RESEARCH PAPER

Liposomal Nanocochleates: A Comprehensive Review of Formulation Strategies and Therapeutic Applications in Cancer and Diabetes

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Abstract

Liposomal nanocochleates (NCs) represent a novel group of lipid-based nanoformulation with the specific spiral structure of these vectors, formed by stacking multilayers through the interaction between divalent cations (Ca^2+ are the most widely used in our experiments) and negatively charged phospholipids. Since they are generally composed of solid lipid bilayer sheets rather than rolling-up without inside aqueous space into large tubular structures, these as-fabricated cylindrical nanostructures demonstrate better stability compared to liposomes and effectively protect encapsulated drugs from degradation and external adverse environment. In this review, we discuss recent formulation strategies for preparation of liposomal nanocochleates [using hydrogel method, trapping method, dialysis methods (A-DSD and SAD-DMD), and new direct lipid–drug bridging techniques] and critically review their therapeutic potential in both antitumor action against cancer as well as treatment of diabetes. In the field of oncology, chemotherapeutics and phytochemicals encapsulated in nano-cochleates have shown improved oral bioavailability, enhanced tumor targeting and efficacy even to multidrug resistant cancers. Similarly, for diabetes management, nanocochleates have been employed for targeted delivery of antidiabetic drugs (metformin, insulin, resveratrol) with improved stability and controlled release properties and prolonged therapeutic action. Despite encouraging preclinical data in those 2 settings, translation has been poor. We outline priority research areas, including scalable manufacturing and long-term safety data, as well as preclinical evaluations that must be addressed by the field to pave its path towards clinical (ie, nanocochleate) based therapy of cancer and diabetes.

Keywords: Nanocochleates; Liposomes; Drug Delivery; Cancer Therapy; Diabetes; Controlled Release; Oral Bioavailability; Nanocarriers.

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Introduction

Nanocochleates are novel lipid-based nanoparticles distinguished by their supramolecular cochlear structure, resembling a rolled-up scroll or cylindrical "cigar-like" roll **[1–3]**. They form when multivalent cations such as Ca^{2+} or Zn^{2+} bind to negatively charged phospholipid headgroups, causing planar lipid bilayers to fuse and curl into continuous multilayered tapes without any internal aqueous core **[2,4]**. Figure 1 illustrates this architecture: a solid phospholipid bilayer wraps in a spiral fashion, generating a rigid, rod-shaped cochleate devoid of internal aqueous compartments **[1,5]**. Unlike conventional liposomes that contain an aqueous lumen, nanocochleates possess a water-free interior, conferring exceptional structural stability and enhanced protection to entrapped bioactive molecules **[3,6]**. Because the assembly consists entirely of densely packed lipid layers, drug molecules "encochochleated" within the structure remain protected even under harsh physiological or environmental conditions **[5,7]**.

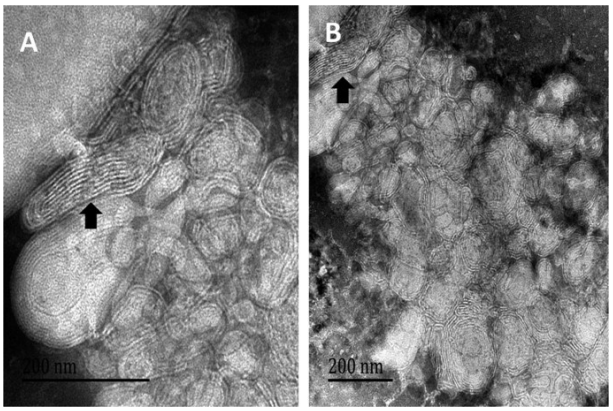

Figure 1. TEM images of lipid vesicles and nanocochleates. (a) Conventional liposomes are spherical vesicles containing an aqueous core, while (b) nanocochleates are elongated multilayer cylinders of closely stacked lipid sheets [1,5]. The thick condensed dehydrated lamellae depicted in (b) account for its high stability towards chemical and enzymatical decomposition [4,6].

Therapeutic Potential:

Nanocochleates have garnered substantial interest as drug delivery platforms on account of their biocompatible nature, low immunogenicity and capacity to encapsulate a broad range of therapeutic entities such as hydrophobic drugs, peptides, proteins and nucleic acids [8–11]. Because of their good stability under acidic pH and enzymatic attack, they are particularly interesting for oral drug administration [10,12]. Furthermore, the multilayered lipid structure 9 gradually uncoils or disperses in vivo when using nanocochleates which not only enhances bioavailability and therapeutic indices but also offers sustained and controlled drug release [13]. Table 1 shows the main structural and functional differences among nanocochleates as compared to conventional liposomes [1,9].

Applications in Cancer and Diabetes:

Recent studies reveal that strategies underpinned on nanocochleate-based formulations might revolutionize current treatment protocols for not only cancer but also diabetes, two of the primary global health concerns against which a success in treatments depends, at least in part, upon an increase on the efficiency of drug delivery [14–18]. In the field of oncology, nanocochleates restore orally administered chemotherapeutics restricted to intravenous delivery and protect these compounds against P-glycoprotein-derived efflux with subsequent accumulation at tumor-cell sites [16,19]. Oral paclitaxel-loaded nanocochleates, for example, exhibited highly enhanced antitumor efficacy in mutant P-gp-overexpressing colon cancer models compared with Taxol® given intravenously [16,20].

Nanocochleates also have been tested for administration of insulin, metformin, and resveratrol among other antidiabetics in diabetes with the greatly improved pharmacokinetics, cellular uptake as well as therapeutic efficacy [21–24]. Cochleate encapsulation also functions as a barrier against enzymatic cleavage of peptides such as insulin and allows for controlled release, thereby enabling oral or less frequent dosing [21, 23]. Phytochemical, e.g., resveratrol, also demonstrated improved protections for the pancreatic β-cell delivered by nanocochleates [24].

