

APPENDIX F: CHAPTER II.5.16 — DRUG DELIVERY SYSTEMS: H, MUCOSAL DRUG DELIVERY

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INTRODUCTION

Mucous membranes line various body cavities and structures that are connected or exposed to the external environment, such as the respiratory, gastrointestinal (GI) and reproductive tracts as well as structures such as the eyes, nose and mouth. A mucosal drug delivery system delivers drugs across the mucosa for both local and systemic therapeutic effects. Mucosal drug delivery is used to increase bioavailability and therapeutic efficacy of drugs both locally and systemically. One of the most fundamental problems is how to overcome the protective barrier functions of the mucosa. Clearly, this requires understanding of the characteristics of the mucosa, the principles and mechanisms of the mucosal drug delivery process, as well as the properties of the dosage form itself that will overcome these barriers while allowing the drug to achieve optimum performance in its target environment. This chapter is designed to

1. Provide an overview of the structure and permeability properties of the mucous membranes.
2. Examine the main principles and mechanisms of mucosal drug delivery, including strategies to enhance mucosal drug delivery mechanisms.
3. Discuss examples of mucosal drug delivery systems.

MUCOUS LAYER

The main functions of the mucous membrane include absorption, secretion, lubrication, entrapment of foreign substances and antibacterial action (Ross, Romrell, and Kaye, 1995). Some mucous membranes are highly specialized for their function, as in the case of the membranes lining the GI tract, especially in the region of the small intestine, which have characteristics that adapt them for efficient absorption. Some mucous membranes are secretory, with secretions that are either watery in consistency or more viscous. Watery mucus is secreted by serous cells and contains numerous active enzymes. These enzymes aid in the metabolic activities of the body, such as digestion. A more highly viscous mucus is secreted by mucous cells with lubrication as their primary function. In the respiratory tract, for example, the viscid mucus helps to trap foreign particles and remove them from the body. Particles here include drug and drug-containing nanoparticles. Depending on its physiological location, the mucous membrane may vary in structure, but all mucous membranes can be considered to comprise

several layers: a mucous layer, an epithelial layer covered by the mucous layer, a basement membrane that anchors the epithelium to underlying tissue layers, and a connective tissue layer (lamina propria) (Smart, 2005).

Mucus is continuously secreted by cells located in the epithelial layer or specialized glands adjacent to tissues. The resulting mucous layer either forms a gel layer that adheres to the epithelial layer or is present as a suspended form adjacent to the epithelial layer. The thickness of the mucous layer varies on different mucosal surfaces. For example, in the human GI tract, the mucous layer is thickest in the stomach (50–450 μm) (Kerss, Allen, et al., 1982) and colon (110–160 μm); in contrast, in the oral cavity, the thickness of the mucous layer is less than 1 μm (Sonju, Christen, et al., 1974). The thickness of the mucous layer is dependent upon the balance between the rate of secretion and the rate of degradation and shedding. On some mucosal surfaces, the mucous secretion is so rapid that it is very difficult for particles to diffuse through the mucous layer against the “upstream” motion of mucous secretion (Cone, 2009). On the other hand, the barrier motion of thinner mucous layers are predominately due to degradation and shedding, where the particles bound to the mucus are cleared before transport across the mucous layer.

The major components of mucus are mucin glycoproteins, lipids, inorganic salts and water, which comprise more than 95% of the total mucus weight (Marriott and Gregory, 1990). Mucin fibers are the structural units of mucus. In general, there are two distinct families of mucin molecules: cell-associated mucins and gel-forming mucins (Cone, 2005). Cell-associated mucins are anchored to the cell surface through a transmembrane domain and range from 100 to 500 nm in length. Gel-forming mucins (or secreted mucins) are formed from mucin monomers linked end-to-end by disulfide bonds, and therefore are much longer and can be up to several microns in length (Carlstedt and Sheehan, 1984). Regardless of the type of mucin molecule, there are several common characteristics of mucin fibers. Each mucin fiber is similar to a flexible string with a densely coated layer of short glycans on the surface (Cone, 2009). These short glycans interact with mucin by forming O-linkages to the threonine and serine residues in the proline, threonine, serine domains of the mucin protein. Many of the glycans terminate in a negatively charged carboxyl group, which makes the glycosylated region highly hydrophilic. In addition, many negatively charged sulfate-bearing glycans are N-linked to the ends of the mucin monomers, further adding to the hydrophilic nature of the mucin. These glycosylated and highly hydrophilic regions are interspersed by “naked” relatively hydrophobic protein regions that fold into globular beads and stabilize themselves by forming numerous disulfide bonds. In mucous gels, each mucin overlaps and entangles with on the order of 10–100 other mucins (Figure II.5.16.1).

