# Challenge Of Cubosomes In Advanced And Targeting Drug Delivery Systems

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**Abstract–** Cubosomes are Nanostructures particles of the bicontinuous cubic liquid crystalline phase. Compared to liposomes, cubosomes have advantages including ease of preparation, better physical stability, and special liquid crystalline properties. Cubosomes drug delivery has achieved a challenging role in various applications and targeting issues. As different approaches have been studied for targeting anticancer cubosomes to cancer cells, Efficient cytotoxicity and cellular uptake of Resveratrol cubosomes were attained with a particle size range 45–76 nm. Cubosomes also have great potential for ocular disease treatment, For example, cubosome drug delivery system for glaucoma treatment was constructed for timolol maleate (TM) which is capable of increasing the corneal permeability and bioavailability of TM. The cubosomeal gel could be considered as a promising carrier for brain targeting of drugs like resveratrol through transnasal route and challenge in oral delivery of numerous compounds including low aqueous solubility, poor absorption, and great molecular size. 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. Furthermore, since cubosomes are known as skin-adhesive, this versatile drug nanocarriers can be promising drug carriers to be administrate by Transdermal route. Interests on cubosomes being formulated as cosmetics products have been increased. chito-cubosomes exhibited anti-digestion effect, much slower in vitro release behavior, and further enhanced oral bioavailability than intact liquid cubosomes. Cubosomal-gel could be considered an innovative dosage-form for the treatment of epileptic children. Cubosomes also show a recent advance in gene therapy. Magnetocubosomes are interesting hybrid nanostructures in nanothoranostics applications. Consequently, cubosmes drug delivery could be a challenge for advanced and targeting drug delivery systems.

**Keywords–** Cubosomes, Liquid crystal, nanocarriers, drug delivery, polaxmer407, monolinolein, cubic phase.

## 1 Introduction

Liquid crystals (LCs) have buildings between those of ordinary liquids and those of solid crystals. Liquid crystals are classified into thermotropic, lyotropic and metallotropic phases. Lyotropic liquid-crystalline phases are abundant in living systems. lyotropic liquid crystals are classified into three types named lamellar phase, cubic phase, and hexagonal phase according to their different internal structures. [1, 2].

Cubic liquid crystals are often spontaneously formed by the addition of certain amphiphilic lipids (such as Glyceryl monooleate (monoolein, GMO or MO), glyceryl monolinoleate (monolinolein, GML or MLO), oleyl glyceryl (OG) and phytanyl glycerate (PG)) in an aqueous environment [3]. When cubic liquid crystals are dispersed into nanoparticles with excess water with the addition of stabilizers (such as Pluronic copolymers [4] and Myrj series [5]), they form stable colloidal dispersions which are termed cubosomes [6–9].

Cubosomes are discrete, sub-micron, nanostructured particles of the bicontinuous cubic liquid crystalline phase Fig. 1 [10]. Cubosomes have been an advanced research field because their structure lends itself well to controlled-release applications. There are three phases that cubic structures can be in: the P-surface, G-surface and, D-surface for primitive, groid and diamond structures respectively [11], Fig. 2 [12]. Accordingly, to Cubosomes complex structure, cubosomes be the superlative drug delivery system that could maintain the structural integrity of the ingredients that it carries [13].

## 2 Cubosomes advantages [10]

1. It is economic.
2. It is non-toxic and biocompatible.
3. The method of preparation is simple.
4. It has excellent bioadhesive properties.
5. It has skin permeation enhancement.
6. For a longer time they are thermodynamically stable.
7. The capability of encapsulating hydrophilic, hydrophobic and amphiphilic substances.
8. Targeted release and controlled release of bioactive agents.
9. Due to the high internal surface area & cubic crystalline structures, there is high drug loading.

## 3 Disadvantages [10]

1. Due to the presence of large amounts of water inside cubosomes there is low entrapment of water-soluble drugs
2. Because of the high viscosity, the large scale production is sometimes difficult.

## 4. The effect of cubosme characterization in various applications challenging and targeting issues (Table 1)

### 4.1 In the cancer cell targeting

Recently some anticancer drugs have been successfully encapsulated in cubosomes [14]. Different approaches have

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been studied for targeting anticancer cubosomes to cancer cells.

