Cubosomes A New Versatile Drug Delivery System

Sushma Awati

Assistant professor

Pharmaceutics, BVVS Hanagal Shri Kumareshwar College of Pharmacy,

Bagalkot,

[sushmawati95@gmail.com](mailto:sushmawati95@gmail.com)

Metre Anil Suresh

Assistant professor

Pharmaceutical Chemistry BLDEAS college of pharmacy

basavan bagewadi, 58203

[metreanil1@gmail.com](mailto:metreanil1@gmail.com)

Sachinkumar wali

Assistant professor

HKE'S matoshree Taradevi Rampure institute of pharmaceutical science, a

kalaburagi

Vinod Babaleshwar

Assistant Professor

Department of Pharmaceutics

Shri Sharanabasaveshwar College of Pharmacy

Vijayapura-586101

vinodbabaleshwar25@gmail.com

ABSTRACT

Cubosomes are self-assembled liquid crystalline particles. They are formed by dispersion of discontinuous cubic liquid crystalline phases.Cubosome are honey comb like structure. Cubic liquid crystals are physically transparent and isotropic phases that are stable in excess water and show a unique system for the production of pharmaceutical dosage forms. The liquid crystals of cubic phase are used in the controlled release of selected water and oil soluble molecules. Cubic phases have a thermodynamically stable structure consisting of two separate, continuous but non intersecting hydrophilic regions divided by a lipid bilayer. This allows the incorporation of hydrophilic and hydrophobic materials and also amphiphilic materials into the system. Lipid based cubic system is biocompatible, and bio adhesive. Mainly two methods are employed for the preparation of cubosome, they are top- down technique and bottom -up technique. Cubosome structure is investigated through electron microscopy, light scattering, X-rays, and NMR, although some researchers are studying the potential of cubosomes as a delivery system.

Key words: Cubosome, Honeycomb, Hydrophilic, Hydrophobic, Drug delivery systems

# INTRODUCTION

Cubosomes get their name from their structure, which is 'phases' suffixed as'some' and they have a cubic crystal lattice. These are nanoparticles which are self-assembled liquid crystalline particles of certain surfactants with proper ratio of water with microstructure. Larsson coined the term Cubosomes to reflect the cubic molecular crystallography and similarity to liposomes. Certain lipids, detergents, and polymer molecules, or amphiphilic molecules, contain both polar and non-polar components. Physically transparent and isotropic phases known as 8 liquid crystals exhibit a novel method for the synthesis of pharmaceutical dosage forms. They are stable in excess water. In the bicontinuous cubic liquid crystalline phase, cubosomes are distinct, sub-micron-sized nanostructured particles. The square and rounded particles with discernible interior cubic lattices are called cubosomes. Because of the complexity of their structure, they can load more drugs. Cubosomes can encapsulate hydrophobic, hydrophilic, and amphiphilic substances. They are thermodynamically stable and have carvenous (honeycomb) structures with sizes ranging from 100 to 500 nm that are tightly packed and twisted into three-dimensional bilayers. Cubosomes are nanoparticles, but instead of the usual solid particles, they are self-assembled liquid crystalline particles with a solid-like rheology that provides unique practical properties. Figure: Cubosomes with various drug loading modalities. Depending on the content substance, the medication-to-polymer ratio is roughly 1:2 or 1:1. 3Cubosomes and the parent cubic phase share the same microstructure; however, cubosome dispersions have a significantly lower viscosity than the cubic in bulk phase. 13 Because 'phases' is prefixed with'some' and contains a cubic crystal lattice, the term cubosomes was coined.9 Cubosomes form at a specific temperature. They exist in three distinct phases: - P-surface, G-surface, and D-surface are used for primitive, gyroid, and diamond structures. [14,15] Temperature, stability, bicontinuous structure, high internal surface area, solid-like viscosity, and low coast raw material make them appealing for consumer and pharmaceutical industrial applications. Despite widespread interest in cubosome applications, no studies have been conducted to investigate the practical aspects of large-scale cubosome processing and production.

