International Journal of Engineering Inventions
e-ISSN: 2278-7461, p-ISSN: 2319-6491
Volume 9, Issue 8 [August. 2020] PP: 01-08

Cubic Lipids:A Bliss For Drug Delivery

[a1]Tanima Bhattacharya,,[a2]Caixia Wang,[a3] Zhaoquan Ai
a. Hubei Collaborative Innovation Center for Advanced Organic Chemical Materials, Ministry of Education Key Laboratory for the Synthesis and Application of Organic Functional Molecules, College of Chemistry and Chemical Engineering, Hubei University, Wuhan 430062, P. R. China
a 1 Post Doctoral Researcher
*First corresponding author:Dorctorl Caixia Wang ;**2.Second corresponding author:Prof.Ai. Zhaoquan email: 2326978832@qq.com

Abstract:*Lipids are existing biopolymers useful in many biomedical applications. It has ,promising characteristics as traditional medicine carriers. Various forms of lipids sought attention for scientists in drug delivery comprising of liposomes, micelles, solid lipid nanoparticles. Traditional carriers are facing some problems of early drug release, bio adhesion property, and enhanced permeability rate, prolong circulation.Thereby to overcome such poor properties, nanotechnology has become an outstanding approach, using lyotropic crystalline lipid nanocubes. In this review the focus will be on day by day newer modified techniques of those cubes formulation to modify surface area for enhancing loading capacity of small drug moiety and membrane proteinswhichcan be applied as Nano therapeutics in drug delivery system.*

Keywords: lyotropic,crystalline, lipid nano cubes, modified techniques, Nano therapeutics,

Abbreviations: SLN: solid lipid nanoparticles, SEM: Scanning Electron Microscopy, TEM: Transmission electron microscopy, DDS: drug delivery system, siRNA: short interfering ribonucleic acid, GEFP: green fluorescent protein ,LET: lauryl ester of tyrosine,PEG-L-NP:pegylated nanoparticles, SAXS :X-ray scattering pattern,CET: cryo electron tomography

Date of Submıssıon: 31-10-2020 Date of Acceptance: 12-11-2020

I. INTRODUCTION

In recent days Nanotechnology has created an important field of dimension in pharmaceutical research especially in drug delivery system. Nano encapsulation is very important and unique technique for bioactive compounds to sustain their bioavailability due to increase surface volume ratio by reducing the size into nano range. Biopolymers with dimension 10nm -1000nm can be used as nanoparticles .Recently biopolymers sought attention of many researchers due to their bio compatibility, easy design and preparations, surface variations and interesting biomimetic characters. Past few decades lipids gain much importance as carrier of poor water solubledrugs. Numerous safety formulations for delivery have been a big attraction for scientists. The absorption rate of drug moiety from lipids depends on particle size, rate of emulsification, rate of dispersion and precipitation of drug upon dispersion **[1].** Liposomes are spherical, self-closed structures formed byone or several concentric lipid bilayers with inner aqueous phases Micelles, which are self-assembling closed lipid monolayers with a hydrophobic core and hydrophilic shell, have beensuccessfully used as pharmaceutical carriers for water-insoluble drugs.

.

II. LIPID BASED DRUG FORMULATION BY CONVENTIONAL APPROACH

The factors to be considered while carrier formulations are solubility [2], dispersion [3], digestion [4] and absorption [5]. The following methods are described here.

2.1.SprayCongealing&SprayDryingTechnique:

This method is known as spray cooling. Here lipid is melted and introduced in a cooling chamber, where congealing occurs.Ultrasonication is required. The lipid thus collected from bottom later modified in to capsules or tablets. Temperature and viscosity are the prime parameters of the process.This method is somewhat similar to the above described process onebut here the temperature of the atomizing spray chamber differs. The drug organic or water solution is sprayed along with lipid moiety resulting in granules and powder form Gelucire lipid excipients is manufactured by this process. [6,7].

2.2.Solid Carrier Adsorption:

Simple approach in which a liquid-lipid formulation is adsorbed onto solid carrier like silicon dioxide, calcium silicate, or magnesium aluminometasilicate. The liquid-lipid formulation is addedto the carrier by mixing in a blender. Here the choice of carrier is important so that it can get adsorbed in the liquid formulation.Labrasols formulations were successfully converted into solid intermediates whose bioavailability was maintained even after adsorption on carriers. [8-10]

2.3.Pelletization Method:

This process involves high sheer mixing of powder mix with drug into granular pellets.Due to friction in the process the bider melts. This is also known as Pump on technique[11]. Reports on Lactose monohydrate melt-agglomeration with a melt ablebinderlikePEG3000ofGelucires50/13inahigh-shear mixer was cited [12].

2.3.Supercritical Fluid Technique:

In this method, the drug and lipid-based excipients are dissolvedinanorganicsolventandsupercriticalfluid(carbon dioxide) by elevating the temperature and pressure [13,14]. The coating process is facilitated by a gradual reduction in pressureandtemperatureinordertoreducethesolubilityof the coating material in the fluid and hence precipitate onto the drug particles to form a coating [15,16]. The solubility oftheformulationcomponents in the supercriticalfluidand stability of the substance during the process are important considerationsofthismethod.

III. MODERN TECHNICAL APPROACH FOR CONVENTIONAL LIPIDS IN DRUG DELIVERY:

Recently new modified Nano carriers are taken into consideration for better DDS, gene therapy to delivery of short interfering ribonucleic acid (siRNA) into a green fluorescent protein (GFP) expressing cell line, using lipid Nano carriers in cubic lyotropic liquid crystal form reported by Guoliang Zhen etal 2012**[17]**

Although lipid nanoparticles created a space in NanoDDS, they often cannot release at tumor site efficiently. Several techniques are tried for the enhanced drug delivery out of which is ultrasound mechanism by Rahul Nahire 2013 etal**[18]**. They observed in their research that lipid Nano carrier in presence of cytosolic glutathione only delivers 76% of the drug to the targeted site where as if the Nano carrier is faced 3MHz for 2minutes, then the release increases to 96%.

