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Formulation and Development of Cubosome Loaded Emulgel - A Review.

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Abstract : Cubosomes are nanoparticles in structure which is mainly made of certain amphiphilic lipids in definite proportion, known as bicontinuous cubic phase liquid crystals. They perform solid like rheology with unique properties of practical interest. They are thermodynamically stable and they have carvenous (honeycomb)structure which are tightly packed twisted into three dimensional bilayers. This type of complex structure allows them to have greater drug-loading ability. All other benefits of this type of structural ability cubosomes.Cubosomes have ability to encapsulate the hydrophobic, hydrophilic, amphiphilic substances. Cubosomes can increase the solubility of poorly soluble drug. Cubosomes are mainly can used in melanoma therapy. Emulgel are having better advantage on topical delivery system of hydrophobic drugs for dermal care. In Emulgel the formulation is prepared by one part of emulsion and one part of 1-2% gel. The Emulgel formulation are used for consideration of analgesic and antifungal drugs. Emulgel are very much effective for chronic skin diseases.
Keywords : Cubosomes, Honeycomb, Emulgel, Hydrophobic Drug, Melanoma Therapy, Analgesic and Antifungal Drugs.

Introduction

Cubosomes[1-5]

The cubosomes were introduced into the literature by Larsson and co-worker. The cubosomes referred as the bicontinuous cubic liquid crystalline structure which forms colloidal dispersion with water using surfactant suitable for it results in nanostructured system. Cubosomes are self-assembled liquid crystalline particles which pusses solid like rheology. Cubosomes have much larger specific area but have same microstructure as parent cubic phase. Bulk cubic phases have higher viscosity than cubosomal dispersion.

Structure

The cubosomes are honeycombed in structure which is separating the two internal aqueous channel along with large internal surface area. Cubosomes are nanostructured particles of a with cubic crystalloghraphic symmetry of a liquid crystalline phase formed by the self-assembly of amphiphilic or surfactant like molecules. Cubosomes are nanoparticles having size range of 10-500nm. They are looks alike Dots, Slightly Spherical. Every single Dot corresponds to presence of pore containing aqueous phase cubic phases in lipid water system in X-ray scattering technique was first identified by Luzzati & Husson.

Preparation of cubosomes

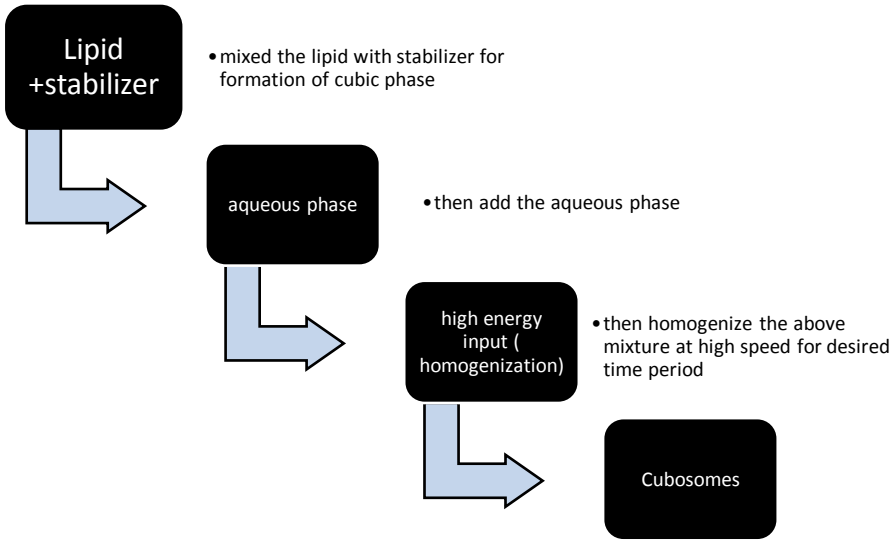
Materials:

Sr. no	Ingrediants	Categories
1	Glyceryl mono oleate	Emulsifying agent
2	Poloxamer 407	Stabilizer

