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ADVANCEMENTS IN NANOCOCHLEATE DRUG DELIVERY SYSTEMS: A COMPREHENSIVE REVIEW

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Abstract:

Nanocochleates composed of bilayer lipids, a novel cigarette-shaped structure, has emerged as a drug delivery system, offering improved stability, improved bio-availability, and targeted drug delivery. This comprehensive review examines the evolution, mechanisms, preparation methods, characterization studies, and several applications of nanocrystals in pharmaceuticals.The review explores the basics of nanocochleates, tracing their discovery in the 1970s and subsequent development. This structure formed by the interaction of liposomes and cationic salts provides a stable matrix for encapsulating hydrophilic, hydrophobic and amphiphilic drugs. The versatility of nanocoats allows for different routes of administration, including oral, parenteral, topical and mucosal.Lipids (phosphatidyl serine, phosphatidic acid, etc.), cations (Ca + 2, Zn + 2) and various drug classes used in the preparation of nanocochleate were identified separately. The drug delivery mechanism describes how nanocochleates are absorbed from the gut and delivered to target cells through membrane fusion events.Advantages include stability, reduced drug dosages, increased bioavailability and control, while acknowledging challenges such as special storage requirements and manufacturing costs. This review provides detailed information on nanocochleate preparation methods, focusing on entrapment methods, hydrogel approaches, and dialysis techniques.Characterization studies including particle size measurements, encapsulation efficiency, surface morphology, and in vitro release studies are reviewed. Furthermore, the review highlights the possibility of industrial scale production using pure lipid feedstock.

Keywords: Oral delivery, Nanocochleate, Phospholipid, Liposome, Laser diffraction.

INTRODUCTION

Improving bioavailability and formulation techniques are always at the forefront of the development of new formulations using nanotechnology, where researchers focus on changes in drug delivery systems. Essentially, liposomes are vesicles containing at least one lipid bilayer composed of phospholipids and cholesterol, which are packaged to deliver nutrients or drugs in the desired form. Among these lipid-based nanocarriers, liposomes, cochleates, and new multilayer nanocarrier systems emerged as hydrophilic and hydrophobic drugs with better and improved stability, efficacy, increased drug permeability, and decreased drug dosage. except special drugs that produce fewer side effects. Nanocochleate drug delivery is based on encapsulating the drug in a multi-layered, lipid crystalline matrix, which can safely and effectively deliver the drug to the target site. Various lipid-based nanocarrier systems such as lipoproteins, lipid nanoparticles, lipid nanocapsules, and liposomes are available, but they show limitations due to stability, oxidation, and incompatibility for the delivery of proteins and peptides. Cochleates have been developed as an alternative to lipid-based drug delivery systems. Many therapeutic agents, especially biological molecules, are not absorbed in the gut due to their inability to penetrate tissue membranes and undergo enzymatic degradation in the GIT wall. Cochleate consists of a special structure, phospholipid bilayer, and hydrophobic and hydrophilic drugs are added to prevent oxidation, increase permeability, and reduce drug dosage. Thus, it provides a potential delivery system for various drugs. This novel nanocarrier system approach is applicable to macromolecules as well as hydrophobic small molecule drugs and drugs with poor oral bioavailability.[1]

Introduction To Nanocohleates

Defination : Nanocochleates are cigarette-like structures formed from an array of lipid bilayers formed by the interaction of negatively charged liposomes with cationic salts, usually calcium ions. Phospholipids play an important role in the formation of nanoclasts because they are the main ingredients in the formation of nanoclasts. Derived from natural lipids, it is an essential requirement for several nanoparticle systems and has superior stability under harsh environmental conditions. Phospholipids bind together with calcium ions and form packed sheets. The high tension at the edges of the lipid bilayer causes the interaction of the nanocochleates with the tissue membrane. The alternative structure of lipids in nanocochleates encapsulates drugs without chemical binding. The hydrophilic and hydrophobic parts of phospholipids enable the transport of hydrophobic, hydrophilic and amphiphilic drugs, presenting a wide range of applications. They have the flexibility to change the direction of administration if necessary, as nanocoats are administered sublingually, parenterally, and topically. This versatility makes it ideal for any treatment you need. Widespread use of nanocochleate technology will provide better outcomes for patients. This review describes the fundamentals and potential applications of nanocochleates.[2]

