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REVIEW ARTICLE

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A REVIEW ON NANOCOCHLEATES: LATEST APPROACH FOR DRUG DELIVERY SYSTEM

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ABSTRACT: Nanococholeates are at the precursor of the rapidly expanding nanotechnology industry in medication delivery. It is a novel technique for administering medications orally and systemically that combines various charged drug molecules into a multilayered structure with a solid-lipid bilayer that is spirally rolled. It is a revolutionary lipid-based system that serves as a special technical platform for a broad range of important therapeutic biological activities, including genes, vaccination antigens, and medications. It has been demonstrated that nanocochleate performs better than liposomes and is more soluble in the human body. They differ from liposomes in terms of structure and body compatibility. In contrast to liposomes, which have an aqueous inner environment, nanocochleates are multilayer lipid matrixes that are charged lipid bilayers without an aqueous inner environment. The cochleate or nano-cochleate system can be utilized for microencapsulation and distribution, and the therapeutic drugs are loaded as bridging agents between lipid bilayers in the cochleate structure. Hydrophobic, positively charged, negatively charged, and tunable small molecule medications are particularly well suited to the nanocochleates formulation process. Nanocochleates can be manufactured in a variety of methods and used to deliver a wide range of active substances for a wide range of applications. Other dosage formulations have more restrictions and potentially effective drug delivery technology than nanocochleates. The definition, composition, their route and dosages form, formulation method, and mechanism of permeation of the Nanocochleate drug delivery system are all covered in this article. The benefits, drawbacks, application of the Nanocochleate drug delivery system and their role in specific diseases are also discussed in depth in the review article.

Keywords: Phospholipid, Nanococholeates, Liposomes, Cochleates

I. INTRODUCTION

In order to demonstrate effective oral absorption, a number of recent developments in medicine administration techniques are either in the preclinical stage or an advanced clinical trial. Among the documented methods for enhancing drug absorption by cross membrane diffusion were prodrug analogue creation, the application of absorption enhancers and enzyme inhibitors, and administration *via* lipids [1, 2]. In recent years, the predominant method of delivering medications has been via vesicles. One tactic that indicates the medicine will stay in the systemic circulation for a longer amount of time is encapsulation of the drug in these vesicular structures [3]. The nanocochleate drug delivery system (cochleate) encapsulates pharmaceuticals in a multilayered, lipid crystal matrix that may administer the treatment in a way that is safe, effective, and potentially efficient. Nanocochleates are microstructures composed of a sequence of cylindrical (cigar-like) lipid bilayers (Figure 1). The hydrophobic and hydrophilic surfaces of nanocochleates make them excellent for encapsulating both hydrophobic and hydrophilic medications [4]. Phospholipid-cation precipitates composed of natural components like phosphatidylserine and calcium serve as nanocochleate delivery carriers. A solid lipid bilayer sheet wrapped in a spiral or stacked sheets with little to no interior aqueous gap make up its multilayered structure. This structure shields comparable "encochleated" chemicals from deterioration. Encochleation of the medication is used in this method to overcome issues including low solubility, permeability, and oral bioavailability. It might therefore be used to give a variety of medications [5-7].

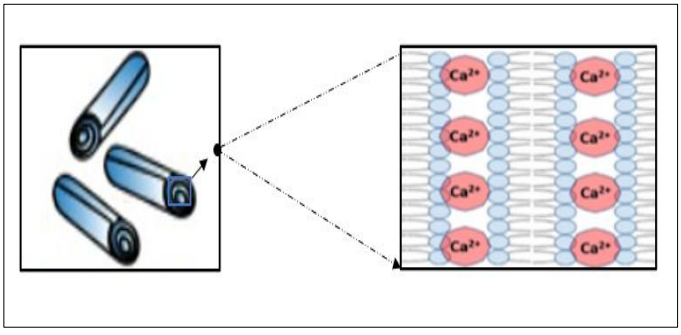


Fig. 1: Nanocochleates (Cigar like structure)

2. What exactly are cochleates?

Using liposomes in various formulations modification, a new family of drug carriers known as "COCHLEATE" was created [8]. Cochleates constitute solid fragments without an internal aqueous phase, composed of massive continuous lipid bi-layer sheets coiled together in a spiral shape. Cochleates are cigar-like microstructures that are created when small unilamellar negatively charged liposomes condense. In contrast to liposomes, cochleates have a rod-shaped structure, a strong, solid structure, and an interior free of water (Figure 2). Massive sheets are formed when tiny phosphatidylserine (PS) liposomes come together in the presence of calcium. These sheets like to coil into a cigar-like cochleate in order to reduce their interactions with water. The elongated form and closely packed bilayers of a typical cochleate cylinder are revealed by freeze fracture electron microscopy [9-10].

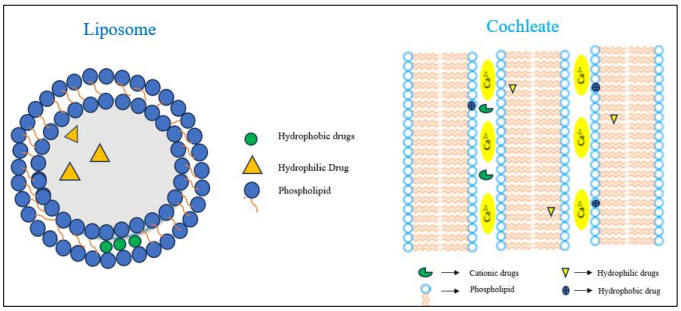


Fig 2: Liposomes and cochleates (structurally different) [3]

3. History of Nanocochleates

Prior to the 1990s, cochleate structures which are created when liposomes contact with cations were used to transport peptides and antigens for vaccine delivery. Dr. Papahadjopoulos and his associates discovered these structures in 1975 [11]. The cochleate structures described in the literature have not always been constant, leading to large needle-like structures in the dialysis procedure or aggregation of stacked sheets and cochleates in the trapping strategy. To produce smaller but more consistent particles with sizes between 50 and 100 nanometers, nanocochleates were initially produced in 1999 [12]. Using a binary phase system, such as two non-miscible hydrogels, cochleates with a mean particle size of less than 500 nm were produced. Bioral TM Amphotericin B was the first product to encapsulate lipophilic medication [13]. The encapsulation of hydrophobic medicines with these nanocochleates was found to be very effective [14].

