

Cubosome – A Review

Vishal B. Patond, Ananta B. Ghonge, Mahesh B. Narkhede

Dr. Rajendra Gode College of Pharmacy, Malkapur, Buldhana, Maharashtra, India

ABSTRACT

This review article covers the detailed about cubosome. Cubosomes are single crystal structures, with visible unilamellar vesicles, dispersed lamellar liquid crystalline phase particles. Increasing polymer-to-monoolein ratios leads to formation of larger vesicles. Cubosomes are nanoparticles whose size ranges from 10-50nm in diameter they appear like dots square shaped, slightly spherical. Each dot corresponds to the presence of pore containing aqueous phase cubic phases in lipid water system in X-ray scattering technique. and also covers some methods of preparation of cubosome along with there characterization methods like Cryo-Transmission Electron Microscopy (Cryo-TEM), Small-Angle X-ray Scattering (SAXS), Particle Size Distribution (PSD). Application of cubosome like vehicle activity of biological substances, controlled release of solubilized substances, Treatment of skin, hair, and other body tissue. Melanoma (cancer) therapy on size delivery system is the key to target cancer through the enhanced permeability and retention effect. With some advantages of cubosome.

KEYWORDS: Cubosome, Monoolein, cubic phases, Suspension, Nanopartical

INTRODUCTION

Lipids, surfactants and polymer molecules have both polar and non polar components are termed as amphiphilic. The hydrophobic effect phases with lengths on nanometer scale. These liquid crystalline phases possess a sufficient average degree of molecular orientation and structural symmetry an interesting example is the Bicontinuous cubic liquid crystalline phase, (Cubosomes).¹ Bicontinuous cubic phases are optically isotropic, very viscous, and continuous but nonintersecting hydrophilic regions divided by a lipid bilayer in to a periodic minimal surface with zero curvature. A special property of the cubic phases formed by certain classes of amphiphiles is their ability to be dispersed in to particles, termed as cubosomes.² Cubosomes are nanoparticles whose size ranges from 10-50nm in diameter they appear like dots square shaped, slightly spherical. Each dot corresponds to the presence of pore containing aqueous phase cubic phases in lipid water system in X-ray scattering technique.³

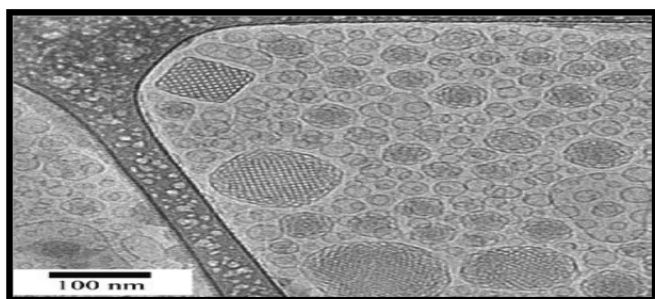


Fig.1: Square or spherical shaped Cubosomes⁴

How to cite this paper: Vishal B. Patond | Ananta B. Ghonge | Mahesh B. Narkhede "Cubosome – A Review" Published in International Journal of Trend in Scientific Research and Development (ijtsrd), ISSN: 2456-6470, Volume-4 | Issue-4, June 2020, pp.1116-1120, URL: www.ijtsrd.com/papers/ijtsrd31428.pdf



IJTSRD31428

Copyright © 2020 by author(s) and International Journal of Trend in Scientific Research and Development Journal. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (CC BY 4.0) (<http://creativecommons.org/licenses/by/4.0>)



THEORY ON CUBIC PHASE STRUCTURE

1. Fontell & Drew Theory: ⁴

Ternary systems of amphiphiles, oil & water, some mono glycerides will exhibits cubic phases. Monoglycerides are polar lipids, having poor water solubility that exhibits aqueous phase behavior, which are structurally mimicking to non-ionic surfactants. Lutton results the Monoglycerides whose hydrocarbon chain lengths between C-12 and C-22 of all the Monoglycerides, particularly monoolein exhibits larger region of cubic phase. Monoolein is unsaturated, C-18 Monoglycerides.

