ejpmr, 2024, 11(5), 412-422

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

CUBOSOMES AS TRANSDERMAL DRUG DELIVERY SYSTEM

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Article Received on 19/03/2024 **Article Revised on 09/04/2024** **Article Accepted on 29/04/2024**

ABSTRACT

Transdermal drug delivery systems (TDDS) are one of the fascinating drug delivery systems offers several advantages over conventional and oral dosage forms for patient compliance but face challenges such as skin penetration barriers and formulation issues. This can be overcome by lipid nanocarriers, namely cubosomes which acts as an interesting and valuable alternative for transdermal delivery, for delivering of both lipophilic and hydrophilic drugs through the stratum corneum for potential local or systemic effects in treating various diseases. They are the stable colloidal dispersions characterized by a bicontinuous lipid bilayer structure arranged in three dimensions, with an uninterrupted cubic symmetrical surface separated by two interwoven, but nonintersecting, aqueous nanochannels similar to a honeycomb-like liquid crystal structure. They are prepared by top-down, bottom-up, spray drying and solvent evaporation methods and characterized by direct and indirect techniques. They act as a promising vehicle for different routes of administration. They are favoured for sustained, controlled, and targeted drug delivery, presenting novel avenues in therapeutic applications.

KEYWORDS: Transdermal, skin penetration, cubosomes, applications.

CUBOSOMES AS TRANSDERMAL DRUG DELIVERY SYSTEM

Transdermal drug delivery systems (TDDS) have gained numerous interests in the past two decades due to their advantages over conventional and oral dosage forms. It offers improved bioavailability, controlled drug release, reduced side effects, and the avoidance of first-pass metabolism.[1] It is a non-invasive and painless delivery system compared to intravenous and intramuscular administration which is particularly effective for poorly soluble and low permeable drugs (BCS II & IV), usually known for their lipophilic nature.[2] As a successful part of a novel drug delivery system, which provides prolonged drug action with low toxicity and better patient compliance. They are self-contained discrete dosage forms when applied transdermally, provide systemic circulation at a controlled rate.[3]

Barriers to transdermal drug delivery: The skin anatomy

The skin is the largest organ of the human body, covering about 1.7 m^2 and accounting for more than 10% of the total body mass of an average person.[4] Skin acts as an essential barrier against external chemical, mechanical, physical, and microbial stresses, thereby protecting against pathogens and water loss.[5]

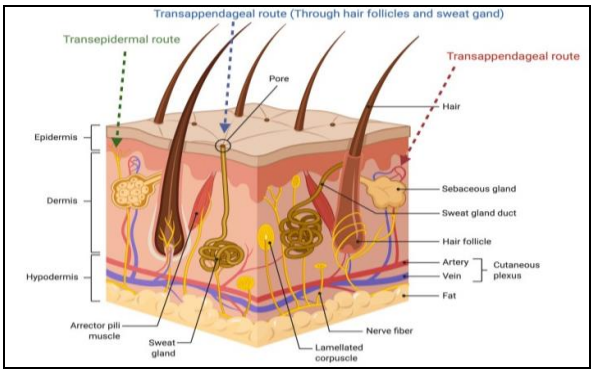

Fig. 1: Schematic illustration of the skin layer and showing penetration routes of the drug administered through the skin.[6]

The skin comprises three distinct functional strata, arranged from the deepest to the most superficial: the hypodermis, the dermis, and the epidermis.[7] These layers are made up of epithelial and connective tissues.[8] Skin appendages such as pilosebaceous follicles, which ensure hair growth as well as the sebum secretion, and the sweat glands, facilitating for water evacuation as a means of maintaining the body temperature.[7]

