CALIFORNIA NORTHSTATE UNIVERSITY
COLLEGE of PHARMACY

PHAR 632

"Ocular and Nasal Drug Delivery"

Objectives:

1. Understand the significance of ocular delivery.
2. What are the limitations associated with ocular drug delivery.
3. Understand the advantages and disadvantages of using ophthalmic dosage form over oral dosage form.
4. List and understand the pharmaceutical requirement for the preparation of ophthalmic dosage for with regards to sterility, preservation, isotonicity, buffering, viscosity, ocular, bioavailability and packaging.
5. List some of the pharmacological categories of drugs that are delivered to the eye?
6. Understand the significance of nasal drug delivery.
7. Describe the structure of the nasal cavity as it relates to the delivery of drugs to the body.
8. Understand the advantages and disadvantages of using nasal dosage form over oral dosage form.
9. What are the limitations associated with drug delivery via the nasal cavity.
10. Understand the approaches used to enhance the absorption of drugs through the nasal mucosa.
11. Explain the proper administration for both dosage forms.

Reading Assignment:

The following pages are your reading from ***Ansel's Pharmaceutical Dosage Form and Drug Delivery*** for the next topic: "**Special Solutions and Suspensions"** Read **Chapter 17** pages;

Pages 606-620. No calculations will be tested <u>for this class</u> but you should understand the concept of isotonicity and pH and solubility. Skip tables 17.1-17.4

Pages 628-630 from "Proper Administration and Use of Nasal Drops and Sprays", **stop** at Otic Preparation.

Read the **additional reading** attached to this document on Nasal Drug Delivery.

<u>Also read the lecture handout once posted.</u>

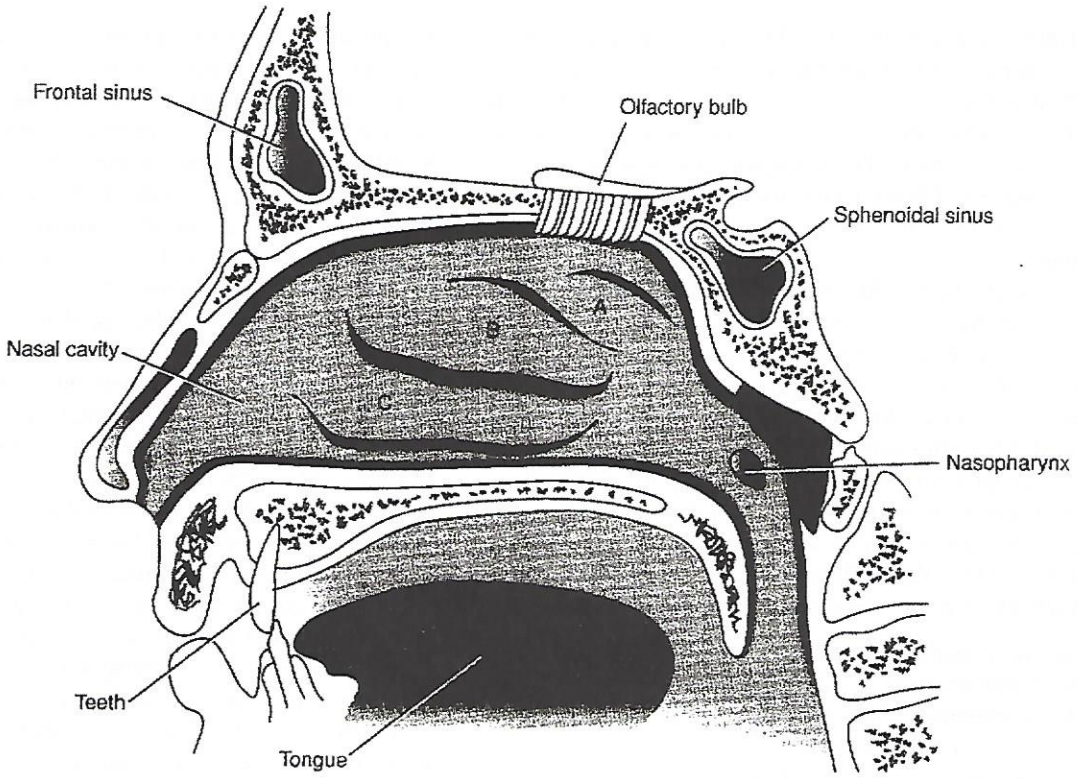

Fig. 22–7. Nasal anatomy. The nasal cavity consists of three passageways or meatuses: (*A*) upper meatus; (*B*) middle meatus; (*C*) lower meatus. The nasal cavity is lined with a mucous membrane.

