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A REVIW ON CUBOSOMES: A NOVEL METHOD FOR DRUG DELIVERY

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ABSTRACT:

Cubosomes are tiny, stable particles with a unique structure that looks like a honeycomb. These particles are made from special fats, called amphiphilic lipids, which are stabilized by a polymer. They have two continuous water-filled regions separated by a lipid layer. Cubosomes are created when a certain ratio of water and surfactant (detergent-like molecules) come together to form self-assembled particles. These particles are useful in delivering drugs because they can hold different types of substances, including both water-loving and fat-loving compounds. They can be applied in many ways, like through injection, by mouth, or on the skin, to treat various body areas. Cubosomes are stable, biocompatible (safe for the body), and can release drugs slowly over time, which makes them great for targeted treatments. They also have other uses, like in creating artificial cells or as biosensors. The process of making cubosomes is simple, and compared to liposomes (another type of particle), cubosomes are stronger and more resistant to breaking. This article explores the different methods used to create cubosomes.

Keyword: Cubosomes, Honey combed structures, Drug delivery systems, Preparation Method of Cubosomes

INTRODUCTION:

Larsson was the first to create the word "cubosomes," which are similar to liposomes in structure.[1] Cubosomes are very tiny particles that are made up of a special structure called a bicontinuous cubic liquid crystal. These particles are formed naturally by assembling smaller components. The structure has water-loving (hydrophilic) parts and water-hating (hydrophobic) parts that don't mix with each other. They are created by breaking down larger materials using high-energy equipment. These cubosomes are stable and can hold certain types of drugs that don't dissolve well in water. They have become popular because they help improve the stability of products, keep them on the skin for a longer time, and are good at carrying hydrophobic (water-hating) drugs.[2] They have a structure that looks like a honeycomb, with many tiny holes or spaces, similar to a sponge. These structures are called "cavernous" because they have lots of small, open areas inside. The size of each structure is very small—between 100 and 500 nanometers—which means they are thousands of times smaller than the width of a human hair.[3] Cubosomes are mainly made from special types of fats called amphiphilic lipids, especially glycerol monooleate (GMO) and phytantriol (PHYT). These lipids have a unique ability to mix with water and arrange themselves into stable, cube-like structures on their own. When placed in water, they naturally organize into these tiny, structured particles called cubosomes without needing much help, thanks to their chemical properties.[4] Cubosomes and the original cubic phase they come from have the same internal structure. However, cubosomes are much easier to handle because they are in a liquid-like form and have much lower thickness or stickiness (called viscosity) compared to the solid or gel-like bulk cubic phase. This makes cubosome dispersions more suitable for various applications.[5] Cubosomes are better than many other drug delivery systems because of their special structure. They have a 3D design made up of water-filled channels and layers of fat-like materials. This structure helps them carry different types of drugs—both natural and man-made, whether they dissolve in water or not. They can also carry large molecules like proteins, DNA, mRNA, and imaging agents. The complex structure of cubosomes protects the drugs inside from breaking down and allows them to be released slowly over time, which is useful for long-lasting effects in the body.[6]

CUBOSOME CHARACTERISTICS[7]

- ✓ Cubosome dispersions are not very thick – they have low viscosity.
- ✓ Cubosomes are tiny, special particles with a unique internal structure.
- ✓ They are very interesting because of their unusual properties.
- ✓ They look clear and stay stable in water, thanks to their structure.
- ✓ Their tiny pores make them great for slowly releasing drugs or other substances.
- ✓ They can hold and carry many types of substances – water-loving, oil-loving, and both.
- ✓ They are also biodegradable, meaning they break down safely in the body.

STRUCTURE OF CUBOSOMES:

Cubosomes have a special structure that looks like a honeycomb. This structure is made up of tiny water channels separated by layers of fat molecules. Because of this design, cubosomes feel thick and gel-like, kind of like a solid, even though they're made mostly of liquid.[8] They look like tiny dots, and each dot shows where there is a pore.

