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Review Article

Cubosomes as Smart Nanocarriers: Advances in Targeted Drug Delivery and Anticancer Therapy

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ABSTRACT

Cubosomes, which are self-assembled nanostructures derived from amphiphilic lipids in the presence of stabilizing agents, represent a significant advancement in the field of nanomedicine. Characterized by their distinctive bicontinuous cubic liquid crystalline phase, cubosomes exhibit a high surface area, structural adaptability, and the capacity to encapsulate hydrophilic, hydrophobic, and amphiphilic compounds. This review offers a comprehensive examination of the physicochemical properties, constituent components, drug loading methodologies, release mechanisms, and fabrication techniques associated with cubosomes. Particular attention is devoted to their application in targeted and controlled drug delivery systems, with an emphasis on cancer therapeutics. The article underscores recent progress in employing cubosomes for the treatment of glioblastoma, lung, colorectal, liver, ovarian, and cervical cancers, highlighting improvements in drug bioavailability, reduction of systemic toxicity, and site-specific therapeutic action. Additionally, this review addresses characterization techniques, formulation challenges, and the potential of cubosomes as innovative nanocarriers in clinical drug delivery contexts.

INTRODUCTION

The bicontinuous cubic liquid crystalline phase comprises unique nanostructured entities termed cubosomes, which typically measure less than one micron in size. The designation "cubosomes" was introduced by Larsson to describe these structures, owing to their cubic molecular crystallography and their resemblance to liposomes. These self-assembling liquid crystalline nanoparticles exhibit an optimal water-to-microstructure ratio and incorporate specific surfactants. Unlike conventional solid particles, cubosomes spontaneously organize into liquid-crystalline

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nanoparticles. Structurally, amphiphilic cubosomes consist of lipids, surfactants, polar and non-polar polymers, among other related constituents. The hydrophobic effect drives the amphiphilic molecules into the polar solvent, prompting their aggregation into nanometer-scale liquid crystalline assemblies upon mutual recognition. Notably, cubosomes feature two distinct aqueous domains within their bicontinuous cubic liquid phases, which are separated by surfactant-regulated bilayers[1].

These materials exhibit cubic crystallographic symmetry and are characterized by their solid, viscous nature and optical isotropy, resembling liquid crystalline solids. By disrupting the cubic phase, it is possible to generate particle dispersions that are both colloidally and thermodynamically stable. Cubosomes, which are integral to nanodrug delivery systems, form a bicontinuous cubic liquid crystalline phase upon hydration of a mixture containing monoolein and poloxamer 407. The resulting particles are typically square to somewhat rounded in shape, with diameters ranging from 10 to 500 nm. Active pharmaceutical molecules are chemically bonded to the polar head groups of the phospholipids within the cubosomes. The polymer-to-drug ratio in these formulations can vary, commonly being either 1:1 or 2:1, depending on the specific materials employed [1].

This phenomenon is primarily attributed to the ability of nanoparticles to accumulate in target tissues either passively, through the enhanced permeability and retention (EPR) effect, or actively, via surface-conjugated targeting ligands. Regardless of the necessity of such targeting, nearly all drug delivery systems exhibit passive targeting, wherein the therapeutic agents preferentially localize around the leaky vasculature characteristic of tumor sites. The EPR effect can be exploited through the intravenous administration of nanoparticles; however, it is widely recognized that the majority (>95%) of these dispersed nanoparticles tend to accumulate in organs such as the liver, spleen, and lungs[2]. Furthermore, the tortuous diffusion of active compounds through the cubic phase's ordered channel structure enables their controlled dissemination. Cubosomes facilitate the controlled release of pharmaceuticals due to their small pore sizes, which enhance the stability and bioavailability of physiologically active substances, including proteins and vitamins [3].

