Formulation and evaluation of Simvastatin liquisolid tablets

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ABSTRACT

Poor aqueous solubility always has been a very challenging obstacle like Simvastatin needs to be enhanced by using Powder solution technology. The present research proving the Propylene glycol, Avicel PH 101 and Aerosil PH 200 suitable for the liquisolid tablets i.e. resulting highest dissolution rate due to the wettability, producing of the super saturated microenvironment around the tablets and good flow properties by changing the 5:1 to 10:1 excipient ratio (R). All Simvastatin liquisolid tablets were showing the highest dissolution rate (99.9%) within the 60 minutes comparison with the direct compressed tablets and marketed tablets.

Keywords: Simvastatin, Liquisolid tablets, Dissolution rate, Flow Properties.

INTRODUCTION

The poor dissolution of water insoluble drugs is a substantial problem confronting the pharmaceutical industry. Different approaches have been attempted to increase aqueous solubility of poorly soluble drugs, such as conversion of crystalline molecule to its amorphous state, a particle size reduction via micronization, solubilization in surfactant systems, co-solvency, hydrotrropic solubilization, cyclodextrin complexation. A more recent technique, entitled "Powdered Solution Technology", has been applied to prepare water-insoluble drugs into rapid release solid dosage forms. Powdered solutions are designed to contain liquid medications in powdered form, thereby possessing mechanisms of drug delivery. Several investigators were reported the results and giving their suggestions on the liquisolid technology for the achieving the flow properties [1-19].

Increased drug dissolution rate and Bio-availability is achieved as a result of greater drug surface area exposed to the dissolution medium of water insoluble drugs can be improved to a...
significant extent as a result due to the increased wettability. Cost of production of liquid solid systems is less compared to that of soft gelatin capsules. Liao [16] proposed mathematical expressions for the calculation of the amount of excipients needed for powdered solution formulations. The major drawback of this approach was that the final product exhibited poor and erratic flowability due to the inadequacy of the proposed model to calculate the appropriate amount of excipients required to produce powder admixtures of acceptable and consistent flow properties. Mathematical model expressions based on power properties and the fundamentals principles and mechanisms of powdered solutions are derived. It is successfully allow for calculation of the optimum amounts of ingredients required to produce liquid/powder admixtures possessing, to a pre-specified desirable degree, acceptable flow characteristics [1].

Simvastatin having the low solubility in the gastric fluids (1-2 pH) and Intestinal fluids (6.5 pH to 8.0 pH), it is needs to be enhancing the solubility, dissolution rate and bioavailability by using Liquisolid technology.

**MATERIALS AND METHODS**

**Materials:** Simvastatin, Avicel PH 101, Aerosil PH 200, Propylene Glycol (PG), Crospovidone.

**Solubility studies**
For the selection of best non volatile solvents solubility studies are used, in this procedure, pure drug was dissolved in five different non volatile solvents. Excess amount of pure drug was adding to the non volatile solvents. From this obtained saturation solution were shaking on the rotary shaker for 48 hours at 25°C under constant vibration. After 48 hours period the saturated solution were filtered through a filter paper, and analyzed by UV spectrophotometer. The liquisolid tablets contain a solution of the drug in suitable solvent, the drug surface available for dissolution is tremendously increased.

**Calculation of loading factor (L_f)**
Loading factors were calculated for carrier material, using various solvents. By using \( L_f = \frac{W}{Q} \) formula (W: Amount of liquid medication and Q: Amount of carrier material), the drug loading factors were obtained and used for calculating the amount of carrier and coating materials in each formulation. The results showed that if the viscosity of the solvent is higher, lower amounts of carrier and coating materials are needed to produce flowable powder [12].

**Simvastatin liquisolid tablet preparation:** By using propylene glycol as a solubilizing non volatile solvent is drug solution i.e. absorption into the carrier material (Avicel PH 101) and onto the coating material (Aerosil PH 200) by changing the excipient ratio \( R \).

**Evaluation of the excipients**
All the excipients undergoes the precompression studies such as Bulk Density; Tapped Density; Measures of Powder Compressibility; Compressibility Index.; Hausner Ratio ; Angle of Repose.
**Thickness**
The thickness of the tablets was determined using a Screw guage. Five tablets from each batch were used and average values were calculated.

**Weight variation test**
To study weight variation, 20 tablets of each formulation were weighed using an electronic balance and the test was performed according to the official method (USP).

**Drug content**
The drug content of the floating matrix was determined according to In house standards and it meets the requirements if the amount of the active ingredient in each of the 10 tested tablets lies within the range of 85% to 115% of the stated amount.

**Hardness**
For each formulation, the hardness of 6 tablets was determined using the Monsanto hardness tester and the average was calculated and presented with standard deviation.

**Tablet density**
The density (D) of Floating tablets was calculated from tablet height, diameter, and weight.

**Friability**
A sample of 6 tablets was taken and was carefully dedusted prior to testing. The tablets were accurately weighed and placed in the drum of the Roche Friabilator. The drum was rotated for 100 times at 25 rpm and the tablets were removed, dedusted and accurately weighed.

