chapter seven

Intranasal and ocular drug delivery

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I. Intranasal drug delivery

A. Introduction

In view of the vascularity of the nasal mucosa, the possibility of bypassing hepato-gastrointestinal (GI) first-pass elimination, and the ease of administration, the nasal route would seem to be an ideal alternative for daily administration of some drugs. The use of the nasal route for the administration of drugs has, in fact, engaged the attention of mankind since ancient times. Nasal therapy, for example, is a recognized form of treatment in the Ayurvedic system of East Indian medicine. Psychotropic drugs and hallucinogens have been used as snuffs by the natives in South America for centuries.

Over the last decade, the possibility that intranasal administration might be useful for many compounds that are not absorbed orally has received

increasing attention. In particular, with the availability of proteins and peptides from advanced biotechnology (e.g., insulin, growth hormone, etc.), the research and development of intranasal drug delivery systems has become even more vital.[1]

Not all drugs can be administered nasally. For example, some drugs cannot be absorbed through the nasal mucosa because of their chemical characteristics. Others are absorbed only with great difficulty and require added permeation enhancers — pharmaceutical ingredients that often produce their own side effects. For drugs that can be delivered nasally, however, there are potential advantages: lower doses, more rapid attainment of therapeutic blood levels, quicker onset of pharmacological activity, and fewer side effects.

Not all of these benefits accrue to every drug that can be delivered nasally. In rare instances, a drug that is absorbed nasally will show none of these benefits. In such cases, the only advantage of nasal delivery may be convenience or compliance of administration — reason enough to continue to evaluate the nasal route of administration. For drugs that can be delivered orally, nasal delivery might not offer the advantages of increased efficacy, absorption rate, compliance, and convenience.

Nudelman[2] has reported that a drug should be considered for development as a nasal product if it fulfills one of the following conditions: it is administered parenterally; it is in an inconvenient dosage form, such as a suppository; it is absorbed poorly; or it is absorbed slowly and produces undesirable side effects when administered orally.

Many drugs absorbed through the rich blood supply of the nasal mucosa enter the systemic circulation more rapidly than when they are administered orally. For example, properly formulated into a nasal dosage form, the beta blocker propranolol can abort a migraine attack even after the symptoms have started. Similarly, nasally administered meclizine (an antihistamine) can reduce or eliminate dizziness and nausea associated with motion sickness.

B. Nasal physiology and intranasal drug administration

Even with a cursory examination of nasal morphology and physiology, it becomes obvious that the nasal passage is quite different from the remainder of the airway. Figure 7.1 illustrates the upper airway as seen from the midline. The dashed line just beyond the nostrils marks the beginning of the nasal valve, while the dotted line shows approximately the beginning of the ciliated epithelium region. Large aerosol particles deposit largely in the zone between the dashed and dotted lines. The dashed line near the nasopharynx indicates the posterior termination of the nasal septum. Materials applied topically to the nasal conjunctiva will enter the nose through the nasolacrimal duct, just beneath the anterior end of the inferior turbinate. The other conducting airways provide conduits permitting the passage of respired air with a minimum resistance to airflow.

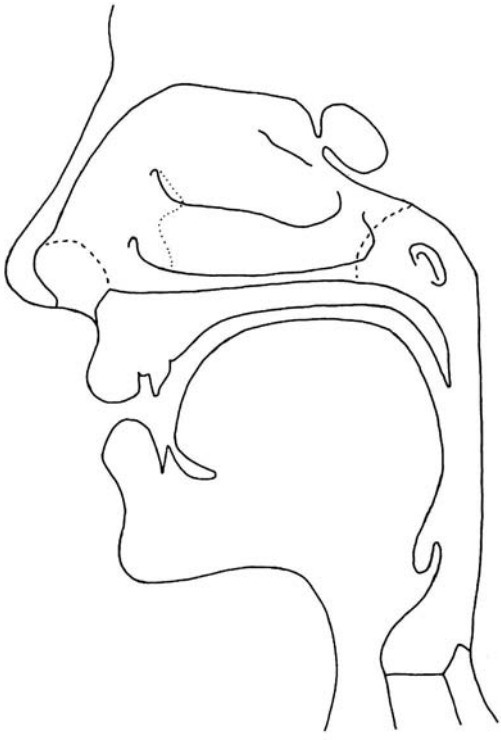

Figure 7.1 The upper airways as seen from the midline. (From Chien, Y.W., Ed., *Transnasal Systemic Medications, Fundamentals, Developmental Concepts and Biomedical Assessments*, Elsevier Science Publishers, Amsterdam, 1985, 102. With permission.)

The nasal airway accounts for as much resistance as all the remainder of the respiratory tract. This results from the bifurcation of the nose into two halves by the nasal septum. Each half, in turn, is convoluted by the folds of the turbinates, an arrangement which, at the cost of added resistance to airflow, permits an intimate contact between the air stream and the mucosal surfaces.[3]

Figure 7.2 illustrates a section through the main nasal passage showing the nasal septum, folds of the turbinates, and airway. The stippled area indicates the olfactory region, which is generally free of inspiratory airflow. Horizontal lines mark the metal spaces, through which there is very little airflow, but in which there exists communications with the paranasal sinuses and naso-lacrimal duct. The clear areas mark the zone of inspiratory airflow and the region lined with richly vascular erectile tissue. This is the site primarily reached by medications applied intranasally (e.g., nose drops or fine aerosol sprays).

Modification of inspired air within the nose includes stabilization of temperature and water vapor content. These adjustments become possible because of the close contact between the narrow airstreams and mucosal

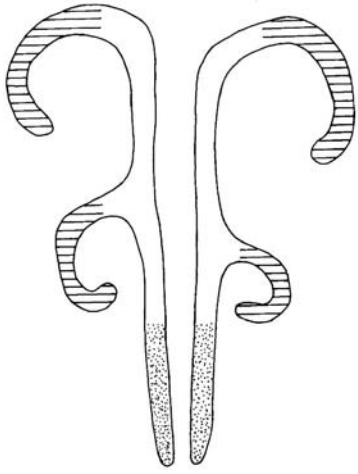

Figure 7.2 Section through the main nasal passage. (From Chien, Y.W., Ed., *Transnasal Systemic Medications, Fundamentals, Developmental Concepts and Biomedical Assessments*, Elsevier Science Publishers, Amsterdam, 1985, 103. With permission.)

surfaces and because of the nature of the circulatory and mucociliary systems. Therefore, the nasal vascular system presents a substantial surface area to inspired materials (e.g., gases or aerosols) that is extremely rich and highly adjustable.[4,5]

The mucociliary system consists of a great number of submucosal glands and goblet cells that provide the mucus and cilia that transport fluids to the nasopharynx, where they can be swallowed or expectorated. Of special importance is the fact that both circulatory and secretory mechanisms are susceptible to a variety of influences. For example, if a factor produces significant vasoconstriction, the capability of the nose to transmit surface materials to the systemic circulation can be significantly reduced.

Since a drug may be introduced into the nose in liquid or nasal spray form (e.g., aerosol or powder), it is necessary to understand the factors that influence these delivery forms. In the anterior area of the nose, there is a constriction known as the nasal valve. To pass this point, air must flow at a high-linear velocity and change direction. These two characteristics result in deposition of most aerosols or dusts in the anterior region of the nose. The larger particles lodge far enough anteriorly to be in front of the exchange region of the nose and, therefore, are not subject to nasal absorption into the body. Insoluble particles, even if they pass this point and deposit in the main passage, are likely to be carried backward by the mucociliary system and dispatched to the stomach. If a drug is introduced as a vapor or in soluble form, it may readily pass through the surface secretions and into the systemic circulation.

The presence of existing nasal pathology is also important. Nasal obstruction as a result of extensive nasal polyposis, for example, would

reduce the capacity of nasal absorption. In addition, atrophic rhinitis or severe vasomotor rhinitis can also reduce the usefulness of the nose to absorb a drug. In some individuals, excessive response of the mucous cells to some irritants may drain away whatever is introduced prior to absorption. Such a tendency may exist in persons with severe nasal allergies.[6,7]

Of all of the parenteral routes, intravenous administration serves as the reference standard for establishing the basis of bioavailability. Not only does it bypass the absorption process, but it results in no presystemic metabolism. Intramuscular injection, unlike intravenous, does not always ensure rapid or complete absorption. Like intramuscular and intranasal, subcutaneous administration also depends upon the vascularity and blood supply at the administration site, and these factors can influence the rate or extent of absorption.[8]

Although surfactants and other absorption promoters may stimulate the absorption of macromolecular drugs by other routes, intranasal administration offers a much more favorable opportunity for the absorption of such large bioactive molecules.[9,10]

In comparison with the more traditional nonoral routes of administration, the intranasal route is experiencing increasing interest, especially for hormones, peptides, vaccines, and other drugs. This is a clear advantage for drugs that undergo extensive hepatic first-pass elimination, gut wall metabolism, or destruction in GI fluids. In some cases, such as with an influenza vaccine, a large population of individuals will be more willing to accept intranasal rather than parenteral administration, and this could have significant public health implications.[11]

C. Nasal drug delivery devices

In the development of nasal drug delivery devices, two principal systems will be discussed: the mechanical pump system and the pressurized aerosol system. Because both systems are capable of delivering drugs accurately, they are widely used. The selection of either the mechanical pump system or the pressurized aerosol system depends upon the nature of the drug to be developed. In general, the mechanical pump system is simpler than the pressurized aerosol system. Once the final formulation has been assured to be stable — both chemically and physically — and compatible with all the components of the delivery device, the use of a pump system should be straightforward. However, the pressurized aerosol system can be more complicated because of the presence of propellants in the formulation.

If an ingredient in the formulation is required to be dissolved or dispersed, the physicochemical compatibility of the drug with the propellant, co-solvents, or dispersing agents will require evaluation. An aqueous system should certainly be the first choice, and then its use with a mechanical system should be straightforward. However, if an active ingredient has solubility and stability problems in an aqueous system, a nonaqueous solvent system

should be considered. Once a specific formulation is determined, three basic vehicle systems can be considered (i.e., solution, suspension, and emulsion).

When a formulation is finalized, it is essential to evaluate how the product will maintain its stability under the variable conditions of time, temperature, and pressure. Accelerated stability testings, in which the final formulation is subjected to the stability evaluation under more extreme conditions, will provide some preliminary information. Stability studies, in addition to assessing the active ingredient, should include testing for weight loss, delivery rate, tail-off, pressure, and pH. The studies must be conducted with the formulation in a glass container to permit the observation of any physical changes if the final product is to be in metal. During storage, the adsorption of a drug by plastic components could occur, leading to a reduction in drug concentration delivered to the patient. Although aerosol products, like oral dosage forms, need not be sterile, they should be free from any bacterial contamination.

