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REVIEW

Intratympanic drug delivery systems to treat inner ear impairments

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Abstract

Background Sensorineural hearing loss (SNHL) is a disorder that significantly affects human quality of life. Current treatment for SNHL is still limited to hearing aids and cochlear implants. A better understanding of the etiological mechanisms of SNHL will facilitate the elucidation of the oto-protective efficacy of various novel therapeutic molecules. Intratympanic (IT) administration appears to be an attractive route for the delivery of these agents into the inner ear due to its advantages over systemic and cochlear administration. However, this administration route is limited by Eustachian tube clearance, transport capacity through the round window membrane (RWM), and the intrinsic structure of the cochlea, leading to the necessity of developing advanced drug delivery systems to improve the efficacy of IT administration.

Area covered In this review, we summarize and discuss various drug delivery systems applied to IT administration, including conventional formulations and combinations of hydrogels and nanoparticles such as polymers, lipids, inorganic, and hybrid nanoparticles.

Expert opinion A variety of innovative injectable systems have been prepared, and they have been demonstrated in several research models to have a significantly better ability to deliver drugs to the inner ear than that of conventional dosage forms. Hydrogels take advantage of prolonged residence time in the middle ear, while nanoparticles can enhance drug stability and cellular uptake, and allow drug targeting to specific cells. The combination of these two strategies is a promising area for future investigation.

Keywords Intratympanic administration · Hydrogels · Nanoparticles · Combination between hydrogels · Nanoparticles

Introduction

Among the five senses, hearing is one of the most important in the interaction between humans and the external environment. Humans sense surrounding airborne sounds based on a complex anatomical structure called the ear. The ear provides the process for converting sound waves into electrical signals that the brain can process. The organ responsible for hearing is the cochlea, which is embedded in the innermost part of the ear. The well-maintained structural integrity and cellular organization of the cochlea play a pivotal role in converting mechanical stimuli into electrical signals (Ekdale 2016; Fettiplace 2017).

SNHL is considered a global problem and a significant handicap that greatly affects quality of life. In 1985, the worldwide disease prevalence of SNHL was first reported by the World Health Organization (WHO) with approximately 1% of the world's population (42 million people) estimated to have moderate to severe hearing disorders or impaired hearing (Davis and Hoffman 2019). From 1990 to 2019, the number of people suffering from moderate to complete hearing loss increased from 225.3 million to 403.3 million (Haile et al. 2021). According to WHO statistics, the most recent estimate shows that more than 1.5 billion people (nearly 20% of the world's population) live with hearing loss, of whom 430 million have hearing loss (over 5% of the world's population) (WHO 2021a). This estimate predicts that nearly 2.5 billion people (1 in 4 people) will live with hearing loss, and at least 700 million people (1 in 10 people) worldwide will develop hearing loss by 2050 (WHO 2021b). Hearing impairment can negatively affect an individual's social and emotional development as well as communication and education. People with hearing impairments tend to avoid social situations and experience with increased rates of depression,

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anxiety, and feelings of inadequacy because they have difficulty acquiring surrounding information.

With the increasing prevalence of hearing loss worldwide, it is necessary to explore and develop treatments for hearing loss due to the negative impact of this condition on quality of life. SNHL can result from several diseases and external stimuli that damage the sensorineural structures of the cochlea (Cohen et al. 2014; Yang and Chung 2016; Vona and Haaf 2016; Cardin 2016; Rizk, et al. 2020; Gacek 2021). The treatment of such inner ear disorders has been a challenge for physicians, as there are few drugs on the market for cochlear indications and it is difficult to achieve effective drug concentrations in the cochlea (Nyberg et al. 2019). In the last two decades, IT administration, a safe procedure that can overcome the pharmacokinetic limitations of systemic administration for the treatment of inner ear diseases, has attracted considerable attention as a potential method for drug delivery to the cochlea. Many conventional dosage forms of medication on the market (e.g., dexamethasone solution 4 mg/mL or 5 mg/mL; prednisolone solution 0.25 mg/mL; methylprednisolone solution 62.5 mg/mL; triamcinolone acetonide suspension 10 mg/mL or 40 mg/mL) are currently used in clinical practice by IT injection instead of systemic application (Lechner et al. 2019; Roßberg et al. 2020). However, although IT administration helps drugs reach the inner ear at a greater level than that achieved through the systemic route, it still has several limitations that make it very difficult to deliver drugs to the cochleae by conventional formulations (including short residence time in the middle ear and low passage of drug through the RWM) (Szeto et al. 2020). These limitations indicate the need for the development of new strategies to improve the efficiency of IT drug delivery systems. A variety of innovative systems have been researched and evaluated in in vitro studies, in vivo studies and clinical trials (Pyykkö et al. 2011; Pararas et al. 2012; El Kechai et al. 2015; Rathnam et al. 2019; Freitas et al. 2021).

The purpose of this review is to provide an overview of drug delivery systems for IT administration. First, we describe the most critical features of the anatomy and physiology of the inner ear that should be considered during the design of drug delivery systems for IT administration. Next, promising systems for future clinical applications and current obstacles to overcome for efficient inner ear treatment are discussed.

Structure of the inner ear and auditory transduction mechanism

Anatomically, the ear is divided into three parts: the external ear, the middle ear, and the inner ear (Fig. 1A). The external ear consists of the pinna, the auditory canal, and the tympanic membrane (eardrum). The middle ear consists of the

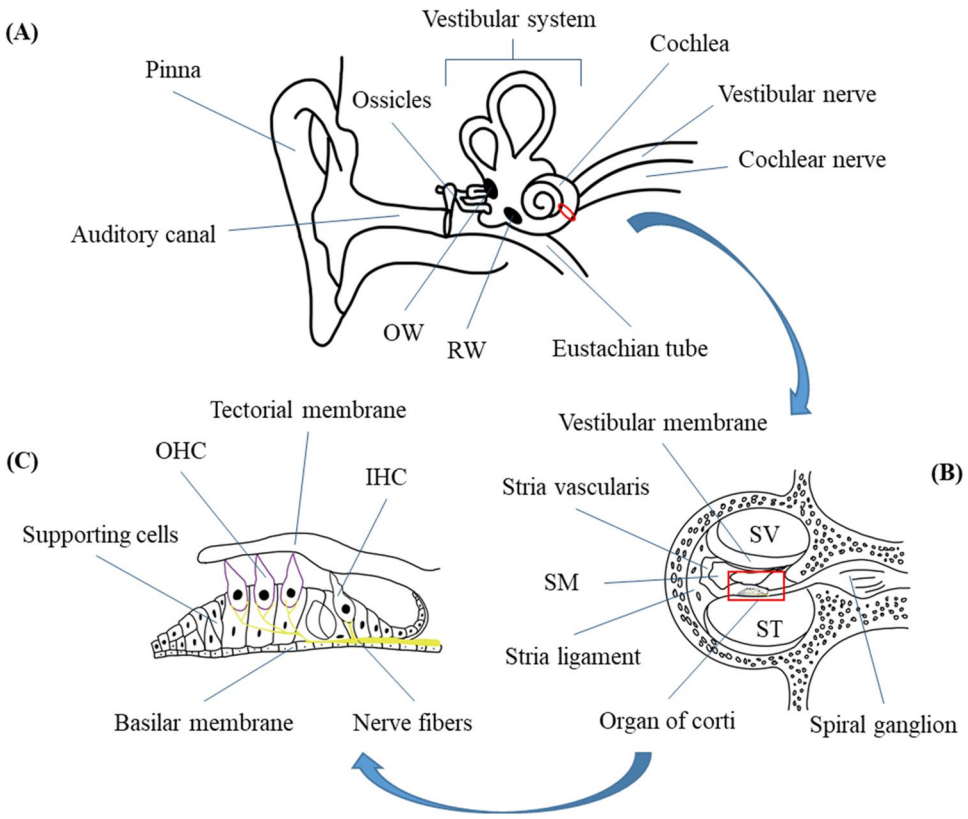

Fig. 1 The anatomic structure of ear and organ of corti. **A** The anatomic structure of mammalian ear composed of external ear, middle ear and inner ear, **B** the cross section of cochlea including 3 compartments [scala vestibuli (SV), scala media (SM) and scala tympani (ST)], and C the anatomic of organ of corti (OC) indicates the relation of cochlear hair cells, tectorial membrane, nerve fibers

tympanic cavity including three auditory ossicles (the malleus, the incus, and the stapes), the round window (RW), the oval window (OW), and the Eustachian tube. The external and middle ears are responsible for guiding and conducting sound waves to the inner ear. The inner ear is an anatomically isolated structure comprising the vestibular system responsible for balance and the spiral cochlea responsible for auditory perception. The cochlea consists of three constitutively fluid-filled cavities. The middle cavity filled with endolymph is called the scala media (SM) and is separated from the superior cavity (scala vestibuli—SV) and inferior cavity (scala tympani – ST) by the vestibular membrane and basilar membrane, respectively. The SV communicates with the middle ear via an OW, whereas the ST communicates with the middle ear via an RW; and both of these cavities are filled with perilymph. The scala media contains the organ of Corti (OC), an essential organ considered to be an auditory receptor that converts sound vibrations into nerve signals (Fig. 1B). The OC is composed of sensory hair cells (inner hair cells (IHC), which are the actual sensory cells, and outer hair cells (OHC), which are cochlear signal amplifiers), supporting cells, basilar membrane, tectorial membrane as well as nerve fibers connecting the organ to the nearby spiral ganglion (SG) (Fig. 1C) (Ekdale 2016). Each auditory hair cell has the potential to detect a distinctive range of sound frequencies varying tonotopically along the cochlear axis. In addition, the scala media includes another vital structure called the stria vascularis that is responsible for producing and maintaining the ionic composition of the endolymph. For sounds to be detected, sound waves must first travel across the external ear canal and middle ear and through the inner ear fluids to stimulate the mechanosensory hair cells housed in the OC to release the neurotransmitters, which are then transferred to the spiral ganglion neurons (SGNs) and further propagated to the auditory cortex of the brainstem, where they are processed to cause auditory sensation (Fettiplace 2017).

