligosaccharide of seven glucose units [11-13]. Studies involving inclusion of solute into cyclodextrins are important due to the resulting improvement of aqueous solubility, stability against chemical degradation and to the possibility of controlled drug released, which presents many potential applications in drug formulations. In addition, the possibility of solute inclusion leads to many other

interesting phenomena such as biomimatic systems, in relation to enzymes, in catalysis, separation of isomers (Chiral recognitions) among others [14, 15].

Materials and Methods

Ketoprofen obtained by BEC Chemicals Pvt. Limited, Mumbai, India. and β-Cyclodextrins (β-CD) and Hydroxy Propyl- β- Cyclodextrins (HP-β-CD) was obtained from HiMedia Laboratories Pvt. Ltd. Mumbai, India.

P_H: The PH of a $3.95X10^{-4}$ M solution in water is 6.5

Dissociation Constant: The pKa in dioxan: water (2:1) is 7.2, acetonitrile: water (3:1) are 5.02, methanol: water (3:1) is 5.937.

Partition Coefficient: The Partition Coefficient of Ketoprofen in an n-octanol/water (phosphate buffer pH 7.35 and initial Ketoprofen concentration of 0.2542 mg/ml in this) is 0.105 and the pH 7.4 (Macilvaine's buffer and initial Ketoprofen concentration of 0.0240mg/ml in this) is 0.97. At these pH's most of the Ketoprofen is ionized and thus an increase in the initial concentration of Ketoprofen in the buffer will cause an alteration in the Partition Coefficient

Ultraviolet Spectrum: The U.V. Spectra of Ketoprofen ($3.95X10^{-4}$m) was determined in 0.1N hydrochloric acid pH 1.2, Distilled water pH 6.5 and 0.1N Sodium hydroxide pH 12.9 solvents. The λ^{max} appears at 261 nm and corresponds to a K band. This maximum is independent of pH but the maximum absorbance is slightly decreased with increasing pH. The λ^{max} in methanol has been reported as 255nm and log € = 4.33. The λ^{max} in ethanol has been reported as 255nm.

Standard Plot

Take the 10mg of Ketoprofen in 100ml 0.1N HCl and heat it up to 60^0C. Prepared the different concentration of drug (10, 20, 30, 40 and 50 mcg/ml) in 0.1N HCl. Filter the solution through filter paper and observed by U.V. spectrometer. The λ^{max} was determined at 261nm.

Preparation of the cyclodextrin complexes of ketoprofen

Kneading Method: β-CD or HP-β-CD and Ketoprofen at a (1:1, 1:2 and 1:3 molar ratios) were wetted with ethanol (96 % V/V): distilled water (4:6) solution. It was kneaded to get a paste and then dried in a vacuum dissector for 4 hr.

Coprecipitation Method: Coprecipitation of Ketoprofen - β-CD or HP-β-CD (1:1, 1:2 and 1:3 mole ratios) were prepared by the solvent method using ethanol in a beaker with constant stirring at 60 0 C which were subsequently dried.

In order to study the effect of processing parameters, drug alone (without Cyclodextrins) was subjected (treated drug) to kneading or co-precipitation method before characterization.

Cyclodextrin Complexation Studies

Phase solubility studies

The phase solubility studies were carried out according to the method reported by Higuchi and Connors. About 10 mM solutions each of β-CD and HP- β-CD in water were

prepared with slight heating. Excess amount (10 mg) of Ketoprofen were weighted in to test tubes, to which were added appropriate volume of aques solution of β-CD or HP-β-CD (0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0 ml) and diluted with appropriate volume of distilled water to make final volume 2 ml to get final concentration of CDs in 1 mM – 10 mM range The suspensions so obtained was then shaken at 25±0.5 ^{0} C for 24 hr, to acquired solubility equilibrium. The aliquot was filtered through membrane filters and analyzed by U.V. Spectroscopy at λ^{max} 261.

Characterization of the inclusion complex and physical mixture

The NIR Fourier transform (FT) Raman spectra were recorded with a Bruker FT-106 Raman module, equipped with a Ge detector cooled by liquid nitrogen and connected to a Bruker FT-IR 66 interferometer. In order to excite the Raman signal, a continuous wave diode-pumped Nd:YAG Laser with a radiation of wavelength 1064nm (9398.4 cm-1) was used. In all cases, the laser power was 300mW and the spectral resolution 2cm-1. FT-IR spectra of the inclusion complex in solid state were obtained using Nujol mulls with infrared spectrophotometer (Perkin-Elimer Mod. 983).

