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Short communication

Time-dependent charge reversal mixed micelles

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Introduction

Overcoming the intestinal mucus barrier requires nanocarriers that reconcile opposing surface-charge requirements: neutral/anionic surfaces favor mucus diffusion by minimizing electrostatic binding to the polyanionic mucin network, whereas cationic surfaces promote epithelial interaction but are prone to mucus immobilization (Watchorn et al., 2022). Zeta-potential-changing micelles address this conflict by maintaining mucus-compatible surface properties during initial diffusion and subsequently exposing cationic domains near the epithelium (Postina et al., 2026). In the present study, Kolliphor RH 40 and Labrasol served as the nonionic micellar matrix, while Eudragit RL/RS–stearate ionic complexes acted as charge-modulating components, following the cationic polymers-fatty acid ion-pairing approach reported by Malkawi et al. (2021). The aim was to evaluate whether these complex-loaded mixed micelles undergo time-dependent negative-to-positive charge reversal and whether this reflects interfacial reorganization rather than conductivity-driven variation.

Materials and methods

Micellar systems were prepared by the thin-film hydration method. Briefly, Eudragit RS or Eudragit RL, stearic acid (SA), Kolliphor RH 40 and Labrasol were dissolved in an acetone/absolute ethanol solvent system rendered alkaline with ammonia solution to promote SA deprotonation and electrostatic association with the cationic quaternary ammonium groups of the polymer. After solvent evaporation, the resulting thin film was hydrated using phosphate buffer pH 6.8 to obtain or Eudragit:SA complex-loaded mixed micelles. For each polymer grade, three formulation groups were investigated: Eudragit-loaded mixed micelles without SA, Eudragit:SA 1:1 complex-loaded micelles, and SA-excess Eudragit:SA 1:10 complex-loaded micelles.

Hydrodynamic diameter and zeta potential were monitored over time after appropriate dilution in 0.01 M phosphate buffer, pH 6.8, using dynamic and electrophoretic light scattering, respectively (Zetasizer Nano series, Malvern Instruments, UK). Conductivity–zeta state maps were used to verify that the observed charge reversal was not primarily attributable to conductivity-related effects, but reflected time-dependent interfacial rearrangement of the Eudragit–stearate complex within the mixed micellar matrix.

Results and discussion

Blank Kolliphor/Labrasol micelles were near-neutral and showed a Z-average diameter of 17.0 ±

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2.0 nm, confirming the low intrinsic electrostatic contribution of the nonionic micellar matrix. Loading with Eudragit–SA complexes caused a concentration-dependent increase in hydrodynamic diameter. RS–SA complex-loaded micelles increased from 123.0 ± 4.5 nm to 168.5 ± 6.5 nm and 194.2 ± 3.7 nm for 10, 20 and 30 mg complex, respectively, while the corresponding RL–SA systems were smaller, 98.1 ± 3.5 nm, 146.0 ± 5 nm and 185.2 ± 5.6 nm. Thus, complex incorporation expanded the micellar assembly in a load-dependent manner, with RL–SA producing more compact nanosized dispersions than RS–SA.

Eudragit-loaded Kolliphor/Labrasol mixed micelles without SA served as cationic controls and confirmed the grade-dependent polymer contribution. RL-loaded micelles shifted from −0.120 ± 0.005 mV to +24.07 ± 0.80 mV, whereas RS-loaded micelles shifted from +0.030 mV to +14.37 ± 0.50 mV, consistent with the higher quaternary ammonium content of Eudragit RL. In contrast, equimolar Eudragit:SA 1:1 complex-loaded micelles showed only weak positive drift, with RL–SA shifting from −0.040 mV to +2.98 ± 0.10 mV and RS–SA from −0.64 ± 0.03 mV to +0.95 ± 0.04 mV. These profiles indicate partial charge attenuation/neutralization rather than true charge reversal.

The SA-excess Eudragit:SA 1:10 systems showed the intended negative-to-positive charge reversal. RL–SA 1:10 shifted from a pronounced anionic phase of −17.36 ± 0.60 mV to a sustained mildly positive terminal phase of +2.30 ± 0.09 mV, while RS–SA 1:10 followed the same direction but with lower amplitude and greater heterogeneity, shifting from −14.60 ± 0.50 mV to +1.05 ± 0.04 mV, within approximately 3h. Thus, both SA-excess systems expressed time-dependent charge reversal, but RL–SA 1:10 gave the cleaner profile and stronger terminal positivity. Isolated transient positive excursions in the RS trace were not interpreted as true reversal, because sustained crossing and persistence above 0 mV are more reliable criteria than a single positive point.

Mechanistically, the initial negative state is consistent with stearate-dominated screening of Eudragit quaternary ammonium groups at or near the slipping plane. Over time, stearate redistribution, relaxation or partial dissociation likely reduces the anionic contribution and progressively unmasks polymeric cationic domains. The terminal ζ-potentials of the 1:10 systems remained far below the polymer-only controls, indicating partial rather than complete cationic exposure, still moderated by residual stearate and the nonionic Kolliphor/Labrasol corona. Conductivity–zeta trajectories further supported time-dependent interfacial rearrangement rather than a conductivity-related measurement effect, because the systems followed loop-like temporal paths rather than a single monotonic conductivity–zeta relationship.

Conclusion

Eudragit RL–SA and Eudragit RS–SA complex-loaded Kolliphor/Labrasol mixed micelles exhibited controllable, time-dependent zeta-potential behavior. Eudragit:SA 1:1 systems mainly attenuated polymer charge, whereas SA-excess Eudragit:SA 1:10 micelles produced clear negative-to-positive charge reversal. RL–SA 1:10 showed the most coherent profile, with stronger terminal positivity and cleaner charge evolution than RS–SA. This is consistent with the higher quaternary ammonium content of Eudragit RL and supports RL–SA 1:10 as the more promising charge-modulating system. Further mucus permeation and cellular uptake studies are required to confirm whether this physicochemical charge-switching profile translates into sequential mucus-compatible and epithelial-interactive oral delivery behavior.

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