With regard to evaluation of the physical stability of an aerosol system, the pertinent parameters include polymorphism, crystal growth, phase separation, dispersability, and dose distribution. Products are subjected to stability testing at temperatures of –8°C, 4°C, room temperature, and a cycling temperature ranging from –8°C to 40°C to mimic shipping conditions. A wrong choice of polymorph can result in some physical instability. Furthermore, the presence of a less stable crystal form may cause crystal growth at a later stage, which may subsequently affect aerosol performance. It should be kept in mind that since the propellant content in the formulation can vary once the product is in use, the dose distribution from the first dose could be significantly different from the last dose. Therefore, dose distribution must be fully studied.

The aerosol release valve plays perhaps the most important role in any aerosol product. It must mechanically function each time and must repeatedly deliver the drug in a specified quantity. Therefore, the valve components need to be compatible with the formulation. Plastic parts used in the valve may be subject to swelling, softening, and cracking. The metal parts of the valve may also be corroded, depending upon the formula involved. Dip tube growth, for instance, is a common problem in aerosols. Therefore, separate testing for each valve part by the total immersion technique should be conducted to detect any incompatibility problems.

The plasticizers and lubricants required in the molding of the plastics may be extracted by various solvents used in the formulation. These materials should not have any adverse effects on the physiological properties of the drug and its efficacy. For example, pumps or aerosol systems employ at least one rubber gasket, which comes in contact with the contents of the product. These gaskets almost always contain plasticizers, antioxidants, lubricants, and other substances. Compatibility of these gaskets with the formula must be evaluated. The gaskets fabricated from rubber products such as buna and neoprene are commonly utilized in the aerosol industry because of their acceptable compatibility with most products.

No matter how well a valve is designed, variation in the volume dispensed will occur from one valve to another and from one actuation to another, even with the same valve. The limits of acceptable variation depend entirely on the formulation to be dispensed and the safety of the medication to be administered.

There is no doubt that drug distribution within the nasal cavity is an important factor for nasal uptake. Because the mode of administration will affect drug distribution, it will, in turn, affect the efficacy of a medication. Mygind et al.[12] have demonstrated that a significant variation in drug distribution occurs in a model cast of the human nose following intranasal drug administration by different drug delivery devices.

The drug, and its final dosage form, must be subjected to both acute and chronic toxicity evaluations. Most of the ingredients used in aerosol formulations are generally regarded as safe, so that no major toxicity issues should be of concern. With regard to the active compound, acute toxicity is fairly easy to evaluate, since toxic manifestations show up within a relatively short period of time during preclinical testing. This data should be available in time for starting preformulation and designing dosage forms. Chronic toxicity presents a greater problem because of the long waiting time required for determination of toxicity under normal conditions of exposure and use. Nevertheless, like other dosage-form products, a 30-day toxicity program on the finished product should be sufficient for single-dose clinical trials and a 90-day toxicity program for multiple-dose clinical trials.[1]

Phasing out of chlorofluorocarbon (CFC) propellants in pressurized inhalers under the terms of the Montreal Protocol, together with the desire to use the lungs as a portal to the systemic circulation, has resulted in the development of many innovative techniques. Since the introduction of the first generation of passive unit dry-powder inhalers (DPIs), Fison's Spinhaler and GSK Rotahaler powder inhalers, many advances with respect to both complexity and performance have been made (see Table 7.1). Inhance Pulmonary Delivery system utilizes compressed air to pre-aerosolize the formulation, independent of the patients' inspiratory effort, into a transparent holding chamber, thereby enabling patients to view the aerosol before inhalation. This device has been designed for the systemic delivery of insulin and other proteins. Marketed multiunit dose devices include GSK Diskhaler and Accuhaler. Other innovative multiunit device systems include Spiros S2, the technology of which involves the use of electro-mechanical energy (breath-actuated, battery-operated propeller) to aerosolize and disperse powdered medication, rather than depending upon the patients' inspiratory effort or propellants. The development of multidose reservoir powder inhalers was pioneered by AstraZeneca with the Turbohaler. The design of this delivery system enables the efficient aerosolization and dispersion of pure aggregated drug material without excipients.

Optimization and control of particle–particle and particle–inhaler interactions is of critical importance in the development of efficient drug-powder inhaler systems. Drug particles should be less than 5 mm aerodynamic

Table 7.1 Dry-powder inhalers at various stages of development

Passive powder inhalers	Classification	Dispersion mechanism
Spinhaler (Fisons)	Unit dose	Pierced capsule rotates on impeller — vibratory dispersion
Rotahaler (GSK)	Unit dose	Capsule separates with dispersion via plastic grid
Inhalator (Boehringer-Ingelheim)	Unit dose	Stationary capsule pierced — dispersion via capillary fluidization
Aerosolizer (Novartis)	Unit dose	Pierced capsule rotates in chamber — dispersion aided by grid
Solo (Inhale Therapeutic Systems)	Unit dose	Dispersion via turbulent airflow pathway
Orbital (BrinTech International)	Unit dose	Dispersion via centrifugal acceleration mechanism
U.S. Patent 6,092,522 (RPR)	Unit dose	Pierced capsule rotates rapidly within a chamber
U.S. Patent 6,102,035 (Astra)	Unit dose	Disposable inhaler — airflow pathway entrainment and dispersion
Diskhaler (GSK)	Multiunit dose	Pierced blister — dispersion via turbulent airflow pathway and grid
Accuhaler (GSK)	Multiunit dose	Pierced blister — dispersion via turbulent airflow pathway
Inhalator M (Boehringer-Ingelheim)	Multiunit dose	Stationary capsule pierced — dispersion via capillary fluidization
Flowcaps (Hovione)	Multiunit dose	Capsule-based device — dispersion via turbulent airflow pathway
Spiros S2 (Elan Corporation)	Multiunit dose	Dispersion via free-floating beads and a dosing chamber
Technohaler (Innovata Biomed)	Multiunit dose	Dispersion via turbulent airflow pathway
U.S. Patent 5,469,843 (3M)	Multiunit dose	Pierced capsule rotates rapidly within a chamber
U.S. Patent 5,724,959 (AEA Technology)	Multiunit dose	Dispersion via impaction and turbulent flow
U.S. Patent 6,182,655 (Jago Research)	Multiunit dose	Dispersion via turbulent airflow pathway
U.S. Patent 6,209,538 (Innova Devices)	Multiunit dose	Airflow diversion around powder until optimal flow rate achieved
U.S. Patent 6,237,591 (Dura)	Multiunit dose	Turbine-powdered inhaler with impeller
Turbuhaler (AstraZeneca)	Multidose reservoir	Dispersion via turbulent airflow pathway
Easyhaler (Orion)	Multidose reservoir	Dispersion via turbulent airflow pathway
Clickhaler (Innovata Biomed)	Multidose reservoir	Dispersion via turbulent airflow pathway

Table 7.1 Dry-powder inhalers at various stages of development (Continued)

Passive powder inhalers	Classification	Dispersion mechanism
Pulvinal (Chiesi)	Multidose reservoir	Dispersion via turbulent airflow pathway
Twisthaler (Schering-Plough)	Multidose reservoir	Dispersion via turbulent airflow pathway
SkyePharma DPI (SkyePharma)	Multidose reservoir	Dispersion via turbulent airflow pathway
Taifun (Leiras)	Multidose reservoir	Dispersion via turbulent airflow pathway
Novolizer (Sofotec GmbH)	Multidose reservoir	Dispersion via turbulent airflow pathway
MAGhaler (Mundipharma)	Multidose tablet	Dispersion via turbulent airflow; formulation present as tablet
U.S. Patent 5,505,196 (Bayer)	Multidose reservoir	Dispersion via turbulent airflow in a "swirl chamber"
U.S. Patent 5,699,789	Multidose reservoir	Dispersion via turbulent airflow pathway
U.S. Patent 5,975,076 (Kings College)	Multidose reservoir	Dispersion via turbulent airflow pathway
Active powder inhalers	**Classification**	**Dispersion mechanism**
Inhance PDS (Inhale)	Unit dose	Gas-assisted — compressed air disperses powder formulation
Spiros (Elan Corporation)	Multiunit dose	Electromechanical energy — battery-operated impeller
Prohaler (Valois)	Multiunit dose	Gas-assisted — built-in pump provides compressed air
U.S. Patent 5,349,947	Multiunit dose	Explosive blister is crushed between piston and anvil
U.S. Patent 5,388,572 (Tenax)	Multiunit dose	Gas-assisted — inhalation-activated piston
U.S. Patent 5,875,776 (Vivorx)	Multiunit dose	Gas-assisted — electrostatic charge discharges on spacer
U.S. Patent 6,142,146 (Microdose)	Multiunit dose	Electronic circuitry with dispersion via vibration
U.S. Patent 6,237,590 (Delsys)	Multiunit dose	Electrostatic powder dosing coupled with electronic release

Source: Russell Publishing, *Am. Pharm. Rev.,* Fall 2001, 38. With permission.

diameter to produce efficient lung deposition, but should also exhibit acceptable flow properties required for accurate dose metering. Therefore, micronized powders are often blended with "coarse" inert carriers (e.g., lactose or glucose), or alternatively pelletized as loose agglomerates to improve powder flow. In recent years, the industry has focused on two types of alternative particle-generation technologies (e.g., spray drying and supercritical fluid

condensation). Generally, spray-drying particles are spherical and often hollow, resulting in a powder with a low bulk density in comparison to the starting material. The major drawback of the spray-drying process is that metastable, high-energy amorphous forms that may crystallize over time and influence product performance are created. Improved aerosol efficiency can be achieved by spray drying with excipients such as sodium chloride, human serum albumin, or carbohydrates (e.g., lactose, mannitol, trehalose, or combinations thereof). Particles of insulin, delta-1-amitrypsin and beta-interferon have been successfully prepared by spray drying with excipients. Proteins are spray dried with "glass forming" sugars to form an amorphous glass state in which the liquid has a high viscosity. The glass state will remain stable for long periods of time when stored well below the glass-transition temperature.

