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CUBOSOMES AND ITS APPLICATIONS-A REVIEW

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ABSTRACT
Cubosomes are square or spherical particles having visible cubic lattices on the inside. Cubosome discovery is a fascinating narrative that involves food science, differential geometry, biological membranes, and digestive processes. Cubosomes have a "honey combed" structure and are thermodynamically stable. Cubosomes are made up of amphiphilic lipids that are held together by a polymer. Cubosomes can be used to treat skin, hair, and other bodily tissues in a variety of ways, including parenteral, oral, mucosal, and transdermal. Cubosome formation may be tweaked to design pore size or include bioactive lipids, and polymers can be utilised to target the outer circle. They're also quite safe under physiological conditions. They have more drug trapping potential with their network topology. Cubosomes are nanostructured liquid crystalline particles that self-assemble and have a different internal cubic structure and content. Cubosomes are formed by hydrating a surfactant or polar lipid that generates a cubic phase and then dispersing a solid-like phase into smaller particles. They have solid-like rheology with unique features that are useful in practise. Cubosomes can encapsulate hydrophobic, hydrophilic, and amphiphilic molecules. Cubosomes can improve the solubility of drugs that aren't very soluble. Applications of cubosomes includes treatment of skin, hair, and other body tissue using cubosome-like vehicle activity of biological substances, regulated release of solubilized chemicals. Melanoma (cancer) therapy based on a size delivery system is the key to effectively targeting melanoma due to increased permeability and retention.

KEYWORDS: Cubosomes, Nano carriers, Lipid, Anticancer therapy.

INTRODUCTION
Larsson was the first to form word "cubosomes," which is similar to liposomes.[1] Cubosomes are nanostructured particles of the bicontinuous cubic liquid crystalline phase, which are discrete and sub-micron in size. The capacity of the bicontinuous cubic phases to control membrane curvature is one of their main advantage. Cubosomes are self-assembled liquid crystalline particles with a solid-like rheology that self-assemble swiftly and efficiently.[2]

Cubosomes are viscous, optically isotropic, solid, and have cubic crystallographic symmetry to liquid crystalline substances.[3] Cubosomes play a critical role in drug delivery systems based on nanotechnology.[4] Recently, the interest in pharmaceuticals has grown to a point that it is now a particle with a diameter of a few hundred nano meters, the range is 10-500 nm diameter.[5] The proportion of medication to polymer is roughly 1:2 or 1:1, depending on the content substance.

Cubosomes and the parent cubic phase have the same microstructure; cubosome dispersions have a substantially lower viscosity in comparison to the cubic phase in bulk.[7] Cubosomes are made up of surfactant-like molecules that self-assemble amphiphilic compounds or molecules.[8]

The word cubosomes was coined because 'phases' is suffixed with 'some' and contains cubic crystal lattice.[9] Cubosomes are created at a specific temperature. They exist in three separate phases: - For primitive, gyroid, and diamond structures, P–surface, G–surface, and D–surface are used.[10,11]

Cubosome Characteristics[12]
- Cubosome dispersions have a much lower viscosity.
- Cubosomes are distinct, sub-micron nanostructured bicontinuous cubic liquid crystalline particles.
- Cubosomes are probably the most intriguing.
- Because they are transparent and isotropic, cubic liquid crystals are physically stable in excess water.
- Because of their small pore size, cubosomes are appealing for controlled release.
- It can solubilize hydrophobic, hydrophilic, and amphiphilic compounds and has biodegradability.

