



A Novel Drug Delivery: Nanocochleates

Dr. Martha Srinivas^{*1}, Markad Pranali Sampat², Pawar Pratiksha Baburao³, Dr. Vishal Bharat Babar⁴

¹Professor & HOD, Dattakala Shikshan Sanstha Institute of Pharmaceutical Science & Research (For Girls), Swami-chincholi, Bhigwan, Pune, Maharashtra, India-413130.

^{2,3}B.Pharm Students, Dattakala Shikshan Sanstha Institute of Pharmaceutical Science & Research (For Girls), Swami-chincholi, Bhigwan, Pune, Maharashtra, India-413130.

⁴Principal & Professor, Dattakala Shikshan Sanstha Institute of Pharmaceutical Science & Research (For Girls), Swami-chincholi, Bhigwan, Pune, Maharashtra, India-413130.

*Corresponding author's E-mail: srinivaaspharma@gmail.com; *1ORCID ID: <https://orcid.org/0000-0002-0264-9095>

Received: 06-04-2024; Revised: 28-05-2024; Accepted: 10-06-2024; Published on: 15-06-2024.

ABSTRACT

Dr. Dimitrios Papahadjopoulos and his team found cochleates as precipitates formed by the interaction of negatively charged phosphatidylserine with calcium. They are used to provide vaccinations by delivering peptides and antigens. In nanocochleates, a new drug delivery vehicle, the targeted drug molecule is enclosed in a multi-layered structure including a solid-lipid bilayer within a spiral-shaped sheet. Encochleation of the drugs is used in this approach to overcome issues such as poor solubility, permeability, and oral bioavailability. They protect the molecule from harsh environmental conditions like pH, temperature, and enzymes. Because it has both hydrophilic and lipophilic forms on its surface and in its structure, it can contain both hydrophilic and lipophilic drug molecules. The loading capacity of the drug molecule to encapsulate is determined by the physical structure of the cochleates, while the encapsulation procedure defines the particle size of the complex formed. It can be used to deliver biologically active substances orally and systemically, including medications, DNA, proteins, peptides, and vaccine antigens. This method can be used for systemic as well as oral therapeutic delivery, and it may eventually be developed into a drug delivery system. These factors will encourage researchers to look into this emerging field of drug delivery technology. There are numerous methods for creating nanocochleates, which can then be used to administer different active compounds for a range of applications. This article discusses the composition and structure of nanocochleates as well as the drug administration mechanism, manufacturing techniques, assessment, uses, and limitations of these compounds.

Keywords: Nanocochleates, solid lipid bilayer, Encochleation, hydrophilic, lipophilic, drug delivery.

INTRODUCTION

Much emphasis has been paid to the recent development of novel drug delivery systems (NDDS) throughout the past few decades. Two basic requirements should be present in a great NDDS: -

1. It should distribute the medicine at a pace determined by the body's needs over the course of treatment.
2. It should transport the active ingredient/chemical moiety to the active site.

It is more appropriate and feasible to develop a novel drug delivery method that raises the therapeutic efficacy of

both existing and new drugs. Consequently, it allows for controlled and long-term drug administration to a specific location¹.

COCHLEATES are a fresh new class of drug carriers that resulted from a variety of alterations to liposome compositions. These are spiral-shaped, solid particles devoid of an internal aqueous phase, formed from massive, unbroken lipid bilayer sheets. Unlike liposomes, cochleates have a water-free interior, a rod form, and a stiff, stable structure (as shown in fig.1). These properties of cochleates are frequently exploited for drug administration when bioavailability is a problem².

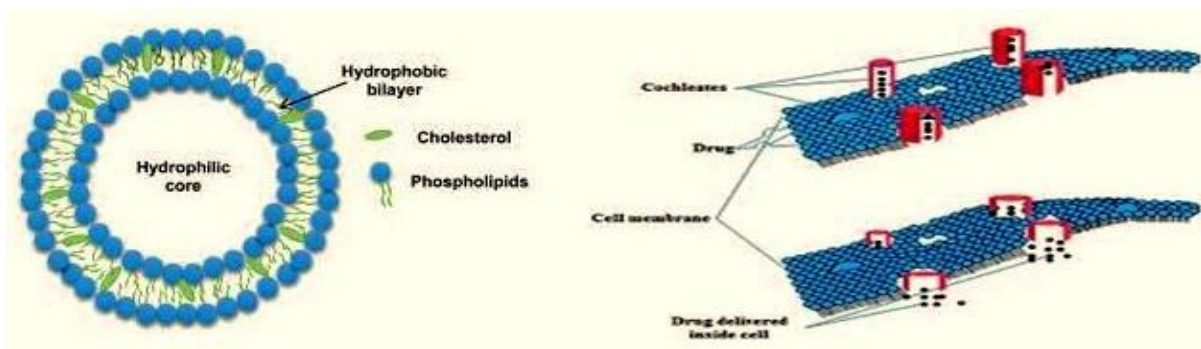


Figure 1: Structural difference between Liposomes and Cochleates

The multi-layered lipid crystal matrix of the nanocochleate drug delivery vehicle encapsulates medications to be delivered to the target region in a manner that is likely both safe and efficacious (a cochleate). These are persistent phospholipid-cation precipitates made out of natural elements such as Phosphatidylserine and Calcium³.

