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Liquid crystalline drug delivery vehicles for oral and IV/subcutaneous administration of poorly soluble (and soluble) drugs

Andrew Otte[a,*], Bong-Kwan Soh[b], Gwangheum Yoon[b], Kinam Park[a,c]

[a] Purdue University, Weldon School of Biomedical Engineering, West Lafayette, IN 47907, USA
[b] Chong Kun Dang Research Institute, 315-20, Dongbaekjukjeondaero, Giheung-gu, Youngin-si, Gyeonggi-do 16995, South Korea
[c] Purdue University, Department of Industrial and Physical Pharmacy, West Lafayette, IN 47907, USA

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ABSTRACT

Poorly soluble drug molecules often have low bioavailability issues and absorption problems in the clinical setting. As the number of poorly soluble drugs increases from discovery, developing technologies to enhance their solubility, while also controlling their release is one of the many challenges facing the pharmaceutical industry today. Liquid crystalline systems, nanoparticulate or macro-matrix, self-assemble in the presence of an aqueous environment and can provide a solubility enhancement, while also controlling the drug release rate. This review examines the fundamentals of liquid crystalline systems through the representative literature, concluding with examples of liquid crystalline systems in clinical trials development. The review focus is on the potential of utilizing liquid crystalline systems for poorly soluble drugs, in the areas of oral delivery and IV/subcutaneous, followed by water soluble molecules. Key considerations in utilizing liquid crystalline systems advantages while also discussing potential areas of key research that may be needed will be highlighted.

1. Introduction

Approximately 40% of currently marketed compounds and most current drug development candidates remain poorly water soluble (Williams et al., 2013). The desire for increased potency, coupled with the realization that receptor binding is mediated, at least in part by hydrophobic interactions, further illustrates the likelihood that drug candidates will have limited aqueous solubility (Williams et al., 2013). The consequences of compounds with low solubility include poor absorption and bioavailability, insufficient solubility for IV dosing, artificially low activity values from bioassays, developmental challenges leading to increasing the development cost and time coupled with expensive formulations, and shifting the burden to the patient (frequent high-dose administration) (Kerns and Di, 2008). One of the major challenges of a formulation scientist is developing viable formulation strategies to enhance the aqueous solubility of drugs, coupled with controlling the drug release rate. This is especially important to class II and IV molecules of the BCS (biopharmaceutical classification system). Oral absorption from class II molecules can be categorized into two types, dissolution rate-limited and solubility-limited, based on the solubility and dissolution rate of the drug, where class IV drugs bring on the added issue of permeability limitations (Sugano et al., 2007).

Early in development, one of the first strategies for solubility limitations is drug substance form selection – including salt, co-crystal, or solid form (polymorph). If form selection was not successful in improving the solubility and/or dissolution rate of the molecule, particle size reduction strategies can often be the simplest means to enhance the dissolution rate of poorly soluble drugs (Liversidge and Cundy, 1995). In addition, co-solvents (Seedher and Kanojia, 2009), nanoparticle engineering (Hu et al., 2004), solid dispersions (Leuner and Dressman, 2000), polymeric surfactant-based systems (Torchilin, 2001), supersaturating drug delivery systems (Brouwers et al., 2008), and lipid based systems such as self-emulsifying drug delivery systems (SEDDS) (Gursoy and Benita, 2004; Pouton, 2000) are all fairly common approaches that can be used for solubility enhancement. A newer technique, liquid crystalline (LC) drug delivery systems (LCDDS) have gained considerable attention in the last few decades as a multifunctional technique that may have the capability to both enhance the solubility and control the drug release rate. While lipid based systems and SEDDS are closely related to liquid crystalline systems, as they often use common excipients, they differ in the resulting 2- and 3-D periodic structural arrangement. This review seeks to provide an overview of the liquid crystalline structure and examples of how this formulation strategy may be used for potential solubility enhancement and/or coupled with sustained drug release. The beginning is structured to provide a fundamental introduction to liquid crystalline structures,

* Corresponding author.
E-mail address: aotte@purdue.edu (A. Otte).

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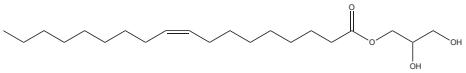
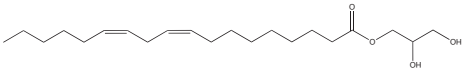
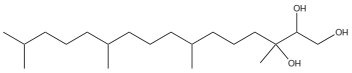
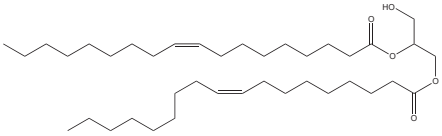
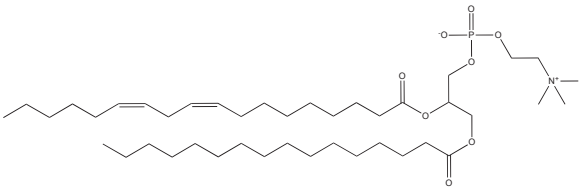
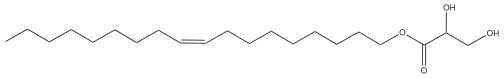
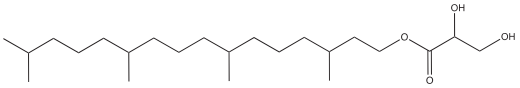
Table 1
Chemical structure of some commonly used LC forming materials for drug delivery.

