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MICRONEEDLE LOADED WITH CUBOSOMES – A REVIEW

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ABSTRACT

This review examines the latest advancements and possible uses of cubosome-loaded microneedle-based drug delivery. For drug encapsulation and delivery, cubosomes nanostructured lipid carriers having a cubic liquid crystalline structure offer special benefits. A viable method for improving transdermal medication delivery and permitting controlled release and increased therapeutic efficacy is the incorporation of cubosomes into microneedles. Reviewing the characterization methods, formulation tactics, and recent advancements in this embryonic field, this paper emphasizes the potential of cubosomes-loaded microneedles as a flexible and efficient platform for targeted drug delivery in a various biomedical application.

Keywords: Cubosomes, Microneedles, Vaccines, Cancer, Nanotechnology

1. INTRODUCTION

The transdermal drug delivery system is one of the most promising delivery systems in recent times. Due to recent advancements, transdermal drug delivery can carry low, moderate, and high lipophilicity drugs. One of the advantages of topical delivery avoidance by degradation throughout the digestive system and avoiding discomfort after receiving an intramuscular or intravenous injection.
Despite the growing interest in transdermal drug delivery systems (TDDS), conventional methods have several limitations. These include low skin permeability, especially for hydrophilic and high-molecular-weight drugs, variability in drug absorption due to skin condition, and potential for skin irritation. The stratum corneum, the outermost layer of the skin, acts as a significant barrier, limiting the penetration of many therapeutic agents. Moreover, passive diffusion-based systems cannot often provide controlled or targeted drug release, making them less effective for drugs requiring precise pharmacokinetic profiles. These limitations have driven the development of advanced delivery technologies such as microneedles and nanocarrier systems.[1]

Device-assisted transdermal delivery, makes use of tools like microneedles (MNs) to distribute various kinds of molecules. The micron-sized needles of MN patches can penetrate the stratum corneum of the skin and approach the skin's deeper, immunologically active areas. A lot of research has been done on using MNs to administer vaccines, increasing their immunogenicity and stability.[2] The tiny needles (>1 mm in length) in microneedle arrays temporarily disrupt the SC, creating micro-channels that allow medication delivery. They have the potential to significantly transform the vaccine delivery industry because of their inexpensive production and distribution costs, and ease of use in administering vaccines. [3]

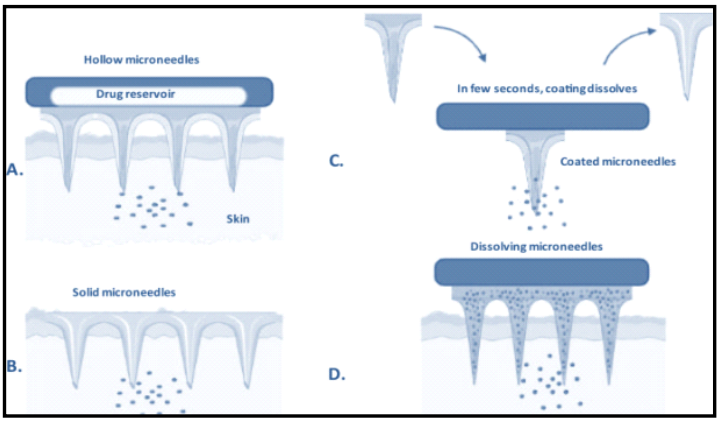

FIG 1: DIFFERENT TYPES OF MICRONEEDLES [16]

Nanotechnology research is one of the emerging areas, it has a major effect on the field of nanomedicine.[4] Cubosomes are unique nanovesicles of bicontinuous cubic arrangements that are made when liquid crystalline cubic aggregates are distributed in aqueous environments. They are manufactured by specific amphiphilic lipids that can self-assemble, such as phytotriol (PHYT) and glycerol monooleate (GMO) to create Cubosomes. Their structure is comparable to a honeycomb's. Cubosomes are becoming more and more popular as one of the novel drug delivery methods; recently, they have been used in cancer, dermatological, ophthalmic, and oral therapy. A hydrophobic medication can be introduced into the hydrophobic core of the micelle, and a hydrophilic bioactive molecule can be integrated into the micelle's outer hydrophilic shell.[5]

