Preparation of Rosuvastatin Orodispersible Tablets and Comparative Evaluation with Brand and Generic Marketed Tablets

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ABSTRACT

Rosuvastatin is a type of a drug class; statins, used for treatment of high level of cholesterol and for avoid of cardio-vascular diseases. The main goals of the current study is to prepared fast dissolved tablets of rosuvastatin using different kinds of super dis-integrants to promote the dis-integration and dissolution of rosuvastatin to enhance bio-availability of a medicine. Many approaches were used to formulate a satisfactory rosuvastatin rapid dissolved tablets by using of direct compression method. The formulated tablets were characterized for different parameters, such as hardness, variation in weight, friability, time of wetting, in vitro dis-integration time and in vitro release of drug. The formulas that formulated by directly compression method showed a good flow ability. Various super dis-integrants were used including croscarmellose and crospovidone. Crospovidone is better than croscarmellose as it is showing faster dis integration time. Among the utilized diluents it was found that spray dried lactose was the best one in formulation of rosuvastatin tablets with rapid dis integration time in mouth. The best formula (F6) was formulated using 10% w/w of crospovidone, by directly compression give the lowest dis-integratoin time in the mouth (11) seconds. In addition to that the optimized formula had a suitable friability and hardness, therefore; it was considered as the best formulation. The net of the results showed that crospovidone was the best super dis-integrant of showing the lowest disintegration time while spray dried lactose was the best diluent used in formulating of rosuvastatin oro-dispersible tablets and this suggesting the probability of utilizing the optimized best formulation (F6) in the formulation of rosuvastatin oro-dispersible tablets as a good dosage form for orally administration.

Keywords: preparation, tablets, comparative, brand.

INTRODUCTION

The poorly water-soluble or water-insoluble molecules lists more than one third of US Pharmacopeia drugs. In new medicinal molecules development decades ago, more than 41 percent of failures are because of poor properties of bio molecules, including water insolubility, and recently, up to fifty percent of drug candidate failures have a low “drug_like” properties. The low solubility of the medicinal compounds lead to prevented absorption of drug from the site of administrati0n. To solve the above discussed problems, pharmaceutical technologists develop a Fast dissolving drug delivery tablet (Orodispensible) tablets. Rosuvastatin, as rosuvastatin calcium is 3-hydroxy—3methyl-glutaryl-CoA reeducates inhibitor used to treat the dys-lipidaemia, benign prostatic hyperplasia, osteoporosis and Alzheimers disease. Rosuvastatin is acrystalline in nature, therefore it reduces its water solubility and results in abioavailability of about 20% .

The goal of this study is to formulate oro-dispersible rosuvastatin’s tablets by using suitable of super disintegrant to promote the dis-integration and dissolution of rosuvastatin to enhance drug’s bioavailability.

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METHODS

Materials
Rosuvastatin calcium (eq to rosuvastatin 10 mg), Avicel ph101, spray dried lactose, crospovidone, calcium phosphate dibasic, aspartame, banana flavor and magnesium stearate were supplied from (sama-alfayhaa drug industry).

Characterization of Rosuvastatin

Determination of Rosuvastatin’s Melting Point.
The drug’s melting point is determined according to USP method. A little amount of medication powder was inserted into a capillary tube to create a compact 6-mercaptopurine powder column. The tube was inserted into the Stuart electrical device. Until the powder was completely melted, the temperature was taken and recorded.3

Determination of the λ max of Rosuvastatin.
The solution of rosuvastatin of 0.1 mg/ml concentration in HCL solution medium (pH 1.2) and phosphate buffer solution (pH 6.8) were prepared, then scanned by spectrophotometer from 200-400 nm, and the λ max of the drug was determined.3

Calibration Curve of Rosuvastatin
Calibration curves were generated using drug stock solutions and series diluted concentrations of HCL solution (pH 1.2) (0.1 mg/ml for methanol and 0.01 mg/ml for HCL solution), methanol, as well as phosphate buffer solution (pH 6.8) the formulated samples were analyzed spectrophotometrically at rosuvastatin λ max. The determined absorbance was assigned and plotted versus the concentration.3

The NMR Spectra
The nuclear magnetic resonance analyses were done at the laboratories of college of sciences, Basra University. 1 H-NMR and 13C-NMR analyses were performed at 400 MHz. DMSO-d6 used as a solvent, with the chemical shifts (δ) expressed in parts per million (δ).4

