Preparation and Characterization of Simvastatin Solid Dispersion using Aqueous Solvent

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ABSTRACT – Simvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol. Simvastatin has good permeability, but it also has low solubility (BCS class II), which reduces its bioavailability. To overcome this problem, a solid dispersion is formed using a spray-dryer with polymeric material carrier to potentially enhance the dissolution rate and extend drug absorption. As carriers for solid dispersion, Gelucire® 44/14 and Gelucire® 50/13 are semi-solid excipients that greatly improve the bioavailability of poorly-soluble drugs. To avoid any toxic effects of an organic solvent, we used aqueous medium to melt Tween® 80 and distilled water. The structural behaviors of the raw materials and the solid dispersion were analyzed by differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD) and scanning electron microscopy (SEM). The DSC and PXRD data indicated that the crystalline structure of simvastatin was transformed to an amorphous structure through solid dispersion. Then, solid dispersion-based tablets containing 20 mg simvastatin were prepared with excipients. Dissolution tests were performed in distilled water and artificial intestinal fluid using the USP paddle II method. Compared with that of the commercial tablet (Zocor® 20 mg), the release of simvastatin from solid dispersion based-tablet was more efficient. Although the stability study is not complete, this solid dispersion system is expected to deliver poorly water-soluble drugs with enhanced bioavailability and less toxicity.

Key words – Solid dispersion, Simvastatin, Zocor®, Gelucire®, Spray-dryer, Bioavailability

The medical treatments for hyperlipidemia include statin class drugs such as atorvastatin, lovastatin, simvastatin and fibrate class drugs like fenofibrate (Koh et al., 2008; Lee, 2008; Bullen et al., 1999). Statin class drugs acts by inhibiting the rate limiting enzyme in cholesterol biosynthesis, the HMG-CoA coenzyme, to lower total cholesterol, LDL cholesterol, and also plasma triglyceride levels in some clinical studies (Kim et al., 2008; Storda and Kontoyannis, 2008; Kang et al., 2003). Simvastatin is a crystalline powder extracted from Aspergillus terreus fermentation product that dissolves well in dichloromethane, chloroform, methanol and ethanol but scarcely in water.

After ingestion of a drug, it is usually dissolved and absorbed in the gastrointestinal tract, then reaching the target organ. In such serial kinetics, there are two key points. One is the solubility of the drug and the other is the permeability of the drug in the gastrointestinal tract. Many drugs of many classes show different solubility and permeability, and BCS classification (FDA, 2000) sorts them into 4 categories. Acetaminophen, barbiturate, metronidazole, and prednisolone are class 1 drugs with high solubility and permeability. Ibuprofen, nifedipine, carbamazepine, and naproxen are class 2 drugs with low solubility and high permeability, while class 3 drugs such as acyclovir, atenolol, cimetidine, and metformin exhibit high solubility and low permeability. Class 4 drugs include fiuosemide, acetazolamide, and ritonavir and have low solubility and low permeability (Craig, 2002). Overcoming the low solubility of class 2 and 4 drugs could increase the bioavailability, especially for class 2 drugs with their high permeability (Noyes and Whitney, 1897).

Methods to increase dissolution or available surface area include physical modifications and chemical modifications. Physical modifications include micronization and nanosuspensioning of particle size, modifications of the crystal habit, polymorphs, pseudopolymorphs (including solvates), complexation/solubilization using surfactants and cyclodextrines, and drug dispersion in carriers using eutectic mixtures, solid dispersion (non-molecular) and solid solutions. Chemical modifications include usage of soluble prodrugs and salts (Khang et al., 2001; Chiou and Riegelman, 1971; Jeong et al., 2002; Ahn et al., 2004; Kang et al., 2004; Chae et al., 2002; Sekiguchi and Obi, 1961).

Sekiguchi and Obi first experimented with sulphathiazole and urea in the solid dispersion of a eutectic mixture (Chiou
and Riegelman, 1969). A hot melt method was used to prepare simple eutectic mixtures. Producing a solid dispersion requires adequate cooling so that no material crystallizes earlier than any other material and the cooling process ought to be quick. Another important limitation to the hot melt method is the thermostability of the drug and the carrier.

