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# Improvement of physical stability and dissolution rate of celecoxib suspensions by complexation with β-cyclodextrins

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Solid dispersions of celecoxib with β-cyclodextrins were prepared by physical mixing, slugging and kneading methods at 1 : 1 and 1 : 2 molar ratios and characterized by differential scanning calorimetry. Celecoxib suspensions were formulated employing its solid dispersions with sodium carboxymethylcellulose as the suspending agent. Stability studies were conducted by subjecting all the suspensions to freeze-thaw cycling. The suspensions were evaluated for particle size, sedimentation volume, viscosity, redispersibility and dissolution rate initially and after stability testing. Celecoxib suspensions formulated employing its solid dispersions exhibited good physical stability and gave higher dissolution rates than those formulated with celecoxib alone. The suspension prepared from solid dispersions (1 : 2) by the kneading method gave the highest improvement in dissolution rate and efficiency. Celecoxib in the inclusion complex with β-cyclodextrin produced suspensions of better physical stability and dissolution rate.

## 1. Introduction

Celecoxib, 4-[5-(4-methylphenyl)-3-(triflouromethyl)-1H-pyrazol-1-yl]benzene sulfonamide (Budavari 2001) is a new non-steroidal anti-inflammatory drug (NSAID) and a selective cyclooxygenase-2 (COX-2) inhibitor. Solubility and permeability of celecoxib are low, hence it is categorised as a class IV drug according to the biopharmaceutics classification system (Amidon et al. 1995). Solutions of the poorly water soluble drug, containing an appropriate dosage, would be of an unacceptably large volume. Suspensions allow the development of a liquid dosage form containing an appropriate quantity of drug in a reasonably small volume. Formulation of an effective and pharmaceutically elegant suspension is usually much harder to achieve than that of a tablet or capsule of the same drug (Rhodes 1990) because of their inherent physical instability. The approaches used to control the physical stability are based on classical concepts like Stoke's law (Staniforth 2002), controlled flocculation (Swarbrick et al. 2001) and structured vehicles (Meyer 1959; Samyn 1961). The disadvantage of these methods is a decrease in dissolution rate due to high viscosity or floccules. Application of drug-cyclodextrin complexes for the improvement of both physical stability and dissolution rate of suspensions is a novel approach in this respect. The inclusion of a drug in the cyclodextrin cavity results in the modification of its physical and chemical properties. There are numerous benefits of cyclodextrin complexes in pharmaceutical formulations (Rajewski 1996). Cyclodextrin complexation has immense application in improving the physical stability of suspensions (Jain 1999). The present work is aimed at studying the influence of β-CD on the physical stability and dissolution rate of celecoxib suspensions.

**Table 1: Celecoxib suspensions prepared**

| Sl. No. | Ingredients (g) | Formulation | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | $F_1$ | $F_2$ 1 : 1 PM | $F_3$ 1 : 1 SL | $F_4$ 1 : 1 KN | $F_5$ 1 : 2 PM | $F_6$ 1 : 2 SL | $F_7$ 1 : 2 KN |
| 1. | Celecoxib | 2.0 | 2.0* | 2.0* | 2.0* | 2.0* | 2.0* | 2.0* |
| 2. | Sod. CMC | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| 3. | Tween 80 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| 4. | Methyl paraben sodium | 0.15 | 0.15 | 0.15 | 0.15 | 0.15 | 0.15 | 0.15 |
| 5. | Propyl paraben sodium | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 |
| 6. | Purified water q.s. (ml) | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

* Solid dispersions of celecoxib and β-cyclodextrin were prepared by different methods. The weight equivalent to celecoxib was taken.
PM = Physical mixing; SL = Slugging; KN = Kneading