4. Construction of Nanocochleate

Multivalent counter ions (Ca^{2+} or Zn^{2+}) act as bridging agents between the negatively charged phospholipid bilayers that make up cochleate and nanocochleate, which are spiral rolls. With the help of calcium, liposome fusion produces enormous multilayer sheets. The interaction with the divalent cation (Figure 3) causes the liposomes to roll up. To restrict water interactions, the hydrophobic surfaces of the huge multilayer sheets tend to form a cigar-like coil [15]. Dehydration of the phosphatidyl head group is the molecular mechanism, which is necessary for bilayers to approach each other and initiate the cochleate cylinder building process [11].

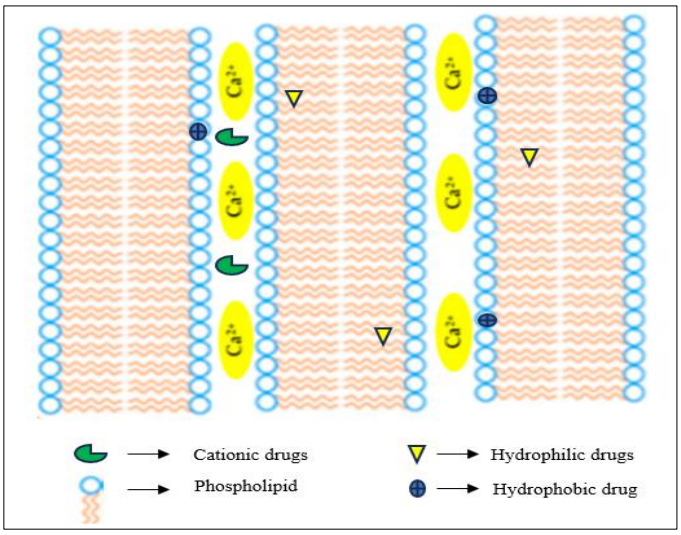


Fig 3: Structure of Nanocochleates

5. Nano-cochleate vs. Liposomes

Liposomes and nanocochleates are both lipid-based compositions. Because nanocochleates are less prone to oxidation than other lipid-based formulations, they are preferred [16]. Table 1 shows the difference between liposomes and Nano-cochleates. Liposome have a significant potential for regulated drug release and improved oral bioavailability [17]. Cochleate is a superior mechanism than liposomes for transporting hydrophobic compounds through the matrix of a lipid bilayer [18].

Both deference are described with parameters as shown in table 1.

Table 1: Nanocochleate *vs.* Liposomes [19-23]

S. No.	*Parameter*	*Liposomes*	*Nanocochleate*
1	Description	An inner aqueous volume is encircled by one or more concentric lipid bilayers.	Cochleates are solid fragments devoid of an aqueous phase that are composed of coiled lipid bilayer sheets.
2	Composition	Phospholipids, cholesterol	Cation required
3	Internal core nature	Aqueous volume	Non-aqueous
4	Efficiency of Entrapment	Low	High
5	Stability	Because lipids are more sensitive to oxidation, they are less stable.	Lipids are more stable than liposomes because of their coiled form, which makes them less susceptible to oxidation [19-23].

6. Composition of nanocochleates drug delivery system

The main ingredients utilized to make nanocochleates are lipids and cations. Nanocochleates include:

Purified soy-based phospholipid contains: At least 75% of the total lipid weight (PI) is made up of phosphatidic acid (PA), phosphatidyl serine (PS), phosphatidylinositol (PI), and dioleoylphosphatidylserine (DOPS). phosphatidyl glycerol (PG), combined with additional lipids, or a combination of these lipids.

Additionally, lipid: Phosphatidylcholine (PC), phosphatidylethanolamine (PE), and diphosphotidylglycerol are examples of phospholipids (DPG). Dipalmitoylphosphatidylgycerol, dioleovlphosphatidic acid (DOPA), distearoylphosphatidylserine (DSPS), and dimyristovlphosphatidylserine (DMPS) (DPPG).

A Cations: Zn^{+2} or Ca^{+2} or Mg^{+2} or Ba^{+2}

A drug which can be: Protein, peptide, polynucleotide, anesthetic, antiviral, and anticancer A vasodilator, vitamin, herbal product, non-steroidal anti-inflammatory drug, immunosuppressant, tranquilizer, or nutritional supplement It has thus been shown to be an effective carrier for a variety of pharmaceuticals [11,24,25].

7. Route of Administration

Since oral medicine distribution improves patient compliance, it is the best way to administer nanocochleate. Possible routes of administration include intrauterine, rectal, topical, sublingual, mucosal, nasal, ophthalmic, subcutaneous, intramuscular, intravenous, transdermal, spinal, intra-articular, intra-arterial, bronchial, lymphatic, intravaginal, or any other mucosal surface [28, 29]. Table 2 lists various dosage forms and routes of administration for the manufacture of nanocochleate.

Table 2: For nanocochleates preparation, there are several different routes of administration and dosages [26, 27]

S. No.	*Route of administration*	*Dosages form*
1	Oral	Capsules, tablets, lozenges, powders, cachets, pills, granules, solutions, suspension and emulsion
2	Topical or Transdermal administration	Powders, ointments, pastes, lotions, gels, sprays, solutions, creams, patches and inhalants.
3	Parenteral administration	Sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions, or emulsions, as well as sterile powders that can be reconstitution into sterile injectable solutions or dispersions immediately before use [26,27].