Cubosomes are tiny particles made from special liquid crystal materials. Inside them, there are two water-filled channels, and between these channels is a large surface area where they meet. You can think of cubosomes like small, organized sponges with a lot of space inside. Because of this unique structure, they are called nanoparticles of liquid crystal phases and are useful for carrying and delivering drugs or other substances in the body.[9]

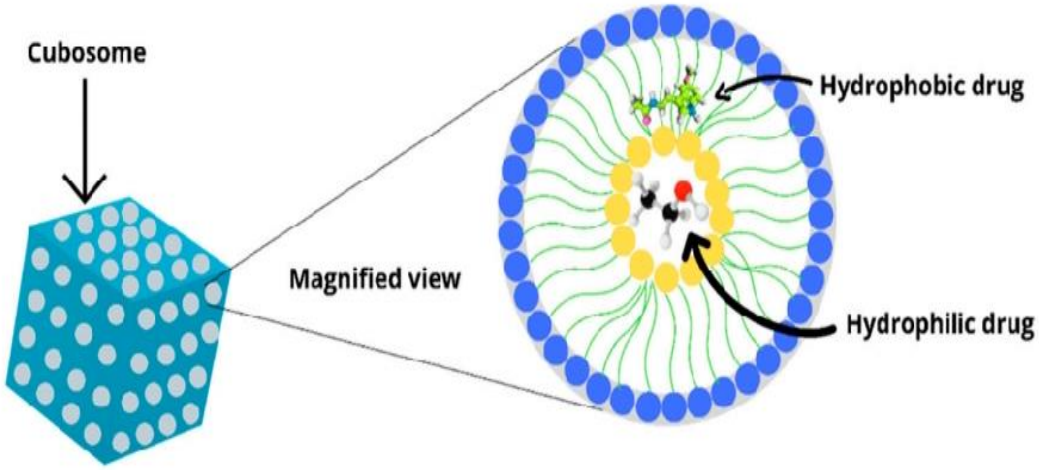

Fig 1. Structure of cubosomes

ADVANTAGES:

i. A very simple procedure can be used to make cubosomes.
ii. They can contain compounds that are amphiphilic, hydrophilic, and hydrophobic.
iii. Cubosomes possess the qualities of biocompatibility and bioadhesivity.
iv. When compared to non-lipid carriers or traditional lipids, cubosomes are superior solubilizers.
v. Cubosomes can be used to treat a variety of promising drugs with high molecular sizes, poor absorption, and poor water solubility.
vi. Low cost of raw materials.
vii. Improves efficacy and decreases risk of drug misuse and misdirection.
viii. The cuboidal system enhances the bioavailability range 20 100 times for water soluble peptides.
ix. Cubosomes increases convenience and compliance.
x. High drug payloads can be achieved due to high internal surface area and cubic crystalline structures.
xi. Cubosomes particles as oil-in- water emulsion stabilizers and pollutants absorbents used in cosmetics.
xii. The fractured and dispersed cubic phase of cubosomes leads to the formation of particulate dispersions that are colloidally and/or thermodynamically stable for longer time.
xiii. Cubosomes serve as an excellent vehicle to protect the sensitive drugs such as proteins and peptides from enzymatic degradation and in-vivo degradation.[2]

DISADVANTAGES:

i. Challenging in large scale production due to the high viscosity of cubic phase.
ii. Because of the significant amount of water in their structure, they have a low entrapment efficiency for pharmacological molecules that are soluble in water.[1]
iii. Large scale production is difficult for sometimes because of high viscosity.[10]

COMPONENTS OF CUBOSOMES:

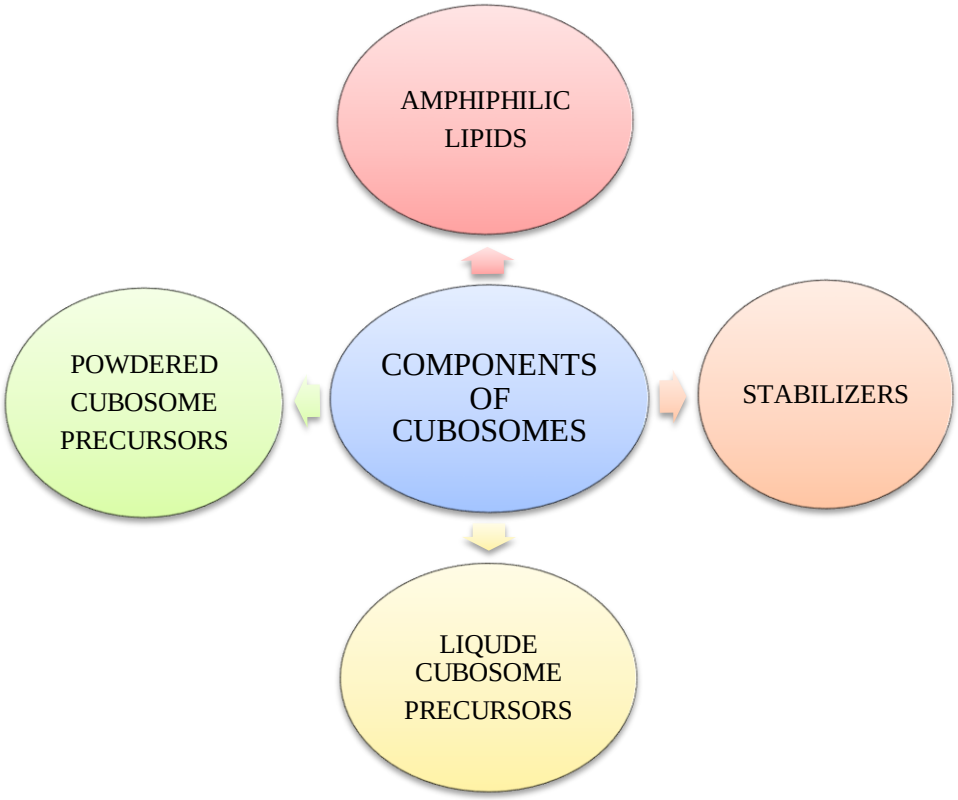

Fig 2. Components Of Cubosomes

a) Amphiphilic lipids:

The most common lipids used to make cubosomes are Glyceryl Monooleate (GMO) and Phytantriol (PHYT). GMO is made mostly of monooleate and belongs to a group of lipids that can form liquid crystals when mixed with water and heat. It's biocompatible, biodegradable, and FDA-approved for use in food. GMO has both water-loving and oil-loving parts, which helps form cubic phases.

PHYT is another lipid with a phytanyl chain, commonly used in cosmetics, and it provides better structural stability than GMO. Both GMO and PHYT show similar phase changes with increased water and temperature, forming cubic and hexagonal phases. PHYT dispersions are more stable, especially with added hydrophilic substances. The purity of these lipids also affects how they behave during phase transitions.[10]

b) Stabilizers:

Surfactants are used to keep cubosomes stable, and the most common one is Poloxamer 407 (P407). It has parts that can mix with both water and oil. In cubosomes, some parts of P407 go inside the structure, and some stay on the surface, helping to stabilize it. Usually, it's used in 2.5–10% concentration, but can go up to 20% depending on the mixture. Studies showed that too much P407 can make smaller particles, but not always the desired cubic structure—sometimes it makes vesicles instead. In PHYT-based cubosomes, P407 stays on the surface, while in GMO-based cubosomes, it mixes into the structure.

Other stabilizers like propylene glycol (PG), PEG400, and MPD were tested with PHYT. MPD made a sponge-like phase, while PG and PEG400 formed cubic or mixed structures. This difference is because PHYT is more hydrophobic and rigid than GMO.

The structure of cubosomes with β-casein and P407 was also studied to understand their internal behavior.[2]

c) Liquid Cubosome Precursors:

Making cubosomes using high shear methods is difficult and costly. A gentler and easier method is hydrotrope dilution, where monoolein is dissolved in ethanol (a hydrotrope) to stop crystal formation. When water is added, cubosomes form on their own through a process like crystallization. This method is cheaper, easier to scale up, and suitable for sensitive ingredients like proteins.[11]

d) Powdered Cubosome Precursors:

Powdered cubosome precursors are better than liquid ones because they are made from dried surfactants coated with a polymer. When mixed with water, they form tiny cubosomes around 600 nm in size. Spray drying is used to make these powders, especially with sticky lipids that are hard to handle. In this process, a spray nozzle creates droplets that dry quickly with hot air, forming solid particles with a polymer coating. This also allows the drug to be loaded before drying. Choosing the right polymer is key, as it affects how the cubosomes behave in water. A 3:1 mix of starch and monoolein works well, giving good drug loading and small particle size.[12]

PREPARATION METHODS OF CUBOSOMES:

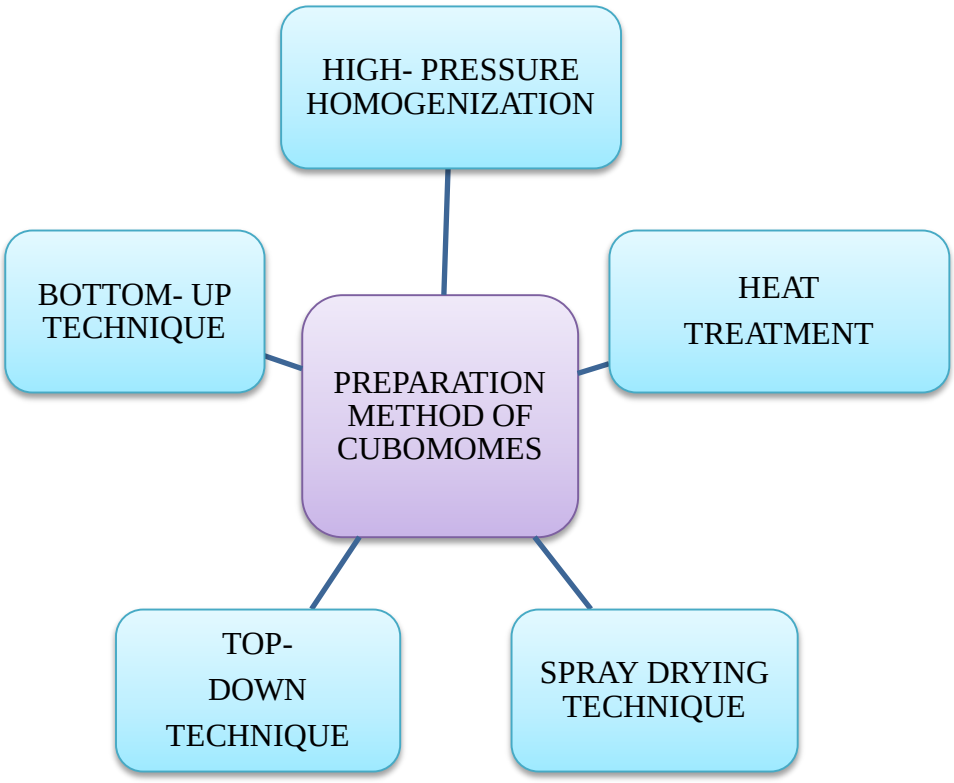

Fig 3. Preparation Methods of Cubosomes

Methd	Advantages	Disadvantages
High-pressure homogenization	**It gives smaller, more evenly sized particles.[20]**	**There is a risk of damage to lipids, drugs, and protein-based molecules due to heat.[23]**
Bottom- Up Technique	**It uses less energy and is easy to carry out.[4]**	**Hydrotropes can cause allergic reactions if taken by mouth.[22]**
Spray-drying Technique	**This method is cheap and easy to use for making larger amounts.[21]**	**The problem with the spray drying method is that a cube-like structure forms when the lipids mix with water. [21]**
Top- Down Technique	**It gives even particle sizes and is a well-known, reliable method.[4]**	**Using high energy makes it hard to add heat-sensitive things like peptides and proteins.[22]**

Table 1. Advantages and disadvantages of Cubosomes Preparation techniques.

1. **High-Pressure Homogenization**

This is the most suitable method for making cubosomes. It helps create very stable cubosomes that can handle high-pressure processes and stay good for a long time. The method has three main steps:

Step 1 – Gel Preparation: In this step, lipids (fats) and special surfactants (ingredients that help mix things) are dissolved in an organic solvent. They are mixed well to make a smooth and even mixture. Then, a rotary evaporator (a device that removes liquid by turning it into vapor) is used to take out the solvent. This leaves behind a thick gel.

Step 2 – Shearing: Next, this gel is mixed with water or another liquid. This breaks it down into tiny particles, forming a liquid mixture. This step is very important because it prepares the mixture for the next stage.

Step 3 – Homogenization (not written, but implied): Finally, this mixture goes through a high-pressure machine to make cubosomes—tiny particles that can carry medicines.[13]

High-Pressure Homogenization: This method is suitable for large sample volumes (around 30 ml) but not for small ones. Since it is sensitive to temperature, the temperature is chosen based on the type of lipid used. In this process, the prepared mixture is passed through a high-pressure homogenizer to mix it thoroughly. However, only one sample can be processed at a time using this method.[9]

2. Heat Treatment

Heat treatment is a helpful step in making cubosomes. While it's not the only process involved, it plays an important role by helping disorganized vesicles turn into well-structured cubic-shaped particles.[14]

