RESEARCH PAPER

Nanocochleate-Driven Antidiabetic Drug Treatment: Advances in Synthetic and Herbal Compounds

Shubham K Sanjekar[1], Sayali S Pawar[2], Jayashri G Mahore[1*]

[1]Sinhgad College of Pharmacy, Affiliated to Savitribai Phule Pune University, Vadgaon (Bk), Pune, Maharashtra, India

[2]Jayawant Shikshan Prasarak Mandal University, Wagholi, Pune 412207

[*]Corresponding author: Dr. Jayashri G Mahore, Sinhgad College of Pharmacy, Affiliated to Savitribai Phule Pune University, Vadgaon (Bk), Pune, India. Email: Jayashri.topale@gmail.com

ABSTRACT

Diabetes mellitus (DM) is a long-term metabolic condition that impacts approximately one in every nine adults globally. Presently, oral antidiabetic medications like metformin and glibenclamide have limited absorption in the intestines, often necessitating higher doses that can cause systemic side effects. Meanwhile, peptide medications such as insulin require frequent injections due to their breakdown by enzymes in the gastrointestinal tract. To address these challenges, drug delivery systems based on nanotechnology have been developed as a promising solution. Among these, nanocochleates ; a new type of lipid-based nanocarrier with a distinctive cigar-shaped, multilayered roll-like structure formed through the interaction of anionic phospholipids and divalent cations (Ca^{2+})have shown significant potential for oral drug delivery.

This review offers an in-depth examination of nanocochleate-based formulations for antidiabetic treatment, focusing on three primary drug types: the small-molecule biguanide metformin, the peptide hormone insulin, and herbal phytoconstituents like curcumin, quercetin, and andrographolide. The article explores preparation methods, such as trapping and direct calcium bridging techniques, and their effects on drug stability and bioavailability. Preclinical results indicate that insulin-loaded nanocochleates provide sustained glucose regulation, metformin-loaded systems show up to a fivefold increase in oral bioavailability, and phytochemical-loaded nanocochleates enhance therapeutic effectiveness and shelf life. Additionally, this review summarizes comparative studies to identify formulation trends and existing research gaps. Despite encouraging results, challenges like aggregation, scalability, and regulatory hurdles need to be overcome for successful clinical application. Overall, nanocochleates offer a promising and innovative platform for the oral delivery of antidiabetic agents, enhancing stability, bioavailability, and patient adherence, which could significantly impact diabetes management in the future.

Keywords: DM, diabetes mellitus; IR, immediate release; NCs, nanocochleates; LBNPs, lipid-based nanoparticles; MTF, metformin; INS: insulin; ADAs: herbal antidiabetic agents and DD: drug delivery.

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1. INTRODUCTION

Diabetes mellitus is essentially a long-term condition characterized by elevated blood sugar levels due to issues with insulin production, function, or a combination of both[1]. According to the most recent International Diabetes Federation (IDF) 2024 report, the number of adults (aged 20–79 years) with diabetes worldwide has risen to approximately 589 million, up from 537 million in 2021, and is expected to reach around 853 million by 2050. This indicates that about 11.1% of the adult population will be affected by this disease[2-3]. If current trends persist, the diabetic population could surpass 1.3 billion by 2050 . These statistics highlight the urgent need for improved management strategies, as poorly managed diabetes can lead to severe complications. Currently, most patients require daily medication, either in the form of oral tablets or insulin injections, to manage diabetes. Metformin tablets or insulin injections are commonly prescribed by doctors to effectively regulate blood sugar levels. These medications help maintain normal glucose levels in the blood. However, traditional delivery methods have significant limitations. Metformin, when taken orally, is only moderately absorbed in the intestines, necessitating high doses that can cause side effects and result in inadequate blood sugar control[4-6]. Insulin and other peptide medications cannot be

administered orally because they are broken down by enzymes and cannot be properly absorbed through the intestines. This necessitates frequent subcutaneous injections, as oral administration is ineffective. The burden of frequent injections often leads to patients skipping their medication[7] . Improved adherence to treatment regimens is crucial for better diabetes management[8] .

Recent research is centered on creating innovative drug delivery systems to enhance the stability and targeted administration of antidiabetic medications. Non-invasive methods, like inhalable insulin, have been investigated; nonetheless, achieving effective oral insulin therapy remains a highly desired objective in diabetes management. In recent times, nanotechnology-based delivery techniques have significantly advanced in diabetes care. These methods are indeed aiding physicians in improving diabetes treatment. Scientists have developed numerous small carriers, such as polymer particles, liposomes, and micelles, to transport insulin and diabetes medications. These tiny carriers are capable of effectively delivering both conventional diabetes drugs and plant-derived therapies.[9-10] They safeguard drugs from degradation and facilitate their passage through biological barriers. Additionally, they offer controlled drug release, which can lower the necessary dosage and reduce side effects.[11-12] For instance, researchers have examined cerium oxide and other inorganic nanoparticles for their antidiabetic properties[13]. This highlights the extensive range of nanomedicine strategies being explored in current studies.

Recent research highlights the growing interest in nanocochleates for drug delivery, as they can effectively transport both hydrophilic and hydrophobic drugs. Essentially, nanocochleates are akin to spiral-shaped lipid particles resembling snail shells, formed when phospholipid layers coalesce upon the addition of specific ions. Notably, recent studies indicate that calcium ions (Ca^2+) are exclusively involved in these processes[14-15]. This technique was initially described in the 1970s by Papahadjopoulos et al., and it has since become a foundational method. Verkleij et al. employed a similar research approach. These structures are composed of continuous solid lipid sheets that coil into tight spirals with minimal water space inside[15-17]. This configuration results in a compact structure with negligible internal aqueous regions. This unique structure endows nanocochleates with several advantageous properties. The rigid layers shield drugs from damage and enable high drug loading of both hydrophilic and hydrophobic molecules. Additionally, the structure itself regulates drug release through gradual uncoiling and ensures safety by utilizing natural phospholipids and calcium. Nanocochleates can be dried into powder and reconstituted with water without losing their structure, making oral administration as convenient as tablets. This method is effective in capsules and provides an extended shelf life[17]. According to recent studies, these attributes make nanocochleates a promising system for the oral delivery of antidiabetic drugs.

