formulation

An introduction to self-emulsifying nutraceutical delivery systems (SENDS)

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Like their counterparts in the pharmaceutical industry, many dietary ingredients are poorly soluble. This article describes how self-emulsifying nutraceutical delivery systems improve solubility and enable formulators to deliver these difficult ingredients in solid dosage form.

The nutraceutical benefits of medium-chain triglycerides (MCTs) are well known. The primary benefit: MCTs are quickly converted in the liver to energy-providing ketone bodies like beta-hydroxy butyrate and acetoacetate. These ketone bodies can be employed as energy substitutes for glucose. For that reason, MCTs have been widely studied and are employed as a dietary treatment for numerous disease states, including epilepsy, Alzheimer's disease, Parkinson's disease, ischemia brain injury, and diabetes [1, 2]. Other research has documented the benefits of a ketogenic diet supplemented with MCT in weight loss, athletics, and energy and replenishment [3].

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In addition to those therapeutic uses of MCT, it can serve as an important primary solubilizing excipient in self-emulsifying nutraceutical delivery systems (SENDS). Other ingredients commonly used as solubilizers in SENDS include long-chain triglycerides and natural oils. As oil-in-water emulsions, SENDS enable formulators to deliver active nutraceutical ingredients (ANIs) composed of triglycerides and/or natural oils, mono- and di-glyceride emulsifiers, and surfactants.

Like many of today's active pharmaceutical ingredients (APIs), a number ANIs exhibit poor aqueous solubility and thus poor bioavailability. Limited bioavailability, in turn, can restrict an ANI's therapeutic efficacy. By formulating a SENDS that delivers the ANI in the form of a highly dispersed micellar system, dissolution of the ANI can reach a molecular level that improves its overall solubility in the digestive system. That ultimately leads to greater absorption of the ANI and better bioavailability and therapeutic efficacy.

Poorly water soluble ANIs include fat-soluble vitamins (A, D, E, and K), botanical actives (carotenoids like lycopene and ß-carotene), as well as other popular nutraceutical supplements, such as co-enzyme Q10 (CoQ10) and quercetin [4]. The practically insoluble nature of these ANIs makes them ideal candidates for a SENDS formulation.

Typical components of a SENDS pre-concentrate

Typically, a SENDS comprises the ANI dissolved in a combination of solubilizer, emulsifier, surfactant, and co-surfactant. This mixture is referred to as the pre-concentrate.

Solubilizers. These are typically fully esterified medium- or long-chain lipids that are manufactured by esterification of fatty acids to a substrate, typically glycerol or propylene glycol. The glycerides that result are highly lipophilic and can dissolve very hydrophobic ANIs.

Emulsifiers. These are typically partially esterified lipids manufactured by the partial esterification of glycerol or propylene glycol with fatty acids. Depending on the fatty acid chain length and degree of esterification, these emulsifiers can be manufactured to generate different hydrophilic-to-lipophilic balances (HLBs). In certain cases—depending on the HLB of the ANI—a partially esterified lipid can serve as a primary solubilizer.

Surfactants and co-surfactants. Manufacturing an optimal SENDS formulation—a stable, finely dispersed ANI-carrying oil-in-water emulsion—often requires high concentrations (greater than 30 percent) of surfactants and co-surfactants. The most common types of surfactants and co-surfactants employed in SENDS formulations are pegylated esters, polyethoxylated sorbitan esters, and polyethoxylated glycerides. Pegylated esters are manufactured through the esterification of polyethylene glycol with respective fatty acids. Polyethoxylated castor oil is prepared by reacting ethylene oxide with castor oil, and polyethoxylated sorbitan esters are made through the esterification of polyethoxylated sorbitan with respective fatty acids after the cyclization of sorbitol.

