Formulation Development and *In-vitro* Evaluation of Mouth Dissolving Tablets of Celecoxib Employing Distinctive Proportion of Disintegrating Agents

Daljit Masih¹, Rajesh Gupta²

¹J.J.T. University, Chudela, Jhunjhunu, (Rajasthan), India  
²Sri Sai College of Pharmacy, Pathankot, (Punjab), India

**Abstract**

In present study we planned to formulate and evaluate mouth dissolving tablets of Celecoxib using superdisintegrants agents namely Crospovidone and Sodium starch glycolate in various ratios. The mouth dissolving tablets were prepared by direct compression method using Crospovidone and Sodium starch glycolate. Tablets blends were evaluated for loose bulk density, tapped bulk density, compressibility index and angle of repose, shows satisfactory results. The compressed tablets were then evaluated for various physical tests like thickness, friability, hardness, weight variation, wetting time, water absorption ratio and disintegration test by using standard procedures. The results of all these tests were found to be satisfactory. The *in-vitro* dissolution study was carried out for 14 min using paddle method in phosphate buffer (pH 6.8) as dissolution media. The data of *in-vitro* dissolution of tablets revealed that 76 to 100% of drug release from various formulations at 14 min. The formulation C7 exhibited better results as compared to other formulations.

**Keywords:** Celecoxib, Crospovidone, Sodium starch glycolate, Mouth dissolving tablets

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**1 Introduction**

The oral route of drug administration is mostly used and acceptable comparable to other dosage form which produces systemic delivery of therapeutic agents. The low cost of oral administration enhance it demands. Among oral route of administration, the tablets are widely used because of their special properties such as suitability to self-administration, improved stability, accurate dosing, ease of handling, versatility with respect to type and dose of the drug, and suitability to scale up. But sometime tablets fails to prove it’s useful in some circumstance. The elderly patient face problem in taking conventional oral dosage forms like solutions, suspensions, tablets, capsules, due to hand tremors and dysphagia. The pediatric patients face difficulties in swallowing of tablets which leads to poor compliance. The mentally ill, developmentally disabled patients, and patients who are uncooperative or who are suffering from severe nausea gets problems in taking conventional oral dosage form¹⁴. However, this form of dosage has some limitation like motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, but one important drawback is ‘dysphagia’ or difficulty in swallowing⁶. Additionally, there are many instances where tablets may not suit the given indication. Above mentioned task can be overcome by substituting conventional tablets and capsules with mouth dissolving tablets.

Celecoxib is the selective COX-2 inhibitor, it belong to nonsteroidal anti-inflammatory category. It has highly demand in the healing of osteoarthritis, rheumatoid arthritis and dysmenorrhea in adult patients. Celecoxib tablets have rate limiting steps in the process of drug absorption due to its poor water solubility properties. Additionally, it displayed poor absorption in large intestine. Conventional Celecoxib tablet available in the market are not suitable for urgent response of drug where quick onset of action of drug is required. The rapidly disintegrating tablets in oral cavity can be swallowed with a small amount of water or saliva⁶⁹. Hence, an attempt was made to improve the dissolution of Celecoxib through the formulation of mouth-dissolving tablets with appropriate mechanical strength, which would disintegrate in oral cavity, in less than 30 seconds, and would provide an immediate relief to patients due to its faster dissolution in gastrointestinal tract.

**2 Materials and Methods**

**2.1 Materials**
Celecoxib was obtained from Centaur Pharmaceuticals Pvt Ltd Goa. Crospovidone and sodium starch glycolate were obtained as gift samples from Micro Labs, Bangalore.

2.2 Methods

2.2.1 Preparation of mouth dissolving tablets

Tablets of Celecoxib were prepared by direct compression method. All the formulation ingredients mentioned in formulation table 1 were weighed accordingly and mixed in a mortar and pestle. This powder blend was then allowed to dry for few moments and then again mixed well and passed through sieve no 60. Then blend were used for further processing.

2.2.2 Evaluation of pre-compression characteristics of powder blend

Powder blend prepared were evaluated for various rheological properties like bulk density, tapped density, Hausner's ratio, angle of repose by using standard procedures. All these properties were carried out in triplicate (n=3) and average values were reported.

