DEVELOPMENT OF A NANOSCALE DELIVERY SYSTEM FOR RESVERATROL USING CHOLINE AND GERANIC ACID (CAGE) IONIC LIQUID AS A CARRIER

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Choline and geranic acid (CAGE) is a unique ionic liquid which has high potential in encapsulation of active pharmaceutical ingredients, because it can self-assemble into nanosized micelles in aqueous solutions. CAGE has been previously employed as a vehicle for the transdermal transport of proteins (e. g. insulin, ovalbumin) and flavonoids (e. g. nobiletin). Resveratrol (trans-3,4′,5-trihydroxystilbene) is one of the most characteristic naturally occurring polyphenols with powerful antioxidant capacity, but its hydrophobic nature leads to its low solubility and bioavailability.

The aim of the present work is the development of a potential novel non-toxic transdermal delivery system for resveratrol. CAGE is synthesized by a one-step metathesis reaction between choline bicarbonate and geranic acid at a molar ratio 1:2. The solubility of resveratrol in an aqueous solution of CAGE 1200mM was 9.9 mg/mL, whereas in water it is reported to be 0.003mg/mL. This result indicates that the solubility of resveratrol is remarkably enhanced in CAGE. The encapsulation efficiency (EE%) of resveratrol in CAGE micelles was found to be 79%. The radical scavenging activity of the nanoscale micellar systems was determined using the DPPH assay. The micellar system prepared of 20mg resveratrol in 1g CAGE shows significant antioxidant activity (IC_{50} 10.34 mg/ml), albeit lower than free resveratrol (IC_{50} 0.03 mg/ml). CAGE shows moderate antioxidant activity (IC_{50} 59.43 mg/ml). Dynamic Light Scattering (DLS) and Nanoparticle Tracking Analysis (NTA) were used to determine the size, polydispersity index and z-potential as well as the concentration of the micellar nanosystems. The average size of the micelles varies between 85.0 nm and 126.5 nm and their concentration between $1.05*10^8$ particles/ml and $2.47*10^8$ particles/ml. Polydispersity index values declare medium to good homogeneity of the size distribution of micelles. According to z-potential measurements (-19.6mV for CAGE micelles and -30.5mV for resveratrol loaded in CAGE at a mass ratio 20mg/g), the dispersions are satisfyingly stable and actually the stability is enhanced with the increase of resveratrol mass loaded.

References: Tzani, A., Karadendrou, M. A., Kalafateli, S., Kakokefalou, V., & Detsi, A. (2022). Current Trends in Green Solvents: Biocompatible Ionic Liquids. *Crystals*, *12*(12), 1776.

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