Thus from the above pic by Nahire etal it is clear that the lipid nanoparticles can exhibit effective Drug Delivery System as well as in Ultrasound imaging with modification in their environment. Researchers are developing self-organized assemblies and different phase structures of amphiphiles with polymer nanoparticles is a promising approach for the design of high performing Nano carriers . According to Angyarkanny etal **[19]**" Nano carriers of Solid Lipid from Micelles of Amino Acids Surfactants Coated with Polymer Nanoparticles" were focus of research. The researchers develop Polymer nanoparticle coated micelle assemblies of lauryl ester of tyrosine (LET) act as potential Nano carriers for the model solid lipid stearyl alcohol. It is significant to mention here, that in dispersions of amino acid surfactant in neat Lauryl ester of tyrosine and Lauryl Esters of Phenylalanine micelles, amino acid surfactant separated spontaneously which suggested an almost negligible encapsulation of amino acid surfactant in the micelles. By this it is proved that polymer coated LET micelles acts as a suitable matrix for the encapsulation of SA, the strength of which must be arising through H bonding interaction between phenolic group in LET and Hydroxyl(OH) of SA.

Day by day newest approach of biopolymers in DDS is being in limelight. Nano carriers may cause half burst release before accumulating at tumor site, thereby circulating materials can sometimes lead to toxicity. Henceforth researchers are emphasizing on stimuli responsive carriers**.** Michelle Stollzoff etal **[20]**, reported a novel, pH responsive lipid coated nanoparticle which expands in size from 100-1000nm in mild acidic pH environment in presence of PolyetheleneGlycated lipids. The surface modified of PEG-NPs allows for the incorporation of folic acid (FA) and folate receptor-targeting. The resulting hybrid polymer/lipid Nano carriers, Folic Acid -PEG-L-NPs, exhibit greater in vitro uptake and potency when loaded with paclitaxel compared to nontargeted PEG-L-eNPs.

IV. CONVERSION OF CONVENTIONAL LIPIDS TO CUBIC LIPIDS:

Liposomes, solid lipid nanoparticles, micelles and Nano Lipid carriers are the most commonly used in Drug Delivery Approach. These promising carriers are nowadays showing some hindrances in drug delivery like large amount of drug is required, sometimes early burst release due to poor bio adhesion properties. Researchers thereby trying to transform the conventional lipid to overcome such problems.Nearly two decades, the research is being conducted on cubic lipids termed as "Cubosomes" [21].These Cubosomes are smart nano lipids

containing bicontinuos phase containing a single lipid layer with interwoven water channels. The outer corona is modified by a polymer coating. This is a non-lamellar type of lipid phase **[22].**

Cubosomes are of more enhanced large membrane surface area than liposomes which can entrap any drug moiety of small amount or protein particles of interest [22]. These are having highly ordered interwoven structures which offer the pharmaceutical substances of various sizes and polarities to release slowly in the matrix [23]. There are number of methods for cubic lipids formulations like including dispersion of bulk cubic phases using sonication,[24-26] homogenization,[27,28] shearing,[29] solvent evaporation,[30,31] the incorporation of hydrotopes, which enable formation via a dilution method,[21, 32] and (less commonly) using mechanical stirring[33,34]So far two types of lipids monoolein and phytantriol are mainly used with plurogenic gel series in reverse phase comprising an aqueous phase[35].Nowadays various amphiphilic lipids like monoglycerides,glycolipids, phospholipids, urea based lipids which are capable of forming self-assembly crystalline structure have been promising in developing these cubic lipids,[36].The conventional approach is further modified by applying vacuum treatment in presence of nitrogen gas, so as to enhance the physiochemical properties[37].Other materials comprising of nonionic tricopolymers, amphilic proteins like caseins, cationic amino acids based surfactant are also used as stabilizing agents for cubic phase dispersion[36, 38]

V. TECHNIQUES OF PREPARING TRANSFORMED CUBIC LIPIDS:

Many pharmaceutical scientists are emphasizing on the ability of preparing nanostructured aqueous dispersion of uniform particle size without aggregation. To decrease viscosity of Cubosomes so that it can be applied Invivo or Invitro surface modification is been done by addition of plurogenic gel series,**[39]**Zahara etal .The existing two methods for cubic lipid preparation are top down technique and bottom up approach. Top down approach is a two way mechanism, where cubic phase of lipids is formed by addition of stabilizers to plant based or animal based lipids. The first step then followed by the second step where the cubic lipid dispersion is added by applying high energy throughput (homogenization or sonication)to aqueous phase**[40].**The cubic lipids of this technique exists in a crystalline form or vesicle like structure**[41].**Reports of particle size distribution is also depicted by Worle etal**[42],** the group observed that at an optimization between 40-60℃, the cubic phase attained is of much promising characteristics whereas increasing of temperature beyond 60 ℃,results in smaller particle size.

