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Recent Dispersion Technology Using Liquid Crystal

Yuji Yamashita

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Abstract

Lyotropic liquid crystals have prospective potentials for several industrial applications and also being a key technology in terms of the quality assurance of a product, drug carrier, as well as interpretation of biological phenomena. This chapter will provide the recent topics on several applications of liquid crystals in the cosmetic and pharmaceutical fields and review how to generate the lyotropic liquid crystals in the amphiphilic material system on the basis of the phase behavior and why the liquid crystal structure can impact the respective application.

Keywords: liquid crystal-based emulsification, nanoemulsion, vesicle, cubosome, hexosome, drug delivery vehicle

1. Introduction

In a few decades, formulation technology in the fields of cosmetics and pharmaceuticals has evolved owing to the advanced nanotechnologies involving theory, computational simulation, and analytical devices, and nowadays, various forms such as a capsule, tablet, poultice, and liquid emulsion can be designed in consideration of usability, quality assurance, as well as efficacy of an active ingredient. Colloid science is a very strong tool to understand and control these points and eventually most of formulations regardless of soft and hard matters. In addition, the stuff we are made of, blood, organ, and bone, contains colloidal particles. Since the industrial era, new kinds of colloid-containing products, including paint, foam, pastes, and so on, have been developed.

The colloidal system is referred to be a system in which one phase is homogeneously dispersed in another phase. It seems to be the similar relation of solute and solvent, while this dispersion system should be little soluble mutually. Both the dispersed phase and continuous phase are

in gas, liquid, solid states, and may be in liquid crystal (LC) state, and generally many industrial products can be categorized by these phase states (**Figure 1**) [1]. Typically, the emulsified products such as milk consist of oil (oil phase) and water (aqueous phase), namely being a liquid-liquid dispersion system. When one liquid is dispersed in another liquid, the dispersion system would be called “lotion” for a transparent solution or “emulsion” for a turbid solution. Thus, the colloid dispersion system can be classified into two types, in which one is “molecular colloid” or “association colloid,” and the other “dispersed colloid.” The molecular colloids are known to be formed in polymer solutions such as starch and protein, and the association colloids are micellar solution consisting of surfactant molecules. These two colloid systems are thermodynamically stable and spontaneously formed in a solvent, generally called “solubilizing system.” This system has been utilized for cleansing, the targeting drug delivery of a poorly soluble compound encapsulated in micelle, and so on. On the other hand, the dispersed colloid is unstable and separated into two phases sooner or later, and many of formulations, such as liquid-liquid emulsion and liquid-solid suspension, are concerned.

This chapter will introduce unstable colloid dispersion systems using LC. One may have doubt on the relation between the colloid dispersion and LC. However, this intermediate state has a potential to generate new value and some liquid crystals have been already contributed to the formulation technology. Here, the following two topics will be separately mentioned because LCs are applied in different manners.

- (1) Emulsification technology using self-assemblies
- (2) LC dispersions

		Continuous Phase		
		Gas	Liquid	Solid
Dispersed Phase	Gas	None	(Foam) Hair mousse, Shave foam 	(Xerogel) Sponge, Styrofoam, Silica gel 
	Liquid	(Aerosol) Hair spray 	(Emulsion) Cream, Lotion 	(Gel) Pomade, Food gelatin, 
	Solid	(Aerosol) Powdery Spray 	(Suspension) Nail enamel, Foundation 	(Solid colloid) Colored glass 

Figure 1. Various colloidal dispersion systems [1].

The first topic will explain emulsion systems stabilized by LCs and the unique properties, and note that LC can be used as a stabilizer for emulsion. The second topic may be more common for the recent researchers of LCs and will review various LC dispersions that are prospective vehicles for the drug delivery system.

2. Lyotropic liquid crystal formed in surfactant system

First, LC used for cosmetics and pharmaceuticals is explained in brief. As known well, the LC can be classified into “lyotropic” and “thermotropic” LCs, which may be defined by their dependent parameters, concentration and temperature, respectively. In some cases, they cannot be definitively distinguished by their features, for example, the nematic phase is often observed in the thermotropic LC, but a peculiar surfactant solution system forms it at certain temperature [2]. In addition, the identical LC structure may be termed independently, for example, hexagonal LC for lyotropic system and columnar LC for thermotropic one. The principal difference between two LCs is constituent; the representative compound to form the lyotropic LC is surfactant, and the thermotropic LC is formed by anisotropic molecules with a mesogen group. Some surfactants have mesogen groups in the molecule as well, whereas the important interactions in the lyotropic LC system should be solvation and hydrophobic interaction rather than molecular interactions via the mesogen group that can provide the translational order and optical anisotropy. Therefore, most of the surfactant cannot work in the absence of solvent and rarely forms LC by itself.

The surfactant is paraphrased by amphiphiles which have the dual character, hydrophilicity and lipophilicity, derived from hydrophilic and lipophilic groups. The thermodynamic properties of amphiphiles in aqueous solution are controlled by the hydrophilic group to avoid contact with water, referring to “hydrophobic effect” [3]. This leads to spontaneous formation of micelle at lower concentration of surfactant (above critical micellar concentration, CMC) and generally liquid crystals at higher concentration. The formation of self-assembled bodies is predominantly determined by an entropic contribution which arises from the local structuring of water, known as iceberg structure.