In another approach, large porous particles (comprising poly[lactic acid-co-glycolic acid] or DL-a-phosphatidylcholine) have been prepared with geometric diameters in the order of 5 to 20 μm. Because of the reduced number of surface contacts, interparticle interactions are minimized, and thus particles are claimed to be less cohesive and demonstrate improved flow and dispersability. Also, these large particles are less likely to be phagocytosed than small particles and can reside in the lungs for relatively long periods of time and offer sustained release characteristics. Spray freeze drying produces large protein particles with light and porous particles, demonstrating improved aerosol performance compared to spray-dried particles. Hollow and porous particles are prepared by a two-stage process. Initially, a drug is dissolved in the continuous phase of a fluorocarbon in water emulsion. The resulting emulsion is spray dried, with the dispersed fluorocarbon serving as a blowing agent, keeping the particles inflated and creating pores in the drying aerosol droplets.

The inhalation particles can also be prepared by using supercritical fluid condensation (SCF) methods. SCFs are fluids at or above their critical temperature and pressure. In this region, SCFs exist as a single phase and possess the solvent power of liquids (also used in high-pressure liquid chromatographic separation of chemicals) together with the mass-transfer properties of gases. Carbon dioxide is the most commonly used SCF because it is nontoxic, noninflammable, inexpensive, and has a critical temperature of 31°C, which allows for easy operation under ambient conditions.

During the past few years, advances relating to formulation-related pMDIs include: incorporation of HFA-miscible co-solvents into the formulation, inclusion of various surfactant systems, encapsulation of drug particles, use of perforated microparticles, and use of other nontoxic stabilizing excipients. Device-related pMDI advances include incorporation of actuation mechanism (e.g., Smartmist, Aradigm, Hayward, CA) and use of spacers and plume modifiers (e.g., Azmacort, Rhone-Poulenc Rorer Co., Collegeville, PA; Aerohaler, Bespak, UK; and Spacehaler, Evans Medical, UK).

Nebulizers are drug delivery systems that can be used to generate solutions or suspensions for inhalation. These are suitable for deep-lung delivery.

Two types of nebulizers are currently marketed: jet and ultrasonic. Jet nebulizers use the Venture Effect to draw solution through a capillary tube and disperse droplets in air at high velocity. Ultrasonic nebulizers use oscillating ultrasonic vibration, which is conveyed by means of piezoelectric transducer to a solution that creates droplets suitable for inhalation. A portable, battery-operated aerosol generator has been developed (AeroGen, Sunnyvale, CA). This device has been used for delivery of liposomes and can be used to store freeze-dried compounds, which can be dissolved in a solution (also stored in a device) immediately before being aerosolized. This is particularly useful in the case of proteins and peptides, which are more stable in the solid state. The AERx (Aradigm) system has been shown to be useful in the delivery of peptide drugs, narcotics, and insulin. A portable, piezoelectric aqueous delivery system has been developed for the delivery of drugs in solution. A portable, breath-activated delivery system, the Halolite (Medic-Aid, UK) has also been developed. This device is capable of producing a precise dose and prevents the waste of drugs during exhalation. A device that uses an electric field to form an aerosol of fine droplets from a liquid has been developed (Battelle Pulmonary Therapeutics, Columbus, OH). The aerosol formed from this system in monodisperse, and the total delivered dose, dose reproducibility, and particle-size distributions generated can be controlled by changes in the drug formulations or electric field.

DPIs can be divided into two classes: passive and active devices. Passive devices rely solely upon the patients' inhalatory flow through the DPI to provide the energy needed for dispersion. Active devices have been under investigation for several years, but no active device has been on the market yet. These devices use an external energy source for powder dispersion. However, complexity of these active devices probably has contributed to their inability to achieve regulatory approval, which could increase their cost. Besides Allen & Hanbury's Rotahaler and Fison's Spinhaler, several passive devices are available (e.g., AstraZeneca's Turbuhaler, Schering-Plough's Twisthaler, and Spiro's inhalers).

The addition of five ternary components has increased fine-particle fraction (FPF) of various drug particles. Ternary components so far examined include magnesium stearate, lactose, L-leucine, PEG-6000, and lecithin. Possible mechanism for improved FPF by ternary components could be the saturation of active sites on the carrier, electrostatic interactions, and drug redistribution on the ternary component.

Current commercial DPI formulations are based on drug agglomerates or carrier-based interactive mixtures. Excipients act as diluents and stability enhancers and improve flowability and aerosol dispersability. Surfactants, such as dipalmitoylphosphatidylcholine, can be incorporated to further improve powder flow, aerosol dispersion, and lung deposition. Large-sized particles have been found to enhance mouth deposition and reduce lung deposition. Commercial formulations predominantly deliver bronchodilators, anticholinergics, and corticosteroids for the local treatment of asthma and chronic airway obstruction. New formulations contain multiple drug

components, such as fluticasone and salmeterol. Several therapeutic agents, such as analgesics (fentanyl and morphine), antibiotics, peptides (insulin, vasopressin, growth hormone, calcitonin, and parathyroid hormone), RNA/DNA fragments for gene therapy, and vaccines, are under investigation for inhalation. A new therapy using DPI formulations is zamamivir (Relenza, GSK, Research Triangle Park, NC), and it is mainly targeted at the upper respiratory tract for the treatment of influenza.

Nanosystems, PDC, and BioSante have technologies dealing with particulates containing drugs and formulation additives and absorption enhancers, such as bile acids and surfactants. The potential advantage of all of the particulate or molecular-transport promoters is that they may improve the bioavailability of the drug, thereby maximizing the proportion of the dose that reaches the site of action. According to one report, self-reported asthma prevalence in the U.S. increased 75% between 1980 and 1994 and to 17.3 million cases in 1998. In children between the ages of 5 and 14, asthma was prevalent in 74.4 children for every 1000 in 1994. Chronic obstructive pulmonary disease (COPD) was the fourth leading cause of death in 1998, with incidence rates of 6.9 per 1000 for all ages and 32.4 per 1000 for age 65 and over. Therapeutic drugs that potentially could be used for lung delivery include antimicrobial agents, such as antitubercular compounds; vaccines; proteins, such as insulin for diabetes therapy; and nucleic acids or oligonuclides for cystic fibrosis gene therapy.

The market for compounds to treat respiratory diseases (e.g., asthma and COPD) was approximately $12 billion worldwide in 2001 and is projected to grow to $20 billion in the next 5 years. In 2001, the DPI share of this market was around 20%, and this percentage is likely to grow as pMDIs are slowly phased out and new products with better therapeutic profiles are phased in. Compounds intended for systemic delivery represent an even larger potential market. The overall systemic market is projected to be nearly $40 billion during the first decade of this millennium.

D. Examples of intranasal drug delivery systems

1. Su et al.[11] have reported nasal absorption studies with compounds such as clofilium tosylate, enkephalin analogs, and dobutamine hydrochloride. In particular, they demonstrated that a compound with a short biological half-life can be designed for mimicking intravenous infusion by applying an intranasal sustained-release formulation approach.
2. Kumar et al.[13] reported that intranasal administration of progesterone and norethisterone can prevent ovulation in rhesus monkeys. These steroids were given to 15 animals to determine their systemic absorption through the nasal mucosa and conjunctival sac and to evaluate the existence of a specific pathway from the eye and nose to the cerebrospinal fluid.

3. Lindsay[14] has reported his observations with 93 patients having nasal surgery whose bleeding was controlled by diathermy and postoperative application of a nasal aerosol called Tobispray. Tobispray is a dry, metered-dose nasal aerosol containing a vasoconstrictor (tramazoline), a steroid (dexamethasone isonicotinate), and an antibiotic (neomycin sulfate). This treatment achieved a success rate of 94.6%.
4. Xylometazoline is a long-acting topical nasal decongestant used for the relief of congestion due to coryza or allergic rhinitis. Hamilton[15] evaluated the ability of xylometazoline nasal spray in the reduction of nasal congestion in normal subjects with coryza as a result of upper respiratory infection.
5. Hyde et al.[16] have reported that sublingual administration of scopolamine is definitely inferior to both the intranasal and subcutaneous routes of administration.
6. Atropine sulfate has been administered intranasally, using an atomizer, to patients with rhinorrhea caused by allergic rhinitis and viral rhinitis. All but one of the 31 patients studied demonstrated a visible reduction in secretions. None of the patients reported the occurrence of common side effects, such as dry mouth or visual disturbance.[17]
7. Ipratropium is a parasympatholytic drug with topical activity and, when supplied in aerosol, has been used as a bronchodilator for the treatment of broncho-constructive diseases. Borum and Mygind[18] developed a simple test for the measurement of nasal reactivity in healthy subjects and patients with perennial rhinitis.
8. Dyke et al.[19] have made a comparative study on the efficacy of cocaine by oral and intranasal administrations. Their results indicated that following intranasal administration, cocaine was detected in the plasma by 15 min, reached peak concentrations at 60 to 120 min, and then decreased gradually over the next 2 to 3 h. On the other hand, by oral administration, cocaine was not detected in the plasma until 30 min, and it then increased rapidly for the next 30 min.
9. Angard[20] topically administered PGE_1, PGE_2, and $PGF_{1\alpha}$ to subjects and reported the observation of increased pharmacological potency in some subjects taking PGE_1 and PGE_2. The most likely mechanism of action for the increase of nasal potency results from the vasodilating effect of prostaglandins on nasal blood vessels.
10. Sulbenicillin, cephacetrile, and cefazoline are poorly absorbed from the GI tract because of their high water solubility and lack of lipophilic properties. Hirai et al.[21] carried out an *in vivo* absorption study in rats to compare the bioavailability of these antibiotics following intranasal, oral, and intramuscular administrations. After oral administration, poor absorption was confirmed for all three drugs. After intranasal administration, the percentage excreted in the urine was one-half of that following intramuscular injection.

