23 Drug Delivery and Targeting

Chapter Objectives

At the conclusion of this chapter the student should be able to:

1. Distinguish between conventional dosage forms and advanced drug delivery systems.
2. Appreciate the need for drug delivery systems and recognize their benefits in enhancing drug bioavailability and reducing adverse effects.
3. Differentiate various routes of administration and the uniqueness of drug delivery systems designed for each route.
4. Identify the basic characteristics of gene and antisense oligonucleotide therapy and their delivery systems.
5. Understand the concept of targeted drug delivery and advantages of drug targeting to specific organs, tissues, intracellular organelles, and molecules.
6. Recognize the prodrug approach and its benefit in drug delivery.
7. Understand the concept of controlled drug delivery.
8. Classify controlled drug release kinetic profiles and recognize the benefits of each type of profile.

Introduction

"Drugs" that are taken by a patient exert a biological effect usually by interacting with specific receptors at the site of action.1 Unless the drug is delivered to the target site (in other words the site of action) at a rate and concentration, which minimizes the side effects and maximizes the therapeutic effect, the efficiency of a therapy is compromised.1 Often, the delivery and targeting barriers are so great that they render an otherwise potent drug ineffective. Dosage forms serve many purposes including facilitating drug administration and improving drug delivery. Traditional dosage forms include injections, oral formulations (solutions, suspension, tablets, and capsules), and topical creams and ointments. Unfortunately, most traditional dosage forms are unable to do all of the following: facilitate adequate drug absorption and access to the target site; prevent nonspecific drug distribution (side effects) and premature metabolism and excretion; and match drug input with the dose requirement.1 Alternative routes of drug administration and advanced drug delivery systems are therefore needed to meet these drug delivery challenges and improve drug therapy. In this chapter, the student will learn about advanced drug delivery systems.2,3

Advanced drug delivery systems aim to overcome limitations of conventional drug delivery using traditional dosage forms by achieving enhanced bioavailability and therapeutic index, reduced side effects, and improved patient acceptance or compliance.3While the first three factors are well appreciated, the improved patient compliance is equally important because it has been estimated that patients take almost one billion prescriptions per year incorrectly resulting in a significant number of hospitalizations and nursing home admissions. Improved patient compliance is achieved by developing "user-friendly" delivery systems that are convenient to take and require lower dosing frequency. During the 1950s and 1960s some of the first attempts were made to transform common dosage forms into advanced delivery systems by sustaining drug release via the oral route.4 The Spansule capsule, consisting of hundreds of tiny-coated pellets of drug substance developed by Smith Kline and French Laboratories, is considered the first such example.1 As a pellet travels through the gastrointestinal (GI) tract, the coating dissolves to release the drug. The pellet thickness is changed to control the drug release pattern. By the 1960s, polymers began to be used to deliver drugs and scientists started using a systems approach to product development that combined an understanding of pharmacokinetics, the biological interface, and the biological compatibility.4 Nanoparticles were introduced in drug delivery in 1970s; transdermal drug delivery system started appearing in 1980s and transepithelial delivery models were developed in 1990s. The phenomenal advances in the field of biotechnology and molecular biology during 1980s and 1990s made possible large quantity synthesis of biologics/biopharmaceuticals such as

peptides, proteins, antisense oligonucleotides, and siRNA. These compounds, although highly potent, are difficult to deliver because of their large molecular size, water solubility, and instability.

Key Concept

Advanced Drug Delivery Systems

Advanced drug delivery systems are defined as a formulation or device that delivers drug to specific site in the body at a certain rate. Advanced drug delivery systems usually represent a more sophisticated system that incorporates advanced technologies such as controlled, pulsatile, or bioresponsive drug delivery.2 Usually some form of targeting technology may also be present.

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There is an economic rationale as well for developing advanced drug delivery technologies.5 It has been estimated that the sales of advanced drug delivery systems in the United States were $64.1 billion by the end of 2006.6 The sales are projected to reach $153.5 billion in 2011. Similarly, the European market for advanced drug delivery systems totaled at $25 billion in 2007 and was expected to reach $47 billion by 2013.7 In 2009, the largest market share is for targeted drug delivery systems (~$50 billion) followed by sustained-release formulations (~$45 billion). While oral drug delivery systems currently represent about half of the drug delivery market, pulmonary, transdermal, and nanodrug delivery systems are expected to show most promising growth in the future.

This chapter aims to provide an overview of advanced drug delivery and targeting technologies. Major drug delivery routes are described and both advantages and disadvantages associated with each delivery route are discussed. An introduction to the concepts of controlled drug delivery and targeting is presented and representative examples of different drug delivery systems are presented.

Terminology2’3

- **Active targeting:** Targeting is achieved by binding to specific antigens or cell surface receptors.
- **ADME:** Abbreviation for absorption, distribution, metabolism, and excretion.
- **Bioavailability:** The rate and extent to which a drug is absorbed and becomes available at the site of action.
- **Biocompatible:** The system is able to perform the desired function without eliciting toxic and immunogenic responses, either systemically or locally.
- **Biodegradable:** The system degrades (chemical breakdown) either chemically or enzymatically by physiological environment.
- **Bioerosion:** The gradual dissolution of the system (mostly polymer matrix).
- **Bioequivalence:** Absence of significant difference in the rate and extent to which the active ingredient or moiety in two formulations becomes available at the site of action. Formulations showing superimposable drug plasma concentration (Cp) versus time (*T*) curve are said to be bioequivalent.
- **Bioresponsive release:** Drug delivery is controlled by a biological stimulus.
- **Blood–brain barrier (BBB):** The permeability barrier present between the brain (brain capillary endothelium) and blood, which prevents substances in blood from entering the brain tissue.
- **Carrier:** Monoclonal antibodies, carbohydrates, proteins, peptides, hormones, vitamins, growth factors, immunotoxins conjugated to the drug for achieving site-specific delivery.
- C_{max}**:** The maximum plasma concentration reached after the drug administration.
- **Drug Delivery System (DDS):** Formulation or device that delivers drug to a specific site in the body at a certain rate.
- **Drug disposition:** All processes involved in the DME of drugs in living organism.

- **Half-life ($t_{1/2}$):** The time required for half of the drug to be removed from the body.
- **Passive targeting:** Exploits the in vivo passive distribution pattern of a carrier for drug targeting.
- **Prodrug:** Pharmacologically inert derivatives that can be converted to active drug molecule in vivo, enzymatically or nonenzymatically, to exert a therapeutic effect.
- **Rate controlled delivery:** Drug delivered at predetermined rate either systemically or locally for a specific period of time.
- **Spatial drug delivery:** Delivery to a specific region of the body.
- **Sustained drug delivery:** Drug delivery, which prolongs or sustains the therapeutic blood or tissue levels of drug for an extended period of time.
- **Targeted drug delivery:** Drug is delivered to specific sites in the body.
- **Temporal drug delivery:** Control of drug delivery to produce an effect in time-dependant manner.
- **Therapeutic index:** Ratio of toxic to therapeutic drug dose.
- **t_{max}:** The time at which C_{max} occurs.
- **Variable release:** The drug is delivered at variable rate.
- **Zero-order release:** Drug release does not vary with time and relatively constant drug level is maintained in the body for longer periods.

Routes of Drug Delivery

The route of administration or delivery is a very important factor in designing a drug delivery system. For example, a conventional oral tablet could not be used to deliver medication in the ear since tablets require a certain amount and type of fluid to disintegrate and dissolve. The ear canal does not have the fluid or volume to be able to accommodate tablets. In addition, many tablets are simply too big to be inserted into the ear canal. Another factor is the therapeutic agent that has to be delivered. Some drugs are so poorly absorbed across the intestine that they need to be injected directly into the bloodstream through a vein (intravenous) or an artery (intra-arterial). It may be desirable to deliver a drug locally to the target organ or tissue without first entering the systemic circulation. This type of drug delivery is usually referred to as local or topical (Greek topikos, “place”). A good example of this is hydrocortisone cream. Hydrocortisone cream is applied topically to the skin where it is expected to exert its action as an anti-inflammatory and antipruritic (i.e., anti-itch) agent. Because of the potency and side effects associated with

steroid drugs, avoiding systemic absorption is often desirable. In contrast, drugs can be delivered to the whole body via the general blood circulation. This is usually referred to as systemic drug delivery. In order to enter the systemic circulation, a drug has to pass through a rate-limiting membrane such as the intestine or vaginal mucosa or it may be directly injected into the body avoiding a transmembrane absorption step altogether (e.g., it may be directly injected into a vein). Often, several dosage forms of the same drug are produced that may be suitable for different routes of administration. In such cases, the selection of the route of administration for the particular drug is generally dictated by the desired onset and duration of drug effect, reliability, patient's discomfort, and compliance.

The common routes of administration are summarized in Table 23-1. It should be stressed that local drug delivery can result in the release of the drug into the systemic circulation and therefore provide systemic drug delivery to many other organs (Fig. 23-1). For example, if a drug is being delivered to the lung, it might penetrate the respiratory barrier and enter the circulation. Similarly, penetration of a drug through the oral mucosa (i.e., sublingual, buccal, or gingival) results in the systemic delivery of the drug. Fundamental differences in the various biologic routes of drug administration critically affect the onset and duration of drug action. Table 23-2compares different routes of administration using nitroglycerin as an example. The selection of route of administration and dosage form depends on the desired drug concentration profiles that need to be achieved, patient issues (e.g., the ability to tolerate treatment

regimens such as the frequency of administration or the ability to swallow a tablet), and the disease state that is being treated. For instance, intravenous drug administration is often used in emergency situations when

fast action is critical. In contrast, extended-release oral tablets or transdermal drug delivery systems are often used to prolong the drug action. Specific drug delivery systems that are used for the various routes of delivery are discussed in detail later in this and other chapters.

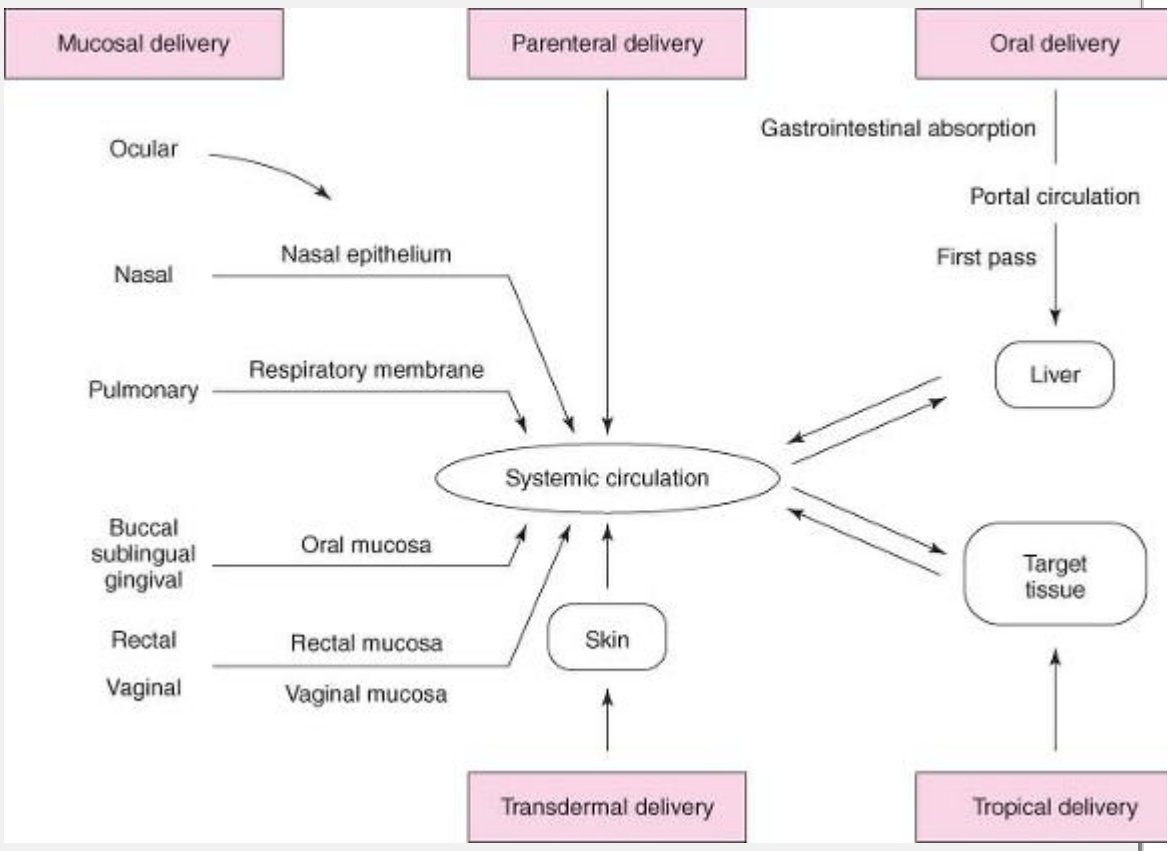

Fig. 23-1. Commonly used routes of drug delivery.

Table 23-1 Common Routes of Drug Administration*

Route	Site of Absorption
Parenteral	Injected directly into body, so the absorption step is usually minimal or nonexistent
Intravenous	Into a vein
Intramuscular	Into a muscle
Subcutaneous	Under the skin
Buccal	In the mouth through the oral mucosa (cheek near the gumline)
Inhalation	By mouth or nose and absorbed by the pulmonary (lung) mucosa
Nasal	In the nose through the nasal mucosa
Ocular	In the eye
Oral	Given by mouth and absorbed through the gastrointestinal mucosa
Rectal	In the rectum
Sublingual	Under the tongue
Topical	On the skin, local action
Transdermal	On the skin, systemic delivery
Vaginal	Into the vagina and absorbed through the vaginal mucosa

*Most of these routes of drug administration can be used for both topical (local) and systemic drug delivery.

Table 23-2 Comparison of Routes of Nitroglycerin Administration*

Route of Administration	Drug Delivery System	Onset of Action	Duration of Action
Intravenous	Parenteral solution	Immediate	Several minutes (dose dependent)
Translingual	Rapidly dissolving tablets	2–4 min	30–60 min
	Extended-release capsules and tablets	20–45 min	8–12 hr
Sublingual	Tablets and drops	1–3 min	30 min
Transmucosal (buccal)	Extended-release tablets	2–3 min	5 hr
	Ointment	20–60 min	4–8 hr
Transdermal	Transdermal patches	40–60 min	18–24 hr

*Nitroglycerin belongs to the class of drugs called nitrates. It dilates (widens) blood vessels (arteries and veins). Nitroglycerin is used to prevent angina attacks (oral tablets, buccal tablets) and to treat attacks once they have started (sublingual tablets, chewable tablets, spray).

Gastrointestinal (Oral, Per Os)

Oral administration of drugs is the simplest, easiest, and most common route of drug administration. After absorption from the GI tract, the drug enters the liver through the portal circulation (Fig. 23-1). During this “first pass” through the intestine and liver, drugs can be metabolically deactivated unless special measures are taken to protect them. Beyond the liver, the drug enters the systemic circulation and is delivered to the target tissues as well as all other tissues. The existence of first-pass intestinal–hepatic metabolism is the most significant challenge of oral drug delivery. In addition, the oral route is not suitable for the systemic delivery of drugs that are poorly absorbed or significantly destroyed in the GI tract.

In many countries, oral administration is the most common and preferred route of administration. The most commonly used dosage forms for the oral route are liquids, dispersed systems, and solids. Liquid dosage forms include oral solutions of drugs with added substances to make the preparation

pharmaceutically stable and aesthetically acceptable. Drugs administered in this form are more rapidly absorbed than other forms when administered on an empty stomach because gastric emptying is rapid and the drug is immediately available for absorption. Dispersed systems include emulsions and suspensions (see Chapters 16 and 17). The drugs in the emulsion or suspension forms are absorbed much more rapidly than in the solid forms since solid forms have to disintegrate, deaggregate, and dissolve. The solid dosage forms include the vast majority of the preparations used for oral administration. The widely used solid dosage forms are powders, tablets, caplets, and capsules. An entire chapter is devoted to this important dosage form and route of administration (see Chapter 22). Powders are administered occasionally for rapid systemic action. A tablet is a compressed form of the powdered drug along with therapeutically inactive ingredients that enable the proper disintegration, dissolution, lubrication, and so on, of the dosage form. A well-formulated immediate-release tablet should disintegrate rapidly and make the drug available for dissolution and absorption. Exceptions are slow-release and delayed-release tablets, which are designed for the continuous delivery of drug over a defined period of time or for delayed dissolution and drug release to target or avoid a specific GI location (e.g., enteric-coated tablets to avoid gastric release and inactivation of drugs). A capsule is a solid dosage form in which the drug with or without other ingredients is enclosed in either a hard or soft soluble shell generally prepared from a suitable form of gelatin.

Many new drugs cannot be delivered in oral form because they are too large, highly charged, or are degradable by stomach acid or the various enzymes in the GI tract. Insufficient amounts of these types of drugs traverse the intestinal barrier and reach the bloodstream. Consequently, these molecules can be delivered only by injection or other nonoral means. Nevertheless, oral ingestion is regarded as the safest, most convenient, and most economical method of drug administration. When compared to other alternatives, patient acceptance and adherence to a dosing regimen is typically higher among orally delivered medicines. Prodrug approaches have been widely used to enhance the oral delivery of small-molecule therapeutics such as acyclovir or ganciclovir (GCV). As described later in this chapter, by orally administering valacyclovir, the valyl-ester prodrug of acyclovir, one obtains blood concentrations of acyclovir similar to those achieved after the intravenous administration. Although the pharmaceutical industry has been successful in delivering small-molecule therapeutic agents orally, successes have been much more limited when it comes to larger drugs with more complex secondary and tertiary structures. Controlled-release drug delivery systems suitable for oral drug delivery are discussed later in this chapter (see Controlled Drug Delivery section).

Parenteral

The word “parenteral” (Greek para, “outside”; enteron, “intestine”), meaning outside of the intestine, denotes the

routes of administration other than the oral route (mainly by injection). Parenteral routes of administration are often used when the administration of drugs through the oral route is ineffective or impractical. It is also suitable for administration of drugs that are poorly absorbed or inactivated in the GI tract. The parenteral route is also used for drugs that are too irritating to be given by mouth. Almost any organ or area of the body can be used to inject drugs. However, the most commonly used routes of injections include the intramuscular (IM), intravenous (IV), subcutaneous (SC), and intradermal (ID) routes (Fig. 23-2). Intravenous injection provides very rapid onset of drug action, precision of dose, and accommodation of a large volume of drug solutions. It is suitable for administration of high–molecular-weight compounds. The other common forms of parenteral administration require that the drug pass through a significant amount of tissues and blood vessels (i.e., the endothelium of capillaries) to enter the circulation. The longer the path to the systemic circulation, the more delayed is the onset of drug reaction. Bioavailability of a parenteral drug also depends significantly on physicochemical characteristics of the drug (e.g., solubility, polarity, degree of ionization, molecular size).

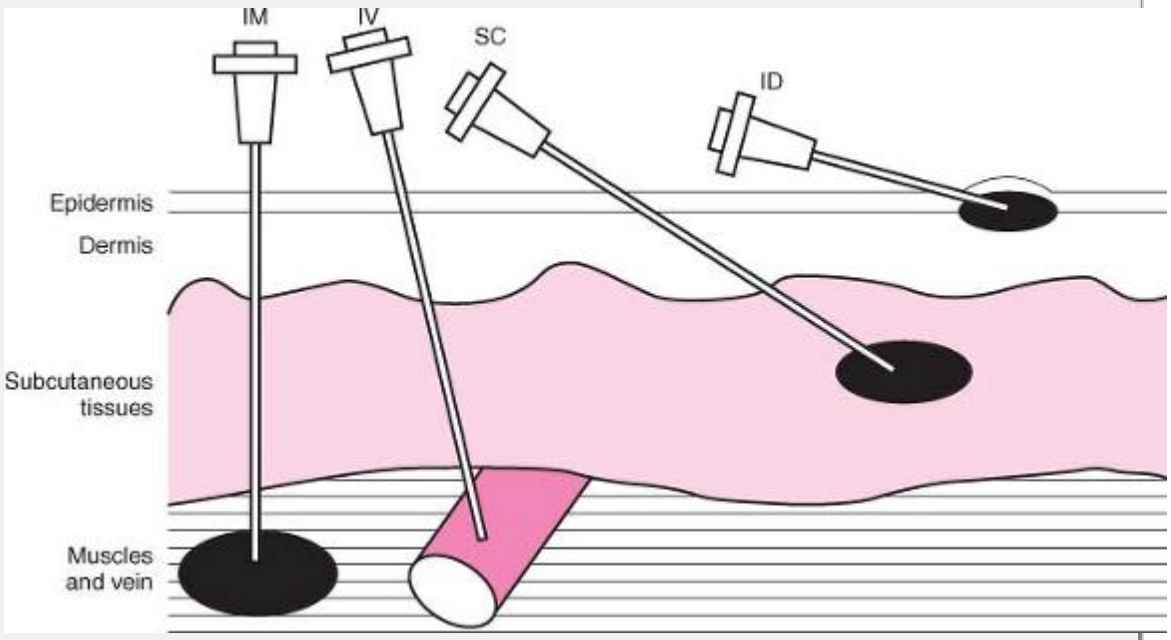

Fig. 23-2. The most common injection routes: into a vein (intravenous, IV); into a muscle (intramuscular, IM); under the skin (subcutaneous, SC, sub-Q, hypodermic, hypo); into the skin (intradermal, ID, intracutaneous).

Protein formulations, when given as injections, show poor pharmacokinetic profiles.8 The proteins are metabolized and rapidly cleared, which limits their therapeutic utility. PEGylation (covalent attachment of PEG to active moiety) reduces the plasma clearance of proteins by reducing their metabolic degradation and receptor-mediated uptake from systemic circulation. It also improves their safety profiles by shielding antigenic and immunogenic epitopes. An important example to consider is that of recombinant interferon-α (IFN), which is approved for the treatment of chronic hepatitis C, cell leukemia, malignant melanoma, non-Hodgkin lymphoma, and chronic myelogenous leukemia. When given subcutaneously, IFN is rapidly absorbed ($t_{1/2}$: 2.3 hr) and reaches a peak plasma level in 1 to 8 hr, which then falls rapidly (elimination $t_{1/2}$: 3–8 hr) and becomes undetectable in 24 hr.9 PEGylation with a 12-kDa linear PEG (peginterferon alpha-2b, PEG-Intron, Schering-Plough) significantly increases the absorption ($t_{1/2}$: 7 hr) and elimination half-lives ($t_{1/2}$: 4-days) of IFN.10 PEGylation with a 40-kDa branched PEG (peginterferon alpha-2a, Pegasys, Roche) enhances the absorption ($t_{1/2}$: 50 hr) and elimination ($t_{1/2}$: 11 days) half-lives to much higher levels.9 The improved pharmacokinetic profile reduces the dosing from three times weekly to once a weekly subcutaneous injection (with ribavirin) for patients with hepatitis C. Both products have safety profiles similar to unmodified IFN.

The advantage of using these routes lies in reliability, precision of dosage, and timed control of the onset of action. Disadvantages of all parenteral routes of drug administration include discomfort, possibility of infection, tissue damage, administration by trained personnel, and so on. Drug delivery systems and devices suitable for parenteral use are discussed later in this chapter.

Mucosal

Delivery of drugs via the absorptive mucosa in various easily accessible body cavities like the buccal, nasal, ocular, sublingual, rectal, and vaginal mucosae offers distinct advantages over peroral administration for systemic drug delivery. The primary advantage of using these routes is that they avoid the first-pass effect of drug clearance. Some of the numerous approaches that have been taken to facilitate mucosal drug delivery are described in the following sections.

Mucosal delivery faces several challenges such as retention on the mucosal surface so that bioavailability can be maximized. Bioadhesive polyacrylic acid nanoparticles are an example of a novel DDS designed for mucosal drug delivery.11 They had a narrow size range, averaging approximately 50 nm, and are stable in buffer. The drug timolol maleate is loaded into the nanoparticles from aqueous drug solutions, which is then released over several hours on dispersal of drug-loaded particles in phosphate buffer solution. Another variant of a mucoadhesive drug delivery formulation is based on H-bonded complexes of poly(acrylic acid) (PAA) or poly(methacrylic acid) with the poly(ethylene glycol) (PEG) of a PEG–drug conjugate.12,13 The PEGylated prodrugs are synthesized with degradable PEG-anhydride-drug bonds for eventual delivery of free drug from the formulation. The complexes are designed to dissociate as the formulation swells in contact with mucosal surfaces at pH 7.4, releasing PEG-bound drug, which then hydrolyzes to release free drug and PEG. It has been found that as the molecular weight of PAA increases, the dissociation rate of the complex decreases, which results in a decreased rate of drug release. On the other hand, drug release from PEG–drug conjugates alone and from a solid mixture of PEG–indomethacin +PAA was much faster than that from the H-bonded complexes. Because of the differences in thermal stability, the poly(methacrylic acid) complex exhibited slightly faster drug release than the PAA complex of comparable molecular weight. These H-bonded complexes of degradable PEGylated drugs with bioadhesive polymers may be useful for mucosal drug delivery.

Buccal and Sublingual

The buccal and sublingual mucosae in the oral cavity provide an excellent alternative for the delivery of certain drugs. The buccal mucosa is located on the cheeks in the mouth, and the sublingual mucosa is located under the tongue and on the floor of the mouth. Both of these mucosae offer an easily accessible area for the placement of dosage forms such as adhesive tablets. The buccal and sublingual routes provide improved delivery for certain drugs that are inactivated by first-pass intestinal/hepatic metabolism or are inactivated by proteolytic enzymes in the GI tract. Although this route shows some promise, it can only be used for potent drugs, as only a small surface area of about 100 cm^2 is available for absorption. Delivery of drugs into the mouth is also potentially limited by the taste of the drug or components of the delivery system.

The delivery of drugs to the oral mucosal cavity can be classified into three categories: (*a*) *sublingual delivery*, which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth; (*b*) *buccal delivery*, which is drug administration through the mucosal membranes lining the cheeks (buccal mucosa); and (*c*)*local delivery*, which is drug delivery into the oral cavity for nonsystemic delivery.

The sublingual mucosa is relatively permeable, giving rapid absorption and onset of drug action with acceptable bioavailabilities for many drugs. This route of drug delivery is also convenient, accessible, and generally well accepted. Sublingual drug delivery systems are generally of two different designs: (*a*) rapidly disintegrating tablets and (*b*) soft gelatin capsules filled with the drug in solution. Such systems create a very high drug concentration in the sublingual region before they are absorbed across the mucosa. Because of the high permeability and the rich blood supply, the sublingual route is capable of producing a rapid onset of action, making it appropriate for drugs with short delivery period requirements and an infrequent dosing regimen.

The most commonly used dosage form for the administration of drug through this route is a small tablet. These tablets are placed under the tongue. The tablets are designed to dissolve rapidly, and the drug substances are readily absorbed to the systemic circulation. Nitroglycerin sublingual tablets are frequently used for the prompt relief from an acute angina attack. The other drug products designed for this route are hormones such as dehydroepiandrosterone, melatonin, and vitamin C, and several metal salts.

The buccal mucosa is considerably less permeable than the sublingual area and is generally unable to provide the rapid absorption properties and higher bioavailabilities as seen with sublingual

administration. Two main differences between sublingual and buccal routes should be considered when designing drug delivery systems suitable for oral mucosa delivery. First, these two oral mucosa routes differ significantly in their permeability characteristics. The onset of action from the buccal mucosa is not as rapid as the sublingual mucosa because it is much less permeable and absorption is not as rapid. Therefore, it is more suitable for a sustained-release approach. Second, the buccal mucosa has an expanse of smooth muscle and is relatively immobile, whereas the sublingual region lacks both of these features and is constantly washed by a considerable amount of saliva. This makes the buccal mucosa a more desirable region for retentive delivery systems used for oral transmucosal drug delivery. Thus, the buccal mucosa is more useful for sustained-delivery applications, delivery of less permeable molecules, and perhaps peptide drugs. Similar to any other mucosal barrier, the buccal mucosa has limitations as well. One of the major disadvantages associated with buccal drug delivery is the low rate of absorption, which results in low drug bioavailability.

Because of the relative low permeability of buccal mucosa, DDSs for this route of administration usually include permeability or penetration enhancers—compounds that promote or enhance the absorption of drugs through the skin or mucosae, usually by reversibly altering the permeability of the barrier. Various compounds have been investigated for their use as buccal penetration enhancers to increase the flux of drugs across the mucosa. These compounds include but are not limited to ethers, cholates, aprotinin, azone, benzalkonium chloride, cetylpyridinium salts, cyclodextrins, dextrans, lauric

acid and its salts, propylene glycol, phospholipids, menthol, salicylates, ethylene diamine tetraacetic acid, several salts, sulfoxides, and various alkyl glycosides.14

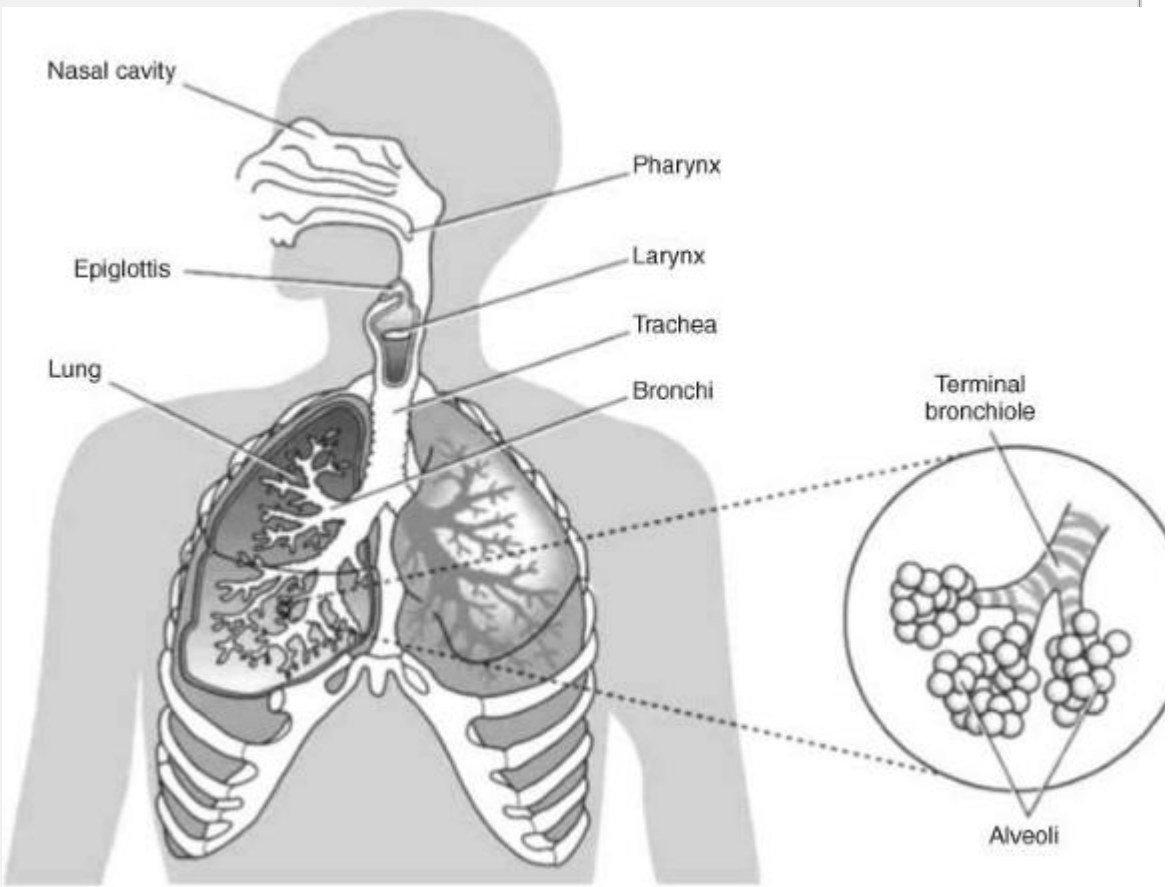

Fig. 23-3. Human respiratory system.

Pulmonary (Inhalation)

The respiratory tract (Fig. 23-3), which includes the nasal mucosa, pharynx, and large and small airway structures (trachea, bronchi, bronchioles, alveoli), provides a large mucosal surface for drug absorption. Utilization of this huge surface for drug delivery might provide a more convenient way compared with parenteral administration. The advantage of this drug delivery route was succinctly stated by J. S. Patton, “Taking advantage of the body's ability to transfer large molecules through the lungs is a better way to deliver drugs than sticking people with needles.”15 This route of administration is useful for the treatment of pulmonary conditions and for the delivery of drugs to distant target organs by means of the circulatory system.

The respiratory tract has a large surface area and therefore can be used for local and systemic drug delivery. The surface increases from the exterior region (nasopharyngeal) to the tracheobronchial and pulmonary regions, the latter consisting of bronchioles and alveoli (Fig. 23-3). One of the oldest examples of pulmonary administration for systemic drug delivery is inhalation anesthesia. An increasing variety of drugs such as beta-agonists, corticosteroids, mast cell stabilizers, antibiotics, and antifungal and antiviral agents are being administered by this route to obtain a direct effect on the target tissues of the respiratory system.

The pulmonary route has been used for decades to administer drug to the lung for the treatment of asthma and other local ailments. Recently, this route has received more attention for the systemic delivery of drugs. The onset of action following the pulmonary administration of drugs is very fast and comparable to the intravenous route. The lungs offer a larger surface area (70 m^2) for systemic absorption of drugs than other nontraditional routes of systemic drug delivery such as the buccal, sublingual, nasal, rectal, and vaginal cavities. The major challenge is the lack of reproducibility in the deposition site of the administered dose. The rate of drug absorption is expected to vary in many regions in the lung owing to the variable thickness of the epithelial lining in the bronchial tree.

Nasal

The uppermost portion of the human respiratory system, the nose, is a hollow air passage, which functions in breathing and in the sense of smell. The nasal cavity moistens and warms incoming air, and small hairs and mucus filter out harmful particles and microorganisms. The nose (Fig. 23-4) consists of two openings (nostrils) separated by a median septum. The vestibule at the entrance of each nostril is covered with hairs, which prevent the entrance of air-suspended particles. The nose cavity is divided by the septum into two chambers called fossae. They form passages for air movement from the

nostrils to the nasopharyngeal space at the back of the nose. Each fossa consists of two parts, an olfactory region at the front of the nose and a respiratory region that accounts for the remainder of the fossae. The nasal cavity is lined with a mucous membrane, called the membrana mucosa nasi, which is continuous with the skin of the nostrils. The respiratory portion of the nasal cavity contains ciliated (hairlike) projections consisting of columnar epithelial cells.

