Lovastatin Fast Dissolving Tablets: Formulation and In Vitro Evaluation

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ABSTRACT

The present study is intended to develop the lovastatin fast dissolving tablets using superdisintegrants to improve the dissolution rate. Lovastatin fast dissolving tablets were prepared using direct compression method and were characterized for both pre-compression and post-compression parameters. From the in vitro drug release studies the F9 tablets showed fast disintegration (38 sec) and almost complete drug release within the 10 min. The percent drug release in 10 min (Q₁₀) and initial dissolution rate (IDR) of F9 tablets was 97.56±0.56%, 9.76%/min. These were very much higher compared to control tablets (38.41±0.23%, 3.84%/min). The relative dissolution rate (RDR) was found to be 2.93. The dissolution efficiency (DE) was found to be 43.26 and it is increased by 3.0 fold with F9 tablets when compared to control tablets. DSC and FTIR studies were carried out to understand the drug-polymer compatibility and revealed that there was no possible interaction between them. From the stability studies, F9 formulation showed the good stability and it was proved by calculating the similarity factor i.e., 82.56. Thus the developed fast dissolving tablets may be suitable to give rapid dissolution and rapid onset of action.

Key words: Dissolution efficiency, Initial dissolution rate, Pre-compression parameters, Post-compression parameters, Similarity factor, Superdisintegrants

Introduction

Even though several novel drug delivery systems were developed, still the oral administration of tablets is the preferred method for the treatment of various disorders due to greater flexibility in design and high patient acceptance (Vangala et al., 2014). But to overcome the common problems of tablets like slow onset of action and dissolution rate, preparation of the fast dissolving tablets (FDT) is one of the useful approaches (Kaushik et al., 2004; Hirani et al., 2009). The following are the common methods to formulate the FDT: i.e., direct compression, wet granulation, molding, spray drying, freeze drying, and sublimation (Seager, 1998; Bandari et al., 2008). In those, direct compression method is the simplest method to formulate the FDTs due to the advantages like conventional equipment and limited number of processing steps (Dobetti, 2010).

Incorporation of superdisintegrants is the simple, basic and most commonly used approach to develop the FDTs that fasten the disintegration and dissolution. In this approach, selection of a suitable disintegrant and its concentration is the challenging factor because it has strong influence on the achievement of fast disintegration as well as dissolution rates. Superdisintegrants are well known to produce fast disintegration with the result of swelling and water absorption by the tablets (Vemula et al., 2011). Due to swelling of superdisintegrant, the wetted surface of the carrier increases that promote the wettability and dispersibility of the system, which directs the improvement in disintegration and dissolution (Vemula et al., 2010). The important properties of oral fast dissolving tablets are fast absorption of water into the core of the tablets, and disintegration of associated particles into individual components for fast disintegration (Vemula and Veerareddy, 2011). FDTs using superdisintegrants is able to lowers the disintegration time without much affecting the tablet properties. In the formulation of FDTs, the concentration of lubricant is critical factor since it prevents wetting and there by increases the disintegration time (Vemula and Veerareddy, 2011).
In the present study, lovastatin is selected as the model drug to prepare FDTs using superdisintegrants. Lovastatin is a hypolipidemic agent that belongs to statins, used for lowering cholesterol in those patients suffering with hypercholesterolemia. It is a poorly soluble drug, with a shorter half life of 1.1-1.7 h and less than 5% bioavailability (Neduri et al., 2013; Leuner and Dressman, 2000). Thus the present study is intended to formulate the lovastatin fast dissolving tablets to enhance the dissolution rate to maximize the therapy.

Materials

Lovastatin is a gift sample from MSN laboratories, Hyderabad, India. Sodium starch glycolate, Crosspovidone, and Crosscarmellose were gift samples from Matrix laboratories, Hyderabad, India. All other chemicals used were of analytical grade.

Methods

Preparation of Fast dissolving tablets

Direct compression method is used to prepare the fast dissolving tablets. Lovastatin, superdisintegrants and other excipients were passed through a mesh # 60. The drug was mixed with proper portion of superdisintegrant with care to ensure the proper mixing of drug and superdisintegrant. Then excipients other than glidant and lubricant were added and mixed in a poly bag for 5-10 min. The obtained blend was lubricated with talc and magnesium stearate for another 5 min and it was compressed into tablets with 6 mm round flat punches using 16 station rotary tabletting machine (Cmach, Ahmedabad, India). Different formulations compositions are given in Table 1. The conventional tablets (control) were prepared in a similar manner with normal disintegrating agent.

