CHAPTER 15

NASAL AND EAR PREPARATIONS

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Abstract

Nasal and ear preparations are specialized dosage forms designed for local or systemic drug delivery through the nasal cavity and ear canal. This section explores the anatomy and physiology of the nasal and auditory systems, highlighting their unique features for drug administration. Various types of nasal formulations, including solutions, suspensions, and gels, are discussed along with their applications in local treatment and systemic drug delivery. The formulation considerations for nasal preparations, such as tonicity, pH, and viscosity, are examined to ensure efficacy and patient comfort. Ear preparations, including drops, ointments, and suspensions, are explored with emphasis on their specific requirements for safety and efficacy. The challenges in developing nasal and ear formulations, such as limited residence time and potential for irritation, are addressed along with strategies to overcome them. Advanced delivery systems, including nasal sprays and metered-dose inhalers for nasal administration, are discussed. Quality control measures specific to nasal and ear preparations, including sterility testing, particle size analysis, and spray pattern evaluation, are detailed.

Keywords: *Mucosal delivery, Absorption enhancers, Otic formulations, Spray systems, Local therapy, Bioavailability*

Learning Objectives

After completion of the chapter, the student should be able to:

- Describe the anatomy and physiology of the nasal cavity and ear.
- Explain the advantages and limitations of nasal and ear drug delivery.
- Classify different types of nasal and ear preparations.
- Discuss the formulation principles of nasal sprays, drops, and ear drops.
- Outline the manufacturing processes for nasal and ear preparations.
- Describe the quality control tests specific to nasal and ear formulations.
- Analyze the factors affecting drug absorption in nasal and ear preparations.

NASAL PREPARATIONS

Nasal Solutions

Nasal solutions are aqueous solutions designed to be administered to the nasal passages in drops or sprays. Other nasal preparations may be in the form of emulsions or suspensions. The adult nasal cavity has about a 20 mL capacity with a large surface area (about 180 cm2) for drug absorption afforded by the microvilli present along the pseudo-stratified columnar epithelial cells of the nasal mucosa. The nasal tissue is highly vascularized, making it an attractive site for rapid and efficient systemic absorption. Another advantage of nasal delivery is it avoids first-pass metabolism by the liver. For some peptides and small molecular compounds, intranasal bioavailability has been comparable to that of injections. However, bioavailability decreases as the molecular weight of a compound increases,

and, for proteins composed of more than 27 amino acids, bioavailability is quite low. Various pharmaceutical techniques and functional excipients, such as surfactants, have been shown capable of enhancing the nasal absorption of large molecules.

Many drugs are administered for their local sympathomimetic effects to reduce nasal congestion, such as Ephedrine Sulfate Nasal Solution, USP, or Naphazoline Hydrochloride Nasal Solution, USP. A few other preparations, Lypressin Nasal Solution, USP, and Oxytocin Nasal Solution, USP, are administered in spray form for their systemic effect for the treatment of diabetes insipidus and milk letdown prior to breast feeding, respectively. Table 24-3 lists examples of commercial products for nasal use.

Nasal solutions are formulated to be similar to nasal secretions with regard to tonicity, pH, and viscosity, so normal ciliary action is maintained. Thus, aqueous nasal solutions are isotonic and slightly buffered to maintain a pH of 5.5–6.5. In addition, antimicrobial preservatives, similar to those used in ophthalmic preparations, and appropriate drug stabilizers, if required, are included in the formulation. Current studies indicate that nasal sprays are deposited mainly in the atrium and cleared slowly into the pharynx with the patient in an upright position. Drops spread more extensively than the spray, and three drops cover most of the walls of the nasal cavity with the patient in a supine position and head tilted back and turned left and right.43,44 It is suggested that drop delivery, with appropriate movement by the patient, leads to extensive coverage of the walls of the nasal cavity. Most nasal solutions are packaged in dropper or spray bottles, containing 15–30 mL of medication. The pharmaceutical scientist should ensure the product is stable in the containers, and the pharmacist should keep the packages tightly closed during periods of

nonuse. The patient should be advised that, should the solution become discolored or contain precipitated matter, it must be discarded.

Examples of Commercial Nasal Preparations

Product Name	Manufacturer	Active Ingredient	Indication
Atrovent Nasal Spray	Boehringer Ingelheim	Ipratropium bromide 0.06%	Seasonal or Allergic Rhinitis
Beconase AQ Nasal Spray	GlaxoSmithKline	Beclomethasone dipropionate, monohydrate 42 mcg	Seasonal or Allergic Rhinitis
Miacalcin	Novartis	Calcitonin-salmon, 2200 I.U. per mL	Postmenopausal osteoporosis
Nasalcrom Nasal Spray	Pharmacia	Cromolyn sodium 5.2 mg	Seasonal or Allergic Rhinitis
Nasarel Nasal Spray	IVAX	Flunisolide	Seasonal or perennial rhinitis
Nicotrol Nasal Spray	Pfizer	Nicotine 0.5 mg	Smoking Cessation
Neo-Synephrine	Bayer	Oxymetazoline hydrochloride 0.05%	Decongestion
Rhinocort Aqua Nasal Spray	Astra-Zeneca	Budesonide 32mcg	Seasonal or Allergic Rhinitis
Stadol Nasal Spray	Bristol-Myers Squibb	Butorphanol tartrate, 1 mg	Pain Relief, Migraines
Stimate	Aventis	Desmopressin	Hemophilia A

Product Name	Manufacturer	Active Ingredient	Indication
Nasal Spray		Acetate 1.5 mg/mL	or von Willebrand disease
Synarel Nasal Solution	Searle	Nafarelin acetate 2 mg/mL	Endometriosis
Tyzine	Bradley Pharmaceuticals	Tetrahydrozoline hydrochloride	Decongestion