The successful ability of nanocarriers' applications in the cancer therapy necessitates efficient cellular internalization[15]. Paracellular and transcellular transport are the two main pathways for nanocarriers' uptake [16]. Paracellular transport is a passive diffusion mechanism via the intercellular spaces and tight junctions. Previous studies reported that negatively charged particles don't influence on disturbing the tight junctions [17]. Consequently, negatively charged nanosystems could be implemented in the transcellular endocytic pathway only. Trans- cellular endocytosis includes macropinocytosis, clathrin-mediated endocytosis, caveolae-mediated endocytosis or caveolae- and clathrin-independent endocytosis [18]. These different endocytic pathways differ in the size it could internalize and the fate of the penetrated nanocarrier [19].

Particle size could be considered one of the major factors that affect cellular uptake mechanism and biodistribution of nanocarriers [20]. Nanocarriers with a size less than 200 nm have superior extravasation and accumulation into tumors by the enhanced permeability and retention effect [21].

A study was performed to improve Resveratrol (RSV) cellular uptake and cytotoxicity against HepG2 human hepatoma cells[22]. Resveratrol (RSV) is an anticancer which suffers from low aqueous solubility, extensive first-pass metabolism, and isomerization to the inactive cis-isomer by light exposure [23]. The prepared RSV cubosomes zeta potential values ranged from -17.32 ± 2.71 to -32.12 ± 1.41 mV. The cubosomes with the highest GMO ratio (The highest fatty acid content) have the highest charge. The negative charge was possibly imparted by the free fatty acids present in the lipid [24]. The mean particle size of the prepared RSV cubosomes ranged from 22 ± 1.26 to 195 ± 2.99 nm with a polydispersity index (PDI) <0.2 which indicated the narrow homogenous particle size distribution of the prepared RSV cubosomes [25].

Cellular penetration of a high particle size prepared cubosome (97.65 ± 4.50 nm) was mainly followed micropinocytosis only, endocytosis was abolished for particles with size more than 80 nm [26]. Formula with the least evaluated size (28 nm), was infiltrated into cells by clathrin-mediated endocytosis mechanism only and had the least efficacy. Particles with size less than 40 nm are unable to produce sufficient free energy to enwrap to the cellular membrane surface which may avert endocytosis. Efficient cytotoxicity and cellular uptake of RSV cubosomes were attained with a particle size range 45–76 nm which was additionally internalized by caveolae-mediated endocytosis [23].

### 4.2 Increasing the corneal permeability

Ocular drug delivery faces different challenges, as low corneal permeability and bioavailability as a result of the distinctive anatomical structure of the human eye.

A cubosome drug delivery system for glaucoma treatment was constructed for timolol maleate (TM) in a study. The TM cubosomes were prepared using glycerol monooleate and poloxamer 407 via high-pressure homogenization. These constructed nanoparticles had an average particle size of 142 nm and zeta potential of -6.27 mV. Ex vivo corneal permeability tests displayed that the total amount of TM cubosomes penetrated was higher than the commercially available eye drops. In vivo studies showed that TM cubosomes decreased the intraocular pressure (IOP) in rabbits from 27.8□39.7 to 21.4□32.6 mmHg after 1-week administration and had more retention time and lower-IOP effect than the commercial TM eye drops. Besides, neither cytotoxicity nor histological affliction in the rabbit corneas was observed [27].

### 4.3 Brain targeting

The blockage in delivering drugs to the brain for the treatment of diseases related to the central nervous system (CNS), lies behind the presence of the blood-brain barrier (BBB). This barrier prevents most of the large and some small molecules from entering the brain, thus posing a considerable challenge in the administration of drugs.

The use of particulate drug carriers, such as nanoparticles, can be a promising non-invasive strategy to increase drug loading into the brain by masking drug properties, to ascertain higher encapsulation efficacy and to enhance the stability of the drugs. One type of lipid-based nanoparticles, cubosomes, had been investigated in a study to determine its suitability as a drug carrier.

