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Cubosomes and its Pharmaceutical Application in Treatment of Cancer

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Abstract: *Cubosomes are lipid-based nanoparticles that have recently gained attention in the field of pharmaceuticals due to their unique physicochemical properties. These nanoparticles are composed of a highly ordered lipid bilayer that forms a cubic liquid crystalline phase, which can encapsulate both hydrophilic and hydrophobic drugs. The unique structure of cubosomes allows for high drug loading and sustained release, making them an attractive option for drug delivery. Cancer treatment is a major focus of research for cubosomes due to their potential for targeted drug delivery. Cubosomes have been shown to be effective in delivering chemotherapeutic agents to cancer cells, increasing drug efficacy while reducing toxicity to healthy tissues. Additionally, the highly ordered structure of cubosomes can be tailored to increase cellular uptake and improve the stability of the drug within the body.Recent studies have demonstrated the potential of cubosomes as an effective drug delivery system for a wide range of anticancer agents, including small molecule drugs, peptides, and nucleic acids. In addition, cubosomes have been explored for use in combination therapy, where multiple drugs can be encapsulated within a single nanoparticle.Overall,cubosomes have shown great promise as a versatile and effective drug delivery system for the treatment of cancer. Further research is needed to fully understand the potential of cubosomes in cancer therapy, including optimization of their structure, improved drug loading efficiency, and increased specificity for cancer cells.*

Keywords: Cubosomes, Lipid-based nanoparticles, Drug delivery, Cancer treatment, Targeted therapy, Combination therapy etc.

I. INTRODUCTION

The “cubosomes” term was firstly coined by Larsson, which is similar to liposomes [1] . Cubosomes are the nanostructured particles and these are the discrete and sub-micron size particles of the bicontinuous cubic liquid crystalline phase. The bicontinuous cubic phases are having a specific benefit, that is, their ability to tune membrane curvature. Cubosomesare self assembled liquid crystalline particles, which have rheology like a solid [2]. Liquid crystals could be a quarter state of matter These cubosomes are made up of lipids, polymers, and surfactants, which are usually amphiphilic. Here, the meaning of bicontinuous is that the enclosures of two different regions of water are divided by surfactant bilayers. Cubosomes are similar to liquid crystalline substance, viscous, optically isotropic as well as solid and having cubic crystallographic symmetry [3]. Cubosomes are highly important in nanotechnology based drug delivery system [4] . Recently, the interest in pharma has increased into a particle with a few hundred nm in diameter that is 10-500 nm in diameter [5] . The ratio of drug to the polymer is around 1:2 or 1:1, which may vary substance to substance. Some anticancer drugs have been successfully formulated in the form of cubosomes. The large-scale production of cubosomes wasdifficult because of their viscosity and behavior of phase. When water is mixed with some specific surfactants, then there is a spontaneous formation of cubic phase [6]. The cubosomes and the parent cubic phase possess the same microstructure; also the cubosome dispersions have much lower viscosity as compared to the bulk cubic phase [7]. The cubosomes have a larger surface area in comparison to the parent cubic phase [8]. Cubosomes are formed by the self-assembly of surfactant-like molecules or amphiphilic molecules [9]. Cubosomes are generally prepared by high energy dispersion of the bulk cubic phase [10]. There is a colloidal stabilization by polymeric surfactants [11]. The cubosomal formulations are either released via diffusion or absorbed [12]. At higher levels of dilutions, most of the liquid crystalline systems are converted into micelles. But, at any dilution levels, the cubosomes remain stable. This is because of the relative insolubility of the cubic phase, which is formed by lipids in water. The

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controlled drug release is nothing but a release of a drug in a pre-designed manner. A drug delivery system is like a device that carries a drug moiety to the specific site of the body (or towards a specific tissue) to achieve an effective concentration at the site of action. There are some benefits of controlled drug release, such as – enhances the therapeutic benefits, minimizes untoward side effects, reduce the need of multiple dosing, increases patient compliance, reduces cost, etc. [13-15]. In the cubosomal vesicles, when drugs are incorporated into it, then it will transport drugs to the site of action (even a high molecular weight drugs). It acts as a penetration enhancer, and it will increase drug transport across skin .[16] Cubosomes are a part of vesicular drug delivery system, which were discovered in 1980.[17] and had great importance in a nanotechnology. [18] Cubic gel phase, cubosomes, and cubic phase precursor are the three forms of cubic phase. Cubosomes acts as a promising delivery system for various substances, such as proteins, amino acids, peptides, low molecular weight substances, nucleic acid, etc. [19, 20] The mechanism of a cubic phase is as a delivery vehicle. They showed better stability than the liposomes [21-23]. Cubic liquid crystals are transparent and stable even in excess of water. Cubosomes are the form of binary systems [24]. Cubosomes have many applications such asantibiotics delivery, analgesics, enzymes, antimuscarinic drugs and peptides delivery [25]. Cubosomes consist of highly twisted lipid bilayers, and they possess a high surface area, which is about 400 m2 /g [26] . The cubosomes size ranges from 10-50 nm in diameter. The cubosomal systems are superior to other novel delivery systems because there is an improvement in the stability of the drug in formulation, maximizing drug loading capacity, controlled drug release, and also optimum particle size. The drug in a cubosome will diffuse through a channel present on cubic phase [27]. Polymers used in cubosomes preparation are responsible for both stability as well as controlled release behavior [28]. These polymers also include block copolymers as well as PEG moieties. This is modifiable with protein molecules. There are few companies (Nivea, L"Oréal, Procter & Gamble) who are engaged in a researching activity for cosmetical (cosmeceutical) applications of cubosomes. Recently, researchers are investigated the cubosomes for the therapy of cancer, cosmetic production, topical applicability as well as other drug delivery systems. In practice, the anticancer drugs which are being formulated are very less [29].

II. THEORY ON CUBIC PHASE STRUCTURE

2.1 Fontell & Drew Theory:[30]

Ternary systems of amphiphiles, oil & water, some mono glycerides will exhibits cubic phases. Monoglycerides are polar lipids, having poor water solubility that exhibits aqueous phase behavior, which are structurally mimicking to non-ionic surfactants. Lutton results the Monoglycerides whose hydrocarbon chain lengths between C-12 and C-22 of all the Monoglycerides, particularly monoolein exhibits larger region of cubic phase. Monoolein is unsaturated, C-18 Monoglycerides.

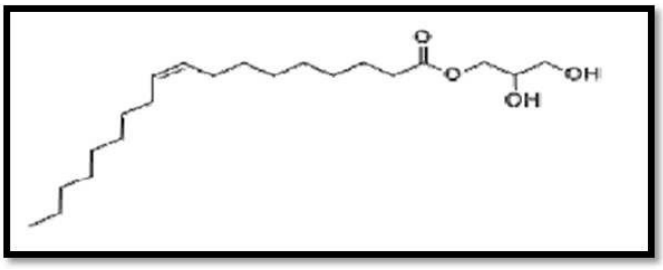

Fig 2. Monoolein StructureMONOOLEIN PROPERTIES

Melting point: 35-37 °CFEMA: 2526
Flash point: 180 °C Storage temp: −20°C
Solubility: chloroform: 50 mg/ml clear, colorless.

