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CUBOSOMES - ADVANCED DRUG DELIVERY SYSTEMS: A REVIEW

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Abstract:
Cubosomes are self-assembled liquid crystalline particles. They are formed by dispersion of bicontinuous 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.
Key words: *Cubosome, Honeycomb, Hydrophilic, Hydrophobic, Drug delivery systems.*

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INTRODUCTION:

Drug delivery systems (DDS) can accurately control the release rates or target drugs to a specific body site have a massive effect on the health care system. The biggest challenge faced by drug industry nowadays is to control the delivery rate of active agents to a predetermined site in human body. Controlled release system is to deliver constant supply of active ingredient, zero order rates by continuously releasing for a certain period of time in the predetermined rate.

Novel Drug delivery System (NDDS) refers to the approaches, formulations, technologies, and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effects.The method by which a drug is delivered can have a significant effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. On the other hand, the very slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues. From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition, and efficacy of drugs were generated. These new strategies, often called drug delivery systems (DDS), are based on interdisciplinary approaches that combine polymer science, pharmaceutics, bioconjugate chemistry, and molecular biology.[1]

CUBOSOMES

Cubosomes are self-assembled liquid crystalline particles with a microstructure that provide unique properties in a size range of 50-1000 nm. They are formed by dispersion of bicontinuous cubic liquid crystalline phases. Bicontinuous cubic liquid crystalline phase is an optically clear, very viscous material that has a unique structure at the nanometer scale. The word 'bicontinuous' refers to the division of the two continuous but non-intersecting aqueous regions by a lipid bilayer that is contorted into a space-filling structure. Hydrating a surfactant or polar lipid that forms cubic phase and then dispersing the solid-like phase into smaller particles usually forms cubosomes. Cubosomes are the liquid crystalline cubic nano particles share features from both liquids and crystalline substances. Due to their intermediate state they are also called as "mesophases". Liquid crystalline nano particles possess nano cavities. In this view, system can be used as a carrier for hydrophilic as well as for lipophilic drug molecules, peptides and proteins.[2]

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. They are isotropic, viscous and solid like liquid crystalline substances with cubic crystallographic symmetry. Liquid crystal is a state of matter that has properties between those of conventional liquids and solid crystals.

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 water and oil soluble materials and also amphiphiles into the system. Lipid based cubic system is biocompatible, and bio adhesive. Bicontinuous nature of such cubic phases differentiates them from micellar or discontinuous cubic system containing micelles packed in cubic symmetry.[3]

HISTORY OF CUBOSOME

Cubosomes are square and round shaped crystal particles with internal cubic lattices. The invention of cubosomes is a distinctive story and spans the fields of differential geometry, food science, biological membrane and digestive processes.

In 1980 Luzzati and Hussondiscovered cubosomes, but its manufacture in large scale was difficult because of their complexity and highviscosity. They are unique as they have viscosity similarto solids. These cubic phases can be broken and spread to thermodynamically/ colloidal particulates which are stable for a longer time. At certain concentrations, some surfactants form cubic phases suddenly when mixed with water. In 1985, determined the honey comb structure of cubosomes. The word "Cubosome" was coined by Larsson, since the structure resembles cubic molecular crystals and liposomes. Attempts were made in scaling up the production of cubosomes. In practice very few anticancer drugs are being successfully formulated and characterized as cubosomes.[4]

STRUCTURE OF CUBOSOMES

Cubosomes are discreate, sub-micron, nanostructured particles of bicontinuous cubic liquid crystalline phase. When cubic phase is dispersed into small particles, these particles are termed cubosomes. The internal and structural changes of

cubosomes could be controlled by adjustment in lipid composition. Cubosomes are discrete, sub- micron nanostructures having the same microstructure as the parent cubic phase.Their size ranges from 10-1000 nm in diameter. They appear like dots square shaped or slightly spherical.[5]

