Electrode Features for Hearing Preservation and Drug Delivery Strategies

C. Jolly\textsuperscript{a} · C. Garnham\textsuperscript{a} · H. Mirzadeh\textsuperscript{b} · E. Truy\textsuperscript{c,d} · A. Martini\textsuperscript{e} · J. Kiefer\textsuperscript{f} · S. Braun\textsuperscript{g}

\textsuperscript{a}MED-EL Hearing Implants, Innsbruck, Austria; \textsuperscript{b}Biomaterials Department, Iran Polymer and Petrochemical Institute, Tehran, Iran; \textsuperscript{c}UMR5020 Neurosciences sensorielles, Comportement, Cognition, CNRS, Université Claude-Bernard Lyon-1 et \textsuperscript{d}Département d’ORL, de Chirurgie Cervico-Maxillo-Faciale et d’Audiophonologie, Hôpital Edouard-Herriot, Hospices Civils de Lyon, Lyon, France; \textsuperscript{e}Department of Audiology, University of Ferrara, Ferrara, Italy; \textsuperscript{f}Hals-Nasen-Ohrenklinik und Poliklinik des Klinikums rechts der Isar der Technischen Universität München, München and \textsuperscript{g}Universitätsklinikum, J.-W.-Goethe-Universität, Frankfurt/Main, Deutschland

Abstract

Background/Aims: Reducing the risk of hearing loss after cochlear implantation requires optimization of the electrode array to minimize the physical trauma caused by insertion and placement. Furthermore, the electrode design must be optimized for atraumatic surgical approaches. Even greater levels of protection may be achieved by the use of a drug during and after implantation. The electrode array offers a potential vehicle for drug delivery.

Methods: This article reviews the laboratory and clinical data available thus far relating to the importance of electrode design parameters for trauma minimization, and the possibility of further reduction through pharmaceutical intervention. Candidate drugs were identified through literature review and laboratory evaluation. The most promising have been investigated in vitro and in animal models of implantation trauma. Three delivery devices are currently under development to satisfy the specific demands of different therapy regimes. The delivery profiles of each were evaluated through both modelling and bench testing and the concepts investigated in vitro and in vivo.

Results: Current evidence favours a thin, flexible electrode array with wires in a zigzag shape. Steroids and an apoptosis inhibitor (AM111) performed well in animal models of electrode trauma and are both good drug candidates for reduction of the risk of hearing loss after implantation. Semi-chronic dexamethasone elution, acute drug delivery by intracochlear catheter, and longer-term delivery through diffusion from a reservoir were all shown to be feasible.

Conclusion: An extensive programme focussed on minimizing hearing loss through device optimization and the development of new technologies has yielded positive results and new concepts for further development and clinical application.

Features of Electrodes Desirable for Electric Acoustic Stimulation Surgery

It is generally assumed that to maximize the chances of hearing preservation during cochlear implant surgery an atraumatic electrode array is required and that the electrode length should be limited to reach the 1,000-Hz region, equivalent to an insertion angle of about 360°, or less. In order to reduce trauma and increase the chance of hearing preservation, the cochlear implant manufacturers offer lateral wall electrodes: from MED-EL GmbH the approved FLEX EAS [1], and a FLEX 20-mm-long prototype in testing [Helbig S., in preparation], from Cochlear Ltd. the Hybrid S [2] and Hybrid L [3], and from Advanced Bionics Corporation a ‘Thin Lateral’ and a HELIX II electrode have been
reported [4]. Preshaped electrodes such as Contour Advance or HELIX increase the risk of hearing loss and are not designed for consistent hearing preservation due to the large number of direct scala vestibuli insertions and deviations from scala tympani to scala vestibuli [5]. Lateral wall electrodes are assumed to be less traumatic than preshaped electrodes and are preferred for hearing preservation.

Histological studies performed in fresh and fixed human temporal bones have demonstrated that electrode arrays inserted in the cochlea can cause mild to severe trauma [6, 7]. With a good electrode design the occasional trauma is limited to a spiral ligament compression and basilar membrane bulging in localized region(s) of the cochlea. The location most at risk from trauma is the point of 1st contact between the electrode and the lateral wall for free-fitting lateral wall electrodes, at an insertion angle of around 90°. With a poor electrode design the trauma can include electrode displacement from scala tympani to scala vestibuli with spiral lamina fracture and rupture or displacement of the basilar membrane, with risks of endolymph and perilymph mixing [8].

The key features to reduce electrode trauma in the cochlea are the size and flexibility of the array. The electrode should be much smaller than the dimensions of the smallest cochlea, but without compromising the pushability of the electrode. Most importantly, the electrode should be flexible to easily adapt to the angulations of the basal and second turn of the cochlea, regardless of lateral or medial wall positioning. A key feature to make an electrode flexible is zigzagging the platinum-iridium wires inside the electrode silicone carrier (fig. 1). A collection of straight wires, even 25 μm in diameter, increases the rigidity and more than doubles the insertion force of the electrode compared to an array with wires in zigzag form. Slightly reducing the diameter of the metallic wire reduces insertion forces, but not as much as wiggling the wire into zigzag shape. Measurements of the insertion force of a commercially available electrode with a network of zigzag wires (fig. 2)
are shown in figure 3 and compared to the insertion force of the same electrode with straight wires. Insertion forces were compared in the same 3-dimensional plastic 1:1 size scala tympani model. In both cases, the electrode wires were platinum-iridium 25-μm wires, Teflon insulated to a diameter of 33 μm.

The least traumatic (and surest) approach for entering the scala tympani is through the round window, after partial removal of the so-called round window niche [3, 9]. The annulus around the round window should be untouched. Entering the cochlea purely through the round window does not cause any disruption of the spiral ligament and associated bleeding from venules that irrigate the lateral wall soft tissues. A round window puncture of the size of the electrode diameter at its most basal end is required. For such a non-cochleostomy approach, the electrode diameter at its most basal end should be smaller than the width of the round window, preferably less than 1 mm in diameter. The success of the electric acoustic stimulation approach demonstrates that partial blockage of the round window by a foreign body does not significantly suppress cochlear mechanics. This fact has also been recently demonstrated by the successful placement of an implantable middle ear mechanical transducer in the round window niche [10].

With the round window approach, the point of 1st contact between the electrode tip and the lateral wall takes place sooner than with a cochleostomy approach. If the front end of the electrode (initial 10 mm) is superflexible, the electrode array has no difficulties engaging the lateral wall of the cochlea with minimal trauma. Superflexible front end electrodes have little chance of deviating from one scala to the other during insertion since the softness of the electrode associated with its flexibility preclude the possibility of developing the force necessary at the electrode tip for basilar membrane perforation or spiral lamina fracture. Contrary to rigid electrodes, superflexible lateral wall electrodes do not have a ‘tip fold-over’ when pushed into an area of increased resistance. Tip resistance to insertion causes basal buckling of a flexible electrode at or near the entrance point, be it round window or cochleostomy [11].

In order to reduce stiffness and increase electrode flexibility it is desirable to keep the channel
density low. A large number of channels over a short length increase stiffness and subsequent risks of trans-scala displacement. Fewer contacts, spaced further apart, increases flexibility. In any case, the front end of the electrode should be especially flexible to engage well into the scala tympani without deviation of the tip. Differential contact density between the front end and the back end of the electrode array may be warranted. In one electrode design, reduction of front end wire and contact density by 50% and an associated reduction in size and volume yielded a significant reduction in insertion force [1].

Low-frequency hearing loss after hearing preservation surgery that includes the insertion of a short or medium electrode array is not directly related to the physical presence of the electrode since the hearing loss is in a region where no electrode carrier is present. Hearing loss in that case is related to the indirect effects of trauma, caused either by the electrode insertion or the surgical opening of the cochlea or a foreign body reaction such as fibrosis. The indirect effects may include inflammatory processes [12], cell necrosis and apoptosis [13], fibrosis [14], and blood diffusion [15].

It has long been assumed that the presence of an electrode near an organ of Corti region with functional hair cells would guarantee the destruction of hearing in this region. There are reports that the presence of an electrode in the low-frequency region does not always prevent hearing preservation [16, 17], just as there are reports that insertion of a very short electrode array is not a guarantee for hearing preservation in the low-frequency region [2].

The optimum electrode insertion depth for hearing preservation is unclear at this time. More prospective studies are needed. Also needed are studies that evaluate the mechanical effects of the electrode on hearing preservation in cochlear implant patients with more or less flat but measurable audiograms, or even in patients with residual high-frequency hearing. In order to better and consistently control the indirect effects that can cause hearing loss in the low-frequency region during hearing preservation surgery, a pharmaceutical strategy is necessary [18].

**Pharmaceutical Approaches for Hearing Preservation**

Experience has shown that most of the causes of postoperative hearing loss after cochlear implantation can be minimized by electrode design, and optimized surgical technique with acute attention to detail. However, the degree of variation in anatomy and underlying pathology, the required level of surgical skill and (as yet undetermined) factors after implantation leave considerable potential risk to hearing. Protection of the cochlea during implantation is likely to have benefits for most cochlear implant candidates, either through hearing preservation or through increased protection of the status of the auditory nerve. Furthermore, as greater success is achieved, audiological boundaries will be pushed, and hearing preservation will be explored with greater insertion depths and greater degrees of residual hearing. Patients with progressive hearing loss might be implanted earlier, and with a better outcome, if the remaining hearing could be maintained. The safe and appropriate development of pharmaceutical approaches for hearing preservation in cochlear implant patients is likely to be a major milestone in the practical development of pharmaceutical therapies against acquired deafness. The invasive nature of cochlear implant electrode insertion itself provides both an opportunity for accurate local drug delivery and a platform for the development of a delivery device.

Effective treatment of hearing loss using a pharmaceutical approach requires an understanding of the underlying mechanisms at the molecular level. Cochlear pathology has traditionally been difficult to analyze due to inaccessibility, size and the difficulties associated with creating models of disease.
However, a number of researchers have made significant progresses in recent years in, for example, animal models of ototoxicity, noise trauma and cochlear implantation. Inflammation and cochlear homeostasis are better understood. A review of current work relating to the protection and repair of inner ear sensory cells is given in Forge and Van de Water [19]. Eshraghi and Van de Water [20] describe how cochlear implantation trauma activates both inflammatory and cell death pathways, and may involve several mechanisms at the molecular level, i.e., necrosis, necrosis-like programmed cell death (type 2 programmed cell death), and apoptosis (type 1 programmed cell death).

Two drugs shown to be very effective in animal models of implantation trauma are the apoptosis inhibitor AM111 (D-JNK-1 inhibitor), currently undergoing clinical trials against acute sensorineural hearing loss (Auris Medical, Switzerland), and steroids, including dexamethasone. Eshraghi and Van de Water [20] demonstrated apoptosis in upper turns of the guinea pig cochlea after implantation trauma and reduction in the degree of hearing loss using AM111. Staecker et al. [unpubl. data] have reported increased levels of TNF-α (an inducer of inflammation) in the cochlea after implantation trauma. Keithley et al. [21] demonstrated that TNF-α can recruit leucocytes into the cochlea at concentrations that are not cytotoxic to sensory cells in the organ of Corti. Dinh et al. [22] demonstrated in organ-specific culture that TNF-α may have a direct toxic effect on hair cells by increasing the Bax/Bcl-2 ratio. A number of groups have investigated the use of steroids (to suppress the inflammatory response) using a variety of delivery methodologies, demonstrating efficacy in the protection of hearing after mild to moderate levels of trauma [23–26] (see also the study of dexamethasone elution by Kiefer et al. [27] reported later in this article). Steroids can have quite a wide spectrum of activity, however, including antioxidant and homeostatic effects. Possible mechanisms specific to this application are reviewed in Eshraghi et al. [13] and Dinh et al. [22]. In another study, Barkdull et al. [28] demonstrated considerable efficacy of AM111 against hearing loss caused by inflammation. Both drugs therefore appear viable for further development. The suitability of a drug for use in the inner ear depends on many factors. Foremost is the issue of safety. Additionally, specific features of the drug and its formulation are important to the design of the delivery system [29]. These include molecular weight and charge, rate of clearance, time of action, adherence to the materials of the system, stability, specificity, and solubility. The ratio between effective and toxic concentrations must be high enough to allow for uncertainties in distribution, and the available formulations and regulatory status of the drug will affect the system development costs.

**Delivery Devices Tailored to the Application**

Each possible therapy identified through basic research requires a delivery system capable of adequate, and accurate, dosage to the target tissues in the required time frame. Some therapies, for example AM111, require application within a few hours. Others, such as steroids, may be most effective using delivery over a number of days or weeks, whereas targeting, for example, long-term fibrosis, or chronic or progressive pathologies, may require extended periods of treatment. The future may even allow treatment extended over many years with either slow release or periodic bolus delivery. Possible delivery mechanisms include systemic (oral or injection), round window delivery (diffusion or injection), and a number of intracochlear delivery methodologies. For many drugs it is anticipated that local delivery will be preferable, and in some cases necessary, to avoid systemic effects, reduce the usage of expensive drugs, and allow accurate local dosage. Proteins, peptides, liposomes and biologics normally require local delivery. Round window diffusion is relatively simple, but is unlikely to be optimal for the electric acoustic stimulation application. Due
to the slow rate of diffusion of substances along the scala tympani, combined with clearance from the perilymph and variability in round window membrane permeability, very high doses or extended treatment times are likely to be required for adequate treatment of the apical turns [30]. Three systems currently under development will be described in the following paragraphs.

**Elution of Dexamethasone from the Electrode Carrier**

Farahmand and colleagues (US patent publication No. 2007/0213799A1) have demonstrated that pharmaceutical grade micronized dexamethasone can, with proprietary techniques, be homogeneously mixed with the medical grade silicone elastomer used in the cochlear implant electrode array, and that the resulting combination product will elute dexamethasone into physiological media in a predictable manner. Depending on the drug percentage loading and the geometry of the eluting silicone, the release rate and duration can be predetermined according to the desired treatment regime. After an initial release burst (dependent on the device constituents and the initial surface treatment), a steady state is rapidly reached in which the rate of release is primarily determined by the surface area in contact with the fluid. The release duration is determined by the cross-sectional area of the device and by the total load of drug substance. Elution of a low dose of dexamethasone from a submillimetre silicone rod such as the implant electrode array is indeed possible for many months, if required – but shorter

<table>
<thead>
<tr>
<th>Drug percentage</th>
<th>Batch</th>
<th>Release amount on the first day μg</th>
<th>Release amount after 1 month μg</th>
<th>Release amount after 2 months μg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>batch 1</td>
<td>0.2479</td>
<td>2.7074</td>
<td>4.4465</td>
</tr>
<tr>
<td></td>
<td>batch 2</td>
<td>0.2366</td>
<td>2.6305</td>
<td>4.4009</td>
</tr>
<tr>
<td></td>
<td>batch 3</td>
<td>0.2728</td>
<td>2.8838</td>
<td>4.7306</td>
</tr>
<tr>
<td></td>
<td>mean ± SD</td>
<td>0.25245±0.0185</td>
<td>2.7405±0.1298</td>
<td>4.5260±0.1786</td>
</tr>
<tr>
<td></td>
<td>RSD</td>
<td>7.35255</td>
<td>4.73822</td>
<td>3.94756</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>0.35</td>
<td>0.097</td>
<td>0.102</td>
</tr>
<tr>
<td>2</td>
<td>batch 1</td>
<td>0.8149</td>
<td>10.0200</td>
<td>17.1006</td>
</tr>
<tr>
<td></td>
<td>batch 2</td>
<td>0.8711</td>
<td>10.2921</td>
<td>17.4384</td>
</tr>
<tr>
<td></td>
<td>batch 3</td>
<td>0.8712</td>
<td>10.1037</td>
<td>17.5676</td>
</tr>
<tr>
<td></td>
<td>mean ± SD</td>
<td>0.8524±0.0324</td>
<td>10.1386±0.1393</td>
<td>17.3689±0.24111</td>
</tr>
<tr>
<td></td>
<td>RSD</td>
<td>3.80810</td>
<td>1.374913</td>
<td>1.38822</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>0.559</td>
<td>0.459</td>
<td>0.344</td>
</tr>
</tbody>
</table>

RSD = Relative standard deviation.
release times can be set by appropriate design parameters.

Dexamethasone was thoroughly mixed with two parts silicone at 0.25, 0.35, 0.5, 1.0 and 2.0% weight for weight of the final cured polymer. Three consecutive batches were prepared for each percentage loading for reproducibility analysis. For each batch and concentration, four samples of the eluting silicone were created with dimensions representative of the intracochlear portion of the electrode array, without contacts or wires, and each underwent in vivo release experiments in both sink (5 ml) and non-sink (1 ml) conditions using normal saline at 37°C as the release medium. The concentration of dexamethasone in the release medium was determined at geometrically spaced intervals using HPLC analysis. Excellent batch-to-batch reproducibility of the samples was found across the range and is illustrated in table 1, for the extremes of the range. Figure 4 shows the cumulative amount of drug released from silicone dummy electrodes of various dexamethasone loading over a 250-day release period, illustrating the dependence of daily dose on drug loading. The release profile was also strongly affected by the specific ratio of the two constituent parts of the silicone used for dummy electrode preparation. This is believed to be a direct consequence of variations in cross-link density, as shown in figure 5.

The silicone produced by this method has very similar properties to that of non-eluting silicone, except for an increase in opacity. Importantly, no change is imparted to the physical properties of the manufactured electrode array, in contrast to significant increases in stiffness typically found after ultrathin coating with drug-releasing biodegradable polymers. Clearly there are many advantages associated with such a delivery regime; the drug can be released uniformly along the electrode array, imparting a large advantage over round window delivery. The steroid-eluting electrode array can be used in the same way as a standard cochlear implant electrode, adding no time or complexity to the surgical procedure. Furthermore, the lack of additional chemical entities (i.e. drug excipients) reduces the risk of toxicity to the inner ear tissues compared to fluid-based approaches.

The optimal delivery period for anti-inflammatory agents after implantation has not been fully established, but there is evidence of efficacy.
in animal studies after delivery of a single application of dexamethasone phosphate [25] and after maintenance of a low dose of dexamethasone base for a period of 8 days [26]. Any possible benefits of extending the treatment regime beyond the first few weeks after implantation would need to be balanced against increased risks due to prolonged exposure to the drug.

Kiefer et al. [27] investigated the efficacy of dexamethasone elution in reducing hearing loss after cochleostomy and insertion of rods of implant grade silicone 3–4 mm into guinea pig cochleae. Rods of dexamethasone-eluting silicone were created, 0.6 mm in diameter, with drug loadings of 2 and 10%. In the animal model, in vivo measurements of drug concentration were made at sacrifice using apical fluid sampling of 10 μl at selected intervals after implantation of dexamethasone-eluting electrodes. The results are shown in figure 6. This figure illustrates the higher dosing achieved with higher drug loading for the same geometry. A burst release is followed by a relatively stable concentration during the first week. After this time, the rapid clearance from the cochlea combined with the small sample volume brought the concentration below the detection limit of the HPLC system. Importantly, there was no evidence of accumulation of drug in the perilymph at the doses used.

In the same model, the degree of hearing loss after implantation of eluting and control (non-eluting) silicone rods was evaluated (n = 18/group). Auditory thresholds were established using tone burst BERA and distortion product otoacoustic emissions. The data are shown in figure 7. At 1 month, there was a significantly lower threshold shift, at mid to high frequencies, after implantation with dexamethasone-eluting rods than in...
animals implanted with control rods. This difference was maintained for 24 weeks.

Ongoing safety studies are now evaluating the effect of steroid elution on infection risk. Locally applied steroids are known for their ability to inhibit wound healing, and this has potential adverse effects for both hearing preservation and postoperative infection (through increase in the time for tissue sealing around the electrode array). This risk should always be borne in mind when introducing steroids to the middle ear during cochlear implant surgery, particularly due to
the rare but potentially catastrophic nature of the risk involved. It is likely that such a risk will be related to the drug dosage and duration of application, in addition to the methods used for electrode array entry to the cochlea and sealing the site of cochleostomy or round window entry. The safety studies will investigate the effect of dexamethasone elution on cochleostomy sealing, and on the risk of meningitis after bacterial challenge, in animal models.

As the device described is an innovative combination product in which a medicinal product performs an ancillary function to an active implantable medical device, at a new location for drug application, the route to device approval will be complex. Comprehensive laboratory evaluation of the product will be required to include assessments of interactions of all constituents, in addition to safety evaluations around the use of dexamethasone in the inner ear. If these have a positive outcome, as anticipated, then evaluation of the finished product will be performed according to the requirements of the competent authorities through a structured programme of clinical trials, with the performance of the drug in reducing the risk of hearing loss after implantation defined as a primary endpoint.

**Intracochlear Drug Injection Prior to Electrode Insertion with a Disposable Single-Use Catheter**

Acute and topical, intraoperative pharmacological treatments of the cochlea have included the use of corticosteroids in crystal (depot) or liquid form to prevent the inflammatory process from spreading [24, 32]. A drop of solution is placed at or very near the cochleostomy site. It has been assumed previously that electrode insertion will carry the solution at some depth into the scala. The hydrodynamics associated with electrode insertion suggest the opposite: the drug, instead of being brought further into the cochlea, is expelled into the middle ear due to flushing of the perilymph out of the scala by the electrode insertion. A volume of perilymph equivalent to the volume of the electrode must be expelled to make room for the electrode. The volume of an electric acoustic stimulation electrode may be 20% of the scala tympani volume for a short insertion of 20 mm, and 40% for an insertion depth of 31 mm with an electrode of standard size.

In order to bring a defined amount of drug into the scala tympani, at a known location and at some known depth into the scala, the use of a disposable single-use catheter delivery is warranted. A prototype disposable catheter is shown in figure 8. The catheter front end is exactly the shape of the intracochlear electrode used by the hearing implants manufacturer MED-EL, with a single opening at the tip. The material is the same as for the electrode (medical grade silicone elastomer). No wires or contacts are included in the catheter, making the device particularly soft and flexible. Insertion depths of up to 20 mm are achievable without significant resistance. Six silicone ink marks are shown on the catheter, 5 mm apart. Catheter insertion up to 20 mm will displace around 7 μl of perilymph (the volume of the catheter). Injection of 10 μl of an isotonic pharmacological solution will backflush another fraction of perilymph, for a total of 17 μl, which is about half the volume of the scala tympani [33]. Electrode insertion after catheter removal will simply replace the disposable device without causing additional fluid displacement. The advantage of the single-use catheter is that a known volume of drug is delivered along the cochlea. The backflush effect ensures that the drug is distributed from the catheter tip back to the insertion point (fig. 9). Further drug diffusion into the apical region of the cochlea will occur after implantation. In situ feasibility of the procedure has been investigated and will be published. In eight temporal bones, the catheter was inserted into the cochlea and a iodine solution injected. CT scans of the temporal bones show that the injected liquid is located in the scala tympani (fig. 10). Histology has revealed no perforation of the basilar membrane after gentle injection of 10 μl of solution with a Hamilton syringe. The effects
of inserting a supersoft catheter and slowly injecting a protective isotonic drug into the cochlea to preserve the apical sensory epithelium need to be investigated in vivo. Insertion and removal of a disposable soft catheter followed by insertion of a permanent flexible electrode may not be detrimental to the cochlea if the long-term protective effect of the drug outweighs the additional catheter trauma, provided this is minimal.

Furthermore, few possess a depot facility to maintain a therapeutic dosage in the cochlea, avoiding its clearance mechanisms. To satisfy the potential need for delivery of such substances uniformly over a substantial length of the cochlea, the concept of delivery from an integral gel or fluid-filled reservoir in the body of the electrode array has been investigated both in vitro and in vivo. The concept involves a single, wide channel extending most of the length of the electrode array and (potentially) beyond the intracochlear portion by several centimetres (fig. 11). Outlets from the reservoir channel to the cochlea would be small in dimension to allow control of the rate of drug release by passive diffusion out of the gel or fluid carrier. The release location could be controlled by outlet positioning, the dosage by the concentration of drug in the reservoir, and the duration

**Delivery of Medicinal Products or Biologics through a Gel-Filled Reservoir in the Electrode Carrier**

A number of medicinal products proposed for inner ear use are hydrophilic (and therefore immiscible with the implant silicone), complex, unstable, or too large to diffuse rapidly throughout the cochlea for treatment of the apical tissues.
by the reservoir size. The device could be pre-filled, or loadable by the surgeon at the time of implantation through a port and septum (to prevent ingress of bacteria and extracellular fluids). The use of a viscous gel to house the drug within the reservoir would prevent drug loss by device flexion during implantation, at the same time as maintaining the electrode carrier flexibility required for trauma reduction. The drug might alternatively be added to the reservoir in powder form, for release by fluid ingress into the outlets. Nanoparticles and biologics could also be delivered in such a manner.

Initial evaluation of the concept has involved in vitro assessment of dexamethasone release profiles, and an analysis of microbial contamination of a simplified reservoir implanted for 90 days in a guinea pig model. This device was a simple tube with a single outlet at the tip, implanted up to 1 mm inside the guinea pig cochlea. Six tubes initially filled with saline or dexamethasone sodium phosphate solution (Fortecortin, Merck, Darmstadt, Germany) were explanted after 90 days, and their contents incubated within 1 of 5 agar preparations specific for bacteria most likely to be found on an implant electrode. No growth of pathogen colonies was demonstrated under these conditions. In a pilot trial, the same reservoir tubes filled with physiological saline or dexamethasone sodium phosphate were implanted for 90 days, during which time frequency-specific hearing levels were assessed using the compound action potential. The results suggested a small but significant advantage of the steroid at
high frequencies, and are shown in figure 12. In conclusion, these preliminary investigations support further work on the device, to ensure safety and to improve its usability. The device also has the potential for long-term or delayed drug delivery, perhaps in response to an audiological or physiological event.

Acknowledgements

The authors would like to acknowledge the contributions of Jochen Tillein from the University of Frankfurt, Houssam Nabih Ibrahim from the University of Lyon, Yi Liu and Claudius Fauser from the Technical University of Munich, Dr. M. Imani and Dr. F. Farahmand from the Iran Polymer and Petrochemical Institute (IPPI), Tehran, and Dr. M. Farhadi from the Iran Cochlear Implant Center (ICIC), Tehran. The project was funded by MED-EL and by EC contract No. 026556-2, NANOEAR.
References