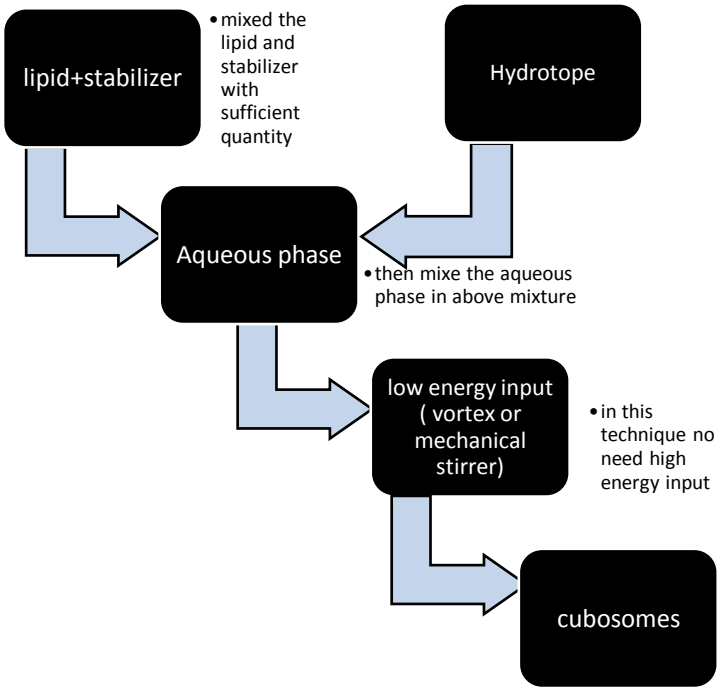
Cubosomes can be manufactured by two defferent techniques:

- Top down technique
- Bottom up technique

Top down technique



Bottom up technique :



Preparation methods of cubosome's:[6-9]

The cubosome dispersion carried out by two methods

1. Fabrication method
2. Emulsification method

1. Fabrication method

GMO/p407 cubic gel GMO 5% and P407 1.0% were melted at 60°c in hot water bath and add the required amount of drug and stir continuously till dissolve. Deionized water is added drop by drop and vortex are set to the homogenisation. It kept upto 48 hrs at room temperature the optically isotropic cubic gel are form and disturbed by mechanical stirring crude dispersion was subsequently fragmented by sonicater probe having the energy 200W under cool temperature at the 20°c in water bath for the 20 min.

2. Emulsification method:

In this method the GMO and P407 are put in to the water and it followed the ultrasonication the 5% GMO and1% P407and 5% ethanol in 89% water are taken GMO and P407 are melted at the 60°C and mixed the ehanolic solution was added to the melting . The resultant mixture are added drop wise to deionized water preheated at the 70°C, it ultrasonicated at maximum power 130kW for 50min at the same temperature the disperse solution are kept in to the ambient temperature and protected from light.

Emulgel[10-12]

Emulgel are emulsion based gel which are mainly used for topical preparation for chronic skin diseases. Emulgel are emulsion either o/w or w/o type mixed with gel which is mainly prepared by gelling agents like HPMC or Carbapol. Emulgel are mainly used for delivery of antifungal or analgesic drugs to avoid first pass metabolism. Presence of good gelling in the water converts a emulsion into the emulgel. Emulgel have properties of being thixotropic, greaseless, spreadable, removable, emolient, nonstaining, long shelf life.

Constituents or material which are important for Emulgel preparation

1. **Aqueous material**
   Aqueous material used are mainly water and alcohol. They form aqueous phase of the Emulsion.
2. **Oils**
   The oil phase of Emulsion are formed by this agents. This are mainly applied emulsion, mineral oils, widely used vehicle for the drug are hard and soft paraffins.
3. **Emulsifier**
   Emulsifying agents are having characteristic nature of emulsification but they control stability during shelf life. for example Polyethethylene glycol 40, GMS, GMO, Sorbitol monooleate, Sodium stearate, Tween 80
4. **Gelling agent**
   This agents are used to enhance the thickness of the solution and increase the consistency of the solution.

Emulgel Preparation:

For preparation of emulgel first of all Gel formulation is prepare by dispersing the Carbapol 934 or 940 in purified water with constant stirring at moderate speed then pH adjust to 6 to 6.5 using tri ethanol amine.

The oil phase of the emulsion were prepared by dissolving span 20 in light paraffin while the aqueous phase was prepared by dissolving tween 20 in purified water. Methyl and propyl paraben was dissolve in propylene glycol whereas drug was dissolve in ethanol and both solution was mixed with aqueous phase. Both the oily and aqueous with continuous stirring until cooled to room temperature and add Glutaraldehyde in during of mixing of gel and emulsion in ratio to obtain the emulgel.

Objective of study

- To develop a new formulation for topical route of administration.
- To improve high payload in cubosomal vesicles.

- To develop % topical gel.
- To improve the solubility of the poorly water soluble drug.
- To develop the emulgel and there characterization.

