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Cubosomal Gel: A Vesicular Drug Delivery System for Topical Application

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ABSTRACT:

Novel Drug Delivery Systems (NDDS) are advanced approaches developed to improve therapeutic efficacy and drug bioavailability while minimizing side effects. Among these systems, cubosomes have gained significant attention as nanostructured vesicular carriers formed from amphiphilic lipids arranged in bicontinuous cubic phases. Their unique honeycomb-like structure contains interconnected aqueous channels and lipid bilayers, enabling the encapsulation of hydrophilic, lipophilic, and amphiphilic drugs. Cubosomes offer advantages such as high drug-loading capacity, biocompatibility, bio adhesion, and controlled drug release. They are widely investigated for oral, topical, transdermal, nasal, ocular, and parenteral drug delivery. Incorporation of cubosomes into gel formulations further enhances viscosity, skin retention, and ease of application. Cubosomal gels are especially promising for topical and transdermal delivery due to their ability to provide sustained and site-specific drug release. These systems also improve drug permeation through the skin and reduce systemic adverse effects. In addition, cubosomal gels exhibit excellent stability and tissue compatibility. Therefore, cubosomal gels represent a promising advancement in modern pharmaceutical drug delivery systems.

Keywords: Cubosome, Bicontinuous cubic phase, Self- assembled nanoparticle, Novel drug delivery system, Topical delivery, Lipid-based nanocarrier.

INTRODUCTION:

A drug delivery system represents the advanced specialized strategy that can be developed to transport therapeutic agent to targeted sites within the body. The Controlled release mechanisms are pre-designed and strategically developed to sustain optimal drug concentrations at the targeted therapeutic effect, minimizing adverse toxic effects meanwhile maximizing medicinal efficacy. Over time, drug delivery has undergone significant advancement, termed as Novel Drug Delivery Systems (NDDS). The novel drug delivery system emerging and growing trend in area of interest in modern pharmaceutical development which represents a major advance over conventional approaches by offering improvement in the therapeutic performance and overcoming the intrinsic limitations of traditional dosage forms such as low bioavailability, poor solubility, frequent dosing, short half-life, and non-specific distribution. The benefits of novel drug delivery system are multidimensional including the minimization of toxic and systemic side effects, drug preservation from acidic degradation in gastrointestinal tract, significant improvement in patient compliance. Current research suggests that NDDS shows considerable promise in the treatment of common disorders. In view of a wide range of delivery vehicles has designed over the preceding decade, and novel carriers are in the process of development in rapid rate. [1,2]

The vesicular drug delivery system (VDDS) one of the newly developed therapeutic delivery systems that achieves the location-specific drug delivery via holding drug within its vesicular matrix. [3] The vesicular drug delivery system represents well-organized structure that is precisely arranged by one or more concentric bilayer which can be generated through the self-organized of amphiphilic molecules in a water-based environment. [4] This system plays a significant role in the targeted drug delivery because they can promote the therapeutic concentration regarding medication at the target site and also its diminishing, minimizing drug exposure and potential toxicity in non-target tissues. [5]

The cubosome is also found to be a vesicular drug carrier system, which can be considered lipid-based colloidal system. Cubosome gaining significant consideration as a newly developed therapeutic delivery system. Cubosome serves as discrete, nanostructured, submicron nanocarrier of bicontinuous cubic liquid- crystalline arrangement. [6] cubosome looks like a honeycomb-like structure, dividing two water-filled channels along with a large interfacial surface. [7] Such new particles are used in the case of poorly water-soluble medicinal compounds. Cubosome are most probably consisting combination of polar and non-polar polymeric components, surfactants, lipids; that's why they called as amphiphilic. The amphiphilic molecules are naturally recognized and aggregate within

the nanometre-sized liquid crystal by hydrophobic interaction in a polar medium. The cubosome comprises structural feature of two continuous cubic phase system with two distinct aqueous channel that are separated by a bilayer and stabilized by the surfactant. [8] Cubosome are thermodynamically stable systems. The size of cubosome ranging from 10 to 500 nm. [9] So, they can provide regulated delivery of therapeutic agents, including anti-diabetics, local anaesthetics, anti-fungal, and anti-cancer medication. [10] The main goal of cubosome is to reduce unwanted effects and maximize the delivery of medication reaching the disease site so it can manage the drug loss and degradation. [11]

Conventional topical drug delivery system includes (creams, gels, ointments, etc.) often face challenges such as: poor retention, irritation, frequent dosing, reduced penetration, and diminished therapeutic efficacy. Cubosomes overcome these issues due to:

- Structural resemblance with stratum corneum → better penetration into skin layers
- High bio adhesion → prolonged drug retention in disease site.
- Prolonged and regulated drug release → improved therapeutic effect.
- Low toxicity, stability, and economical formulation → suitable for gel.[12]

Hence, this review aims to summarize the recent advances in cubosome-based drug delivery systems with special emphasis on their formulation approaches, characteristics, and therapeutic applications in topical and transdermal delivery.

