WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 8, Issue 12, 1570-1581. Review Article ISSN 2277– 7105

CUBOSOMES – AN ADVANCED DRUG DELIVERY SYSTEM – A REVIEW

Shrikant Rajaram Divekar* and Dr. Vaibhav R. Vaidya

Department of Pharmaceutics, Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune.

Article Received on
20 Sept. 2019,

Revised on 10 Oct. 2019,
Accepted on 30 Oct. 2019,

DOI: 10.20959/wjpr201912-16197

***Corresponding Author**
Shrikant Rajaram Divekar
Department of Pharmaceutics, Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune.

ABSTRACT

Cubosomes are the square and rounded particles with internal cubic lattices visible. Cubosomes are self-assembled nanostructured particles shaped by aqueous lipid and surface-active agent systems. Cubosomes are thermodynamically stable; they have a structure like "honeycombed" with bicontinuous domains of water and lipid in which surfactant assembles into bilayers and twisted into a three dimension, periodic, and least surface, forming a tightly packed structure. They exhibit totally {different|completely different} internal cuboidal structure and composition with different drug-loading modalities. Overall, cubosome have nice potential in drug nanoformulations for malignant melanoma treatment because of their potential benefits, as well as high drug payloads thanks to high internal area and isometric crystalline structures, comparatively easy preparation methodology, biodegradability of lipids, the ability of encapsulating hydrophobic, hydrophilic and amphiphilic substances, targeting and controlled release of bioactive agents. Cubosome dispersions are bioadhesive and biocompatible. Because of their properties, cubosome are versatile systems, administrable in different ways such as orally, percutaneously and parenterally. Cubosome structure by means of electron microscopy, "light scattering", x-ray and "NMR", nevertheless few researchers have been studying the potential of cubosome as "delivery systems". Hydrating a surface-active agent or polar lipid that forms cuboidal section and then dispersing a solid like section into smaller particles typically forms a cubosomes. Such novel particles are used to encapsulate guest molecules that are either hydrophilic, lipophilic or amphiphilic, due to the compartmentalization of its structure.

KEYWORDS: Cubosomes, honeycombed, versatile, drug payloads, compartmentalization.

1. INTRODUCTION

1.1 Definitions of Cubosomes

Cubosome is a separate, sub-micron, nanostructured particles of the bicontinuous cubic liquid crystalline phase.[1] Cubosomes are nanoparticles which are self-assembled liquid crystalline particles of certain surfactants with a proper ratio of water with microstructure. Cubosomes are nanoparticles but instead of the solid particles usually encountered, cubosomes are self-assembled liquid crystalline particles with solid-like rheology that provides unique properties of practical interest.