Because of these limitations, the solvent method became more popular. With the discovery of the solvent method, many of the problems associated with the melting method were solved. For example, it was then possible to form solid dispersions of thermolabile substances. Likewise, many polymers that could not be utilized for the melting method due to their high melting points (e.g. PVP) could be now considered as possible carriers. As a result, for many years the solvent method was the method of choice for polymer-based systems. An important prerequisite for the manufacture of a solid dispersion using the solvent method is that both the drug and the carrier are sufficiently soluble in the solvent. The solvent can be removed by any one of a number of methods. The temperatures used for solvent evaporation are usually in the range of 23–65°C (Zein et al., 1998; Betageri and Makarla, 1995). The solvent can also be removed by freeze-drying (Lo and Law, 1996) or by spray-drying (Tran et al., 2008). It must be remembered that when an organic solvent is to be removed, small variations in the conditions used can lead to large changes in product performance. Another point to consider is the importance of thoroughly removing all of the solvent, since most organic solvents have toxicity issues.

In this study, solid dispersion of the poorly water-soluble drug simvastatin was performed to increase the actual solubility, further raising the dissolution rate in an aqueous environment to improve bioavailability. Lauroyl polyoxyl-32 glycerides (Gelucire® 44/14), Stearoyl polyoxyl-32 glycerides (Gelucire® 50/13) and Hypromellose 6cps (Pharmacoat® 606) were used as hydrophilic carriers and Polysorbate 80 (Twee®80) and hydrophilic fumed silica (Aerosil® 200 Pharma) were also added to the solid dispersion solution. Gelucire® 44/14 and Gelucire® 50/13 were both semi-solid state at room temperature and non-ionic, water dispersible surfactant composed of well-characterized PEG-esters. The melting points were 44°C and 50°C, respectively. Twee®80 as surfactant and Aerosil® 200 Pharma with a specific surface area of 200 m²/g as absorbent were used.

Also important is the use of water instead of an organic solvent as the solid dispersion solvent. By using water, the remaining toxicity issues from spray dry methods using organic solvents were solved, and more eco-friendly methods that could be applied in actual manufacturing processes were explored. Considering the poorly water-soluble drug, less toxic surfactant was used.

The characteristics of the solid dispersion product were analyzed by differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), and scanning electron microscopy (SEM). To identify the enhanced dissolution rate, the Zocor® 20 mg tablet and the 20 mg simvastatin solid dispersion product were compared.

**Materials and Methods**

**Materials**

Simvastatin was purchased from Whawan CO. Ltd. Gelucire® 44/14 and Gelucire® 50/13 were from Gattefosse (France). Hydroxypropyl methylcellulose (Pharmacoat® 606) was supplied by Shin-Etsu Chemicals Ltd., Tween®80 and Twee®20 were from Junsei Chemical, and Aerosil® 200 Pharma was from EVONIK Degussa Ltd. Other solvents were of analytical grade and chemicals were of the highest grade available.

**Preparation of simvastatin solid dispersion**

In the preparation of simvastatin solid dispersion, the solvent method was used to manufacture 200 tablets of 20 mg simvastatin per batch. As the solvent, 800ml of distilled water was heated to 60°C. While maintaining the temperature and stirring with a magnetic stirrer, we added 4ml of Twee®80 (0.5% of solvent) as a surfactant. Four types of formulations were added separately as shown in Table I. The main reagent simvastatin, Gelucire® as the carrier and Pharmacoat® 606 were added simultaneously. The ingredients were mixed for two minutes and then for 3 more minutes after adding 2 g of Aerosil® 200 Pharma. The resultant white suspension was homogenized using a mechanical homogenizer at 2000 rpm for 1 minute. While the stirring was maintained using a magnetic bar, the solid dispersion suspension was injected into the spray dryer. The operating condition of the spray dryer was an inlet tem-

