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Biomaterial-based drug delivery systems in the treatment of inner ear disorders

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Abstract

Inner ear disorders are among the predominant etiology of hearing loss. The blood-labyrinth barrier limits the ability of drugs to attain pharmacologically effective concentrations within the inner ear; consequently, delivering drugs systemically is insufficient for effectively treating inner ear disorders. Hence, it is imperative to create efficient, minimal or non-invasive methods for administering drugs to the inner ear. However, the development of such a system is hindered by three main factors: anatomical unavailability, the lack of sustained drug delivery, and individual variability. Advances in biomaterials technology have created new opportunities for overcoming existing barriers, offering great hope for the effective treatment of inner ear disorders. Hydrogel- and nanoparticle-based drug delivery systems can carry drugs to targeted designated anatomical locations in the inner ear for long-term, sustained release. Furthermore, a range of devices, including microneedles, micropumps, and cochlear implants, when paired with biomaterials, enhance the delivery of drugs to the inner ear, making the treatment of inner ear disorders more effective. Therefore, biomaterial-based drug delivery systems offer the possibility for extensive clinical uses and promise to restore hearing to millions of patients with inner ear disorders.

Keywords Drug delivery, Inner ear disorders, Hearing loss, Biomaterials

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Introduction

Hearing loss is a frequent human disorder that predisposes humans to cognitive decline, social impairment, speech complications, autism, and depression [1]. As indicated by the 2021 World Health Organization's publication, about one in five individuals worldwide suffer from hearing loss, with projections indicating a potential increase of over 1.5 times in the next 30 years [2]. In clinical practice, exposure to acoustic trauma [3], ototoxic drug therapies such as cisplatin [4], aminoglycoside antibiotics [5], harmful microbial infections caused by bacteria [6, 7], and genetic factors [8] can lead to irreversible injury to cochlear hair cells and auditory neurons, which is the core causes of hearing loss [9]. The inner ear is composed of the vestibule and cochlea, commonly considered important drug targets for treating treat balance and hearing disorders [10]. Traditional treatment methods involve systemic administration, where drugs enter the vestibule and cochlea through the circulatory system. However, due to limitations such as the blood-labyrinth barrier, the concealed anatomy of the inner ear, its intricate structure, and the insufficient local blood supply, therapeutic drug molecules encounter numerous physical barriers as they attempt to enter the inner ear, resulting in poor treatment efficacy [11]. Current preclinical research on treating hearing loss is focused on promoting the regenerative and repair of auditory neurons or cochlear hair cells. These treatments include delivering cells or bioactive molecules to the inner ear [12], including stem cells [13], exosomes [14], neurotrophic factors [15], and gene therapy [16]. Nonetheless, the intricate structure of the inner ear, coupled with the presence of the blood-labyrinth barrier, poses significant challenges for these treatment methods. Therefore, investigating innovative routes for the application of pharmacotherapeutic compounds to the inner ear to enhance the potency of medical treatments has emerged as a forefront trend in scientific inquiry.

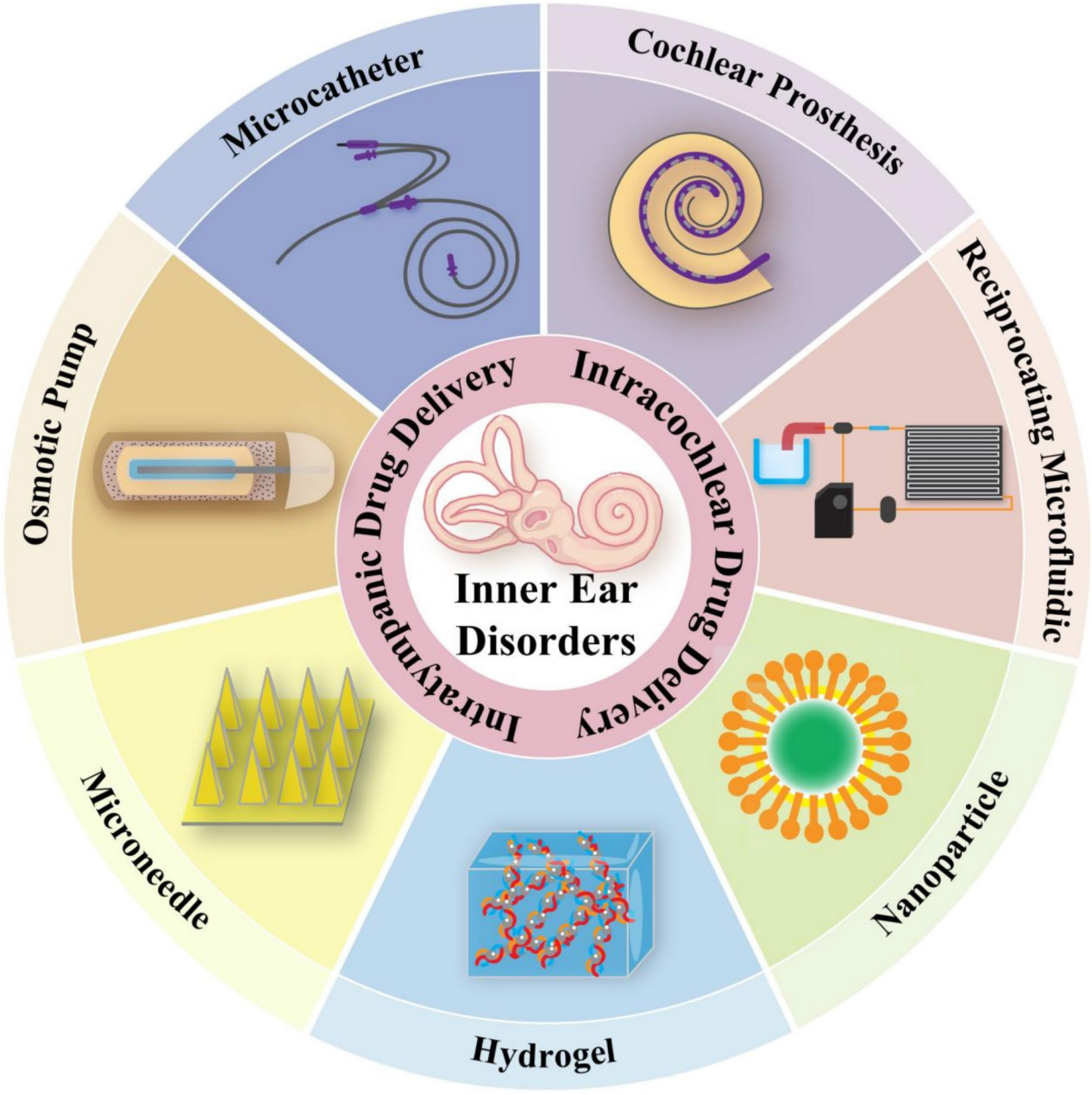
Recently, as biomaterial technology advances, biomaterial drug delivery systems have shown the potential to solve the challenges mentioned. Biomaterials-based approaches are able to improve the bioavailability of drugs through the property of controlled and sustainable release of drugs as compared to existing therapeutic approaches. Constructing degradable, non-toxic biomaterials capable of loading drugs and targeting specific cells and organs has emerged as a prominent research topic. In contrast to systemic drug delivery, targeted pharmaceutical administration to the inner ear confers benefits, including sustained, regulated release of the therapeutic agent and diminished systemic adverse effects [17]. Administering drugs via the intratympanic route is a commonly employed technique for targeted administration to the inner ear, while intracochlear drug delivery is also feasible [18]. Beyond conventional intratympanic injection, intratympanic drug delivery can be facilitated by microcatheters, micro-osmotic pumps, microneedles, and various biomaterials, including hydrogels [19] and nanoparticles, which are designed to maintain effective therapeutic levels of drugs in the tympanic cavity over time [20]. Intracochlear administration includes direct cochlear drug delivery, cochlear prosthesis-based delivery, and reciprocating microfluidic drug delivery [21], which can provide more targeted delivery than systemic drug delivery. These biomaterial-based delivery systems are usually well biocompatible and do not cause serious side effects in the body. As well, the biomaterials can act as tissue scaffolds to support cell adhesion and facilitate the release of bioactive factors [22]. In addition, these systems can also be personalized to the patient's disease state and anatomy. Thus, biomaterial-based delivery systems bring new perspectives to the treatment of inner ear disorders and increase the possibility for patients to receive safer and more effective therapies.

This review offers a comprehensive summary of the methods for the administration of drugs to the inner ear, with a particular emphasis on biomaterial-based delivery systems for localized administration (Scheme 1). Furthermore, we discuss the challenges and future directions that these approaches may encounter as they move toward clinical application, providing innovative strategies to enhance the functional capacity of drug delivery and the management of inner ear disorders.

Anatomy and physiology

The peripheral auditory apparatus is constituted by the external, middle, and inner ear components (Fig. 1). The external ear encompasses the pinna and the external auditory canal. The pinna captures sound vibrations, which are then channelled towards the tympanic membrane via the external auditory canal. Positioned on the lateral side of the round window membrane (RWM) in the inner ear, the middle ear includes the tympanic membrane, tympanic cavity, eustachian tube, and auditory ossicles. These anatomical elements are crucial for the transmission of acoustic energy from the air-containing external auditory canal to the fluid environment of the cochlea [15]. The inner ear is situated in the most profound recess of the ear, positioned at the interface of the tympanic cavity and the bottom of the inner ear canal, encased within dense bone [23]. The inner ear comprises the cochlea, which is dedicated to auditory function, and the vestibule, which is crucial for the preservation of equilibrium. Due to its intricate structure, small dimensions, and inaccessibility, it poses a significant challenge for drug delivery into the inner ear.

