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A Review of Nanocochleates for Enhancing Antifungal Drug Oral Absorption Through a Phospolipid-Based Drug Delivery Method

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Abstract : Genes, vaccinations, and medications can all be delivered orally and systemically using nanocochleate, a lipid-based delivery system. It works especially well for drugs with low oral bioavailability and hydrophobic macromolecules. As excipients, phospholipids are essential for improving permeability and solubility and getting around the drawbacks of conventional drug delivery techniques. This strategy may enhance the oral administration of macromolecules and antifungal medications.

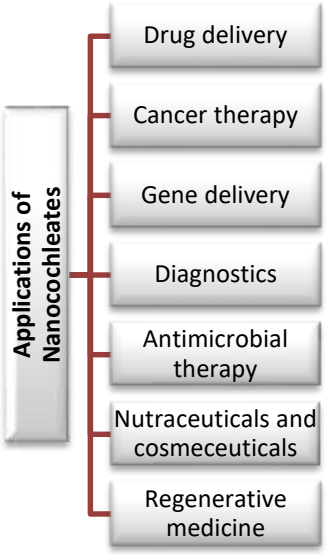
IndexTerms **- Cochleate Nanocochleates, Hydrogel method, Trapping method, Anti-Fungal Drug, liposomes, Nano-Carrier System; Novel Formulations; Oral Delivery; Phospholipids.**

I. INTRODUCTION

Drugs are encapsulated in a multilayered lipid crystal matrix by the nanocochleate drug delivery vehicle, guaranteeing their safe and efficient distribution. Large, continuous, spirally twisted lipid bilayer sheets without an aqueous phase inside make up the crucial particles known as cochleates. Because nanocochleates are more stable than liposomes, they hold promise as a delivery method. It also offers a higher encapsulation efficiency due to its rod-like structure. The bilayered structure allows for more controlled medication storage. Because they require particular storage conditions, they have drawbacks despite their many benefits. (1) Stable phospholipid-cation precipitates, primarily made up of calcium and phosphatidylserine, are essential parts of nanocochleate delivery systems. The solid layers and components that comprise the overall development of the nanocochleate are contained within its core and stay intact, despite the outer layers being subjected to severe circumstances or enzymes. Both hydrophobic and hydrophilic drugs can be encapsulated in nanocholeates due to their surfaces' dual hydrophobic and hydrophilic properties.(2) Encochleation nanotechnology has the potential to improve a wide range of product attributes, including as ease of manufacturing, formulation quality, extended drug release, processing, shelf-life stability, and biodegradability for systemic administration. Physiologically significant substances are shielded by nanocochleate from gastrointestinal and environmental enzyme breakdown. Cochleates preserve phospholipid bilayer structures. Because of their exceptional flexibility, these solid particles may easily extract the bridging counter ions from the interbilayer gaps and transform into liposomes. (3)

Discovery of Nanocochleates

Dr. D. Papahadjoupoulos and associates made the discovery of cochleats in 1975, and in the 1980s and 1990s, they were employed to deliver peptides and antigens for vaccination. Sheet aggregates and cochleates covered by the trap method or large needles similar to the structure by the dialysis method are the results of the non-uniform cochleate structure documented in the literature. In 1999, nanocochleates were developed to create particles that were smaller but more uniform. Cochleates with tiny particle sizes between 104 and 113.5 nm have been demonstrated to develop using a binary phase system, such as two fake hydrogels.



Drug delivery

Drug delivery is one of the main applications for nanocochleates. These nanostructures can encapsulate a variety of drugs, such as small molecules, peptides, proteins, and nucleic acids. Better therapeutic results are achieved because nanocochleates prevent the encapsulated drug from degrading, increase its stability, and offer controlled release.

Cancer therapy

By encapsulating chemotherapeutic chemicals and directing them toward tumor cells, nanocochleates have demonstrated promise in cancer treatment. Chemotherapy's effectiveness can be increased while systemic toxicity and adverse effects are reduced with this focused delivery method.

Vaccine delivery

The use of nanocochleates to deliver adjuvants and antigens in vaccines has been investigated. They are intriguing candidates for vaccine development because they can increase vaccine stability, encourage antigen absorption by antigen-presenting cells, and elicit strong immune responses.

