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*Corresponding author

Wesam R Kadhum, Ph.D, Department of Pharmacy, Kut University College, AL Kut, Wasit 52001, Iraq, Telephone No: 00964-782-825-5935 (Iraq); 0081-80-9462-0134 (Japan)

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Mini Review

Characterizations of Liquid Crystals as A Transdermal Drug Delivery System

Wesam R Kadhum[1*], Saeed AS Al-Zuhairy[1], Radhi K Obaid[1], Muqdad Alhijjaj[2,3]

[1]*Department of Pharmacy, Kut University College, AL Kut, Wasit, 52001, Iraq*

[2] *Department of Pharmaceutics, College of Pharmacy, University of Basrah, Basrah 61004, Iraq*

[3]*Department of Pharmacy, Al-Kunooze University College, Basrah 61029, Iraq*

Abstract

The outermost layer of skin, the stratum corneum, has a role as the primary barrier against water evaporation from the body and drug entry through skin into the body. Thus, overcoming the stratum corneum barrier is important to develop transdermal drug delivery systems. Transdermal administration of drugs represents an excellent alternative to conventional pharmaceutical dosage forms. However, insufficient penetration of the active pharmaceutical substance through the skin is a common problem. Thus, in the present review we discussed the characterizations and the skin permeation enhancing ability of liquid crystal (LC) topical formulations.

Introduction

Liquid crystals (LCs) are semisolids made of lipids with crystalline structures combining the properties of both crystal and liquid states. Molecules in crystal are highly ordered, while those in liquid are free to diffuse in a random way. Thus, molecules in LC phases diffuse like the molecules in liquid but contain some degree of order [1-4]. A generally used term is the mesophase for LC, indicating such a unique structure is between those of true liquid and solid crystals [5]. In general, LCs can be classified into two categories, i.e., thermotropic and lyotropic. Thermotropic LCs are formed by a change in temperature, whereas lyotropic phases are obtained when mixed with some solvent. Lyotropic LCs usually consist of amphiphilic substances like surfactants and solvents. Amphiphilic substances become micelle at a low concentration, having cluster of molecules with their polar groups oriented in the water. This is a liquid isotropic phase, where isotropic means identical properties of the structure in all directions. More ordered structures such as hexagonal, lamellar and cubic phases are formed at higher concentrations. These structures are formed, due to insufficient water to fill up spaces between the spherical or elongated micelles [6,7]. Depending on the solvent concentration and the polarity of solvated mesogen, these systems can undergo phase transitions and structure modifications. Thus, their consistencies and rheological properties can be systematically changed as required [5,8]. Lyotropic LCs formed with aqueous surfactants can absorb water from the environment, inducing spontaneous phase-transition and forming lamellar phase (Lα), cubic phase (V2) and hexagonal phase (H2) [9,10]. Among them, cubic phase and hexagonal phase have received much attention due to their highly ordered internal structures, and can be used as a slow release matrix for active pharmaceutical ingredients with various molecular sizes and polarities [11,12]. Cubic and hexagonal LCs are often spontaneously formed by addition of certain amphiphilic lipids in an aqueous environment [13]. When these LCs are dispersed into nanoparticles by addition of excess water with the stabilizers such as Pluronic copolymers and Myrj series [14], they form stable colloidal dispersions which are termed cubosomes and hexosomes, respectively [15-18]. During the last few decades, increasing attention has been paid to LC formulations including cubosomes and hexosomes because of their remarkable structural complexity and usefulness in diverse applications [19].

LC phase structures:

The confirmation of LC phase structures can be undertaken by Small-Angle X-Ray Scattering (SAXS). The typical reflection patterns; for dispersed LC formulation at nearly √2, √3, √4, √6, √8, √9, revealed the presence cubosomes. On the other hand, the typical reflection patterns at nearly √1, √3, √4, √7, √9 revealed the presence of a hexagonal phase in all prepared LC formulations [20, 21]. In general, if there was any material with high birefringence, the light output by the top layer, a linear polarizer, may cause optical anisotropy to appear on the displayed image, depending on the orientation of the viewer with respect to the display.