The cochlea is a coiled, hollow bone cavity that makes about 2.5 turns, measuring about 31–35 mm in length



Scheme 1 Illustration of a biomaterial scaffold for the targeted therapeutic intervention in inner ear disorders

in humans [24, 25]. The cochlea is structured with three luminal compartments: the scala vestibuli, scala tympani, and scala media, each of which is laden with fluid. The scala vestibuli and scala tympani are bathed in perilymph, while the scala media is occupied by endolymph [26]. The scala vestibuli and scala tympani are located in the superior portion of the cochlea, with the scala media positioned between them, demarcated by the Reissner membrane. The cochlear spiral structure, known as the organ of Corti, is located inside the scala media and is fixed to the basilar membrane, which serves as the cochlea's auditory receptor. The organ of Corti is made up of three rows of outer hair cells (OHCs) and a single row of inner hair cells (IHCs), along with supporting cells and a range of accessory components. Approximately 15,000 hair cells populate the human cochlea, with a distribution of around 3,000 IHCs and 12,000 OHCs [27]. Positioned in the medial helix of the cochlear spiral, the IHCs are supported by inner phalangeal cells, while the OHCs are situated on the outer edge of the cochlear spiral and surrounded by the outer phalangeal cells. The exact organization of hair cells is crucial for decoding sounds with different intensities and frequencies: HCs at the apex detect low frequencies, whereas HCs at the

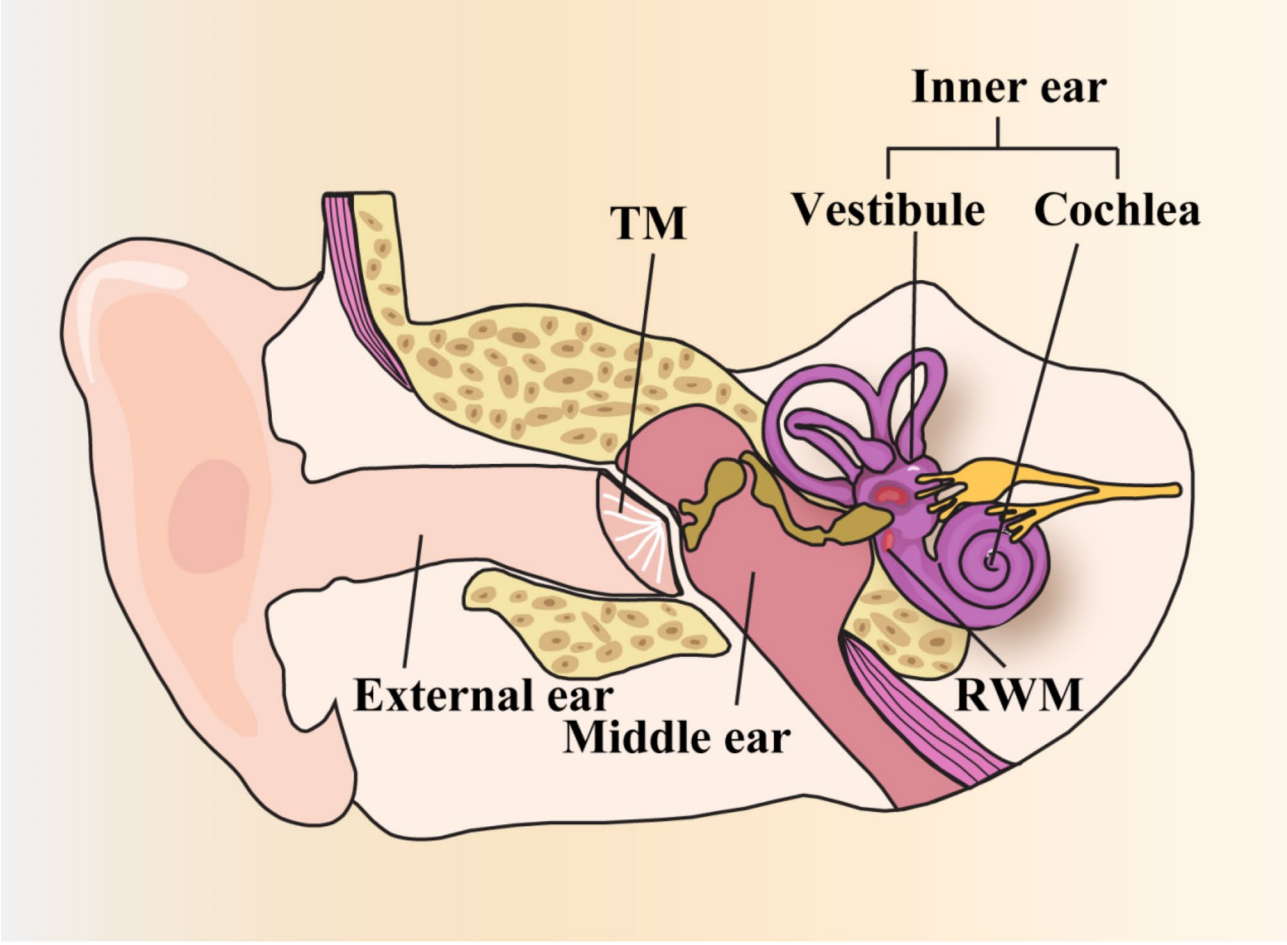


Fig. 1 Diagrammatic representation of the morphological architecture of the peripheral auditory apparatus

base sense high frequencies. The center of the cochlear spiral is the modiolus, which is filled with spiral ganglion neurons (SGNs). The somata of SGNs produce peripheral processes that make contact with auditory receptors in the organ of Corti, while their axons bundle aggregate to constitute the auditory nerve, which extends into the central nervous system [28].

Inner ear disorders

Inner ear disorders are the principal etiology of hearing loss, and the common clinical inner ear disorders include sensorineural hearing loss (SNHL), noise-induced hearing loss (NIHL), cisplatin ototoxic hearing loss, and autoimmune inner ear disease (AIED) [29].

Sensorineural hearing loss

SNHL is a widespread manifestation of auditory dysfunction in humans, frequently caused by hair cell destruction or apoptosis as a consequence of aging, acoustic overexposure, or the use of ototoxic drugs [30]. Approximately 278 million individuals, including more than 1% of children worldwide, suffer from SNHL [30]. Almost all cases of SNHL are irreversible, and current treatment mainly consists of the application of hearing aids and cochlear implantation, which do not promote hair cell regeneration or stop the deterioration of hearing. Consequently, researchers are increasingly focused on advancements in molecular targeting for SNHL therapy, which have promoted the advancement of secure and efficient delivery systems designed for the precise administration of novel therapeutic agents to defined therapeutic targets within the inner ear.

Noise-induced hearing loss

The escalating incidence of NIHL is linked to either acute or prolonged noise exposure. Research has demonstrated that chronic exposed to noise levels exceeding 85 dB can damage hair cells and auditory neurons, leading to a loss of hearing [31]. Intense noise exposure leads to elevated levels of free radicals in hair cells, which consume excessive intracellular antioxidants [32]. Although steroids, growth factors, and antioxidants are commonly employed in clinical studies to treat NIHL, the direct application of these pharmaceuticals to the inner ear

remains impractical, which restricts their therapeutic effectiveness [33]. The combination of nanotechnology as a drug carrier to deliver small-molecule drugs directly to the inner ear is under investigation as a promising curative approach for NIHL [34].

Cisplatin ototoxic hearing loss

Cisplatin, a commonly prescribed chemotherapeutic drug for tumours occurring in the head and neck region, pulmonary neoplasms, and genitourinary cancers, often causes irreversible ototoxic hearing loss, typically manifesting as vertigo and tinnitus [35]. The ototoxic effects of Cisplatin typically commence by impacting high-frequency hearing and can advance to affect lower frequencies with ongoing treatment, resulting in a higher susceptibility of OHCs over IHCs. Studies have indicated an increase in hearing thresholds in 75–100% of individuals who have undergone cisplatin therapy [21]. In addition, ototoxic reactions to cisplatin have been found to be influenced by age, with research suggesting a more pronounced impact on hearing in elderly individuals and children [36, 37]. Although certain research has investigated the application of antioxidants or agents that bind to platinum to reduce hearing loss caused by cisplatin [36], systemic use of these substances has been shown to deactivate cisplatin, diminishing its antitumor properties [38]. Therefore, the localized delivery of antioxidants and platinum-binding agents can protect the hair cells without cisplatin losing its antitumor activity.

Autoimmune inner ear disease

AIED, a form of hearing loss caused by an autoimmune response, was first described by McCabe in 1979 [39], is characterized by progressive sensorineural hearing impairment affecting both ears, accompanied by symptoms such as tinnitus and vertigo, which typically persist for weeks to months. Treatment of AIED has involved high doses of systemic steroids, immunosuppressive agents like methotrexate [40], and certain proinflammatory cytokines, including interleukin-1β (IL-1β) [41]. However, the documented therapeutic efficacy of these interventions remains limited, with notable severe side effects that may lead to discontinuation of drug therapy. Therefore, there is a pressing clinical demand for innovative, more effective, and less risky treatments for AIED. While Cochlear implantation has been validated as a potent intervention for the restoration of auditory function in instances of AIED, individuals with Cogan's syndrome (CS) within the AIED cohort, characterized by inflammatory inner ear involvement, are susceptible to partial or complete intracochlear ducts occlusion due to inflammatory periosteal reaction [42]. Hence, it is advisable to consider cochlear implantation early to middle age for patients with AIED.

Inner ear drug delivery route

Systemic drug delivery

Inner ear disorders can be managed by various systemic administration methods, such as intravenous injection [43], intramuscular injection [44], and oral administration [45]. In 1980, Wilson's study revealed that the administration of steroid hormones was effective in enhancing auditory function in individuals with SNHL, as demonstrated by a randomized, double-blind clinical trial. The trial showed a recovery rate in SNHL patients using oral glucocorticoids, in contrast to a 32% improvement with a placebo among the control group [46]. The 2019 clinical practice guidelines issued by the American Academy of Otolaryngology–Head and Neck Surgery Foundation recommend that corticosteroids should be considered a primary therapeutic approach for managing sudden SNHL in humans. A daily concentration of 1 mg/kg of prednisolone or equivalent, no more than 60 mg/day, is chosen as the preferred clinical treatment for idiopathic sudden SNHL within two weeks of the onset, and a lower dose is applied as the therapy time increases [47]. Meniere's Disease is a chronic condition whose main symptom is intermittent vertigo, usually lasting from minutes to hours, accompanied by symptoms such as hearing loss and tinnitus [48]. Some studies have shown that intramuscular injections of aminoglycosides displace the vestibular structures responsible for balance function, which can help reduce vertigo in individuals who have Meniere's Disease [49, 50].