Cochlear diseases, molecular mechanism, and therapeutic treatment

Any damage to sensory cells or auditory nerves can cause SNHL, which is the most frequent inner ear impairment in humans. This sensory deficit can originate from external stimuli (such as excessive noise (Yang and Chung 2016), infections (Cohen et al. 2014), and ototoxic drugs (Rizk, et al. 2020)) or intrinsic causes such as genetic mutations (Vona and Haaf 2016), aging (Cardin 2016) and Meniere's disease (Gacek 2021). Overexposure to ototoxic compounds (for example, aminoglycoside antibiotics (gentamicin, streptomycin, etc.), chemotherapy agents (cisplatin, etc.), and acoustic injury as well as aging affect the distinct cellular signaling pathways to activate apoptosis leading to the degeneration of hair cells and SGNs. Moreover, both infections and Meniere's disease can cause endolymphatic hydrops, inducing SNHL.

A more comprehensive understanding of the molecular mechanisms related to the degeneration and regeneration of sensory cells and the auditory nerve is of paramount importance in identifying the therapeutic candidates to prevent and treat inner ear diseases (Fig. 2). Most causes of SNHL induce cell death in response to the overproduction of reactive oxygen species (ROS) in both hair cells and SGNs. The high level of ROS activates the MAPK-JNK pathway, triggering the production of pro-apoptotic mediators and pro-inflammatory cytokines, leading to apoptosis or necroptosis (Kurabi et al. 2017). Antioxidants and apoptosis inhibitors as well as anti-inflammatory agents have been investigated to improve the defense capacity of hair cells and SGNs against damage to hinder cell death. On the other hand, the excessive generation of ROS mediates the activation of AMPK to inhibit mTOR, the central regulator of cell growth and cell proliferation, which plays a crucial role not only in cell survival but also in cell regeneration (Zhao et al. 2020; Cortada et al. 2021). Therefore, the stimulation of cell survival which can be achieved by using growth factors is another strategy to prevent hair cells and spiral ganglion nerves from damaging elements. A further approach is the application of molecular candidates (such as ATOH1 and neutrophins) or stem cells for the enhancement of cell regeneration to rescue injured hair cells and SGNs. In addition, gene therapy is a prospective means for treating hearing loss related to the functional deficits caused by genetic mutations (Table 1).

Intratympanic administration

There are two main approaches to the treatment of inner ear disorders: systemic drug delivery and local drug delivery. The presence of the blood labyrinth barrier (BLB), which inhibits the exchange of blood and inner ear fluids, is a major factor in the difficulty delivering drugs into the cochlea with sufficient concentration via systemic administration (Nyberg et al. 2019). The necessity of a more effective delivery route that can maximize the drug concentration in the inner ear and minimize the undesired side effects caused by systemic drug delivery has increased interest in local drug deliveries (including IT and intracochlear administration (Salt and Plontke 2009) from many researchers. Intracochlear drug delivery is rarely applied in clinical practice, as it requires surgical access to the cochlea for the sole purpose of local drug delivery. Therefore, IT administration, which is minimally invasive, opens new horizons for drug delivery to the inner ear for the treatment of SNHL.

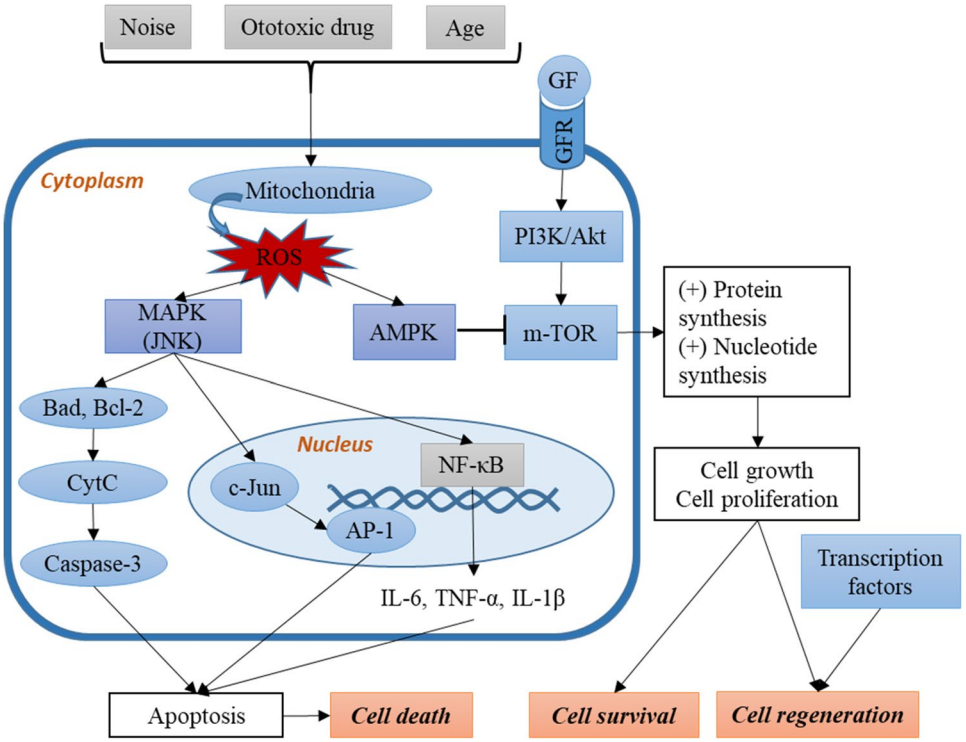

Fig. 2 Cellular mechanism of hearing loss. AMPK, AMP-activated kinase; AP-1, activator-protein 1; CytC, cytochrome c; GF, growth factor; GFR, growth factor receptor; JNK, a-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K, phosphoinositide 3-kinase; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-alpha; m-TOR, mammalian target of rapamycin

In IT administration, the drug is transported directly into the middle ear cavity to diffuse the drug through the RWM into the cochlea. The discovery and development of IT administration over time is presented in Fig. 3. In 1956, this route was introduced by Schuknecht to treat Meniere's disease with gentamicin (Schuknecht 1956). However, it was not until 1996 that IT injections were used in patients with sudden hearing loss (Silverstein et al. 1996), and this drug delivery route has received much attention in the treatment of various inner ear diseases since then. Over the past two decades, much evidence regarding the efficacy of this approach has been reported for the clinical application of steroids, gentamicin, and several other therapeutic candidates in animal studies. More details are described in the section "Drug delivery system for IT administration".

Pharmacokinetics and challenges in intratympanic drug delivery

Similar to the pharmacokinetic processes that occur in the human body after systemic administration, the pharmacokinetics of drugs after IT delivery to the inner ear also include liberation, absorption, distribution, metabolism, and elimination (Fig. 4). Liberation refers to the release of a drug from an administered dosage form; absorption is the entry of drug into the internal fluid from the administration site through an RWM and an OW; distribution is the process by which drugs spread within the inner ear fluid (perilymph and endolymph) and are delivered to cochlear tissues; metabolism is a chemical alteration of drugs catalyzed by the enzymes in the inner ear fluid; and elimination includes removal of the drug and its metabolites from the inner ear and clearance through the Eustachian tube from the middle ear cavity (Salt and Plontke 2009, 2018). The bioavailability of a drug is determined primarily by the permeability of the drug through the RWM, the residence time of the drug in the middle ear, and the basal to peak concentration gradient of the drug within the cochlea, which are the leading challenges for drug delivery into the cochlea via the IT route.

Round window membrane

The RWM that allows drugs in the middle ear to penetrate into the perilymph can be considered the main pathway for drug delivery to the cochlea; however, it is also the fundamental obstacle to this administration route. The RWM, which consists of 3 layers, acts as a semipermeable membrane that allows the passage of low-molecular-weight molecules (such as antibiotics, local anesthetics, and corticosteroids). The permeability of the RWM is affected not only by the characteristics of drugs (lipophilicity and charges) but also by their properties (morphologic strength, thickness, and pathological condition) (Goycoolea and Lundman 1997).

Table 1 Therapeutic candidates for treatment of inner ear disorders

Category	Representatives	Mechanism of action	Route of use	References
Antioxidants	N-acetyl cysteine	Decrease the ROS generation	Local & systemic	Choe et al. (2004) and Somdaş et al. (2020)
	D-methionine			Campbell et al. (2011) and Wang et al. (2019)
	Edavarone			Asplund et al. (2009)
	Melatonin			Gusmão de Araujo et al. (2014) and De Araujo et al. (2019)
	Salvianolic acid B			Guo et al. (2010) and Zheng et al. (2020)
	Panax notoginsenoside			Fujita et al. (2007) and Mungan Durankaya et al. (2021)
	Rosmarinic acid			Fetoni et al. (2018)
	Resveratrol			Erdem et al. (2012) and Şimşek et al. (2013)
	Sodium thiosulfate			Dickey et al. (2005)
Steroids	Dexamethasone	Reduce the level of cytokines	Local & systemic	Alles et al. (2006) and Barreto et al. (2016)
	Methylprednisolone			Özel et al. (2016)
	Triamcinolone acetonide			Dahm et al. (2019)
IL-6 inhibitor	Anti-IL-6-receptor antibody		Local	Wakabayashi et al. (2010)
TNFα inhibitor	Etanercept		Local	Wang et al. (2003)
Apoptosis inhibitors	d-JNKI-1 (AM-111)	JNK inhibitor	Local	Coleman et al. (2007), Eshraghi et al. (2006) and Omotehara et al. (2011)
	PFT-α	p53 inhibitors		Benkafadar et al. (2017)
Aminoglycoside antibiotic	Gentamincin	Treatment of Meniere's disease induced hearing loss	Local & systemic	Postema et al. (2008)
Growth factors	Insulin-like growth factor 1 (IGF-1)	Stimulate mTOR induce regeneration of hair cells	Local	Yamahara et al. (2015)
	Hepatocyte growth factor (HGF)			Kikkawa et al. (2009)
Neural stem cells		Hair cells regeneration	Local	Bas et al. (2014) and Barboza Jr. et al. (2016)
Neurotrophic factors	Brain-derived neurotrophic factor (BDNF)	Hair cells and SGNs regeneration	Local	Fritzsch et al. (2006)
	Neurotrophin 3 (NT3)			Suzuki et al. (2016)
Genes	DNA Plasmids	Induce hair cell regeneration to overcome genetic dysfunction	Local	Chien et al. (2016)
	siRNA			Du et al. (2013b)

Eustachian tube clearance

The Eustachian tube, which connects the middle ear cavity with the nasopharynx to equalize the middle ear pressure (Smith et al. 2016), also removes drugs administered to the middle ear. This drug loss reduces the residence time of the drugs in the middle ear and consequently decreases the amount of drug that diffuses through the RWM into the inner ear (Plontke et al. 2008b).

