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Review Article

Cubosome based Nanocarriers for Drug Delivery: Recent Advances, Clinical Translation, and Future Perspectives

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A B S T R A C T

The bicontinuous cubic liquid crystalline phases are also being exploited as emerging lipid based nanocarriers, providing a novel three dimensional nanostructure with connected lipid bilayers and aqueous channels. This architecture allows the encapsulation of both hydrophilic, lipophilic and amphiphilic drugs with high loading, stability and controlled release properties. Cubosomes have been recently receiving a lot of attention in nanomedicine because of their bioavailability, drug stabilization, and therapeutic efficacy for various drug delivery platforms such as oral, topical, ocular, transdermal, pulmonary and parenteral delivery. With the development of formulation concepts (top down bottom up, hydrotrope dilution, solvent free and microfluidic technologies) their scalability and reproducibility have been enhanced. Furthermore, surface functionalization and stimuli responsive designs have facilitated targeted and theranostic uses in cancer therapy, neurological and ophthalmological diseases. These benefits are accompanied by manufacturing scale up, long term stability, regulatory issues and restricted clinical translation. Future studies will incorporate quality by design principles and advanced manufacturing techniques, which should help to expedite clinical development. Overall, cubosomes represent a versatile and promising platform for next generation drug delivery systems in precision nanomedicine.

Keywords: Cubosomes,Drug Delivery Systems, Targeted Drug Delivery, Liquid Crystalline Nanoparticles, Nanomedicine,Etc.

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INTRODUCTION

Nanotechnology has revolutionized the modern drug delivery system by providing the means to design new carrier systems that overcome the shortcomings of traditional drug formulations namely the problem of poor aqueous solubility, low bioavailability, degradation, non-specific biodistribution, dosedependent adverse effects. Lipid based nanocarriers have attracted significant interest due to their biocompatibility, biodegradability, the ability to load a high amount of drug, and the enhancement of therapeutic efficacy, among the different nanocarriers systems investigated.[11,17]

Cubosomes are a novel class of lipid based nanocarriers that have unique internal nanostructure and superior versatility as drug delivery systems. This unique structure allows the inclusion of therapeutics of widely varying physicochemical properties, and enables controlled drug release, enhanced drug stability, and improved bioavailability.[1, 5] Since then, the formulation science, characterization methods and surface functionalization techniques have advanced greatly and now allow for the development of stable Nano particulate dispersions of the cubic phases, opening the door for their use in a variety of therapeutic applications.

Cubosomes are gaining attention as a drug delivery system due to several physicochemical properties. They have a bicontinuous cubic structure that offers high drug loading capacity, structural stability, protection of encapsulated therapeutics from degradation and sustained drug release behavior. Moreover, the lipids used to prepare cubosomes

have generally excellent self-assembling properties and also good safety profiles, which helps to develop formulations for therapeutic use with low systemic toxicity and high therapeutic performance. Recent studies have shown that cubosomes can be used in various delivery methods such as oral, topical, transdermal, ocular, pulmonary, parenteral and intranasal.

These results demonstrate the potential of numerous cubosome based formulations for delivering drugs across biological barriers, enhancing the bioavailability of poorly soluble drugs, increasing the residence time of the drug in the eye, achieving efficient brain targeting and increasing the drug's accumulation in tumors. In addition to traditional applications, novel developments have targeted the design of stimuli responsive cubosomes, ligand mediated targeted delivery systems, theranostic platforms, and intelligent nanocarriers which are capable of recognizing and reacting to certain physiological conditions.

Simultaneously, the incorporation of quality by design principles, microfluidics manufacturing technologies, and artificial intelligence (AI) has enabled formulation optimization, providing fresh potential to enhance formulation reproducibility, scalability, and clinical applicability, thereby increasing the potential of cubosomes as next generation nanocarriers in precision medicine.[22, 30]

Although these exciting developments are further steps towards the wider commercialization of cubosomes as therapeutics, there are some issues still to be overcome. Strategies to overcome these challenges will be critical to industrializing cubosome technology to commercial, clinically validated pharmaceutical products. This review therefore aims to present a broad and critical survey of the formulation design, structural features, preparation, characterization, drug delivery applications, clinical translation, regulatory aspects, and future prospects related to the cubosome based nanocarriers for drug delivery. This review is designed to highlight the current achievements and the challenges that still remain, and provide future directions for the successful development of cubosome based pharmaceutical systems, by combining fundamental concepts with contemporary developments.

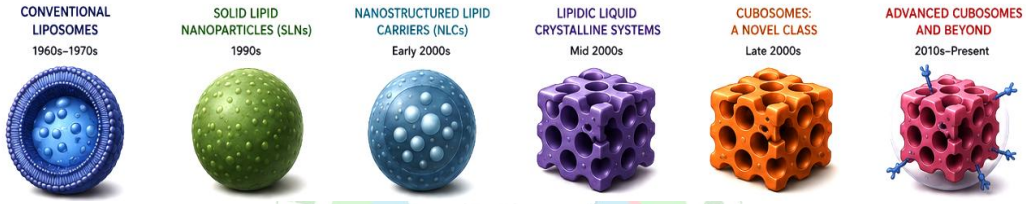

Figure 1: Evolution of lipidbased nanocarriers

Fundamentals of Cubosomes

Definition and Concept of Cubosomes

Cubosomes are nanostructured particles of bicontinuous cubic liquid crystalline phases in aqueous dispersion stabilized by appropriate surfactant. Conventional vesicular systems like liposomes have continuous lipid bilayers that divide two distinct aqueous networks, but cubosomes have bicontinuous internal architecture, consisting of a continuous lipid bilayer between two non-intersecting aqueous networks.[1,2]

Larsson first described the lipid cubic phases and showed that under specific conditions, amphiphilic lipids form thermodynamically stable cubic mesophases when hydrated, which allows for the inclusion of hydrophilic, lipophilic, and amphiphilic therapeutic agents in separate domains for exceptional formulation versatility and controlled drug delivery.[5,6] The special nanostructure has garnered a lot of interest for cubosomes in the oral, topical, ocular, parenteral, pulmonary and intranasal drug delivery formats.[7,11,12]

Major Components of Cubosomes

The main factors determining the performance of cubosomes are the lipids and stabilizers applied during their formulation.

