FORMULATION AND EVALUATION OF FEBUXOSTAT FAST DISINTEGRATING TABLET

Rahul Dass, Sandhya Jaiswal, G.D Gupta
Department of Pharmaceutics Research Div., ASBASJSM College of Pharmacy, BELA (Ropar) 140111-India.

ARTICLE INFO

Article history
Received 10/06/2014
Available online
08/07/2014

Keywords
Febuxostat, β-Cyclodextrin, Locust Bean Gum, Gout, Kneading.

ABSTRACT
Gout is a metabolic disorder characterized by elevated uric acid levels in the body, associated with painful arthritis, tophi and nephropathy. Febuxostat, an antigout drug that is currently approved in many countries for the treatment of gout. It is a BCS class II drug. It exhibits poor bioavailability about 49% which is attributed to its poor solubility. The present work was aimed to overcome these two limitations poor bioavailability and poor solubility. Febuxostat β-Cyclodextrin complex was prepared and characterized by FTIR and DSC studies. In-vitro studies showed that the solubility and dissolution rate of Febuxostat was significantly improved by complexation with β-Cyclodextrin with respect to drug alone. The inclusion complexes with β-Cyclodextrin was prepared by kneading method show highest solubility (378.77%). The Febuxostat containing tablets was prepared by direct compression method using different ingredients such as crosspovidone, crosscarmellose, locust bean gum, lactose, microcrystalline cellulose. Prepared tablets were evaluated for thickness, uniformity of weight, hardness, friability, wetting time, in-vitro disintegration time, drug content and in vitro drug release. The formulation of Locust Bean Gum superdisintegrant in the concentration of (10 %) i.e. F9 batch gives best results. Formulation F9 of Locust Bean Gum superdisintegrant required minimum disintegration time, wetting time as compared to formulations of Crosspovidone and Crosscarmellose with same concentration. So it can be concluded that Febuxostat can be successfully complexed with β-cyclodextrin to prepare fast disintegrating tablet and showed enhanced dissolution rate.

Corresponding author
Prof. (Dr). G.D Gupta,
Director-cum-Member Secretary
[Chairman: Board of Studies, Pharmacy, PTU, JALANDHAR
ASBASJSM College of Pharmacy, Bela(Ropar)-149111, India.
(Affiliated to Punjab Technical University, Jalandar)
919417862160
drgdg@rediffmail.com


Copy right © 2014 This is an Open Access article distributed under the terms of the Indo American journal of Pharmaceutical Research, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

www.iajpr.com
INTRODUCTION
Fast Disintegrating Tablet is solid unit dosage form which disintegrates or dissolves rapidly in the mouth without chewing and water. Various techniques have been used to improve the solubility and bioavailability of poorly water-soluble drugs, in general, include micronization, the use of surfactant and the formation of solid dispersions. Among them, the solid dispersion technique and complexation with cyclodextrin are most frequently used. In solid dispersions, hydrophilic polymers have commonly been used as carriers [3].

Solid dispersion (SD) is defined as the dispersion of one or more active ingredients in inert carriers in the solid state, by fusion, solvent or solvent-fusion methods. The physical state of the drug is often transformed in solid dispersions from crystalline to amorphous and the dissolution surface increases because of particle size reduction [4].

Febuxostat is a novel, orally administered antihyperuricemic drug. Chemically, Febuxostat is (2-[3-cyano-4-(2-methyl propoxy)-phenyl]-4-methylthiazole-5-carboxylic acid). It is a non purine analogue inhibitor of both the oxidized and reduced forms of xanthine oxidase; in contrast, allopurinol an hypoxanthine analog, weakly inhibits the oxidized form [14].

As per literature febuxostat prepared by co-evaporation method using Hydroxy propyl β-Cyclodextrin 1:1 show 330.24% solubility but β-Cyclodextrin in 1:2 (kneading method) showed 387.77 solubility alone. Kneading method is cheap, simple, no wastage and less time consuming as compared to co-evaporation method [22].

The aim of the present work is to improve solubility of drug through complexation with β-cyclodextrin by kneading method and to formulate the rapid disintegrating tablet by incorporating the prepared complexes by direct comparison method using various superdisintegrants. Febuxostat is practically insoluble in water, chemically stable, half life- 5 to 8 hrs, undergoes first pass effect so it is selected as an ideal drug candidate for fast disintegrating tablet.

MATERIAL AND METHOD
Material
Febuxostat (FBX) was obtained as gift sample form Emcure Pharmaceuticals, Pune. The complexing agent betacyclodextrin (β-CD) was purchased from Signet Chemicals Pvt.Ltd., Mumbai. All other chemicals and solvent used were of pharmaceutical and analytical grade.