Gene delivery

Nanocochleates can be used to deliver nucleic acid-based treatments for gene therapy applications, such as mRNA, siRNA, and plasmid DNA. They facilitate cellular uptake, prevent nucleic acids from degrading, and improve targeted distribution to particular tissues or cells.

Diagnostics

Potential uses for nanocochleates in diagnostics include biosensing and imaging. Because they can be functionalized with imaging agents or targeting ligands to allow for the viewing of specific tissues or biomolecules, nanoparticles are helpful tools for disease monitoring and diagnostic imaging

Antimicrobial therapy

Antibiotics, antifungal medicines, and antiviral medications can be encapsulated in nanocochleates to treat a variety of infections. Cochleates' special structure makes it possible to distribute antimicrobial drugs to infected cells or tissues efficiently, which enhances the effectiveness of treatment.

Nutraceuticals and cosmeceuticals

Bioactive substances including vitamins, antioxidants, and phytochemicals can be encapsulated in nanocochleates and used in cosmeceuticals and nutraceuticals. They increase these compounds' stability and bioavailability, which boosts their effectiveness in cosmetics and dietary supplement

Regenerative medicine

In regenerative medicine, nanocochleates can be used to distribute growth factors, cytokines, and other bioactive substances to promote wound healing and tissue regeneration. They can be utilized in regeneration and tissue engineering treatments and customized for particular tissue types.(16)

Structure and composition of nanocochleates

Natural materials such as calcium and phosphatidylserine are used to create the stable, negatively charged phospholipid cations precipitates called nanocochleates. Nanocochleares are cigar-like structures composed of a continuous lipid bilayer. Small unilamellar anionic liposomes form a cigar-like shape as they condense. Cochleates that resemble cigars are created when the negatively charged lipids are arranged by the divalent cations, such calcium, into a solid sheet that rolls up on itself, except for water. When two negatively charged phospholipid bilayers, cochleate and nanocochleate, interact with multivalent counter ions like Zn2+ or Ca2+, bridging agents are created that allow the bilayers to form spiral rolls that resemble cigars. (4) Because of their solid matrix, cochleates have special qualities above liposomes as particulate structures. These qualities include enhanced mechanical stability and better drug protection. The vast multilayer sheets with hydrophobic surfaces have a tendency to coil up in a cigar-like shape to reduce water interactions. Dehydration of the phosphatidyl head group, which is required for bilayers to assemble closely and for the cochleate cylinders to start growing, is the molecular mechanism (Figure 1). Near 54 Å, the lipid bilayer's orientation repeats itself. (5)