Although systemic drug delivery is frequently employed in the therapeutic management of inner ear disorders, several challenges remain. The blood-labyrinth barrier hinders the attainment of adequate therapeutic levels in the inner ear, which constrains the potency of medication treatments. While high doses of drugs, such as gentamicin and streptomycin, may achieve the desired therapeutic effect, they are often accompanied by considerable toxicity and potential damage to the body, including hypertension and increased susceptibility to infections, as well as systemic side effects such as osteoporosis [50, 51].

Intratympanic drug delivery

Tympanotomy and intratympanic injection

Tympanotomy is a surgical procedure in which a needle is used to puncture the tympanic membrane, allowing for the removal of fluid from the tympanic cavity and the delivery of medication. This technique is primarily employed for diagnostic and therapeutic management of secretory otitis media. In addition, an intratympanic injection-a procedure where therapeutic agents are administered into the tympanic cavity via a syringe through an incision in the tympanic membrane (created during tympanotomy)-promotes drug delivery to the

inner ear, primarily through the RWM. This method acts as a vital therapeutic intervention for managing inner ear conditions, including sudden SNHL and Meniere's Disease. Intratympanic injections have attracted great clinical interest since the systemic administration has limitations. This method circumvents the blood-cochlear barrier, thereby enhancing treatment efficacy and minimizing the risk of adverse physical side effects associated with systemic administration. Studies have revealed that the drug concentration in cochlear perilymph and endolymph following intratympanic injection are significantly higher than those observed in the cochlea subsequent oral and systemic administration [52, 53].

Due to these advantages, the use of intratympanic injections has grown in clinical practice for administering corticosteroids and aminoglycosides as treatments for SNHL and Meniere's Disease [24]. To compare the efficacy of oral versus intratympanic corticosteroids in the treatment for SNHL, Rauch et al. conducted a randomized investigational study in which individuals with unilateral sensorineural hearing loss received either oral or intratympanic injections. Evaluating hearing improvements following a 2-month treatment period, the research showed that intratympanic injection is as effective as oral administration in promoting hearing recovery [54]. Recently, Jung et al. prepared dexamethasone sodium phosphate (Dex SP) as a nanosuspension with a particle size of 250–350 nm and administered the drug suspension via intratympanic injection. High drug concentrations were detected in both perilymph and cochlear tissue within 6 h of injection, with no toxicity observed even at concentrations as high as 20 mg/mL [55].

Intratympanic injections, while effective in treating inner ear disorders and circumventing systemic adverse reactions, demonstrate variability in the therapeutic efficacy among different patients due to inconsistent scattering of the medication within the inner ear. The efficacy of drug permeation across the RWM is contingent on the duration of exposure of the drug molecules to the RWM and the volume of the drug that crosses this barrier. Additionally, the scattering of intratympanic injected drugs into the inner ear lacks precision in targeting damaged areas. Moreover, the short duration of drug action in the tympanic cavity often necessitates repeated injections over several days to maintain adequate drug concentration. Therefore, the design and advancement of pharmacotherapeutic delivery systems that lengthen the duration of drug presence within the inner ear while also demonstrating enhanced selectivity and precision is of critical importance.

Microcatheter, micro-osmotic pump and microneedle

Due to the restricted anatomical space for clinical intervention within the inner ear, the deployment of a highly targeted and meticulous drug delivery approach to the cochlea is imperative, often requiring a significant duration for treating inner ear conditions. Consequently, microsystem-based methods such as microcatheters, micro-osmotic pumps, and microneedles offer a viable means to manage drug therapy for inner ear disorders meticulously [56].

IntraEAR has engineered the μ-Cath™ and e-Cath™ microcatheters for round window administration for precision inner ear drug delivery. Specifically, the e-Cath™ features three lumens designated for infusion, pumping, and the detection of auditory signals, respectively [21]. A microcatheter equipped with a controlled-release mechanism (Fig. 2ai) was deployed into the round window niche through a tympanic membrane flap without causing damage to the membrane itself [57]. The microcatheter was externally attached to the spiral and connected to an electronic pump, through which therapeutic drugs such as artificial perilymph, neurotrophic factors, gentamicin, and glucocorticoids were injected into the microcatheter and delivered to the inner ear [58]. To evaluate the therapeutic efficacy of microcatheter-delivered drugs via RWM on hearing loss, patients with hearing impairment received microcatheter-administered drops of dexamethasone or gentamicin, in comparison to an equivalent dose administered of intracochlear injection. After one month of treatment, hearing improvement was observed in 40.6% of the microcatheter group, surpassing the improvement noted in the intracochlear injection group (20.6%) and the control group (7.7%) [59]. The majority of the patients experienced controlled symptoms of vertigo and tinnitus without significant reductions in cochlear or vestibular function (Fig. 2aii) [60]. Furthermore, with the help of optical coherence tomography (OCT), researchers detected the destruction of the RWM by measuring RWM thickness and facilitated the non-destructive identification of endolymphatic effusion (Fig. 2aiii) [61]. The Organ of Corti was excised and underwent immunofluorescent labelling to evaluate the retention of hair cells (Fig. 2aiv). Results showed that while microcatheters may temporarily alter the mechanical properties of the RWM, the delivery of drugs such as BDNF could mitigate hearing loss resulting from microcatheter delivery. Consequently, the influence of microcatheters and continuous "wetting" treatments on the integrity and functionality of the round window membrane throughout the drug administration process necessitates additional investigation.

The micro-osmotic pump is extensively applied for inner ear pharmacotherapy by creating an incision behind the ear, through which a microcatheter is advanced into

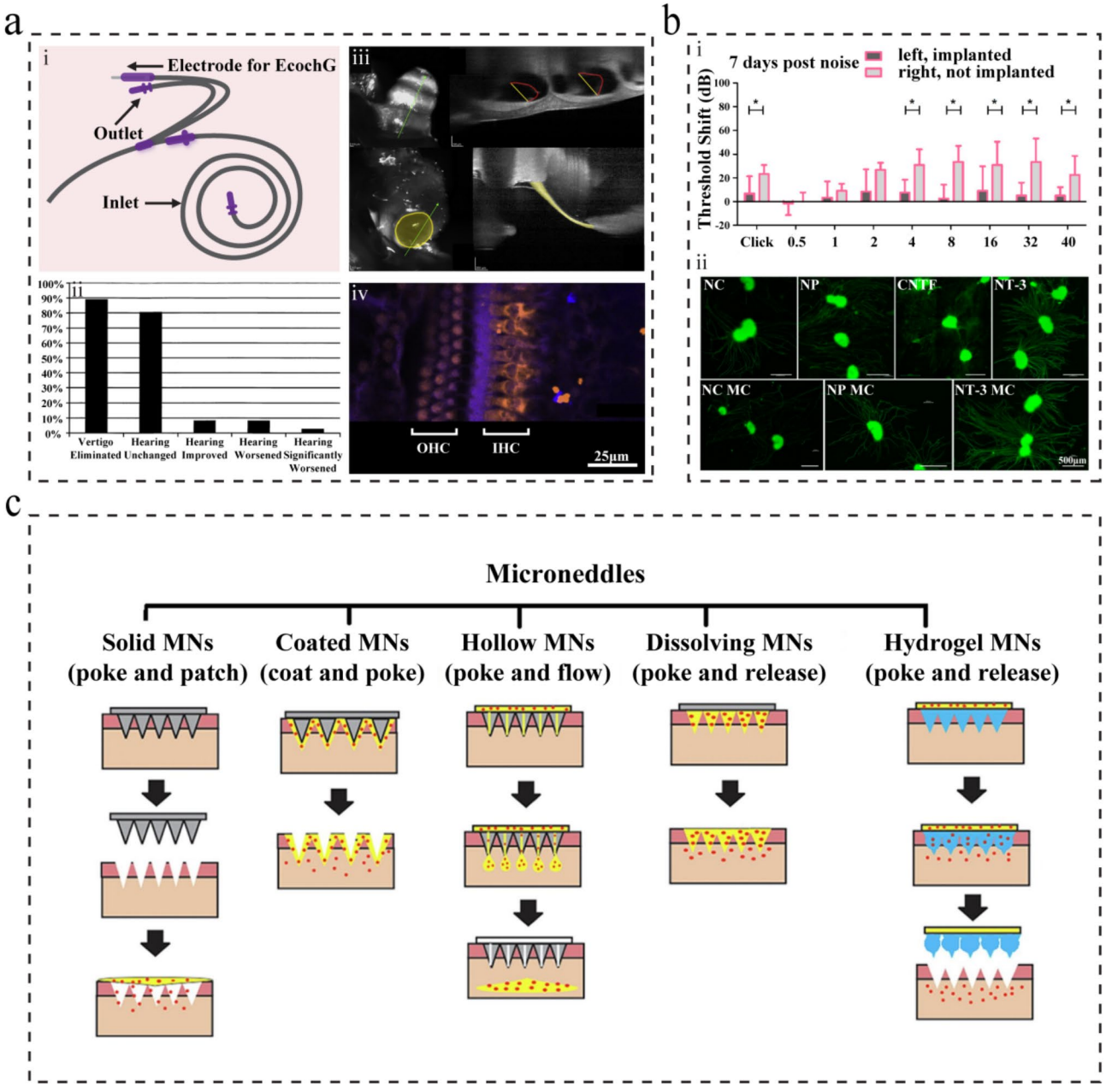


Fig. 2 Microcatheter, micro-osmotic pump and microneedle for inner ear drug delivery applications. (**a**i-iv) i: Round window microcatheter with electrodes for detecting ear signals; ii: Microcatheter delivery of gentamicin for hearing damage; *© 2006, John Wiley and Sons*; iii: Acquisition of optical coherence tomography (OCT) image of the cochlear axis mid-section; iv: OHCs and IHCs, as visualized through immunofluorescent labelling with DAPI (purple) and myosin VIIa (orange); *© 2017 Elsevier B.V. All rights reserved*; (**b**i-ii) i: Hearing recovery in the left (implanted) and right (unimplanted) ears one week after noise injury; *© 2022 by the authors*; ii: Fluorescent microscopy visuals of spiral ganglion explants (SGE) across various therapeutic regimens; *© 2022 by the authors*; (**c**) Drug delivery mechanisms of different types of microneedles; *© 2020 Elsevier B.V. All rights reserved*