Enhancing the delivery of resveratrol to the brain through the transnasal route by cubosomes was studied. Cubosomes were prepared using glycerol monooleate lipid and Lutrol® *F 127* by probe sonication process. A 32 full factorial design was used for the optimization of cubosomes. The batch that has glycerol monooleate (4% w/v) and Lutrol® *F 127 (*1.5% w/v) was optimized cubosomal dispersion, hence it was a cubic shape with

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mean particle size 161.5 ± 0.12 nm. The optimized cubosomal dispersion was dispersed into poloxamer 407 polymer to form in situ gel for nasal use. Ex-vivo permeation and in vivo bio-distribution tests were studied for the optimal cubosomal gel (containing 12% w/v poloxamer 407). It showed significantly higher transnasal permeation and better distribution to the brain, when compared to the drug solution (i.n.) and drug solution (oral) [28].

### 4.4 Oral drug delivery

Cubosomes direct challenges in oral delivery of numerous compounds including poor aqueous solubility, poor absorption, and large molecular size. In an application, large proteins have been encapsulated for local activity in the gastrointestinal tract.

Orally administered amphotericin B (AmB) has low bioavailability, hence the perspective of glyceryl monoolein (GMO) cubosomes to improve the oral efficacy of AmB was studied. A 9:1 ratio of GMO and Polaxmer 407 was used. Orally AmB cubosomes were investigated for its antifungal efficacy in vivo in rats. The adenocarcinoma cell line (Caco-2) of the human colon was used to evaluate transport across a model of the intestinal barrier by in vitro study.

In vivo investigations revealed that Orally AmB cubosomes, could significantly increase oral efficacy, compared against Fungizone®.

In addition in vitro study results showed a significantly more amount of AmB being transported into Caco-2 cells, via both clathrin- and caveolae-mediated endocytosis, but not macropinocytosis. These results propose that GMO cubosomes, as lipid nanovectors, could ease the oral delivery of AmB [29].

### 4.5 Transdermal drug delivery systems

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 [30,31]. Furthermore, since cubosomes are known to be skin-adhesive[32], these versatile drug nanocarriers can be promising drug carriers to be administrable by the transdermal route[33].

Transdermal etodolac-loaded cubosomes were studied to treat patients pain and joints 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, MO [34]. Moreover, the surface negative charge may be due to the PVA hydroxyl group that was anchored on the surface of the cubosomes[35]. 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 [36]. The etodolac-loaded cubosomes showed particle size values ranging from 135.95 to 288.35 nm the p article size of cubosomes is indirectly proportional to the increase in poloxamer concentration.and zeta potential values ranging from −18.40 to −36.10 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 [37].

### 4.6 Cosmetics

L'Oreal and Nivea are trying for the use of cubosome particles as oil-in-water emulsion stabilizers and pollutant absorbents in cosmetics. Cubosomes have been formulated as cosmetics products like skincare, hair care, antiperspirants, and Nivea had filed patents too [38].

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 [39].

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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 [40].

### 4.7 Sustained-release behavior

Drugs with a broad range of molecular weights and water solubilities have showed sustained release in cubic phase liquid crystals, such as aspirin and vitamin E [41], propantheline bromide and oxybutynin hydrochloride [42], metronidazole [43], tetracycline [44], timolol maleate [45], chlorpheniramine maleate [46], propranolol hydrochloride [47], melatonin, pindolol, propranolol and pyrimethamine [48], hemoglobin [49], cefazolin [50], insulin [51, 52], cinnarizine [53], and diclofenac salts [54].

Although GMO-based cubosomes hold the promise for achieving sustained release *in vivo*, they are susceptible to degradation in the gastrointestinal tract catalyzed by lipase, which compromises liquid crystalline structure[55,56] and, thereby, loss of the sustained drug release property *in vivo* [57,58]. A recent study developed cubosomes with surface cross-linked Chitosan (CS) which could prevent the digestion of cubosomes in the intestinal tract, thereby, enabling the sustained drug release and further *in vivo* bioavailability enhancement as a spray-dried vinpocetine VPT cubosomes with surface cross-linked CS were prepared and characterized. After subsequent surface modification of GMO based liquid cubosomes with cross-linked CS, the obtained chito-cubosomes exhibited an anti-digestion effect, much slower *in vitro* release behavior, and enhanced oral bioavailability than intact liquid cubosomes [59].