Research Gap:

Despite this promising evidence, nanocochleate technology has so far not been readily translated to the clinic. Nevertheless, there still remains a significant gap in optimizing the formulation strategies for uniform performance at high scale and improving the reproducibility of therapeutic effects [25–27]. *Key unresolved questions include: Which methods of formulation produce the most stable and bioavailable cochleates for a given class of drugs? What are means at the disposal of mass production that can keep structure in generalized uniformity? What are the potential long-term human safety, biodistribution and pharmacokinetic considerations following chronic nanocochleate administration? [26–28].*

Furthermore, although various investigations have separately investigated their application in either cancer or diabetes, no integrated review has systematically evaluated the dual effectiveness of nanocochleates in both pathologies. The juxtaposition of these realms of knowledge may actually inform cross-applicable strategies – e.g. formulation science learned from oncologic medicine being applied to improve delivery and biodistribution of diabetic drugs, or immune modulatory principles applicable to tumour pathogenesis that have relevance in the pathophysiology of metabolism [18,27].

In the following sections, we discuss the principal strategies to formulate liposomal nanocochleates (and major breakthroughs and continuing challenges) [1,2,29]. We finish by discussing therapeutic prospects in cancer and diabetes with the same emphasis. Major findings and open challenges are summarized for each section in a table. An ‘Opinion’ section then provides our critical

thoughts on emerging trends and paths for innovation, closing with a conclusion and extensive reference list to maintain scientific rigour and citation [30]. By combining this systematic integrative approach, we emphasize how liposomal nanocochleates may connect with unmet needs within the advanced drug delivery for oncology [42] and metabolic disease space and identify the critical research directions that must be pursued to further facilitate clinical translation [21].

Formulation Strategies for Liposomal Nanocochleates

Formulating liposomal nanocochleates involves converting lipid vesicles (liposomes) into cochleate cylinders, typically by introducing a multivalent cation or poly-cationic agent that collapses the liposomal membranes into solid lamellar stacks **[1–3]**. Over the years, several methods have been developed to achieve this transformation, each with its advantages, limitations, and ideal use cases **[2,4]**. The major formulation strategies are summarized in Figure 2 and discussed below **[5]**.

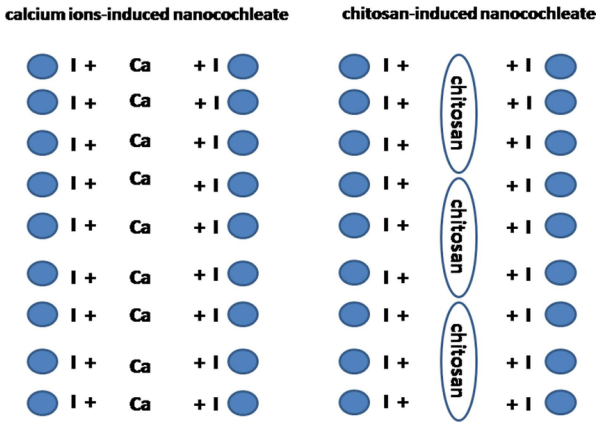

Figure 2. *Schematic representation of two nanocochleate formulation approaches. Left: Calcium-mediated cochleation – negatively charged liposomes are treated with Ca^{2+} ions, which bridge adjacent lipid bilayers and induce rolling into cochleates **[6]**. Right: Polymer (chitosan)-mediated cochleation – a cationic polymer (e.g. chitosan) serves as the bridging agent in place of Ca^{2+}, coiling the lipid sheets into a cochleate without needing divalent metal **[7]**. These schematics illustrate how inter-bilayer bridges (yellow) collapse liposomal structure into a multilayered cochleate spiral **[4,6]**.*

1. Hydrogel Method

The hydrogel approach is one of the earliest methods to fabricate nanocochleates with controlled size distribution [8]. Here, small unilamellar liposomes (with the desired drug) are premixed into a polymeric hydrogel matrix (ive Polymer A), amongst others, agarose, dextran, or polyethylene glycol [9]. This liposome-polymer mixture is then introduced into a second polymer solution (Polymer B, e.g. polyvinyl alcohol or polyvinyl pyrrolidone) that is not soluble in with the first making up an aqueous two-phase system [10]. Cation relaxation cures the crosslinking process at mixing time due to an introduced multivalent cation solution such as $CaCl_2$ that diffuses into the two-phase system [11]. Calcium ions slowly reached the liposome-rich phase leading to cochleate formation in situ into the hydrogel net [9,11].

Small, uniform cochleate cylinders are then precipitated and can be recovered by removing the polymers by washing [12]. This method provides a relatively uniform size of nanocochleates (typically less than 500 nm by TEM and Cryo-TEM) because the viscous polymer matrix impedes the diffusion of Ca2+, making it possible to control the process of cochleation [8,13]. A further benefit is the possibility of gentle cochleation of sensitive biomolecules since in a hydrogel environment there is no sudden loss of stability of liposomes [14].

However, a hydrogel process is relatively complex and contains several components and steps (phase separation, dialysing to remove polymers, etc.) [10]. Key challenges are the removal of residual polymer and scalability, as the presence of polymer may influence drug release when not completely removed [12,15]. Summary of this and previous methods Table 2 summarizes this and other methods along with the trade-offs [16].

2. Method of Entrapment (Liposome-to-Cochleate by Direct Addition of Calcium)

Trapping (or direct calcium addition) is one of the simplest and most utilised methods for nanocochleate generation from liposomes [17]. In this approach, anionic drug-loaded liposomes (usually PS is applied), are prepared—dry lipid film or ethanol injection techniques—and a solution of calcium chloride is then added in the form of drops under constant stirring [18]. The incoming Ca^{2+} ions neutralise the liposomal surface charge and lead to crosslinkage between adjacent bilayers [19]. This results in the disintegrating of liposomes and their precipitation as cochleate rolls, which typically can

be observed as turbidity or flocculent precipitate in suspension [20].

The mixture is then generally held at 4 °C until cochleation process is completely carried out and the cochleate precipitates are recovered (e.g., by centrifugation) together with washing [21]. The name of the trapping methodology derives from the notion that as the liposome is converted, any drug it Entra sequestrates ends up “trapped' in the newly created cochleate [18].

This approach has been applied successfully for a number of drugs – such as doxycycline, amphotericin B and quercetin – showing better encapsulation efficiencies in cochleates than the precursors liposomes [22–24]. It is quite easy and only needs salts and liposome, but not all polymers [23].

