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A Comprehensive Review on Cubosomes

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ABSTRACT

Cubosomes are very stable nanoparticles with honeycomb-like or cavernous features. Some amphiphilic lipids are used to create cubosomes, which are then stabilised by a polymer. Bi continuous cubic phase liquid crystals are what they are called. The two continual but not intersecting watery zones that are separated by a lipid bilayer are referred to be bi continuous. Cubosomes are liquid crystalline particles that self-assemble and have a specified water-to-surfactant ratio. Cubosomes that self-assemble function as active medication delivery systems. They exhibit solid-like rheology. Cubosomes have a stable thermodynamic state, and the dispersions they form are both biodegradable and mucoadhesive. Cubosomes can be administered orally, topically, mucosally, intravenously, or transdermally for the treatment of skin, hair, or other bodily tissues. Cubosomes have the ability to encapsulate both hydrophilic and hydrophobic molecules. Nevertheless, several researchers have been pointing out cubosomes' potential as delivery mechanisms. They use a variety of medication loading methods and large interior surfaces. Cubosomes also have the ability to target and release bioactive substances under controlled conditions. They may also be used as biosensors, artificial cells, membrane bioreactors, etc. They are made using a straightforward process. Cubosomes have a greater breaking resistance than liposomes. This article examines and analyses sophisticated cubosome preparation techniques.

INTRODUCTION:

Polymers and surfactants are frequently employed in controlled medication delivery device. Supra assemblies are created by surfactant and polymer systems, and they are widely used as active delivery methods. These systems comprise cross-linked gel networks (hydrogels) or liquid crystalline aggregates (liposomes, cubosomes, etc.) that load, stabilise, and ultimately transport active components. The possibility for using a certain active with a vehicle depends on their respective physicochemical characteristics. It must be feasible to load sufficient amounts of the active to provide medicinal benefits, which heavily based on how the vehicle and active interaction. Additionally, the active ingredient must maintain its integrity during all phases, including manufacturing, storing, and usage. To get the best drug release profiles, the rates of active delivery should be managed. Simplicity of manufacturing and vehicle stability are also taken into account. All these characteristics must be properly incorporated into an ideal delivery vehicle.

Bi-continuous cubic phase liquid crystals called cubosomes have a variety of features which makes these desirable as a general medication delivery system. Its geometrical model was initially described by Luzzati et al.[1] and later provided by Scriven.[2] Which has been investigated for drug delivery over the last ten years[3]. The surfactant forms phospholipid bilayer which are twisted into a periodic, three-dimensional structure with a minimum surface which resembles a "honeycombed" pattern with bi-continuous domains of liquid and fat.

In order to distinguish them from liposomes, cubosome nanoparticles first were created by mechanically fragmenting the cubic lipid-water phase in a three-phase area containing a liposomal dispersion. Its structure differs from liposomes in that it may hold compounds that are concurrently lipid-soluble, water-soluble, and amphiphilic.[4-9]

Generally, the structure preserves the stability and effectiveness of active ingredients as proteins and vitamins.[10,11] Cubosomes are eternally stable from a thermodynamic perspective.[12] Cubosome colloidal dispersions can be made more stable by addition of polymers.[13] They also have the potential for controlled delivery of actives, with diffusion regulated by the active's tortuous passage through the cubic phase's "regular" channel shape.[14] Cubosomes frequently develop in aqueous surfactant systems at relatively high amphiphile concentrations and have an average degree of molecular orientation order that allows them to be identified by structural symmetry.

