CUBIC LIQUID NANOCRYSTAL SYSTEM FOR DRUG DELIVERY: A STATE OF THE ART


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ABSTRACT
The present review deals with the Cubic liquid nanocrystal systems, in which the submicron-sized particles envelope a unique well-defined self-assembled nanostructured aqueous dispersions. Now a days such systems (reversed bicontinuous cubic and hexagonal mesophases) are attracting more attention to the formulation scientists owing to their unique structures and physicochemical properties. Various therapeutically active molecules can be solubilized in either aqueous or oil phase and be protected from enzymatic degradation, hydrolysis and oxidation. Furthermore, several researchers have proved the sustained type of release behaviour of the bioactive from the lyotropic liquid crystal systems. In this article, an outline of current advancement and status of cubic liquid nanocrystal systems, with respect to their types, fabrication methods and applications in the field of drug delivery are presented. In addition to these, the commercial potential of this system is also summarized.

KEYWORDS: Cubic liquid nanocrystal, Sustained release, Bioavailability, Applications

INTRODUCTION
The field of nanotechnology is evolving everyday and its findings are applied in the wide-spectrum areas, as for diagnostic purpose or for imaging, regenerative medicine or as
pharmaceuticals for drug delivery. A large array of drug delivery systems have been developed ranging from polymeric and lipidic systems to more sophisticated systems such as gold nanoparticles, carbon nanotubes and so on. However, with the advancement in the drug delivery approaches the production methods as well as the factors influencing delivery system has also expanded and become more intricate. Thus a precise control over the different process parameters as well as excipients variables involved in the production of nanoparticles is needed in order to achieve reproducible results.

Nowadays, the self-assembly of biologically significant molecules is drawing attention of researchers from all over the globe due to its importance in various systems with unique properties.\(^1,5\) The development of such well-defined nano-sized aggregates with manageable morphology provides extensive range of application in pharmaceutical formulations.\(^1,4,6,7\) These interesting self-assembled nano systems forms excellent contenders for fabricating novel composite, as well as matrices for mimicking biological system in the formation of new nanoparticulate carriers for delivering functional foods and active biomolecules (drugs, peptides and etc).\(^4,6\)

Cubic liquid nanocrystals (CLNs) has a unique self-assembly structure with well-defined thermodynamically-stable system. It comprises of a curved bi-continuous polar liquid in an aqueous environment extending in three dimensions, with a high interfacial area of 400 \(m^2/g\).\(^8,9,10\) Bi-continuous cubic phase formed through monooloein-Poloxamer 407-water system have been found to act as a carrier for all types of drug molecules.\(^11\) The cubic phase is isotropic, transparent and consists of water channel (fully swollen diameter approximately 5 nm) in between the lipid matrix, which assists both the hydrophilic and lipophilic drugs to be uploaded in it.\(^8\) The following properties of bi-continuous cubic phase makes them an excellent carrier for different drug moieties: (1) low viscosity; (2) bioadhesive property; (3) absorption enhancers (Monooloein / Phytantriol); (4) large surface area; (5) incorporated hydrophilic and hydrophobic drug; and (6) sustained drug delivery.\(^11,12\) Glyceryl monooleate acts as a penetration enhancer for the transcellular route (cross within the cells) because it interacts with the lipidic part of cell membrane and as a result disturbs the lipidic packing within.\(^13\)

They are technically classified as cubic liquid crystals because of their ability to self assemble themselves in the presence of water. However, unlike traditional amphiphiles, lyotropic
chromonic LCs are rigid rather than flexible, and their hydrophobic components are based on aromatic units rather than aliphatic chains. Unlike traditional amphiphilic CLNs, they self-organize in solution into columns via stacking of their rigid cores, rather than forming traditional micellar-based structures.

**Liquid crystal nanoparticles or Cubic Liquid nanoparticles**

The surfactant assembles into bi-layered honeycomb like structure with bi-continuous domains of water and lipid by twisting itself in a three dimensional and periodic way.