Preparation of solid dispersion
Solid dispersions of febuxostat in 2 different weight ratios (1:1 and 1:2) were prepared by the kneading method. Febuxostat and β-Cyclodextrin were weighed according to different weighed ratios. The mixture of febuxostat and β-Cyclodextrin was wetted with ethanol and kneaded thoroughly for 30 min in a glass mortar. The paste formed was dried under hot air oven for 24 h. Dried powder was passed through sieve no. 30 and stored in a desiccator until further evaluation [5].

Phase Solubility Study
Solubility studies was performed according to the method described by Higuchi and Connors. An excess amount of febuxostat was placed into 25 ml glass flask containing different concentrations of β-Cyclodextrin in 20 ml distilled water. All flasks were closed with stopper and covered with cellophane membrane to avoid solvent loss. The content of the suspension was equilibrated by shaking for 72 hr in thermostatically controlled water at 25°C. After attainment of equilibrium, the content of each flask was then filtered through a Whatman filter paper no. 41. The filtrate was diluted and assayed spectrophotometrically for febuxostat content at 315 nm. All solubility measurements were performed in triplicate [6].

Determination of drug content
Drug: cyclodextrin complex equivalent to 10 mg of drug was stirred with 100ml of methanol. From this the concentration of 10 μg/ml was prepared and the drug content was determined spectrophotometrically at 315 nm using methanol as blank.

Characterization of the physical mixture and inclusion complexes
UV spectroscopic study
Complex formation between febuxostat and cyclodextrins were studied by UV spectroscopic method. 10mg febuxostat was weighed accurately and dissolved in 100ml methanol. Diluted suitably and spectra of drug recorded at 315 nm. Same method was used only febuxostat –cyclodextrins complex.

Fourier Transform Infrared spectrophotometry [FT-IR]
FT-IR has been employed as a useful tool to identify the drug excipient interaction. Samples were analyzed by potassium bromide pellet method in an IR spectrophotometer (Varian, Australia) in the region between 4000 to 400 cm⁻¹ [22].

Differential Scanning Calorimetry
The DSC thermograms were recorded on a DSC (model 50, Shimadzu). Samples of 1.3 mg weight were heated in hermetically sealed aluminum pans over a temperature range of 30°C to 300°C at a constant rate of 10°C/min under nitrogen purge (40 ml/min) [22].
In-vitro dissolution studies

Drug release studies were performed in triplicate at 37 ± 0.5°C employing USP apparatus II at 100 rpm. Dissolution study was carried out in one dissolution media (Phosphate buffer of pH 6.8). Dissolution studies were performed on pure drug (40mg) and the complexes containing an equivalent amount of the drug. Aliquots of the periodically withdrawn samples (5 mL) was analysed spectrophotometrically at 315 nm, and was replaced with an equal volume of dissolution medium [7, 9].

Preparation of tablets

Fast-disintegrating tablets (FDTs) was prepared by the direct compression method from an optimized batch of kneaded 1:1 febuxostat-β Cyclodextrin solid dispersion (on the basis of the dissolution and saturation solubility results for the solid dispersions), by adding one of three different superdisintegrants (crospovidone or Doshion). The tablets was prepared separately in the proportions given in Table 1, using a Minipress II 8-station rotary tablet machine (Rimek Ltd.), equipped with 8-mm flat-faced punches (Sammour et al., 2006).

<table>
<thead>
<tr>
<th>Ingredients (mg)</th>
<th>FDT1</th>
<th>FDT2</th>
<th>FDT3</th>
<th>FDT4</th>
<th>FDT5</th>
<th>FDT6</th>
<th>FDT7</th>
<th>FDT8</th>
<th>FDT9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug : β-CD complex</td>
<td>120</td>
<td>120</td>
<td>120</td>
<td>120</td>
<td>120</td>
<td>120</td>
<td>120</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>12.5</td>
<td>18.75</td>
<td>25</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CCS</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>12.5</td>
<td>18.75</td>
<td>25</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LBG</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>12.5</td>
<td>18.75</td>
<td>25</td>
</tr>
<tr>
<td>MCC</td>
<td>45</td>
<td>45</td>
<td>45</td>
<td>45</td>
<td>45</td>
<td>45</td>
<td>45</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>Lactose</td>
<td>67.55</td>
<td>73.75</td>
<td>55</td>
<td>67.55</td>
<td>73.75</td>
<td>55</td>
<td>67.55</td>
<td>73.75</td>
<td>55</td>
</tr>
<tr>
<td>Talc</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>
<td>2</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Evaluation of Super Disintegrating Tablets:

Evaluation of powder blend

The powder blend was evaluated for flow properties. Different tests that were carried out are angle of repose, hardness, friability, disintegrating time, wetting time, in-vitro release bulk density (sb), tapped density (st), compressibility index, and Hausner ratio.