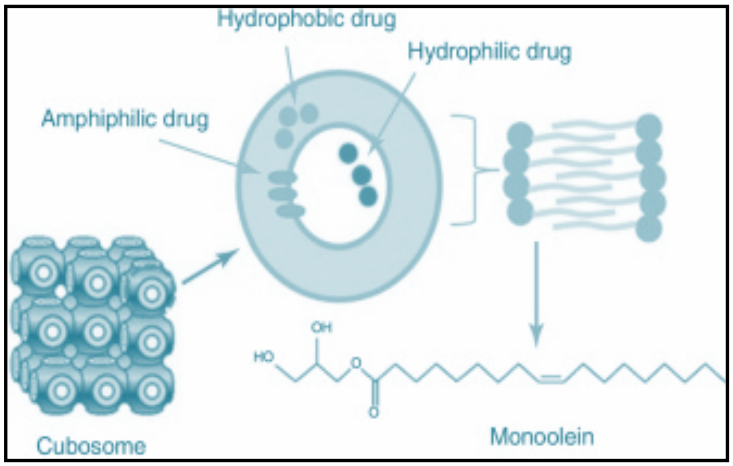

FIG 2: CUBOSOME STRUCTURE [17]

1.1 MICRONEEDLE AS A DRUG DELIVERY SYSTEM

The degree of medication delivery and skin permeability related to transdermal distribution facilitated by microneedles can ultimately be influenced by many parameters. It has been demonstrated that highly soluble, ionized species significantly boost medication delivery rates as compared to their neutral, low-solubility counterparts. The skin treated with microneedles has a low diffusional resistance, which may result in a shift in the transmission rate-limiting step from the skin to the transdermal device. The therapeutic value of this method is limited by the short lifetime of the punctures generated after microneedle administration. Sufficient optimization of multiple aspects of microneedle-assisted transdermal distribution is required to create drug delivery systems with a duration of use that is clinically meaningful. Because of the pores that the MN pretreatment creates, molecules that typically would be thought inadequate to permeate can be transported smoothly through the skin. These molecules encompass macromolecules and nanoparticulate systems. Nanometer-scale particles may penetrate the microchannel as a result of the pore opening's micrometre-scale diameter. [6]

TABLE 1: CLINICAL TRIALS INCORPORATING THE DELIVERY OF MACROMOLECULES BY MICRONEEDLES.

Clinical trial	Disease	Year of publication	References
Insulin delivery	Type 1 diabetes mellitus	2021	[7]
Injectable-Platelet Rich-Fibrin	Periodontoclasia gingiva	2021	[7]
Macro flux parathyroid hormone	Osteoporosis	2011	[7]
Adalimumab	Pain injection	2021	[7]
Pembrolizumab	Skin Cancer	2021	[8]
Tamoxifen	Breast Cancer	2021	[8]

1.2 Cubosomes as drug delivery system:

When there is an excess of water present, the cubic liquid crystals produced by isotropic and transparent Cubosomes remain physically stable. They can dissolve hydrophobic, hydrophilic, and amphiphilic substances and are non-toxic and biodegradable. Polymers can be added to cubosome colloidal dispersions to stabilize them. Because of their

small pore diameters, cubosomes aid in controlling drug release and are essential for maintaining the effectiveness and stability of physiologically active substances including proteins and vitamins. Compared to liposomes, hexosomes, various liquid crystalline drug delivery systems, cubosomes are found to have a lower viscosity. They can exist in water at any dilution and in additional cubic phases. Adhering to the rules of Higuchi-diffusion-controlled kinetics, the cubic shape of cubosomes can encapsulate the moiety and start releasing agents based on different molecular weights and polarity:[9]

$$Q = [D_m C_d (2A - Cd) t] ½$$

1.3 Combined Approach: Microneedles Loaded with Cubosomes:

A broad spectrum of medication molecules belonging to the hydrophilic, lipophilic, and amphiphilic classes can be contained by cubosomes. However, as numerous studies have documented, using cubosomes or any other type of nanocarrier system does not guarantee that therapeutic molecules will completely penetrate the skin barrier, which shall reduce the bioavailability of therapeutic molecules. A combination of two or more methods for enhancing transdermal permeation was proposed in a significant amount of literature to increase the permeation across the skin. The most well-known method for doing so is to combine a patch of microneedles (MNs) with nanocarriers. Administering MN is beneficial because it allows blood to get through the most formidable barrier of the skin, the stratum corneum without causing any pain at all. Microneedles can be composed of various materials, both biodegradable and non-biodegradable. [12]

