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CUBOSOMES AS NOVEL APPROCH OF DRUG DELIVERY

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Abstract

Cubosomes are extremely stable nanoparticles that resemble honeycombs or have hollow interiors. Cubosomes are formed from certain amphiphilic lipids and stabilized with a polymer. A famous tale involving differential geometry, biological membranes, food science, and digestive processes is the discovery of cubosomes. They have distinct drugloading modalities and differ in internal cubic structure and composition. Its features include a high internal surface area, cubic crystalline structures, biodegradability of lipids, targeting and controlled release of bioactive agents, and the capacity to encapsulate hydrophobic, hydrophilic, and amphiphilic substances. Its preparation is also comparatively simple. Cubosomes can be characterized by a variety of evaluation parameters and have a wide range of applications in various fields. Thus, the field of pharmaceuticals is paying more attention to cubosomes. X-rays, NMR, electron microscopy, and light scattering are the methods used to study Cubosome structure; however, some researchers are also looking into the possibility of using cubosomes as a delivery system. **Keywords**

Cubosomes, Cubic Phase, Mono-olein, Liquid crystal, drug-loading, hydrophilic, hydrophobic, amphiphilic.

Introduction [1, 2, 3]

Distinct nanovesicles of bicontinuous cubic structures, known as cubosomes, are created when liquid crystalline cubic aggregates are dissolved in aqueous fluids. Having a same microstructure and a large surface area With relation to its parent cubic aggregates [1]. They're developed by some amphiphilic lipids, such as GMO (glycerol monooleate) and Phytantriol (PHYT) is a substance that may self-assemble in in order to create cubosomes. They include a framework akin to honeycomb (cavernous) formations ranging in size from 100 to 500 nm.[1] Due to their liquid crystalline structure, which is made up of lipid bilayer membranes arranged in periodic 3D topologies and well-defined networks of aqueous channels, cubosomes have an advantage over other delivery methods. Many macromolecular medications (peptides, proteins, DNA, m-RNA, and other imaging agents) as well as synthetic and natural lipophilic, hydrophilic, and hydrophobic medicinal molecules have been encapsulated using biocompatible techniques. Large surface area, intricate cubic lattice networks protect the integrated payload from deterioration and enable the sustained release of encapsulated bioactive substances [2] Cubosomes are gaining a lot of attention as a cutting-edge drug delivery method, and they have recently been applied to cancer, ophthalmology, dermatology, and oral medicine [3]

Structure of Cubosomes [4, 5]

The two internal aqueous channels of cubosomes are separated by honeycombed structures, and a sizable interfacial area is present [Fig. 1] [4]. The term "bicontinuous" designates two distinct (continuous, but non-intersecting) hydrophilic zones divided by the bilayer that are formed by amphiphilic molecules in water and oil channels [4]. In general, the structure preserves the stability and effectiveness of active ingredients like proteins and vitamins.

Surfactants assemble into bilayers within the structure, which are twisted into a three-dimensional, periodic, minimum surface that forms a densely packed structure resembling a "honeycombed" mixture of bicontinuous domains containing lipid and water. Because it may hold molecules that are amphiphilic, lipid soluble, and water soluble, its structure differs from that of liposomes [5]. The structure's interconnectivity produces a transparent, viscous gel with a comparable rheology and appearance.