Discovery of Nanocochleates

Cochleats were discovered in 1975 by Dr. D. Papahadjoupoulos and colleagues and used to transport antigens and peptides for vaccine delivery in the 1980s and 1990s. The cochleate structure reported in the literature is not always uniform, resulting in sheet aggregates and cochleates covered by the trap method or large needles like the structure by the dialysis method. Nanocochleates were introduced in 1999 to develop smaller but more consistent particles. Using a binary phase system such as two false hydrogels, it has been shown that cochleates with small particle sizes ranging from 104 to 113.5 nm can be formed.[3]

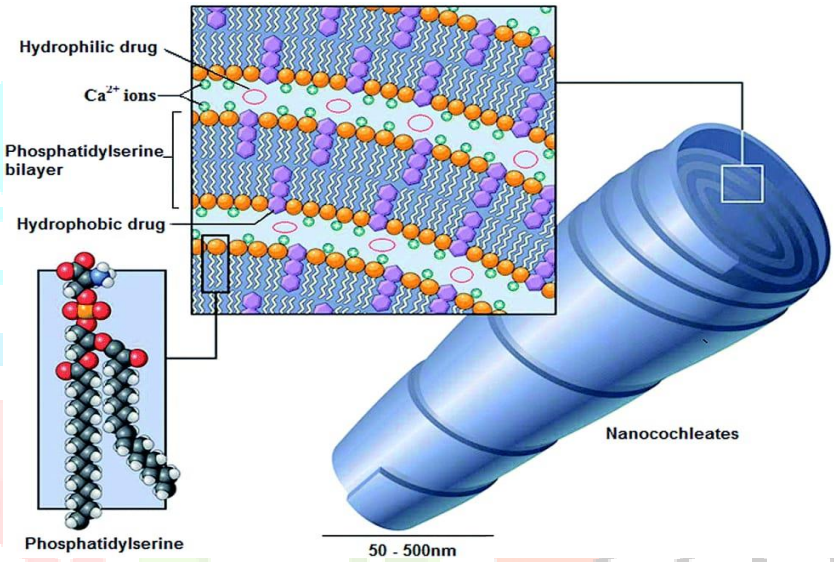

Figure 1: Structure of nanocochleates

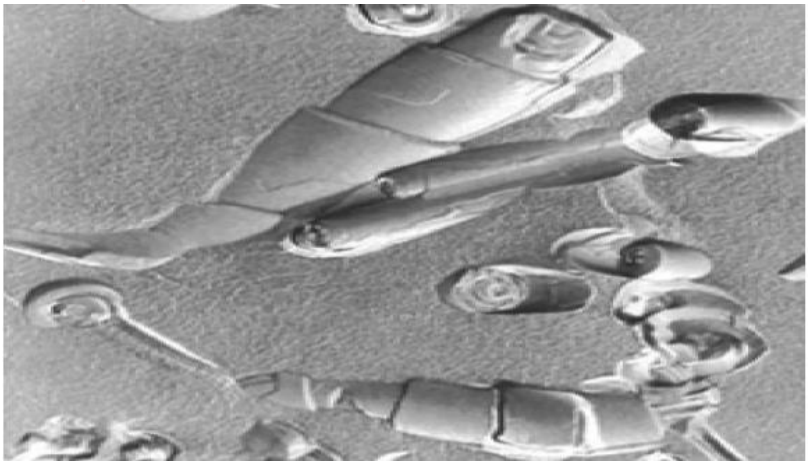

Figure 2: Cigar like structure of nanocochleate

Routes of administration for nanocochleate drug delivery

Nanocochleates as drug delivery devices enable efficient oral delivery of drugs. Alternative routes for administration may include parenteral, rectal, topical, sublingual, mucosal, nasal, ophthalmic, subcutaneous, intramuscular, intravenous, transdermal, spinal, intestinal, arterial, bronchial, lymphatic and intrauterine administration, intrauterine administration. or other mucosal surfaces.[4]

Components Of Nanocochleates

The three main components used in the preparation of nanocochleates are atmospheric pressure ionization (API), lipids, and cations.