2.2.3 Bulk density

Bulk density was determined by placing the powders blend in a measuring cylinder and the total volume is noted. The weight of powder bed was determined by using digital weighing balance. Bulk density was calculated using the following formula:

$$\text{Bulk Density} = \frac{\text{Weight of the powder}}{\text{Volume of the powder}}$$

2.2.4 Tapped density

Tapped density was determined by taking the dried powders in a measuring cylinder and measures the volume of powders after 100 tapping's and take weight of the total powders.

$$\text{Tapped Density} = \frac{\text{Weight of the powder}}{\text{Tapped Volume of the powder}}$$

2.2.5 Angle of repose

Angle of repose was determined by measuring the height and radius of the heap of the powder bed. A cylindrical two side open tube of 6 cm length is place on graph paper. Powders are placed in the tube and slowly removed the tube vertically. With the help of scale the height and radius of the heap were measure and note.

$$\theta = \tan^{-1} \frac{h}{r}$$

Where, h = height of heap of granular bed, r = radius of heap of granular bed.

2.2.6 Hausner's ratio

It is expressed in percentage and is expressed by

$$H = \frac{D_t}{D_b}$$

Where $D_t$ is the tapped density of the powder

$D_b$ is the bulk density of the powder.

2.2.7 Evaluation of compression characteristics of mouth dissolving tablets

The prepared tablets were evaluated for their thickness, friability, hardness, weight variation and dissolution test by using standard procedures.

2.2.8 Weight variation test

20 tablets are taken and their weight is determined individually and collectively on a digital weighting balance. The average weight of one tablet is determined from the collective weight. Note more than 2 of the individual weights may deviate from the average weight by more than the percentage deviation given in the monographs and none should deviate by more than twice that percentage given in the monographs.

2.2.9 Thickness test

The tablets were evaluated for their thickness using a venirer caliper measured in terms of micrometer. Averages of three readings were taken and the results were tabulated (n = 3)

2.2.10 Hardness test

Prepared tablets were evaluated for their hardness by using Monsanto hardness tester. The hardness was measured in terms of kg/cm². Triplicate readings were taken and average was determined.

2.2.11 Friability test

Roche friabilator was used for testing the friability of the tablets. For this test, 20 tablets were weighted accurately and placed in the friabilator chamber and rotated at 25 rpm for a period of 4 min. Tablets were again weighted and the percentage weight loss was determining by using formula given below.

$$\% \text{ Friability} = \left(\frac{(W_1 - W_2)}{W_1}\right) \times 100$$

Where,

$W_1$ = Weight of tablet before test

$W_2$ = Weight of tablet after test.

2.2.12 Drug content

Three tablets were weighed and ground in a mortar with pestle to get fine powder. Powder equivalent to the mass of one tablet was dissolved in pH 6.8 phosphate. This solution was diluted with pH 6.8 phosphate buffer. The absorbance of diluted sample of Celecoxib was measured at 252 nm in UV-Visible Spectrophotometer and drug
content was calculated using equation obtained from a standard calibration curve.

2.2.13 Wetting time

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of purified water, then a tablet was placed on the paper and the time required for complete wetting was measured.

Wetting time corresponds to the time taken for the tablet to disintegrate when placed gently on the tissue paper in a Petridish. Less wetting time indicates more porous tablets.

2.2.14 Water absorption ratio

A piece of tissue paper folded twice was placed in a small petri plate containing 6 ml of distilled water. A tablet was put on the paper and time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio R was calculated using equation.

\[ R = 100 \left( \frac{W_a - W_b}{W_b} \right) \]

Where, \( W_a = \) weight of the tablet before water absorption

\( W_b = \) weight of the tablet before water absorption

2.2.15 In-vitro disintegration time

The process of breakdown of a tablet into smaller particles is called as disintegration. The in vitro disintegration time of a tablet was determined using disintegration test apparatus as per IP specifications. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 (simulated saliva fluid) maintained at 37±2 °C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 6.8 maintained at 37±2 °C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded

2.2.16 In-vitro drug release study

In vitro release study was performed using tablet dissolution test apparatus USP XXIII, apparatus I. The dissolution medium consists of 900 mL phosphate buffer pH6.8 maintained at 37 ± 1°C rotated at 50 rpm. At different interval of time 10 mL sample was withdrawn and replaced with fresh medium. 10 mL sample was diluted to 100 mL phosphate buffer pH 6.8, the aliquots were assayed spectrophotometrically at 252 nm for Celecoxib.

3 Results and Discussion

3.1 Evaluation of pre-compression characteristics of powder blend

The powders were evaluated for bulk density, tapped density, Hausner’s ratio and angle of repose and consistency in data obtained as indicated by their standard deviation values shown in table 2.

Bulk density and tapped density of different formulations were calculated. The result of bulk density range from 0.473 to 0.483 and tapped density from 0.467 to 0.513. Hausner’s ratio was found to be in between 1.12 to 1.19; and Compressibility index from 11.39 to 14.09. Angle of repose showed good to excellent flow properties of the powdered blend (Table 2).