Base-to-apex concentration gradient in the cochlea

The base-to-apex concentration gradient occurs due to diffusion of the drug in the spiral structure of the cochlea after IT administration. This phenomenon poses a challenge to the treatment of disorders in the apex due to the difficulty of drug transport into the apical turn as a therapeutic concentration (Plontke et al. 2007, 2008a).

Strategies for overcoming the challenges of intratympanic administration

To overcome the above hurdles and effectively transport drugs to the treatment site, two parameters affecting drug concentration in the perilymph after IT injection should be considered: (1) residence time in the middle ear and (2) passage of drug through the RWM. Various strategies for the development of devices and drug delivery systems have been studied to increase the residence time of a drug in the middle ear cavity and to enhance drug delivery through the

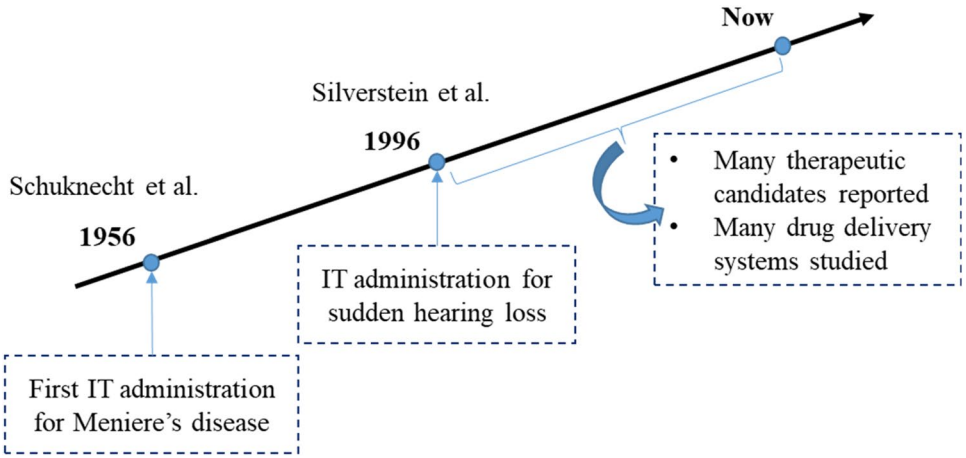

Fig. 3 The diagram presents the discovery and development of IT administration route over time

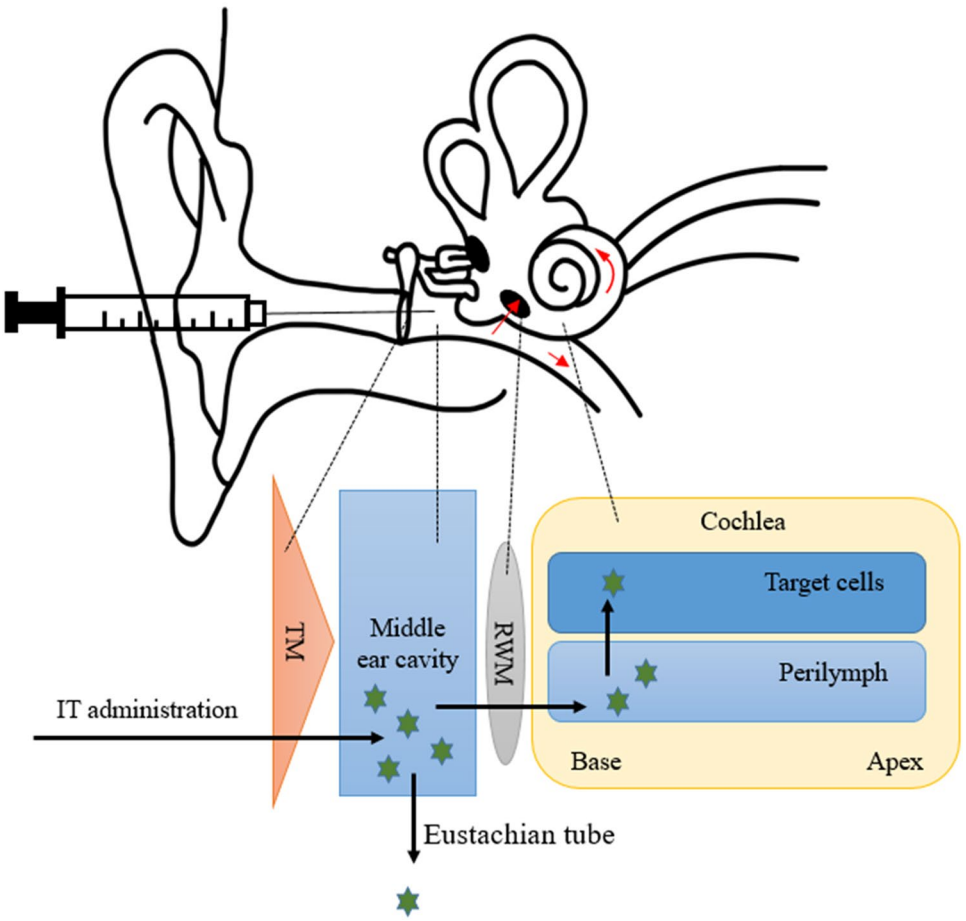

Fig. 4 Pharmacokinetic processes from application position to therapeutic targets including absorption, distribution and clearance of drug after IT administration by direct injection into middle ear cavity. Red arrows indicate the path of the drug into the ear from the middle ear to the cochlea and Eustachian tube. TM, tympanic membrane; RWM, round window membrane

RWM. The former goal can be achieved using either several devices (in particular, microwicks, microcatheters, gelfoam, and Seprapack) (Pararas et al. 2012) or gelling systems (Rathnam et al. 2019). To achieve the latter, there are two main strategies: increasing the permeability of the three-layer barrier by a microneedle or penetrating facilitators and improving cellular uptake based on nanoparticle systems (Pyykkö et al. 2011). Although drug delivery devices are not mentioned in this review, we focus on the advanced technologies applied in preparation for intratympanically administered drug delivery systems.

Drug delivery system for intratympanic administration

Conventional drug delivery systems are still being used to treat inner ear diseases through the IT route, but the development of innovative drug delivery systems that overcome the limitations of these conventional dosage forms has been an attractive field for many researchers. A drug delivery system suitable for this route is a system that provides a prolonged residence time and/or sustained release to achieve a therapeutic concentration of drug in the inner ear with minimal invasiveness. In addition, it should be easily injected, biodegradable, and biocompatible. Various systems including hydrogels, nanoparticles, and combinations thereof, have been designed in recent years.

Conventional delivery systems

Conventional delivery systems, including solutions and suspensions, are the first dosage forms applied intratympanically to deliver streptomycin and dexamethasone into the middle ear cavity for the treatment of Meniere's disease and sudden hearing loss, respectively (Schuknecht 1956; Silverstein et al. 1996). Although these conventional formulations have better therapeutic efficacy than systemic administration, frequent repeated injections (usually 2–5 times per week (Alles et al. 2006)) cause the typical undesired side effects of local injections such as pain, brief caloric vertigo, otitis media or lingering tympanic membrane perforation (Rauch 2011). These limitations are due to the difficulty of reaching therapeutic concentrations in the inner ear fluid due to the rapid drainage of intratympanically injected fluids via the Eustachian tube and the low transportability of the drug through the RWM. In this context, Eustachian tube clearance is the most important route that significantly shortens drug residence time at the absorption site, as demonstrated in the research of Plontke et al. on the IT use of methylprednisolone in humans (Plontke et al. 2008b). Another limitation of treatment with conventional dosage forms is the morphological change of the RWM after some therapeutic agents (e.g., hydrocortisone) come into direct contact with middle ear structures (Spandow et al. 1990; Nordang et al. 2003). Despite these drawbacks, transtympanic injection of conventional solutions or suspensions is widely used to manage common inner ear diseases. Aqueous solutions or suspensions of some therapeutic molecules, such as gentamicin sulfate (Liu et al. 2015a), dexamethasone (Liu et al. 2015a), methylprednisolone (Özel et al. 2016), N-acetyl cysteine (Somdaş et al. 2020), triamcinolone acetonide (Salt et al. 2019), and ciprofloxacin (Mair et al. 2016), have been investigated for the treatment of inner ear impairments through IT application.

Hydrogels

To prevent unintentional leakage via the Eustachian tube described above, viscous hydrogels seem to be a possible strategy to prevent rapid flow through the Eustachian tube, thereby increasing the residence time of the drug in the middle ear cavity and consequently improving the biodistribution of the drug in the cochlea. However, the delivery of formulations to the middle ear is conducted using a long and fine needle (smaller in diameter than G22) (El Kechai et al. 2015). Therefore, the residence time and injectability are two key parameters to consider when developing a hydrogel delivery system for IT administration. Injectability is the ability of a formulation to be injected into the tympanic cavity through a needle with an acceptable force, and residence time is the period of time at the application site calculated from the time the formulation is injected into the middle ear until it is washed out from the middle ear. In general, either injectability or residence time is affected by the viscosity of the hydrogel. The higher the viscosity, the longer the residence time and the harder it is to pass through the needle.

