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Lyotropic liquid crystalline phases for the formulation of future functional foods

Abstract

The especial features and advanced characteristics of Lyotropic Liquid Crystalline (LLC) phases as potent nano materials for encapsulation and the development of novel delivery systems for nutraceuticals and other bioactive compounds are reviewed. Exemplary, a focus is set on the health benefits of flavonoids and their current restrictions in bioavailability. Accordingly, our visions for application of LLC phases in the engineering of enhanced flavonoid-based food supplements and correlated challenges to overcome are highlighted.

Keywords: lyotropic liquid crystals, isasomes, mesosomes, cubosomes, polyphenols, flavonoids, smart foods, nano structured functional foods

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Introduction

Nanostructures Formulation for Food Products: Advances in soft matter nanotechnology are increasingly being realised to offer smart and generic solutions in various production fields including food and agriculture industries.[1] In recent years there have been several studies reporting on nano medicinal applications of Lyotropic liquid crystalline (LLC) phases like in development of novel contrast enhancers for magnetic resonance imaging (MRI).[2,3] Within the food and pharmaceutical research, LLC nano materials have shown potentials in the development of novel delivery systems.[4–6] These nanostructures are self-assemblies of naturally occurring surfactant-like lipid molecules which are closely related to those observed in biological membranes and empower the formation of efficient delivery matrices due to their impressive characteristics:[6] (i) their great interfacial area per volume ratio allow high compound loads; (ii) sustained or controlled release of compounds is supported due to their special and tuneable narrow channel networks (typically, few nano meters thick water-channels); (iii) loading of bioactive molecules with different physicochemical properties is possible, e.g., highly water-insoluble nutraceuticals can be incorporated; (iv) their effective encapsulation capabilities enhance the stability, improve bioavailability and reduce possible toxicity of administered drugs, and (v) their good bio membrane absorption properties increase the compounds transdermal penetration.

Various types of LLCs form under different conditions. Stable inverse bicontinuous cubic (V_2) phases spontaneously form with glycerol monooleate or phytantriol at excess water conditions at ambient temperature. Discontinuous phases such as the inverse hexagonal (H_2) and the inverse micellar (L_2) phase form when increasing amounts of oil are added to the LLC systems. The latter inverse structures can be imagined as isolated water droplets (e.g. L_2 phase) or separated rod-like water channels (H_2 phase) in a continuous oil phase, whereas in the V_2 phases two intertwined, continuous water channel networks are separated by self-assembled lipid bilayers of about 3nm thickness (Figure 1). We note that bicontinuous cubic phases have very good temperature stability and are relatively insensitive to even extreme variations in pH and salinity, which are normally met within the gastrointestinal tract. Their aqueous dispersions were firstly reported in 1981 by Lindström et al. in a fat digestion study.[7] Later in 1996, Landh and Larsson patented the preparation of particles comprising different types of liquid crystalline phases in their interiors.[8] These stabilized particles with Internally Self-Assembled mesophases are sometimes referred to as ISAsomes[9–11] or as in this review simply termed as mesosomes.

