Innovative Preparation Techniques: Boosting Oral Bioavailability of Phenylbutyric Acid Through Choline Salt-Based API-Ionic Liquids and Therapeutic Deep Eutectic Systems

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Abstract : Urea cycle disorders (UCD) are rare genetic metabolic disorders that compromise the body's urea cycle. Sodium phenylbutyrate (SPB) is a medication commonly administered in tablet or powder form to lower ammonia levels. Nonetheless, its high sodium content poses risks to sodium-sensitive UCD patients. This necessitates the creation of an alternative drug formulation to mitigate sodium load and optimize drug delivery for UCD patients. This study focused on crafting a novel oral drug formulation for UCD, leveraging choline bicarbonate and phenylbutyric acid. The active pharmaceutical ingredient-ionic liquids (API-ILs) and therapeutic deep eutectic systems (THEDES) were formed by combining these with choline chloride. These systems display characteristics like maintaining a liquid state at room temperature and exhibiting enhanced solubility. This in turn amplifies drug dissolution rate, permeability, and ultimately oral bioavailability. Incorporating choline-based phenylbutyric acid as a substitute for traditional SPB can effectively curtail the sodium load in UCD patients. Our in vitro dissolution experiments revealed that the ILs and DESs, synthesized using choline bicarbonate and choline chloride with phenylbutyric acid, surpassed commercial tablets in dissolution speed. Pharmacokinetic evaluations in SD rats indicated a notable uptick in the oral bioavailability of phenylbutyric acid, underscoring the efficacy of choline salt ILs in augmenting its bioavailability. Additional in vitro intestinal permeability tests on SD rats authenticated that the ILs, formulated with choline bicarbonate and phenylbutyric acid, demonstrate superior permeability compared to their sodium and acid counterparts. To conclude, choline salt ILs developed from choline bicarbonate and phenylbutyric acid present a promising avenue for UCD treatment, with the added benefit of reduced sodium load. They also hold merit in formulation engineering. The sustained-release capabilities of DESs position them favorably for drug delivery, while the low toxicity and cost-effectiveness of choline chloride signal potential in formulation engineering. Overall, this drug formulation heralds a prospective therapeutic avenue for UCD patients.

Keywords : phenylbutyric acid, sodium phenylbutyrate, choline salt, ionic liquids, deep eutectic systems, oral bioavailability
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