Conventional hydrogels

Several conventional hydrogel-based delivery systems investigated for IT drug delivery have been formulated from a variety of natural polymers including collagen, gelatin, chitosan, and hyaluronic acid (shown in Table 2). Collagen and gelatin are biodegradable polymers that can increase the viscosity of liquid dosage forms. However, since collagen or gelatin alone has limitations in thermal and mechanical stability and aqueous solubility, it cannot be accommodated in the site of administration for a long period of time. For this reason, glutaraldehyde is used as a crosslinking agent for collagen and gelatin, which reduces the degradation rate of collagen and gelatin, enabling long-term applications (Graziola et al. 2016; Peng et al. 2017). Hydrogels generated by glutaraldehyde crosslinking of gelatin or porcine type I collagen have proven effective for the delivery of some proteins, including brain-derived neurotrophic factor (BDNF) (Endo et al. 2005), insulin-like growth factor 1 (IGF-1) (Iwai et al. 2006; Lee et al. 2007; Fujiwara et al. 2008), and hepatocyte growth factor (HGF) (Inaoka et al. 2009). Chitosan is a nontoxic biodegradable cationic polymer that is prepared by alkaline N-deacetylation of chitin obtained from the exoskeleton of crustaceans (Sreenivas and Pai 2008). The positive charge of chitosan prolongs the residence time in the middle ear due to its electrostatic interaction with the negatively charged mucosal surface. In a study by Saber and coworkers, three types of chitosan were investigated to deliver neomycin to the inner ear. In the middle ear, low/medium-molecular-weight chitosan (Ch1 and Ch2) with lower solubility could be observed 7 days after application,

Table 2 Conventional hydrogels for IT administration

Polymers	Drug	Species	Main outcomes	References
Collagen	BDNF	Pigment guinea pigs	- BDNF concentration on day 3rd and 7th post-application of BDNF solution and BDNF hydrogel was (16.39 ± 5.83; 8.26 ± 2.23 pg/mL) and (675.00 ± 230.22; 884.77 ± 100.35 pg/mL), respectively - BDNF-hydrogel significantly reduced the threshold elevation and enhanced survival of SGNs	Endo et al. (2005)
	IGF-1	Sprague–Dawley rats	- IGF-1 hydrogel reduced ABR thresholds elevation and OHC loss after 7 and 30 days of administration	Iwai et al. (2006)
Gelatin	IGF-1	Hartley guinea pigs	- Sustained delivery of IGF-1 - Safety with no systemic and local side effects - The protective effect of IGF-1 was dose-dependent	Lee et al. (2007)
		Adult male Mongolian gerbils	- IGF-1-gelatin hydrogels reduce ABR threshold elevation at frequency of 8 kHz and increase hair cells survival on day 7 after ischemia	Fujiwara et al. (2008)
	HGF	Hartley guinea pigs	- HGF-gelatin hydrogel significantly reduced the ABR threshold shift and OHC loss caused by noise exposure after 21 days of administration	Inaoka et al. (2009)
Chitosan	Neomycin	Albino guinea pigs	- Comparability - Neomycin loaded in chitosan gel can pass through RWM and exert ototoxic effects on the inner ear	Saber et al. (2010)
Hyaluronic acid (HA)	Neomycin	Guinea pigs	- Safety with no inflammatory signs - Neomycin was slowly released from HA hydrogel and transported into inner ear leading to the loss of hair cells	Saber et al. (2009)
	Dexamethasone (Dex)	Hartley albino guinea pigs	- Up to 72 h, the bullae was still filled with gel, while no Dex solution was remained - Dex-HA gel exhibited significantly higher Dex concentration in perilymph compared to Dex solution	Borden et al. (2011)

while oligomeric chitosan (Ch3) with higher solubility was not observed at the same time. All formulations successfully delivered neomycin to the cochlear and chitosans have been demonstrated to be resistant to cochlea tissues (Saber et al. 2010). Hyaluronic acid is an anionic polymer present in the extracellular matrix of many tissues in the body and has mucoadhesive properties, biodegradability, and biocompatibility. The effect of drug delivery into the inner ear by the hyaluronic acid hydrogel was evidenced by the loss of hair cells after placing the neomycin-loaded hydrogel into the RWM, while there was no significant difference between the results obtained with neomycin solution (Saber et al. 2009). Hyaluronic acid can form highly viscous aqueous hydrogels that can extend residence time up to 72 h, as demonstrated in the study by Borden and colleagues (Borden et al. 2011). However, the high viscosity of the hyaluronic acid hydrogel does not affect the syringeability due to the shear-thinning and self-healing property of this polymeric system (Kechai et al. 2016). In addition to the achievement of higher drug concentrations in the perilymph based on prolonged contact with RWM, hyaluronic acid has been reported to facilitate drug diffusion to the inner ear based on its osmotic effect on the perilymph (Bagger-Sjöbäck et al. 1993) and RWM permeability modulating potential (Selivanova et al. 2003). Most conventional hydrogels mentioned above are in liquid form both before and after injection. It is difficult to deliver hydrogels with very high viscosity to the middle ear via the RWM with the aim of a very long residence time. To overcome these limitations, an in-situ gelling system was investigated.

In situ hydrogels

An in-situ hydrogel is a system that remains in a liquid state before entering the body for easy injection and then undergoes sol–gel transition process to form a semisolid gel at the site of administration after a stimulus or a period of time. The unique viscosity-adjustable property makes in situ hydrogels easy to handle compared to conventional hydrogels. The in-situ gelling hydrogel systems studied for IT administration include thermosensitive hydrogels and time-dependent hydrogels (shown in Table 3).

In-situ thermosensitive hydrogels that retain fluidity at room temperature and gel at body temperature are very

Table 3 In situ hydrogels for IT administration

Polymers	Drug	Species	Main outcomes	References
Poloxamer 407	Dexamethasone (Dex)	Guinea pigs	- Residence time and half-life of Dex P407 hydrogel were 25–35 times higher than the ones of Dex solution leading to the higher AUC value of gel - Well tolerant with no histopathological alters despite of conductive hearing loss	Wang et al. (2009)
		Guinea pigs	- Residence time of Dex hydrogel was up to 10 days while that of Dex solution was just more than 1 day	Wang et al. (2011)
		Guinea pigs and sheep	- Increasing OTO-104 concentration caused higher drug levels and a more prolonged residence time in perilymph. Dex could be maintained more than 3 months in guinea pigs and more than 1 month in sheep within the therapeutic range - Tolerability with no histologic alters as well as no acute local and systemic side effects	Piu et al. (2011)
	Methylprednisolone (MPS)	Guinea pigs	- The residence time of MPS P407 hydrogel and MPS solution was 10 days and 3 days, respectively	Wang et al. (2011)
	Triamcinolone acetonide (TA)	In vitro	- The optimized hydrogel was composed of 20% poloxamer 407 and 30% TA	Engleder et al. (2014)
		Pigmented guinea pigs	- Significantly high initial drug level in perilymph (107.5 ± 51.7 μg/mL) at day 1 after application - Safety with minimal drug level in CSF and plasma, no histological or changes or ABR threshold shifts	Honeder et al. (2014)
	N-acetyl cysteine (NAC)	Guinea pigs	- Initial NAC level, AUC0-24 h and drug level after 24 h of NAC hydrogel are all 3–6 times greater than those of NAC solution	Gausterer et al. (2020)
Chitosan glycerophosphate (CGP)	Dexamethasone (Dex)	C57BL/6 mice	- CGP hydrogel provided sustained release profile of Dex over 4 days with a peak of 3.2 ng/μL at 24 h - Safe despite of temporal hearing loss	Paulson et al. (2008)
	Gentamicin	C57BL/6 mice	- Gentamicin loading in CGP hydrogel was distributed in IHCs with a time-dependent and basal-to-apical manner	Luo and Xu (2012)
PLGA-PEG-PLGA	Cidofovir	In vitro	- The gelation temperature of PLGA-PEG-PLGA hydrogels ranged from 18 to 35℃ depending on polymer concentration - Formulation containing 10% PLGA-PEG-PLGA provided the longest sustained drug release profile	Liu et al. (2014)
	Cidofovir	In vitro Guinea pigs	- PLGA-PEG-PLGA hydrogels offered a sustained release profile that could be controlled by the present of additives - No harmful effects on the hearing function	Feng et al. (2014)
Silk-polyethylene glycol (PEG)	Dexamethasone (Dex)	Guinea pigs	- Circulation time was at least 10 days for Dex silk-PEG hydrogel and less than 12 h for Dex solution - Safety with minimal Dex concentration in CSF and plasma and no damages on inner ear structures and functions - Silk-PEG hydrogel retained in middle ear up to 21 days	Yu et al. (2016)
		HEI-OC1 cells Cochlear organ from mice pups Male guinea pigs C57BL/6 mice	- Non-cytotoxic - Dex silk-PEG hydrogel show better protective effect against cisplatin-induced toxicity in all experiments in comparison with Dex solution - Dex was maintained in perilymph at least 21 days after applying Dex hydrogel, but was not detected at 6 h following injection of Dex solution	Chen et al. (2019)

attractive for inner ear drug delivery via transtympanic injection. Such thermoreversible systems can be generated from synthetic copolymers such as poloxamer 407 (P407) and PLGA-PEG-PLGA. Both P407 and PLGA-PEG-PLGA copolymers are triblock copolymers composed of a hydrophobic central chain and two hydrophilic side chains. Because of these amphiphilic properties, these copolymers tend to form micelles in water with a hydrophobic core and a hydrophilic shell above the critical micelle concentration (CMC). Intermicellar crosslinking between different micelles at concentrations higher than the critical gel concentration (CGC) leads to the creation of a gel matrix. Heating reduces the CMC and CGC, causing gelation of the thermosensitive copolymer solution (Gong et al. 2012; Fakhari et al. 2017; Russo and Villa 2019). The hydrogels made of either P407 or PLGA-PEG-PLGA are biodegradable, biocompatible, stable, and suitable for controlled release. The concentration of P407 used in hydrogels is typically in the range of 16–20% (w/v). The obtained hydrogel has a gelation temperature of 37℃ (physiological temperature) or less. P407 hydrogel has been extensively investigated as a drug delivery system for the IT administration of several therapeutic agents, such as dexamethasone, methylprednisolone, triamcinolone, and N-acetyl cysteine (Wang et al. 2009, 2011; Piu et al. 2011; Honeder et al. 2014; Engleder et al. 2014; Gausterer et al. 2020). The PLGA-PEG-PLGA solution dissolves at temperatures of 2 to 15℃ and turns into a gel at body

temperature. The CGC of PLGA-PEG-PLGA solution can be controlled by changing the length of the PLGA or PEG block (Gong et al. 2012; Wang et al. 2017). The PLGA-PEG-PLGA system was reported to be effective in controlling the delivery of dexamethasone acetate, cidofovir, and levothyroxine (Gao et al. 2010; Feng et al. 2014; Liu et al. 2014; Kamali et al. 2020).

Chitosan glycerophosphate (CGP), a chitosan derivative, also has the ability to form a temperature-sensitive gelling matrix. However, unlike the abovementioned copolymers, the mechanism of gel formation in CGP solutions is driven by hydrophobic association of the chitosan molecules with increasing temperature. At low temperatures, the CGP system remains in a liquid state based on a hydrated protective layer of glycerophosphate around the chitosan chains created through weak hydrogen bonds. As the temperature increases, this layer breaks down, allowing the chitosan molecules to interact through stronger hydrophobic bonds and form hydrogels at body temperature. The gelation temperature and gelation rate of the CGP solution are affected by the deacetylation degree of chitosan, the concentration of chitosan, and the concentration of glycerophosphate (Gong et al. 2012; Liu et al. 2016; Rahmanian-Devin et al. 2021). Moreover, CGP hydrogels have a high affinity for mucosa due to their positively charged nature and have the potential to provide a sustained release delivery system due to their slow degradation over time by lysozyme available in the middle ear. Studies by Paulson et al. and Luo et al. demonstrated that the CGP hydrogel system can deliver dexamethasone and gentamicin to the cochlear fluid of guinea pigs with a steady release profile after IT injection (Paulson et al. 2008; Luo and Xu 2012).

