ENHANCEMENT OF DISSOLUTION AND BIOAVAILABILITY OF SIMVASTATIN BY SOLID DISPERSION TECHNIQUE USING SUGAR-BASED CARRIERS

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ABSTRACT

Objective: The research aims to enhance poorly water-soluble drug Simvastatin (SMV) solubility and bioavailability by solid dispersion (SD) using various sugar carriers like lactulose, xylitol, Sorbitol, and soluplus.

Methods: First, the drug was subjected to determine bulk density, carr’s index, Hausner’s ratio, angle of repose, solubility, and dissolution rate. Second, the formulations were tested.

Results: For various physicochemical criteria, all of the formulations were found to be within the allowed pharmacopoeial limits. The results demonstrated the lack of interactions between drugs and excipients. In comparison to the other solvents, 0.1N HCl showed better solubility and dissolution rate. Simvastatin is converted from itsoral form to its b-dihydroxyacid form (simvastatin acid) by the cytochrome-3A system in the liver, where it inhibits the rate-limiting step in the production of cholesterol [2, 3]. It is a Class II medication with a broader range of pharmacological actions and frequently displays oral absorption that is dissolution rate-limited. An improvement in bioavailability could result from advancements in solubility and dissolution rate. SMV’s bioavailability and rate of dissolution have undergone several modifications [1, 4].

INTRODUCTION

Simvastatin (SMV) is a crystalline drug with a poor absorption rate from the G.I tract due to its limited water solubility [1]. This drug efficiently and precisely inhibits the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase, which converts HMG CoA to mevalonate. When combined with nutrition, SMV inhibits a critical stage in the liver’s cholesterol production, hence treating dyslipidemia and hypercholesterolemia. Simvastatin is converted from its oral form to its b-dihydroxyacid form (simvastatin acid) by the cytochrome-3A system in the liver, where it inhibits the rate-limiting step in the production of cholesterol [2, 3]. It is a Class II medication with a broader range of pharmacological actions and frequently displays oral absorption that is dissolution rate-limited. An improvement in solubility could result from advancements in solubility and dissolution rate. SMV’s bioavailability and rate of dissolution have undergone several modifications [1, 4].

The bioavailability of SMV has been improved by converting into solid dispersions using various carriers like several grades of polyethylene glycols [5, 6], hydroxypropyl methyl cellulose (HPMC) [7], β-cyclodextrin (β-CD) and hydroxypropyl β-cyclodextrin (HPβ-CD) inclusion complexes [8], polyvinyl pyrrolidone [9, 10], other methods include self-emulsifying drug delivery system (SMEDDS) [11-14], solid lipid nanoparticles [15, 16]. In addition to polymeric carriers, sugar-based carriers are also used in the solid dispersion generation process. Xylitol, lactose, mannitol, sucrose, lactulose, malto, sorbitol, etc. are common sugar transporters. Medications such as corticosteroids [18], etoricoxib [19], allopurinol [20], and chlordiazepoxide [17]. The goal of the current study is to control how sugar carriers, such as xylitol, lactulose, and sorbitol, as well as a non-sugar carrier called soluplus, affect the solubility of SMV.

Fig. 1: Structure of simvastatin

MATERIALS AND METHODS

Materials

The model drug employed in this study was simvastatin (Aurobindo Pharma Ltd., Hyderabad), and the solid dispersion carriers chosen were sorbitol, xylitol, lactulose, and soluplus. The solvent of choice was ethanol.

Methods

Formulation of solid dispersions

Table 1 displays the design of SMV SDs utilizing a range of carriers.

Original Article

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Experimental

To determine the compatibility of the medicine and excipient, Fourier Transform Infrared Spectrophotometric Analysis (FT-IR) was used.

Fourier transform infrared spectrophotometric analysis (FTIR)

Using the KBr dispersion method, the infrared spectra of SMV lactulose were measured on a Fourier Transform Infrared Spectrophotometer (IRAffinity-1S, Shimadzu). The 4000-400 cm\(^{-1}\) frequency range was used to scan the spectra.

Determination of \(\lambda_{\text{max}}\)

After carefully weighing 10 mg of SMV, 10 ml of the drug was placed in a volumetric flask. It was dissolved and then diluted to volume using 0.1 N HCL buffer to form a stock solution of 1000 g/ml. Following pipetting, 1 ml of the stock solution was transferred to a 10 ml volumetric flask. The next step was to add 0.1 N HCL until the desired concentration of 100 g/ml was reached. After that, 1 ml of the stock solution was pipetted and put into a 10 ml volumetric flask. 0.1 N HCL was then added up to the mark to create a concentration of 10 g/ml. Throughout the U. V. spectrum examination, this solution was contrasted with a blank.

