FORMULATION AND EVALUATION OF FILM COATED DASATINIB IMMEDIATE RELEASE TABLETS

Poreddy Srikanth Reddy1, 2, V. Alagarsamy, P. Subhah Chandra Bose, 3 Damineni Sarita, V. Sruthi
1Department of Pharmaceutics, MNR College of Pharmacy, Sangareddy-502294, TS, India.
2Department of Pharmaceutical Chemistry, MNR College of Pharmacy, Sangareddy-502294, TS, India.
3Department of Pharmaceutics, Sultan-ul-Uloom College of Pharmacy, Hyderabad-500034, TS, India.

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Corresponding Author: Poreddy Srikanth Reddy
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Abstract

Immediate release tablets defined as solid dosage form which contain a medicinal substance or active ingredient which disintegrates rapidly within minutes after administered through oral route. Dasatinib inhibits the growth of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) cell lines over expressing BCR-ABL. Main criterion for immediate release dosage form is poor solubility of the drug and need the immediate action of drug to treat any unwanted defect or disease. Current research work is mainly deals with development of patent non-infringing generic version for sprycel (IR tablets of Disatinib) with direct compression method by using croscarmellose sodium, sodium starch glycolate and crosspovidone as the superdisintegrants with 2.5%, 3.5% and 4.5% concentrations. All the formulations were evaluated for their pre-compression and post-compression parameters. Among all the formulations formulation F3 (4.5 % croscarmellose sodium) was found to be optimized formulation based on its dissolution profile comparison with innovator product before and after stability studies.

Keywords: Immediate release tablets, croscarmellose sodium, cross povidone.

1. INTRODUCTION:

The convenient oral drug delivery has been known for decades is the most widely utilized route of administration among all the routes. It remains the preferred route of administration in the discovery and development of new drug candidates. The popularity of oral route is attributed to patient acceptance, ease of administration, accurate dosing, cost effective manufacturing methods and generally improve the shelf life of the product [1]. Immediate release tablets are designed to disintegrate and release the drug in absence of any controlling features such as coating or other formulation techniques [2].

Immediate release drug delivery system is a conventional type of drug delivery. It is designed to disintegrate and release their medicaments with no special rate controlling features [4,5]. These are the dosage forms in which ≥ 85% of labeled amount dissolves with in 30 min. However for immediate release tablets, tablet disintegrants play an important role in ensuring that the tablet matrix break up on contact with fluid in the stomach to allow the release the active drug which then become available in whole or in part, for absorption from gastrointestinal tract [6-8].

Dasatinib film coated tablets is used as an anti-cancer agent. It comes under BCS II class with low solubility and high permeability. Dasatinib inhibited the growth of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) and cell lines over expressing BCR-ABL.

In the present research work intended to formulate and evaluate film coated tablets (direct compression method) of the Dasatinib tablet is for immediate release.

2. MATERIALS AND METHODS:

Dasatinib, Lactose monohydrate, Crosscarmellose sodium, Sodium starch glycolate, Cross povidone, Hydroxy propyl cellulose and Magnesium stearate.
Experimental methods:

Preparation of Dasatinib film coated tablets:
The Dasatinib film coated tablets were prepared by direct compression method. Sift Dasatinib monohydrate, crosscarmellose sodium/sodium starch glycolate/ crospovidone, lactose monohydrate, hydroxylpropyl cellulose and microcrystalline cellulose (MCC) (PH 102) through sieve no. 40 and blend it for 2 min. Add magnesium stearate to above blend which is previously passed through sieve no. 60 and blend for 1 min. finally the above blend was compressed using 12.5 mm round punch. The formulation chart was showed in Table 1 below [9,10].

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Ingredients (mg)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Dasatinib (API)</td>
<td>70</td>
<td>70</td>
<td>70</td>
<td>70</td>
<td>70</td>
<td>70</td>
<td>70</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>2.</td>
<td>MCC (PH102)</td>
<td>395.32</td>
<td>347</td>
<td>299.77</td>
<td>395.32</td>
<td>347</td>
<td>299.77</td>
<td>395.32</td>
<td>347</td>
<td>299.77</td>
</tr>
<tr>
<td>3.</td>
<td>Lactose monohydrate</td>
<td>43.92</td>
<td>86.75</td>
<td>128.48</td>
<td>43.92</td>
<td>86.75</td>
<td>128.48</td>
<td>43.92</td>
<td>86.75</td>
<td>128.48</td>
</tr>
<tr>
<td>4.</td>
<td>Crosscarmellose sodium</td>
<td>13.75</td>
<td>19.25</td>
<td>24.75</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5.</td>
<td>Sodium starch glycolate</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>13.75</td>
<td>19.25</td>
<td>24.75</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6.</td>
<td>Crosspovidone</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>13.75</td>
<td>19.25</td>
<td>24.75</td>
</tr>
<tr>
<td>7.</td>
<td>Hydroxy propyl cellulose</td>
<td>22</td>
<td>22</td>
<td>22</td>
<td>22</td>
<td>22</td>
<td>22</td>
<td>22</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>8.</td>
<td>Magnesium stearate</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Total wt. (mg)</td>
<td>550</td>
<td>550</td>
<td>550</td>
<td>550</td>
<td>550</td>
<td>550</td>
<td>550</td>
<td>550</td>
<td>550</td>
</tr>
</tbody>
</table>