1. Lipids: Phosphatidyl serine (PS), phosphatidic acid (PA), di-oleyl PS, phosphatidylinositol (PI), phosphatidyl glycerol (PG), phosphatidyl choline (PC), di-myristoyl PS, phosphatidyl ethanolamine (PE), di -phosphatidyl glycerol (DPG), diolyl phosphatidic acid, di-stearoyl phosphatidyl serine, di-palmitoyl PG.
2. Cation: Zn+2 or Ca+2 or Mg+2 or Ba+2.[5]
3. Possible drugs: - Proteins, peptides, polynucleotides, antiviral agents, anesthetics, anticancer agents, immunosuppressants, steroid anti-infective agents, steroid anti-infective agents, sedatives, nutritional supplements, herbal products, vitamins and / or vascular agents . Thus, it proves to be a potential carrier for various therapeutic drugs.[6]

Dosage forms available for nanocochleate drug delivery

- For oral administration: Capsules, cachets, pills, tablets, lozenges, powders, granules, or solutions or suspensions or emulsions.
- For topical or transdermal administration: Powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants.
- For parenteral administration: Sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions, or emulsions, or sterile powders that can be reconstituted into sterile injectable solutions or dispersions before use.[7]

Mechanism of nanocochleate drug delivery [8]

- **Absorption from intestine**

Intestinal absorption of nanocolate occurs after oral administration. Cut through the digestive epithelium, the nanocochleates deliver their active ingredients into the bloodstream. In the case of routes other than veins, they penetrate the epithelial cells and circulate. After reaching the circulation, it is delivered to the target cells.

- **Delivery to targeted cells**

The interaction of calcium with negatively charged lipids has been studied extensively. Most natural binding events require the interaction of calcium with a negatively charged phospholipid (usually phosphatidylglycerol or phosphatidylserine). Calcium-induced membrane disruption involving negatively charged lipids and subsequent membrane fusion events is an important mechanism in many natural membrane fusion processes. Therefore, the cochleate can be considered as an intermediate membrane fusion.

- **Delivery by cell membrane fusion**

First, the nanocochleate approaches the cell membrane, causing disruption and rearrangement of the cell membrane, leading to a fusion event between the outer layer of the nanocochleate and the cell membrane. This combination causes a small amount of a given substance to be brought into the cytoplasm of the cell. This transporter can slowly bind or dissociate from the cell, making it available for another binding event with this or another cell.

