# PREPARATION, CHARACTERIZATON AND DISSOLUTION KINETICS OF CELECOXIB : β AND HP β -CYCLODEXTRIN COMPLEXES

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## ABSTRACT

Celecoxib, a specific inhibitor of cycloxygenase-2 (COX-2) is poorly water soluble non-steroidal anti-inflammatory drug with relatively low bioavailability. The effect of β-cyclodextrin (βCD) and hydroxypropyl β-cyclodextrin (HPβCD) on the aqueous solubility and dissolution rate of celecoxib was investigated. The phase solubility studies indicated that the solubility of celecoxib was significantly increased in the presence of β-cyclodextrin and hydroxypropyl β-cyclodextrin and was classified as $A_L$-type, indicating the 1 : 1 stoichiometric inclusion complexes in water. Solid complexes were prepared by kneading method using β-cyclodextrin and hydroxypropyl β-cyclodextrin. The complexes formed were quite stable. Solid inclusion complexes of celecoxib : β-cyclodextrin and celecoxib : hydroxypropyl β-cyclodextrin were prepared in 1 : 1, 1 : 2 and 1 : 3 weight ratios. *In vitro* studies showed that the solubility and dissolution rate of celecoxib were significantly improved by complexation with β-cyclodextrin and hydroxypropyl β-cyclodextrin with respect to pure drug alone. The celecoxib : βCD (1 : 3) inclusion complex yielded a 20 fold increase in the dissolution rate of celecoxib where as the celecoxib : HPβCD (1 : 3) inclusion complex yielded a 21 fold increase in the dissolution rate of celecoxib, when compared with pure drug. Solid complexes prepared were characterized by differential scanning calorimetry, powder x-ray diffractometry, scanning electron microscopy and IR studies.

**Key words :** Celecoxib, β-Cyclodextrin, Hydroxypropyl β-Cyclodextrin, Phase solubility study, Kneading method, Complexation, Characterization, Dissolution rate.

## INTRODUCTION

Celecoxib, 4-[5-(4-methylphenyl)-3-trifluoromethyl-1H-pyrazol-1yl] benzene sulphonamide, is a specific cyclooxygenase-2 inhibitor[1] (COX-2) and it is widely prescribed for pain and inflammation. It inhibits the conversion of arachidonic acid to the

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prostaglandins that mediate pain and inflammation, while having no effect on the formation of the prostaglandins that mediate homeostasis in the gastrointestinal tract, kidney and platelets and that are formed under the control of cyclooxygenase-1[2]. It is also used in the treatment of arthropathies and adenomatous polyps[3] and dentistry[4]. It has comparable efficacy and superior gastric tolerability[5] and is safer, when compared with conventional nonsteroidal anti-inflammatory drugs. [6] The major drawback of celecoxib is its poor solubility and dissolution rate in gastric fluid. The aqueous solubility of celecoxib is low at 3 to 7 µg/mL when determined *in vitro* at pH 7 and 40°C. Since the $pK_a$ of celecoxib is 11. 1. the solubility of the drug is likely to be also low at physiological pH.[7] The oral bioavailability of celecoxib is between 22% and 50%.[8]

Most of the chemical entities that are being discovered are lipophilic and have poor aqueous solubility. So they pose difficulties to the formulator. Cyclodextrins with their ability to form molecular inclusion complexes with drug substances, will affect many of the physicochemical properties.[9, 10] As a consequence of the inclusion process, many physicochemical properties such as solubility, dissolution rate, stability and bioavailability, can be favorably affected.[11–13] Thus, it is important to enhance the solubility and dissolution rate of celecoxib. In the present work, the complexation of celecoxib with CDs like βCD and HPβCD is undertaken to improve its overall oral bioavailability.  The solubility of poorly soluble drugs can be altered in many ways, such as modification of drug crystal forms, addition of co-solvents, addition of surfactants, addition of cyclodextrins, etc. Among these, the cyclodextrin approach is of particular interest.

Cyclodextrins are cyclic (α-1.4)-linked oligosaccharides of α-D-glucopyranose, with a hydrophilic outer surface and a lipophilic central cavity that can accommodate a variety of lipophilic drugs. The number of applications of CDs in pharmaceutical formulations has been increasing in recent years because of their approval by various regulatory agencies.[14, 15] In this study, investigations were performed on the possibility of complexation of celecoxib with βCD and HPβCD for improving the solubility and dissolution rate; thereby increasing the bioavailability and therapeutic efficacy of this COX-2 inhibitor (NSAID). The complexes of celecoxib with βCD and HPβCD were prepared by kneading method. Selective physicochemical determinations based on differential scanning calorimetry (DSC), powder x-ray diffractometry (PXRD), scanning electron microscopy (SEM) and infra red (IR) studies were used to characterize the complexes. *In vitro* aqueous solubility and dissolution rate profiles of the complexes were performed.

# EXPERIMENTAL

## Materials and methods

## Materials

Celecoxib was a gift sample from M/s Unichem Laboratories, Mumbai, βCD and HPβCD were gift samples from M/s S. A. Pharmachem, Pvt. Ltd, Mumbai. Methanol (Qualigens, Mumbai), dichloromethane (Qualigens, Mumbai) and sodium lauryl sulphate (S. D. finechemicals, Mumbai) were procured from commercial sources.