Pre-compression Parameters

Before going to compression, the powder mixtures of different formulations were measured for angle of repose, bulk and tapped densities and compressibility index. The fixed funnel method was employed to measure the angle of repose (θ) and it was calculated using the following formula:

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

In which, θ is angle of repose, h is height of the cone and r is radius of the cone base. The compressibility index (Carr’s Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities and is calculated using the following formulas:

\[ \text{Carr’s Index} = \frac{[(\rho_{\text{tap}} - \rho_b)]}{\rho_{\text{tap}}} \times 100 \]

In which, \( \rho_b \) is bulk density and \( \rho_{\text{tap}} \) is tapped density.

Post-compression Parameters

The prepared tablets were studied for weight variation, hardness, friability, drug content uniformity, in vitro disintegration time, in vitro dispersion time, wetting time, water absorption ratio and mouth feel. For estimating weight variation, 20 tablets of each formulation were weighed using an Electronic weighing balance (AW 120, Shimadzu Corporation, Japan). The strength of tablet is expressed by measuring hardness (Kg/cm\(^2\)) friability. The hardness of six tablets was measured using Monsanto tablet hardness tester. Friability was determined on ten tablets in a Roche friabilator (Electrolab, Mumbai, India) for 4 min at 25 rpm.

Determination of Drug Content

For estimation of drug content, ten tablets were crushed, and the aliquot of powder equivalent to 50 mg of drug was dissolved in suitable quantity of methanol/1.2 pH buffer solution. Solution was filtered and diluted and drug content determined by UV-Visible spectrophotometer (Systronics 2202, Ahmedabad, India) at 238 nm. The drug concentration was calculated from the calibration curve.

In Vitro Disintegration Time

In vitro disintegration time of FDTs was determined by following the procedure described by Gohel et al. Briefly, 10 ml of water at room temperature was taken in a petridish of 10 cm in diameter. The tablet was then carefully placed in the centre of petridish and the time required for the tablet to completely disintegrate into fine particles was noted. Measurements were carried out in triplicates (Gohel et al., 2004).

In Vitro Dispersion Time

In vitro dispersion time was measured by dropping a tablet in a measuring cylinder containing 6ml of pH 6.8 (simulated saliva fluid). Three tablets from each formulation were randomly selected and in vitro dispersion time is expressed in sec (Narmada et al., 2009).
Wetting Time

Wetting time was determined as described in the literature elsewhere. Briefly, two circular tissue papers were placed in a Petri dish of 10 cm diameter. Ten milliliter of water containing 0.5 (% w/v) of phenol red was added to the petridish. The dye solution was used to identify the complete wetting of the tablet surface. A tablet was carefully placed on the surface of the paper in the petridish at room temperature. The time required for water to reach the upper surface of tablet and to completely wet them was noted as wetting time. Wetting time was recorded using stop watch and the measurements were carried out in triplicates (Bi et al., 1996).

Water Absorption Ratio (R)

The weight of the tablet prior to placement in the petridish was noted (W_b) using digital balance (Shimadzu, Japan). The wetted tablet was removed and reweighed (W_a). Water absorption ratio (R), was then calculated according to the following equation (Battu et al., 2007)

\[
R = \frac{W_a - W_b}{W_b} \times 100 \quad [3]
\]

W_b and W_a were tablet weights before and after water absorption, respectively.

In vitro Dissolution Study

The dissolution studies of prepared FDTs were conducted using USP XXIV Type II dissolution apparatus (Electrolab, TDT-08L) at 100 rpm rotation speed and 37±0.5 °C temperature. The drug release studies were carried out in 1.2 pH buffer. An aliquot of 5 ml was collected at predetermined time intervals (2, 5, 10, 15 and 30 min) and replaced with fresh dissolution medium. The samples were filtered, by passing through 0.45 µm membrane filters (Millipore, USA) and analyzed spectrophotometrically at 238 nm.

