Formulation and evaluation of colon targeted tablets containing simvastatin solid dispersion

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Abstract

Solid dispersions (SDs) of simvastatin with mannitol, Ineutic®, Pluronic® F-68, PEG 4000 and PVP K-30 were prepared and evaluated to deliver simvastatin to the colon in a pre-solubilized form. The formulation of choice was compressed into fast disintegrating tablets using drug compatible excipients and was coated with Eudragit® S100 as a pH-responsive polymer. We investigated the effects of several variables related to both SD preparation (carrier type, combined carriers and drug to carrier ratio) and tablet coating (coat level and type of plasticizer) on drug dissolution. Differential scanning calorimetry (DSC) and scanning electron microscopy (SEM) proved drug amorphization in SDs. The 1:5 simvastatin/Pluronic® SDs showed the greatest improvement in dissolution efficiency (12.2-fold) at the lowest carrier ratio. The coating level was critical for determining the duration of the lag-phase. Best results were given by the 10% coat (20.2:1 w/w Eudragit S100/ triethylcitrate/talc). This formula resisted pre-colonic pH values and showed an adequate lag time for the intended colonic targeting (4 h), followed by an immediate release phase (t50% = 249 min) in pH 7.4. The proposed coated tablets may provide a colonic delivery system for simvastatin with improved bioavailability.

Introduction

Solid formulations targeted to the lower gastrointestinal tract are beneficial for the treatment of many localized and systemic diseases and conditions. Various pharmaceutical approaches have been used to target drugs to the colon. They are mainly based on pH-dependent, time-dependent and/or bacterially degradable polymers.

Simvastatin is an HMG-CoA reductase inhibitor since mevalonic acid, the product of HMG-CoA reductase, is essential for cholesterol synthesis and is a precursor of several non-steroid chemical substances that play a role in the regulation of various cellular functions. Simvastatin has beneficial effects on total cholesterol, triglyceride and HDL cholesterol serum levels as well as on bone mineral density and the incidence of Alzheimer’s disease.

Simvastatin has the disadvantage of low bioavailability due to not being soluble in water and its intestinal metabolism by CYP3 enzymes. Simvastatin colon targeting is promising due to the lower levels of this enzyme in the colon than in the small intestine. Moreover, simvastatin delayed release formulations could offer an additional therapeutic advantage by coinciding with the circadian rhythm of cholesterol synthesis. A recent study proved the benefits of simvastatin colon targeting in improving its oral bioavailability. However, dissolution could be problematic for the absorption of the insoluble simvastatin from the distal intestine. Many factors could hinder drug distribution and dissolution in the colon, such as the lack of fluid, (the large intestinal contents are generally viscous), and the non-uniform transit in the colon (dosage forms are often at rest spending up to 30 min periods with no or minimal propagation).

Various techniques have been used to improve the solubility of simvastatin in water, such as the use of hydrotropic solubilizing agents, microemulsions, cyclodextrin inclusion complexes and solid dispersions. This study aimed to prepare and evaluate a pH-dependent system of pre-solubilized simvastatin for bolus delivery of the drug into the colon.

Materials and Methods

Solubility

An excess amount of simvastatin was placed in contact with phosphate buffer of pH 1.2, 4.5, 6.8 and 7.4 to investigate drug solubility throughout the whole pH range of the gastrointestinal tract (GIT). The samples were shaken for 72 h at 37°C in a horizontal shaker. The supernatant was filtered through a Millipore filter (pore size 0.45 μm). The filtrate was immediately injected at a flow rate of 1.8 mL/min (Hypersil C18 column, Thermo Electron Corporation) and assayed using an HPLC with UV detector (SPD-10A, Shimadzu, Japan) at 240 nm. Acetonitrile: 0.05M ammonium acetate (60:40 v/v) was used as the mobile phase. All experiments were conducted in duplicate.

Preparation of solid dispersions

Eighteen solid dispersion formulae of simvastatin were prepared applying solvent evaporation technique. Mannitol, Ineutic®, Poloxamer®, F-68, polyethylene glycol 4000, polyvinyl pyrrolidone K-30 or polyethylene glycol/sodium lauryl sulfate were applied as carriers at different drug to carrier ratios. Simvastatin and the carrier were separately dissolved in the minimum volumes of the suitable solvent with the aid of ultrasonication for 30 min (Crest Ultrasonics Corp., Trenton, USA). Both solutions were mixed and solvents were evaporated under reduced pressure at 40°C (Rotary Evaporator, Heidolph instrument Model D91126). The resulting solid dispersions were pulverized, passed through a 250 μm sieve and stored in a desiccated environment for further evaluation. Composition of the prepared solid dispersions is shown in Table 1.