2.2 Gustafson et al Theory: [31]

Cubosomes are single crystal structures, with visible unilamellar vesicles, dispersed lamellar liquid crystalline phase particles. Increasing polymer-to-monoolein ratios leads to formation of larger vesicles. Ultra sonication of bulk cubic phases produces mostly vesicles on due course of time they get trace formed into Cubosomes via membrane fusion such meta stability is characteristic of Cubosomes systems because of slow transport processes involved in forming high

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viscous crystalline structure and high energy is required to fragment them (bulk cubic phase).vesicles alsogive colloidal stabilization of Cubosomes.

2.3 Schwarz, Jacob & Anderson Theory:[32]

Cubic phases are often founded sandwiched between lamellar and hexagonal liquid crystalline phases, especiallyin non-ionic surfactant systems. The monoolein-water system uniquely possess a cubic phase region contains broad compositional and temperature range. But surfactant packing concepts are more approaching. Normally monoolein has continues hydrophilic headed, hydrophobic tail end, producing reversed or inversed cubic phases, indicating the phases towards polar medium. So that the cubic phase structures can be described using the concept ofdifferential geometry and periodic minimal surfaces. Minimal surfaces are best described by analogy with soap films. Based on their curvatures, 3 types of minimal surfacesare studied in cubic phases.

Fig: 3. P-surface (primitive surface), D-surface(diamond surface), G-surface (gyroid surface) [32]

The monoolein water system forms the D surfaces at high water levels and the G surface at lower levels. The p-surfaceis formed in the monoolein water system, but only when third component such caseins or amphiphilic. The block copolymer are added. Cubic phases existed can be measured by X-ray scattering technique. Transmission electron microscopy (TEM), freeze fracture electron microscopy is used to visualize the Cubosomes.

2.4 System Forming Cubosomes

The system forming Cubosomes is possible in binary and ternary systems with a sufficiently large miscibility gap between the cubic phase and the solvent. Colloidal stabilization of cubosomes is good when poloxamer 407 issued to provide stabilization against aggregation and coalescence. Cubosomes can be coated with lamellar bilayered 'caps' covers the cubic bilayer opening which is formed by fragmentation which prevents the exposure of hydrocarbon chains to water and provides colloidal stability.[33] Coating of Cubosomes with solid crystalline bilayerprovides more colloidal stability, whereas lamellar liquid crystalline will give rigid coatings. In addition coatings of the sponge phase have been proposed as a stabilizing coating ofcubosomes. The following figures will shows two general forms of the ternary phase diagrams exhibited by system forming Cubosomes. Another molecule with great potential for Cubosomes formation is phytantriol[34]

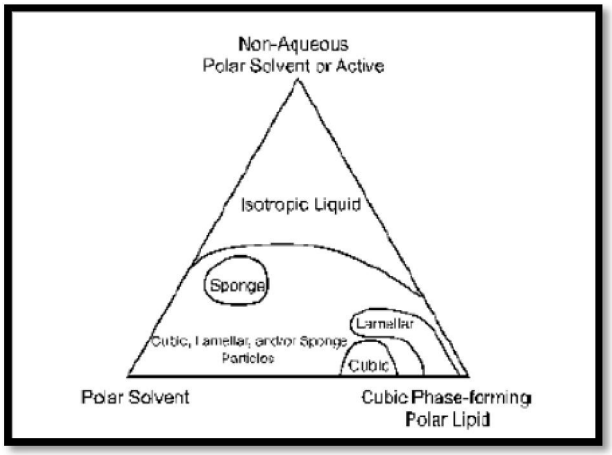

Fig. 4 Phase Diagram [34]

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III. METHOD OF PREPRATION

1. Top-down approach
2. Bottom-up approach
3. Heat treatment
4. Spray drying

3.1 Top-down approach

It is the most widely used in research area, where by bulk cubic phase is first produced and then dispersed by high energy processing in to Cubosomes nanoparticles. Bulk cubic phase is resembling a clear rigid gel formed by water swollen crossed linked polymer chains, whereas cubic phases are like liquid crystalline structure.[30] The cubic phases exhibits a yield stress that increases with increasing amount of bilayer forming surfactant and oils.

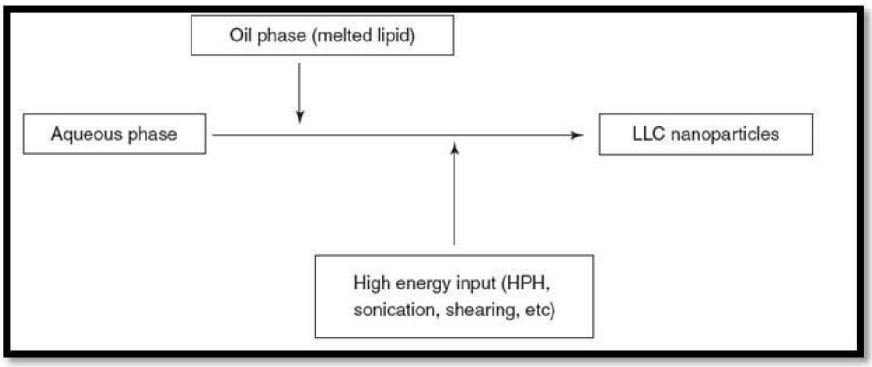

Fig No: 5 -Top Down approach method [35]

Based on most existing studies comparison of dispersion produced by sonication and high pressure homogenization suggests the formation of complex dispersions containing vesicles and Cubosomes with time dependent ratios of each particle type.[36]

Coarse Cubosomes on micron scale possess the same D-surface structure as their originating bulk cubic phase, but after homogenization, the P-surface dominates because of added polymers. The extreme viscous bulk phase is prepared by mixing structure-forming lipids with stabilizers, then the resultant is dispersed into aqueous solution through the input of high energy (such as high-pressure homogenization [HPH], sonication or shearing) to form LLC nanoparticles. At present, HPH is the most extensively used technique in the preparation of LLC nanoparticles (cubosomes).[37]

3.2 Bottom-up approach

In this Cubosomes are allowed to form or crystallize from precursors. Almgren et., al. discuss the formation of Cubosomes by dispersing L2 or inverse micellar phase droplets in water at 80ºC,and allow them to slowly cool, gradually droplets get crystallizes to Cubosomes. This is more robust in large scale production of Cubosomes. Spicer et.al developed Cubosomes at room temperature is by diluting monoolein-ethanol solution with aqueous poloxamer 407 solution. The Cubosomes are spontaneously formed by emulsification[38]

