Original Article

Design and Evaluation of Etoricoxib Fast Dissolving Tablets

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ABSTRACT

The concept of Fast dissolving drug delivery system emerged from the desire to provide patient with more conventional means of taking their medication. It is difficult for many patients to swallow tablets and hard gelatin capsules. Hence, they do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy. In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult. Such problems can be resolved by means of Fast dissolving tablets when put on tongue these tablets disintegrate and dissolve rapidly in saliva without need of drinking water. The faster the drug disintegrates in to solution, the quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and esophagus as saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form. The objective of the present study is to develop Etoricoxib Fast dissolving tablets. In this present study an attempt was made to improve on set of action as well as to enhance bioavailability of drug. Systematic studies were conducted using different concentration of different superdisintegrants i.e. Cross Carmellose sodium and Sodium starch glycolate. All the prepared systems were evaluated for the different properties. Before the preparation of tablets, preformulation studies were conducted like micromeritic properties to assess flowability, compressibility properties and solubility studies. And all the formulations gave good results for above preformulation studies.

Key words: RP-HPLC, Exemestane, method development and validation, acetonitrile, buffer.

INTRODUCTION

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. Oral administration is the most popular route for systemic effects due to its ease of administration, pain avoidance, versatility and patient compliance, less expensive to manufacture. The oral route
remains the perfect route for the administration of therapeutic agents because the low cost of therapy, manufacturing and ease of administration lead to high levels of patient compliance. Many patients have difficulty swallowing tablets and hard gelatin capsules and consequently do not take medications as prescribed. It is estimated that 50% of the population is affected by this problem, which results in a high incidence of noncompliance and ineffective therapy. Oral tablet administration to patients is a significant problem and has become the object of public attention. The problem can be resolved by the creation of rapidly dispersing or dissolving oral forms, which do not require water to aid swallowing. The dosages forms are placed in the mouth, allowed to disperse or dissolve in the saliva, and then are swallowed in the normal way.

The concept of Fast Disintegrating Drug Delivery System emerged from the desire to provide patient with more conventional means of taking their medication. It is difficult for many patients to swallow tablets and hard gelatin capsules. Hence they do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy. In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult. Particularly the difficulty is experienced by pediatric and geriatric patients. Such problems can be resolved by means of Fast Dissolving Tablet. When put on tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva.

**Name of the Drug: Etoricoxib**

**Description:** Etoricoxib is a new COX-2 selective inhibitor. Current therapeutic indications are: treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, chronic low back pain, acute pain and gout. Like any other COX-2 selective inhibitor, Etoricoxib selectively inhibits isoform 2 of cyclo-oxigenase enzyme (COX-2). This reduces the generation of prostaglandins (PGs) from arachidonic acid.

**IUPAC Name:** 5-chloro-3-(4-methanesulfonylphenyl)-2-(6-methylpyridin-3-yl) pyridine

**Molecular formula:** C₁₈H₁₅ClN₂O₂S

**Molecular weight:** 358.84

**Structure:**

![Structure of Etoricoxib](image)

**Category:** Non steroidal Anti inflammatory drug

**Dose:** oral administration contains either 30, 60, 90 or 120 mg of etoricoxib

**PHARMACOLOGY:**

**Mechanism of action:**

Etoricoxib is a member of a new class of agents called Coxibs. Etoricoxib is a potent, orally active cyclooxygenase-2 (COX-2) specific inhibitor within, and significantly above, the clinical dose range. Two isoforms of cyclooxygenase have been identified: cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). COX-1 is responsible for prostaglandin-mediated normal physiologic functions such as gastric cytoprotection and platelet aggregation. Inhibition of COX-1 by nonselective NSAIDs has been associated with gastric damage and inhibition of platelet aggregation. COX-2 has been shown to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. Selective inhibition of COX-2 by etoricoxib (within the clinical dose range) decreases these clinical signs and symptoms.
with decreased potential for GI toxicity and effects on platelet aggregation.

**INDICATIONS**

- Symptomatic treatment of the signs and symptoms of osteoarthritis (OA)
- Treatment of acute gouty arthritis
- Treatment of acute pain, including that related to primary dysmenorrhoea and minor dental procedures

**PREPARATION OF STANDARD CALIBRATION CURVE FOR ETORICOXIB:**

100mg of Etoricoxib pure drug was accurately weighed & transferred into a 100ml volumetric flask, dissolved in little quantities of methanol, then made up to 100ml with methanol (1000µg/ml). From this solution, 10ml of solution was withdrawn into a 100ml volumetric flask & made up to 100ml with 6.8 phosphate buffer to get a concentration of 100µg/ml. From this, again pipette out 10ml of solution & diluted to 100ml with 6.8 phosphate buffer to get a concentration of 10µg/ml. Absorbance of this was measured at 235 nm using UV/VIS spectrophotometer against blank (6.8phosphate buffer).