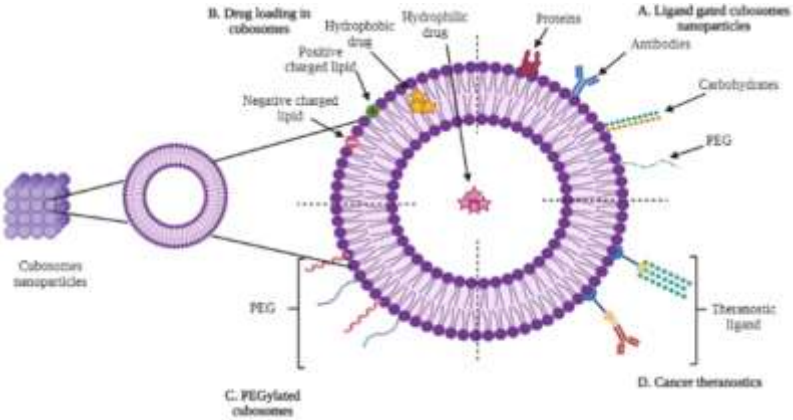

Figure 1:Cubosomes exhibiting internal and cubic structures with potential of drug delivery

COMPONENTS OF CUBOSOMES:

Cubosomes predominantly consist of stabilizers of various grades in combination with amphiphilic lipids. The formation of cubic crystals occurs

through the interaction of amphiphilic lipids, including monoglycerides, glycolipids, phospholipids, and alkyl glycerates. The self-assembly of diverse amphiphilic lipid nanostructures, exhibiting distinct geometries and physicochemical characteristics, is influenced by multiple factors such as lipid composition, electrostatic interactions, temperature, pressure, and the molecular architecture of the lipids [4].

Currently, the most widely employed amphiphilic lipids for the formation of cubosomes are Phytantriol (PHYT) and Glycerol Monooleate (GMO), also known as Rylo MG 19 or monoolein. GMO is a polar, unsaturated monoglyceride with a melting point ranging from 35 to 37 °C. It is a colorless and transparent substance with a hydrophilic-lipophilic balance (HLB) value of 3. The primary constituent of GMO is monooleate, although it also comprises glycerides derived from oleic acid and other fatty acids. The amphiphilic nature of monooleate enables it to form various crystalline structures, which can subsequently organize into lyotropic liquid crystalline phases. This behavior is attributed to the presence of hydrocarbon chains in the lipid tails and hydroxyl groups in the head region, allowing GMO molecules to form hydrogen bonds with water in aqueous environments, thereby exhibiting both hydrophilic and hydrophobic properties [5].

Phytotriol, a compound frequently incorporated in various cosmetic products, is utilized in cubosome formulations as an alternative to glyceryl monooleate (GMO). It has the ability to form a bicontinuous cubic phase in aqueous environments under physiological conditions and temperatures. Among the commonly employed stabilizing agents are Pluronics, with the triblock copolymer poloxamer 407 (F127), composed of PEO99-PPO67-PEO99 segments, being a preferred surfactant for cubosome synthesis. This stabilizer functions by establishing an electrostatic barrier that prevents the dispersed particles from approaching each other closely, thereby preserving their highly stable dispersion state[6].

MECHANISM OF DRUG RELEASE FROM CUBOSOME:

The concentration gradient of a drug across cubosomes serves as the driving force for drug diffusion, which underpins the drug release mechanism from these nanostructures. Consequently, the rate of drug release from cubosomes is frequently described by the Higuchi or Fickian diffusion models. Several factors influence the drug release rate, including the diffusion and partition coefficients, the geometry of the cubic liquid-crystalline phase, pore size and distribution, interfacial curvature, as well as environmental conditions such as temperature, pH, ionic strength of the release medium, and drug solubility. Additionally, the release mechanisms from cubic and inverted hexagonal liquid crystalline phases have been investigated using various hydrophilic model drugs[7].

DRUG LOADING IN CUBOSOMES:

Cubosomes are capable of encapsulating a substantial quantity of biologics, peptides, bioactive compounds, or small-molecule drugs. The primary strategies for drug loading involve incorporation into the aqueous channels of the cubic phase, embedding within the lipid bilayer, or adsorption onto the bilayer surface. Drug molecules can be introduced by co-lyophilizing with the lipid film prior to dispersion or by direct injection into molten lipids. Post-dispersion, drug loading into cubosomes can also be achieved through incubation. Typically, proteins, peptides, and small-molecule drugs are predominantly localized within the lipid bilayers. Investigations have been conducted on drug delivery systems

based on cubic and inverted hexagonal liquid crystalline phases[8]. Compared to liposomes, cubosomes exhibit an enhanced capacity for hydrophobic drug loading due to their larger hydrophobic domain, while also effectively encapsulating hydrophilic drugs. According to Higuchi diffusion-controlled kinetics, the cubic architecture of cubosomes facilitates the entrapment and controlled release of therapeutic agents with diverse molecular weights and polarities.