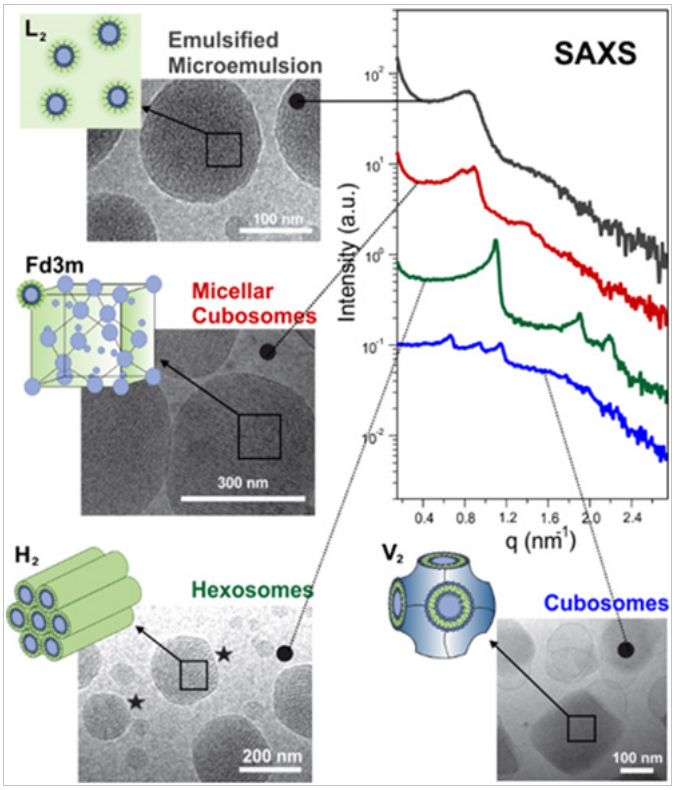

Figure 1 Cryo-TEM observations taken for four different types of monoglyceride-based aqueous dispersions[12] and corresponding Small Angle X-ray Scattering (SAXS) patterns. Control measurements carried out on empty mesosomes demonstrate the different types of delivery systems that can be designed.

Applications of the LLC bicontinuous cubic phase containing mesosomes (cubosomes) and the inverted hexagonal phase based mesosomes (hexosomes) have received considerable attention in recent years.[12–15] In particular various types of stabilizers have been tested in order to formulate mesosomes with improved physico-chemical characteristics, but also to assure food or pharmacological safety aspects, Table 1. Very recently, Pickering stabilisation, in which solid nano particles are attached to the oil-water interface[16] rather than surfactant molecules, have received greater interest in the formulation of mesosomes due to the high stability and surfactant free approach offered by this methodology.[10,17,18]

Table 1 Various types of stabilizers applied for the formulation of mesosomeS

Type of stabilizer	Stabilised internal phase
Clay mineral particles[19,20]	L_2, Fd3m, H_2,V_2*
Silica particles[17,18,21]	L_2, Fd3m, H_2 and V_2 (only partial stabilisation)
Copolymers[22–27]	L_2, Fd3m, H_2,V_2
Proteins[26,28,29]	H_2,V_2
Nanotubes[30]	L_2, Fd3m, H_2,V_2
Biopolymers[31,32]	V_2

*L_2 (inverse micellar phase); Fd3m (inverse micellar face-centred cubic phase); H_2 (inverse hexagonal phase);V_2 (inverse bicontinuous cubic phase)

Alike bulk LLC phases, mesosomes offer loading capacities for both hydrophobic and hydrophilic bioactives, and further allow sustained release of loaded material as long as highly stable and appropriately sized particles are formulated. Alternatively, other studies have pointed out, how in-situ forming depots of LLC phases can be exploited for a sustained release usage.[33] Each of the underlying mesophases vary in their suitability for different administration routes or delivery of various types of bioactive compounds with respect to optimized encapsulation and release behavior.[34] Moreover, mesosomes have the potential to protect the incorporated molecule from oxidation and biodegradation, and structural LLC transitions can be triggered via a range of stimuli including temperature and pH. The later offers the opportunity to actively modulate the delivery system and control the compound release.[34] Further, also the release time can be tuned by varying the size of the carriers, however, submicron-sized particles are commonly favoured due to their high interfacial area.

Health benefits of plant based polyphenols: Plant based bioactives especially polyphenolic compounds, are biomaterials with great potentials in the development of food supplements. Flavonoids are one of the main classes of Polyphenols consisting of two phenyl rings and one heterocyclic group. Among flavonoids anthocyanins and catechins are two main groups having several reported health benefits. For example, anthocyanins from bilberry and blueberry have shown strong intracellular antioxidant activity[35] Epigallocatechin-3-gallate (EGCG), an abundant Polyphenol in green tea, has even shown to prevent tumour formation and growth. For example, colon cancer prevention activity of tea Polyphenols has been demonstrated in animal models.[36] Similarly, lemon verbena (containing Polyphenols from a popular herbal tea) has high antioxidant activity. While many phenolic compounds have shown anticancer and antibacterial activity, efficacy in reducing oxidative stress and other health benefits *in vitro* experiments, often their function *in vivo*, in particular in human, is limited due to their reduced bioavailability or bioactivity. Identified reasons are (i) their interactions with proteins or enzymes throughout the gastrointestinal (GI) tract, (ii) poor solubility in aqueous media and (iii) interactions with the food matrix. An overview of further plant based polyphenols with their health benefits and restrictions is given in Table 2.

