e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:06/Issue:04/April-2024 Impact Factor- 7.868 www.irjmets.com

CUBOSOMES: A UNIQUE DRUG DELIVERY SYSTEM

Mr. Sahil Chandulal Shaikh[*1], Mr. Gaurav Fulchand Nikam[*2], Ms Sana Fakir Sayyad[*3], Ms Sakshi Chandrakant Paygude[*4], Ms Vaishnavi Baliba Jagtap[*5], Ms Saniya Rafik Tamboli[*6], Ms Anusha Echanur[*7]

[*1,2,3,4,5,6]Al-Ameen College's Education And Medical Foundation's Delight College Of Pharmacy, Koregaon Bhima, India.

[*7]Assistant Professor Delight College Of Pharmacy, Koregaon Bhima India.

Corresponding Author: Anusha Echanur

ABSTRACT

Experimenters are interested in lipid- grounded medicine- delivery nanoparticles because of their eventuality for controlled and targeted release of biopharmaceutical medicines. These includenon-lamellar-type, mesophasic nanostructured accoutrements of lyotropic liquid chargers (LLCs). Cubosomes are tone- assembled boxy- phasebi-continuous crystalline nanoparticulate colloidal dissipations that are produced from LLCs. Their lipid bilayers are piled in three confines, with two connected water channels dividing their nonstop, regular, boxy symmetrical face. They therefore have a significant advantage over lamellar liposomes in enabling the effective trapping and dragged release of active medicinal composites due to their enormous face area incorporating several interior parts. The application of cubosomes in cancer treatment and as a possible medicine delivery medium are the main motifs of this review.

Keywords: Cubosomes, Drug Delivery System, Nanoparticles, Lipid Based Drug Delivery.

I. INTRODUCTION

Because amphiphilic molecules self-assemble, they are crucial to drug delivery. abilities in specific circumstances, ultimately resulting in extremely well-organized structures capable of being a part of medication delivery systems. The hydrophobic effect of amphiphilic lipids can cause them to self-assemble into a variety of well-defined, thermodynamically stable structures, including lamellar (Lα), hexagonal (HII), and bicontinuous (QII) cubic phases. These systems are referred to as lyotropic liquid crystal (LLC) systems, and they all have an adequate average degree of molecular orientation and structural symmetry.

Cubosomes are unique nanovesicles of bicontinuous cubic structures that are created when liquid crystalline cubic aggregates are dissolved in aqueous fluids. They share the same microstructure and have a large surface area as their parent cubic aggregates. Usually, high-energy dispersion of the bulk cubic phase is used to form cubosomes, which are then stabilized colloidally with the use of polymeric surfactants. A potential use for cubic phase liquid crystals is the regulated discharge of certain compounds soluble in water and oil. Cubosomes, which are nanoparticle disperse systems with great biocompatibility and bioadhesivity, are produced when cubic lipid phases are emulsified in water. Lipids, surfactants, and polymer molecules that include both polar and non-polar constituents a combination known as amphiphilicity make up cubosomes. Cubosomes, then, are bicontinuous cubic liquid phases that surround two distinct water zones that are separated by bilayers that are regulated by surfactants.

Structure of Cubosomes

Cubosomes are characterized by a wide interfacial area and honeycombed features that divide the two internal aqueous channels. Amphiphilic molecules create bicontinuous oil and water channels. The term "bicontinuous" describes two independent hydrophilic zones that are continuous but do not intersect, kept apart by the bilayer. 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. The structure's interconnectivity produces a transparent, viscous gel with a rheological and visual similarity to cross-linked polymer hydrogels.

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:06/Issue:04/April-2024 Impact Factor- 7.868 www.irjmets.com

Compared to hydrogels, monoglyceride-based cubic gels have longer range order, and their lipid and water composition provides superior biocompatibility.