**ADVANATGES OF CUBOSOMES1**

1. It is economic.
2. It is non-toxic and biocompatible.
3. Method of preparation is simple.
4. They have ability to encapsulate both hydrophilic& hydrophobic & also amphiphilic drugs
5. They have a sustained- release drug delivery characteristics
6. Cubosomes have biocompatibility and bioadhesivity properties.
7. Bicontinuous cubic liquid crystalline phase of cubosomes even stable in excess water
8. Cubic phase materials can be formed by simple combination of biologically compatible lipids and water and are thus well suited for use in treatments of skin, hair, and other body tissue.
9. With respect to liposomes, cubosomes possesses a larger ratio between the bilayer area and the particle volume and a larger breaking resistance
10. Because of their high internal surface area and crystalline cubic structures they have high drug payloads.
11. They can be prepared by simple method and possess lipid biodegradability
12. Targeted release and controlled release of bioactive agents
13. Cubosomes are excellent solubilizers, compared with conventional lipid or non-lipid carriers.
14. They show high drug carrier capacity for a range of sparingly water-soluble drugs.
15. These are an excellent vehicle to protect the sensitive drug from enzymatic degradation and in-vivo degradation, such as peptides and proteins.
16. The cuboidal system enhances the bioavailability range twenty to more than one hundred times of water-soluble peptides.
17. The cubic phases of cubosomes can be fractured and dispersed to form particulate dispersions that are colloidally and/or thermodynamically stable for longer time.

**DISADVANTAGES: 1,4,10**

1. Manufacture of Cubosomes on a large scale embodied
2. difficulty because of their viscosity
3. High energy processes
4. Harmful to fragile temperature-sensitive active ingredients
5. Expensive
6. Difficult to scale up

**Preparation methods of cubosomes**

The cubic lipid phases of cubosomes consists of three macroscopic forms that are typically encountered precursors, bulk phase gel and particulate dispersion. Bulk phase cubic gels that are rigid, strong, optically isotropic, and solid like particles which are in equilibrium with water and are dispersed into cubosome nanoparticles that has been made easier than their dispersions [26]. The nanoparticle dispersions prepared within the cubosomes may be achieved with the aid of several techniques consisting of spray drying, sonication, high stress homogenization and spontaneous emulsification, while sonication and high-stress homogenization and then paperwork the complex dispersions that incorporates vesicle like structures and cubosomes with time dependent ratios of each sort of particle.

1. Top-down approach

2. Bottom-up approach

3. Heat treatment

4. Spray drying

The cubosomes dispersion carried out by

#### Fabrication method

1. Emulsification method.

**Top-down approach**

It is the most frequently performed operation, as first noted by Ljusberg-Wahren in 1996. There are two stages involved in using this technology. Aggregation occurs because the thick bulk cubic phase is first created by combining the lipids with stabilisers. The second stage involves applying high power processing, such as excessive-strain homogenization, sonication, or excessive electricity dispersions, to the bulk cubic segment in order to create Lyotropic Liquid Crystal (LLC) nanoparticles (cubosome dispersions).1

Nanoparticles. The most popular technique for creating LLC nanoparticles is HPH. Cubosomes created using this top-down technique coexist with vesicles like dispersed nanoparticles of lamellar liquid crystalline phase or vesicle-like structures and are stable against aggregation for about a year. However, since it takes a lot of energy to disperse the cubic phase into cubosomes in large-scale manufacturing, it is difficult to incorporate ingredients like proteins and peptides that are sensitive to temperature.5,19

The cubic phases are distinguished by the fact that they are a single thermodynamic phase with a periodic liquid crystalline structure. The energy required to rupture a cubic phase in a direction parallel to the shear direction is proportional to the number of tubular networks. 2 The yield stress in the cubic phase increases with increasing temperature.

The amount of bilayer-forming surfactant and oils. According to Warr and Chen, cubic phases may behave as lamellar phases during dispersion as shear increases, dispersed liquid crystalline particles form at intermediate shear rates, and defect free bulk phase reforms at higher shear rates.

Oil phase (melted lipid)

Liquid + stabilizer

Aqueous phase

LLC nanoparticles

Aqueous phase

High energy input (homoginization..)

High energy input (HPH,Sonication .shearing etc.)

**2. Bottom-up approach**

The bottom-up approach assembles the building blocks into the final material.