Luzzati et al. was the first to recognize the existence of cubic phases in lipid-water system using X-ray scattering measurement.\[^{14}\] Fontell et al. came to similar conclusions regarding cubic phase in ternary systems of amphiphiles with oils and water in parallel although without apparent awareness of the lipid work.\[^{15}\] Landh and Larsson got their preparation of colloidal dispersions of nonlamellar lyotropic crystalline phases patented and have termed the particles — cubosomes.\[^{16}\]

Cubosomes are unique structure with self assembly capability and have well-defined thermodynamically-stable system comprising of a curved bi-continuous polar liquid in an aqueous environment extending in three dimensions, with a high interfacial area of 400 m\(^2\)/g.\[^{8,9}\]

The production of cubosomes requires methods which are usually time consuming as well as involves high-energy input. For instance Gustafsson et al. have investigated the structure and the production of aqueous dispersions of lipid based lyotropic liquid crystalline phases. Liquid crystalline nanoparticles technology (LCNP).\[^{17}\] having following advantages:

1) LCNPs are excellent solubilizers in comparison to conventional lipid or non-lipid carriers, 2) LCNPs show high drug carrier capacity for a variety of sparingly water-soluble drugs, 3) LCNPs are an excellent vehicle to protect the sensitive drug from enzymatic and in-vivo degradation, such as peptides and proteins, 4) The LCNP system enhances the bioavailability range twenty to more than one hundred folds of water-soluble peptides, 5) Low viscosity and bioadhesive property 6) Absorption enhancer (Monoolein / Phytantriol) and large surface area, and 7) It consists of low cost raw materials and have the potential for controlled release through fictionalization; thus they provide an attractive choice for oral drug delivery.\[^{18}\]
Types of Liquid crystal nanoparticles (LCNs)

Liquid crystal nanoparticles can also be termed as ordered fluids. LCs can be subdivided into two general classes—thermotropic LCs and Lytropic LCs—depending on the environmental and molecular factors that govern how they form ordered fluid phases.

1) Thermotropic LCs (TLCs)

TLCs are molecules that form ordered fluid phases in which the temperature of the material decides the degree of average order. In contrast to conventional materials which undergo a melting transition from a crystalline solid directly into an isotropic liquid, thermotropic LCs loses their order incrementally with the increasing temperature by adopting a number of ordered yet progressively more fluid states. In terms of their molecular structure, thermotropic LCs have anisotropic shape (e.g., typically rod- or disk-shaped) with a relatively rigid core and a number of flexible peripheral alkyl tails. The rigid cores of these molecules encourage ordered packing while the flexible tails tend to disorder the system until a compromise is met to produce an ordered fluid state.[19]

2) Lytropic LCs (LLCs)

LLCs are molecules that form ordered fluid phases in which the proportion of LC mesogen relative to an added immiscible solvent such as water influence the degree of order.[20] In addition to morphology which depends on system composition, LLC phases are also sensitive to other external parameters like as temperature and pressure. In terms of molecular structure, LLCs are very different from thermotropic LCs as the former are flexible amphiphillic molecules (i.e., surfactants) that contain both a hydrophobic organic tail section and a hydrophilic head group. The shape and amphiphilic character of these molecules encourage them to self-organize into highly ordered, phase-separated matrices in the presence of a polar solvent such as water. The flexible aliphatic tails of the amphiphiles aggregate into fused hydrophobic regions while the hydrophilic head group (ionic or neutral) encapsulates the extended aqueous regions. Depending on the molecular shape/packing preferences of the LLC molecules and interfacial curvature energy considerations,[21] with the aqueous domains, LLC phases can form molecules ranging from planar bilayer lamellae to extended, cylindrical channels to 3-D interconnected channels and manifolds. Based on their symmetry, these LLC phases are termed lamellar (L), hexagonal (H), bicontinuous cubic [Q (or V)], and discontinuous cubic (I) phases.[20] They are also subdivided into type I (or type 1) and type II (or type 2) phases depending whether they are on the water-excessive (type I) or water-
deficient (type II) side of the phase diagram relative to the central L phase. The L phase is considered to have no intrinsic curvature and often viewed as the midpoint of an ideal, symmetrical LLC phase progression.\[20\]

Type I or II LLC phases are indicated with subscripts after the principal phase label designation. In addition to these more classical LLC phase architectures; there are also a number of less common LLC phases such as —intermediate (e.g., ribbon or mesh) LLC phases and lyotropic nematic phases. Based on their symmetries the intermediate ribbon and mesh-type LLC phases are sometimes called rhombohedral, monoclinic, or tetrahedral LLC phases. These phases are believed to have ribbon-like or porous mesh-like continuous or bicontinuous structures\[22\], but their structures are not well characterized. These intermediate phases can also be type I or type II structures. Lyotropic nematic phases are believed to be composed of collections of discrete disk-shaped or rod-shaped micellar aggregates having a common average orientated direction (i.e. a director) due to their anisotropic shapes and close packing considerations.\[23\]

It can be pointed out that LLC phases are different from the ubiquitous individual, phase-separated aggregate structures commonly formed by amphiphillic molecules or surfactants, such as micelles, reverse micelles, vesicles, and lipid microtubules.