ADVANTAGES OF CUBOSOME:

The cubosomal drug delivery system offers several advantages is as follows:

1. Cubosomes are non-toxic, non-allergic, biodegradable and biocompatible.

2. They feature a large inner surface area, which also contributes to a large drug loading capacity.

3. Cubosomes offers numerous advantages such as, increase in bioavailability, improving the solubility, promoting better dermal penetration, through these properties is considered as a cost-effective drug delivery.

4. It has excellent bio adhesive properties, the method of preparation of cubosome can be easy to perform.

5. Cubosomes acts as highly effective solubilizers, particularly when it is compared to conventional lipid-based carriers. They having an ability to encapsulating or hold drugs with very low water solubility and acts protective vehicle for sensitive drug molecules such as peptides and proteins. Additionally, they can enhance 20–100% of bioavailability of water-soluble peptides can be achieved.

6. It can increase the convenience and compliance; it boosts drug efficacy and also minimizes the risk of drug incorrect targeting or misuse. [13-17]

DISADVANTAGES OF CUBOSOME:

However, like any other drug delivery system, cubosome also have challenges is as follows:

1. Due to high viscosity of cubosome the large scaling up production is getting difficult.

2. Cubosomes containing high aqueous content resulting, lower loading of hydrophilic drug.

3. The use of specific polymer is necessary for the controlled drug delivery.

4. The phase could alter according to the changes in the external environment. [18-20]

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STRUCTURE OF CUBOSOME:

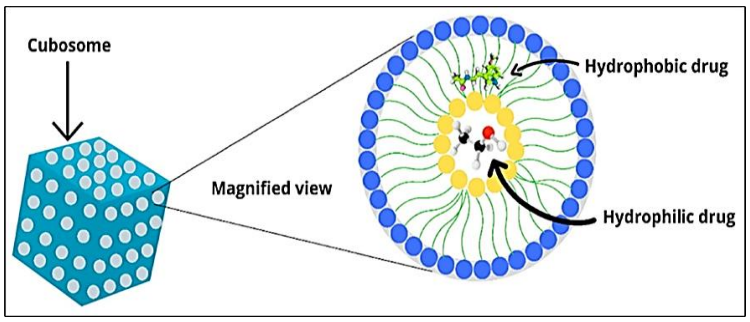

Figure no: 1 Structure of cubosome [21]

The bicontinuous cubic liquid crystalline nanostructure of cubosomes can enable the controlled and sustained release, where the tortuosity of the lipid layer and the aqueous nanochannel serve as a key factor. Cubosomes are stable in vitro, undergo lipolysis in vivo, and improve drug dissolution. They also possess good bio adhesive properties, making them suitable for gastrointestinal, nasal, pulmonary, buccal, rectal, vaginal and topical administration. Based on the principal of the differential geometry the open and closed structure of the cubosomes can be characterized. The open cubosomes consist of both aqueous channel and connecting the exterior environment, Whereas, the close cubosomes have only single aqueous-filled channel exposed to the outside and other remains enclosed. Three structural types of cubosomes have been reported such as Pn3m (Diamond), Ia3d (Gyroid), and Im3m (Primitive), in terms of nodal surface. This structure can help to maintain active ingredients functional efficacy and compound stability. Moreover, the cubosomes exhibits the remarkable thermodynamic stability, which helps preserves the integrity of structure and functional performance over the extended period. The stability of cubosomes can be arises due to their bicontinuous cubic liquid crystalline structure.[22]

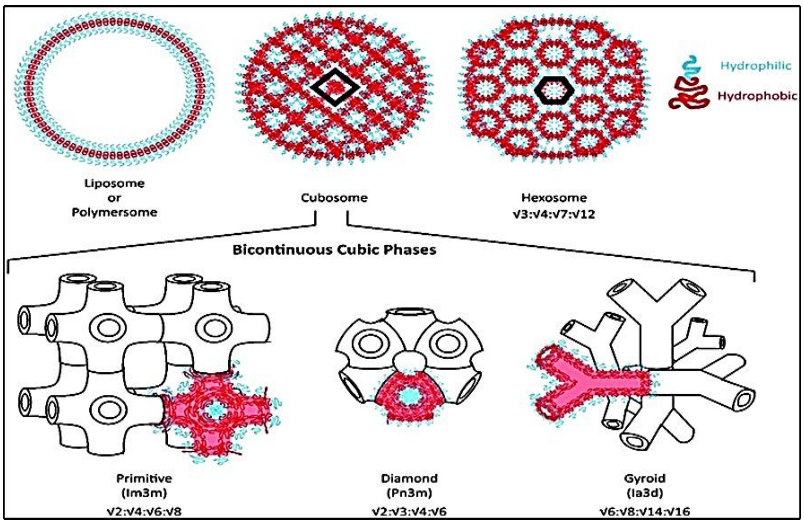

Figure no: 2 Types of structure of cubosome [23]