$$Q = [D_m C_d (2A - C_d)t]^{½}$$

This equation states that the square root of time impacts matrix agent diffusion. Q is the agents' release per unit area of the matrix, Dm is their diffusion coefficient in the cubic matrix, Cd is their solubility, A is the drug's primary quantity per unit volume, and t is the period [9].

PREPARATION TECHNIQUES:

Cubosomes can be manufactured by two different techniques as shown in figure2.

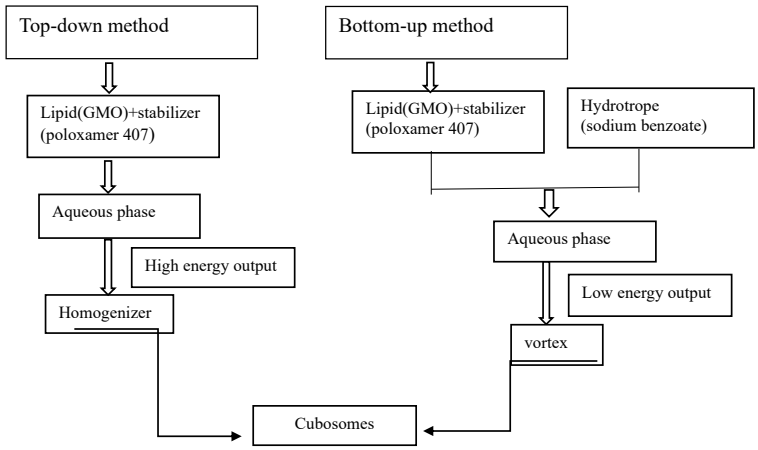

Figure 2: Diagrammatic illustration of cubosomes preparation approaches

Another technique is spray drying technique in figure3.

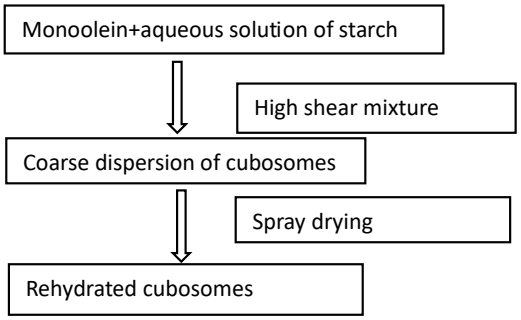

Figure 3: Diagramatic illustration of spray drying technique

CHARACTERIZATION OF CUBOSOMES:

The optical characteristics of cubosomes were evaluated, encompassing parameters such as color, turbidity, homogeneity, and the presence of macroscopic particles. The morphology of the cubosomes was examined using transmission electron microscopy. Particle size distribution was assessed employing dynamic light scattering via a Zeta sizer based on photon correlation spectroscopy, which is considered the gold standard for this purpose. Prior to measurement, samples were diluted with an appropriate solvent to achieve a light scattering intensity of approximately 300 Hz and were analyzed in triplicate at 25 °C [10]. Data were typically represented using the average volume-weighted particle size. Additionally, measurements of zeta potential and polydispersity index were obtained. The magnitude of the zeta potential reflects the

degree of electrostatic repulsion between charged particles and serves as a valuable indicator of formulation stability. Entrapment efficiency of the cubosomes was determined through ultrafiltration techniques [11], wherein the concentration of unencapsulated drug was quantified and subtracted from the total drug amount initially incorporated. Drug quantification was performed using spectrophotometric analysis. Furthermore, physical stability was assessed by monitoring organoleptic and morphological properties over time.

