FORMULATION AND EVALUATION OF IMMEDIATE RELEASE TABLETS OF DASATINIB USING CROSS POVIDONE

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ABSTRACT

Objective: The present investigation is concerned with development and evaluation of immediate release tablets containing Dasatinib drug a selective tyrosine kinase inhibitor (TKI) which is used in the treatment of chronic myeloid leukemia (CML) and acute myeloid leukemia (AML) using cross povidone as super disintegrants to improve its bioavailability and dose-related side effects. Methods: The tablets were prepared by wet granulation method using various excipients, drug and super disintegran such as cross povidone. The prepared tablets were evaluated for pre-compression parameters, post compression parameters, in vitro drug dissolution study and stability study. Results: Fourier Transform Infrared spectroscopy (FTIR) confirms no drug excipients interaction from various batches. Among the prepared formulations F5 Batch shows 89.99 % drug release in 45 minutes. The best formulation F5 batch indicates no significant changes from short-term stability studies(at 40±2°C/75±5% RH). Conclusion: Hence it was concluded that the best formulation F5 was suitable for all evaluation parameters and showed good results.

Keywords: Dasatinib, immediate release tablets, FTIR spectroscopy, in vitro drug release study.

INTRODUCTION

Immediate release tablets are convenient to be manufactured and easy to administer to patients. It is free of side effects, offering immediate release and enhances bioavailability so as to achieve better patient compliance. Oral drug delivery systems [1] preferably tablets are most widely administered dosage forms which offer uniform dose, easy to take and painless delivery to the patients. Tablets the solid dosage forms are a system of choice for all drug delivery system because they do not require special treatment and less expensive to manufacture. Hence immediate release tablets are more acceptable among all the tablets. Immediate release drug delivery [2] is preferable for drugs having long biological half-life, high bioavailability, lower clearance and lower elimination half-life. The drug from immediate release tablets is intended to be released rapidly after administration to gastrointestinal tract or the tablet is dissolved and administered as a solution. IR tablets are those tablets which are designed to disintegrate [3] and release their medication with no special rate controlling features such as special coatings and other techniques. In pharmaceutical industries, manufacturers of generic tablets are usually focused on the optimization of the excipients mixture composition to obtain a product that meets established a standard.

Dasatinib [4] is a selective tyrosine kinase inhibitor (TKI) used in the treatment of chronic myeloid leukemia (CML) and acute myeloid leukemia (AML). It is the first line drug in the pharmacotherapy of patients with CML [5] as it possesses tolerability and safety advantages over the other tyrosine kinase inhibitors. Dasatinib inhibits kinases such as BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, EPHA2 and PDGFRβ at nanomolar concentrations. It binds to multiple conformations of the ABL kinase. It suppresses the growth of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) cell lines overexpressing BCR-ABL. It is able to overcome imatinib resistance resulting from BCR-ABL kinase domain mutations, activation of alternate signaling pathways involving the SRC family kinases (LYN, HCK) and multi-drug resistance gene overexpression. Dasatinib undergoes hepatic [6] first pass metabolism by the cytochrome P450 enzyme 3A4 and terminal elimination half-life between 1.3 to 5 hrs after oral administration. Dasatinib is excreted mainly in faeces (85%) and urine (4%). In the present study IR tablets of Dasatinib were designed using wet granulation method using various excipients and crosspovidone as natural super disintegrants with prime objective arriving of a cost effective product.

MATERIALS AND METHODS

Materials

Dasatinib was received as a gift sample from Natco Pharma. Pvt Ltd., Hyderabad, Telangana. Hydroxy Propyl Cellulose, magnesium stearate, lactose monohydrate, sodium starch glycolate, microcrystalline cellulose, potassium dihydrogen-o-phosphate were procured from SD fine chem. Ltd Mumbai. Sodium hydroxide, crosspovidone and methanol were procured from Qualigens fine chemicals Mumbai.

Drug excipient studies

Fourier Transform Infrared Spectroscopy (FTIR)

The use of FTIR technique [7] offers detection of the different functional groups of drug and excipients by analyzing the significant changes in the shape and position of the absorbance bands. In this technique individual samples, as well as the mixture of drug and excipients, were ground mixed thoroughly with potassium bromide (1:100) for 3-5 minutes in a mortar and compressed into the disc by applying pressure of 5 tons for 5 minutes in a hydraulic press. The prepared pellet was kept in the sample holder and scanned from 4000 to 400 cm⁻¹ in FTIR spectrophotometer. Then the characteristics peaks were obtained of all sample as well as mixtures. Then the peaks of optimized formulation were compared with pure drug and excipients.