The epidermis is a multilayered, dynamic area whose thickness varies, ranging from 0.06 mm on the eyelids to 0.8 mm on the palms and soles of the hands and feet. It is avascular, composed of keratinocytes accounting for 95% of its cells which undergo constant proliferation, differentiation, and keratinization, being responsible for the physiological renewal of the skin. Each layer is known to represent a different level of cellular or epidermal differentiation.[4] Within epidermis there are several layers comprising the strata spinosum (SS), stratum lucidum (SL), stratum granulosum (SG), stratum corneum (SC), and stratum basale (SB). (Fig No.1).[8] Stratum basale is the germinal layer which continuously divides to produce new keratinocytes that move to outer layers finally to form a horny layer of dead cells in the SC. It takes 2 to 3 weeks for the migration of keratinocytes from the basal layer to finally shed off from the SC.[9]

The stratum corneum forms the outermost hydrophobic layer of the epidermis, ranging from 10–30 μm in thickness, and acts as a prominent barrier against skin permeation. The barrier property of the stratum corneum is due to its extreme lipid matrix and corneocyte organization, which are rich in keratin filaments and filaggrin. The corneocytes are entangled in a dense multilamellar lipid composed of glycosphingolipids (ceramides), phospholipids, and lipid-like sterols. The corneocytes embedded within the lipid matrix are well-described as a brick-and-mortar model.[10,11]

The stratum corneum is an essential barrier for the permeation of many drugs, to overcome this barrier, several techniques have been developed, including the use of methods that alter the stratum corneum (SC) continuity, such as ultrasound, electroporation, and iontophoresis, and the use of the vehicle and nanocarriers to improve drug penetration.[12] Passive diffusion enhancement strategies include increasing the thermodynamic activity of the drug in formulations (supersaturations), and use of chemical penetration enhancers.[13]

The dermis lies directly beneath the epidermis and is comprised of living cells with a higher density of blood vessels, that provide nutrition to the skin and maintain thermoregulation.[14] Capillaries within the dermis provide the sink condition for the molecules permeating through the transdermal route.[10]

Below the dermis lies the subcutaneous tissue layer, which consists of fat, adipose tissue, connective tissues, and muscles, which provides mechanical support to the epidermal and dermal layers.[10,14]

Micro and macroparticles can penetrate the skin through three distinct pathways: (1) The intercellular pathway, which is through the lipid matrix fills the intercellular spaces of the keratinocytes, (2) he transappendageal pathway, which crosses sweat glands, sebaceous glands, and hair follicles, and (3) the transcellular pathway, which goes via keratinocytes.[15]

Absorption of the drug

The drug permeation across the stratum corneum obeys Fick's first law with the steady state flux (J) being determined by the diffusion coefficient (D) of the drug within the stratum corneum and the diffusional pathlength or membrane thickness (h), the partition coefficient(P) between the stratum corneum and vehicle, and the applied drug concentration(C_0) which is assumed as constant.[16]

$$dc/dt = J = DC_0P/h$$ [16]

The emergence of nanocarriers, particularly lipid nanocarriers like liposomes, transferosomes, nanostructured lipid carriers, solid lipid nanoparticles, and lipid-based cubic liquid crystalline nanoparticles (cubosomes), presents an interesting and valuable alternative for transdermal delivery, for delivering of both hydrophilic and lipophilic drugs through the stratum corneum, for potential local or systemic therapeutic effects for treating various diseases.[17,18] Among these, cubosomes presented excellent enhanced drug penetration and retention ability, and have attracted much attention in recent decades for transdermal delivery.[18]

Cubosomes, nanostructured lipid-based particles, have gained considerable attention in the field of drug delivery and nanomedicine.[19] The term "Cubosomes" was coined by Larsson in 1980, which reflects their cubic molecular crystallography and resemblance to liposomes.[20,21] They are the stable colloidal dispersions characterized by a bicontinuous lipid bilayer structure arranged in three dimensions, with an uninterrupted cubic symmetrical surface separated by two interwoven, but nonintersecting, aqueous nanochannels similar to a honeycomb-like liquid crystal structure. They exhibit a complex nanostructure and typically range in size from 100 to 300 nm. The three main structures of bicontinuous cubic phases observed in cubosomes are the diamond (Pn3m), primitive (Im3m), and gyroid (Ia3d) phases.[22,24] Due to their unique properties such as thermodynamic stability, bio adhesion, capacity to encapsulate hydrophilic, lipophilic and amphiphilic drugs, as well as the potential for controlled release through functionalization, cubosomes are considered promising vehicles for various routes of administration.[25] It can be developed as a carrier of anti-inflammatory, antibacterial,

anti-viral, anti-cancer, neuroprotective, and anti-dementia drugs.[26]