**In vitro Dissolution Studies**
The dissolution of simvastatin will be carried out by using USP Type 2 (paddle) Apparatus at 50 rpm. 900ml volume of 6.8 pH dissolution medium was used at 37.0 ± 0.5°C. At specific time intervals such as 5, 10, 20, 30, 40, 60 min.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Simvastatin conc. in Propylene Glycol</th>
<th>R</th>
<th>L₇</th>
<th>Avicel®PH 101(mg)</th>
<th>Crospovidone (mg)</th>
<th>Aerosil®PH 200(mg)</th>
<th>Total tablet weight(mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>5% (100mg)</td>
<td>5</td>
<td>0.5</td>
<td>200</td>
<td>15</td>
<td>40</td>
<td>355</td>
</tr>
<tr>
<td>F2</td>
<td>5% (100mg)</td>
<td>10</td>
<td>0.5</td>
<td>200</td>
<td>15</td>
<td>20</td>
<td>335</td>
</tr>
<tr>
<td>F3</td>
<td>10%(50mg)</td>
<td>5</td>
<td>0.5</td>
<td>100</td>
<td>10</td>
<td>20</td>
<td>180</td>
</tr>
<tr>
<td>F4</td>
<td>10% (50mg)</td>
<td>10</td>
<td>0.5</td>
<td>100</td>
<td>10</td>
<td>10</td>
<td>170</td>
</tr>
<tr>
<td>F5</td>
<td>20% (25mg)</td>
<td>5</td>
<td>0.25</td>
<td>100</td>
<td>10</td>
<td>20</td>
<td>155</td>
</tr>
<tr>
<td>F6</td>
<td>20% (25mg)</td>
<td>10</td>
<td>0.25</td>
<td>100</td>
<td>10</td>
<td>10</td>
<td>145</td>
</tr>
</tbody>
</table>

*Note: All formulations should contain 5% crospovidone as a super disintegrant \(L_7\) = Load factor; \(R\) = carrier and coating material ratio.*

**Table 1. Composition of Simvastatin liquid formulations**
RESULTS AND DISCUSSION

Solubility studies were proving the saturation form of the simvastatin in the non volatile solvent propylene glycol when compared with rest of the Poly Ethylene Glycol 200, Poly Ethylene Glycol 400, Polysorbates.

Precompression evaluation studies for Simvastatin liquisolid tablets

Powder flow is a complicated matter and is influenced by so many interrelated factors; the factors list is long and includes physical, mechanical as well as environmental factors [20]. Therefore, in our study, the angle of repose, Carr’s index (compressibility index), and Hausner’s ratio. As the angle of repose (θ) is a characteristic of the internal friction or cohesion of the particles, the value of the angle of repose will be high if the powder is cohesive and low if the powder is non cohesive. All liquisolid systems with acceptable flowability according to the angle of repose measurements, while those having higher angles of repose were considered as non-acceptable.

Powders showing Carr’s index (%) up to 20 are considered of acceptable flow properties. In addition to Carr’s index, Hausner found that the ratio $D_{B\text{max}}/D_{B\text{min}}$ was related to the inter particle friction, so, he showed that powders with low inter particle friction, had ratios of approximately 1.15 indicating good flow [21-22].

Finally, all formulations were proven to be acceptably flowing according to either the angle of repose, Carr’s index and Hausner’s ratio were compressed into tablets and subjected for further evaluation while the rest of formulae were nominated as having unacceptable flowability and therefore excluded from further investigation.

All the simvastatin liquisolid tablets had acceptable friability as none of the tested formulae had percentage loss in tablets weights that exceed 1% also, no tablet was cracked, split or broken in either formula. Since all the prepared formulae met the standard friability criteria, they are expected to show acceptable durability and withstand abrasion in handling, packaging and shipment. Simvastatin liquisolid tablets should be sufficiently hard to resist breaking during normal handling and yet soft enough to disintegrate properly after swallowing [22].

The hydrogen bonds between hydrogen groups on adjacent cellulose molecules in Avicel may account almost exclusively for the strength and cohesiveness of compacts [22]. The high compressibility and compactness of Avicel can be explained by the nature of the microcrystalline cellulose particles themselves which are held together by hydrogen bonds, when compressed, such particles are deformed plastically and a strong compact is formed due to the extremely large number of surfaces brought in contact during the plastic deformation and the strength of the hydrogen bonds formed.

The disintegration time test revealed that the all liquisolid tablet formulations disintegrated in less than 100 seconds, All the formulations should meet the required USP specifications. Since our aim was to improve simvastatin dissolution rate via improving the tablets’ physical characteristics.
In vitro release studies

Spireas et al., [8] clarified that the liquisolid hypothesis suggests that when the drug dissolved in the liquid vehicle is incorporated into a carrier material which has a porous surface and closely matted fibers in its interior as cellulose, both absorption and adsorption take place; i.e., the liquid initially absorbed in the interior of the particles is captured by its internal structure, and after the saturation of this process, adsorption of the liquid onto the internal and external surfaces of the porous carrier particles occur. Then, the coating material having high adsorptive properties and large specific surface area gives the liquisolid system the desirable flow characteristics.

