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NANOCOCHLEATES: INNOVATIVE SOLUTIONS FOR ENHANCED DRUG DELIVERY, A REVIEW

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ABSTRACT

Nanocochleates have emerged as a novel and promising approach in pharmaceuticals, offering unique advantages for drug delivery and therapy. Nanocochleates can encapsulate a variety of drugs, protecting them from degradation. A chelating agent can be designed to release the medication in a regulated way, which results in maintaining therapeutic levels in the body and reduction in side effects The small size of nanocochleates enables them to penetrate biological barriers more effectively, such as BBB, improving the bioavailability of drugs.

In recent years, nanocochleates have gained attention for their potential applications in various disease treatments, including cancer, cardiovascular diseases, and infectious diseases. Their ability to deliver drugs to specific cells or tissues while minimizing systemic exposure holds great promise for personalized medicine.

This review aims to provide an overview of nanocochleates, in the field of pharmaceutical sciences; we seek to clarify the possibility of using nanocochleates as a ground-breaking drug delivery mechanism.

Keywords: Nanocochleates, drug delivery, chelating agent, targeted therapy, bioavailability

INTRODUCTION

Traditional drug delivery methods frequently struggle with issues like poor targeting, low bioavailability, and poor solubility. By offering a platform for precise control over medication release and targeting, nanocochleates overcome these problems. The metal ion core enables the medicine's regulated release, while the chelating agent serves as a protective shell to prevent drug degradation and increase solubility **[1]**. The drug is imprisoned in nanocochleates due to its distinct lipid structure, which prevents chemical bonding **[2]**. Phospholipids hydrophilic and hydrophobic regions enable it to transport hydrophilic, hydrophobic, and amphiphilic medications, indicating the multi-application system. If needed the method of administration can be modified because nanocochleates can be used topically, parentally, or orally. Patients will comply with treatment as it has versatility & wide spread application **[3-4]**. Nanocochleates are stable precipitates of phospholipid plus cation. In 1975 it was first described by Papahadjopoulos **[5]**. They consist of negatively charged phospholipid bilayers that have been rolled up and are connected by multivalent cations **[6]**. A numbers of techniques have been established to prepare this kind of drug delivery system **[7]**. To ascertain the cochleates composition, the maximum amount of medicine that can be entrapped, and to assess the cochleates stability over time, a variety of characterisation procedures are used. As a result, various methods have been used. Techniques like UV spectroscopy, FTIR, TEM, and X-ray diffraction, as well as differential scanning calorimetry (DSC) **[8, 9]** have been employed to analyze the, nanocochleates

Nanocochleates:

Stable phospholipid-cation precipitates, known as nanocochleates, are made up of a tightly arranged, densely packed structure as given in **Figure 1 [10]**. It is composed of up of a spiral continual layer of solid lipid bilayers without an internal aqueous gap **[11]**. Divalent cations and negatively charged liposomes unite to create them **[12]**. Dehydration and self-assembly occur from this, and a spontaneous organization that produces increasingly complex structures with a recognizable cigar form follows:

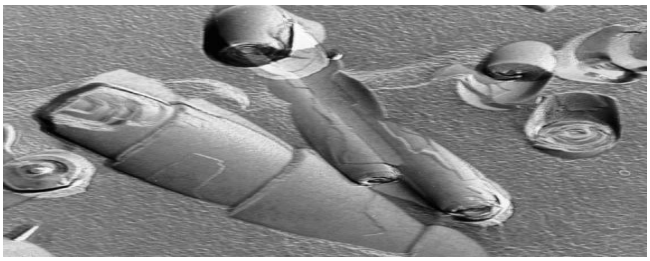

Figure 1: Structure resembling a cigar with a double fold; from Zarif *et al*. [10]

