ISSN: 2320 - 4230

Journal of Drug Discovery and Therapeutics

Available Online at www.jddt.in

CODEN: - JDDTBP (Source: - American Chemical Society)

Volume 10, Issue 04, July-August: 2022, 01-09

Review Article

A Review on Techniques Involved in Preparation of Cubosomes

Ramy Saliheen Mohamed [1], Thadipatri Reshma[2], Nawaz Mahammed[*1]

[1]Department of Pharmaceutics, Raghavendra Institute of Pharmaceutical Education and Research, K.R. Palli Cross, Anantapur, Chiyyedu, Andhra Pradesh-515721.

[2]Department of Pharmaceutical Quality Assurance, Raghavendra Institute of Pharmaceutical Education and Research, K.R. Palli Cross, Anantapur, Chiyyedu, Andhra Pradesh-515721

Article Info: Received 20 July2022; Accepted 25 August 2022

Corresponding author: Dr. Nawaz Mahammed

Conflict of interest: No conflict of interest.

Abstract:

Cubosomes are a type of nanoparticle; however they differ from other nanoparticles in that they are self-assembled liquid crystalline particles with fascinating practical features. In recent years, significant review has contributed to the advancement of the loaded bio active's efficacy in a variety of areas, including manufacture, characterization, target selectivity, and the management of drug release patterns. Cubosomes have peculiar features, such as a cubic structure that enables the incorporation of medications that are very lipophilic, hydrophilic, and amphiphilic. In addition, the formulation of Cubosomes makes use of biocompatible and biodegradable lipid additives. In this review, the pertinent literature on Cubosomes will be examined, with an emphasis on theories of self-assembly, the composition of Cubosomes, preparation methods, and applications in drug delivery.

Keywords: Cubosomes, Self-assembled, Biodegradable, Biocompatible.

INTRODUCTION

Due to improved therapeutic efficiency and bioavailability, Cubosomes, or lyotropic cubic liquid crystalline nanoparticles, have gained appeal as useful carriers for solubilization of a range of pharmaceuticals (1-3). Cubosomes are bicontinuous cubic nanovesicles that arise when liquid crystalline cubic aggregates are dispersed in aqueous fluids. Cubosomes, which are bicontinuous cubic phase liquid crystals, have a number of properties that make them a potential universal carrier for a variety of medicinal actives. Cubosomes are frequently produced using time-consuming and energy-intensive methods. A lipid bilayer divides the continuous but non-intersecting hydrophilic areas of the bicontinous cubic phases into a periodic minimum surface with zero curvature. The capacity of certain kinds of surfactant molecules to form cubic phases

and then disperse into Cubosomes-like particles is a unique characteristic of these phases (4)

To begin, a liposomal dispersion is created by dissolving the cubic lipid-water phase in a three-phase region. These particles have been called Cubosomes to distinguish them from liposomes (5). To load the drug moieties, the medicinal agent could be introduced to the molten lipid or lyophilized with the lipid film before dispersion (6). Cubosomes are nanoparticles that range in size from 10 to 50 nm; they have a dot-like appearance and a somewhat round shape. In the X-ray scattering technique, each dot represents the presence of a pore containing an aqueous phase cubic phase in a lipid water system.

