RESEARCH PAPER

Nanocochleates as Smart Lipidic Nanocarriers for Improved Anticancer Therapy Recent Advances and Future Perspectives

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Abstract
Cancer therapy is frequently limited by poor aqueous solubility, inadequate bioavailability, rapid degradation, nonspecific distribution, systemic toxicity, and multidrug resistance, creating a need for advanced drug-delivery systems. Nanocochleates have emerged as promising lipidic nanocarriers characterized by compact, tightly packed multilamellar structures formed through interactions between negatively charged phospholipids and divalent cations, particularly calcium ions. Their distinctive architecture provides drug protection, improved retention, and potential for sustained and controlled release. This review discusses the development of nanocochleates as smart nanocarriers for improved anticancer therapy, with emphasis on their fundamental characteristics, composition, formation mechanisms, preparation approaches, and physicochemical characterization. Their potential for delivering conventional anticancer agents and poorly bioavailable natural compounds is discussed, including applications involving doxorubicin, fisetin, paclitaxel, curcumin, quercetin, and resveratrol. Particular attention is given to passive and active tumor targeting, folate-, antibody-, peptide-, and tumor-microenvironment-based strategies, as well as pH-, redox-, enzyme-, and reactive oxygen species-responsive systems. The review further highlights nanocochleate-enabled combination therapy, drug/gene co-delivery, immunotherapy integration, and potential approaches for overcoming multidrug resistance. Safety, toxicity, biocompatibility, formulation reproducibility, scale-up, quality control, regulatory requirements, and clinical translation are also considered. Future perspectives include multifunctional and theranostic nanocochleates, artificial intelligence-assisted formulation optimization, Quality by Design, personalized nanomedicine, and scalable manufacturing. Overall, nanocochleates represent a promising platform for precision cancer therapy, although rigorous in vivo validation, standardized manufacturing, long-term safety assessment, and well-designed clinical studies are required to establish their therapeutic and translational value and demonstrate clear advantages over established nanomedicine platforms in efficacy, safety, stability, and patient-specific therapeutic outcomes.

Keywords
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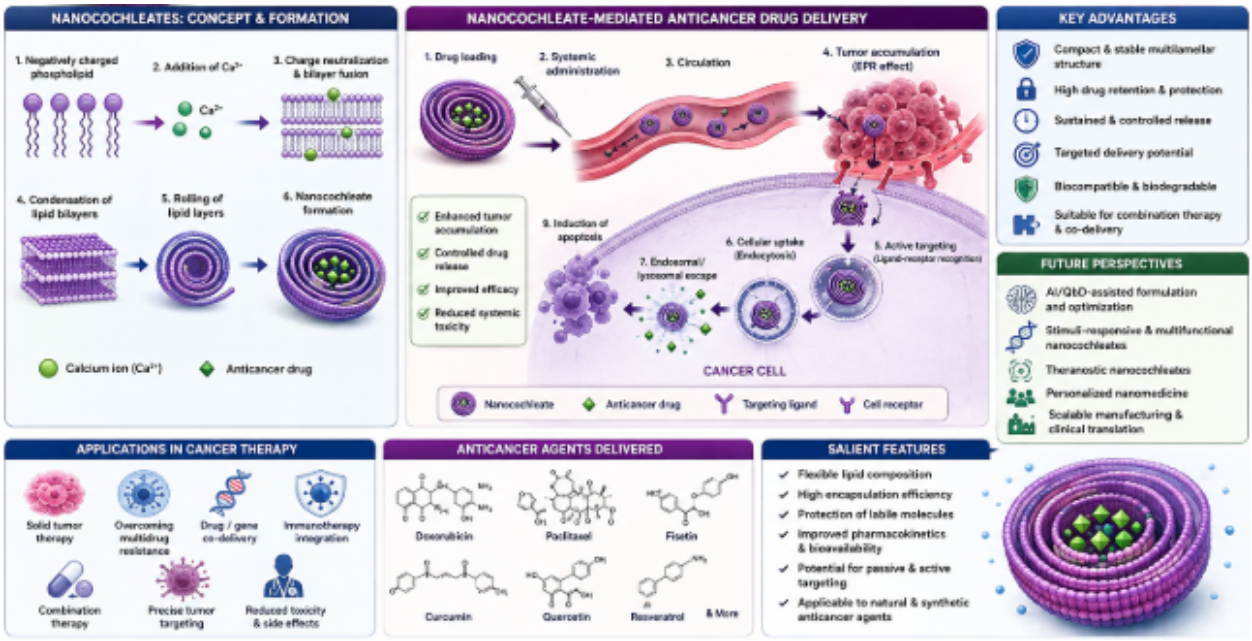

Figure 1: Graphical abstract

1. Introduction

Cancer remains a major global health challenge, and the effectiveness of anticancer therapy is often limited by poor aqueous solubility, inadequate bioavailability, rapid degradation, nonspecific distribution, systemic toxicity, and multidrug resistance. These limitations have encouraged the development of advanced drug-delivery systems capable of improving drug stability, pharmacokinetics, cellular uptake, and selective accumulation at the tumor site [1].

Lipid-based nanocarriers have gained considerable attention in cancer therapy because of their biocompatibility, structural flexibility, and ability to accommodate poorly soluble therapeutic molecules. However, conventional lipidic systems such as liposomes may suffer from drug leakage, physical instability, and limited retention of encapsulated molecules. Nanocochleates have therefore emerged as an alternative lipidic nanocarrier with a highly organized and compact multilamellar structure [2].

Nanocochleates are formed through the interaction of negatively charged phospholipids with divalent cations, particularly calcium ions, resulting in the condensation and rolling of lipid bilayers into stable cochleate structures [1,2]. Their unique architecture provides protection to incorporated drugs and may facilitate sustained release and improved drug retention. These properties make nanocochleates particularly attractive for delivering anticancer agents with poor solubility or stability.

Several studies have demonstrated the potential of nanocochleates for anticancer drug delivery. Fisetin-loaded nanocochleates, for example, showed improved drug delivery, sustained release, enhanced anticancer activity, and increased bioavailability compared with the free drug [3]. Functionalization with targeting molecules such as folic acid may further improve tumor-cell interaction and facilitate targeted delivery of chemotherapeutic agents [4].

Despite these advantages, important challenges remain, including reproducible manufacturing, scale-up, formulation stability, toxicity evaluation, and regulatory translation [5]. Therefore, this review discusses recent advances in nanocochleates as smart lipidic nanocarriers for anticancer therapy, with particular emphasis on their structural characteristics, preparation, anticancer drug delivery, targeting strategies, combination therapy, stimuli-responsive systems, limitations, and future perspectives.