the round window niche. Subsequently, the catheter is subcutaneously guided through a skin incision in the posterior wall of the external ear canal, with continuous medication administration facilitated by an external micro-osmotic pump linked to the catheter. The micro-osmotic pump facilitates the drug's controlled release through the microcatheter into the round window niche at a uniform and continuous rate. The system facilitates a variable drug volume from 0.1 to 2 mL and an adjustable flow rate of 0.1 to 10 μL/h, thereby maintaining a consistent drug concentration within the perilymph. This approach facilitates controlled drug delivery, providing a more accurate estimation of the total drug volume while allowing clearance mechanisms to regulate the overall fluid volume. DURECT Corporation manufactures Alzet osmotic pumps, which are used in experimental animal

research to provide effective long-term drug delivery. Investigators conducted unilateral implantation of micro-osmotic pumps and cannulae in guinea pigs, followed by exposure to a sound pressure level of 120 dB for a duration of 4 h to elicit changes in the auditory threshold. Findings from the auditory brainstem response (ABR) assessments revealed no substantial disparity in threshold shifts between the ears with and without implants prior to noise exposure. However, after 7 days of exposure, there was a marked distinction in threshold shifts (Fig. 2bi), wherein the insertion of a micro-osmotic pump was associated with substantially reduced threshold shifts at 5 of the 8 tested frequencies when contrasted with the non-implanted ear [62]. In addition, Jana et al. integrated a micro-osmotic pump with 3D printing technology to create an inner ear-inspired neural synapse growth cavity (NOC) [63], enabling the pump to facilitate long-term drug delivery. Over two weeks, the micro-osmotic pump's drug delivery function was utilized to treat spiral ganglion explants with neurotrophic factor-3 (NT-3), resulting in a significant enhancement in neural protrusion growth compared to the other groups (Fig. 2bii). These findings suggest that micro-osmotic pumps could be effectively combined with other drug delivery methods to mimic long-term drug delivery in vivo, thereby allowing for the evaluation of the biological efficacy of osmotic pump-delivered factors for periodic replacement of inner ear tissues over several weeks.

Microneedles consist of micron-sized tiny tips arranged in an array on a base, typically exhibiting a body length of 50–2000 μm and a diameter of 1–100 μm. The size, length, shape and material of the microneedles can be individualized according to the specific requirements of treatment. Since the first microneedle arrays were prepared by reactive ion etching techniques in 1998, these devices have seen extensive application in the fields of biological fluid sampling and pharmaceutical delivery systems [64]. Recently, investigators have investigated the utilization of microneedles as a platform for drug delivery in the management of inner ear disorders. The RWM constitutes a prime target for pharmacological administration via the cochlear pathway [65]. The use of microneedles for puncturing the RWM facilitates precise regulation of the dimensions and extent of the perforation, which can minimize anatomical and functional damage. When developing microneedles for drug delivery, three fundamental characteristics must be considered: (1) the high strength and ductility of the materials used, (2) sub-micron precision and accuracy, and (3) design flexibility, which enables the customization of microneedle geometries tailored for targeted pharmacotherapy of the inner ear [66].

Microneedles can be classified based on their characteristics into several categories, including solid microneedles, coated microneedles, hollow microneedles, dissolving microneedles, and hydrogel microneedles (Fig. 2c) [67, 68]. Researchers produced hollow microneedles by two-photon polymerization lithography, which enables penetration of the RWM in both humans and guinea pigs. These hollow microneedles can aspirate perilymph and deliver therapeutic drugs into the inner ear [65]. Pawley et al. engineered a polymer-based microneedle composed of poly (lactic acid-glycolic acid) (PLGA) impregnated with a therapeutic agent, which is intended to perforate the RWM and deliver a consistent drug payload over an extended duration [69]. Utilizing a combination of two-photon photolithography and electrochemical deposition techniques, Aykut manufactured ultra-sharp gold-plated copper microneedles capable of causing minimal tissue damage upon penetration of the RWM for drug administration purposes [66]. Leong has advanced a 3D-printed microneedle platform designed for extralymphatic aspiration in diagnostic applications and for the intracochlear administration of therapeutic substances [70]. In this study, the investigators examined the anatomical, physiological, and proteomic outcomes associated with microneedle-mediated RWM perforations. ABR results demonstrated that microneedle-mediated RWM perforations do not result in hearing loss and can heal within 48–72 h. In conclusion, microneedle-mediated RWM perforation can minimize anatomical and functional loss during drug delivery in the inner ear. Moreover, microneedle technology facilitates accurate regulation of the administered drug dosage and concentration, providing a level of safety and efficacy that intratympanic injection cannot achieve.

Hydrogel delivery system

Hydrogels consist of water-swollen networks formed by cross-linked polymers and usually exhibit a porous three-dimensional structure [71–73]. They are extensively utilized as carriers for drug delivery in tissue and organ regeneration [74, 75]. In the cochlea, drug-encapsulated hydrogels are usually fabricated into microspheres, microneedles, and various other forms, which can adhere to the RWM by modifying adhesion factors such as polydopamine (PDA) for effective delivery drugs [76, 77]. In a contemporary investigation, Chen and colleagues synthesized gelatin methacrylate (GM) microspheres modified with polydopamine (PDA) and encapsulated within Ebselen liposomes, resulting in a novel, sticky, injectable formulation designated as GM@PDA@Lipo Ebselen microspheres [78]. The researchers administered the GM@PDA@Lipo Ebselen by injection onto the RWM, where they adhered firmly facilitated by the adhesive properties of PDA (Fig. 3ai). These microspheres demonstrated extended retention within the middle ear cavity for over a week, maintaining a consistent release of the

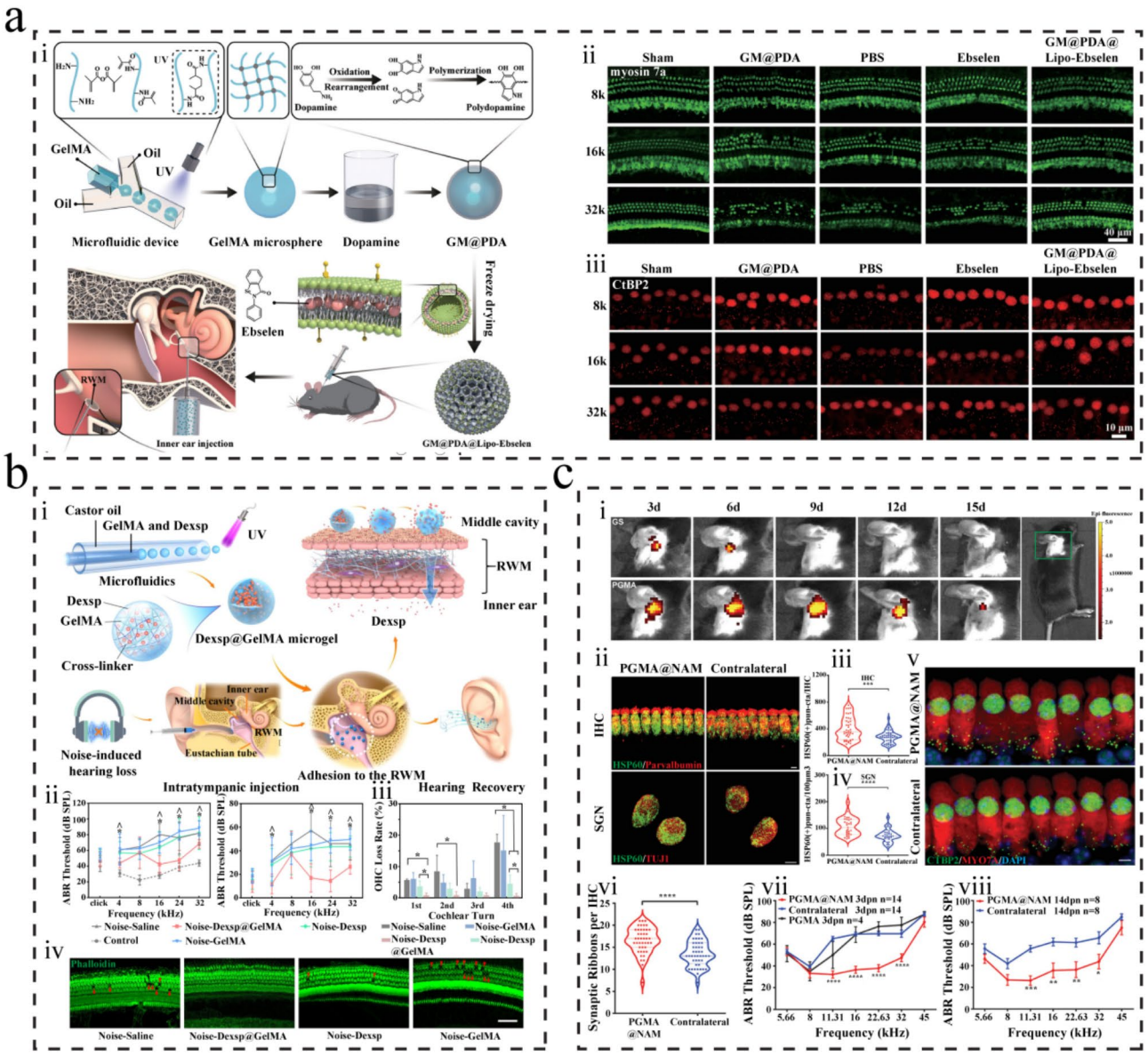


Fig. 3 Hydrogel-based platform for the administration of therapeutic agents to the inner ear. (**a**i-iii) i: GM@PDA@Lipo-Ebselen model via RWM inner ear injection; ii: Immunofluorescence images of OHC at 8 kHz, 16 kHz and 32 kHz; iii: Immunofluorescence images of synapses at 8 kHz, 16 kHz and 32 kHz; *© 2022 Wiley-VCH GmbH*; (**b**i-iv)i: Schematic diagram of tympanic chamber injection of Dexsp@GelMA microgel for the treatment of NIHL; ii: ABR thresholds and threshold shifts within each cohort on the seventh day following acoustic overexposure; iii: Rate of OHC loss in each experimental group; iv: Fluorescent immunolabeling visualizations of OHCs within respective experimental group; *© 2022, American Chemical Society*; (**c**i-viii) i: Mouse at 0, 3, 6, 9, after delivery of agents with GS or PGMA, 12 and 15 days of non-invasive bioluminescence imaging; i-iv: HSP60 and TUJ1 immunofluorescence images of mouse IHC and SGN, and their statistical plots of the number of spots; v-vi: MYO 7a (red) and CtBP2 (green) immunofluorescence images of IHC at 16 kHz, and their statistical plots; vi-viii: At 3 and 14 dpn, with /no ABR thresholds in mouse with or without PGMA or PGMA@NAM delivery; *© 2024 The Authors. Advanced Science published by Wiley-VCH GmbH*

encapsulated drug. Immunofluorescence analysis demonstrated that GM@PDA@Lipo-Ebselen protected against noise-induced damage to OHCs and synaptic proteins (Fig. 3aii-iii). Additionally, the mouse's hearing returned to normal levels across all frequencies after being treated with these microspheres. These findings suggest that GM@PDA effectively deliver load Lipo Ebselen into the middle ear for sustained drug release, offering significant therapeutic benefits for NIHL mice.