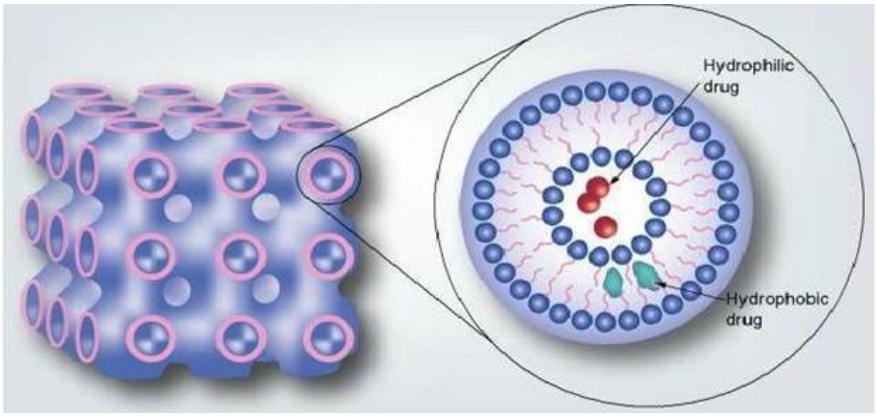

Figure 1: Cubosomes exhibiting its cavernous internal and cubic structure and its membrane composition with different drug loading modalities

Advantages and Disadvantages of Cubosomes

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 continuous release.
3. Biocompatibility and bioadhesivity are characteristics of cubosomes.
4. Even with excess of water, the bicontinuous cubic liquid crystalline phase of cubosomes remains stable.
5. Biologically compatible lipids and water can be combined to create cubic phase materials, which are ideal for treating skin, hair, and other human tissues.
6. Cubosomes have a greater breaking resistance and a bigger ratio between the bilayer area and particle volume than liposomes.
7. Their crystalline cubic shapes and large interior surface area allow them to carry large pharmacological payloads.
8. They are lipid biodegradable and have an easy technique of preparation.
9. Regulated and targeted release of bioactive substances.
10. When it comes to solubilizing, cubosomes outperform traditional lipid or non-lipid carriers.
11. Their drug carrier capacity is high for a variety of medicines that are only weakly soluble in water.
12. These work wonders in shielding the delicate medication from peptides and proteins that break down enzymatically and in vivo.
13. Water-soluble peptides' bioavailability range is increased twenty to over a hundred times by the cuboidal method.
14. Cubosomes' cubic phases can be broken up and dispersed to create particle dispersions that are thermodynamically and/or colloidally stable for extended periods of time.

Limitation of Cubosomes

1. Due to the potential for low drug loading efficiency and drug leakage during preparation, preservation, and in vivo transport, the primary issue with cubosome stability functions as a barrier, hence restricting the application of these systems.
2. The high viscosity can occasionally make large-scale production challenging.

II. APPLICATIONS OF CUBOSOMES

1. **Breast Cancer:** Leflunomide (LEF) loaded cubosomes were successfully created utilizing the emulsification process, according to Haidy Abbas et al., and their TEM pictures revealed a consistent cubic structure. The produced cubosomes exhibited a consistent particle size, a high entrapment efficiency, and a sustained release profile of LEF for a duration of 24 hours. In an ex-vivo skin examination, the chosen formulation had the maximum percentage of LEF penetrated and was constant for three months at 25°C. LEF cubosomes demonstrated greater cell uptake and drastically decreased cell survival in the MDA-MB-231 cell line when compared to LEF suspension, suggesting a possible use for these particles in the treatment of breast cancer.

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:06/Issue:04/April-2024 Impact Factor- 7.868 www.irjmets.com