Angle of repose;

The angle of repose for powder blend was determined by the funnel method. The accurately weighed quantity of powder blend was taken in a funnel. The height of the funnel was adjusted in such away that the tip of the funnel just touches the heap of the powder blend. The powder blends were allowed to flow through the funnel freely onto the wooden surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

\[ q = \tan^{-1}\left(\frac{h}{r}\right) \]

Where ‘h’ and ‘r’ are the height and radius of the cone respectively.

Bulk density;

Bulk density \( \rho_b \) is defined as the ratio for mass of the powder to the bulk volume and is expressed as g/cm\(^3\). Weighed quantity of powder blend from each formulation was taken in a measuring cylinder separately and the initial volume of the powder blend in the measuring cylinder was noted. This was calculated by using the formula

\[ \rho_b = \frac{M}{V_b} \]

Where, \( \rho_b \) - Bulk density, \( M \) - Weight of the sample in gm, \( V_b \) - Final Volume of the blend in cm\(^3\).

Tapped density;

It is the ratio of total mass of the powder to the tapped volume of powder. The volume was measured by tapping the powder blend for 500 times. Then the tapping was done for 750 times and the tapped volume was noted. Tapped density was calculated by using the following formula

\[ p_t = \frac{M}{V_t} \]

Where, \( p_t \) - Tapped density, \( M \) - Weight of the sample in g, \( V_t \) - Tapped Volume of blend in cm\(^3\).

Compressibility index and Hausner’s ratio;

The compressibility index of the powder blend was determined by Carr’s compressibility index and the Hausner’s ratio. It is calculated by using the formula:

\[ \text{Hausner’s ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \]

Carr’s index (%) = \[ \frac{[\text{TBD} - \text{LBD}] \times 100}{\text{TBD}} \]

\( \text{TBD} = \text{Total bulk density}, \text{LBD} = \text{Loose bulk density} \)
Evaluation of Tablets

Tablet thickness

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer.

Hardness:

The hardness of the tablet from each formulation was determined using Pfizer hardness tester.

Weight Variation:

Twenty tablets from each formulation were selected at a random and average weight was determined. Then individual tablets were weighed and was compared with average weight.

Friability

Friability of the tablets was determined using Roche Friabilator. This device subjects the tablets to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and re weighed. The friability (%F) is given by the formula.

\[
\%F = \left(1 - \frac{W}{W_0}\right) \times 100
\]

Where W0 is weight of the tablets before the test and W is the weight of the tablet after the test.

In vitro Disintegration time:

The disintegration time for all formulations was carried out using tablet disintegration test apparatus. Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed. The water was maintained at a temperature of 37°±2°C and time taken for the entire tablet to disintegrate completely was noted.

Drug content:

For the content uniformity test, ten tablets was weighed and pulverized to a fine powder, a quantity of powder equivalent to 10 mg of febuxostat was extracted into phosphate buffer solution pH 6.8 and liquid was filtered through Whatman filter paper. The febuxostat content was determined by measuring the absorbance at 315 nm (Shimadzu-1700 UV-Visible spectrophotometer) after appropriate dilution with phosphate buffer solution pH 6.8. The drug content was determined using standard calibration curve. The mean percent drug content was calculated as an average of three determinations.

Wetting time

The method was followed to measure tablet wetting time. A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small petri dish (ID = 65 cm) containing 10 ml of phosphate buffer (pH 6.8). A tablet was put on the paper, and the time for the complete wetting was measured. Three trials for each batch were performed and the standard deviation was also determined.

In-vitro dissolution study

The release rate of febuxostat from fast disintegrating tablets was determined using USP XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of phosphate buffer solution pH 6.8 as a dissolution medium, at 37 ± 0.5 °C and 75 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at different time interval (min). The samples were filtered through a Whatman filter paper. Absorbance of these solutions was measured at 315nm using a Shimadzu-1700 UV-Visible spectrophotometer. Percentage of drug release was calculated.