Formulating the pre-concentrate

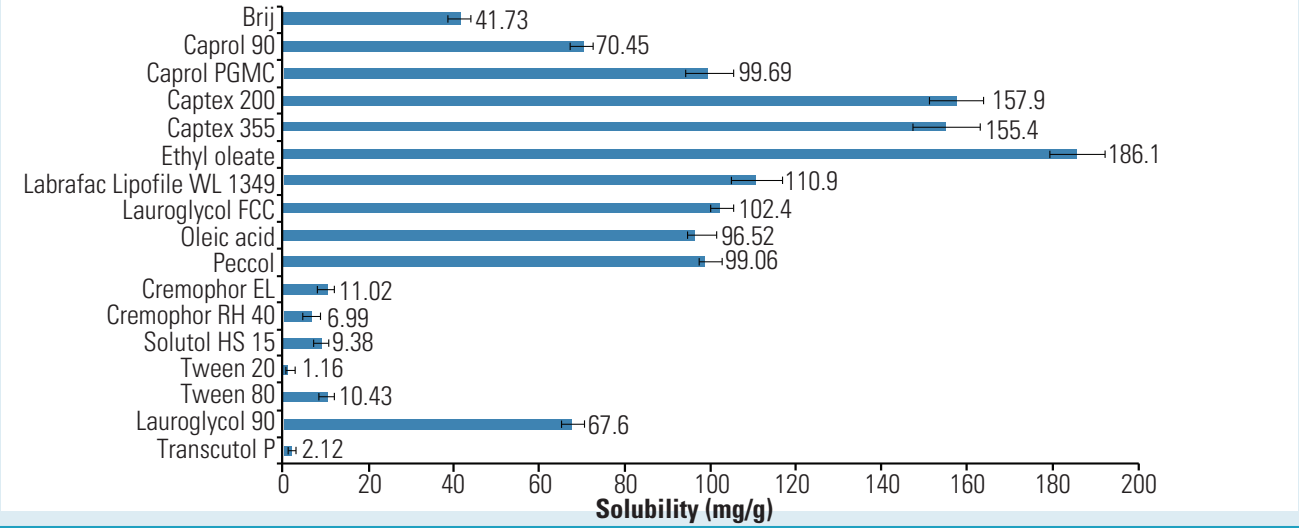
There are four general steps to formulating a SENDS pre-concentrate:

- Select the pre-concentrate component candidates;
- Determine the ANI's maximum solubility in the pre-concentrate component candidates;
- Determine the emulsions' characteristics after diluting the pre-concentrate in aqueous media; and
- Assess the in vitro dissolution of the ANI from the pre-concentrate formulation.

Select the pre-concentrate component candidates. First, determine the aqueous solubility, log P, melting point, and solubility parameter of the API. Typically, a log P greater than 4 indicates that a fully esterified lipid should be employed as the primary solubilizer [5]. By matching the HLB of the ANI to the HLB of the proposed SENDS components, one can select the SENDS pre-concentrate solublizers and emulsifiers to conduct additional studies on maximum solubility.

FIGURE 1

Solubility of CoQ10 in various excipients [7]



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Determine the ANI's maximum solubility. This entails adding an excess of ANI to each of the SENDS pre-concentrate candidate components, individually or in selected combinations. Once the ANI is added, the component-ANI mixtures are vortexed to ensure the ANI is randomly distributed within them. These vortexed combinations are then agitated for 24 hours at 37°C and allowed to stand for 24 hours at 25°C. Next, the solutions are filtered and analyzed for ANI content to determine the maximum ANI solubility in each pre-concentrate candidate.

Determine the emulsions' characteristics. After determining their maximum solubility, the selected SENDS pre-concentrate components are plotted on a phase diagram. Typically, SENDS components are plotted on two vertices of a simplex and water is plotted on the third vertex. Subsequently, binary or pseudo-binary mixtures of the pre-concentrate components are diluted systematically with water, and the phase characteristics of these combinations are observed. Characteristics of interest include clear emulsion formation, emulsion globule size, and phase separation. Emulsion globule size and the stability of the globules are of specific interest because those characteristics can ultimately affect the absorption of the ANI and, therefore, the ANI's bioavailability.

Assess the dissolution characteristics. In vitro dissolution testing is required to demonstrate an improvement in the ANI's aqueous solubility in the optimized SENDS formulation compared to the same ANI in a non-SENDS formulation. Additionally, dissolution testing allows observation of the SENDS formulation's phase behavior under stirred sink conditions. Dissolution parameters and media can be adjusted on an individual formula basis as required. Researchers at St. John's University have suggested an in vitro dispersion test, which employs USP apparatus 2 (0.01N HCl, 37°C, 50 rpm) [6]. The ANI concentration and the emulsion's globule size are analyzed over time during the test to observe both dissolution and phase behavior of the oil-in-water emulsion.