Second approach is another simpler one where lipid precursors are crystalised.Then addition of polymers and hydrotopes are followed by as reported in Spicer etal**[21].**Here the input energy is energy is less compared to that of the previous technique, thereby dealing of temperature sensitive materials become much easier.The hydratope is used to avoid the higher viscosity of these crystalline cubic lipids**,[43].**

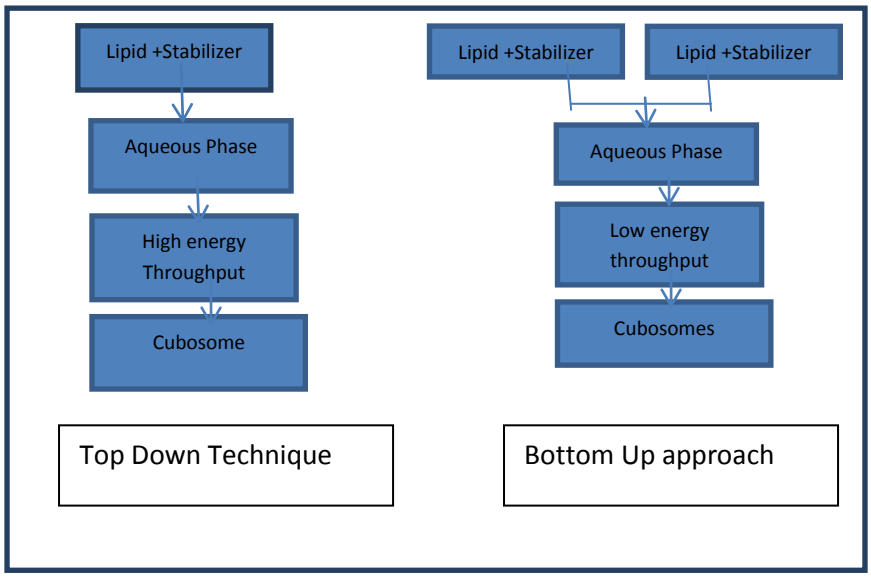

Fig.1.The schematic diagram of the Top down and Bottom up Technique

Comparative studies conducted by researchers showed that bottom up approach is much appreciable as small size cubic crystalline lipids are formed using low energy throughput**,[44].**Recent development of not using hydra tope has also sought attraction among researchers, Here phosphate buffer saline is used to apply in charged lipid where charge shielding occurs thereby altering the bilayered curvature and leads to the restoration

of the bicontinuos cubic phase.The Cubosomes made from bottom up technique also showed enhanced encapsulation efficacy.Research on conventional cubic lipid behavior is also conducted by researchers. They noticed the crystal lattice behavioural changes of traditional cubic lipid to double diamond cubic lipid by adding mono and divalent salt to the bicontinuos lipid phase, resulting in modest crystal lattice parameter up tonanometer**[45].**

VI. CHARACTERISATIONS OF TRANSFORMED CUBIC LIPIDS:

The small angle X-ray scattering pattern[SAXS] is the most commonly used for determining the cubic crystal formation with the hydratope and lipid phase. This was an eye catcher mechanism cited by Spice etal .From another report of researcher SAXS result described that Plurogenic gel series with Phytantriol is much effective in forming diamond cubic phase compared to monoolein,Chongetal.The plurogenic series confirmed the internal stabilistaion of the cubic lipid crystal lattice.ThecryoTEM of the cubic phase also confirmed the same. Particle size and polydispersity was measured by photon correlation spectroscopy.In case of SiRnAcuboplex synthesized under vacuum treatment in presence of Nitrogen**,[37],**the internal structure was determined by Cryo TEM . According to many research, SAXS characterization has limitations because it depends on constructive interfernces in reciprocal space from a large number of ordered scattering planes thereby resulting in obstructions for small particles . This technique does not provide straightforward visualization of the smaller particles.CryoTEM signaling technique also limits in resolution and subsequent structural interpreteions,thus to overcome such problems, a technique "cryo electron tomography was coined**,[46].**The result of the cryoCET depicts the cubosome are internally ordered with a diameter of ranging from 100-500nm,and the possibility of visualizing 3D network comprising of bicontinuos lipid structure with two independent water channels.Morphologicalcharacteristics was also reported by Lukas etal by Differential light scattering technique .Photosensitization was measured by fluorescence microscopy.

Identification of hexagonal phases and other nonlamelar phases are ben readily understood by static NMR. Since Bicontinuos cubic phase do not exist in istropic phase, though gives isotropic peaks at Static NMR it is highly indistinguishable .Thereby group of Researcher from Massachusetts Institute of Technology worked on this problem finally concluding by distinguishing the time relaxation differences between lipid isotropic phases and cubic phases.This technique has sought attention in many protein-induced membrane remodeling phenomena in biology,**[23]**

VII. THERANOSTIC APPROACH AND CANCER TARGETTING COMPATABILITY:

Earlier in the current review , it is already discussed that lipid nano particles have proved their efficacy in drug delivery system.

These liposomes exhibits much less membrane surface area to entrap certain small molecular drug moieties, compared to cubic lipids**[22].**Though past decades, scientists were involved in developing cubic lipids by modifying several techniques and tried to characterized their internal structural stability , theranostic approach is still a challenge in respect to drug delivery system due to high viscosity and practical Invivo Invitro applications. This current review will like to portray the way out of overcoming such problems of "Cubosomes". Recently these cubic crystalline lattice structured lipidsare being utilized in various biomedical applications including carcinoma targeting and early stage detection by optical imaging.

Cubic lipids have many therapeutic reports as better oral bioavailabilitysustained transdermal delivery of Monoolein and phytantriol[**47-49**], anti-inflammatory drug celocoxib enhanced release also cited when encapped by cubic lipid formed from oleic acids**[50].**Report on rheumatoid arthritis treatment by cubosome was depicted by loading monoolein Cubosomes with etodolac, Salah etal[51].Tropical delivery of antimicrobial peptide was also an important approach by Lukas etal**[52].**The group of researchers processed a glycerol monoleate based cubosome with the help of top down technique using high shear force.The Cubosomes was loaded with antimicrobial peptide to target skin disease causing *Staphylococcus areus.*Skin penetration report by Nithyaetal**[53]** is also a promising research. The researchers used pig ear skin ,where Dapsone loaded Cubosomes (DC) were prepared by ultra-sonication of aqueous dispersion containing cubic gelmatrix of glycerylmonooleate (GMO) and Poloxamer 407.This can further be used in tropical delivery without any systemic effects. Reports of overcoming limitations of hydrophilic drug moieties are modified by cubic lipids are depicted in **[23,47,49],** where these crystalline cubes entrapped a diabetic hydrophilic drug portrayed enhanced Drug delivery system.