At high concentrations, surfactants can self-assemble into lyotropic LCs and their structures depend on the concentration. **Figure 2** shows schematic structures of the series of typical lyotropic LCs formed in a surfactant system. Cubic LC is very stiff and optically isotropic, basically divided into two types: discontinuous (I_1) and bicontinuous cubic LC (V_1). These cubic LCs are furthermore classified into 230 kinds of the crystal lattice with symmetries called space group. The space group can be assigned by the characteristic reflection plane relevant to Miller indices. Hexagonal LC (H_1) has the two-dimensional structure that the infinitely elongated rod-like micelles are packed in the hexagonal array and shows optical anisotropy. Lamellar LC ($L\alpha$) consists of one-dimensionally stacked bilayers and also shows optical anisotropy. The reverse-type micelle and LCs except for $L\alpha$ are formed in the surfactant solution; reverse micelle (L_2), reverse discontinuous (I_2) and bicontinuous cubic LC (V_2), and reverse hexagonal LC (H_2).

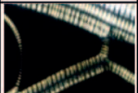
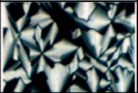
		State	CPP		Structure	Symbol	Texture
Hydrophilic Positive ↑ HLB ↓ Lipophilic Negative Curvature	Micelle		$v/al \leq 1/3$		Sphere	L ₁	—
			$1/3 < v/al \leq 1/2$		Cylinder	L ₁	—
	Liquid Crystal		$v/al \leq 1/3$		Discontinuous Cubic	I ₁	—
			$1/3 < v/al \leq 1/2$		Hexagonal	H ₁	
			$1/2 < v/al \leq 1$		Bicontinuous Cubic	V ₁	—
			$v/al \approx 1$		Lamellar	L _α	
			$1 \leq v/al$		Rev. Bicontinuous Cubic	V ₂	—
			$1 < v/al$		Rev. Hexagonal	H ₂	
			$1 < v/al$		Rev. Discontinuous Cubic	I ₂	—
	Rev. Micelle		$1 < v/al$		Sphere	L ₂	—

Figure 2. Summary of self-assembly structures formed in surfactant systems, and relationship between the structure and three parameters, critical packing parameter (CPP), hydrophilic-lipophilic balance (HLB), and interfacial curvature.

A schematic phase diagram in a binary surfactant/water system is demonstrated in **Figure 3**, indicating that all LCs not always appear over the concentration range. The type of LC formed in the system depends on the kind of surfactant, added oil, and additive as well as surfactant concentration. Temperature is also a factor to determine the micelle and LC structure. The temperature-dependent phase transitions can be observed in **Figure 3**, for example, micellar solution (L₁) → two phase (II), and hexagonal LC (H₁) → L₁. Any phase transitions in a surfactant system are always relevant to interaction between surfactant and solvent, and three important parameters, interfacial curvature, critical packing parameter (CPP), hydrophile-lipophile balance (HLB) number, prevailing in the academic and industrial fields are applied to understanding and controlling the self-assembly structures and the phase transition phenomena. The concentration-dependent LC structures can also be interpreted by these parameters.

2.1. Interfacial curvature

The LC structure is characterized by the interfacial curvature (main curvature). In principle, overall area on the interface can be defined as the mean curvature (*H*) and Gaussian curvature (*G*) using the radii of the main curvatures, *R*₁ and *R*₂

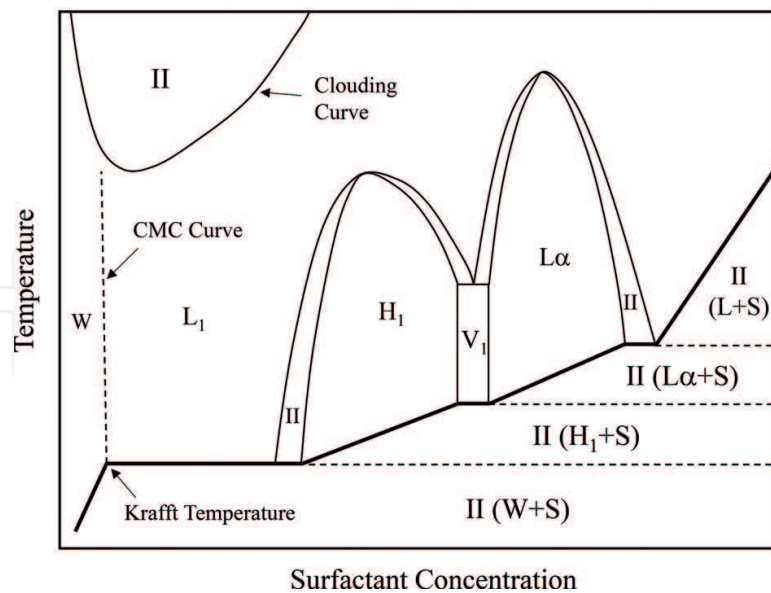


Figure 3. Schematic phase diagram of a binary surfactant/water system. W: monodispersed solution, L_1 : micellar solution, H_1 : hexagonal LC, V_1 : bicontinuous LC, L_α : lamellar LC, S: surfactant solid, and II: two phase.

$$\text{Mean curvature:} \quad H = \frac{1}{2} \left(\frac{1}{R_1} + \frac{1}{R_2} \right) \quad (1)$$

$$\text{Gaussian curvature:} \quad G = \frac{1}{R_1} \times \frac{1}{R_2} \quad (2)$$

In the case of a spherical micelle, which is formed at the low surfactant concentration, the mean curvature corresponds to $H = 1/R$ ($R = R_1 = R_2$) and the Gaussian curvature is $G = 1/R$ [2] because of its isotropic structure. On the other hand, anisotropic structures, such as cylindrical micelle and bilayer structure, give different curvatures; $H = 1/(2R_1)$ and $G \sim 0$ for the cylindrical structure, $H \sim 0$ and $G \sim 0$ for the bilayer structure. In general, the positive curvature indicates convex toward the water phase, and contrarily the negative one is concave. Thus, the curvature continuously changes from positive to negative or from large to small in the order corresponding to L_1 , I_1 , H_1 , V_1 , L_α , V_2 , H_2 , I_2 , L_2 as shown in **Figure 2**.