Structure

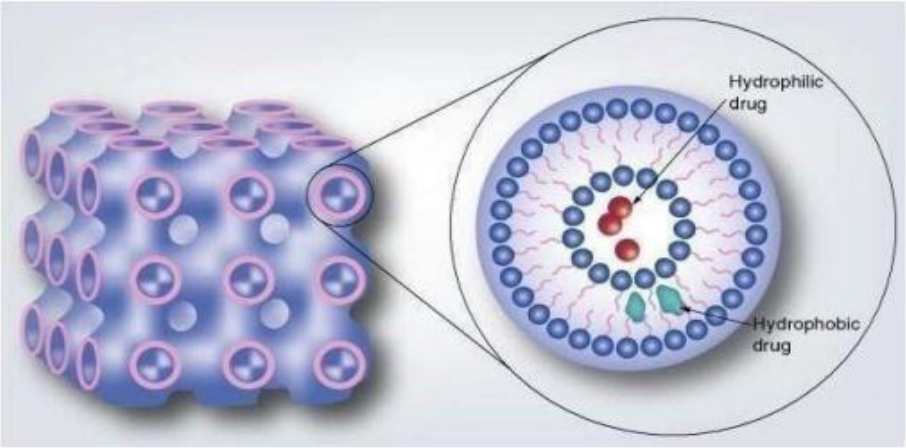

Figure 1: Cubosomes exhibiting its cavernous internal and cubic structure and itsmembrane composition with different drug loading modalities.

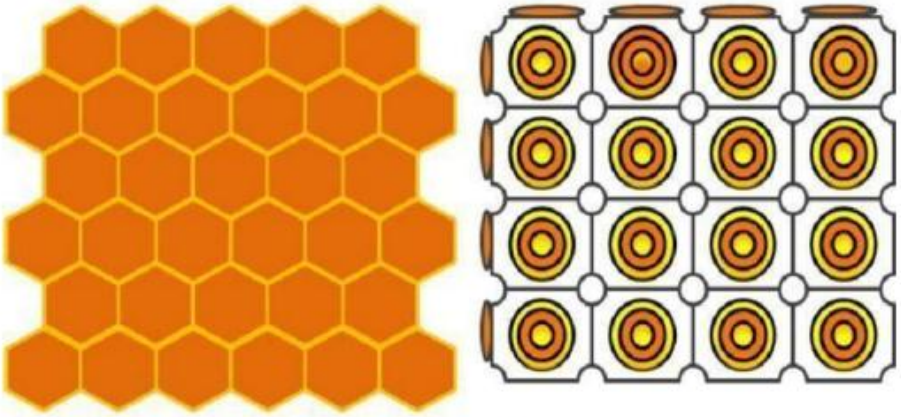

Fig. 2: (a) shows the honey comb structures, (b) shows the structures of primitive (P)cubic cubosomes which is similar to honeycomb.

Advantages

- Cubosomes are biocompatible, biodegradable, and non-irritating.[13]
- It has a simple preparation process.[14]
- Because of their large interior surface area, they have a high drug-loading capacity. for a longer period of time, they are thermodynamically stable.[15]
- They can encapsulate hydrophobic/lipophilic (cinnarizine) and hydrophilic (cyclosporine) molecules.[16,17]
- The usage of a specific polymer allows for the regulated and targeted release of bio-actives.
- Because there is less recurrent administration, the overall cost of health care is reduced.
- They lessen the negative effects of injections that are caused by the burst release.
- Particle volume and bilayer area have a higher ratio in comparison with the liposomes.[18]
- Cubosomes are good solubilizers, especially when compared to other typical carriers (lipid-based). They demonstrated the ability to encapsulate medications that are only slightly water soluble. They serve as a carrier for transporting the enzymatically degraded sensitive drug moiety (proteins, peptides). They increase the bioavailability of water-soluble peptides by roughly 20 to 100 percent.[19]
- Cubosome preparation procedures (such as shear and homogenization techniques) do not necessitate the use of organic solvents.[20,21]

Disadvantages

- Because cubosomes contain a large amount of water, water-soluble drugs are less likely to be trapped. [22]
- Due to its high viscosity, large-scale cubosome manufacture is challenging.[23]
- Without the use of a specific polymer, regulated drug delivery is not possible. They have the

potential to leak during storage or in-vivo transmission.[24]

- When particles are left alone for a long time, they may grow. If the external environment changes, cubosomes can produce a phase change (dynamics).[25]

Selection Criteria for Drugs and Excipients

The fundamental concept of the cubosome formulation was to deliver lipophilic medications such as diazepam, rifampicin, propofol, and griseofulvin to the target region, where the phospholipid coat provides enhanced permeability by lowering the lipophilic moiety's solubility problem. In the event that the permeability of hydrophilic glucose and insulin moieties Despite the fact that the biomembrane is limited, this can be accomplished successfully by integrating them into lipid components, they can be mitigated. As a result, both types of pharmaceuticals can be incorporated into cubosomes, however lipophilic drug encapsulation has been reported to be higher to date. Cubosomes were used to distribute peptides effectively, and the peptides' stability was improved by decreasing their exposure to diverse pH environmental conditions. As a result, the drawbacks of alternative site-specific/targeted drug delivery methods could be mitigated by careful selection of a cubosome carrier that allows drug moiety distribution to specified tissues/organs.[26]

Compatibility of the drug with the polymer and drug distribution in the solid lipid matrix are two physicochemical aspects to consider when selecting excipients.