Particle size and zeta potential of LC

Zeta potential and particle size are important parameters for the evaluation of stability and bio-distribution. By increasing the LC concentration, the particle size tended to be smaller and the zeta potential became more negative, suggesting that the number of LC forming particles can be increased with an increasing of LC concentration. Stable nano-formulations of LC should own small particle sizes ranged between 220 and 280 nm, and the zeta potential of these formulations should range between -17 and -30 mV [22]. In addition, no significant changes should be observed in particle size or zeta potential at 10 days after their preparation. LC formulations characterized by small particle size with high surface charges and electrical repulsion between the particles, can prevent their aggregation even 10 days after preparation. The zeta potential present strong negative values for LC formulations, indicating the predominance of repulsive forces. The reason why LC formulations show negative zeta potential values is due to the present of free oleic acid in the lipid phase may give rise to the negative charge of the particles. In addition, the negative charge can also be explained by preferential adsorption of hydroxyl ions at the lipid-water interface [22, 23].

Preparation

In order to successfully prepare LC formulations with cubic or and hexagonal phase the following Tables show the percentages of the LC forming lipid, incorporated drug, surfactant and the water content that required for topical and oral LC formulations. These formulations were designed based on different ratios of the active ingredient in distilled water (drug solution) and LC-forming lipids. GMO was melted at 70°C before use, but MGE was dispersed with drugs solution without preheating [24-26].

Table 1: Composition of dispersed LC formulations [24].

Formulation	Drug concentration	% Drug solution	% MGE	% GMO
TXA-MGE	19 mM	50	50	---
4-MS-MGE	1 mM	50	50	---
CC-MGE	10 mM	50	50	---
Cal-MGE	3 mM	50	50	---
TXA-GMO	19 mM	50	---	50
4-MS-GMO	1 mM	50	---	50
CC-GMO	10 mM	50	---	50
Cal-GMO	3 mM	50	---	50

Abbreviations: TXA, Tranexamic acid; MGE, C_{17}-monoglycerol ester; 4-MS, 4-Methoxy-salicylic acid; CC, Catechin; Cal, Calcein; GMO, glyceryl monooleate.

Table 2: Composition of petrolatum-LC formulations [25].

Ingredients (%)	WP	WP-GMO5	WP-GMO10	WP-GMO20
White petrolatum	20	20	20	20
Stearyl alcohol	25	25	25	25
Propylene glycol	12	12	12	12
Sodium lauryl glycol	1	1	1	1
GMO	0	10	20	30
PABA solution (purified water)	41	37	32	22
Total %	100	100	100	100

Abbreviations: PABA, *p*-aminobenzoic acid; GMO, glyceryl monooleate; WP, white petrolatum, the concentration of PABA was 10mM.

Table 3: Composition of oral and topical LC formulations [26].

The concentration of PABA, M-PABA, or E-PABA solution was 10 mM and the concentration of Na-FL

