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Review Article

CUBOSOMES: A BOON FOR COSMECEUTICALS AND TOPICAL DRUG DELIVERY

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ABSTRACT

Cubosomes are the nanoparticles of bicontinuous, lyotropic cubic phases, comprised of curved lipid bilayers organized into a three-dimensional honeycomb (cavernous) like structures separating two internal aqueous channels and large interfacial area. Cubic phases are optically isotropic, very viscous, and solid-like (crystalline) with cubic crystallographic symmetry. They can encapsulate hydrophilic, hydrophobic and amphiphilic drug substances, which are able to target and control the release of the bioactive agent. The cosmetic industry has made progress in the development of products to overcome skin as a barrier and deliver the actives through the skin effectively. Drug incorporated cubosomes shows some unique advantageous like, protection from chemical and physiological degradation, *in vivo* drug release in a controlled manner and improving the bioavailability of drug while reducing the side effect. Cubosomes are pharmacologically inactive, non-irritant, non-toxic, effective, and cosmetically acceptable. Topical drug delivery can deliver drugs selectively to the specific site; this avoids fluctuations of drug levels and improves patient compliance and suitable local and systemic therapeutic effects. Cubosomal topical drug formulation shows outstanding potential advantages for their controlled and sustained drug delivery. This review article mainly focuses on cosmetic and topical applications of cubosomes.

Keywords: Nanoparticles, Cubosomes, Bioavailability, Patient compliance, Drug release, Topical drug delivery

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INTRODUCTION

Cubosomes has a three-dimensional network of water channels surrounded by lipid bilayers. Cubosomes are termed as such because they present cubical crystallography, which is attributed to a self-assembled surfactant as well as amphiphilic molecules [1]. Morphological characterization through SAXS (Small-Angle X-ray Scattering) and cryo-TEM (Cryo-TRANSMISSION electron microscopy) reveled that they are square and round-shaped particles in the nanometer range [2, 3]. These cubic phases attract researches as soft materials for the controlled release of pharmaceutically or cosmetically active drugs. Cubosomes size ranges from 10-500 nm. It is said to be large cubosomes if diameter is more than 200 nm and smaller cubosomes and vesicles with a diameter smaller than 100 nm [3, 4].

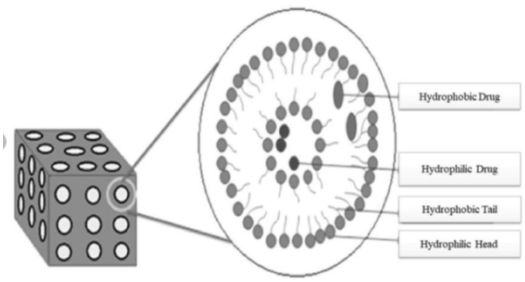

Fig. 1: Structure of cubosomes

Liquid crystals are of two types, thermotropic and lyotropic, the former is temperature dependent, i.e., phase transition occurs into liquid crystalline phase as the temperature changes. The later, lyotropic liquid crystals (LLC) in which phase transition occurs as a function of the concentration of the mesogen in a solvent which is typically water [6]. Lyotropic liquid crystals have importance in drug delivery applications. Many amphiphilic molecules that have distinct polar and non-polar units, which may be ionic, non-ionic or cationic shows lyotropic liquid crystal phase sequence [7].

Amphiphilic molecules are randomly distributed without any order at low concentrations. When the concentration is slightly increased, they tend to arrange themselves into micelles or vesicles. At high concentration, assembly becomes ordered, some structures to hexagonal columnar phase or cubic phase. The principle may be simply by dissolving the drug in the liquid crystal matrix, which carries the drug to the site of action. In general, such a drug delivery might take place in two stages: first, preparation of liquid crystal and the drug solutions and later dissolving of the drug in the liquid crystal. Based on principles of differential geometry, cubosomal structure can exist as open structure and closed cubosomal structure. The two aqueous channels are in contact with the external environment in the open structure, whilst the closed cubosome has one water channel open towards the external environment with the other compartment closed in relation to the outside. The closed cubosome was proposed as the more stable structure of the two forms. Like the bulk parent cubic phase, cubosomes are also classified into gyroid, primitive or diamond [8].

