Compatibility Study Between Simvastatin and Excipients in Their Physical Mixtures

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Simvastatin (SIM) (fig. 1) (1S,3R,7S,8S,8aR)-8-{2-[(2R,4R)-4-hydroxy-6-oxotetrahydro-2H-pyran-2-yl]ethyl}-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate, is a drug used to control hypercholesterolemia by reducing its high concentrations. It is a member of the statin class of pharmaceuticals. All statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A HMG-CoA reductase, the rate-limiting enzyme of the HMG-CoA reductase pathway, the metabolic pathway accountable for the endogenous production of cholesterol [1-5].

Simvastatins are more effective at lowering the LDL-cholesterol concentration than other lipid-regulating drugs but they are less effective than the fibrates in reducing triglyceride concentration. Simvastatin attenuates cardiovascular disease events and total mortality disregarding of the initial cholesterol concentration.

Information on the physical and/or chemical interaction drug/excipient is very important in the elaboration of a new drug formulation. To develop a stable and more effective dosage form of drug it is very important to carefully select the excipients and the constituent components of all pharmaceutical products. Usually the ingredients are considered as “inert”, but there are cases when they can interact with the drug substance, it usually happens when there were changes in their stability, dissolution rate, solubility and bioavailability. Therefore, in order to accelerate drug development, it would be very useful to obtain information and knowledge about potential physical and chemical interactions between drugs and excipients [6-9].

The pharmaceutical product is good when there is no interaction between the active ingredient and excipients or excipients used in the formulation. Preformulation studies are an important stage of the development process directed to the evolution of the drug and excipients compatibility [6].

Thermal analysis is the most used technique in the preformulation stage of solid pharmaceutical forms. Differential scanning calorimetry (DSC) is an important procedure for preformulation researches, which gives information about the possible interactions between the components of pharmaceutical forms, the change or disappearance of endothermic or exothermic peaks, or variations of enthalpy values in thermal curves due to mixing drug substances with excipients.

The main purpose of this paper is to assess the compatibility of simvastatin and some pharmaceutical excipients using thermal analysis techniques (DSC and TG) supported by X-ray powder diffraction (XRPD) and Fourier transform infrared spectroscopy (FTIR) [10-17].

Experimental part

Equipment, materials and methods

All materials were of reagent grade and were used without further purification. SIM is obtained from a company in Romania, made in China. The excipients examined were: lactose monohydrate (Meggle, Germany),

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Magnesium stearate (Union Derivan, Spain), ascorbic acid, citric acid, starch and talcum powder (Merck, Germany).

Binary physical mixtures SIM:each excipient was prepared in different ratios: SIM:lactose monohydrate 1:1, SIM:magnesium stearate 1:0.25, SIM:ascorbic acid 1:0.25, SIM:starch 1:1 and SIM:talcum powder 1:0.25, obtained by grinding in the agate mortar.

All analyses were performed using a sample of SIM, each excipient and of binary mixtures prepared as described above.

The excipients were selected taking into account the characteristic of the drug and its compatibility with other components.

Lactose monohydrate, as anhydrous or hydrated, is used in pharmaceutical formulations (tablets and capsules) as diluents for direct compression. Magnesium stearate is used as lubricant in the tablet making since it decreases friction between the tablet surfaces and dies wall during the ejection process. Starch is often used as a diluent, disaggregated, binder and for its lubricant property. Usually starch is mingled with lactose. Talcum powder is the most used lubricant because of its anti adhesive effect and fluidifies the granulated substance. Ascorbic acid is used as antioxidant synergist and citric acid is used as sequesterant.

Differential scanning calorimetry (DSC)

DSC curves were obtained in a DSC-60 Shimadzu calorimeter cell using aluminum crucibles with about ~2mg of samples, under dynamic N₂ atmosphere (flow rate: 50 mL/min) and at a heating rate of 10°C/min in the temperature range 25-400°C.

