FORMULATION AND IN-VITRO EVALUATION OF CONVENTIONAL TABLETS OF EZETIMIBE BY USING SOLID DISPERSION

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Received: 01 Mar 2013, Revised and Accepted: 11 Apr 2013

ABSTRACT

Objective: The objective of the present investigation was to improve dissolution characteristics of EZE, which might offer improved bioavailability.

Method: The solid dispersion of Ezetimibe was prepared by Solvent evaporation method by using 1:1, 1:2 and 1:3 ratios of drug and polymers (PVP K-30, Sodium starch glycolate).

The tablets were prepared by direct compression method. The compressed tablets were evaluated for various parameters like hardness, friability, uniformity of weight, uniformity of drug content, drug-polymer interactions, in vitro drug release and short term stability studies.

Results: The prepared dispersion showed marked increase in the dissolution rate of Ezetimibe than that of pure drug and the in vitro release studies revealed that there was an improvement in the dissolution characteristics of EZE when prepared as solid dispersions. Solid dispersion with SSG gave better rate and extent of dissolution. The best fit model indicating the probable mechanism of drug release from solid dispersions was found to be first order. The results of characterization of solid dispersions by Fourier transform infrared spectroscopy revealed that there is no chemical interaction between drug and polymers.

Conclusion: It can be concluded that the solid dispersions prepared with SSG has high solubility than PVP K30 and among all the formulations, F6 has highest solubility and in vitro dissolution rate.

Keywords: Ezetimibe, PVP-K30, Sodium starch glycolate, Solid dispersion.

INTRODUCTION

Solubility is one of the important physico-chemical property to be considered for formulation development and it is a predetermined and rate limiting step for drug absorption. There are many methods like salt formation, solubilisation and particle size reduction to enhance oral bioavailability of poorly soluble drugs. However, techniques such as size reduction increases dissolution and bioavailability but, micronization often leads to aggregation and agglomeration, which leads to poor wettability of particles[1]. This problem is rectified by preparation of solid dispersion of poorly water soluble drugs by using water soluble carriers. Poorly soluble drugs when formulated as tablet or capsule dosage forms it disintegrate into large solid particles in GI tract, which leads to poor dissolution and less absorbed into the body system. Significantly, solid dispersion disintegrates into colloidal particle of particle size less than 5 microns which enhances the dissolution rate of the drug. Among all the methods, solid dispersion has been widely used to increase oral bioavailability, solubility and dissolution rate of the drug.

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles[2]. Based on the molecular arrangement solid dispersion is classified into six types. They are solid solutions, glass solution, amorphous precipitations in crystalline matrix, eutectics and glass suspension. Glass suspension is of two types one is matrix in amorphous state and the other is in crystalline state. There are different methods for the preparation of solid dispersion. They are melting method, solvent method, melting solvent method, melt extrusion method, lyophilization techniques, melt agglomeration process, use of surfactants, electrosprining, super critical fluid technology. In the present study solvent evaporation method is used for the preparation of Ezetimibe solid dispersion.

Ezetimibe decreases plasma cholesterol levels by inhibiting the cholesterol absorption in the intestine. Ezetimibe, administered alone is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, and Apo B in patients with primary (heterozygous familial and non-familial) hypercholesterolemia[3]. It is also used in combination therapy with HMG-CoA reductase inhibitors. It has 35-65% of bioavailability due to its low dissolution profile in gastro intestinal tract. In the present investigation an attempt has been made to increase the dissolution profile of EZE by solid dispersion. Various carriers such as PVP-K30[4] and Sodium starch glycolate have been used for the preparation of solid dispersion.

MATERIALS AND METHODS

Ezetimibe obtained as gift sample from Richer pharmaceuticals( kukatpally), PVP K30(Quliteck Pharma, Jeddah), Sodium starch glycolate was purchased from Central Drug House, New Delhi, Talc (Sd fine chemicals Ltd., Mumbai), lactose anhydrous ( Surya Pharmaceuticals Ltd., Himachal Pradesh), micro crystalline cellulose[6] fine chemicals Ltd., Mumbai, Magnesium stearate(Rexer Pharma Private Ltd.,Cherlapallay), Methanol(Ranchem).

Preparation of Ezetimibe solid dispersion[5]

Ezetimibe was dissolve in sufficient quantity of methanol and weighed amount of polymer (according to the formulation table) is taken in the porcelain dish and the drug is mixed with polymer by using glass rod and the solution is left aside for 24 hrs, the solution containing PVP-K30 is poured over a polythene paper and dried until a film is formed which is collected later. The solution containing SSG forms a solid in the china dish which is collected directly.

Formulation of Ezetimibe Tablets[6]

Direct compression method has been used for the preparation of Ezetimibe solid dispersion tablets. Different ratio of drug to polymer were mixed with two types of diluents i.e., microcrystalline cellulose and lactose. In addition, Talc and magnesium stearate were used as glidant and lubricant respectively. Weighed quantity of drug and polymer are mixed with all the excipients as given in table-1 except...
lubricants. All the ingredients were transferred into mortar and mixed geometrically with pestle. Finally magnesium stearate and talc were added and mixed well. Tablets were compressed on a single punch tablet machine (Cadmach, India) using round flat surface punches of 7.5 mm diameter. The hardness of the tablet was maintained around 2.4 kg/cm². The prepared tablets were stored in tightly closed contained and evaluated for following characteristics.