8. Benefits & Drawback of Nanocochleates Over other Drug Carrier Systems

1. Nanocochleates are more stable than liposomes because their lipids are less prone to oxidation. Their inner core is non-aqueous, and their lipids are less prone to oxidation [6].
2. This method of formulation increases the drug's permeability across the intestinal lumen. For example, when compared to regular rifampicin, the apparent permeability of nanocochleate rifampicin is more than two-fold higher [30].
3. As nanocochleates gradually unwind or otherwise disintegrate, they may allow for the gradual or scheduled release of the biologic substance *in vivo*.
4. Simple lipids, which are present in plant and animal cell membranes, make up their lipid bilayer matrix, which acts as a carrier and is non-inflammatory, non-immunogenic, and non-toxic.
5. They may be made safely and easily [31, 32].
6. Cochleates, which are medications that must be given parenterally, can be given orally. Eg. Amphotericin B [33] .
7. They increase the oral bioavailability of a variety of substances, including genes, vaccines, proteins, peptides, and biopharmaceuticals with high lipophilicity that are challenging to give, such as artemisinin and ibuprofen [34].
8. They lessen the encapsulated drug's toxicity, gastrointestinal distress, and other adverse effects.
9. Instead of forming a chemical link with the medication, they encapsulate or trap it within a crystal matrix.
10. Sunshine, water, oxygen, temperature, and gastrointestinal enzymes can all cause environmental degradation of encochleated medicines [35].
11. They make it possible to incorporate biological compounds like nanocochleate insulin that have hydrophobic moieties and a significant molecular weight [36].

Drawbacks

1. They need certain storage conditions because of stability issues.
2. During storage, aggregation may occasionally occur. Aggregation inhibitors can be used to prevent this.
3. Expensive production [37].

9. Drug Delivery Mechanism of Nanocochleates

The suggested method for delivering lipophobic medications across membranes that are loaded into the inter-bilayer spaces of nanocochleates. It is believed that the inter-bilayer contents of cochleates are transmitted into cells when the lipid bi-layer structure of nanocochleates fuses with the cell membrane and releases the medication. It depicts in figure 4 [11, 38].

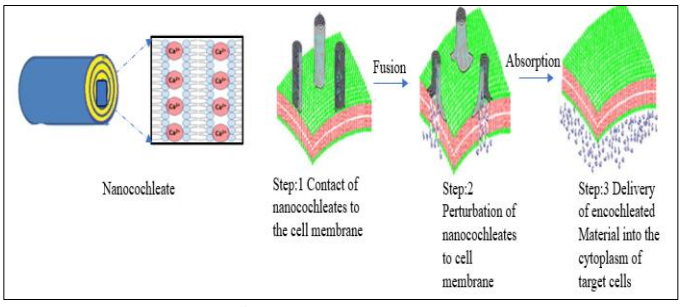


Fig 4: Interaction of nanocochleates with the cell membrane

9.1. Absorption from intestine

The intestinal tract absorbs nanocochleate following oral administration. After passing through the intestinal epithelium, nanocochleates convey their active ingredients to the blood vessel. They bypass the epithelial cell and enter the bloodstream, excluding intravenous techniques. After they reach circulation [39], they are sent to the cell of interest.

9.2 Delivery to targeted cells

Research on calcium's interactions with negatively charged lipids is extensive. Calcium interacts with negatively charged phospholipids in a number of natural fusion processes (usually phosphatidylglycerol or phosphatidylserine). Many natural membrane-fusion techniques involve calcium-induced membrane disruptions and the ensuing membrane-fusion events. Cochleate can therefore be regarded as a membrane-fusion mediator [38, 40]. The exterior layer of the nanocochleate and the cell membrane finally fuse together after the nanocochleate first reaches the cell membrane, disrupting and rearranging it. This fusion causes the cochleated material to be transferred into the target cell's cytoplasm. This carrier has the ability to fuse or break free from the cell over time, allowing it to be accessed [38, 40].

Methods of Formulation of nanocochleates

The cochleate, composed of a series of solid lipid bilayers, is formed by the condensation of small, negatively charged unilamellar liposomes. Large sheets are created when negatively charged phospholipid liposomes fuse together in the presence of calcium. In order to transform the spherical vesicle into a cochleate cylinder, the liposome must first be created. It is then treated with a divalent cation using one of the following techniques.

Method 1: Hydrogel Method
Method 2: Trapping method
Method 3: Liposomes before cochleates (LC) dialysis method
Method 4: Direct calcium (DC) dialysis method
Method 5: Binary aqueous-aqueous emulsion system [29, 41].

9.3. Hydrogel Method

The following are the steps involved in creating nanocochleates using the Hydrogel method:

Step 1: To generate a suspension of microscopic unilamellar liposomes, standard procedures like sonication or micro fluidization are utilized.

Step 2: Polymer-A is then added to drug-loaded liposomes in the form of dextran, phosphatidylserine, or polyethylene glycol.

Step 3: Create a polymer B solution. Polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), and polyvinyl methyl ether (PME) are a few examples of PVME.

Step 4: The polymeric liposomes A solution is introduced into a brand-new polymeric B solution that contains ficoll, polyvinyl pyrolidone, polyvinyl alcohol, and polyvinyl methyl ether. The two polymers' immiscibility creates a two-phase aqueous porosity system. Mechanically, this can be accomplished by using a syringe pump at a regulated rate of 1 to 50 milliliters per minute.

Step 5: The polymers undergo cationic cross-linking with the use of a divalent cation salt solution. It facilitates the synthesis of nano-cochleate.

Step 6: In order to facilitate the removal of polymers, the generated cochleates are immersed in a buffer containing a positively charged molecule.

The cochleate structures are protected and remain precipitates during the washing process thanks to the addition of a calcium cation to the bathing buffer. The medications Amphotericin B and Nelfinavir have been investigated for use in the production of cochleates [42- 44]. The flow chart illustrates the hydrogel process in Figure 5 [6,43].