Commonly cited LC forming materials	Structure
Monoolein/Glycerol Monooletae	
Monolinolein	
Phytantriol	
Glycerol dioleate	
Phosphatidylcholines	
Oleyl glycerate	
Phytanyl glycerate	

followed by the various applications, specifically oral and IV/subcutaneous, this technology platform has been used for solubility enhancement and delivery. These systems started out predominantly for topical administration in the early 1980s, although this route is not covered in this review. In addition, the various phases and phase behavior of LLC systems used for drug delivery, the molecules/combination of molecules, the *in vitro/in vivo* characterization methodology, the drug substances characterized in these systems, and finally an overview of the systems in clinical trials will be provided.

2. Liquid crystal overview

A liquid crystal is a state of matter that exhibits properties between a conventional liquid and a solid crystal, and can be subdivided into two types: lyotropic and thermotropic. Thermotropic liquid crystals exhibit properties dependent on the applied temperature of the system, whereas lyotropic liquid crystalline systems are based upon the self-assembly of amphiphilic molecules induced by a solvent (typically aqueous) environment. The architecture of the system is based upon the amphiphilic molecule(s) structure (Table 1), combination of amphiphilic molecules/additives Table 2 (Dong et al., 2006), temperature (Qiu and Caffrey, 2000), media (Nguyen et al., 2010), pH (Negrini and Mezzenga, 2011), water content (Boyd et al., 2006), pressure (Yaghmur et al., 2010), ions (Awad et al., 2005), and salt concentration (Khvostichenko et al., 2013) among others. Due to the amphiphilic nature of the components used to fabricate these systems, hydrophilic, lipophilic, or amphiphilic molecules can be encapsulated into these systems.

Similar systems, not discussed here are self-(micro) emulsifying drug delivery systems (S(M)EDDS), isotropic mixtures of oils, surfactants, solvents, and/or co-solvents, that form fine relatively stable oil-in-water emulsions upon dilution in aqueous mediums (Gursoy and Benita, 2004). While overlap exists between LLC and SEDDS, as some SEDDS will form liquid crystals depending on the excipients, excipient ratio(s), and water content, these systems will not be discussed in this review. If the reader is interested in these systems, there are a number of well written review articles (Pouton, 1997; Tang et al., 2008; Kohli et al., 2010).

Thus far, two main physical configurations of LLC systems for drug delivery have been explored: (1) so-called cubosomes and hexosomes, sub-micron dispersions of self-assembled reverse mesophases, where the inner structure is in thermodynamic equilibrium with the external excess aqueous environment and (2) as the bulk mesophase, gel, mesophase depot, matrix, etc, essentially describing the LC system in thermodynamic and structural equilibrium with the external environment as a single structure/mass.

2.1. Cubic and hexagonal phase structure

The structure of the cubic phase comprises lipid bilayers arranged in periodic three-dimensional structures by contorting the bilayers into the shape of infinite periodic minimal surfaces. This reverse bicontinuous structural arrangement minimizes stress and free energy, resulting in water and oil domains with a surface area on the order of 400 m^2/g (Lawrence, 1994). The bicontinuous cubic phases can be classified into either the double-diamond lattice (Pn3m, Q^{224}), the body-centered cubic phase (Im3m, Q^{229}), or the gyroid lattice (Ia3d, Q^{230}) (Table 3 (Hyde, 2001). As a bulk phase, it is typically a clear, viscous, semi-solid gel similar in appearance and rheology to cross-linked polymer hydrogels (Spicer et al., 2001).

In addition to the bicontinuous cubic structure, reverse micellar cubic phases exist, consisting of reversed micelles packed on a cubic lattice. This is a discontinuous structure and composed of two populations of reversed micelles, one larger than the other (Seddon et al., 2000). The two sizes of micelles allow for more efficient packing. Due to the discrete, small water domains associated with this structure, it is expected to exhibit the most extended release profiles of the various liquid crystalline phases (Tiberg and Johnsson, 2011).

Table 2
Chemical structure of some commonly used LC additives.

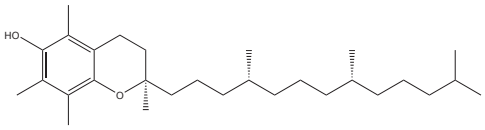
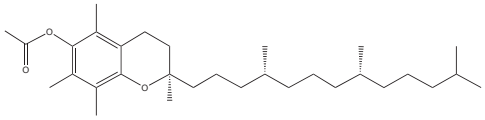
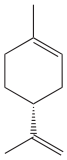
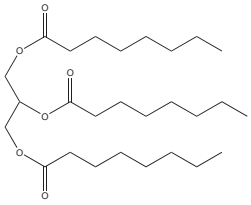
Common LC additives	Structure
α-dl-tocopherol	
tocopherol acetate	
R-(+)-limonene	
tricaprylin	

Table 3
Lyotropic liquid crystalline mesophases and their dimensionality, descriptor, and peak ratios adapted from (Hyde, 2001).

