The Study of the Influence of Formulation and Process Variables on the properties of Simvastatin-Phospholipid Complex

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The Study of the Influence of Formulation and Process Variables on the properties of Simvastatin-Phospholipid Complex

Abstract

Objectives: The aim of the present study was to examine the influence of the formulation and process variables on the entrapment efficiency of simvastatin-phospholipid complex (SPC), prepared with a goal of improving the solubility and permeability of simvastatin.

Method: The SPC was prepared using a solvent evaporation method. The influence of formulation and process variables on simvastatin entrapment was assessed using a central composite design. An additional SPC was prepared using the optimized variables from the developed quadratic model. This formulation was characterized for its physical-chemical properties. The functional attributes of the optimized SPC formulation were analyzed by apparent aqueous solubility analysis, in-vitro dissolution studies, dissolution efficiency analysis, and ex-vivo permeability studies.

Results: The factors studied were found to significantly influence on the entrapment efficiency. The developed model was validated using the optimized levels of formulation and process variables. The physical-chemical characterization confirmed a formation of the complex. The optimized SPC demonstrated over 25-fold higher aqueous solubility of simvastatin, compared to that of pure simvastatin. The optimized SPC exhibited a significantly higher rate and extent of simvastatin dissolution (>98%), compared to that of pure simvastatin (~16%). The calculated dissolution efficiency was also found to be significantly higher for the SPC (~54 %), compared to that of pure simvastatin (~8%). Finally, the optimized SPC exhibited a significantly higher simvastatin permeability (>78%), compared to that of pure simvastatin (~11%).

Implications: The present study shows that simvastatin-phospholipid complex can be a promising strategy for improving the delivery of simvastatin, and similar drugs with low aqueous solubility.

Disciplines
Pharmacy and Pharmaceutical Sciences

Comments


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A Study of the Influence of Formulation and Process Variables on the Functional Attributes of Simvastatin-Phospholipid Complex

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Objective
To examine the influence of formulation and process variables on the entrapment efficiency of simvastatin-phospholipid complex (SPC), prepared with a goal of improving the solubility and permeability of simvastatin.

Methods
The SPC was prepared using a solvent evaporation method. The influence of formulation and process variables on simvastatin entrapment was assessed using a central composite design. An additional SPC was prepared using the optimized variables from the developed quadratic model. This formulation was characterized for its physical-chemical properties. The functional attributes of the optimized SPC formulation were analyzed by apparent aqueous solubility analysis, in vitro dissolution studies, dissolution efficiency analysis, and ex vivo permeability studies.

Results (contd.):
The optimized SPC demonstrated over 25-fold higher aqueous solubility of simvastatin, compared to that of pure simvastatin (Table 1). The optimized SPC exhibited a significantly higher rate and extent of simvastatin dissolution (>98%), compared to that of pure simvastatin (~16%) (Fig. 3). The calculated dissolution efficiency was also found to be significantly higher for the SPC (~54%), compared to that of pure simvastatin (~8%). Finally, the optimized SPC exhibited a significantly higher simvastatin permeability (~78%), compared to that of pure simvastatin (~11%) (Fig. 4).

Conclusions
The present study showed that phospholipid-based complexation can be a promising strategy for improving the delivery of simvastatin, and similar drugs with low aqueous solubility.

Table 1. Apparent aqueous solubility of pure simvastatin, the physical mixture of simvastatin and Phospholipon® 90H (1:1), and the prepared SPC.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Aqueous solubility (mg/mL)*</th>
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<tbody>
<tr>
<td>Simvastatin</td>
<td>0.016 ± 0.001</td>
</tr>
<tr>
<td>Simvastatin: Phospholipon® 90H (1:1)</td>
<td>0.018 ± 0.001</td>
</tr>
<tr>
<td>SPC</td>
<td>0.431 ± 0.02</td>
</tr>
</tbody>
</table>

Figure 1. Pareto diagram for the estimation of effect. The effects presenting P<0.05 are considered as statistically significant.

Figure 2. The response surface plots, and the contour plots based on the entrapment efficiency (Y, %) as a critical quality attribute (CQA) as a function of the ratio of phospholipids and simvastatin (X₁, w:w), the reaction temperature (X₂, °C), and the reaction time (X₃, h).

Figure 3. The in vitro dissolution profiles of simvastatin, the physical mixture of simvastatin and Phospholipon® 90H (1:1), and the prepared SPC.

Figure 4. The ex vivo permeation of simvastatin, the physical mixture of simvastatin and Phospholipon® 90H (1:1), and the prepared SPC across everted rat intestine.