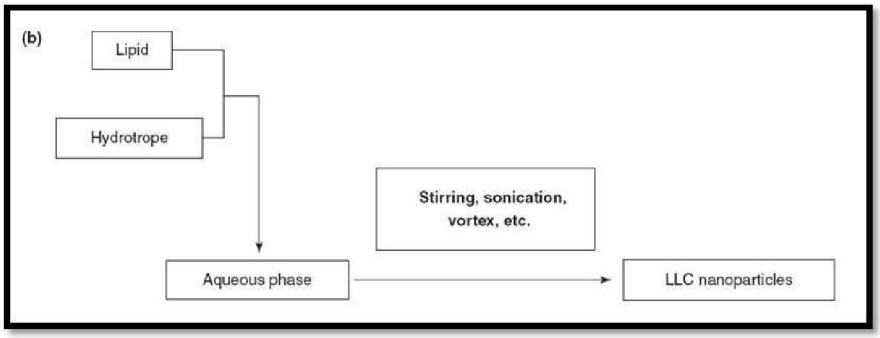

Fig No 6: Bottom-up approach method [39]

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The key factor in the bottom-up approach is hydrotrope, which can dissolve water-insoluble lipids to create liquid precursors and prevent the formation of liquid crystals at high concentration. Compared with the top-down approach, this dilution-based approach can produce Cubosomes without laborious fragmentation. In other words, it needs less energy input. Moreover, this approach is far more efficient at generating small particles. The reason for this might relate to the forming mechanism of Cubosomes. The dilution-based approach can be regarded as a process of small particles forming big particles through aggregation, which is analogous to the use of precipitation processes to produce nanoparticles, whereas the top-down approach is more analogous to the attrition of big particles. In addition, Cubosomes prepared through dilution show long-term stability, which might be attributed to the homodisperse stabilizers onto the surface of Cubosomes. Indeed, the use of hydrotrope can simplify the preparation process and produce Cubosomes possessing similar or even better properties than those fabricated by the top-down approach.

3.3 Heat treatment

In this case, heat treatment can be regarded as a good approach. Note that in the strictest sense, heat treatment is not an integrated process for the manufacture of Cubosomes because it only promotes the transformation from non-cubic vesicles to well-ordered cubic particles. The dispersed particles, therefore, can be produced by a simple processing scheme comprising a homogenization and heat-treatment step. From the reported studies, heat treatment could cause a decrease in the small particle size fraction that corresponded to vesicles and form more cubic phases with narrow particle distribution and good colloidal stability. Taking the whole process of preparation into account, it is obvious that the transition takes place during the procedure of heat treatment. The reason for transition could be speculated as an elevated temperature giving rise to a reduction in solubility and stability. When the temperature was below cloud point, the surfactant had a high solubility and thus the particles could exist stably and the phenomenon of fusion was hardly observed. Once reaching cloud point, the solubility of surfactant decreased notably and a notable fast fusion among vesicles would occur.

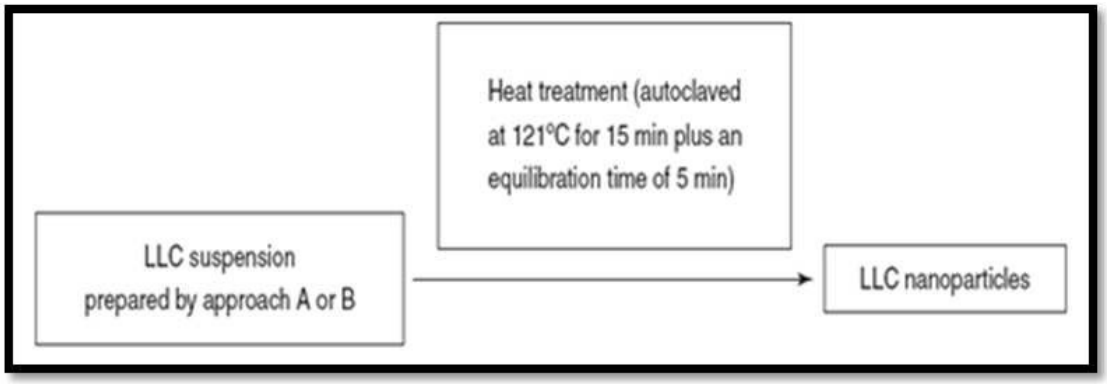

Fig no 7: Heat Treatment method[39]

The lipids used to make Cubosomes are waxy, sticky Solids, rendering them unable to form small discrete particles. It is found that a water-soluble non-cohesive starch coating on the waxy lipid prevents agglomeration and allows control of particle size. Spray drying is an excellent process to produce these particles. Spray drying produces encapsulated particles from an emulsion of liquid droplets or a dispersion of solid particles in a concentrated aqueous polymer solution[30]

The continuous and dispersed phases are sprayed through a nozzle to create suspension droplets that are contacted with a heated, dry air stream flowing in the opposite direction. Excess water immediately evaporates, leaving dry powder particles composed of the dispersed phase encapsulated by a shell of the formerly dissolved polymer. Spray-drying processes are easily scaled up and are already widely employed for manufacturing consumer products like detergents and foods. Further, the process provides an easy route to preload active into the Cubosomes prior to drying. Finally, the polymer coating on the powder imparts surface properties to the hydrated Cubosomes that can be tailored by proper selection of the encapsulating polymer. The liquid feed to the spray-dryer can be tailored to adjust the resultant powder properties. The production of starch- coated Cubosomes powder precursors requires high shear treatment of monoolein in aqueous starch solution to form a coarse Cubosomes dispersion that is then pumped through a nozzle and dried. Full operating conditions are given in Spicer et al. (2002a). The initial composition pumped into the spray-drier is 60% w/w

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water, 30% starch, and 10% monoolein. Drying removes almost all water present and gravimetric tests of the powder generally indicate a final composition of about 4% w/w water, 72% starch, and 24%monoolein in the product powders.
The emulsion of both phases has low viscosity and is easily spray dried. The type of encapsulating starch also affects powder quality. Drying occurs as the dispersion is sprayed into droplets and moisture rapidly evaporates by convective heating. The Cubosomes in the dispersion form the nucleus of many of the sprayed droplets, surrounded by aqueous starch solution. As drying proceeds, the starch remains and forms a coating on the cubic gel particle, thereby encapsulating it. Because the cubic phase itself contains 40% (w/w) water, some drying must also occur at the core of the particles. Low molecular weight starches (84,000 MW) produce superior powders when compared to those made using high (335,000 MW) molecular weight starches. Spicer et al. (2002b) provide a more comprehensive listing of feasible polymers and other materials for use as polymeric coatings to encapsulate Cubosomes.[38]

IV. CHARACTERIZATION

4.1 Cryo-Transmission Electron Microscopy (CryoTEM).[40]

Cryo-Transmission electron microscopy (Cryo-TEM) is a microscopy technique whereby a beam of electrons is transmitted through an ultrathin specimen, interacting with the specimen as it passes through. An image is formed from the interaction of the electrons transmitted through the specimen; the image is magnified and focused onto an imaging device, such as a fluorescent screen, on a layer of photographic film, or to be detected by a sensor. Cryo-TEMs are capable of imaging at a significantly higher resolution than light microscopes, owing to the small wavelength of electrons.