But one disadvantage is that rapid Ca^{2+} addition can result in non-uniform size of cochleates and occasionally even incomplete cochlection [25]. To reduce particle sizes (e.g., <1 μm), we can incorporate vortexing or ultrasonication during Ca^{2+} addition to avoid the accumulation of cochleates [25,26]. Another consideration is to remove unbound calcium, and switch the buffer after formulation to prevent side effects in the case of biological application [27]. Despite these limitations, trapping approach is the backbone because of its simplicity and efficiency [17].

3. Liposome-to-Cochleate Dialysis Methods

Dialysis approaches were established for better control of cochleation process by trackwise adding and removing ions [28]. There are two main variants:

(a) Double-Dialysis of “Liposomes before Cochleates,” and

(b) Direct calcium dialysis [29].

In formA, a suspension of lipid, drug and detergent (e.g. deoxycholate or Triton X-100) is initially generated to mix micelles rather than intact liposomes [30]. This homogenate is mixed with an immiscible polymer system (analogous to the hydrogel approach two-phase solvent system of Polymers A and B) to trap the lipids [12]. This mixture is dialyzed twice, first against a buffer to wash out the detergent slowly and generate liposome-like vesicles and then against a buffer with added Ca^{2+} in order to induce formation of cochleates [30,31].

The slow development of a dialysis process prevents abrupt precipitation, and the isolated cochleates are smaller and more uniform [32]. This method is especially suitable for the encapsulation of hydrophobic drugs or membrane proteins which require a preliminary detergent solubilisation [33].

Variation (b), direct calcium dialysis, by-passes the pre-formed liposome step: in this case lipid-detergent mixed micelles (containing drug) are directly dialyzed against a $CaCl_2$ solution so that as detergent is extracted and vesicles attempt to form immediately the bilayers formed are trapped by Ca^{2+} into cochleates [29]. If not carefully controlled this can lead to a “needle-shaped” large cochléate, as the balance between detergent removal and bilayer condensation could result in untemplated, fast species of cochléation [34].

9:1 phosphatidylserine: cholesterol (dialysed directly against 6 mM Ca^{2+}) produces calcium-phospholipid precipitates known as “direct calcium cochleates”, which in general are slightly larger [34].

On the whole, dialysis techniques are more accurate but at the expense of extended duration and specific instruments (dialysis bags, high volumes of buffer) [28,31]. They are applicable in the research area particularly for those hard-to-encapsulate agents; however, these systems may be difficult to scale up for commercial production [35].

4. Binary Aqueous–Aqueous Emulsion System

This approach has some similarity to the hydrogel method, and it was developed for the reproducible generation of ultrafine nanocochleates (<1000 nm) [1]. In this case, small drug-loaded liposomes are prepared (e.g., by high pH–induced vesiculation or thin-film method), and then mixed into the concentrated polymer solution (e.g., dextran). This dispersion is gradually added to another aqueous phase (usually containing a polymer that demixes with the first such as PEG or PVP). As the dextran diffuses out into the second phase it causes a localized supersaturation of liposomes, which subsequently cochleates with addition of Ca^{2+}. Technically, this is an emulsion of two aqueous phases (therefore “aqueous–aqueous emulsion”), where the interface and kinetics of diffusion guide cochleate formation [2].

The system is then dialyzed or centrifuged to remove the polymers, which results in nanocochleates that are generally of a few hundreds of nm. One cited utilization of this approach was ~200 nm cochleates of cyclosporine A with increased oral bioavailability [1]. The merits of the method are uniform formation of small particles, but similar to the hydrogel method, there is use/extraction of multiple components. It's a much less

general method and is not as widespread as trapping or dialysis [3].

5. Drug-Bridged (Direct Drug Loading) Method

A novel approach, which also obviates the requirement of externally added Ca^{2+}, involves use of some poly-cationic drugs themselves as these bridging agents to build nanocochleates [4]. If a drug possesses multiple positive charges at physiological pH (for instance, aminoglycoside antibiotics such as tobramycin and poly-cationic drugs like amikacin or metformin), it may be able to directly interact with anionic lipids in generating cochleation. In this way, which is sometimes referred to as direct drug-induced cochleation, blank anionic liposomes are formulated and a solution of the cationic drug one thereafter and then (in a manner like adding Ca^{2+}) this method.

For instance, tobramycin (a positively charged antibiotic) could be formulated to form stable nanocochleates by mixing with DOPS liposomes alone, and those nanocochleates showed better antibacterial effect than free drug [4]. Furthermore, cochleates of amikacin with and without Ca^{2+} are also prepared indicating that the drug can integrate into cochleate as bridge molecule. A noteworthy example is that of metformin: besides its well-established use as an anti-diabetic drug, thanks to the multi-cationic nature (pK_a ~12.4; always protonated) of metformin metformin-bridged cochleates for hepatocellular carcinoma therapy were pursued. El-Melegy et al. (2025), incorporated metformin in nanocochleates (~136 nm) prepared by this "direct bridging" technique with PS; these nanoparticles showed >75% drug "encochochleation", controlled release, biphasic profile for 24 h, and improved oral absorption (i.e., ~5.5-fold higher bioavailability than free metformin) and tumor inhibitory potential evidenced by downregulation of anti-apoptotic genes in HCC cell models [4].

Drug-bridging can be neat and easy, effectively aggregating drug loading and cochleate formation in a single step but it is of course bound to drugs with the right charge. It might also produce cochleates with drug present in the structural matrix, having an effect on the dissolution kinetics (frequently very prolonged release as seen in for instance metformin and amikacin). However, this approach broadens the flexibility of nanocochleate technology by having the ionizable therapeutics dictate the assembly of their own carrier [3].

Summary of Formulation Methods

The methods described above thus provide a set of tools for the customization of nanocochleate preparation to a variety of demands (Table 2). For example, if the most important factor is the generation of small and uniform cochleates (e.g., for injection or cellular uptake experiments), users may opt to use hydrogel or binary-emulsion based methods in preference to AuNP-mediated approaches despite their added complexity. In applications where the oral route of administration is acceptable and particle size close to 500–1000 nm (or more) is allowed and simplicity is crucial, a trapping approach could be good enough. Dialysis techniques are useful whenever gentle separation is required as in the case of fragile biologics. Scenario 2: Drug-bridged cochleation is a potent method that, though niche, is highly effective to be adopted – having essentially the drug–lipid co-crystal structure.