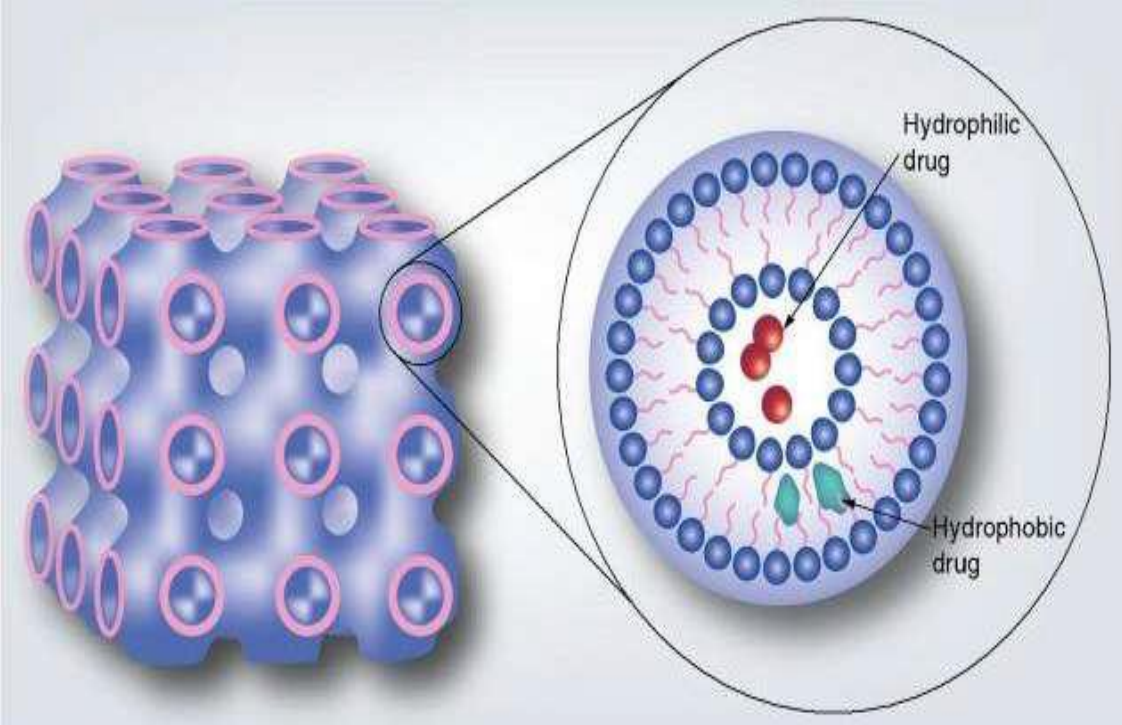

Fig. No. 1: Cubosomes internal cubic structure and its membrane composition with different drug loading properties.

1.2 History

Despite the first recognization (in 1980) massive scale manufacture of cubosomes was difficult because of their complicated phase behavior and viscous properties. The cuboidal phases are unique as possessing very high solid like viscosities due to their intriguing bicontinuous structures. Cubic phases can be fractured and dispersed to form particulate dispersions which are colloidally and/or thermodynamically stable for a longer period of time. Certain surfactants spontaneously form cuboidal phases once mixed with water higher than an exact concentration. Determination of their honeycomb structure was carried out by Luzzati and Husson, Luzzati et al., Larsson and Hyde et al between 1960 and 1985. The term

"Cubosomes" was coined by Larsson, that reflects the cuboidal molecular crystallography and similarity to liposomes. The effort to develop scalable processes to produce cubosomes on large scale is under development. A few anticancer drugs have been successfully encapsulated in cubosomes and characterized.[1]

MECHANISMS OF DRUG TRANSPORT

Drug transportation across cell membrane is dependent on the nature of the activity and composition of the carrier system, the anatomy and physiology of the skin. Small ions are transported through the hair follicles, pores of skin membranes, the tight junctions without much complex mechanism. Mechanisms concerned in skin membrane transport usually involve in intra (trans) and inter (para) cellular transports. By manipulating carriers, drugs can be incorporated either in the core or as an integral part of the vesicles.[2] Paracellular diffusion is that the movement of drug across a membrane by going between, rather than through, two cells. By definition, this process is solely passive and is dependent upon pore size, as well as the size and shape of the xenobiotic. Transcellular diffusion is that the movement of a drug across the cell. When enteric absorption happens by transcellular diffusion, the drug is exposed to the enzymes within the cell, as well as any efflux pumps that are present on the apical region of the membrane. These may result in a reduction in the amount of drug that reaches the systemic circulation. Transcellular diffusion could also be passive, facilitated, or active.[3] Transcellular movement, which involves the passage of drug through cells, is considered as most common route of drug transport. However, some drugs are too polar to go through the lipoidal cell wall and they can pass through the paracellular pathway only.[4]

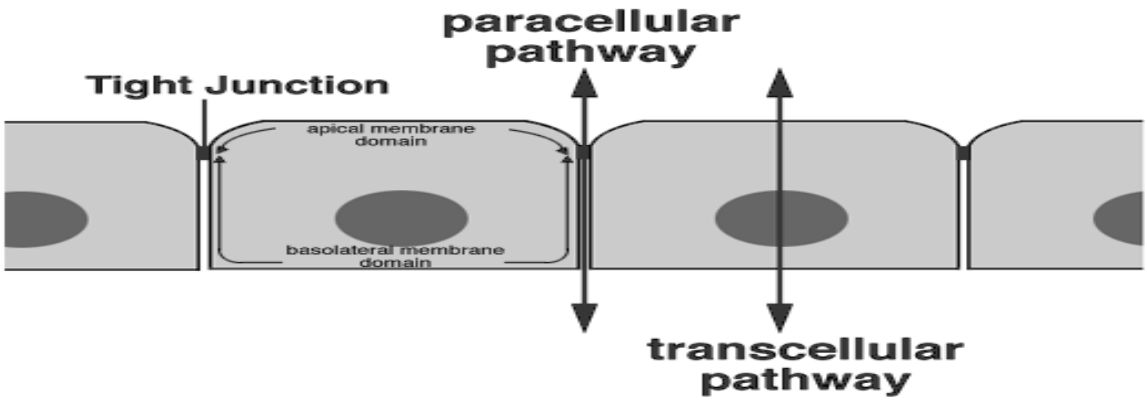

Fig. No. 2: Mechanism of Drug Transport Across Biological Membrane.