Formulation development Of Drug Loaded Cubosomes:

Preparation of Cobosomes :

Table:The different functional categories of ingredients used in formation

Sr. no	Ingredients	Functional categories
1	Polaxamer 407	Stabilizer
2	Glycerylmonooleate	Self-emulsifier
3	Distilled water	Vehicle
4	Carbapol 940	Gelling agent
5	Sodium hydroxide	pH adjustment

Make the cubosomes by emulsification method which make proper emulsion for preparation of good emulgel.

Accurate weighed quantity of 4.5% Glycerylmonooleate (GMO) and 0.5% Poloxamer 407 mix and melt in a water bath at 60°c to this mixture add drug and stir until completely dissolved, then to this solution add drop by drop preheated (upto 70°c) distilled water of suitable quantity (95%) by continuous stirring, after complete addition of water kept aside for one day to attained equilibrium, there is formulation two phase and it is disturbed by stirring.

Take this whole system into subject it for homogenization at 8000-10000 rpm for 2hrs. At room temperature. Thus formed liquid dispersion of cubosomesand kept it at room temperature, avoids direct sunlight and which will use for further study.

Preparation of CubosomeEmulgel Formulation

Cubosomesemul gel can be obtained by the addition of the weighted amount of the carbapol 2% in distilled water and kept it for a half day for gelling and swelling and then addition of 1% sodium hydroxide for pH maintainance to obtain the gelling consistency, then dilute the obtain gel with cubosomes solution containing only the cubosomes which having entrap consistency. stirr continuously until a homogeneous emulgel is formed.

Evaluation parameter of cubosmes loaded with drug:[13-15]

1. pH measurement.
2. Particle size analysis.
3. Zeta potential.
4. Entrapment Efficiency.

1. pH measurement

pH of formulation is determine by using digital pH meter by immigrating the electrodes in gel formulation and pH is measure.

2. Partical size measurement

Particle size analysis determine by the (Nano ZS, Malvern, Worcesterlshire) instrument at 25°c which is based on the Brownian motion. Sample should dilute in particle free purified water to scattering intensity approximately 150-300keps. The mean z-average diameter and polydispersity indices iscanbeobtain by cumulative analysis using MAVERN software.

3. Zeta potential

Zeta potential is key indicator of the stability of formulation. The magnitude of zeta potential indicates the degree of electronic repulsion between adjust, similarly charge particle in dispersion.

4. Entrapment efficiency

Entrapment efficiency is defined as the percentage amount of drug which is entrapped by the cubosomes by the cubosomes. For the determination of entrapment efficiency, the un-entrapped drug is first should separate by centrifugation at 15000 rpm for 30 min. the resulting solution is then separate and supernatant liquid is collected. Estimate using UV visible spectrophotometer at 242 nm.

$$\% \text{ Entrapment} = \frac{\text{Total amount of drug} - \text{Unentraped drug}}{\text{Total amount of Drug}} \times 100$$

Evaluation of CubosomalEmulgel Formulation:[15-17]

1. pH measurement
2. Viscosity measurement
3. Drug content
4. Clarity
5. Diffusion study
6. Drug kinetic release
7. Antimicrobial study
8. Statistical analysis

1. pH Measurment:

The obtain cubosomalemulgel should analyse by digital pH meter by immersing the electrode in gel formulation and pH is measure which is previously calibrated by the pH.

2. Viscosity measurement:

Viscocity of the different formulation should determine at room temperature using a brook field viscometer. A coleparmer viscometer shouldused to measure the viscosity of the prepare gel bases. The spindle was rotated at 10 rpm- 100 rpm and viscosity were observe.

3. Drug content:

Drug loaded cubosmes should mix with methanol and sonicate for 10 min. to obtain a clear solution. Concentration of drug should determine spectrophotometrically at λmax

242 nm.

$$\text{Drug Content} = \frac{\text{Actual Yield}}{\text{Therotical Yield}} \times 100$$

4. Clarity test :

The clarity of the formulation can checked by visual inspection.

5. Diffusion study:

In vitro skin permeation studies can be perform by using a franze diffusion cell with a receptor compartment capacity of 20 and 50 ml. Temperature is should be maintain at 37 ± 0.50 °c.

6. Drug kinetic analysis:

Following equation selected for to analyse the drug release mechanism from topical gel.

a. Zero – order equation: $Q = k0\ t$

Were, Q is the amount of drug of selected at time t, and k0 is zero-order release rate.

b. First –order equation: in (100 – Q) = in 100 – k1 t
   Where, Q is the percent of drug release at time t, and k1 is the first – order release rate constant.
c. Highuchi's equation: $Q = k22\sqrt{t}$
   Where, Q is the percent of drug release at time t, k2 is the diffusion rate constant.