4.2 Small-Angle X-ray Scattering (SAXS). [41]

Small-angle X-ray scattering (SAXS) is a small-angle scattering (SAS) technique where the elastic scattering of Xrays (wavelength 0.1. - 0.2 nm) by a sample which has in homogeneities in the nm-range, is recorded at very low angles (typically 0.1 - 10°). This angular range contains information about the shape and size of macromolecules, characteristic distances of partially ordered materials, pore sizes, and other data. SAXS is capable of delivering structural information of macromolecules between 5 and 25 nm, of repeat distances in partially ordered systems of up to 150 nm.

4.3 Particle Size Distribution (PSD).[42]

The particle size distribution of the dispersions was determined using photon correlation spectroscopy. Measurements were performed at 250C using a refractive index (RI) of Cubosomes at intervals of 100 s. Samples were diluted with water to adjust the signal level. The average particle size (z-average) and poly dispersity index were determined.

4.4 Application of Cubosomes

1. Vehicles for biologically active substance.
2. Control release of solubilized substance.
3. Treatment of skin, hair, and other body tissue.
4. Melanoma (cancer) therapy.
5. As Injectable vehicles.

A. Vehicles for biologically active substance.[30]

Cubic phases were produced at 25 ºC in water monooleinalcohol mixtures. Ethanol was found to be more efficient than propanol and butanol. In the composition range of 49 to 56 wt% water, 31 to 40 wt% monooleine and 10 to 13% wt ethanol we identified a new transparent, low-viscosity (flowing) phase that we called OL. No structures were found by bright field light microscopy and polarized light microscopy, indicating that OL is an isotropic phase. CryoTEM showed large domains of this ordered phase, which by Fast Fourier Transformation was identified as a cubic phase.

B. Control release of solubilized substance.[43]

Cubic phase is more applicable for control release because of its small pore size (5-10nm), ability to solublise hydrophilic, hydrophobic, amphiphilic. The molecules and its biodegradability by simple enzymes.

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C. Treatment of skin, hair, and other body tissue.[44]

Cubic phase materials can be formed by simple combination of biological compatible lipids and water and are thus well suited for use in treatments of skin, hair, and other body tissue. Cubosomes contents is mono-olein i.e. monoglycerides.Monoglycerides has microbicidal property. Cubosomes contents ethanol which causes skin disruption. These increase lipid fluidity cause more permeation through skin. Cubosomes permits inside and fuse with skin lipids and release drug into deep skin layers.

D. Melanoma (cancer) therapy.[43,44]

Cubosomes can be circulate in the body after being injected they have ability to target diseases at the site disorder. This feature of Cubosomes is especially useful in cancer therapy. Where the size of the delivery system is the key to target cancer through the enhanced permeability and retention effect. Diseased cells can also be targeted by attaching ligands (follic acid derivative, peptides, protins, antibodies)to the surface of Cubosomes.

E. As Injectable vehicles.[40]

Cubosomes are highly viscous, and this mechanical stiffness makes them clumsy to handle and difficult to inject. To overcome this defect, some corresponding approaches have been proposed, such as application of flowable precursor forms and use of LLC nanoparticles. According to the phase diagram of structure-forming lipid, the transition from lamellar phases to cubic phases can be completed upon heating from room temperature to body temperature or swelling with water. Therefore, lamellar phases with inherently fluid properties can act as precursors of viscous cubic phases. Once injected into the body via subcutaneous or muscular approach, flow able lamellar phases will gradually absorb water from body fluid or surrounding tissues and, subsequently, convert to cubic phases, which can form the sustained release depot in situ.

4.5 Advantages: [45]

- High drug payloads
- Simple preparation method
- Biodegradability of lipids
- The ability of encapsulating hydrophobic, hydrophilic, amphiphilic substances.
- To targeting and controlled release of bioactive agent.

4.6 Disadvantages: [46]

- Manufacture of Cubosomes on a large scale embodied difficulty because of their viscosity
- High energy processes
- Harmful to fragile temperature-sensitive active ingredients
- Expensive
- Difficult to scale up

4.7 Cubosomes in Cancer Therapy

Globally, cancer is one of the most prevalent diseases which poses an important clinical challenge, owing to its high rates of incidence. GLOBOCAN 2020 estimates reveal the diagnosis of 19.3 million cancer cases, with ~10 million deaths in 2020 [47,48]. This marks cancer as a critical barrier to increasing life expectancy and is also deemed the leading cause of death worldwide [48]. With the advent of biotherapeutic interventions, biomacromolecular drugs have recently garnered substantial attention, primarily in the field of drug discovery and development, due to advance in-vivo functions. Over the recent years, a plethora of drug delivery strategies has been devised for the administration of these biomacromolecular drugs, to overcome the difficulties in their dispensing, like drug instability and restriction by physiological membrane barriers [32]. The tumor microenvironment has several distinct characteristics, of which the most conspicuous include irregular vascular structure, dense stroma, and numerous supporting cells such as cancer-associated fibroblasts and tumor-associated macrophages (TAM) [49]. These characteristics have been leveraged in the efficient diagnosis and treatment of cancer, as the responsiveness of these nanobiotechnological modalities solely relies

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on the release of the active constituents under particular stimuli like enzymes, temperature, pH, redox potential, or other external stimuli based on their distinct physicochemical parameters. Furthermore, the synergistic integration of various nanoparticles with target ligands expedites the evolution of highly efficacious active drug carrier systems. Moreover, the amalgamation of nanotechnology with a contrast agent can substantially increase the sensitivity of in vivo real-time diagnosis for next-generation precision medicine. For instance, clinically approved Poly (Ethylene Glycol)-Polylactide (PEG-PLA) copolymer micelles to combat malignancies; PEG-based Platinum (II) nanoformulation for treating multidrug-resistant cancer; conjugated PEG and β-cyclodextrin (PEGCD) for effectual delivery of Sorafenib and Doxorubicin, among several nanocarriers devised for the treatment of cancer [34]. The utility of novel drug delivery systems for the efficient and patient compliant delivery of biomacromolecular drugs ensures a substantial increment in bioavailability, drug half-life prolongation, and improved patient compliance, thereby promoting their efficacy and potentiality for clinical applications [50].