2. Nanocochleates: Concept and Fundamental Characteristics

Nanocochleates are lipid-based nanocarriers composed of tightly packed, multilamellar lipid bilayers arranged in a characteristic rolled or spiral structure. They are generally formed by the interaction of negatively charged phospholipids with divalent cations, particularly calcium ions, which induce charge neutralization, membrane fusion, and condensation of lipid bilayers [6]. Unlike conventional liposomes, nanocochleates possess a compact architecture with little or no aqueous internal compartment, providing greater structural rigidity and protection of incorporated therapeutic molecules [7].

The physicochemical characteristics of nanocochleates depend on factors such as phospholipid composition, lipid-to-calcium ratio, preparation conditions, particle size, and surface charge. Their tightly organized lipid structure can

minimize drug leakage and protect sensitive molecules from degradation during storage and biological transport [8]. Nanocochleates can also accommodate a range of therapeutic agents, including poorly water-soluble drugs and bioactive phytoconstituents, making them attractive carriers for improving the delivery of compounds with unfavorable physicochemical or pharmacokinetic properties.

An additional advantage is the possibility of modifying their surface with polymers, ligands, or other functional molecules to improve stability, cellular interaction, and targeted delivery [9]. These characteristics, together with their potential for controlled drug release and improved drug retention, make nanocochleates promising candidates for advanced drug-delivery applications, particularly in cancer therapy where efficient tumor delivery and reduced systemic toxicity are important therapeutic objectives.

3. Why Nanocochleates for Cancer Therapy?

Conventional anticancer therapy is frequently associated with poor drug solubility, limited bioavailability, rapid elimination, nonspecific distribution, and toxicity toward healthy tissues. These limitations can reduce therapeutic efficacy and restrict the dose that can be safely administered [10]. Nanocarrier-based systems offer an opportunity to overcome these problems by improving drug solubilization, protecting therapeutic molecules, and modifying their pharmacokinetic and biodistribution profiles.

Nanocochleates are particularly attractive because their compact multilamellar lipid structure can provide enhanced protection and retention of encapsulated drugs. The absence of a large aqueous internal compartment and the strong association between lipid layers can reduce premature drug leakage and improve formulation stability [11]. This may be beneficial for anticancer molecules that are chemically unstable or have poor aqueous solubility.

Another important advantage is the potential for sustained and controlled drug release. Prolonged drug release can help maintain therapeutic concentrations for longer periods and may reduce the frequency of administration. Furthermore, the lipidic nature of nanocochleates may facilitate interaction with cellular membranes and enhance intracellular delivery of the encapsulated drug [12].

Nanocochleates can also be engineered for targeted cancer therapy through surface modification with ligands that recognize receptors overexpressed on tumor cells. Such approaches may improve cellular uptake and increase the concentration of the therapeutic agent within tumor tissues while potentially reducing systemic exposure [13]. Their ability to incorporate different therapeutic molecules further creates opportunities for combination therapy and co-delivery strategies.

4. Composition and Design of Nanocochleates

Nanocochleates are primarily composed of phospholipids and divalent cations, with the selection and ratio of these components strongly influencing their structural and pharmaceutical properties. Phospholipids such as phosphatidylserine are commonly used because their negatively charged head groups interact with divalent cations and facilitate conversion of lipid bilayers into the compact cochleate structure [14].

Divalent cations, particularly calcium ions, play a central role in nanocochleate formation. Calcium-mediated charge neutralization promotes aggregation and fusion of negatively charged lipid membranes, followed by condensation and rolling of the lipid layers. The concentration of calcium and the lipid-to-calcium ratio can therefore affect particle formation, morphology, stability, and drug encapsulation [15].

Other lipid components may be incorporated to modify membrane rigidity, fluidity, stability, and drug-loading characteristics. Cholesterol is frequently considered as a membrane-modifying component because it can influence lipid packing and membrane permeability. The incorporation of suitable stabilizing or surface-modifying agents may further improve colloidal stability and biological performance.

The design of nanocochleates can also be extended through surface functionalization. Polymeric coatings, hydrophilic materials, targeting ligands, peptides, antibodies, and other biomolecules may be introduced to improve circulation characteristics, cellular uptake, or tumor-specific recognition [16]. Such modifications are particularly relevant for anticancer applications because they can transform nanocochleates from passive drug carriers into more sophisticated targeted delivery systems.

Table 1. Comparative characteristics of nanocochleates and other lipidic nanocarriers

Parameter	Nanocochleates	Liposomes	SLNs	NLCs	Nanoemulsions
Basic structure	Rolled multilamellar lipid structure	Phospholipid bilayer vesicle	Solid lipid matrix	Solid–liquid lipid matrix	Oil droplets

Aqueous core	Minimal/absent	Present	Absent	Absent	Present continuous phase
Structural stability	High	Moderate	High	High	Moderate
Drug retention	High	Moderate	High	High	Moderate
Hydrophobic drug loading	Good	Good	Good	Excellent	Good
Controlled release	Possible	Possible	High	High	Variable
Surface modification	Possible	Highly feasible	Feasible	Feasible	Feasible
Targeted delivery	Possible	Well established	Possible	Possible	Possible
Major limitation	Scale-up and limited clinical data	Leakage and stability	Drug expulsion	Complex lipid composition	Physical instability

5. Mechanism of Nanocochleate Formation

The formation of nanocochleates is primarily governed by electrostatic interactions between negatively charged phospholipids and divalent cations. Phospholipids containing anionic head groups, particularly phosphatidylserine, provide negatively charged sites that interact with calcium ions. When a divalent cation is introduced into a suspension of negatively charged lipid vesicles, electrostatic neutralization reduces repulsion between adjacent lipid membranes and promotes membrane aggregation and fusion [17].

Initially, phospholipids organize into bilayer structures in an aqueous environment. Following exposure to calcium ions, the cations associate with the negatively charged phospholipid head groups and induce condensation of neighboring bilayers. Progressive membrane fusion and dehydration result in the formation of tightly packed lipid sheets. These sheets subsequently roll or coil into a characteristic cylindrical or spiral structure, producing the cochleate architecture [18].

The calcium-mediated transformation can be influenced by several formulation variables, including phospholipid concentration, calcium concentration, lipid-to-calcium ratio, temperature, ionic strength, pH, and mixing conditions. Optimization of these parameters is important because excessive calcium concentration or uncontrolled aggregation may produce larger particles or heterogeneous structures, whereas inadequate calcium availability may result in incomplete cochleate formation [19].