Cubosomes are allowed to form from the precursors. The inverse micellar phase droplets are allowed to slowly cool after being dispersed in water at 80C..5,11Gradually These droplets start to form clumps. The cubosomes are produced by mixing monoolein-ethanol solution with a poloxamer 407 solution.Cubosomes are formed by emulsification.The spray drying technique is used to produce the cubosomes. On simple hydration, spray dried powders comprise monoolein coated with starch..5

In large scale production of cubosomes, this method is more useful.The bottom approach assembles the building blocks into the final material.These structures are formed by the dispersion of a mixture consisting of a liquid crystal and a hydrotrope.In liquid precursors, hydrotrope helps in dissolving water insoluble lipids..41,45 Cubosomes are produced through crystallization.This method requires less energy than the top-down approach and is more suited for large scale production.Patric T.In the presence of a hydrotrope, Spicer studied the formation of the cubic phase..8 Hydrotrope here is a particle that is either hydrophilic or hydrophobic yet is unequipped for displaying surfactant conduct (Micelle formation).45 Hydrotropes don't create LLC, however they increment the lipid solvency and afterward show a peculiarity called "salting out" forerunner might be both of a fluid or a strong. The fluid antecedent is made by adding ethanol to the lipid (monoolein) ethanol. Cubosomes are delivered, when the antecedent is weakened. Powdered forerunners involve a dried out substance that is covered with a polymer, structures cubosomes upon the hydration substance that is covered with a polymer, structures cubosomes upon the hydration.12

Hydrotrope

Liquid + stabilizer

Aqueous solution

Low energy input (vortex....)

cubosomes

***Heat treatment approach***

The process described here cannot be considered a comprehensive method for manufacturing cubosomes. Instead, it focuses on transforming non-cubic vesicles into well-organized cubic particles through the application of homogenization and heat treatment. This process leads to a reduction in the fraction of small particles that represent vesicles, while simultaneously promoting the formation of cubic phases with narrow particle distribution and excellent colloidal stability.

**Spray drying** Due to the limited flexibility of liquid precursors for cubosome production, a dry powder precursor was created.

The spray drying process was used for the manufacture of monoolein precursor.The method was limited for powerful medicaments, vitamins, flavours, or smells because the amount of active material loading was reduced.Cubosomes are made when Monoolein and water are combined around 40 C.The gel is dispersed with mechanical or Ultrasonic energy.High-pressure homogenizers are frequently used. The cubosomes have been secured.A lot of energy is input. 3,24

Or A dry powder precursor for cubosome preparation was developed using a spray drying technique. They used spray drying to make monoolein precursor.The method was limited for powerful medicaments, vitamins, flavours, or odours because the amount of active material loading was reduced. Cubosomes are formed by combining monoolein and water at temperatures around 40 C.

The gel is dispersed using mechanical or Ultrasonic energy.Cubosomes are created using high-pressure homogenizers.The cubosomes are protected.A lot of energy is input. 3,24

**Fabrication method**

The required amount of drug was added and stirred continuously after the drug was melted in a hot water bath. Drop by drop, deionized water is added.After being kept at room temperature for up to 48 hours, it was disturbed by mechanical stirring crude dispersion and fragmented by a sonicater probe under a cool temperature of 20C. (16,17,6)

**Emulsification method**

The 1% P407, 5% GMO and 5% ethanol are added to the water and followed by the Ultrasonication method.

Adding the solution that was added to the melting caused the two items to melt at 60.

The dispersal mixture is kept at the ambient temperature and protected from the sun, but it is added dropwise to deionized water at the 70 C, which will give it a maximum power of 130 kilowatts..17,18,6

**Evaluation of Cubosomes:**

**Visual inspection**

The Cubosomes were outwardly evaluated for optical appearance like tone, turbidity, homogeneity, presence of perceptible particles for around 6-10 days after readiness.20,54

**Photon Correlation Spectroscopy**

By utilizing zeta-sizer (photon relationship spectroscopy) molecule size circulations in still up in the air with dynamic laser light dissipating. The example is weakened with appropriate dissolvable and acclimated to light dispersing force of around 300 Hz and estimated at 25°C in three-fold. By utilizing normal volume weight size, the gathered information can be for the most part shown. The zeta potential and polydispersity file can likewise be recorded.