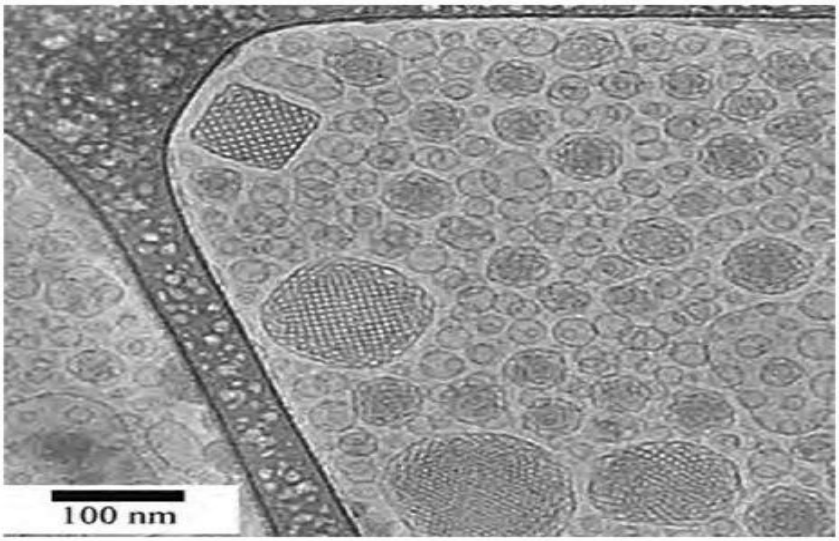

Fig. No. 1: Figure of Cubosomes

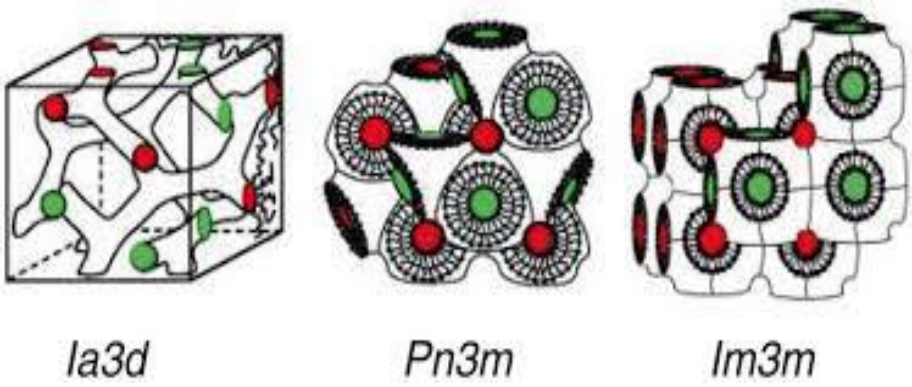

Fig. No. 2: Structure of different Cubosomes

Advantages of Cubosomes:

- Cubosomes are biodegradable, disposable, non-irritating, and non-allergic.[15]
- Its production is straightforward. [16]
- They have a large interior surface area, which increases their ability to carry drugs.
- They are more durable in terms of thermodynamic stability.[17]
- It is physico chemically stable, even in the presence of excess water.[18-20]
- With the application of a specific polymer, regulated and targeted release of bio-actives are possible. Because of its size, bioavailability is good.
- It reduces total health care costs since there is less need for frequent administration.

- They lessen adverse reactions that are linked to injections' burst release.
- When compared to liposome[21], there is a greater ratio between the particle volume and the bilayer area.
- Cubosomes have the feature of being superior solubilizers when compared to other typical carriers (lipid-based).

Disadvantages of Cubosomes:

- Because there is a lot of water inside Cubosomes[22], there is less trapping of medications that are water-soluble.
- Because of its high viscosity, Cubosome manufacture on a big scale is challenging.[23]
- Without the use of a certain polymer, regulated medication delivery is not possible.
- They might cause leaks during in-vivo transfer or storage.[24]
- After some time, there is a probability that the particles will increase.
- If the external environment changes, Cubosomes' dynamics have the potential to bring about a phase transition.

METHODS OF PREPARATIONS OF CUBOSOMES:

High Pressure Homogenization:

It is the best approach for cubosome productions because they are extremely stable throughout the high-pressure homogenization process and have a long shelf life.[25,26] There are three steps to it:

Gel Preparation:

In this stage, an organic phase is used to breakdown the lipids and amphiphilic surface active agents, which are then completely combined to produce what appears to be homogenous mixture. Here, the gel phase of a preparation is produced by rotating evaporating the organic solvent.

Shearing:

At this moment, the produced gel is being sheared.[27] When watery solvents are used, a micro-dispersion is produced. In the process of making cubosomes, it is the critical phase before homogenized.

High Pressure Homogenization:

The small volume sample systems cannot use this procedure, which is only appropriate for the high-volume sample systems (30 ml).

Since this approach is temperature sensitive, the temperature is chosen in this stage based on the characteristics of the lipid. In this, the produced dispersion is homogenised in a higher pressure homogenizer.[28] only one specimen might be handled by such procedure.