This route of administration is useful for the treatment of pulmonary conditions and for the delivery of drugs to distant target organs by means of the circulatory system.

Nasal Mucosa

The uppermost portion of the human respiratory system, the nose, is a hollow air passage that functions in breathing and in the sense of smell. The nasal cavity moistens and warms incoming air, and small hairs and mucus filter out harmful particles and microorganisms. The nose (**Figure 22–7**) consists of two openings (nostrils) separated by a median septum. The vestibule at the entrance of each nostril is covered with hairs, which prevent the entrance of air-suspended particles. The nose cavity is divided by the septum into two chambers called fossae. They form passages for air movement from the nostrils to the nasopharyngeal space at the back of the nose. Each fossa consists of two parts, an olfactory region at the front of the nose and a respiratory region that accounts for the remainder of the fossae.

The nasal cavity is lined with a mucous membrane, called the membrana mucosa nasi, which is continuous with the skin of the nostrils. The respiratory portion of the nasal cavity contains ciliated (hairlike) projections consisting of columnar epithelial cells.

The nasal cavity consists of three passageways or meatuses: upper, middle, and lower meatus. The nasolacrimal duct drains into the lower meatus. The nose is connected to the middle ear through the nasopharynx or postnasal space and through the auditory canal. The compartments of the nose are connected to the conjunctiva of the eye by way of the nasolacrimal and lacrimal ducts, and through several sinuses that drain into the nose. A portion of a drug administered into the conjunctiva of the eye may enter the nose through these ducts and sinuses, and may also pass into the esophagus.[18] The nasal mucosa is the only location in the body that provides a direct connection between the central nervous system and the atmosphere. Drugs administered to the nasal mucosa rapidly traverse through the cribriform plate into the central nervous system by three routes: (*a*) directly by the olfactory neurons located in olfactory bulb (**Figure 22–7**); (*b*) through supporting cells and the surrounding capillary bed; and (*c*) directly into the cerebrospinal fluid.[18a] Therefore, in addition to local and systemic drug delivery, the nasal mucosa can be used to deliver drugs to central nervous system.

Traditionally, the nasal route is used for locally acting drugs. This route is getting more and more attention for the systemic delivery of protein and peptide drugs. The highly vascular nature of the nasal cavity makes it a suitable alternate route for systemic drug delivery. This route is also useful for potent drugs because of its smaller surface area, about 200 cm^2, available for absorption.

The most commonly used dosage form for the administration of drug through this route is liquid solutions of drug. For large polar molecules such as peptides or polysaccharides in

the form of drugs or vaccines, the nasal route provides a viable, noninvasive alternative to injections. For conventional molecules, the nasal route provides other clinical benefits relevant to certain drugs and patient groups: pulsatile or sustained plasma profiles, fast absorption and rapid onset of action, avoidance of first-pass metabolism, and avoidance of the effects of gastric stasis and vomiting often seen in migraine patients.

One of the major challenges is developing nasal formulations that improve the absorption of macromolecules and water-soluble drugs. Another challenge is the problem of short retention time in the nasal cavity, the result of efficient physiologic clearance mechanisms. Good systemic bioavailability after nasal drug delivery can be achieved for molecules with a molecular weight of up to 1000 daltons when no enhancer is used. With the inclusion of enhancers, good bioavailability can be extended to a molecular weight of at least 6000 daltons. Several methods have been used to facilitate the nasal absorption of drugs:

1. *Structural modification.* The chemical modification of the molecular structure of a drug has been used to modify its physicochemical properties, and hence could also be used to enhance its nasal absorption.
2. *Salt or ester formation.* The drug can be converted to form a salt with increased solubility or an ester with better nasal membrane permeability for achieving better transnasal absorption.
3. *Formulation design.* Proper selection of formulation excipients could improve the stability and/or enhance the nasal absorption of drugs.
4. *Surfactants.* Incorporation of surfactants into nasal formulations could modify the permeability of nasal mucosa, which may facilitate the nasal absorption of drugs.

