

Cubosomes: a vehicle for delivery of various therapeutic agents

Abstract

A drug delivery system is a formulation or device that safely brings a therapeutic agent to the specific body site at a certain rate to achieve an effective concentration at the site of drug action. To achieve therapeutic effects, it must be possible to load sufficient amounts of the active, which largely depends on the interaction of the vehicle and active. In this concern, cubosomes are bicontinuous cubic phase liquid crystals have many properties that make them appealing as a universal vehicle for drug delivery and it was considered as the drug nanocarrier due to their great potential as an alternative drug delivery system relative to liposome. Cubosomes are capable of loading lipophilic, hydrophilic, and amphiphilic drugs. This can be prepared by top-down or bottom-up approach. The main precursor of cubosome formation is monoolein whereas poloxamer 407 in a concentration range between 0% and 20% w/w with respect to the disperse phase use as a surfactant.

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Introduction

A drug delivery system is a formulation or device that safely brings a therapeutic agent to the specific body site at a certain rate to achieve an effective concentration at the site of drug action. The release of drug in a pre-designed manner is termed controlled drug release (CR), which is used to promote therapeutic benefits while minimizing toxic side-effects. Sustained release over an extended period of time may reduce the need for multiple dosing which will be a benefit in terms of reduced cost and increased patient compliance. The release rate of drugs must be controlled to achieve optimal drug release profiles. Surfactant and polymers are generally employed in the fabrication of controlled drug delivery systems because they form supra-assemblies, which are extensively exploited as active delivery vehicles. These systems include liquid crystalline aggregates or cross-linked gel networks that load, stabilize and eventually deliver active ingredients. Incorporation of drugs into the complex internal domains of these structures can facilitate diffusion controlled release of drug into the surrounding external aqueous environment.¹⁻³ Providing new ways to modify pharmacokinetic profiles using lipid-based systems.^{4,5} To achieve therapeutic effects, it must be possible to load sufficient amounts of the active, which largely depends on the interaction of the vehicle and active. Further, the integrity of the active must be retained through all stages: preparation, storage, and use. The release rate of actives must be controlled to achieve optimal drug release profiles, while ease of preparation and vehicle stability must also be considered. An optimal delivery vehicle must successfully encompass all these properties.

Cubosome

Cubosomes are bicontinuous cubic phase liquid crystals have many properties that make them appealing as a universal vehicle for drug delivery. Cubosomes are nanoparticles, more accurately nanostructure particles, or self-assembled liquid crystalline particles with a solid-like rheology. However, the cubic phases are unique in that they possess very high solid-like viscosities because of their intriguing bicontinuous structures. Bicontinuous cubic liquid crystalline phase is an optically clear, very viscous material that has a unique structure at

the nanometer scale. Its geometric model was supplied, prepared and examined for drug delivery. In the structure the surfactant assembles into bilayers that are twisted into a three dimension, periodic, minimal surface forming tightly packed structure, like “honeycombed” with bicontinuous domains of water and lipid. Cubosome particles are first prepared by mechanical fragmentation of the cubic lipid-water phase in a three-phase region containing a liposomal dispersion and to differentiate from liposome’s, these particles have been termed as cubosomes. Its structure is different from liposome’s because its structure can simultaneously accommodate water-soluble, lipid-soluble, and amphiphilic molecules. Three structure of cubosomes have been proposed Luzzati V et al.,⁶ (i) $Pn3m$ (D-surface) (Diamond surface), (ii) $Ia3d$ (G-surface) (Gyroid surface), and (iii) $Im3m$ (P-surface) (Primitive surface), in terms of nodal surfaces. The structure generally maintains the efficacy; stability of actives such as vitamins and proteins. Cubosomes are thermodynamically stable; lasting indefinitely. Colloidal dispersions of cubosomes can be stabilized by the addition of polymers. They also possess the potential for controlled delivery of actives, where diffusion is governed by the tortuous diffusion of the active through the “regular” channel structure of the cubic phase. Cubosomes possess a sufficient average degree of molecular orientation in order to characterize by structural symmetry, and often form in aqueous surfactant system at relatively high amphiphile concentrations. In recent years, cubosomes (cubosome dispersions) were considered as the drug nanocarrier due to their great potential as an alternative drug delivery system relative to liposome. Cubosomes, especially made of binary systems, monoolein– water.⁷ That can self assemble into thermodynamically stable biocontinuous cubic liquid crystallize phases.⁸

