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Review on Liquid Crystal Cream for Topical Drug Delivery

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Abstract

Liquid crystal creams represent a novel approach in skincare formulations, leveraging the unique properties of liquid crystal technology to improve skin hydration and barrier function. An overview of current developments in liquid crystal cream formulations is given in this article, with an emphasis on the benefits they offer for skincare and their composition and structure. Liquid crystal creams mimic the lipid bilayers of the skin, offering enhanced compatibility and permeability. Liquid crystal creams have emerged as a promising vehicle for topical drug delivery in pharmaceutical formulations, offering unique advantages for enhancing drug permeation, stability, and efficacy. This comprehensive review explores the application of liquid crystal technology in topical drug delivery systems, with a focus on composition, structure, and therapeutic applications. Liquid crystal creams, by mimicking the organization of biological membranes, facilitate the penetration of drugs across the skin barrier, resulting in improved bioavailability and therapeutic outcomes. Their versatile composition allows for the incorporation of à wide range of drugs, including hydrophilic and lipophilic compounds, peptides, and proteins, enabling targeted delivery to specific skin layers or underlying tissues. Furthermore, the rheological properties of liquid crystal creams can be tailored to optimize drug release kinetics, providing sustained and controlled drug delivery over extended periods. Additionally, the incorporation of penetration enhancers and other excipients into liquid crystal creams can further enhance drug permeation and tissue targeting, expanding their potential applications in dermatology, cosmeceuticals, and wound healing. This review highlights the potential of liquid crystal creams as versatile and effective platforms for topical drug delivery in pharmaceutical formulations, with opportunities for continued research and development to optimize their performance and clinical utility.

Keywords: Liquid crystal, cream, skin, topical drug delivery, penetration, bioavailability

INTRODUCTION

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The characteristics of both liquid and solid states are combined in the liquid crystalline state. Solids have a crystalline structure and are organized, whereas liquids are characterized by their capacity to flow [1]. In 1888, Austrian Botanist Friedrich Reinitzer began research on liquid crystals [2]. Reinitzer studied the substances that display a phase of matter with characteristics halfway between those of a traditional liquid and solid crystals are called liquid crystals. It is frequently referred to as a condition of matter or a mesomorphic state. The degree of molecular order in a mesomorphic state is intermediate between that of isotropic liquids, gases, and amorphous solids, which lack long-range order, and that of perfect three-dimensional, long-range positional, and orientational order seen in solid crystals. Another

name for it is meso (intermediate). Although a liquid crystal may flow like a liquid, its molecules are arranged and/or directed to resemble crystals. Different optical features (such as birefringence) can be used to distinguish between the various types of Liquid Crystal (LC) phases [3].

Preparation of Liquid Crystal

The mesophase is obtained by adding a solvent or raising the temperature from the crystalline state. As a result, thermotropic and lyotropic liquid crystals can be distinguished from one another. Similar to thermotropic liquid crystals, lyotropic liquid crystals can undergo a phase transition between various mesophases in response to temperature changes [4].

TYPE OF LIQUID CRYSTAL

Thermotropic Liquid Crystals

Over a century ago, the first liquid crystals were discovered to be calamitic mesophases. After melting cholesteryl esters, botanist Friedrich Reinitzer noticed birefringence. He consulted crystallization microscopy expert Otto Lehmann, a physicist, who explained the birefringence as a parallel orientation of molecules within a liquid crystal, a novel state. Nevertheless, these cholesteric liquid crystals show that the anisometric molecules are oriented parallelly and that the orientation direction rotates layer by layer in a left- or right-handed helix. Pitch, which is often in the visible light spectrum, is the layer distance at which a 360° revolution has been executed. The distinctive color play of cholesteric liquid crystals is caused by both the phenomena and the temperature change of the pitch. Cholesterics require the addition of a mesogen or an already chiral mesogen [5].