Drug incorporation can occur during or before the conversion of lipid vesicles into nanocochleates. Hydrophobic molecules can associate with the lipid bilayers, whereas hydrophilic or amphiphilic molecules may become entrapped or associated with the lipid layers during structural condensation. The transition from a relatively hydrated vesicular system to a compact cochleate structure can consequently improve retention of the incorporated drug and provide protection against environmental degradation [20].

The resulting nanocochleates possess a highly ordered multilamellar organization that contributes to their characteristic physical stability. Their compact structure can limit exposure of the encapsulated therapeutic agent to the surrounding aqueous environment and may reduce premature drug release. Following administration, interactions with biological membranes and physiological conditions can facilitate structural reorganization and release of the incorporated therapeutic molecule [21].

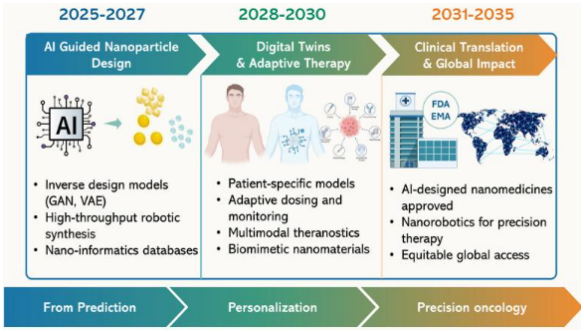

Figure 2: Structure and formation mechanism of nanocochelates

An important advantage of this mechanism is that cochleate formation can be reversible under appropriate conditions. Removal or alteration of divalent cation interactions may promote rehydration or structural transformation of the lipid assembly. This reversible behavior can contribute to drug release following interaction with biological membranes or intracellular environments [22].

6. Methods for Preparation of Nanocochleates

The preparation method plays a critical role in determining the particle size, morphology, drug-loading capacity, stability, and release characteristics of nanocochleates. Several approaches have been investigated, with most methods involving the initial formation of lipid vesicles followed by their conversion into cochleate structures through interaction with divalent cations [23].

6.1 Liposome-to-Cochleate Conversion

The most commonly described approach involves the preparation of negatively charged liposomes followed by calcium-induced conversion. In this method, phospholipids are first hydrated and processed to form vesicles. Calcium ions are subsequently introduced under controlled conditions, resulting in charge neutralization, membrane fusion, and progressive transformation of the vesicles into compact cochleate structures [24]. The method is attractive because liposome preparation and drug loading can be optimized before cochleate conversion.

6.2 Direct Calcium-Induced Method

In the direct method, phospholipids and the therapeutic compound are dispersed or hydrated in an aqueous medium, followed by controlled addition of calcium ions. The interaction between calcium and anionic phospholipids promotes aggregation and rolling of lipid bilayers. The concentration and rate of calcium addition are important because rapid or excessive ion addition can result in uncontrolled aggregation and increased particle size [25].

6.3 Trapping Method

The trapping method involves incorporating the therapeutic molecule within lipid assemblies before inducing cochleate formation. During calcium-mediated condensation, the drug becomes associated with the tightly packed lipid layers. This approach can improve retention of compounds that may otherwise diffuse rapidly from conventional lipid vesicles [26].

6.4 Hydrogel-Based Method

Hydrogel-mediated approaches have also been explored to control the interaction between lipid vesicles and divalent cations. The gradual diffusion of calcium through a hydrogel matrix can provide a more controlled conversion process and potentially improve the uniformity of the resulting cochleate structures. Such approaches may be useful when precise control over particle formation is required [27].

6.5 Solvent-Assisted Approaches

Organic solvents such as ethanol may be employed during lipid processing to improve the solubilization and mixing of phospholipid components. Solvent-assisted techniques can facilitate the formation of relatively uniform lipid assemblies and may be particularly useful for incorporating poorly water-soluble anticancer drugs. However, residual solvent removal and control of solvent-related effects remain important considerations during formulation development [28].

6.6 Factors Affecting Preparation

The final characteristics of nanocochleates are influenced by lipid composition, drug concentration, calcium concentration, lipid-to-calcium ratio, temperature, pH, mixing intensity, hydration conditions, and processing time. Optimization of these variables is therefore essential to obtain reproducible particle size, high drug encapsulation, desirable surface characteristics, and appropriate drug-release behavior [29]. For anticancer applications, preparation methods should additionally provide adequate scalability, reproducibility, and compatibility with pharmaceutical manufacturing requirements.

7. Physicochemical Characterization of Nanocochleates

Comprehensive physicochemical characterization is essential for establishing the quality, stability, reproducibility, and biological performance of nanocochleate formulations. Important critical quality attributes include particle size, polydispersity index (PDI), surface charge, morphology, drug loading, encapsulation efficiency, structural organization, and in vitro drug-release behavior [30].

7.1 Particle Size and Polydispersity

Particle size is an important parameter because it can influence cellular uptake, biodistribution, circulation behavior, and tissue penetration. Dynamic light scattering (DLS) is commonly used to determine the hydrodynamic diameter and PDI of nanocochleates. A low PDI generally indicates a relatively homogeneous particle population, whereas a high PDI may indicate

aggregation or inadequate control of the preparation process [31].

7.2 Zeta Potential

Zeta potential provides information regarding the surface charge and colloidal stability of nanocochleates. Because anionic phospholipids participate in cochleate formation, surface charge can change substantially following calcium-mediated conversion. Measurement of zeta potential can therefore provide useful information regarding successful structural transformation as well as the tendency of particles to aggregate during storage [32].

7.3 Morphological Characterization

Transmission electron microscopy (TEM), scanning electron microscopy (SEM), and cryogenic electron microscopy can be used to investigate the morphology and structural organization of nanocochleates. These techniques can reveal particle shape, surface characteristics, lamellar organization, and aggregation behavior. The characteristic elongated, rolled, or cylindrical architecture provides morphological evidence of cochleate formation [33].

7.4 Encapsulation Efficiency and Drug Loading

Encapsulation efficiency and drug-loading capacity are particularly important for evaluating the suitability of nanocochleates as anticancer drug carriers. Encapsulation efficiency represents the proportion of drug incorporated into the nanocarrier relative to the total drug used during formulation, whereas drug loading describes the amount of drug associated with a given quantity of carrier. These parameters are generally determined after separating free drug from the nanocochleate-associated drug using centrifugation, dialysis, ultrafiltration, or chromatographic techniques [34].

7.5 Structural and Chemical Characterization

Fourier-transform infrared spectroscopy (FTIR) can be used to investigate interactions between the drug and lipid components, whereas differential scanning calorimetry (DSC) can provide information regarding thermal transitions and changes in the physical state of formulation components. X-ray diffraction (XRD) may additionally be used to evaluate crystallinity and structural changes following drug incorporation and cochleate formation [35].