The tablet dimension includes diameter and thickness of tablets. Thickness of all formulations was found to be between 2.25 to 2.84 (Table 3). No significant difference was observed in the thickness of individual tablet from the average value. No significant difference was observed in the weight of individual tablets form the average weight.

From table 3 it has been observed that tablet weights of all batches were found with in recommended USP limits, between 218 ± 1 mg. Hardness of tablets of all batches are in between 3.14 to 3.72 (Kg/cm²) which is acceptable limits, which shows in the literature. Friability of all the formulation showed % friability less than 1% that indicates ability of tablets to withstand shocks, which may encountered. The data of uniformity of content which was performed by UV spectroscopy indicated that tablets of all batches had drug content within USP limits i.e. between 97.43 to 99.34%. In guidance of industrial scientist different parameter of tablet like flow property, dimension hardness, drug content etc. were studied which results in successful trials.

The wetting time and water absorption ratio were found to be 13.25 to 27.38 seconds and 84.73 to 40.62 seconds (Table 4), respectively. The disintegration time of mouth dissolving tablet ranges from 18.16 to 31.84 seconds (Table 4).

From above result it has been observed that C7 formulation exhibited excellent wetting time, water absorption ratio and disintegration time as compared to other formulations. Moreover the C8 formulation exhibited lowest wetting time and disintegration time; and highest water absorption ratio. This parameter enhances due to gelling and its subsequent viscosity producing effects.

3.2 In vitro drug release studies

Figure 1 displayed in-vitro dissolution of tablets, it revealed that 76 to 100% of drug release from various formulations. The 50% of the drug was released from the C7 and C8 within 4 minutes. The rapid drug dissolution might be due to easy breakdown of particle by superdisintegrant action. From in vitro dissolution data, it was...
observed that 98.89% of Celecoxib released in 14 minutes indicates that the tablet complies as per IP specifications, that is, 85%–110%. The dissolution rate was found to increase linearly with increase in the concentration of superdisintegrant. Mechanism it followed was wicking and swelling with minimum gelling. It was observed that C8 formulation released 98.73% drug in 12 minutes. This formulation has maximum amount of superdisintegrant that may cause tablets fragile.

Table 1: Formulation of mouth dissolving Celecoxib tablet

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>C1</th>
<th>C2</th>
<th>C3</th>
<th>C4</th>
<th>C5</th>
<th>C6</th>
<th>C7</th>
<th>C8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Sodium starch glycolate</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>10</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Mannitol</td>
<td>90</td>
<td>88</td>
<td>86</td>
<td>84</td>
<td>88</td>
<td>86</td>
<td>84</td>
<td>82</td>
</tr>
<tr>
<td>Mg. Stearate</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Talc</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Aspartame</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Theoretical Weight</td>
<td>218</td>
<td>218</td>
<td>218</td>
<td>218</td>
<td>218</td>
<td>218</td>
<td>218</td>
<td>218</td>
</tr>
</tbody>
</table>

Table 2: Data of pre-compression characteristics of Celecoxib powder blend

<table>
<thead>
<tr>
<th>Parameters</th>
<th>C1</th>
<th>C2</th>
<th>C3</th>
<th>C4</th>
<th>C5</th>
<th>C6</th>
<th>C7</th>
<th>C8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Angle of repose* ± S.D.</td>
<td>29° 37' ± 0.02</td>
<td>34° 15' ± 0.11</td>
<td>32° 54' ± 0.05</td>
<td>26° 72' ± 0.08</td>
<td>35° 31' ± 0.09</td>
<td>30° 67' ± 0.13</td>
<td>28° 48' ± 0.21</td>
<td>36° 81' ± 0.05</td>
</tr>
<tr>
<td>Mean Apparent bulk density* (g/cm³) ± S.D</td>
<td>0.412±0.01</td>
<td>0.428±0.06</td>
<td>0.439±0.03</td>
<td>0.427±0.05</td>
<td>0.409±0.02</td>
<td>0.483±0.09</td>
<td>0.451±0.03</td>
<td>0.437±0.07</td>
</tr>
<tr>
<td>Mean Tapped bulk density* (g/cm³) ± S.D.</td>
<td>0.467±0.04</td>
<td>0.483±0.08</td>
<td>0.511±0.05</td>
<td>0.495±0.03</td>
<td>0.486±0.07</td>
<td>0.548±0.05</td>
<td>0.513±0.06</td>
<td>0.502±0.03</td>
</tr>
<tr>
<td>Compressibility Index* (%)</td>
<td>11.78</td>
<td>11.39</td>
<td>14.09</td>
<td>13.73</td>
<td>15.84</td>
<td>11.86</td>
<td>12.08</td>
<td>12.94</td>
</tr>
<tr>
<td>Hausner’s Ratio*</td>
<td>1.13±0.05</td>
<td>1.12±0.03</td>
<td>1.16±0.08</td>
<td>1.16±0.06</td>
<td>1.19±0.03</td>
<td>1.13±0.07</td>
<td>1.14±0.02</td>
<td>1.15±0.01</td>
</tr>
</tbody>
</table>