In a separate study, investigators developed GelMA microgels using microfluidics techniques and encapsulated them with dexamethasone sodium phosphate (Dexsp) for the treatment of NIHL [79]. The obtained Dexsp@GelMA microgels were fabricated by coaxial microfluidic chips in a narrow jetting regime, where the

pregel solutions of GelMA and Dexsp were emulsified to create droplet structures. The droplets were subsequently cross-linked and polymerized through ultraviolet (UV) irradiation (Fig. 3bi). The dimensions of the microgels can be modulated by manipulating the microfluidic operational parameters. Microgels of suitable sizes are favorable for conduction within the inner ear, as they do not lead to long-term conductive hearing loss and can be employed for targeted pharmaceutical administration. Subsequent to its development, the efficacy of Dexsp@GelMA microgel in mitigating hearing impairment was investigated utilizing the guinea pig model of NIHL. The noise-Dexsp@GelMA group demonstrated a marked enhancement in auditory function relative to the other lesioned groups, signifying an enhanced protective capacity (Fig. 3bii). Additionally, there was a notale reduction in the OHC loss rate in the noise-Dexsp @ GelMA group (Fig. 3bii-iv). Therefore, microfluidics-based adhesive microgels may offer novel perspectives on the utilization of microfluidic delivery systems within the inner ear.

Nicotinamide mononucleotide (NMN) is an crucial NAD^+ supplement that enhances the stability of the mitochondrial intracellular environment and protects the cochlea from neuroexcitotoxic damage. Feng [80] et al. optimized NAM-encapsulated GelMA by lyophilization, yielding a drug delivery construct tailored for the distinctive architecture of the round window ecological niche in mouse, enabling efficient drug release. The researchers observed significant fluorescence signals in the injected ear, where the fluorescence signal in the gelatin sponge (GS) group disappeared by day 12. Conversely, the PGMA group did not exhibit any reduction in fluorescence intensity over the 12-day observation period, suggesting that small-molecule drugs are continuously released in the inner ear via PGMA (Fig. 3ci). Furthermore, the study team examined the prolonged protective impact of PGMA@NAM on the prevention of NIHL in mice. The researchers documented a significant rise in the number of mitochondria- and synapse-positive areas within the cochlea of the PGMA@NAM treated group relative to the untreated cochlea (Fig. 3ciii-vi). Besides, ABR threshold results also indicated that PGMA@NAM treatment significantly ameliorated hearing loss (Fig. 3cviii-viii).

Nanoparticle delivery system

Nanoparticles (NPs) are nanoscale materials, generally ranging from tens to hundreds of nanometers in diameter, which are fit for conjugating or summarizing a variety of therapeutic agents [81, 82]. In the management of inner ear disorders, a diverse array of nanoparticles are employed, such as PLGA NPs, magnetic NPs, silica NPs, lipid NPs, polymeric NPs, and liposomes, depending on the material employed in their preparation (Fig. 4) [81, 83]. These NPs exhibit significant variations in size, morphology, and surface charge [18]. They confer multiple benefits, including non-invasiveness, enhanced drug loading and regulated release mechanisms, modification for specific indications, and targeted delivery. Therefore, the utilization of NPs for pharmaceutical delivery has arisen as an auspicious therapeutic modality for the management of inner ear disorders in recent years.

NPs have been increasingly utilized for surface-loaded with ligands and encapsulated with therapeutic drugs, allowing for targeted delivery to specific sites in the inner ear and facilitating sustained drug release. Zhao et al. developed a reactive oxygen species (ROS)-responsive OHC-targeted nanoparticle platform for the delivery of berberine (BBR), termed PL-PPS/BBR (Fig. 5ai). This formulation can penetrate the RWM of NIHL guinea pigs via a postauricular approach. The nanoparticles were conducive to scavenging ROS in the reactive oxygen environment, thus stimulating the rapid release of BBR, which possesses antioxidant and anti-inflammatory properties that protect OHC from noise-related damage (Fig. 5aii-v) [84]. The use of mesoporous silica superparticles (MS-SPs) as therapeutic carriers has garnered significant interest due to their numerous benefits in drug delivery, including adjustable pore size adjustability, ease of surface modification, and excellent biocompatibility. The mesoporous architecture of MS-SPs facilitates the encapsulation of a substantial quantity of particles within a confined volume, forming superparticle clusters. Researchers have reported that MS-SPs can be artificially produced through the self-assembly of mesoporous silica (MS) nanoparticles within confined droplets driven by capillary action (Fig. 5b) [85]. Following cochlear implantation, the MS-SPs can continuously release neurotrophic factors and effectively rescue auditory neurons in mice with hearing loss. The utilization of DNA nanotechnology for pharmaceutical delivery systems has gradually gained attention due to the unique advantages of DNA, such as high programmability and controllable surface chemical modifications. Among the various designs of DNA, tetrahedral DNA nano-junctions (TDNs) have gained particular interest in therapeutic and diagnostic nanomedicine. TDNs, characterized by their favourable dimensional structure and mechanical stiffness, facilitate efficient tissue penetration and have emerged as a strong candidate for the targeted administration of therapeutic agents to the inner ear. Xu et al. [86] integrated gelatin nanoparticles (GNPs) with TDNs to successfully construct nanocarrier complexes for loading epigallocatechin gallate (EGCG) (Fig. 5ci-iv). The prepared TDN@GNP demonstrated a prolonged drug clearance. The enhanced in vivo pharmacokinetic profile of TDN@GNP complexes was confirmed in an