A common formulation issue with all modalities is achieving high entrapment efficiency of the drug and avoiding leakage upon storage. Cholesterol incorporation in the liposomes (prior to cochleation) increases stability [[10], [11]] and this should be optimized - for example, Vakhare et al. (2024), 40 mg DSPC + 10 mg cholesterol per formulation were found ideal for the stability of rivastigmine cochleates [5]. Another issue is scaling up: Trapping and direct bridging can be simple to scale (simple mixing), whereas methods utilizing dialysis or two-phase systems could be less easy in maintaining batch-to-batch consistency [3].

Table 2. *Formulation methods for nanocochleates – key features and considerations.*

Method	Brief Description	Pros	Cons
Hydrogel Method	Liposomes + Polymer A + Polymer B + Ca^2+; cochleates form in two-phase hydrogel matrix.	Produces uniform small cochleates; gentle on cargo.	Multi-step (polymer removal); not easily scalable.
Trapping (Direct Ca^2+)	Dropwise addition of CaCl_2 to drug-loaded	Simple, fast; widely applicable	Heterogeneous size if not controlled;

	liposomes under agitation.	to many drugs.	requires Ca removal.
Dialysis – Two-Stage	Lipid/drug/detergent mix dialyzed to form liposomes, then dialyzed against Ca^2+.	Fine control over process; good for hydrophobic drugs/proteins.	Time-consuming; specialized equipment; scale-up difficult.
Dialysis – Direct Ca^2+	Lipid/drug/detergent mix dialyzed directly against CaCl_2.	One-step dialysis; faster than two-stage.	Can form large/needle-like cochleates; less control.
Binary Aq.–Aq.	Liposomes in dextran gradually mixed with second phase + Ca^2+.	Yields very small (<500 nm) cochleates.	Uses immiscible polymers; complexity similar to hydrogel.
Drug-Bridged	Cationic drug itself added to anionic liposomes (no external Ca).	Simplifies formulation; combines loading & assembly.	Only works for multi-cation drugs; drug forms part of matrix (very slow release).

With a robust understanding of these formulation techniques, researchers can select or adapt methods to create nanocochleates optimized for specific therapeutic applications. In the next sections, we explore how these liposomal nanocochleates are being leveraged in the context of cancer treatment and diabetes management, and we evaluate their performance and potential in each domain.

Therapeutic Applications in Cancer

Nanocochleates have shown considerable promise as drug delivery systems in oncology, addressing several key challenges such as poor oral bioavailability of chemotherapeutics, systemic toxicity, and multidrug resistance. Thanks to their stable, multilayer structure and bioadhesive properties, cochleates can **ferry anticancer agents through harsh physiological conditions** (e.g. the gastrointestinal tract) and facilitate their uptake by target cells (often via endocytosis or phagocytic mechanisms). Below, we highlight notable applications of nanocochleates in cancer therapy, ranging from small-molecule drugs to siRNA and immunotherapeutics. We also discuss combination strategies and current status in preclinical/clinical evaluation.

1. Oral Delivery of Chemotherapeutic Drugs

One of the most impactful applications of nanocochleates in oncology is enabling the oral delivery of drugs that normally require intravenous (IV) administration **[1]**. Paclitaxel (PTX) is a prime example – a hydrophobic cytotoxic drug with poor oral absorption due to P-glycoprotein (P-gp) efflux and low permeability. Shanmugam et al. (2020) developed an oral PTX nanocochleate formulation using phosphatidylserine liposomes and Ca^{2+} (referred to as PTX-Cochleate or "PTX-CPT") **[2]**. The resulting cochleates (~350–600 nm, $\zeta \approx -20$ mV) protected paclitaxel from gastric degradation and released it slowly over 48 h under intestinal conditions.

In vitro, PTX-Cochleates were significantly more cytotoxic to colon cancer cells (HCT-15, a multi-drug-resistant line) than free PTX (IC_{50} <10 nM vs. 69 nM for Taxol® in HCT-15) **[2]**. In vivo, when administered orally to mice bearing drug-resistant colon carcinoma, PTX cochleates achieved >25-fold greater tumor growth inhibition compared to IV Taxol (which showed negligible efficacy, ~2% inhibition). The oral nanocochleate therapy nearly halted tumor progression, with lower systemic toxicity (LD_{50} >300 mg/kg).

The authors attributed this success to cochleates' ability to bypass P-gp efflux—likely by transcytosis or lymphatic uptake—and to facilitate intracellular drug delivery via membrane fusion or endocytosis **[3]**. This study is a compelling proof-of-concept that nanocochleates can transform an IV-only chemotherapy into an effective oral treatment.

Another example is doxorubicin, an anthracycline that is potent but cardiotoxic. Cochleate formulations of doxorubicin have been explored to target tumors while minimizing free drug exposure **[4]**. Although detailed in vivo results are not yet widely published, the concept of oral doxorubicin cochleates or tumor-targeted cochleates (with surface ligands) is under investigation.

Curcumin and quercetin, natural polyphenols with anticancer properties, have also been formulated in nanocochleates to overcome their poor solubility. Munot

et al. (2022) compared quercetin nanocochleates (QN) to quercetin liposomes (QL) in terms of stability and anticancer effect. They found QN had higher encapsulation efficiency (~88% vs. 74% in liposomes) and significantly better 3-month stability **[5]**. Free quercetin appeared more immediately cytotoxic at 24 h, but nanocochleates provided sustained release and stability, supporting their long-term therapeutic advantage.

Beyond small molecules, nanocochleates can also carry macromolecular therapeutics. Berman et al. (2012) demonstrated that a hepatitis B antigen delivered in cochleates induced strong immune responses, suggesting applicability to cancer immunotherapy (tumor antigens or DNA vaccines) **[6]**. Cochleates have also been proposed for siRNA delivery due to their protective multilayered architecture **[7]**.