Table 1: Composition of Rosuvastatin Oral Dispersible Tablets

<table>
<thead>
<tr>
<th>Constituents</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin calcium</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Avicel ph101</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium phosphate dibasic</td>
<td>56</td>
<td>56</td>
<td>56</td>
<td>56</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>Aspartame</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Banana flavor</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>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Spray dried lactose up to…. (mg)</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
</tr>
</tbody>
</table>
Ten tablets of each formula were firstly weighed (W, initial) and then putted in the friabilator. The friabilator usually operate at 25 rpm for four minutes or runs up to 100 revolutions. The tablets then also weighed (W final). The percent of friability was estimated by using the following equation.

\[ F = \frac{\text{Initial} - \text{Final}}{\text{Initial}} \times 100 \]

If the percent of friability of the tablets is less than 1% is an acceptable.

**In-vitro Dissolution Test**

The in-vitro disintegration time was estimated using disintegration test apparatus. The tablets were put inside of each 6 tubes of disintegration instrument and then add one disc in every tube. Then the time was detected in a seconds after completion disintegration of each tablet with no palatableness mass remain in the instruments was detected in a seconds.

**In-vitro Disintegration Test**

The dissolution of the orodispersible tablets, as well as the brand and generic marketing tablets, was done to compare the release of drugs from these formulas. All of these studies were conducted out utilizing the USP dissolution paddle method. In this method, dissolving media such as HCL solution (pH 1.2) and phosphate buffer solution (pH 6.8) were used. The stirring speed was 50 ± 2 revolutions per minute. 6-mercaptopurine was present in all formulations at a concentration of 50 mg. Each of the two mediums included 900 mL volume, which were kept at 37°C at all times.

Approximately 5 ml of the sample was taken and then filtered through a 0.45-mm Millipore filter at appropriate intervals (5, 10, 20, 30, 40, 50 and 60 minutes). Because of this, 5 ml of fresh dissolving solution was added to the mixture in order to keep the volume consistent. The samples were evaluated using a UV-spectrophotometer at \( \lambda \) max of rosuvastatin, which was used for the experiment. The drug release of each formulation was estimated by taking the average of three individual measurements.

**Statistical Analysis**

All the results of present studies are taken as triplicate samples ± standard deviation and were analyzed according to the one-way analysis of variances (ANOVA) at the level of \( P < 0.05 \).

**Result and Discussion**

**Characterization of Rosuvastatin**

**Determination of Melting Point**

There is no evidence to suggest that rosuvastatin powder is less pure than the previously reported melting point range of 180°C.

**Determination of \( \lambda \) max of Rosuvastatin**

The UV scan of rosuvastatin in HCL medium (pH 1.2) revealed a maximum at 240.5 nm (Figure 1), which was selected as the previously published value. The UV scan of rosuvastatin in buffer medium (pH 6.8) with (Figure 2) revealed that the maximum wavelength was 241 nm.

**Calibration Curves**

Figures (3-4) illustrate the calibration curves for absorbance versus concentration, which were generated by graphing absorbance versus concentration for acidic medium and buffer medium, respectively. Given enough data and a high correlation coefficient of 0.999, the Beer-Lamberts equation was found to be well-confirmed for the experimental concentration range under consideration.
NMR Spectral Characterization

**HNMR Spectroscopy**

The main peaks showed by 1H NMR spectrum, at 3.41 – 3.55 ppm assigned of hydrogen atom attached to sulfur and nitrogen atom, the peaks at 3.84 ppm represent hydrogen atom in hydroxyl molecule, at 5.513 – 5.565 ppm assigned of hydrogen atom in AGU part of drug and 6.5 – 7.7 ppm assigned of hydrogen atom attached to aliphatic hydrocarbon chain, (Figure 7).

**13CNMR Spectroscopy**

The 13C NMR spectrum was showed the main peaks: at 174.7, and 179.1, which were assigned to methyl group (CH3) and o—c—o., at 161-164 were assigned to carbon atom at aromatic ring, at 69-66 were assigned of hydrogen atom in AGU part and at 21-39 were assigned to carbon atom at aliphatic backbone and chain as shown in figure 6.

Differential Scanning Calorimetrical Analysis (DSC)

The prepared orodispersible tablets and its ingredients were examined by DSC for its solid state. The crystalline behavior of free rosuvastatin is demonstrated in Figure (7) is evaluated by a single strident endothermic peak at 240.4°C. There is only one sharp endothermic peak (19), (41). Semi-crystallinity is evident in the DSC thermographs for avicel ph 101, calcium phosphate and spray dried lactose because of the significant endothermic peak at 351.1 °C, 205.3 °C and 235.5 °C respectively.