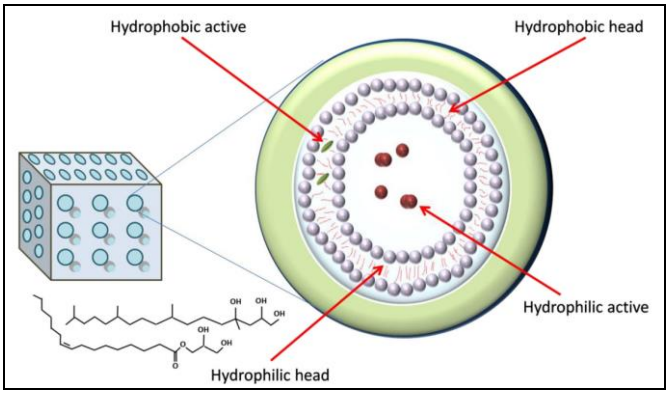

Fig. 2: Structure of Cubosomes.[27]

Advantages of Cubosomes

- The preparation process of the drug delivery system should be simple, easy and costless.[28]
- It should be inert, stable, safe (non-toxic), and biodegradable.[28]
- They are distinguished by high loading capacity for numerous drugs with different hydrophilic properties.[29]
- They facilitate targeted and controlled drug release.[29]
- They improve the stability of the drug.[29]
- The high surface area is attributed to the existence of two uninterrupted water channels divided by the lipid bilayer.[30]
- ability to boost the bioavailability and improve the absorbency of active ingredients.[31]
- Thermodynamically stable in excess water.[31]
- Good bioadhesive properties.[32]

Disadvantages of Cubosomes

- Large-scale production can be challenging at times due to high viscosity.[33]
- They have high water content in their structure, resulting in the low entrapment efficiency of the water-soluble drugs.[25]

TYPES OF CUBOSOMES

Depending upon the method used for formulation, cubosomes are categorized into liquid and powder precursors.[34]

Liquid Cubosomes Precursor: The hydrotrope dilution technique has been found to create smaller and more stable cubosomes by dissolving monoolein in a hydrotrope like ethanol, preventing it from forming liquid crystals Diluting this solution leads to spontaneous cubosome crystallization or precipitation through nucleation, crystallization, and precipitation. The quid precursor technique allows for faster cubosome preparation scale-up while avoiding bulk solids handling and possibly destructive high-energy operations.[35]

Powdered Cubosome Precursor: Powdered cubosome precursors, comprising dehydrated surfactant coated with a polymer, can be hydrated to form cubosomes with a mean size of 600 nm, as confirmed by light scattering and cryo-TEM analysis.[36] By using the spray-drying technique, enables the formation of powdered cubosomes after encapsulation of particles from liquid droplets in emulsion and dispersion. In order to stop agglomeration, this method is used to coat a water-soluble, non-cohesive starch with a waxy lipid.

However, it is better to use cubosomes in a powdered form to avoid the processing of bulk water.[34]

STRUCTURAL COMPONENTS OF CUBOSOMES

Cubosomes consists of target molecule to be enclosed within the particles, a stabilizer, a lipidic mixture. The idea behind cubosome creation is that these parts self-assemble into a bicontinuous cubic phase.[37]