Characterization of solid dispersions

Thermal analysis characterization was based on differential scanning calorimetry and infrared spectroscopic analysis. The DSC studies were performed for the drug, the carriers, for the drug-carrier physical mixtures (PM) and for the prepared solid dispersions (SDs). Physical mixtures of the drug with the used tablet excipients (croscarmellose Na, microcrystalline cellulose (MCC) and Eudragit® S100) were also studied. Samples (3-4 mg) were placed in an aluminum pan and heated at a rate of 10°C/min, with indium in the reference pan, in an atmosphere of nitrogen to a temperature of 350°C. Fourier-transform infrared (FT-IR) spectra of the above combinations were determined using the KBr disc technique between 4000 and 500 cm⁻¹.
In vitro dissolution

In vitro dissolution of simvastatin from the prepared solid dispersions was studied using USP apparatus type I (Hanson Research Corporation, California, USA) in 500 ml phosphate buffer (pH 7.4). Sodium lauryl sulfate (0.5% w/v) was added to assure sink conditions. The experiments were carried out in triplicate at 37°C±0.5°C and 100 rpm for 1 h. Samples (5 mL) were withdrawn at predetermined time intervals, filtered and assayed for simvastatin. The same procedure was carried out for simvastatin powder. Dissolution rate at 4 min (DR4min), dissolution efficiency at 30 min (DE30min) (16) and similarity factor (f2) (17) were calculated to compare the dissolution profiles of simvastatin from different SDs formulae. The similarity factor f2 indicates the similarity in percentage release based on a logarithmic transformation of the sum of squared error, according to the following equation:

\[
f_2 = 50 \times \log \left(1 + \left(\frac{1}{n} \sum (R_t - T_t)^2\right)^{0.5} \times 100\right)
\]

Where \(R_t\) and \(T_t\) are the cumulative percentage of drug released for reference and test assay at time \(t\), respectively, and \(n\) is the number of time points. Generally, a value of \(f_2\) close to 100 (range 50-100) ensure sameness between the profiles.

Preparation and evaluation of the core fast disintegrating tablets

The SDs formula of choice was compressed into 400 mg tablets using 5% croscarmellose as superdisintegrant. Magnesium Stearate (1%) and microcrystalline cellulose (79%) were added as lubricant and filler, respectively. The tablet blend was compressed with a single punch machine (Royal Artist, Bombay, India) using a 13 mm punch and die set. The friability (percentage weight loss) of 10 tablets was measured at 25 rpm for 4 min (Tablet Friabilator, digital test apparatus, Model DFI-1; Veego, Bombay, India). Hardness ± standard deviation was measured for 10 tablets using a tablet hardness tester (Monsanto, USA). Ten randomly selected tablets were evaluated for their thickness using a tablet micrometer. The relative standard deviation (% RSD) values were calculated. Ten tablets were pulverized to a fine powder. Accurately weighed aliquots containing an amount of powder equivalent to a single dose were taken in triplicate and assayed for simvastatin.

The disintegration time of the tablets was measured using a USP Disintegration Tester in phosphate buffer pH 7.4 at 37°C. The basket was raised and lowered at a fixed frequency of 30 cycles/min. The test was carried out in triplicate.

pH dependent film coating of tablets

Ten different coated tablet formulae were prepared using two plasticizers (triethyl citrate or dibutyl phthalate), each at five coating levels (2.5, 5, 7.5, 10 and 15% w/w as total solid applied) (Table 2). The coating solution was prepared by dissolving 25 g of Eudragit® S 100 in 350 g of 95% ethanol under high-speed stirring. The plasticizer was added as 10% w/w of dry polymer. The mixture was stirred for 24 h to ensure sufficient plasticization of the polymer and to obtain a homogeneous solution after the addition of 5% talc as a glidant. Tablets were coated by immersion in the coating solution followed by solvent evaporation using a hot air electric hand dryer. The process was repeated until the desired level of coating per tablet was achieved.

Evaluation of coated tablets

The thicknesses of the prepared tablets was measured before and after coating. Mean values were calculated and the coat thickness for each formula was calculated by subtraction.

The in vitro dissolution was carried out in bio-relevant dissolution media with a sequential pH gradient in order to mimic the mouth-
to-colon transit.20 The paddle was operated at 50 rpm and the system was kept at a temperature 37°C.