2.2. Critical packing parameter (CPP)

The LC structures are governed geometrically by the volume fraction of the self-assembly occupied in space of the solution and the molecular structure of surfactant composed in the system. The surfactant molecules can be arranged in a self-assembly under a given condition so that the interfacial area per molecule will be minimized in order to avoid the contact of the alkyl chain and water. The morphology of the self-assembly is determined by the balance of two opposing forces, hydrophobic attraction at the alkyl chain-water interface, and repulsive force between the head groups of surfactants (ionic repulsion, hydration force, steric hindrance, etc.). The interfacial free energy per surfactant molecule (μ_N^0) can be written as follows [4]:

$$\mu_N^0 = \gamma a + \frac{K}{a} \quad (3)$$

where K is the constant, γ is the interfacial tension, and a is the cross-sectional area of the surfactant head group at the interface. The first and second terms in the equation represent attraction and repulsion, respectively. Assuming that these interactions would operate within the same interfacial area, the optimized effective cross-sectional area per molecule (a_s) is estimated from the minimum μ_N^0 .

Israelachvili proposed “critical packing parameter (CPP),” which allows one to predict the morphology of the self-assembly [4]. CPP has the non-dimensional unit and can be calculated using the volume of alkyl chain (V_L), the length of the extended alkyl chain (l), and a_s

$$\text{CPP} = \frac{V_L}{a_s l} \quad (4)$$

CPP gives a geometric characterization of a surfactant molecule and will be seen to be very useful when discussing the type of self-organized structure formed by a given amphiphile. Considering what surfactants fall into the different categories of the self-assembly structures shown in **Figure 2**, we note that CPP characterizes the self-assembly structure, for example, the $\text{CPP} < 1/3$ for the spherical micelles (L_1, I_1), $1/3 \sim 1/2$ for the cylindrical micelles (H_1), ~ 1 for the bilayer structure ($L\alpha$). For the nonionic surfactant, CPP becomes smaller with increasing the polymerization degree of the hydrophilic group [5–7], indicating that curvature changes toward positive.

2.3. Hydrophile-lipophile balance (HLB) number

The HLB number has been utilized as a parameter which characterizes the surfactant and would be widely spreading in the industrial field because of the chain length distribution of the commercial surfactants.

HLB denotes the nature of surfactant in terms of hydrophilicity and lipophilicity. Griffin [8, 9] codified the HLB numbers for nonionic surfactants. Till now, several equations have been proposed to calculate the HLB number for different surfactants including ionic surfactants [10–14]. Generally, the HLB number can be calculated from the hydrophilic and lipophilic portions of the molecule. The HLB number is a useful parameter for selection of surfactants suitable for various applications (e.g., emulsifier, solubilizer, wetting agent, and antifoamer).

3. Formulation utilizing self-assembly

3.1. Liquid crystal emulsification

Since an emulsion is a thermodynamically unstable system, the state and stability are greatly influenced by the preparation process. This can be understood from the several emulsification

methods such as the phase inversion temperature (PIT) method [15], D-phase emulsification [16], quenching method [17], and liquid crystal (LC) emulsification [18], which are attributed to stability at the oil-water interface accumulated by surfactant molecules or self-assemblies.

The LC emulsification method was discovered by Suzuki et al. and referred to the process that an oil phase was added directly to a lamellar liquid crystal ($L\alpha$) phase, and then dispersed by agitation to produce an emulsion (**Figure 4**) [18]. The key to LC method is to select an appropriate surfactant that preferentially forms $L\alpha$ phase, as well as constituents of aqueous phase. According to CPP, the surfactant with a balanced HLB number, in general, a two tails surfactant tends to form $L\alpha$. This emulsification method is achieved in two steps corresponding to the arrows in **Figure 4**. In the first step, the oil phase is added and dispersed into the $L\alpha$ phase composed of surfactant/glycerol/water. In the second step, water is poured into the oil in $L\alpha$ (O/LC) to form an O/W emulsion. This LC method can form a stable emulsion because the LC phase is present as “third phase” surrounding the dispersed oil phase and physically prohibits coalescence of emulsion droplets. The stabilization mechanism of emulsion can be referred to the other emulsification technologies such as Pickering emulsification [19] and three-phase emulsification [20], collectively named “Active Interfacial Modifier (AIM)” [21, 22].