The most common and widely used amphiphilic lipid for the formulation of cubosomes is glyceryl monooleate (GMO), also referred to as monoolein. The physical and chemical properties of GMO, which are significant for cubosome synthesis, include the polarity of the unsaturated monoglyceride, which has a melting point of 35–37°C, a storage temperature of 20–30 °C, and an HLB value of three, and it is usually colourless and clear in nature. GMOs are made up of a combination of monooleate and glycerides of oleic acid and other fatty acids. There are two kinds of monoolein: distilled monoolein and mixed glyceride. Distilled monoolein is preferred for pharmaceutical purposes because of its high purity. Monoolein swells in water which generates various lyotropic liquid crystalline structures. It is non-toxic, biodegradable, and biocompatible, which is used as an emulsifier in both the food industry and many pharmaceutical preparations.[34,38]

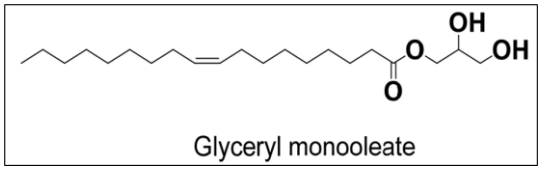

Fig. 3: Molecular structure of Glyceryl monooleate.[34]

Phytantriol, chemically 3, 7, 11, 15-Tetramethylhexadecane-1, 2, 3-triol (PHY) which is biocompatible, has cosmetic applications and displays cubic Pn3m self-assembled structure in excess of water. It has been suggested that PHYT serves as a good alternative to GMOs due to its lack of unsaturation in the alkyl chain. The absence of an ester bond in the polar head group, similar to monoolein, also makes PHYT less prone to chemical degradation.[39] Despite pf having different molecular structures, PHY and GMO exhibit similar phase transition behaviors with an increase in water content and temperature.[40]

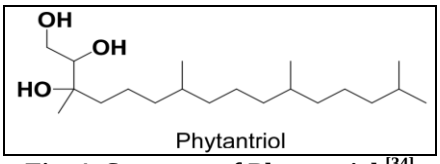

Fig. 4: Structure of Phytantriol.[34]

Stabilizers

Surfactants play an important role in providing colloidal stability for the preparation of cubosomes. They tend to coalesce into the bulk cubic phase. Unfavourable interactions between hydrophobic domains can be prevented by an ideal stabilizer as it encounters between the particles of the cubosomes. Stabilizers can create an electrostatic repulsive barrier between the approaching particles, by protecting the cubic structure without causing any disruption. Therefore, the stabiliser is an essential element required for the formation of cubosomes. Stabilizer sequestration occurs in cubosomes as a result of their high internal surface area.[41]

Poloxamer-407 (P407 or Pluronic F127 or PF127), is a triblock polymer, comprising polyethylene oxide polypropylene oxide-polyethylene oxide (PEO-PPO-PEO) copolymer. This aids in stabilizing Lyotropic nonlamellar liquid-crystalline nanoparticles (LCNs) by preserving their internal liquid-crystalline structure and forming a steric barrier. Furthermore, the hydrophilic nature of the polymer is attributed to the PEO portion, while the hydrophobic nature of the polymer is attributed to the PPO portion. The ability of P407 to stabilise the hydrophobic PPO block on the particle surface for adsorption or functionalization is explained by this action. Simultaneously, the hydrophilic PEO segment imparts steric shielding by extending into the aqueous environment. The P407 dispersions structural kinds, however, may differ depending on how much of them is employed in relation to a certain liquid crystal lipid.[42] Apart from P407, stabilizers such as propylene glycol (PG), polyethylene glycol 400 (PEG400), polysorbate 80 (Tween 80), and 2-methyl-2,4-pentanediol (MPD) are often used alternatives in the production of PHYT-based cubosomes.[43] Additionally, Hydroxypropyl methylcellulose acetate succinate (HPMCAS) is effective for stabilizing GMO-based cubosomes with P407.[40]

METHOD OF PREPARATION

Techniques used for preparation of cubosomes include the top-down, bottom-up, spray-drying, and solvent evaporation methods.[34] However, the top-down and bottom-up methodologies are the two most important methodologies now in use. Both of these strategies use the same colloidal stabilizer, P407, to help disperse cubosomes more easily and stop them from aggregating.