Automated Cubosome Preparation:

There aren't many differences from the probe sonication approach. By using this technique, several cubosomes might be produced. This method of cubosome preparation employs robotic equipment and a probe sonicator. In this procedure, the gels are made using a 96-well plate with a 600-l solvent capacity. A robot is then used to do the sonication.[29]

Probe Ultra Sonication:

Utilizing this technique, small quantity samples production may be completed fast. Even samples 600 l in size may be dispersed with it. based on the size of the probe. The gels are created using stabilisers in this process. The solvent then equilibrates, resulting in the formation of a cubic phase. After that, the cubic phase is passed for ultrasonic treatment.[30] Careful maintenance of the variables, frequency and amplitude, is required to manage the pulse frequency and prevent overheating of the samples.

Top-down Technique:

This method requires a significant energy input and is suited to cubic phases in bulk. It is made by combining lipid and amphiphilic surfactants. The aforesaid mixture is then homogenised under high pressure, followed by sonication, to disperse it in an aqueous phase. Liquid crystal nanoparticles are created as a result.

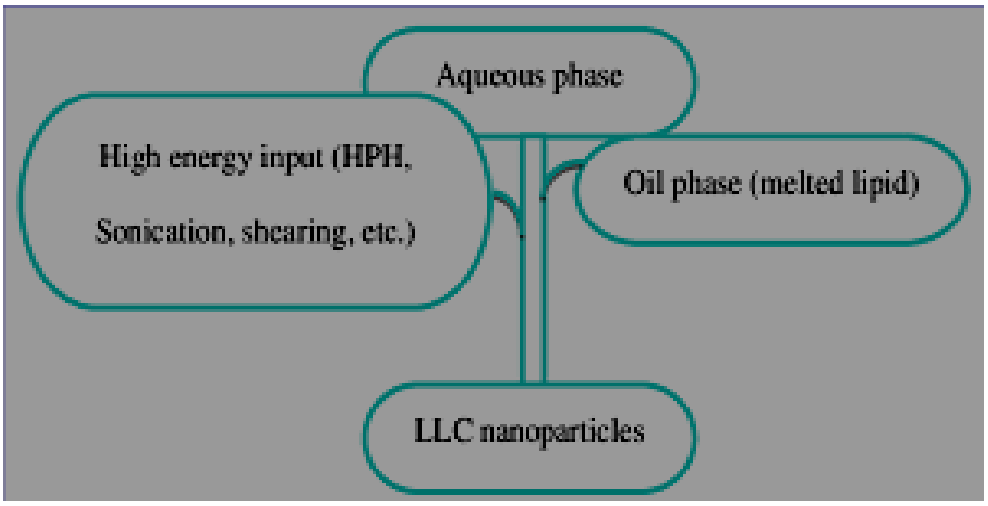

Fig. No. 3: Top-down method of Cubosome formulation

It is a frequently employed method. Ljusberg-Wahren is credited with creating it in 1996. High energy input is needed.[31] Structure like vesicles and cubosomes coexist. The cubic phases are initially generated in bulk using this approach, and then they are dispersed using high energy. Because the cubic phases are rupturing, a large amount of energy input is needed.[32]

Bottom-Up Technique:

This method may be used to produce cubosomes effectively. In the preparation of minute particles, it works incredibly well. It takes relatively little energy to do something.

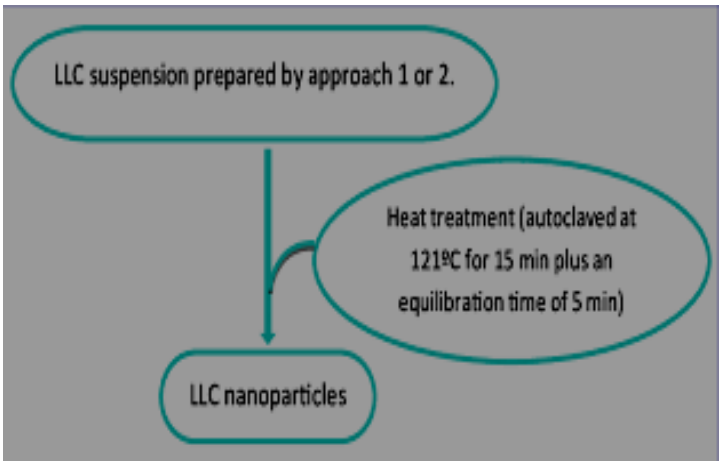

Fig. No. 4: Formulation of Cubosomes by bottom-up method

The cubosomes are created using this process from the precursors. This results in the emulsification process [33]resulting in the spontaneous production of cubosomes. Hydrotrope is

a key component in this approach. It is a procedure in which small particles aggregate to generate big particles (approach: dilution-based). As a result, they show consistency over a longer period of time.