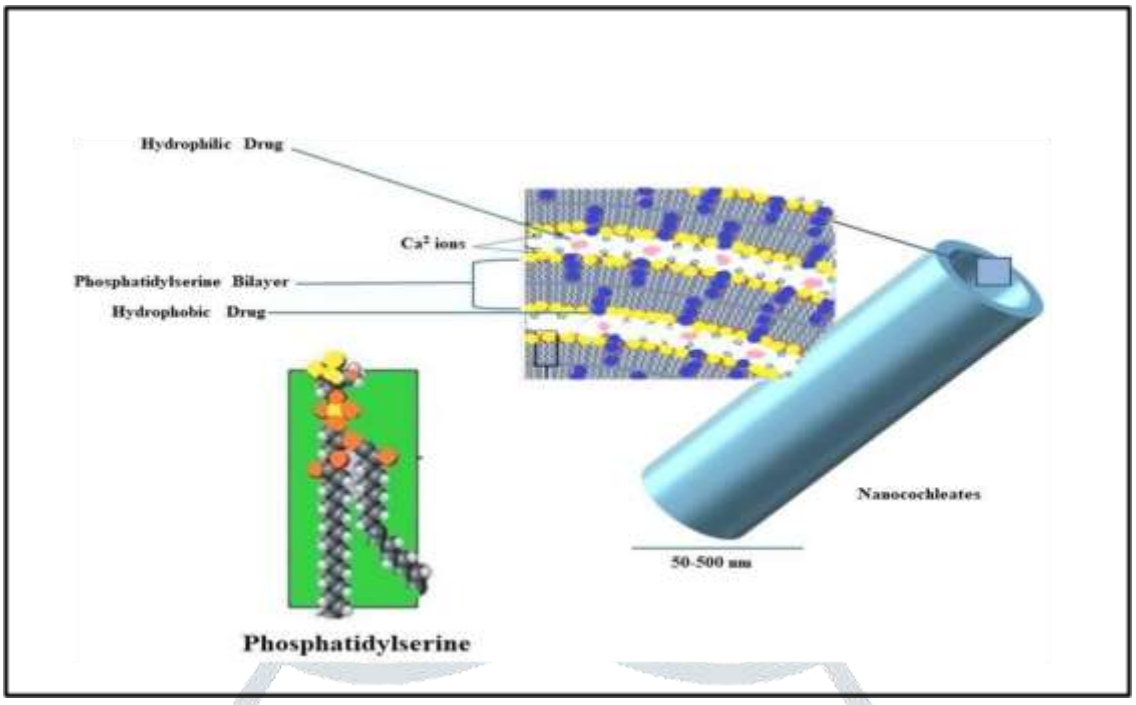


Fig. 1: Structure of Nanocochleates

Components Of Nanocochleates

To create nanocochleates, three main materials are used: lipids, cations, and active pharmaceutical ingredients (API).

1. Phosphatidyl serine (PS), phosphatidylinositol (PI), di-oleyl PS, phosphatidyl glycerol (PG), phosphatidyl choline (PC), di-myristoyl PS, phosphatidyl ethanolamine (PE), di-phosphatidyl glycerol (DPG), diolyl phosphatidic acid, di-stearoyl phosphatidyl serine, and dipalmitoyl PG are examples of lipids.
2. Cation: Ba+2.5, Zn+2, Ca+2, or Mg+2.
3. Potential medications include polynucleotides, proteins, peptides, immunosuppressants, antiviral medications, anesthetics, anticancer medications, steroid anti-infective medications, sedatives, vitamins, herbal products, nutritional supplements, and/or vascular medications. Consequently, it exhibits potential as a carrier for several pharmaceutical drugs. (6)

Routes of administration for nanocochleate drug delivery

Nanocochleates as drug delivery devices provide efficient oral medication delivery. Possible alternative routes of administration include spinal, intestinal, arterial, bronchial, lymphatic, topical, sublingual, mucosal, nasal, ocular, subcutaneous, intramuscular, intravenous, transdermal, and other mucosal surfaces. (7)

Dosage forms available for nanocochleate drug delivery

Capsules, cachets, pills, tablets, lozenges, powders, granules, suspensions, emulsions, or oral solutions are all examples of oral delivery forms.

• Inhalants, pastes, creams, lotions, gels, sprays, ointments, patches, and powders for topical or transdermal delivery.

• Sterile powders that may be concocted into sterile injectable solutions or dispersions before use, as well as sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions, or emulsions, are suitable for parenteral administration. (8)

Merits of nanocochleates

1.Due to less lipid oxidation, they are more stable than liposomes.

2. Because they are found in the membranes of both plant and animal cells, the lipids used to make the nanocochleates are non-toxic, non-immunogenic, and non-inflammatory.

3. While liposome structures are destroyed upon lyophilization, nanocochleates retain their structure even after lyopilization.

4. They increase the oral bioavailability of broad range compounds, including hydrophobic and hydrophilic medications. They are also helpful in delivering specific medications, such as proteins and peptides, genes, vaccines, and antigens.

5. Hydrophobic medications can be adequately encapsulated in the lipid bilayer of the nanocochleate structure. (9)

Demerits of nanocochleates

Nanochleates need certain storage conditions.

Aggregation may occasionally happen in the formulation of nanocochleates when they are being stored; this can be prevented by using surfactants and aggregation inhibitors such polyethylene glycol.