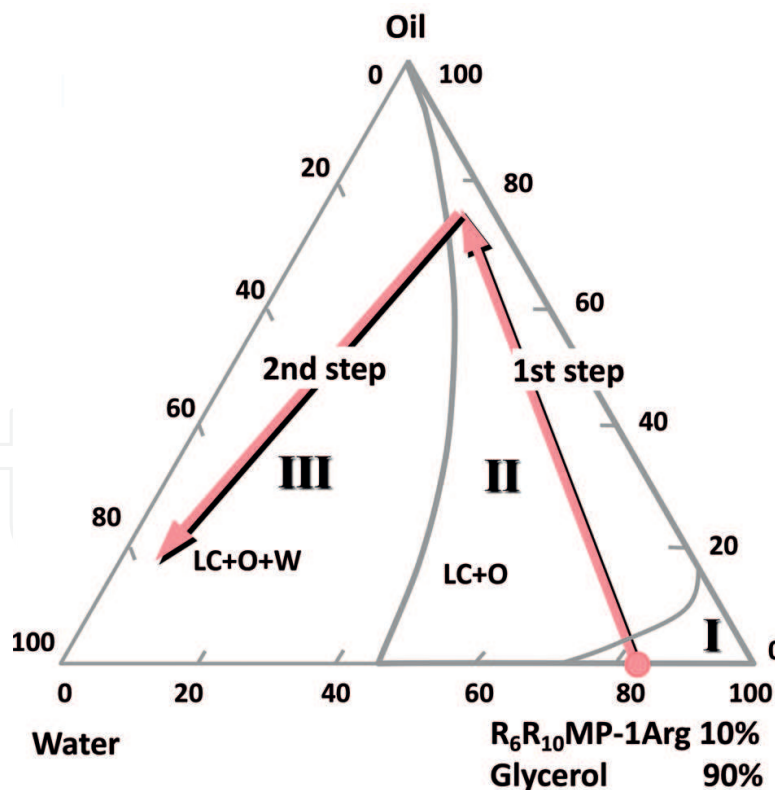


Figure 4. Procedure of LC emulsification in the ternary phase diagram of b-branched L-arginine hexyldecyl phosphate ($R_6R_{10}MP-1Arg$)/glycerol/oil/water system [18]. Premixture of $R_6R_{10}MP-1Arg$ /glycerol/water forms the lamellar LC, in which oil is added then in order to form the two phase LC+O (O/LC) (first step). Finally, O/W emulsion (LC+O+W) is obtained by adding water to the O/LC solution (second step). W: water phase, O: oil phase, and LC: liquid crystal phase.

3.2. Nanoemulsion prepared by cubic liquid crystal

Nanoemulsions are nanosized emulsions, typically, a size of tens to hundreds nanometer, which can be expected to improve the stability of emulsion and the delivery of active ingredients. The term “nanoemulsion” also refers to a mini-emulsion which is fine oil/water or water/oil dispersion stabilized by an interfacial surfactant film. According to the droplet size, the nanoemulsions are apparently transparent or translucent [23–25]. Contrary to the microemulsions, the nanoemulsions are thermodynamically unstable, yet they may have high kinetic stability. Disruption of the nanoemulsions would be processing within hours, days, or weeks through general flocculation, coalescence, and Ostwald ripening. These characteristic properties have put the nanoemulsions to practical use, such as cosmetics [26–28], pharmaceuticals [29–34], reaction media for polymerization [35, 36], and agrochemicals [37].

In industrial fields, it has been paid attention to how to formulate and prepare a stable emulsion. Two major methods for the preparation of fine emulsions are well known: dispersion or high-energy methods, and condensation or low-energy methods [23]. The high-energy method is the most popular procedures to produce a fine emulsion using specific equipment, such as high-shear stirring, high-pressure homogenization, and ultrasonication [24].

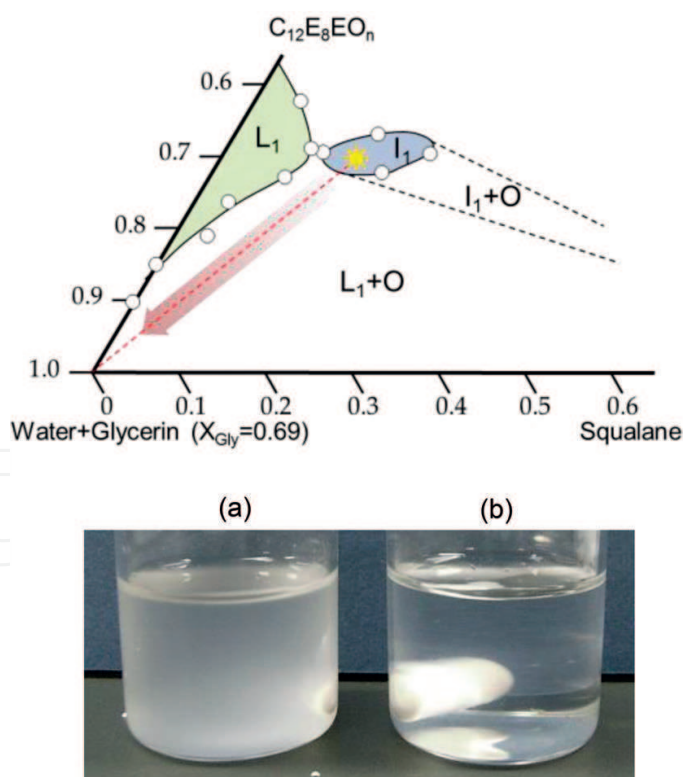


Figure 5. Quasi-ternary equilibrated phase diagram in the polyoxyethylene octyldodecyl ether ($C_{12}C_8EO_n$)/water/glycerol/squalane system at 25°C (top) [46]. The weight ratio of water/glycerol is fixed at 31/69. The arrow in the phase diagram indicates the preparation route of the novel emulsion. Bottom pictures show sample appearances of the solutions prepared by (a) simple mixing and (b) dilution method utilizing the cubic liquid crystal (I_1). L_1 : micellar solution, I_1 : discontinuous cubic LC, and O: excess oil (O).