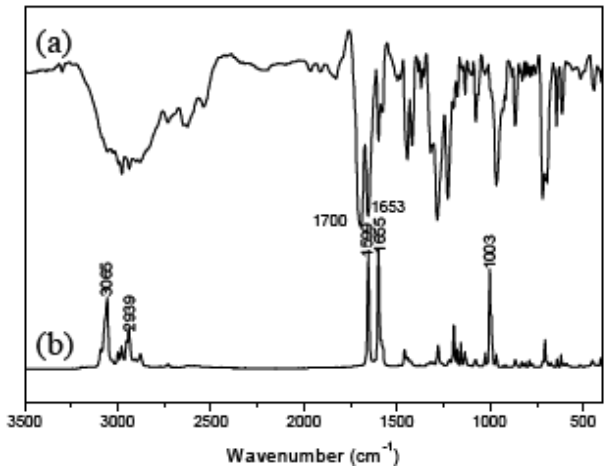

Fig.1 FT-Raman (a) and FT-IR spectra (b) of the ketoprofen.

In FT-Raman spectra, the νC=C stretching of the phenyl group in ketoprofen was recorded at 1595 cm-1 and 1655 cm-1, respectively. In a previous paper, 7, 8 the νC=C stretching of phenyl group onto pure *o*-, *m*-, and *p*-nitrophenol were at 1587, 1595, and 1586 cm-1, respectively. The νC=C stretching of phenyl group onto pure 2-, 3-, and 4-chlorostyrene were at 1593 cm-1. In order to assign νC=C stretching at 1655 cm-1, the terephthalic acid (TPA) and 2-phenylpropionic acid (2-PPA) were recorded by FT-Raman spectroscopy. One νC=C stretching of phenyl group in a pure TPA was recorded at 1610 cm-1. Two νC=C stretching of phenyl group in a pure 2-PPA were recorded at 1605 and 1630 cm-1, respectively. In a previous paper,6 the νC=C stretching of phenyl group in a pure loxoprofen was assigned at 1611cm-1. From the results, the νC=C stretching at 1595 and 1655 cm-1 due to aromatic C=C stretching and cyclic C=C stretching was considered as shown Scheme I. In the 2950-3150 cm-1 region, pure ketoprofen gives three types: namely ν CH=, ring ν CH, and asymmetric ν =CH, respectively. According to results of the previous study,6 the ring νCH at 3065 cm-1 due to phenyl group was assigned.

In IR spectra of the Fig. 1 (b), the keton C=O stretch and carboxylic acid C=O stretch was assigned at 1700 cm-1 and 1650 cm-1, respectively. Carboxylic acids were similar to alcohols and water in that they all contain the O-H group. This structural unit was responsible for hydrogen bonding, and carboxylic acids were so strong that that the acid molecules were bounded together in dimers when in solid.

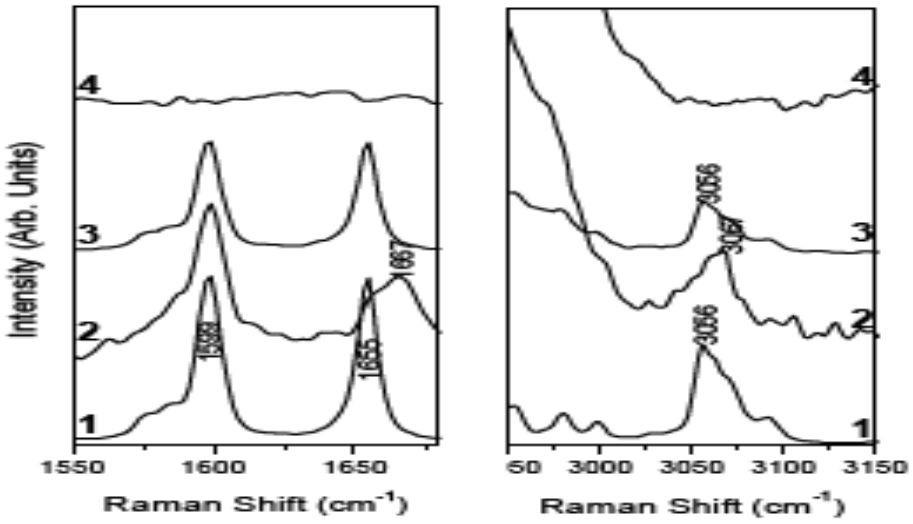

Fig.2 FT-Raman spectra of the ketoprofen in the solid state.