Preparation of standard calibration curve of simvastatin in 0.1 N HCL

A 10 ml volumetric flask was filled with precisely measured 10 milligrams of SMV. It was dissolved and then diluted to volume using 0.1 N HCL buffer to create a stock solution of 1000 g/ml. Using 0.1 N HCL buffer, the standard stock solution was serially diluted to yield 2 to 12 g/ml of Simvastatin. The absorbance of the solution was measured at 230 nm using a UV-visible spectrophotometer, with a 0.1 N HCL buffer used as the reference. Plotting the absorbance values versus the concentration (g/ml) resulted in the creation of the standard calibration curve.

Solubility studies of pure drug

To find out how different buffers influenced the drug, a solubility study was conducted. 10 ml of distilled water, methanol, ethanol, acetone, phosphate buffer solution (pH = 6.8, 7.4), and 0.1N HCL were combined with the drug to dissolve it excessively, and the tubes were sealed with glass stoppered tops. All flasks were covered with cellophane membrane and sealed with stoppers to prevent solvent loss, and they were kept in a water bath shaker at 37 °C for a full day. After reaching equilibrium, the samples were centrifuged at predetermined intervals and replaced with an equal volume of the new medium in order to maintain the volume constant between test periods. A milliliter of a saturated solution sample was diluted with 0.1 N HCL buffer to form a stock solution of 1000 g/ml. Using 0.1 N HCL buffer, the standard stock solution was serially diluted to yield 2 to 12 g/ml of Simvastatin. The absorbance of the solution was measured at 230 nm using a UV-visible spectrophotometer, with a 0.1 N HCL buffer used as the reference. Plotting the absorbance values versus the concentration (g/ml) resulted in the creation of the standard calibration curve.

Preparation of solid dispersion (SD) of SMV by solvent evaporation method

In this process, test tubes were carefully filled with precisely weighed amounts of the carriers in the prescribed ratios and brought to a boil before being dissolved in ethanol. These solutions were mixed with precisely weighed portions of the drug, which were then allowed to dissolve. The dispersions were dried for one hour at room temperature, for two hours at 450 degrees in a hot air oven, and for one hour at room temperature after the solution was transferred to a petri plate. Pulverizing, crushing, and straining each case’s produced material through a 60 mesh screen [26-28].

Preparation of solid dispersion (SD) of SMV by fusion method

The fusion method was used to make the drug and carrier dispersions. The carrier was heated in a water bath with a thermostat of 55 °C/-0.5 °C. Using Xylitol, Sorbitol, Soluplus, and Lactulose, SMV was dissolved in the molten carrier at drug-to-polymer ratios of 1:0.5, 1:1, 1:1.5, 1:2, and 1:3. The resultant liquid was promptly cooled to 10 °C, 20 °C, or 30 °C using an ice-water mixture, and it was maintained there for two hours. After solidifying, the bulk was removed from the ice-water solution and allowed to thaw to ambient temperature. It was pounded in a glass mortar and pestle after being left at room temperature for a full day. The material was placed in a desiccant for twenty-four hours before being ground with a porcelain mortar pestle and desiccant (Singhal Scientific Industries, Haryana, India). The ground-up powder was passed through an 80-mesh Micro Teknic sieve (Manufactured in Haryana, India) to ensure uniform particle size [29].

Evaluation of solid dispersions

Drug content

Standard flasks with a capacity of 10 ml were filled with methanol following the accurate weighing of 10 mg of SD s into the flasks. A UV-visible spectrophotometer (T60 PG Instruments) was used to detect the concentration of SMV spectrophotometrically at 237 nm in relation to a suitable blank.

In vitro dissolution studies

Pure SMV (100 mg) and SMV-equivalent SD s (20 mg) were put into capsules and kept in a dissolving media. The dissolving examination of solid dispersions was conducted in 900 ccs of pH 1.2 HCL acid buffer at 37 °C and 50 rpm using the USP dissolving Testing Apparatus 1 (basket method). An aliquot of 5 ml was removed at predetermined intervals and replaced with an equal volume of the new medium in order to maintain the volume constant between samples. After that, the sample was subjected to spectrophotometric analysis at 237 nm using a UV-visible spectrophotometer (T60 PG Instruments) against a suitable blank.