Preparation of immediate release (IR) tablets
IR tablets each containing 70mg Dasatinib were prepared by wet granulation method. Accurately weighed quantities of ingredients mentioned in Table-1 were passed through sieve no. 40 and magnesium stearate was passed through sieve no.60. All the ingredients except magnesium stearate (lubricant) and talc (glidant) were manually blended homogenous by way of geometric dilution. The mixture was moistened with aqueous solution and granulated with sieve no.20 and placed in hot air oven at 60°C for sufficient 3-4 hrs. Then dried granules passed through sieve no.12 and blended with magnesium stearate and talc. The homogenous mixture was placed into tablet punching machine (10 stations rotary tablet machine, Clint India) getting tablet using deep concave punch.

Table 1: Composition of Dasatinib immediate release tablets

<table>
<thead>
<tr>
<th>Ingredients(mg)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dasatinib</td>
<td>70</td>
<td>70</td>
<td>70</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Micro Crystalline Cellulose</td>
<td>400</td>
<td>395</td>
<td>390</td>
<td>385</td>
<td>380</td>
</tr>
<tr>
<td>Crosspovidone</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>Hydroxy propyl cellulose</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Talc</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total weight(mg)</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
</tr>
</tbody>
</table>

Evaluation of immediate-release (IR) tablets

Pre-compression parameters of immediate release (IR) granules

Angle of repose:
The angle of repose [8] of granules blend was determined by the fixed funnel method. The accurately weighed quantity of granules was taken in a funnel. The height of funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules are allowed to flow through the funnel freely onto the surface. The diameter of powder cone was measured and angle of repose was calculated using the following equation

\[ \tan \Theta = \frac{h}{r} \]

Where \( \Theta \) is the angle of repose, \( h \) is the height of cone in cm and \( r \) is the radius of the cone base in cm.

Bulk density (\( e_b \))
Bulk density [9] was determined by pouring the granules into a graduated cylinder in bulk density apparatus (Sisco, India). The bulk volume (\( V_b \)) and mass (\( m \)) of the granules were determined. The bulk density was calculated using the following formula.

Bulk density (\( e_b \)) = Mass of granules (\( m \))/Bulk volume of granules (\( V_b \))

Tapped density (\( e_t \))
The measuring cylinder containing known mass (\( m \)) of granules blend was tapped 1000 times for a fixed time in bulk density apparatus (Sisco, India). The minimum volume occupied in the cylinder (\( V_t \)) and mass of the granules (\( m \)) were measured. The tapped density [10] was measured by using the following formula.

Tapped density (\( e_t \)) = Mass of granules (\( m \))/Tapped volume of granules (\( V_t \))

Compressibility index (Carr’s index):
The compressibility index [11] determines the flow property characteristics of granules developed by Carr. The percentage compressibility of granules is a direct measure of the potential powder arch and stability. The Carr’s index can be calculated by the following formula.

\[ %\text{Carr’s index (C.I)} = \frac{e_t - e_b}{e_t} \times 100 \]

Where \( e_t \) is the tapped density of granules and \( e_b \) is bulk density of granules

Hausner’s ratio [11] is used for the determination of flow properties of granules. The ratio can be calculated by the taking the ratio of tapped density to the ratio of bulk density.

Mathematically: Hausner’s ratio (H.R) = \( \frac{e_t}{e_b} \)

Post compression parameters of immediate-release (IR) tablets: [12]

Thickness
The thickness of individual tablets is measured by using vernier caliper which gives the accurate measurement of thickness. It provides information of variation of thickness between tablets. Generally, the unit for thickness measurement is mm. The limit of the thickness deviation of each tablet is ±5%.

Hardness
The hardness of a tablet is associated with the resistance of the solid specimen towards fracturing and attrition [13]. The hardness of tablets can be determined by using Monsanto hardness tester and measured in terms of kg/cm².

Friability
Friability [14] of tablets was performed in a Roche friabilator. Ten tablets were initially weighed (WI) together and then placed in the chamber. The friabilator was operated for 100 revolutions and the tablets were subjected to the combined effects of abrasion and shock because the Plastic chamber carrying the tablets drops them at a distance of six inches with every revolution. The tablets are then dusted and reweighed finally (WF). The percentage of friability was calculated using the following equation.

\[ \%\text{Friability} = \left(1 - \frac{WF}{WI}\right) \times 100 \]

Where WI and WF are the weight of the tablets before (initially weight) and after (final weight) the test respectively.

Weight Variation
The weight variation test [15] was done by weighing 20 tablets individually (Shimadzu digital balance), calculating the average weight and comparing the individual tablet weights to the average. The percentage weight deviation was calculated and then compared with USP specifications.

Disintegration test
Six tablets along disc were introduced in each tube of a basket of disintegration test apparatus (Lab care instruments). The basket was positioned into a beaker containing 900 ml of distilled water [16] and operated at 37 ± 2°C. The time of disintegration of the tablet was recorded. The average time and standard deviation were calculated. Three trails were performed.