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Formulations (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin</td>
<td>4 4 4 4</td>
</tr>
<tr>
<td>Gelucire® 44/14</td>
<td>8 - 4 -</td>
</tr>
<tr>
<td>Gelucire® 50/13</td>
<td>- 8 - 4</td>
</tr>
<tr>
<td>Pharmacoat® 606</td>
<td>4 4 8 8</td>
</tr>
<tr>
<td>Aerosil® 200 Pharma</td>
<td>4 4 4 4</td>
</tr>
<tr>
<td>Total</td>
<td>20 20 20 20</td>
</tr>
</tbody>
</table>

*200 Tablets per batch

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perature of 120°C, outlet temperature of approximately 50°C, aspirator 100%, pump 30%, and nozzle clearance step 1. A white powder of solid dispersion product was obtained.

**Characteristic studies**

Simvastatin (API), Gelucire® 50/13, Pharmacoat® 606 and their physical mixture (1:1:1) were used as samples for characteristic study, along with SD-3 and SD-4, which showed significant results in the content study of the solid dispersion product.

**Differential scanning calorimetry (DSC)**

Thermal characteristics like melting point and glass transition temperature were analyzed using DSC. 5~10 mg samples were observed at a rate of 20°C/min from 0°C to 200°C using DSC Q100-1189 (TA Inst. USA) and Indium was used as the standard for correction. Their difference of energy input was calculated by Q100 V9.8 build 296 program.

**Powder X-ray diffraction (PXRD)**

X-ray diffraction of the specimens was performed using Rigaku MAX-3C diffractometer (Rigaku Instrument, Japan) at 40 kV and 40 mA with irradiation from the Cu-Kα1 ray. X-ray diffraction data was collected at a rate of 4°C/min from 5 to 50°C.

**Scanning electron microscopy (SEM)**

SEM was used to examine the morphological and dimensional characteristics of the model drug, the water-soluble polymer and the resultant products. For the SEM photomicrography, reagents were fixed on the metal plate and coated with platinum using argon gas. Platinum-coated reagents were magnified at 10 kV for observation of their characteristics.

**Preparation of solid dispersion tablet**

Three types of tablet were prepared using 20 mg of simvastatin; SD-3 and SD-4 contained 20 mg equivalent simvastatin as the main reagent according to the content study. Lactose was used as diluent and microcrystalline cellulose (Avicel) pH102 as the binder. Crospovidone as a disintegrator and magnesium stearate as a lubricant were combined and mixed as shown in Table II. Using a rotary tablet press, consistent pressure was applied to produce FN-1 (simvastatin), FN-2 (SD-3), and FN-3 (SD-4) tablets.

**Dissolution studies**

The commercially available Zocor® tablet and the produced FN-1, FN-2, and FN-3 tablets were compared. The dissolution fluids used in the comparison were distilled water and artificial intestinal fluid (KH₂PO₄ buffer, pH6.8). Dissolution comparison was carried out by the paddle method of the USP apparatus using the dissolution tester Pharma Test PTWS-1210 (Pharma Test. Germany). Three tablets were used per group and the speed of the paddle was 50 ± 2 rpm. 5 mL of dissolution fluid were collected at 0, 5, 10, 20, and 40 minutes after beginning the dissolution test. Each collected dissolution fluid sample was filtered through a Whatman syringe filter (13 mm, 0.45 µm) into an auto-sampler vial for HPLC analysis.

**Results and Discussion**

**Preparation of simvastatin solid dispersion**

It is particularly important to simultaneously add the main reagent with its carrier Gelucire® and Pharmacoat® 606 when producing a solid dispersion solution because the water-soluble polymer carrier has a dispersing effect on the poorly water-soluble simvastatin molecule in a net-like space via its dissolution and rearrangement in water. The net of water-soluble polymer prevents simvastatin from agglutinating, thereby increasing the actual surface dimension of the solute and ultimately its solubility. Dissolving Gelucire® and HPMC prior to the addition of the API was also tried but the resultant dissolution of API was not as effective as adding them simultaneously. The temperature of the spray dryer at the time of collection of solid dispersion simvastatin is shown in Table III. Considering that the solute constitutes 20 g of the total solid dispersion fluid among the 200 tablets, the yields of SD-1, SD-2, SD-3 and SD-4 were