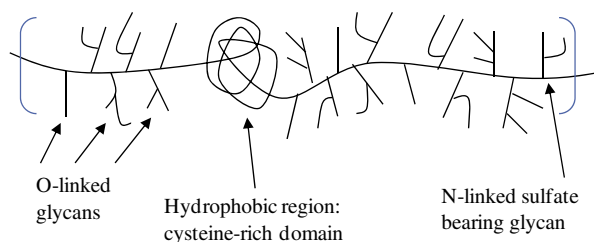


FIGURE II.5.16.1 A basic unit of the mucin structure. Multiple basic units are linked to form a monomer mucin molecule, and the monomers are in turn linked by disulfide bonds to make polymeric structure of mucin.

PRINCIPLES OF MUCOSAL DRUG DELIVERY

Mechanisms of Mucosal Drug Delivery

In mucosal drug delivery, the ability of the drug particles to cross the mucosal membrane barriers is critical to achieving the desired therapeutic effect in the body. Although mucous membranes vary in structure and function, the basic modes of drug transport mechanisms are common to all mucosal drug delivery throughout the body (Chien, 1995). In order for a drug particle to reach the capillaries present in the lamina propria, it must successfully traverse several mucosal barriers.

The basic mechanism of transport in the mucous layer is diffusion. Early views of mucous layer diffusion held that small molecules diffuse readily through the mucous layer, but macromolecules such as globular proteins were assumed to be unable to penetrate this layer (Cone, 2009). However, more recent investigations demonstrated that a number of macromolecules also rapidly diffuse through the mucous layer. Important experiments by the Saltzman and Cone research groups showed that soluble globular proteins diffuse freely through human cervicovaginal mucus, while secreted antibodies such as IgM are only slightly slowed by the same mucus (Saltzman, Radomsky, et al., 1994). Studies conducted by Olmsted et al. (Olmsted, Padgett, et al., 2001) substantiated the claim that viruses with a diameter of 30 nm should be able to diffuse through the cervicovaginal mucus unhindered. Furthermore, they showed that Norwalk virus (38 nm) and human papilloma virus (55 nm) penetrated the mucous layer at diffusion rates approximately equal to that in water. These results demonstrate that particles with a range of sizes are capable of diffusing through the low viscosity pores within the viscoelastic mucous layer matrix (also see Lai et al., 2007; Lai, Wang, and Hanes, 2009). However, due to the restriction set by the size of the mucous pores, not all particles are capable of diffusing through the matrix. Olmsted et al. also established that the herpes simplex virus with a diameter of approximately 180 nm was almost completely unable to cross the mucous layer. This is in accordance with

the obstruction scaling model (Amsden, 1999), which estimated the average mucous pore size to be around 100 nm.

The diffusion of particles through the mucous matrix is not merely determined by their particle size comparative to the mucous matrix pore size. There are also other factors that may facilitate or inhibit the diffusion of these particles. Recent works show that antibodies may have a secretory component that makes them slightly mucophilic (Corthesy and Kraehenbuhl, 1999, pp. 93–111). This characteristic facilitates the transport of antibodies across the mucous layer by forming weak bonds between the antibodies and the mucin fibers. Furthermore, scientists have observed that capsid viruslike particles diffuse freely through the mucous matrix, but polystyrene spheres of similar sizes are trapped by the mucus. This phenomenon is explained by the fact that, although the polystyrene spheres have a diameter smaller than the mucous pores, they form hydrophobic interactions with the hydrophobic regions on the mucin fibers. In addition, charge–charge interactions between the particles and the mucin fibers also play an important role in determining the diffusivity of substances across the mucous layer. As we can see, diffusion of particles through the mucous matrix is by no means a simple process that only involves an unequal distribution (concentration gradient) of particles across a barrier, which we traditionally tend to associate diffusion with. Transport across the epithelium has been described elsewhere as transport across cell layers, and will not be dealt with in this section.