Thermogravimetric analysis (TG)

TG curves were obtained with a TGA/SDTA 851e thermobalance in the temperature range of 25–400°C, using alumina crucibles with approximately 5mg of sample, under dynamic N₂ atmosphere (50mL/min) and at a heating rate of 10°C/min.

X-ray powder diffraction (XRPD)

X-ray powder diffraction pattern was obtained using Bruker D8 Advance diffractometer, sealed Cu tube λ = 1.5406 Å equipped with an incident beam Ge 111 monochromator.

Fourier transform infrared spectroscopy (FTIR)

FTIR spectra were obtained with JASCO 6100 FTIR spectrometer in the 4000–400 cm⁻¹ spectral domain with a resolution of 4 cm⁻¹ using the well known KBr pellet technique.

Results and discussions

The thermoanalytical curves (DSC and TG) of SIM are illustrated in figures 2-3.

Table 1 illustrates the main process that happens to simvastatin and to the mixtures of simvastatin and the excipients which are used and the heat energy released in each decomposition process.

In all binary mixtures it can be seen that the typical melting temperatures of each component of the mixture is slightly changed, because of the second component that is perceived as “impurity”, which decreases the melting temperature of the mixture compared to the melting temperature of the pure substance.

The TG curve of SIM exhibited 97.452% of mass loss between 77.70 and 222.25°C due to the decomposition of SIM.

In the TG curves of SIM and lactose monohydrate 1:1 physical mixture a first Δm = 1.761% mass loss was observed between 10.83 and 23.78°C due to the dehydration followed by a second Δm = 82.815% mass loss between 62.32 and 221.90°C due to the decomposition of the two components in the physical mixture.

The TG curve of the 1:0.25 physical mixture of SIM with ascorbic acid exhibited 90.828% of mass loss between 30.30 and 174.15°C due to the decomposition of SIM and ascorbic acid in the physical mixture.

In the TG curve of SIM and citric acid 1:0.25 physical mixture a first Δm = 41.683% mass loss was observed between 23.01 and 74.27°C due to the dehydration of the mixture followed by a second one, Δm = 50.629% between 77.23 and 189.17°C due to the decomposition of the two components of the mixture.

In the TG curve of the 1:0.25 physical mixture of SIM and magnesium stearate two mass loses can be observed. The first one, Δm = 65.778% was seen between 53.93 and 135.79°C and represents the dehydration of the mixture, while the second one, Δm = 19.586% between 149.95 and 290.67°C represents the thermal decomposition of the mixture components.

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The TG curve of the 1:1 physical mixture of SIM and starch exhibited a first Δm = 0.801% mass loss between 13.78 and 25.87°C due to the dehydration of the starch in the physical mixture followed by a second Δm = 85.264% mass loss between 64.89 and 216.81°C due to the decomposition of SIM and starch in the physical mixture.

TG curve of SIM and talcum 1:0.25 physical mixture presented two mass losses, Δm = 72.799% between 47.59 and 153.73°C and Δm = 1.755% between 248.34 and 296.00°C characteristic for the decompositions of the two substances in the mixture.

All the thermal profiles of mixtures can be considered as a superposition of DSC and TG curves of pure SIM and excipients, as a proof of compatibility between SIM with the used excipients.

To get more information and to support DSC and TG results X-ray diffraction studies were performed on the analyzed mixtures.

X-Ray powder diffraction patterns for starting compounds and for compound obtained by mechanical mixture are shown in figure 4.