TABLE 2: DRUG VEHICLES IN THE CUBIC PHASE HAVE BEEN DOCUMENTED RECENTLY

Therapeutic agent	Route of administration	Disease	References
Cyclosporin A	Topical	Immunosuppressive agent	[10]
Sulforhodamine B	Topical	Treatment of cancer	[10]
d-Aminolevulinic acid	Topical	Actinic keratoses	[10]
Flurbiprofen	Ophthalmic	Pain killer	[11]
Odorranalectin	Internasal	Viral infection	[11]
siRNA	Topical	study gene function	[11]
Doxorubicin	Topical	Cervical Cancer	[9]
Silver sulfadiazine	Topical	Treatment of infected burns.	[5]
Indomethacin	Oral	Anti-inflammatory	[5]
Erythromycin	Topical	Treatment and prevention of acne	[5]
Dapsone	Oral	Anti-inflammatory agent	[5]

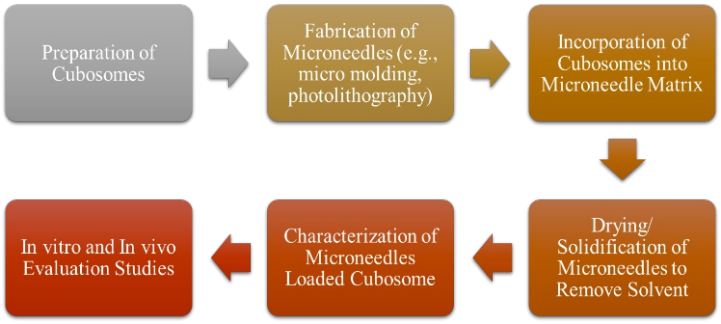

FIG 3: FLOW CHART FOR METHOD OF PREPARATION OF MICRONEEDLE LOADED WITH CUBOSOME

METHOD OF PREPARATION:

Step 1: Preparation of cubosomes:

Phytantriol and Monoolein are the two lipids that are used the most frequently in cubosomes production. An organic solvent is used to dissolve surfactants and lipids. The API is subsequently hydrated into this lipid combination using an aqueous phase. This solution is then added to Pluronic F127 by stirring the mixture. High-frequency ultrasound waves are typically employed for sonication of the hydrated lipid mixture. Lipid bilayers are broken down and cubosomes, which are nanostructured lipid particles with a cubic liquid crystalline structure, are formed as a result of this process. [2]

Step 2: Fabrication of Microneedle:

The intended use and the need for medication dispersion are taken into consideration while designing microneedles. Molds containing microneedle architectures are made via photolithography, laser cutting, micro had moulding and various other fabrication methods. A hydrogel or biocompatible polymer solution is made. Additives like plasticizers or crosslinking agents can be added to the polymer solution to improve its mechanical characteristics and

stability.[13]

Step 3: Incorporation of Cubosomes into Microneedle Matrix

The polymer solution is then combined with the cubosomes dispersion, which was made separately. To guarantee that the cubosomes are distributed evenly throughout the solution, this can be accomplished by combining the cubosomes dispersion directly with the polymer solution. The polymer solution loaded with cubosomes is poured into the microneedle molds. It is possible to guarantee that the molds are filled uniformly.[2]

Step 4: Solidification of Microneedles to Remove Solvent

Depending on the polymer employed, the filled molds are allowed to solidify via air drying, solvent evaporation, or crosslinking. By keeping the cubosomes inside the microneedle matrix, this process guarantees the creation of solid microneedles with the appropriate shape and size. The microneedles are carefully removed from the molds when they're completely set. The drug loading, stability, or insertion qualities may be further improved by performing additional processing processes such as surface modification or coating.[2]