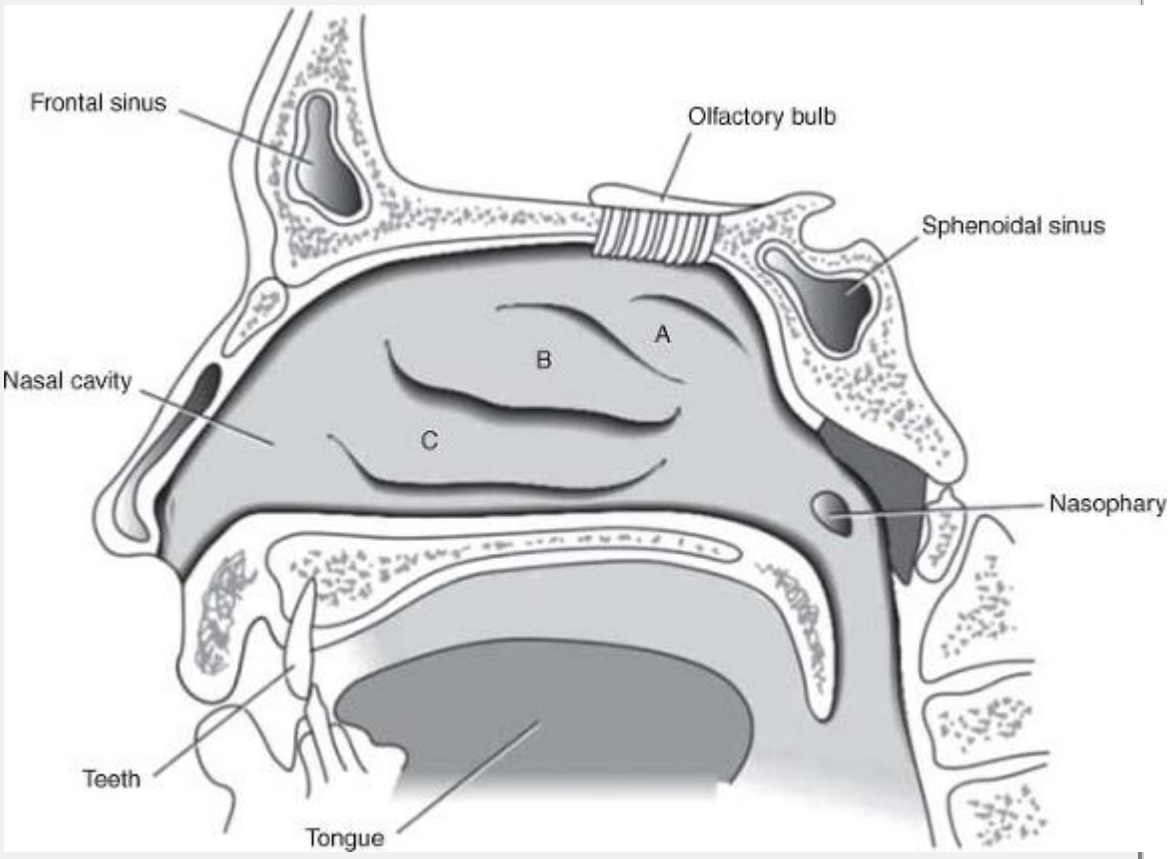

Fig. 23-4. The nasal anatomy. The nasal cavity is lined with mucous membrane and consists of three passageways or meatuses: A: upper; B: middle; and C: lower.

The nasal cavity consists of three passageways or meatuses: upper, middle, and lower meatus. The nasolacrimal duct drains into the lower meatus. The nose is connected to the middle ear through the nasopharynx or postnasal space and through the auditory canal. The compartments of the nose are connected to the conjunctiva of the eye by way of the nasolacrimal and lacrimal ducts, and through several sinuses that drain into the nose. A portion of a drug administered into the conjunctiva of the eye may enter the nose through these ducts and sinuses and may also pass into the esophagus.16 The nasal mucosa is the only location in the body that provides a direct connection between the central nervous system (CNS) and the atmosphere. Drugs administered to the nasal mucosa rapidly traverse through the cribriform plate into the CNS by three routes: (*a*) directly by the olfactory neurons located in olfactory bulb (Fig. 23-4); (*b*) through supporting cells and the surrounding capillary bed; and (*c*) directly into the cerebrospinal fluid.17Therefore, in addition to local and systemic drug delivery, the nasal mucosa can be used to deliver drugs to CNS.

Traditionally, the nasal route is used for locally acting drugs. This route is getting more and more attention for the systemic delivery of protein and peptide drugs. The highly vascular nature of the nasal cavity makes it a suitable alternate route for systemic drug delivery. This route is also useful for potent drugs because of its smaller surface area of about 200 cm^2 available for absorption. The most commonly used dosage form for the administration of drug through this route is liquid solutions of drug. For large polar molecules such as peptides or polysaccharides in the form of drugs or vaccines, the nasal route provides a viable, noninvasive alternative to injections. For conventional molecules, the nasal route provides other clinical benefits relevant to certain drugs and patient groups: pulsatile or sustained plasma profiles, fast absorption and rapid onset of action, avoidance of first-pass metabolism, and avoidance of the effects of gastric stasis and vomiting often seen in migraine patients.

One of the major challenges is developing nasal formulations that improve the absorption of macromolecules and water-soluble drugs.18 Another challenge is the problem of short retention time in the nasal cavity due to the efficient physiological clearance mechanisms. Good systemic bioavailability after nasal drug delivery can be achieved for molecules with a molecular weight of up to 1000 daltons when no enhancer is used. With the inclusion of enhancers, good bioavailability can be extended to a molecular weight of at least 6000 daltons. Several methods have been used to facilitate the nasal absorption of drugs:
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1. **Structural modification.** The drug is chemically modified to alter its physicochemical properties to enhance its nasal absorption.
2. **Salt or ester formation.** The drug is converted to a salt with increased solubility or an ester derivative with better nasal membrane permeability for achieving better transnasal absorption.
3. **Formulation design.** Appropriate formulation excipients are selected, which could improve the stability and/or enhance the nasal absorption of drugs.
4. **Surfactants.** Surfactants are incorporated into the nasal formulations to modify the permeability of nasal mucosa, which may facilitate the nasal absorption of drugs.

Chitosan is used as an absorption enhancer in nasal delivery (as described earlier for oral mucosa drug delivery). The chitosan nasal technology can be exploited as a solution, dry powder, or microsphere formulation to further optimize the delivery system for individual drugs. For compounds requiring rapid onset of action, the nasal chitosan technology can provide a fast peak concentration compared with oral or subcutaneous administration.18,19,20
Two kinds of organic-based pharmaceuticals are used for nasal drug delivery: (*a*) Drugs with extensive presystemic metabolism (e.g., progesterone, estradiol, testosterone, hydralazine) can be rapidly absorbed through the nasal mucosa with a systemic bioavailability of approximately 100%; and (*b*) water-soluble organic-based compounds, which are well absorbed (e.g., sodium cromoglycate). Recently, nasal drug delivery has been used for systemic delivery of peptide-based pharmaceuticals.21,22,23Because of their physicochemical instability and susceptibility to hepatogastrointestinal first-pass elimination, peptide and protein pharmaceuticals generally have a low oral bioavailability and are normally administered by parenteral routes. Most nasal formulations of peptide and protein pharmaceuticals have been prepared in simple aqueous (or saline) solutions with preservatives. Another recent example is a commercially available nasal salmon calcitonin formulation. The calcitonin (Miacalcin) nasal spray is licensed for the treatment of established osteoporosis for postmenopausal women. Unlike injectable calcitonin, it is recommended for long-term rather than short-term use and has been shown to reduce the risk of new vertebral fractures. The extent of systemic delivery of peptides or proteins by transnasal permeation may depend on the structure and size of the molecules, partition coefficient, susceptibility to proteolysis by nasal enzymes, nasal residence time, and formulation variables (pH, viscosity, and osmolarity).

Ocular

The eye is uniquely shielded from foreign substance penetration by its natural anatomic barriers, which makes effective drug delivery to the inside of the eye difficult. Two main barriers that protect the eye are (*a*) the cornea, which protects the front of the eye, and (*b*) the blood–retina barrier, which protects the back of the eye.
Topical medications are frequently impeded in reaching the targeted site due to the eye's natural protective surface. In many situations, less than 1% of the medication applied to the surface of the eye will actually reach the disease site. The solution instilled as eye drops into the ocular cavity may disappear from the precorneal area of the eye by any of the following composite routes: nasolacrimal drainage, tear turnover, productive corneal absorption, and nonproductive conjunctival uptake (Fig. 23-

5). Traditional dosage forms for delivery of drugs into the eye are mostly solutions and ointments; however, as a consequence of its function as the visual apparatus, mechanisms exist for the clearance of applied materials from the cornea to preserve visual acuity. This presents problems in the development of formulations for ophthalmic therapy. A large proportion of the topically applied drug is immediately diluted in the tear film, excess fluid spills over the lid margin, and the remainder is rapidly drained into the nasolacrimal duct. In addition, part of the drug is not available for therapeutic action because it binds to the surrounding extraorbital tissues. These processes lead to a typical corneal contact time of about 1 to 2 min in humans for solutions and an ocular bioavailability that is commonly less than 10%.

To achieve a sufficient concentration of drug delivered to the back of the eye, medications are frequently administered systemically at very high doses to overcome the blood–retina barrier. Drug injections into the back of the eye are occasionally used, but are quickly removed by the eye's natural circulatory process, often necessitating frequent injections that can carry toxicity risks.

To optimize ocular drug delivery, the following characteristics are required: good corneal penetration, prolonged contact time with the corneal epithelium, simplicity of instillation for the patient, nonirritative and comfortable form (i.e., the system should not provoke lacrymation and reflex blinking), and appropriate rheologic properties. Several novel drug delivery systems have been developed to enhance drug delivery to the eye24 (described later in this chapter).

Transdermal

The skin has been used for centuries as the site for the topical administration of drugs, but only recently has it been used as a pathway for systemic drug delivery (i.e., transdermal).25 The barrier function of the skin prevents both water loss and the entrance of external agents; however, some drugs are able to penetrate the skin in sufficient amounts to produce a systemic action. The transdermal route is of particular interest for drugs that have a systemic short elimination half-life or undergo extensive first-pass metabolism, therefore, requiring frequent dosing.

The concept of delivering drugs through the skin was first introduced in the early 1950s. However, the first commercial product was made available in the United States only in the early 1980s. These first-generation, passive, transdermal patches set the foundation for this route of delivery. These

transdermal patches, which were designed to control nausea, vomiting, and angina, however, failed to succeed in the market. The introduction of nicotine patches for smoking cessation gave the necessary impetus to this technology during the initial years. Today, transdermal patches are widely used to deliver hormones and pain management medications. The basic process involved in the development of transdermal drug delivery systems (i.e., patches) is percutaneous or transdermal absorption. Novel transdermal systems, including iontophoresis, thermophoresis, and phonophoresis, were also developed to enhance transdermal delivery of drugs.

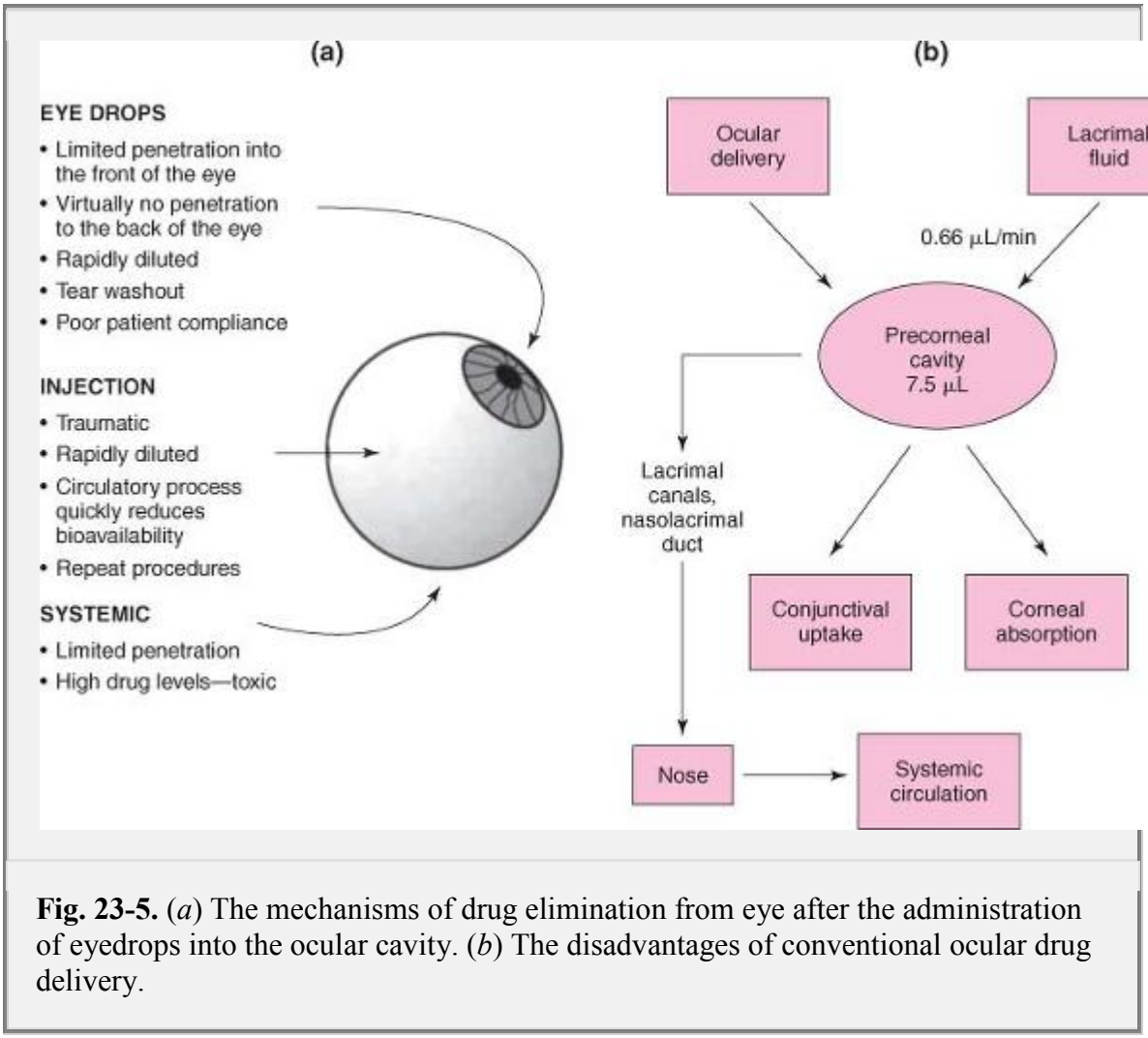

Fig. 23-5. (*a*) The mechanisms of drug elimination from eye after the administration of eyedrops into the ocular cavity. (*b*) The disadvantages of conventional ocular drug delivery.

The skin epidermis consists of three main layers, the stratum corneum, the granular layer, and the basal layer. The stratum corneum is considered the most important barrier to drug transfer. It is a heterogeneous nonliving structure, formed by keratinized cells, protein-rich cells, and intercellular lipid layers. The lipid composition among the epidermal layers is very different. Polar phospholipids, which are components of living cell membrane, are absent in the dead stratum corneum. These lipids form bilayers and their acyl chains can exist in “gel” and “liquid crystalline” states. The transition between these two states occurs at certain temperatures without loss of the bilayer structure.26 The principal lipids of the stratum corneum are ceramide (50%) and fatty acids (25%). Although the stratum corneum does not contain phospholipids, the mixture of ceramides, cholesterol, and fatty acids is capable of forming bilayers. These lipid bilayers provide the barrier function of the stratum corneum.26

To study the percutaneous transfer of drugs, the skin can be considered as a bilaminate membrane consisting of the dead stratum corneum (lipophilic layer) and the living tissue (hydrophilic layer) that comprises the granular and basal layers of the epidermis and the dermis (Fig. 23-6). Diffusion of polar drugs is much faster through the viable tissue than across the stratum corneum.27 The permeability coefficient through the skin, P, can be expressed as:28

$$P = \frac{D_v D_s}{K l_v D_s + l_s D_v} \qquad (23\text{–}1)$$

where K is the partition coefficient of the drug between the stratum corneum (s) and the viable tissue (v) and l_v, l_s, D_v, and D_s are the diffusion path lengths and diffusion coefficients, respectively. The subscripts s and v refer to the stratum corneum and the viable tissue, respectively. If the drug diffuses slowly through the stratum corneum, Kl_vD_s is much less than l_sD_v, and equation (23-1)becomes:

$$P = \frac{D_s}{l_s} \qquad (23\text{–}2)$$

In this case, the skin permeability is controlled by the stratum corneum alone. If the diffusion through the stratum corneum is fast, Kl_vD_s is much greater than l_sD_v, and equation (23-1) becomes:

$$P = \frac{D_v}{l_vK} \qquad (23\text{–}3)$$

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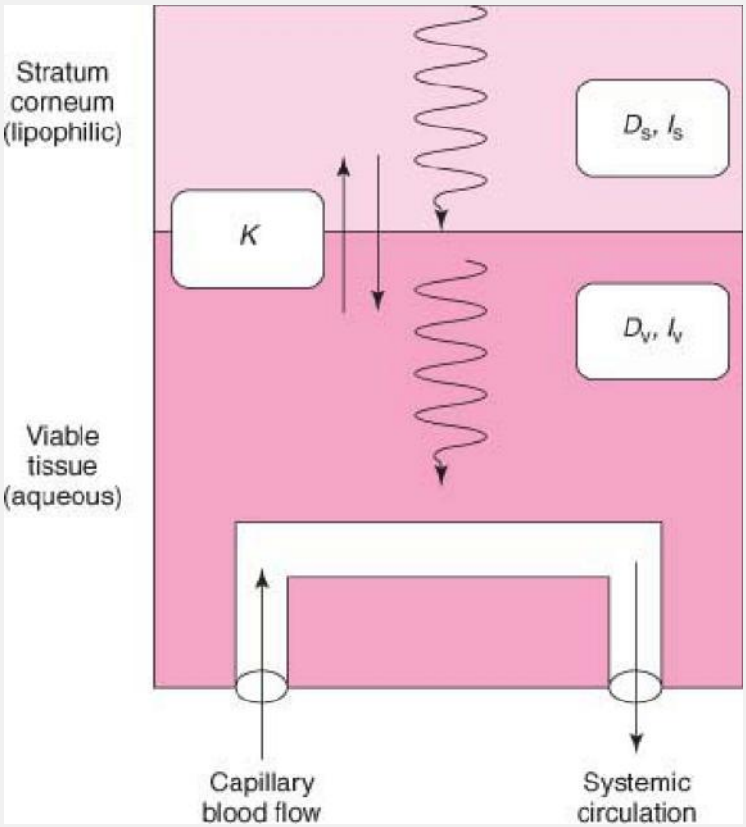

Fig. 23-6. The skin represented as two layers: the dead stratum corneum (*s*) and the viable or living tissue (*v*) (dermis and part of epidermis). The diffusion coefficients, D_s and D_v, and the diffusion path lengths, l_s and l_v, together with the partition coefficient, K, control the transport of the penetrant through the two layers. (Modified from R. H. Guy and J. Hadgraft, Pharm. Res. **5,** 753, 1988. With permission.)

In this case, the partition coefficient may be influential in the permeability. As *K* increases, the transfer from the stratum corneum to viable epidermis becomes less favorable and slower. At large *K*values, partitioning of the drug is the rate-limiting step.28

Example 23-1

Transdermal Permeability

Compute the permeability of a drug across the skin assuming that D_s is 10^{-10} cm^2/sec and D_v is 10^{-7} cm^2/sec. The path lengths are l_s = 350 μm and l_v = 150 μm. The large value for l_s is due to the fact that the molecules follow a tortuous pathway through the intercellular spaces. The value for l_v is the distance from the underside of the stratum corneum to the upper capillary region of the dermis. The partition coefficient is taken to be K = 1.

Because diffusion through the stratum corneum is very slow (D_s = 10^{-10} cm^2/sec) and KI_vD_s = 1.0 × 150 × 10^{-4} × 10^{-10}= 1.5 × 10^{-12} is much less than l_sD_v = 350 × 10^{-4} × 10^{-7} = 3.5 × 10^{-9}, then from equation (23-3),

$$P = \frac{10^{-10}\ \text{cm}^2/\text{sec}}{350 \times 10^{-4}\ \text{cm}} = 2.86 \times 10^{-9}\ \text{cm/sec}$$

Using equation (23-2), we arrive at a similar order of magnitude:

$$P = \frac{(10^{-7}\ \text{cm}^2/\text{sec})(10^{2}\ \text{cm}^2/\text{sec})}{(1.0 \times 150 \times 10^{-4} \times 10^{-10})\ \text{cm} \cdot \text{cm}^2/\text{sec} + (10^{-7} \times 350 \times 10^{-4})\ \text{cm} \cdot \text{cm}^2/\text{sec}} = 2.86 \times 10^{-9}\ \text{cm/sec}$$

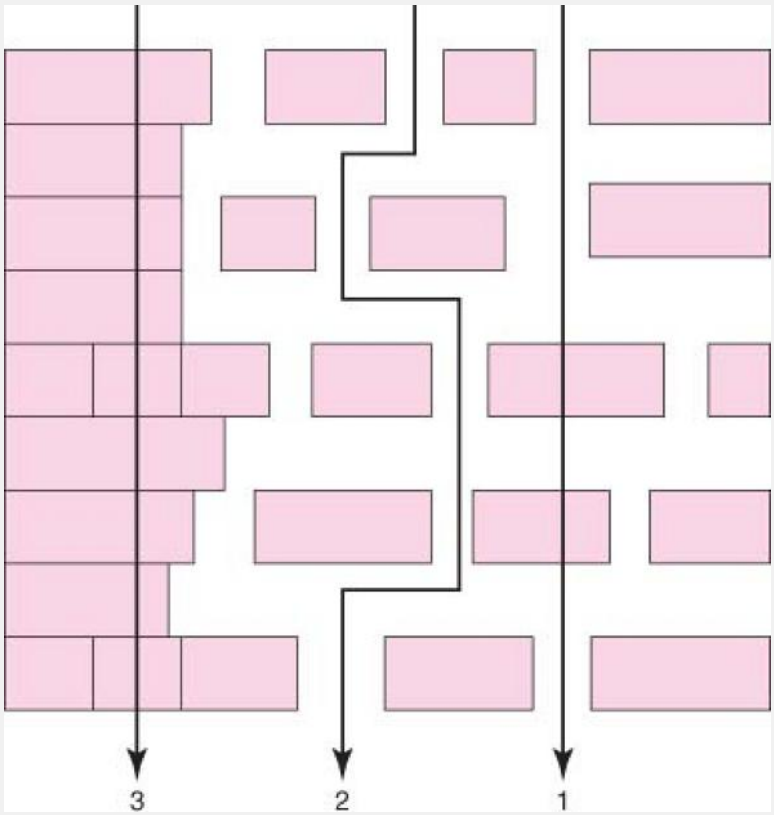

Fig. 23-7. Random-brick model for the stratum corneum. Arrows 1, 2, and 3 show three possible routes of drug diffusion. (Modified from K. Tojo, J. Pharm. Sci.**76,** 889, 1987. With permission.)

Tojo29 proposed a random-brick model for the transfer of drugs across the stratum corneum. As shown in Figure 23-7, the cells rich in proteins separated from one another by thin-layer intercellular lipids represent the stratum corneum. The side length of the cells varies, but the total average surface area is constant. The thickness of the cells and the lipid layer are also assumed to be constant. According to this model, the transfer of a drug is divided into three parallel pathways: (*a*) across the cellular–intercellular regions in series; (*b*) across the lipid intercellular spaces; and (*c*) across thin lipid layers sandwiched between flattened protein cells of the stratum corneum.

According to the brick model, the effective diffusion coefficient, D_{eff}, across the skin is given by:

$$D_{\text{eff}} = 2\varepsilon(1-\varepsilon)D_1 + \varepsilon^2 D_2 + (1-\varepsilon)^2 D_3 \quad \textbf{(23–4)}$$

The first, second, and third terms on the right-hand side represent the three possible routes 1, 2, and 3 in Figure 23-7, respectively; D_1,D_2, and D_3 are the diffusivities across routes 1, 2, and 3, respectively; ε and (1 - ε) are the average fraction of diffusion area of the lipid and protein on the skin surface,

respectively. Substituting D_1, D_2, and D_3 by their corresponding expressions, we find that equation (23-4) becomes:

$$D_{\text{eff}} = \frac{2\varepsilon(1-\varepsilon)(2n+4)}{\frac{n}{D_p} + \frac{n+4}{KD_l}} + \varepsilon^2 KD_l + \frac{(1-\varepsilon)^2(2n+4)}{\frac{2n}{D_p} + \frac{4}{KD_l}} \qquad (23\text{–}5)$$

The term n is related to the volume fraction of lipids in the skin and the average fraction of diffusion area of the lipids,

P.605

ε; K is the lipid–protein partition coefficient, and D_p and D_l are the diffusion coefficients across the protein layer and the lipid layer, respectively.

The flux across the skin is given by:

$$J = \frac{dQ}{dt} = \frac{D_{\text{eff}} C_p}{h} \qquad (23\text{–}6)$$

where C_p is the concentration of drug in the protein cell layer, h is the thickness of the skin, and D_{eff} is defined by equation (23-5).

Example 23-2

Brick Model of Transdermal Penetration*

Compute the flux at the steady state, dQ/dt, of a new drug from the following data: $D_l = 1 \times 10^{-10}$ cm^2/sec, $D_p = 1 \times 10^{-7}$ cm^2/sec, $C_p = 10$ mg/cm^3, ε = 0.02, $h = 0.0020$ cm, K= 0.1, and $n = 14.3$. Use the random-brick model.

We have

$$D_{\text{eff}} = \frac{(2)(0.02)(1-0.020)(2\times 14.30+4)}{\frac{14.3}{1\times 10^{-7}} + \frac{14.3+4}{(0.1)(10^{-10})}} + (0.02)^2(0.1)(10^{-10}) + \frac{(1-0.02)^2(2\times 14.3+4)}{\frac{2\times 14.3}{1\times 10^{-7}} + \frac{4}{(0.1)(1\times 10^{-10})}} = 7.89\times 10^{11}\ \text{cm}^2/\text{sec}$$

The flux is

$$J = \frac{(7.89\times 10^{-11}\ \text{cm}^3/\text{sec})(10\ \text{mg/cm}^3)}{0.0020\ \text{cm}} = 3.95\times 10^{-7}\ \text{mg/(cm}^2\ \text{sec)} = 3.95\times 10^{-4}\ \mu\text{g/(cm}^2\ \text{sec)}$$

Factors Affecting Permeability

Hydration

The skin permeability of a drug depends on the hydration of the stratum corneum; the higher the hydration, the greater is the permeability. The dermal tissue is fully hydrated, whereas the concentration of water in the stratum corneum is much lower, depending on ambient conditions. Hydration may promote the passage of drugs in the following way. Water associates through hydrogen bonding with the polar head groups of the lipid bilayers present in the intercellular spaces. The formation of a hydration shell loosens the lipid packing so that the bilayer region becomes more fluid.30 This facilitates the migration of drugs across the stratum corneum. From the rate of transpiration (i.e., passage of water from inner layers to the stratum corneum) and diffusivity of water in the stratum corneum, the amount of water in the tissue can be obtained.31

Solubility of the Drug in Stratum Corneum

Using the experimental results obtained from intact skin and stripped skin (layers of stratum corneum removed using Scotch tape), the solubility, C, of a drug in the stratum corneum was calculated from the following expression29:

$$C = \frac{1-3\tau+2\eta\tau}{(1+2\eta)(1-\eta)} \cdot \frac{6t_2}{h_2}\left(\frac{dQ}{dt}\right)_2 \qquad (23\text{–}7)$$

where $(dQ/dt)_2$ is the steady-state permeation across the intact skin, τ is the ratio of the two time lags, (t_1/t_2), and η is the ratio $(dQ/dt)_2/(dQ/dt)_1$. The subscripts 1 and 2 refer to the stripped and intact skin, respectively; h_2 is the thickness of the stratum corneum.

Example 23-3

Solubility of Progesterone in the Stratum Corneum

Compute the solubility of progesterone in the stratum corneum. The lag times across the intact and stripped skin are t_2 = 5.49 and t_1 = 1.55 hr, respectively, and the permeation rates across the intact and stripped skin are $(dQ/dt)_2$ = 2.37 μg/(cm^2 hr) and $(dQ/dt)_1$ = 3.62 μg/(cm^2 hr), respectively. The thickness of the stratum corneum is 10 μm (10 × 10^{-4} cm). We have

$$\tau = \frac{t_1}{t_2} = \frac{1.55}{5.49} = 0.28$$

$$\eta = \frac{(dQ/dt)_2}{(dQ/dt)_1} = \frac{2.37}{3.62} = 0.65$$

From equation (23-7),

$$C = \frac{1 - (3 \times 0.28) + (2 \times 0.65 \times 0.28)}{[1 + (2 \times 0.65)](1 - 0.65)} \cdot \frac{6 \times 5.49}{10 \times 10^{-4}} \cdot 2.37$$

$$C = 50816.8\,\mu\text{g/mL} = 50.8\,\text{mg/mL}$$

Excipients

Common solvents and surfactants can affect penetration of drugs though the skin. Sarpotdar and Zatz32 studied the penetration of lidocaine through hairless mouse skin in vitro from vehicles containing various proportions of propylene glycol and polysorbate 20. Propylene glycol is a good solvent for lidocaine and reduces its partitioning into the stratum corneum, lowering the penetration rate. In this study, the effect of the surfactants depended on the concentration of propylene glycol in the vehicle. The decrease of flux for 40% (w/w) propylene glycol concentration can be explained by micellar solubilization of lidocaine. It is generally assumed that only the free form of the drug is able to penetrate the skin. Thus, the micellar solubilization of lidocaine reduces its thermodynamic activity in the vehicle and retards its penetration. At higher propylene glycol concentrations, 60% and 80%, an increase in flux was observed, possibly owing to an interaction of the surfactant with propylene glycol.

Influence of pH

According to the pH-partition hypothesis only the un-ionized form of the drug is able to cross the lipoidal membranes in significant amounts. However, in studies of isolated intestinal membranes, both the ionized and un-ionized forms of sulfonamides permeated the membrane. The diffusion of ionized drug through the skin may be nonnegligible, particularly at pH values at which a large number of ionized molecules are present.33 Fleeker et al.34 studied the influence of pH

on the transport of clonidine, a basic drug, through hydrated shed snakeskin. The contribution to the total flux, J, in μg cm^{-2} hr^{-1} of the nonionized and ionized species for a basic drug can be written as:

$$J = J_B + J_{BH^+} \qquad (23\text{–}8)$$

where B and BH$^+$ represent the basic (nonionized) and protonated forms, respectively. The dissociation of the protonated form is represented as:

$$[BH^+] \overset{K_a}{\longleftrightarrow} [B] + [H^+] \qquad (23\text{–}9)$$

and

$$K_a = \frac{[B][H^+]}{[BH^+]} \qquad (23\text{–}10)$$

Taking the logarithm of both sides of equation (23-10) and rearranging it, we obtain the concentration of the protonated form as:

$$[BH^+] = \frac{10^{(pK_a - pH)}}{1 + 10^{(pK_a - pH)}}[T] \qquad (23\text{–}11)$$

where [T] represents the total concentration of both the charged and uncharged species,

$$[T] = [B] + [BH^+] \qquad (23\text{–}12)$$

The concentration of nonionized form [B] can be computed from equation (23-12). The total flux, equation (23-8), can also be written in terms of the permeability coefficients times the concentrations of each species:

$$J = P_B[B] + P_{BH^+}[BH^+] \qquad (23\text{–}13)$$

From equations (23-11) and (23-12), provided PB [congruent] PBH^+s, we have the following results:

a. When pK_a = pH, [B] = $[BH^+]$, and both species B and BH^+contribute to the total flux.
b. When pH is much greater than pK_a, [B] is much greater than $[BH^+]$, and the total flux, *J*, is approximately PB[B].
c. When pH is much less than pK_a, [B] is much less than $[BH^+]$, and the total flux, *J*, is approximately PBH^+ $[BH^+]$.

Equation (23-13) allows one to compute the permeabilities of both species from the total experimental flux and the values of [B] and $[BH^+]$ from equations (23-11) and (23-12).

Example 23-4

Transdermal Permeability of Clonidine

Compute the permeability coefficients PB and PBH^+corresponding to the nonionized and protonated forms of clonidine. The total fluxes at pH 4.6 and pH 7 are 0.208 and 0.563 μg/(cm^2 hr), respectively. The pK_a of the protonated form is 7.69. The total concentration* of the two species, [T], is 4 × 103 μg/uv, where μg/uv stands for microgram/unit volume.

At pH 4.6,

$$[BH^+] = \frac{10^{(7.69-4.6)}}{1+10^{(7.69-4.6)}}(4\times10^3) = 3.996\times10^3\ \mu g/uv$$

$$[B] = (4\times10^3) - (3.996\times10^3) = 4.0\ \mu g/uv$$

At pH 7,

$$[BH^+] = \frac{10^{(7.69-7)}}{1+10^{(7.69-7)}}(4\times10^3) = 3.322\times10^3\ \mu g/uv$$

$$[B] = (4\times10^3) - (3.322\times10^3) = 678\ \mu g/uv$$

From equation (23-13) with the flux, *J*, expressed in μg/cm^2hr and the permeability coefficient, *P*, in units of cm/hr, at pH 4.6,

$$0.208\ \mu g/cm^2\ hr = P_B(4\ \mu g/cm^3) + P_{BH^+}(3996\ \mu g/cm^3)$$

At pH 7,

$$0.563\ \mu g/cm^2\ hr = P_B(678\ \mu g/cm^3) + P_{BH^+}(3322\ \mu g/cm^3)$$

PB and PBH^+ are calculated by solving the two equations simultaneously:

$$P_B = (0.208 - 3996\,P_{BH^+})/4$$

$$0.563 = 678\frac{0.208 - 3996\,P_{BH^+}}{4} + 3322\,P_{BH^+}$$

$$P_{BH^+} = \frac{-34.693}{-674000} = 5.15\times10^{-5}\ cm/hr$$

$$P_B = [0.208 - (5.15\times10^{-5}\times3996)]/4 = 5.5\times10^{-4}\ cm/hr$$

It is noted that the values found for PBH^+ and PB do not change with pH, whereas the fluxes, *J*, are markedly different at pH 4.6 and pH 7.0.