Structure of Cubosomes

Cubosomes having shape like honeycombed (cavernous) structures whose size range from 10–500 nm in diameter. It appears dots like structure, which are slightly spherical in nature. Each dot contains the presence of pore containing aqueous cubic phase in lipid water system. It was first identified by Luzzati and Husson with the help of X-ray scattering technique.[2]

Liquid Cubosome Precursors

The hydrotrope dilution method is found to give smaller, more stable cubosomes. Particles are formed by nucleation and growth, as employed in crystallization and precipitation processes. This is achieved by dissolving the monoolein into a hydrotrope, such as ethanol, that prevents liquid crystalline formation. Subsequent dilution of this mixture continuously "crystallizes" or precipitates the cubosomes. quid precursor method permits for easier scale up of cubosome preparations and avoids bulk solids handling and probably damaging high energy processes.[5,6]

Powdered Cubosome Precursors

Powdered cubosome precursors are composed of dehydrated surface-active agent coated with polymers. Such powders offer benefits to liquid phase hydrotropic cubosome precursors. Hydration of the precursor powders forms cubosomes with a mean particle size of 600 nm, as confirmed by light-weight scattering and cryo-TEM.[7] The lipids use to build cubosomes are waxy, sticky solids. Water-soluble non-cohesive starch coating on the waxy lipid prevents agglomeration and allows control of particle size. Spray drying is a superb method for his purpose.[6]

Advantages of Cubosomes[1]

1. Targeted release and controlled release of drug delivery system
2. It can encapsulate hydrophilic, hydrophobic and amphiphilic substances.
3. Biodegradability property of lipids.
4. Relatively simple & easy method of preparation.
5. High drug payloads capacity due to its high internal surface area and cubic crystalline structures.
6. The cubic phases of cubosomes can be dispersed to form particulate dispersions that are colloidally and/or thermodynamically stable for longer time.

Disadvantages of Cubosomes

1. Large scale production sometime harder due to its high viscosity property.

Methods of preparation of cubosomes

Three macroscopic varieties of cuboidal phase are usually encountered; precursor, bulk gel and particulate dispersion. The precursor type exists as a solid or liquid material that forms cuboidal phase in response to a input, like contact with liquid. Bulk cuboidal phase gel is associate optically identical, stiff, and solid like material in equilibrium with water can be dispersed into particles called cubosomes. The production of cubosomes entails two distinct technologies:

Top-down technique

Top-down approach begins with an appropriate beginning material then sculpts the functionality from the material. The bulk cuboidal section is initial created then spread by high energy process into cubosome nanoparticles. Bulk cuboidal phase resembles a transparent rigid gel formed by water-swollen cross-linked polymer chains, but cubic phases differ in that they are a single thermodynamic phase and display periodic liquid crystalline structure. Cubic phases may behave as lamellar phases during dispersion with increasing shear: dispersed liquid crystalline particles form at intermediate shear rates, whereas a defect free bulk phase re-forms at higher shear rates. At high oscillatory frequencies, cubic phases become highly elastic.[8]

Bottom-up technique

The bottom-up approach first forms the nanostructure building blocks and then assembles them into the final material. It is a lot of recently developed technique of cubosome formation, allowing cubosomes to form and crystallize from precursors on the molecular length scale. The formation of cubosomes by dispersion of inverse micellar phase droplets in water at 80°C, then by slow cooling to allow the droplets to gradually crystallize into cubosomes.[9]

Dispersion of the nanoparticles produced in the cubosomes formation by several techniques

i. Sonication

ii. High pressure homogenization

iii. Spontaneous emulsification

iv. Spray drying

v. Sonication and high-pressure.