4.8 Anticancer Drugs Loaded onto Cubosomes

The most commonly employed drugs used in adjunct with the cubosomes have been elucidated below:

A. Paclitaxel

Paclitaxel (PTX) is regarded as the first-line chemotherapeutic drug employed in the treatment of Non-Small Cell Lung Cancer (NSCLC). PTX binds with the β-tubulin facilitating the obstruction of the mitotic spindle, further arresting the cell cycle at the metaphase-anaphase junction of mitosis, enhancing its polymerization, thereby leading to the inhibition of cell cycle. Generally, the microtubules are regarded as unstable and dynamic components, but the conjugation of PTX to β-tubulins stabilizes the microtubules, thereby precipitating an obstruction of dynamic rearrangement of the tubule network, which is responsible for maintaining the interphase and mitotic functions that produce unusual bundles throughout the cell cycle [51]. The research conducted by Aleandri et al. employed biotinylated cubosomes, that were stabilized and operationalized using Biotin (Vitamin H or B7)-based copolymer, and had the potential to transport PTX and the hydrophobic fluorescent dye (MO-Fluo), utilized for active targeting or cellular-internalization of the nanoparticles. The cubosomes were further characterized by chemical and physical techniques, particularly small-angle X-ray scattering (SAXS) and dynamic laser light scattering (DLS), and their delivery efficacy on HeLa cells was established. These novel MO-based cubosomal dispersions were designed using a biotin-conjugated stabilizer (PF108- B), which has a great affinity for the sodium-dependent multivitamin transporter (SMVT), which is overexpressed in the membranes of tumor cells. This conjugation of PF108 and Biotin is quantified using HABA (4'- Hydroxyazobenzene-2-carboxylic acid), in a solution containing avidin, HABA, and Biotinylated PF108. The research also underlined the significantly increased anticancer action of PTX at a concentration of 1 µg/mL, in the biotinylated cubosomes when compared to the free PTX or non-targeted cubosomes. This has been accentuated by the promotion in cancer cell uptake via receptor-mediated endocytosis, brought about by the biotin ligand, which further increases the efficacy of PTX against tumor cells, with a concurrent reduction of PTX toxicity to healthy cells and tissues. These biotinylated cubosomes could potentially be employed in the drug delivery, diagnosis, and monitoring of therapeutic responses [52]. Moreover, Murphy et al. (1993) and Chang et al. (1993) calculated response rates of 21% and 24% for a 24-h infusion regimen of PTX for the treatment of NSCLC [35–37]. Additionally, the Studies conducted by Zhai et al. opine Mono-olein (MO)-based cubosomes to be a potential carrier for PTX in the treatment of ovarian cancer. Additionally, by virtue of their encapsulation into a nanocarrier, these nanoparticles aid in overcoming solubility issues, thereby achieving PTX loadings of up to 10 wt% of MO. Furthermore, the active targeting of the cancer cells was attained by bio-conjugating Epidermal Growth Factor Receptor (EGFR)-antibody fragments on the nanoparticle surfaces. These nanoparticles demonstrated a higher in vitro cytotoxic activity against Human Ovarian Cancer Cell Line (HEY) when compared to free PTX. Further research established that the lipid nanoparticles exerted no effect on the HEY cell viability at the effective concentration, indicating an improved anticancer activity attributed to the integration of PTX in the nanocarriers, as the mice administered the same dose (5 mg/kg of body weight) of free PTX had tumors twice as large as the ones administered the cubosome-loaded drug. In HEY-derived ovarian cancer mouse models, a weekly intraperitoneal injection of PTX-Cubosomes and EGFR-PTX-Cubosomes substantially reduced tumor burden, thereby enhancing in vivo survival. These results underscore the

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incorporation of metronomic doses of the drug in a cubosome-based drug delivery system as a promising approach in the treatment of end-stage ovarian cancer patients [53]. Conclusively, the PTX-loaded cubosomebased drug delivery modalities possess the potential to protract the disease-free progression and overall chances of survival in end stages of various cancers.

B. Cisplatin

Cisplatin (cis-diamminedichloroplatinum) is an alkylating agent and a subset of platinum (II) analogs. It acts by producing an immensely reactive moiety that facilitates the cross-linking of DNA, forming DNA adducts, which in turn impede the repair of DNA, subsequently leading to DNA damage and apoptosis in the cancer cells [54]. Cisplatin is among the most frequently administered chemotherapeutic agents for solid tumors but finds its major utility in metastatic testicular and ovarian carcinoma. In a research conducted by Zhang et al., several studies performed on uncoated and poly-ε-coated cisplatin-loaded cubosomes employed the Human Hepatoma (HepG2) cell line. The zeta potential measurement, in vitro release, and entrapment efficiency studies of cubosomes, along with cytotoxicity studies, were performed for further characterization. The zeta potential values for the blank, uncoated, and coated cisplatin cubosomes were noted to be − 24.5 ± 0.3 mV, − 22.4 ± 0.4 mV, and − 2.8 ± 0.1 mV respectively. The complexation of the cubosomal surface takes place following its coating and is validated by the lowering in the zeta potential values of the coated cubosomes. Additionally, the in vitro release studies revealed that the uncoated model had an initial burst release of 55 ± 3%, with a slowrelease post 6 h and no release post 10 h. However, the coated model demonstrated only 23 ± 3% initial release, with a slow yet continual release lasting for about 25 h. Furthermore, the cytotoxicity studies revealed that the free cisplatin was significantly more toxic towards the HepG2 cells when compared to the cubosome-loaded ones. Owing to their high initial burst release, the uncoated models demonstrated lesser cell viability and higher cytotoxicity than the coated models [39]. Conclusively, these studies indicate that the coating prevents the burst release of large amounts of the drug, corroborated by the cell viability of the coated cubosomes being almost comparable to that of the blank cubosomes.

C. Doxorubicin

Doxorubicin is an anthracycline antibiotic repurposed as an antitumor drug, primarily against solid tumors in the breast, ovaries, thyroid gland, urinary bladder, and also in neuroblastomas, sarcomas, and lung cancers. It exerts its effect by inhibiting the synthesis of DNA and RNA, by positioning itself between the DNA strands. Activation of the topoisomerase-2 enzyme with a concurrent formation of quinone-type free radicals catalyzes the cleavage of the DNA strands. The Glycerol Mono-oleate (GMO)-based cubosomes find their utility as vehicles for both the chemotherapeutic drug (Doxorubicin) as well as the radionuclide (low-energy β-emitter, Lutetium-177 or 177Lu). Additionally, these cubosomes were doped with a chelating agent DOTAGA-oleylamine conjugate (DOTAGA-OA) that forms stable complexes with Lutetium177. Owing to its hydrophilic nature, the DOTAGA-metal complex tends to be released from the cubosomal channels but is impeded by the oleylamine hydrophobic chain, being the lipophilic conjugate utilized in the synthesis of DOTAGA-OA. The studies conducted by Cytryniak et al. report the decline in the metabolic activity of HeLa cells, validating its antitumor efficacy. Furthermore, their results reveal that, though the increment in cytotoxicity by the conjugated DOTAGA-OA-177Lu in a single cubosome is minimal, yet these cytotoxicity enhancements become statistically significant only post short incubation times (e.g., 24 h). Despite this, the multifunctional cubosomes facilitate a reduced use of chemotherapeutic doses, thereby lowering the possibility of adverse effects during chemotherapy, particularly in the administration of doxorubicin, that exerts a strong cardiotoxic effect [52].