Barriers to Mucosal Drug Delivery

One of the most fundamental problems encountered in mucosal drug delivery is poor bioavailability due to the numerous barriers the drug must overcome to reach the blood stream. In summary, a barrier can be classified as a physicochemical barrier or a metabolic barrier (Rathbone and Tucker, 1993). Physicochemical barriers stem from the structure and properties of the various mucosal membrane layers, while metabolic barriers arise due to the presence of active enzymes in the mucosal membrane environment.

The mucous layer is a critical barrier in mucosal drug delivery (Cone, 2009; Hanes and Demeester, 2009). In order to penetrate across the mucous layer, a particle must avoid the rapid mucus clearance and adhesion to mucin fibers. This is no easy feat. Mucus is continuously secreted, then shed and discarded, or digested and recycled. The continuous secretion of mucus means that a particle must migrate “upstream” against the mucus flow in order to reach the epithelium. In addition, in some places the mucus is shed and cleared at such a rapid rate that particles are engulfed and removed before having sufficient time to diffuse through the mucous layer. This is especially the case in the eyes, where the shedding of the tear film occurs within a matter of seconds. Besides the dynamic properties of the mucus, the chemical properties

of the mucin fibers also contribute toward the barrier functions of the mucous layer. Mucin fibers contain negatively charged and therefore highly hydrophilic regions interspersed with hydrophobic domains. By conforming to the surface of an incoming particle, a mucin fiber can form multiple, low-affinity hydrophobic and/or hydrophilic ionic or H-bonds with this particle. Although these bonds are easily broken, their number is such that, at any given time, one or more of these types of bonds will “link” the particle to the fiber. The effect is especially important for relatively large hydrophobic molecules, which can simultaneously form many such low-affinity bonds with mucus. Relatively small hydrophobic molecules are less prone to be trapped by the mucous matrix, because they can only bind to mucin fibers monovalently. Furthermore, positively charged molecules bind tightly to mucin fibers via ionic interactions with the large number of negatively charged glycans. When the concentration of such positively charged particles is high, the mucous gel can collapse, causing the formation of large channels within the mucous layer. This phenomenon can actually be utilized to enhance mucosal layer permeability.

The metabolic barriers to mucosal drug delivery mainly refer to the degradation of particles by active enzymes in the mucosal membrane environment. In part, these metabolic barriers evolved out of the body’s defense mechanism, which permits the body to degrade foreign substances that may be potentially harmful. However, this defense mechanism may also function against the successful delivery of useful drug particles. During the mucosal permeation process, there are several main locations that the drug particles may be subjected to premature metabolism: (1) the lumen of the route of delivery, prior to making contact with the mucous layer; (2) on the surface of the mucosal layer; or (3) within the mucosal membrane environment. The effect of metabolism is especially detrimental to the delivery of peptide and protein drugs, which are susceptible to various peptidases present in the mucosal membrane. These peptidases inactivate the peptide and protein drugs by cleaving the peptide bonds, acting as a form of presystemic first-pass effect. The types of molecules subject to degradation and the extent of degradation are dependent upon the specific mucosa. For example, a study conducted by Yamamoto et al. indicated that proteolytic degradation of insulin and proinsulin in the rabbit mucous membrane is consistently high in the rectum and consistently low in the vagina, but in the nose and mouth the degree of proteolytic activity differs with the peptides (Yamamoto, Hayakawa, et al., 1990).

General Strategies to Enhance Mucosal Drug Delivery

In order to enhance delivery of drugs and drug particles across the mucosal membrane, drug transport, absorption and eventual bioavailability all need to be improved.

In order to realize this goal, the drug molecules and nanoparticles must overcome the physicochemical and metabolic barriers described in the previous section. In order to facilitate this, it is often necessary to utilize additional compounds in combination with the drug molecules to enhance mucosal membrane penetration. Currently, there are two main approaches, one involves the usage of permeation enhancers and the other employs compounds that act as mucoadhesives.