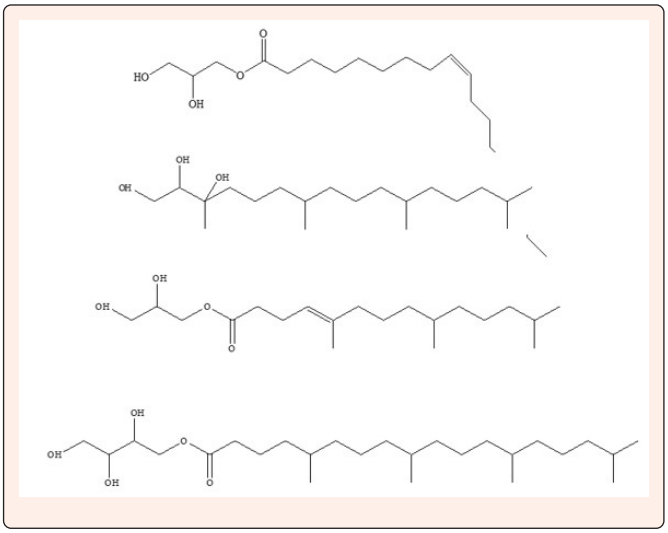
Formulation code	Composition of oral LC formulations
OP5	PABA solution containing 5% Pluronic® F127 and 5% MGE
OP10	PABA solution containing 5% Pluronic® F127 and 10% MGE
OP20	PABA solution containing 5% Pluronic® F127 and 20% MGE
OP30	PABA solution containing 5% Pluronic® F127 and 30% MGE
OP10D	PABA dry powder formulation containing 5% Pluronic® F127, 10% MGE, 10% mannitol and 1% ethanol
OP20D	PABA dry powder formulation containing 5% Pluronic® F127, 20% MGE, 10% mannitol and 1% ethanol
OM5	M-PABA solution containing 5% Pluronic® F127 and 5% MGE
OM10	M-PABA solution containing 5% Pluronic® F127 and 10% MGE
OM20	M-PABA solution containing 5% Pluronic® F127 and 20% MGE
OM30	M-PABA solution containing 5% Pluronic® F127 and 30% MGE
OM10D	M-PABA dry powder formulation containing 5% Pluronic® F127, 10% MGE, 10% mannitol and 1% ethanol
OM20D	PABA dry powder formulation containing 5% Pluronic® F127, 20% MGE, 10% mannitol and 1% ethanol
OE5	E-PABA solution containing 5% Pluronic® F127 and 5% MGE
OE10	E-PABA solution containing 5% Pluronic® F127 and 10% MGE
OE20	E-PABA solution containing 5% Pluronic® F127 and 20% MGE
OE30	E-PABA solution containing 5% Pluronic® F127 and 30% MGE
OE10D	E-PABA dry powder formulation containing 1% Pluronic® F127, 10% MGE, 10% mannitol and 1% ethanol
OE20D	M-PABA dry powder formulation containing 5% Pluronic® F127, 20% MGE, 10% mannitol and 1% ethanol
TF5	Na-FL solution containing 5% Pluronic® F127 and 5% MGE
TF10	Na-FL solution containing 5% Pluronic® F127 and 10% MGE
TF20	Na-FL solution containing 5% Pluronic® F127 and 20% MGE
TF30	Na-FL solution containing 5% Pluronic® F127 and 30% MGE
TF40	Na-FL solution containing 5% Pluronic® F127 and 40% MGE
TF50	Na-FL solution containing 5% Pluronic® F127 and 50% MGE

solution was 5 mM

Formulation code: O = Oral formulation; T = Topical formulation; P = PABA; M = M-PABA; E = E-PABA; F = Na-FL; D = Dry powder; Number = Percentage of MGE.

Drug diffusivity

The drug release profiles from LC formulations can be influenced by the concentration of LC and the physiochemical properties of the entrapped drugs. Although the release profile influenced by the changes in the LC concentration, it can be influenced more dramatically by the changes in the physiochemical properties of the entrapped drugs. For example, a previous study showed that the released amount of Na-FL from TF10 was 18 ± 0.6% compared with the release of E-PABA from OE10 (3.8 ± 0.3%), although both formulations contained the same concentration of LC. A similar phenomenon was observed with other drugs (PABA and M-PABA), and drug release decreased with an increase in lipophilicity. Moreover, the type of selected LC forming lipid can also affect the drug diffusivity in the prepped LC formulation, a previous study showed the release profile of a hydrophilic drug model was higher when prepared with C_{17}-Monoglycerol Ester (MGE) compared to Glyceryl Monooleate (GMO), Phytantriol (PHT) and C22-Erythritol Ester (ERT). These results were due to the low viscosity of MGE compared to other LC forming lipids [26].



Chemical structures of glyceryl monooleate (GMO), phytantriol (PHT), C_{17}-monoglycerol ester (MGE) and C22-erythritol ester (ERT) [27].