## 2. Investigations, results and discussion

Seven celecoxib suspensions ($F_1$–$F_7$) were prepared using sodium carboxymethylcellulose (sod. CMC) at 1% w/v concentration as the suspending agent. The compositions of the prepared suspensions are given in Table 1. $F_1$ contained pure celecoxib as such and $F_2$–$F_7$ contained solid dispersions of celecoxib and β-CD prepared by physical mixing, slugging and kneading methods at 1 : 1 and 1 : 2 molar ratios. Tween 80 was used as a wetting agent, methylparaben sodium and propylparaben sodium were used as preservatives in all the formulations. Stability studies were conducted for the prepared suspensions by subjecting them to 21 freeze-thaw cycles. All the suspensions were evaluated on 0 cycle and after 21 freeze-thaw cycles. The average particle size, sedimentation volume, redispersibility, dissolution efficiency and $T_{50}$ (min.) values were calculated and reported in Table 2.

The drug content was found to be in the range of $100 \pm 5\%$ in all the formulations initially and after 21 freeze-thaw cycles, indicating that celecoxib was chemically stable in all the formulations during the period of study. In $F_1$ the pH was initially 9.31 and after stability testing it was found to be 6.95. In formulations $F_2$–$F_7$ the initial pH was in the range of 6.10 to 7.19 and after stability testing it was in the range of 5.17 to 6.80. These values indicated a significant decrease in pH in all the formulations during the stability studies. A suitable buffer was not present in the formulations and these results indicated its requirement.

The celecoxib particle growth was approximately 13, 7, 5, 5, 6, 5, 4 μm in $F_1$, $F_2$, $F_3$, $F_4$, $F_5$, $F_6$ and $F_7$ respectively. There was a significant particle growth in $F_1$ containing pure celecoxib. The crystal growth was insignificant in the suspensions containing dispersions of celecoxib and β-CD. In a similar report on metronidazole benzoate suspensions, the phase transition of the anhydrous form to the monohydrate, along with the crystal growth during the transition, was suppressed by β-CD complexation (Szejtli 1994).

Formulations $F_2$–$F_7$ containing solid dispersions of celecoxib and β-CD showed higher sedimentation volumes (shown in Table 3) than $F_1$ initially and after 21 freeze-thaw cycles. $F_7$ showed the highest sedimentation volume even after stability testing. Also the same formulations i.e. $F_2$–$F_7$, exhibited good redispersion during and after the stability studies. Uniform redispersion was achieved on mild to moderate agitation. This was an important parameter to achieve dose uniformity to ensure patient compliance. In $F_1$ the redispersibility was poor compared with other formulations. In $F_1$ and $F_2$ the sedimentation pattern was characterized first by a rapid settling rate and further sedimentation appears to be governed by slow rate. In contrast to the biphasic curves, $F_7$ and $F_6$ showed approximately horizontal lines indicating a very slow sedimentation rate.

Compared to $F_1$, in $F_2$–$F_7$ containing solid dispersions of β-CD there was a significant decrease in viscosity as shown in Table 2. This may be due to a collapse of the three dimensional network and solubilization of the hydrated sod. CMC by β-CD. The suspension physical stability depends on the complete compatability among the suspending agent, β-cyclodextrin and drug. Good redispersiblity and high sedimentation volume could be seen even at low viscosity in the case of suspensions of celecoxib and β-CD. A minimum concentration of the suspending agent might be sufficient for this purpose.

The dissolution parameters of celecoxib from various suspensions are reported in Table 2. Dissolution efficiency (D.E.) was calculated by the method proposed by Khan (1975) and $D.E._{15}$ values were calculated from the dissolution data. The dissolute rate and efficiency were decreasing in the following order: $F_7 > F_6 > F_4 > F_3 > F_5 > F_2 > F_1$. The dissolution rate and efficiency was poor in $F_1$ and there