Evaluation and Characterization of Cubosomes:

Visual Inspection Studies:

This entails examining the cubosomes' external features, such as their form, turbid, colour, uniformity, and existence of particles.

Transmission Electron Microscopy:

Using TEM, cubosome morphology may be evaluated. Cubosomal particle forms might be provided by it. For observation, it could provide electron microphotographs, and it also produces a high-resolution picture. Therefore, visualisation is possible. It can offer a significantly greater resolution than light microscopes. It is an excellent instrument for studying the behaviour of soft matter dispersions. All the problems with traditional electron microscopy, such as the vacuum setting, poor image quality, the induction of structural changes in cubic phase, etc., may be resolved.

Zeta Potential:

A preparation's zeta potential might be used to gauge its stability. It exudes a strong repulsiveness.

Viscosity:

A rotational Brookfield viscometer, or viscometer, can be used to measure viscosity.

Particle Size Analysis:

This involves diluting the samples with a suitable solvent and subjecting them to 300 Hz, which is the intensity of light scattering at 25°C.[34] A Zeta sizer is used to measure it via dynamic laser light scattering. Zeta potential and the PDI may both be assessed in this. It provides information about average weight, volume, and size. There is a requirement for the Malvern zeta sizer to determine particle size; thus, the samples could be diluted with water 100 times.

Polarized Light Microscopy:

Polarized light microscopy may be used to evaluate the cubosomal surface coatings, that are optically short ringent or vesicular. This technique might also give the anisotropic and isotropic differentiation.[35] It could track how cubic phases changed. It offers details on the potential coexistence of hexagonal liquid crystals and layered liquid crystals.[36]

Differential Scanning Calorimetry:

DSC may be able to determine if and when a phase transition occurs since liquid crystals are thermodynamic equilibrium processes and phase changes are brought on by endothermic and exothermic processes.

Entrapment Efficiency:

The evaluation of cubosomal entrapment effectiveness might be done using ultrafiltration methods.[37] This approach uses a spectrophotometer to determine the concentration of an unentrapped drug and extrapolate that value to the concentration of an entrapped medication. In this, the sample is diluted with deionized water, and then centrifugation is performed. Following this, there is an ultrafiltration method that uses a certain quantity of medication that is quantified spectrophotometrically.

Drug Loading Determination:

Gel permeation chromatography or ultrafiltration techniques may be used to make the determination.[38] HPLC may then be used to evaluate it.

Drug Release Measurement:

In this, the stability may be evaluated based on morphological and organoleptic traits with regard to the time period.[39] additionally, the assessment of the drug concentration and particle size distribution at time.[40] this looks at assessments of potential alterations over time.

Applications of Cubosomes:

As a Drug Delivery Vehicle:

Some businesses, like L'Oréal and Nivea, are attempting to develop cosmetic formulations that utilise cubosomes as O/W emulsion stabilisers, pollution absorbents, etc. This is an almost ubiquitous use for cubosomes and a fairly typical use for them.[41]

For Topical Drug Delivery System:

Cubosomes are employed in mucosal as well as topical medication delivery systems because of their strong bio-adhesion. They are helpful in protecting skin that is sensitive.

Due to the presence of ethanol, which is responsible for the rupture of the skin, cubosomes have a high level of permeability. The outcome is an improvement in fat fluidity, that also raises the medication's skin penetration.

For Treatment of Viral Diseases:

Monoglycerides are one type of lipid that is utilised to create cubosomes and has microbicidal properties. They can thus be used to treat sexually transmitted illnesses, including those brought on by bacteria and viruses (HIV).[42]

For Cancer Therapy:

Numerous anticancer medications have been effectively encapsulated inside cubosomes. Cubosomes serve as an excellent vehicle for anticancer drugs. In order to get greater effects and retention for anticancer medicines, the delivery system's tiny size is a crucial factor.

For Intravenous Drug Delivery:

In contrast to liposomes, the cubosomes offer the potential property of having a higher pharmacological payload. It also functions as a carrier, making it the perfect carrier for injections. Cubosomes are the source of several insoluble tiny compounds.

FUTURE PROSPECTS:

The cubosomes are good in applying medicine distribution and sustained drug release. Although cubosome study has previously been done, it has to be increased due to it is still quite new. Exact studies are required for drug entrapment capacities and releasing behaviours. Understanding the compatibility of cubosomes with blood and physiological tissues will require further optimization and development. Another need for growth is the necessity for cubosome stability in body fluids. Studies are also required to discover the factors that affect the medication delivery from cubosomes.