Stability study

The formula of choice was stored at 40° C and 75% RH for six months according to the International Conference on Harmonization (ICH) guidelines. The relative humidity was initiated and maintained in desiccators using a saturated solution of sodium chloride and the desiccators were placed in an oven at 40°C±0.5. The withdrawn tablet samples were subjected to visual inspection, drug content, disintegration time and in vitro dissolution tests at time intervals of one, three and six months. The similarity factor (f2) was used to compare the dissolution profile before and after storage. Samples were also checked for presence of crystallinity using DSC and SEM to ensure the SD stability.

Results

Solubility

Solubility values of simvastatin at 37°C in aqueous buffers of pH 1.2, 4.5, 6.8, and 7.4 were 14.498, 8.261, 24.861 and 26.087 mg/mL, respectively. The solubility of simvastatin in other solvents and media has been studied previously.21-22 It was reported that simvastatin is virtually insoluble in water, with solubility of 1.5 mg/mL at 23°C.23

Preparation and characterization of solid dispersions

Thermal analysis characterization

The thermograph of pure crystalline simvastatin showed a sharp melting peak at 139.28°C. This peak was persistent in the thermographs of the physical mixtures (PMs) with Inutec® SP1, mannitol and PVP while it disappeared with the prepared solid dispersions (SDs), indicating absence of drug crystallinity (Figure 1A). Drug amorphization could be a consequence of interaction between the components and the method of preparation. The drug characteristic peak also disappeared in the DSC thermographs of both the PMs and SDs with Pluronic and PEG. Figure 1B shows the DSC thermographs of the PM of simvastatin with the used tablet excipients. The drug melting peak did not change, indicating physical compatibility between simvastatin and the selected excipients.

The FT-IR spectrum of simvastatin present-ed characteristic peaks at 3552.16 cm⁻¹ (alcohol free O-H stretching vibration), 2962.91 cm⁻¹ (methyl C-H asymmetric), 2876.05 cm⁻¹ (methylene C-H symmetric stretching vibration), 1704 cm⁻¹ (ester C=O stretch associated) 1461.34 cm⁻¹ (methylene C-H symmetric bend, methyl C-H asymmetric bend), 1367.79 cm⁻¹ (Gem-dimethyl C-H bend), 1267.11 and 1225.70 cm⁻¹ (lacton C-O-C stretch), 1165.06 cm⁻¹ (ester-C-O-C stretch), 1067.13 and 1053.46 cm⁻¹ (secondary alcohol C-O stretch ) 870 cm⁻¹ (trisubstituted olefinic C-H wag) and 670 cm⁻¹ (cis-olefinic C-H wag). Physical mixtures of simvastatin with all

<table>
<thead>
<tr>
<th>Formula</th>
<th>Coat level (%)</th>
<th>Type of plasticizer</th>
<th>Average coat thickness (mm)</th>
<th>t50% (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>2.5</td>
<td>*DBP</td>
<td>0.17±0.064</td>
<td>69</td>
</tr>
<tr>
<td>D2</td>
<td>5</td>
<td>DBP</td>
<td>0.29±0.030</td>
<td>163</td>
</tr>
<tr>
<td>D3</td>
<td>7.5</td>
<td>DBP</td>
<td>0.42±0.040</td>
<td>214</td>
</tr>
<tr>
<td>D4</td>
<td>10</td>
<td>DBP</td>
<td>0.56±0.066</td>
<td>260</td>
</tr>
<tr>
<td>D5</td>
<td>15</td>
<td>DBP</td>
<td>0.69±0.070</td>
<td>360</td>
</tr>
<tr>
<td>T1</td>
<td>2.5</td>
<td>**TEC</td>
<td>0.20±0.045</td>
<td>31</td>
</tr>
<tr>
<td>T2</td>
<td>5</td>
<td>TEC</td>
<td>0.29±0.054</td>
<td>91</td>
</tr>
<tr>
<td>T3</td>
<td>7.5</td>
<td>TEC</td>
<td>0.40±0.045</td>
<td>152</td>
</tr>
<tr>
<td>T4</td>
<td>10</td>
<td>TEC</td>
<td>0.50±0.063</td>
<td>249</td>
</tr>
<tr>
<td>T5</td>
<td>15</td>
<td>TEC</td>
<td>0.70±0.063</td>
<td>269</td>
</tr>
</tbody>
</table>

*DBP: dibutyl phthalate; **TEC: triethyl citrate.
carriers showed spectra corresponding to a superimposition of their parent components. FT-IR spectra of the prepared SDs were identical to those of the corresponding physical mixtures without any dramatic changes in characteristic peaks of simvastatin frequency, suggesting the absence of chemical interactions between simvastatin and any of the tested carriers. Figure 2 shows the FT-IR spectrum of simvastatin and Pluronic® F-68 in comparison with their PM and SDs as an example.