Calculation of dissolution parameters

Cumulative percent drug release was plotted as a function of time and percent drug release in 10 min (Q_10) was calculated. Initial dissolution rate (IDR) was calculated as percentage dissolved of drug over the first 10 min per min. Dissolution efficiency (DE) was calculated from the area under the dissolution curve at time t (measured using the trapezoidal rule) and expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. Relative dissolution rate (RDR) is the ratio between amount of drug dissolved from optimized formulation and that dissolved from the conventional formulation at 10 min (Vemula and Vangala, 2014).

Drug-Polymer Interaction Studies

To study the possible interaction between Lovastatin and excipients, DSC study was carried out on pure Lovastatin, Sodium starch glycolate, croscarmellose sodium, crospovidone and F9 formulation. Differential thermal analysis thermograms were obtained using DSC (Perkin-Elmer, Shelton, U.S). The analyses were performed under nitrogen (nitrogen flow rate 50 ml/min) in order to eliminate oxidative and pyrolytic effects at a standard heating rate of 15°C/minute over a temperature range of 50°C - 350°C. The infrared spectra of Lovastatin and optimized formulation recorded between 400 to 4000 cm\(^{-1}\) on FTIR to detect the drug-excipient interactions. The FTIR spectra for the test samples were obtained using KBr disk method using an FTIR spectrometer (Perkin Elmer FT-IR, Perkin Elmer Inst. USA). The resultant spectra were compared for any possible changes in the peaks of the spectra.

Stability studies

To assess the drug and formulation stability, stability studies were done according to ICH guidelines. Best formulation (F9 tablets) was sealed in aluminum packaging coated inside with polyethylene, and three replicates were kept in the humidity chamber maintained at 40±2 °C and 75±5% RH for six months (Chaudhary et al., 2011). Samples were collected after six months of storage and analyzed for the drug content and in vitro dissolution rate and they were subjected to statistical analysis using paired t-test to test the significance of difference at 0.05 level of significance (LS). Then the similarity index was calculated between dissolution rates of optimized tablets before and after storage to prove the stability of the dosage form (Vemula and Veerareddy, 2013; Vemula and Bontha, 2013).

Results and Discussion

Pre-compression Parameters

The powder mixtures of different formulations were evaluated for flow properties. From this, the bulk and tapped density values found to be 0.288-0.338 and 0.324-0.391 respectively. The results of angle of repose and compressibility index
Post-compression Parameters

The physical properties of lovastatin FDTs were shown in Table 2 and 3. In weight variation test, the pharmacopoeial limit for the tablets of not more than 7.5% of the average and all the formulations showed weight variation within the above limits (Indian Pharmacopoeia, 1996). The tablet hardness was found to be around 3 kg/cm². Conventional compressed tablets that loss less than 1% of their weight are generally considered acceptable. The percentage friability for all formulations was below 1%, indicating that the friability is within the prescribed limits. The tablets were found to contain 97.1± 0.68 to 99.6± 0.83 % of the labeled amount indicating uniformity of drug content.

The disintegration time of all formulations was found in the range of 38.09±6.01 to 51.8±1.94 sec. Among the formulations F9 showed rapid disintegration (38 sec) and all the formulations were disintegrated below 60 sec. In vitro dispersion time of formulated tablets was found in the range of 30.9±0.45 to 44.8±1.45 sec. The wetting time of formulated tablets was found in the range of 30.14±1.12 to 45.28±1.36 sec and water absorption ratio was 57.53±0.80 to 77.53±0.80. The rapid wetting time in all formulations may be due to high ability of swelling and water absorption of superdisintegrants.

In vitro Dissolution Study

The cumulative amount of lovastatin released from FDTs (F1-F9) was shown in Figure 1 and found to vary from 37.8 ±0.23 to 97.56±0.34 in 10 min. This indicates the fast release of drug is observed from above formulations. The optimized formulation F9 showed the 97.56±0.56% drug release in the 10 min where as the conventional lovastatin tablets (control) showed 38.4±0.48 in 10min. Thus the formulation F9 was considered better among other formulations to produce fast drug release. This can be well correlated with the evaluation parameter disintegration time and wetting time which were very lower for the F9 formulation than the other formulations. Similar kind of results were observed in a study developed by Vemula i.e., flurbiprofen fast disintegrating tablets (Vemula and Veerareddy, 2011).