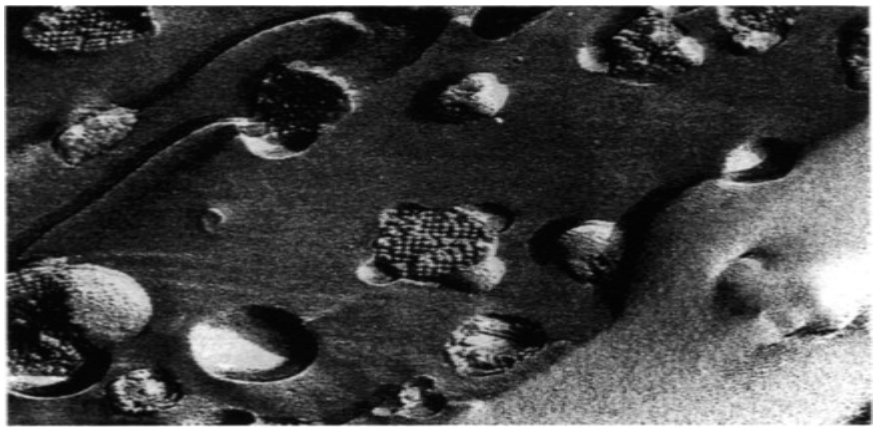

Figure 2: Cubosomes

1.1. Advantages of Cubosomes (7-9):

- They may encapsulate a variety of therapeutic molecules with hydrophilic, hydrophobic, and amphiphilic characteristics, giving a promising technique for improving bioavailability for medications that are poorly water soluble.
- They can be prepared using basic methods.
- They are made up of biodegradable lipids.
- They may encapsulate a variety of therapeutic molecules with hydrophilic, hydrophobic, and amphiphilic characteristics, giving a promising technique for improving bioavailability for medications that are poorly water soluble.
- They can be prepared using basic methods.
- They're made up of biodegradable lipids.

1.2. Disadvantages of Cubosomes (10, 11):

- Due to the cubic phase's high viscosity, large-scale production is difficult.
- Because of the high-water content in their structure, they have low entrapment efficiency for water-soluble drug molecules.

1.3. Cubosomes Application (12, 13):

- It produces nanoparticles with a size of 5 to 10 nm.
- Improves the solubility of a medication that is weakly water soluble.
- Lipid biodegradability.
- Hydrophilic, hydrophobic, and amphiphilic compounds can be encapsulated.
- It created a high dilution level and showed a higher dilution level.

- Cubosomes procedures are used to remove cells from the skin and mucosal surface.
- Cubosomes serve as an excellent vehicle for anticancer drugs. For anti-cancer medications to have more benefits and better retention, the delivery system's small size is a crucial factor.

Because Cubosomes are made of ethanol, which causes the rupture of the skin, they have great skin permeability and can be used to treat sexually transmitted diseases caused by both bacteria and viruses (such as HIV). As a result, lipid fluidity is improved, which also increases the drug's skin permeability.

2. Structure of Cubosomes (14):

Cubosomes have two internal water channels that are separated from one another by honeycombed structures. There is also a substantial amount of interfacial space between the two channels. Cubosomes are nanoparticles, or to be more exact, nanostructure particles of liquid crystalline phases with cubic crystallographic symmetry. They are formed by the self-assembly of molecules that are amphiphilic or surfactant-like. Cubosomes have a cubic crystallographic structure. Because of their fascinating bicontinuous structures, which encompass two distinct regions of water and are separated by a controlled bilayer of surfactant application, the cubic phases have a very high solid-like viscosity, which is a distinctive quality of these phases. This is a feature that sets them apart from other phases. Amphiphilic molecules generate hydrophilic regions that are bicontinuous, which means they are distinct, continuous, but do not intersect with one another. These regions are separated by the bilayer, which in turn generates water and oil channels. The interconnectedness of the structure results in the production of a viscous gel that is both transparent and appears to have the rheology and look of cross-linked polymer hydrogels.