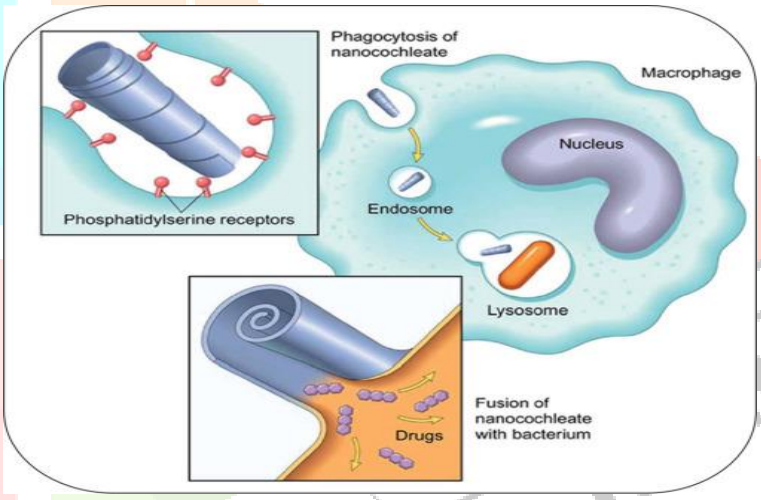

Figure 3: Mechanism of nanocochleate by membrane fusion

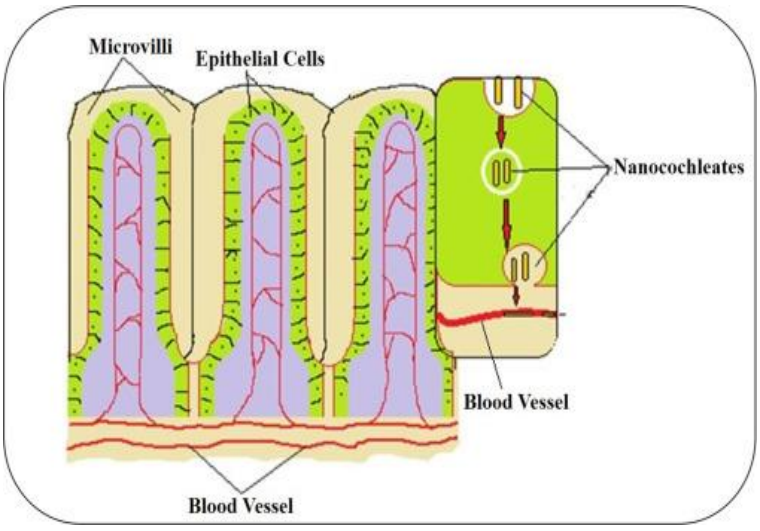

Figure 4: Nanocochleate absorption from intestine

Adventages of nanocochleate drug delivery system[9]

1. Lipids in nanocochleates are more stable than liposomes because they are less susceptible to oxidation. The structure of liposomes is freeze-dried, but the structure is preserved after freeze-drying.
2. It shows that biomolecules, especially those with hydrophobic groups, are efficiently incorporated into the cochleate lipid bilayer.
3. As nanocochleates slowly disintegrate or disintegrate, biomolecules can slowly or supposedly escape in vivo.
4. It contains a lipid bilayer matrix that acts as a carrier composed of simple lipids found in animal and plant cell membranes, so the lipids are non-toxic, non-immunogenic and non-inflammatory.
5. Make it simple and safe.
6. They increase the oral bioavailability of many compounds, including water-insoluble compounds and previously difficult-to-administer biopharmaceutical proteins and peptides. (eg ibuprofen for arthritis).
7. Reduces toxic stomach irritation and other side effects from packaged medications.
8. Instead of chemically encapsulating the drug, they encase or entrap it in a crystalline matrix.
9. Cochlear active substances are protected from degradation and exposure to adverse environmental conditions such as sunlight, oxygen, water and temperature.
10. Formulations can be prepared from specific amounts and ratios of drugs or antigens.

Disadventages of nanocochleate drug delivery [10]

1. Requires special storage conditions.
2. The cost of the product is very high.
3. Agglomeration may occur during storage.

Stability of nanocochleate

Encochleation provides protection and stability to the bound molecules. Because the entire cochleate structure is a lipid bilayer complex, the inner part of this structure remains intact even if the internal part of this structure can be exposed to external environmental conditions or enzymes. The interior of this structure is essentially waterproof and resistant to oxygen penetration, which increases the shelf life of the formula. The nanocochleates can be stored at room temperature or at 4 ° C and lyophilized into powder form. Before in vitro use or in vivo use, lyophilized cochleates can be reconstituted with liquid. No adverse effects on cochleate morphology, structure, or lyophilization function. Safety/biocompatibility of nanocochleate delivery vehicles. The two main components of nanocochleate are PS and calcium. PS is a natural component of all biological membranes and is most concentrated in the brain. Phospholipids used in nanocochleate formulations can be derived from natural sources or synthetically produced from anionic lipids, which are non-swelling and non-biodegradable. Soy PS is available in large and inexpensive quantities and is suitable for human use. Safe, simple, natural ingredients make nanocochleates a safe and biocompatible delivery vehicle. Clinical studies show that PS is very safe in supporting cognitive function in the aging brain.[11]