Cancer is a life threatening disease. Various researches to combat the disease is ongoing. Though Traditional approach of Chemotherapy nowadays has been modified by combination therapies there are certain limitations in the modern therapies as well. Cubic lipids are at the peak of investigation for cancer targeting and further theranostic applications for early detection [Barriga etal].Cubic lipids are formed by inducing low energy/ high energy throughput of aqueous phase and lipid phase.These biopolymer cubes have been nowadays

are been utilized to release poor water soluble anticancer drugs like rapamycin to target breast cancer cell lines. An Invivo study by Fregetal**[54]** compared to free rapamycin. Curcumin has already been proved to be better antitumor agent. Baskaran etal**[55],** enloaded Cubosomes with curcumin and enhanced cellular uptake was observed.Review report of Zabara etal**[56]** , threw a limelight of controlled release of functional ingredients entrapped in these reversed bicontinuos cubic lipids. The study has an overview of symmetrical changes and delivery aspects depending on endogenous and exogenous stimuli of the colloidal environment. Cubosomes as multifunctional drug delivery vesicles are been established by a group of researcher in targeting cancer cells,Mugia etal**[57].**Commercially available starting materials are challenge to develop those multifunctional cubes, thereby Deshpande etal **[58],** developed a cubosome from glycerol monoleate(Rylo,commercially available) coated with single molecular layer of polyline amino acid, which made the cubosome multifunctional.Furthermore the low burst release of non-inflammatory drug naproxen sodium, (which nowadays results in apoptosis of cancer cells) entrapped with the multifunctional lipid cubes was confirmed.The group of researcher also used an image contrast agent to observe the targeting of the cells along with optical imaging. Cubic lipid gels are highly viscous, practical Invitro and Invivo experiments are highly challenging. Cubic dispersion are more advantageous to the gel, in with respect to surface area and high fluidity(low viscosity).The interwoven water channels and small size sometimes hindrance in control release of drug unlike gel cubes. Naser etal **[59]** developed cubosome dispersions from glycerol monoleate cubosome modified with Poloxamer 407 to entrap low molecular weight hydrophilic drug 5 Fluorouracil. The researcher observed that little dosage of the drug can target the hepatic carcinoma cells.

