

Manuscript title: Self-emulsifying Drug Delivery System of Tocotrienols: Concise Review on Pharmacokinetics

Manuscript ID: pharmaceuticals-2489878

Thank you for reviewing our manuscript. Your comments are much appreciated and they are responded as the following with changes highlighted in the revised manuscript:

Reviewer 3

Comment: The author must add other technologies and make some comparisons with SEDDS for better understanding (to enhance the solubility and bioavailability of Tocotrienols).

Reply: Thank you for your suggestion. I already added a few technologies to make the comparison with SEDDS.

“Nanocarriers like solid-lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and polymeric nanoparticles have also been used as vitamin E delivery platforms. SLNs comprise a lipid monolayer surrounding a hydrophobic solid-lipid core, enabling lipid-soluble substances to be incorporated. NLCs, considered the second generation of SLNs, involve the mixture of solid and liquid oil matrices to form a solid colloidal dispersion with particle sizes ranging from 10 to 1000 nm [66]. Mixing lipids with low and high melting points results in irregularities in the crystalline lipid core of NLCs, enhancing their capacity to incorporate compounds [67]. This characteristic offers benefits, especially when dealing with lipophilic compounds such as tocotrienols. A previous study demonstrated that NLCs outperform SLNs in stability and compound loading [68]. Nanoparticles made from polymeric materials consist of amphiphilic polymers with multiple polymer chains exhibiting varying degrees of hydrophobicity. These polymers form self-assembled micelles in an aqueous solution [69]. The active compounds and polymers are dissolved in organic solvents that are immiscible with water, and they are mixed while constantly stirring, resulting in the formation of nanoparticles ranging in size from 10 to 170 nm. Examples include a hybrid system using poly (lactic-co-glycolic) acid (PLGA) and chitosan prepared by synthesizing PLGA-tocotrienol copolymer [70]. Polymers have been demonstrated to provide numerous advantages, especially in improving the solubility and bioavailability of lipophilic substances, such as vitamin E. Meanwhile, SEDDS nanoemulsions represent a kinetically stable mixture of two immiscible phases, aqueous and oil. This formulation yields smaller droplets in the presence of surfactants, leading to a faster lipid digestion rate [71].”

Remarks: Thank you for reviewing the manuscript again. Look forward to receiving a favourable reply from you.