Despite being commonly characterized as cigar-shaped nanostructures, cochleates can have a variety of morphologies depending on the bridging agent and phospholipid type that are employed. Consequently, when palmitoyl oleoyl &soy phosphatidylserine were employed, planar and spherical sheets were produced. whereas with dioleoyl PS homogeneous cigar-shaped particles were produced **[13]**. Furthermore, fibrils and spherical cochleates were observed when bridging agents is other than divalent cation. Physical and chemical characteristics of drug determine whether they can be incorporated within or between phospholipid bilayers **[14]**. Owing to their distinct internal structure, cochleates offer a novel and effective method of synthesizing therapeutic compounds by shielding the encapsulated material from abrasive environments **[15]**. Therefore, this structure offers a number of benefits, such as increased bioavailability, regulated release kinetics, and improved drug solubility **[16, 17, 18]**.

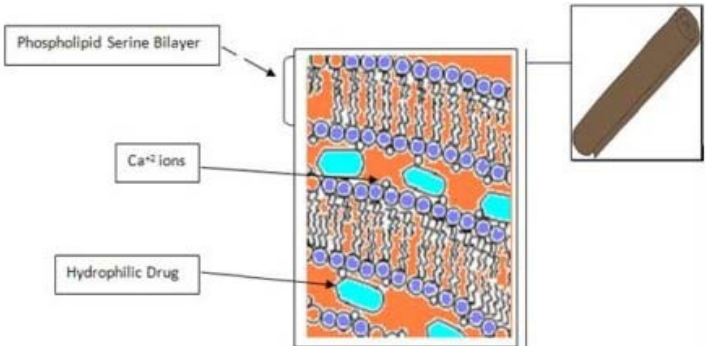

Figure 2: T. S. of a rolled cochleates

Advantages of Nanocochelates [19-22]

1. Nanocochelates are relatively stable than liposomes owing to the less susceptibility of the lipids to oxidation. It retains structure after lyophilization, as lyophilization destroys liposome structures.

2. They show an efficient incorporation of biological molecules in the cochleates structure consisting of lipid bilayers, particularly with hydrophobic moiety.
3. The slowly dissociation or unwinding of nanocochleates, retain the capacity for gradual or controlled release of biological molecules in vivo.
4. Lipid bilayers, typically act as a carrier matrix, are present in nanocochleates. It consists of basic lipids present in both plant as well as animal cell membranes, thus the lipids are harmless, non-immunogenic and non inflammatory.
5. Nanocochleates are simpler also safe to manufacture.
6. Nanocochleates enable the oral administration of intravenous (IV) drugs by enhancing their stability and bioavailability.
7. With the use of this method, a greater range of compounds can be made more bioavailable orally, particularly those that were previously challenging to deliver. such as ibuprofen for rheumatism).
8. Nanocochleates minimize pain in the stomach and mitigate the adverse action of the capsule medication.
9. Nanocochleates contain the medicaments in the form of a crystal matrix, as opposed to chemically binding to the drug.
10. These cochleates protect the drugs substance against degradation caused due to unfavorable conditions such as exposure to air (oxygen), water or temperature.

Mechanism of drug delivery by nanocochleates: Following oral dosing, intestinal absorption of nanocochleates occurs. Through the intestinal epithelium, nanocochleates transport their cargo molecule into blood vessels. When using a different route than intravenous, they pass through the linked cell and enter the bloodstream. Once they enter circulation, they are transported to the specific cell **[22]**.