Oral amphotericin B cochleates proved effective against fungal infections in mice. By 2010, there was increased interest from the industry, with Bio Delivery Sciences International securing patents for oral cochleate formulations for peptides and other biologics. The initial patent for cochleate technology was filed in 1997 by Mannino and Gould-Fogerite, establishing the groundwork for current cochleate applications. Additionally, researchers have begun exploring the use of nanocochleates in diabetes treatment due to their excellent stability and drug delivery capabilities. According to a recent review, researchers have investigated various nanocarriers, including cochleates, for diabetes treatment and discovered that natural compounds perform significantly better when encapsulated in these carriers[18]. In this review article, we concentrate on nanocochleate delivery systems for three primary antidiabetic agents: metformin, insulin, and plant-based antidiabetic compounds. We emphasize their formulation techniques, laboratory testing, animal studies, and system evaluation.

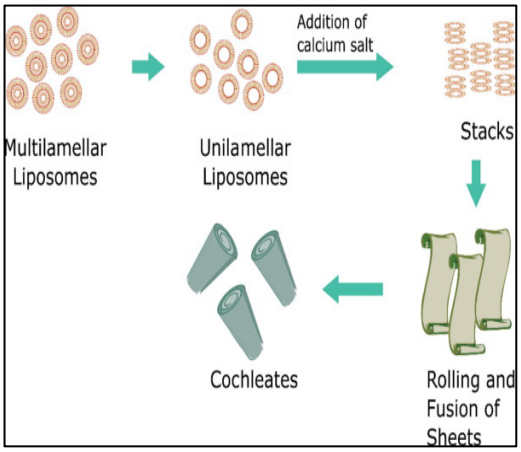

Figure 1. Formation of Nanocochleates[19]

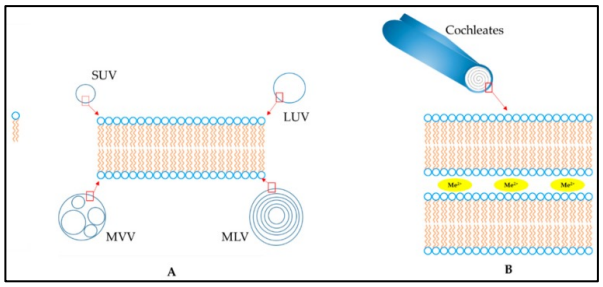

Figure 2. Structural schematic of (A) a liposome (spherical phospholipid vesicle with internal aqueous core) vs. (B) a nanocochleate (solid lipid-cation precipitate rolled up in a cigar-like spiral). Nanocochleates form when anionic lipid vesicles (e.g. containing phosphatidylserine) are treated with divalent cations (Me^2+), which bind and fuse the bilayers into a tightly coiled solid structure. This unique architecture affords high stability (minimal internal water) and protection for the encapsulated drug.[20]

2. NANOCOCHLEATE TECHNOLOGY: STRUCTURE, PREPARATION AND ADVANTAGES

2.1 Structure and Features

Nanocochleates are often described as "rod-shaped lipid cigars" due to their appearance under electron microscopy. These structures originate from a large, flat lipid bilayer that curls into a cylindrical spiral, similar to a jelly roll. During this rolling process, multivalent cations, such as Ca2+, are typically required to neutralize the negative charges on the phospholipid bilayers. This neutralization causes the bilayers to collapse or fuse, resulting in the formation of a tightly coiled, solid laminate[14-15]. The resulting cochleate particle is a solid, multilayered lipid structure that essentially lacks an internal aqueous core.

This design offers exceptional stability. Additionally, the encapsulated drug is shielded from hydrolytic or oxidative degradation because the liposome's interior functions as a solid lipid. For instance, the plant polyphenol quercetin, which typically degrades quickly, became significantly more stable when encapsulated in a (polymerized) nanocochleate and exposed to liver-like oxidative conditions[17]. Similarly, insulin encapsulated within cochleate lipid layers remains unaffected by gastric enzymes until it reaches the intestine for absorption. Another advantage is the ability to freeze-dry nanocochleates into powders that can be rehydrated later while maintaining their structural integrity[17]. Unlike the thin liposomes, the control samples, unilamellar liposomes are generally stabilized with lyoprotectants. This feature is particularly beneficial for creating oral dosage forms, such as capsules, and for the long-term preservation of nanocochleate products.

Advantages of Nanocochleates

Nanocochleates present numerous unique benefits as drug delivery systems. They are highly stable, with a structure that withstands degradation by enzymes, acids, and oxidation, making them more robust than traditional lipid carriers like liposomes. Their substantial loading capacity allows for the encapsulation of both hydrophilic and lipophilic substances, while also safeguarding delicate drugs such as insulin, peptides, and proteins from environmental harm. The cochleate design facilitates controlled and sustained drug release, gradually uncoiling to dispense the active ingredient, thereby decreasing the need for frequent dosing. Nanocochleates also enhance oral bioavailability by preventing drug breakdown in the gastrointestinal tract and boosting absorption, which is particularly beneficial for oral insulin delivery in diabetes treatment. Furthermore, they offer targeted delivery by following lipid absorption pathways that direct the formulation to the liver, the main site of insulin action. Composed of natural or synthetic phospholipids, they ensure biocompatibility and safety, posing fewer risks than many synthetic nanocarriers. Additionally, nanocochleates can be lyophilized, allowing them to be converted into a dry powder form suitable for encapsulation or long-term storage without losing stability.