Fig. 2. Differential scanning calorimetry (DSC) of simvastatin and of its physical mixtures with different excipients
### Table 1
**THERMAL EVENTS AND TEMPERATURES AT WHICH THEY APPEAR FOR SIMVASTATIN, EXCIPIENTS AND FOR BINARY MIXTURES**

<table>
<thead>
<tr>
<th>SIM-EXCIPIENTS</th>
<th>$T_{onset}$ (°C)</th>
<th>$T_{peak}$ (°C)</th>
<th>Heat J/g</th>
<th>Thermal event</th>
<th>Start decomposition (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin</td>
<td>138.48</td>
<td>140.36</td>
<td>-94.32</td>
<td>melting SIM</td>
<td>~230</td>
</tr>
<tr>
<td>Starch</td>
<td>45.35</td>
<td>69.83</td>
<td>-208.14</td>
<td>water elimination</td>
<td>~270</td>
</tr>
<tr>
<td>SIM-Starch</td>
<td>45.50</td>
<td>69.83</td>
<td>-170.48</td>
<td>water elimination</td>
<td></td>
</tr>
<tr>
<td></td>
<td>133.15</td>
<td>137.08</td>
<td>-27.88</td>
<td>melting SIM</td>
<td>~265</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>192.60</td>
<td>194.60</td>
<td>-274.31</td>
<td>melting ascorbic acid</td>
<td>~200</td>
</tr>
<tr>
<td>SIM-Ascorbic acid</td>
<td>133.46</td>
<td>135.10</td>
<td>-49.28</td>
<td>melting SIM</td>
<td>~200</td>
</tr>
<tr>
<td></td>
<td>188.33</td>
<td>190.19</td>
<td>-16.49</td>
<td>melting ascorbic acid</td>
<td>~200</td>
</tr>
<tr>
<td>Citric acid</td>
<td>155.16</td>
<td>156.91</td>
<td>-269.69</td>
<td>melting citric acid</td>
<td>~175</td>
</tr>
<tr>
<td>SIM-Citric acid</td>
<td>114.00</td>
<td>123.01</td>
<td>-40.76</td>
<td>melting SIM</td>
<td>~148</td>
</tr>
<tr>
<td>Lactose</td>
<td>143.56</td>
<td>146.44</td>
<td>-104.64</td>
<td>dehydration lactose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>209.26</td>
<td>217.09</td>
<td>-148.08</td>
<td>decomposition lactose</td>
<td>~150</td>
</tr>
<tr>
<td>SIM-Lactose</td>
<td>128.21</td>
<td>133.45</td>
<td>-23.06</td>
<td>melting SIM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>145.19</td>
<td>148.07</td>
<td>-28.55</td>
<td>dehydration lactose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>208.94</td>
<td>214.79</td>
<td>-77.71</td>
<td>decomposition SIM + lactose</td>
<td>215</td>
</tr>
<tr>
<td>Mg stearate</td>
<td>75.07</td>
<td>86.06</td>
<td>-90.54</td>
<td>water elimination</td>
<td></td>
</tr>
<tr>
<td></td>
<td>96.75</td>
<td>107.40</td>
<td>-11.70</td>
<td>melting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>112.02</td>
<td>114.07</td>
<td>-7.18</td>
<td>melting</td>
<td>~200</td>
</tr>
<tr>
<td>SIM-Mg stearate</td>
<td>63.68</td>
<td>73.86</td>
<td>-21.44</td>
<td>water elimination</td>
<td></td>
</tr>
<tr>
<td></td>
<td>91.58</td>
<td>95.58</td>
<td>-1.91</td>
<td>melting Mg stearate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>135.43</td>
<td>137.44</td>
<td>-9.19</td>
<td>melting SIM</td>
<td>~200</td>
</tr>
<tr>
<td>Talc</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SIM-Talc</td>
<td>132.13</td>
<td>135.21</td>
<td>-50.47</td>
<td>melting SIM</td>
<td>~250</td>
</tr>
</tbody>
</table>

Fig. 3. Thermogravimetry (TG) curves of SIM and of its physical mixtures with different excipients
One can see that the X-Ray powder diffraction patterns for samples obtained by mechanical mixture of active compounds with different ingredient are sum of patterns corresponding to each component, i.e. no new compound is formed and there are no interactions (physical or chemical between drug and excipients).

It could be concluded that XRPD methods sustain the thermal results, showing compatibility between SIM and the used excipients.

The next step was to study the representation and analysis of FTIR spectra of binary card and to observe any chemical interactions between components.