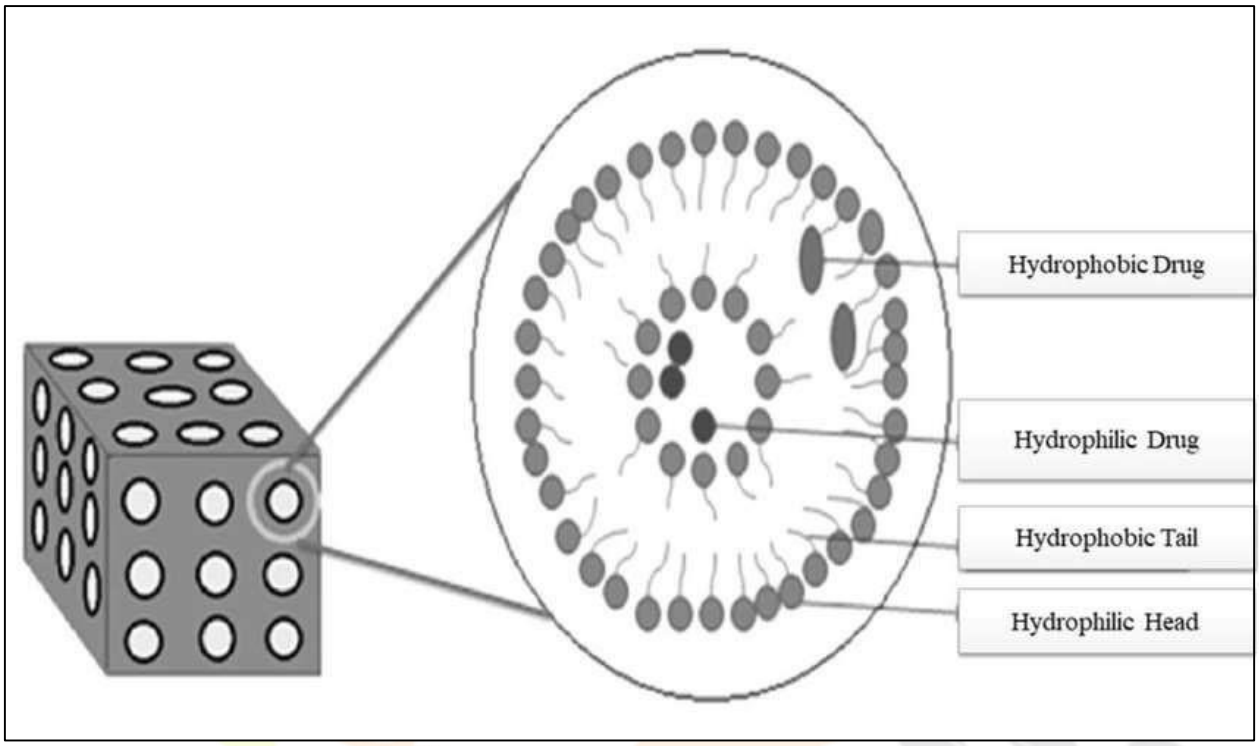

Figure 1: Structure of Cubosome.

GMO, or glycerol monooleate [10-20]

Cubosome component [6, 7, 8, 9]

In his 1980s review on cubic lipid/water phases, Kåre Larsson made the first mention of the cubosome [6]. Patton and Carey then reported their findings in study on the breakdown of fat wherein scattered particles of the Because of this, bicontinuous cubic structures were created. Mixing bile and lipase with the contents of a simulated stomach sodium [7]. But the research on cubic structures was Larsson's work, he found that cubosomes can be produced when dissolved in water from the bulk cubic structure into submicron particles that have interior structures that are the same as the cubic parent structure [8]. Cubosomes are arranged in three different measures as a "honeycomb" configuration, and they are primarily made up of lipids that are amphiphilic and spread in water in the the existence of appropriate stabilisers [9].

Amphiphilic lipids

The most popular amphiphilic lipid for cubosome manufacture is glyceryl monooleate (GMO), which is often known as monoolein [10, 11]. The GMO is polar unsaturated monoglyceride, which melts between 35 and 37 degrees Celsius -20°C storage temperature with an HLB value of 3 [12] GMOs are made up of a blend of oleic acid and other fatty acid glycerides, with monooleate making up the majority. Monooleate belongs to the class of amphiphilic lipids that can form different types of lyotropic liquid crystals [13, 14]. According to reports, GMOs with hydrocarbon chains lengths between 12 and 22 are more likely to produce cubic phases [15]. Amphiphile-based delivery vehicles (DDVs) are quite adaptable since they can include lipophilic [17], amphiphilic [18], and hydrophilic [16] medicines. They've been examined as possible DDVs for numerous treatments and have received FDA and other regulatory agency approval. for the administration of medications via various applications URLs [19-20].

Stabilizers: [21-25]

The stability of hydroxypropyl methylcellulose acetate succinate (HPMCAS) to P407-based GMO-based cubosomes was about equal [21]. The stabilizer's primary job is to provide an electrical barrier between particles to stop them from coming into close contact with one another. Preserving the stable form of the scattered particles. This result is generated as a result of the stabilizer's involvement in the fat-water assembly without causing the cubic liquid to change crystallinity, hence selecting a suitable stabilizer is a crucial phase. The stabilizing agents that are most frequently employed are Pluronics, in particular F127 (Poloxamer 457), which is taken into considered the

"gold standard" [22] Although cubic aggregates in bulk are thermodynamically stable, the dispersed particles in aqueous fluids are not kinetically stable because they tend to aggregation as a result of hydrophobic sections being exposed to the external watery hydrophilic medium [23], so employing stabilizing agents become an essential stage in the development of cubosomes for stop the scattered particles from re-coating inside the parent when distributed in water, a bulk cubic structure [24]. Stabiliser is typically used at concentrations up to 20% w/w, depending on the dispersed particles, while GMO-polymer combination is often utilised at concentrations of 2.5% (w/w) to 10% % based on the dispersion's overall weight [25]

