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Short communication

Simvastatin-loaded charge-reversal micelles

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Introduction

Simvastatin is a highly lipophilic, poorly water soluble neutral lactone prodrug, with very low oral bioavailability (≲5%) resulting from the combined effects of limited intraluminal solubilization, precipitation risk and extensive presystemic metabolisam. Although commonly assigned to BCS class II, refined Developability Classification System (rDCS)/Solubility Limited Absorbable Dose-based interpretation places simvastatin closer to class IIb or IIa/IIb boundary, indicating that relevant limitation is not merely slow dissolution of solid drug, but the insufficient generation and maintenance of a solubilized absorbable fraction during GIT transit. Thus, the central formulation objective is not only to accelerate dissolution, but to generate and maintain a colloidally solubilized absorbable fraction during GIT transit. Enhanced solubilization may also have pharmacokinetic consequences beyond increasing the absorbed fraction. For zeta-potential-changing micelles, an initially neutral-to-negative surface may support diffusion through the polyanionic mucus layer, whereas delayed exposure of cationic domains can increase epithelial interaction, cellular uptake and mucosal residence (Malkawi et al., 2021). This sequential surface-charge modulation is particularly relevant for simvastatin, because increased epithelial drug presentation may hypothetically reduce the relative impact of presystemic metabolism through local enzyme saturation and/or prolonged absorption along the small intestine. In support of this concept, Thomas et al. (2013) showed that supersaturated SNEDDS increased simvastatin relative bioavailability in dogs to 180±53.3% compared with dose-equivalent conventional SNEDDS and reduced the simvastatin acid/parent simvastatin AUC ratio from 0.90±0.30 to 0.57±0.20, which the authors attributed to possible saturation of presystemic metabolizing enzymes and prolonged intestinal absorption. Similar zeta-potential-changing micellar systems have also demonstrated preserved mucus permeation together with improved cellular uptake after delayed conversion toward a less negative or slightly positive surface charge. Accordingly, this study aimed to investigate whether simvastatin-loaded Eudragit RL:stearic acid (SA) mixed micelles can combine rDCS-relevant colloidal solubilization with preserved time-dependent zeta-potential shifting. The effect of simvastatin load and micellar material concentration on hydrodynamic diameter and zeta-potential evolution was evaluated to determine whether increased Kolliphor RH 40/Labrasol content improves size control while maintaining the delayed negative-to-positive charge-shifting behavior of the RL:SA platform.

Materials and methods

Micellar systems were prepared using the thin film hydration method from non-ionic surfactants

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Labrasol and Kolliphor RH 40 loaded with an ionic complex formed between cationic polymer Eudragit RL and SA at a ratio 1:10 and simvastatin. Six formulations were prepared employing three different simvastatin loadings (10, 20, and 30 mg) in combination with two concentrations of non-ionic surfactants, standard (1x) and doubled (2x), and hydration was performed in phosphate buffer pH 6.8. Zeta potential and hydrodynamic size were monitored over time by electrophoretic and dynamic light scattering using Zetasizer Nano, while conductivity was measured in parallel. Raw zeta potential time series were grouped into kinetically coherent negative, near neutral, and positive phases, and phase mean values were calculated for each formulation to capture the dominant charge state. Conductivity-zeta maps were used to assess whether the charge changes followed simple conductivity variation or more complex time-dependent trajectories.

Results and discussion

Simvastatin-loaded RL:SA systems showed clear drug-load and micellar-material-dependent changes in hydrodynamic diameter. Empty micelles were approximately 17±2.0 nm, whereas RL:SA complex incorporation increased the size to approximately 145.0±2.8 nm, confirming structural expansion of the micellar assembly. After simvastatin loading, corrected Z-average values for the 1×systems increased from 178.0±5.0 nm to 220.0±3.0 nm and 260.0±5.4 nm for 10, 20 and 30 mg simvastatin, respectively. The corresponding 2×systems were consistently smaller, 121.0±6.2 nm, 131.1±5.3 nm and 215.0±4.2 nm, indicating that higher Kolliphor RH 40/Labrasol content improved colloidal accommodation of simvastatin and reduced drug-/complex-rich secondary association. Reported PDI values of 0.22–0.25 further indicate acceptable distribution width for the simvastatin loaded systems. Time-resolved zeta-potential analysis showed that simvastatin loading preserved, but attenuated, the charge-shifting behavior of the RL:SA platform. Compared with unloaded RL:SA 1:10 micelles, which shifted from −17.36±0.05 to +2.30±0.07 mV, simvastatin-loaded systems started closer to neutrality, suggesting partial masking of stearate-dominated anionic character by drug incorporation. The most coherent delayed negative-to-positive transition was observed for 1×/20 mg simvastatin, which shifted from a clear negative phase of −1.94 mV to a stable positive phase of +1.42±0.04 mV after 3 h. The 1×/30 mg and 2×/30 mg systems also showed charge conversion, shifting from -2.44±0.03 and -1.51 ±0.02 to final positive means of +1.95±0.06 and +1.40±0.04 mV, respectively. The systems reached terminal positivity after 3 h. The 2×/20 mg systems gave the smallest size among the medium/high-load systems, 131.67±2.5 nm, and the highest terminal positivity, +2.37±0.03 mV, but its weak initial negativity, −0.35±0.04 mV, indicates buffering of the charge-reversal signal by excess nonionic micellar material. Thus, 2× systems were superior for size control, whereas 1×/20 mg better preserved delayed charge-shifting kinetics. At 10 mg simvastatin, charge conversion was weak. Overall, these systems are best described as simvastatin-loaded, sterically stabilized RL:SA micelles with attenuated but temporally structured charge-shifting behavior.

Conclusion

Simvastatin-loaded Eudragit RL:SA mixed micelles successfully combined colloidal accommodation of a poorly soluble drug with preserved time-dependent interfacial charge-shifting behavior. Increasing Kolliphor RH 40/Labrasol improved size control, with the 2×/20 mg formulation showing the most favorable hydrodynamic diameter and terminal positive zeta potential. However, excess micellar material attenuated the initial negative phase, whereas the 1×/20 mg formulation better preserved delayed negative-to-positive conversion. Overall, simvastatin loading moderated but did not abolish the RL:SA charge-shifting platform. Further mucus permeation, cellular uptake, metabolism and pharmacokinetic studies are required before bioavailability enhancement can be claimed.

References

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