![Figure 1. Dissolution profiles of Propylene glycol drug solution of Simvastatin liquisolid tablets](image)

Table 2. Evaluation parameters of tablets containing Propylene glycol drug solution by using Avicel® PH 101 as carrier.

<table>
<thead>
<tr>
<th>Evaluation parameters</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angle of repose</td>
<td>34.9±0.4</td>
<td>34.5±0.5</td>
<td>34.5±0.5</td>
<td>34.4±0.2</td>
<td>35.2±0.6</td>
<td>33.5±0.4</td>
</tr>
<tr>
<td>Bulk density (gm/cc³)</td>
<td>318.3±1.4</td>
<td>313.7±1.6</td>
<td>314.1±1.2</td>
<td>314.2±1.3</td>
<td>216.5±1.6</td>
<td>216.6±1.9</td>
</tr>
<tr>
<td>Tapped density (gm/cc³)</td>
<td>379.7±1.6</td>
<td>369.6±1.2</td>
<td>366.0±1.8</td>
<td>371.6±1.6</td>
<td>245.7±0.2</td>
<td>238.4±0.9</td>
</tr>
<tr>
<td>Hardness (kg/cm²)</td>
<td>4.4±0.3</td>
<td>4.4±0.2</td>
<td>4.4±0.4</td>
<td>4.1±0.3</td>
<td>4.9±0.4</td>
<td>4.8±0.2</td>
</tr>
<tr>
<td>Disintegration time (sec)</td>
<td>100±4</td>
<td>100±5</td>
<td>100±5</td>
<td>90±4</td>
<td>85±5</td>
<td>80±4</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>3.6±0.02</td>
<td>3.5±0.02</td>
<td>3.5±0.02</td>
<td>3.4±0.01</td>
<td>2.0±0.01</td>
<td>2.1±0.01</td>
</tr>
<tr>
<td>Weight variation(mg)</td>
<td>356.5±1.3</td>
<td>325.3±1.7</td>
<td>185.0±1.3</td>
<td>175.8±1.5</td>
<td>158.2±1.7</td>
<td>140.0±1.6</td>
</tr>
<tr>
<td>Friability (%)</td>
<td>0.76</td>
<td>0.45</td>
<td>0.43</td>
<td>0.45</td>
<td>0.33</td>
<td>0.35</td>
</tr>
<tr>
<td>Content of uniformity (%)</td>
<td>98±0.2</td>
<td>98.8±0.8</td>
<td>97.5±0.6</td>
<td>99.2±0.5</td>
<td>99.6±0.6</td>
<td>96.8±0.3</td>
</tr>
</tbody>
</table>
Liquisolid formulations containing 5%, 10%, 20% drug solution, (Figure 1) exhibited similar drug release profiles with a very small variations but these release profiles were found to be higher for the F1, F2, F3, F4 formulations, probably due to the higher amount of Propylene glycol, which might have contributed to the increase in the saturation solubility of the drug at the microenvironment. Table 2 points out the evaluation parameters for F1, F2, F3, F4, F5, F6 formulations.

<table>
<thead>
<tr>
<th>% Cumulative drug release (40min)</th>
<th>72.8±2.4</th>
<th>71.9±1.0</th>
<th>64.1±2.8</th>
<th>64.6±2.2</th>
<th>76.0±3.5</th>
<th>72.5±3.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Cumulative drug release (60min)</td>
<td>99.4±0.2</td>
<td>99.6±1.3</td>
<td>99.4±1.2</td>
<td>99.4±2.3</td>
<td>98.4±1.4</td>
<td>99.4±1.2</td>
</tr>
</tbody>
</table>

Figure 2. Infra red Spectrophotmetry of Simvastatin
At this microenvironment, it may be possible that the infinite amounts of Propylene glycol diffusing with the drug molecules out of a single liquisolid particle [10] and excessive amount of Avicel ® PH 101 responsible for its disintegration property. F1 and F5 formulations also showed the higher dissolution profiles when compared to the rest of the formulations in 5%, 10% and 20%. This may be due to the higher amount of Aerosil ® PH 200 which aid in adsorbing excessive amount of liquid in the physical mixture. Infrared spectroscopy results were confirming there were no any chemical interactions between the pure drug and physical mixtures. Infrared spectroscopy results were confirming there were no any chemical interactions between the pure drug and physical mixtures.

CONCLUSION

All Simvastatin liquisolid tablets were showing the highest dissolution rate within the 60 minutes comparison with direct compressed tablets and marketed tablets due to the producing of the super saturated microenvironment around the tablets. By changing the carrier : coating material ratio 5:1 to 10:1 ratio achieving the good flow properties and harness. Infrared spectroscopy results were confirming there were no any chemical interactions between the pure drug and physical mixtures.

REFERENCES