## Methods

**Phase solubility studies:** Solubility studies were performed according to the method reported by Higuchi and Connors.[16] Excess drug (25 mg) was added to 25 mL of double distilled water containing various concentrations of βCD and HPβCD (3-15 mM) in a series of 50 mL stoppered conical flasks. The mixtures were shaken for 72 hours at room temperature (28 ± 0. $5^0$C) on a rotary flask shaker. After 72 hours of shaking to achieve equilibrium, 5 mL aliquots were withdrawn using a syringe at 1-hour intervals and filtered immediately using a 0. 45 μ nylon filter. The filtered samples were diluted suitably and assayed by using UV-spectrophotometer (SHIMADZU UV-1700 Pharmaspec spectrophotometer) for celecoxib at 254 nm against blanks prepared in the same concentrations of βCD and HPβCD in water so as to cancel out any absorbance that might be exhibited by the CD molecules. Shaking was continued until three consecutive estimations were the same. The phase solubility experiments were conducted in triplicate.

The apparent stability constant ($K_c$) was calculated using the following equation.

$$K = \frac{Slope}{S_0 \ (1 - Slope)} \qquad \ldots(1)$$

The slope is obtained from the initial straight line portion of the plot of celecoxib concentration against CD concentrations, and $S_o$ is the equilibrium solubility of celecoxib in water.

## Preparation of solid complexes

Solid inclusion complexes of celecoxib with βCD and HPβCD were prepared in the weight ratios of 1 : 1, 1 : 2 and 1 : 3 by the kneading method. Celecoxib and βCD were triturated in a mortar with a 5 mL volume of a solvent blend of methanol : dichloromethane (1 : 2). The thick slurry formed was kneaded for 45 minutes and then

dried at 55°C until dry. The dried mass was powdered and sieved through mesh # 100. Similarly the celecoxib with HPβCD were also prepared.

## Estimation of celecoxib

A UV spectrophotometer method based on the measurement of absorbance at 254 nm in water containing 1% sodium lauryl sulphate was developed and used for the estimation of celecoxib. The method obeyed Beer's law in the concentration range of 2-10 µg/mL. The dissolution rate of celecoxib alone and from its CD inclusion complexes was studied using the ELECTROLAB TDT-06N, an 8-station dissolution rate test apparatus with a paddle stirrer. The dissolution rate was studied in 900 mL of water containing 1% sodium lauryl sulphate. Sodium lauryl sulphate was added to the dissolution fluid to maintain sink conditions. Celecoxib (50 mg), or its inclusion complex equivalent to 50 mg of celecoxib, a speed of 50 rpm, and a temperature of 37 ± 1°C were used in each test. Samples of dissolution medium (5 mL) were withdrawn through a filter (0. 45 µ) at different time intervals, suitably diluted and assayed for celecoxib by measuring absorbance at 254 nm. When a standard drug solution was assayed repeatedly (n = 6) the relative error (accuracy) and relative standard deviation (precision) were found to be 0. 8% and 1. 2%, respectively. The dissolution experiments were conducted in triplicate.

## Estimation of drug content in solid inclusion complexes

Solid inclusion complex (20 mg) was taken in a 25 mL volumetric flask. 25 mL of methanol was added and mixed thoroughly. The solution was then suitably diluted with 1% sodium lauryl sulphate and assayed for celecoxib at 254 nm. Inclusion efficiency was calculated using the formula.

$$\text{Inclusion efficienncy} = \frac{\text{Estimated \% drug content}}{\text{Theoretical \% drug content}} \times 100 \qquad \ldots(2)$$

## Differential scanning calorimetry (DSC)

Differential scanning calorimetry thermograms of the drug, CD's and prepared solid binary systems were recorded on the DSC 2920 Model (TA Instruments MDSC 2920, New Castle, DE). Samples (2-5 mg) were sealed in aluminum pans and scanned at a heating rate of 10°C min$^{-1}$ over a temperature range of 40 to 200°C under a nitrogen gas stream.

## Powder X-ray diffractometry (XRD)

The powder X-ray diffraction patterns were recorded using a BRUKER AXS-D8

powder diffractometer with Cu as anode material and crystal graphite monochromator, operated at a voltage of 40 KV and a current of 30 mA. The samples were analyzed in the $2\theta$ angle of $2^{o}$ to $60^{o}$ and the process parameters were set as follows : step size of $0.040^{o}$ ($2\theta$), scan step of 0. 5 sec, and time of acquisitions of 2 hours.

## Scanning electron microscopy (SEM)

The surface morphology of the pure drug and of the binary systems was examined by means of Hitachi S-3000 SEM (Tokyo, Japan). The powders were precisely fixed on an aluminum stub using double-sided adhesive tape and then were made electrically conductive by coating in a vacuum with a thin layer of gold, for 30 seconds and at 30 W. The pictures were taken at an excitation voltage of 10 KV and a magnification of x20 and x 50 or x200.

## Infrared spectroscopy (IR)

The Fourier transmitted infrared spectra of celecoxib and inclusion complexes of celecoxib : βCD and HPβCD prepared by kneading method in different weight ratios were recorded in a KBr pellets using a JASCO FTIR-5300 (Tokyo, Japan) spectrophotometer. The powders of pure drug and the prepared solid inclusion complexes were studied at 400 to 4000 $cm^{-1}$ with a resolution of 4. 00 $cm^{-1}$.