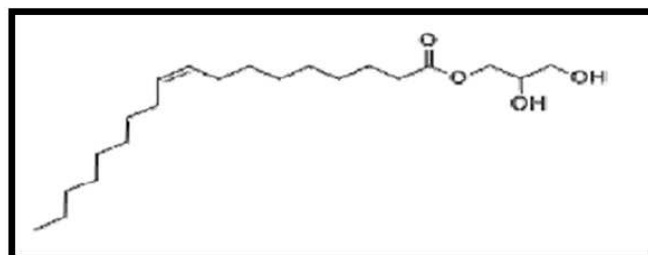


Fig2. Monoolein Structure

MONOOLEIN PROPERTIES

Melting point: 35-37 °C

FEMA: 2526

Flash point: 180 °C

Storage temp: -20°C

Solubility: chloroform: 50 mg/ml clear, colorless.

2. Gustafson et al Theory: ⁵

Cubosomes are single crystal structures, with visible unilamellar vesicles, dispersed lamellar liquid crystalline

phase particles. Increasing polymer-to-monoolein ratios leads to formation of larger vesicles. Ultra sonication of bulk cubic phases produces mostly vesicles on due course of time they get trace formed into Cubosomes via membrane fusion such meta stability is characteristic of Cubosomes systems because of slow transport processes involved in forming high viscous crystalline structure and high energy is required to fragment them (bulk cubic phase). vesicles also give colloidal stabilization of Cubosomes.

3. Schwarz, Jacob & Anderson Theory: ⁶

Cubic phases are often founded sandwiched between lamellar and hexagonal liquid crystalline phases, especially in non-ionic surfactant systems. The monoolein-water system uniquely possess a cubic phase region contains broad compositional and temperature range. But surfactant packing concepts are more approaching. Normally monoolein has continues hydrophilic headed, hydrophobic tail end, producing reversed or inversed cubic phases, indicating the phases towards polar medium. So that the cubic phase structures can be described using the concept of differential geometry and periodic minimal surfaces. Minimal surfaces are best described by analogy with soap films. Based on their curvatures, 3 types of minimal surfaces are studied in cubic phases.

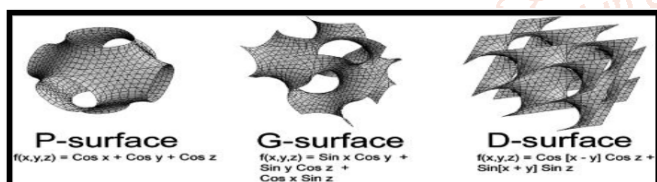


Fig. 3. P-surface (primitive surface), D-surface (diamond surface), G-surface (gyroid surface) ⁶

The monoolein water system forms the D surfaces at high water levels and the G surface at lower levels. The p-surface is formed in the monoolein water system, but only when third component such caseins or amphiphilic. The block copolymer are added. Cubic phases existed can be measured by X-ray scattering technique. Transmission electron microscopy (TEM), freeze fracture electron microscopy is used to visualize the Cubosomes.

1. Top-down approach

It is the most widely used in research area, where by bulk cubic phase is first produced and then dispersed by high energy processing in to Cubosomes nanoparticles. Bulk cubic phase is resembling a clear rigid gel formed by water swollen crossed linked polymer chains, whereas cubic phases are like liquid crystalline structure.⁴ The cubic phases exhibits a yield stress that increases with increasing amount of bilayer forming surfactant and oils.