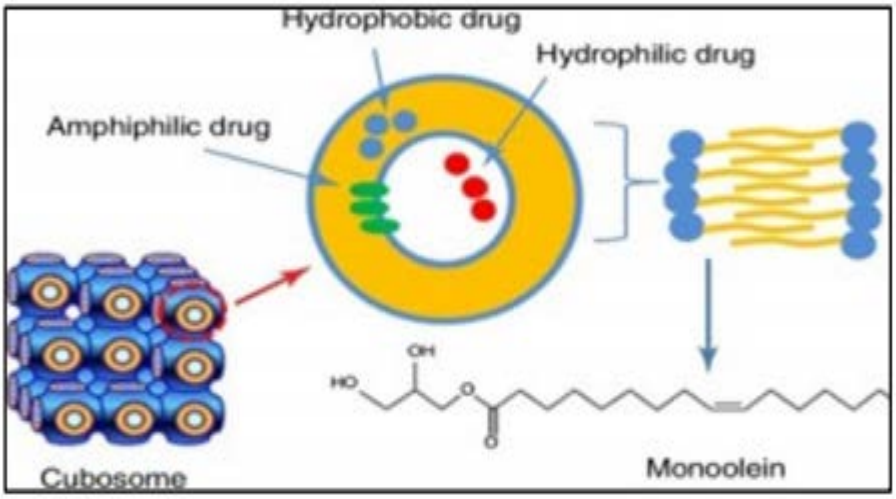

Figure 2: Structure of Cubosomes separating two internal aqueous channels along with large interfacial area

2.1. Structural Components of Cubosomes:

Glyceryl monooleate/ monoolein (GMO) and phytosterol are the amphiphilic lipids utilized in Cubosomes synthesis (PHYT). GMO is very biocompatible and possesses bio adhesive characteristics, although it is destroyed in the gastrointestinal tract by lipase enzymes (14, 15). The stabiliser's act as an electrostatic barrier, preventing near-particle interactions. Pluronic's are the most widely used Cubosomes stabilisers. They're water-soluble triblock copolymers made up of polyethylene oxide and polypropylene oxide organised in a PEO conformation, with the PPO and PEO sections providing hydrophobic and hydrophilic characteristics, respectively (16, 17).

3. Types of Cubosomes:

3.1. Liquid Cubosomes Precursors:

High shear dispersion of viscous bulk cubic phase to manufacture Cubosomes is difficult and expensive due to the aggressive manufacturing procedure. The temperature-sensitive active component is harmed by this high-energy, high-cost, difficult-to-scale-up technique. In order to prevent high energy processing and manufacture Cubosomes in situ, a strong pushing force occurs in Cubosomes for the creation of a liquid phase. As a result, when nucleation crystallisation and precipitation procedures were utilised to develop the particles and grow the Cubosomes, the hydro trophy dilution process consistently produced smaller, more stable Cubosomes (18, 19).

3.2. Powdered Cubosomes Precursors*:*

Dehydrated surfactant wrapped in polymer is the basis of powdered Cubosomes precursors. Compared to liquid-phase hydrotropic Cubosomes precursors, such powders have a number of advantages. Light scattering and cryo-TEM revealed that hydration of the precursor powders produces Cubosomes with a mean particle size of 600 nm. Cubosomes contain lipids, which are waxy, sticky substances. On the waxy lipid, a non-cohesive water-soluble starch layer prevents agglomeration and allows for particle size control. For this purpose, spray drying is an excellent approach for encapsulating particles. Preloading active medicines into Cubosomes before driving is simple with this method. Spray-drying experiments necessitate the use of a Pulvis Basic Unit. There was a cylindrical chamber with a cyclone collector and air, in other words. The nozzle's liquid orifice size is 0.1 cm, and it's used to incorporate liquid into the spray-top. dryer body's The air is pumped at 300 kPa via a 0.25-cm aperture at a pressure of 300 kPa. 8.9 The liquid feed is dried by the heated, drying air that comes down and passes through the nozzle. To keep monoolein from oxidising at high temperatures, a liquid crystalline substance is created, providing significant shear to disperse the high viscosity (20).

4. Preparation Techniques of Cubosomes:

4.1. Top-down technique approach (21):

Combining lipids and stabilisers is the first step in the production of the viscous bulk cubic phase. The next step is to disperse the resulting mixture into an aqueous solution using high energy (such as High-Pressure Homogenization HPH, sonication, or shearing) in order to produce Lyotropic Liquid Crystal (LLC) nanoparticles. The HPH approach is the one that is used the most frequently in the process of preparing LLC nanoparticles. Vesicles, which are dispersed nanoparticles of lamellar liquid crystalline phase, or vesicle-like structures are consistently observed coexisting with Cubosomes created via a top-down approach.