## RESULTS AND DISCUSSION

The phase solubility diagrams for the complex formation between celecoxib and βCD and HPβCD are shown in Fig. 1. The aqueous solubility of celecoxib was increased linearly as function of the concentration of βCD and HPβCD. The phase solubility diagrams of celecoxib : βCD and celecoxib : HPβCD complexes can be classified as type $A_L$ according to Higuchi and Connors[16]. Because the straight line had a slope < 1 in each case, the increase in solubility was due to the formation of complexes in solution with βCD and HPβCD. The estimated $K_c$ values of celecoxib : βCD is 665. 0 $M^{-1}$ and for celecoxib : HPβCD is 474. 3 $M^{-1}$. The values indicated that the complexes formed between celecoxib : βCD and celecoxib : HPβCD are quite stable.

Solid inclusion complexes of celecoxib : βCD and HPβCD in 1 : 1, 1 : 2 and 1 : 3 ratios were prepared by kneading method. The solid complexes prepared were found to be fine and free flowing powders. The angle of repose ($\theta$) was below $20^{o}$. The free flow may be due to the inclusion of the drug in βCD and HPβCD. Low coefficient of variation (CV)

(< 1. 0%) values in the percentage of drug content indicated uniformity of drug content in each batch of solid complex prepared.  The inclusion efficiency was in the range of 96- 98 % with various systems (Table 1).

**Table 1. Celecoxib content in solid βCD and HPβCD inclusion complex systems prepared**

| Complex system | Celecoxib content (%) | Inclusion efficiency (%) |
|---|---|---|
| Celecoxib: βCD (1:1) | 48.2 | 97.00 |
| Celecoxib: βCD (1:2) | 32.1 | 96.30 |
| Celecoxib: βCD (1:3) | 24.2 | 96.80 |
| Celecoxib: HPβCD (1:1) | 47.9 | 95.80 |
| Celecoxib: HPβCD (1:2) | 32.6 | 97.80 |
| Celecoxib: HPβCD (1:3) | 23.9 | 95.60 |
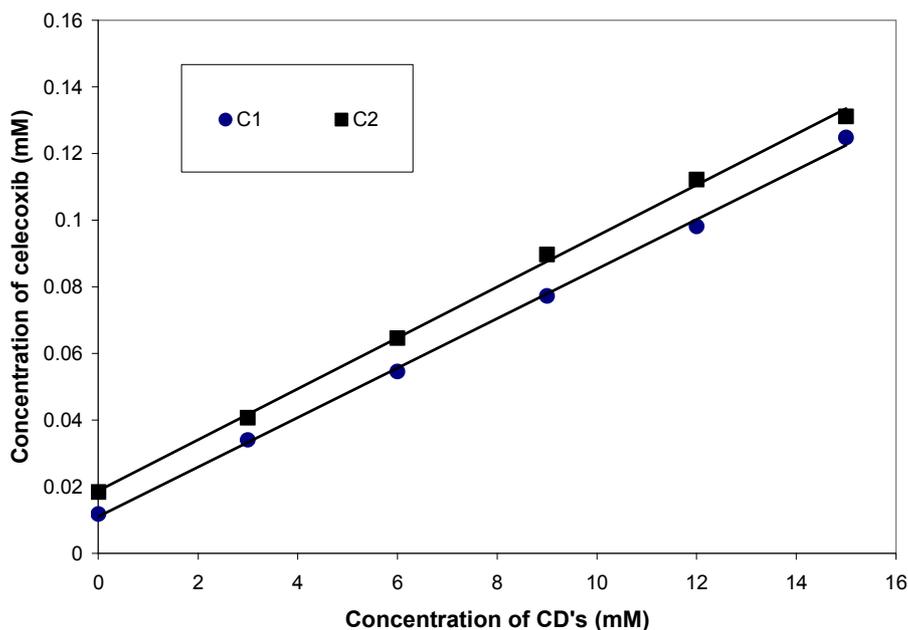


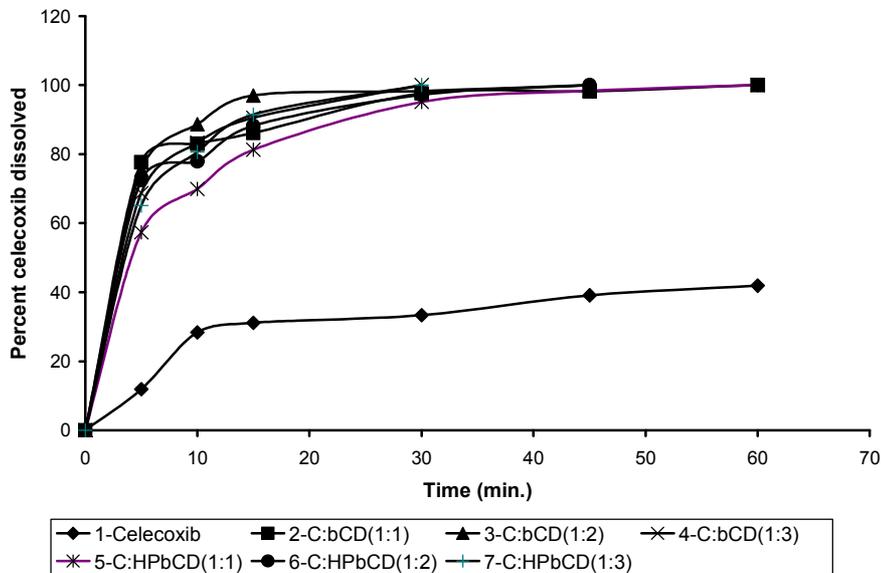**Fig. 1: Phase solubility diagrams of celecoxib : βCD (C1) and celecoxib : HPβCD (C2)**