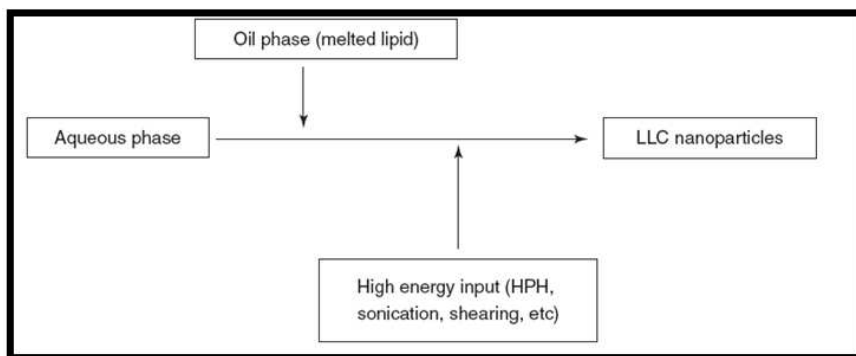


Fig No: 5 -Top Down approach method ¹¹

4. System Forming Cubosomes:

The system forming Cubosomes is possible in binary and ternary systems with a sufficiently large miscibility gap between the cubic phase and the solvent. Colloidal stabilization of cubosomes is good when poloxamer 407 issued to provide stabilization against aggregation and coalescence. Cubosomes can be coated with lamellar bilayered 'caps' covers the cubic bilayer opening which is formed by fragmentation which prevents the exposure of hydrocarbon chains to water and provides colloidal stability.⁷ Coating of Cubosomes with solid crystalline bilayer provides more colloidal stability, whereas lamellar liquid crystalline will give rigid coatings. In addition coatings of the sponge phase have been proposed as a stabilizing coating of cubosomes. The following figures will shows two general forms of the ternary phase diagrams exhibited by system forming Cubosomes. Another molecule with great potential for Cubosomes formation is phytantriol.⁸

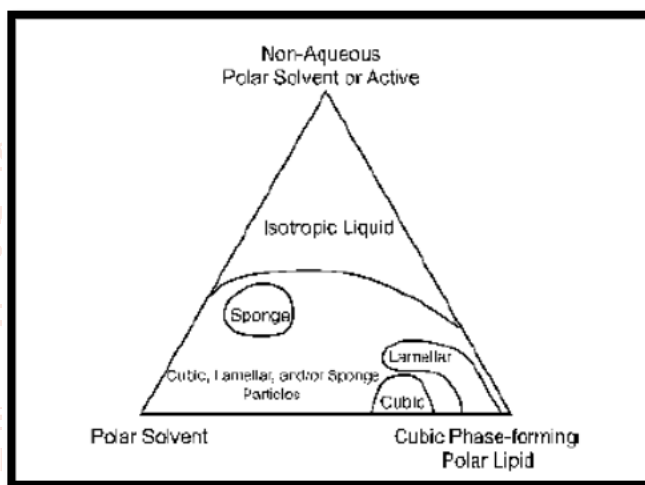


Fig. 4 Phase Diagram ⁸

METHOD OF PREPRATION

1. Top-down approach
2. Bottom-up approach
3. Heat treatment
4. Spray drying

Based on most existing 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.⁸

Coarse Cubosomes on micron scale possess the same D-surface structure as their originating bulk cubic phase, but after homogenization, the P-surface dominates because of added polymers. The extreme viscous bulk phase is prepared by mixing structure-forming lipids with stabilizers, then the resultant is dispersed into aqueous solution through the input of high energy (such as high-pressure homogenization [HPH], sonication or shearing) to form LLC nanoparticles. At present, HPH is the most extensively used technique in the preparation of LLC nanoparticles (cubosomes).¹¹

2. Bottom-up approach:

In this Cubosomes are allowed to form or crystallize from precursors. Almgren et. al. discuss the formation of Cubosomes by dispersing L2 or inverse micellar phase droplets in water at 80°C, and allow them to slowly cool, gradually droplets get crystallizes to Cubosomes. This is more robust in large scale production of Cubosomes. Spicer et.al developed Cubosomes at room temperature is by diluting monoolein-ethanol solution with aqueous poloxamer 407 solution. The Cubosomes are spontaneously formed by emulsification.⁴