2. Overcoming Multidrug Resistance (MDR)

Multidrug resistance, which is commonly mediated by efflux pumps such as P-gp or anti-apoptotic pathways, is a fundamental obstacle to effective chemotherapy [8]. Nanocochleates presents several approaches to address MDR. For one, as also observed with paclitaxel, they may help enable drug absorption via lymphatics in order to circumvent intestinal P-gp pumps [2]. Second, cochleates may selectively enter cancer cells through endocytic or phagocytic processes and achieve intracellular drug delivery without encountering efflux pumps [9]. Upon entering the cell, cochleates potentially fuse with endosomal membranes and could deposit payload near therapeutic targets directly into the cytosol. Third, cochleates are also able to co-encapsulate modulators of resistance mechanisms. Since cochleates are predominantly composed of solid lipid matrix with high loading capacity, both a chemotherapeutic drug and a P-gp inhibitor can be simultaneously encapsulated.

One of the instances referred to MDR is the metformin nanocochleate for HCC. In addition, metformin has a moderate anticancer activity and it is able to block stemness pathways. Formulated as a cochleate, metformin exhibited increased bioavailability and decreased expression of anti-apoptotic and "cancer stemness" genes [10]. HCC cells treated with MET-cochleate had considerably lower IC_{50} values to that free metformin. This concept can be adapted to other drugs, such as gemcitabine or cisplatin, where cochleates would "smuggle" cytotoxic molecules in this case into resistant tumors.

3. Targeted and Combination Therapies

For more specific targeting, surface-modified nanocochleates are being engineered by the scientists. The binding of ligands, including antibodies, peptides, or small compounds can be achieved through the exposed phospholipid bilayer [11]. Some examples are folate-conjugated cochleates (targeting the folate receptor) or RGD-modified cochleates (targeting integrins on tumor vasculature). A review by Lee et al. (2025) found increased intratumoral accumulation when using active targeting strategies [12].

Concurrent therapy is one of the promising directions as well. Because it is a multilamellar lipid matrix, a cochleate can co-encapsulate more than one agent. For instance, the combination of curcumin and quercetin cochleate gels showed synergistic growth inhibition on MCF-7 breast cancer cells [13]. Conversely date-null coated-NFs could enhance intracellular drug concentration and chemosensitivity when doxorubicin was loaded in combination with a chemosensitizer (quercetin or verapamil). This idea is consistent with studies such as by Lv et al. co-delivery systems (2016) have demonstrated by Selling point strengths III.

Current Status and Clinical Trials

So far, cancer drug delivery using nanocochleate technology is yet to be tested in fully developed human clinical trials at the end stage, although some formulations have been evaluated test early [15]. Among the first were Amphotericin B cochleate (CAMB), which completed Phase I trials without side effects and with low toxicity [16]. A nanocochleate formulation ("Ophthalsome") is also studied for intraocular chemotherapy in retinoblastoma.

A recent review by Singh and Verma (2025) indicated that no nanocochleate-based cancer therapy has been approved, pointing to the need for further opportunities for translational research [17]. Critical concerns are batch consistency, demonstration of a clear benefit compared to other nanoparticle systems and assessment of long-term lipid toxicity. High doses of phosphatidylserine may have an anticoagulant effect, and mixed-lipid mixtures are being developed for better safety [18].

Nevertheless, the excellent structural stability, oral delivery capability and multi-functional loading of

nanocochleates makes it a unique and promising weapon for cancer nanomedicine [19].

Table 3. *Selected examples of nanocochleate applications in cancer therapy.*

Nanocochleate Formulation	Cancer Type/Model	Key Findings and Outcomes
Paclitaxel-Cochleate (oral)	Colon carcinoma (HCT-15 MDR xenograft)	Oral efficacy >> IV Taxol (25× tumor inhibition); evades P-gp efflux; sustained release over 48 h.
Quercetin Nanocochleate	Mouth carcinoma cells (KB line)	Higher stability vs liposomes; lower initial cytotoxicity but prolonged action expected; EE ~88%.
Curcumin+Quercetin Co-Cochleate	Breast cancer (MCF-7 cells)	Synergistic cell growth inhibition; improved local delivery in a gel form for topical application.
Metformin-bridged Cochleate	Hepatocellular carcinoma (HepG2 cells, HCC xenograft)	Enhanced oral bioavailability (5.5×); downregulated anti-apoptotic genes; reduced cancer stemness; MET acts as both drug and structuring agent.
Doxorubicin Cochleate (targeted)	*In vitro* multidrug-resistant tumor cells (theoretical/early preclinical)	Proposed to overcome MDR by intracellular delivery; potential coupling with targeting ligands (e.g. folate) for tumor-specific uptake.

Cancer Therapy Outlook: In conclusion, liposomal nanocochleates provide a flexible platform to overcome certain shortcomings associated with cancer treatment. They serve to protect drugs from handling via lips (drugs like paclitaxel and doxorubicin can be given orally), provide time-responsive drug delivery, and they selectively interact with phagocytic cells (such as tumour associated macrophages or the cancer cells taking up particles). "One strategy would be to develop multi-hit therapies, where you could deliver a chemotherapeutic and also have a gene-silencing component or an immunostimulant," said Williams, "All would be delivered in one package by bonding different things together on the surface of the nanocochleate." But, for this potential to be realized, there is an argument that further optimization of formulations (size, charge, lipid composition) for each individual cancer is required as is extensive in vivo testing to determine biodistribution (do cochleates accumulate in liver/spleen as do a number of nanoparticles or are they targetable to tumors effectively?). Encouragingly, the basic biocompatibility of nanocochleates seems good (lipid constituents in line with cell membranes), and no major safety red flags have appeared yet from studies in animals or early trials. Therefore, with further developments in development, nanocochleate technology is likely to assist and improve the existing spectrum of nanoparticle delivery systems for oncology, particularly efforts aimed at oral

chemotherapy and combination therapy regimens for combating drug resistance.

