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Review Paper

Cubogel Technology: A Breakthrough in Drug Delivery

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ABSTRACT

Cubogel technology was an innovative drug delivery system that combined cubic liquid crystalline nanoparticles (cubosomes) with gel formulations to improve the delivery and effectiveness of therapeutic agents. This hybrid system offered the advantages of both cubosomes and hydrogels, including enhanced stability, controlled drug release, improved viscosity and better patient compliance. The unique internal cubic structure of cubogels provided a large surface area capable of encapsulating hydrophilic, hydrophobic, and amphiphilic drugs, making them suitable for a wide range of pharmaceutical applications. Cubogels were widely explored for topical, transdermal, ocular, oral and mucosal drug delivery. The gel matrix enhanced adhesion and prolonged the residence time of drugs at the site of application, thereby increasing therapeutic efficacy and reducing dosing frequency. In addition, cubogels protected sensitive drugs from environmental degradation and helped minimize side effects through sustained and targeted release. Recent studies demonstrated the potential of cubogel formulations in delivering antifungal, anti-inflammatory, antimicrobial, and anticancer drugs. Their biocompatibility and non-toxic properties also made them useful in cosmetic and tissue engineering applications. The performance of cubogels depended on factors such as lipid composition, polymer concentration, and preparation methods. Although challenges such as formulation stability, scalability, and production costs still existed, ongoing advances in nanotechnology and pharmaceutical sciences were expected to improve their commercial and clinical potential. Overall, cubogel technology represented a promising approach for advanced controlled and targeted drug delivery systems

INTRODUCTION

The application of the Cubogel technology in pharmaceutics, especially in developing novel drug delivery systems (NDDS) is the relatively

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young but advanced technique. The traditional drug delivery techniques usually have their weaknesses such as poor solubility, bioavailability, stability of the drug, and the serious systemic toxicity.[1] For this reason, new drug delivery systems that would eliminate these shortcomings were developed using nanotechnology.[2] Nevertheless, having realized that further improvement could be reached for drug delivery, the interest towards cubosomes increases due to their unique structure and properties.[3] Cubosomes are the nanostructured lipid carriers formed in bicontinuous cubic liquid crystalline phase. The cubosomes are formed due to self-assembly of the amphiphilic lipids, for instance, monoolein and water in the presence of the surfactant, for example, poloxamer 407.[4,5] The interior of the cube comprises two aqueous channels which do not intersect each other but are separated by the bilayer of lipids.[6]

Cubosomes have several significant advantages. First of all, they have a high capacity for encapsulating the various kinds of drugs that can be hydrophilic, lipophilic, or amphiphilic. Hence, cubosomes can be used for the delivery of different types of drugs.[7] Moreover, the controlled and sustained release and delivery of the drug ensures that uses of cubogel technology have been demonstrated in the management of several illnesses such as arthritis, fungi infections, burns, and other skin disorders.[8,9]In particular, medications that lead to stomach complications when taken orally such as ketoprofen and diclofenac can be delivered using this method without causing problems. In addition, cubogels ensure that there is no degradation of the drug in the environment.[10,11] Therefore, their capacity of delivering drugs under control while minimizing side effects is quite promising in today's pharmacology and transdermal therapy.[12]

Indeed, cubogel drug delivery system technology is highly innovative because it incorporates nanotechnology and polymer science in one.[13,14] Some of the benefits that come with using the technology include increased bioavailability of the drugs and their efficacy, decreased side effects, and acceptability by patients.[15]

CUBOGEL TECHNOLOGY

The cubogel delivery system is one of the most advanced forms of drug delivery which relies on two different delivery techniques which include cubosomes and hydrogels. Cubogel delivery system is mainly used in skin-based drug delivery applications. Cubosomes represent nanoparticles based on liposome structure consisting of lipid molecules. Molecules of such structure can transport drugs regardless of their solubility since they can carry drugs whether they are water-soluble or fat-soluble. In addition, owing to their special structure, the process of sustained release can be accomplished easily.[16,17]

On the other hand, hydrogels can be defined as polymer-based gels which are capable of holding large amounts of water. It can be used in skin-based drugs because of its gentle nature to the skin. Therefore, in a cubogel delivery system, both cubosomes and hydrogels are used together. First of all, cubosomes play the role of mini carriers carrying drugs whereas hydrogels are supposed to provide higher viscosity, stability, and improved skin adhesion to ensure the controlled release process and penetration of drugs through skin barrier deeper inside the skin.