THEORIES OF CUBIC PHASE STRUCTURE:

Multiple theories have been introduced to describe the cubic-phase arrangement, is as follows:

1. Fontell & Drew Theory

2. Gustafson et al. Theory

3. Schwarz, Jacob & Anderson Theory

4. System Forming Theory

1] Fontell & Drew Theory:

Cubic phase is the unique liquid crystalline structure that are commonly observed in ternary system that can be composed of oil, water and amphiphiles especially with different monoglycerides. The monoglycerides are amphiphilic lipid with poor solubility in water, and it can exhibit aqueous phase characteristics which behaves surfactant-like properties typical of uncharged species. Lutton's studies demonstrate that monoglyceride having hydrocarbon chain length lying between C-12 to C-22, especially, glycerol monooleate it can exhibit the bicontinuous cubic liquid crystalline regions. Monoolein, identifies as C18 monoglyceride, it is classified as unsaturated lipid that has been commonly utilized in the preparation of cubic phase. [24,25]

2] Gustafson et al. Theory:

Cubosome having monocrystalline structure assembly characterized by the unilamellar vesicles which are embedded within dispersed layered liquid crystalline phase units facilitated to form bigger vesicular structure promoted by polymer-to-monoolein ratio is raised. The formation of highly viscous crystalline structure is occurred through slow transport processes, high energy is essential for outcome of fragmentation, generally generated by ultrasonication of bulk cubic phases yields vesicles. Gradually, these vesicles forms cubosome through membrane merging. This temporary stability can be key aspects of cubosomal system. Additionally, cubosome also stabilized by surrounding lipid vesicular bodies.

3] Schwarz, Jacob & Anderson Theory:

Uncharged Surfactant System, The Cubic-Phase are commonly observed between the layered and six-fold (hexagonal) arrangement of liquid- Crystalline Phases. The monoolein water system is exceptional for exhibiting a cubic phase area with various varieties of composition and temperature condition. According to surfactant principle, monoolein possesses a water-soluble and fat-soluble following in inverted cubic Phases, indicates the hydrophilic environment medium phase. Consequently, Cubic structure represents and explained through differential geometry and Periodic minimal Surface. That is analogues to thin liquid film. Three Surfaces categories examining the Cubic- phase according to curvature, under large aqueous content, water containing monoolein system. Diamond, whereas at Low levels, the gyroid. The Primitive it is appeared only when presence of additional constituents, e.g. amphiphiles, casein exists. X-ray diffraction scattering can be employed to identify cubic-liquid crystalline phase, by employing transmission electron microscopy (TEM) and freeze-fracture electron microscopy (FFEM) are employed for visualizing cubosome.

4] System Forming Theory:

The cubosome can be formed from both binary and ternary system when the solvent and cubic phase having a considerable miscibility gap. The incorporation of stabilizer plays crucial role to prevent from flocculation and aggregation, the stability of cubosome in colloidal form. They may be enclosed within the lamina-like bilayer closures, sealing openings in cubic lipid bilayer formed during fragmentation thus it offering the dispersion integrity by preventing the exposure of hydrophobic chains towards water. The cubosomes are covered with the solid crystalline bilayer that demonstrate the superior colloidal stability. On other hand the layered liquid- crystalline coatings are harder. Furthermore, sponge-like phase coating is an alternative approach for stabilizing the cubosome. The molecule phytonadione shows great potential for the development of cubosomes.[26]

DRUG RELEASE MECHANISM FROM CUBOSOME:

The small pore dimensions of cubosomes promote a tortuous diffusion pathway, enabling a sustained, controlled delivery of therapeutic agents, through organized channels which are cubic nanostructure. The release behaviour of encapsulated drugs is primarily governed by their molecular weight and polarity. Hydrophilic drugs tend to be released rapidly because their increased interaction with the surrounding aqueous medium enhances the effective surface area for diffusion. On other hand, water-insoluble compound demonstrates slower liberation profile due to strong preference for lipid-rich water-repelling domains of cubic structure. Mathematical modelling suggests that amphiphilic drugs preferentially orient themselves at the lipid–water interface and consequently display more complex release behaviour. This complexity can be attributed to factors such as the drug's partition coefficient, its diffusivity within the aqueous channels, and its diffusion through the lipid bilayer. Overall, drug release from CBs typically adheres to either the Higuchi diffusion-controlled kinetics (Equation 1) or the Korsmeyer–Peppas model (Equation 2).