The percent drug release in 10 min (Q10) and IDR of F9 tablets were found to be 97.56±0.56%, 9.76%/min and these were improved significantly when compared to control tablets (38.41±0.23%, 3.84%/min). The DE was found to be 43.26 and it is increased by 3.0 fold with F9 FDT formulation compared to control tablet (Table 4) and RDR was found to be 2.93. Hence the improvement of dissolution rate of F9 tablets were described in terms of dissolution parameters (IDR, DE, RDR) in comparison to control tablets. Comparable results were observed in flurbiprofen fast disintegrating tablets using superdisintegrants (Vemula and Veerareddy, 2011).

Drug polymer interaction studies

DSC studies were performed to understand the nature of the drug in the formulated tablets. Thermograms obtained for pure drug, cроссповидоне, and optimized formulation were shown in Figure 2. The DSC of lovastatin showed endothermic peaks equivalent to its melting point at 172.21 °C. The thermograms of the F9 tablets did not show any significant shift in the endothermic peak. The FTIR spectrum (Figure 3) of above mentioned excipients and F9 tablets were compared to that of pure lovastatin. The FTIR spectra of pure lovastatin and optimized formulation of superdisintegrants, exhibit peak at 1275 cm⁻¹ ,1050 cm⁻¹ is due to lactone and ester C-O-C bending vibration stretching and peaks at 2930 cm⁻¹ is due methyl and methylene C-H stretching, though additional peaks were observed with optimized formulation which could be due to the presence of polymers. Thus, it conforms the structure of drug lovastatin.

Stability studies

F9 tablets were subjected to a drug assay and in vitro dissolution studies after storage of six months (Figure 4). From the statistical analysis there was no significant difference between before and after storage (P<0.05). The similarity index value between dissolution profiles of optimized formulation before and after storage was found to be 82.56, which is more than 50 indicates similarity between the dissolution profile before and after storage (Vemula and Veerareddy, 2013; Vemula and Bontha, 2013).

Conclusion

With the intention to enhance the dissolution rate, in the present study, lovastatin fast dissolving tablets were successfully prepared using direct compression method. From the in vitro dissolution studies, F9 tablets were found as best formulation. The percent drug release in 10 min and initial dissolution rate of F9 tablets was 97.56±0.56%, 9.76%/min and improved when compared to control tablets. DSC and FTIR spectral studies revealed that there are no drug-excipient interactions. From the stability studies, similarity factor was found to be more than 50 indicated the stability of formulation. Further the efficacy of the formulations has to be assessed by pharmacokinetic studies. Hence the development of lovastatin fast dissolving tablets using superdisintegrants is able to give rapid dissolution rate to achieve rapid onset of action.
Table 1. Formulation of lovastatin fast dissolving tablets

<table>
<thead>
<tr>
<th>Ingredients (mg/tablet)</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>Lovastatin</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Sodium starch glycolate</td>
<td>2.4</td>
<td>4.8</td>
<td>7.2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Crosscarmelose</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.4</td>
<td>4.8</td>
<td>7.2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Crosspovidone</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.4</td>
<td>4.8</td>
<td>7.2</td>
</tr>
<tr>
<td>Avicel PH102</td>
<td>94</td>
<td>91.6</td>
<td>89.2</td>
<td>94</td>
<td>91.6</td>
<td>89.2</td>
<td>94</td>
<td>91.6</td>
<td>89.2</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Talc</td>
<td>2.4</td>
<td>2.4</td>
<td>2.4</td>
<td>2.4</td>
<td>2.4</td>
<td>2.4</td>
<td>2.4</td>
<td>2.4</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Table 2. Physical properties of lovastatin fast dissolving tablets