Encapsulated material is shielded against deterioration by nanocochleates. Since the nanocochleate structure is composed entirely of solid layers, components enclosed within it stay undamaged, although its outside layers may be subjected to harsh environmental factors or enzymes. Drugs that are hydrophobic and amphipathic will be confined in nanocochleates because they have surfaces that are both hydrophilic and hydrophobic⁴ (shown in fig. 2). The physical makeup of the cochleates can be used to estimate the loading capacity of the drug to encapsulate, while the encapsulation technique determines the particle size of the complex that is produced⁵. The most adaptable method for delivering medications and molecules is nanocochleate. These include proteins and peptides, polynucleotides, tranquilizers, steroidal and non-steroidal anti-inflammatory agents, immunosuppressants, antiviral, anesthetic, and vitamin products⁶.

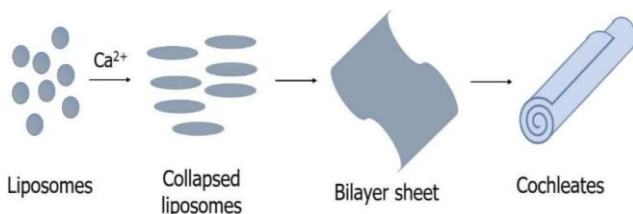


Figure 2: Nanocochleate formation by interaction between negative lipids and cations

HISTORY:

Cochleates were discovered by Dr. Dimitrios Papahadjopoulos and his team as precipitates generated by the relationship between negatively charged phosphatidylserine with calcium. They are employed in the transfer of peptides and antigens for vaccination delivery. Due to their rolled-up appearance, these cylindrical constructions are COCHLEATE, which means SHELL in Greek.

It doesn't seem that cochleate structures form uniformly. With the dialysis process, they can be produced as enormous needle-like structures, or as aggregates of distorted sheets utilizing the trapping approach. Cochleates were first used in 1999 to develop smaller particles utilizing the hydrogel isolation process.

Making use of a binary phase system, similar to non-miscible hydrogels, small mean particles of less than 500nm will be generated. These nanocochleates were especially suitable for encasing medications that are hydrophobic⁷.

STRUCTURE AND COMPOSITION:

Using multivalent counter ions (Ca^{2+} or Zn^{2+}) as combining agents between bilayer structures, negatively charged phospholipid bilayers are rolled up to create

nanocochleates, a form of spiral roll (shown in fig. 3). By eliminating the bridging counter ions from the inner bilayer gaps, these solid particles can be easily transformed into liposomes due to their extreme malleability⁸.

Lipids, cations, and pharmaceuticals are the three main components utilized in the creation of nanocochleates.

1. Lipids:- Phosphatidyl serine (PS), Phosphatidic acid (PA), Dioleoyl PS, Phosphatidylinositol (PI), Phosphatidyl glycerol (PG), Phosphatidyl choline (PC), Dimyristoyl PS, Phosphatidyl ethanol amine (PE), Diphosphatidyl glycerol (DPG), Dioleoyl phosphatidic acid, Distearoyl phosphatidyl serine, Dipalmitoyl PG.
2. Cations:- Zn^{2+} , Ca^{2+} , Mg^{2+} and Ba^{2+} .
3. Drug:- Protein, Peptide, Polynucleotide, Herbal product, Antiviral agent, Anaesthetic agent, Vitamin, Anticancer agent, Immunosuppressant, NSAIDS, Tranquilizer, Nutritional supplement⁹.

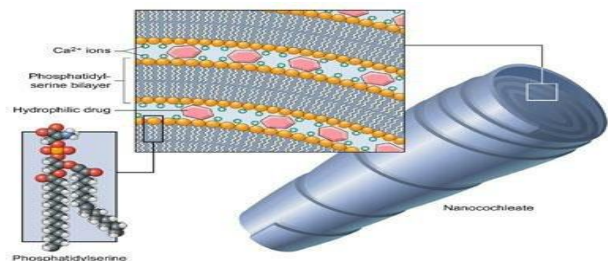


Figure 3: Structure and Composition of Nanocochleates

ROUTES OF ADMINISTRATION:

Effective oral medication delivery is made possible by the nanocochleate drug delivery device. Possible administration routes include intravaginal, parenteral, topical, rectal, sublingual, mucosal, nasal, ophthalmic, subcutaneous, transdermal, intramuscular, intravenous, spinal, intrathecal, intraarticular, intraarterial, subarachnoid, bronchial, lymphatic, and intrauterine¹⁰.

Dosage Form: Oral administration of capsules, sachets, pills, tablets, lozenges, powders, granules, solution, suspension, or emulsion Topical or transdermal delivery agents include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches, and inhalants. Sterile powders can be easily reconstituted into injectable or isotonic solutions, suspensions, or emulsions for parenteral administration.¹¹

Stability: Encochleation provides both protection and stability to linked molecules. Since these cochleates are composed entirely of solid-lipid bilayers, their constituent parts stay intact even when their outside layers—which contain enzymes—are exposed to severe external environmental conditions. This structure's interior is free of water and resistant to oxygen penetration, resulting in a longer shelf life for the formulation. Nanocochleates can be lyophilized to create powder, or they can be kept at room temperature or 40 degrees Celsius. Lyophilized cochleates

are frequently reconstituted with fluids before being used *in vitro* or *in vivo*¹².