**Table 2: Stability evaluation parameters of celecoxib suspensions**

| Sl. No. | Formulation | pH | | Avg. particle size (μm) (x ± S.D.) | | Redispersibility (cycles) | | Viscosity (cPs) | | $D.E._{15}$ (%) (x ± S.D.) | | $T_{50}$ (min) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0C* | 21C | 0C | 21C | 0C | 21C | 0C | 21C | 0C | 21C | 0C | 21C |
| 1. | $F_1$ | 9.314 | 6.958 | 22.16 ± 4.72 | 34.85 ± 4.89 | 15 | 47 | 195.93 | 145.46 | 39.16 ± 3.21 | 37.70 ± 3.01 | 68.3 | 69.4 |
| 2. | $F_2$ | 6.794 | 6.126 | 20.52 ± 4.81 | 28.06 ± 5.51 | 2 | 8 | 91.15 | 63.76 | 39.25 ± 2.59 | 39.92 ± 2.17 | 47.5 | 39.0 |
| 3. | $F_3$ | 6.801 | 6.372 | 18.72 ± 3.61 | 25.73 ± 4.95 | 1 | 6 | 119.92 | 86.72 | 46.55 ± 1.92 | 47.12 ± 1.08 | 15.3 | 11.5 |
| 4. | $F_4$ | 7.190 | 6.807 | 15.85 ± 4.59 | 21.01 ± 3.80 | 1 | 5 | 138.18 | 95.92 | 54.94 ± 0.88 | 56.17 ± 1.92 | 10.5 | 9.3 |
| 5. | $F_5$ | 6.103 | 5.045 | 19.89 ± 5.61 | 26.12 ± 6.02 | 1 | 7 | 87.62 | 59.76 | 43.76 ± 0.29 | 42.93 ± 1.32 | 19.0 | 14.8 |
| 6. | $F_6$ | 6.051 | 5.172 | 15.12 ± 3.76 | 20.08 ± 4.31 | 1 | 5 | 98.79 | 70.57 | 60.07 ± 1.27 | 59.72 ± 3.25 | 10.0 | 8.6 |
| 7. | $F_7$ | 6.538 | 5.560 | 9.12 ± 3.05 | 12.90 ± 3.23 | 1 | 4 | 109.18 | 82.97 | 79.18 ± 1.05 | 80.52 ± 0.98 | 2.8 | 2.4 |

* cycle (s)

**Table 3: Effect of freeze-thaw cycling on sedimentation volume of celecoxib suspensions as a function of time**

| Sl. No. | Formulation | 0 cycle | | | | | 21 cycles | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Time (h) | | | | | Time (h) | | | | |
| | | 0 | 1 | 6 | 12 | 24 | 0 | 1 | 6 | 12 | 24 |
| 1. | $F_1$ | 1.00 | 0.94 | 0.72 | 0.68 | 0.55 | 1.00 | 0.68 | 0.39 | 0.37 | 0.18 |
| 2. | $F_2$ | 1.00 | 1.00 | 0.78 | 0.74 | 0.62 | 1.00 | 0.76 | 0.68 | 0.60 | 0.56 |
| 3. | $F_3$ | 1.00 | 1.00 | 0.96 | 0.90 | 0.88 | 1.00 | 0.84 | 0.76 | 0.72 | 0.70 |
| 4. | $F_4$ | 1.00 | 1.00 | 0.98 | 0.92 | 0.90 | 1.00 | 0.90 | 0.84 | 0.72 | 0.68 |
| 5. | $F_5$ | 1.00 | 1.00 | 0.90 | 0.86 | 0.82 | 1.00 | 0.84 | 0.70 | 0.66 | 0.62 |
| 6. | $F_6$ | 1.00 | 1.00 | 0.96 | 0.94 | 0.90 | 1.00 | 0.92 | 0.84 | 0.80 | 0.74 |
| 7. | $F_7$ | 1.00 | 1.00 | 0.98 | 0.96 | 0.92 | 1.00 | 1.00 | 0.90 | 0.88 | 0.88 |