CONCLUSION:

Both hydrophilic and hydrophobic medications may be encapsulated by cubosomes, and they can also enter the targeted areas, such as the brain or central nervous system. Proteins, immunogenic compounds, medicinal molecules, and beauty formulations can all be included in cubosomes. Despite their tiny size, they have a large surface for loading drugs. The cubosomes have been successfully used for diabetic, melanoma, oral, intravenous, topical, and ophthalmic treatments. Additionally, it possesses a special quality in personal care products. The internal organisation of cubosomes and bodily tissues is comparable. They are useful for treating the skin and different bodily tissues. The pharmaceutical industry advances as a result, both industrially and commercially. Cubosome formulations are made by simply mixing lipids and water, and they provide flexibility in the product's development process. Because lipids are compatible with bodily tissues, they are appropriate. In order to better understand cubosome safety testing and the function of cubosome vesicles in drug delivery systems, more research on cubosomes is necessary.

REFERENCES:

1. Luzzati V., Tardieu A., Gulik-Kryzwicki T., Rivas E., Riess-Husson F., Nature (London), 220, 485—487 (1968).
2. Scriven L. E., Nature (London), 263, 123—124 (1976).
3. Shah J. C., Sadhale Y., Chilukuri D. M., Adv. Drug Deliv. Rev., 47, 229—230 (2001).
4. Larsson K., J. Disper. Sci. Technol., 20, 27—34 (1999).
5. Engstrom S., Alfons K., Rasmusson M., Prog. Coll. Pol. Sci., 108, 93—98 (1998).
6. Larsson K., J. Phys. Chem., 93, 7304—7314 (1989).
7. Spicer P. T., Hayden K. L., Lynch M. L., Langmuir, 17, 5748—5756 (2001).
8. Gustafsson J., Ljusberg-Wahren H., Almgren M., Langmuir, 12, 4611—4613 (1996).
9. Luzzati V., Vargas R., Mariani P., Gulik A., Delacroix H., J. Mol. Biol., 229, 540—551 (1993).
10. Schmidt-Lewerkuhne H., Riedel J. H., Eur. Patent App. EP 0, 67168 A2 (1998).
11. Landau E. M., Rosenbusch J. P., Proc. Natl. Acad. Sci. U.S.A., 93, 14532—14534 (1996).
12. Caboi F., Amico G. S., Pitzalis P., Monduzzi M., Nylander T., Larsson K., Chem. Phys. Lipids, 109, 47—49 (2001).
13. Gustafsson J., Ljusberg-Wahren H., Almgren M., Larsson K., Langmuir, 13, 6964—6971 (1997). 14) Anderson D. M., Wennerstrom H., J. Phys. Chem., 94, 8683—8684 (1990).
14. Rizwan SB, Dong YD, Boyd BJ, Rades T and Hook S: Characterization of bicontinuous cubic liquid crystalline systems of phytantriol and water using cryo field emission scanning electron microscopy. Micron 2007; 38: 478-85.
15. Bei D, Meng J and Youan BC: Engineering Nanomedicine for Improved Melanoma Therapy: Progress and Promises. Nanomedicine (London, England) 2010; 5(9): 1385-99.
16. Tilekar KB, Khade PH, Shitole MH, Jograna MB and Patil RY: Cancer oriented cubosomes – a review. International Journal for Pharmaceutical Research Scholars (IJPRS). 2014; 3: 198-10.
17. Spicer PT: Cubosome Processing Industrial Nanoparticle Technology Development. Chemical Engineering Research and Design 2005; 83(A11): 1283-86.
18. Yingchoncharoen P, Kalinowski DS and Richardson DR: Lipid-based drug delivery systems in cancer therapy: what is available and what is yet to comePharmacol Rev 2016; 68: 701-87.