This method, however, is not preferable from the point of environmental view because of a large amount of energy loss. On the other hand, the low-energy methods utilize unique properties of surfactant and in particular the phase transitions that take place during the emulsification process as a result of a change in the spontaneous curvature of the surfactant. The phase transition with the drastic curvature change can be driven by the phase inversion temperature (PIT) method [15, 38] and the phase inversion composition (PIC) method [39]. The preparation methods of nanoemulsions have been widely reported in the nonionic and ionic surfactant systems, by using both of the high- and low-energy methods [23, 24]. Solans et al. had thoroughly investigated low-energy input methods using PIT and PIC and successfully produced finely dispersed nanoemulsions [40–45]. It was also demonstrated that a liquid crystal formation would play an essential role in forming a fine nanoemulsion [44].

Yamashita et al. proposed a unique nanoemulsion using a discontinuous cubic LC (I_1) [46]. This nanoemulsion is simply obtained by diluting I_1 without any high-energy input (**Figure 5**). Contrary to the common emulsions, the I_1 -based nanoemulsion has an abnormal shear-response: the semi-stable structure of the nanoemulsion is breaking down gradually by applying a mechanical energy (**Figure 6**). On the other hand, H_1 and V_1 do not form such transparent nanoemulsion. Such a new type of emulsion would be applicable for cosmetics and pharmaceuticals as an external application. Since the solution transforms from nanoemulsion to emulsion when shearing force is applied, the solubility of active agent loaded in the hydrophobic compartment of the nanoemulsion should be varied. This can also modulate partition between the formulation and the skin surface (stratum corneum), which is a key factor for transdermal drug delivery systems [47, 48].

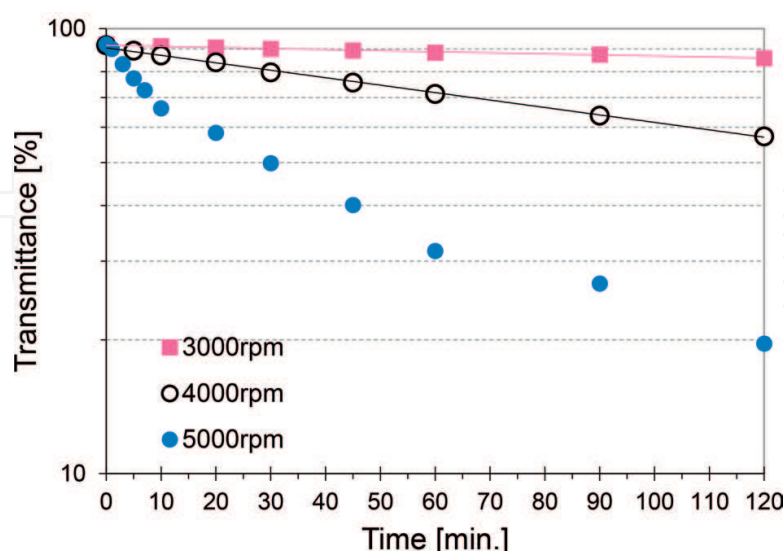


Figure 6. Change in transmittance of the nanoemulsion formed in the polyoxyethylene octyldodecyl ether ($C_{12}C_8EO_n$)/water/glycerol/squalane system as a function of time under different shearing rates; 3000 rpm (■), 4000 rpm (○), and 5000 rpm (●) [46]. The transmittance measurements were carried out using the monochromatic light source ($\lambda = 550$ nm) at room temperature. The surfactant concentration is 1.4 wt.%.

4. Liquid crystal dispersion

Liquid crystal dispersions are promising drug carriers and typically referred to vesicle (liposome), cubosome, and hexosome that have two domains to accumulate both hydrophilic and lipophilic ingredients, although the micelle or reverse micelle has either compartment.

4.1. Vesicle and liposome

A vesicle is a hollow aggregate with a shell made from one or more amphiphilic bilayers. According to the number of bilayer shell, vesicles can be roughly categorized: a vesicle with a single bilayer is called “unilamellar vesicle” and the one with a shell of several bilayers is “multilamellar vesicle (MLV).” MLV is sometimes called “onion vesicle.” **Figure 7** exhibits a unilamellar vesicle. Vesicles formed by lipids are termed “liposomes,” which are of great interest and have been widely studied because they are simple membrane models for cell. Vesicles or liposomes have no biological functionality, while vesicle formation and fusion should be important in many physiological processes. Liposomes are also important technology in cosmetics and for drug delivery. In both cases, the liposome acts as a delivery vehicle for active material contained inside. The aims of encapsulating the active materials (or drugs) in the liposome are mainly targeting and release control, whereby not only effective delivery but reduction of side-effect can be attained. However, this targeting technology has not been established yet, although gradually developed by recent studies such as protein recognition and stealth vehicle.

Vesicles (or liposomes) are usually not in thermodynamic equilibrium, while they can be kinetically stable for quite long period. As seen in **Figure 8** [49], vesicles are formed in a two-phase region, $L\alpha + W$, where excess water is separated from the $L\alpha$ phase. In such systems, the constituent molecules cannot transform to another LC when diluted with water because of their packing restriction of lipophilic chain, and instead vesicles are formed to minimize the energy loss of lamellar membrane edge (E_{edge}) [50, 51].

$$E_{edge} = 2\pi R \gamma_L \quad (5)$$

R is the radius of lamellar sheet (disk) and γ_L is the line tension. On the other hand, the bending energy (E_{bend}) should be required to form the vesicles, expressed by the following equation [52]:

$$E_{bend} = 8\pi\kappa \quad (6)$$

where k is the bending modulus. When E_{bend} is smaller than E_{edge} , vesicles are preferentially formed. The unit structure of vesicle is same with $L\alpha$ and CPPs of both morphologies are assigned to be nearly unity. According to the morphological similarities, the concentric Laphase can be reversibly transformed to a multi-lamellar vesicle (MLV) by applying a certain shearing force (**Figure 9**) [39].