**Polarized Light Microscopy**

The conceivably surface covering of the cubosomes can be uncovered by utilizing enraptured light microscopical technique. This can likewise be utilized to recognize isotropic and anisotropic substances.

**HPLC Procedure**

A verified HPLC densitometry technique was employed to examine the samples. The plates that were created were treated with a mobile phase consisting of cupric sulfate (penta hydrate), phosphoric acid, and water. The quantification was performed using a UV light source that was set at the appropriate wavelength..21,20

**d) Entrapment Efficiency**

For knowing the entanglement proficiency, 1 ml from every one of the scatterings was taken and weakened with 4 ml of deionised water. Again 1 ml of the weakened scattering is taken and further weakened with one more 4 ml of deionised water. This shaped scattering is gone through a needle channel with pore size of 0.1 μm and the filtrate was examined spectrophotometrically at 250 nm. Taking into account the weakening variable, this got focus was increased by the absolute volume of the scattering created. This gives the free convergence of medication (Cf) which when diminished from the all out drug fixation (Ct) gives how much medication ensnared in the cubosomes to get all the more precisely, each trial was rehashed multiple times. Entanglement effectiveness % of cubosomes**e)**

**Particle Size Distribution Measurements**

Characterization of both spray dried powders and the aqueous dispersions of cubosomes is carried out by using laser diffraction.22

**f) Cryo-Transmission Electron Microscopy**

A modest quantity of arranged example is put on an unadulterated flimsy bar 600-network transmission electron microscopy framework at encompassing condition. The arrangement was smudged with channel paper to frame a flimsy film for crossing the openings of transmission electron microscopy matrix. Presently confirmations of test are finished by submerging into fluid ethane close to its edge of freezing over. This is moved to TEM for imaging at a temperature of - 180°C by utilizing a cryo holder. Pictures are carefully recorded.23,51

**g) Pressure Ultra-filtration Method**

Drug release measurement from cubosomes is carried out using the pressure ultra-filtration technique. This method utilizes an Amicon pressure ultrafiltration cell equipped with a Millipore membrane under ambient conditions.temperature **of (22 }2)°**

**h) Thermal Analysis**

To assess the condition of the drug within the Cubosome, DSC analysis was conducted between temperatures of 37°C to 56°C, at which the ingredients of cubosomes appeared to fuse together, potentially causing the glycerol monooleate to become more flexible. The thermal reactions observed between 200°C and 300°C are likely associated with the degradation of glycerol monooleate, as there is no distinct melting peak detected for the drug around 200°C.

**i) Light Microscopy**

The cubosomes that have been prepared are mixed with deionized water and observed under an optical microscope. The microscope has been calibrated using a micrometer slide at magnifications of 400x and 1000x.

**j) Drug content of dispersions**

It is evaluated by diluting the filtered dispersion sample in methanol (1:9 v/v) and analysed by HPLC.52

**k) Transmission Electron Microscopy**

Cubosomes can be utilized to observe the configuration and internal composition of the cubosomes. The cubosomes, which are cubic phase nanoparticles, were treated with a 2% phosphotungstic acid solution to create negative staining.

An acidic solution with a pH of 6.8 was prepared and then applied onto a carbon-coated grid measuring 200 mesh. The grid was allowed to air dry at room temperature. Electron microscope analysis was utilized to capture electron micrographs..

**l) X-Ray Diffraction Measurements**

XRD is used to identify the spatial arrangements of different groups in the sample and this is carried out by using Philips PW 1830 X-Ray generator.53

**m) Gel permeation chromatography**

With the assistance of gel saturation chromatography we can know the ensnarement productivity and medication stacking in cubosomes. By utilizing ultra-filtration procedure the unentraped drug not entirely settled, which is deducted from the aggregate sum of medication added.

**n) Viscosity**

By utilizing Brookfield turning viscometer the thickness of arranged definition of not entirely set in stone at various precise speeds at 25°C. The revolution speed of viscometer was with shaft #18 and 20 rpm. To ascertain the thickness of plan; normal of three readings was taken.