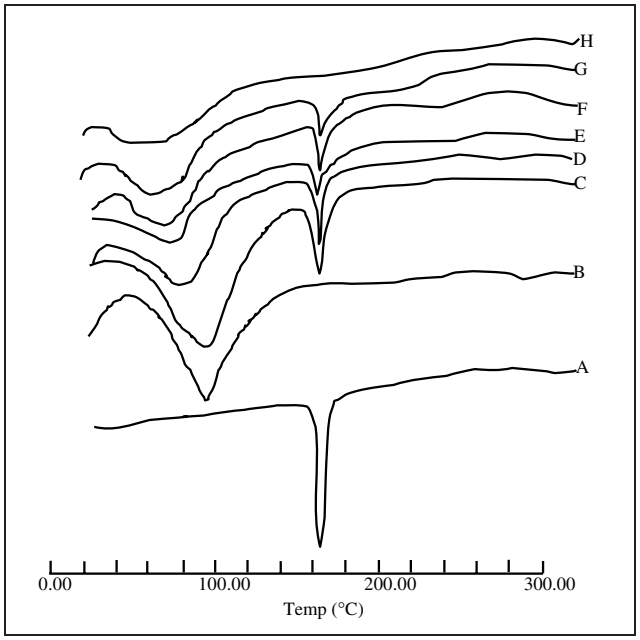


Fig.: DSC thermograms of celecoxib and its inclusion complexes; DSC thermograms (A) celecoxib (B) β-cyclodextrin (C) 1 : 1 physical mixture; (D) 1 : 1 slugged complex (E) 1 : 1 kneaded complex (F) 1 : 2 physical mixture; (G) 1 : 2 slugged complex (H) 1 : 2 kneaded complex

was a good increment in $F_2$–$F_7$. These results were further confirmed after stability studies. $F_7$ gave the highest dissolution efficiency initially and after 21 freeze-thaw cycles. Compared to $F_1$, there was a twofold increase in the dissolution rate and efficiency in the case of $F_7$.

The differential scanning calorimetry (DSC) thermograms of celecoxib and its solid dispersions with β-CD were shown in the Fig. The DSC thermogram of celecoxib exhibited an endothermic peak at 163.9 °C corresponding to its melting point (Budavari 2001). β-CD has shown a broad endothermic peak at 93.0 °C, which was the dehydration peak of crystal water of β-CD (Hees 2002). The thermograms of physical mixtures (both 1 : 1 and 1 : 2) and slugging powder (1 : 1) contained both the peaks of celecoxib and β-CD. In the thermograms of 1 : 2 slugged powder and 1 : 1 kneaded solid dispersions, the intensity of the endotherm at 163.9 °C was reduced in intensity and in the thermogram of the 1 : 2 kneaded solid dispersion the peak had disappeared, indicating the inclusion complex formation between celecoxib and β-CD.

There was a remarkable enhancement in the dissolution rate and physical stability of all the suspensions formulated. Complexation between celecoxib and β-CD might be the reason for this important conclusion.

## 3. Experimental

### *3.1. Materials*

Celecoxib was a gift sample from M/s Ranbaxy Laboratories, Gurgaon. Sodium carboxymethylcellulose (medium viscosity grade) was obtained as a gift sample from M/s Roland Pharmaceuticals, Berhampur. β-Cyclodextrin (Himedia), Tween® 80 (S.D. fine chemicals), methylparaben sodium (Loba Chemie), propylparaben sodium (Loba Chemie), sodium hydroxide (Qualigens fine chemicals) were purchased from a local agency. All other reagents and solvents were of analytical grade.