Practically, unilamellar vesicles with different sizes are used for the drug delivery carrier and cell model, while the bilayers of these vesicles may have different physicochemical properties

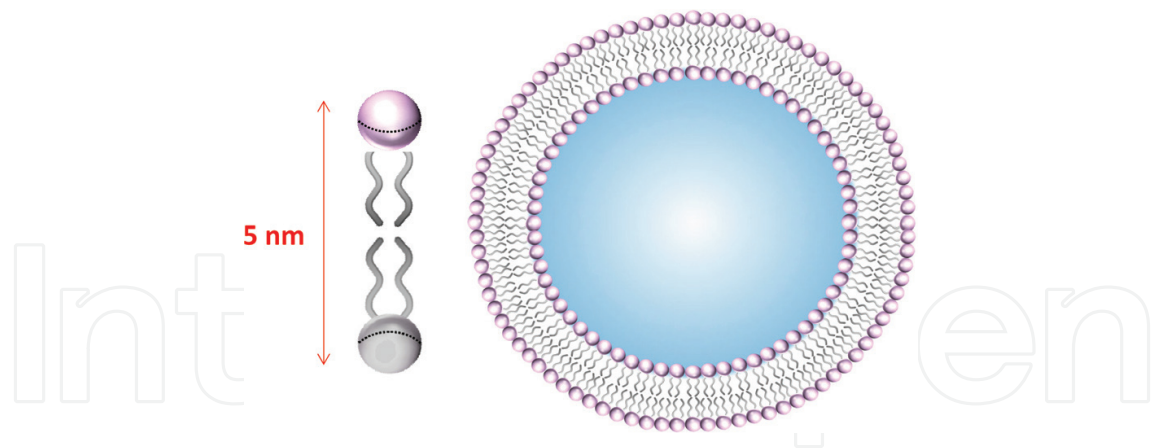


Figure 7. Schematic representation of unilamellar vesicle.

depending on the size. General unilamellar vesicles are listed in **Table 1**, where one can compare to various cell sizes [53, 54]. Regarding the topological effect of the vesicle, the surface energy depends on the curvature as expressed by Laplace equation