One of the methods used in nasal delivery is based on the use of chitosan as an absorption enhancer as described for oral mucosa drug delivery. The chitosan nasal technology can be exploited as a solution, dry powder, or microsphere formulation to further optimize the delivery system for individual compounds. For compounds requiring rapid onset of action, the nasal chitosan technology can provide a fast peak concentration compared with oral or subcutaneous administration.[19–21]

Two kinds of organic-based pharmaceuticals are used for nasal drug delivery: (*a*) Drugs with extensive presystemic metabolism (e.g., progesterone, estradiol, testosterone, hydralazine) can be rapidly absorbed through the nasal mucosa with a systemic bioavailability of approximately 100%; and (*b*) water-soluble, organic-based compounds are well absorbed (e.g., sodium cromoglycate). Recently, nasal drug delivery has been used for systemic delivery of peptide-based pharmaceuticals.[22–24] Because of their physicochemical instability and susceptibility to hepatogastrointestinal first-pass elimination, peptide and protein pharmaceuticals generally have a low oral bioavailability and are normally administered by parenteral routes. Most nasal formulations of peptide and protein pharmaceuticals have been prepared in simple aqueous (or saline) solutions with preservatives. Recently, more research and development work has been done on the development of delivery systems for the nasal delivery of peptides or proteins. One example is a commercially available nasal calcitonin formulation. The Miacalcin nasal spray is licensed for the treatment of established osteoporosis for postmenopausal women. Unlike injectable calcitonin, it is recommended for long-term rather than short-term use and has been shown to reduce the risk of new vertebral fractures. The extent of systemic delivery of peptides or proteins by transnasal permeation may depend on the structure and size of the molecules, partition coefficient, susceptibility to proteolysis by nasal enzymes, nasal residence time, and formulation variables (pH, viscosity, and osmolarity).

The following dosage forms are the most suitable for nasal drug delivery: aerosols, gels, liquids, ointments, suspensions, and sustained-release formulations. Dosage forms for nasal absorption must be deposited and remain in the nasal cavity long enough to allow effective absorption. The standard methods of administration are sprays and drops. The particle size in aerosols is important in determining the site of deposition. Particles less than 0.5 μm in diameter may pass through the nose and reach the terminal bronchi and alveoli of the lungs. A nasal spray requires that the particles have a diameter larger than 4 μm to be retained in the nose and to minimize passage into the lungs. The nasal spray deposits drug in the proximal part of the nasal atrium, whereas nasal drops are dispersed throughout the nasal cavity. A spray clears more slowly than drops because the spray is deposited in nonciliated regions. A metered-dose inhaler (MDI) is most often used for nasal and pulmonary delivery. This device (**Figure 22–8**), when manually compressed, delivers an accurate and reproducible dose of the nasal (or bronchial) formulation.

One of the limitations of nasal drug delivery is rapid removal of the therapeutic agent from the site of absorption. To overcome this, the addition of bioadhesive materials and mixtures with polymers has been investigated. By adding these materials to the drug in solution or powder preparations, drug absorption has been increased by extending the residence time in the nasal cavity. Quadir et al.[25] examined the effect of microcrystalline cellulose on the bioavailability of ketorolac. The investigators found that the bioavailability of spray formulations of ketorolac alone in rabbits was approximately 50% of that after intravenous administration (**Figure 22–9**). Nasal administration of ketorolac with microcrystalline cellulose significantly improved the absolute bioavailability (i.e., compared to intravenous injection) of the drug to 90%.

A new nasal gel drug, Zicam (Gel-Tech LLC, Woodland Hill, Calif.), significantly reduces the length of the common cold. The active ingredient in Zicam is zinc ion, which has long been used in cold lozenges.[26] However, the gel formulation allows the ions to stay within the nasal cavity long enough to interact with the virus. Patients who took Zicam within 24 hr of the onset of three or more cold symptoms

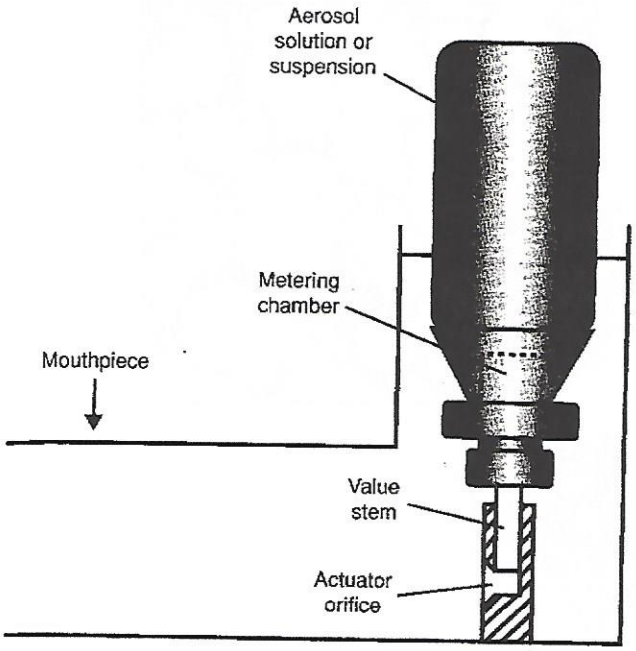

Fig. 22–8. Metered-dose device for drug administration to nasal and pulmonary regions. (Modified from P. R. Byron (Ed.), *Respiratory Drug Delivery*, CRC, Boca Raton, Fla., 1990, p. 171.)