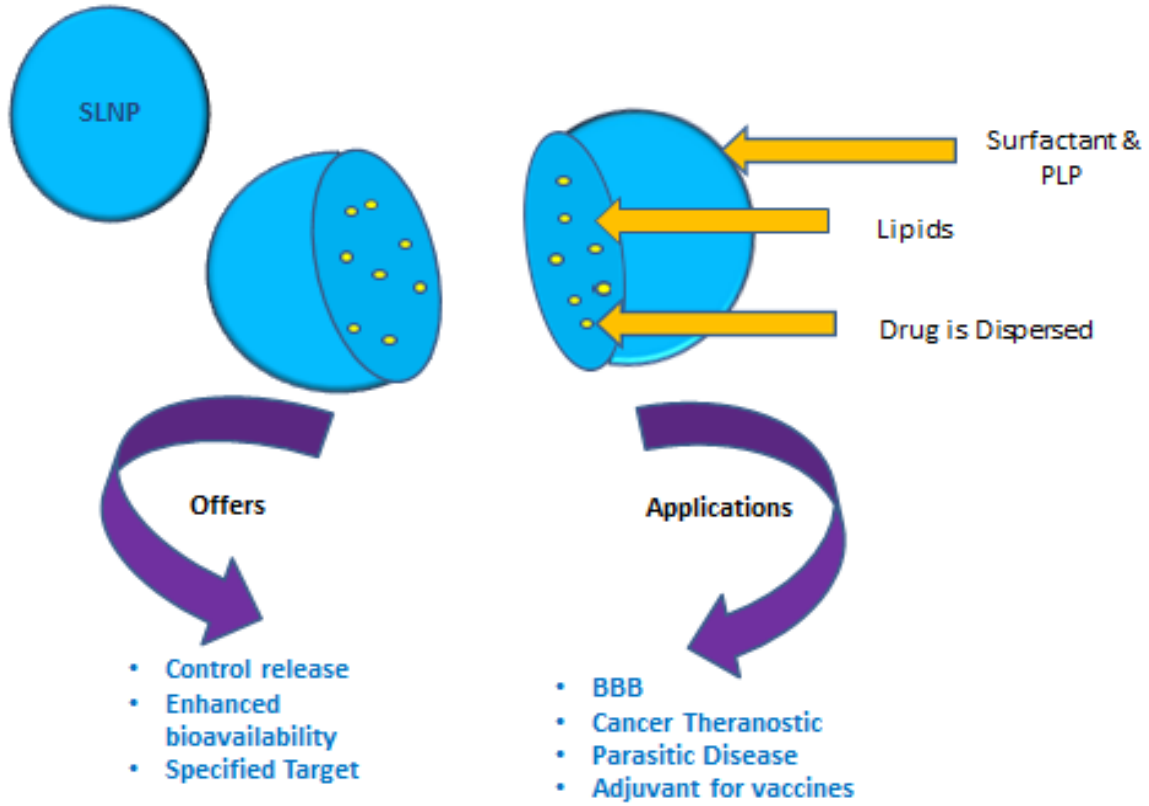

Fig.2. Solid lipid nanoparticles, its characteristics & applications

The cubosome loaded with 5Fluorouracil(FU) has severe dilation and congestion in central vein(CV), in portal vein , sinusoids and exhibited more hepatotoxicity at low dose compared to that of free 5 FU. This approach is a new dimension for hepato-carcinoma, though several further studies are required.Thapa etal **[60]**tried to develop six layer polymer coated cubosome loaded Sorafenib anticancer drug for effective hepatic carcinoma cytotoxicity, enhanced cellular uptake. The coating process is to overcome the drawback of cubic crystalline lipids.Though Cubic lipids are effective nanocarrier for direct intravenous application there are few obstacles like, rapid removal from blood circulation, bioadhesity of non-targeted cells and hemolysis.Monooelin cubic lipids loaded with Sorafenib shows enhanced release rate at acidic pH5.5 leading to hepato carcinoma cell necrosis.According to many researchers multifunctional Cubosomes are very challenging aspects.First report of loading anticancer drug Docotaxel in Monoolein based Cubic lipids along with image contrasting agent folate conjugate rhodamine(40%) is recorded by Meli etal**[61].**The outcome of the research

depicts that this Cubosomes can serve as theranostic tools inspite of the surface modification or decoration by contrasting agent.The anticancer drug moiety is released by Cubosomes in enhanced fashion targeting and imaging moieties of HeLA cells.

The most commonly used amphiphilic lipids for Cubosomes preparation are glycerol monoleate and glycerol linoleate. These two lack ester linkages and the Cubosomes are less stable due to enzymatic hydrolysis.Thus to overcome this problem reseacrchers are trying to use Phytantriol which is easily available and cheap**[62].**The research emphasizes on coformulation of phytantriol cubosome with charged phospholipids along with 5Fluorouracil (anticancer drug to treat Triple negative Breast Cancer).

It is clear that Phytan cubosome modified with charged phospholipid DOTP(N-[1-(2,3-Dioleoyloxy)propyl]-N,N,N-trimethylammonium chloride salt) show a cell viability of 40% compared to that of low lipid concentration, the cell viability was 80%.Therefore this system can be effective in targeting breast cancer cells leading cell death.The current review already stated that cubic lipids viscosity is a problem in practical Invivo and Invitro application, modification of surface membrane area by polymer application also been reported by many group of reserachers.Poloxamer series are applied to fragmentize Cubosomes and the cubic phase is retained in nanolevel.

There are several controversies of using Phytantriol and Monolein cubic lipids. Researchers are having many dimensions in their work proving the best application for either of the two. Group of researcher chose Monolein based Cubosomes for Docotaxel drug delivery to target Gliobastoma cells. The choice for the carrier has a reason ,that phytantriol though showed enhanced toxicity to carcinoma cells compared to those of monoolein based cubic phases, they also exhibitinflammatory responses which was not observed in the later one**[63].**

Table.1.: Types of new cubic lipids, drug entrapment, tumor and cancer targetting cells detailed below

Lipid NP	Drugs	Target	Stage	Ref
Cubic lipids	rapamycin	Breast cancer	Invivo	Freg etal
Bicontinuos cubic	curcumin	tumors	Invitro	Baskaran etal
Multifunctional Cubes	-	cancer cell lines	Invitro	Mugia etal
Glycerol monoleate comnined with polylycine amino acids	naproxen	tumor	Invitro	Deshpande etal
Glycerol mono-oleate with poloxomer 407	fluorouracil	Hepatic cancer	Invitro & Invivo	Naser etal
Six layer coated cubics	Sorafenib	Hepatic cancer	Invitro	Thapa etal
Mnolein	Docotaxel	Hepatic	Invitro	Meli etal

Image contrasting theranostic reportsofriverse phase cubic lipids are very limited. The current review already discussed the new era researches on cubic lipids as contrasting image previously. Further more a study of applying dual imaging modalities NIR –MRI in a single system can be a new focus of both cell targeting and optical imaging**,[64].**Here the accumulation of the nanocube lipids in the spleens, liver, kidneys of mice models are confirmed by NIR imaging whereas also proved potentiality as the contrast agent MR imaging and drug delivery.Here in the review , cubic lipid application in drug delivery system for cancers of liver, breast, brainalready been endorsed. A very recent study on colorectal cancer has been eye catcher in curing the disease. So far the treatment for CRC was prescribed chemotherapy which is already having side effects in patients and also delayed process. The traditional therapy was thereby modified by implementing nanosystems.Researcher tried to develop a carrier from Monolein cubic lipids entrapping cisplatin and metformin as the fate of cytotoxicity for CRC is not known.The result was sucessfully attained, showing that nanocubes containing both the drug showed 45% increased antitumoral activity comparative to the individual loading system (in case of only cisplatin it was 20% and metformin 35%).

VIII. SUMMARY &FUTURE PROSPECT:

Cubic lipids are lyotropic crystalline, bicontinuos reverse phased non lamellar lipids gel matrix. The techniques so far developed are top down and bottom up approach. Limited amphiphilic and stabilizers so far used for surface membrane modifications. Tropical, ant inflammatory, skin permeation, antimicrobial peptide delivery, anticancer delivery approaches are in que. Further researches on internal structural stability, intravenous administration should be taken into account as hemolytic reports are observed. High viscosity of the cubic phase lipid shows resistance in practical applications of Invitro studies, thereby plurogenic gel series are applied, emphasized should be more given in case of cubic dispersion for enhanced characteristics for pharmaceutical applications. Invivo studies of cubic lipids are very limited .Future studies on theranostic approaches of Cubosomes from naturally occurring lipid sources are recommended.