RESULTS AND DISCUSSION

Determination of absorption maxima and construction of calibration curve for Simvastatin

The absorption maxima for SMV were determined by using a UV-visible spectrophotometer, and the \(\lambda_{\text{max}}\) of Simvastatin was discovered to be 237 nm. Plotting the calibration curve for Simvastatin involved producing different dilutions ranging from 2 µg/ml to 12 µg/ml. Fig. 2 displays the SMV calibration plot and U. V. spectrum.
Phase solubility studies

SMV’s saturation solubility was assessed in a range of solvent systems, including methanol, ethanolic buffer, pH 1.2 acidic buffer, pH 6.8 phosphate buffer, and pH 7.2 phosphate buffer. Simvastatin was shown to be soluble in the following solvent systems: pH 1.2 acidic buffer > methanol > ethanol > pH 7.4 phosphate buffer > water > pH 6.8 phosphate buffer. The results are displayed in Table 2 and Fig. 3.

Table 2: Saturation solubility studies of simvastatin

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Solubility (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2 pH acidic buffer</td>
<td>0.282±0.21</td>
</tr>
<tr>
<td>6.8 pH phosphate buffer</td>
<td>0.015±0.54</td>
</tr>
<tr>
<td>7.4 pH phosphate buffer</td>
<td>0.055±0.37</td>
</tr>
<tr>
<td>Methanol</td>
<td>0.211±0.22</td>
</tr>
<tr>
<td>Ethanol</td>
<td>0.160±0.45</td>
</tr>
</tbody>
</table>

The values are presented as mean±SD (n = 3)

The solubility of Simvastatin SDs produced using physical mixing, solvent evaporation, and fusion techniques was assessed in distilled water. The results are presented in Table 3.

Table 3: Saturation solubility studies of Simvastatin SDs

<table>
<thead>
<tr>
<th>Preparation Technique</th>
<th>Solubility (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical mixing</td>
<td>0.282±0.21</td>
</tr>
<tr>
<td>Fusion method</td>
<td>0.291±0.27</td>
</tr>
<tr>
<td>Solvent evaporation</td>
<td>0.301±0.24</td>
</tr>
</tbody>
</table>

The saturation solubility of SMV SDs made via fusion, solvent evaporation, and physical mixing techniques was assessed. The solubility of Simvastatin in water was found to be enhanced by the addition of sugar-based carriers. The drug’s saturation solubility was also impacted by the preparation technique and carrier concentration.

The order of saturation solubility of SMV by various methods was as follows:

Physical mixing < Fusion method < Solvent evaporation method.
Table 3: Saturation solubility of Simvastatin SDs

<table>
<thead>
<tr>
<th>Method</th>
<th>Carrier</th>
<th>Simvastatin: carrier ratio</th>
<th>1:0.5</th>
<th>1:1</th>
<th>1:1.5</th>
<th>1:2</th>
<th>1:3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical mixtures</td>
<td>Xylitol</td>
<td>0.122±0.128</td>
<td>0.219±0.184</td>
<td>0.262±0.158</td>
<td>0.299±1.85</td>
<td>0.277±0.165</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sorbitol</td>
<td>0.196±0.128</td>
<td>0.267±0.145</td>
<td>0.288±0.187</td>
<td>0.312±0.169</td>
<td>0.302±0.159</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lactulose</td>
<td>0.222±0.184</td>
<td>0.310±0.192</td>
<td>0.328±0.135</td>
<td>0.412±0.164</td>
<td>0.322±0.189</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Soluplus</td>
<td>0.219±0.187</td>
<td>0.280±0.101</td>
<td>0.288±0.198</td>
<td>0.328±0.204</td>
<td>0.315±0.162</td>
<td></td>
</tr>
<tr>
<td>Solvent evaporation</td>
<td>Xylitol</td>
<td>0.569±0.165</td>
<td>0.612±0.169</td>
<td>0.649±1.65</td>
<td>0.752±0.132</td>
<td>0.738±0.166</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sorbitol</td>
<td>0.614±0.148</td>
<td>0.708±0.168</td>
<td>0.812±0.125</td>
<td>0.948±0.123</td>
<td>0.758±0.150</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lactulose</td>
<td>0.699±0.162</td>
<td>0.748±0.128</td>
<td>0.849±0.148</td>
<td>0.892±0.184</td>
<td>0.838±0.113</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Soluplus</td>
<td>0.749±0.159</td>
<td>0.89±0.102</td>
<td>0.909±0.104</td>
<td>0.986±0.165</td>
<td>0.898±0.153</td>
<td></td>
</tr>
<tr>
<td>Fusion method</td>
<td>Xylitol</td>
<td>0.542±0.168</td>
<td>0.601±0.102</td>
<td>0.624±0.128</td>
<td>0.739±0.174</td>
<td>0.725±0.153</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sorbitol</td>
<td>0.598±0.128</td>
<td>0.697±0.164</td>
<td>0.801±0.187</td>
<td>0.824±0.194</td>
<td>0.811±0.167</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lactulose</td>
<td>0.614±0.139</td>
<td>0.698±0.164</td>
<td>0.801±0.174</td>
<td>0.828±0.128</td>
<td>0.81±0.154</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Soluplus</td>
<td>0.729±0.173</td>
<td>0.854±0.157</td>
<td>0.895±0.198</td>
<td>0.961±0.121</td>
<td>0.925±0.158</td>
<td></td>
</tr>
</tbody>
</table>