Benefits of Nanocochleates

Nanocochleates present numerous advantages as cutting-edge drug delivery systems. They bolster drug stability by shielding them from degradation due to enzymes, acids, and oxidation, thus prolonging shelf life and preserving therapeutic effectiveness. Their capacity to enhance bioavailability ensures more effective drug absorption, particularly for peptide and protein-based molecules like insulin. The controlled and sustained release characteristic of nanocochleates facilitates a gradual release of drugs, decreasing the frequency of dosing and improving patient adherence. Moreover, they enable targeted drug delivery, especially to organs such as the liver, boosting therapeutic effectiveness while reducing systemic side effects. Composed of biocompatible phospholipids, nanocochleates are safe

and well-tolerated for extended use. Additionally, their ability to undergo lyophilization allows for easy conversion into stable dry powder forms suitable for oral administration and long-term storage[21-23].

2.2 Preparation Methods

A common approach to creating nanocochleates consists of two main steps. Initially, negatively charged liposomes are produced as precursors. Lipids like phosphatidylserine (PS) or phosphatidylglycerol (PG) are generally used to establish the required anionic surface, often in combination with structural phospholipids such as phosphatidylcholine (PC) and cholesterol, which can sometimes enhance stability. Liposomes can be formed using standard techniques like thin-film hydration or ethanol injection to generate nanoscale vesicles[24,17].

In the subsequent phase, the liposome suspension is transformed into cochleates by introducing a solution containing divalent cations. The standard trapping method involves gradually adding a solution with Ca2+ while gently swirling the suspension[24]. Calcium ions penetrate the liposome suspension, attach to the anionic headgroups of the lipids, and prompt the bilayers to spontaneously merge and collapse into flat sheets that curl into cochleates (the solution typically becomes cloudy as cochleates form). Key factors in this process include the Ca^2+: lipid molar ratio and the speed of Ca^2+ addition; for instance, PS-rich liposomes, which require approximately a 4:1 Ca^2+: lipid ratio, can use less Ca^2+ due to decreased charge density in lipid mixing. The resulting cochleate cylinders can be collected through centrifugation.

Alternative cochleation techniques have been explored, notably the direct co-precipitation method, where the drug's own positive charge (if present) aids in cochleation with reduced Ca^2+ levels[25]. This method has been effectively applied to create metformin cochleates by leveraging metformin's cationic properties[25], leading to straightforward preparation and a high drug content.

2.3 Benefits and advantages of Drug Delivery

Nanocochleates offer numerous important benefits and advantages when it comes to drug delivery, particularly for oral administration:

Benefits of Nanocochleates for Drug Delivery

Nanocochleates present numerous advantages in drug delivery, especially when it comes to oral administration. They exhibit a high level of resistance to the challenging conditions of the gastrointestinal tract, such as acidic environments, digestive enzymes, and bile salts, which often break down standard formulations. For instance, nanocochleates loaded with andrographolide retained their structural integrity in simulated gastric fluid, effectively safeguarding the drug in the stomach[26]. This protective feature is particularly useful for transporting acid-sensitive biomolecules like insulin through the gastrointestinal system. Additionally, their unique "scroll-like" multilayered design facilitates a biphasic drug release, characterized by an initial rapid release followed by a prolonged release phase. For example, quercetin nanocochleates released their contents gradually over a period of 6–24 hours, in contrast to free quercetin, which dispersed immediately[27]. This extended release is especially beneficial for managing chronic conditions such as diabetes, as it helps maintain consistent drug levels and reduces fluctuations and side effects.

Advantages of Nanocochleates over Conventional Delivery Systems

In addition to their intrinsic benefits, nanocochleates offer unique advantages over conventional formulations like liposomes or unencapsulated drugs. Research has shown that cochleates can enhance drug transport across biological barriers and increase bioavailability. For example, Liu et al. found that chitosan-encapsulated nanocochleates increased the oral bioavailability of cyclosporine A by more than three times compared to a standard formulation[28] . Similarly, both insulin and metformin demonstrated significantly improved absorption when administered via nanocochleates, with metformin achieving approximately 5.5 times higher systemic exposure (AUC) than a metformin solution[25] . Additionally, their particulate form allows for natural uptake by phagocytic cells, facilitating targeted drug delivery to specific tissues such as the liver or immune cells. This is especially beneficial in type 2 diabetes, where reducing liver inflammation can enhance insulin sensitivity and improve glucose regulation. Furthermore,

surface modifications—such as attaching targeting ligands or antibodies—can further improve site-specific drug delivery. Collectively, these benefits lead to enhanced therapeutic effectiveness, increased stability, improved permeability, and controlled release, potentially enabling lower doses and reduced side effects[29] .

