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CUBOSOMES: A VERSATILE NANOCARRIER FOR DRUG DELIVERY

Angelina Austin[1], Anmol Kumar Upadhyay[1], Aryan Bansal[1], Rajwant Kaur[1]*

[1]University Institute of Pharma Sciences, Chandigarh University, Gharuan, Mohali, Punjab

ABSTRACT

Undoubtedly, nanotechnology has significantly advanced numerous scientific disciplines, particularly nanomedicine. The potential to transport active chemicals to targeted sites holds great potential for enhancing medical therapies. Among the various nanocarriers developed, cubosomes have garnered considerable attention. These Lipid bicontinuous cubic phases, which have an aqueous domain organised in a cubic lattice and a lipidic core, make up nanosized dispersions in water. The discovery of cubosomes intertwines food science, biological membranes, differential geometry, and digestive processes. In essence, cubosomes are precisely balanced nanoparticles covered in an exterior layer of polymer, primarily derived from the lipid cubic state. Their exceptional properties make cubosomes suitable for a wide array of biological applications, spanning from imaging to cancer therapies. Given their remarkable attributes, cubosomes are anticipated to find extensive use across various research domains. This review critically evaluates the pertinent literature on cubosomes, emphasizing commonly utilized methods for describing them, such as nanocarriers, cubosome composition, and their applications in drug delivery. The latest advancements Cubosome technology not only makes research easier, but it also creates standard operating procedures for the methodical creation of novel systems suited for biomedical uses.

Keywords: Nanotechnology; cubic phase nanomedicine; delivery systems; cubosomes, etc.

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INTRODUCTION

Nanotechnology has significantly impacted numerous scientific domains, particularly nanomedicine, where it plays a pivotal role. One notable contribution of nanotechnology is the development of carriers that enhance the efficiency of medication delivery, thereby improving therapeutic outcomes [1-5]. Researchers have suggested that combining active medicinal substances with nanocarriers has led to the creation of effective and safe cancer immunotherapy. This innovative approach enables the selective accumulation of therapeutic agents in targeted sites while minimizing absorption by healthy tissues, consequently reducing side effects. Furthermore, the use of nanocarriers has been shown to enhance the stability and solubility of specific active ingredients [6].

Nanotechnology enables the construction of intricate nano-systems with precise target selectivity. Carriers may be targeted to particular places by functionalization, which makes it easier for cells to internalise them. The payload may be transported into subcellular compartments thanks to this feature [7], which improves the payload's capacity to target tumour cells and increases anti-tumor effects, such as anti-tumor immunity. Immunomodulator delivery may result in the development of tumor-specific immune cell subpopulations, altering the immunological environment surrounding the tumor [8]. Furthermore, it has been suggested that tumor-associated antigens and adjuvants can be intracellularly delivered by nanocarriers to antigen-presenting cells such B cells, T cells, dendritic cells, and macrophages, hence enhancing immune system activation [9].

Advancements in nanocarriers have led to the development of nanoparticles capable of simultaneously encasing various compounds [10, 11]. In order to improve therapy results and increase drug concentration at the target location, nanoparticles may cluster at tumour sites and release encapsulated compounds in a regulated way [12]. Furthermore, nanoparticles might benefit from multidrug resistance transporters, which can confer resistance to drug owing to the size-exclusion effect, which efficiently concentrates drugs inside cells [13].

Certain molecules, such as lipids are able to integrate different active biomolecules and self-assemble. It has been shown in several investigations that adding bioactive molecules to these structures greatly increases the likelihood that different medical treatments will be successful [14, 15]. This is mainly because there are less adverse effects when active molecules are delivered at the intended site in a regulated and sustained way [16–19].

Among lipidic carriers evolved throughout time, there has been a lot of interest in the cubosomic lipid structure. Cubosomes possess the unique capability of incorporating

apolar, polar, and amphiphilic molecules simultaneously, including those with diverse chemical properties. This feature makes it possible to combine drugs with different modes of action to produce a synergistic effect. Cubosomes are water-based, nanoscale lipid bicontinuous cubic phase dispersions. comprising an aqueous domain folded in a cubic lattice and a lipidic core [20].