As far as their structure is a concern, cubosomes are similar to crystals because just as in crystals, in cubosomes a repeating basic building block referred to as the unit cell can be distinguished. However, the similarity is not ideal. In crystals the unit cell consists of a group of typical and always equally spaced atoms or molecules, whereas in cubosomes it is a section of appropriately formed membrane immersed in water. Two cubosomes that are virtually identical externally can have a greatly varying internal structure. This observation is of important practical value due to one of the most important potential applications of cubosomes is the delivery of drugs in the body compared with liposomes, cubosomes have a much richer, less uniform internal structure.

Glyceryl monooleate (GMO) [9] phytantriol (PT, 3,7,11,15-tetramethyl-1,2,3-hexadecanetriol) [10,11] and other lipids such as monolinolein [12-14] monoelaidin [15-17], phosphatidyl ethanolamine [18-20], oleoyl ethanolamide [21], phospholipids [22-25] PEGylated phospholipids [26], alkyl glycerates [27, 28], and glycolipids [29] have been reported to form cubic phase. Among them, GMO and PT are the most commonly studied to form cubic phase liquid crystals as drug delivery systems. Paeonolin cubic gel had higher permeability than that of paeonol in the microemulsion

gel and the control solution; therefore, cubic gel would be a better carrier for paeonol in transdermal delivery. The results suggested that the dominating delivery route of the cubic phases is via micro fissures caused by microscopic clustering of the keratinocytes in the skin. Therefore, sulphorhodamine B delivered by cubic phases diffused into the surrounding intercellular lipid matrix through these micro fissures and acted like a source for its sustained release [30, 31].

Two major structural components of cubosomes are amphiphilic lipids and surfactant/stabilizers. Amphiphilic lipids include glyceryl monooleate/monoolein (GMO) and phytantriol (PHYT). The most extensively used cubosomes stabilizers are Pluronics® which are self-assembling water-soluble triblock copolymers consisting of polyethylene oxide (PEO) and polypropylene oxide (PPO) arranged in PEO-PPO-PEO conformation. The prepared cubosomes are biodegradable and bioadhesive in nature [32, 33]. The sources used to prepare the present article are google, PubMed, and Innovare using keywords cubosomes, cubosomes topical, cubosomes transdermal, cubosomes cosmetic, cubosomes dermal applications. The range of years for the review were between 2000 to 2021. There are many reviews on cubosomes, but cubosomes are having wider topical and cosmetic applications which are covered in this review

Pharma value of cubosomes

Cubosomes are means of solubilizing, encapsulating and transporting APIs. Broadly applicable to small molecules, nucleotides, peptides and proteins. It exhibits enormous surface area of several hundred square meters per gram and has a high drug loading capacity. It allows true controlled release and also targeting e. g., of cancer drugs. It shows Stability improved shelf-life and/or *in vivo* stability. Cubosomes are means of protecting sensitive molecules from degradation *in vivo*. Cubosomes improve bioavailability by solubilization of poorly water-soluble drugs. Cubosomes decrease of unwanted side effects and improves intracellular penetration [34, 35].

Topical and transdermal cubosomal drug delivery

The crucial issue in topical formulations is to increase the thermodynamic activity of the active molecule in the vehicle while decreasing it in the skin, which results in increasing the partition of the molecule from vehicle to skin and decreasing the barrier function of the skin [36].

Since cubosomes improve the formulation in several aspects: they increase skin hydration, which increases formulation viscosity as a result of molecular reorganization, and they increase the permeability and prolong the release of actives [37]. A study described how emulsifiers arranged in liquid crystalline structures in the water phase enhanced the skin penetration of active ingredients [38].

Cubosomes are more bioadhesive in nature, so that they can conveniently use in topical and mucosal delivery of different drugs [39]. Topical delivery systems are based on the exploitation of unique properties of liquid crystal and liquid crystal nanoparticle technologies. Topical drug delivery systems are unique in situ forming bioadhesive liquid crystal systems facilitate controlled and effective drug delivery to mucosal surfaces like buccal, ophthalmic and vagina [40]. It can enclose hydrophilic, amphiphilic, and hydrophobic substances ranging from small-molecular weight drugs to proteins, peptides, amino acids, and nucleic acids [41]. Typically, three forms of cubic phase have been used as drug delivery systems: cubic phase gel; cubic phase precursor; and cubosome. Cubic phase gels have been commonly used for mucosal, vaginal, periodontal, and transdermal drug delivery. It was reported that lipid cubic phase gels significantly increased the delivery of δ-aminolaevulinic acid hydrochloride and methyl δ-aminolevulinate hydrochloride through topical administration as compared with normal ointments [42, 43].

