Indian Journal of Modern Research and Reviews

This Journal is a member of the *'Committee on Publication Ethics'*

Online ISSN:2584-184X

Review Article

Overcoming the Round Window Barrier: A Critical Review of Nanocomposite In-Situ Gels for Inner Ear Therapy

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DOI: https://doi.org/10.5281/zenodo.18505950

Abstract

The escalating global prevalence of inner ear disorders, particularly Sensorineural Hearing Loss (SNHL) and Meniere's Disease (MD), presents a critical public health challenge, with over 430 million people affected worldwide. Current pharmacotherapies are severely limited by anatomical barriers: the Blood-Labyrinth Barrier (BLB) blocks systemic drug delivery (>99% drug exclusion), while standard intratympanic injections fail due to rapid drainage via the Eustachian tube (<20 minutes retention). This "drainage paradox" necessitates frequent, painful injections, compromising efficacy, patient compliance, and safety. To overcome these hurdles, in situ gelling systems represent a transformative advancement. These formulations transition from a low-viscosity liquid *in situ* to a gel depot upon contact with the middle ear, adhering to the Round Window Membrane (RWM). This innovation extends drug residence time from minutes to 24–48 hours (standard gels) or 7–14 days for cutting-edge nanocomposite gels. The latter employs a "Trojan Horse" strategy, utilising drug-loaded nanoparticles (e.g., PLGA, liposomes) engineered to penetrate the RWM via endocytic pathways, dramatically enhancing bioavailability and enabling sustained release. Nanocomposite gels deliver therapeutics for diverse applications: rescuing hair cells in Sudden SNHL, regulating endolymphatic pressure in MD, shielding against chemotherapy-induced ototoxicity, alleviating tinnitus, and facilitating inner ear gene therapy with biologics (e.g., siRNA, growth factors). Rigorous evaluation of sol-gel transition temperature, syringeability, rheology, *ex vivo* drug release, mucoadhesion, and ototoxicity testing ensures safety and performance. Despite promising preclinical data, clinical translation faces challenges, including sterilisation complications (without compromising gel integrity), potential pH alterations from polymer degradation, and regulatory scrutiny. The failure of OTO-104 (a Poloxamer-based gel) in Phase 3 trials highlights the need for robust clinical endpoints that mitigate high placebo responses in neurotology. Future directions prioritise theranostic gels integrating diagnostic agents (e, g., MRI contrast) for real-time placement verification and refining manufacturing. If these hurdles are resolved, in situ gelling systems hold immense potential to revolutionise inner ear therapy, shifting from inefficient injections to precise, patient-friendly, sustained treatment.

Manuscript Information

- **ISSN No:** 2584-184X
- **Received:** 12-12-2025
- **Accepted:** 26-01-2026
- **Published:** 06-02-2026
- **MRR:**4(2); 2026: 41-48

- **Plagiarism Checked:** Yes
- **Peer Review Process:** Yes

How to Cite this Article

Kasture S, Shangrapawar T, Bhosle A. Overcoming the round window barrier: a critical review of nanocomposite in-situ gels for inner ear therapy. Indian J Mod Res Rev. 2026;4(2):41-48.

Access this Article Online

www.multiarticlesjournal.com

KEYWORDS: Transtympanic delivery, In situ gel, Round Window Membrane, Nanocomposite hydrogels, Sensorineural hearing loss, Bioavailability.

1. INTRODUCTION

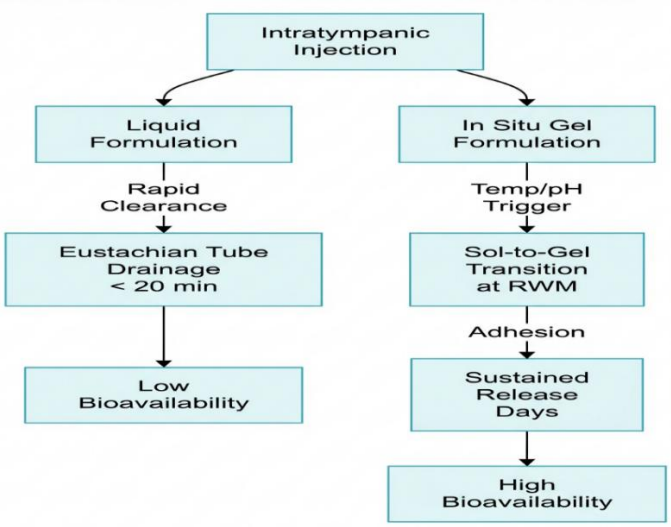
Inner ear disorders, specifically Sensorineural Hearing Loss (SNHL) and Meniere's Disease (MD), are rapidly becoming a major global health concern. The World Health Organisation (WHO) estimates that roughly 430 million people, over 5% of the global population, currently suffer from disabling hearing loss. By 2050, this number is expected to skyrocket to 2.5 billion, meaning 1 in 5 people will likely face some degree of hearing impairment. SNHL is characterised by the permanent destruction of cochlear hair cells, often due to noise exposure or unknown causes. Meanwhile, Meniere's Disease affects up to 513 out of every 100,000 people, causing debilitating symptoms like vertigo and fluctuating hearing loss due to fluid buildup (endolymphatic hydrops). Despite the widespread impact of these conditions, there is a serious gap in medical treatment: currently, no FDA-approved drugs exist to restore lost hearing. Doctors mostly rely on corticosteroids like dexamethasone and methylprednisolone, but these treatments often fail because we lack an effective way to deliver the drug to the injury site.

1.1 The Challenge of Systemic Therapy: Why do standard oral or intravenous treatments fail? The primary obstacle is the Blood-Labyrinth Barrier (BLB). Much like the Blood-Brain Barrier, the BLB is a highly selective physiological shield. It is made of tight junctions between cells in the inner ear's capillaries, designed to strictly control what enters the cochlear fluids to maintain the delicate chemical balance needed for hearing. While this barrier protects the ear, it is a nightmare for drug delivery. When patients take corticosteroids orally or intravenously, the BLB blocks most of the medication, allowing less than 1% of the dose to actually reach the inner ear. To compensate, doctors have to prescribe dangerously high doses to achieve a therapeutic effect. This exposes patients to severe systemic side effects, such as high blood sugar, osteoporosis, and immune suppression, making long-term systemic treatment both inefficient and risky [1].

1.2 The Limitations of Intratympanic Injections: To bypass the BLB, clinicians often use Intratympanic (IT) injections. This involves injecting medicine through the eardrum into the middle ear, hoping it will diffuse across the Round Window Membrane (RWM) and into the cochlea. In theory, this should result in drug concentrations much higher than what systemic treatment can achieve, without the body-wide toxicity. However, in practice, this method is hindered by the "drainage problem." Liquid medications flow down the Eustachian tube very quickly; studies suggest that drugs like dexamethasone stay in the middle ear for only about 27 minutes. Because the drug doesn't stay in place long enough to be absorbed, patients must endure frequent, painful injections, sometimes multiple times a week. This increases the risk of damaging the eardrum and leads to poor patient compliance. Because pills are blocked by the barrier and injections drain away too fast, there is an urgent need for a better solution: in situ gelling systems. These innovative formulations are fluid enough to be injected painlessly but transform into a thick gel once inside the ear. This allows the medication to resist drainage and remain in contact with the round window for days instead of minutes, significantly improving treatment outcomes [2].

The move towards using *in situ* gelling systems for inner ear therapy stems from a major flaw in standard liquid treatments: they simply don't stay in the ear long enough to work well. Conventional liquid drops are usually cleared from the middle ear through the Eustachian tube within just 10 to 20 minutes of injection. In contrast, *in situ* gels are designed to change from a fluid to a semi-solid state once they reach the Round Window Membrane (RWM). This transition drastically increases the time the drug stays in the ear, extending it to 24–48 hours, while some advanced nanocomposite versions can remain for up to 7 days [2,3]. This extended contact time is crucial for successful treatment. Because liquids wash away so quickly, the ear absorbs very little of the drug, forcing patients to endure a difficult schedule of frequent injections, often as many as three times a week. The gel solves this problem by becoming thick enough to resist gravity and the natural movements caused by swallowing. Effectively, it acts as a stable "drug depot," ensuring a steady, continuous release of medication across the RWM rather than a fleeting wash.

Figure 01: Comparison Of Drainage Paradox Vs. The Gel Solution.



1.3 Objectives of this Review: This paper focuses on how *in situ* gelling systems are finally solving the persistent physical barriers involved in delivering drugs across the eardrum. While the difficulty of bypassing the blood-labyrinth barrier is well known, this review zeroes in on a different challenge: the "drainage paradox." This refers to the frustrating reality where liquid medicines are washed down the Eustachian tube before they can be effective, which has historically made intratympanic therapy inefficient.

Instead of simply listing standard polymeric materials, we analyse the breakthrough innovations that have emerged between 2020 and 2025. We specifically look at how nanocomposite hydrogels and multi-stimuli responsive systems are changing the rules of inner ear pharmacokinetics,

successfully extending the time medication stays in the ear from a few minutes to several days. Furthermore, we aim to connect laboratory research with real-world patient care. To do this, we provide a realistic look at the obstacles slowing down clinical adoption, such as the risk of ototoxicity (ear damage), the difficulties of sterilisation, and the complex regulatory landscape that must be navigated to turn these technologies into viable treatments for Meniere's disease and hearing loss.

1.4 Nanocomposite In-Situ Gels: A major standout in recent advancements (2024–2025) is the emergence of "Nanocomposite Gels." These formulations utilise a sophisticated "Trojan Horse" strategy, specifically engineered to sneak therapeutics past the tight permeability defences of the Round Window Membrane (RWM). Unlike traditional gels that simply release free drug, these systems act as a stable "docking station" at the RWM, releasing drug-loaded nanoparticles such as liposomes or PLGA that are specifically engineered to penetrate the membrane via endocytic pathways (e.g., macropinocytosis) inaccessible to free molecules. This dual-
The action mechanism has demonstrated remarkable superiority in pharmacokinetic studies; for instance, PLGA-nanoparticle-loaded gels have been shown to maintain cochlear fluorescence for up to 7 days, a drastic improvement over the <24-hour retention seen with standard gels. [4,5]

Notably, recent work by Le et al. (2023) confirmed that such Dexamethasone-loaded hydrogels achieve significantly higher perilymph concentrations than liquid suspensions without inducing ototoxicity. Beyond small molecules, this platform is proving indispensable for the delivery of fragile biologics. Emerging research is utilising liposomal gels to protect and deliver siRNA and growth factors, thereby opening new avenues for gene silencing and hair cell regeneration therapies that were previously hindered by enzymatic degradation in the middle ear. [6,7]

Table 1: Comparison Between Pharmacokinetic Superiority: Liquid Vs. Gel Vs. Nanocomposite

Feature	Conventional Liquid Drops	Standard In Situ Gel (e.g., P407)	Nanocomposite In Situ Gel (e.g., PLGA-Gel)
Residence Time at RWM	**< 20 minutes** (Rapid drainage via Eustachian tube)	**24 – 48 hours** (Limited by gel erosion)	**7 – 14 days** (Gel acts as depot; NPs retain longer)
Permeation Mechanism	Passive diffusion (poor across 3-layer RWM)	Continuous concentration gradient (passive)	**Endocytosis** (Nanoparticles penetrate RWM cells)
Bioavailability	Low (<1–5% of dose reaches cochlea)	Moderate (Sustained contact improves flux)	**High** (Protects cargo & enhances uptake)
Dosing Frequency	Frequent (e.g., 3x/week for sudden loss)	Weekly (Reduced burden)	**Single Dose** or Monthly (Ideal profile)
Patient Experience	"Salty taste" (drainage), Vertigo, Pain	Improved comfort; minimal drainage	Best compliance; fewer hospital visits

1.5 Mechanism and polymer selection: In situ gelling systems effectively resolve the "drainage paradox" by exploiting a sol-to-gel transition at the site of administration. This unique phase change allows the formulation to be injected as a low-viscosity liquid through a fine-gauge needle (e.g., 27G) for painless administration, before solidifying into a viscous depot that adheres to the Round Window Membrane (RWM) to resist clearance. Among the various triggers, thermosensitive systems utilising Poloxamer 407 (P407) are the "gold standard" due to their reliable gelation at physiological body temperature (37°C); however, unmodified P407 gels often suffer from weak mechanical strength and rapid erosion (1–2 days) [8]. To overcome this, recent strategies (2023–2025) have focused on polymer blending, specifically Poloxamer/Chitosan blends, where the cationic charge of chitosan binds to the negatively charged mucosal surface of the RWM, significantly extending retention time.[9] · Beyond temperature triggers, researchers are increasingly exploring ion-sensitive polymers like Gellan Gum, which crosslink in the presence of middle ear cations (Na^+, K^+, Ca^{2+}) to prevent burst release, as well as novel "Smart Gels" that utilise dual triggers (pH + Temperature). Notably, pH-sensitive hydrogels based on modified hyaluronic acid have been developed to respond specifically to the middle ear's pH microenvironment (~7.4), ensuring precise gelation only at the target site [10]

Table 2: Comparative Analysis of Polymers Used in Transtympanic in Situ Gel

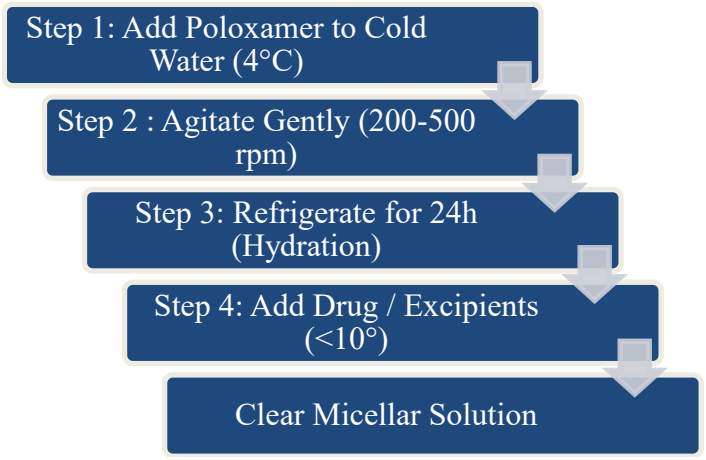
Polymer Class	Specific Polymer	Gelation Trigger	Advantages
Thermosensitive	Poloxamer 407 (Pluronic F127)	Temperature (>32°C)	Reliable sol-gel transition; high drug solubility; FDA approved for other routes.
Ion-Sensitive	Gellan Gum (Gelrite®)	Cations (Na+, Ca2+)	Immediate gelation upon contact with physiological fluids; prevents "burst release."
pH-Sensitive	Carbopol/ Chitosan	pH Change (pH ~7.4)	**Chitosan:** Mucoadhesive (cationic) & opens tight junctions. **Carbopol:** High viscosity at low concentrations.

2. METHOD OF PREPARATION

2.1 The cold method: The preparation of thermosensitive Poloxamer-based gels generally involves the "Cold Method" as described by Schmolka, which is a method of solubilization intended to avoid premature gelation. For this purpose, the required amount of Poloxamer (15-20% w/v) is slowly added to cold distilled water (4°C) under constant and gentle agitation (200-500 rpm) to avoid foam formation. The resulting

dispersion is then refrigerated at 4°C for 24 hours to allow complete hydration of the polymer chains, leading to a clear micellar solution. After the base solution is ready, drugs are added according to their solubility: hydrophilic drugs are added directly to the cold polymer solution, while hydrophobic drugs are usually pre-dissolved in a cosolvent (e.g., PEG 400) or added as a suspension. Finally, performance additives such as bio-adhesive polymers (e.g., Chitosan, Carbopol) are separately prepared and added to the formulation at temperatures kept below 10°C to maintain the liquid state during processing [10].

Figure 02: Preparation Steps in The Cold Method



2.1 Preparation of advanced gelling systems:

The preparation of non-thermal gelling systems, such as ion-sensitive Gellan Gum or pH-sensitive Carbopol, usually requires a Physical Mixing and Neutralization method. This involves the hydration of the polymer in deionised water at 70-80°C to facilitate complete dissolution, followed by cooling to room temperature (<40°C) before adding the drug to prevent thermal degradation of the active compound. One of the most important steps in the preparation of the formulation is the adjustment of osmolarity using non-ionic substances such as Mannitol; ionic tonicity-adjusting agents such as NaCl are strictly prohibited in the formulation because they may induce early cross-linking of ion-sensitive gums. The solution is then filtered using a 0.45 µm membrane filter to remove particulate contaminants. [12]

For the more complex Nanocomposite ("Nanoparticle-in-Gel") Systems, a strong "Two-Step" Process is needed to ensure the stability of the particulate cargo within the hydrogel matrix. In Phase A, drug-loaded nanoparticles (e.g., PLGA or Liposomes) are prepared using conventional methods such as Double Emulsion Solvent Evaporation or Thin Film Hydration. In Phase B, the nanoparticles are lyophilised to a stable powder form and then redispersed in a pre-formed, cold Poloxamer solution (prepared using the Cold Method). A critical control point in this process is the redispersal step, which requires gentle agitation to ensure uniform distribution of the nanoparticles without causing aggregation or disrupting the ordered micellar structure of the thermo-responsive gel [11]

2.3 Sterilisation considerations: Sterility is a non-negotiable requirement for intratympanic formulations to prevent the risk of iatrogenic otitis media; however, selecting an appropriate sterilisation method for in situ gels presents a significant challenge. Autoclaving (121°C for 15 minutes) is effective for thermostable materials but is often unsuitable for hydrogels, as the high heat can induce polymer chain hydrolysis, leading to a detrimental drop in viscosity and altered gelation properties. Sterile filtration (0.22 µm) is the preferred alternative for thermolabile drugs and peptide-loaded systems, yet it is technically difficult for high-viscosity solutions (e.g., >20% Poloxamer); consequently, filtration is typically performed on dilute components before the final concentration step or via aseptic mixing. Gamma irradiation offers a terminal sterilisation option for pre-packed gels, but it requires careful optimisation of the radiation dose to avoid inducing unwanted cross-linking or chain scission that could compromise the gel's rheological performance [12]

3. THERAPEUTIC APPLICATIONS

One of the primaries uses for this technology is addressing Sudden Sensorineural Hearing Loss (SSNHL), a condition where standard treatments often fall short. Typically, doctors prescribe corticosteroids like Dexamethasone, but when administered as standard liquid drops, the medication tends to drain down the Eustachian tube before it can be fully effective. Nanocomposite gels solve this by being injected as a fluid that hardens upon reaching the Round Window Membrane. This creates a stable depot where nanoparticles such as those made from PLGA or liposomes can slowly release the steroid over several weeks, ensuring the inner ear receives a constant anti-inflammatory dose to help rescue hair cells and prevent scarring.

These gels also play a crucial preventative role in shielding the ear from the toxic side effects of aggressive treatments like chemotherapy (using Cisplatin) or heavy antibiotics (aminoglycosides). By delivering potent antioxidants or anti-apoptotic agents directly to the cochlea, the gel acts as a local safeguard. This method allows the nanoparticles to neutralise harmful Reactive Oxygen Species (ROS) within the ear structure itself. Importantly, because the delivery is localised, it protects the patient's hearing without interfering with the cancer-fighting efficacy of the chemotherapy drugs circulating in the rest of the body.

Managing Ménière's disease, which causes debilitating vertigo due to fluid imbalance in the inner ear, requires precise medication control that standard drops cannot offer. Nanocomposite gels are particularly useful here for delivering drugs like Dexamethasone to regulate fluid pressure, or Gentamicin for more severe cases. The key advantage is the controlled release rate; when using potentially toxic drugs like Gentamicin to stop vertigo, the gel limits the exposure to a specific, safe level. This allows effective suppression of vertigo symptoms while significantly reducing the risk of inadvertently damaging the patient's remaining hearing.

Table 3: Therapeutic Applications of Nanocomposite In-Situ Gels for Inner Ear Therapy

Sr. No.	Application	Therapeutic Agents	Mechanism of Action	Key Benefits
1	Sudden Sensorineural Hearing Loss (SSNHL)	Corticosteroids (Dexamethasone, Methylprednisolone)	Injected through the eardrum → gel solidifies on the Round Window Membrane → nanoparticles slowly release steroid into the perilymph	Weeks-long anti-inflammatory effect from one injection; rescues hair cells, reduces fibrosis
2	Protection Against Ototoxicity	Antioxidants (N-acetylcysteine, Vitamin E), Anti-apoptotic agents	Applied before/during chemotherapy or aminoglycosides → nanoparticles deliver protective agents exclusively to the cochlea	Blocks ROS formation in the inner ear; preserves hearing without weakening cancer/antibiotic treatment
3	Ménière's Disease	Dexamethasone (inflammation), Gentamicin (ablation)	Highly controlled, sustained release regulates endolymph pressure or delivers precise low-dose Gentamicin	Controls vertigo attacks; Gentamicin use is safer – spares residual hearing (unlike standard drops)
4	Tinnitus Treatment	NMDA antagonists (e.g., Gacyclidine), Lidocaine, Neurotrophic factors	Direct delivery of neuroprotective agents to spiral ganglion neurons, calming cochlear excitotoxicity	Long-lasting relief from ringing without sedation or systemic side effects of oral drugs
5	Inner Ear Gene Therapy & Regeneration	Neurotrophins (BDNF, NT-3), siRNA, plasmid DNA	Chitosan/lipid nanoparticles inside the gel protect genetic material and enable uptake into Organ of Corti cells.	Promotes regeneration of hair cells from supporting cells and protects remaining neurons

4. EVALUATION PARAMETER

To ensure the safety and efficacy of intratympanic in situ gels, formulations must be subjected to a rigorous battery of in vitro and ex vivo tests. [13,14,15]

a) Sol-gel transition temperature & time

Significance: the gel must remain liquid at room temperature (25°c) and transition to a gel instantly upon contact with the middle ear mucosa (37°c).

Method (tube inversion test): a vial containing 2 ml of the formulation is immersed in a water bath. The temperature is increased at a rate of 1°c/min. The vial is inverted every minute; the point where the meniscus does not move within 30 seconds is recorded as the gelation temperature (sol-gel).

Acceptance criteria: optimal range is 32°c – 36°c. (<32°c risks gelling in the needle; >37°c risks draining before gelling).

b) Syringeability and Injectability

Significance: Intratympanic injections use fine-gauge needles (27g–30g) to minimise tympanic membrane damage. The formulation must flow easily without requiring excessive force.

Method: A texture analyser is used in "compression mode." The formulation is filled into a syringe with a 27g needle. The upper probe pushes the plunger at a constant speed (e.g., 1 mm/s). The "Work of Syringeability" (area under the curve) and "Peak force" are recorded.

Acceptance criteria: force should be < 20–30 n to ensure ease of administration by the otolaryngologist.

c) Rheological Studies (Viscosity)

Significance: Determines the gel's ability to resist gravity drainage down the eustachian tube.

Method: A cone and plate viscometer (e.g., Brookfield) measures viscosity at different shear rates.

Acceptance criteria: sol state: low viscosity (<500 cp) for injection.

Gel state: high viscosity (>10,000 cp) for retention.

Analysis: Formulations should exhibit pseudoplastic (shear-thinning) flow, meaning they become thinner when pushed through the needle and recover viscosity instantly at the target site.

d) In Vitro Drug Release

Significance: Mimics the drug diffusion from the gel across the Round Window Membrane (RWM).

Method (Franz Diffusion Cell):

Donor Compartment: Contains the in-situ gel.

Membrane: Synthetic cellulose membrane or (ideally) excised Round Window Membrane from animal models (guinea pig/sheep).

Receptor Compartment: Simulated Perilymph Fluid (pH 7.4) kept at 37°C.

Data Analysis: Samples are withdrawn at intervals (1h to 7 days) and analysed (HPLC/UV). Release kinetics are fitted to models (Higuchi / Korsmeyer-Peppas) to determine if diffusion is Fickian or anomalous. [13]

e) Ex Vivo Mucoadhesive Strength

Significance: Measures how "sticky" the gel is to the RWM, which prevents it from detaching during swallowing.

Method: A Texture Analyser is used with excised mucosal tissue (e.g., goat/pig nasal or ear mucosa).

The gel is placed on the lower platform. The tissue is attached to the upper probe.

The probe lowers, contacts the gel with a defined force (e.g., 0.5 N), and then pulls up.

The "Peak Detachment Force" represents the adhesive strength. [14]

f) Ototoxicity Evaluation (Safety)

Significance: Essential to prove the polymer does not damage hair cells.

In Vitro Method: HEI-OC1 (House Ear Institute-Organ of Corti 1) cell lines are incubated with the gel extract. Cell viability is measured via the MTT assay.

In Vivo Method: Auditory Brainstem Response (ABR) testing in guinea pigs. A shift in hearing threshold (dB) after gel administration indicates ototoxicity. [15]

5. REGULATORY PATHWAYS AND COMMERCIAL STATUS:

The regulatory landscape for intratympanic in situ gels is complex and evolving, with the FDA typically classifying these systems as "Drug-Device Combinations" or "Extended-Release

Dosage Forms," a designation that mandates rigorous Phase 3 trials demonstrating both superiority over placebo and non-inferior safety compared to standard injections. A definitive case study in this domain is OTO-104 (OTIVIDEX®), a Poloxamer-based dexamethasone gel developed by Otonomy Inc. for the treatment of Meniere's Disease. Despite promising Phase 2 results, the pivotal Phase 3 trial (AVERTS-1) failed to meet its primary endpoint of a significant reduction in vertigo frequency compared to placebo. Critical analysis suggests this failure was not attributable to the formulation's performance, which successfully delivered the drug, but rather to the high "placebo response" inherent in Meniere's patients. This outcome underscores a profound lesson for future development: even a pharmacokinetically perfect delivery system may fail commercially if the clinical trial design cannot robustly account for the subjective nature of patient-reported outcomes in neurology. [16]

Table 04: Case Study of Oto-104 (Otividex®)

Parameter	Details
Product Name	OTO-104 (OTIVIDEX®)
Developer	Otonomy Inc.
Formulation Type	Poloxamer 407-based Thermosensitive Hydrogel
Active Drug	Micronised Dexamethasone (Sustained Release)
Target Disease	Meniere's Disease (Vertigo & Hearing Loss)
Delivery Route	Intratympanic Injection (Single dose)
Phase 3 Outcome	Failed to meet primary endpoint in AVERTS-1 trial.
Reason for Failure	High Placebo Response**:** 60% of placebo patients also reported improvement in vertigo.

6. CURRENT CHALLENGES IN CLINICAL TRANSLATION

Despite the pharmacokinetic advantages of in situ gelling systems, their clinical adoption is stalled by critical manufacturing and safety hurdles. The most significant bottleneck is the "Sterilisation-Viscosity Dilemma": standard autoclaving often degrades the polymer chains of thermosensitive gels, altering their sol-gel transition temperature, while sterile filtration is impractical for high-viscosity formulations, necessitating costly aseptic processing. Furthermore, safety concerns extend beyond simple cytotoxicity; the acidic degradation byproducts of polyester-based nanocomposites (e.g., PLGA) pose a risk of altering the perilymphatic pH, which could induce cochlear inflammation or hair cell damage. Additionally, the physical presence of a stiff gel in the round window niche increases the risk of conductive hearing loss by mechanically dampening sound transmission, a transient side effect that regulatory agencies like the FDA scrutinise closely during Phase 3 trials. [16]

Table 4: Recent Advances in Transtympanic Formulations

Formulation Type	Active Therapeutic	Outcome	Reference
Microneedle + Liposomal Gel	siRNA (Gene Silencing)	**Dual Mechanism:** Microneedles created micro-channels in RWM; Gel sealed them & released siRNA. Significant gene silencing observed.	Feng et al. (2024)
3D Printed Bio-Scaffold	Dexamethasone	**Personalised Implant:** 3D printed to fit the specific anatomy of the Round Window Niche; sustained release > 4 weeks.	Wei et al. (2024)
PLGA-Nanoparticle Gel	Dexamethasone	**Extended Retention:** Fluorescence retained in cochlea for 7 days vs. <24h for standard gel. Superior perilymph concentration.	Kim et al. (2021)
Chitosan-Poloxamer Blend	Ciprofloxacin	**Mucoadhesion:** Cationic chitosan increased RWM residence time by 3-fold compared to Poloxamer alone.	Shau et al. (2023)
pH-Sensitive Hyaluronic Acid	Growth Factors	**Smart Trigger:** Gelation occurred specifically at pH 7.4; supported hair cell regeneration in vitro without toxicity.	Zhang et al. (2025)

7. FUTURE DIRECTIONS

To bridge the gap between clinical promise and commercial success, the next generation of intratympanic gels must evolve beyond simple drug delivery vehicles into precision tools validated by robust data. Future development efforts should prioritise the integration of objective clinical endpoints, moving away from unreliable, subjective measures like "vertigo diaries" in favour of quantifiable biomarkers such as electrocochleography changes. Furthermore, there is a critical need for "Theranostic Gels" smart formulations incorporating contrast agents like Gadolinium, which would allow clinicians to utilise MRI for real-time visual confirmation that the gel has been correctly placed and retained at the Round Window Membrane, thereby eliminating the uncertainty of "blind" intratympanic injections. [17]

8. CONCLUSION

The escalating global prevalence of inner ear disorders, particularly Sensorineural Hearing Loss (SNHL) and Meniere's Disease, presents a critical public health challenge that current pharmacotherapies have failed to adequately address. The fundamental barrier to effective treatment has not been a lack of potent drugs, but rather a lack of effective delivery. As highlighted in this review, the physiological impermeability of the Blood-Labyrinth Barrier renders systemic therapy largely ineffective and toxic, while the "drainage paradox" of the Eustachian tube limits the efficacy of standard intratympanic

injections to mere minutes. In situ gelling systems represent the most promising paradigm shift in resolving these pharmacokinetic bottlenecks. By exploiting unique sol-to-gel phase transitions, these intelligent formulations successfully combine the injectability of liquids with the retention properties of solids. The evolution from simple thermosensitive polymers (e.g., Poloxamer 407) to advanced Nanocomposite Gels marks a significant technological leap. These "Trojan Horse" systems do not merely hold the drug at the Round Window Membrane; they actively facilitate the endocytic uptake of therapeutic payloads, extending drug residence time from less than 20 minutes to over a week. This sustained release capability is clinically vital for rescuing cochlear hair cells in SNHL, managing the fluctuating pressures of Meniere's disease, and providing chemoprotection against ototoxicity with significantly reduced dosing frequencies.

However, the path from laboratory innovation to clinical standard of care remains obstructed by significant translational hurdles. The "sterilisation-viscosity dilemma" continues to complicate manufacturing, and the potential for polymer degradation products to alter perilymphatic pH poses safety risks that require rigorous scrutiny. Furthermore, the commercial failure of OTO-104 (OTIVIDEX®) serves as a cautionary tale regarding the regulatory and clinical trial landscape. It underscores that even a pharmacokinetically superior delivery system cannot succeed without trial designs that mitigate the high placebo response inherent in neurotology disorders. Looking forward, the future of transtympanic therapy lies in the development of "Theranostic" systems, smart gels that combine sustained drug delivery with diagnostic visibility (e.g., MRI contrast) to confirm placement. If the challenges of sterilisation, biocompatibility, and objective clinical assessment can be overcome, in situ gelling systems stand poised to revolutionise otology, transforming the treatment of inner ear disorders from a regimen of frequent, inefficient injections into a precise, sustained, and patient-friendly therapy.

9. CONFLICT OF INTEREST

All authors declare no conflict of interest.

REFERENCES

1. Shau PA, Dangre PV, Potnis VV. Formulation of thermosensitive in situ otic gel for topical management of otitis media. Indian J Pharm Sci. 2015 Nov–Dec;77(6):764–70.
2. Nyberg S, Abbott NJ, Shi X, Steyger PS, Dabdoub A. Delivery of therapeutics to the inner ear: the challenge of the blood-labyrinth barrier. Sci Transl Med. 2019 Mar 6;11(482):eaao0935.
3. Kim DH, Nguyen TN, Han YM, Tran P, Rho J, Lee JY, et al. Local drug delivery using poly(lactic-co-glycolic acid) nanoparticles in thermosensitive gels for inner ear disease treatment. Drug Deliv. 2021;28(1):2268–77.
4. Kim DK. Recent advances in functionalized nanoparticles for targeted and controlled inner ear therapy via localised cochlear delivery. J Audiol Otol. 2025 Jul;29(3):159–65.
5. Zhang L, Xu Y, Cao W, Xie S, Wen L, Chen G. Understanding the translocation mechanism of PLGA nanoparticles across the round window membrane into the inner ear: a guideline for inner ear drug delivery based on nanomedicine. Int J Nanomedicine. 2018;13:479–92. doi:10.2147/IJN.S154968
6. Patel J, Szczupak M, Rajguru S, Balaban C, Hoffer ME. Inner ear therapeutics: an overview of middle ear delivery. Front Cell Neurosci. 2019 Jun 11;13:261.
7. Kurniawansyah IS, Rusdiana T, Sopyan I, Arya IFD, Wahab HA, Nurzanah D. Comparative study of in situ gel formulation based on the physicochemical aspect: a systematic review. Gels. 2023 Aug 10;9(8):645.
8. Zhang L, Bai X, Wang R, Xu L, Ma J, Xu Y, et al. Advancements in the studies of novel nanomaterials for inner ear drug delivery. Nanomedicine (Lond). 2022;17(20):1463–75.
9. Le TP, Yu Y, Cho IS, Suh EY, Kwon HC, Shin SA, et al. Injectable poloxamer hydrogel formulations for intratympanic delivery of dexamethasone. J Korean Med Sci. 2023 May 1;38(17):e135.
10. Paganini V, Tampucci S, Brignone SG, Di Gangi M, Monti D, Burgalassi S, et al. Optimised ion-sensitive hydrogels based on gellan gum and arabinogalactan for the treatment of dry eye disease. Gels. 2025 Oct 1;11(10):787.
11. Barakat SS, Nasr M, Ahmed RF, et al. Intranasally administered in situ gelling nanocomposite system of dimenhydrinate: preparation, characterisation, and pharmacodynamic applicability in chemotherapy-induced emesis model. Sci Rep. 2017;7:9910. doi:10.1038/s41598-017-10032-7
12. Rafael D, Andrade F, Martínez-Trucharte F, Basas J, Seras-Franzoso J, Palau M, et al. Sterilisation procedure for temperature-sensitive hydrogels loaded with silver nanoparticles for clinical applications. Nanomaterials (Basel). 2019 Mar 6;9(3):380.
13. Fathalla Z, Mustafa WW, Abdelkader H, Moharram H, Sabry AM, Alany RG. Hybrid thermosensitive-mucoadhesive in situ forming gels for enhanced corneal wound healing effect of L-carnosine. Drug Deliv. 2022;29(1):374–85.
14. Salerno C, Carlucci AM, Bregni C. Study of in vitro drug release and percutaneous absorption of fluconazole from topical dosage forms. AAPS PharmSciTech. 2010 Jun;11(2):986–93.
15. Basu S, Bandyopadhyay AK. Development and characterisation of mucoadhesive in situ nasal gel of midazolam prepared with Ficus carica mucilage. AAPS PharmSciTech. 2010 Sep;11(3):1223–31.
16. Pang X, Zhang X, Xu D, Bu C, Qiu Y, Feng P, et al. Bioactive hydrogels for the reconstruction of sensorineural hearing loss. Bioact Mater. 2025 Oct 17;56:160–80.
17. Phillips J, Mikulec AA, Robinson JM, Skarinsky D, Anderson JJ. Efficacy of intratympanic OTO-104 for the treatment of Ménière's disease: outcomes of three randomised, double-blind, placebo-controlled studies. Otol Neurotol. 2023 Jul 1;44(6):584–92.

18. Barrett-Catton E, Ross ML, Asuri P. Multifunctional hydrogel nanocomposites for biomedical applications. Polymers (Basel). 2021 Mar 11;13(6):856.
19. Koenen L, Andaloro C. Ménière disease. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK536955/
20. Bakhrushina EO, Afonina AM, Mikhel IB, Demina NB, Plakhotnaya ON, Belyatskaya AV, et al. Role of sterilisation on in situ gel-forming polymer stability. Polymers (Basel). 2024 Oct 21;16(20):2943.
21. Aparna C, Pravalika T, Raju MB. Formulation and evaluation of thermo-reversible in situ gel of felodipine. J Glob Res. 2024;59(2):1–6.
22. Jimoh OO, Ajuwon T, Okonkwo SS, Awoyemi RF, Olaosebikan I, Olahanmi OA, et al. PLGA nanoparticles in otoprotection and inner ear regeneration: a new frontier in nanomedicine for hearing disorders. RSC Adv. 2025;15:1–12.
23. Staecker H, Morelock M, Kramer T, Chrbolka P, Ahn JH, Meyer T. Safety of repeated-dose intratympanic injections with AM-101 in acute inner ear tinnitus. Otolaryngol Head Neck Surg. 2017 Sep;157(3):478–87.

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