Ear diseases can significantly affect the life quality of patient, so the need for effective treatment encourages the development of new active substances and new dosage forms. Otic dosage forms may be solutions, suspensions, or emulsions of drops or spray for washing the ear or for administration to the ear canal. They may be ear-wash preparations in the form of solution or emulsion, or medicated semi-solid or solid preparations in the form of gel, cream, ointment, powders, sticks or buffers. These preparations can contain one or more active ingredients in a suitable vehicle and additionally may contain different excipients for isotonisation, pH adjustment, viscosity or solubility enhancement, buffering, preservation, etc. These excipients should not alter the pharmacological effect of active substances and should not be toxic or irritating. Ear preparations can be packaged in single or multiple doses. It is anticipated that otic dosage forms will be improved and the importance of locally applied, safe and highly controlled drug delivery systems will increase in the future.

Keywords: Drug delivery, ear, excipients, local administration, otic dosage forms, topical.

INTRODUCTION
Potentially life-threatening infections such as sepsis and meningitis, especially for immunocompromised hosts, may spread to the surrounding tissues if not optimally treated. Otic dosage forms are used to treat external ear and auditory canal infections among them. In addition to infections, otic dosage forms are often used against ear diseases such as acute or chronic otitis media, hearing loss, tinnitus and Meniere's disease1. According to World Health Organization criteria, 25 dB loss in hearing frequency pure tone average in both ears is defined as hearing loss and this negatively affects the communication of the individual in daily life. Approximately 300 million people in the world have moderate or severe hearing loss, and this figure is expected to reach 900 million by 20502,3. The ear of human consists of three parts as outer, middle and inner ones. Sound waves reaching the outer ear cause eardrum in the middle ear to vibrate and these vibrations are transmitted to the inner ear with the help of bones. Here, the vibrations are translated by the snail, the original hearing organ, into nerve signals that the brain perceives4. Many diseases such as ear pain, otitis externa, otitis media, tinnitus, ear wax, tympanic membrane perforation, acoustic neuroma, mastoiditis, benign paroxysmal positional vertigo, cholesteroloma and Meniere's disease can affect any of these three main sections. Otitis media is the most common ear disease5,6. Otitis externa, known as swimmer's ear, affecting the outer ear, can be seen with or without infection throughout the ear canal. It can be subdivided into acute (less than six weeks), recurrent acute and chronic (more than three months). The most common clinical case among these is acute otitis externa, which cause is a bacterial infection (90% of cases) or a fungal infection (10% of cases)7. The most prominent feature of this disease is the local feeling of discomfort in the external auditory canal, redness of the canal and swelling with a variable flowing. The causes of acute otitis externa can also be associated with various non-infectious systemic or local dermatological processes8,9. Local anesthetics, cleaning agents (peroxides), anti-infectives and antifungals are among the commonly used categories of otic drugs for humans. Dosages of these drugs can be in liquid, ointment, gel or powder forms that are prepared for administration into the ear10. The solutions are also used to wash the ear, to remove ear wax, infected fluids
and foreign bodies from the ear canal. They can be included surfactants, sodium bicarbonate, boric acid (0.5-1%) or aluminum acetate and usually heated to about 37°C before being applied to the ear. If a long period of drug action is required for treatment of an ear infection, otic suspensions can be used. Otic ointments and gels containing antibacterial, antifungal or corticosteroid components are rarely used and applied directly to the outer parts of ear. Insufflation as solid preparations in the form of fine powders is applied to the ear canal. However, the application of powder into the ear canal is not very common, since ear is free of fluids and dust-plug accumulation may occur. The fine powders comprising antibacterial or antifungal agents may be used for otic delivery via small rubber or plastic bulb, which can be used as powder blower. In the past, use of chloramphenicol has been indicated to deliver high concentration antibiotic to the ear without any contribution to ear moisture.\textsuperscript{11,12}

Since locally administrated topical otic dosage forms and the number of published studies in this group is quite a limited, recent situation and developments in this field are overviewed in terms of available sources in this study.