Application of Nanocochleates

1. Nanocochleates have been used to deliver proteins, peptides and DNA for vaccines and gene therapy.
2. Nanocochleates have been used to deliver amphotericin B as an antifungal agent, and amphotericin B cochleates prepared have improved stability and efficacy at low doses.
3. Antifungal Medication Delivery Ketoconazole (KCZ) is an antifungal medication commonly prescribed for fungal infections such as athlete's foot, candidiasis, and ringworm.
4. Immunizations include measles, mumps, polio, rubella, tetanus, etc. To prevent such diseases, there are usually live or inactive pathogens, to protect antigens, liposomes, cochleates, viruses, etc. vaccine-adjusted system (VADS) with operators used.
5. Delivery of anti-inflammatory compounds.
6. The delivery of volatile oil from Artemisia absinthium L. shows poor solubility and instability. That's why, essential oil (EO) is encapsulated in nanocochlates to increase stability and dissolution, showing better therapeutic efficacy. An in vivo study was conducted to show the EO-Aa-NC-based formulation to reduce the size of the lesions and showed better results than the standard drug glucagon.
7. Delivery of antibacterial agents and combating multidrug resistance in bacteria.
8. Insulin delivery using magnetocolates and prepackaged insulin.
9. Discovery of anticancer drug delivery with nanoliposomes for oral administration of paclitaxel.
10. Nanoparticles are used as carriers for drug delivery.
11. Nanocholesterols have also been used to deliver nutrients such as vitamins and omega fatty acids. Delivery of recombinant factor VIII.
12. Nanocochleates are immunomodulators for nasal vaccination.
13. Biogeod nanocochleates have the ability to stabilize and protect large amounts of micronutrients and increase the nutritional value of processed foods.
14. Nanocochleates have been used to deliver proteins, peptides and DNA for vaccines and gene therapy.
15. The use of cochleates in the delivery of antibacterial agents: Cochleates will have the advantage of reducing toxicity and increasing bacterial activity. Cochleates for aminoglycosides and linear or cyclic peptides should allow oral administration. Proof-of-principle efficacy of cochleates against cancer was achieved using clofazimine as a model antibacterial drug.
16. Nanocholesterols can add omega-3 fatty acids to cakes, muffins, pasta, soups and stews without changing the taste or aroma of the product.
17. Bio Delivery Sciences International has developed nanocochleates that can be used to more efficiently deliver nutrients such as vitamins, omega fatty acids to cells without affecting the color and taste of food, making the concept of superfood a reality. offers a variety of benefits, including increased energy, improved cognitive function, improved immunity, and fighting.[12]