Top-down approach: Bulk cubic phases are initially created and then dispersed into cubosomes nanoparticles using high-energy processes. Bulk cubic phases resemble liquid crystalline structures, while cubic phases resemble transparent, stiff gels made of water-swollen, cross-linked polymer chains. More oils and surfactants in the cubic phases increase yield stress. Lipids and stabilizers are mixed to form the viscous bulk cubic phase, which is dispersed into an aqueous solution using techniques such as High-Pressure Homogenization (HPH), sonication, or shearing to generate Lyotropic Liquid Crystal (LLC) nanoparticles. HPH method is the most frequently used method for this purpose. When cubosomes are created using a top-down approach, vesicles or vesicle-like entities often coexist alongside them.[44]

Bottom-up approach: An alternate method for cubosomes formation at room temperature involves dispersing a mixture of lipid, hydrotrope, and stabilizer in excess water with minimal energy input. Hydrotropes play an important role by dissolving water-insoluble lipids, preventing liquid crystal formation at higher concentrations, and aiding the solubilisation of poorly water-soluble agents. This method provides advantages including low energy requirement, suitability for thermosensitive materials, stable distribution of stabilizer, efficient generation of small particles, use of simple hydrotrope to prepare cubosomes like urea, sodium alginate and sodium benzoate.[45] Several strategies were used to disperse nanoparticles created during cubosome formation like Sonication, Spray drying, High-pressure homogenization and Spontaneous emulsification.[46]

Spray drying method: Spray-drying encapsulation involves mixing liquid droplets or solid particles into a concentrated water-polymer solution, which is then sprayed through a curated nozzle into dry, hot air. As a result of this process, the water quickly evaporates, resulting in the formation of dry powder particles made up of the dispersed phase encased in the previously dissolved polymer. It allows simple preload of actives into cubosomes before drying, with the polymer coating it gives surface property modifications through the choice of encapsulating polymer. By adjusting the liquid

feed, the characteristics of the resulting powder can be varied. For the production of starch-coated cubosome powders, a high shear treatment of monoolein with an aqueous starch solution to form a coarse dispersion. This is then sprayed and dried, leading to a powder final composition of around 72% starch, 4% water, and 24% monoolein, after nearly all water is removed during drying.[47,49]

Solvent evaporation method: Another technique for creating powder cubosomes with a homogenizer or ultra-sonicator is solvent evaporation. With the exception of using a high-energy sonicator, the process is fairly similar to the spray-drying approach. This method involves dissolving the lipids in an organic solvent such as ethanol or chloroform before adding them dropwise to another mixture that contains a stabilizer such as Pluronics in aqueous phase. Under magnetic stirring, the mixture is kept at a high temperature. The drug may be diluted in either an aqueous or lipid surfactant solution. This method involves dissolving the lipids in an organic solvent such as ethanol or chloroform before adding them dropwise to another mixture that contains a stabilizer like Pluronics in aqueous phase. Under magnetic stirring, the mixture is kept at a high temperature. Both the lipid and the aqueous surfactant solution can be used to disperse the medication. Stirring under elevated temperatures removes the volatile organic solvent, and the mixture is homogenized by ultra-sonication or homogenizer, resulting in the formation of cubosomes.[34]