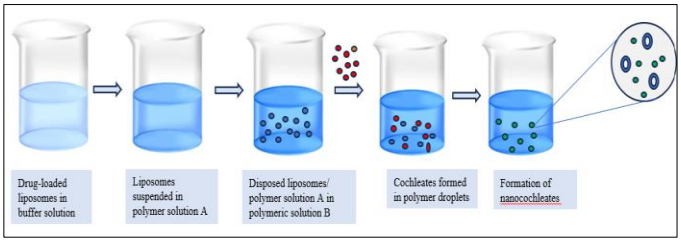


Fig. 5: Hydrogel process

9.4. Trapping method

Both hydrophilic and hydrophobic compounds can be encochleated using this approach. The drug is encapsulated in the aqueous layer of the liposome for hydrophilic pharmaceuticals or intercalated within the bilayers for hydrophobic drugs using a liposomal suspension formulation. Water can be added to phospholipid powder or water phase can be added to phospholipid powder to create liposomes. Cochleates are created when calcium is added dropwise to a liposomal suspension [45, 46]. When compared to other approaches, the trapping method produces cochleates with stronger aggregation, which can be seen following freeze-fracture using electron microscopy.

The following is a description of the procedure:

Step 1: Phospholipids like phosphatidylserine can be used to create liposomes by vortexing the solution for fifteen minutes.

Step 2: Filter the liposomes that were extracted from the previously described solution.

Step 3: To the separated liposomes, add the hydrophobic medication and the trapping solvent (dimethylsulfoxide or ethanol, for example).

Step 4: Dropwise additions of calcium chloride solution to the Step-3 solution precipitate the crystalline cochleates.

Step 5: The leftover solvent is removed by washing the cochleates with a calcium-containing buffer [12]. Paclitaxel, Fisetin, and Quercetin are some of the medications studied by this method.

The modified trapping method uses ethanol to dissolve DOPS (dioleoyl-phosphatidylserine). After adding calcium chloride ($CaCl_2$), it is homogenized for five minutes at 13,000 rpm. It is then agitated for a further hour [47, 48]. The flow chart illustrates the trapping process in Figure 6 [43].

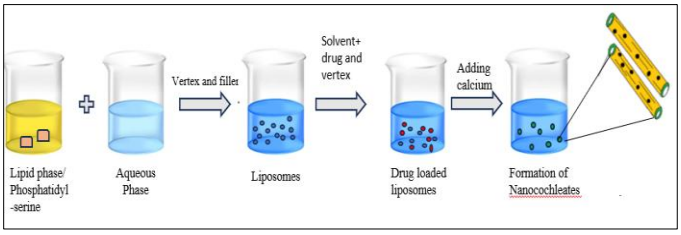


Fig. 6: Trapping method

9.5 Liposomes before cochleates dialysis technique

This method is used to create small cochleates with lipids, a cation, a physiologically significant substance, and detergent. The liposomes are broken apart by the detergent. First, a buffer is used to dialyze the mixture. Calcium chloride is then added to create the cochleates.

The detergent is eliminated by double dialysis. The following are the steps in the technique:

Step 1: Using the lipid-detergent mixture, make an aqueous suspension.

Step 2: Polymer A, such as the suspension created in step 1 is combined with polyethylene glycol (PEG), dextran, or phosphatidylserine.

Step 3: A solution containing polymer B is added to the detergent-lipid/polymer A mixture.

Step 4: A cationic moiety solution is added to the two-phase polymer system.

Step 5: Washing removes the polymer from the two-phase polymer system.

By using the suggested approach, the medications griseofulvin and cyclosporine were attempted to create cochleates. Cochleates of 50-100nm were created using this technology [44, 49, 50].

9.6. Direct Calcium (DC) Dialysis technique

Intermediate liposome synthesis is absent when comparing the Direct Calcium (DC) dialysis method to the Liposome prior to Cochleates dialysis method. Large cochleates are produced with this method. A calcium chloride solution is directly dialyzed against the lipid and detergent mixture. In this method, the removal of detergent from the detergent/lipid/drug micelles and the calcium-induced condensation of bilayers compete to produce enormous, needle-shaped structures.

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

Step 2: A certain concentration of API is combined with a non-ionic detergent and vortexed for five to ten minutes.

Step 3: At room temperature, the colorless solution is dialyzed against three buffer modifications.

Step 4: The colourless solution is dialyzed against three buffer modifications at room temperature. The buffer and Ca+2 (6 mmol) concentrations are in line with the synthesis of cochleate.

Direct calcium cochleate refers to the white calcium-phospholipid precipitates that arise. Cochleates of enormous size are created [50].

9.7. Binary aqueous-aqueous emulsion system

The incompatibility of two-phase polymer solutions that are both aqueous and immiscible with one another is the basis for the technique. An organic solvent is not required while using this method.

Step 1: High pH or a film method are used to create liposomes.

Step 2: Liposomes are mixed with a polymer A, like dextran or polyacrylamide.

Step 3: Next, a non-miscible polymer, such as PEG, is added to the dextran/liposome phase.

Step 4: Following the addition of calcium to the step 3 solutions, the nanocochleates produce a seamless transition between phases. The physiological buffer is then used to wash the gel. It's used to make cochleates that are smaller than 1000 nanometers [46, 50].

10. Stability of Nanocochleates Formulations

Stable lipid-based delivery systems called nanocochleates differ greatly from liposomes in their shapes and characteristics [51]. Associated molecules are stabilized and protected *via* encochleation. Even if the structure's outside layers may be subjected to harsh external environmental conditions or enzymes, the components inside the structure remain intact since the entire structure is made up of solid lipid bilayers. The formulation has a longer shelf life since the inside is virtually water-free and impervious to oxygen penetration. It is possible to lyophilize nanocochleates into a powder and store them at 4°C or room temperature. It is possible to rehydrate lyophilized cochleates with liquid before

administering them *in vivo* or *in vitro*. The morphology and functioning of cochleates are unaffected by lyophilization [52].

11. Evaluation of nanocochleates

11.1. Determination of Particle Size Distribution

The Malvern analyser and laser diffraction technique can be used to determine the average particle size of liposomal and cochleate dispersion. A temperature of 302°C and a detection angle of 90° are used for its analysis. The mean vesicle size is expressed as the volume mean diameter D of a sphere with the same volume as the particle being studied [53-55].