**Scanning electron microscopy (SEM)**

Figure 3 shows the SEM micrographs of (A) simvastatin and (B) simvastatin-Pluronic® F-68 solid dispersions. The drug powder exists as needle-like crystals, whereas the SDs appears in the form of tiny aggregates and amorphous pieces of irregular size.

**In vitro dissolution**

The dissolution profiles of simvastatin from the best prepared SDs (one optimum formula for each carrier type) were formula number 2, 6, 7, 12, 13 and 18 in comparison to simvastatin powder (Figure 4). About 31.28% of the free drug was dissolved after 3 h with dissolution efficiency equal to 16.96%, while the DE_{30 min} values of the prepared SDs were 53.26-97.27% (Table 1). The prepared SDs resulted in 3-6 fold improvements in dissolution efficiency. This could be attributed to the improved wettability of drug particles by the physical presence of hydrophilic amorphous excipients. As also indicated by SEM and DSC, this enhanced drug dissolution could be attributed to the presence of simvastatin in an amorphous form. The method of preparation used helps in drug amorphization. During solvent evaporation, viscosity of the system increases rapidly leading to a decrease in drug mobility. At complete solvent evaporation, the drug molecules are frozen in the polymer matrix in a random order, comparable to that of the liquid state, and exhibit short-range order over only a few molecular dimensions, which is characteristic of an amorphous form.⁵

The similarity factor (f₂) was calculated to compare the dissolution profiles of all formulae. A significant improvement in both the extent and rate of drug dissolution was shown for all the prepared SDs in comparison to drug alone; similarity factor 5.1-25.4. The results showed that this enhancement was concentration-dependent with Inutec® SP1, PEG and PEG/SLS with optimum drug to carrier ratio of 1:15. On the other hand, increasing the carrier concentration had no effect on the calculated DE_{30 min} values in the case of PVP, mannitol and Pluronic based formulae; similarity factor 73.2-89.5. The dissolution rate of all formulae (DR_{4 min}) was 1.66-22.26 %/min with remarkable correlation to the DE_{30 min} values (Table 1).

The similarity factor (f₂) was calculated to select the best SD formula. There was a significant difference in dissolution profiles in formulae 7, 13 and 18 compared to all the prepared formulae (Figure 4). Only formula 13 (1:5 simvastatin/Pluronic® F-68 dispersion) was selected for further formulation studies; it showed the highest dissolution efficiency (97.27%) at the lowest carrier ratio. Furthermore, Pluronic® F-68, being surfactant, is reported to produce more stable SDs than other carrier generations.²⁴ Formula 7 (1:5 simvastatin/PVP K-30) was excluded because of its stickiness while formula 18 (1:15 simvastatin/Inutec® SP1) was excluded because of the high carrier amount used.

**Preparation and evaluation of the fast disintegrating core tablets**

The selection of the optimum superdisintegrant type and level was based on preliminary work. Croscarmellose Na and crospovidone were tested at concentrations of 5-20%. On tabletting, 5% Croscarmellose Na produced tablets with fast disintegration (90 s) and 97.2% drug content. The tablets recorded
an average thickness of 2.190 mm±0.032, moderate hardness of 5.6 kg and acceptable friability of 0.338%.

Coated tablets

The plasticizer concentration was measured according to preliminary trials where, regardless of the plasticizer used, 10% plasticizer resulted in an acceptable viscosity of the coating solution and uniform films. The tablet cores were satisfactorily coated to coating thicknesses of 0.17-0.70 mm. Figure 5 shows the influence of coating level on drug dissolution of simvastatin from the DBP based tablets. Increasing the coating level decreased the rate and extent of drug dissolution. Tablets coated with a 2.5% coating were highly permeable in the acid medium with more than 90% drug dissolved within 2 h. This amount of the dissolved drug decreased at all formulations by increasing coating level. No significant drug dissolution was observed from tablets with 10% coat up to 6 h in gradient pre-colonic pHs, followed by an immediate release phase in pH 7.4 (t50%=260 min). A further increase in the coating level to 15% resulted in a significant delay before coat disintegration and drug dissolution in pH 7.4 (lag period approx. 50 min). This marked effect of the coat level on the drug dissolution could be attributed to longer drug diffusion pathways and more tortuosity at higher coating levels. Triethyl citrate based films acted similarly regarding the pH dependence and the coat level effect but at faster dissolution rates (shorter t50%) (Table 2). This higher coat permeability could be attributed to the higher solubility of TEC in water (1 in 25 at 20°C) compared with DBP (1 in 2500) which creates channels allowing a more rapid penetration of the dissolved drug decreased at all

Stability

The stored coated tablets retained their appearance without any significant changes in drug content or disintegration time during 6-month storage at 40°C and 75% relative humidity. A very slight decrease in dissolution was observed (similarity factor=91.5) with no evidence of crystallinity.