In addition, a time-sensitive silk-polyethylene glycol (PEG) hydrogel that remains in the sol state for sufficient time for injection into the middle ear before the sol–gel transition, has also been investigated for the introduction of dexamethasone into the cochlea (Yu et al. 2016; Chen et al. 2019). Gelation occurs due to the structural transition of silk fibroin from the random coil-dominant structure of the silk solution to the β-sheet structure of the silk hydrogel when the silk solution is incorporated with a polymer (such as PEG). The gelation time depends on the concentration of the silk solution and the type and concentration of PEG (Wang et al. 2015).

In general, due to the advantages of improving residence time and providing sustained release in the RWM, a single IT injection of hydrogel resulted in higher drug levels in the inner ear fluid over an extended period of time that the injection of drug solution. This hydrogel has been proven to be safe and well tolerated. In most studies, only mild conductive transient hearing loss was observed due to interference of the viscous hydrogel with ossicular chain mobility, and no histological damage to the RWM and cochlea after IT administration was observed. However, drug permeability through the RWM is still highly dependent on the drug properties as they do not alter the physicochemical properties of the drug loaded into the gel system. Furthermore, hydrogels cannot stabilize drugs (especially biotherapeutic agents) from degradable reactions or provide targeted delivery. These limitations can be overcome by the application of nanotechnology.

Nanoparticles

Nanoparticle (NP)-based systems have been extensively explored for the IT drug delivery of various therapeutics for the treatment of inner ear disorders due to their potential to stabilize loaded materials, improve diffusion kinetics through RWM, and enhance cellular uptake and specific targeting. NPs encapsulate the drug into a structure, providing a barrier to protect the drug from degradative reactions and providing a controlled and sustained release profile. Likewise, due to the encapsulation of the drug into NPs, the drug properties are modulated by the NPs and the diffusion kinetics of the drug depend on the particle size and surface modification of the NPs. Their small size (typically in the range of tens to hundreds of nanometers in diameter) and surface modifications (including charged, hydrophobic, and tethered cell-penetrating peptides) have been shown to improve the transport of NPs across the row window barrier and increase the uptake and accumulation of drugs in certain cell types of the cochlea. In addition, NP labeling with ligands that interact with specific cellular receptors including tropomyocin receptor kinase B (TrkB) receptor (Bitsche et al. 2011), trisialoganglioside clostridial toxin (GT1b) receptors (Santi et al. 1994), and prestin (Zheng et al. 2000; Liberman et al. 2002), provides targeted delivery to specific cell types such as auditory hair cells and spiral ganglion cells. The advantages of NP-mediated drug delivery mentioned above reduce the dose required and cause unwanted side effects. Many types of NP-based systems for transtympanic administration that can be classified into four main groups: polymer-based, lipid-based, inorganic, and hybrid (Fig. 5).

Polymer-based nanoparticles

Polymer-based NPs are biocompatible, degradable, and maintainable systems prepared from natural and synthetic materials (including preformed polymers and monomers) by a variety of techniques (e.g., emulsification, precipitation, ionic gelation, and microfluidics) for application in the drug delivery of numerous hydrophilic and hydrophobic compounds. The loading efficiency and release kinetics of these drugs can be controlled by modulating formulation parameters such as composition, stability, and surface charge. Nanosystems of this category have been used in

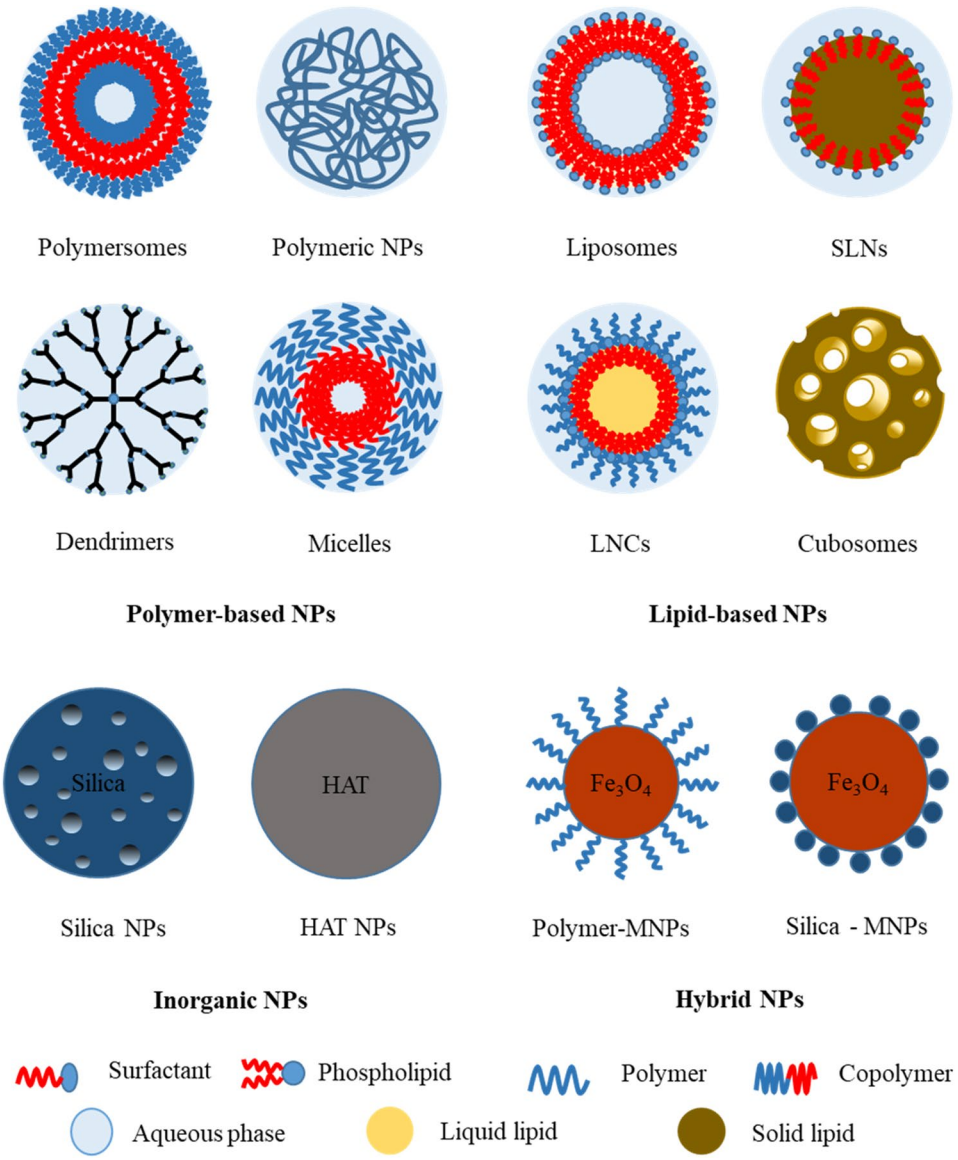

Fig. 5 Structure of various nanoparticle systems used in IT administration. HAT, hydroxyapatite; LNCs, lipid nanocapsules; MNPs, magnetic nanoparticles; NPs, nanoparticles; SLNs, solid lipid nanoparticles

many studies to deliver drugs to the inner ear via IT administration, and according to their structure, they can be further divided into four subsets: polymersomes, polymeric NPs, dendrimers, and micelles.

Polymersomes Polymersomes are a subset of polymer-based NPs with a core–shell structure with a central aqueous core surrounded by an outer bilayer shell composed of a hydrophobic membrane and hydrophilic corona formed by the self-assembly of an amphiphilic copolymer in an aqueous solution. Polymersomes have the ability to encapsulate hydrophilic and hydrophobic drugs with an aqueous core and hydrophobic membrane, respectively, to facilitate codelivery. They are resistant to the immune system due to their biomimetic structure (Lee and Feijen 2012). Many polymersomes studied for transtympanic drug delivery have been manipulated from the di-block copolymer poly(ethylene glycol)-b-poly(ε-caprolactone) (PEG-b-PCL), which showed the ability to penetrate into the inner ear and distribute in various cochlear tissues (Buckiová et al. 2012; Roy et al. 2012). After conjugation to peptides that specifically bind to the surface receptors in selected cell lines (including nerve growth factor-derived peptide (hNgf_EE) and prestin-binding peptides (665 and A666), functionalized PEG-b-PCL polymersomes can specifically target SGNs and outer hair cells, respectively (Roy et al. 2010; Surovtseva et al. 2012). Polymersomes composed of poly(2-hydroxyethyl aspartamide) (PHEA) with or without ligand binding have also been examined to evaluate safety and permeability through RWM (Kim et al. 2015);(Yoon et al. 2015, 2016) (shown in Table 4).