1, pure ketoprofen; **2,** ketoprofen included in β-CD; **3**, physical mixture of ketoprofen and β-CD (1/1, mol-%); **4,** pure β-CD.

Fig.2 shows the FT-Raman spectra of the ketoprofen, for the 1550-1680 cm-1 and 2950-3150 cm-1, in the solid state. **1**, pure ketoprofen; **2**, ketoprofen included in β−CD; **3**, physical mixture of ketoprofen and β−CD (1/1, mol-%); **4**, pure β−CD. In 1550-1680 cm-1, the νC=C peak of phenyl group onto β−CD inclusion complex was shifted to higher wavenumber, and the FWHM intensity of νC=C peak was increased compare to that of pure ketoprofen. On the other hand, the νC=C stretching of physical mixture was not changed. These results clearly indicated that the phenyl group was included in hydrophobic cavity of β−CD. In 2950- 3150 cm-1, the νCH peak of β−CD inclusion complex was shifted to higher wavenumber, whereas the physical mixture was not changed. From the results, the phenyl group of ketoprofen was included in hydrophobic cavity of β−CD.

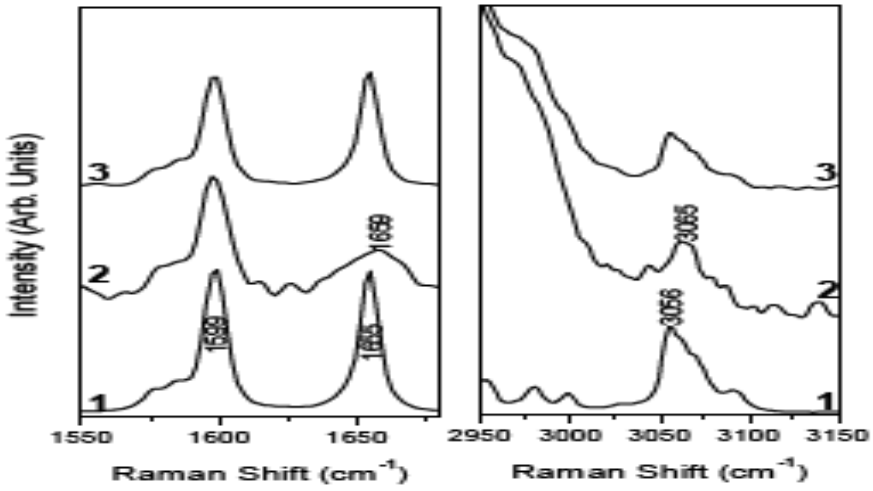

Fig. 3. FT-Raman spectra of the ketoprofen in the solid state.

1, pure ketoprofen; **2**, ketoprofen included in HP-β-CD; **3**, physical mixture of ketoprofen and HP-β-CD (1/1, mol-%)

Fig. 3 shows the FT-Raman spectra of the ketoprofen, for the 1550-1680 cm-1 and 2950-3150 cm-1, in the solid state. **1**, pure ketoprofen; **2**, ketoprofen included in HP β−CD; **3**, physical mixture of ketoprofen and HP β−CD (1/1, mol-%); **4**, pure HP β−CD. In 1550-1680 cm-1, the νC=C peak of phenyl group onto HP β−CD inclusion complex was shifted to higher wavenumber, and the FWHM intensity of the νC=C peak was remarkably increased compared to that of a pure ketoprofen. However, the νC=C stretching of phenyl group in physical mixture (**3**) was not changed. In 2950- 3150 cm-1, the ring νCH peak of HP β−CD inclusion complex was shifted to higher wavenumber, whereas the physical mixture was not changed. From the results, the phenyl group of ketoprofen was included in hydrophobic cavity of HP β−CD.

Dissolution studies

The dissolution studies were carried out as per basket method of USP specified for Ketoprofen capsule. The method is briefly summarized here. 900 ml of 0.1 N HCl was used as dissolution medium. Ketoprofen, physical mixture or complex powder of different molar ratio equivalent to 50 mg of Ketoprofen filled in capsule and placed in basket for dissolution. The studies were carried out at 37^0 C at 75 rpm. The dissolution was performed for 2 hours and sample was withdrawn at a time intervals (5, 10, 20, 30, 45, 60, 90, 120 minutes) and filtered through filter paper and analyzed by U.V. Spectrophotometer.