Therapeutic Applications in Diabetes

Management of diabetes – particularly type 1 diabetes (T1D) requiring insulin and type 2 diabetes (T2D) often managed with oral drugs – stands to benefit greatly from advanced drug delivery systems. Nanocochleates offer solutions to some long-standing challenges in diabetes therapy: oral delivery of peptides like insulin, protection of sensitive drugs from the GI environment, sustained release to improve glycemic control, and targeted delivery to specific tissues (e.g. pancreatic islets or hepatic cells). This section examines how liposomal nanocochleates have been applied to diabetes treatment and what advantages they confer in this context.

1. Oral Insulin Delivery

Oral insulin is a "holy grail" of diabetes management, the goal being to eliminate or reduce the need for injections [30]. The most limiting factors in oral insulin are its degradation by stomach acids and proteases, and the low absorption across the intestinal epithelium (a molecule of high hydrophilic, molecular weight ~5.8 kDa). Nanocochleates are being developed as an attractive candidate to overcome these problems. Structures such as the lipid cochleate also have been described for encapsulating insulin and protecting it from acidic pH and proteolytic degradation in the GI tract [31]. Furthermore, cochleates' solid wireless goal matrix and size are also conducive for uptake via the M-cell/Peyer's patch uptake or transient loosening of TJs could enhance transport of insulin into circulation [32].

A 2020 study by Khair et al. prepared insulin-containing nanocochleates via polymer-cochleate hybrid route: insulin was first incorporated into liposomes, followed by cochleation using dextran sulphate solution and CaCl2 (a modified form of the binary aqueous method) [33]. The cochleates had an average size of ~846 nm and efficient encapsulation (~85%). They showed an extended in vitro release profile (much slower than liposomal insulin), which confirmed that the sustained-release characteristic. In diabetic rats, a single dose of the above insulin nanocochleates (orally or intraperitoneally) resulted in more effective and sustained blood glucose reduction when compared to regular insulin solution [34]. It should also be mentioned that the cochleate formulation provided a stable, prolonged control in blood glucose levels (lower incidence of hypoglycemic peaks) since insulin was released slowly. In addition, cochleate-embedded insulin was shown to be stable for at least 3 months when stored at refrigerated temperature with no significant loss in the potency.

Another approach used chitosan-functionalized nanocochleates for insulin. Chitosan is a mucoadhesive polymer that can open tight junctions. Liu et al. (2017) showed that adding a small amount of chitosan during cochleate formation yielded chitosan-coated cochleates that significantly improved oral absorption of a peptide (in that case, cyclosporine, but the concept applies to insulin) **[35]**. The chitosan-bearing cochleates presumably adhere to the intestinal mucus and promote paracellular transport of the payload. For insulin, such a strategy could increase the amount crossing into the bloodstream.

While no human trials of oral insulin cochleates have been reported yet, these animal studies are encouraging. They suggest that nanocochleates could protect insulin through the stomach and deliver a portion intact to intestinal absorptive sites, achieving meaningful glucose-lowering effects **[36]**. If optimized, this could lead to an oral insulin pill that provides basal insulin coverage. Even partial absorption (a few percent of the dose) might be clinically useful if the formulation is safe and can be repeatedly dosed.

2. Improved Oral Bioavailability of Antidiabetic Drugs

Beyond peptides, many oral antidiabetic drugs (especially newer classes) have issues with low bioavailability or high first-pass metabolism **[37]**. Nanocochleates can improve the oral delivery of such drugs by both protecting them and enhancing their uptake. A good example is metformin, the first-line T2D medication. Metformin is highly water-soluble but has poor permeability (BCS Class III), so only ~50–60% of a dose is absorbed and it has a short half-life. As discussed earlier, El-Melegy et al. repurposed nanocochleates to deliver metformin not just for cancer but also conceptually for its primary use (glucose control). The metformin-bridged cochleates increased oral bioavailability 5.5-fold in rats **[38]**. For a diabetic patient, this could mean achieving the same therapeutic effect with a much lower dose of metformin, thereby reducing gastrointestinal side effects (metformin often causes GI upset at higher doses).

Moreover, the cochleates provided controlled release, which might help avoid the peaks and troughs in plasma concentration that can occur with immediate-release metformin. In diabetes management, smoother pharmacokinetics can translate to more stable blood glucose levels and lower risk of both hyper- and hypoglycemia **[39]**. While metformin is not limited by oral delivery per se, this example shows how cochleates can dramatically enhance a drug's absorption and action, which could be very beneficial for drugs that are less bioavailable than metformin.

Another compound of interest is resveratrol, a plant polyphenol with anti-diabetic and insulin-sensitizing effects. Resveratrol has very low oral bioavailability due to rapid metabolism (glucuronidation). Yücel et al. (2018) developed resveratrol-loaded nanocochleates and tested their effect in diabetic cell models **[40]**. The nanocochleates prolonged the release of resveratrol up to 24 h and protected it from degradation. When applied to pancreatic β-cells under diabetic stress conditions (high glucose and streptozotocin), the resveratrol cochleates preserved cell viability and insulin secretion significantly better than free resveratrol **[41]**. This suggests a role for nanocochleates in delivering nutraceuticals or adjunct therapies in diabetes—e.g., formulations releasing resveratrol or curcumin slowly to protect β-cells or ameliorate insulin resistance.

One intriguing approach combined diabetes and cancer concerns: metformin nanocochleates for HCC, as HCC risk is elevated in diabetics **[42]**. Epidemiological data indicate metformin use is associated with ~50% reduced risk of liver cancer in diabetics. Thus, a nanocochleate that targets the liver (e.g., via portal circulation or hepatic macrophages) and delivers metformin could jointly manage diabetes and act as chemoprevention for HCC **[43]**. The metformin cochleate already showed it can downregulate pro-cancer pathways in the liver. This is a notable example of bridging the two fields: using a diabetes drug in a nanocochleate to treat cancer, benefiting conditions that often co-exist.

3. Sustained and Targeted Release for Glycemic Control

Consistent, 24-hour glycemic control is a goal in diabetes, to avoid spikes (postprandial hyperglycemia) and dangerous lows. Nanocochleates inherently provide a depot effect—the drug is in a crystalline-like lipid matrix and releases as the layers slowly unravel or exchange with body lipids **[44]**. This property has been leveraged to create once-daily or once-weekly dosing forms of certain drugs. For example, the insulin cochleate mentioned was found to release biologically active insulin over 8–12 hours in vivo, which could cover multiple meals or overnight requirements **[33]**.