D. 5-Fluorouracil

5-fluorouracil (or 5-FU) a water-soluble compound, primarily classified as an antimetabolite belongs to the sub-class of pyrimidine analogs. It inhibits DNA replication by inhibiting the action of the thymidylate synthase (TS) enzyme, thereby blocking the synthesis of pyrimidine thymidylate (dTMP). Generally administered as an I.V. Infusion, the 5-FU is commonly employed for solid malignancies, especially within the colon, stomach, pancreas, liver, rectum, or urinary bladder. A study conducted by Nasr et al. compared 5-FU-loaded cubosomes with an aqueous solution of free 5-FU. The in vitro release studies revealed that the aqueous solution demonstrated a rapid release lasting only about 1 h when

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compared to the cubosomes that exhibited a relatively slower release lasting about 4.5 h, post the initial burst releasing 53.6 ± 3.55% of the drug in the first hour. In-vivo biodistribution studies in rat liver revealed that the 5-FU liver concentration of the cubosomal formulation was almost five times higher than the 5-FU solution. Although higher 5-FU concentrations resulted in more hepatocellular damage, the use of cubosomes is believed to increase the efficacy of lower doses of 5-FU. The half-maximal inhibitory concentrations (IC50), obtained from the in vitro cytotoxicity studies were calculated to be 112.70 mg/mL for free 5-FU and 107.78 mg/mL for the cubosomal dispersion. The insignificant difference between the two values indicates that the antitumor activity of the drug hasn't been adversely affected by its loading onto the cubosomes [53].

E. Icariin

Icariin (ICA) is an antitumor agent, primarily obtained from Herba epimedii (Berberidaceae) in the form of flavanol glycoside and has been recently utilized in the treatment of Ovarian Cancer Cell lines (SKOV-3 and Caov 3). Icariin exerts its pharmacological effect via inhibition of PI3K/AKT and Raf1/ERK1/2 signaling pathways, cell cycle inhibition, induction of apoptosis, and inhibition of autophagy by overexpression of autophagy-related p53 in breast cancer cells [54]. Additionally, it modulates the mitochondrial transmembrane potential and expression of caspase-3, which facilitates the induction of reactive oxygen species (ROS) in ovarian cancer cells, thereby exerting a cytotoxic effect. Owing to its hydrophobic nature, the cubosomes loaded with ICA tend to have greater efficacy and better antitumor action, which was regulated by utilizing Box-Behnken statistical design. The in vitro release studies comparing the ICA-Raw (free ICA) and ICA-Cubs (Optimized ICA-loaded cubosomes), observed an initial burst release followed by a gradual release for ICA-Cubs until 96.23 ± 3.231% was attained within a 24-h time-frame whereas ICA-Raw had a slow and incomplete release of ICA of up to 67.34 ± 2.424% within the same time-frame. Additionally, the significant decrease in the release rates of ICA-Raw as compared to ICA-Cubs promotes the use of cubosomes loaded with Icariin as a better intervention for achieving greater antitumor activity. Furthermore, the enhanced ICA-Cubs demonstrated a moderately non-cytotoxic action on the normal EA.hy926 endothelial cells, thereby ensuring a more targetoriented action [55].

F. Irinotecan

Irinotecan (CPT-11) is a derivative of camptothecin, which is decarboxylated or metabolized to its active metabolite, 7-Ethyl-10- hydroxycamptothecin (SN-38), in the hepatic system. The SN-38 exerts its pharmacological activity against tumor cells by blocking the DNA opoisomerase-I enzyme, thereby declining the rate of DNA transcription and replication. Irinotecan finds its utility as a therapeutic agent for metastatic colorectal carcinoma and also in several cancers localized in the lung, cervix, and stomach. However, its clinical development and utility have been impeded by its chemical instability and poor aqueous solubility. In studies conducted by Ali et al., the SN-38 embedded cubosomes were combined with Phytantriol (PHYT), attributed to its chemical stability as an amphiphile and its ability to generate cubic lipid bilayers. Six α-monoglyceride additives (monostearin, monopalmitin, monomyristin, monolaurin, monocaprin, and monocaprylin) were incorporated by probe sonication to yield the PHYT-cubosomes. Additionally, its efficient drug delivery is correlated to the absence of ester linkages or unsaturated double bonds in its orientation. Furthermore, post the quantification, the zeta potential values, polydispersity index, and mean particle size, were estimated to be − 17 to − 22 mV, 0.19–0.25, and 190–230 nm respectively. Moreover, the Small-Angle X-ray scattering analyses revealed that the SN-38-encapsulated cubosomes occurred in Pn3m orientation, both without and with the additives. Additionally, incorporation of the mono-glyceride additives resulted in about a two-fold increment in the SN-38 solubility, in comparison to the PHYT-cubosomes. The drug entrapment efficiency of the PHYTcubosomes with additives was found to be more than 97% with about 55% of SN-38 being gradually released over 96 h in vitro under physiological conditions. Furthermore, the results of the stability studies conducted at 25 ◦C demonstrated no substantial alterations in the polydispersity index or particle size characteristics with a minimum of 85% SN-38 existing in its lactone form post 10 days, exhibiting the high stability of the cubosomal nanocarriers. Recent developments unravel that the PHYT-cubosomes consisting of ionic amphiphilic additives like, cationic di-dodecyl dimethylammonium bromide (DDAB) led to an increment in the solubility and stability of SN-38 [56]. Conclusively, these results indicate that the SN-38-encapsulated-PHYT-cubosomes (with and without additives) could prove to be a

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promising drug carrier for clinical use, following clinical trials, as a novel drug delivery model to deliver drugs to the neoplastic cells, owing to its retention effect and permeability.

G. Curcumin

Curcumin (diferuloylmethane), a drug of herbal origin, primarily isolated from Curcuma longa L., is a polyphenolic compound showing a multitude of pharmacological activities, of which the most acclaimed ones include anticarcinogenic, antidiabetic, anti-inflammatory, antioxidant, hepatoprotective, nephroprotective, myocardial infarction protective, thrombosis suppressing, antirheumatic, and hypoglycemic effects. Additionally, the zeta potential quantification of curcuminloaded nano-cubosomes was done using the SZ-100 nanoparticle analyzer [45]. The resulting zeta potential value of − 24 mV indicated that the formulation was stable, as there was enough charge present to prevent the aggregation of the cubosomes, owing to electric repulsion. Furthermore, the in vitro tests were performed via dialysis method, which demonstrated a rapid release of about 44.2 ± 2.7% of the drug over 24 h, followed by a sustained release of up to 81.3 ± 2.6% over the next 7 days [46]. A study by Chang et al. demonstrated the successful loading of curcumin on cubosomes made up of monoolein (MO), monopalmitolein (MP), and phytantriol (PT). Their studies have indicated a variation in entrapment efficiency and curcumin localization within the bilayer by altering the composition of the lipid used. Additionally, the PT-cubosomes demonstrated the highest entrapment efficiency, due to the deeper penetration of the curcumin molecule into the hydrophobic region of the lipid bilayer, and has been corroborated by the relatively lower maximum fluorescence emission wavelength. Curcumin cytotoxicity for B16F1 and NIH3T3 cell lines is significantly higher in cubosomal formulations, compared to DSPC-liposomes, or when freely solubilized in ethanol. Due to the synergistic impact of between PT and the loaded curcumin, the PT-cubosomes were found to be the most cytotoxic of all formulations, inducing apoptosis even at low concentrations. Furthermore, MO-cubosomes exhibited the greatest increase in cytotoxicity in the B16F1 cancer cell line (compared to the NIH3T3 cell line), suggesting potential utility in anti-cancer treatment modality [57].
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H. Etoposide