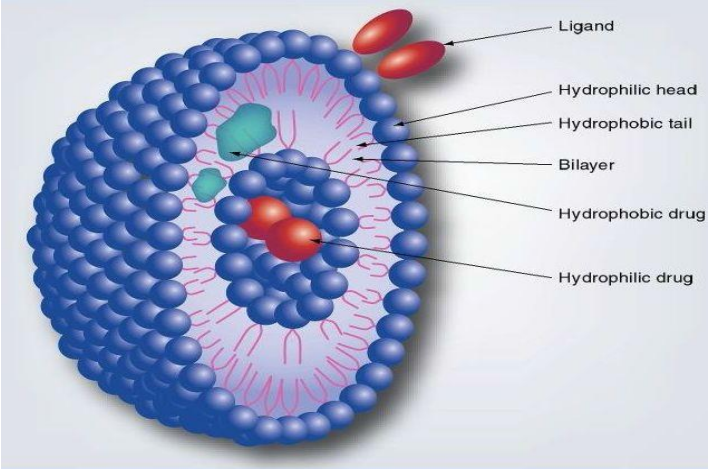

Fig 1.1: Structure of cubosomes

Each dot corresponds to the presence of pore containing aqueous phase cubic phases in lipid-water system. These were first identified using x- ray scattering technique by Luzzati and Husson. Monoglycerides are polar lipids with poor water solubility that exhibit aqueous phase behaviour reflecting their structural similarity to non-ionic surfactants. Bulk cubic phase is formed by hydration of monoolein at levels between 20-40% w/w. Cubic phases are found sandwiched between lamellar and hexagonal liquid crystalline phases. The ability to exist in several different phases is an important property of pure lipids and lipid mixtures; it depends on temperature, hydration and lipid class. In general monoglycerides exhibit different phase behaviours when they exposed to water[6].

Cubosomes are single crystal structures with visible unilamellar vesicles and dispersed lamellar liquid crystalline phase particles. Increasing the polymer to monoolein ratios leads to formation of larger vesicles. Ultra-sonication of bulk cubic phases produces vesicles which in due course of time transforms into cubosomes via membrane fusion. Such meta stability is characteristic of cubosome systems. This is due to slow transport processes involved in forming high viscous crystalline structures. Also high energy is required to fragment these bulk cubic phases.[7]

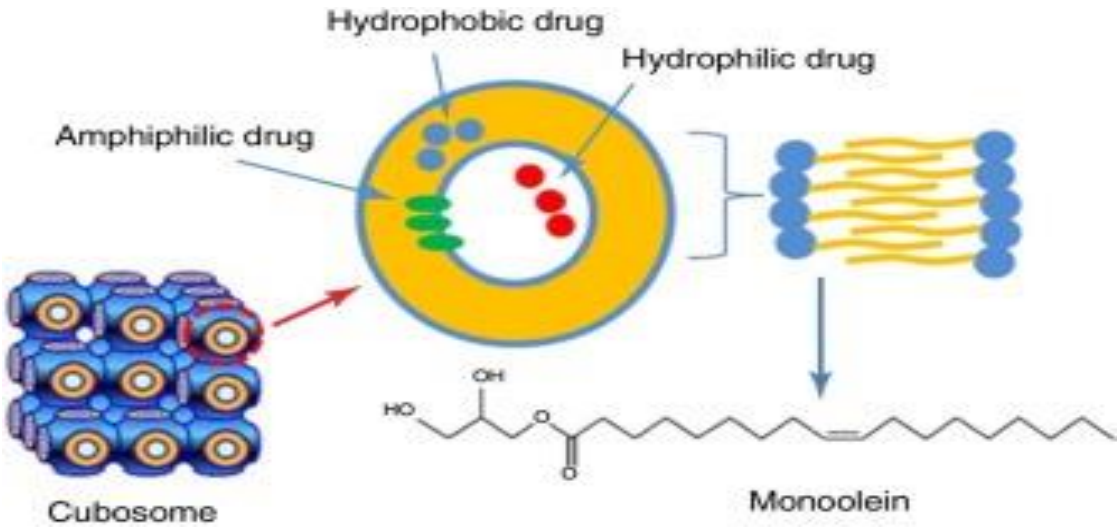

Fig 1.2:Enlarged structure of cubosome

MECHANISM OF CUBOSOME

Cubic phase is more applicable for the controlled release of drug because of its small pore size, ability to solubilise hydrophilic, hydrophobic and amphiphilic molecules.Cubosomes are selected for the drug which comes under BCS classification II, because it has low water solubility and high permeability. Cubosomes will enhance the drugs water solubility and thereby improve its bioavailability. Cubosomes have great potential in drug nano formulations for oral drug delivery owing to their best advantages, like high drug payload due to high internal surface area and cubic crystal structures.[8]