Applications

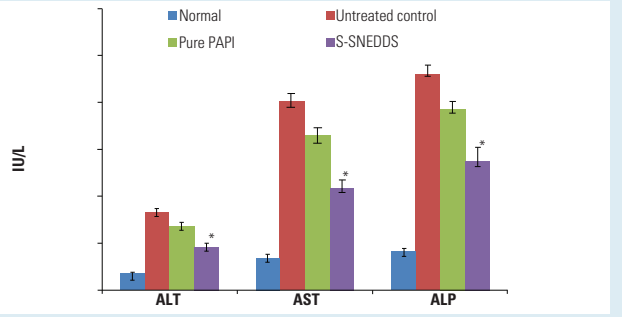
SENDS are suitable for formulating a variety of ANIs, including CoQ10, vitamin E, and quercetin.

CoQ10. This ANI is an endogenous cellular anti-oxidant that is vital for maintaining human health. It is a supplement used by people with various disease states, including diabetes and neurodegenerative disorders [7]. To improve its solubility, Agrawal et al. formulated CoQ10 in a series of SENDS and loaded the individual pre-concentrates onto a silica carrier. Theses formulations were evaluated for dissolution and hepatoprotection against pure CoQ10.

All of the Agrawal SENDS formulations—comprising a primary solubilizer, emulsifier, surfactant, and co-surfactant—underwent emulsification to micro-emulsions (globule size of less than 200 nanometers) upon contact with an aqueous environment. The SENDS formulations attained complete dissolution of the CoQ10 in approximately 30 minutes, while the pure ANI exhibited no dissolution in the aqueous media. Additionally, the SENDS

FIGURE 2

Effects of CoQ10 on CCl4-induced changes in serum ALT, AST and ALP levels (surrogate biomarkers for hepatic injury) [7]



Notes: Data are expressed as mean ± standard deviation.
Asterisk denotes $P < 0.05$ as compared with pure API treated group.

formulations provided better hepatoprotection than pure CoQ10, according the results of a CCl4 hepatic challenge, as is demonstrated by the reduction in serum alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP). See Figure 2. This result is indicative of better bioavailability and therapeutic effect of the CoQ10 due to improved dissolution of the ANI from the SENDS formulation.

Vitamin E. This fat-soluble anti-oxidant interrupts the propagation of free radicals in biological membranes and is a necessary dietary component. Julianto et al. conducted a bioavailability study that compared a standard vitamin E softgel against a SENDS formulation of vitamin E [8]. The SENDS formulation was composed of palm oil, an MCT-rich oil, polysorbate 80, and sorbitan oleate. Each formulation contained 400 IU of vitamin E. The formulations were evaluated for overall bioavailability in healthy human volunteers. The SENDS formulation was found to have a higher maximum serum concentration (C_{max}) and reached it more rapidly (T_{max}). Furthermore, its bioavailability was nearly three times that of the softgel formulation, as determined by the area under curve (AUC). No significant difference in the elimination half-life of the two formulations was observed.

Quercetin. This polyphenolic flavonoid has a wide spectrum of pharmacologic actions, including antiviral, antidiabetic, anti-inflammatory, neuroprotective, and antiproliferative properties. Quercetin exhibits the highest antiradical properties of all the flavonoids [9]. As such, it is a valuable nutraceutical, however, its low aqueous solubility limits its therapeutic use.

Sanyog et al. studied the effects of both a SENDS formulation of quercetin and a formulation of free quercetin on the following: 1) quercetin uptake by caco-2 cells, 2) cell cytotoxicity, 3) in vivo pharmacokinetics, and 4) ability of quercetin to act as a prophylaxis (administered daily 3 days prior to challenge) and as a therapy (administered immediately after challenge) to inhibit drug-induced toxicity due to the oxidative effects of doxorubicin and cyclosporine A.