Cubosomes can be made using different mixing methods like sonication (using sound waves), spray drying, high-pressure homogenization, and spontaneous emulsification. These methods help break down and mix the ingredients to form cubosomes.[15]

Cubosomes have many useful features. They have a special structure with multiple compartments and can carry a high amount of drug. They are easy to make and use safe, biodegradable lipids like glycerol monooleate. Cubosomes can carry different types of substances—those that mix with water, those that don't, and those that do both. This makes them great for targeted and controlled drug delivery.[16]

3. Spray Drying

Another way to make cubosomes is by using a method called spray drying. In this process, a mixture of tiny liquid or solid droplets is sprayed through a special nozzle into hot air. The heat quickly removes the water, leaving behind dry powder particles. These particles contain the cubosome material, which is surrounded by a protective layer made from a polymer (a kind of plastic-like substance). This method is easy to scale up and is already used in everyday products like food and detergents. It also allows you to add active ingredients into the cubosomes before drying. The type of polymer used affects the surface of the cubosomes, and changing the liquid mixture can change the final powder's properties. For example, to make starch-coated cubosome powder, a mixture of monoolein and starch in water is sprayed and dried. After drying, the final powder contains about 72% starch, 24% monoolein, and just 4% water.[17] as shown in Figure 4.

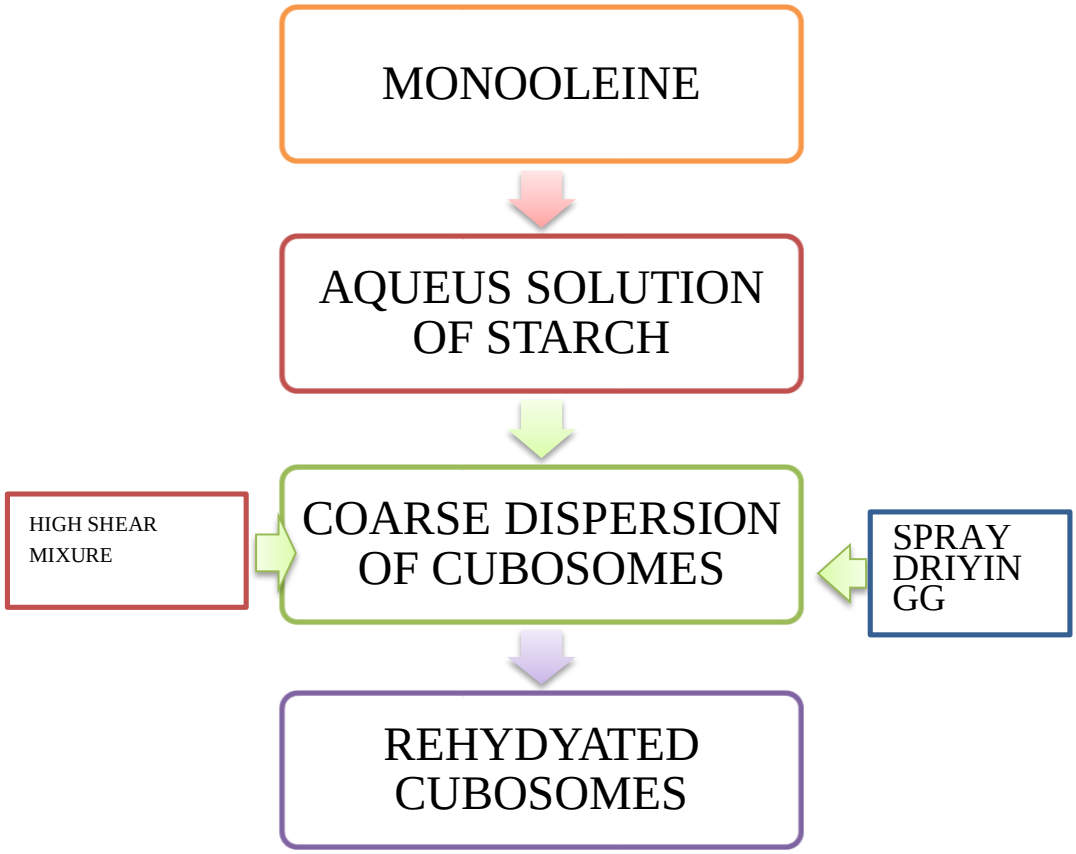

Fig 4. Preparation of Dry Powder Cubosomes

4. Top-Down Technique

The top-down method to make cubosomes, first introduced by Ljusberg-Wahren in 1996, is a commonly used two-step process. First, lipids are mixed with a stabilizer to form a thick, gel-like cubic phase. Then, this bulk mixture is broken down into tiny nanoparticles by using high-energy methods like sonication, high-pressure homogenization, or shearing in water. This creates cubosomes, which are tiny, vesicle-like structures that may also coexist with other types of nanoparticles. The stability and size of the cubosomes depend on factors like stabilizer concentration and temperature, and shearing usually gives more stable particles than sonication.[18]