CUBOSOMES AS TARGETED DRUG DELIVERY FOR TUMORS:

The development of therapeutics that selectively eradicate cancer cells while sparing normal, healthy tissues remains a critical objective in oncology. Protecting healthy tissues and ensuring the targeted delivery of anticancer agents to diseased sites are fundamental to achieving this aim. One of the most promising strategies for drug delivery exploits the unique pathophysiological and structural abnormalities of tumor vasculature, alongside the enhanced permeability and retention (EPR) effect. Nanocarriers, benefiting from the EPR phenomenon, represent some of the most efficient vehicles for the targeted delivery of therapeutics to tumor sites.

One illustrative example involves the functionalization of carrier surfaces with ligands that specifically target or exhibit enhanced affinity for cancer cell receptors. Another approach employs the application of an external magnetic field to improve the delivery of tumor-targeted therapies. It is essential to consider the tumor microenvironment due to its heterogeneous characteristics. The delivery of nanoparticles is particularly challenging in settings characterized by elevated interstitial pressures and a dense extracellular matrix (ECM) [12]. Biocompatible cubic liquid crystals demonstrate excellent adhesive properties and are capable of dispersing in aqueous media. These multifunctional delivery systems can be administered via intravenous, oral, percutaneous, or ocular injection routes, owing to their favorable attributes. This innovative strategy in cancer treatment has garnered significant attention for its potential to mitigate adverse side effects by directing anticancer agents specifically to tumor sites, thereby minimizing their accumulation in healthy tissues [13].

1. Glioblastoma Multiforme Therapy

Cubosomes loaded with AT101 were synthesized using top-down approaches incorporating glyceryl monooleate (GMO) and the surfactant Pluronic F-127. AT101, the R-(-)-enantiomer of the polyphenol gossypol derived from cotton seeds, exhibits potential as a therapeutic agent for glioblastoma multiforme (GBM) due to its capacity to induce apoptosis in tumor cells through autophagic cell death. However, the clinical utility of AT101 is limited by its poor bioavailability and low aqueous solubility, which reduce its therapeutic efficacy. The formulation of AT101 within cubosomes enhances its bioavailability and anticancer activity, thereby overcoming these pharmacokinetic limitations [14].

2. Lung Cancer Treatment

In the treatment of non-small-cell lung cancer (NSCLC), inhalation drug delivery is considered optimal due to its ability to minimize systemic toxicity and reduce dosing frequency. Bedaquiline (BQ), an FDA-approved medication primarily used for tuberculosis, has demonstrated potential anticancer activity. However, its clinical application via pulmonary administration is limited by its poor aqueous solubility. To address this challenge, a novel class of nanocarriers, termed inhaled BQ-loaded cubosomes (BQLCs),

was developed specifically for NSCLC therapy. These BQLCs were formulated using cubosomal nanocarriers characterized by a particle size of 150.2 ± 5.1 nm, a positive zeta potential of 35.4 ± 2.3 mV, and an encapsulation efficiency of 51.85 ± 4.83%. In vitro studies on NSCLC A549 cell lines demonstrated that BQLCs exhibited enhanced cytotoxicity and cellular uptake after 48 hours of treatment, with an IC50 value approximately threefold lower than that of free BQ. Furthermore, BQLCs effectively inhibited colony formation and cancer cell proliferation through the induction of apoptosis, thereby reducing tumor progression in vitro [15].

3. Colorectal Cancer Treatment

In efforts to address colorectal cancer (CRC), researchers have developed cubosome-based delivery systems encapsulating metformin and cisplatin, utilizing genetically modified organisms (GMOs), Pluronic F-127, and polyvinyl alcohol as key components. Colorectal cancer remains a significant global health challenge due to its high mortality rate. Although cisplatin is an effective chemotherapeutic agent, its clinical application is often limited by severe side effects and the development of drug resistance. Therefore, the integration of efficient drug delivery vehicles is essential to enhance anticancer therapy. The formulated cubosomes containing both cisplatin and metformin demonstrated superior cytotoxicity compared to free cisplatin. Notably, the inclusion of metformin reduced the IC30 value to 7 µM, achieving a 50% inhibition of cancer cell proliferation. Furthermore, cisplatin-loaded microcubosomes were observed to decrease cellular energy and glucose levels, concomitantly activating AMP-activated protein kinase (AMPK) and inhibiting the mechanistic target of rapamycin (mTOR) pathway. This formulation also induced a significant increase in reactive oxygen species (ROS) production, attributed to the upregulation of NADPH oxidase and caspase-3 activity, alongside the suppression of lactate dehydrogenase (LDH). Survival fraction analyses indicated that nanoparticles loaded with these drugs exerted enhanced cytotoxic effects relative to the administration of the drugs in their free form [16].