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Permeation Enhancers. Permeation enhancers are compounds that can increase the permeability of the mucosal membrane and/or ability of the drug compound to cross the membrane, thereby increasing the absorption and bioavailability of the drug molecule (Shen and Lin, 1994). Depending on the mechanisms of action, permeation enhancers can be further divided into the following groups: (1) compounds that enhance permeation by altering the permeability of the membrane; (2) compounds that enhance permeation by altering the properties of the drug itself; and (3) compounds that can inhibit the enzymatic degradation of drug molecules in the mucosal environment (Robinson and Yang, 1999; Shen and Lin, 1994). Examples of each class of enhancers are listed in Table II.5.16.1. In general, permeation enhancers are designed to alter the tight junctions and cell membranes, and thus their effects are nonspecific. Not only the drug molecules but also any molecules present adjacent to the permeation enhancer will be absorbed, making this approach rather undesirable.

Mucoadhesives. Another strategy that has been the subject of greater interest than permeation enhancers is the use of mucoadhesive compounds. Mucoadhesives are compounds that prolong the contact between drug and mucosal membrane at the site of action (localized delivery) or at the site of absorption (systemic delivery). One of the primary advantages associated with mucoadhesives is the lengthening of the contact time, which provides drug particles with a longer time to diffuse across the mucous layer. Another major advantage is the strong interaction between drug and mucous layer forms a local barrier that prevents the metabolic activities of the nearby enzymes from degrading the drug particles (Makhlof, Werle, et al., 2008).

Currently, there are six general theories that have been adapted to explain the mechanism of mucoadhesion (Smart, 2005). They are the electronic theory, the wetting theory, the adsorption theory, the diffusion theory, the mechanical theory and the fracture theory. However, due to the relative complexity of this process, no single theory can completely and satisfactorily

TABLE II.5.16.1 Summary of Common Permeation Enhancers Used in Mucosal Drug Delivery

Permeation Enhancers	Mechanism of Action
Ionic Surfactants Sodium deoxycholate	Decrease viscosity of membrane by <ul style="list-style-type: none"> Extracting membrane proteins and lipids
Sodium taurodeoxycholate Sodium glycocholate	<ul style="list-style-type: none"> Fluidizing the membrane Disrupting associated glycoproteins in mucous layer
Sodium lauryl sulfate Sodium laurate	
Chelating and complexing agents EDTA, cytochalasin, citric acid	Alter tight junctions, increasing paracellular transport
Fatty acids and derivatives Oleic acid, lauric acid, sodium caprate, acylcarnitines Mono(di)glycerides	<ul style="list-style-type: none"> Change epithelial cell membrane molecular arrangement Alter tight junctions, increasing paracellular transport
Salicylate and analogs Sodium salicylate	<ul style="list-style-type: none"> Increase solubility and dissolution of drug
3-Methoxysalicylate 5-Methoxysalicylate	<ul style="list-style-type: none"> Calcium chelating Interact with membrane proteins
Others	
Cationic polymers	Ion-ion interaction with mucous membrane, inducing opening of tight junctions
Poly-L-arginine, chitosan Aminated gelatins	
Poly(acrylates), polycarbophil, carbomers	Mucoadhesive, inhibit enzymatic activity
Glycyrrhetic acid	Inhibit leucine aminopeptidase
Azone	Increase membrane fluidization

EDTA, ethylenediaminetetraacetic acid.

explain this phenomenon, and we have to conclude that the mechanism of mucoadhesion is probably due to some combination of the six theories. Regardless of the specific basis for each theory, the general consensus is that there are two major stages in the mucoadhesion process (Wu, 1982): the contact stage and the consolidation stage. In the contact stage, wetting occurs between the mucoadhesive material and the mucus. In the consolidation stage, various interactions occur to consolidate and strengthen the adhesive interaction, leading to a prolonged contact time.