RESULTS AND DISCUSSION

The solubility of febuxostat in phosphate buffer pH 6.8 at 25°C was found to be 40μg/ml. The influence of β-CD upon the solubility of febuxostat is presented in Figure 1. The increase in solubility was linear with respect to the weight fraction of the carrier. The increase in the solubility with increasing β-CD concentration indicates the solvent properties of β-CD for the drug. The increase in solubility in the presence of β-CD can probably be explained by increased wettability of febuxostat. Indeed, β-CD causes a decrease of the interfacial tension between the drug and the dissolving solution.

The dissolution profiles were calculated and are shown in (Table 5). Compared with the pure powdered drug, the presence of β-CD increases the dissolution of febuxostat from the solid dispersions, which increases the dissolution rate (Figure 2). The prepared solid dispersions SD1 and SD2 increase the dissolution rate upto 49.86% and 82.06%. All the release profiles showed 2 different phases of drug release. An initial rapid release phase followed by a slower one. These results could be attributed to the general phenomenon of particle size reduction during the dissolution process.
The chemical interaction between the drug and the cyclodextrin often leads to identifiable changes in the infrared profile of dispersion (Figure 4). Drug spectrum shows prominent peaks at 2928 cm\(^{-1}\) for CH, 2231 cm\(^{-1}\) for C=N, 1714 cm\(^{-1}\) for C=O, 1629 cm\(^{-1}\) for C=N and 1516 cm\(^{-1}\) for C=C. Physical mixture of drug with β-CD (1:1) complexes shows the prominent peaks of drug, but there was reduction in peak intensity of drug peak which was obscured by cyclodextrin peak indicating formation of complexes [22].

Figure 1. Dissolution profile of pure drug and different solid dispersions at 37°C

Table 2: Dissolution release profile of pure drug and from solid dispersions

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Pure drug</th>
<th>SD1</th>
<th>SD2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>5.777554</td>
<td>25.2086</td>
<td>33.44929</td>
</tr>
<tr>
<td>10</td>
<td>10.74427</td>
<td>27.83386</td>
<td>44.59905</td>
</tr>
<tr>
<td>15</td>
<td>12.67016</td>
<td>29.54687</td>
<td>59.80328</td>
</tr>
<tr>
<td>20</td>
<td>15.81237</td>
<td>36.18605</td>
<td>66.79722</td>
</tr>
<tr>
<td>25</td>
<td>17.94093</td>
<td>47.6399</td>
<td>74.19661</td>
</tr>
<tr>
<td>30</td>
<td>20.57632</td>
<td>49.86985</td>
<td>82.30553</td>
</tr>
</tbody>
</table>

*Data are as mean±expressed S.D. (n=3)

Figure 2. FTIR spectra of Pure febuxostat, β-CD and 1:2 solid dispersion of febuxostat β-CD.
DSC enables the quantitative detection of all processes in which energy is required or produced (Figure 3). DSC studies showed that endothermic peaks for pure febuxostat, β-CD were obtained at 205°C, 85.11°C and 280°C respectively. Thermogram of drug: β-CD (1:1) complex showed reduction in the intensity of peak of FBX and shift of endothermic peak of β-CD. These indicate successful complexation with β-CD. Thus, DSC studies confirm the inclusion complexation of drug with β-CD [22].

Figure 3. Represents DSC pattern of (a) pure febuxostat, (b) pure β-CD and (c) 1:2 solid dispersion of febuxostat β-Cyclodextrin.

In order to select the best superdisintegrants, preliminary trials were conducted (Table 3). All the prepared tablets were characterized by a uniform thickness, diameter, and weight. Based on the disintegration and dissolution results, the investigated superdisintegrants can be ranked according to their ability to swell in water as Locust Bean Gum > Crospovidone > Crosscarmellose. The wicking and capillary action are postulated to be major factors in the ability of these superdisintegrants to function. As a result, the superdisintegrants Locust Bean Gum and crospovidone exhibited faster disintegration and dissolution release. Hence, they were selected for further studies [19].