Glyceryl Monooleate (GMO)

Glyceryl monooleate is the most widely studied lipid for cubosome preparation because it readily forms bicontinuous cubic phases in aqueous solvent and is biocompatible and biodegradable.[2, 5]it has a molecular geometry that promotes negative interfacial curvature which causes the spontaneous formation of inverse liquid crystalline structures suitable for drug encapsulation.[7]

Phytantriol

Cubosomes based on phytantriol are often found to be very stable chemically (resistance to hydrolysis higher than GMO) and have excellent structural integrity and controlled drug release.[11,7,9]

Stabilizers

The production of colloidally stable cubosome dispersions requires stabilizers. In addition to Poloxamer 407, which is the most frequently used stabilizer due to its steric stabilization and aggregation prevention capabilities, other stabilizers have been explored for enhancing stability and targeting performance, such as PEGylated surfactants and polymeric coatings.[12]

Structural Characteristics of Cubosomes

The bicontinuous cubic structure of cubosomes allows the formation of a continuous lipid bilayer that creates two distinct adjoining aqueous channel systems, which provide a high interfacial area and multiple compartments for drug incorporation.[1,9] There are three main crystalline cubic phase symmetries: primitive cubic (Im3m), double diamond (Pn3m), and gyroid (Ia3d), which can be seen in cubosomal systems, which vary in their channel

organization, membrane curvature and diffusion pathways, all of which are known to influence drug loading behavior and release kinetics.[7,9]

Advantages over Conventional Nanocarriers

The bicontinuous cubic architecture is beneficial for nanocarriers with high drug loading capacity, structural stability, protecting the encapsulated therapeutics, and controlled drug release versus conventional lipid based nanocarriers.[2,5] Moreover, cubosomes have been shown to have greater interaction with biological membranes, which has led to improved permeation across the skin, mucosal tissues, and the eye and blood brain barrier.[11,12]

They can also be modified with targeting ligands, polymers, and imaging agents to produce more sophisticated targeted, and theranostic, delivery systems.[13,22,23] despite these benefits, there are still issues with large scale manufacturing, longterm stability, and regulatory standardization that prevent broad clinical translation.[11,12,26]

Structure and Self-assembly of Cubosomes

Lyotropic Liquid Crystalline Systems

Cubosomes are derived from bicontinuous cubic liquid crystalline phases that self-assemble in the presence of water. In particular, bicontinuous cubic phases are considered as highly interesting mesophases for drug delivery, due to the combination of long range structural order and liquid like mobility.

The periodic minimal surfaces of lipid bilayers in cubic mesophases create two parallel but connected aqueous channel networks, which can be highly organized, uniquely different from conventional vesicular and particulate delivery systems.

Critical Packing Parameter and Self-assembly Mechanism

For amphiphilic lipids, the molecular geometry determines the formation of the cubic phases mainly by the critical packing parameter (CPP):

$$CPP = v / (a_0 . lc)$$

Where, v represents the hydrophobic chain volume, a_0 is the effective head group area, and $l_{(c)}$ is the critical chain length.[9,12] Inverse liquid crystalline structures with negative interfacial curvature are favoured by lipids with CPP values >1. Thus, lipids like glyceryl monooleate and phytantriol tend to spontaneously form bicontinuous cubic phases when they are hydrated.[7,9] self-assembly involves spontaneous arrangements of amphiphilic molecules to achieve the lowest free energy state of a system. Hydrophobic chains face away from the water and the polar head groups face toward the water, leading to formation of highly ordered nanostructures.[9,11]

Cubic Phase Symmetries

In cubosomal systems three main bicontinuous cubic phase symmetries have been known: primitive cubic (Im3m), double diamond (Pn3m), and gyroid (Ia3d).[7,9]

Primitive Cubic Phase (Im3m)

The Im3m phase has relatively large aqueous channels and lower membrane curvature than other cubic phases. The geometry may support the introduction of hydrophilic molecules and macromolecular therapeutics.[7]

Double Diamond Phase (Pn3m)

The Pn3m phase is one of the most often cited cubic structures in pharmaceutical cubosomes formulations, especially when the formulations were made by glyceryl monooleate. Its highly interconnected channel network facilitates efficient molecular diffusion and it also contributes to structural stability.[5,7]

Gyroid Phase (Ia3d)

The Ia3d phase has a more intricate three dimensional structure with continuous curvilinear channels and clearly defined transport pathways. The release and diffusion of drugs can be affected by the channel organization and the curvature of the membrane.[9] these cubic phases differ in their lattice geometry, dimensions of the channels and channel curvature, and these variations have a profound impact on the encapsulation efficiency, molecular transport and release kinetics. Hence, the internal phase symmetry is a critical factor to optimize cubosome properties.[7,9]

Factors Affecting Cubic Phase Behavior

Lipid Composition

Cubic phases are most likely to form and remain stable in lipids of this type. Glyceryl monooleate and phytantriol are structurally, hydration and phase transition different, and hence show differences in internal geometry and physicochemical properties.[7,11]