**Evaluation of API and Blend (Pre-compression Parameters):**

**Angle of Repose:**

The flow property was determined by measuring the Angle of Repose. In order to determine the flow property, the Angle of Repose was determined. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal. Angle of repose= tan⁻¹ (h/r)

Where, h = height r = radius

**Procedure:**

- The sample was passed through the funnel slowly to form a heap.
- The height of the powder heap formed was measured.
- The circumference formed was drawn on the graph paper. The radius was measured and the angle of repose was determined. This was repeated three times for a sample.

**Bulk density:**

Bulk density is ratio of given mass of powder and its bulk volume. Bulk density was determined by measuring the volume of known mass of powder sample that has been passed through the screen in to graduated cylinder or through volume measuring apparatus in to cup.

\[
\text{Bulk density} = \frac{M}{V_0}
\]

Where M= mass of the powder; V₀= bulk volume of the powder.

**Tapped density:**

A known quantity of powder was transferred to a graduated cylinder and volume V₀ was noted. The cylinder fixed to a density determination apparatus, tapped for 500 times then reading was observed. The density is achieved by mechanically tapped by a measuring cylinder containing the powder sample. After observing the initial volume the cylinder is mechanically tapped and volume reading were taken until little further volume changes is observed.

\[
\text{Tap density} = \frac{M}{V_r}
\]

Where M = mass of the powder, V_r = final tapping volume of the powder.

**Compressibility index and Hausner’s ratio:**
**Basic methods for the determination of compressibility index and Hausner's ratio:** While there are some variations in the method of determining the compressibility index and Hausner’s ratio, the basic procedure is to measure the unsettled apparent volume, \( V_o \), and the final tapped volume, \( V_f \), of the powder after tapping the material until no further volume changes occur. The compressibility index and the Hausner’s ratio are calculated as follows:

\[
\text{Compressibility index} = 100 \times \frac{V_o - V_f}{V_o}
\]

\[
\text{Hausner's ratio} = \frac{V_o}{V_f}
\]

Where, \( V_o \) = apparent volume, \( V_f \) = final tapped volume.

Alternatively, the compressibility index and hausner ratio may be calculated using measured values of bulk density and tapped density as follows:

\[
\text{Compressibility index} = 100 \times \frac{\text{tapped density}}{\text{bulk density}}
\]

\[
\text{Hausner's ratio} = \frac{\text{tapped density}}{\text{bulk density}}
\]

In a variation of these methods, the rate of consolidation is sometimes measured rather than, or in addition to, the change in volume that occurs on tapping. For the compressibility index and the hausner ratio, the generally accepted scale of flow ability is described in the following table.

Flow properties and corresponding Angle of repose, Compressibility index and Hausner’s ratio:

<table>
<thead>
<tr>
<th>S.No</th>
<th>Flow properties</th>
<th>Angle of repose(θ)</th>
<th>Compressibility Index (%) or Carr’s index</th>
<th>Hausner’s ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Excellent</td>
<td>25-30</td>
<td>&lt;10</td>
<td>1.00-1.11</td>
</tr>
<tr>
<td>2</td>
<td>Good</td>
<td>31-35</td>
<td>11-15</td>
<td>1.12-1.18</td>
</tr>
<tr>
<td>3</td>
<td>Fair</td>
<td>36-40</td>
<td>16-20</td>
<td>1.19-1.25</td>
</tr>
<tr>
<td>4</td>
<td>Passable</td>
<td>41-45</td>
<td>21-25</td>
<td>1.26-1.34</td>
</tr>
<tr>
<td>5</td>
<td>Poor</td>
<td>46-55</td>
<td>26-31</td>
<td>1.35-1.45</td>
</tr>
<tr>
<td>6</td>
<td>Very poor</td>
<td>56-65</td>
<td>32-37</td>
<td>1.46-1.59</td>
</tr>
<tr>
<td>7</td>
<td>Very very poor</td>
<td>&gt; 66</td>
<td>&gt;38</td>
<td>&gt;1.6</td>
</tr>
</tbody>
</table>

*EVALUATION OF TABLETS (Post Compressional Parameters):*

The quantitative evaluation and assessment of a tablets chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, disintegration and dissolution characters.