Class	Mesophase	Descriptor	Symmetry	Peak Ratios (observed reciprocal spacings)
Smectic	Lamellar	L_α, L_β	Smectic (1D)	1:2:3:4…, etc
Sponge/Cubic	Bicontinuous cubic (V_1, V_2) or (Q_1, Q_2)	P (Q^{229}, $Im\bar{3}m$)	$Im\bar{3}m$ (2D)	√2:√4:√6:√8:√10…etc
		D (Q^{224}, $Pn\bar{3}m$)	$Pn\bar{3}m$ (2D)	√2:√3:√4:√6:√8…etc
		G (Q^{230}, $Ia\bar{3}d$)	$Ia\bar{3}d$ (2D)	√6:√8:√14:√16:√18:√20…etc
Columnar	Hexagonal (H_1, H_2)	p6m	2D	√3:√4:√7:√12
Micellar	Discrete cubic (I_1, I_2)	—	bcc packing $Im\bar{3}m$ (3D)	√2:√4:√6:√8:√10…etc
			fcc packing $Fm\bar{3}m$ (3D)	√3:√4:√8:√11:√12… etc
			$Pm\bar{3}m$	√2:√4:√5:√6:√8…etc
			$Fd\bar{3}m$	√3:√8:√11:√12:√16

The reverse hexagonal phase (H_2) is a closed, extended micellar columnar structure, where there is no direct contact between water inside and outside the hexagonal phase (Sagalowicz et al., 2006). The bulk and particle structure can be envisioned to be a large micelle with a "core" composed of the extended micellar structures. While the long circular water-filled rods are often illustrated and considered as if they are open to the aqueous environment, it has been reported that these water channels are in fact closed to outside environment (Seddon, 1990; Luzzati and Husson, 1962). Therefore, the release of hydrophilic drugs from the mesophase has been described as a series of dynamic events involving diffusion through water channels and permeation across the lipid bilayers (Martiel et al., 2015). However, for release of large hydrophilic molecules such as the peptide drug leuprolide acetate, random perturbation/dynamic deconstruction-reconstruction events of the reverse micelles may be required (Boyd et al., 2006; Báez-Santos et al., 2016). Fig. 1 illustrates a representative structural comparison between a micelle, liposome, hexosome, and cubosome. The amphiphilicity of the drug molecule will determine the location in the liquid crystalline matrix; hydrophilic drugs will be located close to the polar head of the lipid or in the aqueous channel, lipophilic drugs will be located in the lipid bilayer, and amphiphilic drugs at the interface. Multiple reviews have focused on the self-assembly, structure-packing relationships, drug release mechanisms, and how to control molecular transport in LC systems and the reader is directed to these cited review for more detailed information on these aspects (Zabara and Mezzenga, 2014; Shah et al., 2001; Martiel et al., 2014; Kaasgaard and Drummond, 2006).

2.2. LLC nanoparticle production

The formation and structure of cubosomes was first described in 1989 by Larsson (Larsson, 1989). Since then, a number of reports have been published on the use of the various LC phases, particularly the cubic or "cubosomes" and hexagonal or "hexosomes" for the use in drug delivery. Cubosomes have been proposed as a delivery system which may provide both a solubilization effect and a means for controlling or sustaining release (Boyd, 2003). LLC particles are typically sterically stabilized by a secondary emulsifier (Barauskas et al., 2008), such as polyethylene oxide-polypropylene oxide-polyethylene oxide block copolymers (e.g. Pluronic F127) (Barauskas et al., 2005), due to the high external surface area of the submicron particles.

As Spicer eluded to in 2005, from an industrial perspective, cubosomes have intriguing and fascinating properties, but relying on top-down approaches for production may be problematic due to the potential of multiple passes for the desired properties and the high energy required (Spicer, 2005). Still, most emulsification methods for the lyotropic liquid crystalline nanoparticles (LCNP) production rely on high-energy input from the bulk phase: ultrasonication, microfluidization, and/or homogenization. Additional methods of production, still relying on high energy input, are the hot-melt method were the precursor solution is dispersed with a homogenizer in hot water (80 °C) loaded with a stabilizer and a drug followed by high pressure homogenization (Gustafsson et al., 1997; Boyd, 2003). Reverse to that

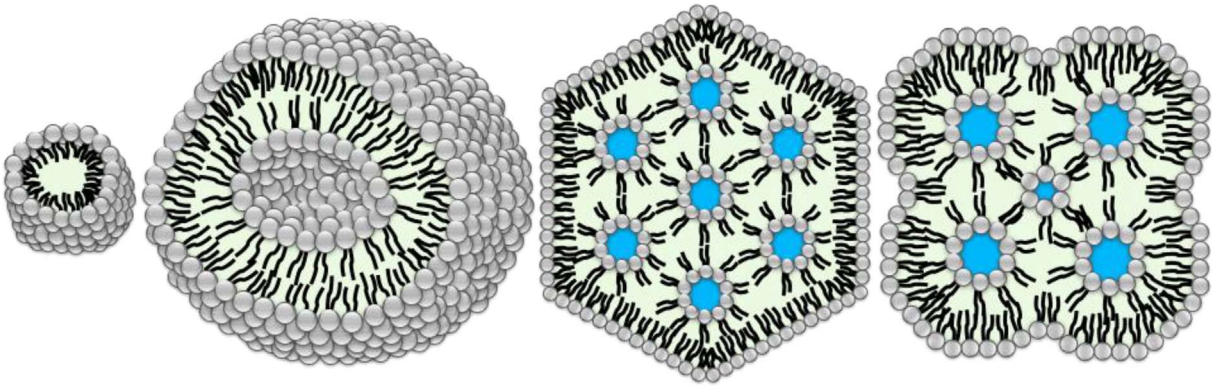


Fig. 1. Schematic representative of a micelle, liposome, hexosome (cross-section), and cubosome (cross-section) (from left to right).

method is the application of microfluidization followed by heat treatment (125 °C) for the formation of dispersions of cubosomes and hexosomes (Barauskas et al., 2005). Other methods not relying on the top down approach have been developed. Cubosomes were shown to be formed by the addition of phosphate buffered saline to phytantriol-based cationic liposomes that contained a charged lipid-dodecyldimethylammonium bromide (Muir et al., 2012). Awad et al., transformed large unilamellar vesicles, composed of dioleylphosphatidylglycerol/monoolein mixtures, into the cubic phase through the addition of low concentrations of Ca^{2+}, where the resultant electrostatic interactions due to the surface charge induced the phase transition (Awad et al., 2005).