The concept behind preparing cubosomes relies on the ability of their constituent parts to self-assemble into a cubic phase. Compounds like lipid monoolein, which exhibit self-assembly into various configurations upon contact with water, can be employed in cubosome synthesis. The adaptability of the cubosome platform makes it suitable for various applications, including transfection systems and cancer therapies [21]. Therefore, this review study will encompass techniques for generating and characterizing lipidic nanosystems, in particular, cubosomes and their possible uses in biomedicine. Specifications of cubosomes in particular, cubosomes and their possible uses in biomedicine.

Properties of cubosomes [22]

- The viscosity of cubosome dispersions is noticeably lower.
- The most intriguing feature of cubosomes may be that they are unique sub- micron nanostructured particles made of bicontinuous cubic liquid crystalline phases.
- Because cubic liquid crystals are transparent and isotropic, they maintain their physical stability in situations with high water content.
- Because of their biodegradability and ability to solubilize hydrophobic, hydrophilic, and amphiphilic chemicals, cubosomes are attractive for controlled release due to their tiny pore size. tiny pore size.

Advantages of Cubosomes [23]

- They are able to encapsulate medications that are amphiphilic, hydrophilic, and hydrophobic.
- Drug delivery cubosomes have sustained-release properties.
- They exhibit qualities of bioadhesivity and biocompatibility.
- Even under high-water conditions, the bicontinuous cubic liquid crystalline phase of cubosomes is stable.
- Cubosomes are superior solubilizers than traditional lipid or non-lipid carriers.

- Cubosomes function as efficient transporters for shielding delicate medications, such peptides and proteins, from enzymatic and in vivo degradation. • They have a high drug carrier capacity for scarce water-soluble pharmaceuticals. The bioavailability of water-soluble peptides is increased twenty to over one hundred times by the cuboidal method.
- Cubosomes have larger bilayer area to particle volume ratios and stronger breaking resistance as compared to liposomes.
- Cubosomes are able to deliver large pharmacological payloads because of their c crystalline cubic shapes and high interior surface area.
- They are lipid biodegradable and may be made with easy techniques.
- The targeted and regulated release of bioactive substances is made possible by cubosomes.
- Cubosomes have a high drug-carrying capability when it comes to water-soluble medications.
- They function as efficient carriers to shield delicate medications, such proteins and peptides, from enzymatic and in vivo breakdown.
- Cubosomes can break apart and distribute their cubic phases to create particle dispersions that are thermodynamically and/or colloidally stable for extended periods of time.

Disadvantages of Cubosomes [24]

- The high viscosity of the cubic phase makes large-scale manufacturing challenging.
- For pharmacological compounds that are soluble in water, their high-water content in the structure leads to a low entrapment efficiency.

Structure of Cubosomes

Cubosomes are characterized by a large interfacial surface and the structure that divides the two interior aqueous channels is honeycombed. These nanostructured particles form when molecules with surfactant-like or amphiphilic properties self-assemble in liquid crystalline phases exhibiting cubic crystallographic symmetry [25]. The high solid-like viscosity of the cubic phases is a unique feature arising from their intriguing bicontinuous structure made up of two different water zones divided by a precisely applied bilayer of surfactant. Bicontinuous water and oil channels are formed in part by amphiphilic molecules; the term "bicontinuous" refers to two distinct but non-intersecting hydrophilic regions that are divided by the bilayer. The structure's interdependencies results in a transparent, viscous gel with rheology resembling

cross-linked polymer hydrogels.

Cubosomes manifest as tiny, round, or square-shaped particles, where Every dot in the lipid-water system represents a pore that holds aqueous phase cubic phases. originally identified by x-ray scattering researchers Luzzati and Husson methods, cubosomes exhibit structural similarities to non-ionic surfactants. Polar lipids like monoglycerides, characterized by poor water solubility, demonstrate aqueous phase behaviour when hydrated at 20–40% w/w, causing bulk cubic phases to develop [26].