PROPERTIES OF CUBOSOME[9]

1. Cubosome dispersions have much lower viscosity.

2.Cubosomes are discrete, sub-micron, nanostructured particles of bicontinuous cubic liquid crystalline phase.

3. Cubic liquid crystals are transparent and isotropic phases that are physically stable in excess water.

4. Due to small pore size, cubosomes are attractive for controlled release.

ADVANTAGES OF CUBOSOME

1. They have ability to encapsulate hydrophilic, hydrophobic and amphiphilic drugs.

2. They have a sustained- release drug delivery characteristics.

3. Cubosomes have biocompatibility and bioadhesivity properties.

4. Cubosomes are excellent solubilizers, compared with conventional lipid or non-lipid carriers.

5. They show high drug carrier capacity.

6. Cubosomes are an excellent vehicle to protect the sensitive drug from enzymatic degradation and in-vivo degradation, such as peptides and proteins.

7. The cuboidal system enhances the bioavailability range, twenty to more than one hundred times of water-soluble peptides

8. Relatively simple method of preparation.

9. Biodegradability of lipids.

10. Targeted release and controlled release of bioactive agents.

11. The cubic phases of cubosomes can be fractured and dispersed to form particulate dispersions that are colloidallyand/or thermodynamically stable for longer time[10].

DISADVANTAGE OF CUBOSOME

1. Large scale production is sometimes difficult because of high viscosity.
2. Cubosomes may lead to drug leakage in preparation.

MANUFACTURE OF CUBOSOMES[11]

Cubosomes can be prepared mainly by two methods,

- Top-down technique
- Bottom-up technique

1. Top-down technique

It is the most widely used method in research area. Here the bulk cubic phase is first prepared. Then by application of high energy such as high-pressure homogenization, it is processed into cubosome nanoparticles. Bulk cubic phase resembles a clear rigid gel formed by water-swollen cross-linked polymer chains. Rupture of the cubic phase occurs as the bilayer breaks under applied shear stresses and flows along slip planes. They rupture in a direction parallel to the shear direction; the energy required is proportional to the number of tubular network branches that rupture. The cubic phase exhibits yield stress that increases with increasing amount of bilayer forming surfactant and oils. Based on most recent studies, comparison of dispersion produced by sonication and high-pressure homogenization suggests the formation of complex dispersions containing vesicles and cubosomes with time dependent ratios of each particle type. [12]

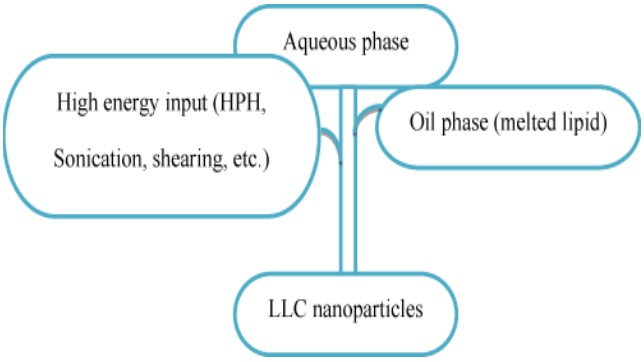

Fig 1.3: Top down technique

2. Bottom up technique

The bottom-up approach first forms the nanostructure building blocks and then assembles them into the final material. In this method cubosomes are allowed to form or crystallize from precursors. The cubosomes are formed by dispersing inverse micellar phase droplets in water at 80°C and are allowed to slowly cool. Gradually these droplets crystallize to cubosomes. This is more useful in large scale production of cubosomes. The cubosomes at

room temperature is produced by diluting monoolein-ethanol solution with aqueous poloxamer 407 solution. The cubosomes are spontaneously formed by emulsification. Another process is also developed to produce the cubosomes from powdered precursors by spray drying technique. Spray dried powders comprising monoolein coated with starch or dextran form cubosomes on simple hydration.[13]