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SD-1</th>
<th>SD-2</th>
<th>SD-3</th>
<th>SD-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inlet temperature (°C)</td>
<td>121</td>
<td>120</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>Outlet temperature (°C)</td>
<td>53</td>
<td>47</td>
<td>47</td>
<td>46</td>
</tr>
<tr>
<td>Yield (g)</td>
<td>15.6</td>
<td>14.4</td>
<td>19.4</td>
<td>14.9</td>
</tr>
<tr>
<td>Percentage (%)</td>
<td>78</td>
<td>72</td>
<td>97</td>
<td>74.5</td>
</tr>
</tbody>
</table>

Table II. *Formulation of solid dispersion based tablet*

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>FN-1 (mg)</th>
<th>FN-2 (SD-3)</th>
<th>FN-3 (SD-4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin</td>
<td>20</td>
<td>110</td>
<td>130</td>
</tr>
<tr>
<td>Lactose</td>
<td>120</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>Avicel pH 102</td>
<td>60</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>215</td>
<td>245</td>
<td>245</td>
</tr>
</tbody>
</table>

Table III. *Result of simvastatin solid dispersion preparation*
78%, 72%, 97% and 74.5%, respectively, and the overall collection yield was 80.38%.

**Standard calibration curve of simvastatin**

According to the concentration and peak dimension of a standard solution, a calibration curve was generated and a regression equation calculated as follows:

\[
Y(\text{concentration}) = 7.564e^{-6} \times (\text{peak}) + 0.370427 \quad (r^2 = 0.9998)
\]

**Content study of solid dispersion product**

The results of the content study of the solid dispersion according to the above regression equation are shown in Table IV. According to the results, the ratio of Gelucire® and HPMC, rather than the grade of Gelucire®, accounts for maintenance of drug content during the solid dispersion process. SD-3 (Gelucire® 44/14) and SD-4 (Gelucire® 50/13) with a 1:2 ratio of Gelucire® : HPMC showed relatively higher contents. These two solid dispersion products were therefore used in subsequent experiments.

**DSC analysis**

The thermal characteristics of the samples are shown in Figure 1. Simvastatin has a specific endothermic peak near the

![DSC thermogram of samples; simvastatin, HPMC, Gelucire, Physical mixture, SD-3, SD-4.](image)

<p>| Table IV. Encapsulation efficiency of solid dispersion |
|---------------------------------------------|-----------|</p>
<table>
<thead>
<tr>
<th>Batch</th>
<th>Encapsulation efficiency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD-1</td>
<td>57.55</td>
</tr>
<tr>
<td>SD-2</td>
<td>65.26</td>
</tr>
<tr>
<td>SD-3</td>
<td>90.36</td>
</tr>
<tr>
<td>SD-4</td>
<td>77.16</td>
</tr>
</tbody>
</table>

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melting point at 141.78°C, suggesting a crystalline form. The endothermic peak of Gelucire® 50/13 was around 47°C and a similar peak was observed from the physical mixture of simvastatin, HPMC and Gelucire®, and from the products SD-3 and SD-4. In contrast, the endothermic peak of simvastatin was only observed in the physical mixture but not in SD-3 and SD-4. A new peak around 37°C suggested that a completely new thermal characteristic developed during the solid dispersion of simvastatin.

**PXRD analysis**

In Figure 2, which shows the PXRD diffraction peak, simvastatin showed many sharp peaks indicative of its crystalline form. In contrast, Pharmacoat® 606 and Gelucire® 50/13 showed no distinctive diffraction peak due to its amorphous characteristic. The peak height appeared to decrease slightly in the physical mixture but still showed the crystalline characteristic of simvastatin. This crystalline diffraction was lost in the solid dispersion samples SD-3 and SD-4, suggesting an amorphous form.