Equations (23-10) and (23-13) can be combined to give:

$$\frac{J}{[B]} = \frac{P_{BH^+}}{K_a}[H^+] + P_B \qquad (23\text{–}14)$$

From equation (23-14), the permeability coefficients of the ionized $[BH^+]$ and nonionized [B] forms can be computed from the slope and intercept of a plot of *J*/[B] against $[H^+]$. The corresponding equation for acids is:

$$\frac{J}{[A^-]} = \frac{P_{HA}}{K_a}[H^+] + P_{A^-} \qquad (23\text{–}15)$$

From equation (23-15), the permeability coefficients of the nonionized [HA] and ionized [A^-] forms are computed from the slope and the intercept of a plot of $J/[A^-]$ against [H^+]. Swarbrick et al.33found that both the ionized and nonionized forms of four chromone-2 carboxylic acids permeated skin, although the permeability of the nonionized form was about 104 times greater.

Binding of Drug to the Skin

The skin can act as a reservoir for some drugs that are able to bind to macromolecules. The drug fraction bound is not able to diffuse, and binding hinders the initial permeation rate of molecules, resulting in larger lag times. Banerjee and Ritschel35 studied the binding of vasopressin and corticotropin to rat skin. Penetration of large molecules such as

collagen, used in cosmetic formulations, is questionable, but partial hydrolysates of collagen are able to reach the deeper skin layers. The sorption process can be represented by the Langmuir equation:

$$\frac{c}{x/m} = \frac{1}{bY_m} + \frac{c}{Y_m} \qquad (23\text{–}16)$$

where c represents the equilibrium concentration of the drug, x is the amount of drug adsorbed per amount, m, of adsorbent (the skin proteins in this case), b is the affinity constant, and Y_m is the maximum adsorption capacity, $(x/m)_{max}$. The sorption isotherm was obtained by Banerjee and Ritschel35 by equilibration of a measured weight of rat epidermis with a known concentration of radiolabeled vasopressin solution and was analyzed by scintillation counting (measured radioactivity). The small value for the adsorption constant in equation (23-16), $b = 6.44 \times 10^{-4}$ mL/μg, suggests low affinity of vasopressin for the binding sites in the skin.

Drug Metabolism in the Skin

The metabolism of drugs during transport through the skin affects bioavailability and can produce significant differences between in vivo and in vitro results. Oxidation, reduction, hydrolysis, and conjugation are kinetic processes that compete with the transport of drugs across the skin. Guzek et al.36 and Potts et al.37 found differences in the in vitro and in vivo extents of enzymatic cleavage in the skin and in the distribution of the metabolites of a diester derivative of salicylic acid. The authors suggested that the in vitro measurements overestimated the metabolism because of the increased enzymatic activity and/or decreased removal of the drug in the absence of capillaries. The fact that the skin contains esterases and other enzymes is useful for the administration of prodrugs. The solubility and absorption can be improved, and the enzymes could be used to cleave the prodrug to give the active drug in the skin.38

*Vaginal*39,40

The vagina has been used for a long time for topical drug administration. The most frequently used vaginal preparations include:39 (*a*) antimicrobials (antibacterial, antifungal, antiprotozoal, antichlamydial, and antiviral) pessaries, or creams such as metronidazole, 5-nitroimidazoles (tinadazole and ornidazole), and imidazole (clotrimazole, econazole, isoconazole, and miconazole); (*b*) estrogen creams; and (*c*) spermicidal foams, gels, and creams such as nonoxynol-9, octoxinol, and p-di-isobutylphenoxy-poly(ethoxyethanol).

Earlier, the vagina was considered as an organ incapable of absorbing drugs systemically and, therefore, systemic absorption of a drug through vagina was considered only from the standpoint of toxicity.40 However, it was shown that a number of topical drugs are able to achieve sufficient blood levels and can achieve systemic effects. Later, it was also shown that vaginal permeability of substances such as water, 17-β-estradiol, arecoline, and arecaidine is in fact higher than the intestinal mucosa.41 As a result, there is an interest in the design of vaginal delivery systems for systemic delivery of drugs such as estrogens, progesterones, prostaglandins, peptides, and proteins. The interest in systemic vaginal drug delivery systems is due to the ease of administration, rich blood supply facilitating rapid absorption, high permeability to certain drugs in different phases of menstrual cycle,

avoidance of hepatic first-pass metabolism, reduction in GI side effects, and decrease in hepatic side effects (e.g., for steroids). The disadvantages associated with vaginal drug delivery on the other hand are that it is limited to only potent drugs; there is a possibility of adverse effects due to the low amount of fluids present, hormone-dependant changes, and possibility of leakage.

The vagina is a tubular, fibromuscular organ extending from the cervix of the uterus to the vaginal vestibule.[39,40] In an adult female, the vaginal tract is about 2 cm in width and comprises an anterior wall of ~8 cm and a posterior wall of ~11 cm in length. Histologically, it consists of four distinct layers: epithelial with underlying basement membrane, lamina propria, muscular layer, and adventicia. Although sometimes considered a mucosal tissue, the normal vagina does not have glands and the vaginal secretions present on the surface is a mixture of fluids from different sources. It must be noted that vaginal characteristics, particularly the pH, changes with the phase of the menstrual cycle. The normal vaginal pH (4.5–5.5) is maintained by *Lactobacilli* present in the vagina. There may be an atrophy of vaginal epithelium, elevation of pH (6.0–7.5), and decrease in secretions, postmenopause. The vagina is normally collapsed on itself and capable of holding about 2–3 g of fluid/gel without leakage. Drug permeation across the vaginal membrane (epithelial) occurs mainly through diffusion, where hydrophilic molecules are absorbed via the paracellular route (diffusion between adjacent cells) and hydrophobic substances are absorbed via the transcellular route (across epithelial cells by passive diffusion, carrier-mediated transport, or endocytic process).[40]

The vaginal route is used for estrogens and progesterone delivery. Controlled-release delivery devices such as suppositories, inserts, and rings are also available. Vaginal route is also being investigated for the delivery of GnRH analogues and insulin. Antiviral vaginal gels and liposomal preparations, vaginal mucosal vaccines, microspheres (starch and hyaluronan), bioadhesive polymers, and gels are under various stages of development. Penetration enhancers such as organic acids and α-cyclodextrin are also being used to enhance the drug absorption across vaginal epithelium but they are associated with side effects.

Central Nervous System[42,43]

The brain is not a route of drug delivery but still an important pharmaceutical target. Drugs that act on the CNS are those

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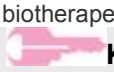
used for psychosis, depression and mania, anxiety, epilepsies, Parkinson disease, Alzheimer disease, pain, and brain tumors. Furthermore, the AIDS virus is also known to attack neuron and glial cells causing memory loss, palsy, dementia, and paralysis.[42] Drug delivery to brain is highly difficult due to the presence of a blood–brain barrier (BBB) regulating the entry of molecules to the brain. The BBB makes the brain inaccessible to CNS-targeted drugs in the systemic circulation, more so for biotherapeutics such as peptides, proteins, and nucleic acids.



Key Concept

Blood–Brain Barrier

In the early 1900s, researchers found the first evidence that the brain had a selective barrier that protects its cells. It is now known as the *blood–brain barrier* (*BBB*) and it is responsible for regulating the entry of molecules into the brain. The BBB separates the blood compartment from the extracellular fluid compartment of the brain parenchyma and consists of monolayer of polarized endothelial cells. The brain endothelial cells are connected by tight junctions, unlike the nonbrain capillary endothelial cells comprising large fenestrations (opening). BBB acts as a selective barrier and performs following functions: (*a*) isolate the brain from systemic influence; (*b*) provide pathway for the transport of nourishment to neurons; and (*c*) clear potentially toxic substance from brain into the blood. Besides the permeability barrier, highly selective enzymes are present in these endothelial cells, which further restrict the entry of substrates to the brain. The problem is further compounded by the presence of efflux transporters such as p-glycoprotein that are active in astrocyte

membranes. All components work in tandem to form a multicomponent BBB.42,43 Most drugs are unable to reach the brain because of their inability to penetrate the BBB.

Various transport mechanisms exist in the brain endothelium for the uptake of nutrients into the CNS, which may also be utilized for the drug delivery. The transport mechanisms available for passage through the BBB are the following (Fig. 23-8):42 passive diffusion, active transport, and receptor-mediated transport.

Physicochemical factors also influence the drug delivery to brain. Increasing the lipid solubility of a drug increases its permeability across the BBB. Highly lipid soluble molecules (barbiturate drugs and alcohol) rapidly cross the BBB into the brain. However, this is true only for low–molecular-weight drugs in the range of 400 to 600 Da. Presence of p-glycoprotein efflux restricts the passive diffusion of drugs that are substrate for p-glycoprotein. Examples include vinblastine, vincristine, and cyclosporin. In addition, the transport of drugs that are highly charged or bind strongly to plasma protein across the BBB is slow.

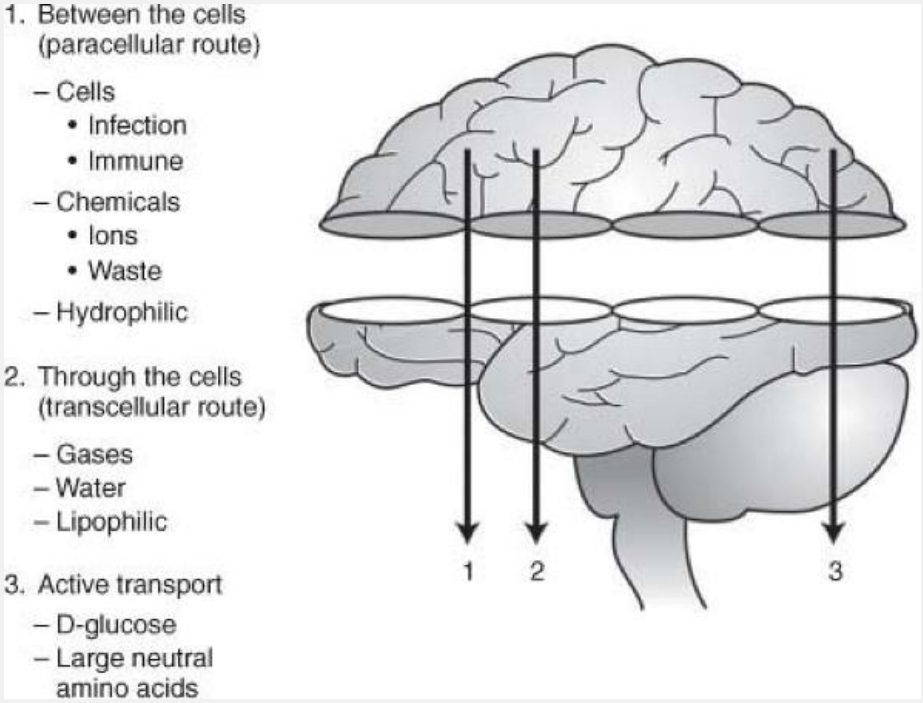


Fig. 23-8. Transport mechanisms available for passage across the blood–brain barrier (BBB).

Delivery of Nucleic Acid Therapeutics

Nucleic Acid Therapeutics

Exogenous nucleic acids can be used to modify gene expression.44Zamecnik and Stephenson45 demonstrated that a short oligodeoxynucleotide (13-mer) that was antisense to the Rous sarcoma virus could inhibit viral replication in cell culture. The existence of natural antisense nucleic acids and their role in regulating gene expression was shown in the mid 1980s.46 This led to the development of technologies employing synthetic oligonucleotides as therapeutics for manipulating gene expression in living cells. Synthetic oligonucleotides (ODNs) are short (<30 nucleotides) nucleic acid strands (DNA or RNA), which are chemically synthesized.

Key Concept

Nucleic Acid Therapeutics

The genetic information in biological systems is transferred from DNA→RNA→proteins (Fig. 23-9). The double helical DNA unwinds and creates a copy of itself by the process called *replication*. As a result, genetic information stored in DNA is faithfully transferred to the next generation of cells or organisms. The information stored in a part of DNA is transferred to mRNA by a process called *transcription.* In eukaryotic cells, the primary transcript (pre-mRNA) is processed further by alternative splicing (mRNA blocks are cut out and rearranged) and it migrates from nucleus to cytoplasm. The mRNA binds to ribosomes in cytoplasm, where information stored in mRNA is read as triplet codon (three base pairs for one amino acid) to assemble proteins (biological activity) by a process called *translation*. Information from proteins cannot be transferred back to either nucleic acids or proteins. Francis Crick47 called this unidirectional flow of information the Central Dogma of Molecular Biology. The importance of *nucleic acid therapeutics* and *gene therapy* lies in the fact that they provide the capability to interfere at different stages of this process with high specificity.

Nucleic acids are polynucleotides comprising sugar (ribose and 2-deoxy-ribose), purine (adenine/A and guanine/G) and pyrimidine (cytosine/C, thymidine/T, and uracil/U) bases, and phosphate. DNA contains 2′-deoxy-ribose sugar and A, G, C, and T bases, whereas RNA contains ribose sugar and A, G, C, and U bases. DNA is a double helical structure, whereas RNA is single stranded but may fold back to form duplex structures. Base and sugar react to form nucleoside and addition of a phosphate group to the nucleoside gives nucleotide. The nucleic acids are linear polynucleotide chains connected through phosphodiester backbone. All nucleic acid hybridizations (DNA-DNA, DNA-RNA, and RNA-RNA) are stabilized by hydrogen bonds (*Watson–Crick base pairing*); G always binds to C with three hydrogen bonds and A always binds to T or U with two hydrogen bonds. This phenomenon is called base complementarity and accounts for target specificity of nucleic acids. AT and GC base pairs in the major groove can establish additional hydrogen bonds with T and protonated C*, respectively. These are called *Hoogsteen base pairing* and used for triplex formation.

Antisense is not the only mechanism available; other mechanisms are now known to cause specific inhibition of gene expression (Fig. 23-10).

1. *Antigene mechanism*: Triplex-helix forming oligonucleotides48 are synthetic single-stranded DNA, which hybridize to purine or pyrimidine-rich region in the major groove of double-helical DNA through Hoogsteen base pairing. If a stable triple helix is formed, it prevents unwinding of double helical DNA necessary for transcription of the targeted region or blocks the binding of transcription factor complexes. This mechanism is not considered efficient for clinical applications even though it provides an opportunity for therapeutic interventions at a very early stage.

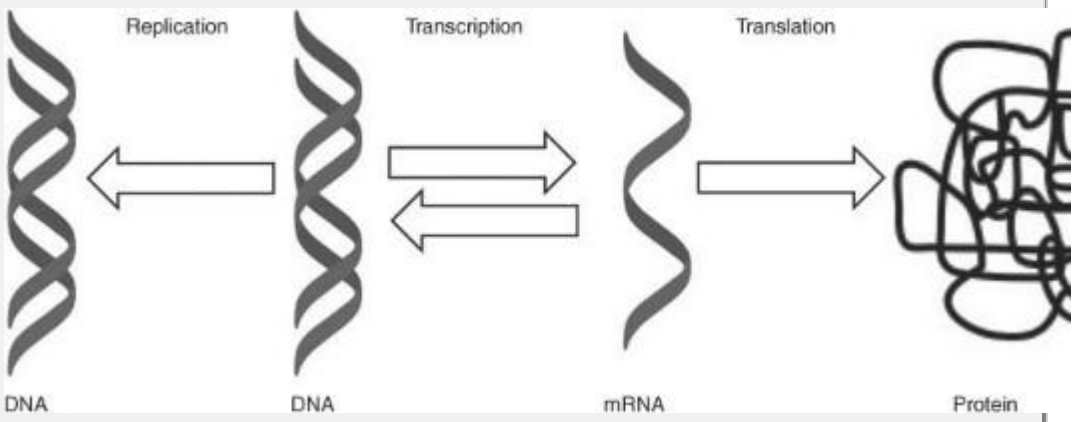


Fig. 23-9. Transfer of genetic information in living organisms (Central Dogma).

2. *Antisense mechanism*: Reverse-complementary (antisense) oligonucleotides, which hybridize to the mRNA strand of the targeted gene.[49,50,51] After hybridization, antisense oligonucleotides block expression either sterically by obstructing the ribosomes or by forming an RNA-DNA hybrid, which is a substrate for RNase H enzyme, thereby causing the cleavage of target mRNA. RNase H is a ubiquitous enzyme that hydrolyzes the RNA strand of an RNA-DNA duplex.
3. *RNA interference*: RNA interference (RNAi) or posttranscriptional gene silencing is a natural process in eukaryotic cells by which double-stranded RNA targets mRNA for cleavage in sequence-specific manner.[52] The mechanism of RNAi involves processing of a very long (500–1000 nucleotides) double-stranded RNA, which is cleaved

into short double-stranded RNA (small interfering RNA or siRNA, 21–25 nucleotides) by the DICER enzyme.[53]Synthetic siRNA can be produced and directly introduced into the cells. Once inside the cytoplasma of the cell, siRNA is incorporated into a large multicomponent complex called RNA-induced silencing complex (RISC). A multifunctional protein (Argonaute 2) in the RISC unwinds the double-stranded RNA and cleaves the sense strand of siRNA. The activated RISC containing the antisense strand of siRNA selectively seeks out and degrades mRNA complementary to the antisense strand. The activated RISC then moves on to destroy additional mRNA targets.[50,54]

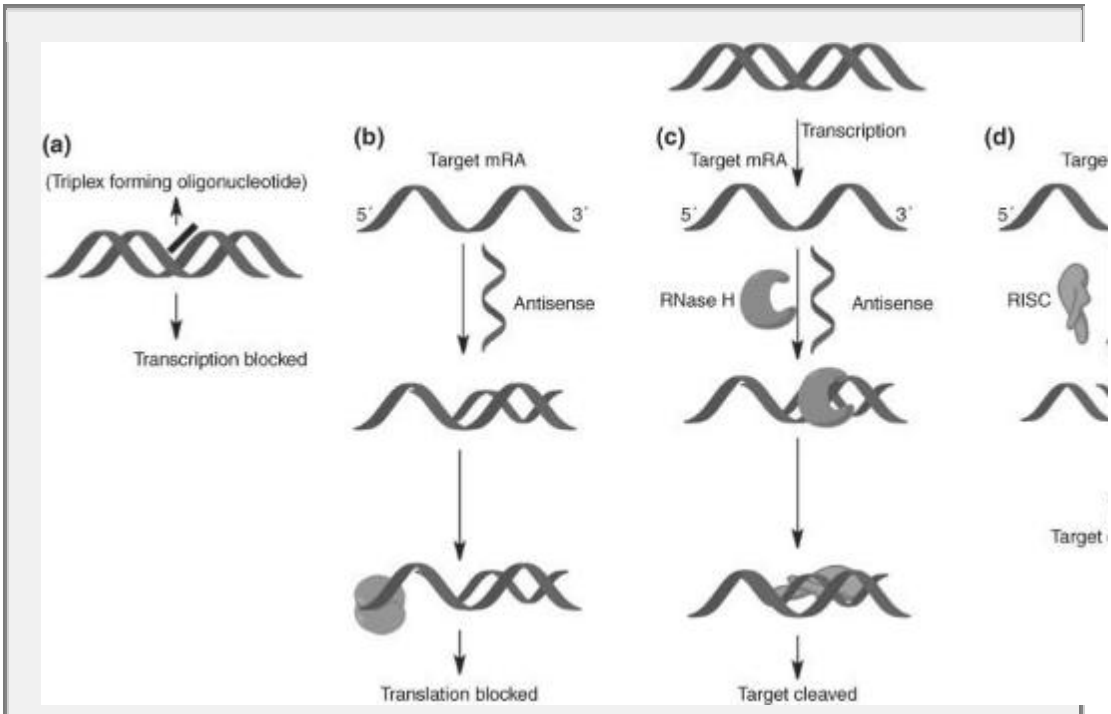


Fig. 23-10. Different mechanisms for selective inhibition of gene expression: (*a*) Triplex-forming oligonucleotide binds to the purine or pyrimidine rich region in the major groove of DNA (antigene); (*b*) antisense oligonucleotide sterically blocks ribosome activity (antisense); (*c*) antisense oligonucleotide forms hybrid with target mRNA, which is a substrate for RNase H (antisense); and (*d*) siRNA forms complex with RISC, which facilitate recognition of target mRNA followed by its cleavage (RNA interference).

4. *Aptamer selection*: Aptamers are nucleic acid ligands (15–40 nucleotides) isolated from combinatorial oligonucleotide libraries by in vitro selection.55 In solution, the oligonucleotide chain forms intramolecular interactions that fold the molecule into a complex three-dimensional shape. Aptamers have capability to tightly and specifically bind to the target molecules ranging from small molecules to complex multimeric structures. The therapeutic potential of aptamers arises from the fact that many aptamers targeted against proteins are able to interfere with their biological activity.

Other nucleic acid agents such as microRNA are also known and so are nucleic acids with catalytic activity: *ribozymes* and *DNAzymes*.*Ribozymes* are RNA molecules containing different catalytic motifs.53 They hybridize (bind) to the substrate RNA through Watson–Crick base pairing and cause sequence-specific cleavage.*DNAzymes* on the other hand are DNA molecules containing a catalytic motif and similar to ribozyme, cleave the substrate RNA after binding to it.

The unmodified nucleic acids have phosphodiester backbone, which are rapidly degraded in biologic fluids and in cells by the nucleases. Moreover, they show extremely poor penetration (diffusion) across the cell membrane.49,50,51 Most of the antisense oligonucleotides or siRNA therefore contain structural modifications. Oligonucleotides for clinical applications mostly have phosphorothioate or morpholino backbone instead of phospodiester. Several advanced antisense oligonucleotides are “gapmers” consisting of a central DNA portion that can recruit RNase H and flanking 2′-modified regions. Other important structural modifications are 2′-OH modifications (e.g., 2′-O-methyl), locked nucleic acids, peptide nucleic acids, and hexitol nucleic acids.

The only nucleic acid therapeutic currently approved for human use is fomivirsen (Vitravene, 1998, Isis Pharmaceuticals) for the treatment of inflammatory viral infection of

the eye (retinitis) caused by cytomegalovirus.53 Vitravene is a 21-mer antisense phosphorothioate oligonucleotide complementary to mRNA transcribed from the main immediate-early transcriptional unit of cytomegalovirus. The drug was later withdrawn from the market. Antisense oligonucleotides in clinical trials are alicaforsen for ulcerative colitis (Isis); ISIS113715 for diabetes (Isis); ATL1102 for multiple sclerosis (ATL/Isis); OGX-011 for prostate cancer (OncoGene/Isis); and Genesense for varied cancer (Genta).50 The siRNAs in clinical trials are AEG35156 for X-linked inhibitor of apoptosis protein (i.v., Aegera Therapeutics); AGN211745 for vascular endothelial growth factor receptor (i.v., Allergan); and ALN-RSV01 for respiratory syncytial virus nucleocapsid (nasal, Alnylam Pharmaceuticals).50,56
Gene therapy is the treatment of human disease by transferring genetic material into the specific cells of the patient.57 It must not be confused with the nucleic acid therapeutics described above. Advances in molecular biology, biotechnology, and the Human Genome Project have led to the identification of several disease-causing genes. Gene-therapy approaches are being suggested for the replacement of genes responsible for genetic diseases like hemophilia, muscular dystrophy, and cystic fibrosis. Gene replacement can also be used for altering the expression of an existing gene, inhibiting or augmenting the synthesis of a particular protein, and producing cytotoxic proteins or prodrug activating enzymes (see GDEPT). Gene therapy is also being investigated for the treatment of cardiovascular, neurological, and infectious diseases and cancer. Clinical success with gene therapy was first reported in 2000 for the treatment of severe combined immunodeficiency.
The limited success of antisense oligonucleotides or siRNA and gene therapy is attributed to the lack of efficient delivery systems.

Systemic Delivery of Nucleic Acids

Local delivery of nucleic acid therapeutics could be achieved in eye, skin, mucus membranes, and local tumors. It is particularly well suited for the treatment of lung diseases and infections. The advantages are higher bioavailability and reduced adverse side effects, but not every tissue is amenable to local or topical delivery.
Systemic delivery of antisense or siRNA oligonucleotides requires that the antisense or siRNA oligonucleotides are able to travel throughout the body to reach the target tissue/organ while avoiding the nontarget tissues. For effective systemic delivery, ODNs must navigate the circulatory system of the body while avoiding rapid excretion by the kidney, degradation by the serum and tissue nucleases, and uptake by the phagocytes of the reticuloendothelial system. Moreover, they should be able to overcome failure to cross the capillary endothelium, slow diffusion/binding in extracellular matrix, and inefficient endocytosis by tissue cells and release from endosomes. The major systemic delivery approaches are described below.57,58

Viral Delivery Systems (Viral Vectors)

A virus carries its genome from one host cell to another. It enters the new target cells, navigates to the cell's nucleus, and initiates expression of its genome, as a part of its self-replication cycle. It is possible to convert a virus into a gene-delivery vehicle by replacing a part of the virus genome with a therapeutic gene. Viruses that are used for delivering genetic material to host cells are called vectors, the process is known as transduction, and infected cells are described as being transduced.
The viral vectors could be nonreplicating or replicating and common examples are:59 (*a*) *retroviruses*, which contain single-stranded RNA molecule as genetic material. Herpes simplex virus (HSV) is a retrovirus, whereas lentiviruses are a subclass of retroviruses; (*b*)*adenoviruses*, which contain the genetic material in the form of double-stranded DNA and cause common cold as well as respiratory, intestinal, and eye infections in humans; and (*c*) *adeno-associated viruses*, which have single-stranded DNA as genetic material. The lesser-used viruses are *baculovirus* and *vaccinia*. Although to a lesser extent, bacteria have also been used as a delivery vehicle. The most prevalent organisms used are *Salmonella*and *Clostridium*; other lesser-used examples are *Bifidobacterium*and *Escherichia coli*.

The evolution of viruses has taken place essentially as gene-delivery vehicles and therefore they are typically very efficient. Viral vectors are used in a large number of preclinical and clinical studies involving gene-delivery. Safety of viral vectors is the major concern limiting their use in clinical applications. The viral vectors are replication deficient and therefore nonpathogenic, but there is a slight risk of reversion to the wild type virus. There is also the possibility of inducing severe immune responses. The introduction of retrovirus vectors may cause mutagenesis of the host genome. The selective delivery and expression of genes (target-cell specificity) may be difficult to achieve and the manufacturing costs are high.

Nonviral Delivery Systems (Synthetic Vectors)

Safety concerns associated with viral vectors have led to the use of synthetic materials (synthetic vectors) for oligonucleotide delivery.[49,57,58] Moreover, they are less expensive, easier and safer to make, and suitable for long-term storage. Synthetic vectors are molecules, which electrostatically bind to DNA or RNA, condensing them into nanosized particles. When nanoparticles are formed by complexation between cationic lipids (or cationic liposomes) and DNA, they are called lipoplexes, whereas when formed by complexation between cationic polymers (or polypeptides) and DNA, they are called polyplexes. This process of delivering nucleic acids into the cell by nonviral methods is called transfection (also lipofection when lipids or liposomes are used).

Cationic liposomes are among the most extensively used synthetic materials for systemic gene delivery due to their relatively higher transfection efficiencies. They electrostatically

interact with the negatively charged phosphate backbone of nucleic acids, which neutralizes the charge and promotes the condensation of nucleic acids into a more compact structure. A common example of cationic liposome is transfection reagent Lipofectin, which comprises 1:1 mixture of *N*-[1-(2,3dioleyloxy)propyl]-*N,N,N*-trimethyl ammonium chloride (DOTMA) and the colipid dioleylphosphatidyl ethanol amine (DOPE). Other examples of cationic lipids are 3β[(*N,N*′-dimethylaminoethane)-carbamoyl] cholesterol (DC-CHOL); 1,2-bis(oleoyloxy)-3-(trimethylamino) propane (DOTAP); and (1,2-dimyristyloxypropyl-3-dimethyl-hydroxy) ethyl ammonium bromide (DMRIE). Recently, stable nucleic acid–lipid particle (SNALP) formulations have demonstrated high efficacy in several models in vivo.

Polypeptides such as polylysine have also been investigated for gene delivery. Polyplexes of DNA and polylysine are poor gene-delivery vectors and require the addition of chloroquine.

Cationic polymers with linear, branched, or dendritic structures also serve as efficient transfection agent due to their ability to bind and condense large nucleic acids into stabilized nanoparticles. Polymers with primary, secondary, tertiary, and quarternary amines as well as other positively charged group like amidines are particularly useful for this purpose. Examples of cationic polymers investigated for gene delivery are polyethylenimine (PEI), polyamidoamine or starburst dendrimer, imidazole-containing polymers, cyclodextrin-containing polymers, and membrane-disruptive polymers (polyethylacrylic acid/PEAA, methylacrylic acid/MAA, polyacrylic acid/PAA, and polypropylacrylic acid/PPAA).

Unlike the ionic complexes, nucleic acid conjugates with cell-penetrating peptides, carbohydrates, and lipid molecules have been used for improved delivery with moderate success.

Liposomes and lipid-based formulation have been mostly used for systemic delivery of oligonucleotides in clinical applications. The disadvantages of using synthetic vectors are low transfection efficiency (polyplexes), reproducibility, toxicity to some cell type's in vitro and in vivo, and colloidal stability upon systemic administration.

Targeted Drug Delivery

Magic Bullet

Paul Ehrlich coined the term “Magic Bullet.”[60,61] He envisaged a treatment of pathogens and toxins in the human body by means of a chemical substance, which is equipped with high affinity for the causative agent. Moreover, this substance should be efficacious in a concentration that is harmless for patients. While screening trivalent arsenic compounds for their potency on *Treponema pallidum*, the causative agent for syphilis, he discovered Salvarsan (magic bullet), which killed syphilis organisms in

most cases without killing the host. Although the concept of the magic bullet was introduced 100 years ago, the challenge of making drugs with selective toxicity (in other words, targeting) has not been broadly achieved.

Key Concept

Targeted Drug Delivery

The main goal of *targeted drug delivery* is to optimize drug's therapeutic index (the ratio of the therapeutic dose to the toxic dose) by strictly localizing its activity at the target (diseased) site.62 Drugs can be targeted to specific organs (organ targeting), systems (systemic targeting), cells (cellular targeting), or specific intracellular organelles, or molecules (molecular targeting). Drug targeting could be achieved by physical, biologic, or molecular systems that result in high concentrations of pharmaceutically active agents at the targeted site, thus lowering its concentrations in the rest of the body. Successful drug targeting results into significantly lower drug toxicities, reduced doses, and increased efficacy.

Drugs administered by routine parenteral administration are distributed throughout the body and reach nontarget (normal/healthy) organs/tissues leading to possible toxic side effects and low efficacy of treatment.62 Besides, there is a possibility of drug metabolism in the liver or other organs and excretion by kidney. As a result, only small fraction of the administered drug dosage will reach the target (diseased) organ or tissues. Targeted drug delivery62 aims to overcome limitations associated with routine drug administration by delivering drugs specifically to diseased cells and tissues while not exposing healthy tissues. Ensuring minimal drug loss during the transit to the target site, protecting the drug from metabolism and premature clearance, retaining the drug at the target site for desired period of time, facilitating the drug transport into the cell, and delivering the drug to the appropriate intracellular target site are other requirements of targeted drug delivery. Last but not least, these targeted drug delivery systems should be biocompatible, biodegradable, and nonantigenic.

Types of Drug Targeting

Drug targeting approaches are grouped into two major categories: (*a*) active targeting and (*b*) passive targeting. A brief overview of major active and passive approaches is provided below.63

Active Targeting

Active targeting is achieved by binding to cell surface antigens and receptors or membrane transporters. A brief overview of different active targeting strategies is provided below.

Carrier-Linked Prodrug Strategy for Targeting Cell Surface Antigens and Receptors

This strategy aims to develop prodrugs by conjugating drug molecules to monoclonal antibodies (mAbs) or ligands for

specific interaction with antigens or receptors expressed on target cell surface. These cell surface targets are distinguished into two categories: noninternalizing and internalizing. In noninternalizing systems, the drug conjugate is cleaved extracellularly, whereas in internalizing systems drug is cleaved intracellularly after endocytosis.

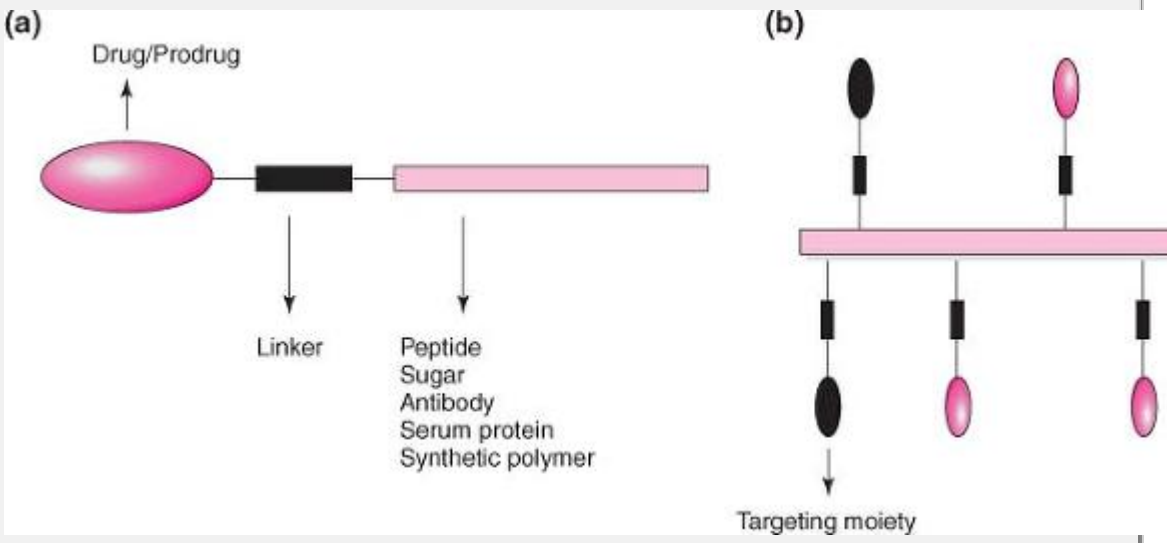


Fig. 23-11. General design of carrier-linked prodrug/conjugate for active targeting.

Active targeting to antigens/receptors is achieved by employing carrier-linked prodrug strategy64 as shown in Figure 23-11. The delivery system has three components: (*a*) drug, (*b*) carrier, and (*c*) the homing device or the targeting moiety. Carrier-linked prodrugs are obtained by conjugating the drug molecules to low- to high–molecular-weight molecules (carriers) like sugars, growth factors, vitamins, antibodies, peptides, and synthetic polymers that can transport the drugs to the target site and subsequently release them there. The drug release in most of the prodrugs is accomplished by conjugating the drug to the carrier through a spacer that incorporates a predetermined breaking point, which allows the drug to be released at the cellular target site. It is achieved by incorporating linkages sensitive to enzymatic cleavage, acidic pH, hypoxia, or thiol-exchange reactions. Drug release is also accomplished by employing self-immolative linkers.