Types of Cubosomes 1. Liquid Cubosome Precursors 2. Powdered Cubosome Precursor

1. Liquid cubosome precursors [26,28]

It has been found that the process of hydrotrope dilution yields smaller and more stable cubosomes. Particles can form during the nucleation process and grow larger through the crystallisation and precipitation processes. Monoolein cannot form liquid crystals since it is properly dissolved in a hydrotrope like ethanol. Consequently, the cubosomes precipitate or spontaneously crystallise when this combination is diluted. The quid precursor technique avoids handling bulk solids and potentially harmful high-energy activities, allowing for speedier cubosome preparation scaleup. It is discovered that the hydrotrope dilution method yields smaller and more stable cubosomes. Particles can form through the nucleation process, and their growth can be observed during the crystallisation and precipitation phases. When monoolein is correctly dissolved in a hydrotrope, like ethanol, it stops from forming liquid crystals. Therefore, the cubosomes precipitate or "crystallise" spontaneously when this combination is diluted. The quid precursor approach has made it possible to scale up cubosome preparations more easily and prevents the handling of bulk materials, which could harm high energy operations.

2. Powdered cubosome precursor [29]

The antecedents of powdered cubosomes are made of polymer-coated, dehydrated surfactant. Compared to liquid phase hydrotropic cubosome precursors, these powders have advantages. Light scattering and cryo-TEM have verified that the precursor powders hydrolyze to create cubosomes with an average particle size of 600 nm. Water-soluble, non-cohesive starch that has a waxy lipid coating on it typically inhibits agglomeration and controls particle size. Spray drying is a good method for his aim. Water-soluble, non-cohesive starch that has a waxy lipid coating on it typically inhibits agglomeration and controls particle size. Spray drying is a good method for his aim.

Properties [30]

Cubosome dispersions have a significantly reduced viscosity.

Cubosomes are unique, sub-micron nanostructured particles that are bicontinuous cubic liquid crystalline.

Cubosomes Seven is arguably the most fascinating. Since cubic liquid crystals are transparent and isotropic, they are physically stable in excess of water.

Cubosomes' small hole sizes make them appealing for controlled release.

It can solubilize molecules that are hydrophilic, amphiphilic, hydrophobic, and biodegradable.

Advantages and limitations of cubosomes:

Advantages of cubosomes [31-34]

1. They can contain medications that are both hydrophilic and hydrophobic as well as amphiphilic.
2. They possess features of a medication delivery system with prolonged release.
3. Biocompatibility and bioadhesivity are characteristics of cubosomes.
4. Even stable in excess of water, the bicontinuous cubic liquid crystalline phase of cubosomes
5. Biologically compatible lipids and water can be combined to create cubic phase materials, which makes them ideal for treating skin, hair, and other human tissues.

6. Cubosomes have a greater breaking resistance and a wider ratio between the bilayer area and particle volume than liposomes
7. They have large pharmacological payloads due to their crystalline cubic shapes and high interior surface area.
8. They have a straightforward preparation process and are lipid biodegradable
9. Bioactive compounds with targeted and regulated release
10. When compared to traditional lipid or non-lipid carriers, cubosomes are superior solubilizers.
11. They have strong drug carrier capacity with a variety of medicines that are only weakly soluble in water.
12. These work wonders in shielding the sensitive medication from peptides and proteins that break down enzymatically and in vivo.
13. The bioavailability range is improved by the cuboidal technique from twenty to more than
14. It's financial.
15. It is biocompatible and non-toxic.
16. The preparation process is easy.
17. Its bioadhesive qualities are superb.
18. It improves skin penetration.
19. They are thermodynamically stable for a longer period.
20. The ability to enclose substances that are amphiphilic, hydrophobic, and hydrophilic.
21. Bioactive agents: targeted and regulated release.
22. There is a substantial drug loading because of the cubic crystalline structures and large interior surface area.

Disadvantages of Cubosomes [35-37]

1. Cubosome stability is a critical issue that limits the adoption of these systems because it can result in low drug loading efficiency and drug leakage during preparation, preservation, and transport in vivo .
2. Due to high viscosity, large-scale production might occasionally be challenging
3. There is little trapping of water-soluble medications because cubosomes contain a lot of water.
4. Due to the high viscosity, large-scale production might occasionally be challenging.
5. Sometimes high viscosity makes large-scale production challenging

Manufacturing of Cubosomes [38,39]

Cubosomes can be produced using two different processes**:**

1. Top down approch
2. Bottom up approach

1. Top-down methodology:

They are the most often utilised techniques in the field of study. Ljusberg-Wahren reported it in 1996 [Fig 2]. Lyotropic Liquid Crystal (LLC) nanoparticles are created by dispersing the resulting mixture into an aqueous solution using high energy methods as sonication, shearing, or high-pressure homogenization (HPH). This process creates the viscous bulk cubic phase. a transparent, stiff gel that resembles the bulk cubic phase and is created by cross-linked polymer chains inflated by water. HPH is the method most frequently employed to manufacture LLC nanoparticles. Using a top-down method, vesicles—dispersed nanoparticles of lamellar liquid crystalline phase—or structures resembling vesicles are created and found to coexist with cubosomes.