Advantages:

1. Because of its non-aqueous inner core, which reduces the lipids' sensitivity to oxidation, cochleates are more stable¹³.
2. The lyophilization process extends the formulation's shelf life and makes room temperature storage possible for extended periods of time.
3. Encochleated pharmaceuticals are protected from degradation induced by environmental variables such as sunshine, water, oxygen, temperature, or gastrointestinal enzymes¹⁴.
4. Drugs that must be delivered parenterally are frequently given as cochleates orally. For example, Amphotericin B¹⁵.
5. They improve the oral bioavailability of many different chemicals, such as high lipophilicity drugs, genes, vaccines, proteins, and peptides, as well as biopharmaceutical items that are challenging to give. For example, ibuprofen with artemisinin.
6. Because the lipid bilayer of nanocochleates is composed of simple, naturally occurring lipids that are nontoxic, non-immunogenic, and non-inflammatory, they are safer and more biocompatible¹⁶.
7. They permit the addition of biological molecules with comparatively large molecular weights and hydrophobic moieties. For example Insulin nanocochleates¹⁷.
8. Hydrophobic drugs and antigens containing hydrophobic fragments can be encochleated into the lipid bilayer of the cochleate structure. For example, Amphotericin B and Clofazimine.
9. This kind of formulation increases the drug's permeability across the intestinal lumen. For example, compared to regular Rifampicin, the apparent permeability of Rifampicin nanocochleates is about two times higher¹⁸.
10. Vaccines frequently contain live organisms that have been attenuated or inactivated in order to prevent sickness. The vaccine adjuvant delivery system (VADS) uses carriers such as liposomes, virosomes, and cochleates to carry antigens to specific cells, results in the faster, stronger, and longer-lasting immune response¹⁹.

Limitations:

1. They must be stored under certain circumstances.
2. Manufacturing costs are astronomically high.
3. Aggregation can happen during storage, which an aggregation inhibitor can prevent²⁰.

Mechanism:

Lipids make up a large part of the cell membrane. When another lipid molecule comes into touch with the cell membrane, the lipid molecules fuse together and the content is distributed throughout the cell. The

nanocochleates drug delivery system used this mechanism. Lipid bilayer structure of nanocochleates merges with the target cell's membrane. causing the medication to slowly release²¹(shown in fig.4).

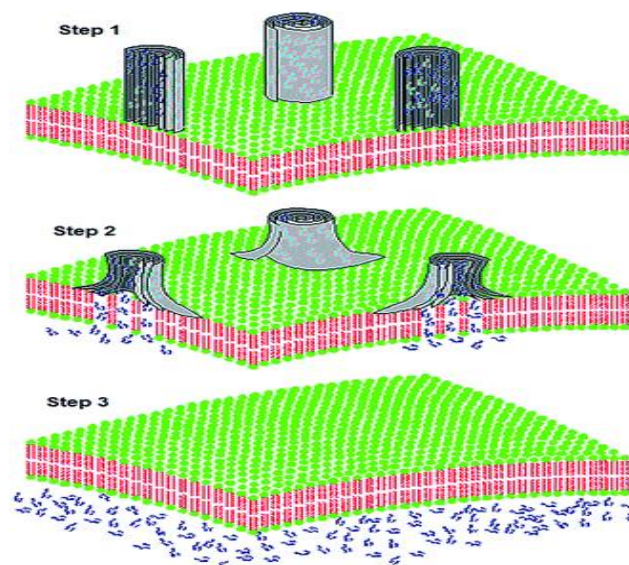


Figure 4: Schematic representation by Nanocochleate interaction with cell membrane

Absorption:

Following oral delivery, nanocochleates are absorbed from the intestine. The intestinal epithelial barrier is crossed by nanocochleates, which then enter blood vessels and release their active chemicals. They pass the related cell and enter circulation via any route other than intravenous (shown in fig.5). Once in the bloodstream, selected cells are given nanocochleates²².

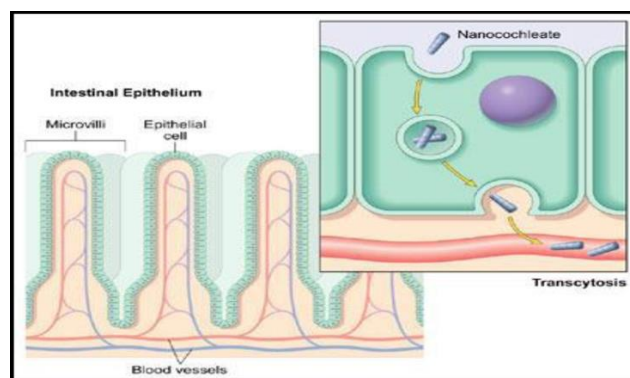


Figure 5: Absorption of Nanocochleates

Delivery to the targeted cell:

The relationship between negatively charged lipids and calcium has been extensively studied. In several naturally occurring membrane fusion processes, calcium ions interact with negatively charged phospholipids. Numerous *in vivo* membrane fusion mechanisms depend on membranes with negatively charged lipids being pertubated by calcium and then undergoing further membrane fusion events (fig. 6). Cochleates are therefore believed to constitute intermediates in membrane fusion²³.