The SENDS formulation comprised quercetin dissolved into a pre-concentrate composed of 40:40:20 w/w of Capmul MCM (a medium-chain mono- and di-glyceride), polysorbate 20, and ethanol. Capmul MCM was chosen as

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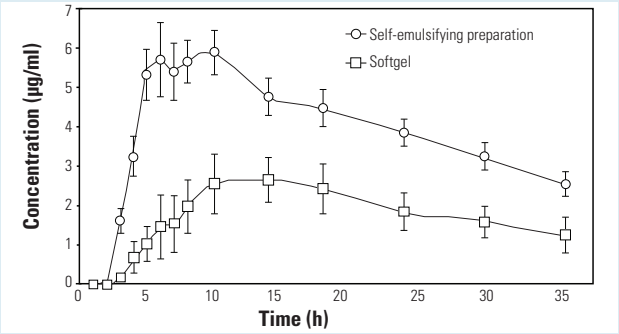
FIGURE 3

Mean plasma concentrations of vitamin E [8]



Notes: Results show plasma concentration (± SEM, n = 8) of gamma tocopherol as a function of time following oral administration of vitamin E (400 IU) in form of self-emulsifying preparation and softgel capsule after subtraction of endogenous vitamin E from each subject.

TABLE 1

Pharmacokinetic parameters following vitamin E administration [8]

Subject	Softgel				Self-emulsifying preparation			
	C_{max} (µg/ml)	T_{max} (h)	$AUC_{0-\infty}$ (h • µg/ml)	$t_{1/2}$ (h)	C_{max} (µg/ml)	T_{max} (h)	$AUC_{0-\infty}$ (h • µg/ml)	$t_{1/2}$ (h)
1	7.4	10.0	254.9	20.4	7.6	5.0	275.3	22.6
2	1.0	8.0	10.0	15.4	3.8	10.0	133.2	18.6
3	3.7	14.0	98.6	14.3	6.3	7.0	224.5	22.1
4	2.1	14.0	61.8	20.9	5.5	10.0	196.4	23.3
5	3.3	14.0	117.2	18.6	7.4	10.0	280.3	21.9
6	1.0	14.0	36.1	14.8	7.5	7.0	194.5	14.1
7	2.0	14.0	71.7	21.3	3.7	5.0	118.6	19.0
8	3.5	8.0	106.4	18.5	10.7	6.0	262.6	20.1
Mean	3.0	12.0	94.6	18.0	6.6	7.5	210.7	20.2
SD ±	2.1	2.8	80.0	2.8	2.3	2.2	63.0	3.0

the primary solubilizer due to its relatively high loading capacity for quercetin (approximately 30 grams per gram). Overall, the SENDS formulation exhibited greater quercetin cell uptake (approximately 24 times higher than free quercetin), no significant cell toxicity compared to free quercetin and quercetin-free pre-concentrate components, significantly increased bioavailability compared to free quercetin, and enhanced cardio-protective (doxorubicin challenge) and nephroprotective (cyclosporine A challenge) activity compared to free quercetin.

Conclusion

Many ANIs exhibit significant solubility challenges that present a barrier to therapy. SENDS constitute an excellent strategy for improving the solubility of these ANIs, thereby increasing their therapeutic utility and efficacy. By dissolving the ANI in an optimized group of pre-concentrate ingredients, the ANI can be carried in a finely dispersed oil-in-water emulsion in the aqueous environment of the gastrointestinal tract, leading to increased solubility and absorption. The ANI-containing pre-concentrate can be readily formulated as a liquid, liquid-filled softgel, or

FIGURE 4

Plasma concentration of quercetin after a single dose of a SENDS formulation and a free quercetin formulation [9]