### 4.8 In the treatment of epileptic children patients

The epilepsy prevalence is very high in children. It was reported that from 187 epileptic patients 41 individuals are children. The development of new dosage forms that are appropriate for children can present significant challenges. TDDS is a preferred dosage form due to their ability to avoid intravenous therapy or incompatibility of other routes of administration like emptying time, gastric pH and first-pass metabolism. For children, transdermal patches are usually very accepted due to its ease of applying and represent a valuable alternative to an oral administration. All children, including neonates, were born with full-term skin which has a thin epidermal layer control the water loss but performs the same adult skin function, A transdermal multilayered patch consists mainly of basic components; polymers and drugs formulated in drug reservoir layer in the patch system. The drug reservoir layer is the most important one as it is the carrier of drug molecules and the controller of the drug release pattern.

Cubosomes were used as a drug reservoir system as they are successfully used for drug transdermal delivery. Clonazepam (Cl) cubosomal-gel was studied to be applicated as a patch reservoir via transdermal-route. Glycerol-monooleate(GMO)/Pluronic-F127(PF127) mixture was used in cubosome preparation. The effect of different stabilizing agents named Ethanol (Et) and polyvinyl alcohol (PVA) and surfactant concentration on cubosomes' particle size and entrapping-efficiency was statistically invistigated. Using PVA or Et as stabilizers with PF127 significantly decreases the average cubosomes' particle size (352□±□2.8 and 264□±□2.16□nm) and increases entrapping-efficiency (58.97□±□4.57% and 54.21□±□3.89%). Cubosomes increase the initial release rate of Cl to ensure a rapid therapeutic effect (37.39% and 46.04% in the first hour) followed by a prolonged release till 4□h. Cub-gel containing PVA showed significantly more Cl-transdermal permeation than Cl-suspension. Moreover, increase the retention-time (89.57% at 48□h) and skin-deposition up to 6-times. It also reduces the epileptic seizures and alters the behavioral parameters induced by piocarpine [60].

### 4.9 Gene therapy

Cubosomes are lipid-based nanoparticles where membranes, instead of enveloping into classic liposomes, intertwine into complex arrays of pores well-ordered in a cubic lattice, hence cubosomes encapsulate more contents of siRNA than liposome. Ordinary methods for cubosomes preparation lead to particle sizes too large to fulfill the state- of the art requirements of delivery vectors. Hence, a microfluidic nanomanufacturing device was utilized to prepare siRNA-loaded cubosomes, termed cuboplexs that overpass commercially available delivery vectors and liposome-based systems [61].

### 4.10 Theranostic Applications

Theranostics is the simultaneous integration of diagnosis and therapy [62]. Nanothoranostics is to apply nanoparticles to diagnose, treat and prevent disease at the cellular and molecular level [62- 64]. Nanothoranostics

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applications include sustained and controlled release, targeted drug delivery, higher transport efficiency by endocytosis [65], stimulus-responsive agent release (i.e. smart delivery) [65-66], synergetic performances (e.g., combination therapy, siRNA co-delivery) [67], multimodality diagnosis and therapies and quality performance (e.g. autophagy inhibition) [68].

Methotrexate is a widely used drug; however, due to its toxic side effects, it should be delivered to organisms encapsulated using an appropriate drug delivery vehicle to prevent healthy cells from being exposed to its toxic influence. the lipidic liquid crystalline cubic phase can be a promising matrix for such a task. Magnetocubosomes are interesting hybrid nanostructures that may accommodate a suitable amount of methotrexate. The rate and efficiency of methotrexate release at the appropriate sites may be controlled, e.g., by applying an alternating magnetic field. The magnetic field can be used to relocate the dispersion of magnetocubosomes without any leakage of the magnetic nanoparticles from the cubosome lipid phase to the solution [69].

## 5. Conclusion

Cubosmes drug delivery could be a challenge for advanced and targeting drug delivery systems. So efforts should be increased to overcome barriers for cubosome scaling up in industries as cubosomes propose a promising system for the treatment of various diseases of the age.