Homogenization suggests the formation of complicated dispersions containing vesicles and cubosomes with time-dependent ratios of every particle type. Coarse cubosomes on the micrometer scale possess identical D-surface cuboidal structure as their originating bulk cuboidal section Spicer pt[10] however once homogenization, the P-surface dominates, either because of the added polymer or other factors.[11] Large-scale produc¬tion of cubosomes and products containing them requires more ro¬bust processes. Smaller and more stable cubosomes are produced than those by high-energy processes, but some vesicles are also produced. A method was also developed to permit cubosome production from a powdered precursor.[11] Spray-dried powders comprising monoolein coated with starch or dextran form cubosomes on simple hydration. The polymers immediately provide colloidal stabilization of the cubosomes.

Material used in cubosomes formation

Bicontinuous cubic phases are found in natural lipids, cationic Boretta M[12] and nonionic surfactants Lynch ML[13] and polymer systems, although the lipid most widely used to construct bicontinuous cubic phases is mainly monoglyceride monoolein, monoglycerides spontaneously form bicontinuous cubic phases upon the addition of water, are relatively insoluble, and are resistant to changes in temperature. The main precursor of cubosome formation is monoolein. Monoolein or glyceryl monooleate is a mixture of the glycerides of oleic acid and other fatty acids, consisting mainly of the monooleate.[14–16] The glycerol moiety may form hydrogen bonds with water in an aqueous environment and is commonly referred to as the head group. The organic compound chain provides hydrophobic characteristics to monoolein and is usually termed the tail. Commercially available monoolein may be obtained in two forms, a mixed glyceride form or as distilled monoolein; the distilled monoolein is preferred for pharmaceutical applications because of its high purity. It swells in water, giving rise to several lyotropic liquid crystalline structures.

When lipid molecule is heated, instead of melting directly convert into an isotropic liquid. Surfactants, which are used in the production of cubosomes, are poloxamer 407 in a concentration range between 0% and 20% w/w with respect to the disperse phase. The concentration of the monoglyceride/surfactant mixture generally takes between 2.5% and 10% w/w with respect to the total weight of the dispersion. Polyvinyl alcohol (PVA) used in addition to poloxamer as a stabilizing agent of the dispersion.

Application of Cubosome

•It used in control release drug delivery system for solubilized substances

•To increase drug solubility because of its ability to solubilize hydrophobic, hydrophilic and amphiphilic molecules

•Due to its small pore size cubic phase is more used for control release.

•Widely used in cancer treatment for delivering anticancer drugs

•Used in topical, mucosal deposition and delivery of various drugs used for topical preparation.

•Mainly utility in skin cancer treatment due to their bioadhesive and skin penetration property

•Properties like bioadhesion and biological membrane penetration enhancement of cubosomes suggest their potential utility in cancerous treatment mainly in skin cancer (e.g., melanoma) treatment.[17]

METHODS FOR CHARACTERIZATION AND EVALUATION OF CUBOSOMES

1. Gel permeation chromatography or ultra-filtration techniques & UV spectrophotometer or HPLC analysis[1]

Entrapment efficiency and drug loading in cubosomes can be determined with the help of gel permeation chromatography or ultra-filtration techniques. In the later technique, unentrapped (means free) drug concentration is determined, which is subtracted from the total amount of drug added. The amount of drug is analyzed with the help of analytical method like UV spectrophotometer or HPLC analysis.

2. Photon correlation spectroscopy[1]

Particle size distributions in cubosomes are determined by dynamic laser light scattering using Zeta sizer (Photon correlation spectroscopy). The sample diluted such a solvent which adjusted light scattering intensity of about 300 Hz and measured at 25°C in triplicate. The collected data generally shown by using average volume weight size. The polydispersity index and zeta potential can also be recorded.

3. Polarized light microscopy[1]

Polarized light microscopical method can be used reveal the optically birefringent (possibly vesicular) surface coating of the cubosomes and also can distinguish between anisotropic and isotropic substances.

4. X-ray scattering[1]

The X-ray scattering can be used to identify the spatial arrangements of different type of groups in the sample. The optical phenomenon (i.e. diffraction patterns) obtained are transfer to plots of intensity versus q value, which enable the identification of peak positions, and their conversion to Miller Indices. This Miller Indices could then be compare with known values for various liquid crystalline structures and space groups to identify the dominant internal nanostructure of the sample.