Several cell-specific receptors are expressed under physiological conditions, which are specific to ligands and therefore could be exploited for targeting.62 Examples are (*a*) parenchymal liver cells, which are specific to galactose, polymeric IgA, cholesterol ester-VLDL, and cholesterol ester-LDL; (*b*) kupffer cells, which are specific to mannose-fucose, galactose, and LDL; (*c*) liver endothelial cells, which are specific to mannose and acetylated LDL; and (*d*) leucocytes, which are specific to chemotactic peptide and complement C3b. Receptors may also become available under pathological conditions. Examples include (*a*) antigenic sites on pathogens (bacteria, viruses, and parasites); (*b*) infected cells expressing specific antigens; and (*c*) tumor-associated antigens/receptors.64

Monoclonal antibodies are used for active targeting because of their high binding affinity for respective antigens. Most mAbs belong to the immunoglobulins of the IgG class, which is smallest in size but most abundant antibody found in all biological fluids. Several standard chemotherapeutic agents including antifolates, vinca alkaloids, or anthracyclines have been conjugated to mAbs mostly through cathepsin-B sensitive peptide linker or disulfide bond. It was found that these antibody conjugates indeed have selectivity toward the cells that expresses the respective antigens. These conjugates, however, failed in clinical trials because the mAbs were of murine origin and invoked immune responses. The problem of immunogenicity was resolved by the development of chimeric and humanized antibodies that do not carry murine sequences. FDA has now approved five chimeric or humanized antibodies such as rituximab (Rituxan), tratuzumab (Herceptin), alemtuzumab (Campath), bevacizumab (Avastin) and cetuximab (Erbitux) for the treatment of hematological and solid cancers. Of several immunoconjugates evaluated in clinical trials, gemtuzumab ozogamicin (Mylotarg, Wyeth, NJ)65 has been approved for the treatment of cancer (Fig. 23-12). This immunoconjugate consists of humanized anti-CD33 mAb linked to the cytotoxic antibiotic ozogamicin (*N*-acetyl-γ-calicheamicin). The linker consists of two cleavable

bonds. Mylotarg65 is used for the treatment of CD33+ acute myeloid leukemia in elderly patients who are not eligible for other chemotherapies and who are suffering from their first relapse. Mylotarg demonstrated clinical efficiency in pediatric patients with advanced CD33+ acute myeloid leukemia. Immunotoxins are antibody conjugates of highly potent drugs (DOX is frequently used) or toxins. Immunotoxins contain a toxin made by plants; insects; or microorganisms and examples include Pseudomonas exotoxin A (PE), diphtheria toxin (DT), and ricin. The primary targets of immunotoxins are tumor cells. BR96-DOX conjugate in an extensively investigated example, where an average of eight molecules of DOX are linked to chimeric mAB BR 96 through an acid-sensitive hydrazone linkage.66 Promising immunotoxins currently in clinical trials include TransMID 107 (transferrin-CRM107) and PRECISE (IL13-PEI-301-R03).64

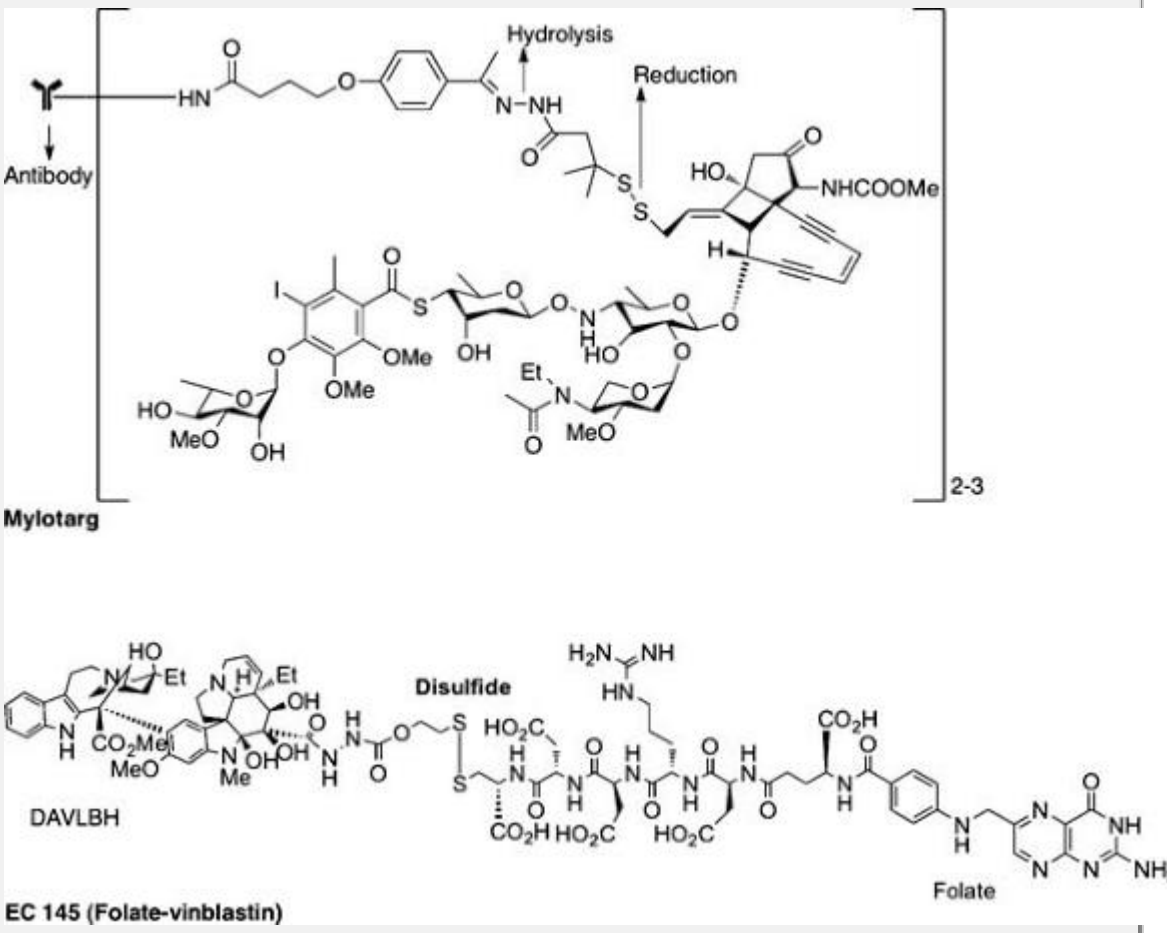


Fig. 23-12. Examples of actively targeted prodrugs: Mylotarg and EC 145.

Besides antigens, cellular receptors also provide targets for prodrug design. Active targeting is achieved by binding drugs to ligands that display high affinity for a particular receptor. The ligands can be low- or high–molecular-weight compounds such as vitamins, peptides, sugars, native or modified proteins, and antibodies. Prodrug is taken up by receptor-mediated endocytosis after binding. The drug is then released in endosomes or lysosomes depending on the route of cellular trafficking of the particular receptor.

Folic acid is one of the most highly used ligands because it retains high affinity for its receptor even after modification with drug/carrier molecules. It is overexpressed in many human types of cancers and a

broad spectrum of low- and high–molecular-weight drug folate conjugates with alkylating agents, platinum complexes, paclitaxel, 5-fluorouracil, camptothecin, doxorubicin, and mitomycin has been investigated. Prodrug EC 145,67 currently in clinical trials, is probably the most promising folate-targeted prodrug (Fig. 23-12). It is composed of vinca alkaloid desacetylvinblastine monohydrazide linked to folic acid through reducible disulfide bridge. EC 145 was found to be more active and better tolerated than the free drug in in vivo preclinical studies and showed superior antitumor activity.

Cyclic peptides that bind to integrins can be used to target vascular receptors. Vascular receptor proteins are crucial for the interaction between a cell and the extracellular matrix and they are involved in tumor angiogenesis. Certain integrins ($\alpha_v\beta_3$, $\alpha_v\beta_5$) are overexpressed on proliferating endothelial cells and some tumor cells. Peptides containing the RGD sequence (Arg-Gly-Asp) that are present in extracellular matrix are used to target integrins and subsequently inhibit angiogenesis. A number of RGD-drug conjugates with cytostatic and diagnostic agents have been prepared to obtain the proof of concept.

The asialoglycoprotein receptor (ASGPR) is a membrane-bound lectin expressed on hepatocytes and liver cancer. It has been used for prodrug targeting for the treatment of hepatocellular carcinoma. ASGPR has high affinity for terminal

β-galactoside or β-*N*-acetylgalactosamine on glycoproteins and is responsible for the endocytosis of several glycoproteins. The strong interaction of glycoproteins with ASGPR receptor is attributed to the cluster effect (multivalency) in which adjacent saccharide group binds to the receptor with high binding constants. The cluster effect is mainly due to the thermodynamic property of multivalent ligands rather than the presence of multiple receptor binding sites. N-(2-hydroxylpropyl) methyl acrylamide (HPMA)-Gly-Phe-Leu-Gly containing galactosamine (PK2, FCE28069) is the only polymer–drug conjugate bearing a targeting ligand to be tested clinically. PK2 has Mw ~25,000, DOX content (~7.5 wt%), and galactosamine content of 1.5 mol% to 2.5 mol%. The prodrug showed 30% delivery to the hepatic region in preclinical studies. The prodrug was found to accumulate in tumors also due to the enhanced permeability and retention (EPR) effect and the ratio of tumor tissue to normal liver uptake was 1:3 in 24 hr. The galactose-mediated liver targeting was about 15% to 20% of dose at 24 hr.

The antigens and receptors described here are only representative and there are many more that have been investigated for active drug targeting. The disadvantage associated with antibody–drug conjugates and drug modified with ligands having affinity for particular receptors is that they are not exclusively target-specific and cross-reactivity of drug conjugate with normal tissue is observed.64

Antibody-Directed Enzyme Prodrug Therapy

Antibody-directed enzyme prodrug therapy (ADEPT) is a two-step mechanism for prodrug targeting, where a tumor-associated mAb linked to drug-activating enzyme (usually antibody–enzyme fusion protein) is administered intravenously in the first step, which binds to specific antigen expressed on the tumor cell surface.68 A nontoxic prodrug is administered systemically in the second step and converted to the cytotoxic drug by the pretargeted enzyme. The enzymes used in ADEPT are divided into following three categories: Class I: enzymes of nonmammalian origin with no mammalian homologues such as alkaline phosphatase and α-galactosidase; Class II: enzymes of nonmammalian origin with mammalian homologues such as carboxypeptidase A, β-glucuronidase, and nitroreductase; and Class III: enzymes of mammalian origin such as β-lactamase, carboxypeptidase, cytosine deaminase, benzylpenicillin amidase, and phenoxymethyl.

Currently, there are two ADEPT systems in Phase I/II clinical trials with prodrug ZD2767P or *N*-{4-[*N,N*-bisamino]phenyloxycarbonyl}-L-glutamic acid. The prodrug is activated by enzyme carboxypeptidase 2 (CPG2) to active drug 4-[*N,N*-bis(2-iodoethyl)amino]phenol or phenol bisiodide mustard and is active against colorectal tumors. The first ADEPT system in a clinical trial uses a recombinant fusion of murine anticarcinoembryonic antigen (CEA) F(ab)2 fused to CPG2 in combination with prodrug ZD2767 for the treatment of advanced colorectal cancer and the second ADEPT study in clinical trials utilizes a

recombinant fusion of CEA sFv fused to CPG2, in combination with ZD2767P for the treatment of CEA-expressing tumors.

The ideal drugs for ADEPT are small molecules with the ability to diffuse into the tumor tissues to cause a bystander effect. The bystander effect is defined as the capability to kill the surrounding nondividing/nonexpressing tumor cells and is an important requirement for this type of therapy as it amplifies the drug effect. To avoid systemic toxicity in clinical application, the time interval between enzyme and prodrug administration should be optimized so that the conjugate accumulates only in tumors and not in blood and normal tissues. The target antigen should be either expressed on tumor cell membrane or secreted into the extracellular matrix of the tumor and use of high-affinity mAb is essential. The drug should be dose dependant and cell cycle independent. For effective therapy, the antibody–enzyme conjugate should remain on the cell surface after binding to the respective antigens and it must also be cleared rapidly from the circulation to prevent toxicity.

The major advantage of ADEPT over antibody conjugates is the amplification of the cytotoxic effects due to catalytic activation of prodrug. Another benefit is the ability to kill surrounding tumor cells thereby reducing the risk of tumor evading therapy by antigen loss. The cytotoxic effects of drugs are largely confined to the tumor target and hence the side effects are reduced as compared to systemic administration of chemotherapy. A significant obstacle for ADEPT is the immunogenicity of enzymes used for prodrug activation and the targeting mAb as both were derived from nonhuman sources. This problem has been resolved by the use of human enzymes in conjunction with humanized or human mAbs.

Another analogous approach is "**Lectin-directed Enzyme-Activated Prodrug Therapy,**" where glycosylated-enzyme conjugates are administered first, which binds to cells surfaces expressing specific lectin receptors.69 The enzyme then activates the systemically administered prodrug at the site of action.

Gene-Directed Enzyme Prodrug Therapy/Virus-Directed Enzyme Prodrug Therapy

Gene-directed enzyme prodrug therapy (GDEPT) is also known as suicide gene therapy and involves physical delivery of a gene for a foreign enzyme (not naturally expressed in the host) to tumor cells by a targeting mechanism that leaves the surrounding noncancerous cells untransformed.59 The transformed tumor cells express the enzyme, which in turn activates the systemically delivered nontoxic prodrug. Viral vectors are mostly used for gene delivery but they suffer from limited amount and size of plasmid-DNA. There is also the possibility of inducing severe immune responses. This approach is recognized as virus-directed enzyme prodrug therapy (VDEPT) when viral vectors are used for gene delivery. Nonviral vectors such as cationic liposomes are less expensive, easier and safer to make, and suitable for

long-time storage, but their gene delivery properties are far from optimal.

An earlier example of GDEPT is herpes simplex virus thymidine kinase and GCV. The drug is phosphorylated by the herpes simplex virus thymidine kinase and then by cellular kinases to produce GCV-triphosphate, which incorporates into the elongating DNA during the cell division (S-phase) and causes inhibition of DNA polymerase and single-strand breaks. These characteristics make HSV TK-GCV useful for eradicating tumor cells invading nonproliferating tissues. Other examples in clinical trials are (*a*) the purinenucleoside phosphorylase enzyme in combination with 6-methylpurine (prodrug); (*b*) carboxylesterases enzyme in combination with prodrug irinotecan (CPT11); and (*c*) cytochrome P450 (CYP450) enzyme in combination with prodrug cyclophosphamide.

For GDEPT to be effective, the expressed enzyme or a related protein should not be present in normal human tissues or expressed only at very low concentrations and must achieve sufficient expression in the tumors to give high catalytic activity. The prodrug should be lipophilic so that it can diffuse into the tumor cells before it can be converted into cytotoxic drug by the suicide enzyme. Alternatively, if the prodrug cleavage takes place extracellularly, the active drug should be capable of diffusing through cell

membranes. The drug should be able to kill surrounding nondividing or nonexpressing tumor cells by bystander effect. The advantage of the GDEPT approach is the possibility of delivering target-specific cancer therapy with reduced systemic toxicity resulting in a better prognosis for patients. There are certain theoretical risks associated with GDPET such as insertional mutagenesis, anti-DNA antibody, local infection, and tumor nodule ulceration, which may restrict its use.

Antibody-Targeted, Triggered, Electrically Modified Prodrug Type Strategy

Antibody-targeted, triggered, electrically modified prodrug type strategy (ATTEMPTS)70 delivery system comprises large complex made of two components: (*a*) targeting component consisting of an antibody chemically linked with an anionic heparin molecule and (*b*) a drug component consisting of the enzyme drug modified with a cationic moiety. The two components are linked through a tight but reversible electrostatic attraction. The cationic species conjugated to the enzyme is relatively small (positively charged peptide) and hence the enzyme conjugates retain its catalytic activity. However, this enzyme conjugate is unable to exert its catalytic activity because it is bound to antibody–heparin conjugate via electrostatic bonds. The ATTEMPTS complex is delivered to the targeted site by the attached antibody and the enzyme drug is released at the site by using a triggering agent such as protamine. Protamine is a heparin antidote, which binds to heparin more strongly than most of the cationic species. The released enzyme is then concentrated at the site of action thereby maximizing its catalytic activity toward drug conjugate at the targeted site while minimizing its toxic effects toward the normal cells. The selection of an appropriate cationic moiety is key to success of ATTEMPTS strategy because retention of prodrug after administration and its conversion to active drug relies on the binding strength of modified enzyme toward heparin. An important aspect of this approach is that both chemical and biological methods can be used to insert the cationic moiety. Yang and colleagues70 modified the tissue plasminogen activator (t-PA) with a cationic species (Arg_7-Cys-) and rendered it inactive by electrostatic binding with negatively charged heparin–antifibrin antibody conjugate. After targeting the complex to the target site, t-PA activity was restored by administration of protamine (heparin antidote).

The approach could be important because prodrug activation in ADEPT depends on chemical conjugation and enzyme cleavage, respectively. ADEPT is therefore restricted to small-molecule drugs only and macromolecular drugs such as proteins are not suitable candidate for ADEPT.

Membrane Transporters

Membrane transporters are integral plasma membrane proteins that mediate the uptake of different substrates including, polar nutrients, amino acids and peptides, nucleosides, and sugars.63,71 They fall into two major families: (*a*) the ATP-binding cassette family, which includes transporters responsible for drug resistance through efflux transporters like Pgp and (*b*) the solute carrier (SLC) transporters, which are capable of influx into the cell. An example of the solute carrier transporters is nucleoside transports, which are responsible for the uptake of nucleosides, the precursors of nucleotides. Transporters can also be selective for different classes of substrates as is the case for the transporters of purine and pyrimidines. Often, transporters require the flux of a secondary substrate, like the peptide transporters PEPT1 and PEPT2, which require the influx of H^+ to facilitate their uptake functions. Because many transporters have nutrients as substrates, prodrug design is manipulated to mask the drug with nutrient moiety so as to initiate prodrug uptake through these transporters (Fig. 23-13).

The use of membrane transporters as prodrug targets has largely stemmed from the discovery of the absorption mechanism of valacyclovir through the PEPT1 transporter.72 The addition of the L-valyl ester to the parent drug acyclovir vastly improves the bioavailability of acyclovir. Upon absorption, valacyclovir is rapidly converted to its parent drug acyclovir via esterase cleavage. Acyclovir is then free to enter the bloodstream, where it is taken up by cells via nucleoside transporters. Valacyclovir is the first example of a novel peptide ester prodrug that actively targets the human transporters, PEPT1, for increased oral absorption. Besides the obvious benefit of increased oral absorption, this method of drug delivery has been tailored to target cancer cells over expressing certain membrane transporters. The malignant ductal pancreatic cancer cell lines AsPc-1 and Capan-2 and the human fibrosarcoma cell line HT-1080 overexpress the PEPT1 membrane transporter. It has been suggested that if

tumor cell uptake of hydrophilic polymer drug conjugates via a specific mechanism of internalization can be achieved; these drugs may avoid the development of or elimination due to multidrug resistance.

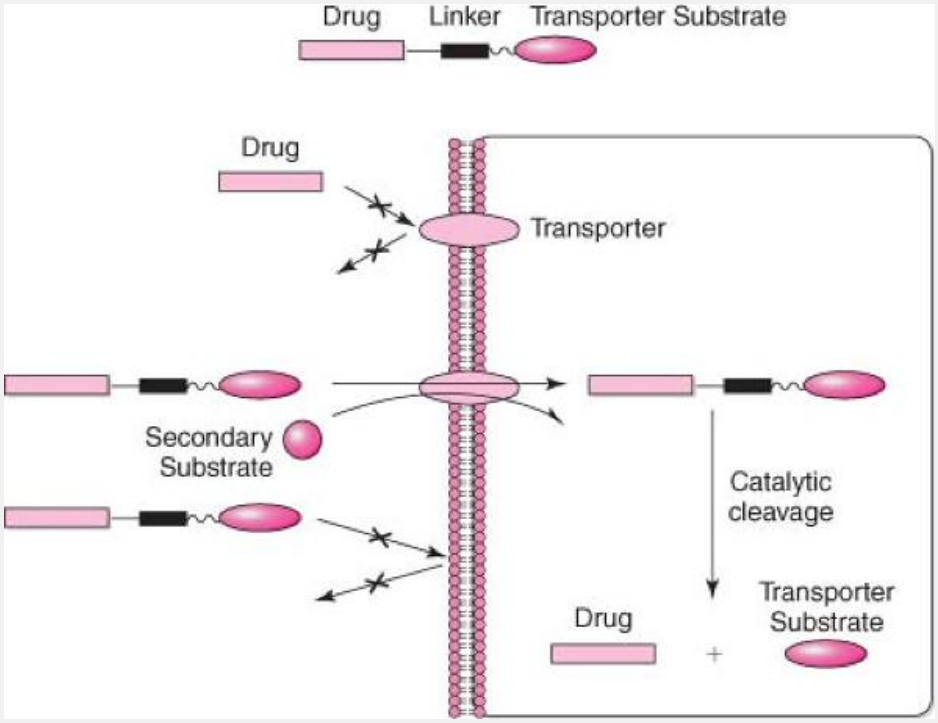


Fig. 23-13. Schematic representation of membrane transporter targeted prodrug uptake. (Source: H.-K. Han and G. L. Amidon, AAPS Pharm. Sci. **2,** 1, 2000.)

The advantage of using transporters like PEPT1 is the potential for increased oral absorption. Thus, prodrugs utilizing the membrane transporters may be afforded the luxury of an oral formulation, which is the gold standard of administration. Amino acid side chains could be varied to alter the physicochemical properties of prodrug. The broad specificity of these transporters for multiple substrates increases the potential flexibility in prodrug design. Also because the transporter-targeting substrates are generally sugars, vitamins, or peptides, the byproducts of the prodrug's conversion yield nontoxic nutrients. The disadvantage associated with this approach is that these transporters are also expressed in cells of the small intestine, kidney, bile duct, and pancreas. Therefore, if PEPT1 substrates are used as targeting moieties, toxicity in these cell types may occur. Another problem could arise if the prodrug upon absorption by the transporter is quickly converted to parent drug. Once this occurs, the parent drug will be passively distributed throughout the systemic circulation, which could in turn cause systemic toxicity.

Passive Targeting

Passive targeting utilizes the natural or passive distribution characteristics of a carrier for drug targeting and no homing device is attached. Some of the major passive-targeting approaches are briefly described below.

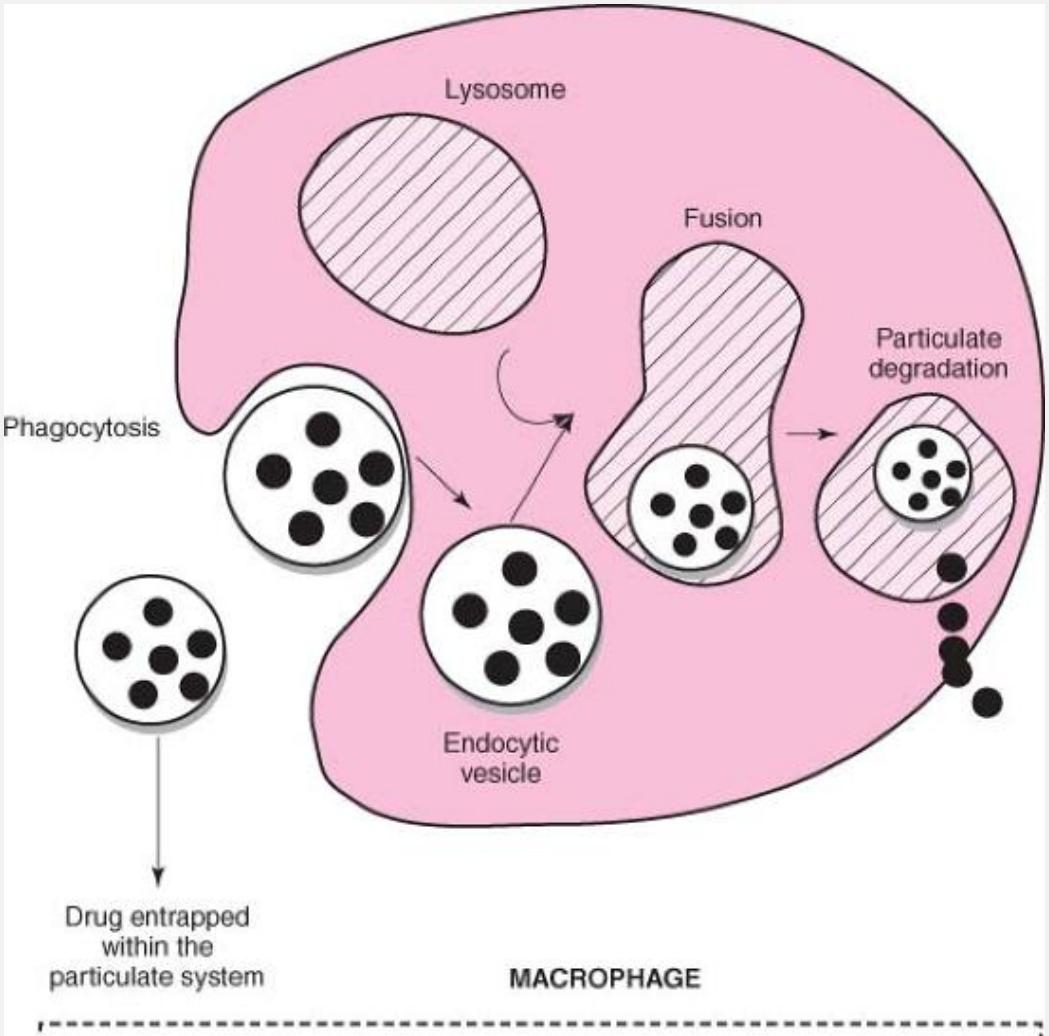
Mononuclear Phagocyte System

Particulate carriers are phagocytosed by the cells of mononuclear phagocyte system (MPS), leading to major accumulation in the liver and the spleen62 (Fig. 23-14). After phagocytosis, the particulate drug/carrier complex is transported to lysosomes, where the complex is disintegrated to release the drug. If the complex is not broken down in the lysosomes, it may be released from the lysosomal compartment into the cytoplasm and may even escape from phagocyte causing a prolonged release

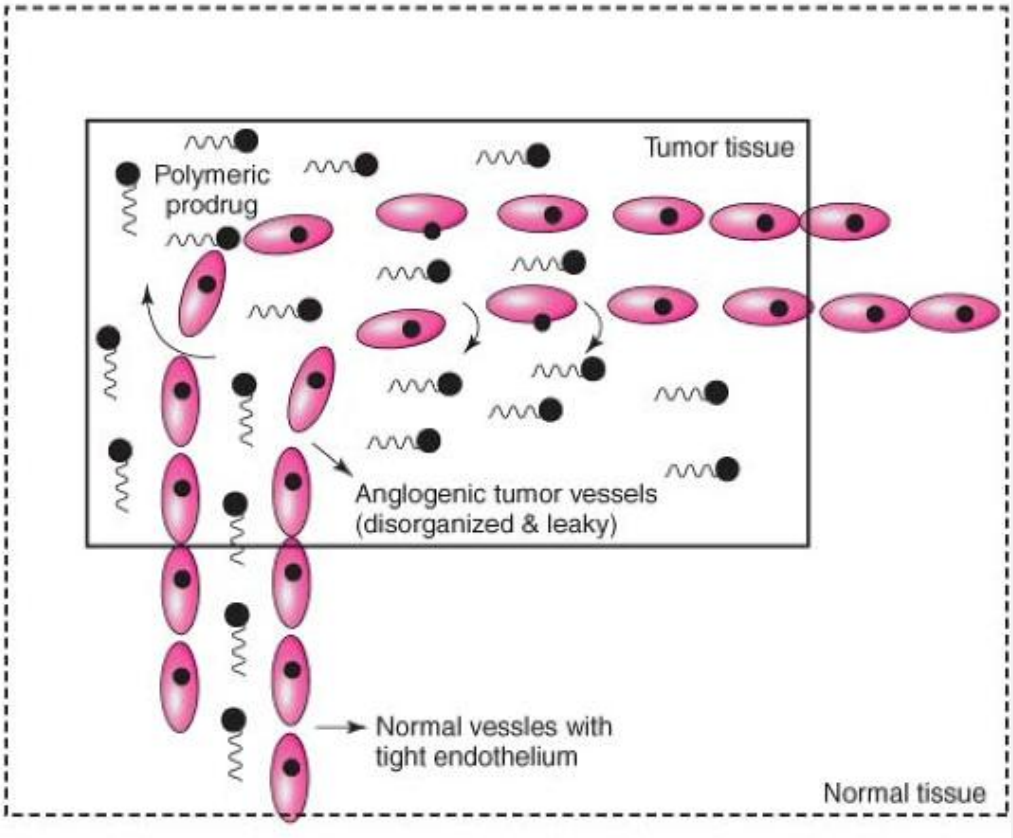
systemic effect. The ability of macrophages to rapidly phagocytose particulate drug/carrier complexes could be diminished by grafting PEG chains on the surfaces of particulate material.
Passive targeting to MPS could be used for the treatment of macrophage-associated microbial, viral, or bacterial diseases and lysosomal enzyme deficiencies.

Enhanced Permeability and Retention (EPR) Effect

Prodrugs could be passively targeted to tumors by exploiting the EPR phenomenon73 (Fig. 23-14). Angiogenesis is induced in tumors to accommodate their ever-increasing demand for nutrition and oxygen as the tumor cells multiply and cluster together to reach the size of 2 to 3 nm.74 Unlike the normal tissue, the blood vessels in tumors become irregular in shape, dilated, leaky, or defective, and the endothelial cells become poorly aligned and disorganized with large fenestrations. The perivascular cells and the smooth muscle layers are frequently absent or abnormal in the vascular wall. Tumor vessels develop wide lumens and the lymphatic drainage in tumor tissues becomes impaired. This results into extensive leakage of blood plasma components such as macromolecules, nanoparticles, and lipidic particles in tumor tissues. These macromolecules and nanoparticles are retained in tumors due to the slow venous return in tumor tissues and poor lymphatic drainage. Longer plasma residence time and neovasculature are known to influence the EPR. This phenomenon has been shown to achieve 10- to 50-fold (1%–5% and in some cases 20% of injected dose per gram of tumor) high local concentration of drugs in the tumor tissues than in normal tissues within 1 to 2 days of injection.



MACROPHAGE



EPR EFFECT

Fig. 23-14. Passive targeting approaches: mononuclear phagocyte system (MPS) and enhanced permeability and retention (EPR) effect. (Modified from D. J. A. Crommelin et al., Drug Delivery and Targeting for Pharmacist and Pharmaceutical Scientists, CRC Press, Boca Raton, FL, 2001, pp. 117 and R. Duncan, Nat. Rev. Drug Discov. **2,** 347, 2003.)

Passive targeting through the EPR effect is achieved by attaching the drug to macromolecules (e.g., synthetic or biopolymers) or nanoparticles (e.g., liposomes, nanospheres) that act as inert carriers. These macromolecules or nanoparticles do not interact with tumor cells but strongly influence the drug biodistribution. Molecular weight is absolutely important but not the sole criterion for predicting the molecule's biodistribution. The chemical nature of polymer, as well as shape and conformation in water, also influences its molecular size. Attachment to polymers results into improved water solubility, prolonged stay in blood circulation, and reduced toxicities. Polymer used for such applications should

be biocompatible (nontoxic, nonimmunogenic, preferably biodegradable), able to carry the required drug payload, able to protect the drug against premature metabolism, display active/passive targeting, able to liberate the drug at a rate appropriate to its mechanism of action, and able to enter tumor cells by endocytosis (if designed for lysosomotropic release).

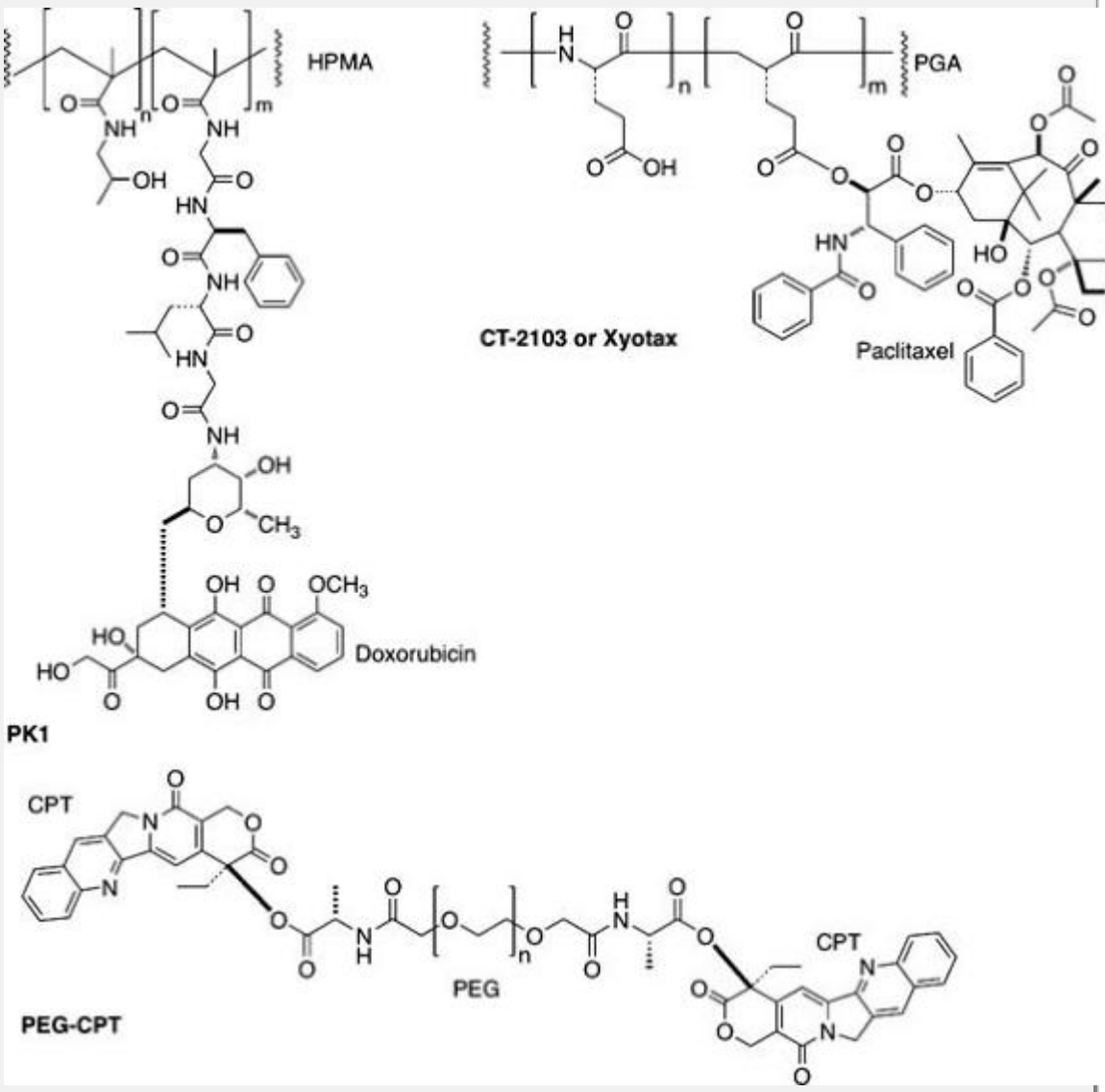


Fig. 23-15. Passively targeted polymeric prodrugs: PK1, Xyotax, and PEG-camptothecin (CPT).