Table 4 Polymersomes for IT administration

Delivery system	Drug	Species	Main outcomes	References
PEG-PCL polymersomes	Disulfiram and DiI	Adult C3H mice (2–3 months old)	- DiI-polymersomes accumulated mainly within the SG, lesser signals in OC, SL and stria vascularis - Safety without any distinct morphological or functional damage - Disulfiram-loaded NPs significantly decreased the number of SG cells up to 2 weeks post-application, while free disulfiram had no damaging effect	Buckiová et al. (2012)
PEG-PGL polymersomes	DiI	Frozen human temporal bones	- DiI-polymersome could across the RWM and distributed in the sensory HCs, nerve fibers and to other cells of the cochlea	Roy et al. (2012)
PEG-PCL polymersomes	DiI	PC12 cells Cochlea from C57BL/6 N mice	- Modified surface with hNgf_EE - Non-toxicity in PC12 cells and ex vivo study - nNgf_EE-conjugated NPs had specific targeting and high binding affinity to SGNs, Schwann cells and the nerve fibers of explant cultures	Roy et al. (2010)
PEG-PCL polymersomes	DiI	Cochlea from newborn rats	- Modified surface with prestin binding peptides - A665 and A666-labeled NPs had effective targeting to the OHCs, while unlabeled NPs had non-specific internalization	Surovtseva et al. (2012)
PHEA polymersomes	Nile red (NR)	C57/BL6 mice	- PHEA NPs had superior permeability into the inner ear - PHEA NPs was safe with inner ear	Kim et al. (2015)
PHEA-C18 NPs (with and without ligand)	Nile red	HEI-OC1 cells Cochlea form C57/BL6 mice C57/BL6 mice	- Comparable with HEI-OC1 cells - The uptake of C18-PHEA NPs was higher than that of PHEA NPs - PHEA-C18-Arg8 penetrated across RWM of mice and accumulated in various inner ear tissues	Yoon et al. (2015)
PHEA-C18 NPs	Dexamethasone (Dex) and DNA/siRNA	HEI-OC1 cells	- Modified surface with Arg8 - Biocompatibility and high cellular uptake in HEI-OC1 cells - Reduction of inflammation of Dex enhanced DNA expression	Yoon et al. (2016)

Polymeric nanoparticles Polymeric NPs are the most commonly used subset of polymer-based NPs with solid matrix structures created from various types of natural and synthetic polymers (shown in Table 5). One of the most extensively investigated polymers is poly(lactic-co-glycolic acid) (PLGA) because of its biodegradability and biocompatibility, approval by the Food and Drug Administration (FDA) and European Medicines Agency (EMA), surface modification ability, and ability to carry either hydrophilic or hydrophobic therapeutics (Tabatabaei Mirakabad et al. 2014). After it was demonstrated in 2005 that PLGA NPs containing rhodamine can cross the RWM after local injection into the middle ear (Tamura et al. 2005), much focus has been placed on PLGA NP systems for drug delivery into the inner ear. PLGA NPs can be used for the delivery of a single drug such as dexamethasone (Sun et al. 2016), or multiple ther-

Table 5 Polymeric nanoparticles for IT administration

Delivery system	Drug	Species	Main outcomes	References
PLGA NPs	Coumarin -6 (Cou-6), Sal B, TS IIA and PNS	Guinea pigs	- Cou-6 was found in perilymph up to 96 h after applying cou-6-loaded PLGA NPs, while no cou-6 was detected after 36 h in perilymph with application of cou-6 solution - The Cmax and AUC of R1, Rg1 and Rb1 delivered by PLGA NPs were significantly higher compared to those of the compound solution	Cai et al. (2014)
PLGA NPs *(Modified surface with hydrophilic molecules)*	Coumarin-6 and DiR	L929 and HEI-OC1 cells Guinea pigs	- All tested formulations were biocompatible with L929 and HEI-OC1 cells. Modified NPs, especially P407-PLGA NPs, had considerable uptake in L929 and HEI-OC1 cells - Safety without any inflammation in the inner ear or morphological alterations - PLGA NP functionalized with hydrophilic molecules, especially with P407, promoted the entry of NPs into the cochlea, enhanced the localization of NPs in cochlear tissues (spiral ligament, stria vascularis, OC and SGNs) compared to the unmodified PLGA NPs	Wen et al. (2016)
PLGA NPs	Coumarin-6 and DiR	HEI-OC1 cells Guinea pigs	- The in vivo cochlear entry of PLGA NPs depended on their particle size and surface chemistry - The uptake of PLGA NPs to HEI-OC1 cells and cochlea was significantly enhanced by incorporating with CPPs (such as TAT, LMWP, penetratin, R8), and the best result belonged to LMWP - The combination of P407-PLGA NPs and LMWP showed synergistic enhancement in accumulation of NPs in OC and stria vascularis without any damages on structure of cochlear tissues and RWM	Cai et al. (2017)
Chitosan NPs	Nile red	L929 and HEI-OC1 cells Cochlea explant from adult guinea pigs Guinea pigs	- Chitosan NPs were biocompatible and had high uptake efficiency in both L929 and HEI-OC1 cells (98,6% and 89,12%, respectively) - Chitosan NPs successfully entered the inner ear and preferentially accumulated in vestibular tissues	Ding et al. (2019)
Bovine serum albumin (BSA) NPs	Rhodamine B	L929 cells Guinea pigs	- BSA NPs was biocompatible with L929 cell line - Compared to suspension, rhodamine B-loaded NPs possessed higher residence time in middle ear and provided controlled release profile	Yu et al. (2014)

apeutic candidates such as the combination of salvianolic acid B, tanshinone IIA, and total panax notoginsenoside (Cai et al. 2014) for the purpose of synergistic actions. The accumulation of PLGA NP-based systems can be increased using surface-modified NPs alone or in combination with cell penetrating peptides (CPPs) (Cai et al. 2017; Wen et al. 2016).

Other polymers of interest for IT drug delivery have also been studied, including bovine serum albumin (BSA) and chitosan. BSA is a biodegradable and nontoxic protein capable of forming spherical NPs that can remain in the middle ear cavity for long periods and can penetrate through the RWM and internalize in the cochlea (Yu et al. 2014). Chitosan NPs can be prepared from chitosan by a different technique from chitosan hydrogels (Agnihotri et al. 2004). The application of chitosan NPs has the potential to successfully introduce drugs into the inner ear fluid in a controlled manner, mainly via the oval window (Ding et al. 2019).

Dendrimers Dendrimers are synthetic polymers with a hyperbranched architecture whose size and shape van be controlled by the creation of repeating units. Dendrimers consist of a hydrophobic core surrounded by hydrophilic branches, and functional groups in hydrophobic core allow it to trap hydrophobic drugs and interact with functional groups to modify the surface (Chauhan 2018). The dendrimers used in otology for IT delivery are commonly formed by polyamidoamine (PAMAM) and hyperbranched poly-L-lysine (HBPL) (shown in Table 6) (Zhang et al. 2011a; Roy et al. 2012; Wu et al. 2013). Activation by heat coupling for surface functionalization with sodium-carboxymethyl-β-cyclodextrin (CM-β-CD) gives dendrimer NPs a higher transfection efficiency for DNA delivery (Wu et al. 2013).

Table 6 Dendrimers and micelles for IT administration

Delivery system	Drug	Species	Main outcomes	References
PAMAM dendrimer *(with and without modified surface)*	pRK4-Atoh1-EGFP plasmid	Adult male Sprague–Dawley rats	- Among unprocessed PAMAM NPs, temperature-activated PAMAM NPs, CD-modified PAMAM NPs and CMAP NPs (PAMAM NPs was thermally activated and then modified with CD), the highest transfection efficiency belonged to CMAP NPs - CMAP NPs was tolerated	Wu et al. (2013)
HBPL dendrimer	Plasmid DNA and FITC	Primary cochlear cell culture from newborn rat and NIH3T3 cells Cochlea from newborn rat Male Sprague–Dawley rats	- HBPL dendrimers had concentration-dependent internalization in primary cochlear cell culture and high transfection efficiency in NIH3T3 cells - FITC-HBPL dendrimer distributed in RWM, middle ear and cochlear tissues including OC and SGNs	Zhang et al. (2011a)
HBPL dendrimer	FITC	Frozen human temporal bones	- Dendrimer had ability to across the RWM and distributed in the sensory hair cells, nerve fibers and to other cells of the cochlea	Roy et al. (2012)

Micelles Another polymer-based NP with core–shell structure is polymeric micelles prepared by the self-association of amphiphilic block copolymers in an aqueous solution, which have many advantages for drug delivery including biocompatibility, low toxicity, and relatively high stability (Ahmad et al. 2014). NPs of a PEG-PLA micellar structure containing Dex prolonged the circulation time of Dex in the perilymph compared to Dex solution (≥ 48 h vs. < 12 h) and were more resistant to cisplatin-induced damage, as evaluated by the ABR test and hair cell counting test (Yu et al. 2015).

Lipid-based nanoparticles

In addition to polymer-based nanoparticles, lipid-based nanoparticle systems have been widely studied to deliver drugs from the middle ear to the inner ear via RWM, including liposomes, lipid nanoparticles, and cubosomes. As a delivery system, lipid-based NPs have many benefits including biocompatibility, large payload, and the ability to regulate their surface properties.

Liposomes Liposomes are a subcategory of lipid-based NPs with a core–shell structure typically composed of phospholipids, a major component of the phospholipid bilayer membrane surrounding an aqueous central core. Similar to polymersomes, liposomes can deliver either hydrophilic therapeutics in the aqueous core or hydrophobic therapeutics in the phospholipid bilayer. Because of their cell membrane-like structure, liposomes are highly resistant. The stability of liposomes is controlled by the particle size, surface charge, lipid composition, number of lamellae, and spatial effect of surface modification (Alavi et al. 2017). Liposomes labeled with traceable agents were observed to have the ability to pass through the middle-inner ear barrier and distribute in the cochlea (Zou et al. 2010a, 2012; Buckiová et al. 2012). Permeation through the RWM of liposomes is size dependent, and smaller NPs have higher transport efficiency (Zou et al. 2012). Many in vivo studies have shown that liposomes can deliver genes for expression in various cochlear organs (Wareing et al. 1999; Jero et al. 2001; Maeda et al. 2007). Surface functionalization with A371 (a TrkB ligand) revealed greater targeted accumulation of therapeutic agents in SGNs and inner hair cells than was achieved by unmodified liposomes (Zou et al. 2009) (shown in Table 7).

Lipid nanoparticles Many other lipid-based NPs lacking an aqueous core-bilayer shell structure, such as liposomes are considered attractive delivery systems for carrying hydrophobic drugs to the inner ear, including lipid nanocapsules (LNCs), solid lipid nanoparticles (SLNs), and cubosomes (shown in Table 8).