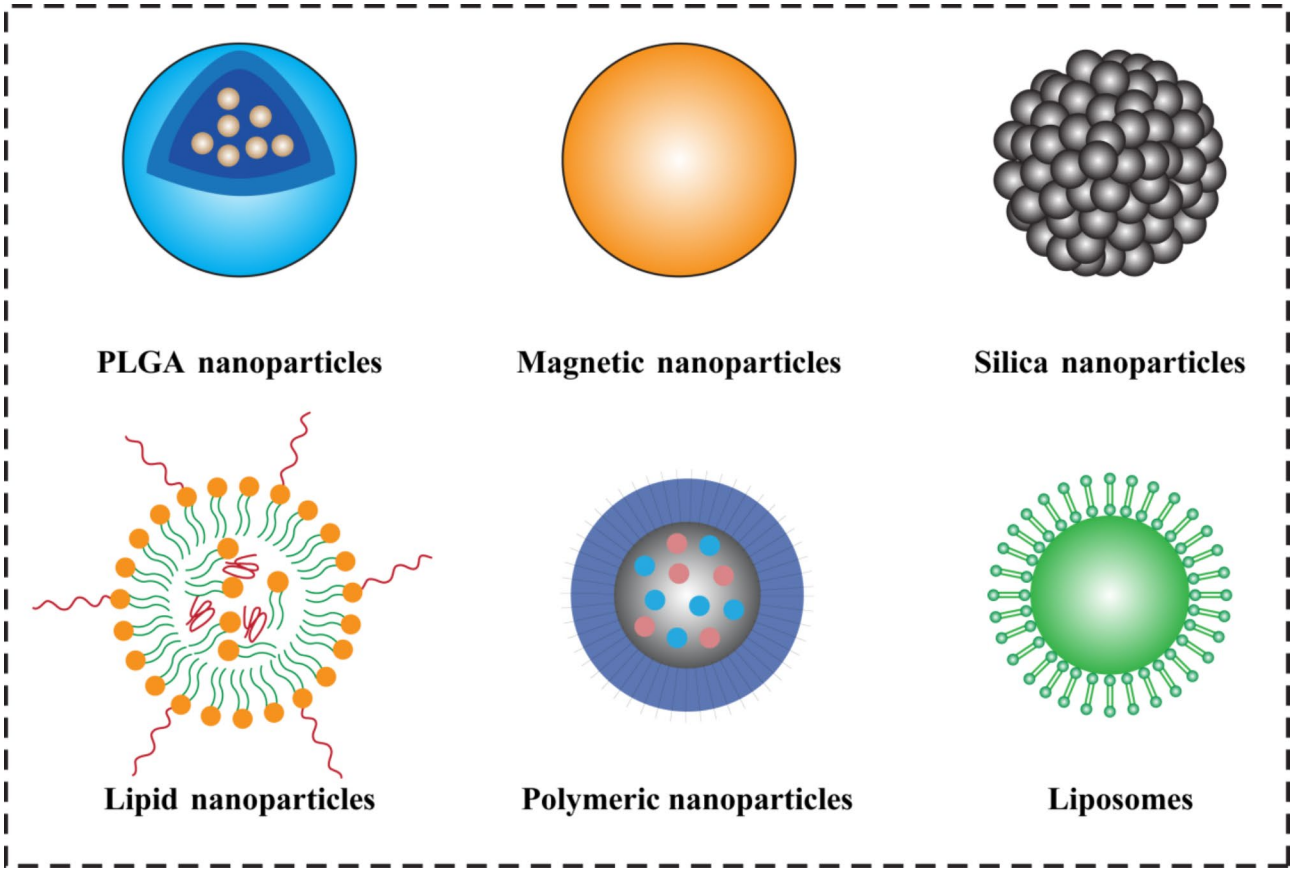


Fig. 4 Graphical depiction of different nanocarriers used for drug delivery

animal model of NIHL. Cy 5-TDN@GNP was detected in connective tissue (CT) and inner epithelium (IE) after injection, indicating a directed transmigration from the tympanic side to the tympanic step side across the RWM. In contrast, the fluorescent signals of Cy 5-TDN were diminished (Fig. 5cv-vi), likely attributable to the surface negativity of the TDNs, which impeded their adhesion on the RWM. TDN@GNP exhibited more efficient transmission through the RWM than naked TDN, making it highly advantageous for inner ear drug delivery. In addition, lipid NPs and polymeric NPs have been used for inner ear protection and hearing restoration. Gao et al. prepared solid lipid nanoparticles (SLNs) of edaravone with an average particle size of 93.6 nm and an encapsulation efficiency of 76.7% by ultrasound technology [87]. SLNs were able to inhibit ROS generation in the cochlea after noise exposure, as observed by the electron spin resonance (ESR) technique. Sergio et al. used pH-sensitive amphiphilic polymeric NPs for the transport and controlled release of dexamethasone in the inner ear to protect against the ototoxic effects of cisplatin [88]. The polymer nanoparticles showed promising results both in vitro (using HEI-OC1 cells) and in vivo (using a mouse model).

Intracochlear drug delivery

In response to the challenge of disproportionate drug distribution within the cochlea associated with RWM delivery and to optimize therapeutic efficacy, a range of intracochlear drug delivery platforms have been engineered for targeted and localized application. These platforms enable precise drug administration to the cochlea via techniques including direct intracochlear injection, cochlear prosthesis-based delivery, and reciprocating microfluidic drug delivery systems.

Direct intracochlear drug injection

Direct intracochlear drug injection is a method of delivering drugs directly to the cochlea utilizing a syringe microinjection or osmotic pump following cochleostomy [89]. This technique effectively overcomes several limitations, including the blood-cochlear barrier, uneven distribution, short residence time, and the variable nature of drug delivery across different cochlea regions [90]. Although the procedure is performed via cochleostomy, which requires a surgical procedure that may cause damage to inner ear structures and lead to potential complications, it is currently employed primarily in conjunction with cochlear implants in clinical practice. De Ceulaer et

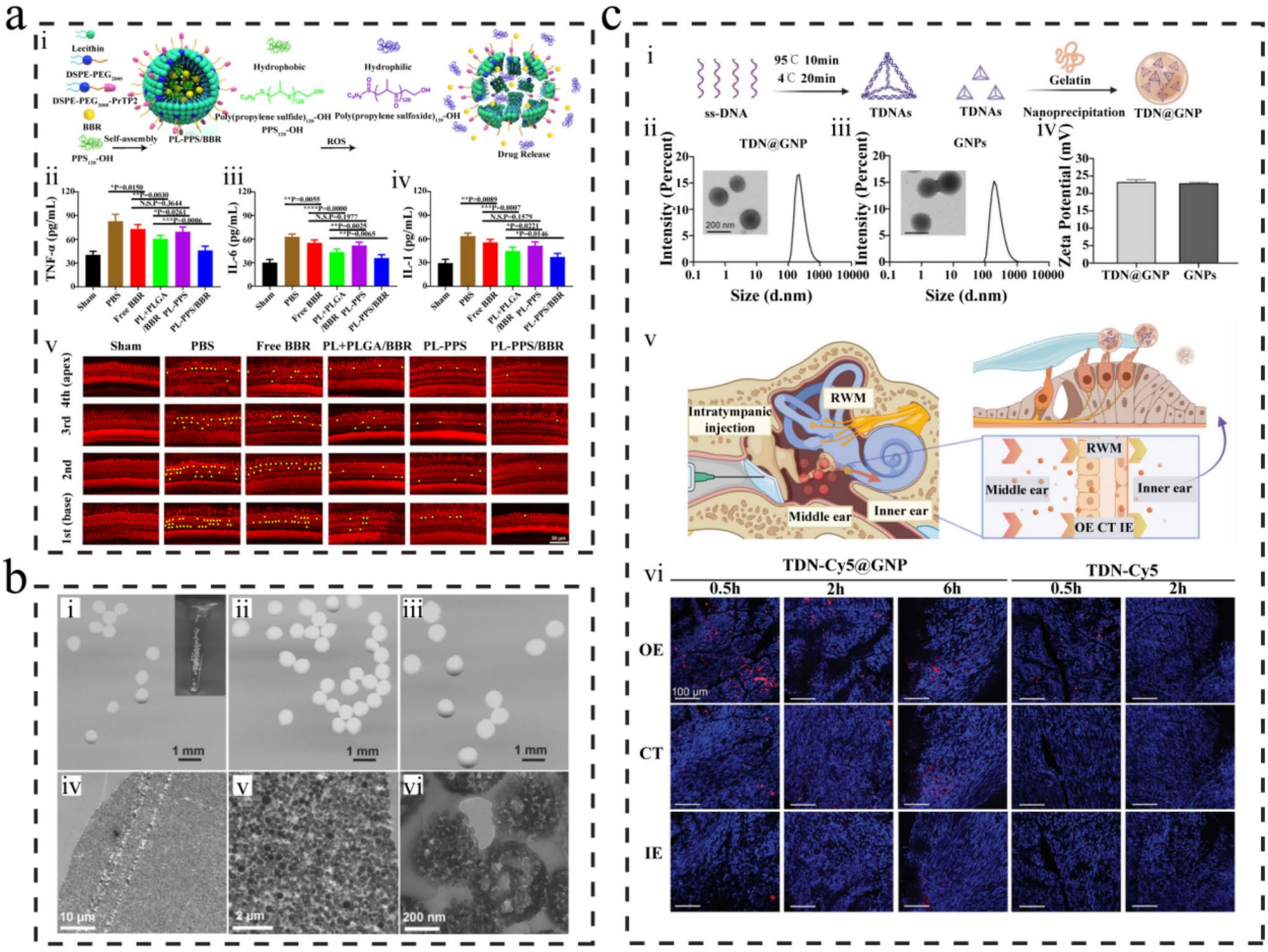


Fig. 5 Nanoparticle microcarriers for inner ear drug delivery applications. (**a**i-v) i: Self-assembly process of ROS-responsive nanoparticles (PL-PPS/BBR); ii-iv: Indirect reduction of inflammation in the cochlea by scavenging ROS by PL-PPS/BBR; v: OHC immunofluorescence images in the guinea-pig cochlea from apex rotation to base rotation; © *2021, American Chemical Society*; (**b**) Transmission electron microscopy characterization of mesoporous silica nanoparticles; © *2014 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim*; (**c**i-vi) i: TDN- EGCGOGNP nanoparticles were prepared; iii-iii: Hydrodynamic diameters and TEM images of TDN@GNP and GNP; iv: Zeta potential of TDN@GNP and GNP; v: Migration schematic of Cy 5-TDN@GNP; vi: Immunofluorescence images of RWM of Cy 5-TDN@GNP and Cy 5-TDNs; © *2024 Wiley-VCH GmbH*

al. performed a retrospective study using steroid input via syringe following the insertion of cochlear electrodes, demonstrating a significant reduction in electrode impedance two months postoperatively [91]. Similarly, the administration of triamcinolone through the cochlear catheter before the insertion of Med-El Flex28 electrodes also reduces electrode impedance and provides a longer-lasting effect [92].

Cochlear implant-based delivery system

Cochlear implants constitute the premier therapeutic modality for the management of individuals afflicted with severe to profound SNHL. Cochlear implant-based drug delivery systems combine therapeutic drugs with devices such as microphones, transmitters, speech processors, and electrode arrays. These electrode arrays are surgically implanted within the cochlea, with each electrode positioned near auditory neurons corresponding to different frequencies. The primaty function of the cochlear implant is to convert external sound input into electrical stimuli, which are delivered discharged through electrodes inserted in the cochlea. This process activates SGNs, resulting in the generation of neural impulses that are conveyed to the auditory pathways of the central nervous system, ultimately producing an auditory response [93]. However, cochlear implants frequently induce symptoms such as inflammation and fibrosis post-implantation. These conditions may contribute to hearing degradation and the degeneration of auditory neurons, thus diminishing the effectiveness of the cochlear electrodes.

To address the limitations of cochlear implant electrodes, researchers have demonstrated that integrating drugs with cochlear implant electrodes presents a

promising approach. The combination of drug molecules, such as neurotrophic factor [94] and therapeutic drugs [95], with electrodes has proven effective in protecting auditory cells and improving hearing in patients with cochlear implants. Furthermore, cochlear electrodes can be paired with gene therapy. In recent years, adeno-associated virus (AAV) gene therapy, a cutting-edge technology, has shown potential in restoring hearing [96]. AAV has excellent gene delivery capabilities and low immunogenicity, making it an ideal vector. However, direct delivery of AAV to the inner ear faces many challenges, such as biocompatibility and delivery efficiency issues. Therefore, optimizing delivery systems for gene therapy using biomaterials has become a hot research topic. Jeremy et al. utilized cochlear electrodes combined with electroporation for gene delivery [97]. By integrating BDNF gene therapy into an auditory implant and implanting it into guinea pigs, the results showed that the auditory implant could regenerate the SGN and shorten the gap between the cochlea and the target neuron, thus improving the therapeutic effect.