Hydration Level

The channel dimensions and lattice parameters of cubic phases are directly affected by water content. Hydration changes can lead to structural changes and alter molecular diffusion pathways.[1,9]

Temperature

The membrane fluidity, lipid mobility and phase stability are influenced by temperature. Depending on formulation composition, alterations in temperature can encourage transitions between cubic, hexagonal, and lamellar mesophases.[7]

Drug Molecules and Additives

The membrane fluidity, lipid mobility and phase stability are influenced by temperature. Depending on formulation composition, alterations in temperature can encourage transitions between cubic, hexagonal, and lamellar mesophases.[7] Drug Molecules and Additives Druglipid interactions are thus critical considerations when designing and optimizing the formulation and should be taken into account.[12,20] The physicochemical properties and therapeutic activity of cubosomes are based on their

Self-assembly properties and internal organization. These structural principles are crucial in choosing the right

manufacturing strategies and in controlling formulation quality. Hence, the next section focuses on the important techniques employed in the preparation of cubosomes, conventional and newer fabrication techniques.

Preparation Methods of Cubosomes

In addition to the unique internal nanostructure of cubosomes, the ability to develop strong and repeatable manufacturing processes is crucial for their use in drug delivery. In the last 20 years, a few methods were developed to overcome the bulk cubic phase problem, and the most used ones are the top down and bottom up.[3,4] Other methods to improve scaleup and formulation reproducibility are the solventfree synthesis processes, microfluidics and continuous manufacturing processes, which are more recent.[12,19,24]

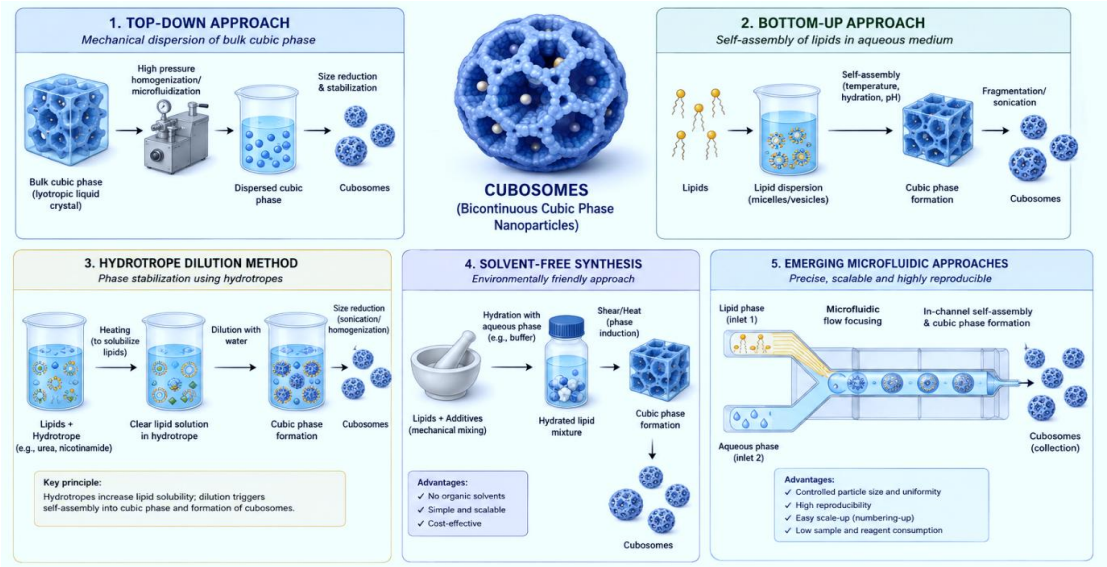

Figure 2: Preparation Methods of Cubosome

Topdown Approach

The classical method and the most widely studied method for making cubosomes is the top down method. This method requires the first step of creating a bulk cubic phase from the components of lipid, water and stabilizer, and then using high energy mechanical forces to break down the viscous cubic matrix into nanoparticles.[3,4]

Usually, glyceryl monooleate or phytantriol is dissolved in water to form a very viscous cubic phase. The poloxamer 407 is then added as a stabilizer. Bulk cubic gel is then processed under high pressure homogenization, ultra-sonication or high shear mixing for the generation of cubosome dispersions.[3,5]

The topdown method offers several advantages, including:

- Wellestablished manufacturing protocols
- Production of highly ordered internal nanostructures
- Good control over particle size distribution
- Applicability to a wide range of drugs

The technique has some drawbacks, however. Furthermore, due to the high viscosity of bulk cubic phases, significant amount of energy is needed during processing, which can lead to higher production costs and batch to batch variability for processing sensitive therapeutic molecules (such as proteins and peptides).[3,4]

This strategy was the first to show that stable cubosome nanoparticles can be produced, laying the groundwork for further applications in the pharmaceutical industry.[3,4] (Fig 2.1)

Bottomup Approach

The bottom up approach was developed because of some of the drawbacks of the top down approach. This approach does not require breaking an existing cubic phase but rather depends on the spontaneous self-assembly of lipid molecules under certain conditions to form cubic nanostructures.[5,19]

The lipids are usually dissolved in a hydrotropic solvent, which is an ethanol or other water miscible organic solvent, in a typical bottom up process. When the solvent is diluted with an aqueous phase in which stabilizers are added, the concentration of the solvent decreases and self-assembly takes place, resulting in cubosomes.[19]

This method offers several advantages:

- Lower energy requirements
- Simpler manufacturing process
- Reduced mechanical stress
- Better suitability for thermolabile compounds
- Easier process scalability

In addition, there are the challenges of removing the residual solvent, and precisely controlling conditions for self-assembly, which must be carefully optimized in the bottom up approach compared with conventional high energy methods.[19,24]

Recent research has shown that bottom up approaches are effective for producing highly uniform cubosomal dispersions with retaining of the structural properties required for efficient drug delivery. (Fig 2.2)

Hydrotrope Dilution Method

Hydrotrope dilution technique is a special case of bottom up approach. This approach involves dissolution of amphiphilic lipids in concentrated hydrotropic solutions which prevent liquid crystalline phase formation. When water is added to the solution, the concentration of the hydrotrope is decreased, and cubic nanostructures form spontaneously.[19]

This approach allows for the preparation of cubosomes under relatively mild conditions, without the need for prolonged mechanical processes. Given the versatility of the method, it is especially applicable for drugs that will degrade under high shear or high temperature.