Thermal investigation of the optimized formulation (F5) shows a peaks of all types of excipients with a very short of the rosuvastatine a typical endothermic peak.

**X-ray Diffractometric Analysis**

The physical characteristics of the drug in the final formula of the drug is critical for achieving the require release pattern. In this study, the physical parameters of the final formulation were determined using an XRD analysis of rosuvastatin and other excipients. Figure 13 depicts rosuvastatin X-ray diffractometric (XRD) reflections, which exhibit many distinct peaks demonstrating the drug's crystalline shape. Crospovidone and avicel ph 101 X-ray diffraction profile exhibits a diffuse backdrop with 2 halo diffractions, indicating that it is amorphous in nature.
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Fig. 8: DSC Thermograms of Avicel ph 101

Fig. 9: DSC Thermograms of calcium phosphate

Figure 10: DSC Thermograms of spray dried lactose.

Fig. 11: DSC Thermogram of crospovidone.

Fig. 12: DSC Thermogram of orodispersible optimized formula

Fig. 13: X-ray Powder diffraction of rosuvastatin

Fig. 14: X-ray Powder diffraction of Avicel ph 101

Fig. 15: X-ray Powder diffraction of Spray Dry Lactose.
This is not the case with spray dried lactose and calcium phosphate, which exhibits a range of reflections emphasizing the polymer’s semi-crystalline structure. As illustrated in Figure (18), the spray dried and crospovidone hump in the X-ray-powder diffraction for the selected formulation (F6) reveals that the rosuvastatin crystallinity in the formula has been decreased, as previously mentioned. This was shown in the X-ray powder diffraction for the formula 6. It appears that the DSC results and the XRD data are in agreement, according to the results of the DSC.

**FTIR Spectroscopy**

For the finished product to have stable, high-quality orodispersible tablets, the medication must be compatible with the excipients in the formulation. Hydrogen bonding, hydrophobic interaction, and electrostatic contact are all examples of second-order interactions that might affect compatibility.

Samples of spray dried lactose, Avicel pH101, pure rosuvastatin, crospovidone, calcium phosphate and optimized formula (F6) were detected by FT-IR spectroscopic analysis, and their spectra at 500 – 4000 cm\(^{-1}\) are shown in Figures (19-24). The characteristic peaks of N–H stretching (in aromatic group) and C=O stretching at 3338.57 cm\(^{-1}\) and 1548.84 cm\(^{-1}\) appeared, respectively.

The characteristic bands of selected formula (F6) and other excipients are clearly visible in the selected formula (figure 24). The pattern of optimized formulation shows that there is no interaction between the excipients and the drug. DSC and XRD measurements support this conclusion.
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Fig. 19: FTIR Spectroscopy of Rosuvastatin

Fig. 20: FTIR Spectroscopy of Avicel PH101

Fig. 21: FTIR Spectroscopy of Calcium Phosphate

Figure 23: FTIR Spectroscopy of Spray Dried Lactose
Evaluation of powder blend
As shown in table 2, all formulas have good flowable properties. The detected values of tapped density, bulk density, angle of repose, percent of compressability and Hausner ratio were within normal range. The good flow ability due to using good flowable excipients such as crospovidone, avicel ph 101 and spray dried lactose.

Evaluation of Rosuvastatin Oro-dispersible Tablet
As shown in table 3, all formulas were within the acceptable limit regarding to hardness test, friability test, weight variation test, diameter of tablets, time of wetting and in vitro disintegration test. The formulation number 6 show the best value for all tests, so it was choose as the selected formula.
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**Table 2: Evaluation of powder blend**