Drug Content
Drug content for immediate release (IR) tablet was done by the assay method. First, the prepared tablet (70mg API) was crushed and added to 70ml of acetate buffer pH 4 with 1 % triton X-100. After 30 minutes the solution was filtered and from 70ml solution 1ml solution was withdrawn diluted up to 10 ml with acetate buffer pH 4 with 1 % triton X-100 producing 100 µg/ml. This 10 ml solution again 1 ml of sample is withdrawn diluted up to 10ml with acetate buffer pH 4 with 1 % triton X-100 obtaining desired concentration 10 µg/ml. This solution concentration for the drug content of formulations was calculated using calibrated standard curve equation \( y=0.04x-0.002 \). The drug content was determined at λmax315 nm by UV-spectrophotometer (ELICO164) against blank.

Diameter of tablet
The diameter of individual tablets is measured by using vernier caliper [15] which gives the accurate measurement of diameter. It provides information of variation of diameter between osmotic pump tablets. Generally, the unit for thickness measurement is mm.
In vitro dissolution studies

In vitro dissolution test was carried out by using USP type II (paddle) apparatus. 1000 ml of acetate buffer pH 4 with 1% Triton X-100 was used as dissolution medium and the paddle was rotated at 60 rpm at a temperature (37°C ± 0.5°C). In specified time intervals (0.5, 10, 15, 20, 25, 30, 35, 40, 45 min) an aliquot of 5 ml samples of the solution was withdrawn from the dissolution apparatus and with the replacement of fresh fluid to dissolution medium. The samples were filtered through filter paper of 0.45 μm. The absorbance of these solutions was measured at λmax 315 nm using a UV/Visible Spectrophotometer (ELICO164). The drug release was plotted against time to determine the release profile of various batches.

Stability studies

Short-term stability studies [16] on the above promising formulation (at 40±2ºC/75±5% RH for 3 months) were carried out for observing significance changes in physical appearance and formulation (at 40±2ºC/75±5% RH for 3 months) were carried out for observing significance changes in physical appearance and drug content.

RESULTS AND DISCUSSION

Drug excipient studies

Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR allows identification of functional groups in various chemicals as well as incompatibilities between the drug and excipients. From the FTIR study, it was found that the drug and excipients were compatible.

Pre-compression parameters of immediate release (IR) formulations:

All the compressible excipients (Table 1) with drug by wet granulation method was prepared. These granules were evaluated for pre-compression parameters (Table 2) such as angle of repose, bulk density, tapped density, Carr’s index and Hausner’s ratio.

Table 2: Pre-compression parameters of IR formulations.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Angle of repose (degree)± S.D</th>
<th>Bulk density (gm/ml)± S.D</th>
<th>Tapped density (gm/ml)± S.D</th>
<th>Carr’s Index (%)± S.D</th>
<th>Hausner’s Ratio± S.D</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>28.65±0.13</td>
<td>0.46±0.17</td>
<td>0.546±0.15</td>
<td>15.56±0.14</td>
<td>1.18±0.16</td>
</tr>
<tr>
<td>F2</td>
<td>29.73±0.12</td>
<td>0.48±0.11</td>
<td>0.536±0.09</td>
<td>9.7±0.06</td>
<td>1.10±0.08</td>
</tr>
<tr>
<td>F3</td>
<td>26.32±0.08</td>
<td>0.47±0.01</td>
<td>0.534±0.03</td>
<td>10.67±0.04</td>
<td>1.11±0.06</td>
</tr>
<tr>
<td>F4</td>
<td>24.41±0.11</td>
<td>0.48±0.04</td>
<td>0.529±0.05</td>
<td>9.07±0.05</td>
<td>1.09±0.04</td>
</tr>
<tr>
<td>F5</td>
<td>30.23±0.12</td>
<td>0.468±0.03</td>
<td>0.533±0.02</td>
<td>12.19±0.06</td>
<td>1.13±0.03</td>
</tr>
</tbody>
</table>

N.B. All values are expressed as mean± S.D, n = 3.

The angle of repose was found in the ranges from 24.41 to 30.23 degrees, bulk density of pre-compression blends was found to be in the range of 0.461 to 0.484 gm/ml, tapped density in the range of 0.529 to 0.546 gm/ml, the Carr’s index values were in the range of 9.07 to 15.56%, and the Hausner’s ratio was in the range between 1.09 to 1.18.

Post-compression parameters of IR formulations

The post-compression parameters such as hardness, weight variation, drug content uniformity, friability and thickness have given below (Table 3).