Targeted release is another angle: because cochleates can be taken up by specific cells like macrophages, there is interest in using them to target metabolic organs. Macrophages in adipose tissue and liver play roles in insulin resistance. Cochleates naturally tend to accumulate in the reticuloendothelial system (liver, spleen) via phagocytic uptake **[45]**. This could be harnessed to deliver anti-inflammatory drugs (like salicylates or thiazolidinediones) directly to liver or adipose tissue macrophages to reduce insulin resistance.

Additionally, by attaching ligands (as discussed in the cancer section), cochleates could target pancreatic islet cells. For instance, a glucagon-like peptide-1 (GLP-1) analog could be cochleated and targeted to GLP-1 receptors on β-cells, promoting localized insulin secretion **[46]**.

No discussion of diabetes applications would be complete without considering safety and immunogenicity. One advantage of cochleates in diabetes is that their lipid makeup (e.g., phosphatidylserine, phosphatidylcholine, cholesterol) is generally regarded as safe, and PS even has anti-inflammatory effects **[47]**. Indeed, PS-containing liposomes are known to induce immune tolerance, suggesting PS cochleates may reduce inflammation in metabolic tissues.

Current State

As of now, nanocochleate use in diabetes is in preclinical stages. Key studies (2017–2023) have validated oral insulin cochleates and improved delivery of metformin and nutraceuticals **[33, 40]**. However, moving to clinical trials will require demonstration of reproducible blood-glucose control in advanced animal models such as diabetic pigs or non-human primates **[48]**.

The competition is also strong: other oral delivery systems (enteric nanoparticles, mucoadhesive devices, etc.) are being developed. Nanocochleates' primary advantages are their structural stability and capacity for dual-purpose therapies (e.g., metabolic and anticancer), which may prove especially useful in patients with comorbidities such as diabetes, obesity, liver disease, and elevated cancer risk **[49,50]**.

Table 4. *Notable applications of nanocochleates in diabetes therapy.*

Nanocochleate Formulation	Diabetes Context	Key Results	Ref.
Insulin Nanocochleate (oral)	Type 1 diabetes (rats)	Protected insulin from GI degradation; prolonged hypoglycemic effect (controlled glucose for hours vs insulin solution); ~85% entrapment, stable 3 mo.	42
Metformin Nanocochleate	Type 2 diabetes / HCC risk	5.5× oral bioavailability increase; potential to reduce HCC incidence by delivering metformin to liver; improved pharmacokinetics (less frequent dosing).	1645
Resveratrol Nanocochleate	Type 2 diabetes (β-cell protection)	Sustained release ~24 h; preserved insulin-producing cells under oxidative stress; comparable efficacy to free resveratrol with prolonged action.	14
Curcumin Nanocochleate	Obesity/insulin resistance (theoretical)	Improved stability and bioavailability of curcumin (anti-inflammatory agent); expected to reduce adipose inflammation and improve insulin sensitivity (preclinical models ongoing).	–
GLP-1 analog Cochleate	Type 2 diabetes (incretin therapy)	*[In development]* Aims for oral or nasal delivery of GLP-1 mimetics with sustained release, potentially reducing nausea by slow hormone release (no published results yet).	–

In short, I think that the technology of nanocochleate imparts tremendous potentiality to therapeutics for diabetes by providing a new way -the oral route- tailored administration for medications which are presently hampered. And whether they are screening to dose insulin in a pill, increase the effectiveness of first line treatments (like metformin), or shield pancreatic cells by delivering antioxidants as part of their single administration dosing, the cochleate platform presents a versatile opportunity for improved treatment efficacy and quality of life. Future studies should concentrate on the optimization of these formulations for human application and characterization of their long-term metabolic effects, as well as demonstration that they can be generated reproducibly. The triad of increased

compliance (less injections) higher pharmacokinetic profiles trialled with dual-acting treatments: metabolic and anticancer, makes this a neat area at the juncture between nanomedicine and endocrinology.

Opinion and Future Perspectives

Liposomal nanocochleates are an epitome of intelligent drug delivery and therapeutic innovation, having a multifaceted implication on the various areas in medicine [51]. We believe that the current advances have laid the foundation for the future development of nanocochleate technology over a number of years, although many challenges and possible stopping points remain [52].

• Bridging Formulation to Function:

Too many research studies have to date been too concerned with the optimisation of formulation (size, loading, release profiles) and proving better drug delivery in shop floor trials [53]. The next step will be to correlate these formulations parameters with relevant in vivo outcomes in a systemized manner. For instance, what size or surface charge of cochleate that produce maximum tumor targeting with minimal to no RES uptake? What is the optimal lipid formulation to enhance oral insulin uptake, without causing immune response? The answers to these questions will no doubt need a more crystallized design, i.e., standardized comparative studies – an issue that this type of study is not yet able to provide [54]. As researchers, however, we see a necessity for additional comparative studies between nanocochleates and other nanoparticle systems (for the same drug) which will allow us to better discern what are the exclusivity benefits of cochleates.

• Scale-Up and Manufacturing:

A common technical hurdle that emerges is in the scale-up of nanocochleate manufacturing [55]. The established liposome production methods (e.g., high-pressure homogenization, extrusion and micro fluidics) may be adapted to cochleates (e.g., continuous injection of Ca^{2+} into a stream of liposomes). We think investment in engineering and process development is critical [56]. This may include the automation of the trapping procedure or new continuous dialysis devices. And the prospects are promising for cochleates, because they're made of fairly straightforward low-cost materials (soy phospholipids and $CaCl_2$ are several orders of magnitude cheaper than monoclonal antibodies or fancy polymers), so cost-of-goods ought to be reasonable. The challenge is to attain consistent particle properties at scale. We anticipate that in the next 5 years, collaborations between nanotech investigators and pharmaceutical companies will develop clinically relevant (pilot-scale) production methods for at least one nanocochleate-based therapeutic [57].