Equation (1): Higuchi Model

$$Q = [Dm\ Cd\ (2A-Cd)\ t]^{1/2} \qquad (1)$$

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This model indicates that the extent of drug liberation can influenced by the proportional relationship to the square root of time, Q represents quantity of drug liberated per unit area, D_m denotes coefficient of diffusion, Cd is solubility of the active ingredient within the system, A indicates starting concentration per unit volume of the system, and t is time.

Equation (2): Korsmeyer–Peppas Model

$$F = \left[\frac{M_t}{M}\right] = K_m t^n \qquad (2)$$

Here, F denotes the proportion of drug released at time t; M_t indicates total amount of drug liberated at time t, M refers to overall drug content in the formulation, K_m represents constant governing release rate and n is the release exponent that characterizes release mechanism.

Makhlouf et al. discussed the release kinetics of minoxidil-loaded cubosomes (MXD-CBs). The prepared CBs exhibited a particle diameter of 131.10 ± 1.41 nm, zeta potential measuring −23.50 ± 0.42 mV, and a polydispersity index value of 0.18. The encapsulation efficiency of minoxidil was reported to be 80.4 ± 4.04%. The release profile of MXD from CBs followed Higuchi diffusion kinetics, supported by a high regression coefficient (R^2). The value of liberated exponent derived from the Korsmeyer–Peppas model was 0.6792, indicating anomalous mechanism, driven by combination of diffusion and erosion processes.[12]

APPROCHES TO PREPARE CUBOSOME:

The preparation of cubosomes can be achieved by using two different approches presented in the figure no:3.

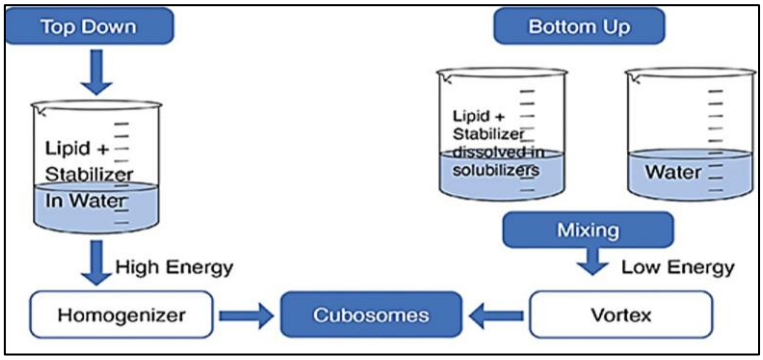

Figure no: 3 Representation of methods of preparation of cubosome [27]

METHOD OF PREPARATION OF CUBOSOMAL GEL: The following preparation methods and formulation procedures are representative methods compiled and adapted from published literature reports is as follows:

Step 1: Formulation of active ingredient loaded cubosome: The active ingredient loaded cubosome may be prepared by using the **Top- down method.**

Accurately weigh the required quantities of Lipid and Stabilizer (Internal Phase). Mix and melt the components on a water bath at 70°C. Add the active ingredient to the melted solution and mix until it gets entirely dissolved. Add this mixture dropwise added into preheated distilled water (External Phase) at 60°C with constant stirring for 2 hours. This entire system treated with bath sonication for 15-45 minutes, accompanied by occasional shaking and stirring. The end product appears as a white dispersion get developed despite the absences of aggregated particles. The cubosomal dispersion kept at room temperature, protected from direct sunlight for 72 hours. [28-30]

Step 2: Method of preparation of cubosome may be prepared by using bottom-up method:

Accurately weigh the required quantity of Lipid and Stabilizer then it is dissolve in an appropriate hydrotrope or solvent. Add Active ingredient to this mixture and stir until a clear solution is obtained, followed by vortexting. Then this solution Gradually diluted with distilled water with continuous stirring at room temperature. After, spontaneous formation of cubosome the cubosomal dispersion incorporated into the gel base, adjust the pH to obtain a homogeneous cubosomal gel. [31]

Formulation of active ingredient loaded cubosomal gel:

The cubogel prepared by adding the cubosomal dispersion into the gel base

Accurately weigh the required amount of Gelling agent. Disperse the gelling agent into the distilled water. Allow the dispersion to stand for about half a day to ensure complete swelling of gelling agent. Add triethanolamine to adjust the pH Mix the prepared gel base with cubosomal dispersion mixed in equal weight ratio 1:1 (w/w), Obtain the final cubosomal gel formulation.[32]

MARKETED LIPID BASED PRODUCT:

Table no 1: List of marketed lipid-based product

Product Name	Drugs	Targeted Disease	References
Doxil/ Caelyx	Doxorubicin	Cancer (Breast, Ovarian)	[33]
Onapattro	Patisiran	Hereditary transthyretin-mediated amyloidosis	[34]
AmBisome®	Amphotericin	Treat fungal Infections and visceral leishmaniasis	[35,36]
Comirnaty	m RNA based Covid-19 Vaccine	SARS-Cov2 Prevention	[37]
m RNA 1273	m RNA based Covid-19 Vaccine	SARS-Cov2 Prevention	[38]
Arikayce®	Amikacin	Non- tuberculous mycobacterial lung cancer	[39]
DepoCyt™	Cytarabine	Lymphomatous meningitis	[40]
Brakiva	Topotecan	Relapsed solid tumour	[41]
CPX-1	Irinotecan HCL	Colorectal Cancer	[42]

EXAMPLES OF TOPICAL, OPTHALMIC, NASAL AND ORAL ADMINISTRED DRUG LOADED IN CUBOSOME:

Table no: 2 List of topical, ophthalmic, nasal and oral administered drug loaded cubosome

Loaded drug	Category of Drug	Therapeutic Use	References
Itraconazole	Anti – fungal	Improved bioavailability, good penetration into the skin	[43]
Capsaicin	Analgesic	It helps to treat psoriasis, pruritus and contact allergy	[44]
Butenafine HCL	Anti – fungal	Use for the treatment of jock itch infection	[45]
Fluconazole	Anti – fungal	Managing cutaneous fungal infection	[46]
Miconazole Nitrate	Anti – fungal	Reduce dose of drug, avoid side effects	[47]
Terbinafine Hydrochloride	Anti- fungal	Used to treat tinea pedis, tinea corporis	[48]
Ketorolac	NSAID	Increased corneal retention and trans-corneal penetration	[49]
Flurbiprofen	NSAID	Promotes trans-corneal delivery while reducing ocular irritation	[50]
Timolol maleate	non- selective β blocker	Reduce intraocular pressure, treat glaucoma	[51]
Dexamethasone	Corticosteroid (Glucocorticosteroids)	Improve ocular tolerance and improve corneal penetration	[52]
Cyclosporine A	Immunosuppressant	Immunosuppressive agent helps to treat inflammation and immune-related ocular disease.	[53]
Risperidone	Antipsychotic	Improved penetration into the brain and increased nasal-to-brain permeation.	[54]
Donepezil HCL	Anticholinesterase	Improved penetration into the brain and increased nasal-to-brain permeation.	[55]
Insulin	Anti-diabetic	Enhanced oral bioavailability	[56]
Piperine	Anti-Alzheimer	Improved cognitive Function	[57]
Simvastatin	Hypolipidemic	Enhanced bioavailability	[58]

FUTURE PROSPECTS:

The cubosomes are nanoparticle that holds a promising avenue in sustained release drug delivery system; however, the further refinement still required, it is depending upon the frequency of dosing, route of administration, mechanism of therapeutic agent release, prior these nanocarrier accurately realizing the effective treatment in a wide range of disorders.[65] It also represents the nano vehicle for the delivery of peptides and protein but the current research remains at a fundamental stage. The various factors related in terms of the characterisation of structural and the morphological attributes, nanocarrier involving the loading ability for biomacromolecules and their release profile must be considered. For upcoming progress of the cubosome is founded on the parenteral nanomedicine, early consideration of the blood compatibility during formulation development is essential. Additionally limited information is currently provided on the stability in Physiological fluids the Physiological factors influencing the therapeutic agent release, such as morphological alterations interact with plasma, interaction with cell membrane, and infusion associate reaction. While the utilization of cubosome related to the intravenous drug delivery system remain ambitious one; Cubosomes may be rapidly used for ocular, topical, oral and poorly water-soluble drug delivery, so thereby delivering economical and encouraging prospect in the formulation studies. [59]

CONCLUSION:

cubosomes represent an advanced and promising nanocarrier system for the effective delivery of both hydrophilic and lipophilic drugs as well as promising nanocarrier systems for controlled and targeted drug delivery due to their unique structure, stability, and biocompatibility. This review may provide valuable guidance for formulation scientists and researchers in the development of advanced nano-drug delivery systems for topical and transdermal applications.

REFRENCES:

1. Porter CJ, Trevaskis NL, Charman WN. Lipids and lipid-based formulations: optimizing the oral delivery of lipophilic drugs. Nature Reviews Drug Discovery. 2007;6(3):231-248. doi:10.1038/nrd2197.
2. Saraf S. Applications of novel drug delivery system for herbal formulations. Fitoterapia. 2010;81(7):680-689. doi: 10.1016/j.fitote.2010.05.001.
3. Jain S, Jain V, Mahajan SC. Lipid-based vesicular drug delivery systems. Advances in Pharmaceutics. 2014;2014:574673. doi:10.1155/2014/574673.
4. Drummond CJ, Fong C. Surfactant self-assembly objects as novel drug delivery vehicles. Current Opinion in Colloid & Interface Science. 1999;4(6):449-456. doi:10.1016/S1359-0294(00)00020-9.
5. Varde NM, Mehta NK, Thakor NM, Shah VA, Upadhyay UM. Phytosomes: a potential phospholipid nanoparticulate carrier for the bioavailability enhancement of herbal extracts. Pharm Globale. 2012;3(10):1-7.
6. Ashara KC, Paun JS, Soniwala MM, Chavda JR, Nathawani SV, Mori NM, Mendapara VP. Vesicular drug delivery system: a novel approach. Mintage Journal of Pharmaceutical & Medical Sciences. 2014;3(3):1-4.
7. Bhosale RR, Osmani RA, Harkare BR, Ghodake PP. Cubosomes: the inimitable nanoparticulate drug carriers. Sch Acad J Pharm. 2013;2(6):481-486.
8. Chandrakala V. Cubosomes: a boon for cosmeceuticals and topical drug delivery. International Journal of Pharmacy and Pharmaceutical Sciences. 2022;14(11):13-17.
9. Sri VR, Reddy AM, Karthikeyan R, Srinivasababu P. A review on cubosomes drug delivery system. Indian Journal of Drugs. 2017;5(3):104-108.
10. Akshata M. A review on cubosomes as a nanoparticulate drug carrier. World Journal of Pharmacy and Pharmaceutical Sciences. 2014;10(2):809-816.
11. Ba A, Xa FG, Sa S. An overview of cubosomes: smart drug delivery system. Sri Ramachandra Journal of Medicine. 2015;8(1):1-5.
12. Nath AG, Dubey P, Kumar A, Vaiphei KK, Rosenholm JM, Bansal KK, Gulbake A. Recent advances in the use of cubosomes as drug carriers with special emphasis on topical applications. *Journal of Lipids*. 2024;2024:2683466. doi:10.1155/2024/2683466.
13. Bei D, Meng J, Youan BB. Engineering nanomedicines for improved melanoma therapy: progress and promises. *Nanomedicine (London)*. 2010;5(9):1385–1399. doi:10.2217/nnm.10.117.
14. Tilekar KB, Khade PH, Shitole MH, Jograna MB, Patil RY. Cancer oriented cubosomes: a review. International Journal of Pharmaceutical Research Scholars. 2014;3:198–210.
15. Rizwan SB, Dong YD, Boyd BJ, Rades T, Hook S. Characterisation of bicontinuous cubic liquid crystalline systems of phytantriol and water using cryo field emission scanning electron microscopy (cryo FESEM). *Micron*. 2007;38(5):478–485. doi:10.1016/j.micron.2006.08.003.
16. Yingchoncharoen P, Kalinowski DS, Richardson DR. Lipid-based drug delivery systems in cancer therapy: what is available and what is yet to come. *Pharmacological Reviews*. 2016;68(3):701-787. doi:10.1124/pr.115.012070.