7.6 In Vitro Drug Release

Drug-release studies are performed to determine the release profile and potential sustained-release behavior of nanocochleates. Dialysis membrane, diffusion-cell, or related methods may be employed using an appropriate release medium maintained under physiological conditions. Release data can subsequently be fitted to mathematical models such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas models to understand the probable mechanism of drug release [36].

7.7 Stability Evaluation

Physical and chemical stability should be assessed under appropriate storage conditions by monitoring particle size, PDI, zeta potential, drug content, encapsulation efficiency, and visible aggregation over time. Stability assessment is particularly important because changes in lipid organization or calcium-mediated interactions may alter the performance of nanocochleates during storage [37].

8. Mechanisms of Anticancer Drug Delivery by Nanocochleates

Nanocochleates can improve anticancer drug delivery through a combination of drug protection, controlled release, enhanced cellular interaction, and potential tumor targeting. Their compact multilamellar structure protects the incorporated drug from premature degradation and may improve retention of the therapeutic payload during systemic transport [38].

Following administration, nanocochleates may interact with biological membranes through adsorption, membrane fusion, or endocytic pathways. These interactions can facilitate internalization of the nanocarrier and increase intracellular exposure to the incorporated drug. Cellular uptake is influenced by particle size, surface charge, lipid composition, surface modifications, and the physicochemical properties of the tumor cell membrane [39].

Once internalized, changes in the intracellular environment can promote destabilization or reorganization of the lipid structure and facilitate drug release. Controlled release from the compact lipid layers may maintain drug exposure over an extended period and potentially reduce the fluctuations associated with repeated administration of free drugs [40].

Nanocochleates may also enhance passive tumor accumulation through the enhanced permeability and retention (EPR) effect. Tumor tissues often exhibit abnormal vasculature and impaired lymphatic drainage, which can favor the accumulation of appropriately sized nanocarriers. However, the magnitude of the EPR effect varies considerably among tumor types and patients, and therefore passive targeting alone may not provide sufficient tumor selectivity [41].

To overcome this limitation, nanocochleates can be functionalized with targeting ligands such as folic acid, antibodies, peptides, aptamers, or other receptor-specific molecules. These ligands can recognize receptors that are overexpressed on tumor cells and facilitate receptor-mediated uptake. Such active targeting strategies may increase intracellular drug delivery while reducing exposure of healthy tissues [42].

The ability to modify nanocochleate surfaces also provides opportunities for tumor-microenvironment-

responsive delivery. Differences in pH, enzyme activity, redox conditions, and reactive oxygen species between tumor and normal tissues can potentially be exploited to trigger localized drug release. Combining targeting with stimuli-responsive behavior may therefore provide a more sophisticated approach to cancer treatment [43].

Another important mechanism is the potential for overcoming multidrug resistance. Nanocochleate-mediated intracellular delivery may increase drug accumulation within cancer cells and partially bypass extracellular drug degradation or certain drug-efflux mechanisms. Co-encapsulation of chemotherapeutic agents with resistance-modifying molecules may further enhance therapeutic activity [44].

9. Nanocochleates for Delivery of Anticancer Agents

Nanocochleates have been investigated as carriers for a range of anticancer agents, particularly drugs and natural compounds that exhibit poor aqueous solubility, low bioavailability, instability, or dose-related toxicity. Encapsulation within the compact lipid structure can improve drug protection and retention while providing opportunities for controlled release and enhanced cellular delivery [45].

9.1 Doxorubicin-Loaded Nanocochleates

Doxorubicin is a widely used anticancer agent; however, its clinical application is limited by systemic toxicity, particularly cardiotoxicity. Nanocochleate-based delivery has been explored as a strategy for modifying the distribution and release of doxorubicin. Incorporation of doxorubicin into lipidic nanocarriers may improve cellular delivery while reducing exposure to healthy tissues. Surface functionalization can further provide opportunities for tumor-specific uptake [46].

9.2 Fisetin-Loaded Nanocochleates

Fisetin is a naturally occurring flavonoid with reported antioxidant, antiproliferative, and pro-apoptotic activities. However, its poor aqueous solubility and limited oral bioavailability restrict its therapeutic application. Fisetin-loaded nanocochleates have demonstrated improved physicochemical characteristics, sustained drug release, enhanced cytotoxicity against cancer cells, and improved bioavailability compared with free fisetin [3]. This example illustrates the potential of nanocochleates for converting poorly bioavailable natural compounds into more effective therapeutic formulations.

9.3 Paclitaxel and Other Poorly Soluble Anticancer Drugs

Paclitaxel is another important anticancer molecule characterized by extremely low aqueous solubility and formulation-related challenges. Although several lipid and polymeric nanocarriers have been developed for paclitaxel delivery, nanocochleates represent a potential alternative for incorporating hydrophobic drugs into a stable lipidic structure. Their ability to accommodate hydrophobic molecules within lipid layers may improve drug dispersion and facilitate controlled delivery [47].

9.4 Natural Anticancer Compounds

Nanocochleates are particularly promising for natural anticancer compounds because many phytochemicals exhibit potent biological activities but suffer from poor solubility, rapid metabolism, and low systemic exposure. Compounds such as curcumin, quercetin, resveratrol, and related polyphenols could potentially benefit from lipid-based encapsulation. Incorporation into nanocochleates may improve their physicochemical stability and enhance their delivery to cancer cells [48].

9.5 Combination Delivery

An emerging application of nanocochleates is the simultaneous delivery of two or more therapeutic agents. Co-delivery can provide synergistic anticancer effects, reduce the required dose of individual drugs, and potentially address multidrug resistance. Nanocochleates may serve as a suitable platform for combining conventional chemotherapeutics with natural compounds, molecularly targeted agents, or resistance-modifying molecules [49].

Table 2. Anticancer agents investigated or proposed for nanocochleate delivery

Anticancer agent	Major limitation	Potential nanocochleate benefit	Therapeutic relevance
Doxorubicin	Systemic toxicity, cardiotoxicity	Controlled and targeted delivery	Breast, ovarian, hematological cancers
Fisetin	Poor solubility and bioavailability	Improved delivery and sustained release	Breast cancer
Paclitaxel	Extremely low aqueous solubility	Lipid-based incorporation	Breast, ovarian, lung cancers

Curcumin	Poor bioavailability and rapid metabolism	Improved stability and delivery	Multiple solid tumors
Quercetin	Poor solubility and bioavailability	Enhanced cellular delivery	Multiple cancer models
Resveratrol	Rapid metabolism and low systemic exposure	Improved stability and retention	Multiple cancer models
Combination agents	Different pharmacokinetics	Potential co-delivery	Multidrug-resistant tumors

10. Targeted Nanocochleates for Precision Cancer Therapy

Targeted drug delivery aims to increase the concentration of anticancer agents at the tumor site while minimizing exposure to normal tissues. Although nanocochleates can provide improved drug protection and controlled release, incorporation of targeting strategies can further enhance their therapeutic potential. Surface modification with specific ligands can promote recognition of receptors expressed at higher levels on cancer cells and facilitate selective cellular uptake [50].