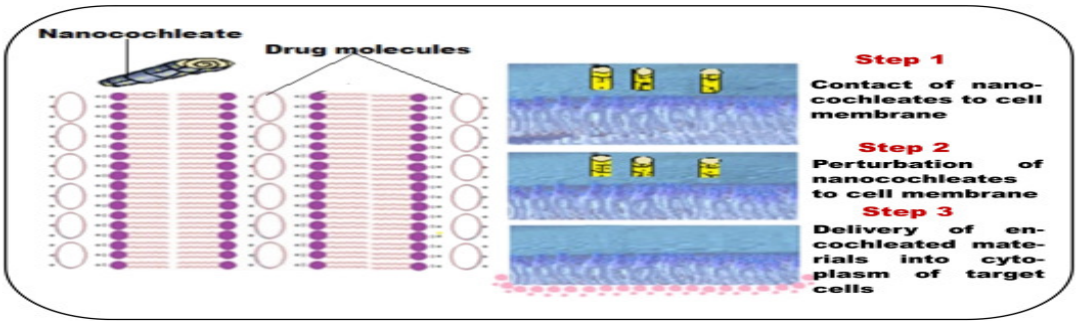

Figure 3: Mechanism of nanocochleates drug delivery [22]

MATERIAL AND METHOD

Components of nanocochleates drug delivery system

The lipids and cations are the main components used to prepare nanocochleates. Lipids such as Phosphatidyl Glycerol, Phosphatidyl Ethanolamine, Phosphatidic Acid, Phosphatidyl Glycerol and Cations such as Ca^{+2}, Zn^{+2}, Mg^{+2} etc. **[22]**

Materials

Lipids: These are the primary components needed to produce nanocochleates. The procedure usually starts with the creation of liposomes having negative charge. Phosphatidylserine (PS), a synthetic form of dioleoylphosphatidylserine (DOPS), having a -ve charged head group at physiological pH **[12, 15, 23]**. Cochleates have also been made from various negatively charged phospholipids, Furthermore, cochleates can be produced by combinations of phospholipids having negative charge and other phospholipids like phosphatidylcholine, however a greater concentration of bridging agents is needed **[18]**.

Cochleates structures can be created from naturally occurring phospholipids, such as soy PS **[24]** and soy PC **[25]**. Synthetic phospholipids with specified acyl chains are not necessary **[25]**.

Bridging agent:

An electrostatic contact between -ve charged head groups of lipids and +ve charged divalent cations in the bilayer help to preserve the shape of the rolled sheet **[18, 26]**. Divalent cations can be employed, including Ca2+, Mg2+, Ba2+, and Zn2+; however, it has been observed that the calcium ion is the most effective **[13, 27]**. Compared to cochleates created with magnesium, The dimensions of those created in calcium were smaller, and their level of dehydration was higher.

Additionally, it was discovered that calcium-based cochleates required a significantly less concentration of bridging ions and were more densely packed and well organized **[28]**. According to certain studies, biologically active compounds including tobramycin, polylysine, and oligo-acyl-lysyls can be used as bridging agents instead of metal cations. More recently, cochleates bridged with amikacin. Amikacin works in concert with low Ca2+ ion concentrations to produce tightly wrapped nanocochleates and regulation in release of drug **[29]**.

Cholesterol: Although not essential to produce the nanocochleates structure, the sterol cholesterol has been included in several cochleate formulations **[25]** This sterol can affect the structure of the nanocochleates, by improving the

phospholipids dehydration and its immobility without affecting the binding agent's stoichiometry or the phospholipid itself by changing the
acyl chain packing **[30]**.

Other components-One disadvantage of cochleates that is frequently mentioned is aggregation. It has been demonstrated that altering the cochleates surface characteristics can prevent aggregation and in turn, prevent cochleate-to-cochleate interaction. In order to keep the cochleates as separate particles, certain inhibitors of aggregation, such as casein, methylcellulose, or albumin, can be added **[15]**.

Following **Figure 4** shows classification of different methods of preparation of nanocochleates.