2. **Glioblastoma Multiforme:** The AT101 medication, which is thought to be a viable treatment for glioblastoma multiforme but has low bioavailability and poor solubility in water-based medium, was successfully encapsulated into cubosomal nanoparticles made of glyceryl monooleate, according to a paper by Dorota K. Flak et al. Stable colloids with a high drug entrapment efficiency and continuous, sustained release of the drug were the GMOAT101 cubosome. By using NMR diffusometry, the effective binding of AT101 to the GMO cubosome was confirmed. GBM cells and 3D tumour spheroids efficiently incorporated the GMO-AT101 cubosome. Normal brain cells were not considerably impacted by AT101 encapsulated in cubosomes, but GBM cells were more susceptible to its in vitro cytotoxic effect, as indicated by the cytoskeletal actin fibers in treated GBM cells being rearranged.. A possible foundational instrument for attempts at alternative therapy for GBM is GMO-AT101 cubosomes.
3. **CD44-Positive Cancer Cells:**According to Arindam Pramanik et al., a formulation of clickable cubosome nanoparticles based on monoolein with an Im3m space group-related internal nanostructure has been disclosed. The clickable chemistry has the benefit of being easily functionalized with any ligand, especially for applications that target cancer. This is the first report of hyaluronic acid-tagged cubosomes that target CD44-expressing cancer cells utilizing copper free click chemistry. We use 3D tumor spheroid models and monolayer cell culture to demonstrate this targeting and specificity. When administered via this targeted nanocarrier, the model medication employed in this work, copper acetylacetonate, successfully killed cancer cells, at least partially by causing apoptosis. Some teams have been successful in encasing various cancer medications into corresponding cubosome formulations; methotrexate, SN38, and paclitaxel are a few examples. As such, we anticipate that our targeting methodology will be widely applicable. The nano formulation is harmless to normal tissues, as our initial in vivo investigation has demonstrated. Since there aren't many published targeted drug delivery studies in the field of cancer that use cubosomes, this work offers a significant advancement with potential clinical utility.
4. **Cubosomes containing 5-fluorouracil used in hepatocellular carcinoma:** Water-soluble fluorinated pyrimidine analog 5-fluorouracil (5-FU) is a commonly used antineoplastic drug in conjunction with or alone in chemotherapy regimens for the treatment of advanced gastrointestinal malignancies, such as hepatocellular carcinoma. However, the hematologic adverse effects, severe bone marrow abnormalities, and gastrointestinal toxicity of 5-FU limit its clinical use. Additionally, due to the drug's rapid metabolism in the body and short plasma half-life (10–20 min), ongoing high dose administration is necessary to maintain a therapeutic blood concentration. 5-FU can have serious adverse effects at elevated plasma levels, and the drug's antitumor effects are dependent more on exposure time than plasma concentration. According to earlier research, 5-FU6-8 formulations with prolonged release and targeted distribution to the tumor site enhance 5-FU's anticancer efficacy while lowering its negative effects as compared to the 5-FU formulation that is already on the market.
5. **Treatment of melanoma:** By creating doxorubicin (DOX) and ICG co-loaded cubosomes (DOX-ICG-cubo), a transdermal delivery system for chemo-photothermal combination therapy of melanoma was established in the study. DOX served as a chemotherapeutic agent model. To the best of our knowledge, this is the first study on topical application of cubosome-based combination therapy for melanoma. It is expected that the transdermal delivery system that was created will enhance melanoma therapy efficaciously in several ways. First, compared to free ICG solution, amphiphilic ICG encapsulated in cubosomes can improve photo and plasma stability, increasing the photothermal effect on melanoma. Second, by using a pH gradient technique, hydrophilic DOX can be efficiently encapsulated within the hydrophilic region of the cubosomes, minimizing skin irritation brought on by direct contact with the skin and facilitating DOX's penetration into the skin's deeper layers to reach the tumor site. Additionally, a promising method for increasing local drug concentrations, lowering systemic toxicities, and enhancing drug efficacy and bioavailability—all of which contribute to a greater treatment response—is the transdermal delivery of chemotherapeutic agents. Not to mention, there is a strong chance that photothermal therapy and chemotherapy will work in concert to improve the therapeutic result of melanoma treatment. For the treatment of melanoma, DOX-ICG-cubo is a potential drug delivery system.
6. **Treatment of Ovarian Cancer Cell:** According to research done by Zhai et al., mono-olein (MO)-based cubosomes may be used as a vehicle for PTX for treating ovarian cancer. Furthermore, these nanoparticles

help overcome solubility problems by virtue of their encapsulation inside a nanocarrier, enabling PTX loadings of up to 10 weight percent of MO. Moreover, bioconjugating fragments of the Epidermal Growth Factor Receptor (EGFR) antibody to the surfaces of the nanoparticles enabled the active targeting of the cancer cells. When compared to free PTX, these nanoparticles showed increased in vitro cytotoxic activity against Human Ovarian Cancer Cell Line (HEY). Further investigation revealed that the mice given the same dose (5 mg/kg of body weight) of free PTX had tumors twice as large as those given the drug loaded into cubosomes, suggesting that the lipid nanoparticles had no effect on the viability of HEY cells at the effective concentration. This suggests an enhanced anticancer activity attributed to the integration of PTX in the nanocarriers.. A weekly intraperitoneal injection of EGFR-PTX-Cubosomes and PTX-Cubosomes significantly decreased tumor burden in HEY-derived ovarian cancer animal models, improving in vivo survival. These findings highlight the medication's inclusion at metronomic levels in a cubosome-based drug delivery system as a potentially effective therapeutic strategy for patients with end-stage ovarian cancer. In conclusion, the drug delivery methods based on cubosomes loaded with PTX have the capacity to prolong the duration of disease-free progression and increase overall survival chances in advanced stages of different types of cancer.