Cochlear implants reconstruct hearing by electrically stimulating auditory neurons, however, variables including electrode size, distance, and the impedance between the electrodes and the target neurons can diminish signal fidelity and impair functionality [98]. To enhance the electrical stimulation efficacy of cochlear implant and bolster the biostability within the inner ear, Chikar et al. [71] have formulated a novel bilayer coating for cochlear implant electrodes. This coating consists of a conductive polymer, poly(3,4-ethylenedioxythiophene) (PEDOT), in conjunction with an RGD-modified alginate hydrogel impregnated with BDNF (Fig. 6ai). The modified cochlear implant demonstrated the ability to continuously supply nutrients (Fig. 6aii), lower electrode impedance (Fig. 6aiii), alter phase angle in vitro EIS (Fig. 6aiv), increase charge storage capacity, and mitigate degeneration of auditory neurons. Richardson et al. [99] fabricated conductive thin films of polypyrrole/p-toluenesulfonic acid sodium containing neurotrophic factor-3 (Ppy/pTS/NT3) thin films, which were integrated into cochlear electrodes and implanted into the guinea pig cochlea for electrical stimulation. Their findings indicated that cochlea implanted with Ppy/pTS/NT3 coating exhibited reduced electrical thresholds for evoked ABR thresholds and an increased density of SGN compared to the unimplanted cochlea. Furthermore, the Ppy/pTS/NT3 coating did not affect electrode impedance or induce cochlear fibrosis (Fig. 6bi-ii). Consequently, The Ppy/pTS/NT3 surface modification of electrodes effectively preserved the number of SGNs while maintaining cochlear function. In addition, the researchers statistically analyzed the effect of cochlear implants on the quality of life of patients with hearing loss through meta-analysis, and the statistical results showed that the implantation of cochlear electrodes can improve the hearing of patients and significantly enhance their quality of life [100, 101].

Reciprocating microfluidic drug delivery systems

From a pharmacological perspective, fluid dynamics and pharmacokinetics facilitate predictable intracochlear drug delivery volumes and concentrations [102]. However, due to the structural limitations of the cochlea, direct and rapid drug infusion can lead to fluid and mechanical damage to hair cells [103]. In clinical studies, drug delivery is often performed by inserting cannulas through cochleostomy; nonetheless, these apparatuses lack the capability for accurate regulation of pharmaceutical flow velocities and dosages. Consequently, a reciprocating microfluidic drug delivery system capable of delivering drugs directly into the cochlea is proposed [104]. The design specifications for this apparatus include an anatomical compatibility with the temporal bone in proximity to the cochlea; an advanced, electronically operated micropump optimized for the recirculation of inner ear fluid (exolymph) with high efficiency; a catheter implanted directly into the tympanic cavity, functioning dualistically as an inlet for the intermittent administration of minute quantities of pharmacological agents into the exolymphatic canal of the cochlea, and as an outlet for the displacement of an equivalent volume of dilute fluid; a drug reservoir with valves; and a sensor for the detection and transmission of relevant information.

The reciprocating microfluidic drug delivery system possesses a unique capability that enables the recirculation of inner ear fluids via an electronically controlled pump, addressing numerous critical issues [105]. First, it enables the delivery of sub-microliter volumes of medicine to the inner ear at fixed intervals, as opposed to a continuous infusion. Second, the drug reservoir of the system can accommodate a highly concentrated solution, allowing for operation over several years without refilling, thereby minimizing the risk of microbial contamination associated with drug replenishment [106]. Third, the circulation rate of inner ear fluid through the catheter operates independently of the drug delivered rate, permitting individual optimization of both flow rates. Finally, the drug reservoirs can take various forms, such as microchip arrays, biodegradable polymers, and combinations of different drug delivery methods [107].

To achieve chronic perfusion of the human inner ear, Kim S developed a reciprocating microfluidic device featuring a reservoir and active dose control, which delivers drugs to the perilymphatic space through a curved perforation at the fundus of the cochlear scala tympani [102]. The device incorporates a catheter that is directly implanted into the tympanic cavity, functioning as both an inlet and outlet to periodically deliver trace amounts

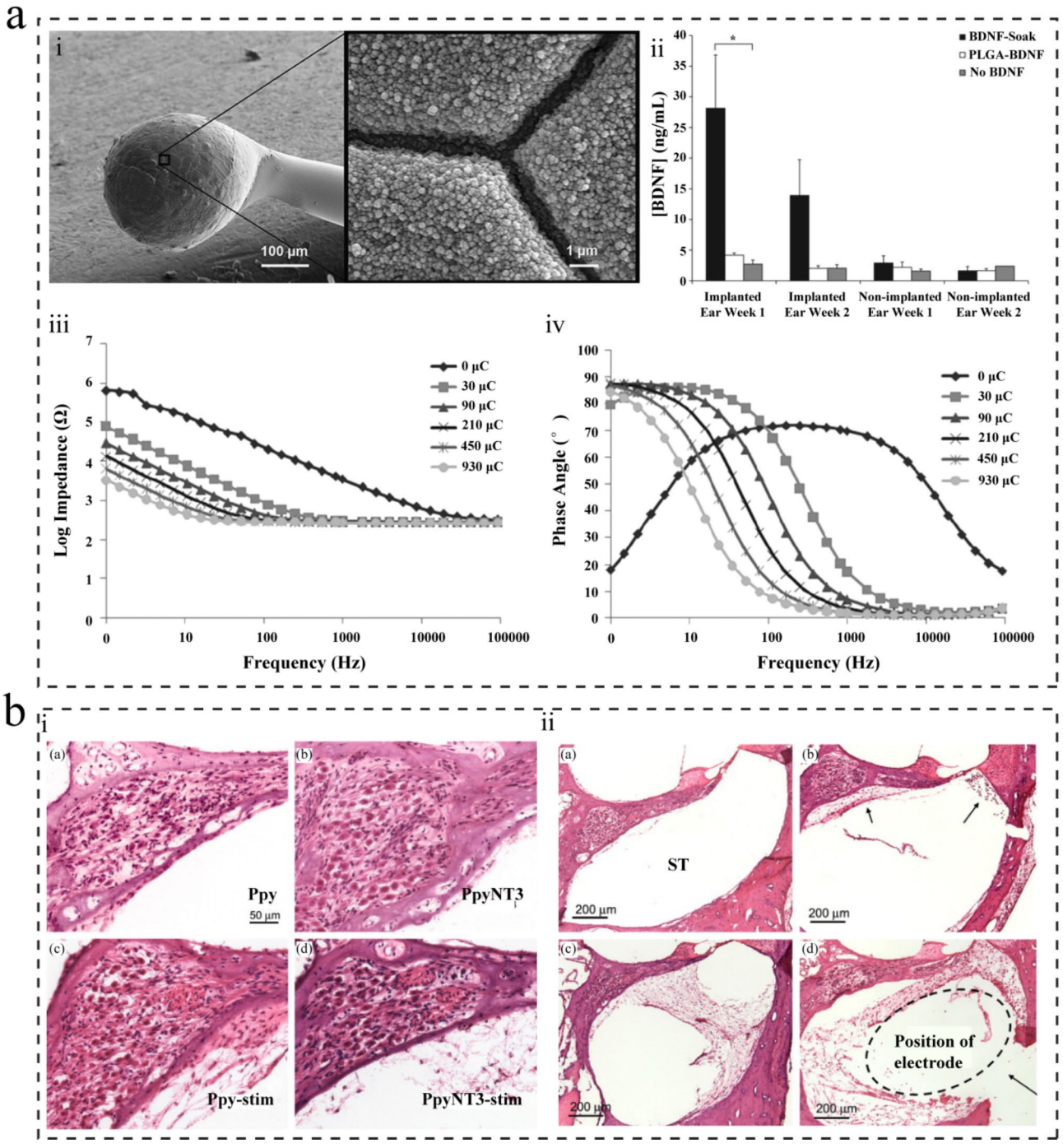


Fig. 6 Platform utilizing cochlear implants for the administration of pharmacotherapeutics to the inner ear. (**a**i-iv) i: Scanning electron micrographs of PEDOT-coated cochlear electrodes; ii: BDNF release from hydrogel coating into the cochlea; iii: PEDOT coating decreases electrode impedance; iv: Phase angle of PEDOT coatings; *© 2011 Elsevier Ltd. All rights reserved*; (**b**i-ii) i: SGN cross-sectional area statistics; ii: HE staining of SGN after cochlear electrode implantation; v: Fibrous tissue formation in the cochlea after electrode implantation; *© 2009 Elsevier Ltd. All rights reserved*

of drug to the outer lymphatic vessels of the cochlea, subsequently expelling an equivalent volume of less concentrated fluid. The reciprocating microfluidic device comprises two distinct pumps and a microfluidic network (Fig. 7ai) that facilitates drug delivery to the cochlea in a sequential manner, as shown in Fig. 7aii [102, 108]. The microfluidic device draws an equivalent volume of fluid into the system after delivering the drug into the cochlea, thereby maintaining a constant fluid volume within the cochlea, even as drug concentration increases [109]. This approach safeguards the hair cells from damage caused by fluctuations in fluid volume and pressure