Several passively targeted polymeric prodrugs are being evaluated in clinical trials[75,76] (Fig. 23-15). Examples are (*a*) PK1 or FCE28068 (HPMA linked to doxorubicin through tetrapeptide linker); (*b*) ProLindac (HPMA linked to diaminocyclohexane platinum [II]); (*c*) Xyotax or CT-2103 (polyglutamate or PGA attached to paclitaxel through ester bond); (*d*) CT-21006 (PGA attached to camptothecin); and (*e*) EZN-2208 or PEG-SN38 (PEG attached to 7-ethyl-10-hydroxycamptothecin). Genoxol-PM is paclitaxel-loaded biodegradabe polymeric micelle of PEG-PLA.

Another example is styrene-malic-anhydride-neocarcinostatin systems (SMANCS) obtained by conjugating neocarcinostatin (NCS, ~12 kDa protein) to two poly(styrene-co-maleic anhydride copolymer. NCS is a small protein, which is rapidly cleared by the kidney and shows nonspecific cytoxicity. Styrene-malic-anhydride-neocarcinostatin, which are targeted possibly by EPR, show improved pharmacokinetic properties. Clinical successes have been reported in patients with hepatocellular carcinomas. Dendritic structures and particulate materials are also being explored for passive targeting of prodrugs.

Polymer-Directed Enzyme Prodrug Therapy and Polymer-Directed Enzyme Liposome Therapy

The polymer-directed enzyme prodrug therapy (PDEPT) and polymer-directed enzyme liposome therapy (PELT) also exploit EPR for drug targeting.75'76 PDEPT is a two-step approach and involves the initial administration of the polymeric prodrug to promote tumor targeting followed by administration of the activating polymer-enzyme conjugate. The process utilizes the EPR effect to target the polymeric prodrug as well as polymer enzyme conjugate. The feasibility of PDEPT for targeted delivery is being evaluated using following: (i) PK1 prodrug and HPMA copolymer-cathepsin B enzyme conjugate; and (ii) HPMA-methacryloyl-GlyGly-cephalosporin-doxorubicin prodrug and HPMA-methacryloyl-Gly-Gly-β-lactamase enzyme conjugate. In another strategy, known as polymer-directed enzyme liposome therapy, liposomes (e.g., HPMA-phospholipase) are used to deliver the prodrug (improved EPR) followed by the polymer enzyme.

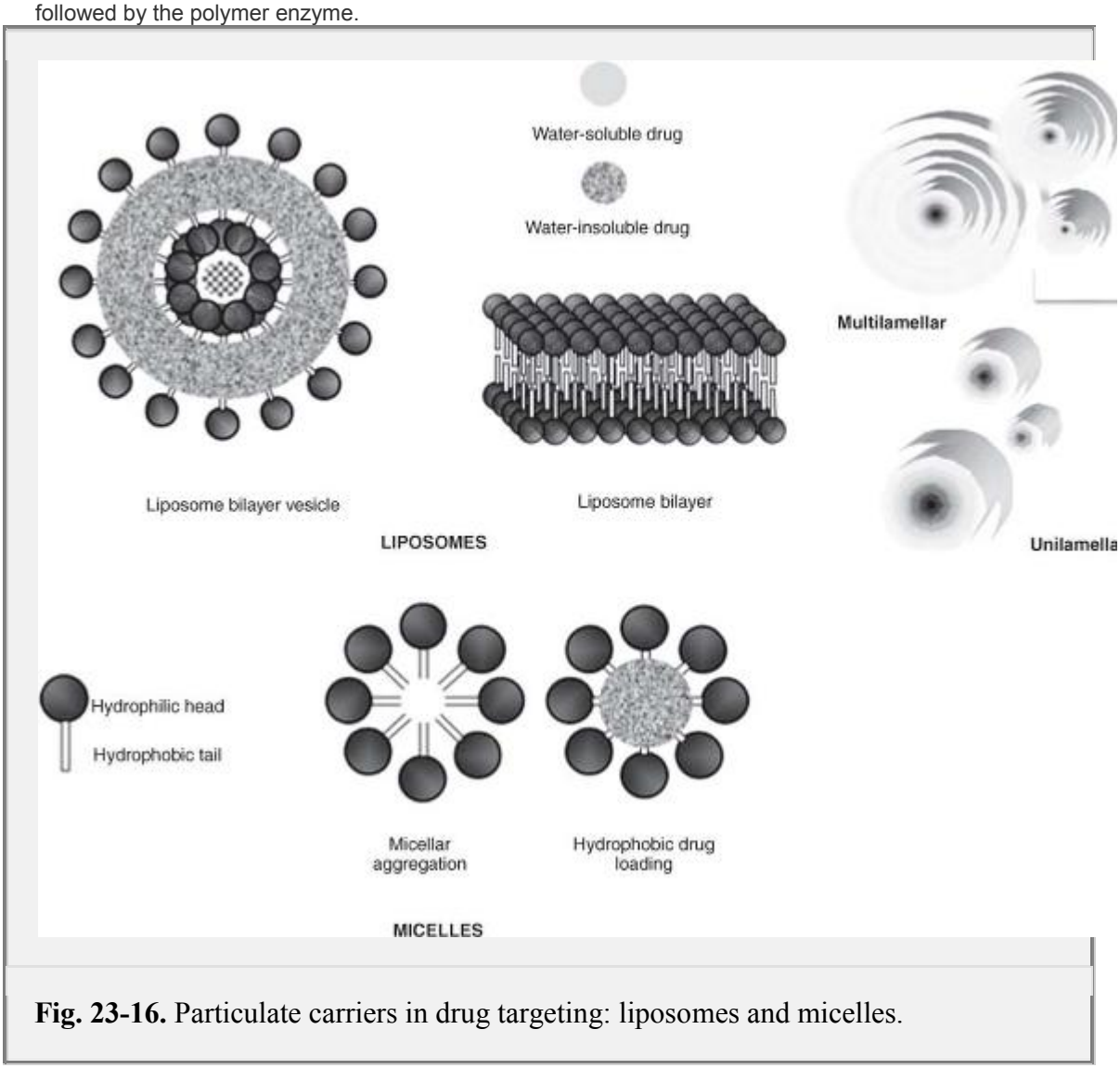


Fig. 23-16. Particulate carriers in drug targeting: liposomes and micelles.

Particulate Carriers in Drug Targeting

Besides the soluble prodrugs/conjugates, particulate carriers have also been used in the targeted drug delivery.62'77 Advantages associated with particulate carriers are (*a*) high drug payload, (*b*) possibility of both covalent and ionic association between the drug and the carrier, and (*c*) high degree of protection available to drug after encapsulation. Several solid-particulate nanosuspensions are in the

market; examples include sirolimus (Rapamune) (immunosuppressant, Wyeth) and aprepitant (Emend) (antiemetic, Merck). Several examples of particulate carriers are briefly described below.

Liposomes

Liposomes are vesicular structures based on one or more lipid bilayers encapsulating an aqueous core (Fig. 23-16).[62,77] The lipid molecules are usually naturally occurring or synthetic phospholipids, amphipathic moieties with a hydrophilic polar head group along with two nonpolar hydrophobic chains

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(tails). These molecules spontaneously arrange themselves in water to give the thermodynamically most stable bilayer structures, where the hydrophilic head groups protrude outside into the aqueous environment, and the hydrophobic chains orient themselves inward, away from water. The flat bilayers self-close into concentric compartments around a central aqueous phase to give spherical liposomes with diameters in the range of 0.02 to 20 μm.

The liposomes are either unilamellar (one concentrically oriented bilayers around an aqueous core) or multilamellar (multitude of concentrically oriented bilayers around aqueous core) (Fig. 23-16). When the liposomes are multilamellar, water may be present in the aqueous core and also between the bilayers. Multilamellar vesicles are formed under low shear agitation with wide size distribution, display relatively low level of aqueous encapsulation, and have relatively short circulation half-lives. The smaller unilamellar vesicles on the other hand have narrow size distribution and therefore preferred for intravenous applications where a long circulation time is demanded. They are also useful for encapsulation of water-soluble drugs but suffer from tendency to aggregate into larger liposomes. Multilamellar vesicles are readily converted to unilamellar vesicles by employing high shear processes such as sonication, homogenization, and extrusion.

Different types of liposomes have been used in drug delivery[62]: (*a*)*liposomes*, which are neutral or negatively charged and used for passive targeting to the cells of MPS; (*b*) *stealth liposomes*, which are sterically stabilized liposomes carrying hydrophilic coating (PEG) for longer circulation times; (*c*) *immunoliposomes*, which contain specific antibody or antibody fragment for active targeting; and (*d*)*cationic liposomes*, which are positively charged and used for gene delivery.

Liposomes are capable of incorporating both water-soluble (inside the aqueous core, e.g., daunorubicin) and water-insoluble drugs (within the bilayer, e.g., amphotericin B). They are biodegradable and nontoxic and proven to improve pharmacokinetic properties of the drugs. Injectable anticancer drugs, which exploit liposome technology, are doxorubicin (Doxil, Alza, CA, 1995), daunorubicin (Daunoxome, Gilead, CA, 1996), and cytarabine (Depocyt, SKYE Pharma, UK, 1999). The technology has also been used for topical antifungal products such as Amphotericin B (Ambisome, Gilead, CA, 1997). Liposomes have been used in pulmonary drug delivery. Lung fluids have a pH of ~6.8 and low protease or lipase activities and, therefore, liposomes are expected to be stable during administration. The drug release from the liposomes depends on the nature of phospholipids, composition of the liposomes, and hydrophilic or lipophilic properties of active ingredients. Multilamellar vesicles are used for nebulization. During the nebulization, the shear force generated by extrusion through the jet orifice reduces the liposome size to 0.2 to 0.3 μm.

Liposomes suffer from drawbacks such as (*a*) physical and chemical instability in liquid state; (*b*) low encapsulation efficiency for several drugs; and (*c*) challenging scale-up and sterilization of the final formulation. Stability of liposomes is dependent on the lipid composition, storage conditions (light, oxygen, temperature, moisture), and stabilizers (cholesterol, α-tocopherols and inert atmosphere) used, and in some liposomal formulations, physical and chemical stability can be improved by lyophilization. Another major concern is the short half-life of liposomes in blood circulation, which can be improved by “stealth” technology (PEGylation).

Micelles

Surfactants molecules aggregate in aqueous solution to form micelles at certain concentrations and temperature[62] (Fig. 23-16). Surfactants have a hydrophilic polar head group attached to a long-chain lipophilic (nonpolar) tail. Surfactant molecule used for micelles formation could be anionic (sodium

dodecyl sulfate or SDS and deoxycholic acid); cationic (hexadecyltrimethyl ammonium bromide); zwitterionic (lecithin or phosphatidylchloline); or nonionic (methyl cellulose and other lipophilic cellulose derivatives). Block copolymers comprising hydrophilic and hydrophobic segments are used to form polymeric micelles. Micelles are formed only when surfactants are present above a certain concentration, known as critical micelle concentration (CMC), which is characteristic for each surfactant. There is also a critical temperature requirement for micelle formation. A high CMC value suggests a rapid exchange of constitutive components and a fast disintegration of the micelles upon dilution, whereas a low CMC value suggests the contrary.

Micelles are used for reducing the surface tension of water, increasing the miscibility of different solvent phases, and stabilizing the emulsions. Micelles used in targeted drug delivery should be of low CMC so that it is stable in blood circulation and does not disintegrate upon contact with blood components. The diameter of the micelles could be chosen in the range where EPR effect is expected to occur (0.2 μm), to allow for accumulation of drug-loaded micelles in tumors or inflammation sites. Micelles obtained from amphipathic block copolymers consisting of hydrophilic PEG block and hydrophobic doxorubicin-conjugated poly(aspartic acid) or poly(β-benzyl-L-aspartate) have been extensively investigated. These drug-loaded block copolymers form micelles in water with spherical core/shell structure with drugs present in hydrophobic core.

Polymersomes and Dendrimers

Polymersomes are polymer vesicles with a core-shell structure similar to liposomes. They are made of diblock copolymers, which contain hydrophilic and hydrophobic portions similar to phospholipids. Since polymersomes are stronger and more stable than liposomes, they display less deformation under load and slower rate of drug leakage. The degree of polymerization and melting temperature (T_g) of the polymer are varied to control the vesicle-like properties such as rigidity, thickness, and permeability. However, polymersomes are not biocompatible, their degradation products are usually toxic, and the drug release from these platforms is generally too slow.

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Polymeric dendrimers on the other hand are treelike or star-shaped polymers that adopt a quasispherical shape. Drugs are incorporated into the internal cavities or attached through the surface functional groups. The main use of polymeric dendrimers is to enhance aqueous solubility of the poorly soluble drugs. Toxicity of the dendrimic polymers remains a major concern. Similar to polymersomes, polymeric dendrimers too are not commercially available.

Lipoproteins, which are endogenous lipid carrier systems comprising a lipid core and a coat where apolipoprotein is found, have also been used for targeted drug delivery. Examples are chylomicrons (10–90 nm); very low-density lipoprotein (VLDL, 30–90 nm); low-density lipoprotein (LDL, ~25 nm); and high-density lipoproteins (HDL, ~10 nm). Other common examples of particulate carriers are albumin microspheres, poly(lactide-co-glycolide) or PLA microspheres, and niosomes.

Prodrug Approaches[78,79]

Conventional prodrug design aims to improve pharmacokinetic and pharmacodynamic properties of a drug by chemically altering its structure, which is usually achieved by attaching a promoiety to the drug through reversible (enzymatic/nonenzymatic) bonds (Fig. 23-17). The most frequently used chemical linkages[78] (bonds) in prodrug design are ester, carbonates, carbamates, amides, phosphates, and oximes. Linkages such as thioethers, thioesters, imines, and Mannich bases have also been used but to a lesser extent. The chemical groups that can produce the aforementioned linkages are carboxylic acid, hydroxyl, amine, phosphate/phosphonate, and carbonyl.

Esters are the most common prodrug linkages constituting about half of marketed prodrugs.[78] They are obtained by attaching the promoiety to the water-soluble charged group (e.g., carboxyl) on the drug through ester bonds and aim to improve the lipophilicity or membrane permeability of the parent drug. Once in the body, the ester bond is cleaved by ubiquitous esterases (blood, liver, and other organs) to release the active drug. Contrary to esters, phosphate ester prodrugs are prepared to enhance the

aqueous solubility of parent drugs for achieving more favorable oral or parenteral administration.78 These display adequate chemical stability and are readily converted to active drugs by phosphatases present at intestinal brush border and in the liver. The amide prodrugs are relatively more stable in vivo and hydrolyzed to active drugs by enzymes such as carboxylesterases, peptidases, and proteases. The carbonates and carbamate prodrugs are converted to active drugs by esterases, whereas oxime prodrugs are converted to active form by microsomal cytochrome P450 (CY450). Enzymatic cleavage is not the only mechanism available for prodrug activation; physicochemical environment at the target site (e.g., acidic pH, hypoxia, glutathione-based thiol-exchange reactions) is also exploited for prodrug activation. Activation is also achieved by incorporating self-immolative linker in the prodrug design.

Key Concept

Prodrugs

The term *prodrug* is used to characterize pharmacologically inert drug derivatives that can be converted to active drug molecules in vivo, enzymatically or nonenzymatically, to exert a therapeutic effect (Fig. 23-17).78,79 It therefore implies a covalent linkage between the drug and the chemical moiety (also called *promoiety*) causing the inertness. The conventional prodrug design aims to overcome (*a*) pharmaceutical problems such as poor solubility, insufficient chemical stability, unacceptable taste or odor, and irritation or pain; (*b*) pharmacokinetic problems such as insufficient oral absorption, inadequate BBB permeability, marked presystemic metabolism, and toxicity; and (*c*) pharmacodynamic problems such as low therapeutic index and lack of selectivity at the site of action. Prodrugs have been earlier referred to as reversible or bioreversible derivatives, latentiated drugs, and biolabile drug carrier conjugates but the term prodrug is now standard. About 10% of the drugs approved worldwide can be classified as prodrugs.

In some cases, a prodrug may consist of two pharmacologically active drugs coupled together into a single molecule so that each drug becomes a promoiety for the other; such derivatives are called *codrugs*. A*bioprecursor prodrug* is a prodrug that does not contain a carrier or promoiety but results from molecular modification of active agent itself (active metabolite). *Soft drugs*, which must not be confused with prodrug, are active drugs designed to undergo a predictable and controllable deactivation or metabolism in vivo after achieving the therapeutic effect. Prodrugs also differ from conjugates in that they are reversible.

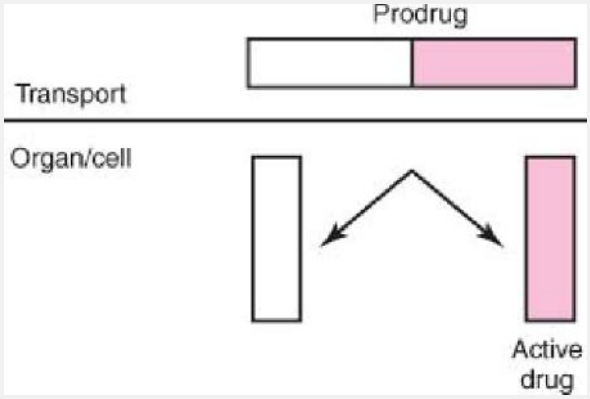

Fig. 23-17. The conventional prodrug design, where inactive prodrugs are transformed into active drugs inside the cell.

Attachment to promoiety through reversible bonds has been used to obtain prodrugs with improved lipophilicity or membrane permeability78,79 (e.g., enalapril, pivampicillin, adefovir dipivoxil, tenofovir disoproxil, famciclovir), aqueous solubility (e.g., sulindac, fosamprenavir, estramustine phosphate, prenisolone phosphate), and parenteral administration (fosphenytoin, foflucanazole, propofol phosphate

etc.). Prodrugs for improved ophthalmic (dipivefrin [propine] and latanoprost) and dermal (tazarotene) delivery and diseases such as Parkinson disease (levodopa), viral (pradefovir), asthma (bambuterol), hypercholesterolemia (simvastatin), and cancer (e.g., capecitabine [Xeloda] and ftorafur [Tegafur]) have also been developed (Table 23-3).

A few specific prodrug examples are discussed below to illustrate the salient features of conventional prodrug design. Enalapril is a prodrug used for lowering the blood pressure, congestive heart failure, and kidney problems (Fig. 23-18). It is an ethyl ester prodrug of enalaprilat, which suffers from low oral bioavailability (36%–44%). Conversion to ester enhances the absorption from 53% to 74% and the prodrug is readily converted to active form by hydrolysis of ester in vivo, which inhibits angiostensin-converting enzyme. Many prodrugs undergo site-selective activation too, common examples being the lipid-lowering bioprecursor prodrugs simvastatin (Zocor, Merck, NJ) (Fig. 23-18) and lovastatin (Mevacor, Merck, NJ) used for the treatment of hypercholesterolemia. Both prodrugs are administered in their inactive hydrophobic lactone form, which are then converted to active β-hydroxyacid form by CYP450 enzymes, mainly in liver. The active form inhibits the 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA), which is involved in cholesterol biosynthesis.

Another example is capecitabine (Xeloda, Roche, Switzerland), which is an orally administered tumor-selective carbamate prodrug of 5′-deoxy-5-fluorouridine (5′-FU) and used for the treatment of breast, colorectal, and gastric cancer (Fig. 23-18). The conversion of capecitabine to active drug is achieved in three-steps: (*a*) a hepatic carboxylesterase converts it into 5′-deoxy-5-fluorocytidine, (*b*) 5′-deoxy-5-fluorocytidine is converted to 5′-deoxy-5-fluorouridine by cytidine deaminase enzyme in the liver/tumor, and (*c*) tumor-associated enzyme thymidine phosphorylase converts 5′-deoxy-5-fluorouridine to 5-fluoruracil, which in turn is converted to 5′-fluoruridine or 5′-fluoro-2-deoxyuridine. The 5′-fluoro-2-deoxyuridine is incorporated into the RNA and DNA, respectively. This prodrug demonstrates satisfactory GI absorption (~100% bioavailability) and low GI toxicity when compared to the parent drug.

Conventional prodrugs are associated with several limitations, most important being their nonspecific activation inside the body. Current prodrug designs are therefore highly focused on the development of targeted prodrugs, where targeting is achieved by employing either active or passive targeting strategies described earlier (see sectionTargeted Drug Delivery).

Key Concept

Controlled Drug Delivery

Controlled drug delivery, also known as *rate controlled drug delivery*, is defined as the delivery of drug or active agent in the body at a predetermined rate.80 A controlled drug delivery system is therefore one that provides some control over the drug delivery in the body: temporal or spatial or both. Controlled drug delivery should not be confused with prolonged or sustained drug delivery because the controlled drug delivery attempts to control drug level in the target tissues or cells, whereas the sustained drug delivery is restricted to maintaining therapeutic blood or tissue levels of drug for extended period of time.

Carrier-linked design has been employed to obtain prodrug targeted to cell/tissue-specific antigens and receptors (Fig. 23-11). A recently approved example in this category is gemtuzumab ozogamicin (Mylotarg, Wyeth)65 (Fig. 23-12). Prodrug systems designed to exploit more advanced active targeting strategies such as ADEPT, GDEPT, and ATTEMPTS are in various stages of development and have been described earlier (see section Targeted Drug Delivery). Examples of prodrugs exploiting carrier-mediated transport (Fig. 23-13) are valacyclovir (Valtrex, GlaxoSmithKline, UK) (Fig. 23-18) and valganciclovir (Valcyte, Roche). These are L-valyl esters (promoiety: amino acid valine) of acyclovir and

GCV, both drugs having limited and variable bioavailability. The prodrugs on the other hand show 3 to 10 times high intestinal permeation, which is mediated by di and tripeptide (hPEPT1) membrane transporters. Following membrane transport, the active drug is released by intracellular hydrolysis. Levodopa is a substrate for neutral amino acid transporter (LAT1) at the BBB. After penetrating the BBB, levodopa is decarboxylated to dopamine, which can act locally, as it is no longer a substrate for amino acid transporter. Other prodrug examples in this category are midodrine (hPEPT1) and XP13512 (MCT1 and SMVT).

Passively targeted prodrugs are also being investigated in clinical trails.[75,76] For example, anticancer prodrugs have been obtained by conjugating (covalent attachment) larger molecules (synthetic or biopolymers) or micro/nanoparticles (liposomes, nanospheres) to active drugs. These macromolecules or particles do not interact with the target tumor cells but strongly influence the drug biodistribution due to the EPR effect. Examples of passively targeted prodrugs and prodrug systems used in advanced passive targeting strategies such as PDEPT and PLEPT have been described earlier (see section Targeted Drug Delivery).

Controlled Drug Delivery

The drug concentration in the plasma does not remain constant and follows a “sawtooth” kinetic profile, where the drug concentration fluctuates between maximum and minimum (Fig. 23-19). As a result, the drug level may rise too high

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leading to toxic side effects or fall too low resulting into the lack of efficacy. Frequent dosing is therefore needed to maintain therapeutically effective plasma drug level, more so for drugs with short half-lives, which is likely to result into toxic side effects and poor patient compliance. Using controlled drug delivery, which involves delivering drug either locally or systemically at a predetermined rate, undesirable fluctuation of drug levels in plasma can be avoided. Designing a controlled drug delivery system requires simultaneous consideration of several factors[2b,3,80] such as the nature of disease and therapy (acute/chronic), drug property, route of drug administration, nature of delivery vehicle, mechanism of drug release, targeting ability, and biocompatibility. It is not easy to achieve all these in one system due to their extensive interdependency. Besides, reliability and reproducibility are also crucial to successful designing of delivery systems12

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Ideally the controlled drug delivery system should be inert, biocompatible, mechanically strong, convenient for the patient, capable of achieving high drug loading, safe from accidental drug release, simple to administer and remove, and easy to fabricate and sterilize.

Table 23-3 Food and Drug Administration–Approved Prodrugs

	Prodrug/Product Name	Chemical Modification	Drug Release Mechanism/Location	Drug Name	References*
1	Valacyclovir (Valtrex)	L-Valyl ester	First-pass metabolism, esterases/intestine, liver	Acyclovir	*a*
2	Valganciclovir (Valcyte)	L-Valyl ester	First-pass metabolism, esterases/intestine, liver	Ganciclovir	*b*
3	Azidothymidine (Zidovudine)	Thymidine analogue	Phosphorylation by kinases/infected and uninfected cells	Zidovudine triphosphate	*c*
4	Capecitabine (Xeloda)	*N*4-pentyloxycarbonyl-5′-deoxy-5-fluoro-cytidine	Thymidine phosphorylase/tumor tissues	5-Fluorouracil	*d*
5	Famciclovir (Famvir)	Diacetyl 6-deoxy derivative	Deacetylation followed by oxidation at the 6 position/liver	Penciclovir	*e*
6	Nabumetone (Relafen)	4-(6-Methoxy-2-naphthyl)-butan-2-one	First-pass metabolism/liver	6-Methoxy-2-naphthyl acetic acid (6-MNA)	*f*

7	Pivampicillin (Pondocillin)	Ester	Nonspecific esterases/gastrointestinal tract	Ampicillin	*g*
8	Irinotecan (Camptosar)	7-Ethyl-10[4-(1-piperidino)-1-piperidino] carbonyloxycamptothecin	Human carboxylesterase/liver	SN-38	*h*
9	Terfenadine (Seldane)	Alkyl derivative	Cytochrome P-450 3A4/hepatic first-pass metabolism	Fexofenadine (Allegra)	*i*
10	Enalapril (Vasotec)	Ester	Hydrolysis by esterase/liver	Enalaprilat	*j*
11	Ramipril (Altace)	Ester	Esterase/liver	Ramiprilat	*k*
12	Dipivefrin (Propine)	Pivalic acid ester	Esterase/human eye	Epinephrine	*l*
13	Omeprazole (Prilosec)	Sulfonamide	Cytochrome P-450/parietal cells	Omeprazole/hfill Sulfonamide	*m*
14	Sulfasalazine (Azulfidine)	Azo modification	Bacterial azo reduction/colon	5-Aminosalicylic acid	*n*

15	Olsalazine (Dipentum)	Azo modification	Diazo-bond cleavage by colonic microflora/colon	5-Aminosalicylic acid	*o*
16	Methenamine (Urex)	Hexamethylenetetramine	Chemical hydrolysis/urine	Formaldehyde	*p*
17	Bambuterol (Bambec)	bis-Dimethylcarbamate	Oxidative metabolism/liver	Terbutaline	*q*
18	Allopurinol (Zyloprim)		Oxidative metabolism/liver	Oxypurinol	*r*
19	Gemcitabine (Gemzar)	Dephosphorylated form	Cellular kinases/deoxycytidine kinase	Triphosphate	*s*
20	Fludarabine (Fludara)	Dephosphorylated form	Cellular kinases/deoxycytidine kinase	Triphosphate	*t*
21	Cladribine (Leustatin)	Dephosphorylated form	Cellular kinases/deoxycytidine kinase	Triphosphate	*u*
22	Simvastatin (Zocor)	Lactone	Biotransformation/liver	β-hydroxy acid	*v*
2	Tegafur	Dehydroxylat	Cytochrome	5-	*w*

3	(Ftorafur)	ed form	P-450, thymidine phosphorylase/liver, cytosol	Fluorouracil	

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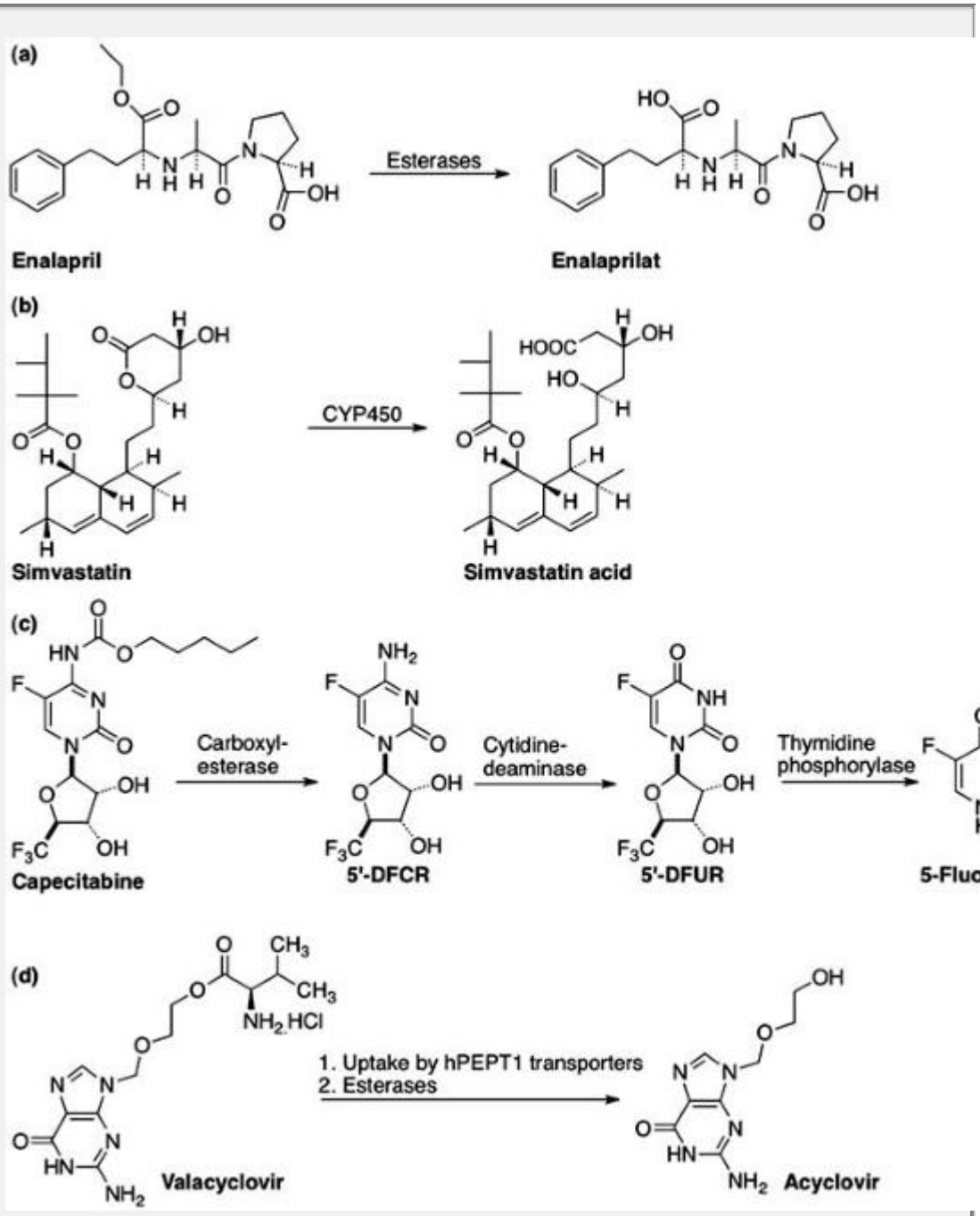

Fig. 23-18. Prodrug activation of (*a*) enalapril, (*b*) simvastatin, (*c*) capecitabine, and (*d*) valacyclovir.

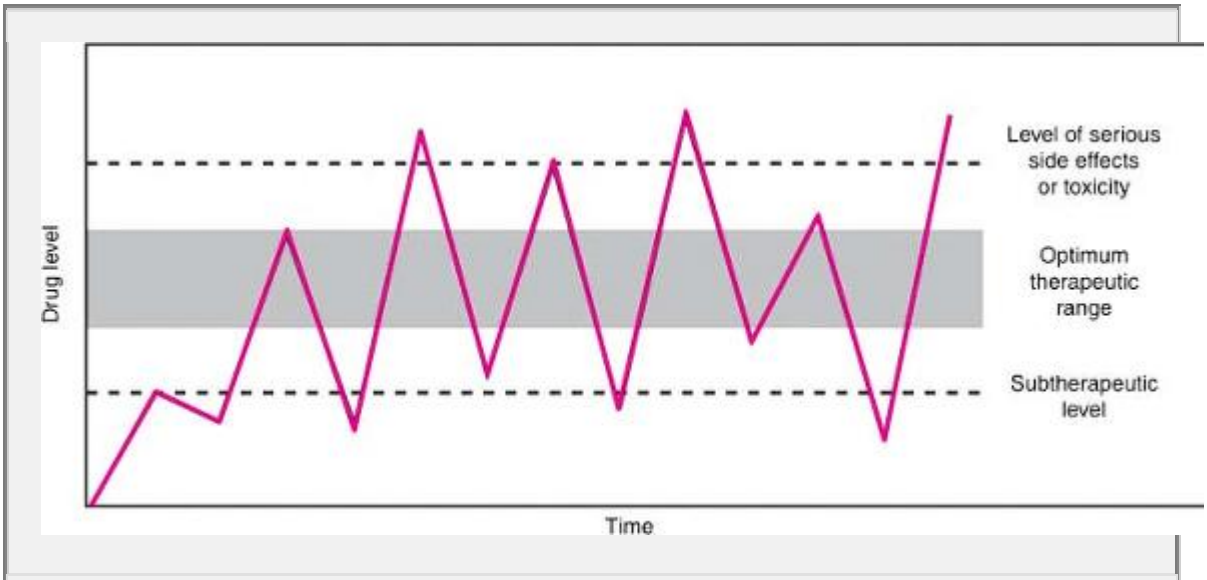

Fig. 23-19. The sawtooth kinetic profile obtained after normal dosing and optimum therapeutic profile obtainable with controlled-delivery devices.