Table 3: Post-compression parameters of IR formulations.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Thickness (mm)± S.D</th>
<th>Hardness (kg/cm²)± S.D</th>
<th>%Friability (%)± S.D</th>
<th>Average tablet (mg)± S.D</th>
<th>wt.of Disintegration time(min.)± S.D</th>
<th>%Drug content± S.D</th>
<th>Diameter (mm)± S.D</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>4.02±0.01</td>
<td>5.7±0.12</td>
<td>0.33±0.03</td>
<td>499.18±1.16</td>
<td>4.2±0.03</td>
<td>97.94±1.32</td>
<td>12.03±0.02</td>
</tr>
<tr>
<td>F2</td>
<td>4.12±0.02</td>
<td>5.8±0.11</td>
<td>0.46±0.02</td>
<td>500.3±1.03</td>
<td>3.8±0.11</td>
<td>99.32±1.41</td>
<td>12.01±0.03</td>
</tr>
<tr>
<td>F3</td>
<td>3.96±0.03</td>
<td>6.2±0.16</td>
<td>0.43±0.03</td>
<td>500.2±1.02</td>
<td>4.1±0.15</td>
<td>98.67±0.98</td>
<td>12.03±0.07</td>
</tr>
<tr>
<td>F4</td>
<td>3.99±0.01</td>
<td>6.4±0.18</td>
<td>0.51±0.02</td>
<td>500.12±1.06</td>
<td>3.9±0.12</td>
<td>98.95±1.4</td>
<td>12.1±0.09</td>
</tr>
<tr>
<td>F5</td>
<td>4.09±0.02</td>
<td>6.3±0.13</td>
<td>0.56±0.01</td>
<td>500.11±1.04</td>
<td>3.7±0.02</td>
<td>99.99±1.5</td>
<td>12.02±0.06</td>
</tr>
</tbody>
</table>

N.B. All values are expressed as mean± S.D, n = 10, a = 20, b = 3

Figure 1: Comparative in vitro drug release study of Dasatinib IR batches.

Table 4: Stability study of the optimized formulation.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>After 30 days</th>
<th>After 60 days</th>
<th>After 90 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical appearance</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Weight variation (mg)± S.D</td>
<td>500.11±1.06</td>
<td>500.10±1.06</td>
<td>500.10±1.06</td>
</tr>
<tr>
<td>Thickness (mm)± S.D</td>
<td>4.09±0.02</td>
<td>4.09±0.02</td>
<td>4.09±0.02</td>
</tr>
<tr>
<td>Hardness (kg/cm²)± S.D</td>
<td>6.3±0.13</td>
<td>6.3±0.11</td>
<td>6.2±0.14</td>
</tr>
<tr>
<td>Friability (%)± S.D</td>
<td>0.56±0.01</td>
<td>0.57±0.01</td>
<td>0.58±0.01</td>
</tr>
<tr>
<td>Drug content (%)± S.D</td>
<td>99.99±1.5</td>
<td>99.99±1.5</td>
<td>99.96±1.5</td>
</tr>
</tbody>
</table>

N.B. All values are expressed as mean± S.D, n = 10, a = 20, b = 20
The thickness of the tablet formulations was found to be in the range of 3.963 to 4.121mm. The hardness of the tablet formulations was found to be in the range of 5.7 to 6.4 kg/cm². The friability values were found to be in the range of 0.33 to 0.56%. The weight of all the tablets was found to be uniform with low values of standard deviation and within the prescribed USP limits. The average weight of one tablet was found to be in range 499.18 to 500.3mg. The disintegration time was in range 3.7 to 4.2min. The percent drug content of all the tablets was found to be in the range of 97.94 to 99.99% of the expected drug content which was within the acceptable limits. The diameter of the tablet formulations was found to be in the range of 12.01 to 12.1mm.

**In vitro drug release study**

In vitro, drug release studies were performed in acetate buffer pH 4 with 1% triton X-100. On the above promising formulation (F5) containing 5%, super disintegrants give the maximum amount of drug release comparing to other formulations. The Percentage of drug release of various batches were F1 (77.93%), F2 (79.12%), F3 (82.96%), F4 (84.59) and F5 (89.99%) respectively. The dissolution profiles of the above formulations are depicted in figure 1.

**Short-term stability studies**

Short-term stability studies on the above promising formulation (at 40±2°/75±5% RH for 3 months) have shown no significant changes in physical appearance, drug content. There was no appreciable changes in vitro drug release upon storage at 40±2°/75±5% RH for 3 months period.

**CONCLUSION**

From the study it can be concluded that immediate-release (IR) tablets of dasanib could be successfully prepared by wet granulation method in a cost effective manner employing cross povidone as super disintegrants. The drug release of dasanib is best in F5 from in vitro drug release study. From the stability study of the formulation carried out by storing at 40±2° / 75±5% RH for 3 months showed that there was no significant change in drug content and percentage drug release. It proved that the product is stable. Hence immediate release (IR) tablets may be considered as a suitable alternative to other dosage forms and it will surely enhance the patient compliance providing rapid onset of action.

**REFERENCES**