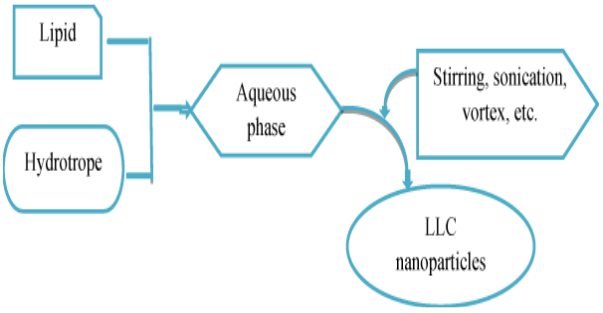

Fig 1.4: Bottom up technique

The bottom-up approach first forms the nanostructure building blocks and then assembles them into the final material. It is more recently developed technique of cubosome formation, allowing cubosomes to form and crystallize from precursors on the molecular length scale. The key factor of this technique is hydrotrope that can dissolve water insoluble lipids into liquid precursors. This is a dilution based approach that produces cubosomes with less energy input when compared top down approach.

FUNCTIONALISATION OF CUBOSOMES

The concept of functionalization is to control the loading and release properties of the active ingredient by changing the properties of the cubic phase. Functionalization is achieved by incorporating amphiphilic molecules into the liquid crystal. The hydrophobic portion of the amphiphile inserts into the bilayers of the cubic phase and the hydrophilic portions extend into the water channels. By customizing the specific properties of the hydrophilic portions, it is possible to control their interactions with the active ingredient. The release properties at long times are also altered as the increased affinity between drug and cubic phase alters the partitioning. Taken together, customizing the properties of the cubic phase is an alternative method to changing the loading and release properties of a drug offering a greater potential for tailored release properties over a broader range of applications and conditions[14].

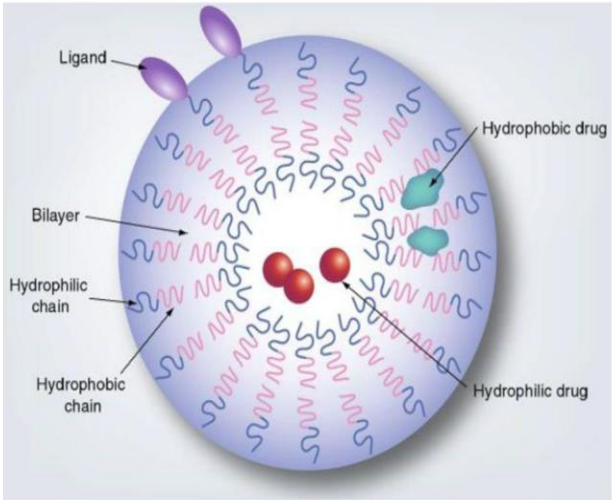

Fig1.5: Drug loading of cubosomes

One approach to functionalization requires formulating small amphiphiles, such as surfactants, into the cubic phase. Surfactants used in this method are often termed ‘anchors’. There must be an optimal set of anchor properties that maximize functionalization without significantly altering the underlying structure of the cubic phase. Ideal anchors have low water solubility, low Krafft Temperature, an accessible hydrophilic group with which the drug can interact, and critical packing parameter (ratio of head group volume and tail volume) close to unity. Such surfactants typically form vesicles in aqueous solutions. Most importantly, several reports suggest that the inclusion of anchors alters the loading and release properties of active ingredients solubilized in the cubic phase. The anchors are added to greater than 20% w/w without altering the bicontinuous structure of the cubic phase.[15] A second approach to functionalization is to formulate large amphiphilic polymers or ‘tethers’ into the liquid crystal. In short, functionalization of cubic phases to control and optimize their loading, release and partitioning of active ingredients is viable across many formulations. Given the relative cost of surfactant and pharmaceutical active ingredients, functionalization seems quite feasible. It also offers greater opportunity for triggered release of drugs as a result of stimuli such as change in pH, salt levels, or addition of solvent. All these tools are at the discretion of the formulator.[16]

CUBOSOMES FOR DRUG DELIVERY

Self-assembled cubosomes are attracting increasing interest as active drug delivery systems as well as biocompatible carriers of large biomolecules including proteins, peptides, DNA and drugs.