3. Solubility and release overview

When considering a poorly soluble hydrophobic molecule in a liquid crystal, it may beneficial to first envision how an oil emulsion may be used to solubilize poorly water soluble drugs first. The oil droplets represent relatively non-polar compartments dispersed in an aqueous environment that may be used to solubilize poorly soluble drugs. A major advantage of nanoparticulate lipid carriers, such as emulsion droplets is that their dissolving power is retained on administration, whereas the use of co-solvents or surfactant micelles may partially lose that power upon dilution with aqueous media (Narang et al., 2007). One example is paclitaxel, which has been observed to precipitate out of the dilutions of Taxol that are prepared prior to administration (Szebeni et al., 2001).

Poorly water soluble drugs do not necessarily display high solubility in lipids/oils. Molecules that have very strong intermolecular forces, resulting in high crystal lattice energies, ultimately demonstrate poor solubility in both water and oil vehicles (Nema and Ludwig, 2010). Emulsions are often useful only for poorly soluble drugs with low melting points, with an inability to interact with water molecules, and have a tendency to be oily-like themselves (Nema and Ludwig, 2010). In addition, the oil type has an effect on the dissolving power. Very non-polar oils such as long chain triglycerides have a lower dissolving power for many drug substances than oils of a more polar nature, for example castor oil or medium chain triglycerides (Malcolmson et al., 1998; Larsen et al., 2002).

Similar to a drug's solubility in an oil, a drug molecule is going to have a certain solubility in the liquid crystal forming material(s). In addition, the drug will also have a solubility in the formed liquid crystalline matrix, and since so many factors can affect the matrix, it is likely the drug will also show a wide range of solubilities depending on the matrix conditions; e.g. ionic strength, water content, pH. While emulsions can provide a solubility advantage, many drugs rapidly dissociate from emulsion droplets post-dilution or administration, as shown with miconazole (Levy and Magenheim, 1993), chlorpromazine (Washington and Evans, 1995), and paclitaxel (Lundberg et al., 2003). If drug solubility is the only objective, this may not be an issue; however, if controlled release in addition to enhanced drug solubility is targeted, this is where emulsion formulations may fail. The solubility in the oil and also the partitioning of the drug between the oil and the aqueous phase needs to be considered when determining the dissolving power of an emulsion. If drug partitioning into the aqueous phase leads to supersaturation, the drug may precipitate. The partition coefficient of the drug should be sufficiently high whereby this issue can be avoided. Both the extent and rate of drug release from emulsions is closely related to the partition coefficient of the drug from the oil. Only drugs with high partition coefficients may be suitable for loading in oil emulsions to provide solubility enhancement and sustained release (Floyd, 1999). Unfortunately, such high values are often uncommon for those with low solubility [eg cyclosporine and paclitaxel logP ~ 3] (Pouton, 1997). Liquid crystalline drug delivery systems may offer an advantage here in both solubility enhancement and controlled drug release. A drug's solubility in the LC matrix will depend on the formulation (e.g. LC excipient/excipient ratios) and environmental conditions; where this solubility may also negatively influence the controlled release characteristics due to LC packing alterations. Therefore, the drug solubility and/or starting concentration may likely have a direct correlation with the controlled release properties of the LC matrix depending on the phase.

3.1. Solubility and release in LLC bulk phase

A monoolein-water liquid crystalline cubic phase systems was used to study the solubility and subsequent release of melatonin, pindolol, propranolol, and pyrimethamine with loadings from 1 to 30 w/w% depending on the molecule (Burrows et al., 1994). The solubility of all drugs was greater in the LC system than their solubility in Sorensen's buffer, thus inferring the drugs were solubilized preferentially in the lipophilic region; the authors also found a general increase in solubility with decreasing monoolein:water ratios (Table 4) (Burrows et al.,

Table 4
Saturation solubilities of drugs in monoolein-water systems and Sorensens's buffer Adapted from Burrows et al. (1994).

Drug	Saturation Solubility in LC system (37 °C) (w/w%)			Solubility in Sorensen's buffer (37 °C) (w/w%)
	Monoolein/water weight ratio			
	4:1	2:1	1:1	
Atenolol	6.1	6.3	8.8	2.55
Melatonin	1.0	1.4	1.0	0.21
Pindolol	3.1	4.1	6.0	0.19
Propranolol	13.2	13.2	14.6	0.31
Pyrimethamine	1.7	2.0	2.3	0.01

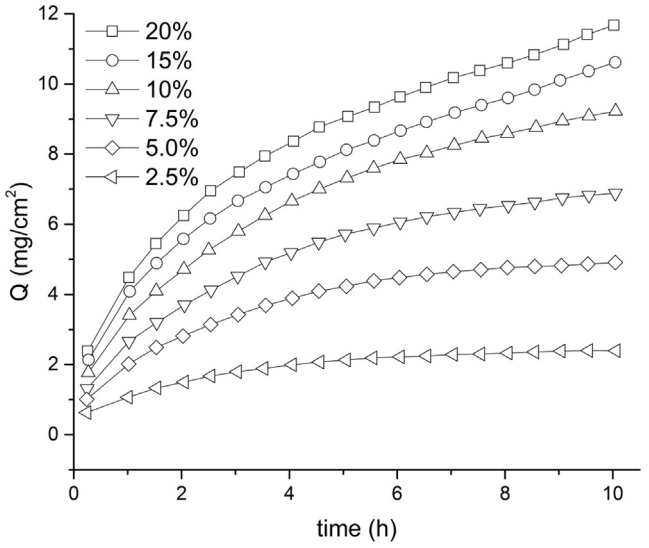


Fig. 2. Cumulative release per unit surface area of a monoolein-water LC system loaded with varying concentrations of atenolol as a function of time. Adapted from Burrows et al. (1994).