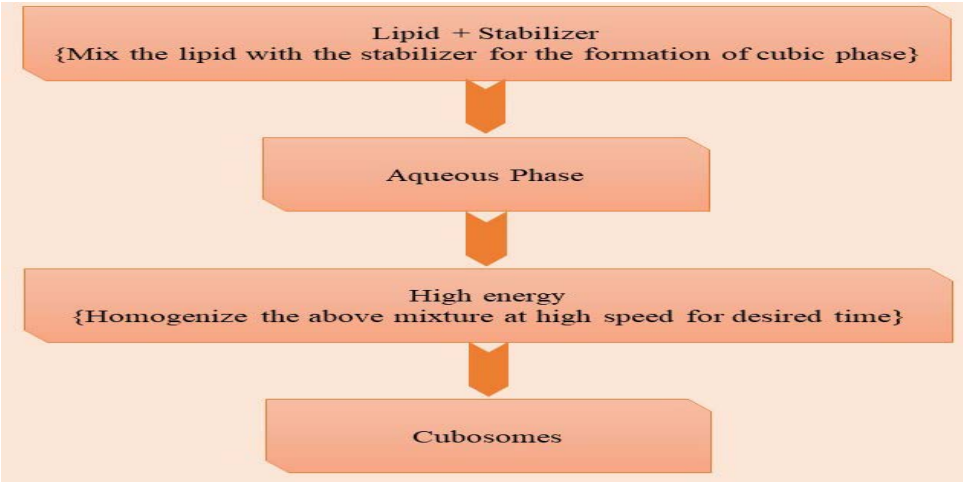

Figure 3: Top-down technique approach

4.2. Bottom-up technique approach (22):

The hydro trope is dissolved in water-insoluble lipids to make liquid precursors and inhibit the production of liquid crystals at high concentrations in the bottom-up strategy, which requires less energy input. Disperse inverse micellar phase droplets in water at 80 °C and allow them to cool slowly to crystallise into Cubosomes to discuss the development of Cubosomes. Emulsification causes the Cubosomes to develop spontaneously. Through cryo-TEM, this bottom-up technique was unable to avoid the formation of vesicles, and several vesicles and vesicle-like structures were discovered coexisting with Cubosomes.

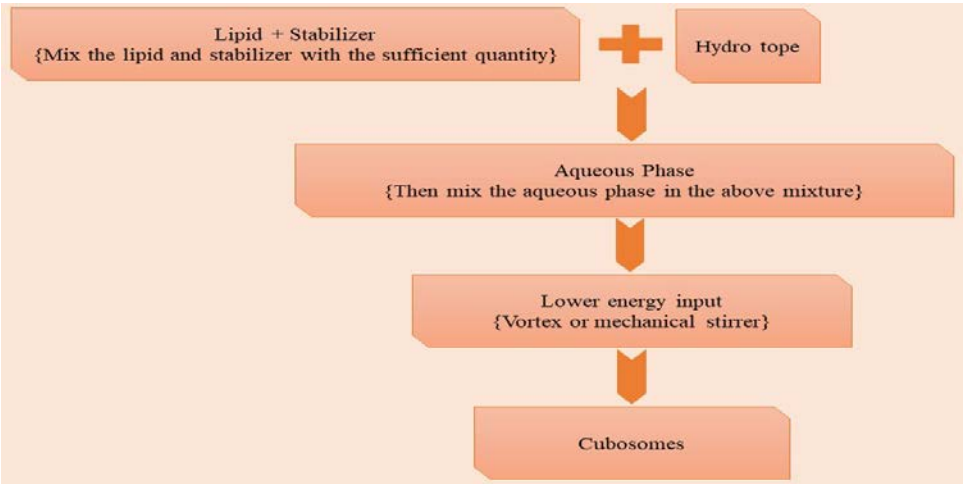

Figure 4: Bottom-up technique approach

4.3. Heat treatment approach (23):

This method is not an integrated Cubosomes manufacturing process because it only promotes the transformation from non-cubic vesicles to well-ordered cubic particles via a homogenization and heat-treatment step. As a result, there is a decrease in the small particle size fraction that corresponds to vesicles, and there is a formation of more cubic phases with narrow particle distribution and good colloidal stability.