10.1 Passive Tumor Targeting

Passive targeting primarily depends on the physicochemical properties of nanocarriers and the abnormal vascular characteristics of tumor tissues. Nanocochleates within an appropriate nanoscale range may accumulate in tumors through enhanced vascular permeability and impaired lymphatic drainage. However, variations in tumor vascularization, interstitial pressure, and lymphatic function can produce considerable differences in passive accumulation between tumor types [51].

10.2 Folate-Mediated Targeting

Folate receptors are overexpressed in several cancer types, including ovarian, breast, lung, and certain colorectal cancers. Folic acid is therefore frequently investigated as a targeting ligand because of its small size, relative stability, low immunogenicity, and strong affinity for folate receptors. Folate-functionalized nanocochleates may undergo receptor-mediated internalization and consequently increase intracellular accumulation of the encapsulated anticancer drug [52].

10.3 Antibody-Mediated Targeting

Antibodies and antibody fragments can provide highly specific recognition of tumor-associated antigens. Incorporation of antibodies onto nanocochleate surfaces may facilitate selective interaction with receptors such as HER2, EGFR, or other tumor-associated markers. This strategy may be particularly useful for cancers in which specific molecular targets are well characterized [53].

10.4 Peptide and Aptamer-Based Targeting

Peptides and nucleic-acid-based aptamers provide additional options for nanocochleate functionalization. Tumor-homing peptides can recognize receptors or extracellular matrix components associated with malignant tissues, whereas aptamers can provide selective molecular recognition with relatively small size and favorable engineering characteristics. These approaches may improve cellular uptake while reducing the nonspecific interaction of nanocarriers with healthy tissues [54].

10.5 Tumor Microenvironment Targeting

The tumor microenvironment contains several characteristics that distinguish malignant tissue from normal tissue, including acidic extracellular pH, elevated enzyme activity, hypoxia, altered redox conditions, and increased reactive oxygen species. Incorporating microenvironment-responsive components into nanocochleates may enable drug release preferentially within tumors or intracellular compartments [55].

10.6 Multifunctional Targeted Nanocochleates

Combining targeting ligands with controlled-release or stimuli-responsive mechanisms could produce multifunctional nanocochleates capable of sequential tumor recognition, cellular uptake, and intracellular drug release. Such systems may also support co-delivery of chemotherapeutic agents and molecular therapeutics, providing opportunities for more personalized treatment strategies.

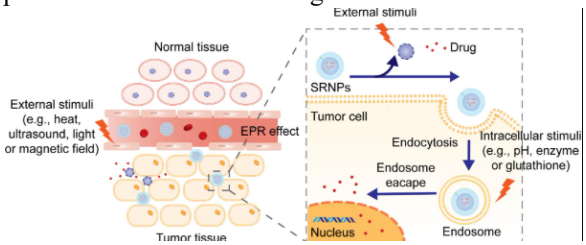

Figure 3: Nanocochelates-mediated Anticancer Drug Delivery

11. Stimuli-Responsive Nanocochleates

Stimuli-responsive nanocochleates represent an emerging approach in which drug release is regulated

by specific physicochemical conditions present within the tumor microenvironment or intracellular compartments. Unlike conventional nanocarriers that release their payload primarily through passive diffusion or gradual degradation, stimuli-responsive systems are designed to respond to endogenous or externally applied triggers, potentially improving spatial and temporal control of anticancer drug release [56].

11.1 pH-Responsive Nanocochleates

Tumor tissues generally exhibit a mildly acidic extracellular environment, while intracellular compartments such as endosomes and lysosomes possess substantially lower pH. This difference can be exploited to develop pH-responsive nanocochleates. Incorporation of pH-sensitive lipids, polymers, or linkers may promote structural destabilization under acidic conditions and facilitate drug release after tumor accumulation or cellular internalization [57].

11.2 Redox-Responsive Systems

The intracellular environment contains higher concentrations of reducing agents, particularly glutathione, compared with the extracellular environment. Redox-sensitive chemical linkers, especially disulfide bonds, can therefore be incorporated into nanocarrier systems to promote intracellular drug release. Redox-responsive nanocochleates may provide an opportunity to maintain structural integrity during systemic circulation while facilitating payload release after cellular uptake [58].

11.3 Enzyme-Responsive Systems

Tumors frequently exhibit increased activity of specific enzymes, including matrix metalloproteinases and other proteolytic enzymes. Nanocochleates can potentially be modified with enzyme-cleavable components that remain stable in normal tissues but undergo degradation in enzyme-rich tumor environments. This approach may enhance tumor-selective drug release and reduce premature drug exposure [59].

11.4 ROS-Responsive Systems

Reactive oxygen species (ROS) are frequently elevated in cancer cells and contribute to oxidative stress, signaling abnormalities, and tumor progression. ROS-sensitive chemical groups can be incorporated into nanocarriers to promote structural disruption and drug release in highly oxidative environments. Such systems may be particularly useful for delivering drugs that act synergistically with oxidative stress-based anticancer mechanisms [60].

11.5 Externally Triggered Systems

External stimuli, including light, magnetic fields, ultrasound, and heat, can also be explored to regulate drug release. Externally controlled systems provide the advantage of applying the trigger at a selected anatomical site or time. However, their clinical application requires suitable tissue penetration, precise control of the stimulus, and demonstration of adequate safety [61].

11.6 Multifunctional Stimuli-Responsive Nanocochleates

Combining two or more stimuli may provide more precise control of drug release. For example, a nanocochleate could be designed to remain stable during circulation, respond to tumor acidity, and subsequently undergo additional destabilization within the reducing intracellular environment. Such sequential responses could minimize premature release and improve intracellular drug availability.

12. Nanocochleates for Combination Cancer Therapy

Combination therapy is an important strategy in cancer treatment because tumors are highly heterogeneous and can develop resistance when exposed to a single therapeutic agent. Simultaneous administration of drugs with different mechanisms of action can produce synergistic or additive effects, reduce the required dose of individual agents, and target multiple pathways involved in tumor growth and survival [62]. However, conventional combination therapy may be limited by differences in drug solubility, pharmacokinetics, biodistribution, and toxicity. Nanocochleates may help address these limitations by providing a common lipidic platform for incorporating and delivering multiple therapeutic agents.