These discrete aggregate structures formed from amphiphiles lacks the periodic order, and are not condensed-phase materials which are the two defining characteristics of LLC phases. For the purposes of this review, LLC phases will be defined as fluid, condensed-phase materials composed of amphiphillic molecules that have periodic order and are formed via phase separation of the amphiphiles around an added solvent which acts as a secondary component. Consequently, functional normal micelle, reverse micelle, Langmuir–Blodgett films, vesicle, and lipid microtubule systems will not be covered in this review, even though micelle and microemulsion systems have historically been assigned phase designations irrespective of the fact that such systems do not have periodic order.\[20\] There is also a small family of LCs called lyotropic chromonic LCs that are in-between traditional thermotropic LCs and LLCs. Lyotropic chromonic LCs typically bears an aromatic organic core with ionic groups lining the periphery, giving them a disk- or plank-like shape (e.g., ionic organic dye molecules).

They are technically classified as LLCs because they can self-assemble into ordered phases in the presence of water. However, unlike traditional amphiphiles, lyotropic chromonic LCs are
rigid rather than flexible, and their hydrophobic components are based on aromatic units rather than aliphatic chains. In contrast to the traditional amphiphilic LCs, they self-organize in solution into columns via stacking of their rigid cores, rather than forming traditional micellar-based structures. They also do not exhibit a critical micelle concentration or a Krafft temperature like traditional flexible amphiphiles in water. In many respects, lyotropic chromonic LCs are closer to thermotropic LCs than conventional LLCs, in terms of their structure and LC behavior. Consequently, lyotropic chromonic LCs will be not discussed in this review. Proposed applications of functional lyotropic chromonic LCs include switchable display materials, optical gratings, polarizers, biosensors, light-emitting diodes, organic transistors, and even drug delivery materials. Their structures, LC behavior, and emerging applications are discussed in two recent review articles.[24]

**Preparation techniques of Cubic liquid nanoparticles**

Three macroscopic forms of cubic phase are typically encountered: precursor, bulk gel and particulate dispersion. The precursor form exists as a solid or liquid material that forms cubic phase in response to a stimulus, such as contact with liquid. Bulk cubic phase gel is an optically isotropic, stiff, and solid like material in equilibrium with water can be dispersed into particles called cubosomes. The production of cubosomes entails two distinct technologies:

**Top-Down Technique**

Top-down approach begins with a suitable starting material and then shape the functionality from the material. In this bulk cubic phase is first produced and then dispersed with the help of high energy application into cubosome nanoparticles. Bulk cubic phase look likes a clear rigid gel formed by water-swollen cross-linked polymer chains, however, cubic phases differ in that they are a single thermodynamic phase and display periodic liquid crystalline structure. Rupture of these cubic phases occurs in a direction parallel to the shear direction and the energy required for this purpose is proportional to the number of tubular network branches that rupture.

reported that rupture of the cubic phase occurs as the bilayer breaks under applied shear stresses and flows along slip planes. The cubic phase exhibits a yield stress that increases with increasing amounts of bilayer-forming surfactants and oils, and that is inversely proportional to the crystalline unit cell dimension. Warr and Chen also suggested but could
not confirm that cubic phases may behave as lamellar phases do during dispersion with increasing shear: dispersed liquid crystalline particles form at intermediate shear rates, whereas a defect free bulk phase reforms at higher shear rates. At high oscillatory frequencies, cubic phases become highly elastic.

**Bottom-Up Technique**

The bottom-up approach first forms the nanostructure building blocks and then assembles into the final material. It is a recently developed technique for cubosome formation, allowing cubosomes to form and crystallize from precursors on the molecular length scale. Almgren et al.,[25] discussed the formation of cubosomes by dispersion of L2 or inverse micellar phase droplets in water at 80 °C, then by slowly cooling it to allow the droplets to gradually crystallize into cubosomes. Dispersion of the nanoparticles produced in the cubosomes formation can be done by several techniques: Sonication, High pressure homogenization, Spontaneous emulsification, Spray drying.