3. NANOCOCHLEATES FOR ANTIDIABETIC AGENTS –CASE STUDIES

3.1 Insulin

For a long time, scientists have been exploring methods to deliver insulin orally instead of through injections, but numerous challenges exist: insulin is broken down by stomach enzymes and has minimal permeability through the gut's lining. The innovation and use of nanocochleates offer a promising solution to these issues. Researchers have created insulin-loaded nanocochleates that safeguard insulin in the gastrointestinal tract and allow it to enter the bloodstream, achieving pharmacological effects akin to injections[29] . Stable oral nanocochleates of insulin were formulated by combining insulin with anionic polymers (dextran sulphate and PEG) to promote interaction with negatively charged lipids, followed by the addition of Ca^2+ to trigger cochleation. The resulting cochleates showed high insulin encapsulation (~85%) and an average particle size of about 850 nm. Functionalized nanocochleates, such as those coated with chitosan, have been developed to improve mucoadhesion and intestinal absorption. For instance, chitosan-functionalized nanocochleates have been tested using cyclosporine A as a model peptide, demonstrating enhanced stability, permeability, and oral bioavailability compared to traditional formulations.[4-5]

In vitro release studies indicate that insulin is gradually released from cochleates. It was observed that insulin cochleates released their contents more slowly in PBS (pH 7.4) compared to a free insulin solution[29] . This prolonged release could help mitigate the rapid insulin surges that occur after dosing. Indeed, a similar two-phase release pattern (initial burst followed by gradual release) has been noted in other systems designed for oral insulin delivery, such as insulin–phospholipid complexes within biodegradable nanoparticles[30] , highlighting a shared design goal to maintain a steady supply of insulin. Previous attempts at oral insulin delivery using lipid vesicles (self-made “liposphere”) achieved only limited success[31,26], underscoring the advancements that cochleates offer through their more robust structure.

Building on these in vitro results, in vivo research has further confirmed the promise of insulin-loaded nanocochleates for oral administration. In diabetic rats induced with streptozotocin, oral delivery of insulin nanocochleates led to superior glycemic control compared to insulin injected subcutaneously, successfully reversing hyperglycemia and insulin resistance[29]. The cochleate formulation achieved a more gradual decrease in blood glucose levels with an extended duration of effect, suggesting the feasibility of once-daily oral dosing for maintaining basal insulin levels. Additionally, Radhakrishnan et al. found that chitosan-coated insulin nanocochleates improved the intestinal transport of insulin across excised intestinal tissues and were more effective in lowering blood glucose than free oral insulin [32] . These findings imply that the combined effects of the cochleate’s protective structure and chitosan’s mucoadhesive and permeation-enhancing properties work together to enhance insulin stability and absorption. According to literature, no oral nanocochleate formulation containing insulin has been tested in humans to date.

A Phase I clinical trial assessed an oral formulation of Amphotericin B cochleate, revealing it to be safe and well-tolerated, with no significant adverse effects. This finding supports the clinical safety of cochleate delivery systems in humans. The trial indicated that cochleates can shield drugs from degradation and facilitate the oral administration of molecules that are typically not absorbable. Conversely, insulin-loaded cochleates have only been examined in preclinical animal studies so far. These studies have shown encouraging outcomes in terms of sustained insulin release and enhanced glycemic control, but no human trials have been conducted for oral insulin cochleate formulations yet [33].

It is noteworthy that numerous advanced oral insulin delivery systems are currently under development, such as inclusion complexes in self-nanoemulsifying systems[34] and cell-penetrating peptide carriers[35]. While each method offers unique benefits, nanocochleates stand out due to their remarkable stability and capacity for carrying payloads. At present, this represents a groundbreaking discovery at an incredibly opportune moment, addressing the pressing need to find alternatives to injectable insulin, provided that ongoing clinical trials continue to show promising results. For insulin, first outline the current options available for oral administration in various nano forms. Present all existing

data, then highlight the significance of insulin in relation to nanocochleates.

3.2 Metformin

Metformin, an oral biguanide, is the primary treatment for type 2 diabetes. Despite this, its low permeability through membranes and significant absorption by the intestinal wall lead to limited oral bioavailability, around 50–60%. This often necessitates high doses, which can result in gastrointestinal side effects. By incorporating metformin into nanocochleate delivery systems, it is expected that its absorption efficiency and therapeutic effectiveness will be enhanced, while minimizing dose-related adverse effects.

Researchers developed metformin-bridged nanocochleates by leveraging metformin's positive charge to promote cochleate formation without needing high levels of external Ca^{2+} [25]. This approach involved combining metformin with a negatively charged lipid, dicetyl phosphate (DCP), to trigger cochleation with only a small amount of calcium. The co-precipitation method resulted in stable nanocochleates with an average size of about 136 nm and a drug loading efficiency of over 75% [36].

The formulation was optimized using a D-optimal design of experiments, highlighting the importance of systematic formulation optimization in creating nanocochleates[36]. This statistical method facilitated the identification of key formulation variables that affect particle size, drug loading, and stability, ensuring the consistent and effective synthesis of nanocochleates [37].

The metformin nanocochleates exhibited beneficial pharmacokinetic and pharmacodynamic properties. In diabetic rats, the oral bioavailability of metformin from these cochleates was about 5.5 times higher than that of a metformin solution in water [36]. This resulted in a stronger antihyperglycemic effect and an extended duration of action. Additionally, the use of metformin cochleates was observed to enhance metformin's effectiveness against hepatocellular carcinoma in preclinical studies, highlighting its known antiproliferative properties and suggesting improved organ targeting [36]. By enhancing metformin absorption and potentially altering its distribution, cochleates may achieve effective concentrations with lower doses, possibly reducing gastrointestinal side effects.

3.3 Mechanism of Action of Nanocochleates in Diabetes Treatment

Nanocochleates are innovative lipid-based nanocarriers composed of negatively charged phospholipids, such as phosphatidylserine, which are stabilized by divalent cations like calcium. These carriers form spiral, multilayered structures that protect bioactive compounds, including peptides, proteins, and small drugs, from degradation. Nanocochleates are particularly effective for the oral or mucosal delivery of insulin, GLP-1 agonists, and other antidiabetic medications in diabetes treatment.