4.4. Spray drying approach (24):

Due to the inflexibility of liquid precursors for Cubosomes synthesis, a dry powder

precursor for Cubosomes manufacture was created. For the manufacture of starch encapsulated monoolein precursor and dextran encapsulated monoolein precursor, they used a spray drying process. Because the number of active elements that could be loaded into the system was limited due to the high proportion of polymer used for encapsulation, the system was only suitable for powerful medicaments, vitamins, flavours, or smells.

4.5. Method of Solvent Evaporation (25, 26):

The lipids are dissolved in an organic solvent like ethanol or chloroform, then dropped into an aqueous solution with a non-ionic surfactant like Pluronic's (F108, F127, F68, P104) to act as a stabiliser. The mixture is kept at a high temperature by magnetic churning. To disseminate the drug, use a lipid or aqueous surfactant solution. Cubosomes form when the volatile organic solvent has been removed through high-temperature stirring and the liquid has been homogenised using ultrasonication or a homogenizer. The lipid-surfactant mixture can also be dissolved in an organic solvent, vacuum-sealed, and then redispersed with an aqueous phase.

5. Characterization of Cubosomes (27, 28):

5.1. Differential Scanning Colourimeter (DSC):

Given that liquid crystals are thermodynamic equilibrium systems and that phase transitions are caused by endothermic and exothermic processes, differential scanning calorimetry (DSC) can reveal whether a phase transition actually occurs or not.

5.2. Zeta Potential:

The amount of zeta potential can be used to gauge how stable a preparation is. It exudes a strong repulsiveness.

5.3. Studies on visual inspection

This involves looking at the Cubosomes' outward characteristics, including shape, turbidity, colour, homogeneity, and particle presence. TEM, or transmission electron microscopy

5.4. Transmission Electron Microscopy (TEM):

Using TEM, Cubosomes morphology may be evaluated. Cubosomes particle forms could be provided by it. It provides a high-resolution image and the potential to produce electron microphotographs for observation. Visualization is thus feasible. In comparison to light microscopes, it can provide substantially higher resolution. It is a great tool for figuring out how soft matter dispersions behave. It might eliminate all the drawbacks of conventional electron microscopy, such as the vacuum environment and weak pictures that cause structural changes in cubic phase.

5.5. Morphology of Cubosomes:

The experiment was carried out using the SEM. The Cubosomes droplet is deposited on a carbon-coated copper gride with a 200-mesh size, the excess fluid is collected by absorbent filter paper. A 1 percent sodium phosphor tungstate solution was used to stain the sample, which was then seen at 1,000,000X magnification.

5.6. Particle size analysis:

The dynamic light scattering source determined the particle size. The material was diluted 100 times with deionized water before being measured in triplicate at 250°C.

5.7. Entrapment efficiency:

The amount of drug in the dispersion was measured spectrophotometrically at the maximum wavelength, allowing the total amount of drug to be removed. 4 mL deionized water was used to dilute 1 mL of each dispersion. After the fluid has passed

through the syringe filter, the spectrophotometer is utilised to examine it.

5.8. Viscosity:

The viscosity is measured using a (Brookfield) Viscometer at varied angular velocities at 250 C. With the Speen #18, the spinning speed was 20 rpm. The viscosity is calculated by taking the average of three readings.

5.9. In vitro release and evaluation of the release mechanism:

In order to determine the amount of medication that is released in vitro from Cubosomes, a dynamic dialysis method is utilised. After loading the samples of the various formulations into dialysis bags (cellulose membrane), they were then submerged in 500 mL of simulated tear at a temperature of 37 degrees Celsius. At each of the predetermined time periods, a sample of 5 mL was collected and then replaced with an equal volume of tear fluid. After then, the concentration of the medication that was ejected is measured.