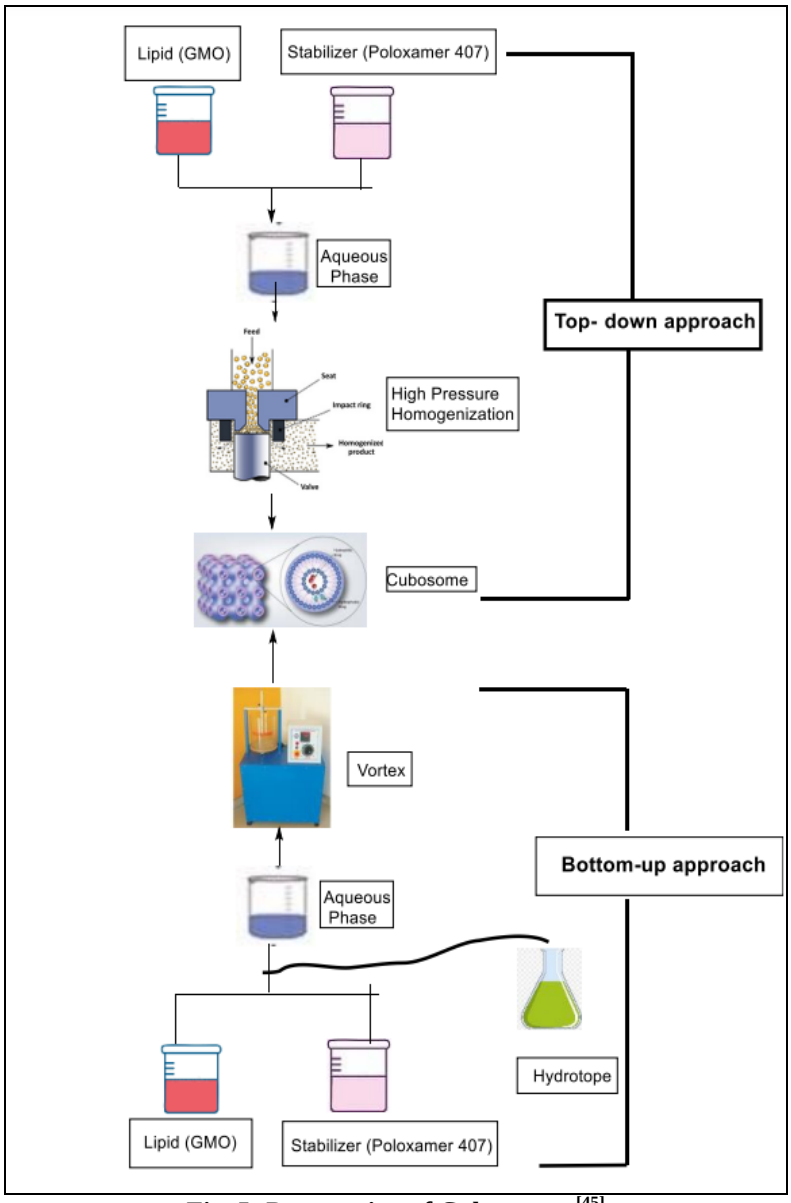

Fig. 5: Preparation of Cubosomes.[45]

Characterisation of cubosomes: Cubosome characterization techniques can be categorized into direct

techniques for phase identification and indirect techniques for phase characterization. Some of the commonly used techniques are given below.[37]

Direct techniques

Cryogenic transmission electron microscopy

Cryogenic transmission electron microscopy (Cryo-TEM) experiments visualized cubosome nanoparticles by preparing vitrified samples at 25°C and 100% humidity using a Controlled Environment Vitrification System (CEVS). After blotting with filter paper and placing a 3µl sample drop on a copper grid coated with perforated carbon film, the grid was submerged in liquid ethane at its freezing point. These samples were then examined in a FEI Tecnai T12 G2 electron microscope at -175°C, using low-dose imaging to minimize electron beam radiation damage, with exposures around 10 to 15 e-/Å2. Images were digitally recorded with a high-resolution Gatan US1000 CCD camera, using Digital Micrograph software.[50]

Small-Angle X-Ray Scattering (SAXS)

SAXS measurements were carried out on a small-angle instrument (SAXSess mc2), featuring a 2084x2084 array with24x24 μm^2 pixel size charged-coupled device detector, at a 311 mm distance from the sample. Samples were held in a capillary tube, equilibrated at 25°C for 45 minutes, and then X-rayed for 90 minutes under vacuum. The two-dimensional scattering data captured by the detector were converted into one-dimensional scattering functions(q) using an equation,

$$q= (4\pi/ \lambda) (\sin\theta/2),$$

where q is the length of the scattering vector, λ the wavelength, and θ the scattering angle. This data helps to determine the relative position of the Bragg peak displayed in the scattering curves. These positions were matched to specific cubic phases—P-type, D-type, and G-type—based on characteristic spacing ratios, aiding in the classification of different cubic phases of cubosomes.[51]