1. **Protection from Degradation**
   • Insulin and other peptide drugs are highly susceptible to degradation in the gastrointestinal tract due to enzymes.
   • Nanocochleates protect these molecules from proteolysis and acidic conditions by encapsulating them within their rigid bilayer structures.
2. **Enhanced Absorption**
   - Their ability to fuse directly with cell membranes, such as those of intestinal epithelial cells or nasal mucosa, facilitates the transcellular transport of insulin or other drugs.
   - Nanocochleates bypass the paracellular tight junction barrier, which typically prevents macromolecules from entering cells[38].
3. **Sustained Release**
   - The spiral structure with multiple layers facilitates a controlled release pattern, ensuring that drug concentrations remain elevated in the bloodstream for an extended period. This is beneficial for diabetes management.
4. **Improved Bioavailability**
   - Nanocochleates significantly enhance the oral bioavailability of insulin by increasing its stability and facilitating its absorption.
   - In their absence, insulin is absorbed minimally. Consequently, this reduces the need for frequent injections, simplifying adherence to the treatment regimen for patients.

5. **Targeted Delivery to Liver**
    - When administered orally, nanocochleates follow a similar path as lipids in the body, eventually reaching the portal circulation and liver, where insulin functions, akin to the natural release of insulin.

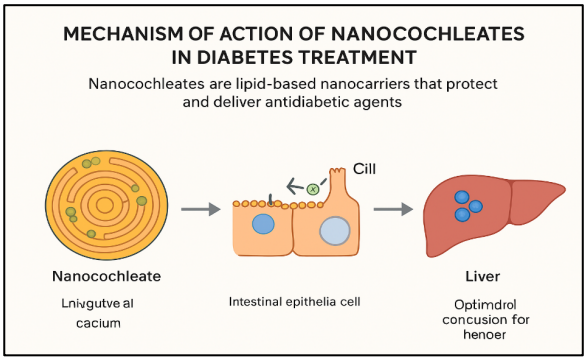

Figure 4. MOA of nanocochleates in diabetes treatment[39]

3.3 Herbal Antidiabetic Compounds

Various plant-derived compounds, known as phytochemicals, including polyphenols and alkaloids such as curcumin, quercetin, resveratrol, and berberine, have been identified for their potential antidiabetic effects. However, these natural hydrophobic substances typically exhibit very low solubility in water and/or are rapidly metabolized, resulting in poor oral bioavailability. To address these limitations and enhance the therapeutic efficacy of these phytoconstituents, nanocochleates have been explored[37,40].

Curcumin nanocochleates were created using the calcium trapping technique. This method achieved an optimized particle size and encapsulation efficiency through the Design of Experiments (DOE)[39] . The resulting cochleates provided a prolonged release of curcumin, lasting approximately 24 hours, and exhibited a significantly higher cytotoxic effect on MCF-7 cancer cells compared to free curcumin, indicating improved cellular delivery[39] . By maintaining curcumin and ensuring its sustained release, cochleates could potentially enhance the anti-inflammatory and insulin-sensitizing properties of curcumin in diabetes.

- Quercetin nanocochleates, approximately 200 nm in size, were developed with an encapsulation efficiency of about 76%[41]. Pharmacokinetic studies indicate that these nanocochleates significantly increased both the peak plasma concentration and the overall exposure (AUC) of quercetin in rats compared to its free form, while also extending the time to reach peak levels [41,42]. Additionally, quercetin was effectively shielded from first-pass metabolism and exhibited greater bioactivity when encapsulated in nanocochleates, surpassing the in vitro bioactivity of quercetin in solution[28]. In the context of diabetes, the improved availability of quercetin, which enhances insulin sensitivity and beta-cell function, could result in more pronounced hypoglycemic effects.
- Andrographolide, a labdane diterpenoid, was encapsulated in nanocochleates to improve its solubility and stability. This formulation achieved a drug encapsulation efficiency of about 71% and maintained stability after freeze-drying and in alkaline conditions that mimic the intestines. The nanocochleates showed a sustained release profile, with nearly 95% of andrographolide being released over a 24-hour period. Furthermore, the formulation was non-toxic to mammalian cells and was easily taken up by macrophages, suggesting its potential for delivering andrographolide's anti-inflammatory effects to immune cells important in diabetes treatment.
- A nanocochleate formulation containing resveratrol was created, which notably improved the oral bioavailability and therapeutic effectiveness of resveratrol in a liver cancer model[39] . While this research was conducted in an oncology setting, the results suggest that nanocochleates can facilitate the systemic delivery of resveratrol with enhanced biological activity. Since resveratrol is recognized for its ability to improve glycemic control and insulin sensitivity, similar formulations might also enhance its anti-diabetic properties. Additionally, in silico studies have proposed that resveratrol encapsulated in cochleates could better manage insulin resistance by optimizing the targeted delivery of the compound to specific action sites.
- Berberine, a natural alkaloid known for its strong blood sugar-lowering effects, faces

challenges with oral bioavailability due to significant P-glycoprotein efflux and first-pass metabolism. When berberine was incorporated into nanocochleates, its oral absorption increased by approximately four times, and there was a notable decrease in blood glucose and HbA1c levels in diabetic rats compared to when berberine was administered in its free form[43]. This improvement highlights the potential of nanocochleates to bypass efflux and metabolic barriers, thereby enhancing the systemic availability of berberine.

Integrating herbal antidiabetic agents into nanocochleates has consistently led to significantly greater in vivo effectiveness compared to their unencapsulated counterparts. This is particularly evident with compounds like berberine and curcumin, where traditional formulations result in low plasma concentrations, making cochleate delivery a revolutionary approach.