## Compliance with ethical standards

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## Disclosure of conflict of interest

All authors declare that they have no conflict of interest.

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**Figures**

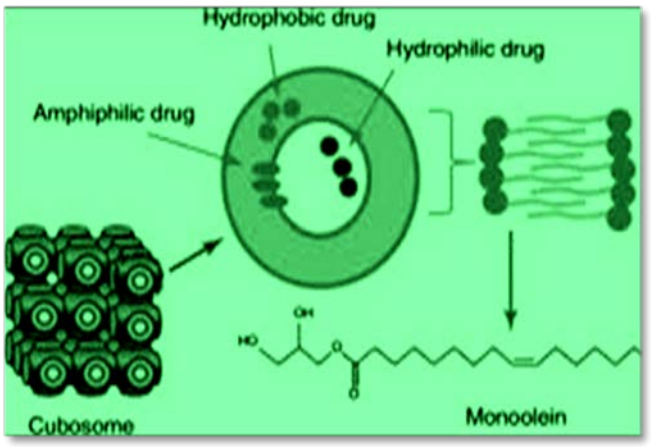


Fig. 1: Structure of cubosome separating two internal aqueous channels along with large interfacial area

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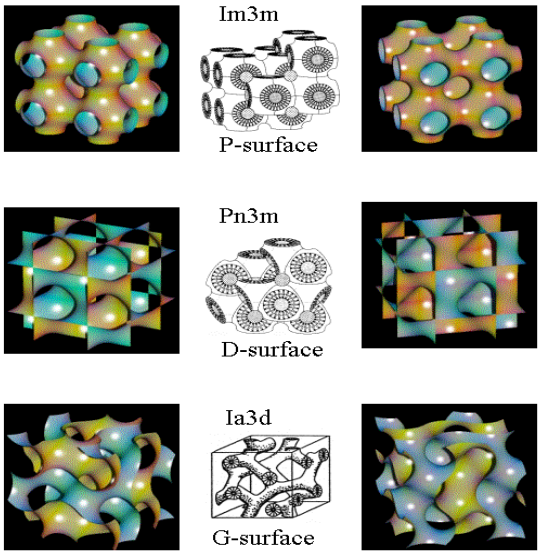


Fig. 2: Biocontinous cubic phases in lipid



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**Tables**

TABLE(1)
CHALLENGE OF CUBOSOMES DRUG DELIVERY SYSTEMS IN VARIOUS APPLICATION

| Trend | Exampble of cubosomal challenge |
|---|---|
| In cancer cell | Efficient cytotoxicity and cellular uptake of RSV cubosomes were attained with a particle size range 45–76 nm which was additionally internalized by caveolae-mediated endo-cytosis |
| Increasing the corneal permeability | TM cubosomes achieved more retention time and lower-IOP effect than the commercial TM eye drops. |
| Brain targeting | A cubosomal gel (containing glycerol monooleate (4% w/v), Lutrol® F 127 (1.5% w/v) and poloxamer 407 (12% w/v) showed significantly higher transnasal permeation and better distribution to the brain, when compared to the drug solution (i.n.) and drug solution (oral). |
| Oral drug delivery | The orally AmB cubosomes, could significantly increase oral efficacy, compared against Fungizone®. |
| Trandermal drug delivery systems | The etodolac-loaded cubosomes propose an encouraging system for the treatment of arthritis simply through skin application |
| Cosmetics | 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. |
| Sustained release behaviour | Chito-cubosomes exhibited an anti-digestion effect, much slower in vitro release behavior, and enhanced oral bioavailability than intact liquid cubosomes |
| In treatment of epileptic children patients | Clonazepam (Cl) cubosomal-gel was studied to be applicated as a patch reservoir via transdermal-route. Cub-gel containing PVA showed significantly more Cl-transdermal permeation than Cl-suspension. It also reduces the epileptic seizures and alters the behavioral parameters induced by piocarpine. |
| Gene therapy | A microfluidic nanomanufacturing device was utilized to prepare siRNA-loaded cubosomes, termed cuboplexs that overpass commercially available delivery vectors and liposome-based systems. |
| Theranostic applications | Magnetocubosomes are interesting hybrid nanostructures in nanothoranostics applications. |

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