Advantages

Cubosomes are capable of loading lipophilic, hydrophilic, and amphiphilic drugs. Because of the three-dimensional nanostructure with hydrophobic and hydrophilic domains, cubic liquid crystalline phases have been applied in pharmaceutical drug delivery. The large interfacial area can provide a complex diffusion pathway for sustained release of entrapped drug molecules, whereas lipid constituents are biocompatible, bioadhesive, and digestible.^{9,10}

Preparation

Cubosomes usually have been produced by means of time-consuming methods involving high-energy input. The dispersions were based either on glyceryl-monooleate/sunflower oil or glyceryl-monooleate/retinylpalmitate mixtures plus a nonionic triblock polymer (Poloxamer 407) in water. Dispersions were produced by drop wise addition of a melt of lipids and poloxamer in water, followed by reduction of size by homogenization under high pressures at 80°C. Recently the preparation and characterization of dispersions constituted of monoolein-rich monoglycerides with or without purified soya phospholipids.¹¹ Dispersions were prepared by equilibration of the monoglyceride/phospholipid/ water cubic phase, subsequent fragmentation by a solution of Poloxamer 407, predispersing by probe sonication and finally high pressure homogenization. Moreover some authors have developed experimental protocols for cubosome production based on the use of organic solvents. Spicer and Hyden have proposed a method based on a dilution process of an ethanolic solution of monoolein with an aqueous solution of poloxamer. Ethanol was used as a hydrotrope to create a liquid precursor, spontaneously forming cubosomes after dilution. Finally Nakano et al. have suggested a method for the production of cubosomes based on hydration of a dry film of monoolein/poloxamer with an aqueous buffer.¹²

Methods of preparation of cubosomes

Three macroscopic forms of cubic phase are typically encountered; precursor, bulk gel and particulate dispersion. The precursor form exists as a solid or liquid material that forms cubic phase in response to a stimulus, such as contact with liquid. Bulk cubic phase gel is an optically isotropic, 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 a suitable starting material and then sculpts the functionality from the material. The bulk cubic phase is first produced and then dispersed by high energy processing into cubosome nanoparticles. Bulk cubic phase resembles a clear 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.¹³

Bottom-up technique

The bottom-up approach first forms the nanostructure building blocks and then assembles them into the final material. It is more recently developed technique of cubosome formation, allowing cubosomes to form and crystallize from precursors on the molecular length scale. The 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.¹⁴

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 complex dispersions containing vesicles and cubosomes with time-dependent ratios of each particle type. Coarse cubosomes on the micron scale possess the same D-surface cubic structure as their originating bulk cubic phase Spicer PT¹⁵ but after homogenization, the P-surface dominates, either because of the added polymer or other factors.¹⁶ Large-scale production of cubosomes and products containing them requires more robust processes. Smaller and more stable cubosomes are produced than those by high-energy processes, but some vesicles are also produced. A process was also developed to allow cubosome production from a powdered precursor.¹⁶ 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 M¹⁷ and nonionic surfactants Lynch ML¹⁸ and polymer systems, although the lipid most widely used to construct bicontinuous cubic phases is the 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.¹⁹⁻²¹ The glycerol moiety may form hydrogen bonds with water in an aqueous environment and is commonly referred to as the head group. The hydrocarbon chain gives hydrophobic characteristics to monoolein and is often 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

- a) Formulations of control release drug delivery system of solubilize substances.
- b) Cubic phase is more applicable for control release because of;
- c) Its small pore size
- d) Ability to solubilize hydrophilic, hydrophobic and amphiphilic molecules

- e) Its biodegradability by simple enzyme
- f) Widely used in cancer therapy
- g) Used in topical, mucosal deposition and delivery of different drugs
- h) The properties of bioadhesion and penetration enhancement of cubosomes suggest their potential utility in skin cancer (e.g., melanoma) treatment, there is currently no formulation addressing this need. Moreover, there is emerging interest in using statistical methods to optimize pharmaceutical formulations.^{22–25}

A short list of applications includes the delivery of actives for periodontal disease and implants *via in vivo* and topical delivery, and as bioadhesives.

Conclusion

Cubosome have great potential to use as a vehicle for drug delivery of various therapeutic agents.

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Conflicts of interest

The author declares no conflict of interest.

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