In the case of SIM-lactose system one can observe that the O-H stretching mode is located at 3547 cm\(^{-1}\) for SIM and at 3528 cm\(^{-1}\) for lactose. In the spectrum of their physical mixture the higher frequency peak was found as a shoulder to the lower frequency, one band showing that a real physical mixture was obtained, without interactions between components. The same action was observed for other characteristic bands of each component. As a consequence, a real physical mixture of these two components was obtained.

The IR spectrum of starch has many stretching vibrations in the region 1300-700 cm\(^{-1}\) originated from the C-C, C-O, glucopyran band and stretching vibration of C–O with the attachment of OH [18-20].

The following peaks are noticeable in the starch spectra: 3445 cm\(^{-1}\) (O–H hydrogen bonding stretching vibration), 2931 cm\(^{-1}\), 1010 cm\(^{-1}\) (specific to the crystalline starch) and at 996 cm\(^{-1}\) (which is related of the hydroxyl group at C-6, was water sensitive).

In the binary mixture' FTIR spectrum, starch's peaks significantly decreased in intensity and are displaced from 3445 cm\(^{-1}\) to 3433 cm\(^{-1}\), one located at 2931 cm\(^{-1}\), corresponding to ethyl group vibration was displaced to 2964 cm\(^{-1}\). SIM peak appeared at 3548 cm\(^{-1}\). Also, the peak from 1010 cm\(^{-1}\) decreased in frequency, and the peak at

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996 cm⁻¹ disappeared, which corresponds to intramolecular hydrogen bonding.

Magnesium stearate is a substance that has not too many vibrations in infrared. Magnesium stearate ethyl group has specific absorption in the spectral range 2920-2851 cm⁻¹ [19].

Other vibrations that can be noticed in the spectrum of physical mixture in the spectral range 1385-870 cm⁻¹ are due to SIM vibrations.

Due to SIM absorptions in infrared, the physical mixture of talcum powder with SIM has the spectrum more "abundant" in vibrations compared to the talcum powder of talcum powder with SIM has the spectrum more "abundant" in vibrations compared to the talcum powder. Due to SIM absorptions in infrared, the physical mixture's spectrum contains SIM vibrations, and also citric acid's vibrations.

Ascorbic acid's most important vibrations are: ν_{OH} at 3525 and 3411 cm⁻¹, ν_{C-OH} at 1316 and 1145 cm⁻¹, δ_{OH} at 1291 cm⁻¹, ν_{C=O} at 1763 and 1683 cm⁻¹, ν_{C=O} at 1280 cm⁻¹, ν_{asym} at 1052 and 823 cm⁻¹, ν_{sym} at 1031 and 875 cm⁻¹, the C=O out-of-plane bending mode (γ) at 761 cm⁻¹, the planar-ring deformation at 693 cm⁻¹ and the C=O in-plane bending vibration (β) at 635 cm⁻¹ [19].

In the binary mixture's FTIR spectrum, the SIM vibrations and ascorbic acid vibrations can be easily noticed without any other vibrations, meaning that there are no interactions between the two.

**Conclusions**

Thermoanalytical results (DSC and TG) supported the absence of incompatibility between SIM and excipients in the physical mixtures.

All the thermal profiles of mixtures can be considered a proof of compatibility between drugs with the used excipients, using the overlap of DSC and TG curves of pure drugs and all the excipients.

One can notice that the X-Ray powder diffraction pattern obtained for samples by mechanical mixture of actives compounds with different ingredients are a sum of patterns corresponding to each component, i.e. no new compound is formed, therefore, there are no interactions (physical or chemical between drug and excipients).

FTIR spectra supported these results. No evidence of interaction in the solid state was identified.

Based on the results supplied by DSC/TG, XRPD and FTIR, all the excipients were found to be compatible with SIM, so they can be used in the formulation of the slow release tablets.

The study demonstrated the applicability of thermal analysis (DSC, TG), XRPD and FTIR methods as fast screening tools to check compatibility of the preformulation process.

**References**


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