CONFLICT OF INTEREST:
Declared None

REFERENCE:

[1]. SudiptaSenapati, Arun Kumar Mahanta, Sunil Kumar , Pralay Mai, Controlled drug delivery vehicles for cancer treatment and their performance, Signal Transduction and Targeted Therapy (2018) 3:7 https://doi.org/10.1038/s41392-017-0004-3.

[2]. P. P. Constantinides, "Lipid microemulsions for improving drug dissolution and oral absorption: physical and biopharmaceutical aspects," *Pharmaceutical Research*, vol. 12, no. 11, pp. 1561–1572, 1995.

[3]. J. B. Cannon and M. A. Long, "Emulsions, microemulsions, and lipid-based drug delivery systems for drug solubilization and delivery, part II," in*Oral Applications*, vol. 16,pp. 227–254, 2008.

[4]. C. W. Pouton, "Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and 'selfmicroemulsifying' drug delivery systems," *European Journal of Pharmaceutical Sciences*, vol. 11, no. 2, pp. S93–S98, 2000

[5]. HinaShrestha, RajniBala, and SandeepArora**,** Journal of Pharmaceutics Volume 2014, Article ID 801820, 10 pages http://dx.doi.org/10.1155/2014/801820

[6]. B. Chauhan, S. Shimpi, and A. Paradkar, "Preparation and evaluation of glibenclamide-polyglycolized glycerides solid dispersions with silicon dioxide by spray drying technique," *European Journal of Pharmaceutical Sciences*, vol. 26, no. 2, pp. 219–230, 2005.

[7]. B. Chauhan, S. Shimpi, and A. Paradkar, "Preparation and characterization of etoricoxib solid dispersions using lipid carriers by spray drying technique," *AAPS PharmSciTech*, vol. 6, no. 3, pp. E405–E409, 2005.

[8]. N.Venkatesan, J. Yoshimitsu, Y. Ohashi et al., "Pharmacokinetic and pharmacodynamic studies following oral administration of erythropoietin mucoadhesive tablets to beagle dogs," *InternationalJournal of Pharmaceutics*, vol. 310, no. 1-2,pp. 46–52, 2006.

[9]. N. Venkatesan, J. Yoshimitsu, Y. Ito, N. Shibata, and K. Takada, "Liquid filled nanoparticles as a drug delivery tool for protein therapeutics," *Biomaterials*, vol. 26, no. 34, pp. 7154–7163, 2005.

[10]. Y. Ito, T. Kusawake, M. Ishida, R. Tawa, N. Shibata, and K. Takada, "Oral solid gentamicin preparation using emulsifierand adsorbent," *Journal of Controlled Release*, vol. 105, no. 1-2, pp. 23–31, 2005.

[11]. A. Seo and T. Schafer, "Melt agglomeration with polyethylene glycol beads at a low impeller speed in a high shear mixer," *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 52, no. 3, pp. 315–325, 2001.

[12]. A. Seo, P.Holm,H.G. Kristensen, and T. Schafer, "Thepreparation of agglomerates containing solid dispersions of diazepamby melt agglomeration in a high shear mixer," *International Journal of Pharmaceutics*, vol. 259, no. 1-2, pp. 161–171, 2003.

[13]. C. Thies, R. Dos Santos, J. Richard, V. Vandevelde, H. Rolland, and J.-P. Benoit, "A supercritical fluid-based coating technology 1: process considerations," *Journal of Microencapsulation*, vol. 20, no. 1, pp. 87–96, 2003.

[14]. I.R.Dos Santos, C. Thies, J. Richards et al., "Asupercriticalfluidbased coating technology. 2: solubility considerations," *Journalof Microencapsulation*, vol. 20, no. 1, pp. 97–109, 2003.

[15]. S. Sethia and E. Squillante, "Physicochemical characterization of solid dispersions of carbamazepine formulated by supercritical carbon dioxide and conventional solvent evaporation method," *Journal of Pharmaceutical Sciences*, vol. 91, no. 9, pp. 1948–1957, 2002.

[16]. S. Sethia and E. Squillante, "In vitro-in vivo evaluation of supercritical processed solid dispersions: permeability and viability assessment in Caco-2 cells," *Journal of Pharmaceutical Sciences*, vol. 93, no. 12, pp. 2985–2993, 2004.

[17]. GuoliangZhen,T. M. Hinton,B. W. Muir,S.Shi,M. Tizard,K.M. McLean,P.G. Hartley,and P. Gunatillake. Glycerol Monooleate-Based Nanocarriers for siRNA Delivery in Vitro, Mol. Pharmaceutics 2012, 9, 2450−2457 dx.doi.org/10.1021/mp200662f |

[18]. Rahul Nahire,M. K. Haldar,S. Paul,A. Mergoum,A.H. Ambre,K. S. Katti, K.N. Gange, D. K. Srivastava,K.Sarkar, S.Mallik, Polymer-Coated Echogenic Lipid Nanoparticles with Dual Release Triggers, Bio macromolecules 2013, 14, 841−853 dx.doi.org/10.1021/bm301894z

[19]. S. Angayarkanny,G.Baskar,A. B. Mandal(2013), Nanocarriers of Solid Lipid from Micelles of Amino Acids Surfactants Coated with Polymer Nanoparticles, Langmuirdx.doi.org/10.1021/la400605v

[20]. Michelle Stolzoff,I. Ekladious,A.H. Colby,Y. L. Colson,T. M. Porter, M. W. Grin staff,(2015),Bio macromolecules Synthesis and Characterization of Hybrid Polymer/Lipid Expansible Nanoparticles: Imparting Surface Functionality for Targeting and Stability, DOI: 10.1021/acs.biomac.5b00336

[21]. Patrick T. Spicer and Kristin L. Hayden, Novel Process for Producing Cubic Liquid Crystalline Nanoparticles (Cubosomes), Langmuir 2001, 17, 5748-5756