LNCs consist of a liquid lipid core composed of triglycerides and mineral oil and an amphiphilic shell composed of nonionic surfactants. It was reported that LNCs could penetrate through the RWM and distribute throughout the cochlear cell populations of human and Sprague–Dawley rat ears without damaging the inner ear structure and function (Zou et al. 2008; Zhang et al. 2011b; Roy et al. 2012). The uptake of LNCs can be altered by the hydrophilicity of the surface. Cationic-PEGylated NPs had the highest cellular uptake in both HEI-OC1 cells and organotypic cultures,

Table 7 Liposomes for IT administration

Delivery system	Drug	Species	Main outcomes	References
Liposomes	Plasmid DNA	Hartley guinea pigs	- Transgene expression was persistent up to 14 days in the spiral ligament, spiral limbus, OC, Reissner's membrane and SGNs without any damaging impacts	Wareing et al. (1999)
Liposomes	hrGFP	Adult brown mice	- Liposome-transgene complex was rapidly and directly delivered to the inner ear compartment, and the transgene expression was detected up to 3 days in Reissner's membrane, spiral limbus, spiral ligament and SGNs with no damage to cochlear structures	Jero et al. (2001)
Liposomes	Plasmid vector $pGJB2_{R75w}$-eGFP	C57BL/6 mice	- $pGJB2_{R75w}$-eGFP was expressed in inner and outer pillar cells, OHCs, claudius cells, spiral limbus and spiral ligament after 3 days of application	Maeda et al. (2007)
Liposomes	Gadolinium	Male Wistar rats	- Liposomes crossing the RWM were visible in inner ear at 3 h after injection and disappeared after 24 h	Zou et al. (2010a)
Liposomes	Gadolinium	Male Wistar rats	- The transport of liposomes via RWM was size-dependent - Gd-DOTA-Liposomes were distributed in utricle, spiral ligament and SGNs	Zou et al. (2012)
Liposomes	Disulfiram and DiI	Adult C3H mice (2–3 months old)	- DiI-liposomes were abundantly identified in the SGNs without any ototoxic impacts - Liposome NPs delivered disulfuram into the inner ear leading to damaging effect	Buckiová et al. (2012)
Liposomes *(Modified surface with TrkB ligand)*	Plasmid DNA (hMGFP)	Primary cochlear cell culture Cochlear explants Male Sprague–Dawley rats Guinea pigs	- A371-functionalized liposomes had potential targeting to SGNs and IHCs compared to unmodified liposomes	Zou et al. (2009)

which resulted in significantly better otoprotective effects (Yang et al. 2018).

SLNs are solid-core lipid nanocarriers composed mainly of fatty acids or mono-, di- or tri-glycerides, which maintain the solid state of the systems at normal body temperature. SLNs have various advantages over liposomes and LNCs: biocompatibility, biodegradability, high stability, extended drug release, and better target delivery ability (Paliwal et al. 2020). SLNs have been reported to be effective in delivering some glucocorticoids (dexamethasone, dexamethasone acetate, hydrocortisone) and antioxidants (edaravone, clozapine) to the inner ear and provide significant protection against ototoxicity induced by noise or cisplatin overexposure (Chen et al. 2008; Gao et al. 2015; Yang et al. 2018; Cervantes et al. 2019; Wang et al. 2020).

Cubosomes are another type of lipid NP that are bicontinuous cubic phase liquid crystalline systems. Due to the honeycomb structure with bicontinuous domains of water and lipid, cubosomes can load hydrophilic, hydrophobic, and amphiphilic drugs and provide sustained release of the entrapped drug (Naveentaj and Muzib 2020). The tested cubosomes composed of amphiphilic lipids (such as phytantriol and glyceromonooleate) exhibit low toxicity and prospective transport ability across the RWM into the inner ear (Liu et al. 2013b, a, 2015b).

Table 8 Lipid nanoparticles for IT administration

Delivery system	Drug	Species	Main outcomes	References
LNCs	FITC or Rhodamine	Primary cochlear cells and mouse fibroblast cells 4-day-postpartum rats	- Toxicity of LNCs in primary cochlear cells and mouse fibroblast cells was dose-dependent - LNC was tolerant without induced hearing loss, cell death or morphological changes in the inner ear	(Zhang et al. 2011b)
LNCs	Nile red and FITC	Frozen human temporal bones	- LNCs had ability to across the RWM and distributed in the sensory hair cells, nerve fibers and to other cells of the cochlea	(Roy et al. 2012)
LNCs	Nile red and FITC	Sprague–Dawley rats	- LNC-DSPI-PEG2000 for longer circulating could migrate through RWM and mainly distributed in SG, IHCs and spiral ligament of the lateral wall	Zou et al. (2008)
Phospholipid-based nanoemulsions (with and without PEGylated)	Nile-red Dexamethasone	HEI-OC1 cells Cochlea from C57BL/6 mice postnatal day 3 C57BL/6 mice 1 months old	- Among neutral, anionic, cationic and cationic PEG phospholipid-based NPs, cationic PEG had the highest cellular uptake in HEI-OC1 cells and in organotypic culture - Dex-NPs exhibited higher Dex internalization in SGNs and IHCs, significantly better hearing function, pro-inflammatory cytokines producing inhibition, and tissue preservation ability than Dex solution	Yang et al. (2018)
SLNs *(Modified surface with DSPI-PEG2000)*	Edaravone	Guinea pigs	- Edaravone-SLN showed significant attenuation of noise-induce threshold shift on the 4th day and ROS generation on the 1st day compared to solution	Gao et al. (2015)
SLNs	Dexamethasone Hydrocortisone Rhodamine	HEI-OC1 cells	- Glucocorticoids-loaded SLNs was more biocompatible and more efficient protection ability against Cisplatin-induced apoptosis as compared to free glucocorticoids at the same dose	Cervantes et al. (2019)
SLNs	Dexamethasone acetate (DA)	Guinea pigs	- DA-SLN showed the higher bioavailability and half-life in perilymph as compared to DA in situ gel	Chen et al. (2008)
SLNs	Clozapine	Guinea pigs	- Treatment of noise-induced ototoxicity by clozapine-SLN showed the lower threshold shift and lower ROS production versus treatment with clozapine solution	Wang et al. (2020)
Cubosomes	Earthworm fibronolytic enzyme (EFE)	L929 cells Guinea pigs	- GMO cubosomes had dose-dependent toxicity - Cubosomes could penetrate through RWM and distribute in the basal turn of the ST and middle portion of the cochlea - $AUC_{0\text{-}24\ h}$ of cubosomes was 2.6-fold higher than solution despite of half-life less than 24 h	Liu et al. (2013b)
	Octodecyl rhodamine B chloride (R18)	L929 cells Cochlea from guinea pigs	- Positive charge GMO cubosomes show higher cellular uptake than negative charge and unmodified cubosomes - Positive charge modified NPs facilitated the permeability and distribution of R18 in cochlea	Liu et al. (2013a)
	Nerve growth factor (NGF)	L929 and PC12 cells Guinea pigs	- Phytantriol Cubosomes showed safety until 20 μg/mL in both two cell lines - Cubosomes did not affect the bioactivity of NGF loaded - Bioavailability of cubosomes was 3.28-fold higher than solution	Liu et al. (2015b)

Inorganic NPs

Inorganic NPs are also attractive for application in drug delivery because of their unique physical, electrical, magnetic, and optical properties. Inorganic NPs can be prepared from metals, silica, and hydroxyapatite (Table 9). However, since metallic NPs alone cannot encapsulate drugs, metallic NPs are used in combination with another type of NP for drug delivery.

Silica-based NPs are biocompatible, biodegradable, porous, and spherical NPs. Silica NPs are the most studied inorganic NPs for drug delivery, enabling a high payload of drug within the pores due to their unique porous structure. In addition, silica NPs release drugs loaded by the pore gating strategy and can be easily surface modified (Şen Karaman and Kettiger 2018). Praetorius et al. reported that silica NPs can cross the RWM and distribute in SGNs and inner hair cells without any harmful impacts (Praetorius et al. 2007), and Wise and colleagues demonstrated an effective strategy for delivering BDNF to the inner ear to improve spiral ganglion neuron survival (Wise et al. 2016). In addition, hollow mesoporous silica NPs have been tested as a system carrying gentamycin for the treatment of Meniere's disease (Xu et al. 2018).

Hydroxyapatite NPs (HAT-NPs) are another widely studied inorganic NP for drug delivery. Hydroxyapatite (a formula formulation of $Ca_{10}(PO_4)_6(OH)_2$) is the principal constituent of bones and hard tissues, and exhibits excellent biocompatibility, biodegradability, bioresorbability, osteogenesis, osteoconductivity, and osteoinductivity. The proprietary properties of large surface area, high loading capacity, and intracellular transportation capacity make HAT-NPs preferred for use in drug delivery systems (Syamchand and Sony 2015; Murata et al. 2018; Ghiasi et al. 2019). Many studies have shown that HAT-NP can mediate NT3 gene transfection into SGNs in both in vitro and in vivo models (Jiang et al. 2007; Sun et al. 2008; Wu et al. 2012).

Hybrid NPs

Hybrid nanosystems are aimed integrating the advantages of these components into nanoscale systems that can combine materials with different properties, including organic-organic, organic–inorganic, and inorganic-inorganic blends. Compared with nonhybrid NPs, hybrid NPs have several advantages, such as improved circulation time, high stability, and outstanding improvements in drug targeting. In addition, the combination of various available ingredients can avoid

Table 9 Inorganic nanoparticles for IT administration

Delivery system	Drug	Species	Main outcomes	References
HAT-NPs	p-EGFPC2-NT3	Guinea pigs	- NT3 was expressed in intracytoplasm of SGNs 1 weeks after injection NT3-HAT NPs inducing protective effect on cochlea injured by kanic acid	Jiang et al. (2007)
HAT-NPs	p-EGFPC2-NT3	Hela cells Guinea pigs	- HAT-NPs was well biocompatible with Hela cells, could mediate NT3 gene transfection into SGNs both in vitro and in vivo model, although the transfection efficiencies were not higher than 30%	Sun et al. (2008)
HAT-NPs *(Modified surface with Polyethylenimine (PEI))*	p-EGFPC2-NT3	Chinchilla	- PEI-HAT-pEGFPC2-NT3 was biocompatibility and had ability to targeting deliver NT3 into vestibular dark cells and vestibular HCs through the conjugation with PEI of HAT-NPs	Wu et al. (2012)
Si-NPs	Cy3	C57BL/6 mice	- Si-NPs was well tolerated with no cytotoxicity and no inflammation. Cy3-labelled Si-NPs was seen in SGNs and IHCs after 4 days after treatment	Praetorius et al. (2007)
Si-NPs	BNDF	Guinea pigs	- BDNF-Si NPs increased the survival of SGNs over a wide extent of the cochlea injured by kanamycin sulfate after 1 month of application - Silica NPs were well tolerated within the cochlea	Wise et al. (2016)
Si-NPs	Fluorescein isothiocyanate (FITC) and Gentamycin	HEI-OC1 cells KM mice	- The hollow mesoporous silica (HMS) coated with zeolitic imidazolate framework (ZIF) (HMS-ZIF) NPs maintained in the cochlea over a longer period of time and provided a sustained release profile - HMS-ZIF showed good biocompatibility and good cellular uptake in HEI-OC1 cells	Xu et al. (2018)

the costly and time-consuming synthesis of new molecules (Hadinoto et al. 2013; Tahir et al. 2020; Ferreira Soares et al. 2020). Inorganic magnetic NPs combined with another inorganic constituent such as silica (Dormer et al. 2005; Kopke et al. 2006) or polymers, such as PLGA and poloxamer 407 (Kopke et al. 2006; Barnes et al. 2007; Ge et al. 2007; Zou et al. 2010b; Du et al. 2013a) have also been tested for otologic treatment by IT application (shown in Table 10).