Table 1: Formulation of Ezetimibe tablets using solid dispersion

<table>
<thead>
<tr>
<th>Ingredients (mg/tab)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezetimibe</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Sodium starch glycolate</td>
<td>-</td>
<td>-</td>
<td>20</td>
<td>-</td>
<td>10</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>PVP K 30</td>
<td>10</td>
<td>30</td>
<td>90.4</td>
<td>-</td>
<td>110.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lactose</td>
<td>110.4</td>
<td>100.4</td>
<td>90.4</td>
<td>110.4</td>
<td>100.4</td>
<td>90.4</td>
<td>120.4</td>
</tr>
<tr>
<td>MCC</td>
<td>36.6</td>
<td>36.6</td>
<td>36.6</td>
<td>36.6</td>
<td>36.6</td>
<td>36.6</td>
<td>36.6</td>
</tr>
<tr>
<td>Talc</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Mg Stearate</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Total weight (mg/tab)</td>
<td>170</td>
<td>170</td>
<td>170</td>
<td>170</td>
<td>170</td>
<td>170</td>
<td>170</td>
</tr>
</tbody>
</table>

Pre formulation studies of Ezetimibe solid dispersion[7]

Preformulation studies such as angle of repose, bulk density, tapped density, Carr’s index, and drug content were performed.

Evaluation of Ezetimibe tablets[6]

Various physical parameters like Friability, Hardness, Uniformity of weight, Thickness were evaluated.

Drug content uniformity of the tablets[8]

Five tablets were powdered in a mortar. From this, powder equivalent to 10 mg of drug was taken in a 100 ml round bottom flask. It is extracted with 20 ml of methanol for half an hour, filtered in a 25 ml volumetric flask and the filtrate was made up to mark with methanol. Further appropriate dilutions were made and the absorbance was measured at 232 nm against blank.

In-vitro Dissolution Studies

In vitro dissolution of EZE tablets was studied in USP dissolution apparatus II employing a paddle stirrer at 50 rpm. 500 ml of 4.5 acetate buffer was used as dissolution medium. The temperature of the dissolution medium was previously warmed to 37±0.5°C and was maintained throughout the experiment. One tablet is placed in each of the baskets, lower down the baskets into each dissolution vessel, start and run the apparatus immediately. 5 ml of the sample of dissolution medium was withdrawn by means of a syringe fitted with prefilter, at known intervals of time. The sample was analyzed for drug release by measuring the absorbance at 242 nm using UV-visible spectrophotometer after suitable dilutions. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The study was conducted in triplicate and the results of in-vitro release profile obtained for all the formulations were plotted in modes of data treatments as follows.

1. Cumulative percent drug released versus time (zero-order kinetic model).
2. Log cumulative percent drug remaining versus time (first-order kinetic model).

Drug excipient compatibility studies[9]

FT-IR studies were carried out for pure drug and in combination with PVP-K30 and SSG.

Short-term Stability Studies[10]

Short-term stability study was performed over a period of three weeks. Sufficient number of tablets (10) were packed in amber coloured screw capped bottles and kept in oven and maintaining the temperature at 45°C. At the end of three weeks period, tablets were checked for any change in physical properties like colour, odour and state.

RESULTS AND DISCUSSION

Pre-Formulation Studies

The powder for matrix tablets were characterized with respect to angle of repose, bulk density, tapped density and Carr’s index (Table-2) Angle of repose was less than 35° and Carr’s index values were less than 21 for all the batches indicating good flowability and compressibility. Hausner’s ratio was less than 1.25 for all the batches indicating good flow properties.

Table 2: Pre formation studies of Ezetimibe solid dispersion

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Angle of repose (degree)</th>
<th>Bulk Density (g/ml)</th>
<th>Tapped Density (g/ml)</th>
<th>Carr’s Index (%)</th>
<th>Hausner’s ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>25.49</td>
<td>0.214</td>
<td>0.251</td>
<td>14.74</td>
<td>1.17</td>
</tr>
<tr>
<td>F2</td>
<td>26.24</td>
<td>0.364</td>
<td>0.364</td>
<td>15.38</td>
<td>1.18</td>
</tr>
<tr>
<td>F3</td>
<td>29.05</td>
<td>0.276</td>
<td>0.322</td>
<td>14.29</td>
<td>1.16</td>
</tr>
<tr>
<td>F4</td>
<td>26.97</td>
<td>0.341</td>
<td>0.388</td>
<td>12.11</td>
<td>1.13</td>
</tr>
<tr>
<td>F5</td>
<td>29.25</td>
<td>0.324</td>
<td>0.376</td>
<td>13.82</td>
<td>1.16</td>
</tr>
<tr>
<td>F6</td>
<td>32.27</td>
<td>0.320</td>
<td>0.397</td>
<td>19.39</td>
<td>1.24</td>
</tr>
<tr>
<td>F7</td>
<td>26.57</td>
<td>0.313</td>
<td>0.356</td>
<td>12.07</td>
<td>1.13</td>
</tr>
</tbody>
</table>