11. Absorption of aminoglycosides from the GI tract can be enhanced by coadministration with a nonionic surfactant. Rubinstein et al.[22] have reported the observation of increased absorption of gentamicin from the nasal passages in healthy human subjects. Apparently, the presence of a surfactant, such as glycocholate, is required to obtain a significant concentration of gentamicin in the circulation.
12. When antiviral drugs are administered as nasal drops to animals infected with viruses in the upper respiratory tract, antiviral activity is always found to be much less than expected. Bucknall[23] studied the factors that may be responsible for the reduction of the effectiveness of antiviral drugs taken intranasally.
13. Enviroxime, a substituted benzimidazole derivative, is virustatic for rhinoviruses. Delong and Reed[24] have studied the clinical prophylactic and therapeutic effects of enviroxime given as a nasal spray in a placebo-controlled, double-blind study in volunteers infected with rhinovirus Type 4 (RV4). A metered-dose nasal spray was used to deliver either the enviroxime or a placebo in an alcohol solution with a freon propellant. No abnormalities were observed in the total or differential leukocyte count, hemoglobin concentration, or renal and hepatic function tests that were attributable to the intranasal administration of enviroxime by nasal spray.
14. The potential of intranasal administration of two antihistamines, prophen-pyridamine maleate and chlorphenpyridamine maleate, was evaluated in patients with allergic rhinitis. The combination was significantly more effective than chlorpheniramine maleate alone. The observations suggest the equal importance of H_1 and H_2 receptors in nasal blood vessels and an additive effect of H_1 and H_2 antihistamines.[25]
15. The efficacy of sodium cromoglycate in powder or solution form has been compared with placebo in a group of patients with allergic rhinitis over a period of 4 weeks. A crossover trial was further carried out in some patients to compare the efficacy of sodium cromoglycate in powder and solution in individuals whose main symptoms were nasal obstruction.[26]
16. The absorptive ability of the sinus membrane for phenol red was studied over 50 years ago by Childrey and Essex in dogs. They found that the dye appeared in the urine 1 hour and 50 minutes after the injection and only faint traces were present at 6 hours and 45 minutes later.[27]
17. Nasal absorption of CsCl, $SrCl_2$, $BaCl_2$, and $CeCl_3$ has been studied in Syrian hamsters and compared with GI absorption. Results indicated that more than 50% of the radioactive Cs, Sr, and Ba deposited on the nasal membrane is absorbed directly into the general circulation, but less than 4% of the Ce is absorbed. For all the isotopes studied, nasal bioavailability was approximately equal to or greater than oral bioavailability in the first four hours postadministration.

The data suggested that the nasopharynx may be the most important site of absorption for aerosols with a median mass aerodynamic diameter greater than 5 microns, where nasal deposition greatly exceeds deposition in all other areas of the respiratory tract.[28]

18. Czeniawska[29] investigated the possibility of penetration of radioactive colloidal gold (Au) from the mucous membrane of the olfactory region into the cerebrospinal fluid of the subarachnoid space in the anterior part of the brain. The results demonstrated that the radioactive isotope Au penetrates from the mucous membrane of the nasal olfactory region directly into the cerebrospinal fluid of the anterior cranial fossa.
19. Nebulized aqueous solutions are similar in efficiency to metered-dose inhalers (MDIs). Nevertheless, penetration of the lung's periphery — as opposed to tracheobronchial deposition — appears to be more effective with nebulized aqueous solutions than with MDIs. DPIs are much less efficient than either MDIs or nebulizers. Byron[30] has discussed pulmonary targeting, especially with aerosols.
20. The invention reported by Mahl et al.[31] is directed toward reducing the transmission of viral infections, such as respiratory, without significantly changing normal behavioral patterns. A substantially dry, flexible, impregnated wipe having virucidal properties against common cold viruses is the basis of this technology.
21. The Food and Drug Administration (FDA) has approved a nasal spray formulation of desmopressin acetate (DDAVP) for the control of nocturnal enuresis. Marketed by Rorer Pharmaceuticals, DDAVP Nasal Spray stimulates production of arginine vasopressin, an antidiuretic hormone that regulates urine production. The absence of a normal nighttime rise in levels of arginine vasopressin is thought to be responsible for many cases of nocturnal enuresis. DDAVP has a biphasic half-life consisting of a 7.8-minute fast phase and 75.5-minute slow phase. Its use results in decreased urinary output, increased urine osmolality, and decreased plasma osmolality.[32]
22. Researchers at the University of Nottingham, UK, and Novo-Nordisk A/S, Gentofte, Denmark, found that administering an insulin solution intranasally in combination with an enhancer produced a 65% decrease in blood glucose levels. They also found that the palmitoyl and stearyl components of lysophosphatidylcholine, in 0.5% concentration, produced effects similar to those produced by the parent compound, indicating that these lysophospholipids are equally potent absorption enhancers when used in nasal delivery.[33]
23. Researchers at the University of Nottingham, UK, have administered a gelling bioadhesive microsphere delivery system containing gentamicin to rats and sheep using the nasal route. The uptake of the drug across the nasal membrane was increased using the microsphere delivery system described. Lysolecithin was incorporated into the delivery system as an absorption enhancer, and the bioavailability of

gentamicin was increased by a factor of 50%, compared with an increase of less than 1% for a simple nasal gentamicin solution.[34]

24. Nasally delivered medications can be effective in treating migraine headaches. As mentioned previously, nasal administration of propranolol is more effective than oral administration, acting faster and avoiding a developing migraine.[35]
25. Sodium taurodihydrofusidate (STDHF) is a novel protein absorption enhancer whose parent compound, sodium fusidate, is isolated from the fermentation products of *Fusidium coccineum*. Interest in this molecule as an absorption enhancer was stimulated by its similarity to the bile salts, which are known enhancers of protein absorption.[36]
26. Other compounds under development for intranasal administration are: flunisolide (Aerobid); narcotic antagonists, such as naloxone and naltrexone; nitroglycerine; LHRH analog-buserelin; hydralazine; interferon; adrenocorticotropin; HOE 471, a synthetic LHRH analog for cryptorchism; oxytocin; nafarelin acetate, an LHRL antagonist for contraception; lypressin; vasopressin; secretin; dye T-1824; pentagastrin; potassium ferrocyanide; dopamine; bradykinin receptor antagonist; insulin using dimethyl-beta-cyclodextrin; physostigmine; arecoline; flurazepam; midazolam; triazolam; amphotericin B; budesonide; benzalkonium chloride; vaccines; epinephrine; thiophene; azelastine; chlorhexidine acetate; acyclovir; nicotine; dextromethorphan HCl; and isosorbide dinitrate.[37]
27. Since it was first described in 1981, nasal continuous positive airway pressure (CPAP) has gained widespread use and is generally accepted as first-line therapy of obstructive sleep apnea. Several types of nasal CPAP devices are currently available at about the same cost as nocturnal nasal oxygen systems. Nasal CPAP is thought to act as a "pneumatic splint," forcing the posterior nasopharynx open to prevent its collapse during sleep. In addition to abolishing apneas, nasal CPAP eliminates snoring. Side effects of nasal CPAP are few, but include conjunctivitis, nasal stuffiness, and ear pain. A minority of patients, however, do not tolerate nasal CPAP. Nasal oxygen is also a logical therapy for sleep apnea, since many of the sequelae, such as arrhythmias and impaired cognition, are thought to result from oxygen deprivation during sleep. Several studies have demonstrated the safety of nasal oxygen and its efficacy in improving oxygenation during sleep.[38–40]
28. The results of a 1-year, controlled, randomized trial of intranasal salmon calcitonin in 79 healthy women have shown that the agent can counteract early postmenopausal bone loss by inhibiting bone resorption and, perhaps temporarily, uncoupling the mechanisms of resorption and formation, according to researchers from the University of Liege, Belgium.[41]

A partial list of transnasal drugs is given in Table 7.2.

Table 7.2 A partial list of transnasal drugs

Drug	Trade name	Use	Producer-marketer
Amiloride	—	Cystic fibrosis	Glaxo
Salmeterol	—	Asthma	Glaxo
Fluticasone	Flixonase	Perennial rhinitis	Glaxo
Pentigetide	Pentyde	Allergic rhinitis	Dura Pharmaceuticals
Vitamin B-12	—	Pernicious anemia	Nastech
Meclizine	—	Antiemetic	Nastech
Cimetidine, ranitidine	—	Antihistaminic	Nastech
Doxylamine, azatidine	—	Antihistaminic	Nastech
Butorphanol tartrate	Stadol NS	Analgesic	Bristol Myers Squibb
Triamcinolone	Nasacort	Allergic rhinitis	Rhone-Poulenc Rorer

E. Recent advances

Ketorolac tromethamine is a potent nonnarcotic analgesic with moderate anti-inflammatory activity. A series of spray and lyophilized powder formulations of ketorolac was administered into the nasal cavity of rabbits, and their pharmacokinetics profiles were assessed. Nasal spray formulations were significantly better absorbed than powder formulations. A nasal spray formulation of ketorolac tromethamine showed the highest absorption, with an absolute bioavailability of 91%. Interestingly, the absolute bioavailability of ketorolac tromethamine from a powder formulation is only 38%, indicating that the drug may not be totally released from the polymer matrix before it is removed from nasal epithelium by mucociliary clearance.[79]

Nasal glucagon delivery using microcrystalline cellulose in healthy volunteers was reported by Teshima et al.[80] The spray solution caused strong irritation, but the powder form did not. Their results suggested usefulness of the powder form of glucagon for the treatment of pancreatectomized patients.

Biodegradable microparticles containing gentamicin were prepared using chitosan hydroglutamate (CH), hyaluronic acid (HA), and a combination of both polymers by a solvent evaporation method. The bioavailability of gentamicin was poor when administered as a nasal solution (1.1%) and dry powder (2.1%) when compared with IV. However, the microparticulate systems composed of CH and HA/CH considerably enhanced the bioavailability of gentamicin (31.4 and 42.9%, respectively).[81]

Carboxymethyl cellulose (CMC) powder formulation of apomorphine was prepared by lyophyilization and characterized with respect to the *in vitro* and intranasal *in vivo* release of apomorphine in rabbits. This was compared to apomorphine release from degradable starch microspheres (DSM) and lactose. *In vitro* apomorphine release from CMC was sustained, unlike that of DSM and lactose. The sustained plasma level of apomorphine by CMC was achieved, with relative bioavailabilities equivalent to subcutaneous injection.[82]

Emulsion formulations of testosterone for nasal administration were reported by Ko et al.[83] Three differently charged testosterone submicron-size emulsion formulations with various zeta potentials were prepared as nasal spray formulations. Both the positively and negatively charged emulsion formulations provided a better bioavailability than the neutrally charged emulsion, probably indicating that the charged particle interactions between emulsion globules and the mucus layer prolong the contact of the drug with nasal membrane, thus enhancing drug absorption.

Lizio et al.[84] reported on the pulmonary absorption and tolerability of various formulations of the decapeptide cetrorelix acetate in rats by aerosol delivery system (ASTA-ADS) for intratracheal application. The histologic examination of the lungs revealed different tolerability of the various tested formulations, ranging from locally intolerable to well tolerated. The measurement of the lung-function parameters did not reveal any compound or formulation-related changes.