1. Delivery following phagocytosis: Macrophages and neutrophil membranes include phosphoryl-serine (PS) receptors, which phagocytose nanocochleates. The liposome membrane then undergoes perturbation and reassembles when nanocochleates come in close proximity to it. As a result, the liposome membrane and the outer layer of the nanocochleates fuse together. Consequently, a small quantity of the encocchleated material is introduced into the target cell's cytoplasm.

2. Delivery by cell membrane fusion: When nanocochleates come into contact with a natural membrane, the cell membrane is disrupted and then reassembled, fusing the outer layer of the nanocochleates with the membrane. This fusion results in the delivery of a tiny quantity of the encocchleated material into the target cell's cytoplasm. In order to prepare for fusion with this or another cell, the nanocochleate may progressively fuse or break free of the cell.²⁴

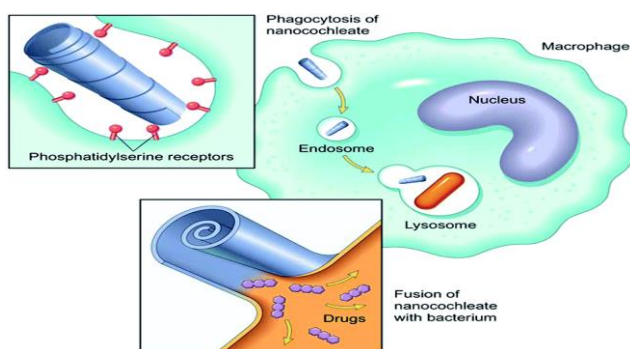


Figure 6: Nanocochleate delivery by direct membrane fusion

Characterization of Nanocochleate formulation:

1. Determination of particle size: Particle size has a significant influence on absorption phenomena. Micrometer-sized particles, which have a smaller surface area for absorption, compared to the nanometer-scale particle size. Using a Malvern analyzer, laser diffraction techniques can be utilized to determine the particle size of nanocochleates dispersion. The analysis must be performed at a temperature of $30 \pm 20^\circ\text{C}$ with a 90° angle of detection²⁵.

2. Density: The density of nanocochleates is measured using a pyranometer.

3. Content of drugs: Following centrifugation, the dispersed nanocochleates suspension is centrifuged at 15,000 rpm for 40 minutes at 25°C to extract the free medication from the supernatant. The complimentary medication After an appropriate dilution, the concentration in the supernatant can be measured using ultraviolet UV-Vis spectrophotometry.²⁶

4. Entrapment efficiency (EE): This is calculated by isolating nonencapsulated centrifugation of suspension for 30 minutes at 5000 rpm 27°C . The sediment vesicles were disrupted with solution of disodium EDTA to break nanocochleates structure in to nanoliposome then add ethanol to release the entrapped drug The absorption of

resulting solution determine using UV- Visible spectroscopic tech and entrapment efficiency is calculate.

Entrapment efficiency = Amount of drug present in nanocochleates / Total amount present

5. Stability study: For the stability study the nanocochleates dispersion can be kept at $2-8^\circ\text{C}$ and $25 \pm 2^\circ\text{C}/60\% \text{RH}$ for 3-month to check the stability of nanocochleates dispersion. The stability of nanocochleates is determined. Check the particle size and percent entrapment efficiency, drug release through nanocochleate formulation after their stability study.

6. Specific surface area: The sorptometer is used to determine the specific surface area of freeze dried nanocochleates following equation use to calculate the specific surface area of nanocochleates.

$$A=6/pd$$

Here A=specific surface area,

P=Density

d=Diameter of cochleates

7. Surface charge: The surface charge of the nanocochleate molecules determines the stability of the formulation; if the surface charge of one or more nanocochleate molecules is the same, there will be a strong repulsion between one or more aggregates are not seen because of nanocochleates. Strong attraction between molecules of nanocochleates occurs when their charges are opposing, leading to increased aggregation.

The velocities of nanocochleates are measured using laser light scattering methods as Laser Dropller Anemometry (LDA) and Laser Dropller Velocimetry (LDA). Electrophoretic mobility of nanocochleates is another method for measuring the surface charge of colloidal particles.

8. In vitro study of release: Standard dialysis, diffusion cell, or modified ultra-filtration methods are used to investigate the nanocochleate release profile in vitro²⁷.

METHOD OF PREPARATION:

Nanocochleates are made from liposomes suspended in an aqueous two-phase polymer solution, which allows for phase separation and differential partitioning of polar molecule-based structures. Liposomes with a two-phase polymer solution that has been treated with positively charged molecules like Ca^{2+} or Zn^{2+} . As a result, a nanocochleate precipitate with a particle size of less than one millimetre forms. The method could be utilised to make nanocochleates with biologically important molecules²⁸.

1. Hydrogel method
2. Trapping method
3. Liposomes before cochleates (LC) dialysis method
4. Direct calcium (DC) dialysis method
5. Binary aqueous-aqueous emulsion system

6. Solvent drip method

1. Hydrogel method: The following steps are involved in the creation of nanocochleates using the hydrogel method:

Step 1: A suspension of small unilamellar liposomes or molecule-loaded liposomes is made that are biologically relevant. Standard procedures like as sonication, microfluidization, and other comparable processes can be used to accomplish this.

Step 2: Polymer A such as Dextran (mol.wt – 2, 00,000– 5, 00,000), Polyethylene glycol (mol.wt – 3400– 8000), or Phosphatidyl serine is added to the liposome solution.