The advantage of this method is the ability to minimize side effects resulting from oral medication administration as well as from drugs possessing poor solubility characteristics. Cubogel formulations have been explored extensively for conditions such as arthritis, skin infection, inflammation, and wound healing. As a result of their advantages such as slow drug release and excellent absorption properties, cubogel

formulations have emerged to be among the promising pharmaceutical products.[18]

COMPOSITION OF CUBOGEL TECHNOLOGY [19, 20]

Cubogel is an example of the combination of technologies where cubosomes are mixed with hydrogel as the basic material. The key elements of the compound are the following:

1. Lipid Phase (Lipid for Cubosome Formulation)

Monoolein (glyceryl monooleate) was the main lipid used. It created the cubic structure within the cubosome, encapsulated the drug, and provided controlled drug release.

2. Stabilizer/Surfactant

Poloxamer 407 was the main stabilizer/surfactant used. It stabilized the nanocubosomes, prevented aggregation, and determined the particle size.

3. Aqueous Phase

Distilled water was used as the aqueous solvent. It formed the cubic lattice and acted as the dispersing medium.

4. API

Ketoprofen, Diclofenac, and Miconazole were used as examples of drugs. They provided pharmacological activity and exhibited hydrophobic/lipophilic characteristics.

5. Gel Forming Agent

Carbopol 934, HPMC, and Chitosan were used as examples of gelling agents. They formed gels from the aqueous phase dispersed cubosomes, enhanced viscosity and spreading ability, and improved skin adherence capacity.

6. pH Adjusting Agent

Triethanolamine was used as an example of a pH-adjusting agent. It maintained the pH of the formulation.

Methods of Cubogel Technology[20,21]

Cubogel preparation uses cubosome preparation methods. These methods are classified into two groups:

1. Top-Down method

2. Bottom-Up method

1. Top-Down method

Steps involved in cubosomes preparation

1. Lipid Phase preparation:

The lipid phase consisting of monoolein (glyceryl monooleate) was weighed and melted. The drug was then mixed with the lipid phase.

2. Aqueous Phase Addition:

The aqueous phase contained distilled water and surfactants such as Poloxamer 407. The aqueous phase was then added to the lipid phase.

3. Formation of Bulk Cubic Phase:

A bulk, gelatinous, and highly viscous cubic phase was formed as a result of mixing the lipid and aqueous phases. The bulk cubic phase contained channels of lipid and water.

4. Homogenization/Size Reduction:

Homogenization is done to reduce gel size into small cubosomes.

5. Sonication (optional):

The mixture was subjected to sonication to obtain a small particle size, achieve uniformity, and provide stability.

6. Cubosomes formation:

The obtained mixture formed a stable dispersion of cubosomes with a milky appearance. The stability of the dispersion was confirmed by verifying the particle size and uniformity.

7. Formation of Cubogels:

A hydrogel network, such as Carbopol 934, was prepared. The cubosome dispersion was then added to the hydrogel base matrix.

Bottom-up approach:

1. Preparation of lipid mixture[19,20,21]

A proper form of lipid, including monoolein, was selected. The lipid was dissolved in an aqueous solvent such as ethanol, and the drug compound was then added to the lipid phase.

2. Aqueous Layer Addition[20,21]

An aqueous layer containing Poloxamer 407 as a stabilizer was prepared independently. The aqueous layer was gradually added to the lipid layer under continuous stirring.

3. Cubosome Formation[16,19,20,21]

When water was added, diffusion of the organic solvent took place. The self-assembly of the lipid molecules then caused the formation of a cubic liquid crystalline phase.Cubosomes are formed without using any mechanical energy.

4. Removal of Organic Solvent[19,20]

The organic solvent, such as ethanol, was eliminated from the mixture. Thus, a cubosome dispersion was obtained through this method.

5. Dispersion Stabilization[18,21]

The surfactant stabilized the cubosomes, and the resultant dispersion became stabilized.

6. Cubogel Formation[10,11,20]

The hydrogel component was composed of a carbomer such as Carbopol 934. The cubosomal dispersion was slowly added to the gel layer and stirred gently.