Method of preparation of Nanocochleates

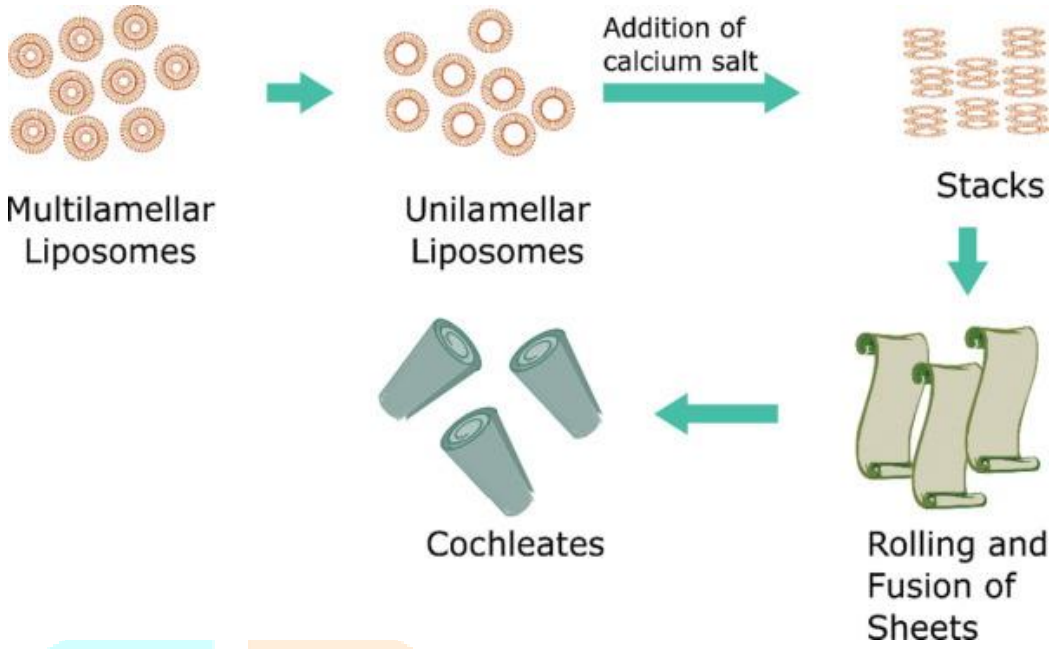

Figure 5: method of preparation of nanocochleates

Nanocochleates are usually prepared by the following methods :

1) Trapping method
2) Hydrogel Method.
3) Aqueous- aqueous emulsion system.
4) Liposome before cochleates dialysis method.
5) Direct calcium dialysis method.

1. Trapping Method

This method involves forming phosphatidylserine liposomes followed by the judicious addition of calcium chloride solution. Liposomes can be formed by adding water to a phospholipid matrix or by adding an aqueous phase to a phospholipid film. Due to the poor solubility of aqueous solutions, the solubility of the cargo after the addition of the liposomal suspension is important: it involves the following steps:

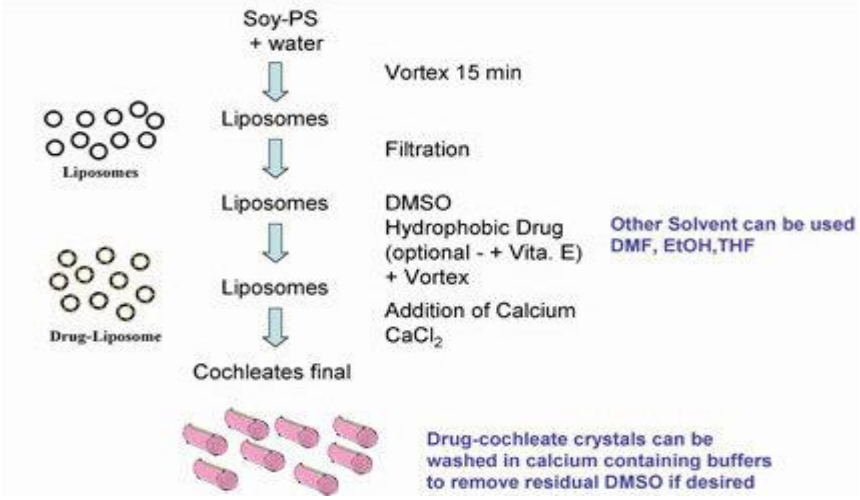

Figure 6: Schemetic representation of trapping method

Step 1: Prepare liposomal form of phosphatidylserine by vortexing the solution for 15 min.

Step 2: Separate the liposomes from the above solution with a filter.

Step 3: Add a solvent and a hydrophobic drug to the trap above that separates the liposomes (ethanol, dimethylsulfoxide).

Step 4: Add calcium chloride solution to the solution from step 3, crystal cochleates appear in the resulting solution.

Step 5: The resulting cochleates were washed with calcium buffer to remove residual solutes.[13]

2. Hydrogel Method

This method consists of the following steps:

Step 1 : A suspension of thin unilamellar liposomes or liposomes loaded with biological molecules is prepared. This can be achieved by conventional methods such as sonication or microfluidization or other related techniques.

Step 2 : Liposome suspensions are mixed with polymers A such as dextran (mol wt-200,000-500,000), polyethylene glycol (mol wt- 3400-8000) or phosphatidylserine.

Step 3 : Preferably, by injection, liposomes/polymer B are suspended in other polymers such as polyvinyl pyrrolidone, polyvinyl alcohol, ficol (mol wt30,000-50,000) and polyvinyl methyl ether (PVMB) (mol wt-60,000). 160,000) leads to an aqueous two-phase polymer system in which polymer A does not separate. This can be achieved mechanically by using a syringe pump with appropriate control, for example at a rate of 0.1 ml/min to 50 ml/min, preferably 1-10 ml/min.