The formulation, however, is a function of the type of hydrotrope, dilution rate, and nature of the lipids. Control of these variables which is not carried out in a proper manner may lead to undesirable phase changes or to the formation of a population of different particles.[19,20] (Fig 2.3)

Solvent Free Preparation Approaches

While the traditional bottom up methods use organic solvents, increasing focus on sustainability and pharmaceutical safety has spurred the development of solvent free preparation methods. Bryant et al. reported a bottom up approach to making cubosomes without the need for any organic solvents and with desired structure and colloidal properties.[24]

Solventfree approaches offer several advantages:

- Elimination of solvent toxicity concerns
- Simplified regulatory compliance
- Reduced environmental impact
- Lower purification requirements
- Improved industrial applicability

Crossing over to the clinical translation aspect, solvent free manufacturing would be favourable in terms of current regulatory expectations of minimizing residual solvents and pharmaceutical green processing.[24] (Fig 2.4)

Characterization of Cubosomes

Systematic physicochemical characterization is crucial for the development and quality evaluation of cubosome based drug delivery systems. Due to their internal nanostructure, several analytical methods are needed to assess particle size, morphology, cubic phase organization, drug loading, release behavior and stability. These parameters are important and are classified as critical quality parameters as they have a direct effect on formulation performance and reproducibility.[12,14]

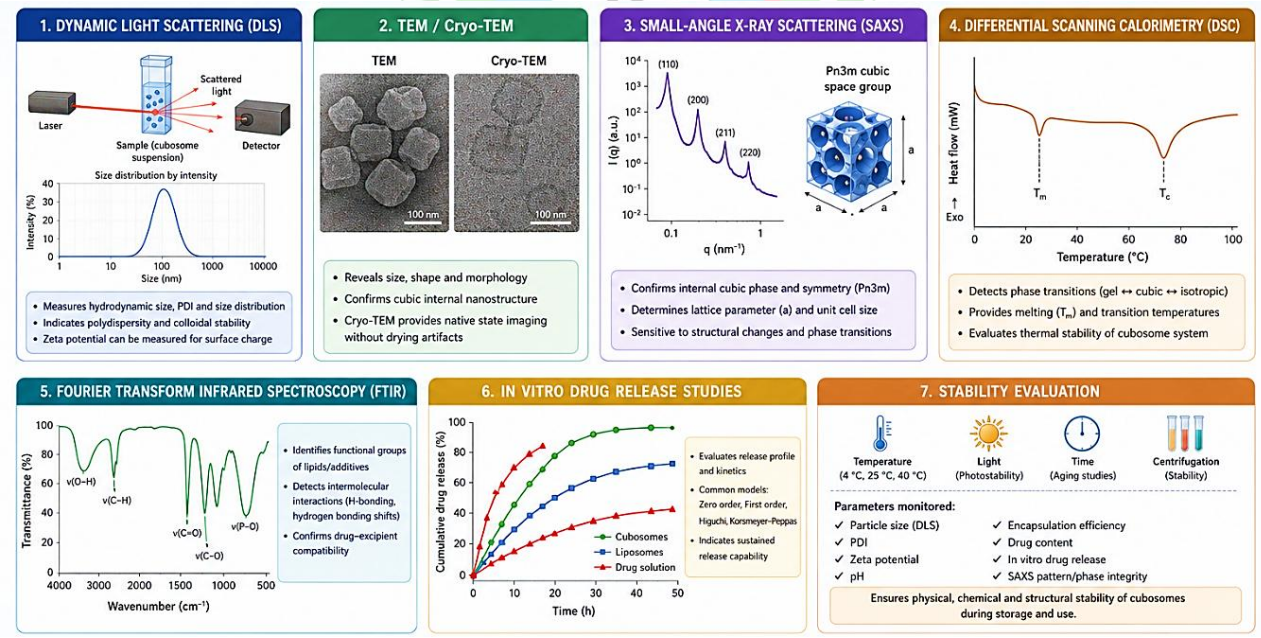

Figure 3: Characterization techniques used for cubosomes

Particle Size, Polydispersity Index, and Zeta Potential

Particle size is one of the key factors that can affect cellular uptake, biodistribution, tissue penetration as well as drug release. In most cases, cubosomes prepared for pharmaceutical use have a particle size within the nanometer range, usually in the range of 100-300 nm, depending on the type of lipids and how they are prepared.

Dynamic light scattering is the most common method to measure hydrodynamic particle size and size distribution. Polydispersity index (PDI) gives information about the formulation homogeneity, and a value below 0.3 is

considered acceptable uniformity for Nano particulate systems.[8]

The most frequent method used to measure the colloidal stability is the measurement of zeta potential. While steric stabilization is the main stabilization mechanism in most cubosomes, surface charge it is a good indicator of particle aggregation tendency and storage stability.[8,12](Fig 3.1).