| Function category          | Exipients                                         | Dosage forms                |
|----------------------------|---------------------------------------------------|----------------------------|
| pH adjusting agents        | Acetic acid, calcium carbonate, citric acid       | Solution, suspension,      |
|                            | hydrochloric acid, benzy alcohol, lactic acid,    | liquid, drops               |
|                            | mono potassium phosphate, sodium acetate, sodium |                           |
|                            | borate, sodium citrate, sodium phosphate (dibasic,|                           |
|                            | monobasic), sodium hydroxide, sulfuric acid,     |                           |
|                            | tris (hydroxymethyl) amino methane                |                           |
| Antimicrobial preservatives| Aluminum acetate, benzalkonium chloride,         |                           |
|                            | benzethonium chloride, benzy alcohol, boric acid,|                           |
|                            | chlorobutanol, isopropyl alcohol, phenethyl     |                           |
|                            | alcohol, methyl paraben, potassium               |                           |
| Suspension agents          | Aluminum sulphate, cetyl alcohol, hydroxethyl    |                           |
|                            | cellulose, methyl paraben, polyvinyl alcohol     |                           |
| Stabilizing and            | Creatinine, hydrogenated soybean lecithin,       |                           |
| thickening agents          | polyvinyl pyrrolidone K30, polyvinyl             |                           |
| Softeners                  | Cupric sulphate, glycerol, polyoxyyl 40         |                           |
| Solvent agents             | Polysorbate 20, Polysorbate 80, Tyloxapol        |                           |
| Tonicity adjusters         | Sodium chloride, sodium sulphite                 |                           |
| Ointment base              | Mineral oil, peanut oil, petrolatum               | Oil, ointment              |

**Local and topically applied otic dosage forms**

In general, dosage forms for topical otic drug administration are eardrops, foams, gels, creams and ointments.\textsuperscript{13} The active ingredients may be dissolved or dispersed in water or diluted alcohol, polypropylene glycol and anhydrous glycerin.\textsuperscript{14} Carriers should exhibit the properties of especially softening the ear wax and skin, inert, non-irritating and viscous vehicle properties that extend the contact time of the active agent with the ear canal surface. The viscosity of a topical formulation is important to provide sufficient contact time of dosage form to release the active agent to the site of infection effectively. Otic foams are commonly used to increase drug contact time in the ear canal.\textsuperscript{15,16} Due to the dose volume applied to the otic site is low, the concentration of active substance in dosage form need to be high, so that the solubility of the active substance is taken into consideration when selecting the proper solvent. Generally, topical otic preparations are prepared in the form of acidic solutions or suspensions with a pH of 3-4 for inhibition of bacterial growth. Commonly used excipients are summarized in Table 1, based on the FDA inactive content database and on the market-approved current otic products.\textsuperscript{17,18}