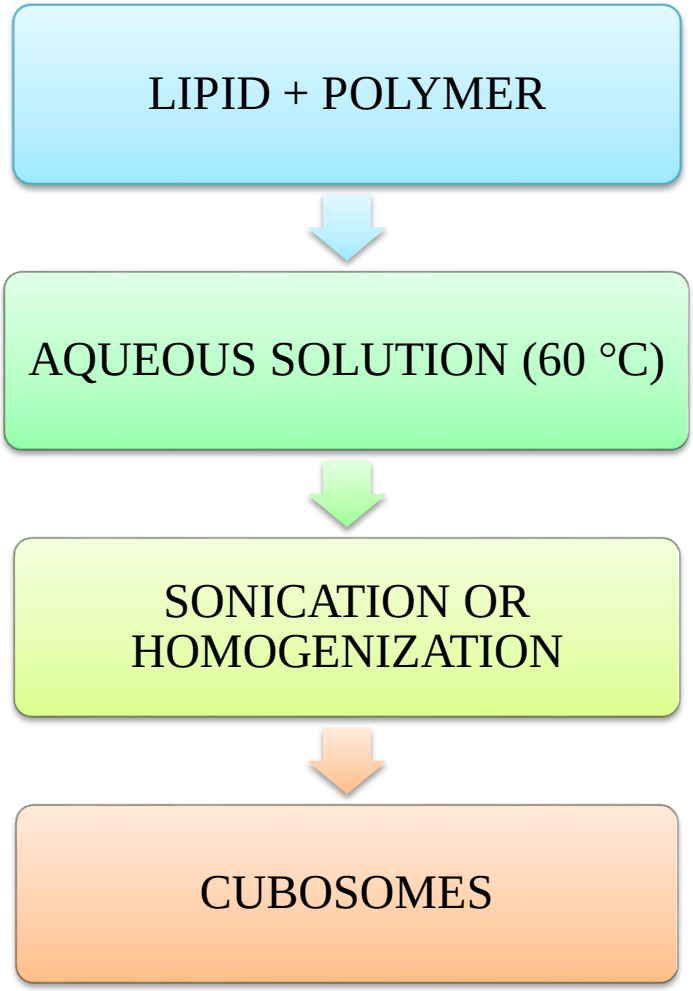

Fig 5. Top- down Technique For Cubosomes

5. **Bottom- Up Technique**

This technique is a simple and efficient way to prepare cubosomes, which are tiny, stable particles used in drug delivery. It uses very little energy and starts with basic ingredients called precursors. When mixed with water and a special substance called a hydrotrope, the cubosomes form on their own through a process called spontaneous emulsification. This method is known as the dilution-based approach and helps create small particles that can later cluster into larger ones. The cubosomes made this way are stable and last a long time.[19]