They have been reported as a burst release delivery system where drug is released by diffusion from the cubic phase matrix, and that pressure ultrafiltration may have benefits over dialysis methods for measurement of drug release from colloidal particle-based drug delivery systems. Research of cubosomes as a drug delivery system has involved oral, intravenous and percutaneous routes of administration.[17]

- **Oral drug delivery**
  Cubosomes address the varied challenges in oral delivery of numerous promising compounds including poor aqueous solubility, poorabsorption, and large molecular size. In an alternative application large proteins have beenencapsulated for local activity in thegastrointestinal tract. Liquid crystallinenanoparticles technology carriers can be combined with controlled release and targeting functionalities.The particles are designed to form in situ in a controlled rate, which enables an effective *in vivo* distribution of the drug. Cubosomestechnology carriers can also be released at different absorption sites, for example in the upper or lower intestine, which is important for the drugs that have narrow regional absorption window.
- **Intravenous drug delivery system**
- Lipid nanoparticles comprising interior liquid crystal structures of curved lipid membranesare used to solubilize encapsulate and deliver medications to disease areas within the body.While emulsions and liposomes have found use as intravenous carriers in drug products, liquid crystal nanoparticle structures increased payloads of peptides, proteins and many insoluble small molecules, and are ideal carriers for injection or infusion of many actives.
- **Topical drug delivery systems**
  Cubic phases are more bio adhesive in nature, sothat they can conveniently use in topical and mucosal depositions and delivery of different drugs. Topical delivery systems are based on the exploitation of unique properties of liquid crystal (LC) and liquid crystal nanoparticle (LCNP) technologies. Topical drug delivery systems are unique in situ forming bio adhesiveLC systems facilitate controlled and effective drug delivery to mucosal surfaces (buccal, ophthalmic, vaginal and others). This fascinating system forms a thin surface film at mucosal surfaces consisting of a liquid crystal matrix which nanostructure can be controlled for achieving an optimal delivery profile and provides good temporary protection of sore and sensitive skin.[18]
- **Melanoma (cancer) therapy**
  Recently few anticancer drugs have beensuccessfully encapsulated in cubosomes and characterized physicochemically. The unique structure of this promising nanocarrier suggests its application in melanoma therapy. In order to specifically target nano medicines to tumours, different approaches have been envisaged, with passive and active targeting of cancer cells having been shown to be valid approaches in preclinical and clinical studies. Passive targeting exploits the pathophysiological properties of the tumour vasculature which is generally highly disorganised with enlarged gap junctions betweenendothelial cells and compromised lymphatic drainageallowing for the extravasation of nanocarriers with sizes up to several hundred nanometres. Objects of this sizecannot pass through the tight junctions that exist withinthe endothelial cell lining of the vessels of healthy tissues. Passive targeting is largely dependent on the ability of a drug nanocarrier to exhibit an increasedcirculation lifetime resulting in enhanced accumulationat the target site.
- **Drug delivery vehicle**
  Drug delivery vehicle is a common applicationfor such new materials. The rapid expansion of the life-sciences industry is expected to drive previously “exotic” delivery vehicles and ingredients into broader marketplaces, such as personal care and consumer products. Consequently, self-assembled surfactant phases have been extensively examined for compatibility with numerous medical active ingredients and their applications. The number of research in association with cosmetic companies like L’Oreal and Nivea are trying for the use of cubosome particles as oil-in-water emulsion stabilizers and pollutant absorbents incosmetics. Moreover, these researches have also discovered that a second amphiphile,phytantriol, has an aqueous phasebehaviour sufficiently close to that of monooleinto form cubosomes under similar conditions.[19]
- **As sustained release behaviour**
  Even more recent patent activity by points tocubosome use in personal care product areas as varied as skin care, hair care, cosmetics, and antiperspirants. Despite recent activity, there remains a lack of the practical elements like manufacturing scalability and material

