A BIOCOMPATIBLE LIPID-BASED SYSTEM FOR THE ENHANCED ORAL DELIVERY OF PALM-TOCOTRIENOLS

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Tocotrienols exhibited multifaceted health benefits, catering to the needs of specific populations (Meganathan & Fu, 2016). However, being a small molecule lipophilic compound, tocotrienols require innovative delivery systems to develop products with targeted nutritional benefits. Lipid-based drug delivery system (LBDDS) provides the solution allowing end application in soft gel encapsulation. Previous studies with self-emulsifying delivery system (SEDDS) were reported to be effective in improving the oral bioavailability and biodistribution of tocotrienols by up to 2-fold enhancement (Mohamad, 2023). Nevertheless, to ensure efficient emulsification properties, water-soluble surfactants with high hydrophilic-lipophilic balance (HLB) were needed. Most of these surfactants are chemically modified by polyglycolysis of vegetable oils with polyoxyethyleneglycols (PEG) of certain molecular weight (varying from 200 to 2,000 g/mol) under heating and in the presence of an alkaline catalyst. These PEGylated compounds could cause side effects upon long-term use, including the production of anti-PEG antibodies, hypersensitivity reactions, and the accelerated blood clearance (ABC) phenomenon.

In this technology, we developed a novel formulation of tocotrienols using PEG-free and regulatory-accepted excipients, venturing into the space of clean and natural dietary supplements. The efficacy of this formulation to enhance the oral absorption of tocotrienols is comparable to marketed products that use chemically modified excipients.

THE TECHNOLOGY

We successfully developed a bioenhanced delivery system for tocotrienols using naturally-derived excipients for enhanced oral absorption. This formulation is designed for use as a pre-mixed ingredient primarily for soft-gel encapsulation, also suitable to be used in formulations for functional food and health supplements.

METHODOLOGY (FIELD TRIAL STUDY)

A single dose bioavailability study was conducted in female Sprague Dawley rats aged between 4–6 weeks, randomised to two groups (n = 6) receiving the following treatments: 1) Tocotrienol-rich fraction diluted in palm olein (Reference Group); 2) PEG-free formulation containing tocotrienol (PEG-free SEDDS). Treatments were given via oral gavage with the volume of preparations being adjusted to less than 1.2 mL. At 0.0, 0.5, 2.0, 4.0, 6.0, 8.0, 10.0 and 24.0 hr post-treatment, blood samples (0.5 mL) were collected and analysed for tocotrienol concentrations.

The Reference Group showed a typical oral absorption profile of tocotrienols with a gradual increase within the first 4 hr, the highest plasma concentration detected between 4–6 hr, and returned to baseline within 24 hr (*Figure 1*). A typical dual-peak profile due to entero-hepatic recirculation was observed in all tocotrienol isomers from the Reference Group. In contrast to the Reference Group, groups treated with PEG-free SEDDS showed a rapid absorption within the first 0.5 hr. Plasma concentration of tocotrienols was distinctively higher compared to Reference Group in most time points. For alpha-tocopherol, the plasma concentration over time profile showed negligible difference in PEG-free SEDDS compared to Reference Group. Endogenous alpha-tocopherol was observed in all time points, remained high at baseline and 24 hr post-administration. Pharmacokinetic parameters were calculated using non-compartmental

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analysis for extravascular administration. The maximum concentration (C_{max}) after treatment of PEG-free SEDDS showed 2.2-, 3.0- and 3.9-fold higher than the Reference Group for α-, γ-, δ-tocotrienol, respectively. Up to 3-fold increment in area under the curve (AUC) was observed in the group treated with PEG-free SEDDS. Relative bioavailability (F_{rel}) was enhanced by at least 200%–300% in PEG-free SEDDS Group, calculated based on AUC_{0-24}.

NOVELTY OF THE TECHNOLOGY

This technology describes a food grade self-emulsifying formulation (SEDDS) using naturally-derived and PEG-free excipients, shown to improve the solubility and oral absorption of vitamin E, especially palm-tocotrienols. The formulation is designed for use as a pre-mixed ingredient primarily for soft-gel encapsulation, also suitable to be used in formulation for functional food and health supplements.

BENEFITS AND ADVANTAGES

1. Superior formulation as substitution of current tocotrienol products.
2. Clean label formulation suitable for applications to other oil-based nutraceutical ingredients.
3. Food grade ingredients.
4. Superior absorption of tocotrienols extends the application to health supplements, nutrition, functional ingredients and functional food products.