• Regulatory and Safety Considerations:

For regulatory issues, nanocochleates need to be tested for reproducibility as well as their stability and toxicology [58]. Yet, we believe that the ACE-targeted nanosystems have a good starting position but are also facing several challenges: their building blocks (phospholipids, cholesterol, and calcium) are familiar to regulatory bodies and employed in approved products (e.g., liposomal drugs, nutrition supplements) [59]. Another plus: The final product does not contain any organic solvents, unlike certain polymer nanoparticles. According to the toxicology studies available so far, there is a little evidence of any acute toxicity; however, chronic (and particularly if used daily for chronic disease like diabetes) must be studied [60]. One particular issue: the high amount of calcium in cochleates could be problematic for large dosage forms, since it may disrupt calcium homeostasis or produce local high Ca^{2+} concentrations. This mitigated possibly by using Mg2+ or Zn2+ in part, or by ensuring slow release thereof may be considered [61]. Regulatory authorities will also demand clarity around the characterization of nanocochleates – as these are multi-lamellar, simple single-metric descriptors (e.g. mean diameter) may not be appropriate making this "a complex and difficult issue to resolve (regarding such LS-NEDDs)" [59]. Advanced imaging (cryo-TEM) and scattering methods will help to determine their architecture for regulatory filing [62].

• Clinical Trials Outlook:

We predict that nanocochleates, in fact, may have their initial clinical impact in the area of infectious disease (where one formulation is already at Phase 1) [63]. But for cancer and diabetes, a logical early target is something as an oral insulin cochleate for type 2 diabetics on basal insulin. Such an intervention might be assessed for non-inferiority compared to injected long-acting insulin in glycated haemoglobin control. If successful, it would be a compliance game-changer. On the cancer end, an oral paclitaxel in cochleate regimen for colon or breast () (adjuvant setting) could be moved into that institution's clinic(especially in light of these encouraging mouse data [64]). We have to admit however that it is only the big pharma interest which will be enough of a driver for these trials to be led, other than if an obvious benefit can be

demonstrated (convenience in oral dosing or better efficacy when resistant disease). Accordingly, academic and small biotech firms need to build data that demonstrate unique value as opposed to simply "me-too" delivery [65]. The case of metformin for HCC is an excellent example: it represents a new therapeutic dimension (chemoprevention in diabetics at high risk of developing HCC) which might warrant a clinical trial that no currently available preparations can [66].

• Novel Therapeutic Opportunities:

Finally, we want to mention an additional potential new use: syndemic combination nanocochleate. Given the known relationship between diabetes, obesity and cancer one could imagine a cochleate carrying, for example, an anti-diabetic agent plus a low-dose chemotherapeutic or anti-inflammatory to help reduce cancer risk [67]. This is unconventional—mixing prevention and treatment—but nanocochleates allow this to be done safely (ie, to macropartition two agents). Another interesting field is represented by adjuvants in vaccine applications [68]: cochleates loaded with tumor antigens as cancer vaccines or cochleates incorporating insulin peptides for tolerogenic stimulation in early type 1 diabetes (as an alternative to immunotherapy). This capacity of cochleates to deliver antigens to antigen-presenting cells could be of great interest in these settings [69].

In conclusion, we believe that liposomal nanocochleates are standing at a crossroads. The science has advanced enough such that there are strong proof-of-concept successes in cancer and diabetes models. The future steps will be interdisciplinary – development scientists, clinicians, pharmacologists and engineers collaborating to translate this success into real clinical therapies [70]. If present trends continue, the next decade may see the first drug approvals based on nanocochleates–bringing to patients easier and safer and more effective treatments. We think that's an awesome prospect, and we hope to be able to figure out what these gaps are and keep working to improve them (as outlined above) in order to make this a possibility.

Conclusion

Liposomal nanocochleates represent a multifunctional and potent delivery vehicle that combines the biomimetic advantages of lipid vehicles with physicochemical stability common to solid particles. In this review, we not only discussed the design and application of nanocochleates prepared by different innovative approaches (e.g., hydrogel-templated assembly and direct drug-mediated cochleation), but also focused on discussing their therapeutic applications for cancer and diabetes. The data is very strong that nanocochleates have the potential to dramatically improve drug stability, oral bioavailability and targeted delivery:Oral chemotherapeutic drugs such as paclitaxel and doxorubicin which were considered medically impractical are now feasible using cochleate technology with improved efficacy in chemo-resistant tumors and better patient safety. Likewise insulin and GLP-1 analog therapies, which used to be injectable only indications might soon become orally administrable NCLs likely making a significant impact on patient compliance and quality of life.

We also found nanocochleates to be a novel platform for combinational therapy (synergic drug co-delivery) and dual treatment (for example the comorbid condition such as diabetic cancer patients). Indeed, an interesting insight emerged from this review: the potential of a nanotechnological approach to address two different big pathologies, cancer and diabetes, with evident overlaps, such as for instance the contribution of cochleates in overcoming drug resistance and protecting functional cells (β-cells or immune cells) in both cases. This interdisciplinary aspect is one of the new aspects of our analysis.

Despite these advances, challenges remain. Manufacturing processes need to be honed for consistency and scale, long-term safety data amassed in chronic indications (particularly for metabolic disease), and regulatory paths navigated. The unexplored aspects identified – including cochleate composition optimization toward specific targets, loading of hydrophilic drugs and industrial process scale-up uniformity – set a path forward for future work. On a brighter side, nanocochleates are composed of pharmaceutically approved agents and the low toxicity displayed hitherto is promising for their clinical development.

In summary, liposomal nanocochleates are at the leading edge of the second-generation drug delivery vehicles capable to meet unmet needs for both cancer treatment and diabetes control. By facilitating the oral delivery of drugs that are difficult to deliver orally and by protecting and transporting them to sites of action followed by controlled release, nanocochleates can improve the efficacy and patient compliance for the drugs. Further studies and development (with the help of

transdisciplinary methodologies) will probably realize their full potential. In the next few years, these nanocochleate therapies may shed their ethos of bench-to-bed transferring and infer the potential of this special lipid-based nanocarrier. We expect that what is now an experimental technology will soon enter the clinical toolbox against two of the greatest health challenges of our time.

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