**Fig. 2: Dissolution profiles of celecoxib and its βCD and HPβCD complxes**

The dissolution rate of celecoxib from both the cyclodextrin complex systems was studied in water containing 1% sodium lauryl sulphate (SLS) as dissolution medium. SLS was included in the dissolution medium to maintain sink conditions. The dissolution profiles of celecoxib and its various βCD and HPβCD complex systems are shown in Fig. 2. The dissolution of celecoxib was rapid and higher from all the solid inclusion complexes, when compared with celecoxib pure drug. The dissolution of celecoxib as such and from various βCD and HPβCD complex systems followed first order kinetics (r > 0.998). Dissolution rate constants ($k_1$) were calculated from the slopes of the first order linear plots of the dissolution data. Dissolution efficiency values ($DE_{30}$) based on the dissolution data were calculated as per Khan[17]. Time taken for 50% dissolution ($T_{50}$) values were recorded from the dissolution profiles. The dissolution parameters are summarized in Table 3.

All CD complexes exhibited higher rates of dissolution and dissolution efficiency values than celecoxib, indicating rapid and higher dissolution of celecoxib from its βCD and HPβCD complexes. The $k_1$ and $DE_{30}$ values were increased as the proportion of βCD and HPβCD in the complex was increased. The increase in $k_1$ (folds) with various CD systems is shown in Table 3. Thus, the dissolution rate of celecoxib was markedly enhanced by complexation with βCD and HPβCD.

**Table 2. Dissolution profiles of celecoxib and its βCD and HPβCD complex systems (Dissolution fluid water containing 1% sodium lauryl sulphate)**

| Time (min) | Percent of Celecoxib dissolved ($\pm$ s.d.) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Celecoxib (C) | C : βCD (1 : 1) | C : βCD (1 : 2) | C : βCD (1 : 3) | C : HPβCD (1 : 1) | C : HPβCD (1 : 2) | C : HPβCD (1 : 3) |
| 5 | $11.90 \pm 1.10$ | $77.65 \pm 1.34$ | $75.46 \pm 1.20$ | $68.75 \pm 0.70$ | $57.32 \pm 0.40$ | $72.48 \pm 1.10$ | $65.13 \pm 1.10$ |
| 10 | $28.40 \pm 1.06$ | $83.02 \pm 1.21$ | $88.62 \pm 0.50$ | $83.32 \pm 1.20$ | $69.91 \pm 1.30$ | $77.94 \pm 1.04$ | $80.61 \pm 1.34$ |
| 15 | $31.20 \pm 0.90$ | $86.10 \pm 1.20$ | $96.98 \pm 0.40$ | $90.53 \pm 0.90$ | $81.23 \pm 0.80$ | $88.20 \pm 1.20$ | $91.46 \pm 1.20$ |
| 30 | $33.40 \pm 1.20$ | $97.60 \pm 1.10$ | $98.29 \pm 1.10$ | $100.00 \pm 0.80$ | $95.10 \pm 1.10$ | $97.19 \pm 1.20$ | $100.00 \pm 1.20$ |
| 45 | $39.10 \pm 0.50$ | $98.19 \pm 1.85$ | $100.00 \pm 1.20$ | - | $98.34 \pm 0.40$ | $100.00 \pm 1.20$ | - |
| 60 | $41.90 \pm 1.20$ | $100.00 \pm 0.90$ | - | - | $100.00 \pm 0.30$ | - | - |

**Table 3. Dissolution parameters of celecoxib and its βCD and HPβCD complex systems.**

| CD-system | $T_{50}$ (min) | $DE_{30}$ (%) | $k_1$ ($min^{-1}$) | Increase in $k_1$ (No. of folds) |
|---|---|---|---|---|
| Celecoxib (C) | >60 | 25.46 | 0.007625 | -- |
| C: βCD (1:1) | 03 | 79.90 | 0.0836 | 10.9639 |
| C: βCD (1:2) | 03 | 84.25 | 0.01317 | 17.2721 |
| C: βCD (1:3) | 03 | 80.63 | 0.1540 | 20.1967 |
| C: HPβCD (1:1) | 04 | 72.04 | 0.0881 | 11.5540 |
| C: HPβCD (1:2) | 03 | 78.75 | 0.1106 | 14.5049 |
| C: HPβCD (1:3) | 03 | 79.78 | 0.1595 | 20.9180 |