5. Transmission electron microscopy (TEM)[1]

Transmission electron microscopy can be used to view the shape and internal structure of the cubosomes. Kim et al. described that the suspensions of cubic section (phase) nanoparticles were negatively stained with freshly prepared phosphotungstic acid solution (2%, pH 6.8) and were transferred onto a formvar/carbon coated grid (200 mesh), air dried at room temperature. The electron microphotographs were conduct on an electron microscope. SEM analysis not perform on cubosomes and vesicular systems because the integrity and robustness of the formulation may be loss in contact exposing to electron array.

6. Pressure Ultrafiltration Method[1]

Drug release measurement of cubosomes can be done with the help of pressure ultrafiltration method. It is based closely on that proposed by Magenheim et al. using an Amicon pressure ultrafiltration cell fitted with a Millipore membrane at ambient temperature (22±2) °C.

7. Stability studies[1]

The physical stability can be studied by investigation of organoleptic and morphological characteristic with respect to time. Particle size distribution and drug content can be assessed at different time intervals can also be used to evaluate the possible variations by time.

8. Visual inspection[18]

About 1 week (6-10 days) after preparation, the dispersions were visually assessed for optical appearance (e.g., colour, turbidity, homogeneity, presence of macroscopic particles).

9. Lightmicroscopy[18]

Prepared sample of cubosome diluted with deionized water and examined using an optical microscope (Lecia DMRXP) calibrated with a micrometer slide at magnification of x 400 and x1000.

10. Entrapment efficiency[18]

For determining the entrapment efficiency (EE), it was mandated to separate free ALA from cubosome associated ALA. The amount of free drug in the dispersion was then analyzed spectrophotometrically at λmax 250 nm, this was then subtracted from the total amount of drug initially added. A volume of 1 ml from each of the dispersions was diluted with 4 ml of deionized water. Then a volume of 1 ml from this diluted dispersion was further diluted with another 4 ml of deionized water. This form dispersion the pass through a syringe filter which pore size of 0.1 μm. The filtrate was then analyzed spectrophotometrically at wavelength (λmax) 250 nm. This concentration was then multiplied by the total volume of the dispersion produced, considering the dilution factor. This shown the concentration of free drug (Cf, shown the drug which not encapsulated in cubosomes). This was reduced from the total drug concentration (Ct) in the formulation to give the amount of drug that was successfully entrapped into the cubosomes. Each experiment was repeated for three times for greater accuracy.

Entrapment Efficiency % of cubosomes = [(Ct – Cf) / Ct] x 100

11. Viscosity[18]

The viscosity of the prepared formulation of cubosome was determined at different angular velocities at 25^{o}C using a rotary viscometer (Brookfield). The rotation speed of viscometer was 20 rpm, with spin # 18. The average of three readings was used to calculate the viscosity of formulation.

Future prospects

The cubosome nanoparticles hold promise in the field of drug delivery and sustained drug release, but further optimization is still required, depending on the route of administration, frequency of dosing and the mode of drug release, before such nanocarriers can truly realize their therapeutic potential in many diseases.[19] They are also attractive nanovehicles for loading and delivery of proteins and peptides but the reported studies are still on a fundamental level[20] and different aspects in terms of structural and morphological characterstics of these soft nanocarriers, loading capacity of bio macromolecules and their release should be addressed. Future development of cubosome based intravenous nanomedicines should address blood compatability at early stages of formulation development. Further, little information is also still available on their stability in biological fluids and biological factors controlling drug release from cubosomes, structural

transformation upon contact with biological fluids such as plasma, interactions with cell membranes, and infusion-related reactions to name a few.[21] The application of cubosomes for intravenous drug delivery is an ambitious one; however, these nanocarriers may find accelerated applications for oral, ocular and topical delivery of poorly water soluble drugs, there by offering an alternative, yet, a cost effective opportunity in formulation science.