<table>
<thead>
<tr>
<th>Formulation codes</th>
<th>Average Weight(mg)</th>
<th>Thickness (mm)</th>
<th>Hardness (kg/cm²)</th>
<th>Friability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>247.9±2.12</td>
<td>3.053±0.187</td>
<td>3.083±0.069</td>
<td>0.77</td>
</tr>
<tr>
<td>F2</td>
<td>248.3±1.98</td>
<td>3.020±0.091</td>
<td>3.000±0.058</td>
<td>0.61</td>
</tr>
<tr>
<td>F3</td>
<td>248.3±2.07</td>
<td>3.018±0.090</td>
<td>3.000±0.100</td>
<td>0.56</td>
</tr>
<tr>
<td>F4</td>
<td>248.3±2.25</td>
<td>3.006±0.094</td>
<td>3.033±0.111</td>
<td>0.81</td>
</tr>
<tr>
<td>F5</td>
<td>248.7±1.85</td>
<td>3.027±0.088</td>
<td>3.117±0.090</td>
<td>0.68</td>
</tr>
<tr>
<td>F6</td>
<td>248.3±2.16</td>
<td>3.007±0.086</td>
<td>3.183±0.090</td>
<td>0.59</td>
</tr>
<tr>
<td>F7</td>
<td>249.0±1.54</td>
<td>3.018±0.089</td>
<td>3.267±0.094</td>
<td>0.74</td>
</tr>
<tr>
<td>F8</td>
<td>248.8±1.76</td>
<td>3.016±0.086</td>
<td>3.334±0.094</td>
<td>0.63</td>
</tr>
<tr>
<td>F9</td>
<td>248.4±1.98</td>
<td>3.030±0.083</td>
<td>3.467±0.095</td>
<td>0.52</td>
</tr>
</tbody>
</table>

*Data are expressed as mean ± S.D. (n = 3)
Stability Studies
Temperature dependent stability studies

The fast disintegrating tablet of febuxostat F9 was packed in wide mouth air tight glass container and stored at (40 ± 2 °C and 75 ± 5 % RH) for a period of 2 months. The tablets was withdrawn after a period of 15 days and analyzed for physical characterization and drug content spectrophotometrically at 315nm Among several methods investigated for dissolution profile comparison [21]
**Table- 6. Effect of storage conditions of F9 formulation.**

<table>
<thead>
<tr>
<th>No. of days</th>
<th>Avg. weight (mg)</th>
<th>Hardness(kg/cm²)</th>
<th>Friability(%)</th>
<th>D.T. (sec)</th>
<th>Drug Content(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>248.93±0.99</td>
<td>3.33±0.1</td>
<td>0.56±0.051</td>
<td>36±1.24</td>
<td>99.88±0.312</td>
</tr>
<tr>
<td>15</td>
<td>248.95±0.76</td>
<td>3.33±0.1</td>
<td>0.56±0.033</td>
<td>35±1.09</td>
<td>99.53±0.017</td>
</tr>
<tr>
<td>30</td>
<td>248.98±0.85</td>
<td>3.33±0.2</td>
<td>0.57±0.072</td>
<td>35±1.55</td>
<td>99.35±0.009</td>
</tr>
<tr>
<td>45</td>
<td>248.76±1.24</td>
<td>3.30±0.2</td>
<td>0.57±0.043</td>
<td>34±1.10</td>
<td>99.23±0.014</td>
</tr>
<tr>
<td>60</td>
<td>248.57±0.31</td>
<td>3.30±0.2</td>
<td>0.58±0.069</td>
<td>34±1.44</td>
<td>99.20±0.021</td>
</tr>
</tbody>
</table>

*Data expressed as mean ± S.D.(n=3)*

**Table -7. Comparison of drug release data before and after storage.**

<table>
<thead>
<tr>
<th>Time(min)</th>
<th>Percent Drug Released ± S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
</tr>
<tr>
<td>5</td>
<td>42.85±0.52</td>
</tr>
<tr>
<td>10</td>
<td>51.22±0.68</td>
</tr>
<tr>
<td>15</td>
<td>66.55±0.20</td>
</tr>
<tr>
<td>20</td>
<td>74.69±0.59</td>
</tr>
<tr>
<td>25</td>
<td>85.94±0.90</td>
</tr>
<tr>
<td>30</td>
<td>93.76±0.3</td>
</tr>
</tbody>
</table>

* Data expressed as mean ± S.D (n=3)

**Figure 5. Comparison of drug release before and after stability studies.**

The similarity factor was calculated for the comparison of the dissolution profile before and after stability studies.

**CONCLUSION**

The present study showed the suitability of β-CD as a carrier for the preparation of febuxostat solid dispersions. The complex formation offered better dissolution rate from its solid dispersion. Disintegration time decreased with the increase in concentration of superdisintegrants. Formulations Locust Bean Gum (10%) and Crosspovidone (10%) showed faster disintegration. Solid dispersions technique for poorly soluble drug will grow due to its recent advancement in the technology with respect to method of preparation, scale-up and newer methods for better predictability of solid state structure and will continue to grow and offers greater possibilities and applications for oral drug delivery.

**REFERENCES**

5. Ghareeb MM., Abdulrasool AA., Hussein AA., Noordin MI., Kneading Technique for Preparation of Binary Solid Dispersion of Meloxicam with Poloxamer 188, AAPS PharmSciTech. 2009; 1206-1215.