Table 1: Standard curve for the pure Ketoprofen

Concentration(µg/ml)	Absorbance
10	0.159
20	0.302
30	0.441
40	0.585
50	0.738

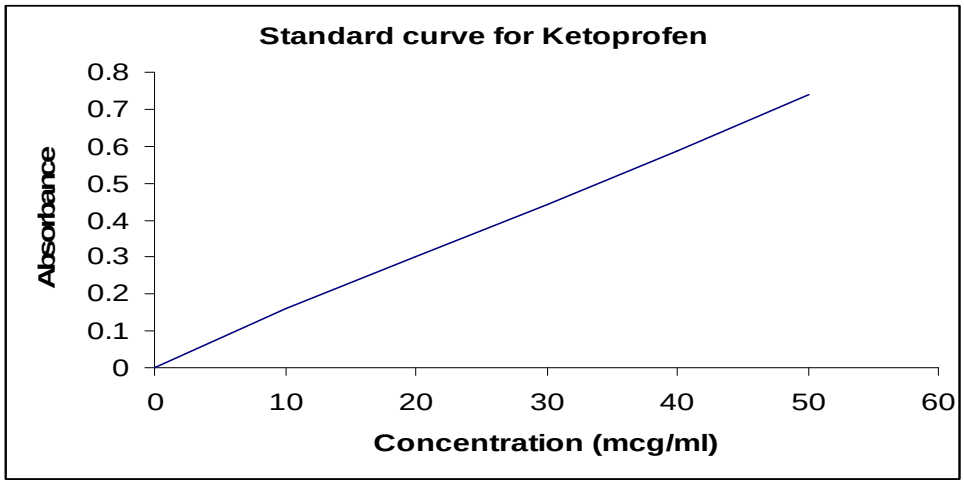

Figure 4. Standard curve for Ketoprofen

Results and Discussion

The λ^{max} appears at 261 nm and corresponds to a K band. This maximum is independent of pH but the maximum absorbance is slightly decreased with increasing pH.
The phase solubility plot of Ketoprofen in the presence of β-CD and HP- β-CD in water at 25^0C showed. In the phase solubility study solution were shaken for 24 hours and analyzed immediately contrary to 48 hours shaking followed by 7 days equilibrium. Further the U.V. Spectroscopy based analytical methodology used. In order to visualize a similar case we summed molar amounts of Ketoprofen against β-CD and HP- β-CD concentration. Initially the apparent solubility of Ketoprofen is increased with increasing concentration of β-CD and HP- β-CD.

Dissolution studies

The dissolution profile of Ketoprofen and Ketoprofen complexes is shown in figure 11. The dissolution profile of most of systems reached a plateau phase with in 30 minutes.

Table 2: % Cumulative amount of drug release from drug: polymer complex:

Time (min)	Pure KTF %	KTF:β-CD (1:1 ratio) %	KTF: β-CD (1:2 ratio) %	KTF:β-CD (1:3 ratio) %	KTF: HP-β-CD (1:1 ratio) %	KTF: HP-β-CD (1:2 ratio) %	KTF: HP-β-CD (1:3 ratio) %
0	0	0	0	0	0	0	0
5	3.6	25.2	23.4	27.0	59.4	34.2	41.4
10	21.6	34.2	43.2	37.8	66.6	43.2	43.2
20	32.4	54.0	54.0	54.0	63.0	46.8	45.0
30	41.4	59.4	61.2	66.6	68.4	48.6	46.8
45	48.6	64.8	68.4	68.4	73.8	54.0	48.6
60	55.8	66.6	72.0	73.8	77.4	57.6	52.2
90	57.6	68.4	73.8	82.8	79.2	59.4	55.8
120	57.6	68.4	73.8	82.8	79.2	59.4	55.8

The results of dissolution were compared then the order of dissolution follows: KTF: β-CD (1:3 ratio) (F3) > KTF: HP- β-CD (1:1 ratio) (F4) > KTF: β-CD (1:2 ratio) (F2)> KTF: β-CD (1:1 ratio) (F1) > KTF: HP- β-CD (1:2 ratio)(F5) > Pure KTF (F) > KTF: HP- β-CD (1:3 ratio) (F6).The dissolution of all the complexes was significantly having a greater dissolution compared to pure Ketoprofen. The Ketoprofen with HP- β-CD (1:3 ratios) have no significant dissolution.