1994). The authors attributed this to an increase in the interfacial area of the cubic phase, potentially aiding the solubilization process. The location of the drug in the LC and the potential mechanism of release therefore can depend on any number of factors including but not limited to the LC component(s), the drug's hydro-/lipophilicity, and/or the water content. As one might expect, the release profiles showed the higher drug loadings lead to an increase in release rate and amount released (Fig. 2). In addition, the higher aqueous solubility of the drug the greater the amount of drug released over a specified time interval for a given initial drug concentration.

Cinnarizine's solubility in phytantriol (PHY) and glycerol monooleate (GMO) was found to be 7.7 mg/g and 29.9 mg/g in PHY and GMO, and diazepam's was 23.6 mg/g and 47.2 mg/g respectively, while their aqueous solubilities are 1.5×10^{-4} mg/mL for cinnarizine and 0.06 mg/mL for diazepam (Nguyen et al., 2010). They also looked at vitamin E acetate, where PLM observations showed that at 10% vitamin E acetate concentrations formed H_2 and L_2 (lamellar) phases rather than the cubic phase. At physiological relevant conditions (37 °C excess simulated fluids), no phase change was noted for PHY alone (Q_2 − reverse bicontinuous cubic) and PHY + drug at solubility (Q_2) or GMO + drug at solubility (Q_2). In a follow up study, the authors looked at these systems as oral controlled release vehicles for the cinnarizine formulation (Nguyen et al., 2010). A dramatic difference in cinnarizine systemic exposure was noted between the PHY and GMO phases. The PHY phase showed sustained absorption consistent with slow diffusion, where the GMO phase is most likely degraded in the stomach due to lipase activity. Cinnarizine was also loaded into GMO and oleyl glycerate (OG), where the OG revealed a relative oral bioavailability of 344% to the aqueous control suspension (t = 120 h), whereas the GMO was 117% (t = 30 h). The drug loading for each LC formulation was ~2.5% (Boyd et al., 2007).

As a means to slow the release from cubic phase, a process was developed for modifying native cubic phases with charged or long-chain molecular anchors that increased the affinity of solubilized actives for the cubic phase, thereby slowing the release (Lynch et al., 2003). The inclusion of di(canola ethyl ester) dimethyl ammonium chloride formulated to 20 wt% or greater while undisturbing the native cubic structure, demonstrated a slower release profile than the unmodified cubic structure. This was based on the slopes of the concentration of ketoprofen in the gel versus the square root of time fit to a matrix model. The release of ketoprofen was only performed at 2.0 wt %. Lynch et al., states about 10 wt% (relative to the cubic phase) is the typical practical upper limit to loading lipid-soluble actives (Lynch et al., 2003). Determining at what drug loading concentration the release converged to the unmodified cubic phase would have been a very interesting follow-up study.

3.2. Solubility and release from LLC nanoparticles

Release of the lipophilic drugs griseofulvin, rifampicin, diazepam, and propofol from cubosomes was found to reach a plateau within 20 min, concluding it is unlikely any therapeutic benefit, by virtue of controlled release, could be obtained using cubosomes as a delivery system for lipophilic drugs (Boyd, 2003). To measure the release from colloidal delivery systems, it is necessary to dilute the dispersion and monitor subsequent release of drug from the particles into the surrounding free solutions (Boyd, 2003). Therefore, in the absence of any *in vivo* pharmacokinetic data, all *in vitro* release studies from such structures should be heavily scrutinized. Similar results of the burst release from hexosomes using irinotecan, an anticancer drug, in either oleyl glycerate or phytanyl glycerate based hexosomes was found (Boyd et al., 2006). The hexosomes did offer a stability enhancing effect whereby it improves the retention of irinotecan in the lactone form at near neutral pH (Boyd et al., 2006). While these two studies demonstrated evidence these systems did not provide a controlled release effect from cubosomes or hexosomes, these types of systems may be capable of delivering stability or solubility enhancement effects that may limit some drugs. Regarding hydrophilic drug release from these systems, the main obstacle remains the burst release typically found when utilizing sub-micron particles (Boyd, 2003). To circumvent this issue, utilizing more hydrophobic drugs or large molecules such as proteins, or utilizing ionic interactions or covalent bonds between the drug and mesophase matrix could be performed.

Propofol was loaded and dosed as a 1:2.5 wt/wt ratio with LC excipients Soy Phosphatidylcholine/Glycerol Dioleate/Polysorbate 80 (Soy PC/GDO/P80) as nanoparticle dispersions providing a high loading capacity and kinetic stability (Johnsson et al., 2006). This formulation was compared with Diprivan®; an o/w emulsion with the highest drug loading being 1:5.6 wt/wt - both formulations dosed at 10 mg/kg to rats. The total drug exposure for the LCNP formulation was significantly higher than the Propofol-Lipuro (compositionally identical to Diprivan) product, concluding this LCNP formulation could be an alternative to current emulsion products.