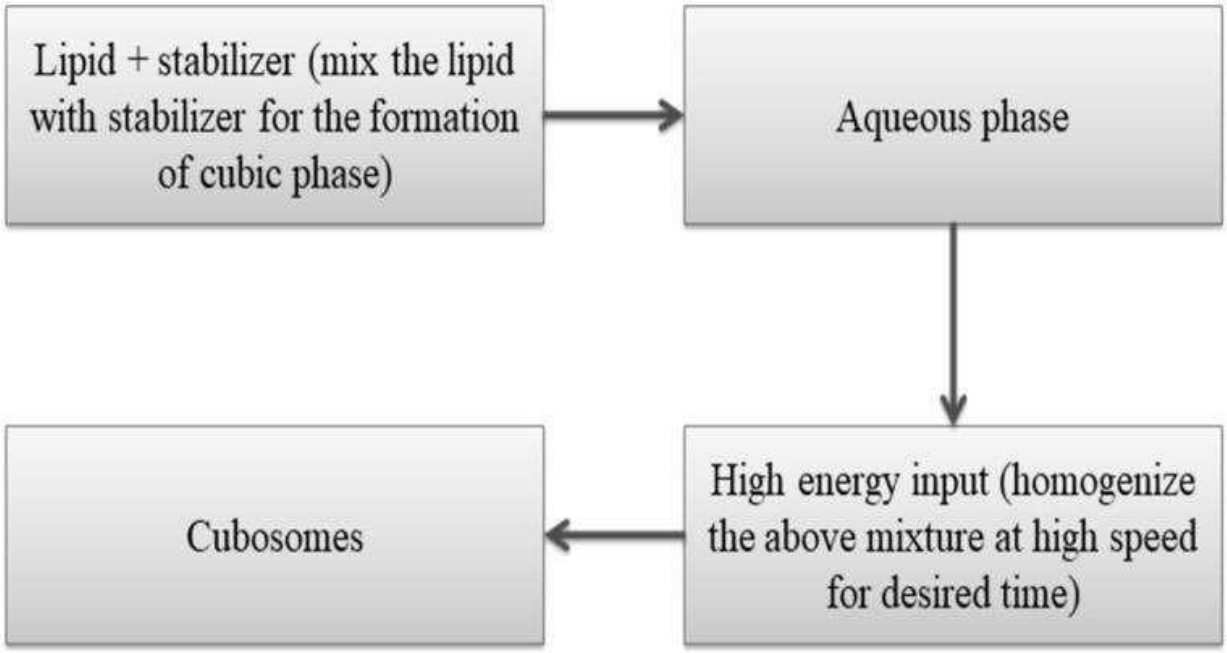

Figure 2: Cubosomes by Top down Technique

Bottom-up approach:

This method creates the building elements of the nanostructure before assembling them to create the finished substance [Fig 3]. The hydrotrope dissolves in water-insoluble lipids to produce liquid precursors. At high concentrations, less energy input is required to inhibit the formation of liquid crystals. When inverse micellar phase droplets are dispersed and allowed to gently cool in 80°C water, cubosomes arise from the droplets crystallising into cubosomes. At room temperature, an aqueous poloxamer 407 solution made by cubosomes is added to the monooleinethanol solution. Emulsification is the process by which cubosomes develop. Through crow -TEM, the bottom-up technique is unable to prevent vesicles from developing; numerous vesicles and vesicle-like structures have also been seen to coexist alongside cubosomes.