Mechanism of Drug Transport

The transportation of drugs across biological membranes is affected by a number of variables, including as the carrier's activity and content, as well as the physiology and structure of the skin. Simple movement of small ions is facilitated by tight junctions, pores in the epidermis, and hair follicles. Mechanisms involved in skin membrane transfer include both transports that occur within (trans) and between (para) cells. Medications can be added to vesicles as an inherent part or by changing the carriers such that they are integrated into the core. Paracellular diffusion occurs when a substance crosses a membrane by passing across two cells rather than between them. This process is passive and is influenced by the size and shape of the xenobiotic as well as the pore size [27]. The term "transcellular diffusion" describes how a material passes across a cell. The drug is exposed to cell enzymes and any efflux pumps on the apical part of the membrane during enteric absorption by transcellular diffusion, which may lessen the quantity of medication that enters the systemic circulation as depicted in figure 1. Transcellular diffusion can occur in three states: assisted, active, and passive. Drug transit across cells, known as transcellular migrations, is the most common form of drug delivery. However, some medications are too polar to traverse the lipoidal cell membrane; in such cases, the paracellular route, which connects the cells, is typically the only accessible route [28].

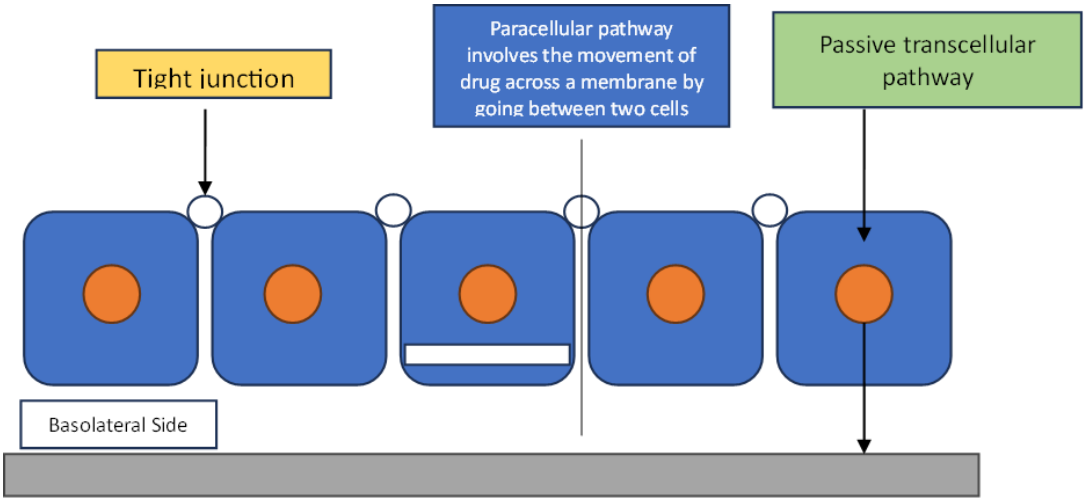

Figure 1: Mechanism of drug transport via skin

Cubosome types

1. Precursors of liquid cubosomes
2. Second, Cubosome Powder Forerunner

Components of cubosomes

Bicontinuous cubic phases can be observed in:

1. Lipids occurring naturally
2. Polymer systems
3. Ionic and non-ionic surfactants

Natural lipids

Monoglycerides and monoolein are the lipids that are most frequently utilised to generate bicontinuous cubic phases. Monoglycerides spontaneously form bicontinuous cubic phases with addition of water. They exhibit resilience to temperature changes and are highly insoluble, facilitating the formation of colloidal dispersions in cubosomes [29].

Monoolein

Monoolein stands as the foremost precursor in the creation of cubosomes. Also known as glyceryl monooleate, monoolein is a blend of various fatty acids and oleic acid glycerides, with monooleate being the main element. There are two types of monoolein that are sold commercially: distilled monoolein and mixed glyceride. Because of its great purity, distilled monoolein is preferred for use in medicinal applications. monoolein characterized by its yellow, waxy consistency and distinct odor, is non-toxic, biodegradable, and biocompatible. It is included in non-parenteral medications listed in the UK and FDA's roster of inactive ingredients. Understanding monoolein's mesomorphic phase is crucial for discerning its

potential medical applications [30].