1. **Physical Appearance:**
   The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, color, presence or absence of odour, taste etc.

2. **Size & Shape:**
   It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micro-meter or by other device. Tablet thickness should be controlled within a ± 5% variation of standard value.
3. Weight variation test:

This is an in process quality control test to ensure that the manufacturers control the variation in the weight of the compressed tablets, different pharmacopoeia specify these weight variation tests. These tests are primarily based on the comparison of the weight of the individual tablets (xi) of a sample of tablets with an upper and lower percentage limit of the observed sample average (x-mean). The USP has provided limits for the average weight of uncoated compressed tablets. These are applicable when the tablet contains 50mg or more of the drug substance or when the latter comprises 50% or more, by weight of the dosage form.

Method:

Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

Table 6: Limits for Tablet Weight variation test:

<table>
<thead>
<tr>
<th>Average weight of tablet (mg)</th>
<th>% Difference allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>130 or less</td>
<td>10 %</td>
</tr>
<tr>
<td>From 130 to 324</td>
<td>7.5 %</td>
</tr>
<tr>
<td>&gt; 324</td>
<td>5 %</td>
</tr>
</tbody>
</table>

4. Content Uniformity:

The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch. Due to increased awareness of physiological availability, the content uniformity test has been included in the monographs of all coated and uncoated tablets and all capsules intended for oral administration where the range of size of the dosage form available include 50mg or smaller sizes.

Method: Randomly select 30 tablets. 10 of these assayed individually. The Tablet pass the test if 9 of the 10 tablets must contain not less than 85% and not more than 115% of the labeled drug content and the 10th tablet may not contain less than 75% and more than 125% of the labeled content. If these conditions are not met, remaining 20 tablets assayed individually and none may fall outside of the 85 to 115% range.

Friability:

Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator.

Method: A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked.

The percentage friability was determined by the formula:

\[
\% \text{ friability} = \frac{(W_1 - W_2)}{W_1} \times 100
\]

\(W_1 = \) Weight of tablets before test and \(W_2 = \) Weight of tablets after test

Wetting time: Five circular tissue papers of 10-cm diameter were placed in a petridish with a 10-cm
diameter. 10 ml of water at 37\(^{0}\)C\(\pm\)0.5\(^{0}\)C containing eosin, a water-soluble dye, was added to the petridish. A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time. Six tablets from each formulation batch were tested randomly and the average reading noted.

**Water absorption ratio:** A piece of tissue paper folded twice was placed in a small Petri dish containing 6ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed.

Water absorption ratio R, was determined using following equation

\[
R = \frac{W_a - W_b}{W_b} \times 100
\]

Where \(W_a\) = weight of tablet after absorption

\(W_b\) = weight of tablet before absorption

**Disintegration time:**

According to the European pharmacopoeia the fast disintegrating or Oro-dispersible tablets should disintegrate within 3minutes without leaving any residue on the screen.

**Disintegration test:**

For a drug to be absorbed from a solid dosage form after oral administration, it must first be in solution, and the first important step toward this condition is usually the break-up of the tablet; a process known as disintegration. The disintegration test is a measure of the time required under a given set of conditions for a group of tablets to disintegrate into particles which will pass through a 10 mesh screen. Generally, the test is useful as a quality assurance tool for conventional dosage forms.

**Method:** The U.S.P. device to test disintegration uses 6 glass tubes that are long open at the top and 10 mesh screens at the bottom end. To test for disintegration time, one tablet is placed in each tube and the basket rack is positioned in a 1-L beaker of water, simulated gastric fluid or simulated intestinal fluid at 37 \(\pm\) 20 \(^{0}\)C such that the tablet remain 2.5 cm below the surface of liquid on their upward movement and not closer than 2.5 cm from the bottom of the beaker in their downward movement. Move the basket containing the tablets up and down through a distance of 5-6 cm at a frequency of 28 to 32 cycles per minute. Floating of the tablets can be prevented by placing perforated plastic discs on each tablet. According to the test the tablet must disintegrate and all particles must pass through the 10 mesh screen in the time specified. If any residue remains, it must have a soft mass. If one or two tablets fail to disintegrate, the test is repeated using 12 tablets.