7. **Treatment of leukemia:** One of the most well-known and effective anticancer medications is methotrexate (MTX), which is a member of the folate antagonists subclass of the antimetabolites class. In addition to treating psoriasis, rheumatoid arthritis, and other autoimmune diseases, MTX is frequently used to treat leukemia, lung, breast, head & neck, skin, and uterine malignancies. Dihydrofolate reductase (DHFRase) is an enzyme that MTX competitively inhibits, preventing dihydrofolic acid (DHFA) from being converted to tetrahydrofolic acid (THFA). Thymidine synthesis is essential to DNA synthesis, and THFA is a component of that process. A study by Janakiraman et al. recently examined methotrexate-loaded cubosomes (MTCs). Several cubosomal formulations (MTCs 1 to MTCs 8) were created, each with a unique ratio of cetyl palmitate, Poloxamer 188, and water. The zeta potential values were measured and found to be between -33.0 ± 0.21 mV and -7.84 ± 0.03 mV; the formulation's good dispersion and stability are shown by the negative value. The formulation was detected in the in vitro investigations in comparison with free MTX release profiles. When the in vitro studies compared the cubosomes' release profiles to those of free MTX, they found that the former showed a release of only 7.2 ± 1.1% of the drug for up to 8 hours, while the latter showed an initial burst release of 80-4 ± 0.9% of the drug, lasting about 1.5 hours.
8. **Anti-cancer medicament in patients with NSCLC:** Scientists are interested in non-small cell lung cancer (NSCLC) since it is thought to be the primary cause of cancer-related fatalities globally. Additionally, new drugs and delivery methods are thought to be essential for achieving safe and efficient treatment outcomes in light of the growing resistance to conventionally administered anti-cancer medicines and the serious systemic toxicities connected to cutting-edge treatment modalities. The FDA-approved anti-mycobacterial medication bedaquiline (BQ) has been repurposed and developed as a possible anti-cancer medication for use in patients with non-small cell lung cancer. Using the solvent evaporation method, Patil et al.'s study showed how to synthesize and load inhalable BQ-loaded cubosomes (BQLC) against NSCLC. These BQLCs had a zeta potential of (+) 35-4 ± 2.3 mV, a particle size of 150 ± 5.1 nm, and an encapsulation efficiency of 51.85 ± 4.83%. DSC and X-ray diffraction (XRD), two solid-state characterisation techniques, demonstrated that the drugs were encapsulated in these nanoparticles in an amorphous form. The BQLC also showed good aerodynamic qualities after nebulization. Furthermore, in the NSCLC (A549) cell line, the BQLC exhibited better cytotoxic effects and cellular internalization than free BQ after 48 hours of treatment, along with a simultaneous 3-fold IC50 decrease.These findings therefore highlight the advantages of medication-loaded cubosomes over traditional treatment in obtaining a better and safer therapeutic outcome.
9. **Human Hepatoma (HepG2) cell line:** The Human Hepatoma (HepG2) cell line was used in multiple experiments by Zhang et al. on uncoated and poly-e-coated cisplatin-loaded cubosomes. For additional characterisation, cubosome entrapment efficiency, zeta potential measurement, and in vitro release tests were carried out in conjunction with cytotoxicity investigations. The uncoated, coat, and blank cisplati cubosomes were found to have zeta potential values of -24.5 ± 0.3 mV, -22-4 ± 0-4 mV, and -2.8 ± 0.1 mV, respectively. The cubosomal surface undergoes complexation after coating, which is confirmed by a decrease in the coated cubosomes' zeta potential values. The uncoated model also showed an initial burst