Table 3: Physical Evaluation of Ezetimide Tablets

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Hardness (kg/cm²)</th>
<th>Thickness (mm)</th>
<th>Weight (mg)</th>
<th>Friability (%)</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>4.50±0.44</td>
<td>0.62±0.17</td>
<td>148.8±1.48</td>
<td>0.36</td>
<td>98.25±1.37</td>
</tr>
<tr>
<td>F2</td>
<td>4.30±0.31</td>
<td>0.67±0.25</td>
<td>158.4±0.54</td>
<td>0.39</td>
<td>95.28±0.80</td>
</tr>
<tr>
<td>F3</td>
<td>4.08±0.40</td>
<td>0.64±0.80</td>
<td>169.6±0.41</td>
<td>0.33</td>
<td>99.12±2.47</td>
</tr>
<tr>
<td>F4</td>
<td>4.66±0.55</td>
<td>0.60±0.20</td>
<td>149.8±1.64</td>
<td>0.12</td>
<td>101.22±0.88</td>
</tr>
<tr>
<td>F5</td>
<td>4.25±0.57</td>
<td>0.68±0.66</td>
<td>159.6±1.14</td>
<td>0.34</td>
<td>100.24±1.25</td>
</tr>
<tr>
<td>F6</td>
<td>4.08±0.30</td>
<td>0.63±0.25</td>
<td>168.2±0.83</td>
<td>0.48</td>
<td>100.53±1.87</td>
</tr>
<tr>
<td>F7</td>
<td>4.01±0.61</td>
<td>0.59±0.14</td>
<td>169.1±0.67</td>
<td>0.54</td>
<td>100.57±1.23</td>
</tr>
</tbody>
</table>

Physical Evaluation of matrix tablets
The results of the uniformity of weight, hardness, thickness, friability, and drug content of the tablets are given in Table 3. All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied between 148.8 and 168.8 mg. The hardness of the tablets ranged from 4.08 to 4.50 kg/cm² and the friability values were less than 0.5% indicating that the matrix tablets were compact and hard. The thickness of the tablets ranged from 0.62 to 0.68 mm. All the formulations satisfied the content of the drug as they contained 95 to 102% of Ezetimibe and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found to be practically within control.

In-Vitro Drug Release Studies of Ezetimibe

In vitro dissolution of EZE tablets was studied in USP dissolution apparatus II employing a paddle stirrer at 50 rpm. 500 ml of 4.5 M acetate buffer was used as dissolution medium. To enhance the solubility of drug solid dispersion was prepared by using PVP-K30 and super disintegrant (SSG). Dissolution data for all the formulations F1-F7 was shown in figure 1. Among all the three formulations F1-F3, F3 had shown a highest dissolution rate profile. Similarly, among formulations F4-F6, the amount of drug dissolved for F6 was twice to that of F5 and thrice to that of F4. Significantly, formulations prepared with SSG has highest dissolution rate compared to formulation prepared with PVP-K30. Formulation F7 composed of pure drug has less dissolution profile. So, by formulating EZE solid dispersion by using PVP-K30, SSG the dissolution rate of the drug has been increased. It was observed that as the concentration of PVP-K30 and SSG increased there was an increase in the dissolution rate of EZE. Among all the formulations, F6 was chosen as a best one and it followed first ordered release kinetics.
Drug-Excipients compatibility studies

Infrared spectra of pure drug and with excipients were recorded on a FTIR spectrophotometer by using KBr dispersion method. All samples were recorded in the range of 400-4000 cm\(^{-1}\) and the spectra was illustrated in figure 4,5,6.

Characteristic peaks of pure drug (Ezetimibe) at 3415.12 cm\(^{-1}\) (O-H bending), 2970.50 cm\(^{-1}\) (C-H stretching), 1718.65 cm\(^{-1}\) (C=O stretching), 1511.29 cm\(^{-1}\) (N-H bending), 1221.96 cm\(^{-1}\) (O-C stretching), 1616.42 cm\(^{-1}\) (N-H bending) was observed.

The characteristic peaks of Ezetimibe were observed when in combined with PVP K30 and SSG. This indicates that there is no chemical interaction between the drug and excipients in formulation of tablets by using solid dispersion method.

Stability studies

Optimized formulation F6 of Ezetimibe were packed, maintained at 40°C and 75% RH for 3 months. The samples were withdrawn periodically and evaluated for drug content, hardness, and release studies. The results of the accelerated stability studies are given in table 4. It shows that a slight reduction in %drug content at the end of 2 months.

CONCLUSION

The solid dispersions of Ezetimibe with PVP K30 and SSG were prepared in different weight ratios using solvent evaporation method. Solubility studies show a solubilizing effect of these polymers on EZE. The highest improvement in solubility and in vitro drug release was observed in solid dispersions prepared with SSG by the solvent evaporation method. Although there was no marked difference with the use of PVP K30 or SSG but when compared with each other there was a slight increase in rate of drug release from SSG (i.e- 1:3 ratio,F6 formulation).

REFERENCES