[22]. Hanna M. G. Barriga, Margaret N. Holme, and Molly M. Stevens, Cubosomes: The Next Generation of Smart Lipid Nanoparticles? Angew. Chem. Int. Ed. 2018, 57, 2–23

[23]. Yulin Chen, Ping Ma , Shuangying Gui, Cubic and Hexagonal Liquid Crystals as Drug Delivery Systems,Hindawi Publishing Corporation BioMed Research International Volume 2014, Article ID 815981, 12 pages http://dx.doi.org/10.1155/2014/815981

[24]. C. Caltagirone, A. M. Falchi, S. Lampis, V. Lippolis, V. Meli, M. Monduzzi, L. Prodi, J. Schmidt, M. Sgarzi, Y. Talmon, et al.,Langmuir 2014, 30, 6228 – 6236.

[25]. D. Demurtas, P. Guichard, I. Martiel, R. Mezzenga, C. Herbert, L. Sagalowicz, Nat. Commun. 2015, 6, 8915.

[26]. M. Duss, L. S. Manni, L. Moser, S. Handschin, R. Mezzenga, H. J. Jessen, E. M. Landau, ACS Appl. Mater. Interfaces 2018,10, 5114 – 5124

[27]. S. Deshpande, E. Venugopal, S. Ramagiri, J. R. Bellare, G. Kumaraswamy, N. Singh, ACS Appl. Mater. Interfaces 2014, 6,17126 – 17133.

[28]. J. Gustafsson, H. Ljusberg-wahren, M. Almgren, Langmuir 1997, 13, 6964 – 6971.

[29]. S. Salentinig, A. Yaghmur, S. Guillot, O. Glatter, J. Colloid Interface Sci. 2008, 326, 211 – 220.

[30]. D.-H. Kim, S. Lim, J. Shim, J. E. Song, J. S. Chang, K. S. Jin, E. C. Cho, ACS Appl. Mater. Interfaces 2015, 7, 20438 – 20446.

[31]. I. Martiel, L. Sagalowicz, S. Handschin, R. Mezzenga, Langmuir2014, 30, 14452 – 14459.

[32]. S. B. Rizwan, D. Assmus, A. Boehnke, T. Hanley, B. J. Boyd, T.Rades, S. Hook, Eur. J. Pharm. Biopharm. 2011, 79, 15 – 22

[33]. A. Yaghmur, O. Glatter, Adv. Colloid Interface Sci. 2009, 147 –148, 333 – 342.

[34]. J. Barauskas, A. Misiunas, T. Gunnarsson, F. Tiberg, M. Johnsson, Langmuir 2006, 22, 6328 – 6334

[35]. Monoolein: a magic lipid?Chandrashekhar V. Kulkarni, Wolfgang Wachter, Guillermo Iglesias-Salto, Sandra Engelskirchenb and Silvia Ahualliac, Phys. Chem. Chem. Phys., 2011, **13**, 3004–3021.

[36]. Xin Pan, Ke Han, XinshengPeng, Zhiwen Yang, Lingzhen Qin, Chune Zhu, etal,Nanostructed Cubosomes as Advanced Drug Delivery System, *Current Pharmaceutical Design*, 2013, *19*, 6290-6297

[37]. Hojun Kim, Cecilia Leal, Cuboplexes: Topologically Active siRNA Delivery ACS Nano, Just Accepted Manuscript • DOI: 10.1021/acsnano.5b03902 • Publication Date (Web): 21 Sep 2015

[38]. Rosa M, Infante MR, Miguel MG, Lindman B. Spontaneous formation of vesicles and dispersed cubic and hexagonal particles in amino acid-based catanionic surfactant systems. Langmuir 2006; 22: 5588-96.

[39]. Zahra Karami, Mehrdad Hamidi, Cubosomes: remarkable drug delivery potential, Drug Discovery Today, (21) 5,2016,789-801, http://dx.doi.org/10.1016/j.drudis.2016.01.004

[40]. Esposito, E. et al. (2003) Lipid-based supramolecular systems for topical application: a preformulatory study.AAPS PharmSci. 5, 62–76

[41]. Rosen, M., ed. (2005) Delivery System Handbook for Personal Care and Cosmetic Products: Technology, Applications and Formulations, William Andrew

[42]. Worle, G. et al. (2007) Influence of composition and preparation parameters on the properties of aqueous Monoolein dispersions. Int. J. Pharm. 329, 150–157

[43]. Um, J.Y. et al. (2003) In vitro cellular interaction and absorption of dispersed cubic particles. Int. J. Pharm. 253, 71–80

[44]. Sherif, S. et al. (2013) The design and evaluation of novel encapsulation technique for topical application of alpha lipoic acid. J. Adv. Pharm. Res. 4, 13–22

[45]. Christopher Brasnett, Georgia Longstaff, Laura Compton1 &AnnelaSeddon, Effects of Cations on the Behaviour of Lipid Cubic Phases,SCientifiCReports| 7: *8229* | DOI:10.1038/s41598-017-08438-4

[46]. Davide Demurtas, Paul Guichard, Isabelle Martiel3, Raffaele Mezzenga, Ce´cile He´bert & Laurent Sagalowicz, Direct visualization of dispersed lipid bicontinuos cubic phases by Cryo-electron tomography, Nature Communications | 6:8915 | DOI: 10.1038/ncomms9915 |www.nature.com/naturecommunications

[47]. Madheswaran, T. et al. (2014) Enhanced topical delivery of finasteride using glycerylmonooleate-based liquid crystalline nanoparticles stabilized by Cremophor surfactants. AAPS PharmSciTech 15, 44–51