The formulation of nanocochleates has a high manufacturing cost. (9,10)

Stability of nanocochleate

Encochleation stabilizes and protects the connected molecules. Since the entire structure is a lipid bilayer complex, the outside part of the cochleate structure remains intact even when the inner part may be exposed to external environmental variables or enzymes. The interior of this construction is essentially oxygen-proof and watertight, prolonging the formula's shelf life. The nanocochleates can be stored at 4 °C or room temperature after being lyophilized into a powder. Before being used in vitro or in vivo, lyophilized cochleates can be reconstituted with liquid. No adverse effects on cochleates' morphology, structure, or lyophilization function. Nanocochleate delivery systems: biocompatibility and safety. The two main components of nanocochleate are calcium and PS. PS is naturally present in all cellular membranes and is primarily abundant in the brain. Phospholipids in nanocochleate formulations can be derived from natural sources or synthesized from anionic lipids, which are non-biodegradable and non-swelling. Soy PS is available in large, reasonably priced quantities and is safe for human consumption. Because nanocochleates are composed of simple,

natural ingredients, they are a safe and biocompatible delivery method. Clinical studies have shown that PS is a fairly safe method of promoting cognitive performance in the aging brain. (11)

Methods for Preparation:

The following techniques are often used to prepare nanocochleates.

- Hydrogel technique,
- Trapping technique,
- Liposome before cochleates dialysis technique.
- Direct calcium dialysis technique
- Binary aqueous- aqueous emulsion technique.
- Hydrogel method

Tiny unilamellar drug-loaded liposomes are made via the hydrogel technique and subsequently added to polymer-A. Next, polymer-B is mixed with two dispersions. The two polymers combine to generate an aqueous two-phase system due to their immiscibility. A cation salt solution diffuses into the second polymer and then into the particles that contain the polymer in a two-phase system. As a result, the polymer creates cationic cross-linkage and tiny cochleate (Figure 2). The generated cochleates can subsequently be resuspended in physiological buffer after the polymer is eliminated through washing. (12)

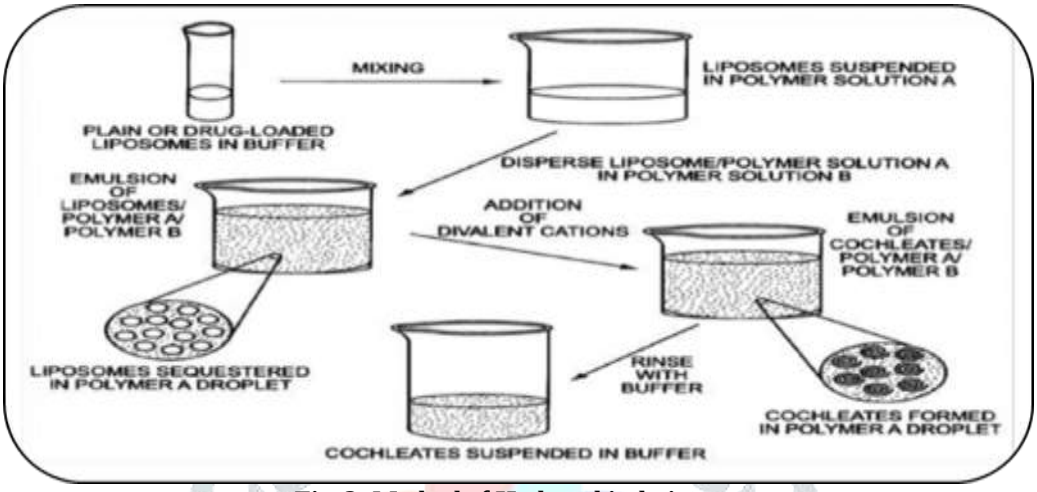


Fig. 2: Method of Hydrogel isolation

Trapping method

Making a phospholipid solution and dissolving the target drug in an appropriate solvent are two crucial phases in the trapping technique. The lipid solution is then mixed with an aqueous buffer and mechanically agitated to promote the formation of lipid bilayers that ultimately develop into cochleate structures. During this procedure, the drug is integrated into the cochleates. Centrifugation or dialysis are used to remove unbound components from the nanocochleates after synthesis (Figure 3). Characterization techniques including transmission electron microscopy and dynamic light scattering are used to assess the size, shape, and efficacy of drug loading in order to decide whether the nanocochleates are suitable for drug delivery applications. (13)