In transdermal drug delivery, the stratum corneum, which is a highly organized outermost layer of skin, represents a strong barrier for skin penetration of topically applied drugs [44]. However, cubosomes with their unique structure and properties, provide a promising vehicle for transdermal drug delivery. Because of the bioadhesive properties of cubosomes to the stratum corneum as a function of GMO, they can be effectively used in topical and mucosal drug delivery [45]. Recently there are several dermatological applications of cubosomes. An important dermatological application is a vaccination through transcutaneous (TCI) immunization. However, microneedles (MNs) and cubosomes have been effectively used as synergistic approach for the delivery of vaccines through the skin. Results showed that the use of MNs enhances the permeation of the aqueous peptide mixture through the skin layers and cubosomes formulated peptide showed longer retention within the skin. Consequently, the use of combined approaches of both MNs and cubosomes were found to be an efficient system for local delivery of antigen to the targeted cells in the skin [46].

Cubosomes have been investigated as topical delivery agents in part because of their ability to influence permeability. This has applications in a number of disease areas, including the treatment of burns, rheumatoid arthritis, post-operative pain and ocular delivery [47, 48].

Cubic phases are more bioadhesive in nature so that they can conveniently use in topical and mucosal deposition and delivery of different drugs. Topical delivery systems are based on the exploitation of unique properties of liquid crystal and liquid crystal nanoparticle technologies.

Topical drug delivery systems are unique in situ forming bioadhesive systems that facilitate controlled and effective drug delivery to mucosal surfaces (buccal, ophthalmic, vaginal and others). This fascinating system forms a thin surface film at mucosal surfaces consisting of a liquid crystal matrix which nanostructure can be controlled for achieving an optimal delivery profile and provides good temporary protection of sore and sensitive skin [49]. Cubosomes for topical delivery of the antimicrobial peptide (AMP) LL-37 was investigated, no skin irritation potential of the cubosomes was found, thus enabling topical administration of cubosomes [50]. Due to the similar cubic phase structure between the cubosomes and the stratum corneum, the cubosomes have penetration enhancing the effect on the skin as the lipid part of the particles mix with the lipids of the stratum corneum and consequently fluidize the stratum corneum [51, 52]. Furthermore, since cubosomes are known to be skin-adhesive [53, 54] these versatile drug nanocarriers can be promising drug carriers to be administrable by the transdermal route [55]. Transdermal etodolac-loaded cubosomes were studied to treat patients' pain and joint stiffness by providing stable etodolac concentration at the targeting sites by controlled drug delivery through the noninvasive skin route with higher sustaining and lower frequent dosing. Cubosomes dispersions were prepared by emulsification of the cubic lipid phase consisting of monoolein (MO) and poloxamer 407 in water containing Poly (vinyl alcohol). The results of the zeta potential study show that etodolac-loaded cubosomes nanoparticles carried a negative charge with mean values of–18.40 to–36.10. This might be due to the presence of the fatty acid [56]. Moreover, the surface negative charge may be due to the PVA hydroxyl group that was anchored on the surface of the cubosomes [57-59]. Generally, adding poloxamer 407 to the cubosomal dispersion resulted in cubosomes with more negative charge values due to the interaction between poloxamer 407 hydroxyl ions with the aqueous medium [60]. The etodolac loaded cubosomes showed particle size values ranging from 135.95 to 288.35 nm the particle size of cubosomes is indirectly proportional to the increase in poloxamer concentration and zeta potential values ranging from−18.40 to −3 6.10 mV. Increasing poloxamer concentration in etodolac-loaded cubosomes developed cubosomes with less particle size and faster drug release. Furthermore, investigated cubosomes showed fast drug penetration through excited mice skin followed by slower drug penetration for up to 24 hr. The *in vivo* study in human volunteers exhibited that the selected etodolac-loaded cubosomes increased the bioavailability of etodolac as compared to the oral capsules (266.11%) with a longer half-life and higher MRT that reached 18.86 and 29.55 hr., respectively. The etodolac-loaded cubosomes propose an encouraging system for the treatment of arthritis simply through skin application [61, 62]. Cubosomes proved to be a promising non-

invasive nanocarrier for transdermal hormonal delivery. Cubosomes can be loaded into gels or emulgels [63, 64].