12.1 Co-delivery of Chemotherapeutic Agents

Nanocochleates can potentially accommodate two or more anticancer drugs within the same carrier. Co-encapsulation may improve the pharmacokinetic synchronization of drugs that otherwise exhibit different distribution and elimination profiles. Maintaining both agents within the same nanocarrier can also increase their simultaneous delivery to cancer cells, potentially improving therapeutic synergy [63].

12.2 Chemotherapy–Phytochemical Combination

The combination of conventional chemotherapeutic drugs with bioactive phytochemicals represents another promising strategy. Natural compounds such as curcumin, quercetin, resveratrol, and other polyphenols have demonstrated anticancer and chemosensitizing activities but are frequently limited by poor solubility and bioavailability. Nanocochleates may improve the delivery of these compounds while allowing their combination with conventional anticancer agents [64].

12.3 Drug and Gene Co-delivery

Nanocochleates may also provide opportunities for incorporating small interfering RNA (siRNA), microRNA, or other nucleic-acid-based therapeutics alongside conventional drugs. Such combinations could simultaneously suppress resistance-associated

genes and deliver cytotoxic agents. This approach may be particularly useful for targeting molecular pathways responsible for tumor survival, proliferation, and drug resistance [65].

12.4 Combination Therapy for Multidrug Resistance

Multidrug resistance remains a major obstacle to successful chemotherapy. Combining cytotoxic drugs with resistance-modifying agents can potentially improve intracellular drug accumulation and restore sensitivity in resistant tumor cells. Nanocarrier-mediated co-delivery may ensure that both therapeutic components reach the same cancer cell at an appropriate ratio, which is difficult to achieve with separate administration [66].

12.5 Immunotherapy and Nanocochleate-Based Combination Strategies

The integration of nanocarrier-based chemotherapy with immunotherapeutic approaches represents an emerging direction in cancer nanomedicine. Nanocochleates could potentially be engineered to deliver immunomodulatory molecules together with anticancer drugs, thereby combining direct tumor-cell killing with stimulation of antitumor immunity. Such multifunctional systems may be particularly relevant for tumors with complex immunosuppressive microenvironments.

12.6 Advantages and Challenges

The major advantage of combination nanocochleates is the possibility of coordinated delivery of multiple therapeutic agents within a single formulation. Nevertheless, co-loading drugs with substantially different physicochemical properties can complicate formulation development and may affect encapsulation efficiency, particle characteristics, stability, and release behavior. Establishing the optimal drug ratio is also essential because synergistic activity may depend strongly on the relative concentration of the individual agents.

13. Nanocochleates for Overcoming Multidrug Resistance

Multidrug resistance (MDR) is one of the major causes of chemotherapy failure and is characterized by reduced sensitivity of cancer cells to structurally and mechanistically unrelated anticancer drugs. Although several mechanisms contribute to MDR, increased drug efflux mediated by ATP-binding cassette transporters, particularly P-glycoprotein (P-gp), multidrug resistance-associated proteins (MRPs), and breast cancer resistance protein (BCRP), is among the most extensively studied mechanisms [67]. Consequently, strategies that increase intracellular drug concentrations or interfere with resistance pathways are important for improving anticancer treatment.

Nanocarrier-based delivery systems can potentially overcome some limitations associated with free anticancer drugs by altering their cellular entry and intracellular distribution. Nanocochleates may facilitate drug uptake through membrane interaction and endocytic pathways, thereby increasing the intracellular availability of encapsulated drugs [68]. Their compact lipidic structure can also protect the therapeutic payload during extracellular transport and provide controlled release following cellular internalization.

Another potential advantage is the ability to co-deliver an anticancer drug with a resistance-modulating agent. For example, inhibition of P-gp-mediated efflux has been investigated using pharmacological inhibitors and molecular approaches. Incorporating both components into a single nanocarrier may provide synchronized delivery and maintain an appropriate intracellular drug-to-modulator ratio [69].

Nanocochleates may also be functionalized with targeting ligands to preferentially interact with resistant cancer cells. Targeted delivery could increase the amount of drug reaching malignant cells while reducing nonspecific exposure. When combined with controlled release, this strategy may increase intracellular drug concentration sufficiently to improve the response of resistant tumor cells [70].

RNA-based approaches provide another potential strategy. Delivery of siRNA or other nucleic acids targeting resistance-associated genes could suppress the expression of efflux transporters or survival pathways. A nanocochleate capable of simultaneously delivering a chemotherapeutic agent and a gene-silencing molecule could therefore address both the cytotoxic requirement and the underlying resistance mechanism [71].

14. Nanocochleates for Delivery of Natural Anticancer Compounds

Natural products have attracted considerable interest in cancer research because of their diverse pharmacological activities, including antiproliferative, pro-apoptotic, anti-inflammatory, antioxidant, antiangiogenic, and chemosensitizing effects. However, many phytoconstituents exhibit poor aqueous solubility, low membrane permeability, rapid metabolism, and extensive systemic elimination, which substantially limit their therapeutic application [72]. Nanocochleates may provide an effective lipidic platform for improving the delivery of such compounds.

14.1 Curcumin

Curcumin is one of the most extensively investigated natural compounds for cancer therapy. It can modulate multiple molecular pathways associated with proliferation, apoptosis, inflammation, angiogenesis, and metastasis. Nevertheless, its clinical translation is

restricted by extremely low aqueous solubility, poor absorption, rapid metabolism, and limited systemic bioavailability [73]. Incorporation into nanocochleates may improve its dispersion, protect it from degradation, and facilitate sustained delivery.

14.2 Quercetin

Quercetin is a flavonoid with reported antiproliferative, pro-apoptotic, and antiangiogenic activities. Its therapeutic potential is restricted by poor water solubility and limited bioavailability. Lipid-based nanocarriers can improve quercetin solubilization and cellular delivery, suggesting that nanocochleate-based encapsulation may be useful for enhancing its anticancer performance [74].

14.3 Resveratrol

Resveratrol exhibits multiple biological activities relevant to cancer prevention and treatment, including modulation of apoptosis, cell-cycle progression, inflammation, and oxidative stress. However, rapid metabolism and limited systemic availability remain important limitations. Incorporation into lipidic nanocarriers may protect resveratrol and improve its delivery to target tissues [75].