Discussion

Results showed that simvastatin has low solubility in an aqueous medium regardless of pH, which shows the need for drug solubilization. We used a solid dispersion technique to improve the aqueous solubility of simvastatin because it can be easily scaled up. Literature includes some examples for the preparation of simvastatin SDs using amorphous type carriers only. Patel and Patel prepared simvastatin SDs with PEG 4000 by fusion-cooling and solvent evaporation techniques, and with PVP K30 by solvent evaporation technique in different drug to carrier ratios. Ambike et al. successfully prepared amorphous SDs of simvastatin and PVP by spray drying with the aid of Aerosil 200 as adsorbent and compressed them into tablets. In our study, five carriers were selected to represent the different generations of SDs carriers; manitol as a representative of crystalline carriers forming 1st generation SDs, PVP by spray drying with the aid of Aerosil 200 as adsorbent and compressed them into tablets. In our study, five carriers were selected to represent the different generations of SDs carriers;26 manitol as a representative of crystalline carriers forming 1st generation SDs, PEG and PVP as 2nd generation amorphous carriers, Pluronic® F-68 and Inutec® SPI as 3rd generation or surfactant SDs. In addition, sodium lauryl sulfate was used in combination with PEG to study the effect of combining amorphous polymers and surfactants.

DSC thermograph proved the existence of simvastatin in an amorphous form in the prepared SDs. SEM showed a change in the original crystalline morphology of the drug suggesting some sort of interaction between the drug and the carrier, and indicating perfect miscibility of the drug and the carriers to form uniform SDs. This was reflected in enhanced drug dissolution in pH 7.4. Third generation SD carriers showed the greatest improvement in simvastatin dissolution. The used carriers can be arranged in a descending order according to their enhancements effect: Pluronic® F-68>Inutec® SPI>PVP K-30>mannitol>PEG/SLS>PEG

Similarly, SDs prepared with PVP were reported to show a greater improvement in dissolution rate of simvastatin compared to those containing PEG (1:10 simvastatin:PVP solid dispersion showed an 8.5-fold improvement in the percentage of drug dissolved within 30 min).14 Spray dried 1:2:2 simvastatin:PVP:Aerosil SDs resulted in an approximately 5-fold increase in the amount of drug released from SDs compared with pure drug during the initial 5 min.15

The SD formula with the highest dissolution efficiency (1:5 simvastatin/Pluronic® F-68 dispersion) was selected for the preparation of fast disintegrating tablets. The prepared tablets recorded fast disintegration with acceptable physical properties and were coated with Eudragit® S 100 to target the colon. Dibutyl phthalate (DBP) and triethyl citrate (TEC) were tested as lipophilic and hydrophilic plasticizers. Both are organic esters and were selected to be compatible with the insoluble Eudragit® S 100 to ensure good mechanical properties of the films. Less than 3% drug release was observed from tablets coated with 10% Eudragit in organic solution at acidic conditions. Once pH 7.4 was reached, the coat was immediately dissolved and the tablets were disintegrated releasing their drug
loading. Such bolus release is supposed to ensure complete drug absorption in the colon regardless of any unfavorable factors present there. Results show that stable tablets of affordable component prices and simple reproducible method of preparation were obtained.

**Conclusions**

Amorphous solid dispersions of simvastatin were successfully prepared by solvent evaporation. The presence of amorphous form in SDs was confirmed by DSC and SEM, and was reflected in the significant improvement in rate as well as extent of in vitro drug dissolution. Proper selection of the Eudragit® S 100 coat level and plasticizer type is essential to deliver simvastatin to the colon. The optimized simvastatin tablets could be promising in reducing the drug dose and improving its bioavailability based on the protection from the intestinal metabolism. Such a delivery system could be applied for similar water insoluble drugs liable to intestinal enzymatic degradation. Additional studies are needed to assess its performance in vivo.

**References**