Indirect techniques

Dynamic Light Scattering (DLS)

Dynamic light scattering method (Nano ZS, Malvern Instruments, UK) is used to measure the average particle size, zeta potential, and polydispersity index (PDI) drug–loaded cubosomes. All the measurements are conducted in triplicate at a scattering angle of 90° and 25°C temperature. The zeta potential of the samples was measured using capillary zeta cells. Using the Helmholtz- Smoluchowski equation, the zeta potential is determined. The procedure involved the use of software to determine the zeta potential.[52]

NMR

NMR spectra were obtained using a 14 T Agilent NMR spectrometer DD2 with a DOTY DSI-1372 diffusion probe. The "dbppste_wg" pulse sequence was used to calculate self-diffusion coefficients. For cubosome samples in water, ^{1}H NMR spectra were obtained with the "water_3919_watergate" sequence, while for pure drug in methanol spectra were recorded using "dpfg_water" with excitation sculpting for methanol resonance lines, all utilizing the Pulsed Gradient Spin Echo (PGSE) method. The frequency selective rf pulse for double-resonance methanol suppression was designed using the pbox tool in VnmrJ software. Finally, data were analysed using MestReNova 12.0.4 software, applying the Stejskal-Tanner equation to calculate self-diffusion coefficients based on NMR signal attenuation in magnetic field gradients.[53]

Rheology

The rheological behaviour of gels was analysed using small-amplitude oscillatory shear tests with a rotational rheometer at 25 and 45°C. These tests measured the elastic modulus or shear storage (G') to assess elasticity and the viscous modulus (G") for viscosity with an oscillation frequency ranging from 0.1 to 10 Hz, Hz and a strain amplitude at which linear viscoelasticity was attained. To investigate the gelation temperature of the polymeric systems, the moduli changes between 25 to 45°C were observed at a fixed frequency of 0.01 Hz and a valid strain amplitude. The gelation temperature was recognized as the temperature at which the sample switched from a predominantly from viscous behaviour (G" > G') to a prevailing elastic behaviour (G' > G").[54]

Morphology of Cubosomal Nanoparticles

The morphology of drug-loaded cubosomes was observed using a Wet-SPM Scanning Probe atomic force microscope. After cleaving the muscovite mica squares, a drop of cubosomal dispersion was adsorbed on them, and any excess water was dried by air. The sample was mounted in a microscope scanner for viewing and imaging in the non-contact mode at a frequency of 312 kHz and a scan speed of 2 Hz.[55]

Differential Scanning Calorimetry (DSC)

A thermal analysis study was conducted on the cubosomal dispersion, each of its components separately and with pure drug to determine the physical state of the drug-encapsulated separate. The DSC thermograms were achieved at a temperature from 25-450°C using DSC-60, Shimadzu, Kyoto, Japan. The aluminium pan was filled with 5 mg of each sample, heated with a 10 ◦C/min heating rate under a purgative nitrogen. A comparable empty pan was used as the control. The location and width of the melting peak were used to analyse the sample's crystallinity.[56,57]

Entrapment Efficiency (%EE)

By ultrafiltering the prepared cubosomes through Vivaspin ultra filter tubes, the entrapment efficiency (%EE) was ascertained. The drug-loaded cubosomal dispersion (3 mL) was added to the centrifuge tube and centrifuged against placebo cubosomes for 15 minutes at 4°C at 3,000 rpm (Cooling centrifuge, Sigma 3-30K). A UV-VIS spectrophotometer was used to measure the

absorbance of the separated supernatant in order to determine the amount of drug that was not entrapped.[58]