4. Liver Cancer Treatment

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5. Ovarian Cancer Treatment

Icariin (ICA), a flavanol glycoside predominantly extracted from the herb Herba epimedii of the Berberidaceae family, has recently been investigated for its therapeutic potential against ovarian cancer cell lines, specifically SKOV-3 and Caov-3. ICA has been shown to inhibit key signaling pathways involved in breast cancer progression, including PI3K/AKT and Raf1/ERK1/2, while also modulating cellular processes such as the cell cycle, apoptosis, and autophagy through the upregulation of autophagy-related p53. Moreover, ICA affects the expression of caspase-3 and mitochondrial transmembrane potential, thereby facilitating the generation of cytotoxic reactive oxygen species (ROS) within ovarian cancer cells. [18].

6.Cervical Carcinoma

Doxorubicin is a pharmaceutical agent widely employed as an anticancer drug. It is primarily indicated for the treatment of solid tumors, including those of the thyroid, bladder, breast, and ovaries, while also demonstrating efficacy against neuroblastomas, sarcomas, lung cancer, and various other malignancies. The mechanism of action involves intercalation between DNA strands, thereby inhibiting the synthesis of both DNA and RNA. Additionally, doxorubicin activates topoisomerase II, which not only generates quinone-type free radicals but also facilitates DNA strand breaks. Cubosomes composed of glycerol mono-oleate (GMO) have been utilized as delivery vehicles for the radionuclide lutetium-177 (177Lu) in combination with doxorubicin. Furthermore, these cubosomes were functionalized with a chelating agent, DOTAGA-oleylamine conjugate (DOTAGA-OA), which forms stable complexes with lutetium-177, enhancing the delivery system's stability and efficacy[19].

ANTICANCER DRUGS LOADING ON TO CUBOSOMES:

1. Docetaxel

Docetaxel (DTX), a first-line chemotherapeutic agent, demonstrates efficacy in the treatment of breast and ovarian cancers. This taxane-class drug induces cell death through the phosphorylation of B-cell lymphoma 2 (Bcl-2) and the monomerization of tubulin. For the delivery of docetaxel, glycerol monooleate (GMO) cubosomes stabilized with Pluronic-F127 and Pluronic-F68 were employed. A thermo-responsive gelling depot system was developed to achieve controlled drug release, allowing the formulation to remain in a liquid state at ambient temperature and transition into a gel at elevated temperatures. Subsequently, the DTX-loaded cubosomes (DTX-Cubs) were incorporated within this depot system[20].

2. Etoposide

Chemotherapy for malignancies of the lung, testicles, and ovary, as well as lymphoma, leukaemia, and neuroblastoma, makes use of Etoposide (ETP), a semisynthetic derivative of podophyllotoxin, a plant glycoside. Etoposide blocks cells in the G2 phase of cell-loaded cubosomes (ETP-Cubs) and folate-modified cubosomes by blocking the topoisomerase-2 enzyme, which cleaves DNA. After being produced by bulk gel fragmentation under homogenisation settings of 1500 bar, these cubosomes were found to have a limited size distribution, with an average particle size of approximately 180 nm [21].

3. Methotrexate

Among the various antimetabolites, methotrexate (MTX) stands out as one of the most established

and enduring agents. MTX functions as a folate antagonist and is employed in the treatment of multiple autoimmune disorders, including psoriasis, rheumatoid arthritis (RA), and leukemia. Its therapeutic effect is mediated through the inhibition of the enzyme dihydrofolate reductase (DHFR), which catalyzes the conversion of dihydrofolic acid (DHFA) to tetrahydrofolic acid (THFA). This conversion is critical for the synthesis of thymidine, an essential nucleotide for DNA replication. In a recent investigation, Janakiraman et al. developed methotrexate-loaded cubosomes (MTCs) by utilizing varying ratios of Poloxamer 188, cetyl palmitate, and water to formulate multiple cubosomal preparations (MTCs 1–MTCs 8). The zeta potential measurements of these formulations ranged from -33.0 ± 0.21 mV to -78.84 ± 0.03 mV, with the negative values indicating enhanced stability and favorable dispersion characteristics of the cubosomal systems [22].