Structural Characteristics Of Cubosomes

Importance Of Structure[27- 29]

Liquid bicontinuous cubic crystals, whether in bulk or cubic form, have unique properties that appeal to the cosmetics sector. Cubosomal personal care products are made by combining biocompatible lipids with an aqueous phase, allowing them to be used in skin, hair, and other body care products. Because of the probable interaction between stratum corneum with lipids utilised in cubosomal formulations, which promote drug absorption, cubosomal skin care products are gaining popularity.

Because Cubosomes are self-assembled cubic crystals, they are biocompatible and bio adhesive, making them ideal for oral administration, as demonstrated by the oral administration of insulin-loaded cubosomes for hyperglycaemic effect.

Applications of Cubosomes

Melanoma therapy[30]

Recently, a few anticancer drugs have been encapsulated in cubosomes and physico-chemically characterised. This promising nanocarrier's distinct structure suggests that it can be used in melanoma therapy. Different outlook have been proposed to specifically target nanomedicines to tumours, with passive and active targeting of cancer cells having been shown to be valid approaches in preclinical and clinical studies.

Passive targeting have advantage of the pathophysiological character of the tumour vasculature, which is generally disorganised, with large gap junctions between endothelial cells and compromised lymphatic drainage, making for the extravasation of nanocarriers with sizes ranging from a few hundred nanometres to hundred micrometres. Objects of this size are not able to pass through the tight junctions found within the endothelial cell lining of healthy tissue vessels.

The most common modification used to avoid detection is Capture and expansion of macrophages. The circulation time is achieved by making the surface hydrophilic nanoparticles via the the incorporation of a polyethylene glycol (PEG) coating on the outside. The vast majority of nanoparticle drug formulations used in clinical trials and in development is primarily based on passive targeting. As a means of increasing awareness of Nanoparticles have been used to target cells, and active targeting has been developed. been put into action Active targeting makes use of peptides and antibodies are examples of specific ligands. that bind to molecules that are expressor target cells are overexpressed As a result, active Targeting has no effect on overall performance accumulation at the site of the tumour, but rather improves the cellular uptake of particles after passive extravasation because of the leaky vasculature Transferrin and its derivatives Two examples of commonly used ligands are folate ligands and In nanomedicine, active targeting moieties are used.

Oral Drug Administration[31]

Cubosomes faces issues such as poor aqueous solubility, poor absorption, and large molecular size in the oral delivery of many promising compounds. Large proteins have been encapsulated in an alternative application for local activity in the gastrointestinal tract. Carriers based on liquid crystalline nanoparticles technology can be clubbed together with controlled release and targeting capabilities. The particles are designed to form in situ at a controlled rate, which makes them effective for drug distribution in vivo.

Cubosomes carriers can also be released at different absorption sites, such as the upper or lower intestine, which is needed for drugs with a limited regional absorption window.

Intravenous Drug Administration Systems[32]

Lipid nanoparticles with interior liquid crystal structures of curved lipid membranes are used to solubilize, encapsulate, and deliver medications to disease sites throughout the body.

While emulsions and liposomes have been used as intravenous carriers in drug products, liquid crystal

nanoparticle structures have increased payloads of peptides, proteins, and many insoluble small molecules, making them ideal carriers for injection or infusion of many actives

Topical Drug Delivery Systems[33]

Cubic phases are more bioadhesive in nature, making them suitable for topical and mucosal depositions as well as drug delivery. The unique properties of liquid crystal (LC) and liquid crystal nanoparticle (LCNP) technologies are used to create topical delivery systems. Topical drug delivery systems are distinct in that they form bioadhesive LC systems in situ, allowing for controlled and effective drug delivery to mucosal surfaces (buccal, ophthalmic, vaginal, and others). This fascinating system forms a thin surface film at mucosal surfaces composed of a liquid crystal matrix, the nanostructure of which can be controlled to achieve an optimal delivery profile, and it provides good temporary protection of sore and sensitive skin.