Docetaxel (0.27 mg/mL) loaded into a LCNP dispersion (70/20/10 wt/wt/wt ratio of 50:50 PC:GDO:Polysorbate 80 (P80):ethanol) was compared to the commercial product Taxotere (0.405 mg docetaxel/mL) (Cervin et al., 2010). The LCNP formulation showed a greater effect on tumor regression relative to Taxotere® as indicated by the lower proliferation index (3.6 ± 1.2% vs 9.8 ± 5.6% for LCNP and Taxotere, respectively). Unfortunately, the liquid crystalline structure, any studies on the actual solubility of docetaxel in the LC matrix, or release from the matrix relative to taxotere, a P80 micelle dispersion, was disclosed in the manuscript.

A LLC nanoparticle delivery system composed of Soy PC, GDO, and P80 (composition not explicitly stated) was shown to improve the oral bioavailability of the poorly water-soluble agent, paclitaxel (Zeng et al., 2012). An *in vivo* pharmacokinetic study showed that the oral bioavailability of paclitaxel-loaded cubic phase nanoparticles (13.16%) was greater than that of Taxol (the commercial formulation of paclitaxel, 6.39%). Unfortunately, no definitive structural information was obtained through either SAXS or TEM, therefore it is difficult to conclude the actual LLC structure used in the study.

Cyclosporin, a poorly water-soluble cyclic peptide was administered orally in dispersed particles of a cubic phase, predispersed L_2 phase (an oil phase with very low interfacial tension towards water), and an oily L_2 phase, with all three yielding improved bioavailabilities of 27%, 34%, and 38% respectively, relative to the 8% to the marketed product (Sandimmune®) (Bojrup et al., 1996). They found low variabilities in

the two L2 phases, and suggested these formulations were self-emulsifying in the GI tract.

Omapatrilat, an antihypertensive agent, was loaded into monoolein nanoparticles and administered orally to rats and provided a rapid and more pronounced antihypertensive effect relative to omapatrilat suspension (Tamayo-Esquivel et al., 2006). Unfortunately, the pharmacokinetic data was not presented, nor was the particle size of the omapatrilat used in the suspension, creating difficulty in truly delineating the difference between the two formulations. While it cannot be argued that the cubic phase nanoparticles provided a greater antihypertensive effect compared to the control suspension, a more thorough description of the differences in the physico-chemical parameters between the formulations would have provided the reader a potentially clearer picture of the advantages of the cubic phase nanoparticles.

A system of simvastatin loaded into GMO/poloxamer cubic nanoparticles (at a loading of 3–5%) had a relative bioavailability to micronized crystalline powder of ~241% (Lai et al., 2009). While the study shows the potential of the system, the control was crystalline powder sized with a mean diameter of < 5 μm, whereas the cubic nanoparticle size, depending on the formulation, was in the range of 110–140 nm. A study comparing the dissolution rate of simvastatin microparticles vs nanoparticles (14 μm to 360 nm) showed more than 80% of the 360 nm simvastatin dissolved within 60 min whereas only ~20% of the 14 μm particles dissolved (Jiang et al., 2012). In the bioavailability comparison, the $AUC_{0\text{-}24h}$ was 1.44 times greater in the nanoparticles than the microparticles (Jiang et al., 2012). These two studies illustrate that appropriate controls should be taken when comparing various formulations as similar results can be obtained with a simple particle size change.

As most molecules in clinical development are poorly soluble, it is a safe hypothesis to say the molecule will be mostly/preferentially located in the hydrophobic (lipidic) domain of the LC, therefore release from these systems may be due to erosion/breakdown of the matrix. Therefore, studies including some form of enzyme such as lipases or esterases may be required. Cinnarizine, a molecule with a log P of 5.8 and aqueous solubility of $< 1.5 * 10^{-4}$ mg/mL was loaded into PHY and GMO cubosomes (2.1 mg cinnarizine/300 mg lipid) and *in vivo* oral experiments were performed in rats (Nguyen et al., 2011). The PHY cubosomes resulted in sustained release beyond 48 h for cinnarizine due to prolonged retention in the stomach due to the non-digestible nature of the lipid and the stability of the cubosome structure in the gastric environment, acting as a drug-releasing reservoir. Whereas within 18 h, under simulated intestinal fluids and pancreatic enzymes, the GMO cubosomes were broken down from the cubic V_2 structure to H_2 to micellar, accounting for the lack of sustained release capabilities relative to PHY cubosomes. In a previous study, the maximal capacity of a lauric acid (LA), monolaurin, and simulated endogenous intestinal fluid cubic phase to solubilize cinnarizine was 53.1 ± 2.0 mg/mL (Kossena et al., 2004). The extent of release from the aforementioned cubic phase was 3.9% cinnarizine whereas 12.4% from a lamellar phase utilizing the same components. Cinnazarine is a good poorly water soluble model compound for these systems, as the dose is fairly low (12.5 or 15 mg three times daily typically). The formulation used in this study is 5 mg cinnarizine and 245 mg cubic phase (38 w/w% LA/monolaurin), a loading of only 5.1%. For low dose compounds such as cinnarizine, this type of loading may be acceptable, but looking at higher dose compounds, additional studies may need to be done to determine the feasibility of using such systems. In addition, looking at the crystallization tendencies of such molecules in the precursor LC materials need to be performed to assess whether this type of dosage form may be clinically relevant. As mentioned in Kossena et al., detailed investigations of drug concentration/release dependencies are required before advantages in oral, rectal, and transdermal drug delivery can be envisaged (Kossena et al., 2004). Countless studies have been performed on these types of systems, often neglecting the upper limit of potential loading of these systems whereby the effect on release may be noticed.