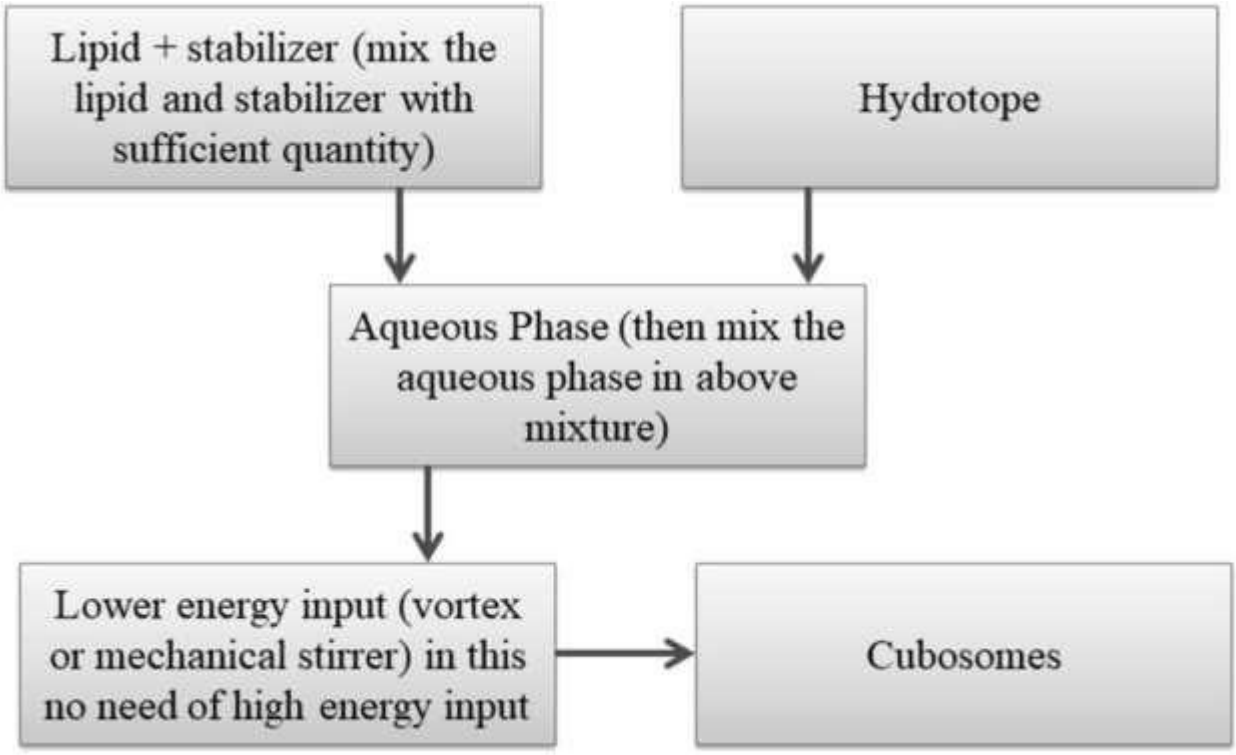

Figure 3: Cubosomes by Bottom up Technique

Heat treatment approach

Because it only facilitates the conversion of non-cubic vesicles into well-ordered cubic particles through a homogenization and heat-treatment step, this technique is not an integrated cubosome manufacturing process. Instead, it leads to a decrease in the small particle size fraction associated with vesicles and the formation of more cubic phases with narrow particle distribution and good colloidal stability.

Materials and Methods [40-45] Material

The wonderful donation of glycerol monooleate (GMO) came from Mohini Organics Pvt. Limited in Mumbai, India. A gift from BASF Limited in Mumbai, India was Poloxamer 407. Donepezil HCl was kindly supplied by the lab of
Dr. Reddy in Hyderabad, India. Glucomannan from konjac was kindly a present from Mumbai, India's Gangwal Chemicals Pvt. Ltd. We bought gellan gum from Balaji. medications Pvt. Ltd., India's Gujarat state. Analytical grade substances were all used in the investigation.

Bicontinuous cubic phases are found in-

A. Natural lipids
B. Cationic and non-ionic surfactants
C. Polymer systems

A. Natural lipids

The lipid that is most frequently used to create bicontinuous cubic phases is monoglyceride monoolein. Monoglycerides spontaneously form bicontinuous cubic phases upon the addition of water, are relatively insoluble, and are resistant to changes in temperature. Monoolein is the primary precursor of cubosome formation. Monoolein, also known as glycerylmonooleate, is a mixture of the glycerides of oleic acid and other fatty acids, primarily consisting of the monooleate

Method of preparation

Cubosomes can be manufactured by two defferent techniques as shown in figure 3, Manufacturing techniques of cubosomes,

1. Fabrication method 2. Emulsification method 1. Fabrication method

Melted at 60°C in a hot water bath, GMO/P407 cubic gel GMO 5% and P407 1.0% were added, and the medication was continually stirred until it was dissolved. Drop by drop, deionized water is added, and the vortex is adjusted for homogenization. The optically isotropic cubic

gel formed after up to 48 hours at room temperature was agitated mechanically, and the crude dispersion was then broken up by a sonicater probe with 200 watts of energy while the mixture was cooled to 20 °C in a water bath for 20 minutes.