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:06/Issue:04/April-2024 Impact Factor- 7.868 www.irjmets.com

release of 55 ± 3% in the in vitro release assays, followed by a gradual release after 6 hours and no release after 10 hours. On the other hand, the coated model showed just 23 ± 3% initial release and a sluggish but continuous release over approximately 25 hours. Moreover, the results of the cytotoxicity tests showed that the HepG2 cells were considerably more susceptible to the free cisplatin than to the cubosome-loaded version.. The uncoated models showed lower cell survival and more cytotoxicity than the coated versions because of their strong initial burst release. These investigations conclude that the coating inhibits the large-scale release of the drug in a burst, as seen by the coated cubosomes' nearly identical cell survival to that of the blank cubosomes

10. **Anti-cancer treatment modality:** Curcumin was successfully loaded onto cubosomes composed of phytantriol (PT), monoolein (MO), and monopalmitolein (MP), according to a study by Chang et al. By changing the lipid's composition, their research has shown differences in entrapment efficacy and curcumin localization inside the bilayer. Furthermore, the PT-cubosomes showed the best entrapment efficiency, which was supported by the comparatively lower maximum fluorescence emission wavelength. This was caused by the curcumin molecule penetrating deeper into the hydrophobic portion of the lipid bilayer. When curcumin is freely dissolved in ethanol or in cubosomal formulations as opposed to DSPC-liposomes, it exhibits much more cytotoxicity for the B16F1 and NIH3T3 cell lines. The PT-cubosomes were discovered to be the most lethal of all formulations, triggering apoptosis even at low concentrations, because of the synergistic effect of PT and the loaded curcumin. Additionally, compared to the NIH3T3 cell line, MO-cubosomes showed the largest increase in cytotoxicity in the B16F1 cancer cell line, indicating possible use as an anti-cancer therapeutic mechanism.
11. **Chemotherapeutic agent for neuroblastoma:** A semisynthetic derivative of podophyllotoxin, a plant glycoside, etoposide (ETP) is being used as a chemotherapeutic treatment for lung, testicular, and ovarian malignancies, leukemia, neuroblastoma, and lymphoma. Because it inhibits the enzyme topoisomerase-2, which catalyzes DNA cleavage and stops cells in the G2 phase of the cell cycle, it has anticancer properties. Tian et al. manufactured both regular etoposide-loaded cubosomes (ETP-Cubs) and folate-modified cubosomes carrying etoposide (ETP-Cubs-FA). These cubosomes, which had an average particle size of about 180 nm and a narrow size distribution, were discovered to have been created by bulk gel fragmentation at 1500 bar homogenization conditions. Furthermore, Etoposide was added to Glycerol Monooleate (GMO)-based cubosomes along with the P407-FA stabilizer. Furthermore, the active targeting of the tumor through the folate-mediated pathway is further triggered by embedding the cubosomal surface with P407-FA. This is explained by the upregulation of folate receptors on the malignant cancer cells, which results in a targeted anticancer impact. Moreover, the human breast cancer cell line (MCF-7) was used to examine the cytotoxic action of ETP-Cubs and ETP-Cubs-FA in vitro. The MTT assay was then used to assess the antiproliferative effect of free ETP. In contrast to the administration of the free medication, the in vitro release of ETP from the cubosomes was shown to be approximately 82.5% post 36 hours, demonstrating a sustained-release feature. As confirmed by in vivo Rhodamine B-based tumor imaging, our work showed that ETP-cubs-FA have a stronger cytotoxic effect on MCF-7 than free ETP and non-transformed ETP because of the active Folate targeting
12. **Improved oral bioavailability of anticancer drug:** Making use of cubosomes' special composition and characteristics to increase a medicine's oral bioavailability. Research has indicated that cubosomes boost the oral bioavailability of 2o(S) protopanaxadiol (PPD), an anticancer medication with poor oral absorption. This effect may be ascribed to cubosomes' bioadhesive qualities.
13. **Uses in oncology:** A unique monoolein-based cubosome was reported by Meli et al. for potential theranostic uses in oncology**.** To gain targeting, therapeutic, and imaging properties, rhodamine- and folate-conjugated Pluronic® F 108 was used to stabilize the docetaxel-loaded nanoparticles in water. The nanoparticles had a strong short-term (4-hour incubation) cytotoxic effect against the cancer cells and were successfully employed to photograph living HeLa cells.
14. **Controlled release of drugs:** A variety of medications with various physicochemical characteristics have been added to cubosomes, and the behavior of their prolonged drug release has also been investigated. Particles called cubosome remnants were responsible for the cubosomes' sustained behavior. For topical administration, such as mucosal or percutaneous, monoglyceride-based cubosomes have been suggested.