Step 5: Characterization:

Some of the characterization tests done are:

1. Shape and Surface Morphology:

TEM (Transmission electron microscopy) has been used to evaluate the surface morphology and form. To see the size, shape, and surface morphology of microneedles, methods like optical or scanning electron microscopy (SEM) are used in examinations. The consistency and integrity of the microneedle formations are aided by this.[14]

2. Total Drug Content (% Assay):

Approximately 1 ml of the dispersion was taken and dissolved in ACN (10ml) to calculate the total amount of medication present in the produced formulation. After that, the chemically produced samples were examined at an appropriate wavelength using a UV-visible spectrophotometer. The equation to calculate the percentage of total drug content: [14]

$$\text{Total drug content \%} = \frac{\text{The amount of total drug estimated}}{\text{Total drug added}} \times 100$$

3. Axial Fracture Force:

The axial needle fracture force has been measured using the Brookfield CT3 texture analyzer. To do this, MN arrays were placed on the mobile probe of the texture analyzer using double-sided sticky tape. This action is carried out cautiously in a way that the mobile probe's axis and the MN's axis line up. Subsequently, an automated probe is used to press the MNs on a flat, stiff steel surface. Using Texture Pro CT data collecting software, the needle strength graph was created during testing. Axial fracture force is calculated via the equation and the peak load that was discovered from the Texture Pro CT-generated graph.[13]

$$F = mg$$

where: m = mass applied for the breaking of the microneedle. g = gravitational force.[14]

4. Zeta Potential Measurement:

The Nano-ZS zeta sizer is used to analyze the sample's zeta potential. To do this, the sample was dispersed and diluted up to ten times, using distilled water that had been previously filtered. The dispersion was then measured for zeta potential using disposable folded capillary cells.[14]

5. Entrapment efficiency (%):

The number of active substances, successfully enclosed within lipid-based nanoparticles is

measured by the entrapment efficiency of microneedle-infused cubosomes, which is essential for maximizing the accuracy of medication delivery. Targeted transdermal drug delivery systems are more effective and have more therapeutic potential when this efficiency is increased by formulation improvement.[3]

6. FTIR study:

Fourier-transform infrared spectroscopy can be used to examine the drug's compatibility with other components. Every sample was pressed into a disc with potassium bromide present. A Shimadzu 435 U-O4 IR spectrometer can be used to scan the compressed disks from 4000 to 400 cm−1.[15]

7. Headspace Gas Chromatography (HS-GC) Examination for Solvent Residue:

An essential step in guaranteeing product safety and regulatory compliance is the evaluation of solvent residues in microneedle-infused cubosomes using Headspace Gas Chromatography (HS-GC). The vapor phase above the sample is analyzed by HS-GC, which provides precise quantification of volatile organic components, including leftover solvents. This technique makes it possible to precisely determine the solvent levels, which aids in quality control and validates the formulation's appropriateness for use in pharmaceutical applications.[14]

8. Transmission electron microscopy:

The nanostructure and morphology of microneedle-infused cubosomes are revealed by Transmission Electron Microscopy (TEM) analysis, which clarifies their applicability for drug delivery applications. The visual data obtained from TEM analysis is vital for refining formulation parameters and improving medicinal efficacy.[15]

9. Scanning Electron Microscopy:

SEM was used to analyze the needle shape and size, and other physical properties of the microneedle patch morphology. The samples were treated with a gold solution and functioning at 10 kV for 15s under a low vacuum for enhanced contrast.[15]

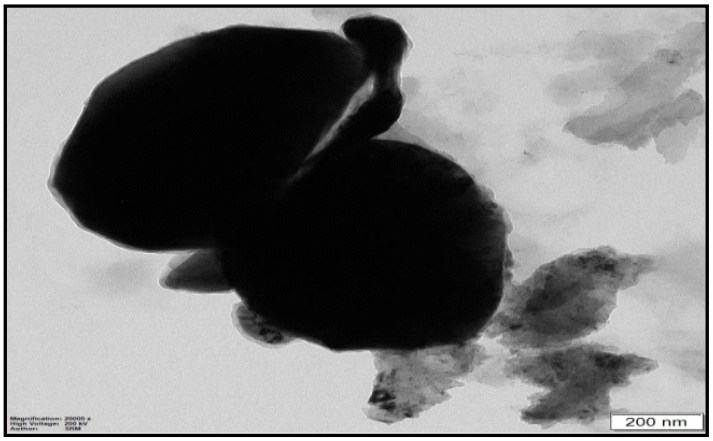

FIG 4: IMAGE OF MICRONEEDLE-INFUSED CUBOSOME UNDER TEM [15]