2. Emulsification method

This process involves dissolving the GMO and P407 in 89% water, followed by ultrasonication of the mixture containing 5% GMO, 1% P407, and 5% ethanol. The melting of the GMO and P407 at 60°C is then combined with the addition of an ethanolic solution. The final combination is gradually added to deionized water that has been heated to 70°C. The water is then ultrasonically sonicated for 50 minutes at a maximum power of 130kW while the dispersion solution is let to cool naturally and is shielded from light

Preparation of Blank and AT101- Encapsulating Cubosomal Nanoparticles

Cubosomes were made via the standard top-down method .The lipid responsible for generating the structure was 3,26 Glyceryl monooleate (GMO, 90%, IOI Olea GmbH, Hamburg, DE), whereas the surfactant stabilising the cubosome dispersion was Pluronic F-127 (Merck, Darmstadt, DE). In order to create blank cubosomes, GMO and Pluronic F127 were combined in a weight:weight ratio of 1:0.25, and the mixture was melted at 40°C to produce a viscous, transparent result. In order to create drug-encapsulating nanoparticles, AT101 (Tocris Bioscience, Bristol, UK) was added to the lipid and surfactant combination at a 10% (w/w) concentration after being diluted in ethanol (99.8%, Avantor Performance Materials, Poland S.A.).

Drug loading in Cubosomes [46-48]

The produced cubosomes can hold a suitable quantity of peptides, biologics, small-molecule medications, or bioactives. Loading the cargo across the lipid bilayer, binding to the lipid membrane, or localising the medication within the cubic phase's water channels are the three primary methods. One possible method to load the drug moieties into the lipid is to either co-lyophilize with the lipid film prior to dispersion or add the therapeutic agent to the molten lipid. As an alternative, drug moieties could be added by incubating them after being dispersed onto cubosomes that have already been created. The majority of proteins, peptides, and small-molecule medications are loaded into the lipid bilayer. Moreover, single or binary lipid compositions, primarily consisting of phytantriol and monoolein, are used in the manufacture of cubosomes. While there are several ways to quantify drug loading, small-angle X-ray scattering (SAXS) is still the most commonly used technique. Consequently, these investigations demonstrated the promise of cubosomes as a drug delivery method, particularly for the administration of anticancer drugs. The main benefit of cubosomes over other particles, such as liposomes, is their bigger hydrophobic region, which increases the amount of hydrophobic medications that may be loaded while allowing hydrophilic pharmaceuticals to be loaded as well. Curcumin in phytantriol cubosomes has a higher loading capacity than curcumin liposomes, according to the research. Additionally, the particle membrane curvature can be adjusted independently of particle size because of the lattice structure of cubosomes. This feature is especially crucial when replicating highly curved structures, which have larger membrane loading capabilities and a greater membrane to surface area to volume ratio

According to the law of Higuchi-diffusion-controlled kinetics, the pharmaceuticals can be entrapped by the cubic structure of cubosomes and subsequently released based on various molecular weights and polarity.

$$[Dm.Cd (2A – Cd) t] = Q¾$$

This equation states that the square root of time determines the agents' release (diffusion) from the matrix. A is the primary amount of the drug per unit volume of the matrix, t is the time, Dm is the diffusion coefficient of the agents in the cubic matrix, Cd is the solubility of the agents in the matrix, and Q is the amount of the agents released per unit area of the matrix. The amount and rate of medication release can be calculated using this equation.

Biochemical tests

On day 22, or 24 hours following the final behavioural test, the animals were decapitated and slaughtered. The hippocampi were dissected after the brains were removed and cleaned with ice-cold saline. Then, ten times (w/v) icecold, phosphate-buffered saline solution (pH 7.2) containing a cocktail of protease inhibitors was used to homogenise the hippocampus samples. The homogenates underwent a 15-minute, 10,000× g centrifugation at 4°C. Following this, aliquots of the supernatant were separated in order to measure the activity of acetylcholine esterase (AChE) and the markers of oxidative stress (OS), such as malondialdehyde (MDA), total antioxidant capacity (TAC), and superoxide dismutase activity (SOD).

Characterization of drug release from cubosomes [49-51]

Sustained release drug delivery systems are helpful for keeping medication concentrations in the therapeutic concentration range for extended periods of time. It helps prevent harmful side effects and lowers the frequency of medicine administration. The cubosomes have been suggested as a medication delivery system and other bioactive agent delivery system based on two key rationales:

- Solubilization of medicines with low water solubility
- Managed or extended release of the loaded pharmaceuticals

The cubic phase regulates and incorporates the release of medications with different molecular weights and polarity. The cubic phase matrix from which the drug releases obeys Higuchi-type diffusion-controlled kinetics, which exhibits a linear dependence upon the square root of time when diffusion is out of the matrix.