Synthetic compound

Insulin, metformin, and synthetic compounds primarily differ in their origins, structures, and mechanisms of action. Insulin is a naturally occurring peptide hormone that regulates blood sugar levels, but it cannot be taken orally because it is broken down by enzymes and poorly absorbed. In contrast, metformin is a synthetic biguanide compound that reduces blood sugar by enhancing insulin sensitivity and decreasing liver glucose production, though it struggles with low membrane permeability and moderate oral bioavailability. Meanwhile, other synthetic compounds, such as small-molecule drugs or analogues, are often engineered for greater stability and specific action, yet they may still encounter issues with poor solubility or limited bioavailability. Consequently, drug delivery systems like nanocochleates are being investigated to enhance the stability, absorption, and therapeutic effectiveness of both natural biomolecules like insulin and synthetic drugs like metformin and similar compounds.

Table 1 Summarizes selected studies of nanocochleate formulations for antidiabetic agents, including the formulation approach, the specific challenges addressed, and key outcomes.

Ref	Antidiabetic Agent (Study & Year)	Challenge / Objective	Formulation Strategy	Key Outcomes
[29]	**Insulin** (Khair *et al*., 2020)	Oral insulin is degraded and poorly absorbed	Insulin–polymer complex in PS liposomes + Ca^2+ (trapping method); dextran sulfate/PEG added to improve loading	The formulation showed high insulin entrapment efficiency (~85%). It provided sustained *in vitro* insulin release. In diabetic rats, orally administered insulin cochleates produced longer and smoother glycemic control compared to injected insulin (Lantus/Humulin).
[28]	**Insulin** (Liu *et al*., 2017)	Low intestinal permeability of peptides like insulin	Chitosan-coated nanocochleates (model tested with cyclosporine A)	The cochleate formulation led to about a threefold increase in the oral bioavailability of cyclosporine A. Chitosan coating further

Ref	Antidiabetic Agent (Study & Year)	Challenge / Objective	Formulation Strategy	Key Outcomes
				enhanced mucoadhesion and facilitated absorption by opening tight junctions. This strategy could be applied to improve the oral delivery of insulin.
[36]	**Metformin** (El-Melegy *et al*., 2025)	Metformin has high solubility but low permeability (requires high doses)	*Metformin-bridged* nanocochleates using DCP lipid (co-precipitation with drug's own positive charge); optimized by mixture design	– Nanocochleates ~136 nm with >75% metformin loaded. – 5.5× higher oral bioavailability vs. free metformin. [25] – >5-fold higher AUC and enhanced glucose-lowering effect; also improved metformin's anti-
				HCC efficacy (indirect anti-diabetic benefit).
[44]	**Curcumin** (Nadaf & Killedar, 2018)	Curcumin is unstable and poorly bioavailable orally	Curcumin nanocochleates via Ca^2+ trapping; formulation optimized by DOE for particle size and EE	– Extended curcumin release (~24 h). – Higher cytotoxicity against MCF-7 cells vs. free curcumin (indicative of improved cellular delivery). – Cochleates protected curcumin from degradation, boosting stability.
[43]	**Quercetin** (Kapare *et al*., 2024)	Quercetin has low bioavailability (poor solubility & rapid metabolism)	Quercetin nanocochleates (PC/PG liposomes + Ca^2+) optimized to	– Particle size ~206 nm; EE ~76%. – Higher C_max and AUC of quercetin in rats vs.

Ref	Antidiabetic Agent (Study & Year)	Challenge / Objective	Formulation Strategy	Key Outcomes
			~200 nm size	free quercetin; prolonged T_max (sustained release). – Stronger in vitro anticancer effect than free quercetin (due to better protection and uptake).
[27]	**Quercetin** (Munot *et al*., 2022)	Compare cochleates vs. liposomes for quercetin delivery	Prepared quercetin liposomes (DMPG-based), then added Ca^2+ to form cochleates; evaluated stability & efficacy	– Cochleates (~500 nm) vs. liposomes (~111 nm). – Quercetin in cochleates was far more protected from metabolic degradation than in liposomes. – Cochleates showed higher anticancer activity (KB cells) and greater stability over time than liposomes.
[26]	**Andrographolide** (Asprea *et al*., 2019)	Andrographolide has poor solubility and GI instability (t_½ ~1.3 h)	AN-loaded PC (or PS) liposomes + cholesterol; Ca^2+ trapping to form cochleates; included freeze-drying for stability	– Encapsulation Efficiency ~71%. – Cochleates remained stable after lyophilization and in alkaline pH (intestinal conditions). – ~95% of AN released over 24 h (controlled release). – High uptake by macrophages (useful for targeting inflammation) with no cytotoxicity.
[45]	**Resveratrol**	Resveratrol has	Trans-resveratr	– High resveratrol

Ref	Antidiabetic Agent (Study & Year)	Challenge / Objective	Formulation Strategy	Key Outcomes
	(Mehanna *et al*., 2024)	low oral bioavailability; needs better delivery	ol nanocochleates (similar method to metformin cochleates with Ca^2+/ DCP)	loading achieved. – Improved oral absorption and greatly enhanced anti-tumor efficacy in HCC model (indicative of better systemic delivery). – Suggests potential for improved anti-diabetic effects (antioxidant/anti-inflammatory) via higher bioavailability.

Table 1: Representative studies of nanocochleate formulations for antidiabetic agents, highlighting each study's focus, formulation approach, and key outcomes.

3.5 Efficacy and Trend-Analysis Discussion

The research discussed above has clearly shown that encapsulating antidiabetic drugs in nanocochleates consistently improves their bioavailability and effectiveness. For instance, formulations of insulin, metformin, quercetin, and andrographolide[25,29,39,46] exhibited significantly higher bioavailability and pharmacological activity compared to their unencapsulated counterparts. These results indicate that the benefits of nanocochleates—such as protection from degradation, solubilization, and controlled release are applicable across various drug categories, including peptides, small molecules, and phytochemicals.