customization that is necessary to lead formulators to consider using cubosomes in commercial products. The cubic phase has been shown to provide a vehicle for several *in vivo*delivery routes, including depot, transdermal, mucoadhesion and ophthalmic. Because of fusogenic property of monoolein it increases the penetration of macro molecules·A wide variety of drugs with different physicochemical properties has been incorporated in cubosomes, and their sustained release behaviour was also studied. Sustained behaviour of cubosomes was because of cubosomes remnant particles. Monoglyceride based cubosome dispersion can be proposed for topical use, such as for perctuneous or mucosal applications.

- **In treatment of viral diseases**
  Because of the microbicidal properties of monoglycerieds, could be used to design intravaginal treatment of sexually transmitted diseases caused by viruses or by bacteria. Due to similarity between the cubic phase structure and the structure of the stratum corneum, it is reasonable to suppose the formation of mixture of cubosomalmonolein with stratum corneumlipids. This kind of interaction might lead to the formation of a cubosome depot in this layer, from which drug can be released in a controlled fashion. Thecubosome technology is used to develop a synthetic vernix– the cheesy whitesubstance that coats infants in late gestation – tohelp premature infants who are born without it. The vernix is a complex mixture of lipid (, proteins and water. It is formed late in gestation and has an integral role in normal skin development.
- **In topical and mucosal depositions**
  Cubic phases are more bioadhesive in nature, sothat they can conveniently use in topical and mucosal depositions and delivery of different drugs.
- **Controlled-Release Drug Delivery**
  Controlled release of solubilized actives is themost popular application pursued by cubosomeresearchers, and excellent reviews exist of attempted delivery applications as well as pharmaceutical actives that have been solubilized in bulk cubic phase and cubosomes. Cubic phase is attractive for controlled release because of its small pore size (5–10 nm); its ability to solubilize hydrophobic, hydrophilicand amphiphilic molecules; and its biodegradability by simple enzyme action. Cubic phase is strongly bioadhesive and is thought to be a skin penetration enhancer,suggesting excellent compatibility with topical and mucosal deposition and delivery of active ingredients. Recent studies have emphasized similarities between the bicontinuous structures formed in human skin layers and those comprising cubic phases, offering the promise of better skintransport understanding and treatment.

- **In Materials Synthesis**
  From a materials science perspective, thecreation of ordered structures with nano scale pore geometries is of great interest to numerous fields including electronics, photonics, catalysis,and medicine. The creation of solid structuresusing cubic phases as a template usually entails either polymerization or reaction to form solids from precursors that are solubilized in, or comprise, the cubic phase matrix. One of the earliest and most successful materials formed in a cubic phase template is the alumina silicate zeolite MCM-48, used for catalytic processing of petroleum.
- **As biologically active substances**
  Cubic phases were produced at 25°C in water mono olein-alcohol mixtures. Ethanol was found to be more efficient than propanol and butanol. In the composition range of 49 to 56 wt% water, 31 to 40 wt% monooleine and 10 to 13 wt% ethanol we identified a new transparent, lowviscosity (flowing) phase that we called OL. No structures were found by bright field light microscopy and polarized light microscopy, indicating that OL is an isotropic phase. Cryo-TEM showed large domains of this ordered phase, which by Fast Fourier Transformation was identified as cubic phase. The symmetry was also confirmed by SAXS. Bioactive compounds were incorporated into the OL phase, and the phase was then dispersed into cubosomes of 100 – 250 nm in diameter by homogenization, in the presence of Pluronics127 as the stabilizing agent[20].
- **Current application**
  1. An application area under current development by L"Oreal is the use of cubosome particles as oil-in-water emulsion stabilizers and pollutant absorbents in cosmetics.
  2. Inmelanoma therapy.

CONCLUSION:

Cubosomes is a new concept for the successful development of controlled release formulation. It is a self-assembled liquid crystalline nano particle; they have ability to incorporate both hydrophilic and hydrophobic drugs. Recent studies shows that

cubosomes are best suited for the controlled delivery of poorly soluble drugs and also targeted drug delivery. The cubosome technology is relatively new with high output and would have wide scope of research in developing new formulation.