5.10. Stability study:

This test can be carried out by looking at organoleptic and morphological properties, DEE which can be assessed at different time intervals. It was stored at a temperature of 4-80°C for three months in amber-coloured glass vials sealed with aluminium foil. The samples were extracted and vortexed for 3 minutes in deionized water at the conclusion of the experiment. The resulting

Future Prospect:

The application of medication delivery as well as sustained drug delivery is where the Cubosomes excel. Cubosomes research has previously been done, however it has to be expanded because it is still in its very early stages. For the drug loading capabilities and release behaviour, precise research is needed. Future optimization and research will be necessary to determine the compatibility of Cubosomes with blood and bodily tissues. The stability needs of Cubosomes in the bodily fluids are a further prerequisite for development. Additionally, research is necessary to learn the parameters that influence the drug release from Cubosomes.

Conclusion:

A survey of the relevant published research reveals that Cubosomes are inverse bicontinuous curved cubic phase lyotropic liquid crystals. These crystals are produced by combining specific amphiphiles, such as glyceryl monooleate, with water and the appropriate stabilisers under conditions that are optimal in terms of hydration and temperature. Because of their unique internal structure, Cubosomes have a far larger membrane surface area than liposomes do, which makes them more suitable for loading with active chemicals. In contrast to liposomes and other drug delivery methods that take the form of emulsions, Cubosomes have the ability to simultaneously solubilize hydrophobic and hydrophilic pharmacological actives, in addition to amphiphilic compounds. A survey of the relevant published research reveals that Cubosomes are inverse bicontinuous curved cubic phase lyotropic liquid crystals. These crystals are produced by combining specific amphiphiles, such as glyceryl monooleate, with water and the appropriate stabilisers under conditions that are optimal in terms of hydration and temperature. Because of their unique internal structure, Cubosomes have a far larger membrane surface area than liposomes do, which makes them more suitable for loading with active chemicals. Cubosomes, in contrast to liposomes and other drug delivery methods that take the form of emulsions, have the ability to simultaneously solubilize hydrophobic and hydrophilic pharmacological actives, in addition to amphiphilic compounds.

Acknowledgements:

Authors are extremely thankful to Raghavendra Institute of Pharmaceutical Education and Research (RIPER) management, Anantapur for their support.

References:

1. Date AA, Vador N, Jagtap A, Nagarsenker MS. Lipid nanocarriers (GeluPearl) containing amphiphilic lipid Gelucire 50/13 as a novel stabilizer: fabrication, characterization and evaluation for oral drug delivery. Nanotechnology. 2011;22(27):275102.
2. Salim M, Minamikawa H, Sugimura A, Hashim R. Amphiphilic designer nano-carriers for controlled release: from drug delivery to diagnostics. MedChemComm. 2014;5(11):1602-18.
3. Li Y, Lin J, Yang X, Li Y, Wu S, Huang Y, et al. Self-assembled nanoparticles based on amphiphilic anticancer drug–phospholipid complex for targeted drug delivery and intracellular dual-controlled release. ACS applied materials & interfaces. 2015;7(32):17573-81.
4. Patond VB, Ghonge AB, Narkhede MB. Cubosome-Review. Int J Trend Sci Res Dev. 2020;4:1116-20.
5. Garg G, Saraf S, Saraf S. Cubosomes: an overview. Biological and Pharmaceutical Bulletin. 2007;30(2):350-3.
6. Caltagirone C, Falchi AM, Lampis S, Lippolis V, Meli V, Monduzzi M, et al. Cancer-cell-targeted theranostic cubosomes. Langmuir. 2014;30(21):6228-36.
7. Gaballa SA, El Garhy OH, Abdelkader H. Cubosomes: composition, preparation, and drug delivery applications. Journal of advanced Biomedical and Pharmaceutical Sciences. 2020;3(1):1-9.
8. Anbarasan B, Grace XF, Shanmuganathan S. An overview of cubosomes—smart drug delivery system. Sri Ramachandra J Med. 2015;8(1):1-4.
9. Gan L, Han S, Shen J, Zhu J, Zhu C, Zhang X, et al. 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):179-87.
10. Kulkarni CV, Wachter W, Iglesias-Salto G, Engelskirchen S, Ahualli S. Monoolein: a magic lipid? Physical Chemistry Chemical Physics. 2011;13(8):3004-21.
11. Luzzati V, Husson F. The structure of the liquid-crystalline phases of lipid-water systems. The Journal of cell biology. 1962;12(2):207-19.
12. Spicer PT, Lynch ML, Visscher M, Hoath S. Bicontinuous cubic liquid crystalline phase and cubosome personal care delivery systems. Personal Care Delivery Systems and Formulations. 2003.
13. Bei D, Meng J, Youan B. Engineering nanomedicines for improved melanoma therapy: progress and promises. Nanomedicine (Lond) 5: 1385–1399. 2010.
14. Urvi S, Dhiren D, Bhavin P, Patel U, Shah R. Overview of Cubosomes: A Nanoparticle. Int J of Pharmacy and Integrated Sci. 2013;1(15):36-47.
15. Karewicz A, Bielska D, Gzyl-Malcher B, Kepczynski M, Lach R, Nowakowska M. Interaction of curcumin with lipid monolayers and liposomal bilayers. Colloids and Surfaces B: Biointerfaces. 2011;88(1):231-9.
16. Eldeeb AE, Salah S, Ghorab M. Formulation and evaluation of