**Morphological observation using SEM**

The morphologies of simvastatin, physical mixture, SD-3 and SD-4 were observed using SEM (Figure 3). Simvastatin showed a needle-like structure with a mean particle size of (length of structure) 100 µm. The physical mixture of simvastatin, HPMC and Gelucire® retained the crystalline structure of simvastatin as a simple mixture of water-soluble amorphous polymer. No crystalline structure was found in the solid dispersion products SD-3 and SD-4, which consisted of much smaller round particles between a few hundred nm to approximately 2 µm in size. Thus, the solid dispersion enhanced solubility by increasing the surface diameter ratio.

![Figure 2](image-url) **Figure 2.** PXRD spectra of samples; Simvastatin, HPMC, Gelucire, Physical mixture, SD-3, SD-4.
Dissolution studies of solid dispersion tablet in distilled water and artificial intestinal fluid

In the dissolution profile in DW, FN-2 and FN-3 tablets exhibited a much higher dissolution rate than the comparison group (FN-1) or the Zocor® tablet (Figure 4). More specifically, FN-3 from Gelucire® 50/13 showed a 68.02% dissolution rate at 60 minute and the dissolution rate of FN-2 at the same time was 56.12%. The comparison group showed a lower dissolution rate than Zocor®. This result indicates an enhanced dissolution rate in an aqueous environment for a solid dispersion product using a water-soluble polymer as carrier. Zocor® shows only 5% of low bioavailability after oral administration due to its poor aqueous solubility (De Angelis, 2004; K. Maggon 2005). According to our knowledge, the higher release rate on dissolution test, the better increased bioavailability in case of BCS class II.

The results in artificial intestinal fluid were similar to those in distilled water in that the dissolution rates of FN-2 and FN-3 were markedly higher than those for Zocor® and FN-1 (Figure 5). However, the rates were slightly lower than the respective dissolution rates in distilled water (FN-2 43.79%; FN-3 51.57% at 60 min.) The pattern of dissolution rate in the dis-
tilled water group showed a zero-order pattern, whereas that in artificial intestinal fluid more closely resembled a first-order pattern.

Conclusions

The intention of this study was to produce a solid dispersion of a poorly water-soluble drug, simvastatin, to increase solubility. The solvent method used to manufacture a solid dispersion with distilled water and surfactant instead of an organic solvent was more cost efficient, eco-friendly and had less concerns in terms of remaining toxins. After analyzing the solid dispersion product by DSC, PXRD, and SEM and comparing the dissolution rate with that of Zocor®, the following conclusions were reached:

1. By using the surfactant, it was possible to produce a solid dispersion of a poorly water-soluble drug without completely dissolving it, but instead adequately adjusting the solubility.
2. Therefore it was possible to use distilled water rather than organic solvents, allowing for a more eco-friendly as well as a

Figure 4. Dissolution profiles of solid dispersion tablets and Zocor® in DW.

Figure 5. Dissolution profiles of solid dispersion tablets and Zocor® in artificial intestinal fluid.
solution to the problem of remaining toxins.
3. As a carrier, HPMC and Gelucire® at a 2:1 ratio worked best for containment of the drug.
4. DSC, PXRD, and SEM results showed that solid dispersion particles of simvastatin changed from a crystalline structure into an amorphous form.
5. Solid dispersion tablets (FN-2, FN-3) showed markedly higher dissolution rates than the Zocor® tablet in distilled water and artificial intestinal fluid.
6. When comparing the solid dispersion tablets, the dissolution rate of FN-3 (Gelucire® 50/13) was higher than that of FN-2 (Gelucire® 44/14) in every dissolution media.
7. With a higher dissolution rate in artificial intestinal fluid, the conditions of which are quite similar to the actual gastrointestinal tract, an actual increase in bioavailability is expected.

Therefore, it was possible to produce a solid dispersion tablet of simvastatin through a more efficient and safer method using HPMC and Gelucire® as a carrier, distilled water and surfactant. The dissolution rate experiments showed a better outcome for the prepared tablets than for the commercially available Zocor® tablet, leading to the expectation of increased bioavailability for the solid dispersion.

Solid dispersion is an old method, but it is expected to be essential in pharmaceutical manufacturing once the process has been optimized to eliminate risk factors and to reach optimal efficiency.

References


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