Surfactant

Poloxamer 407 serves as a surfactant employed in cubosome fabrication, with concentrations in the dispersion phase varying from 0% to 20% w/w. Typically, the concentration of the monoglyceride/surfactant blend ranges between 2.5% and 10% w/w concerning the total weight of the dispersion [31].

Polymer system

Polyvinyl alcohol (PVA) is employed in conjunction with poloxamer to serve as a dispersion stabilising agent.

Cubosomes are a better medication delivery method than others.

Cubosomes excel in delivering medications through the skin due to their enhanced skin penetration rates, making them an efficient vehicle for distributing numerous peptides and proteins. According to scholarly literature, the lipids employed in cubosome formulation are biocompatible, biodegradable, and present a low risk profile [32]. The preparation process requires no specialized equipment and is straightforward. Compared to other carrier systems, cubosomes demonstrate an elevated degree of constancy. This passive, non-invasive nano vesicular technology is about to enter a fast-growing commercial market. appealing to consumers with its unique features [33].

Characterization and Evaluation of cubosomes

The Characterization parameters of Cubosomes are depicted in figure 2

Figure 2: Characterization parameters of Cubosomes

Applications in Dermatology

Transdermal drug delivery is facilitated by the strong barrier known as the stratum corneum, which is the skin's highly structured outermost layer. This barrier prevents drugs applied topically from penetrating the epidermis. However, because of their special structure and characteristics, cubosomes present a viable method for transdermal drug delivery [34]. Through genetic modification, cubosomes have demonstrated the ability to adhere to the stratum corneum, enabling successful topical and mucosal medication delivery. Cubosomes have found various applications in dermatology, with transcutaneous immunization (TCI) being a notable use. The combination of microneedles (MNs) and cubosomes has proven effective in administering vaccines through the skin. MNs facilitate the cubosome-formulated peptide shows extended retention in the skin, whereas the aqueous peptide combination penetrates deeper layers of the skin. The use of MNs with cubosomes in a synergistic manner has become an efficient method for delivering antigens to targeted cells within the skin [35].

Oral applications

Cubosomes have attracted significant interest for their potential application in oral drug

delivery, especially for high molecular weight and poorly absorbed/water-soluble medications. The absorption of oral drugs may be facilitated by their bioadhesive qualities, contact with intestinal cell membranes, or capacity to stimulate the formation of physiological surfactants during lipid breakdown in the gastrointestinal tract [36].

Anticancer applications

Cubosomes are essential for the topical and oral delivery of anticancer drugs. Chemotherapeutic drugs have been successfully delivered using cubosomes as a new drug delivery method, showing enhanced bioavailability, pharmacokinetics, and safety characteristics [37]. Optimising the distinct structure and properties of cubosomes has demonstrated potential in augmenting the oral bioavailability of pharmaceuticals. Research suggests that cubosomes, maybe as a result of their bioadhesive qualities, increase the oral bioavailability of 20(S) protopanaxadiol (PPD), an anticancer medication with restricted oral absorption. Furthermore, it has been noted that administering 5-Fluorouracil (5-FU) to tumour areas via cubosomes in a targeted and protracted manner increases both the drug's anticancer activity and side effects [38]. The water-soluble drug 5-FU has been successfully delivered into liver tissue thanks to cubosomes. Biphasic drug release kinetics from the cubosome formulation were demonstrated by in vitro release profiles, exhibiting a burst release at first and a progressive release over time. Additionally, the cubsomal formulation resulted in greater liver concentrations of 5-FU when compared to the solution form. This difference may be related to the cubosomes' increased systemic absorption rate, which is caused by structural similarities between the lipid bilayers of cubosomes and the microstructures of cell membranes [39].