Cosmetic application of cubosomes

Cubosomes are biodegradable and hence suitable for cosmetic use and also can be used for controlled and targeted drug delivery and hence attractive candidate for cosmetic preparations [65]. Cubosomes can be used as a challenging technique and these particles can solve the problem associated with dermal drug delivery [66] Cubosomes easily evacuate their contents to the epidermis as they have almost same structure to that of the stratum corneum, as well as the properties of adhesion and penetration enhancement of cubosomes suggest their potential utility in skin cancer (melanoma) treatment [67-69]. **T**he first cosmetic products appeared on the market recently; Juvena in 2007 (rutin) and La Prairie in 2008 (hesperidin). Rutin and hesperidin are two, poorly soluble, plant glycoside antioxidants that could not previously be used dermally. Once formulated as nanocrystals, they became dermally available as measured by antioxidant effect. This dermal use of nanocrystals is protected by patents. Other examples are resveratrol and ascorbyl palmitate nanocrystals. Incorporation of nanocrystals into cosmetic products is a straight forward process. Nanocrystals dispersed in water (i.e., a nanosuspension) is admixed with a cosmetic product (typical dilution factor: 50) [70].

The controlled release application of these nanoparticles is of a great significance in the cosmeceutical and pharmaceutical fields. Cubosome has become an attractive vehicle for *in vivo* drug delivery due to their low cost, versatility and potential for controlled release and functionalization. The personal care industry shows particular interest on cubosomes due to their unique features. It substantiates the use of cubosome during manufacture/formulation and also enhances the flexibility for product development. Dermal application of cosmetic actives with properties such as high molecular weight, hydrophilicity, polarity, or susceptibility to enzymatic degradation remains highly challenging. Nano-sized vesicular delivery systems used for drug delivery are of particular interest to the cosmetic industry. Liquid nano-sized systems are significantly more effective as vehicles for extremely hydrophilic agents than classical enhancer emulsions [71].

Alpha-lipoic acid (ALA) is a naturally occurring fatty acid with a potent antioxidant activity which exists in the mitochondria of all kinds of prokaryotic and eukaryotic cells. A recent study has demonstrated that the formulation of ALA in cubosome dispersion has excellent results in reducing facial lines with almost complete resolution of fine lines in the periorbital region and upper lip area with improvement in skin texture and color in most volunteers [72, 73].

An area under modern development by L'Oreal is the use of cubosomal particle as oil-in-water emulsion stabilizers and pollutant absorbents in cosmetics. They revealed that a second amphiphile, glycerol monooleate and phytantriol have an aqueous phase behavior sufficiently close to that of monoolein to form cubosomes. Interests on cubosomes being formulated as cosmetics products like skin care, hair care, antiperspirants have been increased and Nivea had filed a patent too. In spite of new activity, there resides a need on practical problems like scale-up and material customization. Some of the recent Examples of the dermatological applications of cubosomes for topical delivery of drugs are shown in table 1.

Table 1: Examples of the dermatological applications of cubosomes for topical delivery of various drugs

S. No.	Drug	Purpose	Reference
1	Quercetin	Development and Optimization of Quercetin Cubosomes Incorporated in Glyceryl monooleate Aided by Design Expert Software	74
2	Clotrimazole	Formulation and Evaluation of Cubosomes as Skin Retentive System for Topical Delivery of Clotrimazole	75
3	Atazanavir	Design, Formulation, *In vitro* and Ex-Vivo Evaluation of Atazanavir Loaded Cubosomal Gel	76
4	Itraconazole	Formulation, Development and Optimization of Itraconazole Cubosomal Gel for the Treatment of Candidiasis	77
5	Fluconazole	Fluconazole Loaded Cubosomal Vesicles for Topical Delivery	78
6	alpha lipoic acid	The clinical efficacy of cosmeceutical application of liquid crystalline nanostructured dispersions of alpha lipoic acid as anti-wrinkle	79
7	Vitamin E	Preparation and Physicochemical Characterization of Glyceryl Monoolein Bearing Cubosomes to Improve Vitamin E delivery into the Skin: A Proposal for Skin Cancer Prevention	80

CONCLUSION

Cubosomes are nanoparticulate cubic crystals with enormous surface area, stability with unique advantage of encapsulating hydrophilic, lipophilic or amphiphilic materials. Cubosomes serve as excellent carriers, especially in topical and transdermal drug delivery and also in cosmetic industry. The structural characteristic especially makes them the material of choice for topical and transdermal drug delivery. Various drugs are successfully encapsulated in cubosomes with improved dermatological characteristics.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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