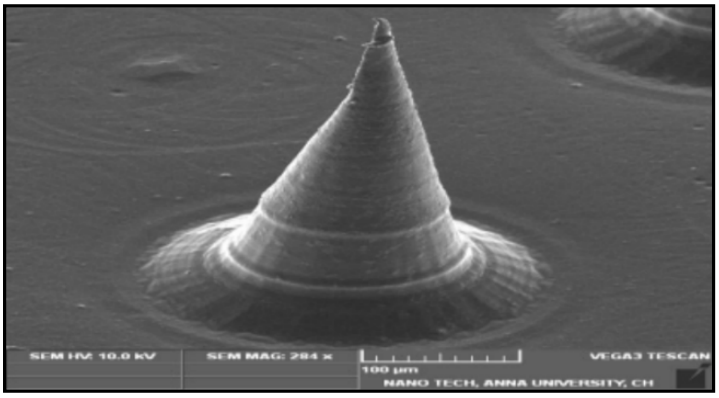

FIG 5: IMAGE OF MICRONEEDLE-INFUSED CUBOSOME UNDER SEM [15]

Step 6: In vitro Evaluation Studies:

1. In vitro drug release:

Studies on the controlled release kinetics of microneedle-infused cubosomes in vitro shed the spotlight on their potential for applications associated with targeted and long-lasting drug administration. Through evaluation of the release profile of encapsulated medicines in physiologically mimicked environments, formulation development for improved therapeutic efficacy is guided by these experiments.[2]

2. In vitro penetration studies:

Double-sided adhesives were used to fix the MNs on the movable probe of the Brookfield CT3 texture analyzer to test the skin penetrability. The axis of the MN was parallelly positioned to the mobile probe axis. The probe

was programmed to press the MNs under strain across the whole thickness of the pig ear skin on a soft sponge pad to replicate in situ mechanical support. The moving probe was set up to insert at a 20 mm/s rate. Trypan blue dye was administered to the skin area where MN was applied, and the treatment lasted for 5 minutes. The excess dye had been wiped using tissue paper. Additionally, a digital camera was used to capture images of the discolored pores.[14]

3. In Vitro Drug Release Study:

Microneedle-infused cubosomes in vitro drug release studies evaluate the controlled release kinetics of encapsulated pharmaceuticals and offer important new information about their potential for transdermal delivery applications. To study the release profile over time and inform the adjustment of formulations for targeted and sustained medication release, these tests replicate physiological conditions.[14]

4. In Vitro Fluorescence Microscopy Study:

Studies using microneedle-infused cubosomes and in vitro fluorescence microscopy show how the cubosomes distribute and penetrate the skin's layers, providing information about their potential for transdermal drug delivery. Fluorescently labeled cubosomes are used in these investigations to follow the mobility and localization of the particles, which helps optimize formulations for the effective and focused administration of medicinal medicines.[14]

Applications:

TABLE 3: MICRONEEDLES LOADED CUBOSOMES THAT ARE RESEARCHED ON

SR NO.	API	TREATMENT	IN- VIVO MODEL USED	YEAR OF PUBLICATION	REFERENCE
1	Rapamycin	Psoriasis treatment	-	2020	[2]
2	Vaccine	-	Mice-C57BL/6,	2013	[3]
3	Febuxostat	Hyperuricemia	Sprague–Dawley rats	2022	[14]
4	ß-Sitosterol	Alopecia	Wistar rats	2023	[15]

Challenges and Limitations:

1. Compliance and User Acceptance:

The acceptance of microneedle-based delivery systems can be influenced by characteristics like treatment regimen compliance, patient acceptance, and convenience of use. Achieving a successful adoption requires educating both patients and medical professionals about the advantages and appropriate use of these devices.