Vehicle for Drug Delivery

A common application for such new materials is drug delivery vehicles. The rapid growth of the life sciences industry is expected to propel previously "exotic" delivery vehicles and ingredients into broader markets such as personal care and consumer products.

As a result, self-assembled surfactant phases have been thoroughly tested for compatibility with a wide range of medical active ingredients and applications. A number of studies in collaboration with cosmetic companies such as L'Oreal and Nivea are attempting to use cubosome particles as oil-in-water emulsion stabilisers and pollutant absorbents in cosmetics. Furthermore, these researchers discovered that phytantriol a second amphiphile, has an aqueous phase behaviour similar enough to monoolein's to form cubosomes under similar conditions.

Sustained Drug Release Behaviour

Recently, there has been a lot of patent activity by. Use of cubosomes in personal care products as skin care, hair care, cosmetics, and so forth.antiperspirants. Despite recent effort, there is still a lot of work to be done.

There is still a dearth of practical features such as material scalability and manufacturing scalability customization that is required to be a leader.

Cubosomes should be considered by formulators. commercially available goods The cubic phase has been completed. demonstrated to be a carrier for various in vivo experiments depot, transdermal, and other delivery methods ophthalmic adhesion and mucoadhesion as a result Monoolein's fusogenic property raises the macromolecular penetration. It also improves macromolecule penetration. Drugs with a range of physicochemical features have been integrated into cubosomes, and their sustained release behaviour has been investigated. Cubosome residual particles were responsible for the cubosomes' long-term activity. Topical usage of monoglyceride-based cubosome dispersion, such as for perctuneous or mucosal applications, is possible.

In The Treatment of Viral Infections

Monoglycerieds could be utilised to develop intravaginal treatments for sexually transmitted illnesses caused by viruses (e.g. HSV, HIV) or bacteria (e.g. Chlamydia trachomatis and Neisseria genorrticae) due to their microbicidal characteristics. The creation of a mixture of cubosomalmonolein and stratum corneum lipids is reasonable due to the similarity between the cubic phase structure and the structure of the stratum corneum. This interaction could result in the establishment of a cubosome depot in this layer, from which drugs could be delivered in a regulated manner. The cubosome technique is being used to create a synthetic vernix – the cheesy white fluid that coats children in late pregnancy – to aid premature babies born without it.

The vernix is made up of lipids (fats), proteins, and water in a complicated composition. It develops late in pregnancy and plays an important function in appropriate skin development.

In Topical and Mucosal Dispositions

Cubic phases are more bioadhesive in nature in topical and mucosal depositions, making them more practical to utilise in topical and mucosal depositions and drug delivery.

Controlled-Release Drug Delivery

The most common use pursued by cubosome researchers is controlled release of solubilized actives, and comprehensive evaluations of attempted delivery applications as well as pharmaceutical actives that have been solubilized in bulk cubic phase and cubosomes exist.

Because of its tiny pore size (5–10 nm), capacity to solubilize hydrophobic, hydrophilic, and amphiphilic compounds, and biodegradability by simple enzyme activity, cubic phase is appealing for controlled release. Cubic phase is highly bioadhesive and is assumed to be a skin penetration enhancer, implying great compatibility with topical and mucosal deposition and active ingredient administration.

Recent research has found parallels between the bicontinuous structures created in human skin layers and those found in cubic phases, promising a better understanding and treatment of skintransport. Cubic phase's tortuous structure is ideal for slowing diffusive release of solubilized actives. According to theory, a solute's free solution diffusivity will be reduced by 33%. Small molecule diffusivity in cubic phases is measured to be on the order of 10 10 m2/sec in experiments. Other than a periodontal disease treatment based on

triglyceride–monoolein combinations paired with the antibiotic metronidazole, no commercial applications of cubic phase delivery vehicles are known. When the lipid–drug mixture is applied to the gums and comes into contact with saliva, it hydrates to form a bulk cubic phase, which subsequently distributes the drug to the gums. Despite the bulk cubic phase's potential as a delivery vehicle, several applications need the employment of cubosomes due to the bulk cubic phase's exceptionally high viscosity. Although the foregoing controlled-release limits apply to small molecule solutes and unmodified cubosomes, different controlled-release pathways for cubosomes may exist.