Advantages of controlled drug delivery are that fluctuations in drug plasma level associated with conventional dosage forms are avoided and therapeutic drug concentration is maintained, which leads to more effective therapies with lesser side effects. Fewer doses are required resulting into improved patient compliance. While the therapeutic considerations are prime driving force for the development of drug delivery systems, there are economic considerations too.[2b,3,80] Once the patent on the new drug has expired (20 years), the pharmaceutical company responsible for its discovery starts loosing its market share to generic competitors, which supply the same drug at lower prices. Repackaging the drug in a new delivery system allows the company to extend the patent life of its product. The disadvantages on the other hand are higher costs compared to conventional formulations, possible toxicity or nonbiocompatibility of the material used, and undesirable by-products. More importantly, many controlled drug delivery systems are invasive and require surgical intervention for their insertion and removal from the body.

Types of Controlled Drug Delivery

Drug release from a controlled drug delivery system is of three types: zero-order, variable, and bioresponsive[2b,80] (Fig. 23-20).

1. **Zero-order release.** The drug release does not vary with time and relatively constant drug level is maintained in plasma over an extended period of time. Since the typical “sawtooth” kinetic profile is not obtained, the risk of drug achieving toxic peak plasma level is abated and so is the possibility of symptom breakthrough resulting from drop in drug plasma level.
2. **Variable release.** The drug is released at variable rates to match circadian rhythms or mimic natural biorhythms. It is characterized by an episodic increase in drug concentration followed by a “rest” period, where drug level falls below the therapeutic level. It may also be fluctuating or pulsatile (release pulses at predetermined lag times). Variable release is used in situations where changing level of response is needed. For example, in hypertension, blood pressure is lower in the night but increases in the early morning, and consequently maximum drug levels are needed in the early morning. Similarly in nocturnal asthma, bronchoconstriction is worse at night.
3. **Bioresponsive release.** The drug release is triggered by biological stimulus like changes in pH, temperature, or concentration of certain biologically active substances12

Blood glucose level triggering the release of insulin from a drug delivery system is an example of bioresponsive release.

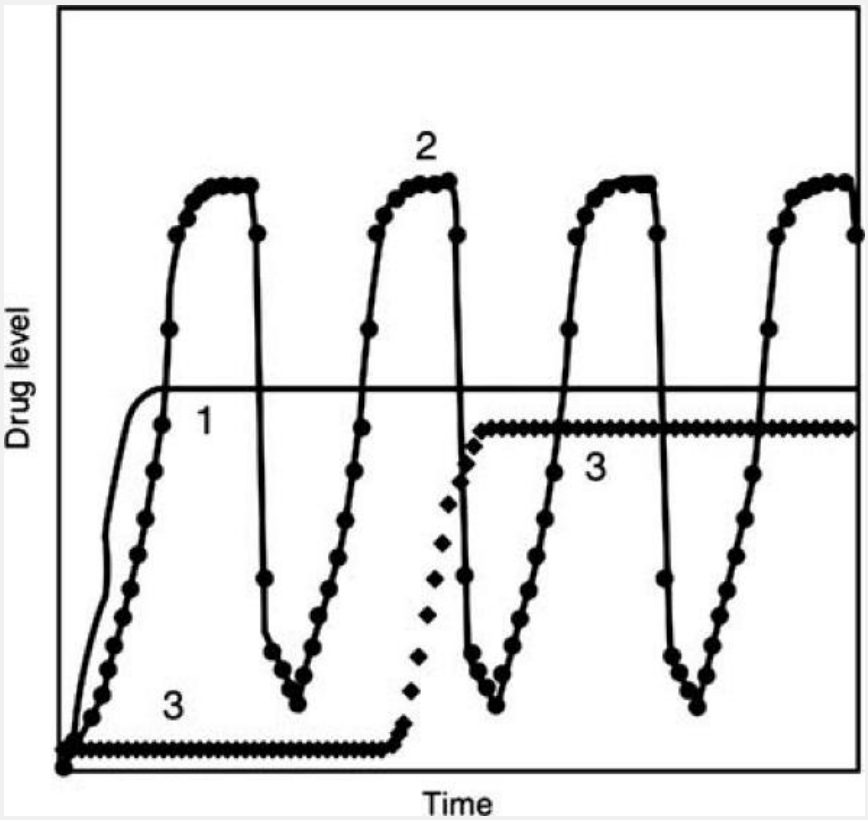

Fig. 23-20. Typical kinetic profiles obtained from controlled drug delivery systems: (1) zero-order, (2) variable, and (3) bioresponsive.

Mechanisms of Controlled Drug Delivery

Only a small number of mechanisms are involved in the drug release from a controlled drug delivery system[2b,80]: (1) diffusion controlled release mechanism, (2) dissolution controlled release mechanism, (3) osmosis controlled release mechanism, (4) mechanical controlled release mechanism, and (5) bioresponsive controlled release mechanism. Any or all of the above mechanisms may be involved in the drug release from the system.

1. **Diffusion controlled release mechanism.** The drug is released by diffusion through either a polymeric membrane or a polymeric/lipid matrix (Fig. 23-21). Diffusion controlled devices could be grouped into two categories: reservoir devices and matrix devices. In reservoir devices, the drug is surrounded by a rate controlling polymer membrane (nonporous, microporous). The rate of diffusion follows Fick's law and depends on partition and diffusion coefficients of the drug in the membrane, the available surface area, the membrane thickness, and the drug concentration gradient. If the drug concentration gradient remains constant, zero-order drug release is attained. Examples include Norplant subdermal implant (parenteral), Vitrasert intravitreal and Ocusert implant (ocular), Transderm-Scop transdermal patch system and

Catapres-TTS transdermal system (transdermal), and Cervidil vaginal insert and Estring vaginal ring (vaginal).

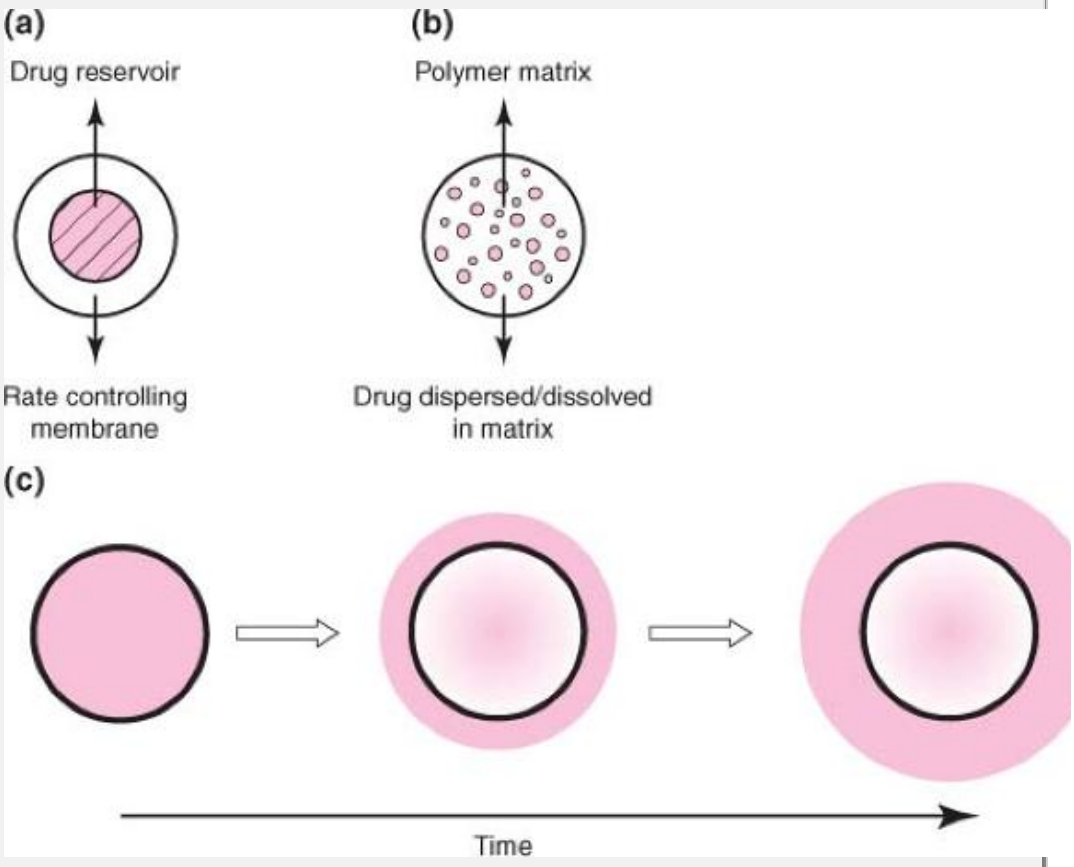

Fig. 23-21. Diffusion controlled controlled-delivery devices: (*a*) reservoir and (*b*) matrix. (*c*) Drug diffusion from a homogeneous controlled drug delivery system. (Modified from H. Sah et al., Drug Delivery and Targeting for Pharmacist and Pharmaceutical Scientists, CRC Press, Boca Raton, FL, 2001, pp. 83.)

2. In matrix (monolith) devices, the drug is distributed throughout a continuous phase composed of polymer or lipid. As release continues, the rate of drug release decreases with square root of time. This decrease in drug release is due to the fact that as the drug present at the surface is being released, the drug present in the center of the matrix has to migrate longer distances for release, which takes more time. Such devices usually do not provide zero-order release. Polymeric controlled release microspheres represent an example of a matrix-controlled release system.81 Commercial examples are Compudose cattle growth implant (parenteral) and Deponit transdermal patch (transdermal).
3. **Dissolution controlled release mechanism.** The drug release is controlled by dissolution rate of employed polymer. Similar to diffusion controlled devices, dissolution controlled devices are also either the reservoir type or the matrix type. Since the drug release is dissolution controlled, the polymer must be water soluble and/or degradable. In reservoir devices, the release is controlled by the thickness and/or the dissolution rate of polymer membrane surrounding the drug core. Once the coating is dissolved, the drug is available for dissolution and absorption. Polymer coatings of different thickness can be employed to delay the drug release for certain

period of time. Such systems are used for zero-order oral drug delivery and examples include Spansule, Sequel, and SODAS capsules.

In matrix-type devices, on the other hand, the drug release is controlled by the dissolution of matrix and decreases with time due to the decrease in the size of the matrix. Examples of matrix dissolution devices are goserelin (Zoladex) subcutaneous implant comprising

poly(lactide-co-glycolide) or PLGA matrix system for goserelin delivery and leuprolide (Lupron) depot comprising PLGA microsphere for parenteral goserelin delivery.

4. **Osmosis controlled or active efflux controlled release mechanism.** Osmosis is defined as diffusion of water through a semipermeable membrane from a solution of low concentration (hypotonic) to a solution of high concentration (hypertonic) resulting into an increase in the pressure of the solution. The pressure difference is termed as osmotic pressure and defined as pressure required for maintaining equilibrium, with no net movement of water. Osmotic pressure can be used to deliver drug at a constant rate, and device and formulation parameters can be controlled to obtain zero-order release. Osmotic pressure is a colligative property and therefore depends only on molar concentration of solute and not its identity. An important consequence is that osmosis controlled devices operate independently of environmental factors. Examples include osmotic mini pumps from Alza Corporation used in experimental animal studies, DUROS implant pump for controlled delivery of peptides and proteins, and Oros osmotic pump for oral delivery. Commercial examples are nifedipine (Procardia XL) and chlorpheniramine (Efidac 24).
5. **Mechanical controlled release mechanism.** Mechanically driven pumps used for drug administration in hospital settings. These pumps can be programmed to achieve zero-order or intermittent release.
6. **Bioresponsive controlled release mechanism.** Drug is released in response to changes in the external environment. The external stimulus could be a change in pH or ionic strength, which might cause drug release by influencing the swellability of polymeric delivery systems. Similarly, there are systems incorporating enzymes, which may cause localized change in pH or substrate (e.g., glucose) concentration to trigger drug release by causing change in swelling or permeability of polymeric systems.

Examples of Controlled Drug Delivery Systems

The characteristic features of implants and Oros osmotic pump are provided below. More examples are discussed in later sections of this chapter.

Implant

An implant is a single unit drug delivery system designed for delivering drug at predetermined rate over an extended period of time.[2b,3,80] It is available in many forms and the two most frequently used implants are (*a*) polymeric implant made of either nondegradable or biodegradable polymer (available in shapes like rod, cylinder, ring, film etc.) and (*b*) minipumps powered by osmotic pressure or mechanical force. Usually, an implant is placed (implanted) subcutaneously into the loose interstitial tissues of the outer surface of the upper arm or the anterior surface of the thigh or the lower portion of the abdomen. Implants may also be surgically implanted in places like the vitreous cavity of the eye or intraperitoneally. Implants have been mostly used for sustained parenteral administration, including ocular and subcutaneous drug delivery.

Polymeric implants are made from either nondegradable or degradable polymers. Examples of nondegradable polymers used in implants include silicone rubber, silicone– carbonate copolymers,

poly(ethylene-vinyl acetate), polyethylene, polyurethane, polyisoprene, polyisobutylene, polybutadiene, polyamide, polyvinyl chloride, plasticized soft nylon, hydrogels of polyhydroxyethyl methyl acrylate, polyethylene oxide, polyvinyl alcohol, polyvinyl pyrrolidone, cellulose esters, cellulose triacetate, cellulose nitrate, modified insoluble collagen, polyacrbonates, polysulfonates, polychloroethers, acetal polymers, and halogenated polyvinylidene fluoride. Implants such as Norplant subdermal and Vitrasert are made from nondegradable polymers such as dimethylsiloxane/methylvinylsiloxane copolymer (containing levonorgestrel) and poly(vinyl alcohol)/poly(ethylene-co-vinyl acetate), respectively.
Implants are also made of degradable polymers. Degradation is achieved by either biodegradation or bioerosion. Biodegradation is the degradation of polymer structure by chemical or enzymatic processes, whereas bioerosion is gradual dissolution of polymer matrix. Bioerosion can be of two types: (*a*) bulk erosion and (*b*) surface erosion. In bulk erosion the entire polymer matrix is subject to chemical or enzymatic processes whereas in surface erosion, polymer degradation is limited to the surface of implant exposed to the medium, and therefore takes place layer by layer. Polymers in biodegradable implants are either water soluble and/or degradable in water. The water-soluble polymers are PAA, PEG, and poly(vinyl pyrrolidone), whereas degradable polymers include poly(hydroxy butyrate), poly(lactide-co-glycolide), poly(orthoesters), poly(caprolactone), and polyanhydrides. Naturally occurring biodegradable polymers are proteins (albumin, casein, collagen, and gelatin) and polysaccharides (cellulose, chitin, dextran, hyaluronic acids, insulin, and starch). Zoladex implant and Lupron depot are made of PLA/PLGA, whereas Gliadel is poly[bis(p-carboxyphenoxy propane: sebacic acid in 20:80 ratio.
There are mechanical implants too and a very recent example is Medtronic IsoMed Constant-Flow Infusion system. The system was approved for (*a*) delivering chemotherapy (floxuridine) in hepatic arterial infusion therapy for patient with colorectal liver cancer and (*b*) delivering morphine to the spinal fluid for patient with chronic intractable pain. The implant comprises two basic parts: (*a*) pump made of an outer round titanium shell (biocompatible) with a silicone rubber septum containing a drug reservoir (20, 35, and 60 mL) and (*b*) catheter made of silicone rubber tube, which is tunneled under the skin to the site of action for delivering drug from the pump. The whole pump is about 3-inches wide and weighs 6 oz with standard flow rates of 0.5, 1.0, and 1.5 mL/day. The reservoir is surrounded by a propellant, which forces the drug content through the catheter to the site of the delivery and can be refilled. The pump is implanted surgically in

the abdomen and the catheter is placed in blood in case of chemotherapy and within the sheath around the spinal cord for pain relief. The system is ideal for patients with stable dosing requirements. Other examples of mechanical implants are SynchroMed pumps for chemotherapy (floxuridine, doxorubicin, cisplatin, methotrexate), intractable cancer pain (morphine sulfate), osteomyelitis (clindamycin), and spasticity therapy (muscle relaxant baclofen); MiniMed insulin pumps; and Arrow pumps (floxuridine, morphine sulfate, baclofen, heparinized saline).

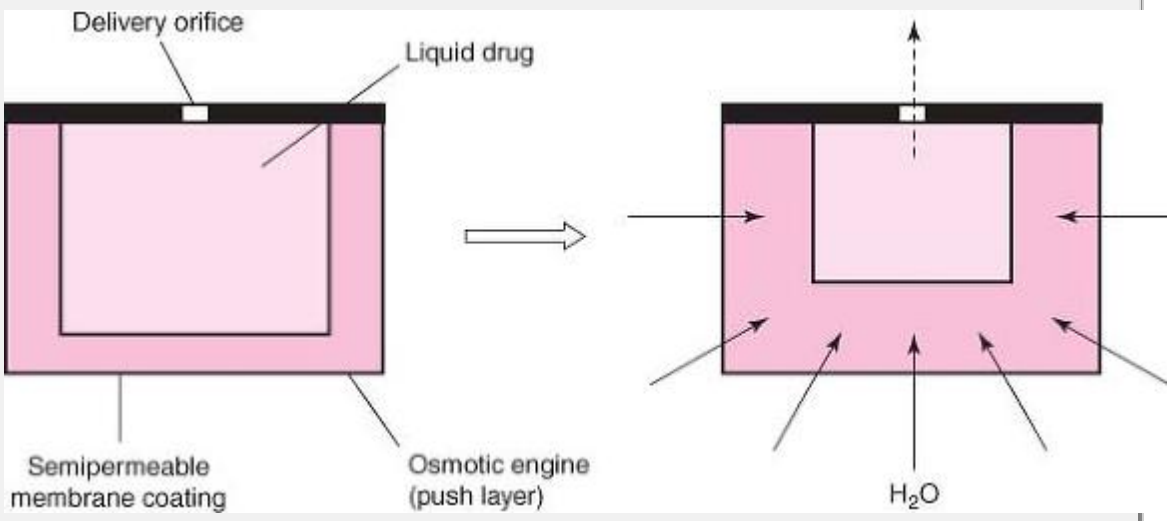

Fig. 23-22. Schematic representation of L-OROS osmotic drug delivery system. The drug is liberated through the small orifice due to the osmosis of fluids through the semipermeable membrane into the osmotic push layer.

Implants are more convenient because they eliminate the need for continuous intravenous infusion or injections for maintaining the drug concentrations and they improve patient compliance by reducing or eliminating the patient-involved dosing. Implants are capable of providing controlled drug release and deliver drug either locally or directly to systemic circulation bypassing the GI tract and liver. Implants are considered new drug product and therefore provide patent exclusivity of 5 years to new drugs and 3 years to existing drugs. However, implants are invasive and require surgical interventions. If not degradable, they have to be retrieved from the body, and if degradable, it is difficult to terminate the drug delivery. Invasiveness is probably the most serious limitation associated with implants. Danger of device failure, possibility of adverse reactions, and biocompatibility are other concerns. Developing implants is highly cost-intensive and therefore limited to only potent drugs.

Osmotic Pump

The elementary osmotic pump, also known as Oros or the GI therapeutic system, was first described by Theeuwes and Yum82'83and introduced by Alza Corporation. The system is composed of core tablet surrounded by a coating of semipermeable membrane containing a laser-created hole (orifice). The core tablet contains two layers, one with drug and the other with the electrolyte. When the tablet is swallowed, a semipermeable membrane permits the entry of fluid from the stomach and intestines to the tablet, which dissolves/suspends the drug. As pressure increases due to the movement of water, drug is pumped out of the orifice. Only the drug solution is able to pass through the orifice and the system is so designed that only few drops of water are drawn in the tablet every few hours. Drug delivery is controlled by osmotic gradient between the contents of the core tablet and fluids in the GI tract. Surface area, thickness or composition of membrane, and diameter of orifices are altered to control the drug delivery rate. Other systems based on this technology are L-Oros softcap and hardcap systems (Fig. 23-22).
In L-Oros softcap, the drug formulation is encased in a soft gelatin capsule surrounded by a barrier layer, an osmotic engine, and a semipermeable membrane. The barrier layer separates the soft gelatin capsule from the osmotic engine, thus minimizing its hydration and mixing with the drug layer. In the L-Oros hardcap system, the drug layer and osmotic engine are encased in a hard capsule surrounded by the semipermeable membrane. Drug release of about 2 to 24 hr is obtained. Other examples in this category are nifedipine (Procardia XL) and Efidac 24.

Example 23-5
Elementary Osmotic Pump

Theeuwes84 first tested the elementary osmotic pump for drug delivery using potassium chloride to serve as both the osmotic agent and the drug model. In a later report, Theeuwes et al.85 designed a therapeutic system based on the principle of the osmotic pump to deliver indomethacin at a constant zero-order rate. For zero-order rate, these workers used following equation:

$$\left(\frac{dM}{dt}\right)_z = \frac{S}{h}k'\pi_s C_s \qquad (23\text{–}17)$$

where $(dM/dt)_z$ is the rate of delivery of the solute under zero-order conditions, S is the semipermeable membrane area (2.2 cm^2), h is the membrane thickness (0.025 cm), k' is a permeability coefficient, 2.8×10^{-6} cm^2/atm hr, and $\pi_s$is the osmotic pressure, 245 atm, of the formulation under zero-order conditions (saturated solution) ($k'\pi_s = 0.686 \times 10^{-3}$ cm^2/hr). The concentration of the saturated solution,C_s, at 37°C is 330 mg/cm^3. The zero-order delivery rate for this system is calculated as follows:

$$\left(\frac{dM}{dt}\right)_z = \left(\frac{2.2\,\text{cm}^2}{0.025\,\text{cm}}\right)(0.686 \times 10^{-3}\,\text{cm}^2/\text{hr})(330\,\text{mg/cm}^3)$$

$$\left(\frac{dM}{dt}\right)_z = 19.9\,\text{mg/hr}$$

Some of the drug is released from the device by simple diffusion through the membrane. Equation (23-17) should therefore be modified as follows:

$$\left(\frac{dM}{dt}\right)_z = \frac{S}{h}k'\pi_s C_s + \frac{S}{h}PC_s$$

or

$$\left(\frac{dM}{dt}\right)_z = \frac{S}{h}(k'\pi_s + P)C_s \qquad (23\text{–}18)$$

where P is the permeability coefficient for passage of KCl across the semipermeable membrane ($0.122 \times 10^{-3}$$cm^2$/hr).
We have following:

$$\left(\frac{dM}{dt}\right)_z = \left(\frac{2.2\,\text{cm}^2}{0.025\,\text{cm}}\right)(330\,\text{mg/cm}^3)(0.686 \times 10^{-3}\,\text{cm}^2/\text{hr} + 0.122 \times 10^{-3}\,\text{cm}^2/\text{hr})$$

$$\left(\frac{dM}{dt}\right)_z = 23.5\,\text{mg/hr}$$

The time, t_z, in which the mass of the drug, M_z, is delivered (disregarding the start-up time required to reach equilibrium) is

$$t_z = M_t\left(1 - \frac{C_s}{\rho}\right)\frac{1}{dM/dt} \qquad (23\text{–}19)$$

where M_t is the total mass of drug in the core (500 mg KCl) and ρ is the density of the drug (2 g/cm^3 or 2000 mg/cm^3):

$$t_z = (500\,\text{mg})\left(1 - \frac{330\,\text{mg/cm}^2}{2000\,\text{mg/cm}^3}\right)\frac{1}{23.5\,\text{mg/hr}}$$

$$t_z = 17.8\,\text{hr}$$

Beyond t_z, the drug is delivered under non–zero-order conditions.

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Drug Delivery Systems

Representative examples of drug delivery systems designed for different routes of drug delivery are described below.

Buccal Drug Delivery Systems

Most of the buccal drug delivery systems are designed to overcome two major limitations: (*a*) low flux and (*b*) the lack of drug retention at the site of absorption, which is due to the saliva produced by the salivary glands. The major determinant of the salivary composition is its flow rate, which is influenced by

the time of day, the type of stimulus, and the degree of stimulation. The salivary pH ranges from 5.5 to 7, but at high flow rates, the sodium and bicarbonate concentrations increase, which further increases the salivary pH. The daily salivary volume is between 0.5 and 2 liters, which is enough to clear the released drug. Hydrophilic polymeric matrices are used for oral transmucosal drug delivery systems. Some drug delivery systems are discussed below.

Polymers

Bioadhesive (mucoadhesive when the substrate is mucosal tissue) polymers are capable of adhering onto a biologic substrate. Diverse classes of polymers have been investigated for their potential use as mucoadhesives. Examples include synthetic polymers like polyacrylic acid, hydroxypropyl methylcellulose, polymethacrylate derivatives, polyurethanes, epoxy resins, polystyrene, and naturally occurring polymers such as cement, hyaluronic acid, and chitosan.14 *Chitosan* is derived from a material called chitin, which is an amino polysaccharide extracted from the powdered shells of crustaceans like shrimps and crabs. Chitosan is similar to cellulose in chemical structure, a plant fiber, and has many of the same properties, except that chitosan is positively charged and actively attracts fat. Chitosan works like a “pollution magnet” to soak up pollutants and make them easier to remove. It is bioadhesive and binds to the mucosal membrane, prolonging retention time of the formulation on the mucosa.

Gels

The dosage forms designed for buccal administration should not cause irritation and they should be small and flexible enough to be accepted by the patient. Gels meet these requirements. Gels are hydrophilic matrices that are capable of swelling in water, without loosing their shape.86 When drug-loaded gels are placed in water, chain relaxation occurs due to the swelling, and the drug is released through the spaces or channels within the gel network. Examples include natural gums and cellulose derivatives. These “pseudohydrogels” swell, and the component molecules dissolve from the surface of the matrix. Drug release occurs through the spaces or channels within the network as well as through the dissolution and/or the disintegration of the matrix. A buccal mucoadhesive device (copolymer hydrogel disk) was developed for the controlled release of buprenorphine.87 The device was applied for a 3-hr application time, and steady-state levels were maintained during the time of application. In general, mucoadhesive oral drug delivery systems are used for both sublingual and buccal drug delivery. They provide an onset of drug action in 1 to 3 min and duration of about 30 min to 5 hr for sublingual and buccal drug delivery systems, respectively.

Adhesive Patches: Systemic Mucosal Delivery

Adhesive patches for mucosal sustained release consist of an impermeable backing layer and a mucoadhesive polymer layer containing the drug (Fig. 23-23a). The shape and size varies depending on the site of administration: the buccal, sublingual, or gingival mucosa. The duration of mucosal adhesion depends on the polymer type and the viscosity of the polymer used. The release of the drug is controlled by the dissolution kinetics of the polymer carrier rather than the drug diffusion out of the polymer.

Adhesive Patches: Local Oral Delivery

Adhesive patches for local oral sustained release generally consist of three layers (Fig. 23-23b): the upper layer of a nonadhesive and flavored waxy material containing the drug, the middle layer prepared from antiadhesive material

(magnesium stearate), and the lower layer designed for adhering to the oral mucosa. This three-level device sustains a constant saliva level of drugs, usually anti-infective drugs, over a 3-hr period.14

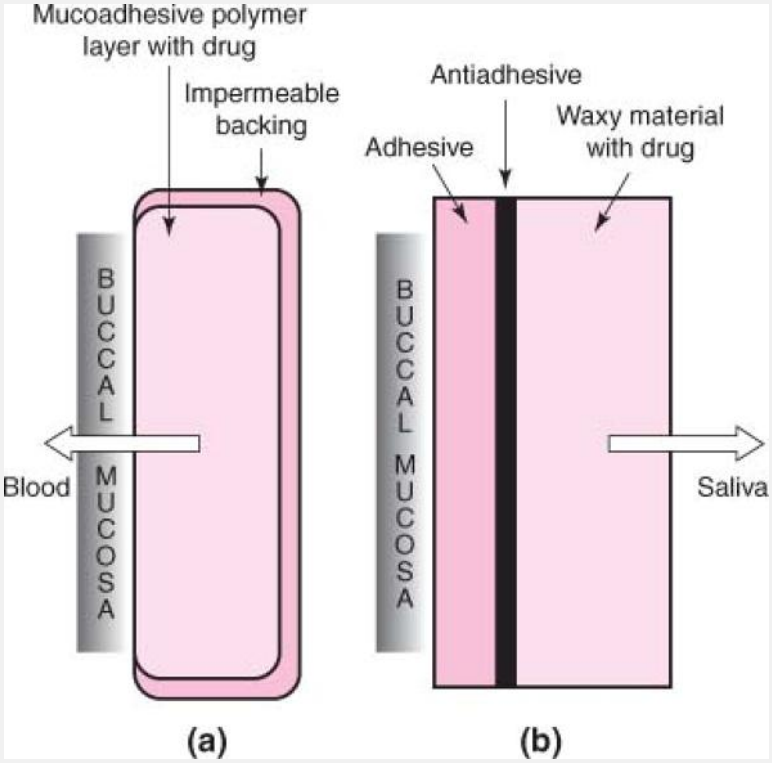


Fig. 23-23. Adhesive patches for drug delivery: (*a*) systemic mucosal and (*b*) local oral.

The buccal mucosa offers several advantages for controlled drug delivery: (*a*) the mucosa is well supplied with both vascular and lymphatic drainage; (*b*) first-pass intestinal/hepatic metabolism and presystemic degradation in the GI tract are avoided; (*c*) the area is well suited for a retentive device and is usually acceptable to the patient; and (*d*) with the right DDS design, the permeability and the local environment of the mucosa can be controlled and manipulated to accommodate drug permeation.

Pulmonary Drug Delivery Systems

Aerosols are widely used to deliver drugs in the respiratory tract. The deposition mechanism of the particles depends on the inhalation regime, the particle size, shape, density, charge, and hygroscopicity. The size of solid particles or liquid droplets in aerosols normally ranges from 1 to 10 μm and expressed as the *aerodynamic diameter,* $d_{ae} = \rho^{½}d$, where ρ is the density of the particle and d is the observed diameter. The particles are delivered via mouth inhalation to bypass the nasopharyngeal cavity and the total retention of particles is only between 50% and 60% of the administered dose.

Liquid jets and ultrasonic nebulizers, metered-dose inhalers (MDIs) (Fig. 23-24), and breath-activated dry powder inhalers (DPIs) have proved useful in the management of asthma.

Nebulizers

These are the device for converting drug solution or suspension into an aerosol suitable for inhalation. There are different types of nebulizers, but the most common are *air jet nebulizers*, which are connected to compressed air source that causes air and oxygen to blast through the solution at high velocity, converting them into an aerosol. Another category is *ultrasonic nebulizers* where high-frequency waves are used to create vertical capillaries of drug solution, which breaks up at high energy to provide an aerosol. Nebulizers generate small particles with high delivery capacities but suffer from inconvenience, long inhalation time, and poor dose control. They have been used for the delivery of insulin (diabetes), penicillin (lung infection), isoprenaline and hydrocortisone (asthma), and DNAse and tobramycin (cystic fibrosis).

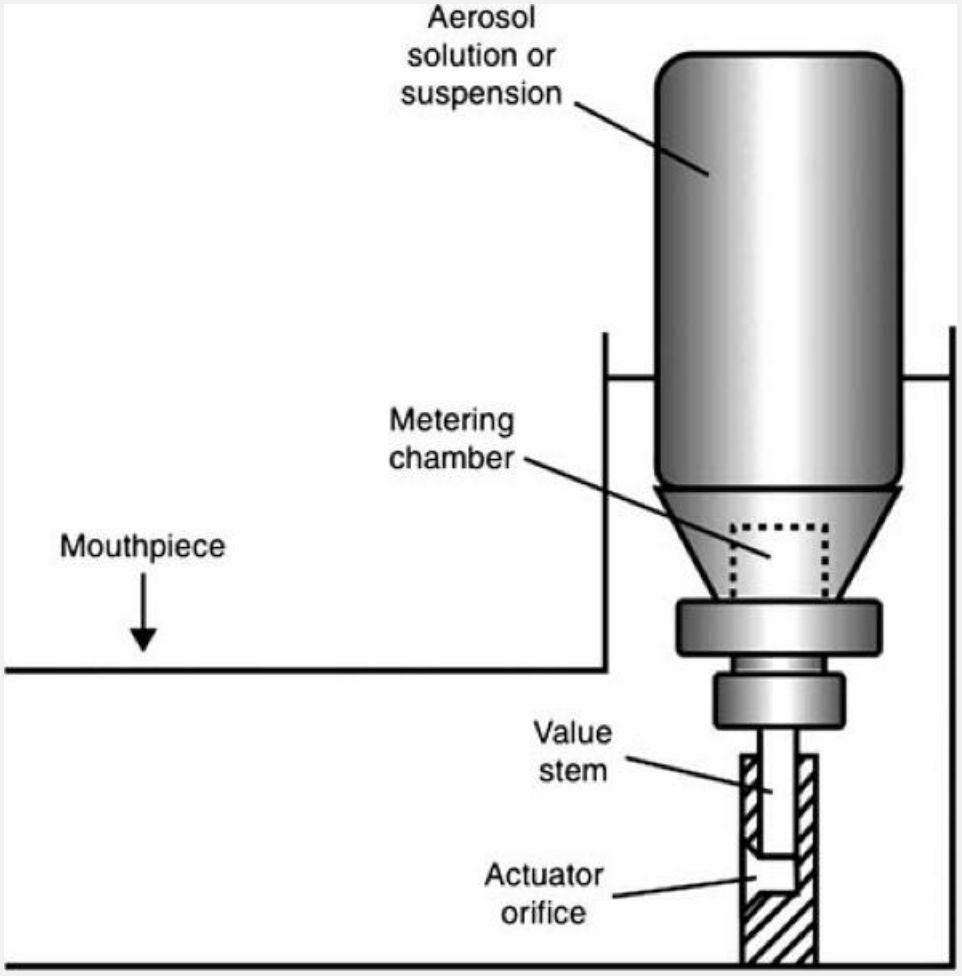


Fig. 23-24. Metered-dose inhaler (MDI) for pulmonary and nasal drug delivery. (Modified from P. R. Byron (Ed.), *Respiratory Drug Delivery*, CRC Press, Boca Raton, Fl, 1990, p. 171.)

Pressurized Metered-Dose Inhalers (MDIs)

MDIs have drug solution or suspension in a volatile propellant. They are equipped with metering valves in conjunction with a propellant and therefore provide multiple dosing capabilities. A typical unit contains a container (10 mL), metering valve (for releasing drug volumes in the range of 25–100 μL), elastomer seal (critical to valve performance), and actuator (propellant). MDIs have been used for delivering albuterol (asthma).

Dry Powder Inhalers (DPIs)

DPIs deliver the drugs to the airways as a dry powder aerosol. They are mostly breath-actuated; a cloud of drug powder (aerosol) is produced in response to patient's breathing. Use of DPIs avoids coordination problems and there is a lower drug loss, but they are associated with problems such as requirement of high inspiratory effort from patient and more inconvenient coughing reflexes as compared to other devices. DPIs have been used for the delivery of noradrenaline and terbutaline (asthma) and insulin (diabetes).