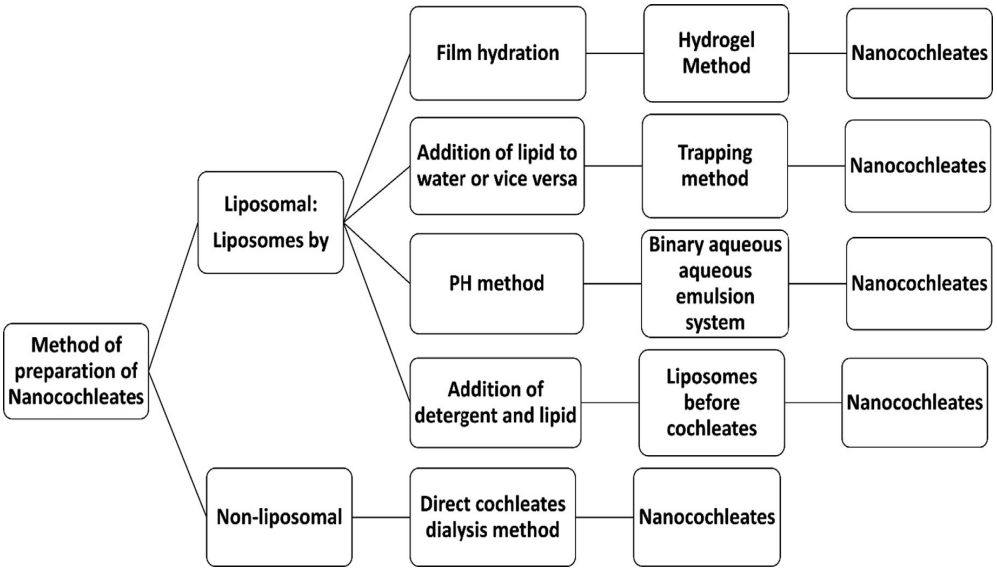

Figure 4: Classification of different method of preparations [32]

Hydrogel method [33]

The creation of cochleates is a multi-step process. Initially, the hydrogel approach was used to generate the medication-loaded small unilamellar liposomes that were connected to polymer A (phosphatidyl serine, polyethylene glycol, dextran, etc.). Polymer B (Ficoll, polyvinylpyrrolidone, polyvinyl methyl ether, polyvinyl alcohol, etc.) was mixed with the aforementioned produced dispersion. It is insoluble for the two polymers to mix together. These polymers' immiscibility aids in the formation of a two-phase aqueous solution. By adding a cationic salt solution it eventually enters a liposome or polymer particle, causing the polymers to undergo cationic cross-integration. leads to the development of tiny cochleates as shown

in **Figure 5**. After producing the nanocochleates, the polymer was extracted and lyophilized into a physiological buffer, or other suitable pharmaceutical vessel.

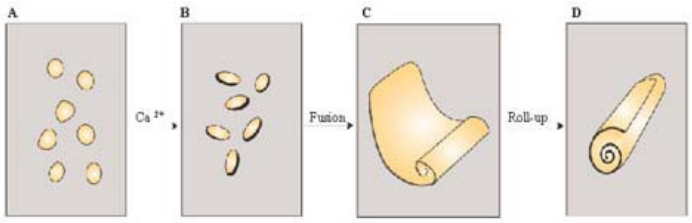

Figure 5: Formation of cochleate cylinder after addition of cation to liposomes [34]

2) Trapping method [35-41]

The method by which phosphatidyl serine liposomes were created. The procedure called for adding CaCl2 drop by drop. Either a film or the addition of water to the phospholipid substance produced liposomes. With this method, substances that are hydrophilic or hydrophobic can be encochleated. It consists of a liposomal solution formulation that, in the case of hydrophilic medications, encloses the drug in the liposome's aqueous layer or, in the case of hydrophobic drugs, intercalates the drug within the bilayers. To create a liposome, addition of water in to phospholipid or water phase can result in to formation of phospholipid film. Cochleates are formed when drop wise addition of calcium in liposomal solution occurs. Here is an explanation of the procedure:-1: liposomes are produced from lipids. By vortexing the mixture for fifteen minutes, phospholipids such as phosphatidylserine can be removed.2: Filtration is used to separate the liposomes prepared from the aforementioned solution. 3: Add trapping solvent and the hydrophobic drug to the separated liposomes, for example, ethanol or dimethylsulfoxide for the trapping solvent. 4: A drop wise addition of calcium chloride solution to the Step-3 solution results in the precipitation of crystalline cochleates. 5: To remove any remaining solvent, the cochleates are rinsed with calcium-containing solution.