The values are presented as mean±SD (n = 3)

Drug-to-carrier proportions ranging from 1:0.5 to 1:3 were used to manufacture SDs. The saturation solubility of SMV was influenced by carrier concentration as well. Up to a certain point, an increase in carrier concentration increased the drug's solubility; beyond that point, it lowered the drug's solubility.

Increased solubility in the solid dispersion of simvastatin may result from the formation of hydrogen bonds between the carbonyl group of simvastatin and Soluplus. These hydrogen bonds will stop molecular movement in the solid solution, inhibit crystal formation, and stabilize the solid dispersion in an amorphous form. Hydrophobic drugs can interact with Soluplus, which has a lipophilic chain and a carbonyl-amide group, to hydrate the medication in an aqueous solution. Furthermore, because Soluplus is amphiphilic, it will form micelles in water, which will dissolve the Simvastatin molecule [30]. Like soluplus, all the sugar-based carriers may also form an intermolecular hydrogen bond with SMV [31].

Characterization of Simvastatin solid dispersion

Interactions between the medicine and the carrier often result in detectable differences in the I. R. profile of SDs. The I. R. spectra of SDs were compared to the standard spectrum of Simvastatin. Pure Simvastatin’s I. R. spectra showed a peak at 3551 cm⁻¹, which denotes the presence of α-O. H bond. Peak at 2965, 2929, and 2874 cm⁻¹ suggests a CH₂, CH₃, and CH₃ bond. The carbonyl group is present, as indicated by the existence of the peak at 1700 cm⁻¹. Peaks between 1268 and 1225 cm⁻¹ confirm that the C=O-C is extending, C-O(H) is represented by the peaks at 1071, 1054 cm⁻¹, and 1011. Aromatic rings can be seen in I. R. spectra between 900 and 600 cm⁻¹ and SMV and characteristic O–H stretching of vibration peaks, 3359.7 cm⁻¹ (in case of solid dispersions using lactulose). The observations recorded might indicate that the possibility of inter-molecular hydrogen bonding.

Fig. 4: FTIR spectrum of pure Simvastatin

![Fig. 4: FTIR spectrum of pure Simvastatin](image1)

Fig. 5: FTIR spectrum of Simvastatin-Lactulose solid dispersion

![Fig. 5: FTIR spectrum of Simvastatin-Lactulose solid dispersion](image2)
Drug content

Various SMV solid dispersions using sugar carriers like xylitol, sorbitol, lactulose, and nonsugar carrier soluplus at different ratios (1:1 and 1:3) were prepared by solvent evaporation and fusion technique to enhance the solubility and/or dissolution of BCS class II drug simvastatin. The percentage drug content in various prepared SMV SDs ranged from 94.26±1.24% to 100.06±1.26% and the drug content in formulations made using the fusion approach, ranged from 86.37±1.87-99.37±1.97%, as reported in table 4. This indicated that SMV was uniformly distributed in all of these prepared solid dispersions.