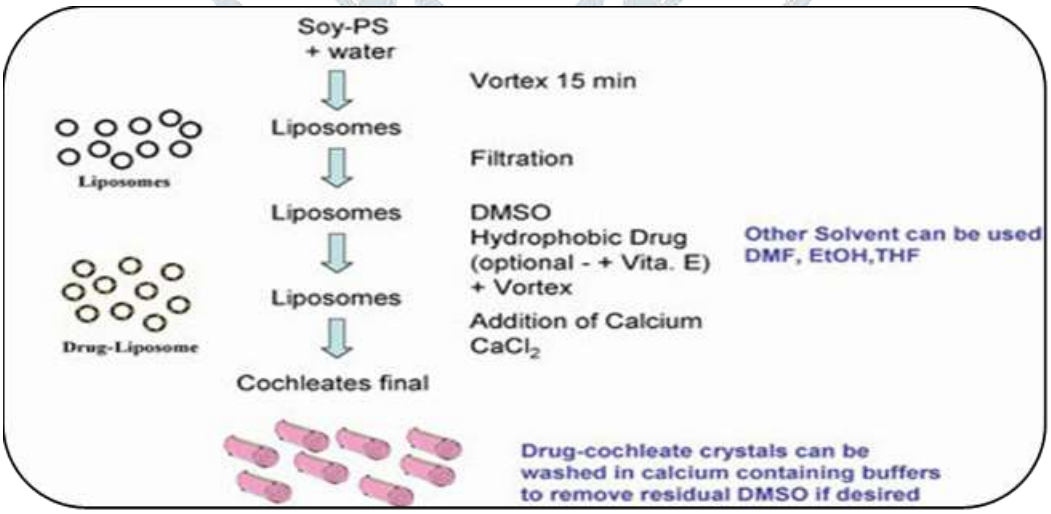


Fig. 3: Method of Trapping

Liposome before cochleates dialysis method

This process involves adding lipid and detergent to create the liposomes initially. It takes two steps to make liposomes. Dialysis is used to eliminate the detergent in the first stage. After the generated liposomes are used for dialysis against a calcium chloride (CaCl2) solution, nanocochleates are created. The modest size of the intermediate liposomes results in small nanocochleates. It is a typical method for treating hydrophobic materials, such as membrane proteins. This technique might produce nanocochleates that range in size from 50 to 100 nm. (14)