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:06/Issue:04/April-2024 Impact Factor- 7.868 www.irjmets.com

15. **Polytherapy based approach to combat antimicrobial resistance using cubosomes:** According to Hsien-Yi Hsu et al. An increasing number of Gram-negative "superbugs" and a depleted antimicrobial medication pipeline have raised interest in nanotherapies as a means of treating antibiotic resistance. We here investigate the antimicrobial activity of polymyxin-loaded cubosomes and investigate an alternative approach via the polytherapy treatment of pathogens with cubosomes in combination with polymyxin. Both cubosomes and polymyxins disrupt the outer membrane of Gram-negative bacteria via distinct mechanisms. Comparing the polytherapy treatment to either polymyxin B-loaded cubosomes or polymyxin and cubosomes alone, there is a significant increase in antibacterial activity. Two steps appear to be involved in achieving the better polytherapy action, according to confocal microscopy and neutron reflectometry. First, the outer membrane is first made unstable by polymyxin and lipid A's electrostatic interactions. The membrane is then further disrupted by an inflow of cubosomes through a lipid exchange mechanism.These results suggest that nanoparticle-based polytherapy treatments could be superior than the current practice of treating "superbugs" with drug-loaded lipid nanopart
16. **AT101-Loaded Cubosomes as an Alternative for Improved Glioblastoma Therapy:** Flak et al.'s findingsAT101, the R-(-)-enantiomer of the polyphenol gossypol produced from cottonseed, is a promising medication for the treatment of glioblastoma multiforme (GBM) since it can both induce autophagic cell death and help tumor cells undergo apoptosis. It does have several drawbacks, like a reduced bioavailability due to its poor solubility in water-based media, which lowers its response rate during therapy. In order to address this limitation and enhance AT101's anti-tumor potential, the application of a cubosome-based formulation for AT101 drug delivery has been suggested. This is the first study on the application of cubosomes in GBM cells as drug carriers for AT101.
17. **Cubosomes for topical delivery of the antimicrobial peptide LL-37:-** The application of cubosomes for topical administration of the antimicrobial peptide (AMP) LL-37 was studied by Lukas Boge et al. The application of AMPs topically is a promising therapeutic approach for bacterial skin infections, as those caused by Staphylococcus aureus. Cubosomes containing AMP were prepared using three distinct methods, which were then compared: i) pre-loading, in which LL-37 was added to a liquid crystalline gel and then dispersed into nanoparticles; ii) post-loading, in which LL-37 was allowed to adhere to pre-formed cubosomes; and iii) hydrotrope-loading, in which LL-37 was added to spontaneously formed cubosomes in a mixture of ethanol and glycerol monooleate. Using dynamic light scattering (DLS), small angle x-ray scattering (SAXS) to investigate liquid crystalline structure, and a fluorescamine test to measure LL-37 release, the size and distribution of the particles were examined. Investigations were conducted on the proteolytic defense of LL-37 and the bactericidal effect upon enzyme exposure. Using an in vitro epidermis model, cubosomes' propensity to cause skin irritation was investigated. The ability of the cubosomes to destroy germs was finally tested using an ex vivo Staphylococcus aureus skin wound infection model. Data indicated that when cubosomes were prepared by sonication (pre-loading), a high loading of LL-37 stimulated the production of vesicles. Strong peptide-particle interaction is indicated by the absence of LL-37 release from the cubosomes. Proteolysis investigations demonstrated that LL-37 was completely shielded from enzymatic assaults when it was linked to the cubosomes, indicating a strong peptide-particle bond. Consequently, the bactericidal action persisted following enzyme exposure in contrast to pure LL-37 that underwent proteolysis. The cubosomes' inability to cause skin irritation allowed for topical application. According to the ex vivo wound infection model, LL-37 in pre-loaded cubosomes was the most effective way to kill bacteria.
18. **Cubosomes for ophthalmic delivery of flurbiprofen:** The purpose of this work was to develop a novel cubosome-based ophthalmic delivery system for FB that would enhance bioavailability and lessen ocular irritation. Atomic force microscopy (AFM) and cryo-TEM were used to evaluate the morphological characteristics of cubosomes. Using a dynamic dialysis technique, the in vitro release patterns of FB cubosomes were examined, and an in vitro study was conducted to examine the corneal penetration of the created vehicle. The Draize method was used to measure eye discomfort, and histological analysis was used to determine any potential injury to the ocular tissues. Finally, research was done on FB's in vivo bioavailability.