11.2. Density

Air or helium are used in a gas pycnometer to measure the density of nanocochleates. At 25°C and 15,000 rpm, the dispersed nanocochleate suspension is centrifuged for 40 minutes. The unrestricted medicine After adequate dilution, a method such as UV-Vis spectrophotometry can be used to determine the concentration in the supernatant. Due to the specific surface, the value produced with helium and air is significantly more noticeable [45, 56].

11.3. Measurement of molecular weigh

The molecular weight and distribution of the polymer in the matrix can be ascertained by gel permeation chromatography (GPC) with a refractive index detector. Using GPC, it was shown that numerous small oligomeric subunits entangle to create polyalkylcynoacrylate nanocochleates instead of one or a few big polymer chains rolling up [56].

11.4. Entrapment efficiency (%) determination

An aliquot of 100 l of cochleates is put in centrifugation tubes. Each tube is vortexed with 1 ml of ethanol and 60 l of pH 9.5 EDTA. A transparent, colorless solution is the end outcome. A spectroscopic method is used to measure the absorbance of the resultant solution, and the following equations are used to calculate the EE. [57, 58, 59]

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

11.5. Determination of Structure and surface morphology

The morphology of the nanocochleate can be investigated using transmission electron microscopy (TEM). A drop of diluted substance is applied to a copper grid covered with carbon to create a thin liquid layer. A Zeiss EM 109 transmission electron microscope with an accelerating voltage of 80 Kv is used to examine and take pictures of the sample after the surplus solution has been removed [60, 61].

11.6. Content of drug

At 25°C, the dispersed nanocochleate suspension is centrifuged for 40 minutes at 15,000 rpm. The free medication After appropriate dilution, a technique like UV spectrophotometry can be used to determine the concentration in the supernatant [62, 63].

11.7. Specific surface area

It is possible to determine the specific surface area of freeze-dried nanocochleate using a sorptometer. Calculate a specified surface using the following equation:

$$A = 6/\rho d$$

Here, A = Specific surface area,
ρ = Density,
d = Diameter [63]

11.8. Surface charge determination

How a nanocochleate interacts electrostatically with bioactive substances and the biological environment depends on the type and strength of its surface charge. The surface charge in an electrical field can be estimated from the particle velocity. Laser diffractometry, such as Velocimetry or Laser Doppler Anemometry, is used to quantify the velocities of nanocochleate [63].

11.9. Cochleates-cell interaction study

Fluorescent liposomes are created by adding 2% fluorescent lipid to the negatively charged lipid in order to investigate the interaction of cochleates with the cell membrane [33]. Under fluorescent microscopes, cell surfaces turn fluorescent when cochleates contact with cell membranes through a fluorescent lipid transfer [55,64].

11.10. Fourier transforms IR spectroscopy study

A study using Fourier transform infrared spectroscopy can identify the compound's functional groups and purity. To prepare samples, they are mixed with KBr. Samples are then put inside the holder. At room temperature, the spectra are scanned across the specific wave number ranges [55].

11.11. Differential scanning by calorimetry study

The lipid status is ascertained via a differential scanning calorimetry examination. The samples are heated at a constant rate of 10 °C/min between -10 and 180 °C while being hermetically packed in perforated aluminium pans. To keep the atmosphere inert, nitrogen gas is pumped through the system at a rate of 100 ml per minute [55].

11.12. Stability study

To test their stability, cochleate dispersions can be stored at 2 to 8 °C and 252 °C/60 percent relative humidity for three months. The stability of the formulation is assessed by comparing changes in cochleate particle size and entrapment efficiency (percent EE) [65].

12. *In vitro* release study

12.1. Diffusion cell method

The diffusion cell method frequently uses double chamber diffusion cells on a shake stand. The Millipore low protein binding membrane is maintained between the two chambers. The formulation is in the donor chamber, while the phosphate buffer is in the receiver chamber. The receptor compartment is tested for the released drug at different intervals using standard analytical techniques [66].

12.2. Modified ultra-filtration method

This technique can also be used to measure the drug concentration of nanocochleates that are discharged. A buffer-filled stirred ultra-filtration cell is directly filled with nanocochleates. Aliquots of the medium are filtered using the membrane at different intervals of time. Then, using any relevant analytical procedures, the drug concentration is determined [31].

13. Applications

13.1. ApoA1 Formulation

To treat atherosclerosis brought on by hypercholesterolemia, a formulation of Apoprotein (ApoA1) based on nanocochleates has been developed. Hypercholesterolemia, a well-known risk factor for atherosclerosis and other cardiovascular diseases, is characterized by high levels of low-density lipoproteins (LDLs) and low levels of high-density lipoproteins (HDLs). ApoA1 lipoprotein administered parenterally enhances HDL's capacity to carry cholesterol to the liver and prevent atherosclerosis. Since ApoA1 is a protein, its intrinsic permeability is minimal. GIT enzymes break it down quickly, and following absorption, it is eliminated. Nanocochleates can be an excellent alternative to oral ApoA1 administration and can bring a lot of benefits [47].

13.2. Delivery of anti-inflammatory agents

Anti-inflammatory drugs could be delivered via nanocochleates. Cochleate delivery vehicles could be used to mix and administer anti-inflammatory medications, including acetaminophen, aspirin, ibuprofen, naproxen, and COX-2 inhibitors, according to studies. Doses ranging from 0 to 40 mg/kg of body weight/day were administered orally for 14 days in a mouse model of systemic aspergillosis. A 70% survival rate and decrease in the amount of colony cells in the lungs, livers, and kidneys were the outcomes of oral doses of cochleate containing amphotericin B (CAMB) (20 and 40 mg/kg/day). CAMB given orally has shown potential in the treatment of aspergillosis [11].

13.3. Antifungal drug delivery

The use of amphotericin B (AmB), an antifungal drug, is restricted by its limited therapeutic index and adverse effects, especially nephrotoxicity. Santangelo *et al.* claim that AmB-loaded cochleates are very effective at distributing AmB orally, something that can only be done with injectable formulations at this time. It demonstrates that it improved overall efficacy, stability, and efficacy at low dosages [67].