Step 4 : A cationic salt solution is added to the two-phase system in step 3, so that the cations dissociate into polymer B and then the liposome/polymer A particles form small cochleates.

Step 5 : Now, to isolate the cochleate structure and remove the polymer solution, the cochleate sediment is washed with a buffer containing a positively charged molecule, preferably a dissociated cation. The addition of positively charged molecules to the wash buffer ensures that the cochleate structure holds and precipitates during the wash step.[8]

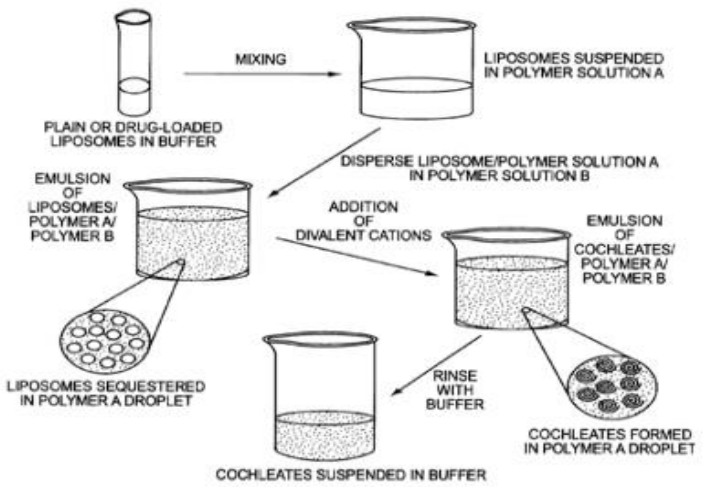

Figure 7: Schemetic representation of hydrogel method

3. Aqueous-aqueous emulsion system

This method involves the formation of small single-cell vesicle liposomes by high pH or the film method, and then the liposomes are mixed with polymers such as dextran. The dextran/liposome phase is then injected into the second, pseudopolymer (ie, PEG). Calcium is then added and slowly dispersed from one phase to another forming nanocrystals, after which the gel is washed. Cochleates produced using this method have a particle size below 1000 nm.

4. Dialysis method

Liposomes before cochleate dialysis (LC) The second method of preparing small cochleates consists of detergents and biologically relevant molecules and cations. Liposomes are added to disrupt the liposomes. The method consists of the following steps:

- An aqueous suspension containing a lipid-solvent mixture is prepared.
- Solvent-lipid suspensions are mixed with polymers A such as dextran, polyethylene glycol, or phosphatidylserine.
- Lipid-solvent/polymer B consists of polyvinyl pyrrolidone polymer, polyvinyl alcohol and polyvinyl methyl ether (PVMB), polymer A and polymer B are integrally formed. phase polymer system.
- A cationic surfactant solution is added to the two-phase polymer system.
- Now wash the biphasic polymer system to remove the polymer and cochleates formed.[15]

5. Direct calcium (DC) dialysis method

This method does not involve the formation of intermediate liposomes, but involves the direct removal of the detergent by dialysis against a calcium chloride solution. In this method, the release of detergent/lipid/drug from micelles and the competition between calcium and double layer condensation. As a result, the length and diameter of the cochleates are needle-shaped structures.[15]

Charecterization Study of Nanocochleates[16]

❖ **Particle size determination**

Laser diffraction technique was used to determine the average particle size of cochleate dispersion and liposomal dispersion. The analysis was carried out at 30 ° 2 ° C at a detection angle of 90 °.

❖ **Entrapment efficiency (EE)**

The entry efficiency of the nanocochleate suspension was determined by centrifugation at 5000 rpm at 270C for 30 min. By adding EDTA and ethanol to slightly dissolve the suspension of nanoclays, the absorption of the resulting solution is determined by spectroscopic techniques and calculate the penetration efficiency of nanoclays.

$$\text{Entrapment efficiency} = \frac{\text{Amount of drug present in cochleates}}{\text{Total Amount of Drug}}$$

❖ **Surface morphology study**

Surface morphology of nanocochlite was determined by transmission electron microscopy. To prepare samples for this study, a drop of carbon-coated copper pores was deposited to form a thin liquid film. After removing the excess solution, the sample was examined and photographed using a transmission electron microscope at an acceleration voltage of 80 kW.