INHALATIONS AND INHALANTS

Inhalation preparations are so used or designed that the drug is carried into the respiratory tree of the patient. The vapor or mist reaches the affected area and gives prompt relief from the symptoms of bronchial and nasal congestion. The USP defines Inhalations in the following way:

Inhalations are drugs or solutions or suspensions of one or more drug substances administered to the nasal or oral respiratory route for local or systemic effect. Solutions of drug substances in sterile water for inhalation or in sodium chloride inhalation solution may be nebulized by the use of inert gases. Nebulizers are suitable for the administration of inhalation solutions only if they give droplets sufficiently fine and uniform in size so that the mist reaches the bronchioles. Nebulized solutions may be breathed directly from the nebulizer, or the nebulizer may be attached to a plastic face mask, tent or intermittent positive pressure breathing (IPPB) machine. Another group of products, also known as metered-dose inhalers (MDIs) are propellant-driven drug suspensions or solutions in liquefied gas propellant (chlorofluorocarbons and hydrofluoroalkanes) with or without a cosolvent and are intended for delivering metered doses of the drug to the respiratory tract. An MDI

contains multiple doses, often exceeding several hundred. The most common single dose volumes delivered are from 25 to 100 μL (also expressed as mg) per actuation. Examples of MDIs containing drug solutions are Epinephrine Inhalation Aerosol, USP, and Isoproterenol Hydrochloride and Phenylephrine Bitartrate Inhalation Aerosol, respectively. Both the solubility and stability of the drug in the propellant mixture must be investigated during formulation development. Ethanol is commonly used as a cosolvents for hydrofluoroalkane propellants, and was reported to significantly increase the solubility of steroids.

As stated in the USP, particle size is of major importance in the administration of this type of preparation. It has been reported that the optimum particle size for penetration into the pulmonary cavity is of the order of 0.5–7.0 μm. Fine mists are produced by pressurized aerosols and, hence, possess basic advantages over the older nebulizers; in addition, metered aerosols deliver more uniform doses. A number of inhalations are described in the USP.

The USP defines "inhalants" as follows: A special class of inhalations termed "inhalants" consists of drugs or combinations of drugs that, by virtue of their high vapor pressure, can be carried by an air current into the nasal passage where they exert their effect. The container from which the inhalant is administered is known as an inhaler. Amyl nitrate, USP, and Propylhexedrine Inhalant, USP, are two examples. Amyl nitrite is a clear, yellowish, volatile liquid that acts as a vasodilator when inhaled. The drug is prepared in sealed glass vials covered with a protective gauze cloth. Upon use, the glass vial is broken in the fingertips, and the cloth soaks up the liquid, which is then inhaled. The vials contain 0.3 mL of the drug substance. The effects of the drug are rapid and are used in the treatment of anginal pain. Propylhexedrine is the active ingredient in the widely used Benzedrex and Dristan Inhalers.

Propylhexedrine is a liquid, vasoconstrictor agent that volatilizes slowly at room temperature. This quality enables it to be effectively used as an inhalant.

The official inhalant consists of cylindrical rolls of suitable fibrous material impregnated with propylhexedrine, aromatized to mask its amine like odor, and contained in a suitable inhaler. The vapor of the drug is inhaled into the nostrils when needed to relieve nasal congestion due to colds and hay fever. It may also be employed to relieve ear block and the pressure pain in air travelers. Each plastic tube of the commercial product contains 250 mg of propylhexedrine with aromatics. The containers should be tightly closed after each opening to prevent loss of the drug vapors

EAR PREPARATIONS

These solutions are occasionally referred to as ear or aural preparations. Other otic preparations include suspensions and ointments for topical application in the ear. Ear preparations are placed in the ear canal by drops or in small amounts for the removal of excessive cerumen (ear wax) or for the treatment of ear infections, inflammation, or pain. The main classes of drugs used for topical administration to the ear include analgesics, such as benzocaine; antibiotics, such as neomycin; and anti-inflammatory agents, such as cortisone. The USP preparations include Antipyrine and Benzocaine Otic Solution. The Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Solutions may contain appropriate buffers, solvents, and dispersants in an aqueous solution. The main solvents used in these preparations include glycerine or water. The viscous glycerin vehicle permits the drug to remain in the ear for a long time. Anhydrous glycerin, being hygroscopic, tends to remove moisture from surrounding tissues, thus, reducing swelling. Viscous

liquids like glycerin or propylene glycol are used either alone or in combination with a surfactant to aid in the removal of cerumen (ear wax). To provide sufficient time for aqueous preparations to act, it is necessary for patients to remain on their side for a few minutes, so the drops do not run out of the ear. Otic preparations are dispensed in a container that permits the administration of drops.

Table. Examples of Commercial Otic Preparations

Product Name	Manufacturer	Active Ingredient	Indication
Americaine-Otic	Celltech	Benzocaine	Local Anesthetics
Cerumenex Ear Drops	Purdue	Triethanolamine polypeptide oleate-condensate	Removal of earwax
Chloromycetin Otic	Pfizer	Chloramphenicol	Antiinfective
Cipro HC Otic	Alcon	Ciprofloxacin hydrochloride and hydrocortisone	Acute otitis externa
Cortisporin	GlaxoSmithKline	Neomycin and Polymyxin B Sulfates and Hydrocortisone	Antibacterial and anti-inflammatory
Debrox Drops	GlaxoSmithKline	Carbamide peroxide	Removal of earwax
Floxin Otic	Daiichi	Ofloxacin	Antiinfective
Tympagesic	Savage	Antipyrine, Benzocaine, and Phenylephrine Hydrochloride	Topical anesthetic