**p) Stability Studies**

By exploring the organoleptic and morphological attributes concerning time, the actual soundness studies can be performed. Drug content and molecule size conveyance canbe evaluated, throughout the time.55

**REFERENCE**

1. Blessy M.R et al, **Cubosomes - advanced drug delivery systems: A review.,** Indo Am. J. P. Sci, 2020; 07(12).
2. Chaudhary K, Sharma D, Cubosomes: A Potential Drug Delivery System ,Asian Journal of Pharmaceutical Research and Development. 2021; 9(5):97-101.
3. Thadanki M, Kumari PS and Prabha KS: Overview of cubosomes: a nano particle.International Journal of Research in Pharmacy and Chemistry, 2011; 1(3): 535-41.
4. Anbarasan B, Fatima G, Shanmuganathan S. An Overview of Cubosomes- SmartDrug Delivery System. Sri Ramachandran J Med. 2015; 8(1): 1-4.
5. Madhurilatha T, Paruchuri SK, Suria P. Overview of Cubosomes: A NanoParticle. Int J Res Pharm & Chem. 2011; 1(3): 535-541.
6. Sadhu Venkateswara Rao 1 \*, Beram Naga Sravya :A review., GSC Biological and Pharmaceutical Sciences, 2018, 05(01), 076–081
7. Karami, Z. and M. Hamidi, Cubosomes: remarkable drug delivery potential. Drug Discovery Today, 2016. **21**(5): p. 789-801.
8. https://dx.doi.org/10.22159/ijcpr.2021v13i6.1926 Journal homepage: <https://innovareacademics.in/journals/index.php/ijcpr>
9. Bhosale RR, Osmani RA, Harkare BR, Ghodake PP. Cubosomes: the inimitable nanoparticulate drug carriers. Scholars Academic Journal of Pharmacy, 2013; 2(6): 481-6.
10. Antony LP, Seevaka K. Advancement of Cubosomes Nanomedicine. Int J of Pure & Applied Mathematics 2018;119(2): 7847-54.
11. Spicer PT, Hayden KL, Lynch ML, Ofori-Boateng A, Burns JL. Novel Process for Producing Cubic Liquid Crystalline Nanoparticles (Cubosomes). Langmuir. 2001;17: 5748-5756.
12. Khalifa MK. Miconazole nitrate based cubsosome hydrogels for topical application. Int J Drug Deliv. 2015;7:1-12.
13. Tilekar KB, Khade PH, Shitole MH, Jograna MB and Patil RY: Cancer oriented cubosomes – a review. International J for Pharmac Res Scholars (IJPRS), 2014; 3: 198-10.
14. Sadhu Venkateswara Rao, Beram Naga Sravya and Kantamneni Padmalath. A review on cubosome: The novel drug delivery system. GSC Biological and Pharmaceutical Sciences, 2018; 05(01): 076–081.
15. Spicer PT, Hayden KL, Lynch ML, Ofori-Boateng A, Burns JL. Novel process for producing cubic liquid crystalline nanoparticles (cubosomes). Langmuir, 2001; 18,17(19): 5748-56.
16. Abdelrahman F.E, Elsayed I, Gad M.K., BadrA, Mohamed M.I, “ Investigating the cubosomal ability for transnasal brain targeting: In 2 vitro optimization, ex vivo permeation and in vivo biodistribution.” International Journal of Pharmaceutics, 2015.IJP, 14934 1–11,
17. Sherif S, Bendas E.R, Badawy S. **“**The Design and Evaluation of Novel Encapsulation Technique for Topical Application of Alpha Lipoic Acid”Journal of Advanced Pharmaceutical Research. 2013 ISSN: 2229-3787, 4(1), 13-22
18. Nasr M, Mohamed G.K, Abdelazem A. “In vitro and in vivo evaluation of cubosomes containing 5-fluorouracil forlivertargeting” a Department of Pharmaceutics and Industrial Pharmacy, FacultyofPharmacy,HelwanUniversity,,Egypt b Department of Pharmaceutical Chemistry, Faculty of Pharmacy,Helwan University, Cairo11790, Egypt Received 11October 2014; received inrevised form 4 November 2014; accepted 28 November 2014. 80-87.