❖ **Specific surface area**

Using a sorptometer to determine the specific surface area of freeze-dried nanocochleates. The following equation is used to calculate the specific surface area of nanoparticles.

$A = 6/\rho d$

Here,

A = Specific surface area,

ρ = Density,

d = Diameter of the cochleat

❖ **Fourier transform infrared spectroscopy study**

Fourier transform infrared spectroscopy determines the presence of functional groups and compound purity. Samples were prepared by mixing with KBr. The specimen is then placed in a container. Spectra were tested at ambient temperature over a range of wavelengths.

❖ **Differential scanning calorimetry study**

Differential scanning calorimetry test determines lipid status. Samples are hermetically packed in permeabilized aluminum containers and heated continuously from 10°C to 180°C at 10°C/min. The system was purged with nitrogen gas at a rate of 100 ml/min to maintain the atmosphere.

❖ **Drug content**

A suspension of nanocochleates processed in 15,000 cycles was centrifuged at 250C for 40 min to separate the free drug in the supernatant. To obtain an adequate drug concentration, the free drug concentration can be determined using a UV-Visible spectrophotometer.

❖ **Cochleates-cell interaction study**

In this study, approximately 2% fluorescent lipids were used to form fluorescent liposomes to investigate the interaction of the cochleate with the cell membrane. When the cochleate interacts with the fluorescent membrane, the surface of the cell under a fluorescence microscope becomes fluorescent.

❖ **Surface charge determination**

The nature and intensity of the nanocochleate surface charge determine its interaction with the biological environment and its electrostatic interaction with bioactive compounds. By measuring the speed of particles in an electric field, the surface charge can be determined. Laser light scattering techniques such as Velocimetry or Laser Doppler Anemometry are used to determine the velocity of nanocochleats.

❖ In vitro release study

1) **Diffusion cell method**

In the diffusion cell method, a double chamber diffusion cell on a shaking stand is used. Between the two chambers there is a millipore, a low protein binding membrane. The receptor chamber is filled with phosphate buffer. The donor chamber is filled with the formulation and standard analytical methods are used to test the receptor site at various time intervals for the drug released.

2) **Modified ultra-filtration method**

This method is also used to determine the concentration of drugs released from nanocochleates. Here, nanoparticles are introduced directly into the ultra-filter cells of the buffer mixture. Aliots are filtered through the membrane at different time intervals. Then, the drug concentration is determined using all analytical methods

❖ **Stability study**

To check the stability, spread cochleate can be stored at 2 to 8 ° C and humidity 25 ± 2 ° C/60% for 3 months. Formulation stability was determined by entrapment efficiency (%) and particle size change.

❖ Future Perspective

Cochleates are a practical platform for drug encapsulation and delivery. Recently, they have attracted considerable interest in academia and industry. In addition, the availability of cheap, low-purity lipid raw materials and the development of methods for preparing cochleates using these lipids may facilitate the industrial production of cochleate-based formulations.

❖ Conclusion

The evolution of nanocochleate drug delivery systems represents a significant leap in drug technology. These structures offer unparalleled advantages in delivering a variety of drugs, including hydrophilic and hydrophobic compounds, proteins, peptides, and DNA. With promising applications for vaccine delivery, gene therapy, antifungal agents, and more, nanocochleates show potential in various therapeutic areas.

Despite its great advantages, challenges remain, especially in terms of storage and production costs. However, ongoing research and advances in preparation methods and characterization methods promise to overcome these challenges, leading to wider use and commercial viability.

The comprehensive understanding presented in this review serves as a valuable resource for researchers, the pharmaceutical industry, and healthcare providers, demonstrating the tremendous potential of nanocochleate drug delivery systems in drug administration and changing therapeutic outcomes.

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