The upgraded trapping method involves dissolving phospholipid in ethanol. After adding, calcium chloride (CaCl2) It is homogenized for five minutes at 13,000 rpm. Then for one hour, it is further stirred.

Liposomes prior to the cochleate dialysis technique [42]

This procedure uses a lipid and detergent mixture as initial ingredients, and two times dialysis is employed to take out the detergent. Lipid detergent mixtures such as polyethylene glycol, dextran, or

phosphatidylserine are blended with polymer A. When solution A is added in to a mixture having polymer B the two polymers become non-miscible and form two-phase polymer system. There are couple of stages involved in adding a cation moiety solution to the polymer structure. Cochleates are formed by dialyzing the mixture first with a buffer and then with a calcium chloride solution. Encapsulating hydrophobic materials or drugs with hydrophobic regions is appropriate for this strategy.

4) The direct calcium dialysis technique [42-43]

Calcium dialysis technique done directly without synthesis of intermediate liposomes, in contrast to the above-mentioned method, and the nanocochleates will be of a certain size. This approach direct dialysis ofCaCl2solution with detergent-lipid mixture, creates a big, needle-shaped structure as a result of the battle between calcium's condensation bi-layer. A polynucleotide of predetermined concentration is added to cholesterol and phosphatidylserine mixture (1:9 weight proportion) in extraction buffer and detergent which is non-ionic. Then the mixture is vortexed for five minutes at room temperature.

5.A system of binary aqueous emulsion [42]

The process entails the production of tiny liposomes. Either using a film approach or a higher pH was used to manufacture liposomes. Next, the liposomes and dextran polymer were mixed together. In the procedure described above, another insoluble polymer is added. The following stage involves applying and diffusing calcium to make nanocochleates. The gel can be removed by washing. There is evidence that the nanocochleates help with oral medication administration. The cochleates made with this method have particles that are less than 1000 nm in size

Application nanocochleates [44-46]

1. Creation of an Apo-A1 formulation based on nanocochleates in order to reduce coronary blockage and other cardiovascular conditions.
2. Proteins, peptides, and DNA use in gene therapy and vaccination applications have been delivered by nanocochleates
3. A wide variety of micronutrients can be stabilized and protected by nanocochleates, which also have the ability to raise the nutritious content of processed meals.

4. Omega-3 fatty acids can be incorporated to biscuits, cakes, muffins, spaghetti and soups using nanocochleates without change in aroma or flavor.
5. Antifungal drug like Amphotericin B in nanocochleates form, at low dosages exhibit more stability and effectiveness They exhibit higher levels of patient adherence.
6. Nanocochleates, bringing the idea of "super foods" to life, as can be used to released nutrients like vitamins and lycopene more effectively at cells without compromising food's quality. These are anticipated to have a variety of potential benefits, such as boosted energy, enhanced immunological response, improved cognitive function, and anti-aging advantages.
7. Anti-inflammatory drugs are delivered by nanocochleates.

Characterization of nano cochleate formulation

1. **Determination of size of particle**: Technique of Laser diffraction using Malvern analyzer is used Tat a temperature 30 ± 2°C while maintaining angle of detection at 90°C **[47, 13]**.
2. **Density**: Using helium or air, the density of nanocochleates is measured with a gas pycnometer. As result obtained with it are more pronounced **[48]**.
3. **Molecular weight**: Gel permeation chromatography is used to determine molecular weight and distribution of the polymer within the matrix **[49]**.
4. **Drug content:** Nano cochleates suspension is centrifuged for 40 minutes at 15,000 rpm at 25°C which result into separation of medication in supernatant. UV-Visible spectrophotometer can then be used to determine the drug's concentration in the supernatant after the correct dilution **[3]**.
5. **Entrapment efficiency (EE):** Centrifugation requires dividing a 100 µl volume of cochleates into tubes. While vortexing 60 micro-liters of ethylene diamine tetra acetic acid of pH 9.5 and 1 ml of ethyl alcohol is added into each tube. Using spectroscopic analysis, the resultant solution absorbance is determined, and equation is used to determine EE **[13, 34]**.
6. **Stability study**: For three months, cochleates dispersions are kept at