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Weight variation*</th>
<th>Hardness†</th>
<th>Friability</th>
<th>Drug content uniformity‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>119.2±1.73</td>
<td>3.06±0.25</td>
<td>0.34</td>
<td>98.6±1.05</td>
</tr>
<tr>
<td>F2</td>
<td>119.6±0.57</td>
<td>3.43±0.25</td>
<td>0.27</td>
<td>98.5±1.30</td>
</tr>
<tr>
<td>F3</td>
<td>120.5±1.23</td>
<td>3.54±0.51</td>
<td>0.32</td>
<td>99.2±0.65</td>
</tr>
<tr>
<td>F4</td>
<td>119.6±0.57</td>
<td>3.26±0.32</td>
<td>0.33</td>
<td>98.2±1.60</td>
</tr>
<tr>
<td>F5</td>
<td>122.4±0.67</td>
<td>3.26±0.41</td>
<td>0.28</td>
<td>97.1±0.68</td>
</tr>
<tr>
<td>F6</td>
<td>121.3±1.52</td>
<td>3.31±0.36</td>
<td>0.42</td>
<td>99.6±0.83</td>
</tr>
<tr>
<td>F7</td>
<td>121.1±0.84</td>
<td>3.39±0.34</td>
<td>0.34</td>
<td>98.1±0.36</td>
</tr>
<tr>
<td>F8</td>
<td>121.6±0.57</td>
<td>3.36±0.3</td>
<td>0.36</td>
<td>97.8±0.62</td>
</tr>
<tr>
<td>F9</td>
<td>118.3±0.45</td>
<td>3.82±1.02</td>
<td>0.43</td>
<td>97.2±0.34</td>
</tr>
</tbody>
</table>

*All values represent mean ± standard deviation, n = 20
†All values represent mean ± standard deviation, n = 6
‡All values represent mean ± standard deviation, n = 3

Table 3. Physical properties of lovastatin fast dissolving tablets

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Disintegration time*</th>
<th>Wetting time*</th>
<th>Water absorption time*</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>50.43±0.97</td>
<td>42.9±0.45</td>
<td>57.53±0.80</td>
</tr>
<tr>
<td>F2</td>
<td>46.81±1.5</td>
<td>38.14±0.79</td>
<td>66.02±0.60</td>
</tr>
<tr>
<td>F3</td>
<td>44.62±0.92</td>
<td>35.49±1.32</td>
<td>68.85±0.73</td>
</tr>
<tr>
<td>F4</td>
<td>51.83±1.94</td>
<td>44.84±1.45</td>
<td>59.51±1.55</td>
</tr>
<tr>
<td>F5</td>
<td>42.21±0.90</td>
<td>39.19±0.42</td>
<td>64.83±1.05</td>
</tr>
<tr>
<td>F6</td>
<td>41.19±6.01</td>
<td>34.24±0.70</td>
<td>71.92±0.84</td>
</tr>
<tr>
<td>F7</td>
<td>47.69±1.67</td>
<td>37.16±0.76</td>
<td>69.09±0.17</td>
</tr>
<tr>
<td>F8</td>
<td>44.08±0.71</td>
<td>35.38±1.60</td>
<td>71.26±1.09</td>
</tr>
<tr>
<td>F9</td>
<td>38.92±6.01</td>
<td>30.92±0.45</td>
<td>77.53±0.80</td>
</tr>
</tbody>
</table>

*All values represent mean ± standard deviation, n = 3

Table 4. Dissolution parameters of optimized and conventional lovastatin formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>(Q10)*</th>
<th>IDR(%/min)</th>
<th>DE</th>
<th>RDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDT (F9)</td>
<td>97.56±0.56</td>
<td>9.756</td>
<td>43.26</td>
<td>2.93</td>
</tr>
<tr>
<td>Conventional</td>
<td>38.41±0.23</td>
<td>3.841</td>
<td>14.75</td>
<td>2.93</td>
</tr>
</tbody>
</table>

Q10=percent drug release in 10 min, IDR-initial dissolution rate, DE-dissolution efficiency and RDR relative dissolution rate.

*All values represent mean ± standard deviation, n=3.

Figure 1. Dissolution profile of lovastatin fast dissolving tablets (F1-F9)
Figure 2. DSC thermograms of the Lovastatin, Crosspovidone and F9 tablets

Figure 3. FTIR studies of the Lovastatin, Crosspovidone and F9 tablets

Figure 4. Stability studies of lovastatin F9 fast dissolving tablets
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Conflict of Interests

The authors of present manuscript do not have any conflict of interest.

References