Morphological Characterization

Morphological evaluation is crucial for the confirmation of the formation of nanoparticles and for the evaluation of their structural integrity. The most commonly used methods for the visualization of cubosomes are transmission electron microscopy (TEM) and cryogenic transmission electron microscopy (Cryo TEM).[2,13]

TEM can deliver high resolution images of particle shape and morphology, while Cryo TEM can visualize the cubosomes in near native conditions, with minimum structural changes due to sample preparation. Therefore, Cryo TEM has been regarded as one of the most reliable methods for the verification of the cubosomal architecture and internal organisation.[2,13] In addition, surface morphological analysis and nanoscale topographical characterisation have been done by scanning electron microscopy (SEM) and atomic force microscopy (AFM).[19] (Fig 3.2)

Structural Characterization of Internal Cubic Phases

One of the most critical features in the characterization of cubosomes is the confirmation of their internal cubic phase organization, since the special performance of the nanocarriers is directly linked to their internal structure.[1,9] Small angle X ray scattering (SAXS) is considered a gold standard method for structural characterization of cubosomes. SAXS gives the information of lattice parameters, phase symmetry, and structural transitions, and the main cubic phases in cubosomal systems, such as primitive cubic (Im3m), double diamond (Pn3m), and gyroid (Ia3d) can be identified.

The method is especially useful for monitoring phase transitions that can be caused by variation in lipid composition, hydration, and temperature or drug incorporation. Reliable identification of cubic phase identity is crucial, since only the size of the particles cannot confirm the existence of a bicontinuous cubic structure.[7,9] otherstructural information can be gained by x ray diffraction (XRD) and polarized light microscopy (PLM) which help to distinguish the cubic phases from other liquid crystalline structures.[12]

Drug Loading and Encapsulation Efficiency

Drug loading capacity and encapsulation efficiency are important parameters that influence the therapeutic performance and feasibility of the formulations. Drug loading capacity is the ratio of the quantity of incorporated drug to the total quantity of formulation, while encapsulation efficiency is the percentage of drug that was successfully entrapped in the carrier system.[12,29] Free and encapsulated drug fractions are typically separated by chromatographic or spectrophotometric separation methods and the parameters are determined.

The lipid composition, the internal cubic geometry and the physicochemical properties of the therapeutic agent, as well as the interactions between the drug and the lipid, all affect drug loading behavior.[5,6] High drug loading and encapsulation efficacy are desirable to ensure high therapeutic efficacy and to minimize the amount of carrier material needed for drug delivery.[12]

Thermal and Physicochemical Characterization

The integrity of the formulation and drug excipient compatibility is usually assessed using thermal and spectroscopic analyses. Differential scanning calorimetry (DSC) is a broad method for studying thermal transitions and determining the physical state of the drugs inside cubosomal matrices.[12,14]

Fourier transform infrared spectroscopy (FTIR) is often used to detect possible interactions between the formulation components and to ensure the incorporation of the drug into the formulation. Thermogravimetric analysis (TGA) can also be applied to assess moisture and temperature induced changes and thermal stability.[12] (Fig 3.)

In Vitro Drug Release Studies

In vitro drug release studies are conducted to investigate the release kinetic and to predict the performance of the formulation. Cubosomes also exhibit a bicontinuous cubic structure which creates tortuous diffusion pathways, thereby leading to sustained and controlled drug release profiles in many cases.[2,23,24]

To investigate drug release, dialysis membrane techniques or Franz diffusion cells or any diffusion based technique, depending on the route of administration, is commonly used. Kinetics models like the zero order, first order, Higuchi and KorsmeyerPeppas are commonly used to interpret release mechanisms by releasing data.[2,24,23] The variations in both the lipid composition and the internal phase geometry and dimensions of the channels can have a significant effect on the drug diffusion behaviour and release rate, allowing modulation of therapeutic delivery to be achieved in a formulationspecific manner.[6,24]

Stability Assessment

Stability evaluation is important to ensure the long term quality and performance of cubosome formulations. The stability studies usually include three parameters during the storage: the particle size, the polydispersity index, and the zeta potential. Other important parameters that are usually monitored are the drug content and the internal phase structure.[11,12]

To ensure formulation robustness and shelf life characteristics, both accelerated and long term stability testing are required, as the following potential instability mechanisms may occur: particle aggregation, lipid oxidation, hydrolysis, drug degradation, and phase transitions between cubic and other liquid crystalline structures.[7,11]

Drug Loading and Release Mechanisms

This special bicontinuous cubic structure of cubosomes allows for incorporation of a large variety of therapeutic molecules of different physicochemical properties. Cubosomes are versatile drug delivery systems, as they harbour many microenvironments for drug localization, owing to the existence of lipid bilayers, aqueous channels, and large interfacial regions.[5,6,7]

Drug Loading Strategies

The physicochemical properties of therapeutic agents, such as molecular size, solubility, lipophilicity and charge are the main factors influencing drug incorporation into cubosomes. The bicontinuous structure of cubosomes allows them to host molecules with hydrophilic, lipophilic, and amphiphilic properties in various parts of the nanostructure.[5,6] the hydrophilic drugs are mainly associated with the interconnected aqueous channels while the lipophilic drugs partition into the lipid bilayer domain. Amphiphilic molecules can tend to gather at the boundary between the lipids and the water.