temperature 2–8°C and 25 ± 2°C/60% RH. Changes in particle size and % EE are used to assess the stability of the vesicles **[24]**.

7. **Cell-Cochleates interaction:** Interaction of cochleates with cell membrane is studied by forming fluorescent liposomes. This is done by addition of 2% fluorescent lipid **[25, 26]** Cell surfaces become fluorescent under fluorescent microscopes when cochleates make contact with the membrane of the cell through a fluorescent lipid transfer.
8. **Specific surface area:** Is measured using Asorptometer. Equation used is, $A = 6/\rho d$ Here, d is the cochleates diameter, ρ is its density, and A is its specific surface area **[28]**.
9. **Surface charge:** Nanocochleates interactions with biological tissue measured with type and strength of their surface charge. Nanocochleates velocities can be quickly and accurately measured using techniques like laser light scattering, laser Doppler anemometry or velocimetry. Another way to quantify the surface charge of colloidal particles is through electrophoretic mobility. The medicine containing nanocochleates biodistribution is determined by the composition of the charge. The electrophoretic mobility of nano cochleate is measured in human serum and phosphate saline buffer **[2]**.
10. **In vitro release study**: Standard dialysis, diffusion cell, or modified ultra-filtration procedures are utilized. Typically, phosphate buffer is employed. A low protein binding membrane made by Millipore divides the two compartments. After pouring nanocochleates into the donor chamber, the receptor compartment is checked periodically using standard techniques to check for the release of medication and submitted to standard procedures to identify the released drug **[25]**.
11. **Analysis of surface morphology**: The transmission electron microscope is used. Sample which is diluted, drop is applied on copper grid coated in carbon in order to prepare the sample for this research. Following the removal of surplus solution, Using TEM sample is examined and photographed at an 80 kV accelerating voltage **[30, 50]**.
12. **Differential scanning calorimetry** – is widely used in different industry

especially pharmaceutical. The application of this technique is to reveal important information about the physicochemical properties of drug and excipient molecules, such as stability, purity, and formulation compatibility. DSC is thermo-analytical method that measures the variation in heat needed to raise a sample's temperature relative to a reference as a function of temperature. The samples are heated at a constant rate of 10 °C/min while being hermetically packed in perforated aluminum pans and subjected to temperatures between -10 and 180 °C. To maintain the atmosphere's inert state, nitrogen gas is purged at a rate of 100 ml/min. **[13, 28, 31]**

13. **Fourier transform infrared spectroscopy**- An investigation using Fourier transform infrared spectroscopy confirms the compound's purity and the presence of functional groups. To prepare samples, blend them with KBr. Samples are then put inside the holder. The specific wave number ranges are covered by scanning the spectra at ambient temperature **[13]**.

CONCLUSION

Nanocochleates have demonstrated widespread applicability to a variety of biologically significant compounds. Encapsulation can improve a finished product by enhancing its qualities during processing, increasing shelf-life stability, improving bioavailability, lowering toxicity, and increasing efficacy.

Because of its distinct multilayered structure, nanocochleates shields the active substances that are intended to be transported inside. As a result, nanocochleates overcome the drawbacks of alternative medication delivery methods. The number of patent applications and publications pertaining to nanocochleates has skyrocketed, suggesting a growing interest in medication delivery from both industry and academia. Because of this, the use of nanocochleates drug delivery systems in pharmaceutical development is becoming more significant in order to deliver appropriate amount of medicine into the body with promising results.

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