When medications are integrated and diffuse, their surface area often increases due to the bulk cubic phase dividing into scattered nanostructured particles known as cubosomes. It is not anticipated that the primary characteristics of the cubic phase—namely, solubility, drug loading, and drug diffusion throughout the cubic matrix—will transform into cubosomes upon division. The cubosomes have a diameter of approximately 200 nm, which is actually 200 000 times larger than its surface area.38. For in-vitro release kinetics, a number of model hydrophilic medicines were assessed at different molecular weights. As a result, the matrix was changed from QII GMO to QII PHYT, which resulted in a decrease in drug release rates. Nguyen et al. revealed that cubosomes produced from PHYT displayed the continuous release of cinnarizine over 48 hours after oral administration to rats. Within 24 hours of employing GMOs to produce the cubosomes, the medication plasma concentrations decreased. Clogston et al. looked on the incorporation of certain big and tiny compounds whose enhanced size on release profile from the cubic phase of GMO.

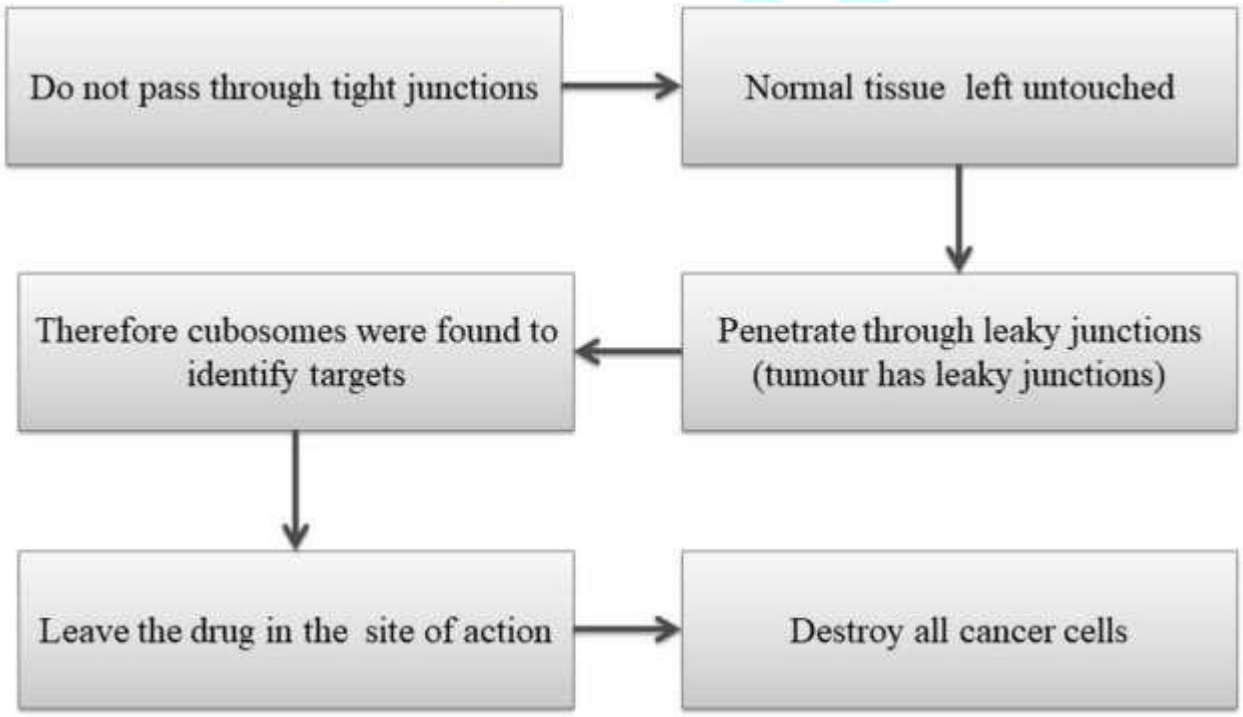

Figure 4: Action of Cubosomes incorporated drugs on tumors.

Toxicity Studies [52-57]

Even though cubosome-based targeting methods are now widely available, research on the toxicity of cubosomes in various cell lines is still rather scarce. and how this may be impacted by the stabilisers. There is some proof. that surface architecture and phase morphology may have an impact on absorption and cytotoxicity, although more research is required to acquire a more lucid image.