DSC was used to characterize the celecoxib : βCD and celecoxib : HPβCD complexes. The DSC thermograms of various products are shown in Fig. 3. The DSC thermogram of celecoxib exhibit an endothermic peak at $166.7^{o}C$ corresponding to its melting point, the endothermic peak of βCD showed a broad peak at $101:2^{o}C$, which may be attributed to a dehydration process. The DSC thermograms of celecoxib : βCD (1 : 1 and 1 : 2 w/w) inclusion complexes prepared by kneading method showed slight shift in peaks which indicates interaction between celecoxib and βCD. But in case of celecoxib : βCD (1 : 3 w/w), the inclusion complex prepared by kneading method showed the greater shift in peak and considerable reduction in the peak area as compared to the inclusion complexes prepared at 1 : 1 and 1 : 2 w/w ratios, which indicates the presence of celecoxib molecule inside the β-CD cavity. DSC thermogram of HPβCD exhibited a broad endothermic peak at $80.3^{o}C$, may be due to the loss of water molecules. In the thermograms of celecoxib : HPβCD inclusion complexes prepared at 1 : 1, 1 : 2 w/w ratios peaks were observed at $157.99^{o}C$ and $157.43^{o}C$, respectively. This shift in peak indicates an interaction of celecoxib with HPβCD where as in the prepared complex of celecoxib : HPβCD at ratio1 : 3 w/w, the peak was observed at $157.75^{o}C$ with an marked reduction in the peak area indicating the absence of crystalline drug and its complete complexation with HPβCD.
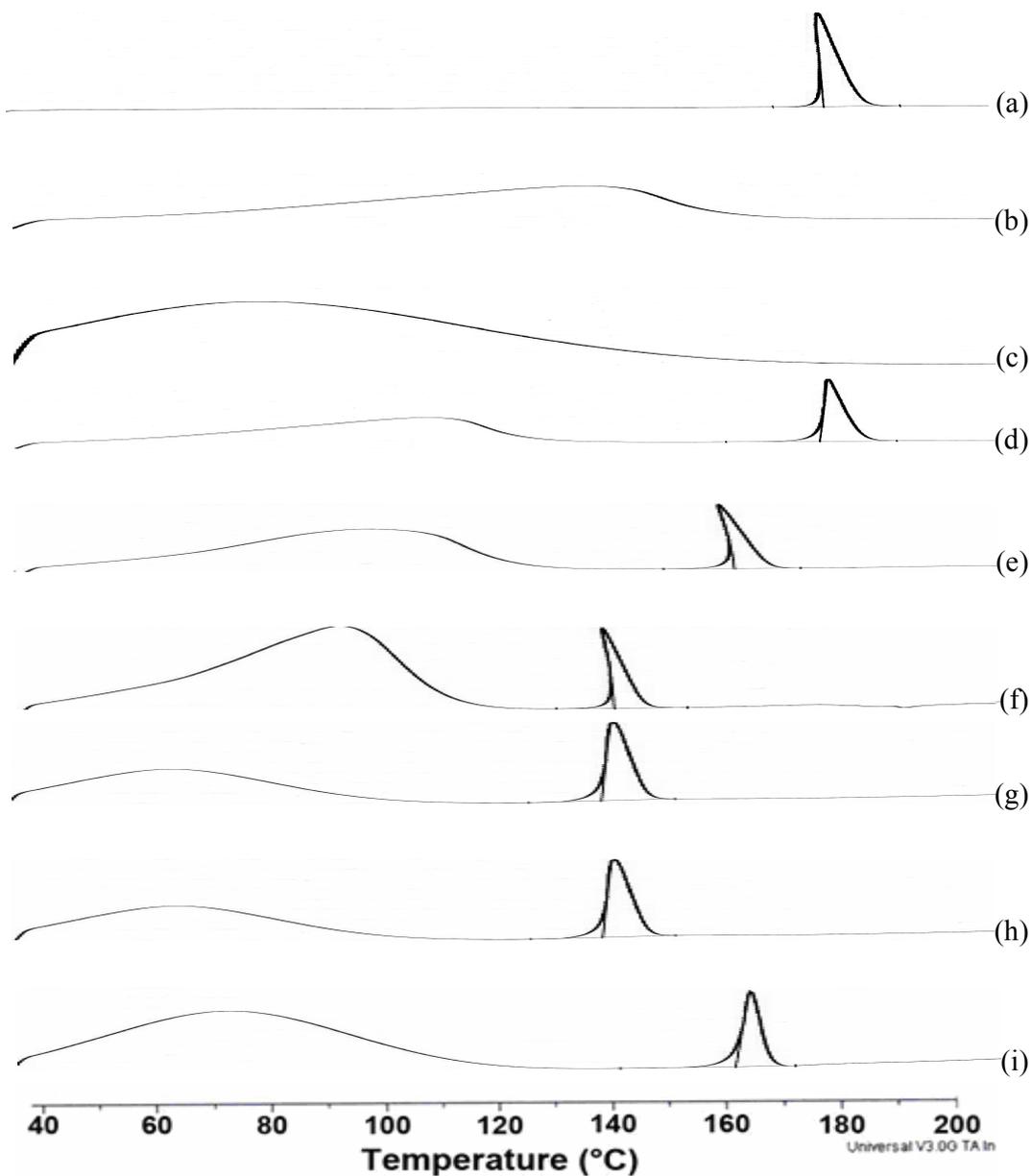