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:06/Issue:04/April-2024 Impact Factor- 7.868 www.irjmets.com

19. **Cubosomes for Parenteral Drug Delivery** Since they exhibit a distinct solubilization, good encapsulation, prolonged release behavior, and in vivo stabilization, cubosomes have been created as appealing drug release platforms. Furthermore, cubosomes retain their controlled release characteristic while having a lower viscosity than the liquid crystalline phase. Cervin showed that when somatostatin cubosomes were intravenously injected into rats, their terminal half-life was significantly longer than six times longer than that of the corresponding somatostatin solution. Moreover, because of its excellent syringeability and minimal solvent consumption during preparation, cubosomes are a desirable alternative to standard microspheres and implants. However, some studies claimed that self-assembled monoglyceride and genetically modified organisms (GMOs) could cause hemolysis in vivo when administered intravenously; as a result, parenteral delivery of cubosome-based drug delivery systems was limited.
20. **Intravenous drug delivery systems:** Lipid nanoparticles having liquid crystal formations inside curved lipid membranes are utilized to encapsulate, solubilize, and transport drugs to illness sites inside the body. Liquid crystal nanoparticle shapes boosted payloads of peptides, proteins, and many insoluble small molecules, making them suitable carriers for injection or infusion of numerous actives, whereas emulsions and liposomes have found usage as intravenous carriers in therapeutic products.
21. **Oral drug delivery:** Cubosomes provide a solution to the many problems associated with the oral delivery of many promising medicines, such as high molecular size, poor absorption, and poor aqueous solubility. These products, which use our self-emulsifying liquid crystalline nanoparticles technology (LCNP), come in liquid and powder forms within capsules. Large proteins have been encapsulated for local action in the gastrointestinal tract in an alternate use. Targeting and controlled release capabilities can be added to liquid crystalline nanoparticle technology carriers. The medicine can be distributed effectively in vivo thanks to the particles' ability to develop in situ at a regulated rate. Technology carriers for liquid crystalline nanoparticles can also be delivered at various absorption sites, such as the upper or lower intestine, which is crucial for medications with a limited window for regional absorption.

III. 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 utilized 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.

IV. REFERENCES

[1] Rohit R. Bhosale, Riyaz Ali Osmani, Bhargav R. Harkare, Prasanna P. Ghodake. Cubosomes: The Inimitable Nanoparticulate Drug Carriers. Scholars Academic Journal of Pharmacy (SAJP). 2013; 2(6):481-486.

[2] Sherif A. Gaballa, Omar H. El Garhy, Hamdy Abdelkader. Cubosomes: composition, preparation, and drug delivery applications. Journal of Advanced Biomedical and Pharmaceutical Sciences 2020; 3:1-9.

[3] Zahra Karami and Mehrdad Hamidi. Cubosomes: remarkable drug delivery potential. Drug Discovery Today, Elsevier. 2016:1-38.

[4] Dhadwal Avantika, Sharma Dev Raj, Pandit Vinay et al. Cubosomes: A Novel Carrier for Transdermal Drug Delivery. Journal of Drug Delivery & Therapeutics. 2020; 10(1):123-130.

[5] Mariam Zewali, Passent M.E Gaafar, Mai M Ali, Haidy Abbas. Lipidic cubic phase leflunomide nanoparticles (Cubosomes) as a potential tool for breast cancer management. Drug Delivery, Taylor and Francis. 2022;29(1):1663-1674.

[6] Dorota K Flak, Vivian Adamski, Grzegorz Nowaczyk et al., AT101-Loaded Cubosomes as an Alternative for Improved Glioblastoma Therapy. International Journal of Nanomedicine. 2020:15; 7415–7431.