13.4. Topical agents drug delivery

An antifungal drug called ketoconazole (KCZ) is used to treat fungal infections such candidiasis, ringworm, and athlete's foot. Ketoconazole was successfully entrapped in cochleates and used for topical and transdermal drug delivery [52].

13.5. Antibacterial drug delivery

Cochleates have the dual benefit of enhancing bactericidal activity and decreasing toxicity. Often used for long-term treatment, antibacterial drugs such clofazimine, aminoglycosides, beta-lactam/beta-lactamase combinations, vancomycin, imipenem, and ethionamide cause toxicity and drug resistance in the host. Clofazimine is 500 times more hazardous than Clofazimine cochleate, according to a study [12], hence Clofazimine cochleate reduces toxicity while improving bactericidal action. In the presence of other anti-TB medications, rifampicin has variable absorption, thus it must be administered in a large dose. Rifampicin nanocochleate was created to solve this problem. Rifampicin nanocochleate, according to Yadav *et al.*, increased the apparent permeability of the medication significantly [68].

13.6. Delivery of Fisetin

Fisetin is an anticancer flavonoid that is found in nature. Poor water solubility and substantial in-vivo metabolism are two problems in Fisetin administration. Fisetin-loaded nanocochleates was developed to address this issue. Fisetin-loaded nanocochleate showed increased *in-vitro* anticancer activity and prolonged release, according to Bothiraja *et al.* With modest tissue distribution, nanocochleates improved systemic bioavailability [69].

13.7. Insulin delivery

Magnetocochleate can be produced by embedding ferrite nanoparticles in a fused lipid microstructure. They're employed to contain biologically important macromolecules. By changing the lipid phase transition from fluidic lamellar to gel at pH 2, insulin is encapsulated in magnetocochleate. Dwivedi et al. claim that magnetocochleate could be injected subcutaneously to disperse macromolecules. The use of magnetocochleate to encapsulate medicines improves their bioavailability, stability, and shelf life [70].

13.8. Oral Mucosal VADS (Vaccine Adjuvant-Delivery System)

Vaccines help to prevent diseases like polio, rubella, tetanus, measles, and mumps by containing live-attenuated or inactivated microorganisms. The vaccine adjuvant delivery system (VADS), which was developed using cochleates, protects antigens while delivering them to certain cells to

provide immune responses that are quicker, more powerful, and more durable. Cochleates are taken up by antigen-presenting cells (APCs) by receptor-mediated phagocytosis, which results in the production of antibodies. Cochleates are hampered by traditional vaccine preparation methods, which entail many time-consuming processes. In one work, Wang et al. created adjuvant lipid-A embedded cochleates (LACs) that trap an antigen bovine serum albumin (BSA) using the emulsification-lyophilization process. According to the findings, LACs elicit a mixed response to antigens, resulting in systemic and mucosal immunity against infections [71].

13.9. Factor VIII delivery

A glycoprotein is factor VIII. It starts the formation of a blood clot by reacting with factor IX to create a series of reactions. Haemophilia is the term used to describe the lack of factor VIII. It lengthens the clotting time, which worsens the bleeding and may result in the patient's death. Due to its protein composition, factor VIII has low stability and solubility. As a result, when given directly to the body, antibodies are produced against these proteins. Cochleates are made to lessen immunological response and harmful effects, preventing the production of antibodies. Matthew *et al.* came to the conclusion that factor VIII-containing cochleates are immune to the quick RES-mediated clearance seen with PS liposomes. This formulation is a feasible delivery strategy due to the delayed-release feature and low immunogenicity of factor VIII [47]

14. Commercial Status of Bioral Technology

The idea of superfoods is now a reality thanks to the development of nanocochleates by the US-based company Bio-delivery Sciences International (BDSI), which can be used to more effectively deliver nutrients like vitamins and omega fatty acids to cells. These are anticipated to provide a wide range of potential benefits, such as enhanced energy, better cognitive and immune function, and antiaging effects. The United States Food and Drug Administration (USFDA) has accepted Bio-Delivery Sciences' first Innovative New Drug Application (INDA) for the company's Bioral® Cochleate technology, which produces an enchocleated form of the powerful antifungal drug Amphotericin B (CAMB) [72]

15. Marketed formulations of nanocochleates

There are some marketed formulations of nanocochleates as shown in table 3.

Table 3: There are so many formulations related to nanocochleates

Drug name	*Brand name*	*Route*	*Category*
Liposomal Amphotericin B	Abelcet	IV infusion	Antifungal infection [24]
Liposomal Amphotericin B	Ambisome	Parental	Antifungal and anti protozoal infections [24]
Liposomal cytarabine	Depocyt	IV	Malignant lymphomatous meningitis [24]
Liposomal daunorubicin	Daunoxome	IV	Hiv-related kaposi's sarcoma [24]
Liposomal doxorubicin	Myocet	IV infusion	Combination therapy with cyclophosphamide in metastatic breast cancer [24]
Liposomal vaccine	Inflexal	IV	Influenza [24]
Liposomal morphine	Depodur	Epidural	Postsurgical analgesia [24]
Liposomal verteporfin	Visudyne	IV infusion	Age-related macular degeneration, pathologic myopia,ocular histoplasmosis [24]
Liposome-PEG doxorubicin	Doxil/caelyx	Parentral	Hiv-related kaposi's sarcoma, metastatic breast cancer, metastatic ovarian cancer [24]
Micellular estradiol	Estrasorb	Transdermal	Menopausal therapy [24]
Liposomal iriv vaccine	Epaxal	IV	Hepatitis A [24]
Paclitaxel	Toxol	Parentral, oral	ovarian cancer, breast cancer, lungs cancer, cervical cancer [32]
HIV-1 Proteins DNA	-	Oral	Anti- HIV [73]
Influenza Glycoprotein	-	Oral	Anti-influenza [73]
Andrographolide	Windose 100 mg	Oral, parental	Anti-inflammatory, Anti-diabetic [74]

16. Role of nanocochleates in specific diseases

16.1. Role of nanocochleates in cancer diseases

One of the main causes of death globally, cancer can affect every organ in the body, including the skin, colon, lung, and breast. The condition known as cancer arises from the unchecked proliferation of aberrant body cells. Drug delivery methods based on nanocochleates have become widely used in a range of cancer treatments due to their capacity to target tumors, lower systemic toxicity, and prolong drug residence time in the blood.