Lyotropic Liquid Crystals

Lyotropic liquid crystals differ from thermotropic liquid crystals. Mesogens, or the hydrates or solvates of molecules as well as the associates of hydrated or solvated molecules, produce them instead of the molecules themselves. The degree of hydration or solvation, respectively, in the presence of water or a combination of water and an organic solvent—the most significant solvents for drug molecules—depends on the amphiphilic characteristics of the drug molecule. Hydration of the mostly rod-shaped molecule—and the same holds for solvation—results in different geometries, cones, or cylinders [6].

IDEAL CHARACTERISTICS OF LIQUID CRYSTAL

1. There are two types of liquid crystal such as lyotropic and thermotropic liquid crystal.
2. The liquid crystal can flow similarly to liquid due to the transition phase.
3. Discotics phases are flat having disc-like molecules which have cores adjacent to aromatic rings.
4. Many chemical compounds are known that can exhibit one or several liquid crystal phases.
5. Liquid crystal phases are mostly cloudy in appearance and they scatter light in the same way as colloids.

METHODS FOR THE CHARACTERIZATION OF LIQUID CRYSTALS

1. Polarized light microscopy
2. Transmission electron microscopy (TEM)
3. X-ray scattering
4. Differential scanning calorimetry (DSC)

APPLICATIONS

Liquid Crystalline Formulations for Dermal Application

Amphiphilic excipients in medication formulations can also produce lyotropic liquid crystals, and pharmacological molecules with amphiphilic characteristics can form lyotropic mesophases. Particularly after dissolving in a solvent, surfactants—which are frequently utilized as emulsifiers in cutaneous formulations—associate with micelles.

The likelihood of contact between these micelles rises with increasing concentration, which leads to the development of liquid crystals.

Surfactant Gels

Gels are the only applications for monophasic lyotropic liquid crystal systems, which are very uncommon. In the presence of water, a range of polar surfactants, such as ethoxylated fatty alcohols, become hydrated and form spherical or ellipsoidal micelles. At high surfactant concentrations, these associates are densely packed and thus are identified as cubic liquid crystals [7].

Ointments and Creams

Typically, ointments and creams have a much lower surfactant content than surfactant gels. Ointments are nonaqueous preparations, whereas creams derive from ointments by adding water. The microstructure of both ointments and creams may consist of liquid crystals, as far as a liquid crystalline network or matrix is formed by amphiphilic molecules. In the case of a liquid crystalline matrix, the system is easier to be deformed by shear. Such formulations show plastic and thixotropic flow behavior on shear. While the crystalline matrix is often irreversibly damaged by shear, a liquid crystalline matrix shows a short regeneration period of the sheared matrix. It is necessary to choose amphiphilic surfactants that form lyotropic liquid crystals at room temperature to create a liquid crystalline matrix. Preferably lamellar liquid crystals should be formed that can solubilize high amounts of ingredients and to spread through the whole formulation as a network-forming cross-linked matrix. In contrast, ointments that contain long-chain fatty alcohols such as cetyl and/or stearyl alcohol, have a crystalline structure at room temperature [8].

Transdermal Patches

For a systemic effect by percutaneous penetration of a pharmacological component, there must be a high potency of the drug for the low dose to be delivered, as well as a high permeability through the stratum corneum and the living tissue underlying.

For situations when the biological half-life is brief, controlled-release transdermal systems are a suitable option. With zero-order kinetics or regulated release of the medicinal material from a reservoir, transdermal patches are advanced medical devices. One type of control element is a matrix or a membrane. The earliest patches on the market were membrane-controlled. Nevertheless, if the membrane is harmed during handling, these patches have the drawback of "dose-dumping." Even liquid crystalline polymers have been studied for their potential utility in membrane-controlled transdermal patches to guarantee the intended medication control [9]. The porous polymer matrix, which functions as both a drug reservoir and an adhesive element in addition to controlling drug release, is the single functional component of the matrix-controlled transdermal patch. Worldwide, transdermal patches containing glycerol triturate, testosterone, estradiol, clonidine, scopolamine, fentanyl, and nicotine are commercialized. The patch must stay at the designated body spot for a maximum of one week. In this instance, there is a significant amount of medication in the reservoir. It is advised to use liquid crystalline vehicles with lamellar microstructure as transdermal patch reservoirs because of their excellent solubilization capacities [10]. Although the lamellar liquid crystal's high surfactant content could irritate skin. The membrane-controlled patch prevents skin irritation by keeping the liquid crystalline vehicle out of direct contact with the skin.