This structural versatility is another characteristic that sets cubosomes apart from numerous traditional nanocarriers and enhances their potential for use in pharmaceutical applications.[5,6,11] the drug loading can be performed either during cubosome preparation (passive loading) or by post formulation loading methods. The strategy of passive loading has been the most commonly used approach due to its simplicity and high encapsulation efficiency.[12]

Mechanisms of Drug Release

The diffusion of drugs through the bicontinuous channel network and the interaction between the drug and the lipid matrix is the main factor controlling drug release from cubosomes. Highly ordered internal structure produces tortuous diffusion pathways which often produce sustained and controlled release profiles.[23,25]

Release for hydrophilic drugs is typically via the aqueous channel system. Lipophilic compounds on the other hand, have to partition out of the lipid bilayer into the surrounding release medium before they diffuse, which may lead to slower release kinetics.[5,6] Drug release behavior may also be influenced by other release mechanisms depending on formulation composition and environmental conditions, including matrix erosion, restructuring and phase changes.[23]

Therapeutic Applications of CubosomeBased Drug Delivery Systems

Cubosomes are a unique bicontinuous cubic nanostructure that has been successfully used in drug delivery via several routes of administration. Their biological properties such as high internal surface area, capacity to encapsulate molecules with a wide range of physicochemical properties, bioadhesive properties, and controlled release behaviour have helped to enhance the therapeutic efficacy in certain disease conditions. Within the last few years, the study of cancer therapy, targeting of the brain, ocular delivery, transdermal administration, and multifunctional theranostic systems has been the focus of recent research.[7,11,15,16]

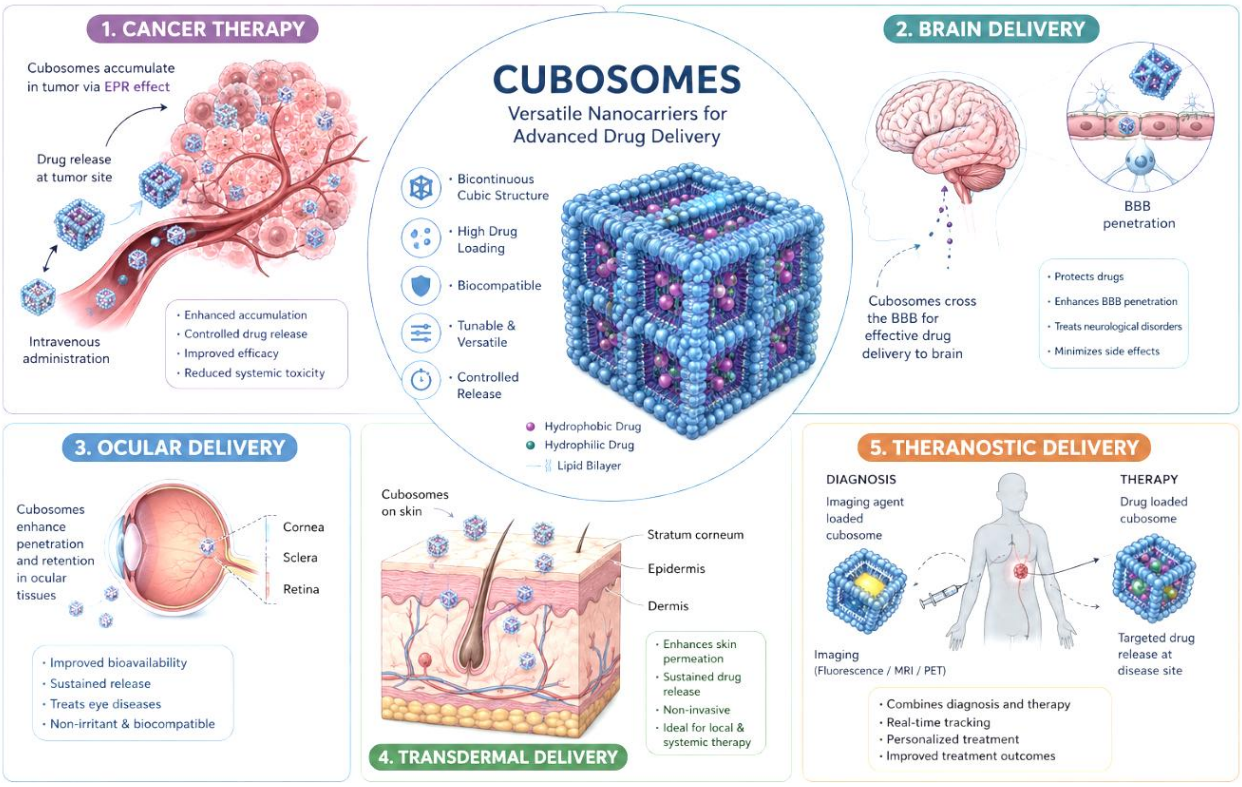

Figure 4: Therapeutic Applications of Cubosomes

Cancer Therapy

Cubosomal nanocarriers are among the most widely studied nanocarriers for cancer therapy. Traditional chemotherapeutic drugs have poor water solubility, rapid systemic clearance, non-specific biodistribution, and high dose limiting toxicity. Cubosomes provide these advantages and are an attractive platform to address these limitations, including improved drug solubilisation, sustained release, and tumor accumulation.[11,31]

Various hydrophobic chemotherapeutics have been successfully encapsulated into cubosomes, and several anticancer drugs such as cisplatin, doxorubicin, and irinotecan have been successfully introduced to cubosomal formulations. Moreover, surface functionalized cubosomes have been found to exhibit greater selectivity to tumor tissues with lower off target toxicity.[33]

More recently multifunctional cubosomes, which deliver both chemotherapy and photothermal or imaging, have been the focus of studies. Cubosomes are also advanced platforms for combination cancer therapy when delivered with other drugs, as is reported for co loading with other chemotherapeutic agents (doxorubicin) and photosensitizers (indocyanine green) to yield synergistic chemo photothermal effects against melanoma models.(Fig 4.1)

Brain and Neurological Drug Delivery

The blood brain barrier (BBB) is very restrictive and delivery of therapeutics to the central nervous system (CNS) remains a significant pharmaceutical challenge. The nanoscale size, lipid composition, and interaction with biological membranes have made cubosomes promising carriers for brain targeted drug delivery.[8,30]