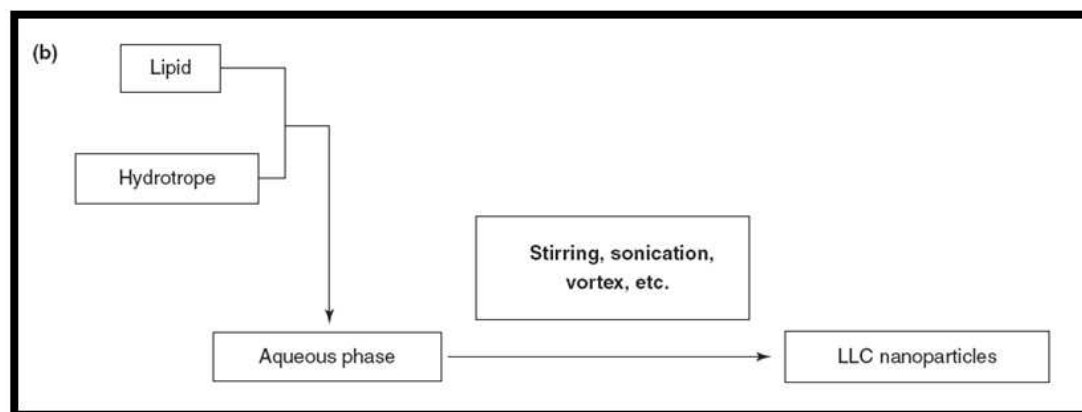


Fig No 6: Bottom-up approach method ¹¹

The key factor in the bottom-up approach is hydrotrope, which can dissolve water-insoluble lipids to create liquid precursors and prevent the formation of liquid crystals at high concentration. Compared with the top-down approach, this dilution-based approach can produce Cubosomes without laborious fragmentation. In other words, it needs less energy input. Moreover, this approach is far more efficient at generating small particles. The reason for this might relate to the forming mechanism of Cubosomes. The dilution-based approach can be regarded as a process of small particles forming big particles through aggregation, which is analogous to the use of precipitation processes to produce nanoparticles, whereas the top-down approach is more analogous to the attrition of big particles. In addition, Cubosomes prepared through dilution show long-term stability, which might be attributed to the homodisperse stabilizers onto the surface of Cubosomes. Indeed, the use of hydrotrope can simplify the preparation process and produce Cubosomes possessing similar or even better properties than those fabricated by the top-down approach.

3. Heat treatment

In this case, heat treatment can be regarded as a good approach. Note that in the strictest sense, heat treatment is not an integrated process for the manufacture of Cubosomes because it only promotes the transformation from non-cubic vesicles to well-ordered cubic particles. The dispersed particles, therefore, can be produced by a simple processing scheme comprising a homogenization and heat-treatment step. From the reported studies, heat treatment could cause a decrease in the small particle size fraction that corresponded to vesicles and form more cubic phases with narrow particle distribution and good colloidal stability. Taking the whole process of preparation into account, it is obvious that the transition takes place during the procedure of heat treatment. The reason for transition could be speculated as an elevated temperature giving rise to a reduction in solubility and stability. When the temperature was below cloud point, the surfactant had a high solubility and thus the particles could exist stably and the phenomenon of fusion was hardly observed. Once reaching cloud point, the solubility of surfactant decreased notably and a notable fast fusion among vesicles would occur.

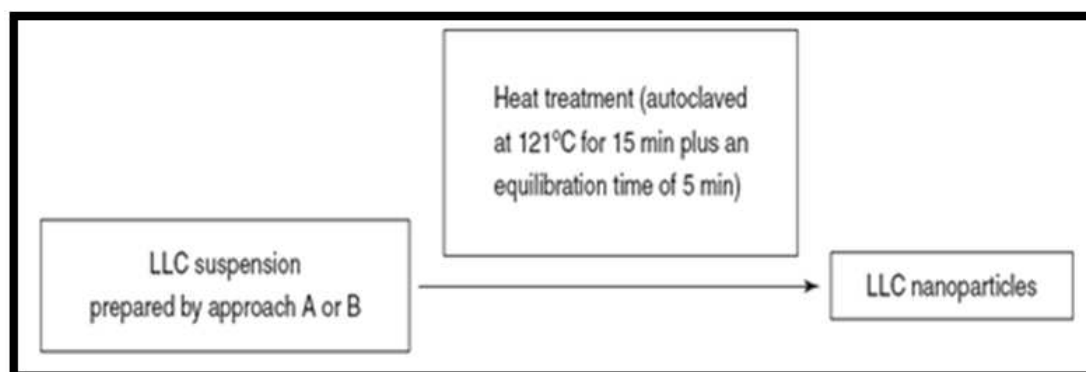


Fig no 7: Heat Treatment method ¹¹

The lipids used to make Cubosomes are waxy, sticky Solids, rendering them unable to form small discrete particles. It is found that a water-soluble non-cohesive starch coating on the waxy lipid prevents agglomeration and allows control of particle size. Spray drying is an excellent process to produce these particles. Spray drying produces encapsulated particles from an emulsion of liquid droplets or a dispersion of solid particles in a concentrated aqueous polymer solution.⁴