Biocompatibility

Biocompatibility is a general term describing the property of a material being compatible with living tissue. A previous study has demonstrated the safely profile of LC for topical application, when human keratinocytes cells (HaCaT) treated with Petrolatum-LC formulation the results showed that with concentrations of 0.1 and 0.5 mg/mL for 12 and 24 hours, the HaCaT cell viability was more than 98%, with no significant difference from the control group. Even at 1 mg/ml vehicle concentration, cell viability remained more than 90%, suggesting that the Petrolatum-LC formulations were safe for HaCaT cells. In addition, the impact of the Petrolatum-LC formulations on DNA damage was also evaluated. There was no apparent DNA damage in the HaCaT cells treated with Petrolatum-LC formulations up to 1 mg/mL [25].

LC for topical application

Several studies have demonstrated the usefulness of LC formulations for the topical application. The penetration enhancing effectiveness of non-lamella LC in topical formulations was evaluated by measuring permeation of a mal-absorbable compound, tranexamic acid, calcein and catechin through excised hairless rat skin using GMO and MGE. Significant improvement in the skin permeation of different drugs was observed after application of MGE and GMO formulations. The enhancement of the skin permeation ratio of MGE formulations was higher than those of GMO formulations. These results showed that MGE formulations managed to improve the skin permeation enhancement effect compared with GMO formulations. These findings could be related to the low viscosity of MGE formulations, and this might offer better drug diffusivity and influence the movement and permeation of the drugs in and across the skin. The detailed mechanism of the skin permeation enhancing ability by LC systems is not fully understood [28]. It was speculated that cubic structure with similar nano-structure as the skin, increases the interaction between skin and formulation and enhances the skin permeation [29,30]. A previous study reported that the hexagonal phase may facilitate the fusion of LCs with the stratum corneum and deeper skin layers and thereby may improve drug delivery to the skin. Moreover, the hexosome system, owing to its larger surface area to interact with the skin and high fluidity, can be incorporated into compounds independently of their solubility [31]. Further studies are needed to clarify the mechanism and effect of LC phase structure on the skin permeation of drugs. A previous study [26] showed that the *in vitro* skin permeation results were dramatically affected by the LC concentration. Significant improvement in the skin penetration of Na-FL was observed in 20% and 30% LC forming lipid with enhancement ratios of 4.3 and 2.9, respectively. However, no marked improvement was observed in 10% and 40% LC forming lipid, suggesting that a low concentration of LC forming lipid such as 10% could lead to a reduction in hexosomes particles. Thus, it is necessary to overcome the barrier function of stratum corneum. On the other hand, a high concentration of LC forming lipid such as 40% reduced drug release from the formulation.

Typical reflection patterns at nearly 1, √3, and √4 for topical LC formulations indicated that these formulations successfully managed to form an H2 inverted hexagonal phase. Previous studies [32-34] have reported that the hexagonal phase has several advantages. It has a larger surface area to interact with biological membranes with high fluidity, and greater amounts of drugs can be incorporated independent of their solubility. Other studies have demonstrated the presence of cubosomes using different types of LC-forming lipids such as Glyceryl Monooleate (GMO) or Phytantriol (PHT). We strongly believed that several factors might affect the phase structure of LC formulations, such as temperature, type of LC-forming lipid, physiochemical properties of the entrapped drugs, lipid concentration, and type of surfactant. Further studies are necessary to understand in full the effect of such factors on the phase transition of LC formulations. The key point is to successfully prepare hexosomes or cubosomes by design with LC formulations. No clear mechanism or clear evidence has been proposed to indicate that cubosomes have more potential than hexosomes, or vice versa, as a drug delivery system.

Conclusion

LC formulations are promising to improve transdermal penetration of drugs. The present review explained that the concentrations of LC-forming lipid and the physiochemical properties of entrapped drugs are very important factors that should be considered by researchers in this field to improve the performance of LC formulations in various pharmaceutical applications. Understanding the effect of these factors on LC formulation performance could enable researchers to develop LC formulation approaches that intended to improve the oral absorption and skin permeation of drugs.

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