Both nasal and systemic delivery routes have shown improved delivery of encapsulated drugs across the brain. Likewise, BBBpenetrating cubosomal formulations of antiepileptic and neuroprotective drugs have shown enhanced brain uptake and efficacy over standard formulations.[11]

The potential for sustained drug delivery, reduction of systemic exposure and enhanced delivery efficiency for poorly BBB permeable compounds is attracting growing interest in cubosomes for neurological applications.[8,30] (Fig 4.2)

Ocular Drug Delivery

Rapid tear turnover, nasolacrimal drainage, and low corneal permeability are some of the factors that limit ocular drug delivery. The cubosomes possess mucoadhesive property and prolonged precorneal residence characteristic making them ideal for ophthalmic applications.[9,23]

Several studies have shown that cubosome based formulations have resulted in increased ocular bioavailability and therapeutic efficacy. Cubosomal in situ gels of voriconazole have been found to be more effective in terms of antifungal action and longer ocular retention times, while cubosomal systems of ketoconazole and latanoprost have been shown to exhibit improved corneal permeation and sustained drug release. Cubosomes could decrease the frequency of dosing and increase patient compliance in the treatment of eye disorders by maintaining therapeutic drug levels for longer periods.(Fig 4.3)

Transdermal and Topical Drug Delivery

Cubosomes are lipidic structures with high order which allows close contact with the stratum corneum and thus facilitates permeation through the barrier. Hence, cubosomes are of great interest as transdermal and topical drug carriers.[1,34]

Many studies have documented the increased penetration and retention of the drug in the skin and better therapeutic results from topical formulations with cubosomes. They have been used for antifungal treatment, wound healing, treatment of inflammatory skin diseases, and osteoarthritis and transdermal administration of poorly permeable drugs.[34,37,38]

Moreover, the introduction of cubosomes into a hydrogel matrix has led to the development of hybrid delivery systems, which combine the controlled delivery properties of cubic phases with the patient friendly properties of topical gels.[3,34,37](Fig 4.4)

Emerging Theranostic and Multifunctional Applications

Cubosomes have been used in a drug delivery system, and, in recent years, there have been significant advances in nanomedicine to extend the possibilities of cubosomes. Development of multifunctional cubosomal systems for simultaneous diagnosis and therapy has been enabled by surface engineering, incorporation of imaging agents, and integration of stimuli responsive materials.[13,21,31] These include magnetic nanoparticle loaded cubosomes for external control of drug release, formulations that are fluorescent or imaging active for disease monitoring, and systems that are responsive to pH, temperature, enzymatic activity or other physiological stimuli and change the drug release characteristics.[17,21]

These versatile platforms significantly align with precision medicine principles and could help pave the way for more personalized therapeutic approaches in the future. Most of the studies are still preclinical but the development of theranostic cubosomes is one of the most promising research directions in cubosomes.[13,31] (Fig 4.5)

Targeted and StimuliResponsive Cubosomes

In recent years, the research of cubosomes has shifted from simple drug delivery to intelligent drug delivery systems with site specific targeting and controlled drug release. The therapeutic potential of cubosomes has been greatly enhanced by the application of surface modification strategies and stimuli responsive designs that have improved their biodistribution properties, their ability to be taken up by the cells of interest, their therapeutic selectivity, and the therapeutic efficacy.[13,15,30]