- **BOTTOM- UP TECHNIQUE**

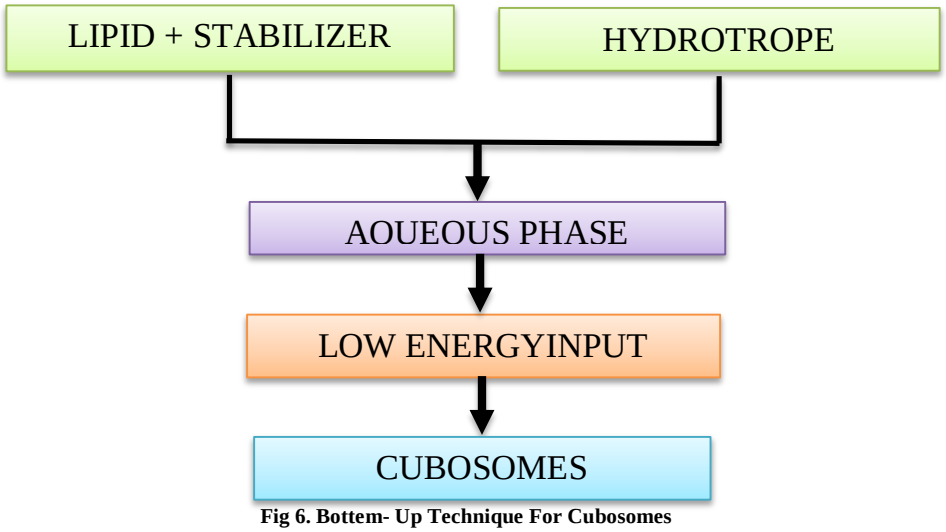

Fig 6. Bottem- Up Technique For Cubosomes

IMPORTED STUDY[23]:

Sr No.	Disease	Marketed formulations
	Skin cancer	**5-Fluorouracil 0.5% (Carac® cream, Valeant Pharma North)**
	Acne vulgaris	**Adapalene 0.1% and benzoyl peroxide 2.5% (EPIDUO® gel, Galderma Laboratories), adapalene 0.1% (Differin® gel, Galderma Laboratories)**
	Fungal infections	**Miconazole nitrate (Daktarin® T cream, Johnson and Johnson), and bifonazole (Canespor® cream, Kern Pharma S.L.)**
	Psoriasis	**Tacrolimus 0.1% (Protopic ointment Astellas®), calcipotriol, and betamethasone (Dovobet® ointment, LEO Pharma)**
	Glaucoma	**Timolol maleate (Timoptic-XE, Merck & Co.) and Nyogel (Novartis AG)**
	Fungal keratitis	**Natamycin 5% (Natacyn®, Alcon)**

Table 2. Marketed formulation of Cubosomes

SIGNIFICANCE:

A. Enhanced Stability and Controlled Release

- Post-2021 studies emphasize the ability of cubosomes to encapsulate and release drugs in a controlled and sustained manner, which is crucial for treating chronic diseases.
- Their internal cubic structure allows for gradual diffusion of the drug, reducing dosing frequency and improving patient compliance.[24]

B. Versatile Drug Loading Capacity

- Recent research confirms cubosomes can effectively carry hydrophilic, lipophilic, and amphiphilic drugs, making them highly versatile.
- They're particularly effective for poorly water-soluble drugs, solving a key formulation challenge in pharma.[25]

C. Biocompatibility and Targeted Delivery

- Cubosomes, made from GRAS (Generally Recognized As Safe) lipids, are non-toxic and biocompatible.
- Post-2021 studies have explored surface functionalization (e.g., with ligands, antibodies) to enhance targeted delivery, especially for tumor and brain tissues.

D. Emerging Applications

- Cancer therapy: Cubosomes have been used to co-deliver chemotherapeutic drugs and genetic material (like siRNA), offering a multifunctional platform for combination therapy.
- Ocular and transdermal delivery: Studies show improved penetration and retention time, suggesting cubosomes are ideal for these routes.
- Vaccines and proteins: Post-2021 work highlights cubosomes as promising carriers for antigens, peptides, and proteins, aiding in mucosal and systemic immunization.

E. Scalability and Industrial Relevance

- Advances in top-down and bottom-up production techniques (like microfluidics and high-pressure homogenization) have improved the scalability of cubosome production.
- Their long-term stability makes them suitable for commercial pharmaceutical formulations.

CONCLUSION:

Cubosomes can carry many types of drugs, including those that dissolve in water (hydrophilic) and those that don't (hydrophobic). They can also deliver drugs to special areas in the body like the brain and the central nervous system. Cubosomes are useful for carrying different medicines, vaccines, proteins, and ingredients used in cosmetics.

Even though they are very small, they can hold a large amount of drug. They are already being used for eye treatments, oral medicines, injections, skin treatments, cancer therapy (like melanoma), and diabetes. They are also helpful in personal care products because their inner structure is similar to the structure of human body tissues, making them safe for skin and other tissues.

Thanks to their ability to target specific parts of the body, cubosomes have a lot of potential. This technology is still quite new, and there is a lot of opportunity for more research to create new and better products.

This can help grow the pharmaceutical industry. Making cubosomes is simple — just mixing lipids and water — and the process is flexible for different products. Because lipids are naturally compatible with our body tissues, cubosomes are very suitable for treatments. However, more research is needed to fully understand how safe cubosomes are and how they work in delivering drugs in the body.

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