### *3.2. Preparation of celecoxib solid dispersions*

The solid dispersions of celecoxib and β-CD were prepared in 1 : 1 and 1 : 2 (celecoxib : β-CD) molar ratios according to three methods i.e. physical mixing, slugging and kneading. The physical mixtures of celecoxib and β-CD were obtained by triturating the accurately weighed powders for 30 min in a clean and dry mortar with a pestle. In the slugging method, accurately weighed quantities of celecoxib and β-CD were dry blended, compressed into slugs on a tablet machine at higher pressure and then powdered (Mitchell et al. 2003). In the kneading method, β-CD was wetted with water in a mortar and kneaded to form a paste. Then celecoxib dissolved in a sufficient amount of acetone was added. The sample was kneaded for approximately 60 min and dried to constant mass at 105 °C and then powdered (Cwiertnia et al. 1999).

### *3.3. Thermal analysis*

DSC patterns of the samples were obtained with Shimadzu DSC-50 instrument using vented aluminium pans. The analysis was performed in a nitrogen atmosphere. All samples were run at a scanning rate of 10 °C $min^{-1}$, from 30 to 300 °C. The instrument was calibrated with standard indium.

### *3.4. Preparation of celecoxib suspensions*

Suspensions containing 100 mg of celecoxib in 5 ml were prepared (Table 1). Accurately weighed quantities of celecoxib or its solid dispersions was taken in a mortar and were levigated with a solution of wetting agent and a small portion of sod. CMC mucilage. When a smooth paste has been formed, the rest of the mucilage was added in divided portions while triturating the contents. Other ingredients were added one after another, mixed, and the suspension was transferred to a measuring jar and adjusted to 100 ml.

### *3.5. Stability testing*

Stability studies were conducted by subjecting all the suspensions to freeze-thaw cycling (Nash 1996). The suspensions in triplicate were first kept in a refrigerator at 6 ± 0.5 °C for 24 h. After removing from refrigerator, the samples were allowed to attain room temperature and then exposed to 40 ± 0.5 °C in a thermostatically controlled oven for 24 h. The samples were then removed and allowed to cool to attain room temperature. This completes one freeze-thaw cycle. The process was repeated and the samples were collected after 21 of freeze-thaw cycles.

### *3.6. Particle size measurement*

Size of celecoxib particles in the suspensions was measured by optical microscopy. The eye piece micrometer was calibrated using a stage micrometer of American Optical Company, New York. Average particle size and standard deviation of 200 particles was determined in each case.

### *3.7. Sedimentation analysis*

The suspensions were transferred to 50 ml stoppered measuring cylinders and were subjected to stability testing. The volume of sediment formed was noted at suitable time intervals. The sedimentation volume (Swarbrick 1974), ratio of the ultimate height ($H_u$) of the sediment to the initial height ($H_o$) of the suspension was calculated. The number of cycles for complete redispersibility was noted by rotating the suspension containing bottles clockwise upside down through 180° in a semicircle path and back in anticlockwise direction repeatedly.

### *3.8. Other parameters*

The viscosity of the suspensions prepared was measured using a Brookfield viscometer (Model: DV-I+) at 100 rpm with spindle no.1 at 35 °C. The pH of the prepared suspensions was measured by using ELICO INDIA, pH ANALYSER (Model LI 612).

### *3.9. Estimation of celecoxib*

Celecoxib was estimated by measuring the absorbance at 252 nm (Shankar DG et al. 2001) with an ELICO SL-159 UV-vis spectrophotometer and 0.1 N NaOH as the reagent. The method obeyed beer's law in the concentration range of 5–25 μg/ml.

### *3.10. Dissolution rate study*

The dissolution rate of celecoxib from various suspensions was studied (Abdou 1989) on Tab machines six stage digital dissolution rate test apparatus USP XXI using 900ml of purified water containing 0.2% w/v sodium lauryl sulphate as dissolution medium at a paddle speed of 50 rpm and a temperature of 37 ± 1 °C. A sample of suspension equivalent to 100 mg of celecoxib was employed in each test. A 5 ml aliquot of dissolution medium was withdrawn at different time intervals for about 60 min, filtered, and suitably diluted. Drug content was estimated spectrophotometrically at 252 nm using 0.1 N NaOH as the reagent. The test was repeated six times and the average values were reported.

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