In the development of otic formulations physicochemical factors such as solubility, viscosity, toxicity, surfactant and preservative properties, serum diffusion activity, impregnation properties, serumolytic activity and rheological properties play an important role.\textsuperscript{19} Many active substances could be soluble in the commonly used carriers for these dosage forms, however, in case of active substances do not dissolve in carriers or have different solubilities, otic formulations can be prepared as suspension. Since most of the carriers having a proper viscosity, addition of deflocculating agents may be necessary. Obtaining optimum viscosity for these dosage forms will provide longer contact time with the ear surface and prevent the leakage of formulation. In this context, while low viscosity may cause shorter contact time of formulation, high viscosity may cause lack of reach of the formulation to the inner parts of ear or may be delayed the delivery of active substance.\textsuperscript{20} The toxicity and hygroscopicity properties are important because they help drawing liquid from the immediate area of the ear. If an otic formulation is hypertonic some liquid may be drawn from the ear thereby releasing some of the pressure, on the contrary if the formulation is hypotonic there may be some fluid flow into the area. Surfactant content in these preparations, helps to spread the drug and break the cerumen. This also facilitates the removal of impurities. 0.5% Chlorobutanol, 0.01% thimerosal, and paraben combinations are commonly used preservatives for otic preparations. Antioxidants (sodium bisulphite, etc.), dehumidifying agents and other stabilizers (such as isopropyl alcohol), which reduce the moisture that is necessary for bacteria to survive are also included in otic formulations, when it is necessary. Dosage forms for ear disorders are usually packaged in small glass or dropper plastic containers with volume of 5 to 15 mL.\textsuperscript{12,21,22} Quality control studies for conventional ear dosage forms are usually performed according to standard quality control procedures such as active substance identification and quantification, volume/weight, pH, viscosity, density, appearance and sometimes odor control. Additionally, quality control parameters can also be used depending on the dosage.
form or existing of in house quality control tests\textsuperscript{23,24}. Otic formulations development should follow aforementioned basic formulation principles to provide effective and specific treatment for each type of ear disease. Otic drug administration can be divided into systemic and local drug administration. Despite potential side effects, systemic drug delivery is a minimally invasive approach and is well suited for self-administration. Systemic administration, therefore, continues to play an important role in the delivery of otic drugs. In terms of pharmacological activity commonly used topical dosage forms include antibiotics and antifungals in the form ear drops, gels or foams\textsuperscript{18,25,26,27}. Topical drug administration to the otic area provides several advantages\textsuperscript{28}. The most important advantage is that a higher local drug concentration is achieved rather than by systemic administration. This is usually necessary for therapeutic purposes; for example, removal of biofilm bacteria requires an antibiotic concentration of 10-1000 times higher than that of planktonic bacteria. Other advantages of topical drug administration include rapid dispersion, good patient compliance and the ability to combine different drugs into a single formulation. The most important disadvantage of topical drug administration is the potential ototoxicity of some drugs, especially if the active substance concentration is too high\textsuperscript{29}. Antibiotic eardrops show the benefits of ototopical administration for patients with punctured tympanic membranes or tympanostomy tubes. However, the stratum corneum provides penetration barrier and restricts the clinical use of such drops to patients with non-intact tympanic membranes. In this context the most appropriate drug delivery route for otic applications should be optimized taking into account for the disease, possible side effects and the patient’s needs. Strategies to cope with the stratum corneum barrier including lipid nanoparticles, chemical permeation enhancers, iontophoresis and micro-injection, have been extensively explored for use in transdermal drug delivery applications. Investigations in otic drug delivery have a tendency to achieve an effective medication with more than local effect with local application. In this direction studies with nanomedicine and particular drug delivery systems (polymersome, lipid based nanoparticles, etc.) associated otic dosage forms have been focused\textsuperscript{30-36}. Treatment of inner ear disorders has shown challenges both due to anatomical and physiological barriers of the ear. Additionally in case of need to prolonged release of drug, the stability problems of the drug molecules in the inner ear have been occurred as another challenge. Recent approaches to overcome these challenges have included use nanoparticles in formulations for targeted drug delivery into the inner ear. Mittal et al., have been summarised, nanoparticles used for drug delivery into the inner ear in their study\textsuperscript{33}. Since biologic treatment options are limited for sensorineural hearing loss due to lack of noninvasive targeted delivery systems. Li et al., have studied nanoparticles containing nanohydrogel that may offer noninvasive and sustained biotherapeutic delivery into specific inner ear cells. Nanoparticles can be stabilized and carry biomaterials across the round window membrane into the inner ear, and ligand bioconjugation onto nanoparticle surfaces allows for specific targeting\textsuperscript{35}. In the treatment of noise exposure related hearing loss, antioxidants and the duration of treatment are noticeably effective on hearing recovery. Gao et al., have studied nanoparticle delivery of edaravone, which is an antioxidant and used in the treatment of noise-induced hearing loss. They investigated the protective effects of edaravone solid lipid nanoparticles and found that solid lipid nanoparticles show noticeable slow release effects and have certain protective effects against noise induced hearing loss on steady noise exposed guinea pigs\textsuperscript{36}. The proven safety and efficacy of lipid-based carriers allowing for controlled/sustained drug delivery make them potential carrier materials for drugs which encounter penetration and absorption problems as well as attractive candidates for preparing lipid-based formulations. Commonly topically administered gentamicin is toxic to the sensory cells of the ear. To overcome this, Kenechukwu et al., reported the delivery of gentamicin by tactical engineering using PEGylated lipid-based drug delivery system\textsuperscript{31}. They formulated solidified reverse micellar solution consisting of P90G and heterolipids from I. gabonensis, and PEGylated solidified reverse micellar solution-based solid lipid microparticles containing gentamicin using melt-emulsification technique and concluded that PEGylated solidified reverse micellar solution-based solid lipid microparticle is better to be used to control the release of gentamicin, because of enhancement its permeation and potential reduction in its toxicity\textsuperscript{31}. Khoo et al., have studied formulations for the sustained trans-tympanic delivery of ciprofloxacin which has established ototopical use in children with acute otitis media with tympanostomy tubes. They incorporated chemical permeation enhancers like sodium dodecyl sulfate, limonene, and bupivacaine into formulations to improve drug flux across the intact tympanic membrane and examined the consequence changes in trans-tympanic drug permeability across intact chinchilla's tympanic membrane\textsuperscript{35,36}.

**CONCLUSION**

As a conclusion although many difficulties in developing otic drugs continue, the sustained progress towards understanding the biology of the ear has led to the development of new drug delivery systems including hydrogels, particulate systems, and other minimally invasive drug delivery methods. Modern delivery systems offer better treatment options for individuals, with minimal side effects and a better life quality for patient suffering from ear diseases. As the advanced technology for delivery systems is focusing on polymers and lipid based nanoparticles, the recent studies for improving local topical products are highly rare. But significant improvements in the study of drug release from otic dosage forms associated nanotechnology and advanced drug delivery systems will encourage further studies in this area.
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