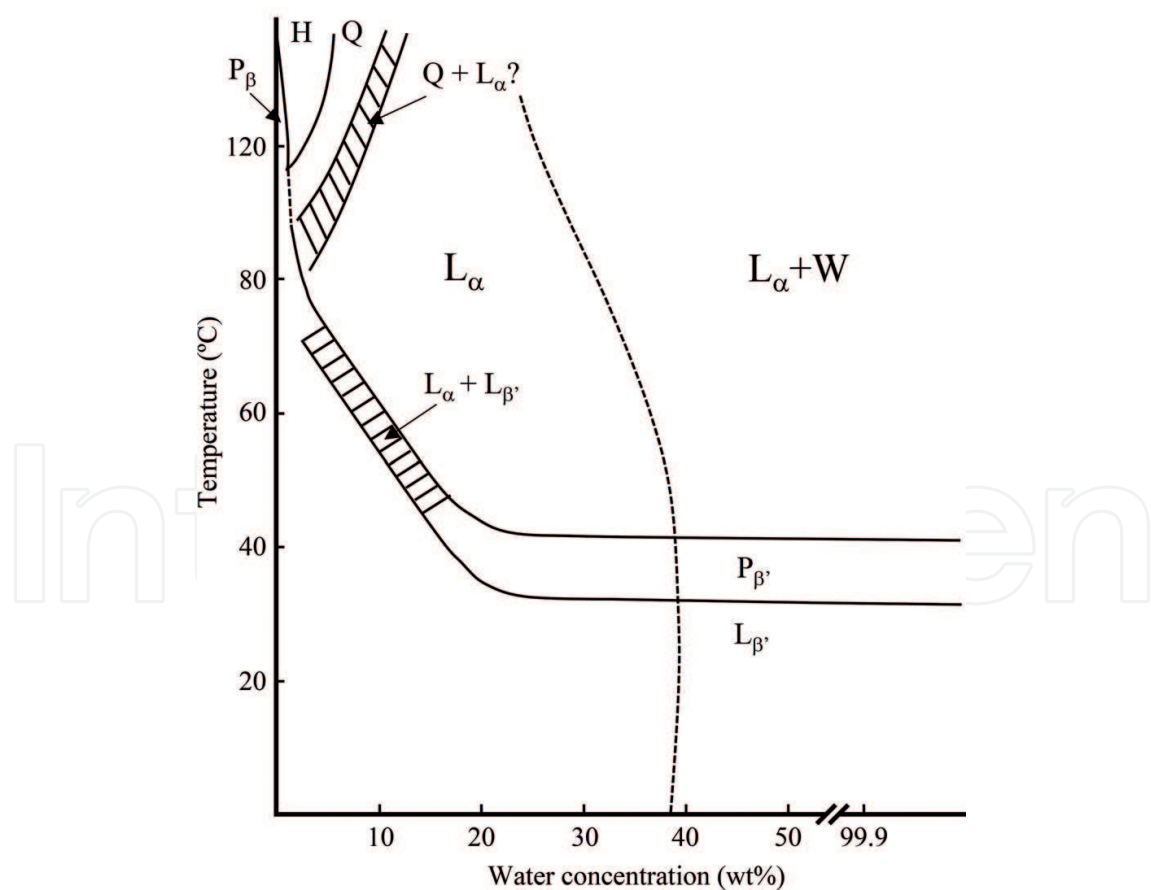


Figure 8. Phase diagram of the binary DPPC/water system [49]. La: lamellar LC, H: reverse-type hexagonal LC, Q: reverse-type bicontinuous cubic LC, P_b: flat ripple phase, P_b': non-flat ripple phase, L_b: gel phase, and W: excess water.

$$P_{in} = P_{out} + \frac{2\gamma}{r} \quad (7)$$

where P_{in} and P_{out} are the inside and outside pressure, γ is the interfacial tension, and r is the radius of curvature. As shown in **Table 1**, P_{in} for large unilamellar vesicle (LUV) and small unilamellar vesicle (SUV) are 25 and 250 times larger than giant unilamellar vesicle (GUV), respectively. In other words, E_{bend} of the membrane becomes larger with decreasing the vesicle size and then the molecules are less mobile and more ordered. Sakamoto suggested that the bilayer curvature had a significant effect on not only stiffness, but also function of the bilayer membrane [55].

Many methods can be applied to prepare various vesicles, which result in different types of vesicles and size distributions [56, 57]. First of all, it should be noted that vesicles are formed in a specific composition range depending on the kind of surfactant and phospholipid used in the system, and generally in the diluted lamellar phase which refers to the region coexisting the lamellar LC ($L\alpha$) and excess water (W) in the phase diagram. In this region, vesicles can be easily prepared by simple shaking, but many of them are MLV. Sonication is typical treatment to form vesicles with single bilayer; the high-frequency sound waves can break up the inhomogeneous stacked bilayers, inducing reassembly of bilayer. Such rough preparation produces SUV with a broad size distribution since the mechanical action is very uneven. Instead, an alternative procedure can be taken to form in particular LUV and GUV, referring to the thin film method: (1) the amphiphile is dispersed in an organic solvent, (2) the organic solvent is distilled away under vacuum to form a thin film of the amphiphile, and then (3) an excess of water is added to the thin film. In addition, dialysis and filtration (extrusion) are often utilized to fractionate the different sizes of vesicles. However, these methods deliver only formation of vesicles with a desirable size and membrane structure, and further technical methods are required to attain the prospective functions of uniform vesicles such as targeting and a large encapsulating ratio.

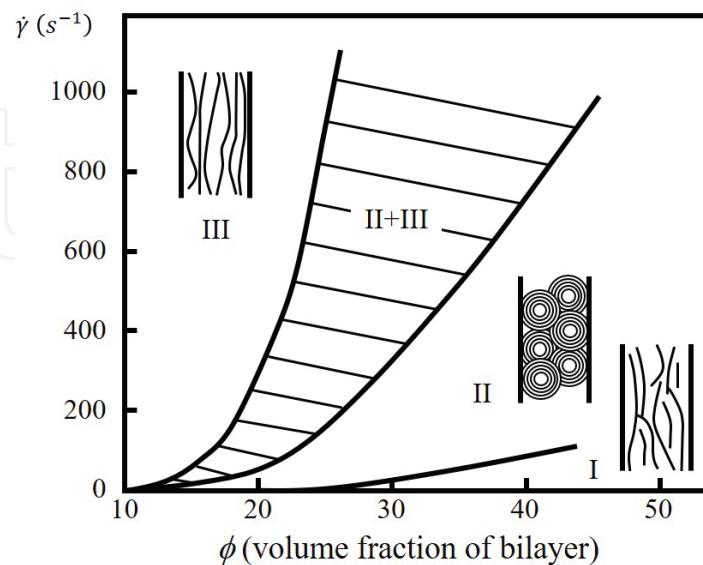


Figure 9. Dynamic phase diagram of SDS/pentanol/water/dodecane system as functions of the volume fraction of bilayer (ϕ) and shear rate ($\dot{\gamma}$) [77]. I region: defected lamellar LC, II region: multilamellar vesicle (MLV), and III region: non-defected lamellar LC.

	Size	Relative pressure difference $P_{in} - P_{out} = 2\gamma/r$
Thickness of cell membrane	ca. 5 nm	
Small virus	30 nm	
Small unilamellar vesicle (SUV)	~ 40 nm	1
Lysosomes	200–500 nm	
Large unilamellar vesicle (LUV)	~200 nm	50
<i>E. coli</i> —a bacterium	2 mm	
Human red blood cell	9 mm	
Giant unilamellar vesicle (GUV)	10 mm	250
Human egg	100 mm	

Table 1. Classification of vesicles by size and relative pressure difference by Laplace equation [53, 54].