17. Sastri KT, Radha GV, Pidikiti S, Vajjhala P. Solid lipid nanoparticles: preparation techniques, their characterization, and an update on recent studies. *Journal of Applied Pharmaceutical Science*. 2020;10(6):126–141. doi:10.7324/JAPS.2020.10617.
18. Nanjwade BK, Hundekar YR, Kamble MS, Srichana T. Development of cuboidal nanomedicine by nanotechnology. *Austin Journal of Nanomedicine and Nanotechnology*. 2014;2(4):1023.
19. Karami Z, Hamidi M. Cubosomes: remarkable drug delivery potential. *Drug Discovery Today*. 2016;21(5):789–801. doi:10.1016/j.drudis.2015.12.007.
20. Garg G, Saraf S, Saraf S. Cubosomes: an overview. *Biological & Pharmaceutical Bulletin*. 2007;30(2):350–353.
21. Achouri D, Alhanout K, Piccerelle P, Andrieu V. Recent advances in ocular drug delivery. *Drug Development and Industrial Pharmacy*. 2013;39(11):1599–1617. doi:10.3109/03639045.2012.736515.
22. Bachhav AA, Pingale PL, Upasani CD, Ahire SA. Cubosome: a novel vesicular drug delivery system. *Int J Pharm Sci Res* 2024;15(1):323-329.
23. Kulkarni CV, Vishwapathi VK, Quarshie A, Moinuddin Z, Page J, Kendrekar P, Mashele SS. Self-assembled lipid cubic phase and cubosomes for the delivery of aspirin as a model drug. *Langmuir*. 2017;33(38):9907–9915. doi:10.1021/acs.langmuir.7b02486.
24. Luzzati V, Husson F. The structure of the liquid-crystalline phases of lipid-water systems. *Journal of Cell Biology*. 1962;12(2):207–219.
25. Varghese R, Salvi S, Sood P, Kulkarni B, Kumar D. Cubosomes in cancer drug delivery: a review. *Colloids and Interface Science Communications*. 2022;46:100561. doi:10.1016/j.colcom.2021.100561.
26. Luzzati V, Tardieu A, Gulik-Krzywicki T, Rivas E, Reiss-Husson F. Structure of the cubic phases of lipid–water systems. *Nature*. 1968;220(5166):485–488.
27. Singhvi G, Banerjee S, Khosa A. Lyotropic liquid crystal nanoparticles: a novel improved lipidic drug delivery system. In: *Organic Materials as Smart Nanocarriers for Drug Delivery*. 2018 Jan 1;471–517. doi:10.1016/B978-0-12-813663-8.00011-7.
28. Sadhu Venkateswara Rao A. A review on cubosome: the novel drug delivery system. *GSC Biological and Pharmaceutical Sciences*. 2018;5(1):76–81.
29. Venkatesh S, Indira. Formulation and evaluation of miconazole nitrate as a cubosomal topical gel. *Journal of Global Trends in Pharmaceutical Sciences*. 2014;5(4):2037–2047.
30. Khalifa MKA. Miconazole nitrate based cubosome hydrogels for topical application. *International Journal of Drug Delivery*. 2015;7(1):1–12.
31. Spicer PT, Hayden KL, Lynch ML, Ofori-Boateng A, Burns JL. Novel process for producing cubic liquid crystalline nanoparticles (cubosomes). Langmuir. 2001;17(19):5748-5756.
32. Karthika VT, Sheri PS, Kuriachan MA. Fabrication & evaluation of ketoprofen loaded cubogel for topical sustained delivery. *International Journal of Research and Review*. 2018;5(8):149–159.
33. Thi TTH, Suys EJA, Lee JS, Nguyen DH, Park KD, Truong NP. Lipid-based nanoparticles in the clinic and clinical trials: from cancer nanomedicine to COVID-19 vaccines. *Vaccines*. 2021;9(4):359. doi:10.3390/vaccines9040359.
34. Urits I, Swanson D, Swett MC, Patel A, Berardino K, Amgalan A, Berger AA, Kassem H, Kaye AD, Viswanath O. A review of patisiran (ONPATTRO®) for the treatment of polyneuropathy in people with hereditary transthyretin amyloidosis. *Neurology and Therapy*. 2020;9(2):301–315. doi:10.1007/s40120-020-00208-1.
35. Meunier F, Prentice HG, Ringdén O. Liposomal amphotericin B (AmBisome): safety data from a phase II/III clinical trial. *Journal of Antimicrobial Chemotherapy*. 1991;28(Suppl B):83–91. doi:10.1093/jac/28.suppl_B.83.
36. Meyerhoff A. US Food and Drug Administration approval of AmBisome (liposomal amphotericin B) for treatment of visceral leishmaniasis. *Clinical Infectious Diseases*. 1999;28(1):42–48. doi:10.1086/515085.
37. Husni P, Lim C, Oh KT. Tumor microenvironment stimuli-responsive lipid-drug conjugates for cancer treatment. *International Journal of Pharmaceutics*. 2023;639:122942. doi:10.1016/j.ijpharm.2023.122942.
38. Griffith DE, Eagle G, Thomson R, Aksamit TR, Hasegawa N, Morimoto K, Addrizzo-Harris DJ, O'Donnell AE, Marras TK, Flume PA, Loebinger MR. Amikacin liposome inhalation suspension for treatment-refractory lung disease caused by *Mycobacterium avium* complex (CONVERT). A prospective, open-label, randomized study. *American Journal of Respiratory and Critical Care Medicine*. 2018;198(12):1559–1569. doi:10.1164/rccm.201807-1318OC.
39. Kim S, Chatelut E, Kim JC, Howell SB, Cates C, Kormanik PA, Chamberlain MC. Extended CSF cytarabine exposure following intrathecal administration of DTC 101. *Journal of Clinical Oncology*. 1993;11(11):2186–2193. doi:10.1200/JCO.1993.11.11.2186.
40. Rattanapak T, Birchall J, Young K, Ishii M, Meglinski I, Rades T, Hook S. Transcutaneous immunization using microneedles and cubosomes: mechanistic investigations using Optical Coherence Tomography and Two-Photon Microscopy. *Journal of Controlled Release*. 2013;172(3):894–903. doi:10.1016/j.jconrel.2013.08.018.
41. Abourehab MAS, Ansari MJ, Singh A, Hassan A, Abdelgawad MA, Shrivastav P, Abualsoud BM, Amaral LS, Pramanik S. Cubosomes as an emerging platform for drug delivery: a review of the state of the art. *Journal of Materials Chemistry B*. 2022;10(15):2781–2819. doi:10.1039/D2TB00031H.
42. Nikita IK, Sultana Y. Formulation, development, and optimization of itraconazole cubosomal gel for the treatment of candidiasis. *International Journal of Pharmacy and Analytical Acta*. 2020;3(1):016–019.
43. Chaudhary K, Sharma D. Cubosomes: a potential drug delivery system. *Asian Journal of Pharmaceutical Research and Development*. 2021;9(5):93–101. doi:10.22270/ajprd.v9i5981.