The use of lungs for the delivery of peptides and proteins, which are otherwise injected, is possibly the most

exciting development in pulmonary delivery.88 Lungs provide higher bioavalabilities for macromolecules than any other noninvasive route of delivery. However, unlike the smaller molecules, which undergo minimal metabolism in lungs, macromolecules (unless modified) are subject to enzymatic hydrolysis. As the molecular mass increases, possibility of enzymatic hydrolysis is decreased or even eliminated, which significantly increases the bioavailability.88 After 15 years of development effort, inhaled human insulin was approved in Europe and United States for the treatment of diabetes in adult (insulin inhalation [Exubera, Pfizer]).88 It has been reported that 4% of the insulin dose reaches the deep lung after the inhalation of single dose and it maintains effective glycemic control comparable to subcutaneously administered fast-acting insulin for type 1 and 2 diabetes. Exubera consists of blisters containing human insulin powder, which are administered using the Exubera inhaler (DPI) before each meal. Each unit dose blister contains 1 to 3 mg of insulin along with the excipients. After the blister is inserted into the inhaler, the patient pumps the handle of the inhaler and then presses a button, causing the blister to be pierced. The insulin inhalation powder (aerosol) is then dispersed into the chamber, which is inhaled by the patient. A major problem associated with this device is inability to delivery precise insulin doses. The product was withdrawn, reasons cited being commercial rather than safety. The key challenge for pulmonary drug delivery is to provide drug penetration deep into the lung to the smaller airways and the alveoli. The aerosol formulations are unable to move the medication into the deep lungs. The lungs are endowed with a sophisticated defense system that protects the body from the penetration of exogenous particles (Table 23-4**)**. Upper airways provide filtering mechanisms that trap and eliminate particles with size >10 μm. Two reflexes, sneezing and coughing, also eliminate large foreign particles. Mucovisciliar transport in conducting airways removes smaller particles out of the respiratory tract into the mouth. In addition, immunoglobulins produced by plasma cells in the submucosa help fight against infections. Alveolar macrophages and neutrophils provide a defense against the smallest foreign matter that penetrates into the gas exchange area of the respiratory system.

Table 23-4 Defense Mechanisms of the Lung

In the upper airways
Filtering mechanisms in the nasal cavity trap and eliminate larger particles (>10 μm)
Two reflexes: sneezing and coughing
In conducting airways
Mucociliary escalator, immunoglobulin A, produced by the plasma cells in the submucosa
In alveoli
Alveolar macrophages with some interplay with and by neutrophils

Immunologic mechanisms: interplay between the alveolar macrophages and T and B lymphocytes; immunoglobulin G

Larger particles (>10 μm) are either filtered in the nose or impacted in the nasal and oral pharynx and cleared by coughing or sneezing. Consequently, drug delivery systems of such size do not penetrate further. Moderate-size particles (5–10 μm) are trapped in a mucous blanket in the conducting airways and move cephalad (i.e., toward the head) by ciliary action (cilia move only in the cephalad direction). At the level of the larynx they are either swallowed or expectorated. Small particles of aerodynamic diameter (<2 μm) can penetrate into the lower airways (e.g., bronchial and alveolar regions) and can be phagocytosed by alveolar macrophages. Therefore, submicron-size drug delivery systems can be used for drug delivery to lower airways, alveoli, and systemic circulation through the gas–blood barrier (i.e., the alveolocapillary barrier). The duration of local therapeutic activity is a complex function of particle deposition, mucociliary clearance, drug dissolution or release (for solid aerosols), absorption, tissue sequestration, and metabolism kinetics.

Byron89 proposed a mathematical model for calculating drug residence times and dose fractions in the three functional regions of the respiratory tract: the nasopharyngeal, the tracheobronchial, and the alveolar. The deposition in the ciliated airways was largely unaffected by breath holding, and the particles showed a maximum d_{ae} between 5 to 9 μm (slow inhalation) and 3 to 6 μm (fast inhalation). Alveolar deposition was dependent on the mode of inhalation and breath holding. The latter is a common practice and allows deposition of small particles that otherwise would be exhaled. To determine the effect of breath holding on the deposition of particles, the *sedimentation efficiency*, *S*, was defined as

$$S = \frac{\text{Distance the particle falls during breath holding}}{\text{Mean regional airway diameter}} \qquad \textbf{(23–20)}$$

The mean regional diameters for the three areas considered are 5 cm for the mouth, 0.2 cm for the tracheobronchial region, and 0.073 cm for the alveoli. In cases where the sedimentation efficiency is greater than 1, *S* is assigned a value of unity. A total lung volume after inhalation, V_t, of 3000 cm^3 is divided into 30, 170, and 2800 cm^3 for the mouth (M), tracheobronchial (TB) region, and alveolary (P) region. For each particle size, the *exhaled dose fraction, E*, is given by

$$E = 1 - (f_M + f_{TB} + f_P) \qquad \textbf{(23–21)}$$

where the terms f_M, f_{TB}, and f_P stand for the respective fractional depositions in the three regions. During breath holding, additional fractions will sediment, depending on the sedimentation efficiency and the ratio of the regional volume to the total volume of the lungs. The *sedimentation dose fraction*, SDF, after breath holding is calculated from the expression

$$\text{SDF} = E\left(\frac{SV_r}{V_t}\right) \qquad \textbf{(23–22)}$$

where V_r is the regional volume of the M, TB, or P regions and V_t is the total volume after inhalation (3000 cm^3).

Example 23-6

Aerosol Deposition in the Lung

For a 3-μm monodisperse aerosol inhaled at 22.5 L/min, the fractional depositions were found to be $f_M = 0.04$, $f_{TB} = 0.14$, and $f_P = 0.55$. Compute the undeposited or exhaled fraction,*E*, and the additional sedimentation of the undeposited fraction in the mouth and tracheobronchial and alveolary regions after 10 sec of breath holding. The velocity of sedimentation of the particles is 0.027 cm/sec.

From equation (23-21) the undeposited (exhaled) fraction is

$$E = 1 - (0.04 + 0.14 + 0.55) = 0.27$$

After 10 sec of breath holding, the distance of particle fall is 10 sec × 0.027 cm/sec = 0.27 cm. Substitution of this value and the mean diameter of the alveolary (P) region in equation (23-20) gives the sedimentation efficiency in the pulmonary region, S_P:

$$S_P = \frac{0.27}{0.073} = 3.70$$

Because $S_P > 1$, a value of $S_P = 1$ is taken. From equation (23-22) the sedimentation dose fraction becomes

$$\mathrm{SDF_P} = 0.27 \times 1 \times \frac{2800}{3000} = 0.252$$

Analogously, for the tracheobronchial zone (mean diameter 0.2 cm), a value of $S_{TB} > 1$ is obtained, so S_{TB} is taken as equal to unity, and for the sedimentation dose fraction, one obtains

$$\mathrm{SDF_{TB}} = 0.27 \times 1 \times \frac{170}{3000} = 0.0153$$

For the mouth region, M, the mean diameter, is 5 cm, and so

$$S_M = \frac{0.27}{5} = 0.054$$

and

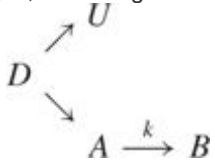
$$\mathrm{SDF_M} = 0.054 \times \frac{30}{3000} = 5.4 \times 10^{-4}$$

Thus, the total additional dose deposited after 10 sec of breath holding is

$$\mathrm{SDF} = \mathrm{SDF_P} + \mathrm{SDF_{TB}} + \mathrm{SDF_M} = 0.252 + 0.0153 + 5.4 \times 10^{-4} = 0.268$$

These results show that for 3-μm particles, breath holding is adequate for depositing particles in the alveolar region ($SDF_P = 0.252$), whereas breath holding is inadequate for depositing these particles in the mouth ($SDF_M = 0.00054$) and in the tracheobronchial region ($SDF_{TB} = 0.0153$).

Byron et al.90 studied the deposition and absorption of disodium fluorescein from solid aerosols having an aerodynamic diameter of 3 to 4 μm. The aerosols were administered for 20 min under different inhalation regimes (respiration frequency, RF, in cycles/min). The total dose administered, *D*, was divided into a transferable amount, *A*, which diffuses into the perfusate according to a first-order rate constant *k*, and an untransferable amount, *U*, according to the scheme.



Assuming instantaneous dissolution of *A* and first-order kinetics, the amount in the perfusate, *B*, at any time *t* is given by the product of perfusate concentration and volume. The amount transferred to *B*can be computed from*

$$B = \frac{A}{20\,\mathrm{RF}}\left[n - \frac{(1 - e^{-\frac{nk}{\mathrm{RF}}})e^{-\frac{k}{\mathrm{RF}}}}{1 - e^{-\frac{k}{\mathrm{RF}}}}\right] \quad \text{for} \quad t \le 20 \qquad (23\text{–}23)$$

and

$$B = B_{20} + A_{20}\left[1 - e^{-k(t-20)}\right] \quad \text{for} \quad t > 20 \qquad (23\text{–}24)$$

where B_{20} is computed from equation (23-23) at time t = 20 min, and A_{20} is calculated using the following expression:

$$A_{20} = \left[\left(\frac{A}{20\,\mathrm{RF}}\right)\left(1 - e^{-20k}\right)e^{-\frac{k}{\mathrm{RF}}}\right]\left(1 - e^{-\frac{k}{\mathrm{RF}}}\right) \qquad (23\text{–}25)$$

The term A/20 RF in equations (23-23) and (23-25) is the transferable amount deposited after each inhalation. The inhalation or dose number, n, is equal to t × RF for $t \le 20$, where RF is the respiratory frequency.

The ratio of transferable amount to amount deposited increases at high respiratory frequency, RF, large tidal volume, and decreasing aerosol particle size. *Tidal volume* is the amount of air that enters the lungs with each inspiration or leaves the lungs with each expiration.

Example 23-7

Small-Particle Transfer

Compute the transfer, B, of 3-μm particles at t = 20 min, knowing that the transferable amount, A, is 37.7 μg, the respiratory frequency RF is 28, and k = 0.049 min^{-1}.

The inhalation or dose number is n = 20 min × 28 cycles/min = 560 cycles; from equation (23-23)

$$B = \frac{37.7}{560}\left[560 - \frac{\left(1 - e^{\frac{-560 \times 0.049}{28}}\right) \times e^{\frac{-0.049}{28}}}{1 - e^{\frac{-0.049}{28}}}\right] = 13.69\,\mu\mathrm{g}$$

The pulmonary route provides effective administration of beta-adrenergic agonists in asthma treatment. Corticosteroids have been added to the therapeutic regime, in particular triamcinolone acetonide and beclomethasone, which are safe and effective in aerosol formulations.91 However, this route has shown to be of limited usefulness for antimicrobial drugs. The pulmonary route can be useful for controlled delivery of drugs to the respiratory tract, depending on the characteristics of the drug and the aerosol device. It is unlikely that this route will be a substitute for the administration of more conventional oral or parenteral drugs in foreseeable future.

Nasal Drug Delivery Systems

The most suitable dosage forms for the nasal drug delivery are aerosols, gels, liquids, ointments, suspensions, and

sustained-release formulations. Dosage forms for nasal absorption must be deposited and remain in the nasal cavity long enough to allow effective absorption. The standard methods of administration are sprays and drops. The particle size in aerosols is important in determining the site of deposition. Particles <0.5 μm in diameter pass through the nose and reach the terminal bronchi and alveoli of the lungs. A nasal spray requires that the particles have a diameter >4 μm to be retained in the nose and to minimize passage into the lungs. The nasal spray deposits drug in the proximal part of the nasal atrium, whereas nasal drops are dispersed throughout the nasal cavity. A spray clears more slowly than drops because the spray is deposited in nonciliated regions. An MDI is most often used for nasal and pulmonary delivery. This device (Fig. 23-24), when manually compressed, delivers an accurate and reproducible dose of the nasal (or bronchial) formulation.

One of the limitations of nasal drug delivery is rapid removal of the therapeutic agent from the site of absorption. To overcome this, the addition of bioadhesive materials and mixtures with polymers has been investigated. By adding these materials to the drug in solution or powder preparations, increased drug absorption was observed because of increased residence time. Quadir et al.92 examined the effect

of microcrystalline cellulose on the bioavailability of ketorolac. They found that the bioavailability of spray formulations of ketorolac alone in rabbits was approximately 50% after the intravenous administration (Fig. 23-25). Nasal administration of ketorolac with microcrystalline cellulose significantly improved the absolute bioavailability (i.e., compared to intravenous injection) of the drug to 90%.

A new nasal gel drug, zinc gluconate (Zicam) (Gel-Tech LLC, Woodland Hill, CA), significantly reduces the length of the common cold.[93,94] The active ingredient in Zicam is zinc ion, which has long been used in cold lozenges. The gel formulation allows the ions to stay within the nasal cavity long enough to interact with the virus. Patients who took Zicam within 24 hr of the onset of three or more cold symptoms recovered in an average of 1.5 to 3.3 days, whereas patients who received a placebo recovered in an average of 9.8 days.

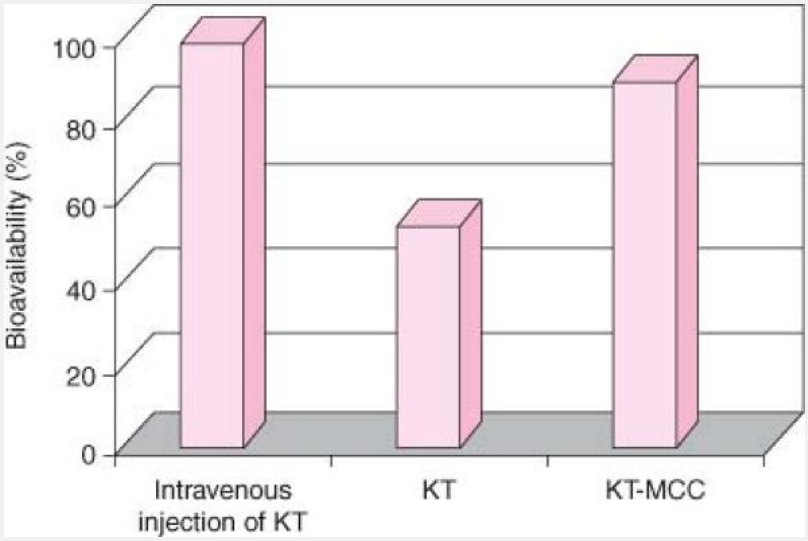


Fig. 23-25. Comparison of bioavailability of injection and spray formulations of ketorolac (KT) alone and with a microcrystalline cellulose (MCC) in rabbits. (Replotted from M. Quadir, H. Zia, and T. E. Needham, Drug. Deliv. **7,**223, 2000.)

Major advantages and limitations of nasal drug delivery are summarized in Table 23-5.

Table 23-5 Advantages and Limitations of Nasal Mucosal Drug Delivery

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

Relative ease and convenience	

Controlled Ocular Drug Delivery Systems

The action of a drug for ocular delivery is prolonged by (*a*) reducing drainage by using viscosity-enhancing agents, suspensions, emulsions, and erodible and nonerodible matrices and (*ii*) enhancing the corneal penetration by using the prodrugs and liposomes. The optimal viscosity range for reducing drainage loss is between 12 and 15 cp when polyvinyl alcohol95 or methyl-cellulose96 is used as viscosity enhancer. To minimize potential irritation, ophthalmic suspensions are prepared by micronization techniques. The dissolution rate of large particles is smaller than that of small particles. To obtain the desired bioavailability, the dissolution rate of the drug must be greater than the clearance of the dose from the conjunctival sac and approximately equal to the absorption rate. Many drugs do not satisfy these requirements.

Using water-soluble matrices, where the drug is either dispersed or dissolved, increases the precorneal retention and duration of action. The delivery of drugs from hydrophilic matrices is fast because the tear fluid rapidly penetrates into the matrix. The prolonged action is not controlled by the vehicle but by the precorneal retention of the drug. The penetration of water into the matrix can be reduced by hydrophobic polymers such as alkyl half-esters of poly(methyl vinyl ether–maleic anhydride) (PVM–MA). The matrix surface is water soluble above certain pH, owing to the ionizable carboxylic groups. However, the hydrophobic alkyl ester groups avoid the penetration of water into the matrix. The diffusion of drug from the matrix is impeded and it is released at the rate at which the polymer surface is dissolved. In one study, pilocarpine was released from PVM–MA polymers according to zero-order kinetics and controlled by the erosion of the

polymer surface.97 Grass et al.98 prepared erodible and nonerodible dry films for sustained delivery of pilocarpine. The polymers used in both cases were polyvinyl alcohol and carboxyl copolymer (carbomer 934). The release of drug from the films fitted either the Hixon–Crowell dissolution cube root equation or the diffusion-controlled dissolution equation proposed by Cobby et al.,99,100 the latter providing the best fit.

The ocular delivery of drugs from matrices can be improved by the use of bioadhesive polymers. Johnson and Zografi101 measured the adhesion (i.e., adhesive strength) of hydroxypropyl cellulose to solid substrates as a function of dry film thickness. A “butt adhesion test” used by them provided a constant slow rate of film detachment to maintain the viscoelastic contribution of the film relative to the adhesion measurements as a constant. For thickness less than 20 μm, there is a linear relationship between the adhesive strength, Y(in g/cm^2) and the film thickness, h (in μm). The adhesive failure, Y_0, can be obtained by extrapolating the adhesive strength to zero film thickness.

Example 23-8

Adhesion Properties of Hydroxypropyl Cellulose

The adhesion, *Y*, of hydroxypropyl cellulose to polyethylene surfaces as a function of the film thickness, *h*, of the adhesive is given as follows:

Y(g/cm^2)	3850	2800	1750	700
h (μm)	5	10	15	20

Compute the adhesive failure, Y_0. A regression of *Y*(dependent variable) against *h* (independent variable) gives

$$Y = -210\,h + 4900$$

The adhesive failure is given by the intercept, Y_0 = 4900 g/cm^2.

The *work of adhesion*, W_a, of the dry film on the solid surface can be computed from the surface tension of the polymer and the solid surface101:

$$W_a = \frac{4\gamma_s^d\gamma_p^d}{\gamma_s^d + \gamma_p^d} + \frac{4\gamma_s^p\gamma_p^p}{\gamma_s^p + \gamma_p^p} \qquad (23\text{–}26)$$

where γ_s and γ_p are the surface tensions of the solid and the polymer, respectively. The superscripts d and p represent the contribution to the total surface tension from nonpolar and polar portions of the molecule.

Example 23-9

Work of Adhesion

Compute the work of adhesion of hydroxypropyl cellulose films to a solid surface of polyethylene from the following data: γ^d_s = 34.2 ergs/cm^2; γ^p_s = 3.4 ergs/cm^2; γ^d_p = 24.7 ergs/cm^2; and γ^p_p = 16.3 ergs/cm^2.

We have

$$W_a = \frac{4 \times 34.2 \times 24.7}{34.2 + 24.7} + \frac{4 \times 3.4 \times 16.3}{3.4 + 16.3}$$

$$W_a = 68.6\,\text{ergs/cm}^2$$

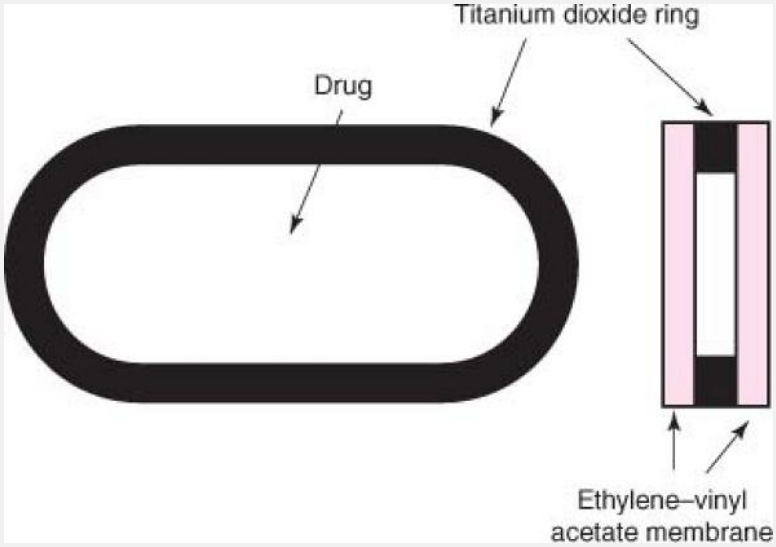


Fig. 23-26. The Ocusert system consisting of a pilocarpine core (drug) sandwiched between two rate-controlling ethylene–vinyl acetate copolymer membranes. When the device is placed under the upper or lower eyelid, the pilocarpine molecules dissolved in the lacrimal fluid are released at preprogrammed rates through the rate-controlling membranes.

Ocusert System

Alza Corporation introduced the pilocarpine-containing device Ocusert. Made of an ethylene–vinyl acetate copolymer, the device (Fig. 23-26) has a central core or reservoir of pilocarpine between two membrane surfaces that control the rate of release of the drug. The oval device, slightly larger than a contact lens, is placed under the upper or lower lid, where pilocarpine is released at a zero-order rate and absorbed into the cornea of the eye. Two products are available, Ocusert P-20, which delivers a dose of 20 µg/hr, and Ocusert P-40, which delivers a dose of 40 µg/hr.

Because of the close contact with the eye and continuous release of drug from the Ocusert over a period of a week, only about one fourth of the pilocarpine dose is administered, when compared to drops. With drugs that are only sparingly soluble in water, such as chloramphenicol, release in the eye is calculated from a form of Fick's law:

$$M = \frac{SDKC_s}{h}t \qquad (23\text{–}27)$$

where M is the accumulated amount released and t is the time. S is the surface area of the device in contact with the eye, D is the diffusion coefficient of the Ocusert membrane, K is a liquid–liquid partition coefficient between the Ocusert and the eye fluids, C_s is the solubility of the drug in water, and h is the Ocusert membrane thickness. As observed in Figure 23-27, a plot of accumulated drug release against time is linear, showing a break at point *A* (125 hr), then becoming horizontal, indicating that chloramphenicol is depleted, and no more is released after 125 hr. A plot of *release rate*, rather than amount, versus time results in a straight horizontal line to point *A*, then tends toward zero (Fig. 23-27**, inset**). The curve does not fall vertically following point *A* but is attenuated parabolically as observed in the inset of Figure 23-27. These plots indicate that the release rate of a sparingly soluble drug

is almost constant, that is, a zero-order release rate over most of the lifetime of the device. The flux or rate per unit time for a water-soluble compound is not horizontal (Fig. 23-27**, inset**) but becomes

attenuated as the release proceeds. By the proper choice of membranes for the Ocusert, the release rate of pilocarpine can be held essentially constant (zero-order drug release) for up to 7 days of delivery.

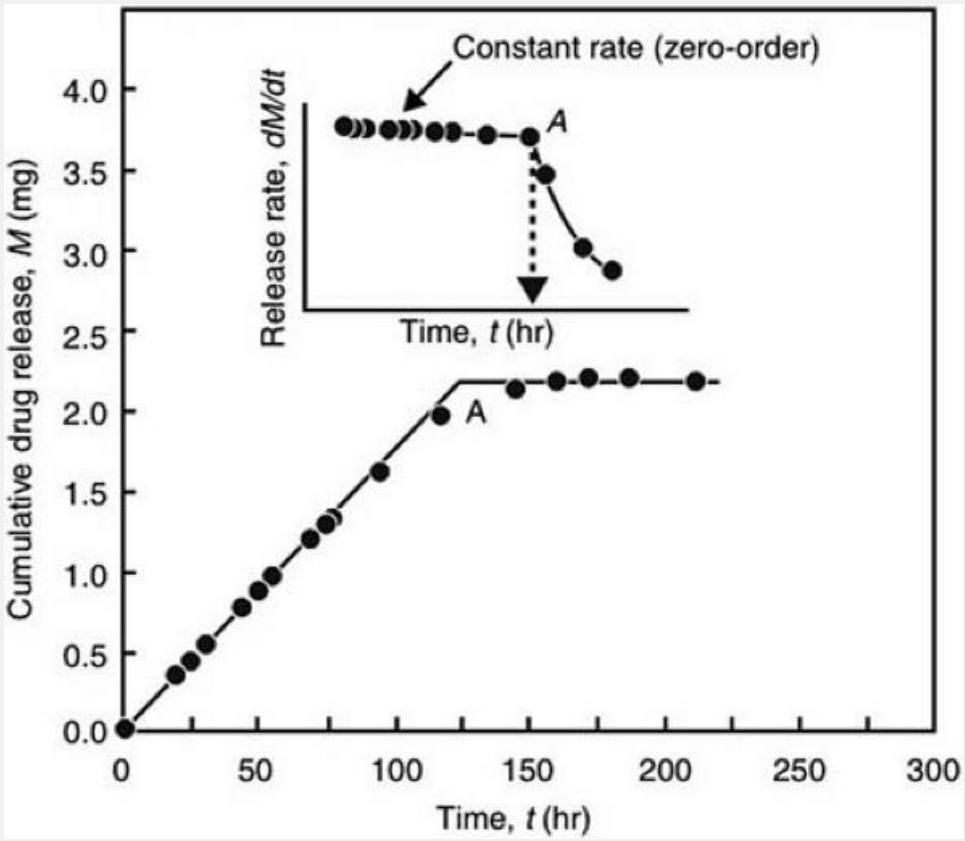


Fig. 23-27. Controlled drug delivery of chloramphenicol through the Ocusert membrane. The graph shows the cumulative release versus time (inset: release rate versus time).

These preparations present some disadvantages, such as noncompliance, especially in elderly people, and many patients lose the device sometimes without becoming aware of it. From the point of view of patient acceptability, a liquid dosage form is preferable.

Example 23-10

Chloramphenicol Analogue Release from Ocusert

The diffusion coefficient of a new chloramphenicol derivative in the Ocusert device is 3.77×10^{-5} cm^2/hr. The surface area, S, of the Ocusert is 0.80 cm^2, the partition coefficient,K, between the Ocusert and ocular fluids is 1.03, the thickness of the membrane, h, is 0.007 cm, and the solubility, C_s, in water (25°C) of the new compound is 3.93 mg/cm^3. By use of equation (23-27), calculate the cumulative amount of drug released in 125 hr.

We have

$$M = \frac{(0.80\,\text{cm}^2)(3.77 \times 10^{-5}\,\text{cm}^2/\text{hr})(1.03)(3.93\,\text{mg/cm}^2)(125\,\text{hr})}{0.007\,\text{cm}}$$

$$M = 2.18\,\text{mg released in 125 hr}$$

Biodegradable Drug Delivery System

Oculex Pharmaceuticals (Sunnyvale, CA) developed the biodegradable drug delivery (BDD) system, which is based on a microsized polymer system that enables microencapsulated drug therapies to be implanted within the eye. Unlike any other intraocular drug delivery system, this technology is

completely biodegradable. This allows biodegradable microsystems to release therapeutic agents directly into the area requiring medication for a predetermined period of time, enabling treatment of a broad spectrum of conditions and diseases that occur within the back of the eye. The key features of this technology include programmable site-specific drug delivery, a biodegradable therapeutic solution, minimally invasive delivery, versatile drug delivery platform, and better patient compliance. Two types of BDD systems have been developed. The first system (Surodex BDD) is inserted in the front of the eye, whereas the second (Posurdex BDD) might be inserted in the back of the eye by elective surgery. BDD delivery systems are designed to provide continuous, controlled release drug therapy directly to the targeted site for periods ranging from several days to several years. Several drug delivery systems based on this technology are undergoing clinical trials.

Mucoadhesive Drug Delivery Formulation

It is based on an ionic complex of partially neutralized PAA and a highly potent beta-blocker drug, levobetaxolol hydrochloride (LB × HCl), and used for the treatment of glaucoma.12'13 PAA is neutralized with sodium hydroxide to varying degrees of neutralization. Aqueous solutions containing varied concentrations of LB × HCl equivalent to the degree of PAA neutralization are added to the PAA solutions to form insoluble complexes. Complexes are prepared with different drug loading, such that the same PAA chain would have free—COOH groups for mucoadhesion along with ionic complexes of LB × H^+ with COO—groups. From thin films of the complexes, drug is released by ion exchange with synthetic tear fluid. The film thickness attenuated continuously during the release of the drug and dissolved completely in 1 hr. Solid inserts of these films could be useful as a mucoadhesive ophthalmic drug delivery system.

Transdermal Drug Delivery Systems

Enhancers for Percutaneous Absorption

The transport of molecules through the skin is increased by the use of adjuvants known as *enhancers*. Ionic surfactants enhance transdermal absorption by disordering the lipid layer of the stratum corneum and by denaturation of the keratin. Enhancers increase the drug penetration by causing the stratum corneum to swell and/or leach out some of the structural components, thus reducing the diffusional resistance and increasing the permeability of the skin.102

Nishihata et al.103 proposed a mechanism for the enhancing effect of reducing agents such as ascorbate and dithiothreitol. The poor permeability of the skin is due to the ordered layer of intercellular lipids and the low water content. Proteins in keratinized tissue are rich in cysteine residues, and the strong disulfide bonds are possibly responsible for the insoluble nature of the protein. The reducing agents cause a decrease in the number of disulfide bridges, leading to an increase in the hydration of the proteins, which results into increased membrane permeability. Azone or laurocapram (1-dodecyl-azacycloheptan-2-one) is the most efficient enhancer

for percutaneous absorption. It greatly improves the penetration of hydrophilic and hydrophobic compounds, though the latter to a smaller degree. Azone is an oily liquid, insoluble in water, but freely soluble in organic solvents. Most of the azone applied remains on the skin surface; the small fraction absorbed is located mainly in the stratum corneum.

The compound has been found to be the most effective enhancer in the percutaneous absorption of dihydroergotamine, a drug widely used in the prevention and/or treatment of migraine. The effect of azone increases in the presence of propylene glycol. A possible mechanism could be the fluidization of the intercellular lipid lamellar region of the stratum corneum by azone. Azone is a very nonpolar molecule, enters the lipid bilayers, and disrupts their structure (Fig. 23-28).104 In contrast, a strongly dipolar solvent, dimethyl sulfoxide (DMSO), enters the aqueous region and interacts with the lipid polar heads to form a large solvation shell and to expand the hydrophilic region between the polar heads. As a result, both azone and DMSO increase the lipid fluidity, thus reducing the resistance of the lipid barrier to the diffusion of drugs. Alcohol derivatives of *N,N*-disubstituted amino acids and hexamethylene lauramine also enhance the permeability of drugs.

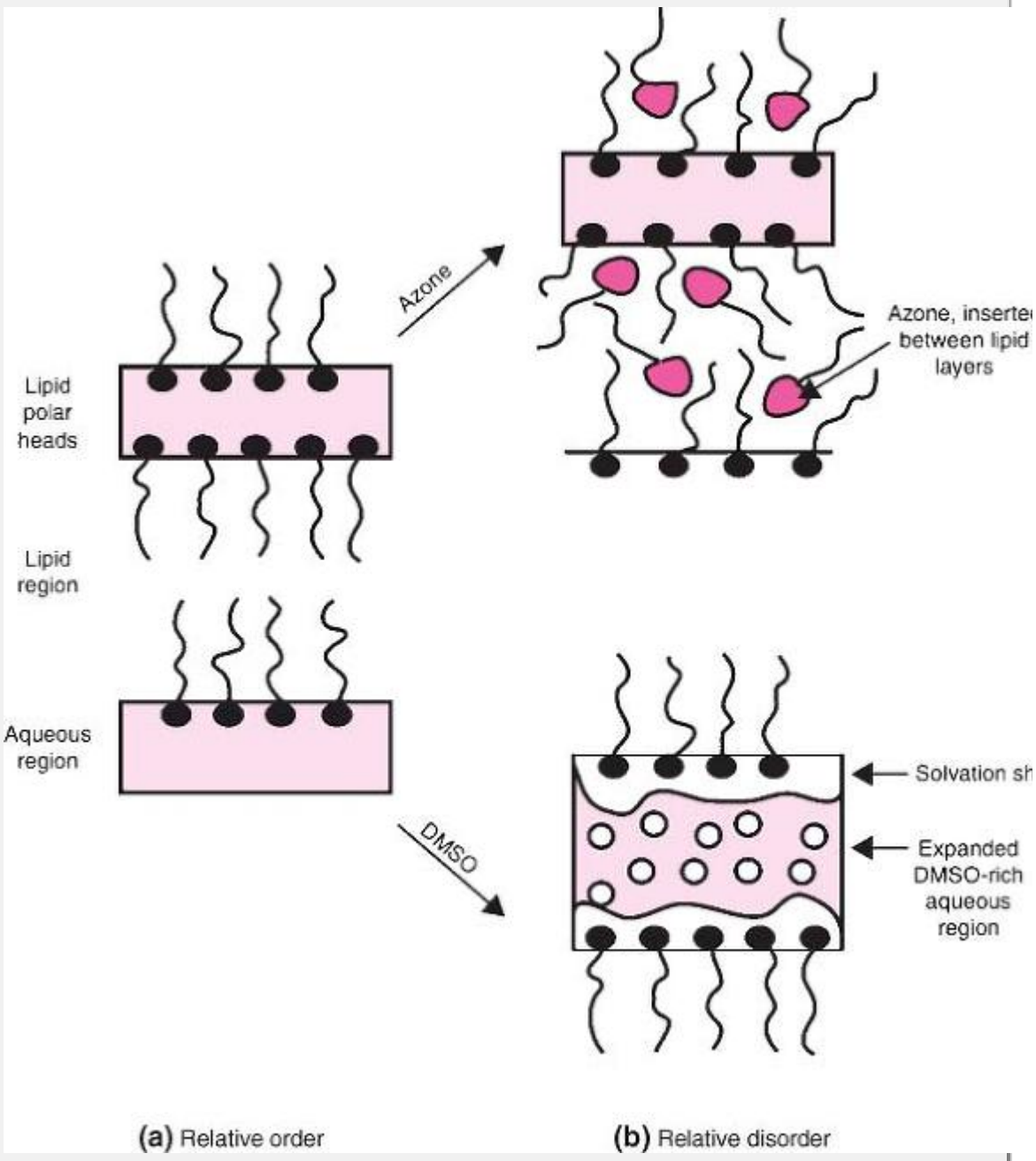


Fig. 23-28. Schematic representation of the interaction of the enhancers azone and dimethyl sulfoxide (DMSO) with the intercellular lipids of the stratum corneum: (*a*) Relatively ordered structure of the lipid bilayers. (*b*) Disordered lipid array due to the azone and DMSO activity. (Modified from B. W. Barry, Int. J. Cosmet. Sci. **10,** 281, 1988. With permission.)