19. Bei D, Meng J, Youan BB. Engineering nanomedicines for improved melanoma therapy: progress and promises. Nanomedicine. 2010; 5:1385-99.
20. Lakshmi Prasanna Yalavarthi et al / Int. J. Res. Ayurveda Pharm. 11 (5), 2020
21. Bhosale RR, Osmani RA, Harkare BR and Ghodake PP. Cubosomes. The Inimitable Nanoparticulate Drug Carriers.Sch Acad J Pharm 2013; 2(6): 481-6.
22. Bei D, Marszalek J, Youan BBC. Formulation of Decarbazine loaded Cubosomes- Part I: Influence of formulation variables. AAPS Pharma Sci Tech 2009; 10:1032-9.
23. Sagalowicz L, Michel M, Adrian M, Leser ME, Frossard P,Rouvet M, et al. Crystallography of dispersed liquid crystalline phases studied by cryo-transmission electron microscopy. J Microscopy 2006; 221(2): 110- 121.
24. Lyla P.A.Seevakan.k. Advancement of Cubosomes Nanomedicine.Int J of Pure and Applied. Mathematics.2018;119 (12):7847-7854.
25. Patrick T. Spicer, Matthew L. Lynch; Bicontinuous Cubic Liquid Crystalline Phaseand Cubosome Personal Care Delivery Systems. Available from [http://www.nonequilibrium.com/CubicLiquid CrystallineRosen.pdf](http://www.nonequilibrium.com/CubicLiquid%20CrystallineRosen.pdf)
26. Zahra K, Mehrdad H. Cubosomes: Remarkable drug delivery potential. Drug Discovery Today 2016; 21(5): 789- 801.
27. Ramya SV, Madhusudhan RA, Karthikeyan R, Srinivasababu P. A Review on: Cubosomes drug delivery system. Indian J of Drugs 2017; 5(3): 104-8.
28. Bhosale RR, Osmani RA, Harkare BR and Ghodake PP. Cubosomes. The Inimitable Nanoparticulate Drug Carriers. Sch Acad J Pharm 2013; 2(6): 481-6.
29. Bei D, Marszalek J, Youan BBC. Formulation of Decarbazine loaded Cubosomes- Part I: Influence of formulation variables. AAPS Pharma Sci Tech 2009; 10:1032-9.
30. Sagalowicz L, Michel M, Adrian M, Leser ME, Frossard P, Rouvet M, et al. Crystallography of dispersed liquid crystalline phases studied by cryo-transmission electron microscopy. J Microscopy 2006; 221(2): 110- 121.
31. Murgia S, Falchi AM, Mano M, Laropis S, Angius R, Cameup AM. Nanoparticles from lipid-based liquid crystals: emulsifier influence on morphology and cytotoxicity. J Phys Chem B 2010; (114): 3518-25.
32. Dr. Kala, Aiswarya CS. Cubosomes – A Novel drug delivery system and its functionalization. WJPPS 2017; 6(3): 286- 300.
33. Bei D, Zhang T, Murowchick JB, Youan BB: Formulation of dacarbazine-loaded Cubosomes, part III, Physiochemical characterization. AAPS Pharma Sci Tech 2010; 2:124349.
34. Shrikant RD, Dr. Vaibhav RV. Cubosomes- An advanced drug delivery system- A Review. World J Pharm Res 2019;8(12): 1570-81.
35. Akshay RB, Dhanashri NG. Cubosomes: The novel drug delivery system. World J of pharm Res 2020; 9(8): 1170-85.
36. Mayuri A, Shilpa S. In vitro and in vivo evaluation of cubosomal in situ nasal gel containing resveratrol for braintargeting. Drug Development and Industrial Pharmacy 2017;43(10): 1686-1693.40. Yang Z, Chen M,
37. Spicer, P.T., et al., Novel process for producing cubic liquid crystallinenanoparticles (cubosomes). Langmuir, 2001. **17**(19): p. 5748-5756.
38. Dan, Y. and M.-m. Poo, Spike timing-dependent plasticity of neuralcircuits. Neuron, 2004. **44**(1): p. 23-30.