Table 4: Drug content uniformity of the SMV SDs

<table>
<thead>
<tr>
<th>Solid dispersion</th>
<th>Ratio</th>
<th>Solvent evaporation</th>
<th>Fusion</th>
<th>Solid dispersion</th>
<th>Ratio</th>
<th>Solvent evaporation</th>
<th>Fusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMV: Xyletol</td>
<td>1:0.5</td>
<td>88.42±1.24</td>
<td>86.37±1.87</td>
<td>SMV: Lactulose</td>
<td>1:0.5</td>
<td>94.12±1.82</td>
<td>98.74±1.74</td>
</tr>
<tr>
<td></td>
<td>1:1</td>
<td>92.64±1.81</td>
<td>90.78±1.71</td>
<td></td>
<td>1:1</td>
<td>92.68±1.38</td>
<td>90.85±1.10</td>
</tr>
<tr>
<td></td>
<td>1:1.5</td>
<td>94.98±1.37</td>
<td>91.25±1.21</td>
<td></td>
<td>1:1.5</td>
<td>95.89±1.40</td>
<td>94.31±1.84</td>
</tr>
<tr>
<td></td>
<td>1:2</td>
<td>96.62±1.79</td>
<td>94.74±1.39</td>
<td></td>
<td>1:2</td>
<td>93.68±1.98</td>
<td>92.62±1.38</td>
</tr>
<tr>
<td></td>
<td>1:3</td>
<td>95.66±1.87</td>
<td>93.66±1.35</td>
<td></td>
<td>1:3</td>
<td>95.02±1.10</td>
<td>94.92±1.67</td>
</tr>
<tr>
<td>SMV: Sorbetol</td>
<td>1:0.5</td>
<td>90.28±1.02</td>
<td>88.36±1.45</td>
<td>SMV: Soluplus</td>
<td>1:0.5</td>
<td>94.26±1.32</td>
<td>93.48±2.17</td>
</tr>
<tr>
<td></td>
<td>1:1</td>
<td>95.26±0.99</td>
<td>93.98±1.74</td>
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<td>1:1</td>
<td>98.11±1.19</td>
<td>97.37±2.01</td>
</tr>
<tr>
<td></td>
<td>1:1.5</td>
<td>94.22±1.99</td>
<td>91.78±1.20</td>
<td></td>
<td>1:1.5</td>
<td>99.02±1.32</td>
<td>99.37±1.97</td>
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<td></td>
<td>1:2</td>
<td>98.26±1.40</td>
<td>97.36±1.98</td>
<td></td>
<td>1:2</td>
<td>99.68±1.74</td>
<td>99.31±1.6</td>
</tr>
<tr>
<td></td>
<td>1:3</td>
<td>95.22±1.12</td>
<td>97.57±1.25</td>
<td></td>
<td>1:3</td>
<td>99.42±1.98</td>
<td>99.26±1.71</td>
</tr>
</tbody>
</table>

The values are presented as mean±SD (n = 3)

In vitro drug release studies

Studies on the in vitro release of solid dispersions and pure Simvastatin were conducted.

In 60 min, the pure SMV yields 56.48±1.45% of release. A non-sugar-based carrier called Soluplus released 80.24±1.87% to 99.23±2.09% in 60 min, while formed solid dispersions with sugar-based carriers such as xylitol, Sorbitol, and lactulose released 83.26±1.35% to 99.22±1.02%, 74.56±1.74% to 98.11±1.28%, and 91.85±1.98% to 100.02±1.73%, respectively. Fig. 6 and 7 depict the drug release patterns obtained from the solvent evaporation and fusion methods, respectively.

Better dissolution behavior of SMV was observed in all physical mixture and solid dispersion samples compared to pure SMV. The key factors contributing to the enhanced dissolution include the drug’s larger surface area when exposed to large carrier molecules, its increased wettability, and its subsequent solubility as a result of the polar impact of sugars with polar groups [32]. This could also be explained by the increased hydrophilic sugar carriers, which can lessen the interfacial tension between the dissolution media and the medication that is poorly soluble in water [33]. Once more, compared to the corresponding physical mixture samples, all of the solid dispersion samples displayed more enhanced SMV dissolution.

In contrast to physical mixes and pure drugs, where the drug is present in crystalline form, this observation suggested that the presence of the drug in an amorphous state causes an enhanced dissolution of SMV from solid dispersion [34].

For SMV solid dispersions, sorbitol<xylitol<lactulose was the sequence of sugar carriers that increased dissolving in pH 1.2HCl.

Fig. 6: In vitro drug release studies of Simvastatin solid dispersions by solvent evaporation, the values are presented as mean±SD, (n = 3)
The SDs, including xylitol, sorbitol, and sulphas carriers, showed a maximum of 83% of drug release at lower concentrations; at higher concentrations, they released 99% of the drug release, according to the in vitro drug release experiments. Conversely, SDs with lactulose as the carrier released 91% of the medication at lower concentrations. The drug-to-carrier ratio was raised to 1:2 by increasing the percentage of drug release. Following that, there was a decrease in drug release and an increase in carrier concentration.

CONCLUSION

The present study investigated the phase solubility studies and dissolution behavior of SMV with several types of sugar-based carriers at various concentrations. The results indicated that there was a massive enhancement of SMV solubility with the presence of sugar-based carriers. Dissolution of the drug in turn, indicated the extent of bioavailability of the drug. A marked enhancement in dissolution of SMV was observed in SDs of SMV with sugar carriers which indirectly indicates the bioavailability of SMV was enhanced in the presence of sugar carriers.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

There is no conflict of interest.

REFERENCES