*Value shown in tables is mean of three determinations

4 Conclusions

It was concluded that mouth dissolving tablets of Celecoxib can be successfully prepared by direct compression techniques using various superdisintegrants for the better patient compliance and effective therapy. It was also found that the superdisintegrants are effective at an optimum concentration, on increasing the ratio of Crospovidone and Sodium starch glycolate concentration above their optimum concentration this enhance the gelling effects of formulation. The formulation C7 exhibited better results as compared to other formulations. Further these formulations can be select for in vivo study.
5 References


Table 3: Evaluation of Celecoxib mouth dissolving tablets

<table>
<thead>
<tr>
<th>Parameters</th>
<th>C1</th>
<th>C2</th>
<th>C3</th>
<th>C4</th>
<th>C5</th>
<th>C6</th>
<th>C7</th>
<th>C8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniformity of weight (mg)*</td>
<td>218.19±1.53</td>
<td>218.53±1.28</td>
<td>217.62±1.17</td>
<td>217.35±1.82</td>
<td>218.47±1.54</td>
<td>217.73±1.47</td>
<td>218.26±1.63</td>
<td>217.86±1.34</td>
</tr>
<tr>
<td>Thickness (mm)*</td>
<td>2.25±0.02</td>
<td>2.84±0.03</td>
<td>2.41±0.05</td>
<td>2.64±0.04</td>
<td>2.36±0.06</td>
<td>2.47±0.02</td>
<td>2.73±0.05</td>
<td>2.28±0.01</td>
</tr>
<tr>
<td>Friability (%)*</td>
<td>0.18±0.03</td>
<td>0.15±0.05</td>
<td>0.21±0.02</td>
<td>0.27±0.06</td>
<td>0.22±0.03</td>
<td>0.28±0.02</td>
<td>0.23±0.04</td>
<td>0.21±0.05</td>
</tr>
<tr>
<td>Tablet Hardness (Kp)*</td>
<td>3.43±0.05</td>
<td>3.59±0.02</td>
<td>3.14±0.04</td>
<td>3.72±0.01</td>
<td>3.38±0.05</td>
<td>3.19±0.06</td>
<td>3.24±0.05</td>
<td>3.17±0.02</td>
</tr>
<tr>
<td>Assay (%)</td>
<td>99.21±0.18</td>
<td>98.53±0.35</td>
<td>98.81±0.48</td>
<td>97.43±0.52</td>
<td>98.59±0.05</td>
<td>99.34±0.41</td>
<td>98.17±0.37</td>
<td>98.28±0.85</td>
</tr>
</tbody>
</table>

*Average of three times measure

Table 4: Evaluation of wetting time, water absorption ratio and in-vitro disintegration time of mouth dissolving tablets

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Wetting time (sec)</th>
<th>Water absorption ratio (sec)</th>
<th>In-vitro disintegration time (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>27.38±0.18</td>
<td>40.62±1.35</td>
<td>31.84±0.14</td>
</tr>
<tr>
<td>C2</td>
<td>25.19±0.21</td>
<td>48.45±1.17</td>
<td>29.47±0.08</td>
</tr>
<tr>
<td>C3</td>
<td>21.45±0.02</td>
<td>59.81±1.24</td>
<td>26.53±0.19</td>
</tr>
<tr>
<td>C4</td>
<td>19.62±0.08</td>
<td>70.53±1.56</td>
<td>20.28±0.03</td>
</tr>
<tr>
<td>C5</td>
<td>22.85±0.12</td>
<td>55.91±1.09</td>
<td>26.46±0.07</td>
</tr>
<tr>
<td>C6</td>
<td>19.73±0.06</td>
<td>66.48±1.42</td>
<td>25.78±0.11</td>
</tr>
<tr>
<td>C7</td>
<td>16.54±0.05</td>
<td>74.12±1.26</td>
<td>22.34±0.08</td>
</tr>
<tr>
<td>C8</td>
<td>13.25±0.11</td>
<td>84.73±1.85</td>
<td>18.16±0.04</td>
</tr>
</tbody>
</table>

Value shown in tables is mean of three determinations

Fig 1: In-vitro drug release profile of Celecoxib mouth dissolving tablets