2. Difficulty with Microneedle:

When fabricating MNs, polymers need to be carefully chosen. The regulatory authorities place the utmost importance on the availability of polymer safety data and the capacity for scaled-up manufacturing, given the rapid advancement of the MN area towards clinical trials. Another important selling point for MN technology that hasn't been fully realized is the therapeutic indications that long-acting MN devices can treat.[12]

3. Limiting drug dose:

The quantity of medication that microneedles can administer is restricted due to their small size. Consequently, their use is challenging when a high dosage or continuous drug release is necessary.[13]

4. High viscosity of Cubosomes:

The primary hurdle is getting beyond the high viscosity, which occasionally makes large-scale production difficult, and the poor water-soluble medicine trapping since cubosomes include a significant amount of water.[9]

5. Regulatory Acceptance:

Approval from regulatory bodies is necessary before introducing novel drug delivery methods, such as cubosomes-infused microneedles, into clinical practice. Adhering to safety, effectiveness, and quality control regulations can be a laborious and cost-prohibitive procedure.[7]

6. Packaging of MN:

Microneedles must be packaged airtight to maintain their stability and effectiveness over time. This keeps the needles safe from air and moisture and guarantees long-term storage integrity. Preserving an airtight seal reduces the possibility of sensitive drug formulations oxidizing or degrading while also protecting the sterile environment necessary for safe use. Reliability and product shelf life are increased by efficient airtight packing techniques, which are essential for preserving the caliber of microneedle-based treatments. [14]

Future Perspectives:

Significant advances in several study fields, most notably medicine, were prompted by the creation of nanocarriers. Because nanocarriers can target specific cells, research on them has shown to boost the effectiveness of medicinal therapies. Cubosomes are one of the nanocarriers that have garnered the most interest recently out of all those that have been created and characterized. [14]

Novel vaccination approaches are made possible by the creation of cubosome-infused microneedles. Compared to standard injection techniques, transdermal vaccination delivery with microneedles has several benefits, such as enhanced patient acceptance, easier administration, and the possibility of self-administration. Cubosomes have the potential to function as efficient vectors for vaccination antigens, augmenting their immunogenicity and stability. This could potentially support global vaccination efforts and disease prevention campaigns by facilitating the development of needle-free immunization programs, especially in areas with limited access to healthcare infrastructure. [3]

Microneedles-infused cubosomes may also be applied to treat cancer. First off, a variety of therapy approaches are made possible by cubosomes' capacity to encapsulate a broad spectrum of medications, such as immunomodulators, chemotherapeutic medicines, and targeted therapies. [4]. Additionally, cancer patients benefit from the minimally invasive aspect of microneedle delivery. When it comes to administering drugs, microneedles provide a more comfortable and convenient alternative to conventional intravenous or oral routes. This could raise the overall quality of life during cancer therapy and increase patient compliance with treatment plans. Sustained investigation and advancement in this domain possess the capability to revolutionize the field of cancer treatment, providing patients with renewed optimism and augmenting their chances of survival.

Conclusion:

To sum up, cubosomes-infused microneedles represent the cutting edge of novel drug delivery technologies, providing effective and focused treatments for a range of medical conditions. The minimally invasive administration of microneedles combined with the versatility of cubosomes to encapsulate a wide range of medications holds great promise. These innovative delivery methods provide new opportunities to enhance treatment effectiveness and patient outcomes by permitting the targeted and continuous release of therapeutic medicines to tumor locations with the least amount of systemic side effects possible.

To fully realize the promise of this strategy, more research and development in the areas of cubosomes formulations and microneedle technology will be necessary. Further advances in drug loading capacity, release kinetics, and biocompatibility will improve cubosomes-infused microneedles' efficacy and safety. These innovative platforms have the potential to have a big influence on health care by giving patients more effective, efficient, and tailored treatment options in the future with continued innovation and multidisciplinary collaboration.

Data Access Statement:

This publication is supported by multiple datasets which are openly available at locations cited in the 'References' section of this paper.

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Declaration of patient consent:

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Conflicts of interest:

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation:

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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