14.4 Fisetin

Fisetin represents a particularly relevant example because its delivery through nanocochleates has already been investigated. Fisetin-loaded nanocochleates demonstrated improved formulation characteristics, sustained drug release, enhanced anticancer activity, and improved bioavailability compared with free fisetin [3]. This provides direct evidence supporting the use of nanocochleates for poorly bioavailable natural anticancer compounds.

14.5 Other Phytoconstituents

Other natural compounds, including epigallocatechin-3-gallate, berberine, luteolin, genistein, and related polyphenols, have demonstrated promising anticancer activities but face pharmacokinetic and formulation challenges. Their incorporation into nanocochleates could potentially improve stability, solubility, cellular uptake, and therapeutic exposure [76]. However, direct evidence for each compound should be established through systematic formulation, pharmacokinetic, and in vivo efficacy studies rather than extrapolated solely from other nanocarrier systems.

15. Nanocochleates for Combination of Chemotherapy and Immunotherapy

The integration of chemotherapy with immunotherapy has emerged as an important strategy for improving cancer treatment outcomes. Chemotherapeutic agents can directly eliminate malignant cells, whereas immunotherapeutic approaches stimulate or restore the ability of the immune system to recognize and destroy tumor cells. However, systemic administration of these therapies may result in suboptimal tumor exposure, systemic toxicity, and inadequate coordination between the two therapeutic modalities [77]. Nanocochleates may provide an opportunity to combine these approaches within a single lipidic delivery platform.

Nanocochleates can potentially encapsulate or associate with immunomodulatory molecules together with cytotoxic drugs. Localized delivery of these agents may increase their concentration within the tumor microenvironment while reducing unnecessary systemic exposure. This approach is particularly relevant because several anticancer drugs can induce immunogenic cell death, leading to the release of tumor-associated antigens and danger-associated molecular patterns that stimulate antitumor immune responses [78].

The combination of nanocarrier-mediated chemotherapy with immune checkpoint inhibition is another promising direction. Immune checkpoint proteins such as programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) can suppress antitumor immune responses. Nanocochleate-based delivery could potentially be used to improve tumor accumulation of chemotherapeutic agents while immunotherapy promotes sustained immune-mediated tumor recognition [79].

Nanocochleates may also be explored for the delivery of immune-stimulating molecules, including cytokines, nucleic acids, tumor antigens, or adjuvants. Encapsulation can protect sensitive biological molecules from premature degradation and may provide controlled exposure to immune cells. Such systems could potentially stimulate dendritic-cell activation and enhance antigen presentation, thereby strengthening adaptive antitumor immunity [80].

16. Safety, Toxicity and Biocompatibility of Nanocochleates

Safety and biocompatibility are critical considerations in the development of nanocochleates for anticancer therapy. Although lipid-based nanocarriers are generally considered favorable because their components can resemble naturally occurring biological lipids, nanoscale formulations may exhibit biological interactions that differ substantially from their individual components. Therefore, toxicity should be evaluated at the level of the complete nanocochleate formulation rather than solely on the basis of its individual ingredients [81].

The composition of the lipid system is an important determinant of safety. Phospholipids are generally well tolerated; however, their concentration, chemical structure, purity, and degradation products can influence biological responses. Similarly, calcium ions are essential for cochleate formation, but excessive concentrations or inappropriate release may disturb

cellular ion homeostasis. Consequently, the lipid-to-calcium ratio and residual free calcium should be carefully controlled during formulation development [82].

Particle size, surface charge, morphology, and aggregation can also influence the interaction of nanocochleates with biological membranes and immune cells. Highly charged or aggregated nanoparticles may exhibit increased nonspecific protein adsorption and uptake by the mononuclear phagocyte system. Formation of a protein corona following exposure to biological fluids can further alter nanoparticle identity, biodistribution, cellular uptake, and biological activity [83].

Hemocompatibility is particularly important for nanocochleates intended for intravenous administration. Interaction with erythrocytes, platelets, complement proteins, and coagulation pathways should be investigated to identify potential hemolytic, thrombotic, or immunological effects. Complement activation-related pseudoallergy is another consideration for intravenously administered nanomedicines and should be evaluated during preclinical development [84].

In vitro cytotoxicity studies using normal cell lines can provide an initial assessment of formulation-related toxicity. However, cytotoxicity toward cancer cells should be interpreted separately from toxicity toward healthy cells because the therapeutic objective is selective tumor-cell killing. In vivo studies should subsequently evaluate changes in body weight, hematological parameters, serum biochemical markers, histopathology, organ distribution, and major organ toxicity.

Long-term safety is another important consideration. Persistent accumulation of lipidic nanocarriers or their degradation products in organs such as the liver and spleen may influence repeated-dose safety. Therefore, chronic toxicity, immunogenicity, biodistribution, and clearance should be investigated before clinical translation. Standardized safety protocols and well-characterized formulations will be essential for establishing the therapeutic index of nanocochleate-based anticancer systems.

17. Advantages and Limitations of Nanocochleates in Anticancer Therapy

Nanocochleates possess several characteristics that make them attractive for anticancer drug delivery. Their compact multilamellar architecture provides a relatively stable environment for encapsulated therapeutic molecules and can reduce premature drug leakage. The lipidic composition also provides opportunities for incorporating drugs with different physicochemical properties, including poorly water-soluble compounds [85].

One important advantage is the potential to improve the stability and bioavailability of anticancer agents. Encapsulation can protect sensitive molecules from degradation and may modify their pharmacokinetic behavior. Controlled release from the condensed lipid structure can additionally prolong drug exposure and potentially reduce the frequency of administration [86].

Nanocochleates also offer considerable flexibility for surface engineering. Targeting ligands, polymers, peptides, antibodies, and other functional components can be incorporated to modify biodistribution and promote interaction with specific cells. This provides opportunities for developing targeted systems that combine drug protection with receptor-mediated tumor-cell uptake [87].

Another potential advantage is their suitability for combination therapy. Different therapeutic agents can potentially be incorporated into the same nanocarrier, allowing simultaneous delivery to tumor cells. Such systems may be useful for combining conventional chemotherapy with phytochemicals, resistance-modifying agents, gene therapeutics, or immunomodulatory molecules.

Despite these advantages, several limitations currently restrict the broader application of nanocochleates. One major challenge is formulation reproducibility. Small variations in phospholipid composition, calcium concentration, mixing conditions, and processing parameters can affect particle size, morphology, encapsulation efficiency, and drug release [88].

Scale-up is another important limitation. A formulation that performs well at laboratory scale may not maintain the same structural and physicochemical characteristics during large-scale production. Manufacturing processes must therefore be optimized to achieve consistent critical quality attributes while maintaining acceptable production costs.