Step 3: The liposome/polymer A solution is combined with another polymer B, such as Polyvinyl pyrrolidone, Polyvinyl alcohol, Ficoll (mol.wt – 30,000 – 50,000) and Polyvinyl methyl ether (PVMB) (mol.wt – 60,000 – 1,60,000), resulting in an aqueous two-phase polymer system. Mechanically this could be accomplished using a syringe pump set to the right rate.

Step 4: A cation salt solution is introduced to the two-phase system of steps 3 so that the cation diffuses into polymer B and then subsequently into the particles that make up the liposome/polymer A, causing miniature cochleates to develop.

Step 5: Cochleate precipitates are periodically washed with a buffer solution containing a positively charged molecule, particularly a divalent cation, to isolate the cochleate structures and remove the polymer solution. (As depicted in fig.7)

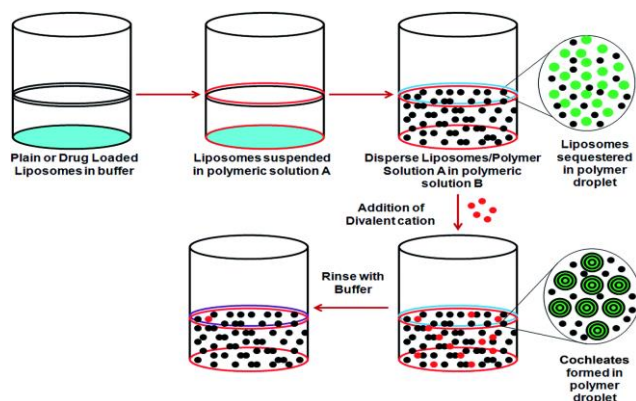


Figure 7: Schematic representation of Hydrogel method

2. Trapping method:

Enochleation of both hydrophilic and hydrophobic compounds is possible with this approach. It comprises of a liposomal solution formulation that encloses the drug in the aqueous layer of the liposome for hydrophilic drugs or intercalated within the bilayers for hydrophobic drugs. Water could be added to phospholipid powder or water phase could be added to phospholipid film to make liposomes. The addition of calcium to a liposomal suspension drop creates a cochleate assembly. (as depicted in fig.8)

When comparison to other approaches, cochleates created utilising the trapping method have more aggregation, which can be evaluated by electron microscopy after freeze fracture. It entails the following procedures:

Step 1: To make liposomes from phospholipids like phosphatidyl serine, vortex the fluid for 15 minutes.

Step 2: Filtration is used to separate the prepared liposomes from the aforementioned solution.

Step 3: A capturing solvent, such as ethanol or dimethyl sulfoxide, is added to the separated liposomes, followed by the hydrophobic medication.

Step 4: Precipitate crystalline cochleates by adding a calcium chloride solution dropwise to the step 3 solution.

Step 5: To remove any remaining solvent, the cochleates are rinsed with a calcium-containing buffer.

Dioleoyl phosphatidyl serine (DOPS) is dissolved in ethanol in the modified trapping method. Calcium chloride (CaCl_2) is added and homogenised for 5 minutes at 13000 rpm before being agitated for 1 hour²⁹.

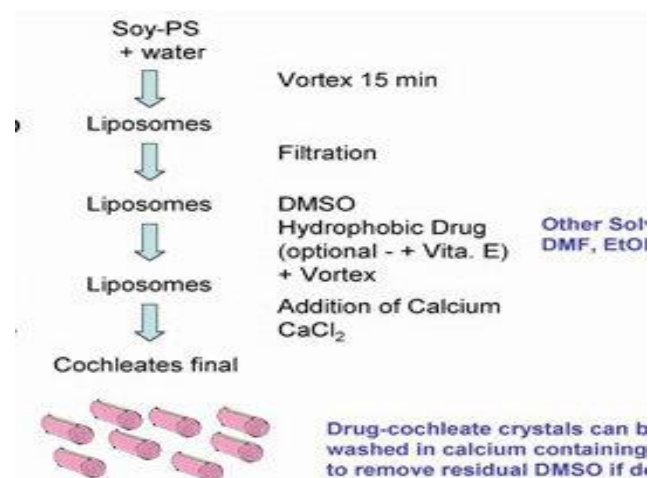


Figure 8: Schematic representation of Trapping Method

3. Liposomes before cochleates (LC) dialysis method:

This approach is used to make tiny cochleates, which are made up of lipids, detergent, a physiologically relevant chemical, and a cation. Adding detergent has the primary goal of disrupting the liposomes. After dialyzing the mixture with a buffer, calcium chloride is added to produce the cochleates. Double dialysis is used to clear away the detergent. The steps in this procedure are as follows:

Step 1: Using the lipid detergent mixture, an aqueous suspension is made.

Step 2: Combine polymer A with the suspension generated in step 1, such as polyethylene glycol (PEG) dextran or phosphatidyl serine.

Step 3: The detergent – lipid/polymer A. Polymer B, such as polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), and polyvinyl methyl ether (PVME), is added to a solution containing polymer A. Polymer A and polymer B are immiscible and form a two-phase polymer system.

Step 4: To the two-phase polymer system, a cationic moiety solution is introduced.

Step 5: Polymer is removed by washing the two-phase polymer system³⁰.