39. Chong, J.Y., et al., Steric stabilisation of self-assembled cubic lyotropicliquid crystalline nanoparticles: high throughput evaluation of triblock polyethylene oxide-polypropylene oxide-polyethylene oxide copolymers. SoftMatter, 2011. **7**(10): p. 4768-4777.
40. Esposito, E., et al., Lipid-based supramolecular systems for topical application: a preformulatory study. AAPS PharmSci, 2003. **5**(4): p. 62.
41. Um, J.Y., et al., In vitro cellular interaction and absorption of dispersed cubic particles. International journal of pharmaceutics, 2003. **253**(1-2): p. 71-80.
42. Mezzenga, R., et al., Shear rheology of lyotropic liquid crystals: a case study. Langmuir, 2005. **21**(8): p. 3322-3333.
43. Maheshwari, R., S. Chaturvedi, and N. Jain, Novel application of hydrotropic solubilization in the analysis of some NSAIDs and their solid dosage forms. Indian journal of pharmaceutical sciences, 2007. **69**(1): p. 101.
44. Dandekar, D.V. and V. Gaikar, Hydrotropic extraction of curcuminoids from turmeric. Separation science and technology, 2003. **38**(5): p. 1185-1215.
45. Ali, Z., P.K. Sharma, and M.H. Warsi, Fabrication and Evaluation of Ketorolac Loaded Cubosome for Ocular Drug Delivery. Journal of Applied Pharmaceutical Science Vol, 2016. **6**(09): p. 204-208.
46. Verma, P. and M. Ahuja, Cubic liquid crystalline nanoparticles: optimization and evaluation for ocular delivery of tropicamide. Drug delivery,2016. **23**(8): p. 3043-3054
47. Murgia S, Falchi AM, Mano M, Laropis S, Angius R, Cameup AM. Nanoparticles from lipid-based liquid crystals: emulsifier influence on morphology and cytotoxicity. J Phys Chem B 2010; (114): 3518-25.
48. Dr. Kala, Aiswarya CS. Cubosomes – A Novel drug delivery system and its functionalization. WJPPS 2017; 6(3): 286-300.
49. Bei D, Zhang T, Murowchick JB, Youan BB: Formulationof dacarbazine-loaded Cubosomes, part III, Physiochemicalcharacterization. AAPS Pharma Sci Tech 2010; 2: 1243-49.
50. Shrikant RD, Dr. Vaibhav RV. Cubosomes- An advanceddrug delivery system- AReview. World J Pharm Res 2019;8(12): 1570-81.
51. Akshay RB, Dhanashri NG. Cubosomes: The novel drugdelivery system. World J of pharm Res 2020; 9(8): 1170-85.
52. Spicer PT. Cubosomes bicontinuous cubic liquid crystalline nanostructured particles. Cincinnati: Procter and Gamble Company; 2004. doi: 10.1081/E-ENN, PMID 120014156.
53. Shah JC, Sadhale Y, Chilukuri DM. Cubic phase gels as drug delivery systems. Adv Drug Deliv Rev. 2001;47(2-3):229-50. doi: 10.1016/s0169-409x(01)00108-9, PMID 11311994.
54. Drummond CJ, Fong C. Surfactant self-assembly objects as novel drug delivery vehicles. Curr Opinion Colloid Interface Sci. 1999;4(6):449-56. doi: 10.1016/S1359-0294(00)00020-0.
55. Chong JYT, Drummond XMBBCJ. Steric stabilizers for cubic phase lyotropic liquid crystal nanodispersions (Cubosomes). Adv Planar Lipidic Bilayers Liposomes. 2015;21:131-87.
56. Larsson K, Fontell K, Krog N. Structural relationships between lamellar, cubic and hexagonal phases in monoglyceride-water systems. possibility of cubic structures in biological systems. Chem Phys Lipids. 1980;27(4):321-8. doi: 10.1016/0009-3084(80)90026-2.
57. Anbarasan B, Grace XF, Shanmuganathan S. An overview of cubosomes- smart drug delivery system. Sri Ramachandra J Med. 2015;8:1-4.
58. Khedekar PB. Cubosomes: a vehicle for delivery of various therapeutic agents. MOJ Toxicol. 2018;4(1):19–21. doi: 10.15406/mojt.2018.04.00083