7. Antimicrobial study:

For the determination of antifungal activity an agar method is can use for selected formulation.

8. Statistical analysis:

In order to compare the results ANOVA is use. Stability data is compare using ANNOVA test. Data which has to be report a significant difference is considered at not less than 0.05.

References:

1. KomalTilekar, PrashantKhade, SujitKakade,SachinKotwal and Ravindrapatil "Cubosomes- A Drug Delivery System". International Journal of Pharmaceutical, Chemical And Biological Sciences 2014;4(4):812-824.
2. Zahra karami, mehrdadhamidi"Cubosomes: Remarkable drug delivery potential", Drug Discovery today 2016; 01.004.
3. JyotiBachhav, Bhushan Bhairav, RavindraSaudagar, "Cubosomal Technique: A Review", International Journal of Pharmacy and Technology,2015;6(2):3263-3272.
4. MadhurilathaT handanki, ParuchuriKumari, SuriaPrabha, "Overview of Cubosome: A Nano Particle" International journal of Research in Pharmacy and Chemistry,2011;1(3):536-541.
5. Yallappamaharaj Hundekar, Dr.J.K.Saboji, S.M.Patil, Dr.B.K.Nanjwade "Preparation and Evaluation of Diclofenac Sodium Cubosomes for Percutaneous administration". World Journal of Pharmacy and Pharmaceutical Sciences, 3(5),523-539.
6. Created 2003. Last modified 30 dec 2015@ 2016 Derm net New Zealand Trust.
7. DebjitBhowmik, Harish Gopinath, B. Pragati Kumar, S.Duraivel, K.P.Samoath Kumar, "Recent Advances In Novel Topical Drug Delivery System" Pharma journal.com, Vol.1,No.92012, 2298-2341.
8. Y.S.Thorat, I.D.Gonjari, A.H.Hosmani, "Solubility Enhancement Technique: A Review on Conventional and Novel Approches, International Journal of Pharmaceutical Science and Research, 2011, Vol.2, 2501-2511.
9. B.Venkatesh, S.Indira, Dr.S.Pratima, "Formulation and Evaluation Glimipride oral Capsule", International Journal of Pharmaceutical science Invention, 2014. Vol.3. 2319-6708.
10. Ankur Jain, Surya Gautam, Yashwant Gupta, HemantKhambete, Sanjay Jain, "Development and Characterization of ketoconazole Emulgel for Topical Drug Delivery", Pelagia research Library, 2010, 1(3): 221-331
11. Sonam vats, CharuSaxena, T.S. Easwari, V.K.Shukla, "Emulsion Based Gel Technique: Novel Approach for Enhancing Topical Drug Delivery of Hydrophobic Drugs, International Journal for Pharmaceutical Research Scholars, 2014, 3(1),649-660.
12. A.S.Panwar, N.Upadhyay, M.Bairagi, S.Gujar,G.N.Darwhekar,D.K.Jain, "Emulgel: A Review", Asian Journal of Pharmacy and Life Science, Vol. 1 (3), July-Sept 2011, 333-343.
13. Elizabeth S. Dodd's Ashley, Russel Lewis, james S. Lewis, Craig Martin and David Andes "Pharmacology of Systemic Antifungal Agents" Supplemental article of Oxford Journal, vol.43,S-28 – S-39.
14. Q2B: Validation of analytical procedure: Methodology, Availability in International conference on Harmonisation. Federal register 1997:62(96):27463-27467.
15. Abounassif, M.A; El-Shazly, B.E.D.M. D1- "Differential Potenciaometric and 1H-NMR Spectrometric determination Of ketoconazole and It's Formulations" Anal.Lett, new York, 1989,Vol.22,2249-2263.
16. P.T.Spicer, K.L.Hayden, M.L.Lynch, A.Ofori-Boateng&J.L.Burns, "A Novel Process for Producing Cubic Liquid Crystalline Nanoparticles (Cubosomes)," 2001.5748-5756

17. R.R.Bhonsale, R.A.Osmani, R.Bhargav, "Cubosomes: Inimitable Nanopartucalated Drug Carrier" Department of Pharmaceutical ,Satara College of Pharmacy, SAJP 2013;2(6), ISSN 2320-4206; 481-486.

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