Liquid Crystals in Cosmetics

In cosmetics, liquid crystals are mostly utilized as ornamental elements. Because of their iridescent color effects, cholesterol liquid crystals are especially useful and are used in lipsticks, nail polish, and eye shadow. Body temperature causes these thermotropic liquid crystals' structures to alter, producing the desired color effect. These liquid crystals, which are spread in a hydrogel, are thermotropic cholesteric and have been used in body care cosmetics recently. The iridescent liquid crystalline particles are distributed statistically in the gel (Este Lauder Time Zone Moisture Recharging Complex) or concentrated locally (Vichy Re structure Contour des Yeux) to give the formulation the desired appearance, depending on whether this dispersion requires stirring or a special spraying process. So far, there have been no published tests evaluating the liquid crystalline components' cosmetic efficacy [11].

Solubility Enhancement of Poorly Soluble Drugs

A wide range of compounds dissolve better in lyotropic liquid crystals. Hydrocortisone is one such instance. Although it is frequently applied topically, its applications have been restricted because the maximum concentration that can be achieved is just 1%. as soon as hydrocortisone reaches 4%. Liquid crystals might eventually take the lead as the main solvent for topical treatments [12, 13].

Biological and Chemical Sensing

It has been successfully shown that LCs can detect and analyze a variety of bacteria and viruses. Furthermore, certain non-toxic lipophilic compounds (LCs) have been identified and employed to promote the proliferation of mammalian cells and to describe the interfacial cell-protein interaction. Droplets of LCs coated with polyelectrolytes help identify charged macromolecules in a solution. Bipolar-to-radial ordering transitions are produced when these positively charged dendrimers are adsorbed on negatively charged polyelectrolyte-coated droplets. These transitions are primarily influenced by the size and quantity of droplets in the solution [14, 15].

Drug Delivery Utilizing Liquid Crystal Structure

Since the active drug component dissolves directly onto vitamin E TPGs to generate a genuine molecular solution—not an emulsion or microemulsion—vitamin E TPGS/drug compositions and procedures are offered that eliminate the need for surfactants or evaporated cosolvents. The invention provides a TPGS/sedate framework that dissolves gradually and absorbs gastrointestinal liquid into the grid at the liquid interface of the measuring shape, where a gel-like liquid crystal forms [16, 17]. This gel front forms a liquid crystal boundary where the greatest breakdown of tranquilizers occurs. Synchronization occurs at this liquid crystal/GI fluid barrier, where the rate of liquid crystal creation equals the rate of liquid crystal breakdown at the water interface, allowing for controlled order release of the medication into [16, 18]

Stability of Drug

Stable hydrocarbon foam has been produced using lyotropic liquid crystals. Because hydrocarbons have a surface tension so low that adsorption to an oil-soluble surfactant would not significantly affect the material, producing hydrocarbon foams has proven to be challenging in the past. In the absence of adsorption, hydrocarbons function as liquids. While the surfactant and water can interact and dissolve in one another, the surfactant cannot dissolve in water. Instead, it can dissolve in the hydrocarbon [12, 19].

Ophthalmic Delivery

This is another area of interest for which LLC NPs are being investigated as potential therapeutic candidates. Cubosomes can be used as nanocarriers for ocular medications to achieve benefits including better pre-ocular retention, decreased ocular irritancy, and increased bioavailability, according to recent findings published by Gan et al. When dexamethasone (DEX) and flurbiprofen are formulated in cubosome form, their trans-corneal permeability is improved. In fact, the ocular bioavailability of the drug-loaded cubosomes is increased because they stay in the pre-ocular region for a longer period of time than similar solutions applied through eye drops. Furthermore, it has been established that the DEX-cubosome formulation does not affect the cornea's tissue integrity or structure. The composition of cubosomes for flurbiprofen lessens its natural irritancy [19–22].