Both sonication and high-pressure homogenization suggests the development of composite dispersions containing vesicles and cubosomes in the time-dependent ratios of each particle type.[12] Large scale production of cubosomes and products containing them requires more robust processes. Spicer et al.,[9] developed a room temperature process to produce cubosomes, diluting monoolein–ethanol (or other hydrotrope) solutions with aqueous Poloxamer 407 solutions by spontaneous emulsification, producing nano-particle dispersions in the near absence of energy input beyond that required for simple blending of the two liquids. The cubosomes which are produced are more stable than those by high-energy processes, but some vesicles are also produced. A second process was also developed to allow cubosome production from a powdered precursor. Spray-dried powders comprising monoolein coated with starch or dextran form cubosomes on simple hydration. The polymers immediately provide colloidal stabilization of the cubosomes.

Hongbing et al. showed that most of the peptides and proteins with considerable potential in the treatment of brain diseases are susceptible to enzymes in vivo and hold a poor ability to cross BBB, the current work succeeded in developing a protocol for surface engineering of PEGylated cubosomes with functional molecules, mediating S14G-HN transport into the brain for ameliorating learning impairment in rats.[26]
Manish H Shah et al. demonstrated that the in situ cubic phase transforming system can be used as a carrier for protein molecules by altering the microenvironment and water uptake by the matrix. Incorporation of magnesium trisilicate (MTS) was found to improve stability of seratiopeptidase (STP) and control its release from GMO matrix.\(^{[27]}\)

Sung et al. showed that Monooloein cubosome effectively damped the fluctuation I time-dependent size and zeta potential KIOM-C. At all PH tested (PH 2.0-10.0), baicalin, a major component of KIOM-C, was found to be chemically stable for 48 h at a room temperature. With the aid of cubosome, baicalin suspension remained homogenous without significant sedimentation for 180 minutes.\(^{[28]}\)

Di Bei et al. showed that various factors influence the loading and encapsulation efficiency of Dacarbazine loaded cubosomes. Taek et al.,\(^{[30]}\) concluded that the nanoparticles of the cubic phases (cubosomes containing HKL) were stable in terms of size even at 16% ethanol concentration. In addition, the cubosomes enhanced the in vitro skin permeation of HKL. Therefore, cubosomes contains HKL are thought to be one of the potent carriers in hair tonics claiming hair growth promotion.\(^{[29]}\)

Xin Jin et al. aimed to improve the bioavailability of 20(S)-protopanaxadiol (PPD) by using cubic nanoparticles to enhance absorption in which piperine was loaded for inhibition of metabolism. This novel carrier containing piperine showed an increase in the absorption and inhibition of metabolism which can be exploited for anticancer drugs that are extensively metabolized and have low absorption.\(^{[11]}\)

Zhiwen Yang et al., formulated phytantriol based cubosomes containing amphotericin B as a formulation for oral delivery. Cubosomes having nanometer-sized particles with reproducible narrow particle size distribution were optimally obtained under homogenization at 1200 bar for 9 cycles.\(^{[31]}\) These cubosomes will be utilized in subsequent studies to determine the oral adsorption of cubosomes as a mean to control loading and release of AmB. Idit et al., worked on designing the cubosome with varying internal and external compositions in sizes ranging from 100 nm – 10μm. These structures are stable for period of years and can be delivered orally, intravenously as well as topically. Cubosomes attains a defined structure when surfactants are added to water at high concentration and they self-assemble themselves to form thick fluids which are called liquid crystals, the most viscous liquid crystal is a
continuous cubic phase, a unique material that is clear and resembles stiff gelatin. When these cubic phases are dispersed into small particles, these particles are termed as cubosomes.\[32\]

Nakano et al., have proposed a method for the fabrication of cubosomes based on hydration of a dry film of monoolein/poloxamer with an aqueous buffer. Monoolein is a nontoxic, biodegradable and biocompatible material classified as GRAS (generally recognized as safe) and it is included in the FDA inactive ingredients guide and in non-parenteral medicines licensed in the United Kingdom. Surfactants, which are used in the production of cubosomes, are poloxamer 407 in between the concentration range of 0% to 20% w/w with respect to the disperse phase. The concentration of the monoglyceride/surfactant mixture generally takes between 2.5% and 10% w/w with respect to the total weight of the dispersion. Most cubosome research over the last two decades has focused on top-down techniques, whereby bulk cubic phase is first produced and then dispersed by high energy processing into cubosome nanoparticles.