Evaluation of Cubogel Formulation [22,23]

It is important to evaluate cubogel formulation for understanding its quality, effectiveness, stability and safety issues. Taking into account that the nature of cubogel includes nano carrier and gel formulation, both of which should be assessed separately.

1. Physical Characteristics

It includes Color, Transparency, Consistency and Appearance. Formulation of cubogel is expected to demonstrate homogenous consistency and absence of phase separation.

2. Measurement of pH Level

It is performed with help of pH digital meter.The range of pH is expected to be from 5.5 to 7.0 which fits human skin.If the pH level is either above or below this pH may lead to skin irritation.

3. Drug Content Homogeneity

A measurement was made by dissolving a certain amount of cubogel in an appropriate solvent. The obtained solution was then filtered and analyzed using UV-Vis spectrophotometry. This analysis confirmed the even distribution of the drug and the precision of the formulation.

4. Rheological Properties Study (Viscosity & Flow Behavior)

The viscosity was evaluated using a Brookfield viscometer to assess the flow behavior, whether Newtonian or non-Newtonian. This evaluation was significant because it controlled the drug release rate.

5. Spreadability Test

The assessment was carried out by filling the gel between two glass plates and pressing them uniformly. The spreading time was then recorded. Good spreadability provided easy application and ensured uniform distribution on the skin.

6. Extrusion Test

The test was performed to assess the extrusion of the gel from the tube. Good extrusion made the formulation easier for patients to use and ensured accurate dosage administration.

7. Particle Size Measurement

The analysis was carried out through Dynamic Light Scattering (DLS). It determined the average particle size and particle size distribution. A small particle size enhanced penetration and improved bioavailability.

8. Zeta Potential

The test was performed to quantify the surface charge of the cubosomes. It provided meaningful information regarding nanoparticle stability. A high zeta potential indicated good stability and the absence of aggregation.

9. Entrapment Efficiency

The test was conducted to determine the quantity of drug entrapped in the cubosomes after separating the free and entrapped drugs. Higher

entrapment efficiency ensured a high drug loading capacity and enhanced efficacy.

10. In Vitro Drug Release Studies

The study was conducted using Franz diffusion cells or dialysis membranes. It measured the kinetics of drug release and demonstrated controlled and sustained release.

11. Skin Permeation Study In vitro

The study was carried out using either animal or human skin. It evaluated the ability of the drug to penetrate various skin layers and determined the rate of drug permeation. The cubogel was required to be non-irritating and safe for topical administration.

12. Irritation Test

The test was conducted on the skin to evaluate irritative reactions such as erythema and edema. The cubogel was required to be non-irritating and safe for topical application.

13. Stability Test

The study was conducted by storing the formulation under various environmental conditions such as different temperatures and humidity levels. The testing included pH stability, drug stability, and viscosity stability. This helped evaluate the stability and shelf-life of the formulation.

14. Microbial limit test (optional)

The test was performed to check the product for microbial contamination. It was important for ensuring the safety of the product and determining its shelf-life.

15. Texture Analysis (advanced testing)

Tests the properties like hardness, adhesion of the gel.

Applications of Cubogel Technology

Cubogel technology has attracted much interest among researchers working in advanced drug delivery technologies because of the presence of both cubosomes and polymeric hydrogel in this technology.[22] This unique combination in this revolutionary technology enables the formulation to exhibit high solubilization ability, controlled release ability and also skin permeation capability thereby making it very suitable for use in various pharmaceutical and biomedical applications.[10,23]

1. NSAID Delivery[24]

Extensive research was conducted on the application of cubogel technology for delivering NSAIDs such as Ketoprofen and Diclofenac. The incorporation of these drugs into the formulation enabled skin absorption and sustained drug delivery. This improved the local activity of the drug, reduced the side effects associated with the oral administration of NSAIDs, and enhanced patient compliance.

2. Management of Arthritis and Musculoskeletal Disorders[25]

Cubogel technology proved to be an excellent carrier for anti-arthritis drugs. It provided localized drug delivery at the joint site, minimized systemic drug levels due to reduced systemic exposure, and maintained a high concentration of the drug at the site of action for an extended duration.