APPLICATION OF CUBOSOMES:

Numerous studies have employed cubosomes as carriers for anticancer drugs, demonstrating encapsulation efficiencies ranging from 71% to 103%. These results highlight the effectiveness of cubosomes as a drug delivery platform, particularly for anticancer therapeutics. Recent research has shown that alpha-linolenic acid (ALA) incorporated within cubosome dispersions significantly diminishes facial wrinkles, achieving near-complete resolution of fine lines in the periorbital and upper lip regions, along with enhancements in skin texture and coloration among study participants. The integration of multiple nanoparticles with specific targeting ligands further facilitates the development of highly efficient active drug delivery systems. In commercial applications, treatments for periodontal disease have utilized cubosome-based formulations combining triglyceride-monoolein with the antibiotic metronidazole. This lipid-drug complex targets the gingival tissues; upon exposure to saliva, it undergoes hydration to form a bulk cubic phase that enables uniform drug dispersion [23].

Cubosomes have been recognized as a highly effective platform for oral drug delivery, particularly in enhancing the oral bioavailability of drugs with poor aqueous solubility [24]. Empirical evidence demonstrates that cubosomes substantially improve the apparent permeability and bioavailability of dexamethasone and flurbiprofen, which are employed as carriers in ocular therapeutics [25]. Their unique solubilization capabilities, high encapsulation efficiency, sustained release profiles, and in vivo stability have established cubosomes as a promising drug delivery system [26]. 2Recent investigations have focused on the application of cubosomes in ocular drug delivery, highlighting their biodegradability and versatility in encapsulating hydrophilic, hydrophobic, and amphiphilic compounds, as well as their ability to facilitate targeted and controlled release of bioactive agents. The enhanced ocular bioavailability observed with cubosome formulations is attributed to their prolonged retention time on the corneal surface when administered alongside therapeutic agents. Moreover, the mucoadhesive properties of glyceryl monooleate (GMO)-based cubosomes contribute to increased ocular permeability, thereby augmenting drug bioavailability. Notably, cubosomes loaded with dexamethasone have demonstrated the ability to penetrate excised rabbit corneas in vitro, underscoring their potential in ocular drug delivery research. Pharmacokinetic analyses of aqueous humour samples, coupled with precorneal residence time assessments, revealed a significant extension in preocular retention time relative to dexamethasone sodium

phosphate eye drops. Correspondingly, the concentration of dexamethasone in the aqueous humour was markedly elevated, indicating improved drug delivery efficiency [27].

Transcutaneous immunisation (TCI) is a vaccination method that employs cubosomes. Cubosomes and microneedles (MNs) have been effectively utilised in this method as a complementary strategy for vaccine delivery via the skin. Cubosomes containing peptide demonstrated prolonged retention in the skin, while the microneedle enhanced the penetration of the peptide mixture through the skin layers in aqueous conditions. Subsequently, it was demonstrated that the integration of cubosomes with microneedles serves as an effective method for the localised delivery of antigens to targeted skin cells [28].

CONCLUSION:

The development of cubosomes as nanocarriers constitutes a notable advancement in the domain of targeted drug delivery, especially within oncology. Owing to their self-assembled, thermodynamically stable, and structurally adaptable characteristics, cubosomes exhibit high drug encapsulation efficiency alongside customizable release profiles. This review synthesizes the expanding evidence base that underscores their therapeutic efficacy across a range of cancers, including glioblastoma, lung, liver, colorectal, ovarian, and cervical malignancies, by enhancing the therapeutic index and mitigating adverse effects. Furthermore, cubosomes have shown considerable promise in augmenting patient adherence through alternative routes of administration and decreased dosing frequency. Despite encouraging outcomes in preclinical investigations, clinical translation remains constrained, highlighting the need for further research focused on scalability, biocompatibility, and long-term safety. Nevertheless, cubosomes emerge as a next-generation nanoplatform with the potential to transform the delivery and efficacy of anticancer agents.

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