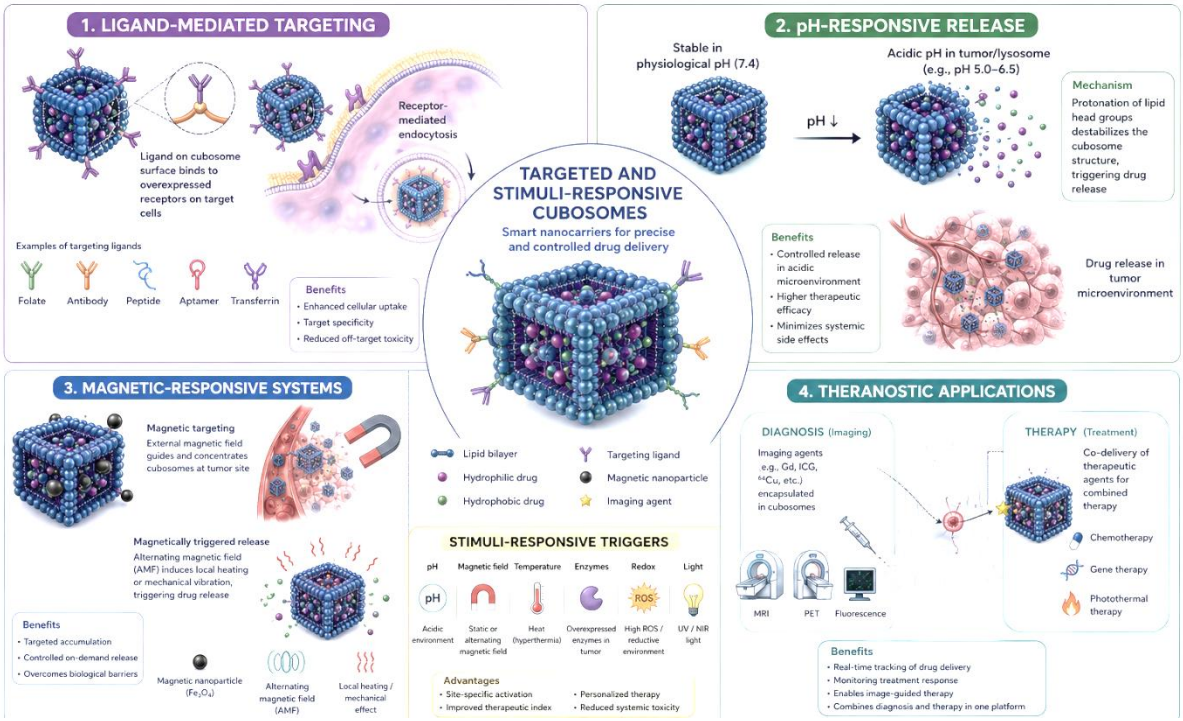

Figure 5: Targeted and Stimuli Responsive Cubosomes

Targeted CubosomeBased Drug Delivery

Targeted drug delivery is designed to enhance the specificity of the drug delivery to the target site with a view to reducing systemic exposure and toxicity. The high surface area and the tunable lipid interface of cubosomes offer superb opportunities for targeting ligands, polymers, peptides, antibodies, and receptor specific molecules to be attached to the surface.[11,30,] Active targeting approaches have been extensively explored in cancer and brain drug delivery applications.

Ligand functionalized cubosomes are able to target and bind to an overexpressed receptor on a diseased cell which aids in receptor mediated endocytosis and increases the delivery of the drug to the interior. For instance, angiopep 2 functionalized cubosomes have shown a better BBB crossing capability and improved therapeutic efficiency against gliomas (GBM).[30] Besides the ligand mediated targeting, polymer coated cubosomes have been explored to achieve prolonged circulation, low opsonization, and EPR effect. These changes can result in enhanced pharmacokinetic properties and therapeutic efficacy relative to their nonfunctionalized counterparts.[11,21]

Stimuli Responsive Cubosomes

Stimuli responsive cubosomes are prepared to change their structural characteristics or drug releasing property upon stimulation by internal or external stimuli. This allows for the controlled release of a drug to the target site, while simultaneously minimizing the amount of drug released before it reaches its systemic destination.[13,24] Typical internal stimuli investigated are pH changes, enzymatic activity, redox gradient and biochemical signals during disease. For instance, tumor microenvironments, which frequently exhibit an acidic pH, can be used to trigger the release of a drug from a responsive cubosomal system, and changes in the expression of enzymes are also characteristic of these environments.[13,15]

Thermally, magnetically, ultrasonically and light responsive drug release has also been attempted. Such systems are capable of structural transition in response to environmental stimuli, thus facilitating the controlled modulation of drug diffusion pathways, with the potential for on demand drug delivery and better spatial and temporal control.[24] Recent investigations have reported pH responsive, coacervation responsive and lysosome targeting cubosomal formulations, which have been shown to deliver superior therapeutic selectivity and controlled release profiles.[1,16]

Multifunctional and Theranostic Cubosomes

Multifunctional cubosomal systems are now emerging, resulting from the combination of targeting ligands, imaging agents, and responsive materials. These advanced formulations can simultaneously carry therapeutic and diagnostic functions, also known as theranostics.[21,31] this includes nanoshells containing magnetic nanoparticles, photothermal agents and fluorescent probes that allow for real time imaging and drug delivery. Magnetic nanoparticle loaded cubosomes have been shown to exhibit externally controlled release behavior, while in the case of systems based on cubosomes combined photothermal and chemotherapeutic effects have enhanced anticancer activity.[1,3]

The multifunctional platforms have been reported to be promising for precision medicine because they facilitate the detection, treatment monitoring, and personalised therapeutic intervention with the same nanocarrier system. While translating to the clinic is still limited,

theranostic cubosomes represent one of the most innovative avenues in today's cubosome research.[13,31]

Current Challenges and Future Opportunities

Although good progress was made, a few obstacles remain to the development of targeted and stimuli responsive cubosomes. Surface functionalization can add complexity, cost, and scalability issues to the formulation. Further, long term stability without compromising targeting efficiency and responsiveness is of concern.[12,16]

The other major drawback is that there is not much clinical evidence supporting the superiority of such advanced systems over traditional formulations. The majority of the reported investigations have occurred in vitro or at the preclinical level, indicating the necessity for in depth pharmacokinetic, toxicological and clinical evaluation.[15,31]

However, the development of next generation intelligent cubosome systems is anticipated to be further aided by ongoing developments in nanotechnology, surface engineering, biomaterials science and artificial intelligence, which will facilitate formulation design. Future studies likely will concentrate on the development of multifunctional systems that integrate targeted delivery, controlled release, imaging, and therapeutic monitoring within a single clinically translatable nanocarrier.[13,15] (Fig 5.)

CONCLUSION

Bicontinuous cubic liquid crystalline structure, high internal surface area and the capability to include therapeutic agents with a wide range of physicochemical properties make cubosomes one of the most promising lipid based nanocarrier systems. They are particularly engineered for high drug loading efficiency, protection of labile molecules, controlled drug release, enhanced bioavailability and improved interaction with biological barriers. With the advent of new formulation strategies, surface engineering, and functionalisation techniques, the use of cubosomes in cancer therapy, brain targeting, ocular drug delivery, transdermal therapeutic delivery and other advanced biomedical formulations has further been expanding. While significant advances have been made at the preclinical level, challenges remain for achieving clinical translation in the areas of scalable manufacturing, long term stability, regulatory standardization, and comprehensive safety evaluation. It is anticipated that future advances in stimuli responsive systems, targeted delivery platforms, continuous manufacturing technologies and artificial intelligence to aid formulation design will further bring cubosome technology from the lab to a clinically viable pharmaceutical product. The evidence available together indicates that cubosomes have a great potential to be an important next generation platform for precision and advanced drug delivery.

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