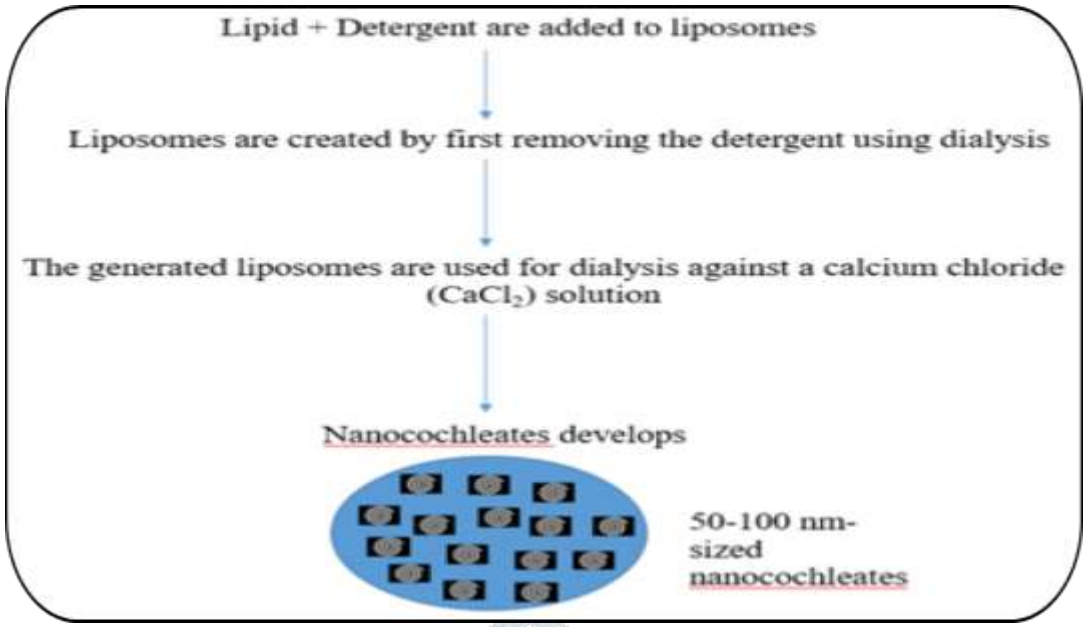


Fig. 4: Liposome before cochleates dialysis method

Direct calcium dialysis method

The cochleates will be the same size, and unlike the liposome utilized in the previous cochleate dialysis procedure, this method does not involve the creation of transitional liposomes. The calcium chloride arrangement dialyzes against the lipid instantly, making it a more effective combination. This creates a thin, highly layered structure due to the tension between the release of the cleanser from the cleanser/lipid/drug micelles and the production of calcium. In a non-ionic cleaner and extraction cushion, phosphatidylserine, cholesterol, and a predetermined concentration of polynucleotide are combined, and the mixture is vortexed for five minutes. The resulting clear solution is then dialyzed against three distinct buffer modifications at room temperature. The final dialysis is performed in a solution containing 6 mM Ca2+, even though 3 mM Ca2+ is sufficient. The resultant whitish calcium phospholipid is called DC cochleate.(15)

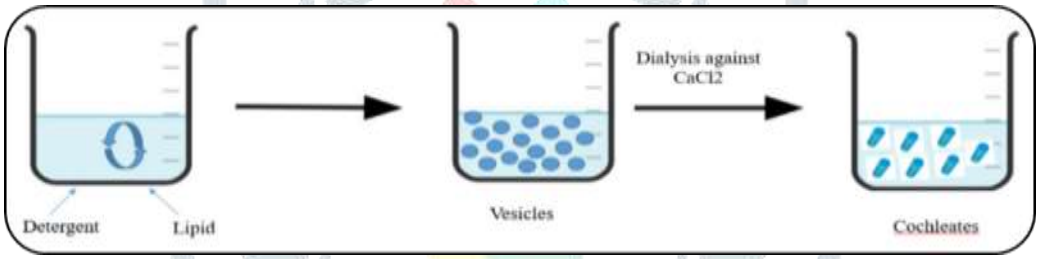


Fig. 5: Direct calcium dialysis method

Binary aqueous-aqueous emulsion system

Using a film process or a high pH, tiny liposomes are encapsulated in this manner before being mixed with a polymer, such as dextran. A second, non-miscible polymer (such Stake) is then introduced into the dextran/liposome phase. The calcium was then gradually administered and distributed, first to one stage and then to the framing nanocochleates that followed. The cochleates framed with this method contain molecules smaller than 1000 nm. (14)

Antimicrobial therapy

Antibiotics, antifungal medicines, and antiviral medications can be encapsulated in nanocochleates to treat a variety of infections. Cochleates' special structure makes it possible to distribute antimicrobial drugs to infected cells or tissues efficiently, which enhances the effectiveness of treatment.

Nutraceuticals and cosmeceuticals

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Charecterization Study of Nanocochleates

Particle Size and Size Distribution

The Malvern 2000SM (Malvern, UK) is used in the laser diffraction technique to assess the average particle size of distributed cochleates. It is analyzed at a temperature of 30±2°C and a detection angle of 90°. The average diameter of a sphere with the same volume as the particle being measured, or volume mean diameter D, is used to express the mean vesicle size.(17)

Polydispersity Index (18)

PDI (Polydispersity Index) reflects the uniformity of the nanoparticle diameter and measures the particle homogeneity. The Polydispersity Index was computed using the below mentioned formula:-

Polydispersity Index = **Mw**/**Mn***100

Here,

Mw= average molecular weight &

Mn= No of average Molecular weight.

Entrapment Efficiency (19)

Nanocochleates are transferred into centrifugation tubes in an aliquot of 100 µl. 60 µl of pH 9.5 EDTA and 1 ml of ethanol are added to each tube while being vortexed. The end product is colorless and transparent. In order to determine entrapment efficiency using equations, the samples were appropriately diluted, and absorbance was measured.