% Entrapment efficiency was calculated by the following equation[58]

$$EE\% = \frac{\text{Total drug} - \text{free drug}}{\text{Total drug}} X\ 100$$

Stability studies

Cubosomes, nanostructured particles formed from cubic phases in water, are stabilized by polymers such as poloxamer 407 to prevent coalescence and aggregation. Bilayered apertures expose them to the aqueous phase, which decreases stability. Solid or liquid crystalline coatings can compensate for this, with solid coatings having a higher level of stability than liquid lamellar coatings. Though- the diameter of cubosomes is 50 nm, solid rigid coating results in the cubosomal diameter of 100 nm due to restrictions in curvature. Besides this, sponge phase coatings also contribute to stabilization. Ingredients such as GMO and monoolein ensure the formulation's stability and the controlled release of drugs. The most widely used lipid, GMO, is included in cubosomal formulations along with a variety of surfactants, polymers, and natural lipids. GMO has the ability to form spontaneous stable colloidal dispersions, which provides thermal stability.[59]

Utility of Cubosomes in transdermal Applications

Sr No.	Polymers used	Active ingredient	Method of Preparation	Applications/ Utility	Ref
1	GMO, Phytantriol, Poloxamer 407	Capsaicin	Emulsification, homogenization	Targeted and sustained transdermal drug delivery.	[60]
2	GMO, Pluronic-F127	Clonazepam	Emulsification	Reduces the epileptic seizures.	[61]
3	GMO, poly vinyl alcohol	Febuxostat	Bottom-up approach	Treatment of gout in the form of transdermal patches.	[62]
4	Phytantriol, Pluronic-F127	Ketotifen Fumarate	Fragmentation method	Sustained drug release for effective treatment of asthma.	[52]
5	GMO, Poloxamer 407	Triamcinolone	Bottom-up approach, Sonication	Management of Psoriasis.	[63]
6	GMO, Poloxamer 407	Leflunomide	Emulsification	Management of breast cancer	[64]
7	GMO, Pluronic F 127, Cetyltrimethylammonium bromide	Atazanavir	Emulsification, homogenization	Antiretroviral treatment.	[65]
8	Monoolein, Poloxamer 407	Etodolac	Emulsification, homogenization	Management of Rheumatoid arthritis.	[66]
9	GMO, Pluronic F 127	Raloxifene	Ethanol injection method, microfluidization technique	Prevention of osteoporosis	[67]
10	GMO, Poloxamer 407	Colchicine	Box-Behnken factorial design	Treatment of gout	[68]
11	Poloxamer 188, Cetyl palmitate	Methotrexate	Emulsification	Treatment of rheumatoid arthritis	[69]
12	Phytantriol, Pluronic F127, PVA, PVP	Rapamycin	Solvent shifting method	Microneedle patches in the management of Psoriasis.	[70]
13	GMO, Pluronic F127	Doxorubicin	pH gradient method,	Treatment of	[18]

		Hydrochloride, Indocyanine green	Top-down method	Melanoma	
14	GMO, Poloxamer 407, Carbomer 940	Dexamethasone acetate	Hot melt ultrasonic method	Treatment skin inflammation	[26]
15	Monoolein	Salbutamol	Melt emulsification, Sonication	Treatment of paediatric asthma	[71]
16	GMO, Poloxamer 407, PVA	Progesterone	Emulsification, Quality by design approach	Management of hormonal disturbances	[72]
17	GMO, Poloxamer 407, Pluronic F127	Dacarbazine	Adapted coarse method, Box–Behnken design	Treatment of Melanoma	[73]
18	GMO, Poloxamer 407	Capsaicin, Thiocolchicoside	Modified emulsification method	Management of gout	[74]

CONCLUSION

Transdermal drug delivery encounters a formidable barrier to skin penetration from topically applied medications: the stratum corneum, the highly structured outermost layer of skin. In contrast, cubosomes present a viable means of transdermal drug delivery because of their distinct features and structure. Cubosomes can be embedded with broad variety of hydrophilic and lipophilic drugs and distribute them in a controlled and targeted way. Top-down, bottom-up, Spray drying and solvent evaporation are some of methodologies to prepare cubosomes. They act as a promising vehicle for different routes of administration. Cubosome technology is new and has a high yield, there is plenty of space for development into new economically and industrially feasible formulation.

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