The purpose of investigation reported by Moore and Pham[85] was to assess hydraulic high-pressure nebulization as a means for respiratory drug delivery. A hydraulic high-pressure nebulizer was designed and constructed. The efficiency of the hydraulic high-pressure nebulizer appears to be correlated with the calculated properties of the liquid jet. For respiratory drug delivery, the hydraulic high-pressure nebulizer provides reasonably high outputs of respirable particles, independent of time, from a single pass of liquid through the nebulizer.

The effect of mixing of fine carrier particles on dry powder inhalation property of salbutamol sulfate was investigated by Iida et al.[86] They concluded that this could be a suitable method for improving the dry powder inhalation properties of therapeutic agents.

Direct delivery of medication to the sinuses with standard nebulizers is sometimes difficult to achieve. The nasal inhalation of aerosolized medications is dependent on the size of the particles and the pressure with which they are delivered. The ability of topical medications to treat sinus disorders can be improved if the medication could be delivered directly to the sinuses. The authors tested the ability of the RinoFlow nasal aerosol delivery device to deposit aerosol directly to the paranasal sinuses. Tc99m was used nasally, and nuclear scanning was used to detect deposition in the frontal and maxillary sinuses. The results of this study were promising.[87]

Particle-size distribution of the sodium cromoglycate preparations, CROPOZ PLUS and CROMOGEN EB, generated with MDI and for underpressure releasing methods were measured. Results of measurements indicate a significant repeatability of each sample properties. An average contribution of mass of the respirable fraction for both aerosolized pharmaceuticals is in the range of 40% of the generated dose. High contribution of submicron particles of CROMOGEN EB with optimizer gives efficient penetration and deposition of these particles in the lungs.[88]

In one study reported by Musoh et al.,[89] the bronchoconstriction induced by histamine inhalation was significantly inhibited by tulobuterol tape in

comparison with its placebo tape. Twenty-four hours after binding, the inhibitory effect of tulobuterol tape gradually diminished. These results suggest that tulobuterol tape has a long-lasting bronchodilatory action.

Pulmonary vasodilation with a 100-ppm concentration of Nomin (NO), given as a short burst of a few milliliters at the beginning of each breath was compared with conventionally inhaled NO, in which a full breath of 40 ppm of NO was inhaled (NOCD). A small volume of NO inhaled at the beginning of the breath was equally effective as NOCD, but reduced the dose of NO per breath by 40-fold.[90]

The incidence of invasive pulmonary aspergillosis has increased in patients receiving immunosuppressive therapy or organ transplantation. For prophylaxis against aspergillus infections, amphotericin B may be a useful drug when inhaled as aerosol. In this reported study, the aerosolization of amphotericin B was investigated using eight different medical nebulizers under various operating conditions and with different amphotericin B concentrations in the solution. Three out of eight devices proved suitable for amphotericin treatment via inhalation.[91]

Kraemer[92] reported on Babyhaler, a new pediatric aerosol device. Nebulizers have, until recently, been the mainstay of drug delivery by inhalation in babies and young children. The willingness of a young child to cooperate, however, is limited, and the 10 to 12 minutes needed to deliver a drug using a nebulizer often limits the compliance with this mode of administration in infants. Therefore, drug delivery systems using the MDI as the aerosol generator attached to valves holding chambers were developed. In brief, the Babyhaler consists of a tubular chamber 230 mm long, with a volume of 350 ml and low-resistance inspiratory and expiratory valves, among other things.

Fuller[93] reported on the Diskus, a new multi-dose powder device. The mass of drug substance (mass median aerodynamic diameter [MMAD]), less than 6 microns, delivered from the Diskus remains relatively constant at different flow rates, unlike the reservoir powder inhaler, in which the fine particle mass is more dependent on flow rate. The doses of drug in the Diskus are protected from moisture. In clinical studies, salmeterol, 50 micrograms twice daily, and fluticasosne propionate, 50 to 500 micrograms twice daily, have been shown to be equally effective and well tolerated when delivered by Diskus as compared with Diskhaler.[94–96]

II Ocular drug delivery

A. Introduction

Ophthalmic preparations, including solutions, suspensions, and ointments, can be applied topically to the cornea or instilled in the space between the eyeball and lower eyelid (the cul-de-sac or conjunctival sac of the lower lid). When drops of an aqueous solution are applied onto the cornea, through which the drug must penetrate to reach the interior part of the eye, the solution in the drops is immediately diluted with tears and washes away

rapidly through the lachrymal apparatus. Consequently, eye drops do not remain in contact with the eye for a long time, and they must be administered at relatively frequent intervals. Suspensions have the advantage of longer contact time in the eye, but also the disadvantage of an irritation potential, due to the particle size of the suspended drugs. Irritation may produce excessive tearing and, consequently, rapid drainage of the instilled dose. Ointments have the advantages of longer contact time and greater storage stability, but also the disadvantage of producing a film over the eye, thereby blurring vision. In addition, ointments can interfere with the attachment of new corneal epithelial cells to their normal base. The disadvantages of various types of ophthalmic preparations can be overcome by controlled delivery systems that release a drug at a constant rate for a relatively long time.

The typical administration of an ocular drug delivery system has been pulse entry of the drug, followed by a rapid, first-order decline of drug concentration. Adequate therapy from eyedrops may be achieved either by providing a sufficient magnitude of the pulse, so that its effect is extended for a useful period of time, or by giving more frequent applications of a less-concentrated pulse.[42]

Some of the new ophthalmic drug delivery systems have been reported to have enhanced corneal absorption. While these systems prolong the desired effect with less frequent applications than eyedrops require, side effects are also enhanced. Thus, these systems are limited to use with drugs with dose-related side effects that are not serious or that can be tolerated by the patient. Representative examples of these delivery systems are described in this section.

B. Relevant anatomy and physiology of the eye

The human eye (see Figure 7.3) has a spherical shape with a diameter of 23 mm. The structural components of the eyeball are divided into three layers: the outermost coat comprises the clear, transparent cornea and the white, opaque sclera; the middle layer comprises the iris anteriorly, the choroid posteriorly, and the ciliary body; and the inner layer is the retina, which is an extension of the central nervous system.[43]

The cornea (see Figure 7.4) is often the tissue through which drugs in ophthalmic preparations reach the inside of the eye. Because the structure of the cornea consists of epithelium–stroma–epithelium, which is equivalent to a fat–water–fat structure, the penetration of nonpolar compounds through the cornea depends on their oil/water partition coefficients. The fluid systems in the eye — the aqueous humor and the vitreous humor — also play an important role in ocular pharmacokinetics. The aqueous humor fills the anterior and posterior chambers of the eye and is secreted continuously from the blood through the epithelium of the ciliary body. This fluid is transported from the posterior to the anterior chamber, and hence escapes through Schlemm's canal. The vitreous humor has the same origin as the aqueous

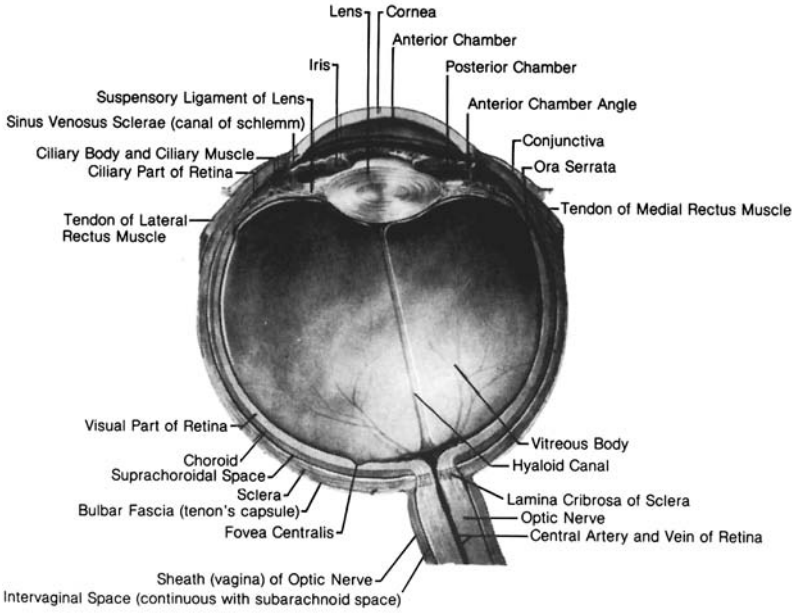

Figure 7.3 Cross-sectional view of the eye. (From Robinson, J.R., Ed., Ophthalmic drug delivery systems, *J. Pharm. Sci.*, 1, 1980. With permission of the American Pharmaceutical Association.)

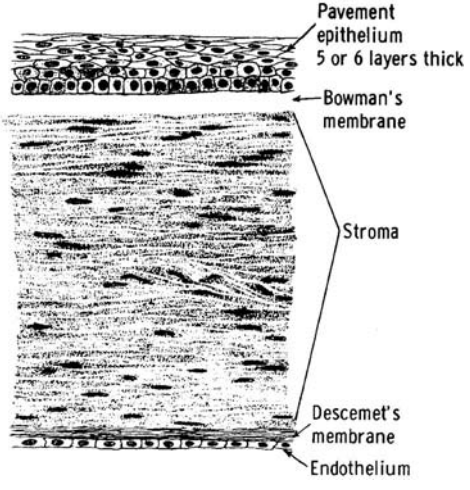

Figure 7.4 Corneal cross-section. (From Robinson, J.R., Ed., Ophthalmic drug delivery systems, *J. Pharm. Sci.*, 10, 1980. With permission of the American Pharmaceutical Association.)

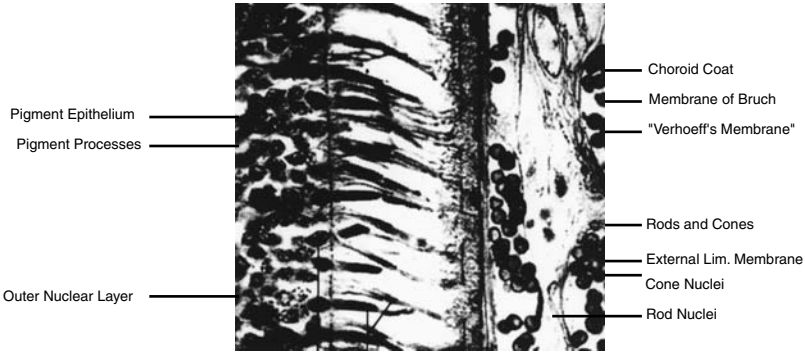

Figure 7.5 Structural detail of the retina. (From Robinson, J.R., Ed., Ophthalmic drug delivery systems, *J. Pharm. Sci.*, 94, 1980. With permission of the American Pharmaceutical Association.)

humor, but diffuses through the vitreous body and escapes from the eye through the uveo-scleral route.