3. Antifungal and Antibiotic[26]

The efficacy of antifungal agents and antibiotics was successfully enhanced using cubogel formulations. The formulations improved the solubility of the drugs and were effective in the treatment of bacterial infections.

4. Wound Healing and Burn Treatment[27]

The presence of hydrogel in the cubogel created a moist environment, which was essential for successful wound healing. It enhanced the tissue repair process, increased drug penetration at the wound site, and prevented microbial infection.

5. Skin Disorder Treatment[27]

Cubogel technology found applications in the treatment of chronic skin diseases because of its superior drug delivery properties. It ensured controlled drug release, minimized skin irritation,

and increased drug penetration through the stratum corneum layer. Examples of such conditions included psoriasis, eczema, and acne.

6. Systemic Medication Delivery through Transdermal Route[28]

Cubogel formulations were used to deliver systemically acting medications through the transdermal route. They bypassed the first-pass effect, helped maintain a constant plasma concentration, and enhanced bioavailability.

. Drug Solubilization[29]

Cubosomes were able to solubilize drugs because of their lipophilic nature. This resulted in fast drug dissolution, enhanced bioavailability, and stabilization of drug molecules. As a hydrogel formulation, cubogel was easier for patients to apply. Its nongreasy nature made application convenient, provided a cooling effect, and improved patient acceptance.

8. Prolonged Stay at Application Area[30]

The hydrogel component in the formulation enhanced viscosity and thereby prolonged its retention at the application site. This resulted in a better drug retention period and improved therapeutic efficacy.

9. Flexible Formula that Can Work with Different Drugs[31]

This formulation was compatible with various types of drugs, including anti-inflammatory agents, antifungal agents, and painkiller agents.

10. Safety and Biocompatibility[32]

Hydrogels and cubosomes were relatively safe formulations. They caused minimal irritation and toxicity, making long-term administration possible.

11. Simplicity in Preparation and Production[33]

Cubogel-based systems were feasible to synthesize through relatively simple procedures. They were suitable for bulk manufacturing and were relatively inexpensive compared to other advanced systems.

Limitations of Cubogels[34]

- Complex Manufacturing Process
- Consumption of More Energy (Top-down Strategy)
- Utilization of Organic Solvents (Bottom-up Strategy)
- Tendency Towards Instability
- Inadequate Ability to Accommodate High Drug Loads for Some Pharmaceutical Substances
- Hard to Scale up the Process
- Cost Factors (Materials and Equipment)
- Skin Sensitization (Occasionally)
- Storage and Transportation Requirements
- Limited Availability

Challenges of Cubogel Technology [35-39]

1. Complex Formulation Procedure[35]

The development of cubogels is quite complex because it requires creating a cubosome first and then incorporating it into the matrix of hydrogels. The process involves several steps, and the formulation procedure takes much time overall.

2. Energy Intensive Processes[36]

If the top-down technique is applied, the only two feasible processes involve high pressure homogenization or sonication, which consume much energy and make it more expensive.

3. Organic Solvents[37]

The bottom-up method requires ethanol as solvent. This causes problems since it might leave residual solvents after incorporation, which may lead to toxicity.

4. Inconsistent Stability[38]

There might arise stability issues such as aggregation, phase separation, and changing the particle size over time, which affects the shelf-life and activity of the medication.

5. Difficult Scale-Up Process[39]

It is easy to produce a successful formulation in laboratory conditions, while scaling up is associated with many problems, including

necessity in special equipment and reproducibility issues.

6. Limited Drug Loading Capacity[39]

There are cases when the drug does not bind effectively with cubosomes; therefore, loading capacity remains quite low.

7. Skin Irritation Hazard[35]

They are normally safe; however, when it comes to choosing proper surfactants or polymers, they may become irritating to the skin, making fine-tuning necessary.

8. Expensive[37]

The main components of this carrier are expensive, and the process cannot be conducted using simple equipment. As a result, production costs increase significantly.

9. Stabilization Difficulties[35]

As cubogels are not very stable, their manufacturing requires certain care since they dislike moisture and heat. Any mistakes will lead to a decrease in stability.

10. Poor Availability[38]

It is impossible to buy cubogels in the pharmacy since they are still laboratory creations; besides, there is no enough clinical data to launch commercial products.

11. Long Regulatory Approval Process[36]

Regulation and certification of cubogels require a lot of time because there are no particular norms regarding nanoparticles.