16.2. Nanocochleates in breast cancer

Poudel *et al.* to achieve controlled drug release, improved bioavailability, targeted delivery, and enhanced anticancer potency with DTX's lower systemic toxicity, new biotinylated chitosan (BI-CHI) decorated Docetaxel anhydrous and Paclitaxel (Internal Standard) docetaxel (DTX) loaded nanocochleates (BI-CHI-DTX-NC) were developed for breast cancer targeting. By converting cholesterol-bearing liposomes and dimyristoylphosphatidylglycerol-na (DMPG-Na) with calcium ions, the researchers loaded DTX into nanocochleates (DTX-NC). They then encapsulated DTX-NC with BI-CHI (BI-CHI-DTX-NC) and compared it to DTX and DTX-NC. Significant pH dependence was seen in the release of DTX, suggesting a robust hydrogen bond between nanocoils. Increased *in vitro* anticancer activity was demonstrated by biotin-expressed human breast cancer MCF-7 cells in BI-CHI-DTX-NC-formulated BI-CHI-DTX-NC-formulated BI-CHI-DTX-NC-formulated BI-CHI-DTX-NC-formulated BI-CHI-DTX-NC-formulated BI-CHI-DTX-NC-formulated BI-CHI-DTX-NC-formulated BI-CHI-DTX-NC- The effect of the BI-CHI-DTX-targeting NC was also demonstrated. Additionally, DTX from BI-CHI-DTX-NC had a 10-fold higher bioavailability than DTX solution, a longer circulation time, slower plasma clearance, and poor tissue distribution.

According to the results, anticancer medications may be precisely delivered using the BI-CHI-DTX-NC.

Table 4: Development of nanocochleates-based formulations for breast cancer research

Drug (technique)	*Lipids*	*Solvents*
Docetaxel anhydrous and Paclitaxel (Internal Standard) (Trapping method)	Dimyristoylphosphatidylglycerol (DMPG)	Calcium carbonate [75]

16.3. Nanocochleates in colon cancer

T. Shanmugam *et al*. investigated paclitaxel (PTX) encapsulated in a new nanocochleates (CPT) technology for oral treatment of resistant colon cancer. PTX encapsulated nanocochleates (PTX-CPT), which are constructed of phosphatidylserine and range in size from 350 to 600 nm, demonstrated continuous PTX release over a 48-hour period at intestinal pH settings. Furthermore, in an HCT-15 drug-resistant colon cancer xenograft mouse model, the in vivo effectiveness of five oral doses of 30 mg/kg PTX-CPT revealed a 25-fold reduction in tumor growth suppression in comparison to intravenous Taxol, which only showed 1.94 percent inhibition. The findings suggested that PTX-CPT could be a promising oral treatment option for drug-resistant colon cancer.

Table 5: Development of nanocochleates-based formulations for colon cancer research

Drug (technique)	*Lipid*	*Solvent*
paclitaxel	Dioleoyl phosphatidylserine (DOPS)	chloroform-methanol (2:1) [76]

16.4. Nanocochleates in pulmonary cancer

Paclitaxel (PTX) is a powerful anticancer drug that is used to treat pulmonary metastases in patients with various malignancies. It is given as an infusion. The use of systemic PTX injections to treat pulmonary metastasis from various malignancies is promising, but it comes with a slew of serious side effects. Using an inhalable phospholipid-based nanocochleate platform, researchers validated a noninvasive technique for delivering PTX to deep pulmonary tissues in this study and showed that it was effective in treating pulmonary metastases of melanoma cancer. Anticancer medications have been delivered orally using nanocochleates in the past. Overall, it seems that a recently created CPT system, which acts as both a pulmonary surfactant and a drug delivery carrier in the treatment of pulmonary metastases, can safely administer PTX as an aerosol [77].

17.5. Nanocochleates in tissue cancer (fibrosarcoma)

Drug resistance and inadequate dosages at the target site are the primary challenges in using chemotherapeutics to treat cancer; greater dosages may result in adverse consequences by damaging nontarget organs. Recent research indicates that nonsteroidal anti-inflammatory drugs (NSAIDs) have anticancer effects and can be used in conjunction with conventional chemotherapeutics to increase their safety and effectiveness. In order to develop targeted surface-modified liposome and nanocochleate formulations for the treatment of fibrosarcoma, imatinib mesylate and dexketoprofen trometamol were selected as model pharmaceuticals. Select formulations were then evaluated in model mice with fibrosarcoma using histopathological observations and tyrosine kinase receptor inhibition assays. In the fibrosarcoma model, a PEGylated nanocochleate formulation was the most effective. These findings lay the groundwork for creating more effective fibrosarcoma and cancer treatment formulations and chemotherapeutic techniques [78].

Table 6: Development of nanocochleates-based formulations for fibrosarcoma cancer research

Drug (technique)	*Lipid*	*Solvent*
Resveratrol (RSV) (trapping method)	Dioleyil phosphatidiylserine (DOPS)	Chloroform [78]

17.6. Role of nanocochleates in other specific diseases

17.6.1. Nanocochleates in diabetes

A chronic metabolic disease known as diabetes mellitus (DM) is characterized by inadequate or poor insulin production. The two primary categories are Type I and Type II. The primary function of the pancreatic beta cells is to release enough bioactive insulin to maintain normal plasma glucose levels. Numerous plants contain the polyphenolic compound RSV (3,5,4'-trihydroxystilbene). By strengthening insulin action, protecting beta cells that produce pancreatic insulin, and boosting insulin activity, RSV, a potent antioxidant, lowers blood glucose levels. Nanocohleates are non-vesicular, cylindrical drug delivery devices based on lipids. The stability of biopharmaceutical compounds that enhance low bioavailability can be increased by encapsulating a broad range of medications. Numerous drugs can be encapsulated to increase low bioavailability and stability of biopharmaceutical compounds. In our investigation, pancreatic beta cell groups that had been rendered diabetic by streptozocin and glucose were used to produce, characterize, and test RSV-loaded nanocochleates for their impact on diabetes. Furthermore, the proposed formulation's antioxidant potential was investigated [79].