From the perspective of ocular pharmacokinetics, the dynamics of the aqueous humor are more important than those of the vitreous humor because ocular drugs are usually applied to the cornea and the aqueous humor has a relatively fast turnover rate. The structural details of the retina, which belongs to the inner coat of the eye, are illustrated in Figure 7.5.

Drug disposition in the eye following topical application is a complex phenomenon resulting from both drug-dependent and independent parameters. In order to describe the pharmacokinetics of ocular drugs, it is necessary to consider the distribution and disposition of drugs in three areas of the eye: the precorneal area, the cornea, and the interior of the eye.

The internal ocular structures are critical to a comprehensive understanding of ocular drug pharmacokinetics. Binding to both aqueous humor and tissues, aqueous flow and turnover, partitioning into and binding within tissues, and various distribution equilibria are all determinants in drug-disposition kinetics in the eye.[43]

When a drug is instilled into the eye, there exist a large number of factors that can influence its distribution and movement into various parts of the eye or the body as a whole. Topically applied ocular drugs may be intended to exert a local effect, or to penetrate into the anterior chamber, to be distributed to various eye tissues. The events that take place in the precorneal area of the eye are critical factors in determining how much of any instilled or applied dose is available to exert its pharmacologic effect. These precorneal factors include the effects of tear production and instilled fluid drainage, protein binding, metabolism, tear evaporation, and nonproductive absorption/adsorption.

The role of the cornea in ocular drug disposition is important. The cornea comprises the anterior one-sixth of the globe and is the membrane through which drugs must pass if they are to reach the inner areas of the eye, such

as the anterior chamber and the iris. As such, the cornea is critical to an overall understanding of ocular drug disposition after topical dosing. It is generally conceded that there are three main factors contributing to the efficiency of corneal penetration of topically applied ophthalmic drugs: the corneal structure and its integrity, the physical–chemical properties of the applied drug, and the formulation in which the drug is prepared.[43]

Once a drug has penetrated the cornea, there are several factors that need to be considered in the ultimate pharmacokinetic description of that drug's fate: the volume or spaces (tissues) into which the drug distributes; binding of drug in both aqueous humor and tissues; partitioning behavior of drug between aqueous humor and the various ocular tissues, such as iris, lens, and vitreous humor; possible differences in equilibration time between aqueous humor and the various ocular tissues; possibility of drug metabolism in eye fluid or tissues; and drug effects to either stimulate or inhibit aqueous humor production and turnover.

The traditional ophthalmic dosage forms have been solutions, suspensions, and ointments, although there have been several other forms tried. Relatively few new efforts have seen any real success, and the newest, the ocular insert, is still uncertain as to its real place in drug delivery. The characteristic parts of an ophthalmic dosage form — the drug, the vehicle, the preservative, and the other additives — occupy the same general relationship to each other as they do in other drug solution, suspension, and ointment products. However, the eye itself has several specific characteristics that affect the expected performance of each of these parts.

In order of economic importance, the topical dosage forms used to treat diseases fall into three specific and one rather broad category: solutions, suspensions, ointments, and a rather amorphous group. Solutions are without question the most generally used and accepted forms. They are relatively straightforward to make, filter, and sterilize, and they all use the standard formulation parameters. Suspensions, while not as common as solutions, are widely used for formulations involving ocular steroids and came into broad, general use with the post-World War II availability of these drugs for the treatment of inflammatory diseases. Ointments have traditionally been the cheapest form of ocular therapy, but for years presented significant problems. They could not, for example, be effectively filtered to free them from particles; they could not be made truly sterile; and no adequate test had been devised to indicate the suitability of added preservatives.

In 1970, with the advent of oil-stable microbial filters, most of these problems were solved. Shortly thereafter, sterile, filtered ophthalmic ointments appeared on the U.S. market, although they are certainly still a distant third in economic importance. Inserts have been described in the pharmaceutical literature for more than 50 years, but a resurgence of interest has been stimulated by the fundamental improvement over the original gelatin leaflet offered by the Ocusert®.[44]

Unlike most systemic drug therapy, the major portion of a topically instilled drug leaves the potential absorption site (the cornea) unused, unab-

sorbed, and lost to therapy. This occurs, in part, because some drug forms do not penetrate the corneal epithelium well and, more important, because tear dilution and subsequent washout eliminate the drug rapidly. This produces, in some cases, an undesired drug load for the systemic circulation when adequate concentrations are used to provide the desired ophthalmic effects. Physiologic factors prevent some areas of the optical globe from being treated with topical products. For example, the posterior parts of the eye are protected from externally applied drugs by the intrinsic flow patterns within the globe. Efforts to treat posterior-chamber inflammation and retinal disease, where the aqueous flow opposes the diffusion path from cornea to the ciliary body, require large systemic doses, and topical therapy is largely ineffective.

While normal saline is an acceptable vehicle for ophthalmic drugs, slightly more viscous solutions are generally recognized by physicians and patients as more satisfying to use. However, this satisfaction results only over a relatively narrow range of viscosity. This narrow band of acceptable viscosity is dictated by the fact that these products must have negligible visual effects if they are to be used during waking hours, as well as be comfortable, filterable, and sterilizable.

Ophthalmic products, with their application methods and multiple-use characteristics, are, unfortunately, highly susceptible to "suck-back" contamination. Preservation, as opposed to single-use containers, has answered the problem satisfactorily, but the limited number of preservatives available has presented problems of compatibility and pH stability for the formulator. For the most part, only three preservatives are in common use — benzalkonium chloride, thimerosal, and chlorobutanol, although mixtures and enhancers, such as EDTA, have increased the spectrum of possibilities.[44]

C. *Examples of ocular drug delivery systems*

1. The Ocusert, introduced commercially by Alza, is a membrane-controlled reservoir system used in the treatment of glaucoma. The active agent in Ocusert is pilocarpine, a parasympathomimetic agent that acts directly on target organs in the iris, ciliary body, and trabecular meshwork, increasing the outflow of aqueous humor and decreasing the intraocular pressure. The copolymer used in the Ocusert is ethylene-vinyl acetate. Pilocarpine is surrounded on both sides with two polymer membranes (see Figure 7.6). Alginic acid, a carbohydrate extracted from seaweed, is also placed in the core of the Ocusert to act as a carrier for pilocarpine. There is also a white annular border around the device consisting of the ethylene-vinyl acetate copolymer impregnated with titanium dioxide, a powdered pigment. The border makes the Ocusert easier for the patient to visualize. To use the Ocusert, the patient places the device in the eye's cul-de-sac where it floats on the tear film. No major complications occur with the

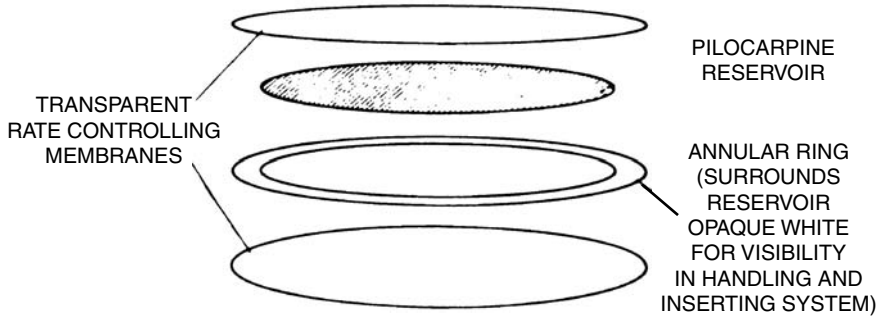

Figure 7.6 Schematic diagram of Ocusert. (From Langer, R.S. and Wise, D.L., Eds., *Medical Applications of Controlled Release*, Vol. II, CRC Press, Boca Raton, FL, 1984, 67.)

Ocusert. The patients who are candidates for Ocuserts are those in whom drugs such as beta blockers do not produce adequate pressure control and who respond well to pilocarpine eyedrops, but are too young to tolerate the marked variation in visual acuity that occurs with pulsed-drop medication.

2. Patients with dry eyes (keratitis sicca) are one of the most common and difficult management problems in ophthalmology. These patients generally demonstrate a wide range of abnormalities of tear production and lid function. In an effort to augment tear function, liquid tear substitutes have been designed to replace the aqueous component of tears and to stabilize the tear film in much the same way that mucous does. The Lacrisert, a substitute for artificial tears, has been developed by Merck. The Lacrisert is inserted into the eye with a special reusable applicator. The system is placed in the conjunctival sac, where it softens within 1 hour and completely dissolves within 14 to 18 hours. The Lacrisert acts to stabilize and thicken the precorneal tear film and prolong the tear film break-up time, which is usually accelerated in patients with dry-eye states.

   At least 25 products have been marketed for dry-eye syndrome since 1955. Currently, product formulators and clinical research groups are examining the influence of immunological factors on dry-eye syndrome. It is anticipated that these factors may offer considerable additional insight into establishing more precise rational approaches to dry-eye syndrome.
3. An ophthalmic gel used for the delivery of pilocarpine is poloxamer 407. This vehicle was chosen because of its low viscosity, optical clarity, and mucomimetic properties and for its previous acceptability in ophthalmic preparations. This formulation enhances pilocarpine activity, as indicated by miosis measurements in rabbits, compared to an aqueous pilocarpine solution of equal drug concentration. A pilocarpine emulsion in eyedrop form (Piloplex) reportedly[45] pro-

longs therapeutic effectiveness compared with pilocarpine hydrochloride eyedrops. In this formulation, pilocarpine is bound to a polymeric material, and this complex makes up the internal, dispersed phase of the emulsion system. Facilitated transport in animals has been used successfully to enhance the movement of the mast cell stabilizer sodium chromoglycate (the dianion) across the cornea.[46]

4. The first ophthalmic pro-drug, dipivalylepinephrine (Dipivefrin, Propine), was recently described in 1980. By diesterification, the compound was made more lipophilic, resulting in a tenfold increase in its corneal absorption. Upon absorption, esterases within both the cornea and the aqueous humor act rapidly to liberate the epinephrine.[47]