According to the above results release after 120 minutes, the release is 28.8 µg/ml for pure Ketoprofen, 34.2 µg/ml for KTF: β-CD (1:1 ratio), 36.9 µg/ml for KTF: β-CD (1:2 ratio), 41.4 µg/ml for KTF: β-CD (1:3ratio), 39.6 µg/ml for KTF: HP- β-CD (1:1 ratio), 29.7 µg/ml for KTF: HP- β-CD (1:2 ratio), 27.9 µg/ml for KTF: HP- β-CD (1:3ratio).

The percentage release after 120 minutes, the release is 57.6 % for pure Ketoprofen, 68.4 % for KTF: β-CD (1:1 ratio), 73.8 % for KTF: β-CD (1:2 ratio), 82.8 % for KTF: β-CD (1:3ratio), 79.2 % for KTF: HP- β-CD (1:1 ratio), 59.4 % for KTF: HP- β-CD (1:2 ratio), 55.8 % for KTF: HP- β-CD (1:3ratio).

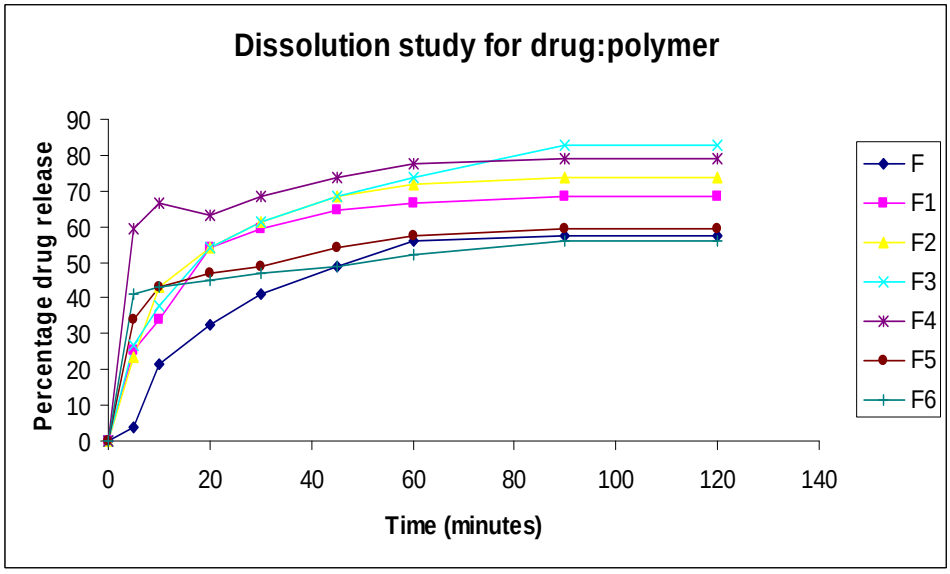

Figure 5: Graph for % Cumulative amount of drug release from drug: polymer Complex (Dissolution profile of Ketoprofen for two hour with 1:1, 1:2, 1:3, KTF/CD complexes)

Conclusion

The phase solubility of Ketoprofen in the presence of β-CD and HP- β-CD in water at 25^0C showed. Initially the apparent solubility of Ketoprofen is increased with increasing concentration of β-CD and HP- β-CD.

The dissolution profile of most of systems reached a plateau phase with in 30 minutes. The result of dissolution were compared then the order of dissolution follows: KTF: β-CD (1:3 ratio) (F3) > KTF: HP- β-CD (1:1 ratio) (F4) > KTF: β-CD (1:2 ratio) (F2)> KTF: β-CD (1:1 ratio) (F1) > KTF: HP- β-CD (1:2 ratio)(F5) > Pure KTF (F) > KTF: HP- β-CD (1:3 ratio) (F6). The dissolution of all the complexes was significantly having a greater dissolution compared to pure Ketoprofen. The Ketoprofen with HP- β-CD (1:3 ratios) have no significant dissolution.

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The result of phase solubility and dissolution studies demonstrate that complexation with CDs have more phase solubility and more dissolution rate. The Ketoprofen complexes with β- Cyclodextrin (1:3 ratios) have better solubility than other complexes.

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