**2.2.1.3. Drug release**

The drug release from the Etoricoxib tablets was investigated in a USP-II (paddle) apparatus, 900 ml of 6.8 pH Phosphate buffer (50 rpm, 37\(^{0}\)C). At predetermined time intervals, 5ml samples were withdrawn and then analyzed with UV spectrophotometry at \(\lambda_{max}=235\)nm.

**Dissolution study of Etoricoxib of fast disintegrating tablets:**

- **Bath temperature** : 37 \(\pm\) 0.5\(^{0}\)C
- **Dissolution media** : 6.8 pH buffer
- **Volume of dissolution media** : 900 ml
- **Aliquot withdrawn** : 5 ml
- **Dissolution apparatus** : USP type II (paddle)
- **Revolutions per minute (Speed)** : 50

**FORMULATION DEVELOPMENT**

**Procedures:**
The Purposes of key ingredients included in the formulation.

Table 7: List of used Excipients in the formulation:

<table>
<thead>
<tr>
<th>S.NO</th>
<th>API CHARACTERISATION</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Physical Appearance</td>
<td>a white to slightly pink crystalline powder</td>
</tr>
<tr>
<td>2</td>
<td>Melting point</td>
<td>137 °C</td>
</tr>
<tr>
<td>3</td>
<td>solubility</td>
<td>Slightly soluble in Water, Soluble in Chloroform, DMSO and Methanol</td>
</tr>
</tbody>
</table>

Formulation:

1. Sieve the Drug, Lactose anhydrous, Mannitol pass through 40 # mesh and then transfer it to poly bag containing above mixture and mix it for 3 minutes then transferred into mortar and pestle and granulated by non aqueous granulation method using Isopropyl alcohol and dried for 10min.
2. Remaining excipients (Super disintegrants and Sweetner) pass through 40 # mesh and then transfer it to poly bag containing above mixture and mix it for 3 minutes.
3. And finally add the Glidant (Magnesium Stearate) and Lubricant (Talc) to the above blend mix it for 2min.
4. Compressed the above lubricated blend by using 6mm round punches.

RESULTS AND DISCUSSION

The present investigation was undertaken to formulate and evaluate the fast disintegrating tablets of Ondansetron by direct compression method using different concentrations of different superdisintegrants i.e. Premellose (Cross carmellose sodium) and Sodium starch glycolate. Superdisintegrants are generally used by formulation scientists for developing FDTs or for improvement of solubility and bioavailability for active pharmaceutical ingredients. The primary requirement for both dosage forms is quicker disintegration.

Physical properties and Flow properties of API:

Preparation of standard graph for Ondansetron

Standard solutions in the range of 2 to 10 mcg/ml were prepared and absorption values were recorded at 235 nm against the reference. From this data, the standard curve of Etoricoxib was obtained by plotting absorbance on Y-axis against concentration on X-axis.
The most important parameter that needs to be optimized in the development of fast disintegrating tablets is the disintegration time of tablets. In the present study disintegration time of all batches were found in the range of 15 to 30 sec fulfilling the official requirements (less than 1 min) for disintegrating tablets.

**Wetting time of all formulations**

Wetting time was used as a parameter to correlate with disintegration time in oral cavity. This is an important criterion for understanding the capacity of disintegrants to swell in the presence of little amount of water. Since the dissolution process of a tablet depends upon the wetting followed by disintegration of the tablet. The wetting time of the formulated tablets were found in the range of 19 to 25 sec.

**Water absorption ratio of all formulations**

Depicts the relation between the formulation and water absorption ratio was performed to know the water absorption and water uptake properties of superdisintegrants. Water absorption ratio was increased and disintegration time was decreased with an increase in concentration of superdisintegrants.

### Disintegration time of all formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Disintegration time (sec)</th>
<th>Wetting time (sec)</th>
<th>Water Absorption Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>20</td>
<td>15</td>
<td>21.95</td>
</tr>
<tr>
<td>F2</td>
<td>21</td>
<td>20</td>
<td>24.39</td>
</tr>
<tr>
<td>F3</td>
<td>18</td>
<td>16</td>
<td>26.82</td>
</tr>
<tr>
<td>F4</td>
<td>22</td>
<td>25</td>
<td>19.5</td>
</tr>
<tr>
<td>F5</td>
<td>24</td>
<td>20</td>
<td>21.5</td>
</tr>
</tbody>
</table>
CONCLUSION:
Above graph indicates that % Drug release of F3 formulation shows better drug release when compared with other formulations.

REFERENCES