<table>
<thead>
<tr>
<th>Formula code</th>
<th>Bulk Density</th>
<th>Tapped Density</th>
<th>Angle of Repose</th>
<th>% of Compressibility</th>
<th>Hausner’s Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.56</td>
<td>0.66</td>
<td>25.57</td>
<td>15.15</td>
<td>1.118</td>
</tr>
<tr>
<td>F2</td>
<td>0.54</td>
<td>0.65</td>
<td>24.91</td>
<td>16.92</td>
<td>1.203</td>
</tr>
<tr>
<td>F3</td>
<td>0.53</td>
<td>0.61</td>
<td>24.54</td>
<td>13.1</td>
<td>1.15</td>
</tr>
<tr>
<td>F4</td>
<td>0.54</td>
<td>0.62</td>
<td>23.63</td>
<td>12.9</td>
<td>1.148</td>
</tr>
<tr>
<td>F5</td>
<td>0.49</td>
<td>0.56</td>
<td>26.32</td>
<td>12.5</td>
<td>1.142</td>
</tr>
<tr>
<td>F6</td>
<td>0.56</td>
<td>0.63</td>
<td>22.13</td>
<td>11.11</td>
<td>1.11</td>
</tr>
</tbody>
</table>

**Table 3: Physical parameters of mouth dissolving tablets, brand and generic marketed tablets**

<table>
<thead>
<tr>
<th>Formula code</th>
<th>Weight Variation</th>
<th>Thickness (mm)</th>
<th>Hardness (Kg/cm²)</th>
<th>Friability %</th>
<th>Time of wetting (sec)</th>
<th>In vitro disintegration time (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>pass</td>
<td>9.43 ± 1.02</td>
<td>2.4 ± 0.3</td>
<td>0.67 ± 0.02</td>
<td>40 ± 1</td>
<td>23 ± 2</td>
</tr>
<tr>
<td>F2</td>
<td>pass</td>
<td>10.2 ± 0.82</td>
<td>2.8 ± 0.2</td>
<td>0.68 ± 0.05</td>
<td>35 ± 2</td>
<td>19 ± 2</td>
</tr>
<tr>
<td>F3</td>
<td>pass</td>
<td>9.61 ± 0.78</td>
<td>2.6 ± 0.3</td>
<td>0.72 ± 0.04</td>
<td>32 ± 2</td>
<td>21 ± 1</td>
</tr>
<tr>
<td>F4</td>
<td>pass</td>
<td>10.01 ± 0.62</td>
<td>2.9 ± 0.4</td>
<td>0.70 ± 0.04</td>
<td>41 ± 6</td>
<td>20 ± 3</td>
</tr>
<tr>
<td>F5</td>
<td>pass</td>
<td>9.34 ± 0.56</td>
<td>2.7 ± 0.2</td>
<td>0.66 ± 0.06</td>
<td>33 ± 1</td>
<td>17 ± 1</td>
</tr>
<tr>
<td>F6</td>
<td>pass</td>
<td>9.96 ± 0.91</td>
<td>2.5 ± 0.2</td>
<td>0.69 ± 0.07</td>
<td>22 ± 3</td>
<td>11 ± 1</td>
</tr>
<tr>
<td>Brand tablet</td>
<td>pass</td>
<td>2.87 ± 0.09</td>
<td>5.3 ± 0.62</td>
<td>0.83 ± 0.05</td>
<td>-</td>
<td>174 ± 15</td>
</tr>
<tr>
<td>Generic tablet</td>
<td>pass</td>
<td>3.1 ± 0.08</td>
<td>5.02 ± 0.41</td>
<td>0.72 ± 0.06</td>
<td>-</td>
<td>234 ± 13</td>
</tr>
</tbody>
</table>

**In-vitro Drug’s Release**

In order to assessment the dissolution properties of all formulation, the dissolution have been done in time interval of sixty minutes at 37 °C in (900) ml 0.1 N HCL and buffer system (pH 6.8). During the first five minutes, the rosvastatin optimized formulation released 78 percent of the medication, but the generic tablet released only 5 percent of the medication and the brand tablet released only 16 percent of the medication in 0.1 N HCL dissolution medium. It took less than five minutes for the rosvastatin-optimized formulation to release most of its active ingredient (84%) but the generic tablet released only 11 percent of the medication and the brand tablet released only 24 percent of the medication in buffer system.

During the period of 60 minutes, all the formulas were able to release the medication in a complete pattern. As shown in figure 25 and 26. It has been demonstrated that the hydrophilic nature of crospovidone, and avicel increase in wettability and improve dissolution.

**Conclusion**

The best super disintegrant was a crospovidone because it showing the lowest disintegration time while spray dried.
lactose was the best diluent in formulation of Rosuvastatin oro-dispersible tablet. This study confirm the capability of using the optimized formulation (F5) in the formulation of oro-dispersible tablet of Rosuvastatin as a new dosage form for oral route due to the required properties of the formulated tablets regarding to enough hardness, small value of friability, rapid disintegration and dissolution.

REFERENCES