When lipid molecule is heated, instead of melting directly convert into an isotropic liquid. The ability to exist in several different phases is an important property of pure lipids and lipid mixtures; it depends on temperature, hydration and lipid class. In general monoglycerides exhibit different phase behaviours when they are exposed to water.\[31\]

In spite of enormous advantages of cubosomal delivery, it is still not so much popular commercially. There are two major constraints in the commercialisation of cubosomal preparations:

1. First, the lipids needed for their preparation should be of high purity and hence, are expensive.
2. Secondly, liposomal preparations are characteristically unstable and require special storage conditions (below 0ºC) even when the products are freeze-dried.

As a result of this stability problem, the dosage forms are limited to injection (freeze-dried) powders for reconstitution immediately before use. Because of these constraints only a few products have actually been commercialised in spite of the large volume of research on cubosomes.
Sung Kyeong Hong et al. showed that Monoolein (MO) cubosomes were investigated in terms of in vitro skin permeation enhancer of KIOM-MA-128 (MA-128), a natural product known to be efficacious against atopic dermatitis. First, an aqueous suspension of MA-128 was prepared by homogenizing the powder in Pluronic F-127 (a dispersant) solution in water. The Pluronic F-127 concentration and the pH have no significant effect on the size and the zeta potential of MA-128 particles. The mean diameter and the zeta potentials fell within 1000–1500 nm and -10 to -20 mV, respectively. The sedimentation rate of the particles was found to be lower at a higher concentration of the polymeric dispersant, possibly because the polymeric surfactant can act as a spring and push away approaching particles. The size of MO cubosomes was found to be in between 10 to 100 of nanometers and exhibited black and white stripes. Cumulative amount of MA-128 permeated through hairless mouse skin was obviously higher when the cubosome was included in the MA-128 suspensions. However, the cumulative permeation amount was found to be inversely proportional to the content of cubosomes, when the contents of cubosome in the suspension was increased from 0.5% to 2.0% with MA-128 concentrations kept constant (2%).

Xin Jin et al. showed that 20(S)-protopanaxadiol (PPD), similar to several other anticancer agents, has low oral absorption and is extensively metabolized. These factors limit the use of PPD for treatment of human diseases.\textsuperscript{[11]} The in vitro release of PPD from these nanoparticles was less than 5% at 12 hours. PPD-cubosome and PPD-cubosome loaded with piperine (molar ratio PPD/piperine, 1:3) increased the apical to basolateral permeability values of PPD across the Caco-2 cell monolayer from 53% to 64%, respectively. In addition, the results of a pharmacokinetic study in rats showed that the relative bioavailabilities of PPD-cubosome [area under concentration–time curve (AUC)\textsuperscript{0–\infty}] and PPD-cubosome containing piperine (AUC\textsuperscript{0–\infty}) compared to that of raw PPD (AUC\textsuperscript{0–\infty}) were 166% and 248%, respectively. The increased bioavailability of PPD-cubosome loaded with piperine is due to an increase in absorption and inhibition of metabolism of PPD by cubic nanoparticles containing piperine rather than because of improved release of PPD. The cubic nanoparticles containing piperine may be a promising oral carrier for anticancer drugs with poor oral absorption and that undergo extensive metabolism by cytochrome P450.\textsuperscript{[11]}

Rizwan et al. showed that the new generation vaccines increasingly utilize highly purified peptides and proteins as the target antigen, however these are often poorly immunogenic. One of the most promising strategies for improving immunogenicity of such subunit vaccines is
through their incorporation into particulate carriers. Here we report the preparation, physicochemical characterization and in vivo immunological activity of cubosomes, a novel lipid-based nanostructured particulate carrier, modified to include the Toll-like receptor agonists monophosphoryl lipid A and imiquimod. The immunological activity of cubosome formulations was compared to that of liposome and alum formulations. Sustained release from the model antigen ovalbumin (Ova) was observed in vitro and in vivo from cubosomes. Cubosomes with adjuvants induces robust CD8+ and CD4+ T cell proliferation and interferon-γ production, as well as the production of Ova-specific antibodies. Cubosomes with adjuvants were found to be more efficient at generating Ova-specific cellular responses and were equally as effective in generating humoral responses when compared to liposomes+ adjuvants and alum. Overall, the results strongly supports that cubosomes have the potential to act as effective sustained release vaccine delivery systems.