4. Direct calcium (DC) dialysis method:

This approach is used to produce large cochleates. The lipid and detergent mixture is dialyzed directly against a calcium chloride solution. The steps in this procedure are as follows:

Step 1: In an extraction buffer, phospholipids and cholesterol (9:1) are combined in a 9:1 weight ratio.

Step 2: A non-ionic detergent is combined with a predetermined concentration of API and vortexed for 5 minutes.

Step 3: At room temperature, the clear solution generated in step 2 is dialyzed against three different buffers.

Step 4: The last dialyses are carried out in a 6mM Ca²⁺ solution, however 3mM Ca²⁺ is enough. The white calcium phosphor lipid that results is DC cochleate³⁰.

5. Binary aqueous-aqueous emulsion system:

The incompatibility of two-phase systems of polymer solutions, both of which are aqueous and immiscible with one other, is the basis for this approach. This approach does not necessitate the use of an organic solvent. It's utilised to make cochleates with a diameter of less than 1000nm. The steps in this procedure are as follows:

Step 1: Liposomes are created using either a high PH or a film technique.

Step 2: Liposomes are combined with a polymer A like Dextran.

Step 3: The dextran/liposome phase is then combined with a non-miscible polymer, such as PEG.

Step 4: Calcium is then added to the step 3 solution, causing Nanocochleates to diffuse softly from one phase to the next. The gel is then rinsed in physiological buffer³¹.

6. Solvent drip method:

It entails making a liposomal suspension from Soy PS and a hydrophobic or amphipathic cargo moiety solution separately. Dimethyl sulfoxide or dimethyl formamide should be used as the solvent for hydrophobic drugs. After that, the solution is added to the liposomal suspension. Because the solvent is miscible with water, the cargo moiety's solubility is reduced, which is linked to the lipid hydrophobic liposomal bilayers at least in part. Addition of calcium leads to the production of cochleates. The excess solvent should be washed.

EVALUATION:

1. Density: A gas pycnometer with helium or air is used to determine the density of nanocochleates. Due to the specific surface area and porosity of the structure, the

value obtained with air and helium is substantially higher.

- 2. Particle size determination:** The mean particle size of liposomal and cochleate dispersion can be calculated using a Malvern analyzer and a laser diffraction technique. This analysis should be performed at a temperature of 30±2°C with a detection angle of 90°.
- 3. Molecular weight determination:** Using a refractive index detector, the molecular weight of the polymer and its distribution in the matrix can be determined using gel permeation chromatography (GPC). Polyalkylcynoacrylate nanocochleates are formed by the entanglement of many small oligomeric subunits rather than the rolling up of one or a few large polymer chains, according to GPC³².
- 4. Drug content:** The redispersed nanocochleates suspension is centrifuged at 15,000 rpm for 40 minutes at 250°C to extract the free drug in the supernatant. After appropriate dilution, the concentration of medication in the supernatant can be measured using ultraviolet UV-Vis spectrophotometry.
- 5. Entrapment efficiency:** 100L of cochleates are aliquoted into centrifugation tubes to increase entrapment efficiency (EE). While vortexing, add 60L PH 9.5 ethylenediamine tetra acetic acid and 1ml ethanol to each tube. The spectroscopic approach is used to quantify the solution's absorbance, and the EE is computed using equation.

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

- 6. Stability study:** Cochleates dispersions could be stored at 2-8°C and 25±2°C/60% percent RH for three months to test their stability. The vesicles stability is measured in respect of particle size change and percent EE³³.
- 7. Cochleate-cell interaction:** Fluorescent liposomes are formed using 2% fluorescent lipid in addition to negatively charged lipid. Cell surfaces become fluorescent under fluorescent microscopes when cochleates contact with cell membranes via a fluorescent lipid transfer.

8. Area of specific surface:

A sorptometer can be used to determine the specific surface area of freeze-dried nanocochleates. To calculate a certain surface, use the following equation³⁴: -

$$A=6/pd$$

Where, A=Specific surface area

p=Density

d=Diameter of the cochleate.

- 9. Surface charge:** The particle velocity in an electric field is used to determine surface charge. For determining nanocochleate velocities, laser light scattering



techniques such as laser doppler anemometry or velocimetry are used as quick and high resolution approaches. Electrophoretic mobility is a measurement of colloidal particle surface charge. The electrophoretic mobility of nanocochleate is determined in a phosphate saline buffer and human serum. The absolute charge value of nanocochleate is reduced by the phosphate saline buffer (PH 7.9) due to ionic interaction of buffer components with the charged surface of nanocochleate.

10. Study of in vitro release:

Standard dialysis, diffusion cell, or modified ultrafiltration procedures are used to determine the nanocochleate release profile in vitro. The most common method is to utilise double chamber diffusion cells with phosphate buffer on a shake stand. Between the two chambers is a Millipore low protein binding membrane. Nanocochleates have been placed in the donor chamber. Standard protocols are used to test the released medication in the receptor compartment at various time intervals.

In vitro release behaviour of nanocochleates is also studied using a modified ultrafiltration approach. Nanocochleates are immediately introduced to a stirred ultrafiltration cell with a buffer in this method. At varied time intervals, aliquots of the medium are filtered through the ultrafiltration membrane and tested for the released drug using established procedures.