Entrapment efficiency = Amount of API present in cochleates / Total amount of API× 100

Fourier transform infrared spectroscopy study:

Fourier transform infrared spectroscopy study determines the functional groups as well as the purity of the compound. Samples are formulated by mixing with KBr. Then samples are located in the holder. The spectra are scanned at ambient temperature over the particular range of wave numbers. (26)

Differential scanning calorimetry study

Differential examining calorimetry study determines the lipid status. The samples are stored hermetically in perforated aluminum pans and heated over the temperature range of-10 to 180 °C at a constant Degree of 10 °C/min. The system is eliminated at a speed of a 100 ml/min with nitrogen energy to protect the atmosphere inert. (27)

Specific Surface Area (20)

The specific surface area of frozen nanocochleates is usually measured using a sorptometer. The following formula can be used to calculate the specific surface area.

where A is the specific surface area of the cochleate, d is its diameter, and ρ is its density.

Although there may rarely be a difference in the observed results because of residual surfactant, the calculated and measured specific surface areas normally coincide very well. (20)

Electron Scanning MicroscopyScanning Electron Microscopy

A gas pycnometer and either air or helium can be used to measure the density of nanocochleates. Because of the structure's porosity and particular surface area, the value obtained by combining helium and air is much more noticeable. (22)

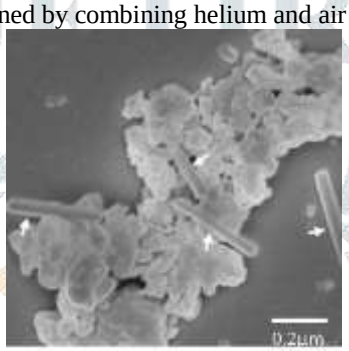

Fig.6. SEM of nanocochleates.

Density

The density of nanocochleates can be determined using a gas pycnometer and either air or helium. The value achieved by combining helium and air is much more evident due to the structure's porosity and specific surface area. (22)

Molecular weight measurements

Using a refractive index detector, gel permeation chromatography (GPC) can determine the molecular weight and distribution of polymers inside a matrix. Using GPC, it was shown that the coupling of many small oligomeric monomers produces poly-alkyl-cyano-acrylate (PACA) nanocochleates rather than one or longer polymer strands rolled up. (25)

Drug content

For 40 minutes at 25°, the redispersed suspension of nanocochleates is centrifuged at a rate of 15,000 revolutions per minute. The purpose of this process is to separate the unbound drug from the residue. UV-visible spectrophotometry can then be used to determine the amount of medication present in the supernatant following the proper dilution. (22)

Stability study

To test the stability of the nanocochleates dispersion, the stability research can be conducted for three months at 2-80C and 25±20C/60%RH. Nanocochleates' stability is assessed. Examine the drug release using nanocochleate formulation, particle size, and entrapment efficiency percentage following their stability investigation (24)

In-vitro Release

The profile of in vitro release of nanocochleates can be evaluated using diffusion cells, modified ultra-filtration, or standard dialysis. These methods use phosphate buffers and dual chamber diffusion cells on shake stands. A Millipore membrane is placed between the two chambers, and the top chamber, also known as the donor, is filled with a suspension of nanocochleates. After introducing Nanocochleates straight into a stirred ultra-filtration cell, aliquots are filtered over the membrane at different intervals using a modified ultra-filtration technique. (23)

CONCLUSION

Because they can encapsulate both hydrophilic and hydrophobic therapeutic molecules, nanocochleates offer a substantial development in drug delivery technology. This ensures increased stability, bioavailability, and decreased toxicity. They make a compelling argument for their potential usage as adaptable drug carriers by demonstrating promising applications in a variety of domains, including gene therapy, vaccine delivery, and infection treatment. Ongoing research and technology advancements have the potential to overcome these barriers, opening the door for wider adoption and economic success in pharmaceutical applications, even in the face of issues like storage and production costs. This cutting-edge device has the ability to completely transform therapeutic results and establish new standards for medication delivery techniques.

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