**Fig. 3: Differential scanning calorimetry thermograms of celecoxib and its cyclodextrin complex systems. Celecoxib (a); β-CD (b); HP β-CD (c); celecoxib: β-CD(1:1) (d); celecoxib: β-CD(1:2) (e); celecoxib: β-CD(1:3) (f); celecoxib:HPβ-CD(1:1) (g); celecoxib: HPβ-CD(1:2) (h); celecoxib: HPβ-CD(1:3) (i);**
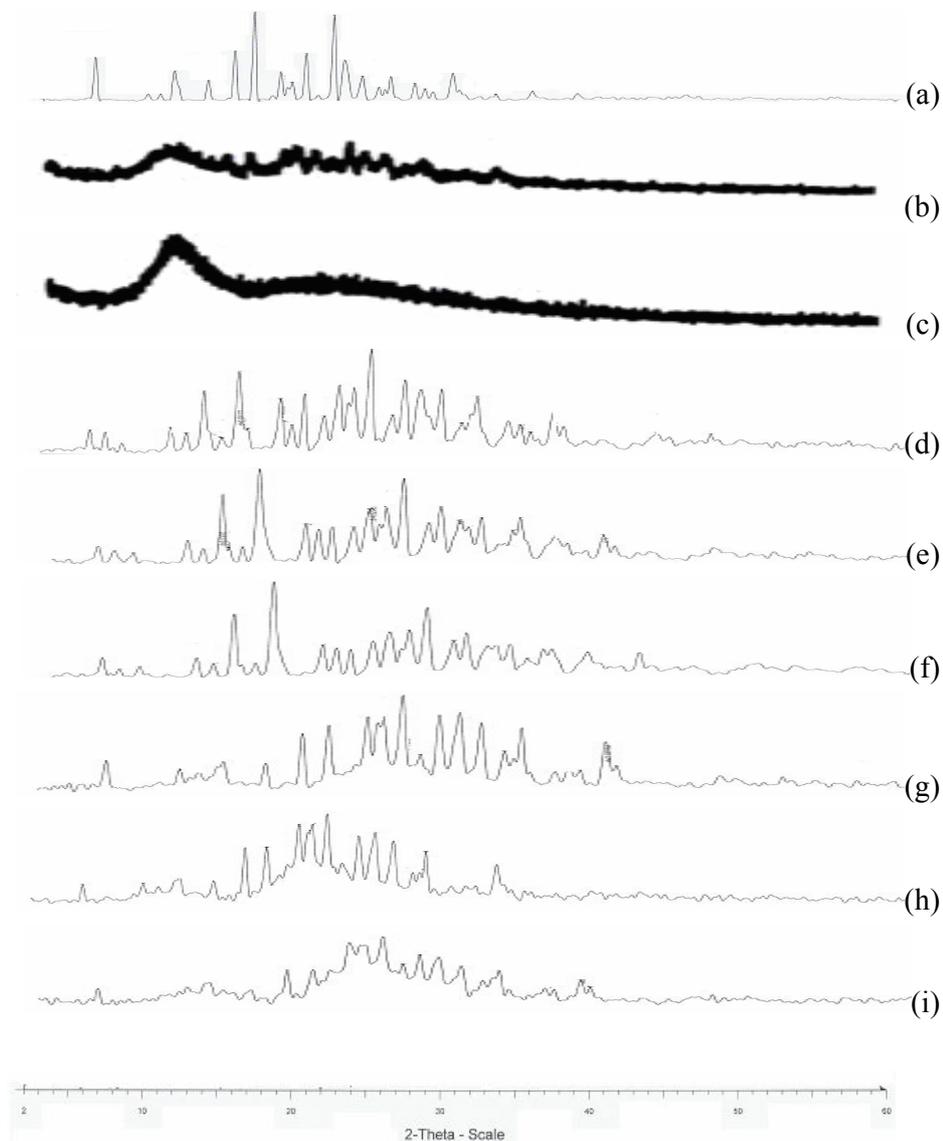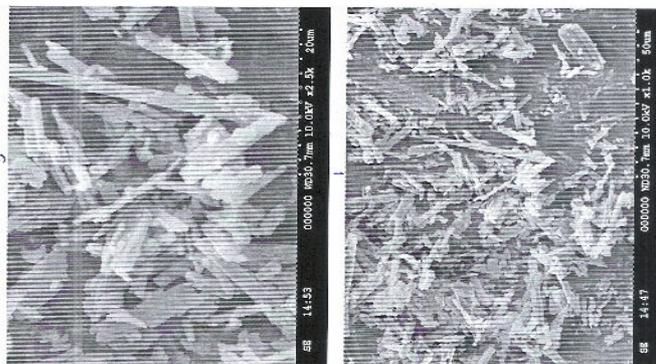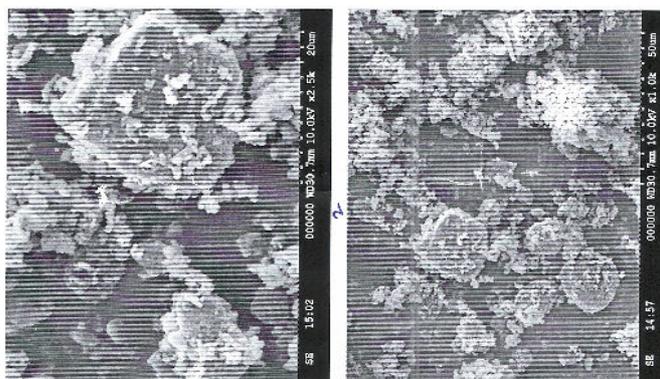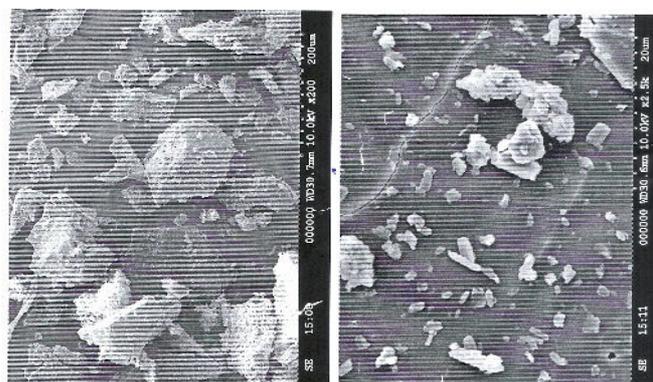
**Fig. 4: X-Ray diffractograms of powder samples of celecoxib and its cyclodextrin complex systems. Celecoxib (a); β-CD (b); HP β-CD (c); celecoxib: β-CD(1:1) (d); celecoxib: β-CD(1:2) (e); celecoxib: β-CD(1:3) (f); celecoxib:HPβ-CD(1:1) (g); celecoxib: HPβ-CD(1:2) (h); celecoxib: HPβ-CD(1:3) (i);**
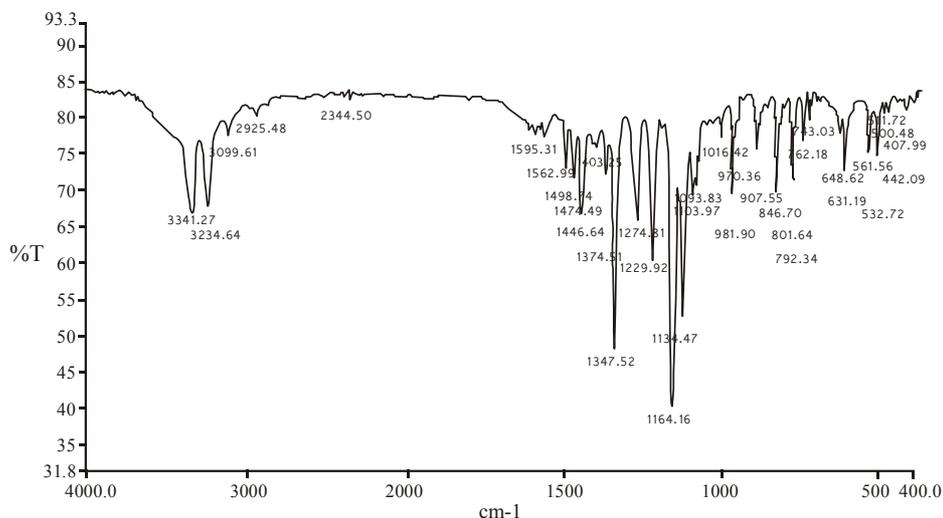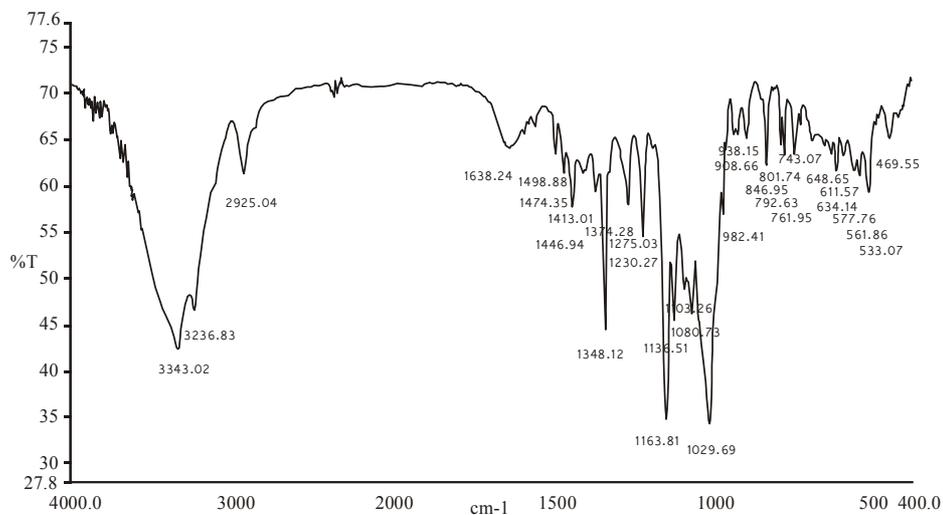
(a)