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:06/Issue:04/April-2024 Impact Factor- 7.868 www.irjmets.com

[7] Arindam Pramanik, Zexi Xu, Nicola Ingram et al., Hyaluronic-Acid-Tagged Cubosomes Deliver Cytotoxics Specifically to CD44-Positive Cancer Cells. Mol. Pharmaceutics.2022:19(12); 4601–4611.
[8] Rarokar NR, Khedekar PB. Cubosomes: a vehicle for delivery of various therapeutic agents. MOJ Toxicol. 2018; 4:19–21.
[9] Bei D, Meng J, Youan BB. Engineering nanomedicines for improved melanoma therapy: progress and promises: Nanomedicine. 2010;:1385-99.
[10] U.S. Food and Drug Administration (FDA). Inactive Ingredient Search for Approved Drug Products. [cited 2018 2018-10-11];
[11] Voss V, Senft C, Lang V, et al. The Pan-Bcl-2 Inhibitor (-)-gossypol triggers autophagic cell death in malignant glioma. Mol Cancer Res. 2010;8(7):1002–1016. doi:10.1158/1541-7786.MCR-09-0562
[12] Nilsson C, Østergaard J, Larsen SW, Larsen C, Urtti A, Yaghmur A. PEGylation of Phytantriol-Based Lyotropic Liquid Crystalline Particles. The Effect of Lipid Composition, PEG Chain Length, and Temperature on the Internal Nanostructure. Langmuir. 2014;30:6398-407.
[13] Cervin C, Vandoolaeghe P, Nistor C, Tiberg F, Johnsson M. A combined in vitro and in vivo study on the interactions between somatostatin and lipid-based liquid crystalline drug carriers and bilayers. Eur J Pharm Sci 2009; 36: 377-85.
[14] Ueno H, Okada S, Okusaka T. Ikeda M, Kuriyama H. Phase I and pharmacokinetic study of 5- fluorouracil administered by 5-day continuous infusion in patients with hepatocellular carcinoma. Cancer Chemother Pharmacol 2002:49:155-60.
[15] Sagnella S and Drummond C. (2012). Drug delivery a nanomedicine approach. Australian Biochemist. (43), 5-7.
[16] E. Nazaruk, A. Majkowska-Pilip, R. Bilewicz, Chem PlusChem 2017,82,570- 575.
[17] J. Zhai, R.B. Luwor, N. Ahmed, R. Escalona, F.H. Tan, C. Fong, et al. ACS Appl. Mater. Interfaces, 10 (30) (2018 Jul 2), pp. 25174-25185.
[18] G. Liu, F. Pei, F. Yang, L. Li, A. Amin, S. Liu, et al. Int. J. Mol. Sci., 18 (2) (2017 Feb 10), p. 20367
[19] Z. Zhang, L. Zhou, N. Xie, E.C. Nice, T. Zhang, Y. Cui, et al. Ther., 5 (1) (2020 Jul 2)
[20] V. Parvathaneni, R.S. Elbatanony, M. Goyal, T. Chavan, N. Vega, S. Kolluru, et al. Int. J. Mol. Sci., 22 (9) (2021 Apr 30), p. 4783
[21] L. Zhang, J. Li, D. Tian, L. Sun, X. Wang, M. Tian, 11 (1) (2020 Jan), 10.1038/s41419-019-2182-024.
[22] M.A. Ali, S. Noguchi, Y. Iwao, T. Oka, S. Itai Chem. Pharm. Bull, 64 (6) (2016), pp. 577-584
[23] C. Chang, T.G. Meikle, C.J. Drummond, Y. Yang, C.E. Conn Soft Matter, 17 (12) (2021), pp. 3306-3313
[24] Y. Tian, J. Li, J. Zhu, N. Zhu, H. Zhang, L. Liang, et al. Med. Sci. Monit., 23 (2017 May 22), pp. 2426-2435
[25] U.A. Fahmy, 0. Fahmy, N.A. Alhakamy Pharmaceutics, 13 (1) (2020 Dec 24), p.20
[26] Meli. fluorescent V. et al (2015) Docetaxel-loaded nanoparticles for cancer theranostics. Langmuir 31,9566-9575
[27] Jin, X., et al., A nanostructured liquid crystalline formulation of 20 (S) protopanaxadiol with improved oral absorption. Fitoterapia, 2013. 84: p. 64-71