REFERENCES:

1. Mannivannan R, Kugalur G. Recent Advanceses in Novel Drug Delivery System.Int J Res Ayurveda Pharm. 2010; 1(2): 316-326.
2. Shakthipal P, Amrapali M, Dharmedra M. A Review on Novel Drug DeliverySystem: A Recent Trend. J Curt pharma &clin res. 2016; 6(2): 82-93.
3. Archana A, Vijaya K, Madhuri M. Curcumin Loaded Nano Cubosomal Hydrogel;Preparation, *In Vitro* Charecterisation and Antibacterial Activity. ChemSci Trans. 2015; 4(1): 75-80.
4. Anbarasan B, Fatima G, Shanmuganathan S. An Overview of Cubosomes- SmartDrug Delivery System. Sri Ramachandran J Med. 2015; 8(1): 1-4.
5. Jyothi K, Bhushan A, Bhairav. Cubosomal Technique; A Review. Int J PharmTech. 2015; 7(2): 3263-3272.
6. Tilekar KB, Khade PH, Shitole MH. Cancer Oriented Cubosomes- A review. Int JPharm Res Scholars. 2014; 3(4): 198-210.
7. Komal T, Prashant K, Sujit K. Cubosomes- A Drug Delivery System. Int J PharmChem&Biol Sci. 2014; 4(4): 812-824.
8. Kala D, Aiswarya CS, Cubosomes -A Novel Drug Delivery System and ItsFunctionalisation. World J Pharm Pharm Sci. 2017; 6(3): 286-300.
9. Rajesh S, Radhika G, Simran S. A Review on Cubosome and Virosome. Austin JNanomedicine. 2017; 3(1): 24-33.
10. Madhurilatha T, Paruchuri SK, Suria P. Overview of Cubosomes: A NanoParticle. Int J Res Pharm & Chem. 2011; 1(3): 535-541.
11. Basavraj N, Yallappamaharaj RH, Meghana SK. Development of CuboidalNanomedicine by Nanotechnology. Austin J Nanomedicine. 2014; 2(4):1-8.
12. Venkatesh, Indira S, Prathima S. Formulation and Evaluation of Glimepiride OralCapsules. Int J Pharm Sci Invent. 2014; 3(10): 1-13.
13. Bhargavi K, Indhira S, Prathima S. Formulation and Evaluation of AceclofenacCubosomal Oral Capsules. World J Pharm Pharm Sci. 2015; 4(11): 1167-1181.
14. Indira S, Dinesh R, Bhagavan R. Formulation and Evaluation of GlibenclamideCubosomal Oral Capsules. World J Pharm Pharm Sci. 2018; 7(1): 784-810.
15. Amala T, Sujith A. Formulation and Evaluation Capsules Containing Cubosomesof Omeprazole for Improving Its Bioavailability. Int J Inst Pharm Life Sci. 2016;6(4): 2249-6807.
16. Ashraf A, Noriko K, Abdul HR. Enhancing the Solubility and OralBioavailability of Poorly Water-soluble Drugs Using MonooleinCubosomes. Chem Pharma Bulletin. 2017; 65(1): 42-48.
17. Ruchi S, Gurvinder K, Deepak NK. Fluconazole Loaded Cubosomal Vesicles forTopical Delivery. Int J Drug Deve& Res. 2015; 7(3): 32-41.
18. Maha KA, Khalifa. Miconazole Nitrate Based Cubosome Hydrogels for Topical Application. Int J Drug DelivSci Tech. 2015; 7(1): 1-12.
19. Yallappamaharaj R, Hundekar, Saboji. Preparation and Evaluation of DiclofenacSodium Cubosomes for Percutaneous Admimistration. World J Pharm Pharm Sci.2014; 3(5): 523-539.
20. Ola M, Belgamwar. Process Optimization for the Formolation of an Oral Pyrazinamide Cubosome. Int J Recent Sci Res. 2017; 8(9): 20138-20141.