44. Chauhan R, Nirmala. Formulation and evaluation of butenafine hydrochloride loaded cubosomal gel. *International Journal of Pharmaceutical Sciences & Research*. 2023;14(11):5441–5450.
45. Sharma R, Kaur G, Kapoor DN. Fluconazole loaded cubosomal vesicles for topical delivery. *International Journal of Drug Development & Research*. 2015;7(1):32–41.
46. Parashar B, Kabra A, Chandel A. Formulation and evaluation of gel containing miconazole nitrate an antifungal agent. *International Journal of Pharmaceutical Research & Reviews*. 2013;2(6):18–28.
47. Gauri G. Sakpal et al, J. Global Trends Pharm Sci, 2020; 11 (3): 8028 – 8039.
48. Ali Z, Sharma PK, Warsi MH. Fabrication and evaluation of ketorolac loaded cubosome for ocular drug delivery. *Journal of Applied Pharmaceutical Science*. 2016;6(9):204–208. doi:10.7324/JAPS.2016.60930.
49. Han S, Shen JQ, Gan Y, Geng HM, Zhang XX, Zhu CL, Gan L. Novel vehicle based on cubosomes for ophthalmic delivery of flurbiprofen with low irritancy and high bioavailability. *Acta Pharmacologica Sinica*. 2010;31(8):990–998. doi:10.1038/aps.2010.98.
50. Huang J, Peng T, Li Y, Zhan Z, Zeng Y, Huang Y, Pan X, Wu CY, Wu C. Ocular cubosome drug delivery system for timolol maleate: preparation, characterization, cytotoxicity, ex vivo, and in vivo evaluation. *AAPS PharmSciTech*. 2017;18(8):2919–2926. doi:10.1208/s12249-017-0763-8.
51. Gan L, Han S, Shen J, Zhu J, Zhu C, Zhang X, Gan Y. Self-assembled liquid crystalline nanoparticles as a novel ophthalmic delivery system for dexamethasone: improving preocular retention and ocular bioavailability. *International Journal of Pharmaceutics*. 2010;396(1–2):179–187. doi:10.1016/j.ijpharm.2010.06.015.
52. Surabhi S, Krishnananda K, Shabaraya AR. Cubosomes and its applications—A review. *European Journal of Biomedical and Pharmaceutical Sciences*. 2022;9:111–116.
53. Abdelrahman FE, Elsayed I, Gad MK, Badr A, Mohamed MI. Investigating the cubosomal ability for transnasal brain targeting: in vitro optimization, ex vivo permeation and in vivo biodistribution. *International Journal of Pharmaceutics*. 2015;490(1–2):281–291. doi:10.1016/j.ijpharm.2015.05.064.
54. Patil RP, Pawara DD, Gudewar CS, Tekade AR. Nanostructured cubosomes in an in situ nasal gel system: an alternative approach for the controlled delivery of donepezil HCl to brain. *Journal of Liposome Research*. 2019;29(3):264–273. doi:10.1080/08982104.2018.1552703.
55. Chung H, Kim JS, Um JY, Kwon IC, Jeong SY. Self-assembled "nanocubicle" as a carrier for peroral insulin delivery. *Diabetologia*. 2002;45(3):448–451. doi:10.1007/s00125-001-0819-9.
56. Spicer PT. Progress in liquid crystalline dispersions: cubosomes. *Current Opinion in Colloid & Interface Science*. 2005;10(5-6):274–279. doi:10.1016/j.cocis.2005.09.004.
57. El-Laithy HM, Badawi A, Abdelmalak NS, El-Sayyad N. Cubosomes as oral drug delivery systems: a promising approach for enhancing the release of clopidogrel bisulphate in the intestine. *Chemical and Pharmaceutical Bulletin*. 2018;66(12):1165–1173. doi:10.1248/cpb.c18-00615.
58. Angelova A, Angelov B, Drechsler M, Garamus VM, Lesieur S. Protein entrapment in PEGylated lipid nanoparticles. *Int J Pharm.* 2013 Oct 1;454(2):625–632.
59. Wibroe PP, Azmi ID, Nilsson C, Yaghmur A, Moghimi SM. Citrem modulates internal nanostructure of glyceryl monooleate dispersions and bypasses complement activation: towards development of safe tunable intravenous lipid nanocarriers. *Nanomedicine: Nanotechnology, Biology and Medicine*. 2015;11(8):1909–1914. doi:10.1016/j.nano.2015.08.00.

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