   A number of soluble, solid-state drug carriers have been utilized for ophthalmic medication. "Lamellae," described as early as 1948 in the British Pharmacopoeia, were atropine-containing gelatin wafers intended for placement beneath the eyelid. Delivery of an antibiotic by an ocular insert made of succinylated, enzyme-solubilized collagen has also been described, and this approach appears promising for the treatment of ocular infection. One study compared ^{14}C-gentamicin levels in rabbit tear film and in ocular tissue when the drug was administered by eyedrops, ointments, subconjunctival injection, or by solid wafers. The inserts gave superior levels of drug in the tears, sclera, and cornea. Prolongation of the pulse entry, as compared to ointment delivery or periocular injection, are evident.[48]

   Experimental continuous-delivery systems based upon the osmotic properties of an incorporated drug have been developed and have undergone early clinical testing. Several sizes and shapes have been developed. They range from a thin, flat layer of different shapes to a contoured, three-dimensional unit designed to conform to the supratarsal space of the upper cul-de-sac. The latter system has been utilized in the delivery of diethylcarbamazine in ocular onchocerciasis. The nonhydrophilic polymer matrix contains the incorporated drug, which is dispersed in the solid state as numerous, extremely small domains, each as a discrete compartment separated by polymer material. Drug delivery proceeds at a fairly constant rate for the life of the system, at which time the device is removed and replaced. The useful life of these systems is limited to a large extent by drug-volume constraints; there being an upper limit to the size of the device the eye will tolerate and retain. Systems have been developed that deliver therapeutic drugs levels for 2 weeks.[49–51]

5. Topically applied peptides can also be absorbed into the bloodstream via the blood vessels in the conjunctival mucosa. Indeed, in one study, the conjunctival mucosa played a more significant role than did the nasal mucosa in the systemic absorption of [D-ala^2] met-enkephalinamide. This is demonstrated by the small change in the area under the curve of concentration plotted against time when the drainage apparatus was blocked to deny the peptide access to the nasal mu-

cosa. When contact between the peptide and the conjunctiva was prolonged by increasing the viscosity of the aqueous solution, the percentage of [D-ala^2] metenkephalinamide systemically absorbed was doubled, but absorption was still far from complete. To achieve systemic delivery of peptides using the ocular route, absorption of the peptide must be enhanced by ensuring that peptidase-mediated degradation of the peptide in the corneal epithelium is prevented.[52]

6. Transport of drugs across the corneal barrier can sometimes be facilitated by formation of a chemical derivative. A distinction is made between temporary derivatives (pro-drugs), from which the active parent compound is regenerated following absorption and derivatives that are made to improve some useful property, such as their bioavailability. A recently reported success with the latter approach involves removing one alkyl group from the quaternary nitrogen of carbachol and converting it into a tertiary nitrogen. The new derivative, N-demethylated carbachol, possesses an enhanced ability to penetrate the cornea with retention of miotic activity.[53]
7. Clinical studies have been conducted on 466 patients waiting for senile cataract surgery and receiving chloromycetin, gentamycin, or carbenicillin subconjunctively or through New Sauflon 70 and New Sauflon 85 lenses. Soft contact lenses provided significantly higher drug penetration than subconjunctival therapy. Both modes of treatment provided therapeutically effective levels against most common ocular pathogens for intervals of 2 to 12 h.[54]
8. Development of an extended-duration ocular drug delivery system is particularly challenging, due to extensive precorneal-loss parameters, as evidenced by the fact that very few ocular products are available for once-daily/weekly therapy. Patient comfort, compliance, and dosing are additional constraints of the product profile. Researchers at the University of Wisconsin have developed an ocular device, the Minidisc, that resolves patient compliance issues with design features that are based on eye anatomy and pharmacokinetic aspects of ocular drug disposition. The disc can be hydrophilic or hydrophobic to permit use of both water-soluble and water-insoluble drugs. For developmental purposes, the researchers selected sulfisoxazole and gentamicin as model drugs. It was found that the Minidisc is an effective and versatile prolonged-release ocular drug delivery system.[55]
9. Corneal penetration and bioconversion of ocular pro-drugs for an anticataract drug, catalin, has been investigated using freshly excised rabbit cornea. A horizontal-type *in vitro* apparatus was developed for studying long-term transcorneal drug penetration/bioconversion kinetics. The appearance rate of the drug after the bioconversion of methyl, ethyl, propyl, and butyl esters was much higher than the penetration rate of the parent drug. The appearance rate of catalin after pro-drug bioconversion improves with increasing alkyl chain length of the esters.[56]

10. Investigation of the impact of the dosage form, whether suspension or ophthalmic film, and formulation variables in the film delivery system on dexa-methasone pharmacokinetics in ocular tissue has been carried out. The results reveal some characteristic features for the disposition of the drug in ocular tissues when the drug is applied in suspension form.[57]
11. An objective in the development of an ophthalmic formulation is the close resemblance of *in vitro* or animal models with the clinical situation. For this reason, experiments with pilocarpine nitrate in conventional eyedrops or adsorbed to poly-(butyl cyanoacrylate) nanoparticles has been carried out.[58]
12. Extensive drug loss due to the highly efficient precorneal elimination process occurs upon eyedrop instillation. The addition of viscosity-enhancing polymers increases precorneal retention and hence bioavailability. A mucoadhesive polymeric solution (Carbopol 934 P) has been compared with an equiviscous (60 cps) nonmucoadhesive solution (PVA), measuring pilocarpine bioavailability and polymer-retention times in the rabbit eye. The polymers were labeled with radioactivity in and their deposition and clearance studied by lachrymal scintigraphy. Different clearance kinetics were observed for the Carbopol 934 P and the PVA, with the former exhibiting extended corneal retention.[59]
13. An ocular therapeutic system for releasing a drug to the eye at a controlled and continuous rate for a prolonged period of time has been described. The system is shaped, sized, and adapted for insertion and retention in the eye. The system contains an ophthalmically acceptable drug, such as hydrocortisone, and it is formed of a polymeric material permeable to the passage of drug by diffusion.[60]
14. 6-Hydroxy-2-benzothiazolesulfonamide is useful for the topical treatment of elevated intraocular pressure. Ophthalmic compositions, including drops and inserts, have been described.[49]
15. Polymers and hydrogels of polymers have been described. The hydrogels are preferably used for the formation of contact lenses. The hydrogels can be impregnated with a solution containing a drug. A material (e.g., drug for ocular therapy) can then be administered to a patient, and the material will gradually be released to the patient. As the drug is removed from the surface of the hydrogel, it will be replaced with a fresh supply of drug migrating to the surface from its interior.[42]
16. A treatment for glaucoma or ocular hypertension by ophthalmically applying an effective amount of 2-(3-tert-butylamino-2-hydroxy-propylthio)-4-(5-carbamoyl-2-thienyl)-thiazole has been described.[61]
17. Waltman and Kaufman[62] have used hydrophilic contact lenses (Bionite, Griffin Labs, and Soflens, Bausch & Lomb) as devices for maintaining high drug concentration in the anterior chamber of the eye. They used fluorescein as a model drug. A Bionite lens presoaked

with the drug yielded a fluorescein concentration in rabbit aqueous humor four times greater than that from drops. In human studies, a Bionite lens could maintain the fluorescein concentration in ocular tissues for 24 h, despite the known rapid exit of the drug.

18. Kaufman et al.[63] have shown the usefulness of soft contact lenses for drug delivery to the eye in several experiments: antiviral idoxuridine (IDU) drops plus a soft contact lens significantly improved the therapeutic index for eyes infected with McKrae herpes virus; polymyxin B 0.25% and a lens soaked in polymyxin solution were administered to rabbit corneas infected with *Pseudomonas aeruginosa* (the presence of the lens in the eye had neither a beneficial nor a harmful effect); and the advantage of a soft contact lens on the effect of pilocarpine on the eye was investigated.
19. Praus et al.[64] have studied the release of antibiotics from presoaked (0.1% chlor-amphenicol or tetracycline) hydrogel contact lenses. In an *in vitro* experiment, the amount of released antibiotics was determined spectrometrically. During the first 3 hours, lenses of 0.3- and 0.9-mm thickness released 50% and 40% of tetracycline and 75% and 60% of chloramphenicol, respectively. The duration of release was up to eight hours for the thinner lens and more than 4 hours for the thicker one.
20. Corticosteroids are useful for the treatment of ocular inflammation. Hull et al.[65] studied the ocular penetration of prednisolone in the rabbit eye and the effect of a hydrophilic contact lens on penetration. The contact lenses made from PHP (hefilcon-A) copolymer (80% 2-hydroxyethyl methacrylate and 20% N-vinyl-2-pyrrolidone) were 16 mm in diameter and 0.3 mm thick, and their hydration was 40% to 45%. Lenses presoaked in prednisolone for 2 min were able to maintain the aqueous and corneal levels two to three times higher, at 4 h, than the levels after topical administration without the lens.
21. Other polymeric devices for drug delivery are soluble ocular inserts, such as the poly(vinyl alcohol) insert (PVAI); the soluble ophthalmic drug insert (SODI); and polypeptide devices.[66] Seven different combinations of SODI and drugs including pilocarpine, atropine, neomycin, kanamycin, sulfapyridazine, tetracaine, and idoxuridine have been studied. These studies established that SODIs are well tolerated by eye tissue and that when an SODI is inserted into the conjunctival sac, it absorbs tears rapidly, swells, and dissolves in about 30 to 90 minutes, releasing the active substance. The dissolution property of the SODIs frees the patient from the task of removing the device after the drug has been released completely.
22. An interesting enzymatically degradable pharmaceutical carrier has been produced by Capozza,[67] and it is made of poly(N-acetyl-D-glucosamine)(chitin), an important structural polysaccharide of invertebrates. Chitin is converted enzymatically to a decomposed form, which serves as a matrix for the ocular inserts. Pilocarpine, which is

released from the eroding surface of the insert, produces pupillary miosis for 6 h.

23. Ueno and Refojo[68] have investigated the sustained release of chloramphenicol and lincomycin from closed-cell, silicone-rubber, scleral-buckling material (sponge) (Dow Corning Silastic sponge, Lincoff design). The sponge was immersed in a saturated solution of lincomycin in propylene oxide for three days at room temperature and then dried. The antibiotic was released into seeded agar plates at a nearly constant rate for about 3 weeks from the cylindrical sponge and for more than one month from the oval-shaped sponge. The cylindrical sponge also released chloramphenicol at a nearly constant rate for about 2 weeks, but then the release rate slowly declined.