When big poly(amidoamine) dendrimer molecules are entrapped in cubic phases, their free diffusivity is reduced by 100.

In Materials Synthesis

From the standpoint of materials science, the nanoscale production of organised structures Many people are interested in pore geometries.Electronics, photonics, and catalysis are only a few examples.as well as medication constructing sturdy buildings Typically, cubic phases are used as a template. either polymerization or a reaction to produce solids derived from solubilized precursors in, or The cubic phase matrix is made up of. Among the elements created in the earliest and most successful The aluminosilicate is a cubic phase template. MCM-48 zeolite for catalytic processing of petroleum. Yang et al. completed the project successfully .Inside cubosomes, polymerization occurs, resulting in a cubic solid nanostructured particle symmetry. Photonic and semiconductor applications could benefit from the employment of such particles. Lu et al. have created unique aerosol techniques that produce nanometer-scale particles by evaporating solvent from isotropic phase liquid droplets, pushing them into cubic phase structures, and hardening the particles. As the cubic phase template area becomes more sophisticated, structure optimization will become a major focus.

Larson argues that prior to templating, the cubic phases could be aligned by steady or large-amplitude oscillatory shearing, resulting in materials with unique and highly anisotropic characteristics.

Biologically Active Substances

Cubic phase is produced at 25 ºC in water monoolein and alcohol mixtures. Ethanol was found to be more appropriate than propanol and butanol. In the composition range of 49 to 56 wt % water, 31 to 40 wt% mono oleine and 10 to 13% wt ethanol identified a new transparent, low-viscosity phase that is called OL. No structures were found by bright field light microscopy and polarized light microscopy, indicating that OL is an isotropic phase. CryoTEM showed large domains of this ordered phase, which by Fast Fourier Transformation was identified as a cubic phase.[34]

Treatment of Skin, Hair and Body Tissue

Cubic phase materials can be formed by a simple combination of biologically compatible lipids and water, making them ideal for use in skin, hair, and other body tissue treatments. Cubosomes contain mono-olein, or monoglycerides. Microbicidal properties of monoglycerides Cubosomes contain ethanol, which disrupts the skin. Because of the increased lipid fluidity, there is more permeation through the skin. Cubosomes allow drugs to enter the skin, bind to skin lipids, and be released into deep skin layers.[35]

REFERENCES

1. Vinod KR, Sravya K, Sandhya S, Banji D, Anbazhagan S and Rani PA: Tailoring active compounds across biological membranes by cubosomal technology: an updated review. Journal of Chinese Pharmaceutical Sciences, 2013; 22(4): 303-11.
2. Almeida JD, Brand CM, Edwards DC and Health TD: Formation of virosomes from influenza subunits and liposomes. Lancet, 2: 899-01.
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. Spicer PT: Cubosomes bicontinuous cubic liquid crystalline nanostructured particles. The Procter and Gamble Company, West Chester, Ohio, USA.
5. Dierking I: A review of polymer stabilized ferroelectric liquid crystals. Materials, 2014; 7(5): 3568-87.
6. Wibroe PP, Azmi ID, Nilsson C, Yaghmur A and Moghimi SM: Citrem modulates internal nanostructure of glyceryl monooleate dispersions and bypasses complement activation: towards development of safe tunable intravenous lipid nanocarriers. Nanomedicine, 2015; 11(8): 1909-14.
7. 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.
8. Spicer PT: Cubosome Processing Industrial Nanoparticle Technology Development. Chemical Engineering Research and Design, 2005; 83(A11): 1283-86.
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. 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.
11. 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.