Thus far, a limited number of toxicity studies have been conducted with cubosomes and stabilisers based on phytantriol and monoolein, such as Pluronics F108 and F127, and PEG. fats conjugated. Typically, cytotoxicity has been first found for cubosomes at lipid concentrations of 1–100 mgmL1. between a number of cell lines (Tables 1 and 2). The. most research have used MTT to assess cytotoxicity. or Alamar Blue cell viability tests, albeit occasionally Assays for hemolysis have also been employed. Specifics are provided in every instance. Hinton and colleagues contrasted the impacts of F127 with lipids MO and Phy on the Alamar Blue assay's toxicity. It was discovered that Phy-based cubosomes were more hazardous than MO. It was determined that the cubic phase and its foundational ones Component It is the component lipid, not the pluronic, that is the main cause of toxicity. Additionally, hemolysis tests demonstrated that Phy-based cubosomes produced a noticeably greater release of haemoglobin compared to MO ones. 74 conducted tests for hemolysis Barauskas and colleagues similarly ascribed variations to the lipid as opposed to the Pluronic.

It has been demonstrated that brush polymers made by the RAFT polymerization technique lessen cytotoxicity when measured by the Alamar Comparing the blue assay in monoolein cubosomes with stabilized Using the Pluronic F127, they also benefit from not having to

Unlike cubosomes, influencing the cubosome cubic phase created using F127, when solutions greater than roughly 2 weight percent F127 causes primordial rather than diamond to develop. crystalline phases.

Evaluation of cubosomes [58-60] 1. Visual inspection 2. Shape of the cubosome 3. Particle size distribution 4. Zeta potential 5. Entrapment efficiency 6. Measurement of drug release 7. Stability studies

1. Visual inspection

The cubosomes are visually examined for optical appearance (e.g colour, turbidity, homogeneity, presence of macroscopic particles).

2. Shape of the cubosome

The cubosomes' form can be observed by transmission electron microscopy.

3. Particle size distribution

Zeta sizer (photon correlation spectroscopy) dynamic laser light scattering is the primary method used to determine the particle size distributions of cubosomes. A appropriate solvent is used to dilute the sample, which is then set to a light scattering intensity of roughly 300 Hz. The measurement is done in triplicate at 25°C . The average volume weight size can be used to collect and display the data. It is also possible to record the polydispersity index and zeta potential.

4. Zeta potential

The strength of the electrical repulsion between an adjust, similarly charged particle is indicated by the zeta potential. One important measure of the formulation's stability is the zeta potential.

5. Entrapment efficiency

The amount of unentrapped drug is calculated and deducted from the total amount of drug added. Spectrophotometers are used to assess medicine dosage.

6. Measurement of drug release

The pressure ultrafiltration approach can be used to liberate drugs from cubosomes . It is based on a method by Magenheim et al. that uses an Amicon pressure ultrafiltration cell at room temperature (22±2) °C that is equipped with a Millipore membrane.

7. Stability studies

An examination of the organoleptic and morphological characteristics as a function of time can be used to study the physical stability. To analyse potential fluctuations over time, the drug content and particle size distribution can be measured at various intervals .

Future prospects[61-63]

Moreover, they are appealing nanovehicles for protein and peptide loading and distribution; yet, the presented experiments remain essentially basic and several facets of the loading capacity of bio macromolecules and their release, as well as the structural and morphological characteristics of these soft nanocarriers, ought to be addressed. The blood compatibility of cubosome-based intravenous nanomedicines should be considered early in the formulation development process. Furthermore, not much is known about their stability in biological fluids, biological factors regulating drug release from cubosomes, interactions with cell membranes, structural transformation upon contact with biological fluids like plasma, and reactions related to infusion, to mention a few . Cubosome nanoparticles have great potential for drug delivery and sustained release; however, more optimisation is needed to fully realise the therapeutic potential of these nanocarriers in various diseases, depending on the mode of release, frequency of dosing, and route of administration.

Conclusion

Unlike solid nanoparticles, cubosomes are self-assembling liquid crystalline particles that exhibit targeted and prolonged drug delivery. They can contain a wide range of hydrophilic and lipophilic medicines. Cubosomes might be readily produced using two strategies, such as top-down and bottom-up approaches, using high pressure homogenization or ultrasonication procedures. Cubosomes have use in immunological compounds, proteins, cosmetics, and a broad spectrum of therapeutic possibilities. Owing to their possible site specificity, cubosomal preparations have the potential to be extensively utilised as targeted drug delivery systems for diabetes, ophthalmology, and anticancer therapy. Since cubosome technology is relatively new and has a high output, there is a lot of room for research into creating new formulations that will be viable in the marketplace and industry.

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