    The uptake mechanism was thought due to propylene oxide swelling the silicone rubber of the sponge, converting it to a gel; and the antibiotics dissolved in propylene oxide diffuse through the network of the swollen rubber into the cells of the sponge. After the propylene oxide evaporates, the swollen sponge shrinks and returns to its original shape, but the antibiotics remain in the cells of the sponge. These antibiotic-impregnated materials, used in conjunction with standard pre- and postoperative therapy, can reduce even further the rate of infection in scleral-buckling procedures.

24. Ueno and Refojo[68] also have developed a device for the delivery of hydrophobic drugs consisting of a silicone-rubber system. The methodology is especially useful for the treatment of intraocular malignancies with 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU). BCNU is a useful chemotherapeutic agent for the treatment of a variety of human cancers. It has also been found effective against Brown–Pearce epithelioma and Greene melanoma implanted in the anterior chamber of the rabbit eye, which are useful animal models for ocular cancer research. BCNU is a liposoluble drug that decomposes rapidly to yield alkylating and carbamoylating intermediates at physiologic pH. BCNU produces various adverse effects, particularly when administered in therapeutic doses to the whole body. Ueno and Refojo have worked on the basis that ideally one should minimize the amount of drug given to the whole body while maximizing drug level at the tumor site. The silicone-rubber drug delivery device fulfilled these goals for the administration of BCNU to eye tumors in the rabbit.

25. The double-stranded complex of polyriboinosonic acid and polyribocytidylic acid (poly I:C) has been successfully used to induce resistance to systemic, as well as localized, viral infections through production of endogenous interferons. Of particular interest, poly I:C has been applied topically for clinical treatment of herpetic infections of the cornea and conjunctiva of the eye. However, a disadvantage associated with topical ophthalmic application of poly I:C has been the apparent need for frequently repeated applications to ensure

adequate exposure of the infected tissue. Major improvements in ophthalmic medication systems can be realized either by providing for the controlled release of drug subsequent to instillation in the medication of the eye or by increasing the contact time for the drug with eye tissues.[69]

D. Recent advances

The objectives of the study were to prepare a biodegradable polyisobutylcyanoaacrylate (PIBCA) colloidal particulate system of pilocarpine to incorporate it into a Pluronic F127 (PF 127)-based gel delivery system and to evaluate its ability to prolong the release of pilocarpine. PIBCA nanocapsules of pilocarpine were prepared by interfacial polymerization. This system can also be used for other, more hydrophobic drugs.[97]

The purpose of the study reported by Kim and Gao[98] was to prepare a chemically and physically stable rhEGF/HP-bta-CD poloxamer complex gel to investigate its possibility of ophthalmic delivery. The poloxamer gel containing the complex increased the area under the concentration-time curve, or area under the curve (AUC), rhEGF in tear fluid compared with gel containing rhEGF solution. This also indicated that rhEGF may be retained in the precorneal area for prolonged periods.

The objective of the study reported by Kawakami et al.[99] was to examine the ocular absorption behavior of an amphiphilic pro-drug after instillation onto the cornea of rabbits. A micellar solution of O-palmitoyl tilisolol (PalTL) an amphiphilic pro-drug, was prepared. After instillation of tilisolol (TL) and PalTL, the drug concentrations in the tear fluid, cornea, aqueous humor, iris-ciliary body, vitreous body, and blood were measured. PalTL exhibited increased retention in the precorneal area compared with the parent drug, TL, resulting in improved ocular absorption of the parent drug.

Poly(ortho esters) (POE) are hydrophobic and biodegradable polymers that have been investigated for pharmaceutical use since the early 1970s. Among the four described generations of POE, the third (POEIII) and fourth (POEIV) are promising viscous and injectable materials that have been investigated in numerous biomedical applications. POEIII has been extensively studied for ophthalmic drug delivery since it presents an excellent biocompatibility, and is currently under investigation as a vehicle for sustained drug delivery to treat diseases of the posterior segment of the eye.[100]

The report by Ghelardi and Tavanti[101] describes the efficacy of a novel mucoadhesive polymer, the tamarind seed polysaccharide, as a delivery system for the ocular administration of hydrophilic and hydrophobic antibiotics. The increased drug (e.g., gentamicin or ofloxacin absorption) and the prolonged drug-elimination phase obtained with the viscosified formulations indicate the usefulness of the tamarind seed polysaccharide as an ophthalmic delivery system for topical administration of antibiotics.

Systemic absorption of insulin from a Gelfoam ocular device was reported by Lee and Yalkowski[102] Gelfoam ocular devices containing 0.2 mg

of sodium insulin prepared with either water or 10% acetic acid were evaluated in rabbits. The results suggest that a change in the Gelfoam upon treatment with acid is responsible for the efficient systemic absorption of insulin from these enhancer-free devices.

The overall objective of the study was to develop pluronic F127 (PF127)-containing formulations of pilocarpine HCl suitable for controlled-release ocular delivery of PHCl. On the basis of the *in vitro* results, the PF127 formulations pf PHCl containing methylcellulose or hydroxypropyl methylcellulose as an additive showed potential for use as controlled-release ocular delivery systems for PHCl.[103]

Sodium insulin and zinc insulin ocular devices are developed for the systemic delivery of insulin. Commercially available Humulin R was selected as another source of zinc insulin and was used as an eyedrop, as well as one device preparation. Only 10% acetic acid solution-treated insulin devices produce significant blood glucose reduction. The dose of insulin used in this study is less than 50% of that used in the reported insulin devices.[104]

Mitomycin C was studied in the rabbit eye. The mitomycin C concentrations in the target tissues were dose-dependent and decreased rapidly over 24 hours. Both the initial mitomycin C concentrations, as well as AUCs in these eyes treated with mitomycin C, dissolved in a reversible thermosetting gel, were higher than those in eyes treated similarly in a study in which the gel was not used. Therefore, applied subconjunctively in the rabbit eye, mitomycin C dissolved in the reversible thermosetting gel-enhanced transfer of the agent to the sclera and the conjunctiva.[105]

Rafferty and Elfaki[106] reported on the preparation and characterization of a biodegradable microparticle antigen/cytokine ocular delivery system. They found that the inclusion of cytokines in the antigen-containing biodegradable microparticles enhanced teat IgA antibody levels following ocular optical delivery P2o, while elevated VW IgA responses occurred following intraperitoneal delivery of P2o and P3o. These data demonstrate that antigen/cytokine-loaded microparticles can potentiate long-term mucosal antibody responses at both target and distal effector sites, as well as elicit circulating antibodies.

E. Conclusion and future outlook

Experimental and clinical studies have confirmed that nasal and ocular routes of administration are practical approaches to therapy with many drugs, with the advantages of rapid absorption in some cases, along with ease of administration and good local tolerance. Nasal spray formulations, especially, have facilitated the diagnostic applications of peptides and biotechnology products by reducing side effects commonly observed in IV testing and treatment of infants and children in which repeated injections are a disadvantage[70,71] (see Figure 7.7).

The potential therapeutic advantages offered by ophthalmic and nasal drug delivery systems are numerous and significant. Despite this, the avail-

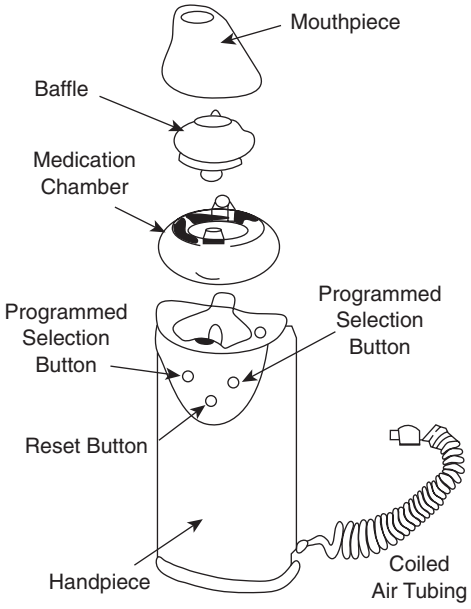

Figure 7.7 Halolite delivery system (Medic-Aid, Profile Therap. Subsidiary, U.K.).

able systems have not yet gained widespread acceptance. This situation may change as improved delivery systems are developed and as continuous administration systems are mandated by the emergence of important new drugs that have short half-lives.

When drugs are given in eyedrop form, 80% or more of the volume of an administered eyedrop, which is known to drain rapidly through the nasolacrimal canal, avoids the first-pass effect and is totally available for systemic absorption through the highly vascularized mucosa. Thus, an eyedrop is more like an intravenous dose.

Until recently, the side effects of frequently used and relatively safe ophthalmic drugs have been of little consequence, or at least have not been serious enough to alter prescribing habits in favor of new drug delivery systems. The development and rational use of more potent drugs, however, which may have serious side effects, may require concomitant development and use of improved methods for their controlled (i.e., non-pulsed) delivery.

Another feature of some ophthalmic and nasal delivery systems that may encourage their eventual acceptance is their freedom from the need for preservatives and other vehicle ingredients. The deleterious effects of these agents are not widely appreciated, but they are certainly real. Systems that provide continuous, controlled drug release to the eye may in time find important uses in the treatment of ophthalmic diseases, which, due to special circumstances, are otherwise difficult to treat effectively. The most important example is trachoma, an infectious ocular disease that is the leading cause of blindness worldwide.[72]

Finally, controlled-release systems could prove beneficial in a number of other ocular indications. These have been summarized by Jones[73] as follows: short, topical, ocular half-life (e.g., heparin for ligneous disease); small, topical, ocular therapeutic index (e.g., pilocarpine for chronic open-angle glaucoma, possibly nucleoside, or antiviral); systemic side effects (e.g., timolol for glaucoma and cyclosporin A for graft rejection); need for combination therapy (e.g., cromoglycate and corticosteroid for asthma and allergies, corticosteroid and indomethacin, or possibly corticosteroid, cyclosporin A, and indomethacin for prevention of corneal graft rejection; combination of antibiotics for septic keratitis (e.g., gentamicin or other aminoglycosides with methicilin or a cephalosporin); the need for a predetermined profile of drug delivery over a prolonged period of days, weeks, or months (e.g., acute corneal infections, acute-becoming chronic inflammation, and corneal graft rejection episodes); and long-continued low dosage for therapy or prophylaxis (e.g., for prevention of corneal graft rejection, prevention of recrudescence of inflammation, and prevention of or recurrence of herpetic disease).

In forecasting the future of rate-controlled topical delivery of nasal and ophthalmic drugs based on the examples cited, it is important to note that certain arbitrary choices about design were made early in this field. Much subsequent work needs to be done regarding reassessment of these early design features in the search for greater ease of system insertion, placement, and removal.[74,75]

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