recovered in an average of 1.5 to 3.3 days, whereas patients who received a placebo recovered in an average of 9.8 days.[27]

Novel nasal dosage forms that provide a sustained release are being investigated. Most of them are based on the use of micro- and nanoencapsulated spheres or particles. These particles are produced by spray drying, solvent-free prilling, coextrusion, solvent evaporation, coacervation, interfacial polymerization, polymerization in dispersed media, melt emulsification, and other methods. In addition, liposome-encapsulated drugs are also being tested for sustained nasal drug delivery.

Major advantages and disadvantages of nasal drug delivery are summarized in **Table 22–4.**

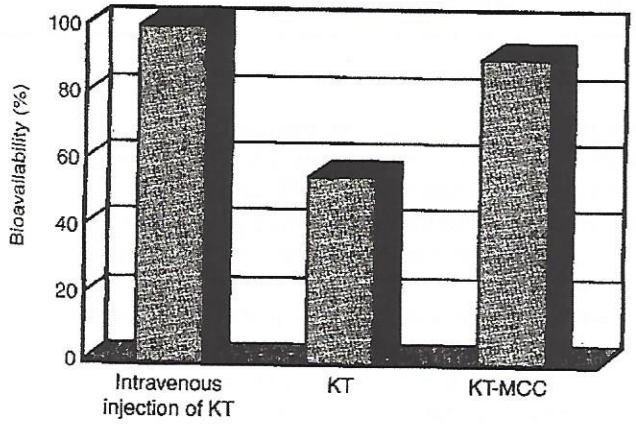

Fig. 22–9. Comparison of bioavailability of injected and spray formulations of ketorolac (KT) alone and KT with a microcrystalline cellulose (MCC) in rabbits. (Replotted from M. Quadir, H. Zia, and T. E. Needham, Drug Deliv. **7**, 223, 2000.)

TABLE 22–4
ADVANTAGES AND LIMITATIONS OF NASAL MUCOSAL DRUG DELIVERY

Advantages	Limitations
Avoidance of hepatic first-pass elimination and destruction in the gastrointestinal tract	Possible local tissue irritation
Rapid absorption of drug molecules across the nasal membrane	Rapid removal of the therapeutic agent from the site of absorption
Can be used both for local and *systemic drug delivery*	Pathologic conditions such as *cold* or allergies that may alter significantly the nasal bioavailability
Relative ease and convenience	

Pulmonary Administration

The respiratory tract has a large surface area and therefore can be used for local and systemic drug delivery. The surface increases from the exterior region (nasopharyngeal) to the tracheobronchial and pulmonary regions, the latter consisting of bronchioles and alveoli (**Figure 22–6**). One of the oldest examples of pulmonary administration for systemic drug delivery is inhalation anesthesia. An increasing variety of drugs, including beta-agonists, corticosteroids, mast cell stabilizers, antibiotics, and antifungal and antiviral agents, are being administered by this route to obtain a direct effect on the target tissues of the respiratory system.

The pulmonary route has been used for decades to administer drug to the lung for the treatment of asthma and other local ailments. Recently, this route has received more attention for the systemic delivery of drugs. The onset of action following the pulmonary administration of drugs is very fast and comparable to the intravenous route. The lungs are an attractive site for the systemic delivery of protein and peptide drugs. They offer a larger surface area (70 m^2) for systemic absorption of drugs than other nontraditional routes of systemic drug delivery such as the buccal, sublingual, nasal, rectal, and vaginal cavities.

The major challenge for this route is the lack of reproducibility in the deposition site of the administered dose. The rate of absorption of drug is expected to vary at various regions in the lung owing to the variable thickness of the epithelial lining in the bronchial tree.

Aerosols are widely used to deliver drugs in the respiratory tract. The deposition mechanism of the particles depends on many factors: the inhalation regime and the particle size, shape, density, charge, and hygroscopicity. The size of solid