Membrane-Controlled Systems for the Percutaneous Absorption Route

A transdermal device is a laminated structure consisting of four layers, as shown in Figure 23-29. It consists of (*a*) an impermeable backing membrane, which is the mechanical support of the system; (*b*) an adjacent polymer layer, which serves as the drug reservoir; (*c*) a microporous membrane filled with a

nonpolar material (e.g., paraffin); and (*d*) an adhesive film to make close contact with the skin and maintain the device in the desired position.

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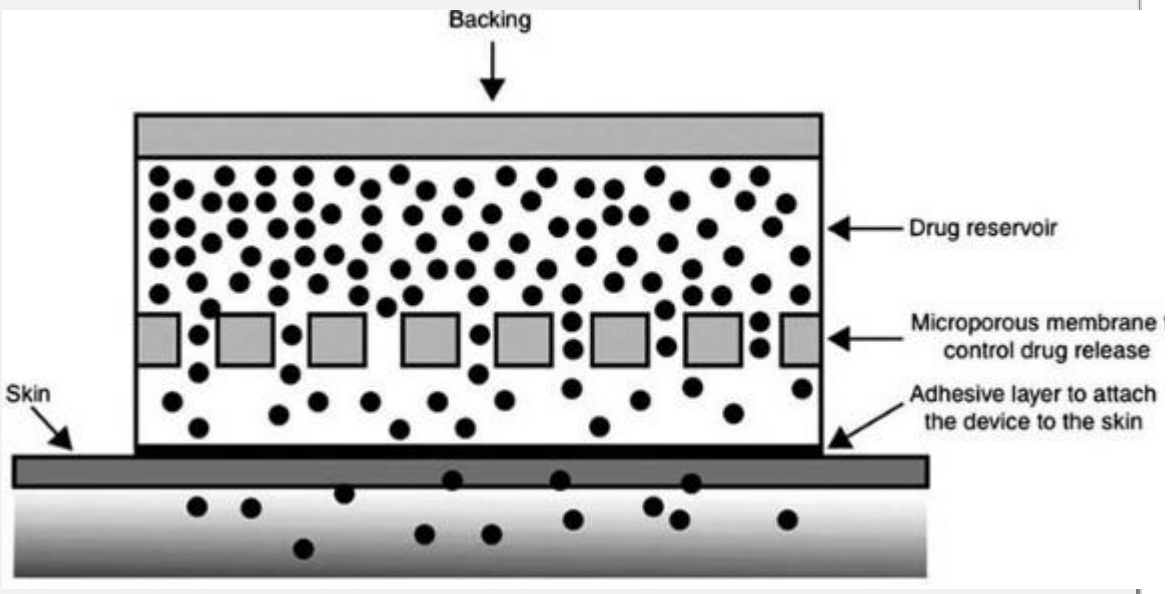

Fig. 23-29. A schematic representation of the transdermal therapeutic system. (Modified from K. Heilmann, *Therapeutic Systems*, Georg Thieme, Stuttgart, 1978, p. 53.)

Guy and Hadgraft[105,106] proposed a model for the transport of clonidine across the skin (Fig. 23-30) from a membrane-controlled adhesive system. The constant k_0 represents the zero-order rate constant for the membrane-controlled leaching of the drug, and $k_R$represents the partition between the patch and the skin surface. The system should be designed so that the partitioning favors the skin and k_R remains negligibly small. The first-order constants k_1 and $k_2$in Figure 23-30 are for drug transport across the stratum corneum and the living part of the epidermis. These constants are directly proportional to the diffusion coefficients for passage through the layers of the skin and therefore inversely proportional to the penetrant molecular weight as observed from the Stokes–Einstein equation:

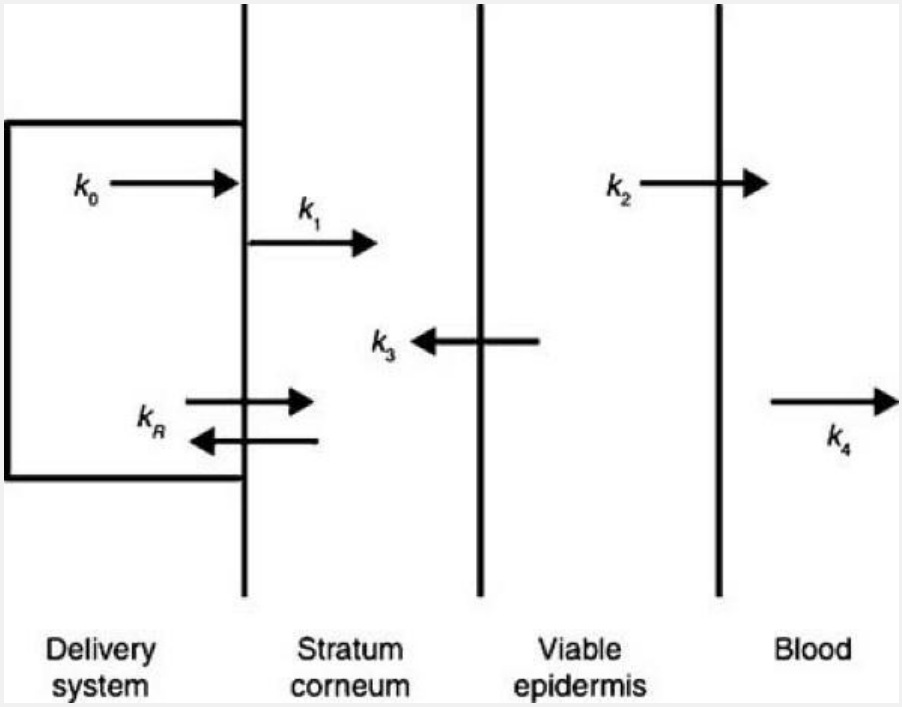

Fig. 23-30. Transdermal delivery of clonidine from a membrane-controlled patch. (Modified from R. H. Guy and J. Hadgraft, J Pharm. Sci. **74,** 1016, 1985. With permission.)

$$D = \frac{RT}{6\pi\eta N}\sqrt[3]{\frac{4\pi N}{3M\bar{v}}} \qquad (23\text{–}28)$$

The rate constant k_3 of Figure 23-30 is included to express any tendency for reverse drug transport from epidermis to the stratum corneum and, in conjunction with k_2, can be considered as a partition coefficient. The authors computed the values of k_1 and $k_2$for benzoic acid and used them to compute these rate constants for other drug molecules. The expressions are

$$k_1 = k_1^{BA}\left(\frac{M^{BA}}{M}\right)^{1/3} \qquad (23\text{–}29)$$

$$k_2 = k_2^{BA}\left(\frac{M^{BA}}{M}\right)^{1/3} \qquad (23\text{–}30)$$

where $k^{BA}{}_1$, $k^{BA}{}_2$, and M^{BA} are the rate constants and molecular weight of benzoic acid and M is the molecular weight of the drug for which the constants k_1 and k_2 are calculated. The ratio k_3/k_2 was found to be a function of the octanol–water partition coefficient, K:

$$K \cong 5(k_2/k_3) \qquad (23\text{–}31)$$

Using this model, one can predict the constants k_1, k_2, and k_3 from the physicochemical properties of the drug. The rate constant k_4 inFigure 23-30 represents the first-order elimination of the drug from the blood and cannot be predicted. It must be measured experimentally.

Examples of membrane-controlled systems are the Transderm-Nitro (Ciba, Basel, Switzerland, and Alza, Mountain View, CA) for the delivery of nitroglycerin, Transderm-Scop (Alza and Ciba-Geigy) for scopolamine, and Catapress TTS (Alza and Boehringer Ingelheim, Germany) for clonidine.107

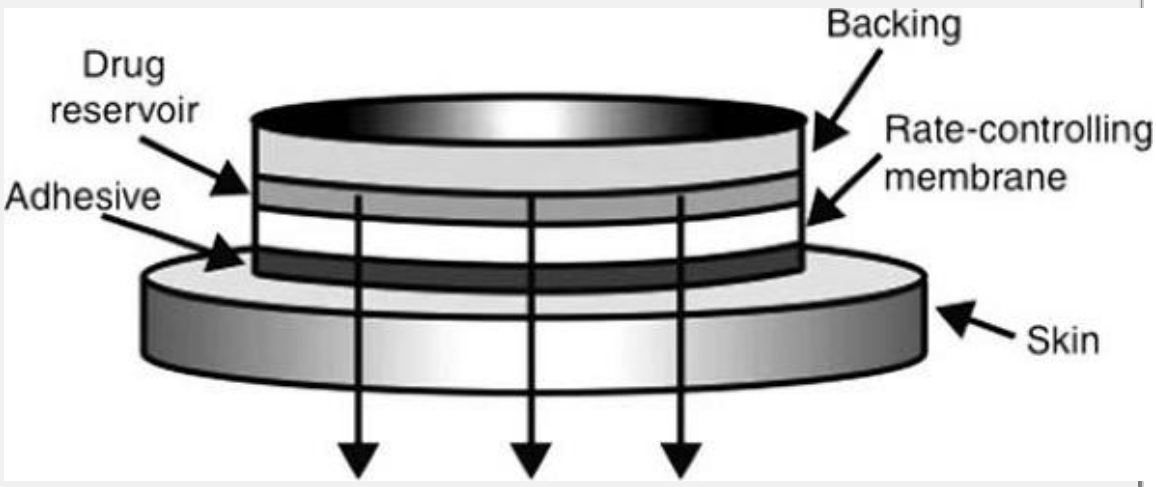

Fig. 23-31. A schematic representation of an adhesive diffusion-controlled transdermal drug delivery system.

Example 23-11
Clonidine Release from a Transdermal Patch

(*a*) Compute the rate constants k_1, k_2, and k_3 for the transport of clonidine from a membrane-controlled patch. The first-order rate constants k_1^{BA} and k_2^{BA} are 5.11×10^{-5} and 80×10^{-5} sec^{-1}, respectively. The octanol–water partition coefficient of clonidine is $K = 6.7$. The molecular weight of benzoic acid is 122.12 g/mole, and the molecular weight of clonidine is 230.10 g/mole.

We have:

$$k_1 = 5.11 \times 10^{-5}(122.12/230.10)^{1/3} = 4.14 \times 10^{-5}\,\text{sec}^{-1}$$
$$k_2 = 80 \times 10^{-5}(122.12/230.10)^{1/3} = 64.77 \times 10^{-5}\,\text{sec}^{-1}$$

From equation (23-31),

$$k_3 = \frac{Kk_2}{5} = \frac{6.7 \times 64.77 \times 10^{-5}\,\text{sec}^{-1}}{5} = 8.68 \times 10^{-4}\,\text{sec}^{-1}$$

(*b*) The steady-state plasma concentration of clonidine, C^{SS}, can be computed from

$$C^{SS} = Ak_0/V_dk_4 \qquad (23\text{–}32)$$

where A is the area of the patch, k_0 is the zero-order rate constant for the delivery of clonidine from the patch, and $V_d$is the *volume* of *distribution*,* the amount of drug in the body divided by the plasma concentration. For the most efficient membrane-controlled patch, which contains 2.5 mg of clonidine, A, the area of the patch is 5 cm^2 and k_0 is 1.6 μg/cm^2 hr. The volume of distribution V_d for clonidine is 147 liters and the first-order constant, k_4, is 0.08 hr^{-1}. From equation (23-31),

$$C^{SS} = \frac{5\,\text{cm}^2 \times 1.6\,\mu\text{g/cm}^2\,\text{hr}}{147,000\,\text{cm}^3 \times 0.08\,\text{hr}^{-1}} = 6.8 \times 10^4\,\mu\text{g/mL}$$

Adhesive Diffusion-Controlled Systems

The basic difference between this system and the one previously described is the absence of microporous membrane (Fig. 23-31**)**. The device consists of an impermeable plastic barrier on the top, a drug reservoir in the middle, and several rate-controlling adhesive layers next to the skin. The rate of drug release, *dQ*/*dt*, depends on the partition coefficient, K, of the drug between the reservoir (r) and the adhesive layers (a), the diffusion coefficient, D_a, the sum of the thicknesses of the adhesive layers, h_a, and the concentration C_r of the drug in the reservoir layer108:

$$\frac{dQ}{dt} = \frac{KD_aC_r}{h_a} \qquad (23\text{–}33)$$

Examples of these devices are the nitroglycerin (Nitrodisc) (Searle, Chicago, IL) and glyceryl trinitrate (Deponit) (Swarz Pharma, Monheim, Germany) for the delivery of nitroglycerin.

Matrix-Controlled Devices

In a matrix-controlled device, the drug reservoir consists of a hydrophilic or hydrophobic polymer containing the dispersed drug, attached to a plastic backing that is impermeable to the drug. The drug reservoir is in direct contact with the skin, and the release of drug is matrix controlled, that is, it is a function of the square root of time. To obtain zero-order release of the drug across the skin from such systems, the stratum corneum must control the rate of drug delivery. This can be achieved if the release rate of the drug from the device is much greater than the rate of skin uptake. Example is Nitro-Dur system (Schering-Plough Corp., Kenilworth, NJ).

Iontophoresis

It is an electrochemical method that enhances the transport of some soluble molecules by creating a potential gradient through the skin tissue with an applied electrical current or voltage (Fig. 23-32). This technique is used to enhance the transdermal transport of drugs by applying a small current through a reservoir that contains ionized species of the drug. Positive or negative electrodes are placed between the drug reservoir and the skin. Positive ions are introduced in the skin from a positive electrode and negative ions from a negative electrode. Figure 23-32 shows an iontophoresis circuit with the active electrode being negative. A second electrode, positive in this case, is placed a short distance away on the body to complete the circuit, and the electrodes are connected to a power supply. When the current flows, the negatively charged ions are transported across the skin, mainly through the pores. The isoelectric point of the skin is between 3 and 4 pH

units; below pH 3 the pores are positively charged and above pH 4 they are negatively charged. Owing to the negative charge in the upper skin layers, basic drugs are relatively easy to introduce.

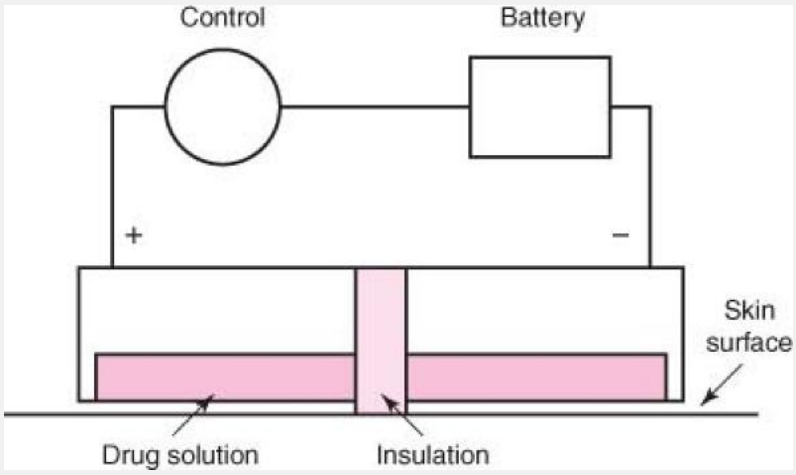

Fig. 23-32. A schematic representation of iontophoresis apparatus on skin.

In vitro systems designed to study iontophoretic transport involve the use of diffusion cells in which a skin membrane is placed vertically between the two halves of the cell. The “active” electrode, say the positive electrode for the transport of positive ions, is placed on the epidermal side. The other side of the cell contains a passive (oppositely charged) electrode in a conductive fluid. Iontophoresis enhances the transdermal absorption of insulin. At a pH below the isoelectric point of insulin (pH 5.3) the drug acts as

a positive electrode, whereas at a pH above the isoelectric point, the drug reservoir acts as a negative electrode. The greatest transport of insulin was found at pH 3.68 rather than at 7 or 8 owing possibly to low aggregation and a high charge density of insulin at pH 3.68.109

The rate of skin permeation depends on the drug concentration, the ionic strength of the buffer solution, the magnitude of current applied, and the duration of iontophoresis.110 Iontophoresis is a promising method for delivering peptides through the skin. Burnette and Marrero111 showed that the flux of both ionized and nonionized species of thyrotropin-releasing hormone was greater than the flux obtained by passive diffusion alone. The increased flux was proportional to the applied current density. Transport through the pores is favored for positive ions, whereas transport of negative ions is probably smaller. Faraday's law states that equal quantities of electricity will deposit equivalent quantities of ions at either electrode. However, the correlation between the prediction by Faraday's law and the experimental values is not good owing to several factors involved in iontophoretic transport. Kasting et al.112 used an electrodiffusion model to study the transport of etidronate disodium, a negatively charged bone resorption agent, through excised human skin. At steady state, the flux, J_i, of drug through the membrane is given by the Nernst–Planck flux equation:

$$J_i = -D_i \frac{dc_i}{dx} + \frac{D_i z_i e E c_i}{kT} \qquad \textbf{(23–34)}$$

where D_i is the diffusion coefficient for the ion i (in the x direction), $z_i$is its charge, and c_i is its concentration. The term kT is the thermal energy of the system, where k is the Boltzmann constant and T is the absolute temperature. The Goldman approximation112 provides a solution of equation **(**23-34**)**:

$$J_i = \frac{-D_i K v}{h} \frac{c_i - c_0 e^{-v}}{1 - e^{-v}} \qquad \textbf{(23–35)}$$

where K is the partition coefficient, h is the thickness of the membrane, and c_i and c_0 are the concentrations at either side of the membrane. Assuming that the concentration $c_0 = 0$, in the limit as $v \rightarrow 0$, equation **(**23-35**)** becomes the flux passive diffusion, J:

$$J_i = \frac{-D_i K c_i}{h} \qquad \textbf{(23–36)}$$

The term v is a dimensionless driving force, defined as:

$$v = \frac{z_i e \mathrm{V}}{kT} \qquad \textbf{(23–37)}$$

where e is the electronic charge, z is the charge on the drug, k is the Boltzmann constant, T is the absolute temperature, and V is the applied voltage across the membrane. The *iontophoretic enhancement factor*, J_i/J_0, is given by:

$$\frac{J_i}{J_0} = \frac{v}{1 - e^{-v}} \qquad \textbf{(23–38)}$$

Equation **(**23-38**)** measures the increase in transport of a drug relative to the passive diffusion due to the electrical current applied. For positive values [z_i and V of the same sign in equation **(**23-37**)**], equation **(**23-35**)** predicts that the enhancement in flux is proportional to v. For negative v values, the flux will fall exponentially with increasing magnitude of v.

Example 23-12

Iontophoretic Enhancement Factor

(*a*) Compute the iontophoretic enhancement factor, J_i/J_0, across human excised skin for a 10% etidronate solution. The voltage applied is 0.25 V, the average number of charges, z, per ion is 2.7. The charge on the electron is 1 eV. The value of kT at 25°C is 0.025 eV.

From equation (23-37),

$$v = \frac{2.7 \times 1 \times 0.25}{0.025} = 27$$

Using equation (23-38), we find the iontophoretic enhancement factor

$$\frac{J_i}{J_0} = \frac{27}{1 - e^{-27}} = 27$$

Thus, we see that the flux for the drug promoted by iontophoresis is 27 times that expected for passive diffusion.

(*b*) Compute the flux under the driving force of iontophoresis, knowing that the passive permeability coefficient, *P*, of the drug is 4.9×10^{-6} cm/hr and the concentration, *c*, is 1.02×10^5 μg/cm^3.

Because $P = DK/h$ cm/hr from equation (23-36),

$$J_0 = 4.6 \times 10^{-6} \times 1.02 \times 10^{-5} = 0.5\ \mu g(cm^2 \cdot hr)$$

From equation (23-35), using the value 27 obtained in part (*a*) for J_i/J_0, we obtain

$$J_i = 0.5 \times 27 = 13.5\ \mu g(cm^2 \cdot hr)$$

Kasting et al.113 found that equation (23-35) applies up to 0.25 V. At higher voltages, the flux of etidronate disodium rises much faster than the predicted values because of alteration of the membrane and because the diffusion coefficient is no longer a constant value, as assumed in equation (23-36). Burnette and Bagniefski114determined the skin electrochemical resistance, *R*, after iontophoresis. The decrease in resistance suggested that the current alters the

ion-conducting pathways of the skin even at the clinically acceptable current densities, leading to tissue damage.115

The main advantages of iontophoresis include (*a*) controlling the delivery rates through variations of current density, pulsed voltage, drug concentration, and/or ionic strength; (*b*) eliminating GI incompatibility, erratic absorption, and first-pass metabolism; (*c*) reducing side effects and interpatient variability; (*d*) avoiding the risk of infection, inflammation, and fibrosis associated with continuous injection or infusion; and (*e*) enhancing patient compliance with a convenient and noninvasive therapeutic regimen. The main disadvantage of iontophoresis is skin irritation at high current densities, which can be eliminated by lowering the current of administration.

Phonophoresis

It is defined as transport of drugs through the skin using ultrasound (synonyms: *ultrasound*, *ultrasonophoresis*, *ultraphonophoresis*) (Fig. 23-33). It is a combination of ultrasound therapy with topical drug therapy to achieve therapeutic drug concentrations at selected sites in the skin. The ultrasonic unit has a sound transducer head emitting energy at 1 MHz at 0.5 to 1 W/cm^2. In this technique, the drug is mixed with a coupling agent, usually a gel, but sometimes a cream or an ointment, which transfers ultrasonic energy from the phonophoresis device to the skin through this coupling agent. The exact mechanism of phonophoresis action is not known.

Vaginal Administration, Intrauterine, and Rectal Drug Delivery Systems

Vaginal delivery systems are in use for estrogen replacement therapy, which when used alone carries the risk of endometrial cancer. Traditionally, this risk is overcome by treatment with progesterone for about 14 to 30 days but it is associated with low oral bioavailability, lack of efficacy, and high level of metabolites. Consequently progesterone tablets, suppositories, and gels have been developed for vaginal administration.39,40 Vaginal administration provides higher and sustained plasma levels and low amount of metabolites. Various vaginal preparations of estrogens and progesterones are now available for use as contraceptives, in hormone replacement therapy, and in vitro fertilization programs.

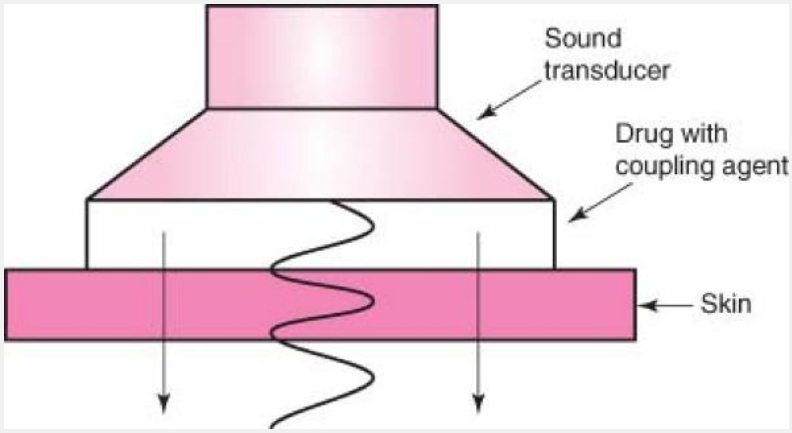

Fig. 23-33. A schematic representation of phonophoresis apparatus on skin.

Suppositories

As mentioned earlier, suppositories are solid dosage forms intended for insertion into body orifices where they melt, soften, or dissolve, and exert localized or systemic drug delivery (suppository, from the Latin sup, “under,” and ponere, “to place”). Once inserted, the suppository base melts, softens, or dissolves, distributing the medications it carries to the tissues of the region. Suppositories are preferred for their safety, suitability for sustained systemic and/or local drug delivery, and nonmessy, nonstaining, and convenient administration. The progesterones and estrogens vaginal suppositories are available commercially.

Vaginal Rings

Vaginal rings containing various progesterones and estrogens are available as steroidal contraceptives (Fig. 23-34a). These rings consist of a drug reservoir surrounded by a polymeric membrane. These are pliable drug delivery system that can be inserted into the vagina, where they slowly release the drug, which is absorbed into the bloodstream. The most common one being Silastic toroidal-shaped ring, which is about 2¼″ in diameter and the size of the outer rim of a diaphragm, designed for insertion into vagina and positioned around the cervix for about 21 days. Levonorgestrel (progesterone analog) is released from the device at a concentration of 20 μg/day with nearly a zero-order release. These rings are easy to use with the advantage of reversibility, self-insertion and removal, continuous drug administration at an effective dose level, and better patient compliance. This above device was

however associated with irregular bleeding. Another vaginal Silastic silicone ring (Estring) was launched in the United States in 1997 for treating postmenopausal women with symptoms of urogenital aging. The ring provides a constant release (6.5–9.5 μg/day) of estradiol over 3-month period and gives better results when compared to estradiol containing pessaries and creams.

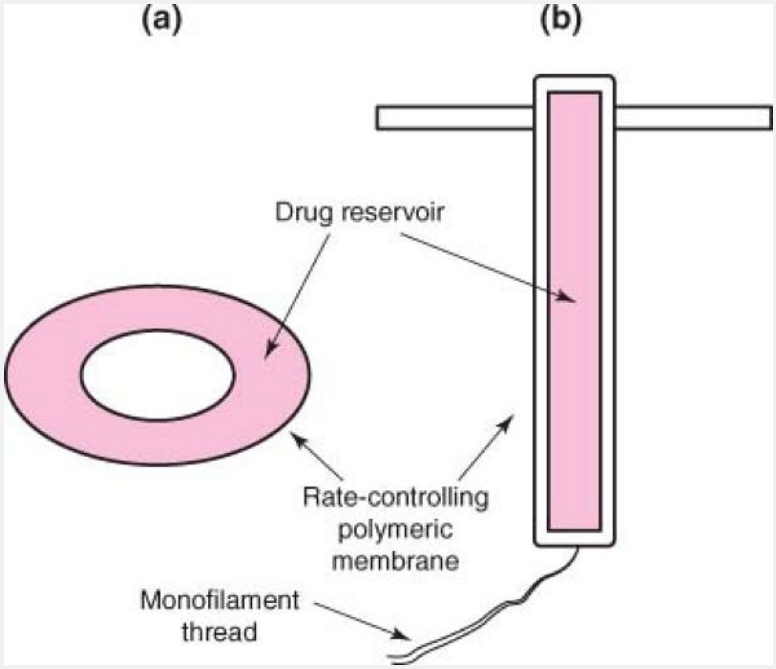

Fig. 23-34. A schematic representation of (*a*) vaginal ring and (*b*) intrauterine device.

Vaginal Inserts

Vaginal inserts are in use for prostaglandin delivery. Prostaglandin E2 (PGE2) is used to ripen the cervix for induction of labor and for second trimester abortion. Prostaglandins provide benefits such as reduced time for onset of labor, reduced need for oxytocin, and shortened time for vaginal and caesarean-operated delivery. These inserts are polymeric hydrogel material, which has the ability to absorb fluid and swell without losing its physical form. As it swells, the incorporated drug is released in a controlled manner. An example is Cervidil Vaginal, which contains 10 mg of dinoprostone and provides release at a rate of 0.3 mg/hr in vivo. The retrieval system comprises Dacron polyester net, which surrounds the insert and has a long ribbon end (net plus ribbon = 31 cm). Another example is the Hycore (CeNeS Pharmaceuticals, Cambridge, UK), which exists in two main forms, Hycore-V, a hydrogel pessary used to deliver drugs locally via the vagina, and Hycore-R, a rectal delivery system used to deliver drugs systemically. Misoprostol (prostaglandin E1 analog used for terminating second trimester pregnancy) is also given through the vaginal route at a dose 100 to 200 µg every 12 hr and provides three times higher bioavailability when compared to oral administration.

Intrauterine Device

An intrauterine device (IUD) is a small plastic device that is placed into the uterine cavity for sustained intrauterine drug release and is usually used for contraception. A typical IUD is shaped like a T and contains a drug, usually progesterone, in its vertical arm (Fig. 23-34b). The progesterone release causes the cervical mucus to become thicker, so sperm cannot reach the egg. It also changes the lining of the uterus so that implantation of a fertilized egg cannot occur. The IUD is inserted through the cervix and placed in the uterus. A small string hangs down from the IUD into the upper part of the vagina and is used to periodically check the device. A shorter-than-normal string can be a warning sign of an imbedded IUD.

Central Nervous System Drug Delivery Systems

Over the years, various strategies have been developed to overcome the BBB and deliver the drugs to the CNS.[42,43]

Invasive Strategies

The invasive strategies are:42,43 (*a*) *intracerebroventricular (ICV) drug infusion*, where the drug is directly injected into the ventricles (large cavities in the middle of the brain). Following the infusion, drug diffusion to brain is still limited by physical barriers, catabolic enzymes, high and low affinity uptake sites, and low diffusion coefficients of high–molecular-weight drugs; (*b*) *implants*, where either genetically engineered cells secreting a drug or polymer matrix/reservoir containing the drug is implanted within the brain. Polymeric implants such as Gliadel are commercially available (Guilford Pharmaceuticals, Baltimore, MD). Gliadel is a small, white, dime-sized wafer made of a biodegradable polymer containing chemotherapy (carmustine or BCNU). Up to eight wafers are implanted in the cavity created, when a brain tumor is surgically removed. Once implanted, they slowly dissolve over a period of 2 to 3 weeks, delivering the drug directly to the tumor site in high concentrations. First approved in 1996 for use as an adjunct to surgery for prolonging patient survival, these wafers are now approved for patients undergoing initial surgery for malignant glioma; and (*c*) *reversible BBB disruption*, where transient disruption or opening of BBB is achieved by the intracarotid infusion of hyperosmolar (2M) solution of mannitol, leukotrienes, or bradykinin. This approach has significant side effects. All the above-mentioned strategies are invasive and require intervention by trained professionals.

Noninvasive Strategies

Besides the invasive strategies for local drug delivery to CNS, there are pharmacology and physiology-based strategies for systemic delivery to CNS. The most common strategy is to increase the lipophilicity (lipidization) of the drug for improved drug penetration into the brain (Fig. 23-35). This is achieved by either blocking the hydrogen bond forming functional groups in the drug or covalent attachment of lipophilic moieties such as long chain fatty acids. For example,42 O-methyation of morphine to form codeine or di-O-methylation to form heroin enhances the BBB permeability. Multivesicular liposomes (diameter <2 μm) are retained in the brain following systemic administration and therefore used for systemic drug delivery to CNS. A further

improvement in liposome-based technologies is achieved by employing immunoliposomes, where antibodies are attached to the liposomes through bifunctional PEG linker to exploit receptor-mediated transcytosis.

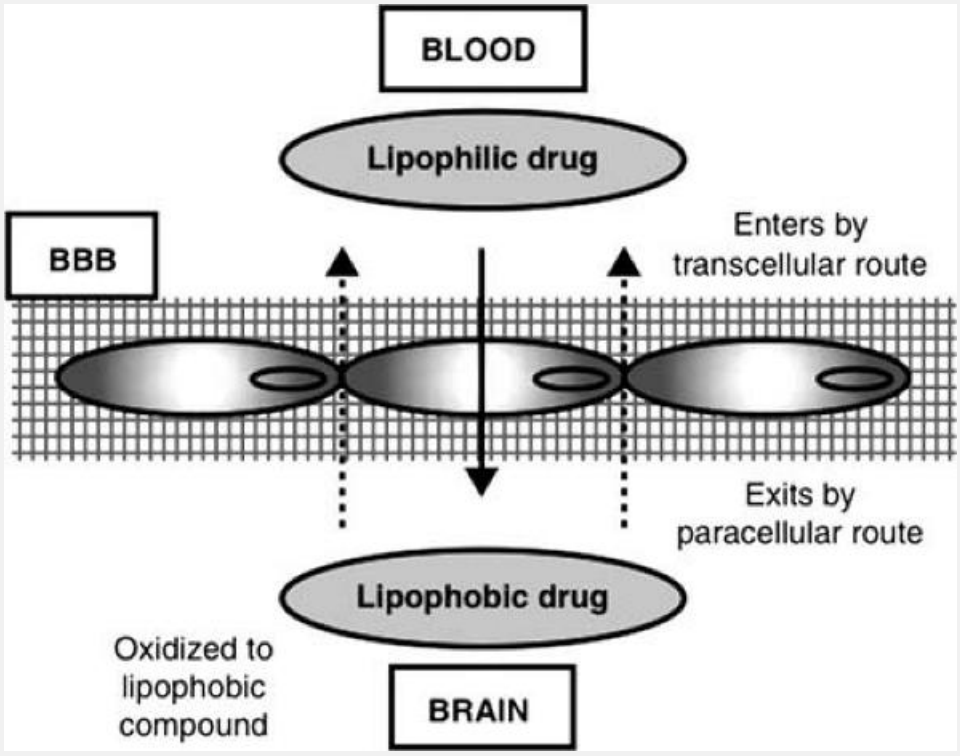

Fig. 23-35. Improving the drug penetration across the blood–brain barrier (BBB) by increasing its lipophilicity.

Carrier-mediated transport mechanism is also used for drug delivery to CNS.[42,43] As explained earlier, nutrients are transferred to the CNS by various carrier-mediated systems. Drugs containing molecular structure similar to the nutrient are designed for transport to the CNS by appropriate carrier-mediated system. Drugs such as L-dopa and α-methyldopa are transported across the BBB by neutral amino acid carrier system. Similarly, receptor-mediated transcytosis is also exploited to achieve systemic delivery to CNS. This strategy (prodrug) involves coupling of the drug to a peptide or protein vector (insulin, insulinlike growth factor, and transferrin) through reversible linker, which undergoes receptor-mediated transcytosis. Once it has been exocytosed into the brain interstitial fluid, the linker is cleaved releasing the drug. Pep:trans peptide-derived vectors (Synt:em, Nimes, France) are examples of such vectors. This vector family is derived from the optimization of natural mammalian antimicrobial peptides involved in an ancestral immune response system. Drugs linked to Pep:trans typically show up to 100-fold enhancement in the brain uptake. This approach suffers from rapid clearance of peptide from the bloodstream. Monoclonal antibodies such as anti-insulin (mAb83–7 or 83–14) and anti-transferrin (OX26) receptor antibodies have been alternatively used as vectors. The limitation with receptor-mediated transcytosis is that it is a saturable process.

Chapter Summary

The objective of this chapter was to provide a perspective on advanced drug delivery. The two key characteristic features of advanced drug delivery systems are controlled delivery and targeting. Oral route remains the most preferred route of drug delivery but not always feasible, and therefore alternative routes of drug delivery are being explored. Each drug delivery route has its own merits and limitations, and the delivery systems depending on the route of drug delivery, must meet characteristic design requirements. The delivery of biotherapeutics (peptides, proteins, and nucleic acids) is more challenging because of their inherent disadvantageous delivery features.

Practice problems for this chapter can be found at thePoint.lww.com/Sinko6e.

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Chapter Legacy

Fifth Edition: published as Chapter 22 (Drug Delivery Systems). New chapter by Tamara Minko.

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