Coating of Tablets:
The compressed tablets were obtained by direct compression machine and they were coated by pan coating technique. The coating formula was given in Table 2.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Uses</th>
<th>Qty/1000 Tablets (gm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypromellose</td>
<td>Film forming agent</td>
<td>6.57</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>Filler</td>
<td>0.73</td>
</tr>
<tr>
<td>Titanium dioxide</td>
<td>Opacifier</td>
<td>4.03</td>
</tr>
<tr>
<td>Triacetin</td>
<td>Plasticizer</td>
<td>1.65</td>
</tr>
<tr>
<td>Opadry white</td>
<td>Color</td>
<td>0.02</td>
</tr>
<tr>
<td>Purified water</td>
<td>Vehicle</td>
<td>87</td>
</tr>
</tbody>
</table>

Evaluation of immediate release tablets of Dasatinib monohydrate Pre Compression Parameters:
The powder blend is evaluated for various precompression parameters such as bulk density, tapped density, angle of repose, Hausner’s ratio, compressibility index to determine the flow properties of the powdered blend [11].

Post Compression Parameters [12,13]:
Thickness:
The thickness of ten tablets was measured using Vernier calipers. The extent to which the thickness of each tablet deviated from ± 5% of the standard value was determined.

Hardness:
Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of
each formulation is determined by using Monsanto Hardness tester.

**Friability:**

The friability of the tablets was determined using Roche friabilator. It is expressed in percentage. 20 tablets were initially weighed and transferred into the Friabilator. The Friabilator was operated at 25 rpm for 4 min. After four minutes the tablets were weighed again. The % friability was then calculated using below formula.

\[
\text{Friability} \% = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100
\]

**Weight variation:**

Twenty tablets were individually weighed and average weight was calculated. The individual weight was compared to the average weight. The tablets pass the test if not more than two tablets are outside the percentage limit and if no tablet differs by more than two times the percentage the percentage limit. The weight variation tolerance for uncoated tablets is as follows:

\[
\% \text{ deviation} = \frac{\text{individual weight} - \text{Average weight}}{\text{Average weight}} \times 100
\]

**Disintegration Test:**

Disintegration test, measured by using USP tablet disintegration test apparatus (ED2L, Electro lab, India) using 900ml of distilled water at room temperature (37±2 °C). Disintegration time is measured for six tablets by inserting each tablet in the each disk.

**Dissolution Test:**

In vitro dissolution test is carried out by using USP type-2 (paddle) apparatus. 1000ml of acetate buffer pH 4 with 1 % triton X-100 is used as dissolution medium and the paddle was rotated at 60 rpm at temperature (37 °C±0.5 °C). Sampling was done at regular intervals (10 min, 15 min, 30 min and 45 min.) and was replaced by media after each sampling interval. The samples are then analyzed spectrophotometrically at λ max of the drug (FDA method) [14,15].

**Drug formulation compatibility studies [15-17]:**

**Fourier transforms infrared (FTIR) spectroscopy:**

The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany(Alpha T).The solid powder sample directly place on yellow crystal which was made up of ZnSe. The spectra were recorded over the wave number of 4000 cm-1 to 400cm-1.

**Differential scanning calorimetry (DSC):**

The possibility of any interaction between the drug and the polymer during preparation of tablets was assessed by carrying out thermal analysis of drug and polymer alone as well as physical mixture. DSC analysis was performed using Hitachi DSC 7020, on 5 to 15 mg samples. Samples were heated in sealed aluminum pan at a rate of 10 °C/min conducted over a temperature range of 30 to 350 °C under a nitrogen flow of 50 mL/min.

**Stability study for optimized formulation:**

For the determination of stability of prepared optimized formulation, accelerated stability study was carried out on optimized formulation. Tablets were stored according to ICH guidelines at 40±2 °C/75±5% RH for three months by storing the samples in (Lab-care, Mumbai, Indis.) stability chamber. After completion of required duration time, samples were withdrawn and tested for different tests such as hardness, drug content and in- vitro drug release [18].