[48]. Liang, X. et al. (2017) HII mesophase as a drug delivery system for topical application of methyl salicylate. Eur. J. Pharm. Sci. 100, 155–162 48

[49]. Madheswaran, T. et al. (2017) In vitro and in vivo skin distribution of 5a-reductase inhibitors loaded into liquid crystalline nanoparticles. J. Pharm. Sci. 106, 3385–3394

[50]. Dante, M. and de, C.L. et al. (2018) Liquid crystalline systems based on glycerylmonooleate and penetration enhancers for skin delivery of celecoxib: characterization, in vitro drug release, and in vivo studies. J. Pharm. Sci. 107, 870– 878

[51]. Salwa Salah, Azza A. Mahmoud & Amany O. Kamel, Etodolac transdermal cubosomes for the treatment of rheumatoid arthritis: ex vivo permeation and in vivo pharmacokinetic studies, Drug Delivery, 24:1, 846-856, DOI: 10.1080/10717544.2017.1326539

[52]. Lukas Boge,KarinHallstensson, LovisaRingstad, Jenny Johansson, Therese Andersson, Mina Davoudi, etal, European Journal of Pharmaceutics and Biopharmaceutics 134 (2019) 60–67, https://doi.org/10.1016/j.ejpb.2018.11.009

[53]. RadhakrishnanNithya, Prince Jerold, KarthikSiram, Cubosomes of dapsone enhanced permeation across the skin, Journal of Drug Delivery Science and Technology 48 (2018) 75–8 https://doi.org/10.1016/j.jddst.2018.09.0021

[54]. Freag, M.S. et al. (2016) Layer-by-layer-coated lyotropic liquid crystalline nanoparticles for active tumor targeting of rapamycin. Nanomedicine 11, 2975–2996 46

[55]. Baskaran, R. et al. (2014) Entrapment of curcumin into monoolein-based liquid crystalline nanoparticle dispersion for enhancement of stability and anticancer activity. Int. J. Nanomedicine 9, 3119–3130

[56]. A. Zabara, R. Mezzenga, Controlling molecular transport and sustained drug release in lipid-based liquid crystalline mesophases, J. Control. Release (2014), http://dx.doi.org/10.1016/j.jconrel.2014.05.052

[57]. Murgia, S.; Bonacchi, S.; Falchi, A. M.; Lampis, S.; Lippolis, V.; Meli, V.; Monduzzi,M.; Prodi, L.; Schmidt, J.; Talmon, Y.; et al. Drug-Loaded Fluorescent Cubosomes: VersatileNanoparticles for Potential Theranostic Applications. *Langmuir* **2013**, *29* (22), 6673–6679.

[58]. Sonal Deshpande, Neetu Singh, Influence of Cubosome Surface Architecture on its Cellular Uptake Mechanism, *Langmuir*, Just Accepted Manuscript • DOI: 10.1021/acs.langmuir.6b04423 • Publication Date (Web): 21 Mar 2017 Downloaded from http://pubs.acs.org on March 27, 2017

[59]. Mohamed Nasr,Mohamed K. Ghorab, Ahmed Abdelazem, In vitro and in vivo evaluation of Cubosomes containing 5-fluorouracil for liver targeting, ActaPharmaceuticaSinica B 2015;5(1):79–88

[60]. Raj Kumar Thapa, JuYeon Choi, Bijay K Poudel, Tran Tuan Hiep, Shiva Pathak, Biki Gupta, Han-Gon Choi, Chul Soon Yong, and Jong Oh Kim, Multilayer-coated liquid crystalline nanoparticles for effective sorafenib delivery to hepatocellular carcinoma,ACS Appl. Mater. Interfaces, Just Accepted Manuscript • DOI: 10.1021/acsami.5b06203 • Publication Date (Web): 28 Aug 2015Downloaded from http://pubs.acs.org on August 31, 2015

[61]. Valeria Meli, Claudia Caltagirone, Angela Maria Falchi, Stephen T Hyde, Vito Lippolis, Maura Monduzzi,etal,Docetaxel Loaded Fluorescent Liquid CrystallineNanoparticles for Cancer Theranostics, *Langmuir*, Just Accepted Manuscript • DOI: 10.1021/acs.langmuir.5b02101 • Publication Date (Web): 20 Aug 2015Downloaded from http://pubs.acs.org on August 25, 2015

[62]. Paola Astolfi, ElisabettaGiorgini, ValentinaGambini, Barbara Rossi, Lisa Vaccari,Francesco Vita, etal Lyotropic Liquid Crystalline Nanosystems as Drug Delivery Agents for 5-Fluorouracil: Structure and Cytotoxicity, Langmuir, Just Accepted Manuscript • DOI: 10.1021/acs.langmuir.7b03173 • Publication Date (Web): 12 Oct 2017 Downloaded from http://pubs.acs.org on October 13, 2017

[63]. RenataBilewicz, EwaNazaruk, AgnieszkaMajkowska-Pilip, Lipid Cubic phase Nano Particles-Cubosomes For Improved Efficiency Of Drug Delivery To Cancer Cells ,*ChemPlusChem*10.1002/cplu.201600534 Link to VoR:http://dx.doi.org/10.1002/cplu.201600534

[64]. Nhiem Tran, Nicole Bye, Bradford A. Moffat, David K.Wright, Andrew Cuddihy,Tracey M. Hinton, etal, Dual-modality NIRF-MRI cubosomes and hexosomes: High throughput formulation and in vivo Biodistribution, Materials Science and Engineering C 71 (2017) 584–593, http://dx.doi.org/10.1016/j.msec.2016.10.028

Tanima Bhattacharya, et. al. "Cubic Lipids: A Bliss For Drug Delivery." *International Journal of Engineering Inventions*, Vol. 09(08), 2020, pp. 01-08.