Jain et al. showed that A PEGylated drug delivery system of paclitaxel (PTX), based on glycercyl monooleate (GMO) was prepared by optimizing various parameters in order to explore its potential in anticancer therapy. The prepared system was characterized through polarized light microscopy, TEM, AFM and SAXS to reveal its liquid crystalline nature. As GMO based LCNPs exhibits high haemolytic toxicity and faster release of entrapped drug (66.2 - 2.5% in 24 h), PEGylation strategy was utilized to increase the haemocompatibility (reduction in haemolysis from 60.3 - 10.2 to 4.4 - 1.3%) and control the release of PTX (43.6 - 3.2% released in 24 h). The cytotoxic potential and cellular uptake was assessed in MCF-7 cell lines. Further, biodistribution studies were carried out in EAT (Ehrlich Ascites tumor) bearing mice using 99mTc-(Technetium radionuclide) labeled formulations and an enhanced circulation time and tumor accumulation (14 and 8 times, respectively) were observed with PEGylated carriers over plain ones, in a 24 h study. Finally, tumor growth inhibition experiment was performed and after 15 days, control group exhibited 15 times enhancement in tumor volume, while plain and PEGylated systems exhibited only 8 and 4 times enhancement, respectively, as compared to initial tumor volume. The results suggest that PEGylation enhances the haemocompatibility and efficacy of GMO based system that may serve as an efficient i.v. delivery vehicle for paclitaxel.[33]

Tri-Hung Nguyen et al. demonstrated the aptitude of nanostructured liquid crystal particles to prolong the assimilation of a poorly water soluble drug after oral administration. Cubic liquid crystalline particles developed by utilizing phytantriol (PHY) were found to be prolonging
the absorption of cinnarizine (CZ) more than 48 h after administering orally to rats. Concentrations of drug in the plasma were sustained, that was in the range of 21.5±1.5 ng/mL during 12 to 48 h. In harsh contrast, cubosomes formulated using glyceryl monooleate (GMO) did not prolong the absorption of CZ and the drug concentrations fell below the limit of quantification levels after 24 h.[33]

Thapa et al. found that Liquid crystalline nanoparticles exhibits unique structures which can be used in the delivery of various active pharmaceutical ingredients. The effect of saturated fatty acids on tacrolimus-loaded liquid crystalline nanoparticles stabilized with poloxamer 407 was also observed. Characterizations of nanoparticles were done using optical and transmission electron microscopy, particle size, and encapsulation efficiency examination. Microscopic data revealed the formation of hexosomes for monoolein-fatty acid and cubosomes for monoolein dispersions systems. Encapsulation efficiency of tacrolimus was reported to be about 99 %. In vitro release study confirmed that the monoolein and carbon chain lengths of the fatty acid were the different factors which affected the drug release from the developed systems.[34]

Cubic phase of cubosomes is attractive for controlled release because of its small pore size (5-10 nm); its ability to solubilize hydrophobic, hydrophilic, and amphiphilic molecules; and its biodegradability by simple enzyme action. Cubic phase is strongly bioadhesive and is thought to be a excellent skin penetrator having compatibility with topical and mucosal deposition and delivery of active ingredients. Recent studies have emphasized similarities between the bi-continuous structures formed in human skin layers and those comprising cubic phases, offering the promise of better skin transport and consequently the treatment. The tortuous structure of cubic phase tends itself well to slowing diffusive release of solubilized actives. Theory predicts the minimum reduction of a solute’s free solution diffusivity by 33%. Commercial applications of cubosomes have been developed for periodontal disease that is based on triglyceride–monoolein mixtures combined with Metronidazole as drug. The lipid–drug mixture forms a low-viscosity liquid that, when applied to the gums and placed in contact with saliva, hydrates to form a bulk cubic phase which then delivers the drug to the gum. A short list of applications includes the delivery of actives for periodontal disease and implants via in vivo[35] and topical delivery[36] and as bioadhesives.[37]
Oral drug Delivery
Cubosomes address the varied challenges in oral delivery of numerous promising compounds including poor aqueous solubility, poor absorption, and large molecular size. These are both liquid and powder in capsule products comprising our self-emulsifying liquid crystalline nanoparticles technology (LCNP), which bears the following advantages: LCNPs are an excellent vehicle to protect the sensitive drug from enzymatic degradation and in-vivo degradation, such as peptides and proteins (Scriven., 1976). The LCNP system enhances the bioavailability range from 20-100 folds of water-soluble peptides.