12. Low Reproducibility[37]

Maintaining consistency in particle size and drug release is a complicated procedure, which leads to numerous difficulties in large-scale production.

Scope of Cubogel Technology in the Future [40-41]

1. Drug delivery by means of advanced drug delivery systems by employing Cubogel technology.
2. Stability and scale-up of cubosomes for commercialization.
3. Site-specific delivery of cubosomes for cancer treatment.
4. Transdermal delivery of drugs by the use of cubosomes.
5. Application of the technology in the development of ocular and nasal drug delivery systems.
6. Modifying cubosomes with new biocompatible lipids and polymers for enhanced drug delivery systems.
7. Increasing the solubility profile of poorly soluble drug candidates.
8. Conjugating nanoparticles and cubosomes for smart drug delivery systems.
9. Further clinical trials for regulatory approval.
10. Economical synthesis for mass production.

Challenges [42,43]

(1) Cubogel development is quite a complicated process. Someone firstly has to make the cubosomes for the cubogels, and then incorporate them into a hydrogel matrix after which both operations are finished. Therefore, developing a cubogel is very time consuming and difficult to complete.

(2) Many of the top to bottom techniques used to produce cubogels, such as high-pressure homogenizing or sonication, require a considerable amount of energy to create, thereby making the process expensive and inefficient.

(3) The bottom-to-top method for producing cubogels requires the use of organic solvents (e.g., ethanol) which leave behind residual amounts of solvent. If some solvent remains in the cubogel when it is used as a drug delivery system, there may be some toxicity associated with that residual solvent.

(4) Cubogels tend to experience instability issues, such as: aggregation/phase separation and large variances/changes in the size of the particles that are used to create the cubogels. Instability will

affect the shelf-life of the product, as well as how effective the cubogel is at delivering a drug.

(5) Cubogels can easily be produced in a laboratory setting. However, attempts to produce cubogels on a commercial scale are generally difficult to achieve because of problems with reproducibility during production and the use of specialized equipment.

(6) There are a number of different drugs that do not properly incorporate into the cubosomes utilized in making cubogels, thereby limiting the amount of drug that can be loaded into the cubogel. Thus, the availability of drugs that can be delivered with cubogels is limited.

(7) Improperly selecting the surfactant or polymer that is used to create the cubogel may produce skin irritations. To prevent skin irritation from occurring when cubogels are made using different polymer and surfactant combinations, it is very important that the component of the cubogel is properly developed.

(8) The overall cost of producing cubogels will be significantly greater at commercial level compared to producing conventional drug delivery systems, because the lipids and surfactants used to produce cubogels are specialized lipids and surfactants, as well as the equipment used to make cubogels are specialized in nature.

(9)Challenges with Stabilization

Environmental conditions (e.g., temperature, moisture) affect the stability of cubogels requiring them to be stored under controlled environments.

(10)Limited Availability for Commercial Use

Due, in part, to insufficient clinical evidence, most cubogel formulations are still under study and are not available for commercial use.

(11)Regulatory Hurdles

There are currently no standardized regulations for nanocarrier systems, which can result in an extended time period for obtaining approval from the FDA before these products can be commercially available.

(12)Consistency of the Particle Size and Other Characteristics

Maintaining consistent particle size, drug loading, or drug release profiles is difficult and represents a challenge when scaling up the production process.

CONCLUSION

Cubogel technology is an advanced drug delivery system that combines cubosomes and hydrogels for controlled, targeted and sustained drug release. Its unique cubic structure allows it to carry hydrophilic, hydrophobic, and amphiphilic drugs, making it highly versatile in pharmaceutical applications. Cubogels improve drug stability, bioavailability, and residence time while reducing dosing frequency, leading to better therapeutic effectiveness and patient compliance. It show strong potential in topical, transdermal, ocular, oral and mucosal drug delivery, especially for anti-inflammatory, antifungal, antimicrobial, anticancer, and anti-arthritic treatments with fewer side effects. Cubogels are also useful in cosmetics and tissue engineering due to their biocompatibility and non-toxic nature. Although challenges such as large-scale production, stability and cost remain. Advancement in the field of science and technology such as nanotechnology may overcome these issues. As a result, cubogels emerged as a promising platform for future drug delivery systems.

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