APPLICATIONS:

1. An Apo – A1 formulation based on nanocochleate was created to treat coronary atherosclerosis and other coronary heart diseases³⁵.
2. Nanocochleates are utilised in vaccination and gene transfer therapy applications to transport proteins, peptides, and DNA.
3. Nanocochleates has the potential to increase the nutritional value of processed meals by stabilising and protecting a wider spectrum of micronutrients.
4. Nanocochleates can supply omega-3 fatty acids to cakes, muffins, pasta, soups, and cookies without changing the taste or odour of the final product³⁵.
5. Cochleates have the benefit of lowering toxicity and increasing bactericidal activity³⁶.
6. Nanocochleates has the potential to deliver Amphotericin B, an antifungal drug, orally and parenterally while maintaining a better safety profile and lowering treatment costs³⁷.
7. Bio delivery sciences international (BDSI), a US-based company, has developed nanocochleates that can be used to deliver nutrients such as vitamins, omega fatty acids, and lycopene to cells more effectively without modifying the colour or taste of food, bringing the concept of superfoods closer to reality³⁸.

FUTURE PROSPECTS:

Antigens, proteins, polynucleotides, polypeptides, vitamins, minerals, and amino acids are among the physiologically relevant compounds delivered as nanocochleate. Cochleates will be utilised to mask harsh taste and odour in medications that are photolabile and vulnerable to oxidation. Alternative routes of administration, including as intranasal, transdermal, and vaginal, may be investigated in the future. In cancer, diabetes, tuberculosis, and neurological illnesses, it acts as a carrier for targeted drug delivery by active targeting, which is frequently performed utilising ligand targets or magneto – cochleates. Combining DNA plasmids and proteins with cochleates is a common way to transfer genes into the genome of a faulty cell or hematopoietic cells. This method has the potential to cure an extensive range of genetic disorders.

CONCLUSION

Nanocochleates have a multi-layered structure that protects the active pharmacological component or substances being transported. It protects encocochleated molecules against harsh environmental factors such as temperature, pH, and enzymes. Due to the bilayer nature of lipids, this system can transport both hydrophilic and hydrophobic drugs. Nanocochleates are widely employed to deliver various active therapeutic medicines, overcoming the difficulties of traditional drug delivery techniques. For efficient delivery, several medication candidates can be encased in nanocochleates. Patent filings and publications of nanocochleates have increased dramatically, indicating a surge in both industrial and academic interest in the drug delivery field.

Acknowledgement: The Authors hope to showed heartfelt appreciation to Dattakala Shikshan Sanstha Institute of Pharmaceutical Science & Research (For Girls), Swami-chincholi, Bhigwan, Pune, Maharashtra, India-413130.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

1. Li V, Robinson J, Lee V. Influence of drug properties and routes of drug administration on the design of sustained and controlled release systems. *Controlled drug delivery: Fundamentals and Applications*. 1987;29:3-61.
2. Dharmesh Gol, Viral Shah. Nanocochleates: A novel approach for drug delivery. *World Journal of Pharmaceutical Research*. 2014;2(3):1920-1944.
3. Rohit Rajendra Bhosale, Prasanna Prasad Ghodake, Abhyang Shree Nandkumar Mane, Amruta Avinash Ghadge. Nanocochleates: A novel carrier for drug transfer. *Journal of Scientific and Innovative Research*. 2013;2(5):964-969.
4. Egan W.J., Lauri E. Prediction of Intestinal Permeability. *Adv. Drug delivery review*. 2002;54: 273-289.