Despite these advantages, similar to conventional delivery systems, the use of nanoparticles alone has some limitations with respect to rapid clearance from the middle ear cavity through the Eustachian tube, reducing the contact of nanoparticles with the RWM for permeation.

Hydrogels combined with nanoparticles

As described above, hydrogels and nanoparticles are beneficial for drug delivery to the inner ear via IT injection. However, there are still individual limitations to the single use of each system. That is, hydrogels are hampered by RWM permeability, whereas nanoparticles are limited by leakage through the Eustachian tube. Therefore, synergistically increasing the control of drug delivery by incorporating hydrogel and nanoparticles in a single formulation is a highly promising strategy to utilize both hydrogel and nanoparticle systems and overcome the drawbacks of each system used alone. Many studies have been conducted to evaluate the effectiveness of the combination of NPs and hydrogels for inner ear drug delivery (shown in Table 11). SPIONs in hydrogel form can pass through the RWM and can be prominently located in the perilymphatic fluid space and over the cochlear tissues in either in vitro or ex vivo model studies without the use of magnetic forces (Thaler et al. 2011). The combination of liposomes and hyaluronic acid hydrogels significantly prolonged the residence time (30 days) compared to liposomes alone (15 days), which facilitated dexamethasone transport into the inner ear (El Kechai et al. 2016). Liposomes could also be entrapped into CGP hydrogels and exhibit higher fluorescence intensity colocalized to inner ear cells than NPs alone (Lajud et al. 2015). The integration of PLGA NPs and CGP hydrogels has the advantage of a longer mean residence time in the perilymph than is achieved by either NPs or hydrogels alone (Dai et al. 2018). In addition, enhancement of the residence time of particle-based carriers in the middle ear cavity is also achieved by using microsphere carriers in combination with film forming agents that can create a dry film to retain drug-loaded particles in the RWM (Dormer et al. 2019). A recent study of our research group on thermosensitive poloxamer hydrogels containing dexamethasone-loaded PLGA NPs also demonstrated the superiority of the combination between PLGA NPs and hydrogel versus PLGA NPs alone for delivering dexamethasone into the inner ear. In vivo studies in BALB/c mice showed that NP-gel remained in the application position for more than 2 days, which led to significantly greater absorption of dexamethasone in the cochleae (7.20 ± 1.76 ng versus 1.83 ± 0.14 ng and 2.71 ± 0.53 ng of dexamethasone solution and dexamethasone-NPs, respectively) (Kim et al. 2021).

Current status, development, and future perspectives of the application of the intratympanic route

The most commonly used therapeutic agents currently administered through the IT route in the treatment of inner ear disorders are steroids prepared in conventional dosage forms commercially available on the market (for example, dexamethasone solution 4 mg/mL or 5 mg/mL; prednisolone solution 0.25 mg/mL; methylprednisolone solution 62.5 mg/mL; triamcinolone acetonide suspension 10 mg/mL or 40 mg/mL) (Lechner et al. 2019; Roßberg et al. 2020). However, these conventional formulations have limitations of a short residence time in the middle ear and a low degree of passage of drugs through the RWM, as described in the above section. To overcome these limitations, many advanced drug delivery systems have been developed with preeminent characteristics for the effective delivery of drugs into the inner ear. Hydrogels with a variety of tunable behaviors that allow prolonged retention in the middle ear cavity can serve as a reservoir for sustained release from the site of application to support drug transport through the RWM. A suspension of ciprofloxacin in poloxamer 407 hydrogel (OTO-201) was developed and approved by the FDA as Otiprio for otitis treatment (Edmunds 2017). In addition, some other products are currently in clinical trials and are expected to enter the market, such as AM-101 (clinical trial Phase III for treatment of Tinnitus of a hyaluronic hydrogel containing esketamine hydrochloride) (van de Heyning et al. 2014), AM-111 (clinical trial Phase III for treatment of acute unilateral sudden deafness of a hyaluronic hydrogel containing brimapitide – a JNK inhibitor) (Staecker et al. 2019), and OTO-104 (clinical trial Phase IIb for treatment of Meniere's disease of a poloxamer 407 hydrogel containing dexamethasone) (Lambert et al. 2012). In addition to the hydrogel product, a lipid-based formulation of gacyclidine – an N-methyl-D-aspartic acid (NMDA) receptor antagonist (OTO-313) exhibiting sustained delivery was also undergoing phase 1/2 clinical evaluation for the treatment of tinnitus (Maxwell et al. 2021). Although no clinical trials are currently underway for nanoparticles for IT administration, these systems are still considered potential delivery vehicles for the future based on their ability to enhance stability, cellular uptake, and drug targeting to specific cells. In addition, the integration of various drug delivery systems to form a versatile platform with superior properties that increase the

Table 10 Hybrid nanoparticles for IT administration

Delivery system	Drug	Species	Main outcomes	References
MNP coated with silica (Silica-MNP)	Without drug	Artificial 3-layer membrane Frozen human temporal bones Sprague–Dawley rats and guinea pigs	- Silica-MNPs had traversed the RWM and presented in perilymph - Silica-MNP did not affect the proliferation of non-dividing ARPE-19 cells and did not induce hair cell damage or loss in organotypic culture	Dormer et al. (2005)
	Without drug	Sprague–Dawley rats and guinea pigs	- Silica-SPION was compatibility with no evidence of inflammation and apoptosis - PLGA-SPION NPs with or without the magnetic exposure were pulled through RWM	Kopke et al. (2006)
SPION + PLGA NPs	Without drug	MDCK cells RWM model of MDCK and fibroblast cells Organotypic culture from organ of corti of mouse pups Human temporal bone Sprague–Dawley rats and guinea pigs	- Compatibility with no harmful effects on the growth of MDCK cells, little detectable hair cell loss or supporting cell scar formation in organotypic culture, and no inflammatory response and no evidence of apoptosis in vivo - Under the effect of external magnetic forces, SPION had ability to cross the RWM much more rapidly than diffusion	Kopke et al. (2006)
	Without drug	Tripartite cell culture membrane Guinea pigs	- The magnetic force required to pull PLGA-SPION in in vivo was 140 times lower than that in in vitro ($9{,}69 \times 10^{\wedge -20}$ N and $5{,}04 \times 10^{\wedge -16}$ N)	Barnes et al. (2007)
	Without drug	Chinchilla	- PLGA-SPION was successful transported via RWM and distributed in perilymph, endolymph, spiral ligament and OC after 40 min of application with or without magnetic exposure	Ge et al. (2007)
	Dexamethasone acetate and coumarin-6	RWM model Guinea pigs	- The magnetic targeting induce faster, more complete and twofold higher delivery of dexamethasone acetate compared with diffusion alone	Du et al. (2013a)
SPION + oleic acid & Pluronic 127	Without drug	Male Wistar rats	- SPION NPs coated with oleic acid and pluronic F127 (POA-SPION NPs) passed through the RWM and stayed in the perilymph for 3 days	Zou et al. (2010b)

Table 11 Nanoparticle-loaded hydrogels for IT administration

Delivery system	Drug	Species	Main outcomes	References
Ferrogel Magnetic nanoparticle + P407 hydrogel	Without drug	Organotypic culture from mouse inner ears Cadaver human temporal bones	- Without magnetic forces, SPIONs in hydrogel could pass the RWM and noticeably locate in the perilymph and within the cytoplasm of various cell types (HCs, SGNs, stria vascularis, Reissner's membrane and fibroblasts	Thaler et al. (2011)
Liposome + Hyaluronic acid hydrogel	Dexamethasone	Guinea pigs	- Liposomal hydrogels had more prolonged residence time (30 days) as compared to liposome alone (15 days) - Non-toxicity with no negative effects on hearing thresholds	El Kechai et al. (2016)
Liposme + Chitosan glycerophosphate hydrogel	Rhodamine B and CF (5(6)-carboxyfluorescein)	C56BL/6 J mice	- Liposomal hydrogel showed higher accumulation in the inner ear cells as compared with NPs alone	Lajud et al. (2015)
PLGA NPs + Chitosan glycerophosphate hydrogel	Interferons (IFN-α)	Guinea pigs	- The PLGA NPs-CGP hydrogel had longer mean residence time over either NPs or hydrogel alone - Compatibility without any obvious histological changes in the inner ear	Dai et al. (2018)
PLGA microspheres + film forming agents (FFAs)	Betamethasone	C57/BL6 mice	- PLGA microspheres in combination with FFA was safe system drying fast within 15 min and offered extended and controlled release up to 35 days	Dormer et al. (2019)
PLGA nanoparticles + Poloxamer hydrogel	Dexamethasone	BALB/c mice	- DEX-PLGA NPs-gel was biocompatibility, remained longer in middle ear, had better absorption into the inner ear	Kim et al. (2021)

efficacy and accuracy of targeted drug delivery is also a promising approach.

Conclusion

In conclusion, ae profound understanding of the etiopathological mechanisms underlying inner ear impairments contributes to the development of new therapies as well as better strategies for the treatment and prevention of hearing loss. A deep understanding of the anatomical structure of the ear and inner ear helps researchers recognize the obstacles for delivering drugs into the inner ear through the IT administration route and to develop formulations with unique properties to overcome these obstacles to reach the targets more effectively. Various efforts have been made to develop an innovative injectable system that can replace conventional formulations for drug delivery into the inner ear with the goals of effectively treating inner ear damage with minimal invasiveness, improving the development of possible new therapeutic candidates, and utilizing the feasibility of IT administration. Many studies on advanced systems, such as hydrogels, nanoparticles and hydrogel-nanoparticles combinations, have accomplished many achievements, laying the foundation for future research concerning IT drug delivery systems.

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Declarations

Conflict of interest All authors (T.N. Nguyen and J.S. Park) declare that they have no conflicts of interest.

Research involving human and animal rights This article does not contain any studies with human and animal subjects performed by any of the authors.

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