3.3. Understanding release of water soluble compounds from LLCs

Water soluble drug release from LC matrices has been extensively characterized and the internal water channel diameter has been shown to determine the drug diffusion rate for hydrophilic compounds (Clogston and Caffrey, 2005). Using glucose as a model hydrophilic compound, the release from glyceryl monooleate based bicontinuous cubic (V_2), inverse micellar (L_2), inverse hexagonal H_2, and inverse micellar cubic (I_2) was determined (Phan et al., 2011). The V_2 showed the greatest diffusion coefficient, whereas minimal release was observed from the L_2, H_2, and I_2 phase. The water channels are closed to the external environment in the H_2 (Sagalowicz et al., 2006; Kaasgaard and Drummond, 2006; Johnsson et al., 2005), the I_2 phase is a closed structure composed of closely packed inverse micelles (Luzzati and Vargas, 1992; Pouzot et al., 2007), and inverse micelles have a water core at the CMC and have been stated to be stable in excess aqueous environment (Phan et al., 2011) or eventually transforms into lamellar liquid crystals with increasing solubilized water (Mueller-Goymann and Hamann, 1993). Bicontinuous cubic phases, by nature of their interpenetrated water channels following triply periodic minimal surfaces have been directly shown that the water channel dimensions correlate with the release and/or separation performance (Negrini and Mezzenga, 2012). Many, if not all studies focus mainly on the diffusion/release from the preformed LC matrix. While it has been stated the LC precursor spontaneously transforms into the cubic phase, few studies have looked at the release from varying the aqueous content and the rates and effect of release on the transformation stage, rather the end result of loaded drug from the cubic phase. Depending on how these systems will be delivered orally, as preformed matrices, precursor matrices, or somewhere in between, future research will need to be performed to determine the optimal dosage form for delivery, coupled with cost, storage, stability, and manufacturing capability.

Propranolol hydrochloride, a water-soluble amphiphilic molecule, was loaded into monoolein and phytantriol systems up to 20 w/w% (Costa-Balogh et al., 2010). In general, they found that higher viscosity cubic phases result in slower drug release rates. Also, due to its amphiphilic nature, they found incomplete release at 48 h of dissolution testing due to drug partitioning into the lipid bilayers (Costa-Balogh et al., 2010). It has also been hypothesized that incomplete release from LC phases may be due to pH dependency of the drug molecule and complexing with free fatty acids present in the monoglyceride (Chang and Bodmeier, 1997). Although, some differences exist experimentally between the two studies. Costa et al., performed the dissolution studies in deionized water and the formulations were allowed to equilibrate for 7 days prior to measurement, whereas Chang et al., performed the dissolution studies in PBS 7.4 buffer and tested the release on precursor LC, therefore some kinetic and ionic differences between the two studies exist complicating the mechanism of propranolol HCl retention in the LC. More importantly, since these are newer systems, extensive detailed information on test conditions must be provided since every study may be slightly different, as a single accepted condition on how to prepare or test the release from these systems does not appear to be agreed upon.

Salicyclic acid was loaded into a cubic GMO-water based system, and the drug loading (2.0, 4.0, or 8.0 w/w%), swelling rate (initial water 0, 20, or 35 w/w%), and water content (20 or 35 w/w%) had no effect on the drug release (Lara et al., 2005). Orally administered insulin loaded into GMO cubic phase particles provided a hypoglycemic effects comparable to IV administration of insulin over a 6 h period post administration (Chung et al., 2002), yet the exact mechanism providing the hypoglycemic effect was not elucidated, and it was hypothesized the 'nanocubicles' will absorb in the intestinal epithelia since monoolein based cubic phases are known to be mucoadhesive based on a previous study (Nielsen et al., 1998).

The release of 3 model compounds, glucose, proflavine, and caffeine was extensively characterized from various surfactant/oil

(monolinolein and soybean PC/tocopherol and limonene) systems (Martiel et al., 2015). While multiple studies have previously shown direct correlation between lattice parameter and diffusion coefficient, in this study, the structural control of the diffusion coefficient was strongly controlled by the type of oil and drug, where the bilayer permeability of the drug appeared as the most meaningful descriptor. Other reports have also eluded to random perturbations and/or dynamic deconstruction-reconstruction events for release of structures that may be influenced by the structure and/or membrane permeability (Báez-Santos et al., 2016; Boyd et al., 2006).

The potential utility of these systems for poorly soluble and soluble compounds as both solubilizing and controlled release vehicles needs to be considered. Using caffeine as an example from the Martiel et al., study, mesophases of 300 mg were prepared with 0.7 wt% or 1.0 wt% caffeine, with the phases ranged from 10 to 35 wt% water contents. Using the 1.0 wt% caffeine, the lower water content system (10 wt%) contained 0.3 mg of caffeine where the higher water content system (35 wt%) contained 1.05 mg of caffeine. It is generally agreed upon that 300–400 mg of caffeine can be consumed daily without any adverse effects (Heckman et al., 2010); with those numbers as reference, a significant amount of mesophase would be required to deliver that amount of caffeine daily. While the study is focused on the LC structural elucidation and effects on release using caffeine as a model drug compound, it would be interesting to see the potential utility for higher dose compounds or more applicable loadings.

