Encapsulation of Alendronate-Polyethyleneimine Complexes into Nanostructured Lipid Carriers Enhances Intestinal Permeation In Vitro

B. N. Abd El-Hamid1, N. K. Swarnakar1, G. M. Soliman2, M. A. Attia2, G. M. Pauletti1

1University of Cincinnati, 2Assiut University

Purpose

Unfavorable physicochemical properties of the anti-osteoporotic drug alendronate (AL) limit oral bioavailability in humans to ≤1%. The main objective of this research was to explore whether a combination of hydrophobic ion pairing with a lipid-based nanodelivery system successfully enhances the flux of this highly polar drug across the intestinal mucosa in vitro. Furthermore, it was attempted to delineate the influence of the external environment present in the gastrointestinal tract on the release kinetics of AL from nanostructured lipid carriers.

Methods

Electrostatically stabilized AL-polyethyleneimine 25 kDa (PEI) complexes were formed at a molar ratio of 1:0.152 in acetate buffer, pH=5. The hydrophobic ion pairs were encapsulated into biodegradable nanostructured lipid carriers (NLCs) comprised of Precirol® ATO5 and medium chain triglycerides using a modified solvent injection method. As a control, AL alone was incorporated into NLCs using the same encapsulation protocol. Encapsulation efficiency for AL and AL-PEI complexes was determined spectrophotometrically ($\lambda$=300 nm) after ultrafiltration. Release kinetics of AL and AL-PEI ion pairs as well as AL-PEI complex stability were quantified in vitro at 37°C using Hanks’ Balanced Salt Solution, pH 7.4 (HBSS) or Fasted State Simulated Intestinal Fluid, pH 6.5 (FaSSIF-V2). Intestinal in vitro permeation studies were performed across confluent Caco-2 cell monolayers cultured for 21-28 days on semi-permeable filter support. For these experiments, a trace of $^{14}$C-labeled AL was incorporated during ion pair formation and encapsulation into NLCs to enhance analytical sensitivity via liquid scintillation counting.

Results

Complexation of AL with PEI increased drug encapsulation efficiency in NLCs from 10% to 84%. In the presence of HBSS, the hydrophobic AL-PEI ion pair remains stable for 6 hrs. Incubation with FaSSIF-V2, however, induces complex dissociation at a rate of 15%/hr. In comparison to AL, release kinetics of the AL-PEI ion pair from NLCs was significantly slower yielding a cumulative drug amount released after 24 hrs that corresponded to ~30% of AL released from NCLs in the same time period. Release properties measured for AL-PEI in FASSIF-V2 were significantly slower than in HBSS resulting in an overall 42.5% reduction in cumulative drug released within 24 hrs. Estimation of intestinal permeation properties of dissolved AL across Caco-2 cell monolayers revealed a Papp value of 2.74±0.42×10^{-6} cm/s (n=3). In contrast, the flux of this drug encapsulated as PEI ion pair complex in NCLs was ~3-fold increased (Papp = 8.43±0.14×10^{-6} cm/s, n=3).

Conclusion

Hydrophobic ion pairing of AL with PEI appears a promising strategy to significantly increase encapsulation efficiency of this hydrophilic drug within lipid-based nanodelivery system such as NLCs. The reduced release rate measured for AL-PEI ion pairs from NCLs in biorelevant media, which was demonstrated to enhance complex dissociation, implies that a greater fraction of the dose will be absorbed across the gastrointestinal mucosa inside of the colloidal nanocarrier. Extrapolating from the in vitro permeation data obtained using the Caco-2 cell culture model, lipid-encapsulated AL/PEI ion pairs have the potential dramatically improve oral bisphosphonate therapy for the prevention and treatment of osteoporosis in the future.