The continuous and dispersed phases are sprayed through a nozzle to create suspension droplets that are contacted with a heated, dry air stream flowing in the opposite direction. Excess water immediately evaporates, leaving dry powder particles composed of the dispersed phase encapsulated by a shell of the formerly dissolved polymer. Spray-drying processes are easily scaled up and are already widely employed for manufacturing consumer products like detergents and foods. Further, the process provides an easy route to preload active into the Cubosomes prior to drying. Finally, the polymer coating on the powder imparts surface properties to the hydrated Cubosomes that can be tailored by proper selection of the encapsulating polymer. The liquid feed to the spray-dryer can be tailored to adjust the resultant powder properties. The production of starch-coated Cubosomes powder precursors requires high shear treatment of monoolein in aqueous starch solution to form a coarse Cubosomes dispersion that is then pumped through a nozzle and dried. Full operating conditions are given in Spicer et al. (2002a). The initial composition pumped into the spray-drier is 60% w/w water, 30% starch, and 10% monoolein. Drying removes almost all water present and gravimetric tests of the powder generally indicate a final composition of about 4% w/w water, 72% starch, and 24% monoolein in the product powders.

The emulsion of both phases has low viscosity and is easily spray dried. The type of encapsulating starch also affects powder quality. Drying occurs as the dispersion is sprayed into droplets and moisture rapidly evaporates by convective heating. The Cubosomes in the dispersion form the nucleus of many of the sprayed droplets, surrounded by aqueous starch solution. As drying proceeds, the starch remains and forms a coating on the cubic gel particle, thereby encapsulating it. Because the cubic phase itself contains 40% (w/w) water, some drying must also occur at the core of the particles. Low molecular weight starches (84,000 MW) produce superior powders when compared to those made using high (335,000 MW) molecular weight starches. Spicer et al. (2002b) provide a more comprehensive listing of feasible polymers and other materials for use as polymeric coatings to encapsulate Cubosomes.¹¹

Characterization

1. Cryo-Transmission Electron Microscopy (Cryo-TEM).¹²

Cryo-Transmission electron microscopy (Cryo-TEM) is a microscopy technique whereby a beam of electrons is transmitted through an ultrathin specimen, interacting with the specimen as it passes through. An image is formed from the interaction of the electrons transmitted through the specimen; the image is magnified and focused onto an imaging device, such as a fluorescent screen, on a layer of photographic film, or to be detected by a sensor. Cryo-TEMs are capable of imaging at a significantly higher resolution than light microscopes, owing to the small wavelength of electrons.

2. Small-Angle X-ray Scattering (SAXS).¹²

Small-angle X-ray scattering (SAXS) is a small-angle scattering (SAS) technique where the elastic scattering of X-rays (wavelength 0.1 - 0.2 nm) by a sample which has inhomogeneities in the nm-range, is recorded at very low angles (typically 0.1 - 10°). This angular range contains information about the shape and size of macromolecules, characteristic distances of partially ordered materials, pore sizes, and other data. SAXS is capable of delivering structural information of macromolecules between 5 and 25 nm, of repeat distances in partially ordered systems of up to 150 nm.

3. Particle Size Distribution (PSD).¹³

The particle size distribution of the dispersions was determined using photon correlation spectroscopy. Measurements were performed at 25°C using a refractive index (RI) of Cubosomes at intervals of 100 s. Samples were diluted with water to adjust the signal level. The average particle size (z-average) and poly dispersity index were determined.

Application of Cubosomes

1. Vehicles for biologically active substance.
2. Control release of solubilized substance.
3. Treatment of skin, hair, and other body tissue.
4. Melanoma (cancer) therapy.
5. As Injectable vehicles.

1. Vehicles for biologically active substance.⁴

Cubic phases were produced at 25 °C in water monoolein-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, low-viscosity (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 a cubic phase.

2. Control release of solubilized substance.¹⁴

Cubic phase is more applicable for control release because of its small pore size (5-10nm), ability to solubilise hydrophilic, hydrophobic, amphiphilic. The molecules and its biodegradability by simple enzymes.

3. Treatment of skin, hair, and other body tissue.¹⁵

Cubic phase materials can be formed by simple combination of biological compatible lipids and water and are thus well suited for use in treatments of skin, hair, and other body tissue. Cubosomes contents is mono-olein i.e.monoglycerides.Monoglycerides has microbicidal property. Cubosomes contents ethanol which causes skin disruption. These increase lipid fluidity cause more permeation through skin. Cubosomes permits inside and fuse with skin lipids and release drug into deep skin layers.

4. Melanoma (cancer) therapy.^{14, 16}

Cubosomes can be circulate in the body after being injected they have ability to target diseases at the site disorder. This feature of Cubosomes is especially useful in cancer therapy. Where the size of the delivery system is the key to target cancer through the enhanced permeability and retention effect. Diseased cells can also be targeted by attaching ligands (follic acid derivative, peptides, protins, antibodies)to the surface of Cubosomes.