Etoposide (ETP) is a semisynthetic imitation of podophyllotoxin, a plant glycoside finding utility as a chemotherapeutic agent for lymphoma, leukemia, neuroblastoma, and cancers of the lung, testicles, and ovaries. Its anticancer property is exerted by the inhibition of the topoisomerase-2 enzyme which catalyzes the cleaving of the DNA, in turn arresting the cells in the G2 phase of the cell cycle. The studies conducted by Tian et al. synthesized folate-modified cubosomes containing Etoposide (ETP-Cubs-FA) as well as normal etoposide-loaded cubosomes (ETP-Cubs). These cubosomes were synthesized through bulk gel fragmentation under 1500 bar homogenization conditions and were studied to have a narrow size distribution with an average particle size of around 180 nm. Additionally, Glycerol Monooleate (GMO)-based cubosomes were loaded with Etoposide in adjunct with the P407-FA stabilizer. Moreover, embedding the cubosomal surface with P407-FA further initiates the active targeting of the tumor via the folatemediated pathway, which is attributed to the overexpression of folate receptors on the malignant cancer cells, thereby eliciting a targeted antitumor effect. Furthermore, the cytotoxic action of ETP-Cubs and the ETP-Cubs-FA were tested on the human breast adenocarcinoma cell line (MCF-7) in vitro, following which the antiproliferative action of free ETP was evaluated by the MTT assay. The in vitro release of ETP from the cubosomes was found to be about 82.5% post 36 h, exemplifying a sustained-release property, contrary to the administration of the free drug. This study demonstrated that the ETP-cubs-FA have a greater cytotoxic effect on MCF-7 as compared to free ETP and non-transformed ETP, owing to the active Folate targeting, as validated by in vivo Rhodamine B-based tumor imaging [59].

I. Methotrexate

Methotrexate (MTX), one of the oldest and highly efficacious anticancer drugs, belongs to the folate antagonists, a subclass of the antimetabolites class. MTX is widely used for the treatment of leukemia, lung, breast, head & neck, skin, and uterine cancers, as well as for the treatment of psoriasis, rheumatoid arthritis, and other autoimmune disorders.

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MTX works by competitively inhibiting the enzyme dihydrofolate reductase (DHFRase), which further blocks the conversion of dihydrofolic acid (DHFA) to tetrahydrofolic acid (THFA). THFA is a necessary component in the synthesis of thymidine, which is imperative in DNA synthesis. In a recent study conducted on methotrexate-loaded cubosomes (MTCs) by Janakiraman et al., different cubosomal formulations (MTCs 1 to MTCs 8) were formulated, each with different ratios of Poloxamer 188, cetyl palmitate, and water. The zeta potential values were quantified to be in a range of − 33.0 ± 0.21 mV to − 7.84 ± 0.03 mV, where the negative value indicates the stability and good dispersion qualities of the formulation. In comparison with free MTX release profiles, the in vitro studies observed that the cubosomes displayed an initial burst release of 80.4 ± 0.9% of the drug, lasting about 1.5 h, followed by a sustained release for up to 8 h, compared to the free MTX that demonstrated a release of only 7.2 ± 1.1% of the drug for up to 8 h [60]. 5.12. Bedaquiline Non-small cell lung cancer (NSCLC) is considered the leading cause of cancer deaths worldwide and thus has piqued the interest of scientists [60]. Furthermore, with increasing resistance to traditionally administered anti-cancer therapies and severe systemic toxicities associated with emerging treatment modalities, novel medications and delivery technologies are considered the need of the hour to provide safe and effective treatment results [61]. Bedaquiline (BQ) is an FDA-approved anti-mycobacterial drug, that has been repurposed and formulated as a potential anti-cancer medicament in patients with NSCLC [61]. A study conducted by Patil et al. demonstrated the synthesis and loading of inhalable BQ-loaded cubosomes (BQLC) against NSCLC, using the solvent evaporation approach. These BQLCs had a particle size of 150 ± 5.1 nm, with 51.85 ± 4.83% encapsulation efficiency and a zeta potential of (+) 35.4 ± 2.3 mV. The solid-state characterization tests like differential scanning calorimetry (DSC) and X-Ray diffraction (XRD) established drug encapsulation in an amorphous form within these nanoparticles. Post the nebulization, the BQLC also demonstrated good aerodynamic properties. Additionally, after 48 h of administration, the BQLC showed improved cytotoxic effects and cellular internalization, with a concurrent 3-fold IC50 lowering, than free BQ in NSCLC (A549) cell line [62]. Thus, these studies underscore the potential of drugloaded cubosomes over conventional therapy in achieving a better and safer therapeutic outcome. Table 1 elucidates more studies that include various anticancer drugs that have been loaded onto the cubosomal nanoparticles: (See Figs. 1–3.) Additionally, Table 2 gives a brief about the various parameters that have been quantified for the anticancer drug-loaded cubosomes:

Utility of cubosomes in theranostic applications Theranostics being a portmanteau of therapeutics and diagnostics [64], aims to clinically develop agents or carriers for efficient diagnosis and therapy, facilitating improved prognoses of diseases, like cancer [65]. Cancer theranostics refers to a combinatorial therapeutic-cumdiagnostic approach in treating cancer that aims to reduce treatment delay, thereby easing patient care, especially in personalized cancer therapy [66]. The LCNs, especially cubosomes, bear numerous traits, particularly the ease of surface functionalization with imaging and targeting moieties. Furthermore, the viscosity of cubosomes is comparable to that of water, which is imperative for intravenous administration, dual-loading with imaging agents or drugs, and surface functionalization of several cancer-specific targeting moieties [67]. For instance, a theranostic cancer nanomedicine employed monoolein-based cubosomes loaded with docetaxel, and were stabilized using Pluronic (PF108), Rhodamine-conjugated PF108, and Folate-conjugated PF108 which further imparted imaging, targeting, and therapeutic capabilities. These docetaxel-loaded cubosomes demonstrated potent cytotoxic effects, by inducing cell toxicity in the Human Adenocarcinoma (HeLa) cell line. Additionally, the comparison of hydrophobicity and surface area of the cubosomes with multilamellar liposomes unravelled that despite 60% of the cubosomal surface being exposed to water, the hydrophobic volume of its nanostructure was 3 times greater than that of the single-bilayer liposomes, but gains equivalence when the liposomal bilayers increase (like, multilamellar liposomes). Alternatively, monoolein-based docetaxel-loaded cubosomes coated with a cancer celltargeting ligand and an imaging probe were acclaimed for their cancer theranostic potential. These docetaxel-loaded cubosomes demonstrated substantial cytotoxic effects against HeLa cells (greater than 1 order of magnitude higher compared to the molecularly dispersed drugs). Therefore, these studies indicate the utility of cubosomes as a promising