Moreover, nanocochleates offer adaptability for creating formulations that meet specific requirements. For drugs that are highly soluble in water but have low absorption rates, like metformin, cochleates improve permeability. In the case of lipophilic and unstable drugs, such as curcumin or andrographolide, cochleates provide a lipophilic environment that enhances stability and allows for gradual release. This adaptability suggests that a range of other antidiabetic medications, including new peptides or combination therapies, could potentially be suitable for cochleate formulation.

4. FORMULATION CHARACTERIZATION AND ASSESSMENT OF NANOCOCHLEATE PROFILES

Thorough characterization of nanocochleate formulations is crucial for both their development and regulatory approval. Key factors include particle size and distribution, surface charge (zeta potential), morphological characteristics, drug loading and release rates, stability in terms of shelf life and in biological fluids, and biocompatibility.

Particle Size and Morphology: Dynamic light scattering (DLS) is typically used to assess particle size, focusing on the hydrodynamic diameter and polydispersity index. However, since cochleate particles are not spherical, DLS results need confirmation through imaging[45]. The multi-layered, rolled structure of cochleates can be directly observed using transmission electron microscopy (TEM) or SEM[45]. For instance, Lipa-Castro et al. pointed out that DLS might underestimate size due to the rod-like shape, recommending a combination with TEM/SEM for more precise size assessment[45]. Achieving uniform size, often in the range of hundreds of nanometers, is essential for consistent absorption, and

forming micro-spherical aggregates was one method to improve uniformity[7] .

Zeta potential is an indicator of surface charge, affecting both the stability of colloids and their interaction with biological membranes. Nanocochleates made with PS or PG lipids exhibit a negative zeta potential (e.g., –20 to –40 mV) due to the anionic lipids on their surface, which help maintain suspension through electrostatic repulsion. When coated with a cationic polymer like chitosan, the zeta potential can shift to positive values, likely after cholesterol loading; for instance, Liu et al. reported a shift to +10 mV with chitosan coating, which improved mucoadhesion in the colon[26]. A suspension can be stabilized at a moderate zeta potential, whether positive or negative, ranging from +15 to −40 mV in magnitude.[55-56]

Drug Loading and Release: To determine the encapsulation efficiency (EE) of a drug, the excess drug is removed from the cochleates, typically through centrifugation or filtration, and the drug content is then analyzed. Many cochleate formulations have shown high EE, often exceeding 70% (e.g., 75–85% for insulin, metformin, quercetin in cited studies), due to the ability of these drugs to intercalate within numerous lipid layers. Release testing is conducted in vitro under simulated gastrointestinal conditions, such as 2 hours in an acidic pH followed by a neutral pH, or in a squared-type buffer at 37°C. It is almost always observed that cochleates display a two-phase release pattern: an initial burst release (typically 10–25% within the first hour) followed by a gradual, sustained release over 12–48 hours [28,37]. This release profile can be described by fitting it to kinetic models, such as a biphasic or diffusion model. The ability to maintain therapeutic levels for extended periods is a significant benefit of cochleates for chronic dosing.Stability studies involve evaluating stability under various conditions, such as long-term storage at 4 °C or room temperature, accelerated stability at elevated temperatures like 40 °C, and stability in simulated gastrointestinal fluids. Generally, cochleates exhibit physical stability, with minimal changes in size and drug loss, as long as they are stored properly for extended periods. Their solid lipid structure makes them less susceptible to drug efflux compared to fluid liposomes. For example, Khair et al. found that insulin cochleates retained 90% of their insulin content over three months at 4 °C, and Asprea et al. demonstrated that cochleates could be dried into a powder and rehydrated with only minor changes[46]. Regulatory guidelines strongly advise comprehensive stability data for any new delivery system[47]. The FDA specifically requires that applications for lipid-based nanosystems include information on particle size distribution, zeta potential, and drug retention over time[48], which are likely requirements that developers of nanocochleates will need to fulfill using advanced analytical techniques as previously discussed.

- Compatible and Safe: Nanocochleates are composed of phospholipids and calcium, which are inherently biocompatible. In vitro studies have shown that proteins from cochleates exhibit low cytotoxicity, meaning they do not reduce the viability of Caco-2 intestinal cells or L929 fibroblasts in proliferation assays[39,46]. Animal studies have reported no toxicity or inflammation following cochleate administration, as the particles eventually break down and the lipids are either metabolized or excreted[33]. A Phase I human trial involving amphotericin cochleates found no severe side effects beyond those of a placebo[49]. Nevertheless, it is crucial to evaluate any immunogenic reactions and the potential for long-term accumulation in all new cochleate formulations. Current evidence suggests that nanocochleates are as safe as similar traditional lipid supplements, such as liposomes, which is a significant advantage for their clinical application.[57,58]

In summary, advanced methods of characterization and testing have verified that nanocochleates can be consistently produced with uniform quality, exhibiting excellent stability and safety characteristics. Shende et al. also highlight that cochleates provide a protective environment for drugs while enhancing therapeutic effectiveness, potentially allowing for reduced dosage levels[32]. The effectiveness and safety of this pegylated nanocochleate present a compelling case for advancing a nanocochleate-based treatment to clinical trials.