Table 2 Reported health benefits, health risks and restrictions of some selected natural polyphenolic compounds

Type of polyphenol	Health benefits	Health risks	Restrictions	Natural sources
Naringenin	Antioxidant, anti-inflammatory and chemoprotective activity[37]	Active chelator of metallic ions[37]	Low absorption (6%) and rapid elimination[38]	Citrus fruits
Hesperetin	Antioxidant, anti-inflammatory, blood lipid and cholesterol lowering activity[38]		Low absorption (4%) and rapid elimination[38]	Citrus fruits
Genistein	Anticancer activity[39]		Low water solubility, low absorption (9%)[40]	Pomegranate seeds[41]
Daidzein	Antioxidant activity		30% bioavailability measured in urine[40]	Pomegranate seeds[41]
Luteolin	Anticancer, anti-hypertension and anti-inflammatory activity[42]		Poor water solubility[42] low oral absorption[43]	Green pepper, celery, broccoli, and parsley

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Table continued...

Type of polyphenol	Health benefits	Health risks	Restrictions	Natural sources
Apigenin	Anti-inflammatory, antioxidant and anticarcinogenic activity[44]		Poor water solubility and unsatisfactory cutaneous permeability[44] Low absorption (1.2%)[45]	Parsley and onion[44]
Quercetin	Anticancer activity (breast, lung and prostate cancer)[46]	Interactions with soy proteins[47]	Limited bioavailability, reduced antioxidant activity through interactions with proteins[48]	Berries
Kaempferol	Antioxidant, anti-inflammatory, antimicrobial, anticancer, cardioprotective, neuroprotective, antidiabetic activity[49]		Poor water-solubility and low bioavailability (2%)[50]	Broccoli, apples
Tiliroside	Antioxidant activity,[51] Inhibiting of neuroinflammation,[52] anti-hyperglycemic effects[53]		Inhibitory effects on carbohydrate digestion[54]	Potentilla species[53]
Epigallocatechin-3-gallat (EGCG)	Neuroprotective, stroke risk lowering[55] and anticancer (colon cancer) activity[36]	Complex formation thorough interaction with proteins[56,57]	Low bioavailability (0.2-2%)[58]	Green tea
Cyanidin	Anticancer (skin and colon cancer)[59] and anti-diabetic activity[60]		Low bioavailability (<1%) and unstable *in-vivo*[61,62]	Wild mulberry/ raspberries

LLCs as the basis for novel food supplements: The applications of LLCs in encapsulation and the delivery of pharmaceuticals have been widely considered in recent years. Camptothecin,[15] protopanaxadiol,[63] dacarbazine[64] and fluorouracil[65] are the examples of nutraceuticals encapsulated into cubosomes in order to improve their delivery and hence their therapeutic behaviour. A comprehensive list of various bioactive molecules loaded into mesosomes have been reported recently in a review by Chong et al.,[4] Nevertheless, the opportunities for enhancing the nutritional values of food by addition of flavonoids are largely unexploited. In particular, the interactions of flavonoids with lipid self-assemblies, formulation of polyphenol-rich mesosomes and eventually engineering of nano structured food supplements with proper taste, stability and digestibility behaviour are scarcely considered. In this respect, the challenges for highly stable and effective encapsulation of flavonoids through formulation of fully food-grade mesosomes which are able to protect bioactives throughout the different digestion stages and guarantee efficient delivery to the small intestine, still remains an essential task for the development of future functional food.

Conclusion

LLC mesosomes are potential nano materials to overcome the challenges concerning the restricted bioavailability, and thus, limited health benefits of current flavonoid-based food supplements. The flavonoids interactions with, and their release behaviour from various types of mesosomes have yet to be understood and further studies are required in order to provide intelligent formulations of mesosomes loaded with flavonoids as future smart food supplements.

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Conflict of interest

Author declares that there is no conflict of interest.

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