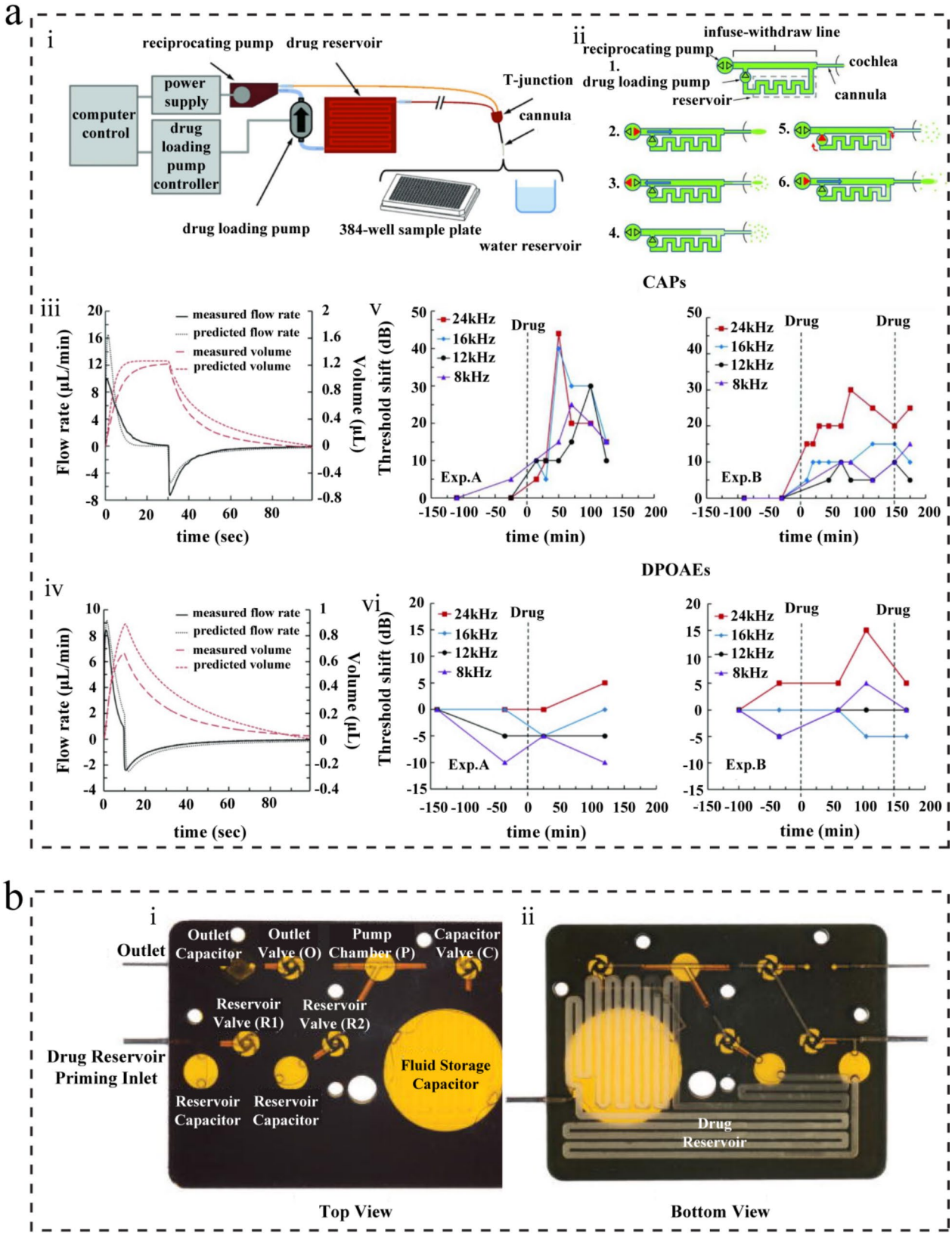


Fig. 7 (See legend on next page.)

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Fig. 7 Reciprocating microfluidic drug delivery systems for the administration of pharmaceuticals to the inner ear. (**a**i-vi) i: Controlled-dose reciprocating microfluidic system (including reciprocating pump, reservoir, and drug-carrying pump); ii: Schematic of the sequence of operation of the reciprocating microfluidic system; iii-iv: Output flow rates and volumes of the reciprocating microfluidic system under different conditions; v-vi: Threshold variations of the CAP and the DPOAE at eigenfrequencies from 8 to 24 kHz; © *The Royal Society of Chemistry 2014*; (**b**i-ii) i -ii: Bright field photographs of the top and bottom of the reciprocating microfluidic system; © *The Royal Society of Chemistry 2016*

within the cochlear [21]. The reciprocating microfluidic device developed by Kim S enables the adjustment of flow rates by varying the applied voltages and durations (Fig. 7aiii-iv). The operational characteristics of the microfluidic system were evaluated through animal experiments, wherein a cannula loaded with 6,7-dinitroquinoxaline-2,3-dione (DNQX) was surgically inserted into the cochlear structure of a guinea pig. Compound action potentials (CAPs) of the auditory nerve and distortion-product otoacoustic emissions (DPOAEs) were recorded across a spectrum of characteristic frequencies from 8 kHz to 24 kHz. The thresholds for DPOAEs remained stable throughout the monitoring period, while the thresholds for CAP increased over approximately 60 min before either returning to pre-DNQX levels or stabilizing (Fig. 7av-vi). The results indicate that reciprocating microfluidic systems are capable of efficiently administering pharmacological agents to the inner ear, resulting in detectable alterations in auditory function. Furthermore, these microfluidic devices can administer a variety of drugs to the cochlea, including salicylic acid [107] and DNQX [102, 108], all of which have demonstrated therapeutic benefit.

In addition to providing precise control over the volume and flow rate of delivered drug, microfluidic devices intended for inner ear delivery must be implantable and capable of delivering multiple drugs in a timed manner [110]. Tandon [108] et al. designed a reciprocating micropump for the automated delivery of inner ear medications. The pump generates a three-dimensional (3D) microfluidic structure by integrating multiple microfluidic primitives (Fig. 7bi-ii) and is equipped with a miniature electromagnetic brake to regulate the valve. The system incorporates an integrated drug reservoir, regulated by a valve, which enables controlled drug delivery as well as reciprocal drug delivery for clinical applications. Owing to the highly regulated nature of the system, the application of this method in cochleostomy facilitates the programmed administration of a sequence of pharmacological agents in a timed manner, thereby enhancing dosage precision, minimizing systemic drug exposure, and improving the potential for hair cell regeneration therapy. Consequently, the reciprocating microfluidic device exhibits wide applicability in treatments for hearing loss that necessitate precise control over localized drug dosage.

Biomaterial-based drug delivery systems are a growing field in the clinical trials. Cochlear implants are already in clinical use, and the results of several clinical trials have shown that cochlear implants are an effective method of enhancing hearing and speech perception in patients with hearing loss [111, 112]. However, cochlear coatings based on biomaterials are not currently in clinical use. In addition to this, the application of delivery systems such as microneedles, hydrogels, and NPs for the treatment of inner ear disorders also lacks experimentation in the clinical setting. But some studies have reported that NPs have brought new breakthroughs in clinical cancer treatment, and their precise targeting reduces adverse effects and improves the prognosis of patients [113]. In addition, gene therapy is now in clinical phase III. Thus, these studies and cases show that biomaterial-based drug delivery systems have great potential for the treatment of inner ear diseases.

Conclusion

Hearing loss resulting from various inner ear disorders represents a significant global concern, highlighting the urgent need for effective treatments. Traditional systemic drug delivery approaches, encompassing oral, intramuscular, and intravenous injections, are limited by the presence of the blood-labyrinth barrier and the intricate structure of the cochlea. Achieving precise targeting of the inner ear is essential for the management of hearing loss associated with these disorders. In response to the limitations of systemic drug delivery, researchers have developed biomaterial-based local drug delivery methods to address hearing loss. This review discusses the clinical challenges in treating inner ear disorders and explores the application of biomaterials in topical drug delivery for these conditions.

In the past decade, inner ear therapies based utilizing drug delivery systems have experienced undergone significant advancements and extensive development. The growing demand for effective drug delivery to the inner ear has driven the creation of various delivery mechanisms, including microneedles, hydrogels, and nanoparticle systems, as well as implantable devices like micro-osmotic pumps, cochlear implants, and reciprocating microfluidic systems. Among the intratympanic drug delivery routes, round-window microcatheters, micro-osmotic pumps, and microneedle delivery systems allow continuous drug delivery across the blood-cochlear barrier through minimally invasive procedures. Adhesive hydrogel microspheres with micron-sized particle can adhere to the RWM for extended durations, facilitating

a higher concentration of therapeutic drugs to enter and remain in the inner ear. Nanoparticles designed for slow release and high loading capacity can deliver drugs such as neurotrophic factors to the cochlea, offering protection to OHC from noise-related damage. The cochlear implant-based delivery system is a method of direct intracochlear drug delivery, in which a coating of biomaterial electrodes with electrical stimulation activity capabilities administers neurotrophic factors into the cochlea, thereby preserving the amount of surviving SGN. Various microfluidic devices for intracochlear pharmacotherapy has exhibited the proficiency to enable chronic perfusion of cochlear drugs by integrating a micropump with an electronic control system. Biomaterial-derived drug delivery platforms show considerable potential in meeting the therapeutic requirements of individuals afflicted with a series of inner ear disorders. The emergence of these delivery methods in mid- to late-stage clinical trials indicates that they are poised to become mainstream options for future clinical treatment of inner ear disorders.

Currently, these systems are not frequently employed in the clinic practice and continue to face significant challenges. For example, the clinical application of drug delivery systems is subject to a rigorous clinical testing and approval process to ensure their safety and efficacy. As well, the current lack of clarity in regulatory regulations, lack of harmonization in international standards, and difficulty in determining the precision and degree of invasiveness of the drug delivery process also limit the application of drug delivery systems. Drug delivery procedures need to be further optimized to achieve minimal invasiveness and enhanced precision, thereby reducing potential damage to the cochlea associated with these interventions. Additionally, the pharmacokinetics and drug release characteristics of delivery system within animal models of hearing loss should be investigated, with a specific focus on tissue permeability and elimination dynamics, in order to advance the design of precisely controlled drug delivery platforms. Furthermore, microfluidic delivery systems ought to be engineered for enhanced precision in drug administration, operating at minimal flow velocities and reduced electrical potential, thus ensuring controlled fluid pathways. Cochlear implants possess significant potential for progress, particularly through the enhancement of electrode technology and the integration of cochlear implants. Besides, the synthesis of innovative biomaterials in conjunction with drug delivery systems for the management of inner ear disorders holds substantial importance. The synergistic application of gene and cellular therapy with biomaterial-based drug delivery platforms has confirmed efficacy, and the convergence of comprehensive therapeutic strategies is anticipated to open novel pathways for the future management of inner ear disorders. Additionally, the establishment of reliable in vitro organoid models and RWM models will contribute to the assessment of safety, efficacy, and drug penetration of various delivery systems. In conclusion, while biomaterial-based drug delivery systems encounter challenges in the management of inner ear disorders, it is anticipated that they will ultimately lead to clinical applications and significantly enhance the realm of cochlear drug delivery.

Author contributions

R.C., T.L.,H.W., Y.H., H.C. conceptualized the review. The methodology was developed, and the investigations were carried out by H.C. and B.Z. The original draft was written, and all sections were prepared by H.C., D.X. P.J., Y.W. illustrated all figures. M.L., X.G. and H.C. prepared and validated all tables. All co-authors were reviewing and editing the study. R.C., T.L., H.W., Y.H., B.Z.and H.C. acquired the funds.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participants

Not applicable.

Consent for publication

All authors have given consent for publication.

Competing interests

The authors declare no competing interests.

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