3. RESULTS AND DISCUSSION:

**Evaluation of tablets:**

The results of the hardness, thickness, weight variation, friability and disintegration of tablets are given in Table 3. All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limit. The hardness of the tablets ranged from 6.92±0.68 - 8.50±0.95 kg/cm² and the friability values were < than 0.53±0.03 % indicating that the tablets were compact and hard. The thickness of the tablets ranged from 4.98±0.8 - 6.14±0.2. All the formulations satisfied the content of the drug as they contained 98.53-101.49 % of Dasatinib monohydrate and good uniformity in drug content was observed. The weight variation test was performed for randomized selected tablets and the results found within the limits. The disintegration time all tablet formulations showed less than 6 minutes. Thus all physical attributes of the prepared tablets were found to be practically within control limits.
Table 3: Evaluation test results of Dasatinib film coated tablets

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Hardness (Kg/cm²)</th>
<th>Thickness (mm)</th>
<th>Wt. variation (mg)</th>
<th>Friability (%)</th>
<th>Disintegration (min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>7.25±0.56</td>
<td>5.81±0.2</td>
<td>552±2</td>
<td>0.52±0.02</td>
<td>4</td>
</tr>
<tr>
<td>F2</td>
<td>8.46±0.25</td>
<td>6.06±0.6</td>
<td>556±1</td>
<td>0.26±0.03</td>
<td>2.6</td>
</tr>
<tr>
<td>F3</td>
<td>7.81±0.71</td>
<td>5.72±0.3</td>
<td>552±2</td>
<td>0.09±0.02</td>
<td>2.1</td>
</tr>
<tr>
<td>F4</td>
<td>7.56±1.25</td>
<td>4.98±0.8</td>
<td>551±2</td>
<td>0.42±0.05</td>
<td>4.6</td>
</tr>
<tr>
<td>F5</td>
<td>8.24±0.52</td>
<td>5.93±0.4</td>
<td>560±2</td>
<td>0.31±0.06</td>
<td>5.2</td>
</tr>
<tr>
<td>F6</td>
<td>6.92±0.68</td>
<td>6.14±0.2</td>
<td>559±1</td>
<td>0.53±0.03</td>
<td>3.1</td>
</tr>
<tr>
<td>F7</td>
<td>8.50±0.95</td>
<td>5.25±0.1</td>
<td>548±3</td>
<td>0.21±0.04</td>
<td>2.4</td>
</tr>
<tr>
<td>F8</td>
<td>7.66±0.26</td>
<td>5.65±0.9</td>
<td>552±2</td>
<td>0.43±0.09</td>
<td>5.1</td>
</tr>
<tr>
<td>F9</td>
<td>7.25±0.75</td>
<td>6.04±0.5</td>
<td>556±2</td>
<td>0.26±0.07</td>
<td>4.8</td>
</tr>
</tbody>
</table>

In vitro drug release:

The drug release rate from the prepared tablet formulations were studied using the USP type II dissolution test apparatus. The dissolution medium was 1000 ml of acetate buffer pH 4.0 at 60 rpm at a temperature of 37±0.5 °C. Samples of 5 ml were collected at different time intervals up to 45 Min (10 min, 15 min, 30 min and 45 min.) and has analyzed after appropriate dilution by using UV spectrophotometer. The results obtained were showed in Figure 1 below. As per the results F3 formulation was showed good drug release.

Drug formulation compatibility studies:

FTIR studies:

FT-IR spectroscopic study was carried out to find out drug excipients interaction. The characteristic peaks between IR spectrum of pure drug and optimized formulation were identified by absorption peaks at 2926 cm⁻¹ (secondary amine N-H stretch), 2921 cm⁻¹ (=C-H aromatic ring), 869.56 cm⁻¹ (C-H bending), 1130.32 cm¹ (C-N stretch), 1552 cm⁻¹ (C=O stretch) and 1298.48 cm⁻¹ (C=C) stretch, aromatic ring. The principal peaks of pure drug and optimized formulation were observed and indicated that no interactions had been observed an the FTIR graph was depicted in Figure 2.

DSC studies:

Drug formulation compatibility studies DSC thermogram for optimized formulation F3 was obtained. The thermogram showed a peak at 282.6 °C which lies around the melting point of the drug (280-286 °C) which indicates that there is no effect of compression force on the formulation. The thermographic results show that the drug retains its identity in the tablet formulations. The DSC thermogram for pure drug and optimized formulation was showed in Figure 3.
Stability study:
There was no major change in the various physicochemical parameters evaluated like description and in vitro dissolution pattern at the various sampling points. There was no statistically significant difference between the initial values and the results obtained during stability studies. The stability data of optimized formulation (F3) was showed in Table 4.

Table 4: Stability data of optimized formulation

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Parameters</th>
<th>Specifications</th>
<th>Test Condition (Accelerated)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>40±2 °C &amp; 75±5 % RH</td>
</tr>
<tr>
<td>1</td>
<td>Description</td>
<td>White to off-white round shape coated tablet</td>
<td>Complies</td>
</tr>
<tr>
<td>2</td>
<td>Dissolution</td>
<td>NLT 80% of labeled amount of Dasatinib</td>
<td>97.8%</td>
</tr>
</tbody>
</table>

CONCLUSION:
In the present research work Dasatinib film coated tablets were prepared by direct compression method. Various formulation trails of Dasatinib were conducted using three super disintegrants like crosscarmellose sodium, sodium starch glycolate and crospovidone. These three super disintegrants were used at three different concentrations like 2.5%, 3.5% and 4.5%. Based the above results, the optimized formulation was found to be formulation containing crosscarmellose sodium at 4.5%. The optimized formulation was subjected to stability studies and it was found to be stable.

REFERENCES: