Original Review Article

A RECENT OVERVIEW OF LOCALLY ADMINISTERED TOPICAL OTIC DOSAGE FORMS

ABSTRACT

Ear diseases can significantly affect the quality of life of people, 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 semi-solid preparations of gel, cream or ointment form, or preparations in the form of powders, sticks or buffers. These preparations may contain one or more active ingredients in a suitable vehicle. In addition to the active ingredient, isotonisation, pH adjustment, viscosity or solubility enhancement, buffering, preservation, etc. excipients may be included forthe above mentioned purposes. These substances should not alter the pharmacological effect of the active substance 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 non-invasive, safe and highly controlled drug delivery systems will increase in the future.

Keywords: Otic dosage forms, ear, topical, local administration, drug delivery, excipients.

INTRODUCTION

Potentially life-threatening infections, especially for immunocompromised host, 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 disease [1]. 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. Around 300 million people worldwide have moderate or severe hearing loss, and this figure is expected to reach 900 million by 2050 [2, 3]. The human ear consists of 3 parts as outer, middle and inner ones. The sound waves reaching the outer ear cause the eardrum in the middle ear to vibrate. 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 perceives [4]. Many diseases such as ear pain, otitis media, otitis externa, Meniere's disease, tinnitus, ear wax, tympanic membrane perforation, acoustic neuroma, mastoiditis, benign paroxysmal positional vertigo, cholesteatoma can affect any of these three main sections. Otitis media is the most common ear disease [5, 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 6 weeks), recurrent acute and chronic (more than 3 months).The most common clinical case among these is acute otitis externa whose cause isa 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 variable flowing. The causes of acute otitis externa can also be associated with various non-infectious systemic or local dermatological processes [8,9].

Local anesthetics, cleaning agents (peroxides), anti-infectives and antifungals are among the commonly used categories of otic drugs for the human ear. Doses of these drugs can be in liquid, ointment, gel or powder forms. Otic solutions and suspensions in liquid dosage form are prepared for administration into the ear. The solutions are also used to wash the ear. Otic wash solutions such as surfactants, weak sodium bicarbonate, boric acid (0.5-1%) or aluminum acetate may be heated to about 37 °C before being placed in the ear to accommodate body temperature. These washing solutions; usually used to remove ear wax, infected fluids and foreign bodies from the ear canal. If a long period of drug action is required for the treatment of ear infection, otic suspensions in which the active ingredient is not dissolved in the liquid are used. Otic ointments and gels containing antibacterial, antifungal or corticosteroid components are semi-solid preparations that are rarely used but are applied outside the ear. These ointments are applied directly to the outer parts of the ear. Insufflation as solid preparations in the form of finely divided powders is applied to the ear canal. However, the application of a powder into the ear canal is not very common, since the ear is free of fluids and dust-plug accumulation may occur. The finely divided powders may comprise an antibacterial and/or an antifungal agent which will form a depot for the medicament. A small rubber or plastic bulb can be used as a powder blower for this purpose[10].

TOPICAL DRUG APPLICATIONS IN OTIC FIELD

In general, dosage forms for topical otic drug administration are eardrops, foams, gels, creams and ointments [11]. The active ingredients may be dissolved or dispersed in water or diluted alcohol, particularly polypropylene glycol and anhydrous glycerin. Among the carriers, polypropylene glycol is inexpensive but it shouldn't be forgotten that it has an ototoxic effect. Carriersshould exhibit the properties of especially softening the earwax and skin, inert, non-irritating and viscous vehicle properties that extend the contact time of the active material with the ear canal surface. The viscosity of a topical formulation is important because the drug must be able to reach the site of infection effectively. Agents to increase formulation viscosity may be added to protect the formulations in the ear. Otic foams are commonly used to increase drug contact time in the ear canal [12,13]. Because the dose volume applied to the otic site is low, the concentration of the drug to be prepared should be high, so that the solubility of the active substance is taken into consideration when selecting the 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 [14,15].

Table 1. Commonly used excipients for topical otic drug delivery systems.

Function category	Excipients	Dosage forms
pH adjusting agents	Acetic acid Calcium carbonate Citric acid Hydrochloric acid Benzyl alcohol Lactic acid Monopotassium phosphate Sodium acetate Sodium borate Sodium citrate	Solution, suspension, liquid, drops

	Sodium phosphate, dibasic, monobasic Sodium hydroxide Sulfuric acid Tris(Hydroxymethyl)aminomethane	
Antimicrobial preservatives	Aluminum acetate Benzalkonium chloride Benzethonium chloride Benzyl alcohol Boric acid Chlorobutanol Isopropyl alcohol Phenethyl alcohol Methylparaben Potassium metabisulfite Propylparaben	
Suspension agents	Aluminum sulfate Cetyl alcohol Hydroxyethyl cellulose Methylparaben Polyvinyl alcohol	
Stabilizing and thickening agents	Creatinine Hydrogenated soybean lecithin Polyvinylpyrrolidone K30 Polyvinylpyrrolidone K90 Poloxamer 407	
Softeners	Cupric sulfate Glycerol Polyoxyl 40 Stearate	
Solvent agents / Wetting agents	Polysorbate 20 Polysorbate 80 Tyloxapol	
Tonicity adjusters	Sodium chloride Sodium sulfite	
Ointment base	Mineraloil Peanutoil Petrolatum	Oil,ointment

Physicochemical Properties

Physicochemical factors such as solubility, viscosity, tonicity, surfactant and preservative properties, serum diffusion activity, impregnation properties, serumolytic activity and rheological properties play an important role in the development of otic preparations [16]. Although sterility is generally ignored, products must be clean. In the carriers commonly used for the preparation of these products, many active substances are soluble. However, if an active substance does no dissolve or there are more than one active substance which are insoluble in these carriers or they have different solubility profiles, the product can also be prepared as a suspension. Since most of these carriers are relatively viscous agents, the addition of defloculating agents may not be necessary. The optimum viscosity of the preparation that increases the contact time of the active agent with the ear surface and provides avoidance from the leakage from the ear is important for sufficient pharmacological activity. If the viscosity of the preparation is low, the contact time will be short. On the other hand, if the drug is very viscous, it may not reach the inner parts of the ear or the delivery of the active substance to the intended site may be delayed [17].

The tonicity and hygroscopicity properties are important because they help drawing liquid from the immediate area of the ear. If the product is hypertonic, some liquid may be drawn from the ear, thereby releasing some of the pressure. However, if the product is hypotonic, there may be some fluid flow into the area. The presence of a surfactant in the preparation helps to spread the drug and break the cerumen, as there are often difficult conditions to clean the ear. This also facilitates the removal of impurities. Microbial contamination does not occur in otic preparations due to the high concentrations of substances such as glycerin, propylene glycol, polyethylene glycol 300 or 400. If these agents are not present, preservatives should be added to minimize microbial contamination. Some liquid otic preparations also need to be protected against microbial growth. When protection is required, agents such as chlorobutanol (0.5%), thimerosal (0.01%), and combinations of parabens are commonly used. Antioxidants such as sodium bisulfite, dehumidifying agents and other stabilizers that reduce the moisture necessary for bacteria to survive, such as isopropyl alcohol, are also included in the otic formulations, when necessary. Ear preparations are usually packaged in small (5 to 15 mL) glass or dropper plastic containers [10, 18, 19].

Advantages and Disadvantages

Topical drug delivery systems have long played an important role in the treatment of ear diseases. This treatment includes direct administration of a drug to the ear canal. Commonly used topical drugs include topical antibiotics and drop-shaped antifungal drugs, gels or foams [15, 20, 21]. Topical drug administration to the otic area provides several advantages [22]. The most important advantage is that a higher local drug concentration is achieved than can be achieved 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 drug concentration is too high [23].

Quality control

While performing quality control studies, standard quality control procedures such as active substance identification and quantification, volume / weight, pH, viscosity, density, appearance and sometimes odor control are followed.

ADVANCED LOCAL TOPICAL OTIC MEDICINE RELEASE SYSTEMS

Significant progress has been made in the distribution of otic drugs in the last decade. In the past few years, patent applications have been filed on new compounds and drug delivery systems for the treatment of inner ear diseases. A better understanding of the mechanisms of inner ear diseases has led to the development of new drugs targeting voltage-gated potassium ion channels, glutamate receptors, and notch developmental signaling pathway inhibitors to treat hearing loss, tinnitus, and peripheral vestibular dysfunction [24, 25].

Local drug administration to the inner ear was first used more than half a century ago for the treatment of meniere's disease with local anesthetics and antibiotics. In the 1990s, locally

administered gentamicin became widespread when it was recognized that it provided an effective treatment for vestibular symptoms in patients with limited hearing risk and meniere's disease. In addition to aminoglycosides and anesthetics, a variety of drugs have been administered to the round window region of the inner ear in humans, including neurotransmitters and neurotransmitter antagonists for tinnitus, monoclonal antibodies for autoimmune inner ear disease, or apoptosis inhibitors (AM-111) for noise-induced hearing loss. However, although the evidence supporting the use of glucocorticoids is limited, they have become the most widely used drugs for local administration to the inner ear and have been used for the treatment of Ménière's disease, idiopathic sudden sensorineural hearing loss, autoimmune inner ear disease, and tinnitus. Currently, the choice of dosage protocols and drug systems is almost entirely empirical, and there is still limited knowledge of the pharmacokinetics of drugs administered to the ear [26, 27].

Local application to the ear is essential for sustained drug release to the round window region (*Fenestra cochleae*). In a guinea pig model, El Kechai et al. have developed a hyposuronic acid liposomal gel for continuous delivery of a corticoid to the inner ear after local middle ear injection. It was observed that the gel remained at the injection site and round window for a long time without affecting the hearing thresholds of the animal. The presence of liposomes in the formulation was able to achieve sustained drug release for 30 days [28].

Yu et al. have developed a hydrogel formulation in the form of an injectable PEG-Silk structure to provide sustained release of glucocorticoid. According to the results, the glucocorticoid concentration in the ear is above 100 ng/mL for at least 10 days when the PEG-Silk formulation is used, whereas for the control formulation containing free glucocorticoid it is less than 12 hours [29].

With new therapies using new polymers and nanoparticles, alternative strategies are provided to improve drug delivery through the inner ear membrane and to target specific sites in the inner ear [30, 31]. Yoon et al. have developed Arg8 conjugated nanoparticles as a controlled drug delivery system for the treatment of diseases in the inner ear. The results of the study show that the prepared nanoparticles are a promising formulation for drug or gene release [32]. It has been reported that the preparation of nanoparticle systems in a hydrogel increases the nano-carrier retention time in the middle ear, thereby increasing drug concentration in the inner ear. In a study by Lajud et al.,a nanohydrogel formulation in which the liposome is contained in a chitosan hydrogel has been developed [33]. They demonstrated that nanohydrogel was able to achieve a controlled and sustained release of the active substance, and by *in vivo* studies that liposomes were introduced into the periliphatic area and reached the cellular structures of the scale media.

Zhang X, Chen G et al. have developed new multiple agents loaded with poly (D, L-lactide-coglycolide acid) (PLGA) nanoparticles and evaluated their potential for drug delivery to the brain through inner ear administration. PLGA nanoparticles loaded with salvianolic acid B (Sal B), tanshinone IIA (TS IIA) and panax notoginsenoside (PNS) were prepared by double emulsion / solvent evaporation method. Optimized nanoparticles were shown to exhibit satisfactory encapsulation efficiency and desired sustained release properties. After intratympanic administration (IT) in guinea pigs, the distribution of drugs in the inner ear, cerebrospinal fluid (CSF) and brain tissues with nanoparticles was found to be better than intravenous administration. After intratympanic administration (IT) in guinea pigs, the distribution of drugs in the inner ear, cerebrospinal fluid (CSF) and brain tissues with nanoparticles was found to be better than intravenous administration. Pharmacodynamic studies have shown that nanoparticles significantly inhibit oxidative reactions and protect the brain from cerebral ischemia/reperfusion (I/R) damage by restoring superoxide dismutase (SOD) activity in both serum and brain tissues, as well as significantly reduce

malondialdehyde (MDA) levels and nitric oxide synthase (NOS). Moreover, intratympanic administration did not cause cochlear function damage by preliminary toxicity examination. Moreover, according to preliminary toxicity examination, intratympanic administration did not cause cochlear function damage. These findings suggest that the PLGA nanoparticle-based delivery system through inner ear administration is a promising candidate for delivering drugs to the brain for the treatment of brain diseases [34, 35].

CONCLUSION

Otic drug applications are developing rapidly, especially for the inner ear, and many new chemicals are in the preclinical or clinical stages. Many of these compounds have the potential to produce promising results for the effective and targeted treatment of inner ear disorders. Since noise, ototoxic drugs, ischemia, infection, inflammation, mechanical trauma, and other movements have been shown to cause damage to the inner ear in preclinical studies, it is very important to develop applicable and safe methods for the targeted delivery of drugs to specific areas of the inner ear. 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. Local drug delivery can also be classified as topical, intratympanic and intralocal. Local drug delivery has the unique advantages of achieving high therapeutic concentration in the ear and minimizing systemic side effects. The most appropriate drug delivery route should be optimized taking into account for the disease, possible side effects and the patient's needs.The development of otic formulations should follow aforementioned basic formulation principles to provide effective and specific treatment for each type of ear disease. 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, nanoparticles, and other minimally invasive drug delivery methods. These delivery systems offer better treatment options for individuals with side effects and a better quality of life for people suffering from ear diseases. Significant improvements in the study of drug release from otic dosage forms will encourage further studies in this area.

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