19. Sastri KT, Radha GV, Pidikiti S and P Vajjhala: Solid lipid nanoparticles: preparation techniques, their characterization, and an update on recent studies. J Appl Pharmaceut Sci 2020; 10: 126-41.
20. Rizwan SB, Dong YD, Boyd BJ, Rades T and Hook S: Characterization of bicontinuous cubic liquid crystalline systems of phytantriol and water using cryo field emission scanning electron microscopy. Micron 2007; 38: 478-85.
21. Tilekar KB, Khade PH, Kakade S, Kotwal S and Patil R: Cubosomes a drug delivery system. International Journal of Chemical and Biochemical Science. 2014; 4: 812-24.
22. Karami Z and Hamidi M: Cubosomes: Remarkable drug delivery potential. Drug Discovery Today 2016; 21: 789- 01.
23. Nanjwade BK, Hundekar YR, Kamble MS and Srichana T: Development of cuboidal nanomedicine by nanotechnology. Austin J Nanomed Nanotechnol 2014; 2: 1023.
24. Barriga HMG, Ces O, Law RV, Seddon JM and Brooks NJ: Engineering Swollen Cubosomes Using Cholesterol and Anionic Lipids. Langmuir 2019; 35: 16521-27.
25. Thapa RK: Liquid crystalline nanoparticles encapsulating cisplatin and docetaxel combination for targeted therapy of breast cancer. Biomater Sci 2016; 4: 1340-50.
26. Leung SSW and Leal C: The stabilization of primitive bicontinuous cubic phases with tunable swelling over a wide composition range. Soft Matter 2019; 15: 1269-77.
27. Mansoori B, Mohammadi A, Davudian S, Shirjang S and Baradaran B: The different mechanisms of cancer drug resistance: a brief review. Adv Pharm Bull 2017; 7: 339-48
28. Sagalowicz L, Leser ME, Watzke HJ and Michel M: Monoglyceride self-assembly structures as delivery vehicles. Trends Food Sci Technol 2006; 17: 204-14.
29. Dong YD, Larson I, Hanley T and Boyd BJ: Bulk and dispersed aqueous phase behavior of phytantriol: Effect of vitamin E acetate and F127 polymer on liquid crystal nanostructure. Langmuir 2006; 22: 9512-18.
30. Bei D, Meng J and Youan BB: Engineering nanomedicines for improved melanoma therapy: progress and promices. Nanomedicine 2010; 5: 1385-99.
31. Urvi S, Dhiren D, Bhavin P, Patel U and Shah R: Overview of Cubosomes: A Nano Particle. International Journal of Pharmacy and Integrated Life Sciences 2013; 1(5): 36-47.
32. Thadanki M: Overview of cubosomes: a nanoparticle, Int. J Res Pharm and Chem 2011; 1: 535-41.
33. Bhosale RR, Osmani RA, Harekar BR and Ghodake PP: The Inimitable Nanoparticulate Drug Carriers. Scholars Academic Journal of Pharmacy 2013; 2(6): 481-86.
34. Saly S, Ehab RB, and Sabry B: The design and evaluation of novel encapsulation technique for topical application of alpha lipoic acid. Journal of Advanced Pharmaceutical Research 2013; 4(1): 13-22.
35. Wibroe PP, Azmi ID, Nilsson C, Yaghmur A and Moghimi SM: Citrem modulates internal nanostructure of glyceryl monooleate dispersions and bypasses complement activation: towards development of safe tunable intravenous lipid nanocarriers. Nanomedicine 2015; 11(8): 1909-14.
36. Thorat YS, Gonjari ID and Hosmani AH: Solubility enhancement techniques: a review on conventional and novel approaches. International Journal of Pharmaceutical Sciences and Research 2011; 2(10): 2501.
37. Wu H, Li J, Zhang Q, Yan X, Guo L and Gao X: A novel small Odorranalectin-bearing cubosomes: Preparation, brain delivery and pharmacodynamic study on amyloid - 25-35-β treated rats following intranasal administration. Eur J Pharm Biopharm 2012; 80: 368-78.
38. Thorat YS, Gonjari ID and Hosmani AH: Solubility enhancement techniques: a review on conventional and novel approaches. International Journal of Pharmaceutical Sciences and Research 2011; 2(10): 2501.
39. Pitzalis P, Monduzzi M, Krog N, Larsson H, LjusbergLahren H and Nylander T: Characterization of the liquid crystalline phases in the glycerol monooleate/diglycerol mono-oleate/water system, Langmuir 2000; 16, 6358-65.
40. Angelov B, Angelova A and Drechsler M: Identification of large channels in PEGylated cubosome nanoparticles by synchrotron radiation SAXS and Cryo-TEM imaging. Soft Matter 2015; 11(18): 3686-92.
41. Thadanki M, Kumari PS and Prabha KS: Overview of cubosomes: a nanoparticle. International Journal of Research in Pharmacy and Chemistry 2011; 1(3): 535-41.
42. Bei D, Meng J and Youan BB: Engineering nanomedicines for improved melanoma therapy: progress and promoses. Nanomedicine 2010; 1385-99.