4.9 Utility of Cubosomes in Theranostic Applications

Theranostics being a portmanteau of therapeutics and diagnostics [68], aims to clinically develop agents or carriers for efficient diagnosis and therapy, facilitating improved prognoses of diseases, like cancer [69]. Cancer theranostics refers to a combinatorial therapeutic-cumdiagnostic approach in treating cancer that aims to reduce treatment delay, thereby

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Sr	Polymer used	Active ingredient	method of preparation	Application /utility
1	Monoolein (MO), PoloXamer 407 (PF127)	20 (*S*)-protopanaxadiol, Piperine	Melting Hydration Vortex miXing	Drug Delivery
2	Monoolein (MO), PoloXamer 407 (PF127), Folic acid	3-bromopyruvate	Injection method combined with high-pressure homogenization	Tumor Targeted Delivery
3	Monoolein (MO), PoloXamer 407 (PF127)	Berberine hydrochloride	Emulsification method	Drug Delivery
4	Squarain-based NIR-emitting fluorescent probe, Pluronic F108 (PF108), Monoolein	Camptothecin	Ultrasonic processing	Theranostic and Bioimaging
5	Monoolein (MO), Polyethylene Glycol (PEG), ethoXy unit	Carboplatin	Heating Vortex miXing Centrifugation Spread	Drug Delivery
6	Monoolein (MO), PoloXamer 407 (PF127)	Cisplatin-Metformin	Emulsification technique	Tumor Targeted Delivery
7	Polyethylene glycol 400 (PEG-400), RH40, and Monoolein (MO)	Curcumin	Vortex mixing Sonication	Anticancer activity
8	Monolinolein, Pyridinylmethyl linoleate	DoXorubicin (DOX)	Hydration Heating	Tumor Targeted Delivery
9	Monoolein (MO), Phytantriol	DoXorubicin (DOX)	Melting Hydration	Drug Delivery
10	Monoolein (MO), N-Oleoyl glycine N-(2- aminoethyl)-oleamide	DoXorubicin (DOX)	Melting Hydration Centrifugation	Drug Delivery
11	Monoolein (MO), MES sodium salt, PoloXamer 407 (PF127)	DoXorubicin (DOX)	Melting Desiccation of DoX sol with molten MO Hydration	Drug Delivery

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12	Monoolein (MO)	DoXorubicin (DOX) and Brucea javanica oil	High-Pressure homogenizer	Dual drug delivery
13	Monoolein (MO)	Gambogenic acid	Lipid recrystallization of homogeneous	Drug delivery in cancer therapy

Table 1: The various drugs loaded onto cubosomes for anticancer theranostics and drug delivery

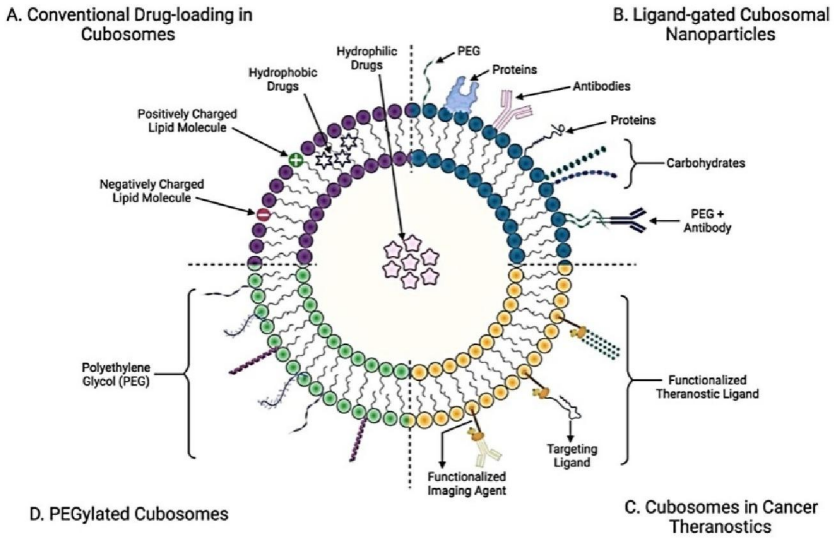

Fig. 1. Graphical abstract on the various utilities of cubosomes in the treatment and theranostics of various cancers.

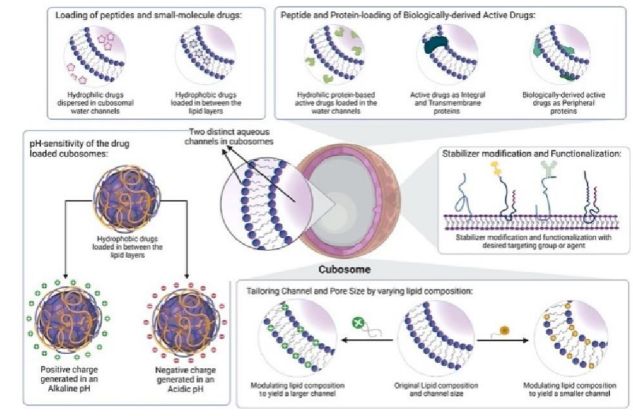

Fig. 2. Various properties in the designing and modulation of cubosomes for the treatment and theranostics of various cancers.

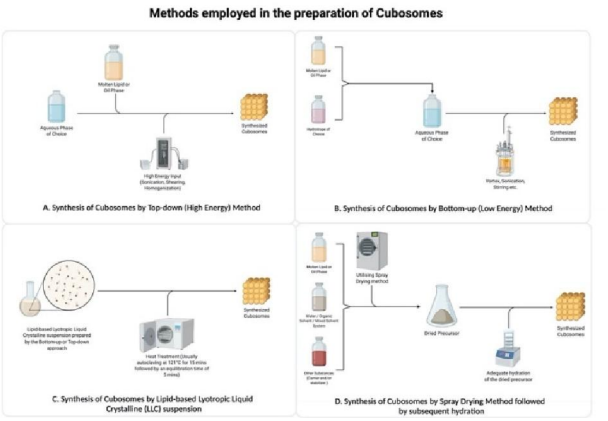

Fig. 3. Various methods utilized in preparation of cubosomal nanoparticles.

V. CONCLUSION

Cubosomes have emerged as a promising drug delivery system for the treatment of cancer. The unique structure and properties of cubosomes make them a versatile and effective tool for targeted drug delivery, enabling high drug loading and sustained release. Various studies have shown the potential of cubosomes in delivering chemotherapeutic agents, peptides, and nucleic acids to cancer cells, with reduced toxicity to healthy tissues. However, further research is needed

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to optimize the structure and increase drug loading efficiency of cubosomes. Additionally, there is a need to improve the specificity of cubosomes towards cancer cells to minimize off-target effects. The use of cubosomes in combination therapy is also an exciting avenue of research, with the potential to enhance the efficacy of cancer treatment by combining multiple drugs within a single nanoparticle. In the future, it is expected that cubosomes will play an increasingly important role in cancer treatment. The development of more advanced cubosomes, including those incorporating stimuli-responsive materials, will allow for even greater control over drug release and targeting. With continued research and development, cubosomes have the potential to become a mainstay in cancer treatment, providing patients with more effective and less toxic therapies.

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