Table 7: Development of nanocochleates-based formulations for diabetes research

Drug (technique)	*Lipid*	*Solvent*
Resveratrol (RSV) (trapping method)	Dioleyil phosphatidiylserine (DOPS)	Chloroform [79]

The purpose of this study is to examine and contrast the effects on glucose levels of insulin, embryonic stem-cell (ESC) loaded liposomes (LPs), nanocochleate formulations, and their PEGylated counterparts. Particle size, zeta potential, polydispersity index, and encapsulation efficiency were the metrics used to assess each formulation. Franz-type diffusion cells were used to determine the amount of insulin released *in vitro* from the formulations. In cell culture, the formulations' effects on glucose and streptozotocin (STZ)-induced diabetic cells were examined. When diabetic pancreatic beta TC cells were incubated with the formulations in mouse testing, blood glucose levels were successfully lowered, and all formulations were shown to be beneficial in lowering blood glucose levels

in diabetic animals. Although ESC-loaded LPs were shown to be the most effective, LPs and nanocochleate formulations may be employed for pancreatic cell healing. This proposed ESC treatment is viewed as a potential approach to diabetes cell replacement therapy [80].

Table 8: Development of nanocochleates-based formulations for diabetes research

Drug (technique)	*Lipid*	*Solvent*
Insulin and embryonic stem-cell (ESC) (dry film hydration method)	Dioleyil phosphatidiylserine (DOPS)	Chloroform [80]

17.6.2. Nanocochleates in leishmaniasis

Treatment of life-threatening visceral leishmaniasis has become more challenging due to the emergence of Leishmania strains resistant to currently available treatments. Amphotericin B (AmB) and miltefosine (hexadecyl-phosphocholine, HePC), two active medications, are combined in innovative lipid formulations (nanocochleates) that should increase efficacy, reduce toxicity, and lessen the chance of resistance emerging. Drug-absorbable, cigar-shaped nanocochleates are composed of rolled, negatively charged lipid bilayers consisting of cholesterol (Cho) and dioleoylphosphatidylserine (DOPS) that are connected by calcium. The drugs were applied at the air-water interface after being mixed with lipids (DOPS or 9DOPS/1Cho).

Phase diagrams and BAM images demonstrate that DOPS maintains AmB in the "erect" form at the interface, as opposed to the "horizontal" form, even at low pressure. Cho amplifies this effect. These results allowed us to predict the optimal drugs/lipids ratio as well as the shape and direction of these medications in nanocochleates.

Table 9: Development of nanocochleates-based formulations for leishmaniasis

Drug (technique)	*Lipid*	*Solvent*
amphotericin B (AmB)and miltefosine (trapping method)	Dioleyil phosphatidiylserine (DOPS)	ethanol/chloroform 4:1 [81]

Leishmania parasitic protozoans are the cause of a range of tropical disorders known as leishmaniasis. Both *Dysphania ambrosioides* (L.) Mosyakin & Clemants and *Bixa orellana* L. (EO-Bo) have demonstrated antileishmanial activity (EO-Da). In this study, tests were conducted on the EO-Bo and EO-Da nanocochleates (EO-Bo-NC and EO-Da-NC, respectively). The enhanced *in vivo* activity of EO-Bo-NC indicates that lipid-based nanoformulations, like nanocochleates, should be studied for their potential in drug administration, especially for the delivery of hydrophobic materials for the successful treatment of cutaneous leishmaniasis.

Table 10: Development of nanocochleates-based formulations for leishmaniasis research

Drug (technique)	*Lipid*	*Solvent*
amphotericin B (AmB)and miltefosine (trapping method)	Dioleyil phosphatidiylserine (DOPS)	ethanol/chloroform 4:1 [82]

17.6.3. Nanocochleates in osteoporosis

By delivering vitamin D3 (Vit-D3), phosphatidylserine nanocochleates (Nanocochs) are novel delivery systems that may help prevent osteoporosis. This work was conducted to describe a vitamin D3-containing Nanococh (Nanococh-D3) and assess its possible role in enhancing GIO in a rat model. In the 320 nm size range, nanococh-D3 particles with a roll-shaped structure and the ability to release continuously were created. Oral Nanococh-D3 enhanced bone mechanical strength, increased vitamin D bioavailability, and improved osteogenic markers such B-ALP, osteocalcin, calcium, and OPG in GIO rats. Histomorphometric studies showed that Nanococh alone, such as Nanococh-D3, improved bone strength more effectively than AL, a common anti-osteoporotic medication. Finally, our findings revealed Nanococh-potential D3's function in the prevention of osteoporosis in rats.

Table 11: Development of nanocochleates-based formulations for osteoporosis research

Drug (technique)	*Lipid*	*Solvent*
Trapping method	Dioleyil phosphatidiylserine (DOPS)	ethanol/chloroform 4:1 [83]

17. CONCLUSION

Nanocochleate protects active substances or compounds that are to be transported because of its unique multilayered structure. Nanocochleate is a one-of-a-kind lipid-based system that overcomes liposome's limitations. It is utilized to encapsulate drug molecules and protect them from environmental harshness, increasing their stability and shelf life. The limitations of conventional drug delivery methods have been addressed by the widespread usage of nanocochleates to administer a range of active medicinal medications. By enhancing formulation qualities, boosting processing and shelf-life stability, boosting bioavailability, reducing toxicity, and boosting efficacy, encochleation can raise the quality of a final product. It is a promising tool for delivering vaccinations, antigens, proteins, peptides, even API genes. Because of this, the nanocochleate drug delivery system is becoming more and more popular in pharmaceutical development as a way to deliver a desired and appropriate drug molecule with high therapeutic potential into the body.

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