5. As Injectable vehicles.^{11, 16}

Cubosomes are highly viscous, and this mechanical stiffness makes them clumsy to handle and difficult to inject. To overcome this defect, some corresponding approaches have been proposed, such as application of flowable precursor forms and use of LLC nanoparticles. According to the phase diagram of structure-forming lipid, the transition from lamellar phases to cubic phases can be completed upon heating from room temperature to body temperature or swelling with water. Therefore, lamellar phases with inherently fluid properties can act as precursors of viscous cubic phases. Once injected into the body via subcutaneous or muscular approach, flow able lamellar phases will gradually absorb water from body fluid or surrounding tissues and, subsequently, convert to cubic phases, which can form the sustained release depot in situ.

ADVANTAGES: ^{1, 4, 9}

- High drug payloads
- Simple preparation method
- Biodegradability of lipids
- The ability of encapsulating hydrophobic, hydrophilic, amphiphilic substances.
- To targeting and controlled release of bioactive agent.

DISADVANTAGES: ^{1,4,10}

- Manufacture of Cubosomes on a large scale embodied difficulty because of their viscosity
- High energy processes
- Harmful to fragile temperature-sensitive active ingredients
- Expensive
- Difficult to scale up

REFERENCES

- [1] Jain A. Cubosomes: a novel approach for nanotechnology. Int J applied Bio & Pharm tech 2011; 2: 19-21.
- [2] Patrick T. Cubosomes: bicontinuous cubic liquid crystalline nanostructured particles. US Patent No-120014156.
- [3] Patrick T. Spicer. Novel process for producing cubic liquid crystalline nanoparticles (cubosomes). American Chemical Society 2001; 17:5748-56.

- [4] Thadanki M. Overview of cubosomes: a nano particle. Int. J Res Pharm. & Chem. 2011; 1: 535-41.
- [5] Patrick T. Progress in liquid crystalline dispersions: cubosomes, cur. Opinion in Colloid & Interface Sci 2005; 10: 274-79.
- [6] Patrick T. Cubosome processing industrial nanoparticle technology development. Chem. Engineering Res. and Design 2005; 83: 1283-86.
- [7] Patrick T. Cubosomes formation via dilution – kinetic effects and consumer product implications. Spicer Cubosomes ACS.doc 2003:1-14.
- [8] Bansal S. A comparative review on vesicular drug delivery system and stability issues. Int J Res Pharm & Chem. 2012; 2:704-13.
- [9] Prashar D. Cubosomes: a sustained drug delivery carrier. Asian J Pharm Sci 2011; 1: 59-62.
- [10] Guo C. Lyotropic liquid crystal systems in drug delivery. Drug Discovery Today 2010; 15:1032-40.
- [11] Esposito E. Production and characterization of cubosomes. Asian J Pharm Sci 2006; 1-2.
- [12] Rizwan S. Characterization of bicontinuous cubic liquid crystalline systems. J Pharm Micron 2007; 38:478-85.
- [13] Ding B. Biodegradable methoxy poly (ethylene glycol)-poly (lactide) nanoparticles for controlled delivery of dacarbazine: preparation, characterization and anticancer activity evaluation. African J Pharm and Pharmacology 2011; 5:1369-1377.
- [14] Chacko R. Polymer nanogels: A versatile nanoscopic drug delivery platform. J Pharm and Pharmacology 2012; 836-51.
- [15] Murphy E. Targeted nanogels: A versatile platform for drug delivery to tumors. Aacro J 2012; 972-82.
- [16] Jan P. A new era for liquid crystal research, Curr appl phy. 2012; 12:1387-1412.
- [17] Kare L. Aqueous dispersion of cubic lipid-water phases. Curr Opinion In Colloid & Interfaces Sci 2000; 5:64-69.
- [18] Clogston J. Controlling release from the lipidic cubic phase. J controllred rel 2007; 107:97-111.
- [19] Patrick T. Bicontinuous cubic liquid crystalline phase and cubosomes & personal care delivery systems. Int J Pharm Tech 2001; 5:1-43.
- [20] Siekmann B. Preparation and structural investigations of colloidal dispersions prepared from cubic monoglycerides–water phases. Int J Pharm 2002; 244:33–43.