(b)



(c)

**Fig. 5: Scanning electron photomicrographs of Celecoxib (a); celecoxib:β-cyclodextrin complex(b) and celecoxib: HPβ-cyclodextrin complex(c)**

**(a)**



**(b)**

**Fig. 6: (a) I.R. Spectra of celecoxib (b) celecoxib:β-cyclodextrin complex**

The XRD patterns of celecoxib, celecoxib : βCD and celecoxib : HPβCD systems are represented in Fig. 4. The diffractograms of celecoxib, βCD and HPβCD exhibited intense peaks, which indicate the crystalline nature. X-ray diffraction of celecoxib : βCD at 1 : 1 w/w ratio has showed many peaks as that of pure drug; thus indicating that a new structure has not been formed.
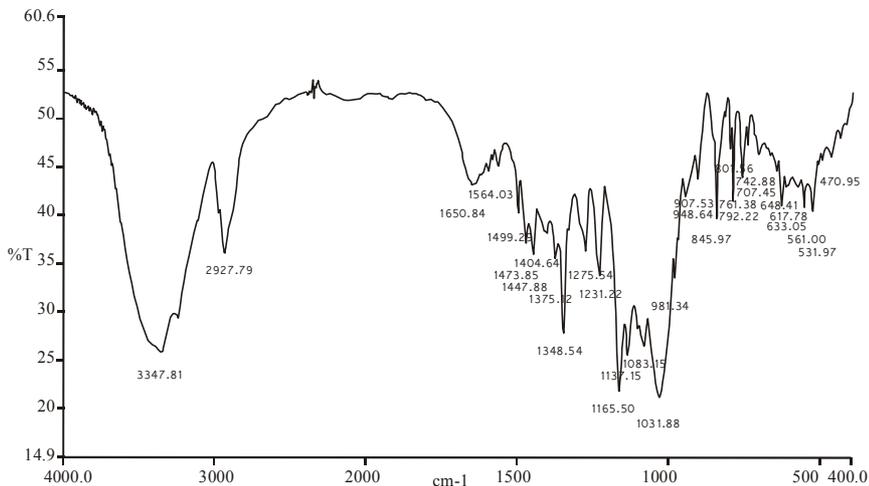
**Fig. 6: (c) Celecoxib: HPβ-cyclodextrin complex**

The kneaded mixture celecoxib : βCD at 1 : 2 ratio presented a diffractogram quite similar to that of complex prepared at 1 : 1 ratio, while that obtained at 1 : 3 ratio showed fewer, broader and less intense peaks indicateing a reduction in crystallinity of celecoxib in prepared complexes. There was a considerable reduction in the diffraction peaks of celecoxib : HPβCD complexes prepared at 1 : 1 and 1 : 2 w/w ratios, when compared to diffraction peaks obtained from pure celecoxib. The diffraction peaks were much reduced or absent in case of complex prepared at 1 : 3 w/w ratio of celecoxib : HPβCD. The disappearance of celecoxib crystalline peaks confirmed the stronger drug amorphization and entrapment in HPβCD.

The SEM of celecoxib, celecoxib : βCD and celecoxib : HPβCD are shown in Fig. -5. The SEM of celecoxib showed the presence of long irregular shaped crystals. The SEM of celecoxib : βCD and celecoxib : HPβCD inclusion complexes prepared exhibited marked change in the morphology of the celecoxib. The complexes appeared as agglomerates rather than individual crystalline structures observed in pure celecoxib. The drastic change of the particle shape was indicative of a presence of a new solid amorphous state of the complexes.

The IR spectrum of celecoxib, celecoxib : βCD and celecoxib : HPβCD are shown in Fig. 6. The IR spectrum of celecoxib exhibited peak at 3099.61 cm$^{-1}$ due to N-H stretching, while peaks at 1347.52 cm$^{-1}$ and 1164.86 cm$^{-1}$ due to –SONH$_2$ stretching confirms structure while of celecoxib. The IR spectrum of βCD and HPβCD showed peaks

at 3399.8 cm$^{-1}$ and 3408.0 cm$^{-1}$ respectively. The IR spectrum of celecoxib : βCD prepared kneaded inclusion complex has shown peaks at 3030.1 cm$^{-1}$, 1348.12 cm$^{-1}$ and 1163.81 cm$^{-1}$. The shift in peak due to N-H stretching indicates interaction between celecoxib and βCD. The IR spectrum of celecoxib : HPβCD kneaded complex has shown peaks at 2927:79 cm$^{-1}$, 1348:54 cm$^{-1}$ and 1165:50 cm$^{-1}$. The shift in peaks indicates interaction between celecoxib and HPβCD.

## CONCLUSIONS

Celecoxib formed inclusion complexes with βCD and HPβCD at all the prepared ratios. Solid complex systems of celecoxib- βCD and celecoxib :  HPβCD gave rapid and higher dissolution of celecoxib than celecoxib alone. The dissolution of celecoxib as such and from various βCD and HPβCD complex systems followed first order kinetics. Celecoxib :  βCD and celecoxib :  HPβCD complex systems exhibited higher rates of dissolution and dissolution efficiency. The aqueous solubility and dissolution rate of celecoxib can be increased by inclusion complexation with βCD and HPβCD. Phase solubility profile indicated that the solubility of celecoxib and apparent stability constant was significantly increased in the presence of βCD and HPβCD. Results obtained by different characterization techniques clearly indicate that the kneading method leads to formation of solid state complexes between celecoxib, βCD and HPβCD. Thus, complexation of celecoxib with cyclodextrins lends for better therapeutic efficacy.

## ACKNOWLEDGEMENTS

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