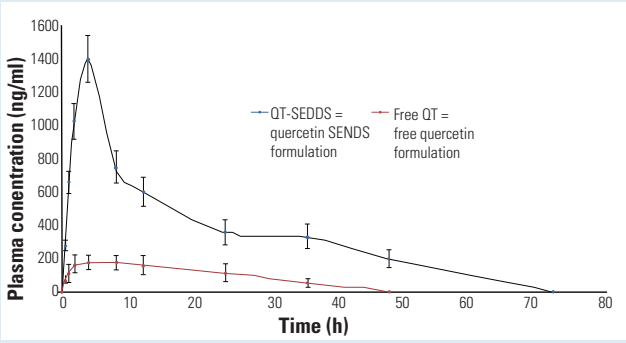
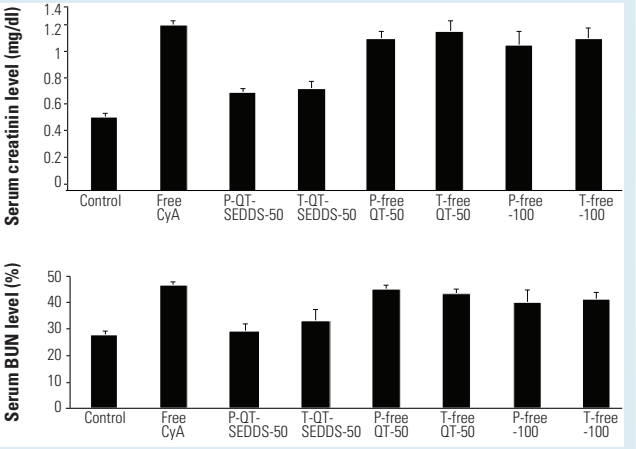


FIGURE 5

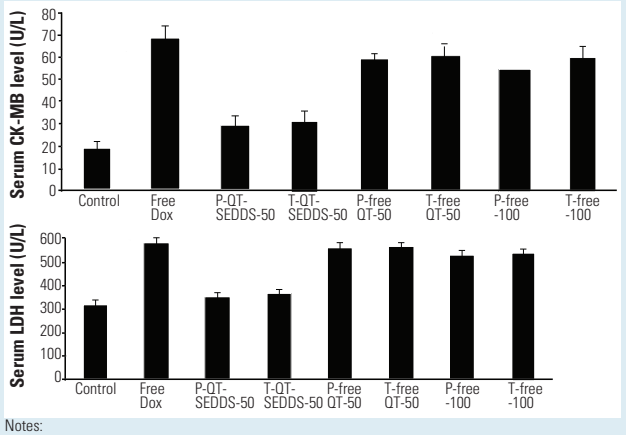
Nephroprotective effect markers after cyclosporine A challenge [9]



Notes:
CyA = Cyclosporine A
P-QT-SEDDS-50 = Prophylactic quercetin SENDS formulation 50 mg/kg dose
T-QT-SEDDS-50 = Therapy quercetin SENDS formulation 50 mg/kg dose
P-free QT-50 = Prophylactic free quercetin formulation 50 mg/kg dose
T-free QT-50 = Therapy free quercetin formulation 50 mg/kg dose
P-free-100 = Prophylactic free quercetin formulation 100 mg/kg dose
T-free-100 = Therapy free quercetin formulation 100 mg/kg dose

FIGURE 6

Cardioprotective effect markers after doxorubicin challenge [9]



Notes:
Dox = Doxorubicin
P-QT-SEDDS-50 = Prophylactic quercetin SENDS formulation 50 mg/kg dose
T-QT-SEDDS-50 = Therapy quercetin SENDS formulation 50 mg/kg dose
P-free QT-50 = Prophylactic free quercetin formulation 50 mg/kg dose
T-free QT-50 = Therapy free quercetin formulation 50 mg/kg dose
P-free-100 = Prophylactic free quercetin formulation 100 mg/kg dose
T-free-100 = Therapy free quercetin formulation 100 mg/kg dose

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liquid-filled hard capsule for per-oral administration. Additionally, the pre-concentrate can be layered onto multi-particulate systems and then filled into hard capsules.

Additionally, lipid-based excipients are being employed in a variety of new areas of drug delivery, ranging from spray-congealing for solid oral dosage forms to applications of nano-structured lipid carriers for the noninvasive delivery of macromolecules. The versatility and functionality of today's lipid excipients provides formulators with numerous options and capabilities to address and overcome many delivery and performance challenges. While there remains a need to further understand the physical and chemical stability of various ANI classes within lipid-based systems, it is clear that lipids will play an expanding and pivotal role in enhancing the bioavailability of poorly soluble ANIs. *T&C*

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