Cubosomes in Nasal route

Treating problems of the central nervous system (CNS) with direct nasal administration of medicine has become popular due to its non-invasive nature and ability to circumvent the blood-brain barrier (BBB). When coumarin was used as a marker, Wu et al. showed that designed PEGylated cubosomes with functional odorranalectin molecules showed around 3.46-fold greater relative absorption in the brain than untreated cubosomes. In addition, Gly14-human (S14G–HN) was added to cubosomes, and its potential as an Alzheimer's disease therapy was studied. According to the research, odorranalectin cubosomes may improve S14G-HN's effects in Alzheimer's patients. Mayuri Ahirrao et al. also investigated the usage of cubosomes to treat Alzheimer's disease by administering resveratrol via the nasal route. The probe sonication technique was used to create GMO P407 cubosomes, and throughout almost

twenty-four hours, the in vitro drug release showed a consistent pattern [40].

Brain targeting

The blood-brain barrier (BBB), which prevents both tiny and big chemicals from entering the brain, makes treating CNS illnesses difficult. One kind of lipid-based nanoparticle that has been studied to help in medication transport over the BBB is cubosomes. For instance, cubosomes have been explored to improve resveratrol's transnasal distribution to the brain. Lutrol® F 127 and glycerol monooleate lipids were used to create these cubosomes by the use of a probe sonication process. An in situ nasal gel was produced by mixing Poloxamer 407 polymer with cubosomal dispersion that had been optimised. This gel showed better transnasal penetration and dispersion than the medication solution [41].

Cosmetics

The mitochondrial fatty acid alpha-lipoic acid (ALA), which is well-known for its strong antioxidant qualities, has been incorporated into cubosomes to formulate hair care, skin care, antiperspirant, and various other cosmetic products. These formulations have demonstrated outstanding reduces wrinkles on the face and enhances the texture and tone of the skin [42, 43].

Drugs Incorporated in Cubosomes

Table 2: demonstrates a list of medications included in cubosomes for different research outcomes.

S. No.	Outcome of the study	Drug used
1	Cubosomes loaded with doxorubicin provide improved drug loading, pH sensitivity, and regulated release at the intended location. This carrier method increases cell cytotoxicity while reducing undesirable side effects.	Doxorubicin
2	A refined formulation of ketorolac-loaded cubosomes resulted in nanoparticles with increased levels of ketorolac encapsulation. Additionally, improvements were observed in retention and transcorneal permeability.	Ketorolac
3	This formulation could potentially facilitate oral administration of AmB. Cubosomes were employed	Amphotericin B

	to achieve controlled release of AmB for oral delivery.	
4	A formulation of SSD dispersions was created to lessen the negative effects of silver by controlling the release of SSDs. These nanoparticles, referred to as cubosomes, exhibited enhanced wound healing with reduced adverse effects compared to commercial formulations. Additionally, they facilitated a decrease in the SSD dosage to 0.2 percent.	Silver sulfadiazin
5	A homogenized formulation of cubosomes containing monoolein and poloxamer was achieved for the continuous transdermal administration of lipophilic medication.	Indomethacin
6	Cubic nanoparticles enhanced both the absorption and transport of flurbiprofen to the cornea.	Flurbiprofen

CONCLUSION

The development of nanocarriers has sparked significant advancements in various fields of study, particularly medicine. Nanocarriers offer the potential to target specific cells, thereby enhancing the efficacy of therapeutic interventions. Among the diverse array of nanocarriers, cubosomes have recently emerged as a focal point of research and exploration. This article comprehensively addresses the fundamental physicochemical principles and limitations governing the construction of cubosomes, the commonly employed characterization techniques, and several proposed biomedical applications of cubosomes.

The importance of cubosomes in the biomedical field stems from their capacity to hold molecules with a variety of physicochemical characteristics, including polar and apolar compounds. This characteristic enhances treatment efficacy by facilitating the concurrent delivery of synergistic molecules. Moreover, cubosomes exhibit versatility beyond mere multi-molecule encapsulation; they have proven effective as a theranostic tool. The discovery of cubosomes has paved the way for the development of novel and potent therapies with reduced side effects. Ongoing improvements in cubosome preparation techniques are anticipated to unlock new avenues for application and innovation in the field.

CONFLICTS OF INTEREST

The author had no competing interests.

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