ECONOMIC ANALYSIS

Economic analysis	Value
Capital investment (manufacturing plant)	RM2,000,000.00
Production capacity	1,000 kg / year
Net present value (NPV)	RM1,411,708.00
Internal rate of return (IRR)	35%
Benefit-cost ratio (BCR)	1.82
Payback period	2.22 year

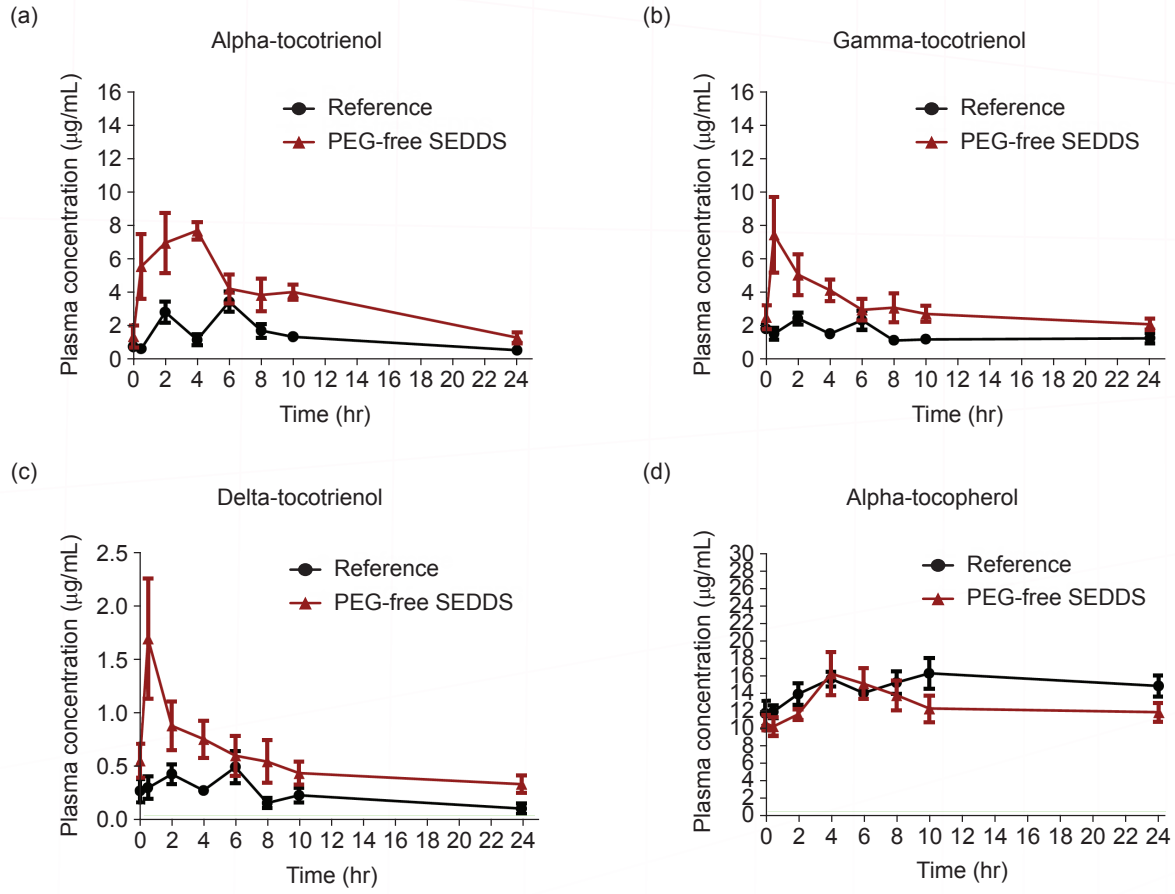

Figure 1. Plasma concentration over time profile for (a) alpha-tocotrienol, (b) gamma-tocotrienol, (c) delta-tocotrienol and (d) alpha-tocopherol after a single dose oral administration PEG-free bioenhanced formulation (red) and Reference (black).

BENEFITS/COMMERCIALISATION POTENTIAL

In this work, we systematically investigated the replacement of PEG-surfactants in SEDDS formulations of palm-tocotrienols. This project aims to resolve the PEG-dilemma limited by the detrimental side effects after prolonged use, especially important for the nutraceutical and health supplements industry. In a proof-of-concept pre-clinical study, this formulation showed enhanced oral bioavailability of palm-tocotrienols that was comparable to marketed products.

IMPACT

This research highlights the prospective application of PEG-free surfactants to improve the oral delivery of tocotrienols, making it a promising strategy for enhancing oral bioavailability and facilitating their absorption. This development offers exciting possibilities for the design and formulation of efficient drug delivery systems, offering an attractive approach for a new product range for clean and natural labels.

CONCLUSION

Self-emulsifying drug delivery systems (SEDDS) for palm-tocotrienols were developed using PEG-free surfactants and co-surfactants. From pre-clinical study, PEG-free SEDDS demonstrated enhanced tocotrienol bioavailability between 200%–300% after a single dose oral administration, comparable to commercially available SEDDS formulated using synthetic surfactants.

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