Cancer Therapeutics

Is the most extensively documented use of cubosome (liquid crystal) systems? In vitro cubosomes have been used to deliver cancer medications to cell lines, such as human hepatocellular carcinoma (HepG2) cells, glioma T98G cells, and mouse 3T3 fibroblasts. These medicines include doxorubicin [12], sorafenib, 5-fluorouracil, and quercetin. As the microenvironment of tumor cells is more acidic, pH stimulation can help deliver chemotherapy payloads. Although early signals are promising, a significant amount of in vivo study is required to establish cubosomes as viable choices in cancer therapies [23–27].

Topical Treatment

The barrier function of the highly structured stratum corneum, the skin's outermost layer, limits the amount of medicine that can penetrate the skin during the transdermal distribution of active molecules. To increase skin permeability, several methods have been suggested, such as iontophoresis, application of skin permeation enhancer, and chemical modification of the active molecule. It is crucial to increase the thermodynamic activity of the active ingredient in the vehicle and decrease it in the skin when using topical preparations. This will decrease the function of the skin's barrier and improve the molecule's partition from the vehicle to the skin [12, 28]. The capacity of cubosomes, or liquid crystals, to alter permeability has drawn attention to them as potential topical delivery systems. One of the most effective topical treatments for burns is silver sulfadiazine, but it requires a delivery system. Cubosomes stabilized with F127 and polyvinyl alcohol were created from monoolein, loaded with silver sulfadiazine, and then added to hydrogels (cubogels) as a possible burn treatment. Compared to the currently available product, an in vivo study demonstrated the efficacy of the cubic nano-structured vehicle in treating deep second-degree burns. This could lead to improved patient compliance, great healing outcomes, and fewer side effects [12, 29].

Temperature Modulated

drug penetration via cellulose membranes coated with liquid crystals. Sensitivity-sensitive membranes can function as "permeability valves" or "on-off switches," generating pulsating release patterns in which environmental or external stimuli regulate the mass transfer's pace and period. Thermo-responsive cellulose nitrate (CN) and cellulose acetate (CA) monolayer membranes with thermotropic liquid crystals were created to prevent drug permeability. To control drug permeability, 4'-methyl-2-cyanobiphenyl, a low molecular thermotropic liquid crystal with a nematic to the isotropic phase transition temperature of 41.5°C, was used. The cellulose membranes without liquid crystal were found to be insensitive to changes in temperature when it came to drug permeation, but the membranes with liquid crystal entrapment showed a clear increase in permeability when the temperature was elevated to above the drug's liquid crystal transition temperature [30, 31].

Vaccines

In addition to their use in cancer treatments, cubosomes are important components of vaccinations. Antigens, adjuvants, and/or proper delivery of immunostimulants, including polysaccharides, into the cubosome membrane can be used to load cubosomes. In a study, inactivated viruses were administered subcutaneously together with phytantriol cubosomes containing polysaccharides. It was shown that by encouraging antigen delivery into lymph nodes and boosting the immunological response, cubosomes containing polysaccharides could magnify the immune effects of immunostimulants [12, 32].

ADVANTAGES OF LIQUID CRYSTAL IN PHARMACEUTICALS

Increased Stability

Coalescence is inhibited by the multilayers surrounding the oil droplets' emulsion stability. When oil droplets combine, the emulsion fractures. The emulsion's greater stability is a result of this coalescence barrier.

Prolonged Hydration

Lamellar liquid crystalline and gel networks contain water layers, suggesting that these structures can bind half of the water in the oil in an oil-in-water emulsion.