CONCLUSION

Cubosomes are nanoparticles but instead of the solid particles, cubosomes are self-assembled liquid crystalline particles, they have ability to incorporate many hydrophilic and lipophilic drugs and shows sustained and targeted drug delivery. Two methods such as top down and bottom up approaches could be easily employed to produce cubosomes either by ultrasonication techniques or high pressure homogenization. Cubosomes are applicable to wide range of drug candidates, proteins, immune substances and also to cosmetics. Due to the potential site specificity, the cubosomal preparations may be widely employed as targeted drug delivery systems for ophthalmic, diabetic and also for anticancer therapy. The cubosome technology is relatively new with high output and would have wide scope of research in developing new formulations with commercial and industrial viability.

REFERENCES

1. Bhosale RR, Osmani RA, Harkare BR and Ghodake PP. Cubosomes. The Inimitable Nanoparticulate Drug Carriers. Sch Acad J Pharm, 2013; 2(6): 481-486.
2. Vinod KR, Sravya K, Sandhya S, Banji D, Anbazhagan S, Prameela Rani A; Tailoring active compounds across biological membranes by cubosomal technology: an updated review. Journals of Chinese Pharmaceuticals Science, 2013; 22(4): 303-311.
3. Passage of Xenobiotics Across Biological Membranes; Pharmacokinetics and Biopharmaceutics (46:138), Lecture Tutorial. Available from http://www.uiowa.edu/~c046138/tut-mem.htm
4. Rowland M, Tozer TN; Membranes and Distribution. In Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications. 4th edition, Lippincott Williams & Wilkins, 2010.
5. 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.

6. Spicer PT, Small WB, Lynch ML, Burns JL; Dry Powder Precursors of 'Soft' Cubic Liquid Crystalline Nanoparticles (Cubosomes). Journal of Nanoparticle Research, 2002a; 4: 297-311.
7. Spicer PT, Small WB, Spicer PT, Lynch ML; Bicontinuous Cubic Liquid Crystalline Phase and Cubosome Personal Care Delivery Systems. Available from http://www.nonequilibrium.com/CubicLiquidCrystalline Rosen.pdf
8. Radiman S, Toprakcioglu C, Mcleish T. Rheological study of ternary cubic phases. *Langmuir*, 1994; 10(1): 61–67.
9. Almgren M, Edwards K, Gustafsson J. Cryotransmission electron microscopy of thin vitrified samples. *Curr Opin Colloid Interface Sci*., 1996; 1(2): 270–278.
10. Siekmann B, Bunjes H, Koch MHJ, et al. Preparation and structurals investigation of colloidal dispersion prepared from cubic monoglyceride–water phases. *Int J Pharm*, 2002; 244(1–2): 33–43.
11. Spicer PT, Small WB, Lynch ML, et al. Dry powder precursors of cubic liquid crystallines nanoparticles (cubosomes). *Journals of Nanoparticles Research*, 2002; 4(4): 297–311.
12. Boretta M, Cantu L, Corti M, et al. Cubic phases of gangliosides in water: Possible role of the conformational bistability of the headgroup. *Physica A*., 1997; 236(1–2): 162–176.
13. Lynch ML, Kochvar KK, Burns JL, et al. *Langmuir*, 2000; 16(7): 3537.
14. Guerrero QD, Buri P. Monoolein: A Review of the Pharmaceutical Applications. *Drug Development and Industrial Pharmacy*, 2000; 26(8): 809–820.
15. Shanmugam T, Banerjee R. Nanostructured self assembled lipid materials for drug delivery and tissue engineering. *Ther Deliv*, 2011; 2(11): 1485–1516.
16. Moquin PHL, Temelli F. Production of monoolein from oleicacid and glycerol in supercritical carbon dioxide media: A kinetic approach. *The Journal of Supercritical Fluids*, 2008; 44(1): 40–47.
17. Rarokar NR, 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
18. 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.
19. Angelova A, Angelov B and Lesieur S. (2008). Dynamic control of nanofluidic channels in protein drug delivery vehicles. Journal of Drug Delivery Science and Technology, 2008; 18(1): 41–45.

20. Angelova A, Angelov B and Drechsler M. (2013). Protein entrapment in PEGylated lipid nanoparticles. International Journal of Pharmac, 2013; 454(2): 625–632.
21. Wibroe PP, Azmi ID, Nilsson C, Yaghmur A and Moghimi SM. (2015). Citrem modulates internal nanostructure of glyceryl monooleate dispersions and bypasses complement activation: towards development of safe tunable intravenous lipid nanocarriers. Nanomedicine, 2015; 11(8): 1909–1914.