Patents:[44]

Patent No.	Inventors' names	Class of medication	Result
US 2021/ 0015,74 9 A1	Godarzi et al.	Alendronat e and vitamin D3	Prevent osteoporosis in animal tests.
US 8,546,5 55 B2	GouldFog erlte et al.	si RNA (small interfering RNA)	In neurological illnesses, the interference of

		nanocochleates	Ribonucleic acid (RNA) is facilitated by the nanocochleate of siRNA, which acts against the target mRNA responsible for protein expression.
US 2014/0220,108 A1	Lu et al.	Antibiotic (Amickacin) Antifungal (Amphotericin B) Viral protein	Amikacin nanocochleates were effective against Mycobacterium avium infections, but amphotericin B nanocochleates were effective against Candida albicans infections. Nanocochleates of viral proteins from influenza viruses elicit strong cellular immunity.
US 15/567,299	Lu et al.	Amikacin	Amikacin nanocochleates were shown to be much less toxic and more effective at treating tuberculosis than an intravenous version of Amikacin.
US 8,642,073 B2	Mannino et al	Nanocochleates of NSAID's Antibiotic (Tobramycin) Antifungal (Cospofungin)	Nanocochleates of Aspirin and Acetaminophen, combined with a grouping inhibitor, make nanocochleates that are stable and help reduce rat paw oedema. Tobramycin nanocochleates stopped the growth of bacteria. Capspofungin nanocochleates stopped the growth of fungus.
US 2015/0297,725 A1	Mannino et al	Curcumin (Anticancer) Antibiotic (Amikacin and Gentamycin) Antifungal (Amphotericin B)	Amikacin and Gentamycin cochleates, whether given orally or intravenously, significantly reduced the bacterial load in vivo within the spleen.
WO2016/205,654 A1	Mannino et al	Non-steroidal anti-inflammatory drugs (NSAIDs)	NSAIDs that are encochleated increased their impact on rat paw edema in vivo and reduced

			toxicity in the gastrointestinal tract.
WO2018/013,711 A1	Mannino et al	Amphotericin B (Antifungal)	If someone has a brain infection with Cryptococcus neoformans, specially engineered nanocochleates lower the amount of colony-forming units (CFUs). V
WO2017/205,550 A1	Mannino et al	Vaccine adjuvant	Nanocochleates with integrated antigens have immune-modulating characteristics.
WO2016/141,203 A1	Mannino et al	Amphotericin B (antifungal) Si RNA	When comparing commercially available fungizone 1 mg/kg intravenous with the produced nanocochleates of amphotericin B 0.5 mg/kg oral, both therapies are similarly effective in reducing fungal infection.
US 2011/0256,214 A1	Martin et al.	Vaccine	The developed vaccine was administered mucosally, resulting in elevated quantities of IgA and IgG antibodies.
EP 2689,775 A1	Martin et al.	Vaccine adjuvant	The immunopotentiation resulted from the vaccine's antibiotic component and the pathogens' demise via mucosal or parenteral injection.

5. CHALLENGES AND FUTURE PERSPECTIVES [52,53,54]

Challenge: Nonetheless, several hurdles must be overcome before nanocochleates can be effectively utilized in clinical diabetes treatment. A significant challenge is the large-scale production. Achieving a consistent cochleate size (under approximately 300 nm to ensure uniform oral absorption and immunogenicity) in bulk quantities is complex. Techniques like controlled microfluidic mixing or the micro-spherical composite method could potentially enhance batch uniformity. Additionally, cochleates are susceptible to aggregation if not prepared or stored under optimal conditions. The use of steric stabilizers (such as a small amount of PEGylated lipid) or adjusting ionic strength might help minimize aggregation, but these parameters must be meticulously optimized for each specific formulation.

Another obstacle is obtaining regulatory validation. For these emerging drug carriers to be considered viable drug delivery options in the future, they must undergo comprehensive characterization as required by regulatory bodies. This includes ensuring consistency between batches, stability across various conditions, and precisely engineered release profiles. The field has made progress in creating characterization protocols. Nonetheless,

converting these protocols into standard quality control tests for industrial manufacturing continues to be a hurdle.Future Directions: Nanocochleates offer promising potential for antidiabetic treatments. The development of an oral insulin nanocochleate could have a profound effect. By reducing the need for frequent injections, patient compliance and overall quality of life may see significant improvements. Notably, the American Diabetes Association and other organizations have highlighted the importance of innovative delivery systems in improving diabetes outcomes, indicating their readiness to embrace these technologies once they are proven effective.Beyond insulin and metformin, nanocochleates can also facilitate combination therapies. For example, insulin paired with a GLP-1 agonist or a polyphenol combined with metformin can be encapsulated together in a single cochleate, allowing for a multi-targeted treatment through one oral dose. This approach addresses the multifaceted nature of type 2 diabetes, which involves multimodal drug interventions targeting various pathways. The high loading capacity and ability to transport both hydrophilic and hydrophobic agents make cochleates suitable for such combinations.The cochleate approach could be applied to other metabolic conditions. One can imagine entirely oral cochleate formulations of GLP-1 and amylin analogues for treating obesity and diabetes. In a theoretical study by Khedr et al., an oral GLP-1 cochleate was suggested, which demonstrated a decrease in glucose levels in mice a result that might be anticipated given the successes of insulin and cyclosporine cochleates. Additionally, nanocochleates could act as a delivery system to enhance new therapies, such as gut microbiome modulators or gene-silencing drugs for diabetes, which require protection from the gastrointestinal environment.

CONCLUSION:

Nanocochleate drug delivery systems have shown significant promise in pre-clinical diabetes studies by enhancing the stability, bioavailability, and effectiveness of insulin, metformin, and various nutraceuticals. Although challenges such as scaling up and regulatory hurdles remain unresolved, advancements in formulation engineering and analytical characterization are addressing these issues. This technology is under close scrutiny by the industry. The outlook is optimistic, with expectations that oral cochleate formulations for proteins and vaccines are imminent. Should this delivery system continue to progress in clinical trials, it is anticipated that diabetes treatment will soon enter a new phase with oral nanocochleate-based drugs, significantly transforming diabetes management and improving patient adherence and outcomes.

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