This type of water is less likely to evaporate when applied topically, allowing for a prolonged moisturizing and hydrating impact that is essential for the absorption of drugs.

Controlled Drug Delivery

The medicine dissolved in the oil phase of an emulsion is not allowed to release quickly thanks to liquid crystals. The lamellar liquid crystalline multilayer is responsible for this, as it lessens the drug's

interfacial transit as it dissolves in the oil droplets. Under polarized light, microscopic observations reveal the extraordinarily thick liquid crystalline lamellar layer around the oil droplets [33].

METHOD OF PREPARATION LIQUID CRYSTAL CREAM USING DIFFERENT DRUG

Itraconazole

A liquid crystalline emollient cream was prepared containing poly oxyethylene stearyl ether as a surfactant, cetostearyl alcohol as a cosurfactant, and silicon as an oil phase (A). The aqueous phase (B) contains propylene glycol, preservatives, and water. The oil phase (A) was melted at 70°C in the water bath, and 1% itraconazole was added and mixed well. The aqueous phase was heated to the same temperature. The oil phase was added dropwise to the aqueous phase while mixing at high-speed using a blender and then cooled to room temperature. The system was then stored for about 48 hours until equilibrium was reached before being subjected to evaluation [34].

Tolnaftate

A Lyotropic liquid crystalline emollient cream was prepared by containing Brij 78 as a surfactant, cetostearyl alcohol as a cosurfactant, and silicon as an oil phase. The aqueous phase contains propylene glycol, preservative, and water. The oil phase was melted at 70°C in the water bath, and 1% tolnaftate was added and mixed well. The aqueous phase was heated to the same temperature. The oil phase was added dropwise to the aqueous phase while mixing at high-speed using a blender and then cooled to room temperature. The system was then stored for about 48 hours until equilibrium was reached before being subjected to evaluation [3].

Garcinia mangostana Extract

Garcinia mangostana liquid crystal cream was prepared as an oil-in-water emulsion cream. The process started with using NIKKOMULESE LC, cetostearyl alcohol, caprylic/capric triglyceride, and *G. mangostana* partially purified extract (0.1% w/w) as oil phase adding into 1,3-butylene glycol, Carbopol ultrez, L-arginine and water at 80°C. The mixture was homogenized and left to cool down to 50°C before DMDM hydantoin was added and mixed. The product was evaluated with polarized light microscopy [35].

Germinated Brown Rice

The formulation strategy for this research was to use Montanov 202 (a natural, on-ionic, oil-in-water emulsifier that is palm oil-free) to create liquid crystals. Liquid crystal creams were formulated by mixing phase A (aqueous phase), phase B (emulsifier), phase C (Sepiplus 400), and phase D (skin conditioning agent, preservative, and fragrance) separately. Afterward, phase A was gently added to phase B under the heated condition at 70–75°C and using a homogenizer at 6000 rounds/minute for 8 min. Then, phase C was added into the homogenizer and continually mixed for 2 min. After cooling down to 40°C, the homogenizer's speed was adjusted to 800 rounds/minute for 30 min. Lastly, phase D was added and continually mixed with the homogenizer using the same homogenizing speed for 10 min and the final pH of the product was adjusted to 5.00. Liquid crystal creams were prepared as two formulations, without and with germinated brown rice extract (1.00–1.20% w/w) as F1 and F2, respectively. The proper liquid crystal cream for his work was a cream, that absorbed quickly and did not leave a greasy feeling on the skin, and felt light-weight, supple, and soft to the touch [36].

CONCLUSION

The conclusions of the article on liquid crystal cream for topical drug delivery highlight its potential as a promising vehicle for enhanced drug penetration and controlled release, offering advantages such as improved stability, biocompatibility, and versatility in formulation. Further research and clinical studies are warranted to fully explore its efficacy and safety across different therapeutic applications, ultimately paving the way for its integration into mainstream pharmaceutical practice.

Conflict of Interest

None.

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None.

Ethics Statement
None.

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