The limited availability of comprehensive long-term toxicity and clinical efficacy data also represents a significant barrier. Although several preclinical studies have demonstrated promising results, relatively few nanocochleate systems have progressed toward clinical evaluation. Furthermore, regulatory requirements for complex nanomedicines can be demanding because both the active pharmaceutical ingredient and nanocarrier characteristics must be carefully controlled [89].

Therefore, the future development of nanocochleates requires a balanced approach that retains their structural and therapeutic advantages while addressing reproducibility, scalability, stability, toxicity, and regulatory challenges.

Advantages

- Improved protection of encapsulated drugs
- Potential enhancement of drug retention

- Sustained and controlled drug release
- Delivery of poorly soluble compounds
- Potential improvement in bioavailability
- Surface functionalization for targeting
- Possibility of combination drug delivery

Limitations

- Complex formulation optimization
- Batch-to-batch variability
- Scale-up difficulties
- Limited long-term safety data
- Limited clinical evidence
- Potential aggregation during storage
- Need for stringent quality control

18. Translational and Clinical Perspectives of Nanocochleates

The translation of nanocochleates from laboratory research to clinically useful anticancer formulations requires integration of formulation science, pharmacology, toxicology, manufacturing, and regulatory considerations. Although preclinical studies have demonstrated their potential for improving drug delivery, clinical translation requires reproducible manufacturing and convincing evidence of safety, pharmacokinetic benefit, and therapeutic superiority over existing treatments [90].

One of the major translational advantages of nanocochleates is their potential to improve the delivery of drugs with poor solubility, instability, or unfavorable pharmacokinetic characteristics. Improved drug retention and controlled release may contribute to increased therapeutic exposure while reducing unnecessary systemic distribution. However, these benefits must be demonstrated using comparative pharmacokinetic and pharmacodynamic studies rather than inferred solely from favorable physicochemical properties.

Manufacturing and scale-up represent important challenges. Nanocochleates require careful control of lipid composition, calcium concentration, particle size, morphology, drug loading, and surface characteristics. Changes in manufacturing conditions may alter these critical quality attributes and consequently affect biological performance. Application of Quality by Design (QbD) principles can help identify critical material attributes and critical process parameters and establish a scientifically controlled manufacturing process [91].

Regulatory evaluation of nanomedicines also requires detailed characterization of both the active drug and the nanocarrier. Parameters such as particle size distribution, surface properties, morphology, encapsulation efficiency, drug release, impurities, stability, and degradation products may need to be evaluated throughout development. Standardized analytical methods are therefore essential for establishing product consistency [92].

From a clinical perspective, nanocochleates may be particularly valuable for anticancer drugs with significant formulation limitations. Their potential applications include improving the delivery of poorly soluble chemotherapeutic agents, enabling targeted therapy, facilitating combination treatment, and incorporating natural anticancer compounds. However, clinical development should progress through appropriately designed pharmacokinetic, dose-escalation, safety, and efficacy studies.

The clinical status of nanocochleates remains considerably less developed than that of established nanomedicines such as liposomal formulations. This highlights the need for systematic translation rather than relying solely on promising laboratory findings. Future clinical programs should establish clear evidence of improved therapeutic index, reduced toxicity, enhanced tumor accumulation, or other clinically meaningful benefits.

19. Future Perspectives

Nanocochleates have considerable potential as next-generation lipidic nanocarriers for anticancer therapy. Future research should focus on targeted, stimuli-responsive, and multifunctional systems capable of improving tumor-specific drug delivery while reducing systemic toxicity [93].

Integration of nanocochleates with combination therapy, gene delivery, immunotherapy, and theranostic approaches may further expand their therapeutic applications. Artificial intelligence and Quality by Design approaches could facilitate formulation optimization, reproducibility, and scalable manufacturing [94]. However, long-term safety, manufacturing consistency, regulatory requirements, and clinical validation remain essential before widespread translation.

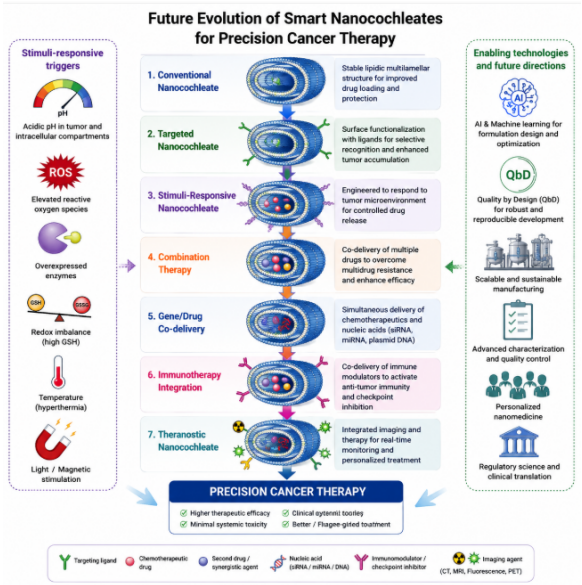

Figure 4: Future Evaluation of smart nanocochelates for precision cancer therapy

Table 3. Current challenges and future opportunities of nanocochleates

Current challenge	Impact on development	Future opportunity
Batch variability	Inconsistent formulation performance	QbD-based optimization
Scale-up difficulties	Limited industrial translation	Scalable manufacturing
Particle-size variation	Alters biodistribution	Process standardization
Limited clinical evidence	Uncertain therapeutic advantage	Well-designed clinical trials
Long-term toxicity	Limits repeated administration	Comprehensive toxicological studies
Drug-loading limitations	May restrict therapeutic payload	Optimized lipid composition
Tumor targeting	Variable tumor accumulation	Ligand-functionalized systems
Multidrug resistance	Reduced chemotherapy response	Combination and gene delivery
Conventional release	Limited spatial control	Stimuli-responsive nanocochleates
Complex formulations	Difficult quality control	Simplified multifunctional designs

20. Conclusion

Nanocochleates represent a promising class of lipidic nanocarriers for improving anticancer drug delivery. Their compact multilamellar structure provides drug protection, improved retention, and potential for controlled release. Surface functionalization can further enable targeted delivery, while their ability to accommodate different therapeutic agents supports combination strategies.

Despite encouraging preclinical findings, challenges related to formulation reproducibility, scale-up, long-term safety, regulatory requirements, and limited clinical evidence remain. Continued research focused on standardized manufacturing, targeted and stimuli-responsive systems, and rigorous in vivo and clinical evaluation is necessary. With these advances, nanocochleates may become valuable platforms for more effective and precise cancer therapy.

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