5. Swapnil E. Yeole, Smita S. Pimple, Pravin D. Chaudhari. A review on nanocochleate – A novel lipid based drug delivery system. *Journal of Biomedical and Pharmaceutical Research*. 2013;2(1):1-7.
6. Papahadjopoulos D, wilschut J. Calcium induced fusion of phospholipids vehicles. *Nature*. 1979; 281:690-692.
7. Sangita Fulchand Pawar, Sunil S. Bothara, Paresh R. Mahaparale and Vikram L. Musale. Nanocochleate - an important drug delivery system offering unique features. *World Journal of Pharmaceutical Research*; 2020;9(9):621-637.
8. Thiruganesh Ramasamy, Umadevi Khandasamy, Ruttala Hinabindh, Kiran Kona. Nanocochleate - a new drug delivery system. *FABAD J.Pharm.Sci*. 2009;34:91-101.
9. Sashi K, Satinder K, Bharat P. A complete review on liposomes. *International Research Journal of Pharmacy*. 2012;3:10-6.
10. Zarif L, Jin T, Segarra I, Mannino RJ. Novel hydrogel isolated cochleate formulations, process of preparation and their use for the delivery of pharmaceutical agents. PCT Application wo 01/52817 A2. Filed 1/22/2000. US patent 6,153,217.
11. O' Donnell, Francis Ejr, Gould-Fogerite S, Mannino RJ. Apoprotein-cochleate compositions. US Patent Application 2006/0019870 A1.2006.
12. Delmorre D, Lu R, Tatton N, Krouse-Elsmore S, Gould-Fogerite S, Mannino RJ. Formulation of hydrophobic drugs into cochleate delivery vehicles: A simplified protocol and formulation kit. *Drug Deliv Technol*. 2004;4:64-9.
13. Agardan NBM, Degim Z, Yilmaz S, Altintas I and Topal T: the effectiveness of Raloxifene-Loaded Liposomes and cochleates in Breast Cancer Therapy. *AAPS Pharm Sci Tech* 2016;17(4):968-977.
14. Asprea M, Tatini F, Piazzini V, Rossi R, Bergonzi MC and Bilia AR. Stable, monodisperse, and highly cell-permeating nanocochleates from natural soy lecithin liposomes. *Pharmaceutics* 2019;11(1). Doi: 10.3390/Pharmaceutics 11010034.
15. City SL (12) Patent Application Publication (10) Pub.no: US 2014/0265900 A1 Se156 Yv Patent Application Publication 2014;1(19):36-42.
16. Shuddhodana, Wong Pwk and Judch Z: Continuous, high-throughput production of Artemisinin-loaded supramolecular cochleates using simple off the shelf flow focusing device. *Mater Sci Eng C* 2020;108:110410. Doi:10.1016/j.msec.2019.110410.
17. Yucet C, Altintas Y and Degim Z. Novel approach to the treatment of Diabetes: embryonic stem cell and Insulin-loaded liposomes and nanocochleates. *J Nano Sci Nanotechnol*; 2019;19(7):3706-3719.
18. Yadav A and Chaudhary S. Formulation development and characterization of nanocochleates for the improvement of permeability of drug. *JAPE and Res*. 2016;6(3):14-21.
19. Wang N, Wu T and Wang T. Liposomes used as a vaccine adjuvant – delivery system. *Liposomes* 2017. Doi:10.5772/intechopen.68521.
20. Ashish Y. Pawar, Khanderao R. Jadhav, Nishigandha B. Sonkamble, Manisha R. Kale. Nanocochleates: a novel drug delivery system. *Asian Journal of Pharmaceutics*. 2016: 10(3):234-242.
21. Wasankar S, Makeswar K, Deshmukh A. Nanocochleate : A review. *Research J. Pharm. Dosage Forms and Tech*, 2012;4(3):153-159.
22. Panchangnula R., Sood A.. Peroral route: an opportunity for protein and peptide drug delivery. *Chem. review*. 2001;101:3275-3304.
23. Panwar Vijeta, Mahajan Vivek, Panwar A.S, Darwhekar G.N, Jain D.K. Nanocochleate : As drug delivery vehicle. *International Journal of Pharmacy and Biological Sciences*. 2011;1(1):31-38.
24. Bio delivery sciences international (2005). Retrieved September 13, 2006 from <http://www.biodeliverysciences.com/Aboutnanocochleatetechnology.html>
25. Ashish Y. Pawar, Khanderao R. Jadhav, Nishigandha B. Sonkamble, Nanocochleate: A Novel Drug Delivery System .*Asian Journal Of Pharmaceutics*, 2016; 10(3):18-26.
26. Zarif L, Graybill J, Perlin D . Cochleate New Lipid Based Drug Delivery System. *Journal Of Liposome Research*, 2000; 10(4):523-538.
27. Bhosale RR, Ghodake PP, Nandkumar.A, Mane AG. Nanocochleates: A Novel Carrier for Drug Transfer. *J. Sci Innov Res.*, 2013;2:964-9
28. Mannino.R.J., Gould-Fogerite, S., Krause Elsmore, S.L., Delmarre, D., and Lu, R. 2005. Novel Encochleation methods, cochleates and methods of use, U.S. patent application 2005/0013854 A1.
29. V. Yadav, B. Parab and S. Shidhaye. Nanocochleate: A novel approach for delivery of biological molecules. *International Journal of Pharmaceutical Sciences and Research*. 2021;12(7):3581-3592.
30. Khairnar SB and Sandagar RB. Nanocochleates : An overview. 2017;3(1):17-24.
31. Road AB. Nanocochleate : As drug delivery vehicle. *Int J. Pharm Boil Sci* 2011;1(1):31-38.
32. Villa AM, Caporizzo E, Papagni A, Miozzo L, Del Buttero P, Grilli MD. Choline and phosphatidylcholine fluorescent derivatives localization in carcinoma cells studied by laser scanning confocal fluorescence microscopy. *Eur J Cancer*. 2005;41:1453-1459.
33. Landge A, Pawar A, Shaikh K. Investigation of cochleates as carriers for topical drug delivery. *Int J Pharm Sci.*;2013;5:314-325.
34. Syed UM, Woo AF, Plakogiannis F, Jin T, Zhu H. Cochleates bridged by drug molecules. *Int J Pharm.*; 2008;363:118-125.
35. Zarif L., Perlin D. Amphoteric B Nanocochleates : Formulation to oral efficacy. *Drug Delivery Technology*. 2002;4:34-37.
36. Zarif.L. Elongated supramolecular assemblies in drug delivery. *J Control Rel*. 2002;81:7-23.
37. Zarif.L., Gray Bill. J. Cochleates: new lipid-based drug delivery system. *Journal of Liposome Research*. 2000;10:523-553.
38. Sankar R.V., Reddy D.Y. Nanocochleate – a new approach in lipid drug delivery. *International Journal of Pharmacy and Pharmaceutical Sciences*. 2011;4:220-223.

For any questions related to this article, please reach us at: globalresearchonline@rediffmail.com

New manuscripts for publication can be submitted at: submit@globalresearchonline.net and submit_ijpsrr@rediffmail.com