12. Bansal S, Kashyap CP, Aggarwal G. A Comparative Review on Vesicular Drug Delivery System and Stability. IJRPC., 2012; 2: 704-13.
13. Rizwan SB, Dong YD, Boyd BJ, Rades T and Hook S: Characterization of bicontinuous cubic liquid crystalline systems of phytantriol and water using cryo field emission scanning electron microscopy. Micron, 2007; 38: 478-85.
14. Bei D, Meng J and Youan BC: Engineering Nanomedicine for Improved Melanoma Therapy: Progress and Promises. Nanomedicine (London, England), 2010; 5(9): 1385-99.
15. Tilekar KB, Khade PH, Shitole MH, Jograna MB and Patil RY: Cancer oriented cubosomes – a review. International Journal for Pharmaceutical Research Scholars (IJPRS), 2014; 3: 198-10.
16. Yingchoncharoen P, Kalinowski DS and Richardson DR: Lipid-based drug delivery systems in cancer therapy: what is available and what is yet to comePharmacol Rev., 2016; 68: 701-87.
17. Sastri KT, Radha GV, Pidikiti S and P Vajjhala: Solid lipid nanoparticles: preparation techniques, their characterization, and an update on recent studies. J Appl Pharmaceut Sci, 2020; 10: 126-41.
18. Rizwan SB, Dong YD, Boyd BJ, Rades T and Hook S: Characterization of bicontinuous cubic liquid crystalline systems of phytantriol and water using cryo field emission scanning electron microscopy. Micron, 2007; 38: 478-85.
19. Spicer PT: Cubosome processing industrial nanoparticle technology development. Chemical Engineering Research and Design, 2005; 83(A11): 1283-86.
20. Mathews PD, Patta, ACMF, Gonçalves JV, Gama GDS, Garcia ITS and Mertins O: Targeted Drug Delivery and Treatment of Endoparasites with Biocompatible Particles of pH-Responsive Structure. Biomacromolecules 2018; 19: 499-10.
21. Attama AA and Muller Goymann CC: Effect of beeswax modification on the lipid matrix and solid lipid nanoparticle crystallinity. Colloids Surf A: Physicochem Eng Aspects, 2008; 315: 189-95.
22. Tilekar KB, Khade PH, Kakade S, Kotwal S and Patil R: Cubosomes a drug delivery system. International Journal of Chemical and Biochemical Science, 2014; 4: 812-24.
23. Karami Z and Hamidi M: Cubosomes: Remarkable drug delivery potential. Drug Discovery Today, 2016; 21: 789- 01.
24. Nanjwade BK, Hundekar YR, Kamble MS and Srichana T: Development of cuboidal nanomedicine by nanotechnology. Austin J Nanomed Nanotechnol, 2014; 2: 1023.
25. Garg G and Saraf S: Cubosomes: An overview. Boil Pharm Bull, 2007; 30(2): 350-3.
26. Mehnert W, Mader K. Solid lipid nanoparticles: production, characterization, and applications. Adv Drug Deliv Rev., 2001; 47: 165-96.
27. Daharwal SJ, Verma E, Saudagar RB. Semi solid dosage forms. Farmavita Net., 2014; 13: 10.
28. Yang Z, Peng X, Tan Y, Chen M, and Zhu X. Optimization of the preparation process for an oral phytantriol-based Amphotericin B cubosomes. J Nanomater, 2011; 10. Article ID 308016.
29. Bei D, Zhang T, Murowchick JB, Youan BB. Formulation of Decarbazine- loaded cubosomes. Part 111. physicochemical Charecterization, AAPS PharmsciTech, 2010; 11(3): 1243-9.
30. Chung H, Kim J, Um Y, Kwon IC, Jeong SY. Self-assembeled Nanocubicle as a carrier for peroral Insulin Delivery, Diabetologia, 2002; 45(3): 448-5
31. Sagnella, S., and Drummond, C. Drug Delivery: A Nanomedicine Approach. Australian Biochemistry, 2012; 43: 5-7.
32. Yosra SRE, Samar ME, Doaa AA, Ossama YA. Novel piperineloaded tween-integrated monoolein cubosomes as braintargeted oral nanomedicine in Alzheimer's disease: pharmaceutical, biological and toxicological studies. Int J Nanomed, 2015; 10: 5459-73.
33. Rizwan SB. Bicontinuous cubic liquid crystals as sustained delivery systems for peptides and proteins. Expert Opin Drug Delivery, 2010; 7: 1133-44.
34. Bhosale RR, Osmani RA, Harkare BR and Ghodake PP. Cubosomes. The Inimitable Nanoparticulate Drug Carriers. Sch Acad J Pharm., 2013; 2(6): 481-486.
35. Murphy E. Targeted nanogels: A versatile platform for drug delivery to tumors. Aacro J., 2012; 972-82.