cubosomes drug delivery system for treatment of glaucoma: Ex-vivo permeation and in-vivo pharmacodynamic study. Journal of Drug Delivery Science and Technology. 2019;52:236-47.
17. Karami Z, Hamidi M. Cubosomes: remarkable drug delivery potential. Drug discovery today. 2016;21(5):789-801.
18. Jung H, Earmme T, Choi S-H. Effect of end-block chain length on rheological properties of ABA triblock copolymer hydrogels. Korea-Australia Rheology Journal. 2021;33(2):123-31.
19. Thandanki M, Kumari S, Prabha K. Overview of cubosomes: A Nanoparticle. International Journal of Research in Pharmacy and Chemistry. 2011;1(3):535-41.
20. Prashar D, Sharma D. Cubosomes: a sustained drug delivery carrier. Asian journal of research in pharmaceutical science. 2011;1(3):59-62.
21. Rizwan S, Dong Y-D, 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):478-85.
22. Spicer P. Cubosome processing: industrial nanoparticle technology development. Chemical Engineering Research and Design. 2005;83(11):1283-6.
23. Spicer PT, editor Cubosome formation via dilution: Kinetic effects and consumer product implications. ACS Symposium Series; 2003: Citeseer.
24. Barauskas J, Johnsson M, Joabsson F, Tiberg F. Cubic phase nanoparticles (cubosome): principles for controlling size, structure, and stability. Langmuir. 2005;21(6):2569-77.
25. Lodha A, Jadhav G, Pande V. Liquid crystals as a cubo-hexagonal topical controlled drug delivery system. Pharmacophore. 2014;5(3):430-41.
26. Rosa A, Murgia S, Putzu D, Meli V, Falchi AM. Monoolein-based cubosomes affect lipid profile in HeLa cells. Chemistry and physics of lipids. 2015;191:96-105.
27. Murgia S, Falchi AM, Meli V, Schillén K, Lippolis V, Monduzzi M, et al. Cubosome formulations stabilized by a dansyl-conjugated block copolymer for possible nanomedicine applications. Colloids and Surfaces B: Biointerfaces. 2015;129:87-94.
28. Liu H, Pan W-S, Nie S-F, Yang X-G, Yan T-X. Study on in vitro release empirical method and the release mechanism of budesonide colonic localization tablet. Yao xue xue bao= Acta Pharmaceutica Sinica. 2008;43(11):1147-51.