4. LC safety and degradation

The digestion of GMO after oral dosing was shown to be responsible for a lack of sustained-release effect for the model drug, cinnarizine (Nguyen et al., 2010; Boyd et al., 2007). Relative to GMO, both oleyl glycerate (Phan et al., 2011) and phytantriol (Gustafsson et al., 1997) were able to sustain the absorption of cinnarizine over approximately 48 h after oral dosing. Oleyl glycerate is a less readily digested GMO structural analogue and phytantriol is a non-digestible lipid demonstrating similar phase behavior to GMO. Phytantriol was found to be retained for an extended period of time in the stomach relative to GMO also, establishing a link between digestibility, gastric retention, and a sustained release effect (Gustafsson et al., 1997). Interestingly, despite this link that was found, very few studies have focused on the digestibility/enzymatic breakdown of these systems, let alone the potential gastric retention of these systems.

Considering intravenous or subcutaneous administration, the biodegradation of these LC systems, whether as LCNPs or as a depot, lipolytic degradation will be the ultimate endpoint for these delivery systems. If naturally occurring lipids, such as GDO and Soy PC are used in a system, such as in Wadsäter et al. (2014), the biodegradation of systems composed of these lipids will be effected by triacylglycerol lipases and phospholipases. Cubic micellar (Fd3m) nanoparticles, composed of 50/50 Soy PC/GDO, were shown to transform from I_2, to the H_2 (< 5 min), V_2 (~ 4 h 15 min), and L_3 ("sponge") phases (~8 h), prior to the final lamellar phase, where GDO is degraded to GMO, oleic acid and glycerol (Wadsäter et al., 2014). The use of monoglycerides (GMO w/Pluronic F127), were shown to have concentration dependent hemolytic properties, whereas LCNPs based on long-chain diacyl lipids (Soy PC and GDO) were found to be practically inert towards hemolysis and lipid mixing with model membranes, where mixtures of long chain mono-acyl and diacyl lipids (diglycerol monooleate/GDO) displayed an intermediate behavior (Barauskas et al., 2010). They concluded the difference in associated toxicities is based on the molecules chemical activity, but the bilayer membrane structure of the cell also plays a role. In contrast, Bode et al. (2013), found nanoparticles based on GMO/Polaxamer 407 only have a low, but detectable tendency toward hemolysis. They also found a low hemolytic potential for LCNPs based on Soy PC and GDO. While the safety debate is still ongoing for intravenous LCNPs, other physico-chemical properties such as nanoparticle size, stabilizer type and concentration, LC forming materials ratio (assuming LC structure remains the same for varying ratios), among others may all have a significant effect on the LC breakdown.

5. Additional utilities of LLC systems in drug delivery

LLC systems can also be designed as "smart" systems, where a blend on monolinolein and linoleic acid exhibiting pH dependent self-assembly, where the reverse bicontinuous phase (Im3m) is present at pH 7, and the inverse hexagonal phase at pH 2 (Negrini and Mezzenga, 2011). Using a model hydrophilic compound, phloroglucinol, and a homemade diffusion setup, they showed diffusion at pH 7 occurred 4 times faster than at pH 2. Future studies may need include enzymes and food effects to determine the utility *in vivo*, as monolinolein is susceptible to esterase catalyzed hydrolysis, and if any fatty acids present in food may affect the packing and/or release of compounds from this system.

6. LLC phases in clinical trials

Despite increasing attention in liquid crystals as drug delivery vehicles for poorly soluble and soluble drugs, clinical trials of liquid crystalline systems are sparse. This may partly be due to patent issues, as only Camurus®AB have ongoing clinical trials utilizing their injectable sustained release depot – Fluidcrystal® – in the clinical setting. The molecules included in the clinical trials are low dose peptide compounds (Leuprolide Acetate – CAM2032 (Camurus, 2017) Octreotide – CAM2029 (Tiberg et al., 2015; Camurus, 2017),) along with 1 week and 1 month buprenorphine (CAM2038) (Albayaty et al., 2017; Walsh et al., 2017; Haasen et al., 2017). The lowest diffusion coefficients and optimal structural control have been obtained by utilizing a drug with a high hydrophilicity and large size, coupled with a LC additive molecule which stiffens the hydrocarbon tails, making these peptide compounds great candidates for controlled release. In addition to the peptide molecules, buprenorphine, a small molecule (mw = 467.64 g/mol) that is practically insoluble as a free base and with limited solubility as a hydrochloride salt is also being used. It is unknown whether the formulation uses the free base or a salt form of buprenorphine, so the potential location in the LC matrix is unknown. Interestingly, it was found that formulations having at least 16% buprenorphine are found to provide more effective release than similar formulations with a lower drug loading (Tiberg et al., 2016), further complicating the understanding of non-hydrophilic compound release from LC matrices.

7. Conclusion

This review has attempted to explain the fundamentals of liquid crystalline systems on their potential for solubility enhancement and controlled release. Liquid crystalline systems have been investigated for both oral, IV, and subcutaneous administration of both poorly soluble and soluble drugs, in addition to topical, percutaneous, and dental. Based on the data presented thus far, oral, IV, and subcutaneous delivery via liquid crystal systems for enhancing the solubility and controlling the release appears to be a viable technology platform. While there have been countless mechanistic studies on these systems, the availability of studies on *in vivo* characterization – release, compatibility, degradation – is lacking in comparison. Continuing with the *in vitro* characterization, several studies focused on the solubility of the drug in LC forming materials and LC matrix is needed, coupled with the release of the drug from different loadings with various release methods. Depending on the patent situation, several of these studies may have occurred and have not been disseminated to the public yet.

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