4.2. Cubosome and hexosome

Cubosome and hexosome are aqueous dispersions of inverted-type bicontinuous cubic [58–62] and hexagonal LCs [63, 64], respectively. Such nanostructured aqueous dispersions with internal hierarchical self-assemblies have received much attention because of their potential applications such as functional food and drug carriers [65–68]. **Figure 10** shows one example of phase diagram in the monoolein/water system [69], where bicontinuous cubic LC (Ia3d, Pn3m) are observed in the composition and temperature ranges. In addition, likely vesicles, two phase, Pn3m + water, is present in the water-rich region where cubosome can be formed. The fully hydrated inverted-type LCs with distinctive nanostructures are internally confined in the

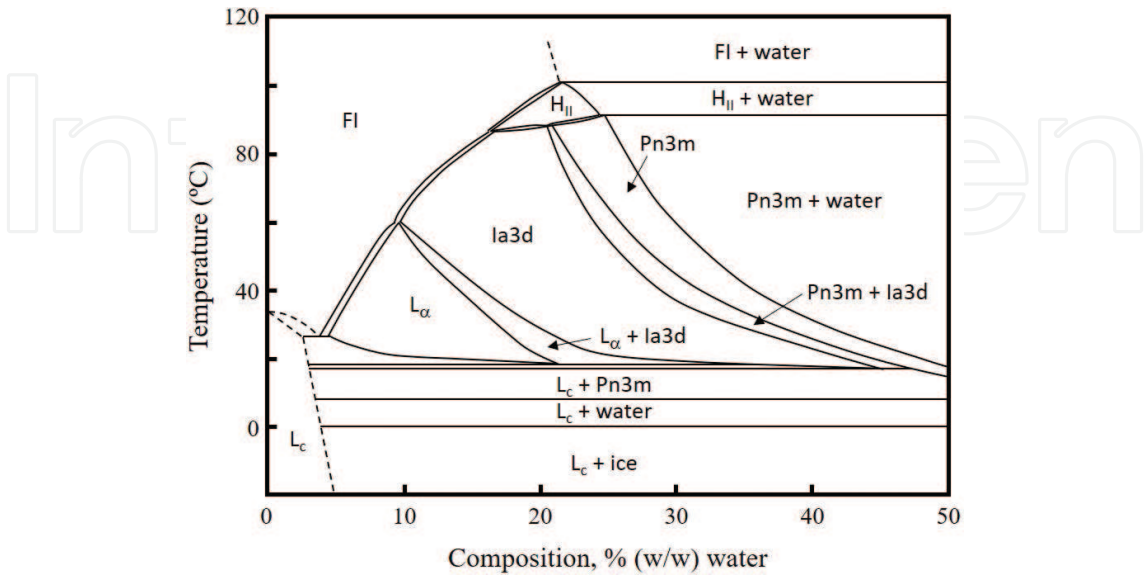


Figure 10. Phase diagram of monoolein/water system [69]. FI: fluid isotropic phase, La: lamellar LC, H_{II}: reverse-type hexagonal LC, Ia3d and Pn3m (space group): reverse-type bicontinuous cubic LC.

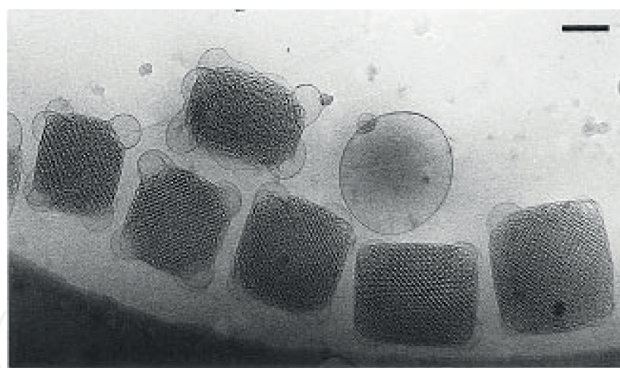


Figure 11. Cryo-TEM micrograph of cubosome [70]. The bar corresponds to 100 nm.

kinetically dispersed particles upon application of high-energy input in the presence of a suitable stabilizer like surfactant [58, 59, 68]. The internal nanostructures are controlled by CPP of amphiphilic molecule and have specific curvatures H and G . These aqueous dispersions, cubosome and hexosome, are often characterized by small-angle X-ray scattering (SAXS) and cryo-TEM. As seen in **Figure 11**, the cryo-TEM micrograph clearly demonstrates the internal nanostructures in the dispersions [70].

The feasibility of the nanostructured aqueous dispersions as drug carrier has been investigated since the 2000s, and the advantages of utilizing these dispersions have been reported, for example, solubilization of drug, bioavailability, efficient delivery, reduction of side effects, percutaneous penetration, protection of drug degradation, and release control [71–76]. However, the number of studies on drug delivery system utilizing these dispersions is still limited regardless of the unique properties so far, and further investigations will be required to understand their potentials for drug carries and also to reveal the interaction of bioactive materials and LC carries while taking the phase behavior of LC into consideration.

5. Conclusion

Beyond expectation, lyotropic liquid crystals are the soft matter familiar to our life, even managing biological functions such as homeostasis in the living system. Recently, we intend to learn or mimic many things from nature to construct artificial products with some function; on the other hand, the scientific technologies that we have ever accumulated would be applicable to reveal a new mechanism of biofunction by integrating several academic fields.

The formulations utilizing the liquid crystals have been contributed to the development of industry and supported our life. This may be a reason why the liquid crystals are constructed by self-assembling of numerous molecules and possess the properties of both liquid and solid. Still, there are many questions on the several applications utilizing the liquid crystals, and thus further investigations of the liquid crystals will clarify and find out unknown phenomena leading to novel functions of the liquid crystals.

Author details

Yuji Yamashita

Address all correspondence to: yyamashita@cis.ac.jp

Faculty of Pharmacy, Chiba Institute of Science, Chōshi, Chiba, Japan

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