In an alternative application large proteins have been encapsulated for local activity in the gastrointestinal tract. LCNP carriers was combined with controlled release and targeting functionalities. The particles are designed to form in situ in a controlled rate, which enables an effective in vivo distribution of the drug. LCNP carriers can also be released at different absorption sites, for example in the upper or lower intestine, which is important for the drugs having narrow regional absorption window.

Topical Drug Delivery Systems
Topical delivery systems are based on the exploitation of unique properties of liquid crystal (LC) and liquid crystal nanoparticle (LCNP) technologies. Topical drug delivery systems are unique in situ forming bioadhesive LC systems which facilitates controlled and effective drug delivery to mucosal surfaces (buccal, ophthalmic, vaginal and others). This fascinating system forms a thin surface film at mucosal layer consisting of a liquid crystal matrix in which nanostructure can be controlled for achieving an optimal delivery profile and to provide good temporary protection of sore and sensitive skin. Their unique solubilizing, encapsulating, transporting and protecting capacity are advantageously exploited in liquid and gel products in order to increase transdermal and nasal bioavailability of small molecules and peptides.

Intravenous Drug Delivery Systems
Lipid nanoparticles comprising interior liquid crystal structures of curved lipid membranes are used to solubilise, encapsulate and deliver medications to diseased areas within the body. While emulsions and liposomes have found use as intravenous carriers in drug products, LCNP structures increased payloads of peptides, proteins and many insoluble small molecules, and are ideal as carriers for injection or infusion of many actives.
Commercial product of Cubic liquid nanoparticles

Some cubosomal products which are either launched or investigated in the field of oral delivery (Table 1) such as Camurus gel technology is known as Fluid Crystal and their nanoparticle systems are known as Fluid Crystal Nano-Particles. The three varieties of Fluid Crystal NP carriers are Cubosomes, Hexosomes, and Flexosomes. Camurus technologies are found to be applicable in oral, topical and parenteral drug delivery (http://en.wikipedia.org/wiki/Camurus). The first drug product based on LC delivery systems to reach the market using the special properties of liquid crystal phase structures was Elyzol® Dental Gel. This was introduced on the market in 1992 by Dumex on a license from Camurus and is now sold by Colgate® Oral Pharmaceuticals.

Table 1: Various marketed cubic liquid nanoparticles

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<th>S. No.</th>
<th>Industries</th>
<th>Products</th>
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<tbody>
<tr>
<td>1</td>
<td>Camurus Technologies</td>
<td>Fluid crystals</td>
</tr>
<tr>
<td>2</td>
<td>Dumex Corporation</td>
<td>Elyzol Dental Gel</td>
</tr>
<tr>
<td>3</td>
<td>Camurus Technologies (Phase III)</td>
<td>CAM 2028 (Bioadhesive fluid crystal film)</td>
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CAM2028 is administered as a lipid-based liquid that spreads on the intra-oral mucosal surfaces and gets transformed into a strongly bioadhesive Fluid Crystal film which mechanically protects the sensitized and sore epithelium of the oral cavity. In a recently completed phase II clinical trial, CAM2028 has been demonstrated to give an immediate and significant reduction of pain (http://www.camurus.com/).

A number of companies including L’Oréal, Nivia and Procter and Gamble are investigating cubosomes for its cosmetic applications. Despite this interest, cubosomes have not yet led to products. The methods of formation must be efficient and cost-effective for scale up before this type of technology can be applied in a mass scale. The presence of large amounts of water during cubosomes formation makes it difficult to load water soluble actives.

CONCLUSION

It is a very fascinating challenge in drug delivery research to develop potentially safe and effective nanosystems as novel carriers for delivery of bioactive molecules. Cubic liquid nanocrystal systems are flexible pharmaceuticals which can be administered through all common routes of administration like oral, topical, ocular and parenteral. Taking into account potential advantages and higher bioavailability, lyotropic liquid crystal systems are considered as suitable candidates for delivery of both water soluble and insoluble bioactive
molecules. Cubic liquid nanocrystal systems modified with functionalized ligands presents a new way of these systems by being able to target desired organs with better results. Furthermore, these systems also provide a platform to produce a choice for currently available high cost drugs. In conclusion, engineered cubic liquid nanocrystal systems have huge potential to deliver bioactive molecules in a more satisfactory and efficient dosage form with high commercial applicability.

REFERENCE