A number of polymeric materials have been shown to display mucoadhesive properties (Table II.5.16.2). The most widely investigated groups of mucoadhesive materials are poly(acrylates) and chitosan (Makhlof, Werle, et al., 2008). Recently, new materials that allow specificity or prolonged and strengthened contact have also been investigated. Examples of these new materials are

TABLE II.5.16.2 Common Mucoadhesive Polymers Used in Mucosal Drug Delivery

Mucoadhesive Polymers	Mechanism of Action
Poly(acrylates)	Interact with the mucus via physical chain entanglement accompanied by hydrogen bonding
Chitosan and derivatives	<ul style="list-style-type: none"> Form hydrogen bonds Cationic nature allows interaction with negatively charged mucus
Thiolated polymers Chitosan conjugates with TGA, TBA, TEA, or glutathione	<ul style="list-style-type: none"> Form disulfide bonds with thiol groups on the cysteine-rich domains of mucin fibers Ionic interactions with mucous substrate
PAA conjugates with glutathione or cysteine	<ul style="list-style-type: none"> Hydrophobic interactions with mucous substrate
Other polymers Hyaluronic acid, CMC, HPMC and PEG	Physical entanglement, ionic interactions

TGA, thioglycolic acid; TBA, thiobutylamide; TEA, thioethylamide; PAA, poly(acrylic acid); CMC, carboxymethyl cellulose; HPMC, hydroxypropylmethyl cellulose.

thiolated polymers, polyethylene glycol (PEG), poloxamer gels, dihydroxyphenylalanine and lectins.

MUCOSAL DRUG DELIVERY SYSTEMS

While the concepts presented thus far can be applied to all mucosal drug delivery systems, it is important to realize that each route of mucosal drug delivery system has unique physiological characteristics that may change the specific formulation strategy used to deliver drugs via that particular route. In the following section, we will examine the major mucosal drug delivery systems in more detail, with particular emphasis on the appropriate strategies and materials used for each route of the mucosal delivery system.

Nasal

The principle location for nasal drug penetration is in the respiratory region of the nasal passage. The respiratory region is highly vascularized, with a dense network of fenestrated capillaries in the lamina propria. The nasal mucosa is generally considered to be penetrable for small molecules, while larger molecules may need the help of permeation enhancers to cross (Worakul and Robinson, 2002). Enzymatic activity in the nasal mucosa is low compared to other mucosal membranes in the body (Sarkar, 1992). However, the rapid rate of mucociliary clearance presents a major barrier to mucosal delivery in the nasal passage.

One approach to prolong absorption is to increase the viscosity of the dosage form. However, highly viscous

formulations are difficult to administer. Thermogelling systems were introduced as a way to circumvent this problem. These systems have low viscosity at room temperature, but can form a viscous gel at body temperature. Some examples are Poloxamer 407 solution (Juhász, Lenaerts, and Ong, 1990), ethyl (hydroxyethyl) cellulose combined with small amounts of sodium dodecyl sulfate in water (Pereswetoff-Morath, Bjurstrom, et al., 1996) and gellan gum (Gelrite).

Another approach to sustain drug release at the site of administration and avoid rapid mucociliary clearance is the use of bioadhesives and bioadhesive microspheres. An early study by Nagai et al. (Nagai, Nishimoto, Nambu, Sozaki, and Sekine, 1984) demonstrated that the bioavailability of freeze-dried powder form of insulin combined with Carbopol 943 (Carbopol® is a lightly cross-linked polyacrylic acid) was equivalent to the parenteral administration of insulin solutions of three times the dose. In another study, Morimoto et al. (Morimoto, Tabata, et al., 1987) developed a nasal delivery system for nifedipine using a mixture of the drug, PEG 400 and Carbopol 941 as mucoadhesives. The results showed that a relatively high plasma drug concentration was achieved and maintained. Nakamura et al. (Nakamura, Ohta, et al., 1996) experimented on several different mucoadhesives in the nose. Their study demonstrated that xanthan gum had the longest residence time, followed by tamarind gum, hydroxypropyl cellulose (HPC) and polyvinyl alcohol. Microspheres not only have increased residence times through strong adhesive interactions with the mucous layer, but also can widen the tight junctions temporarily (Pereswetoff-Morath, 1998). Illum et al. (Davis, Illum, et al., 1987) showed that the half-life clearance of the starch microspheres was approximately 240 min compared to 15 min for control formulations of liquids and powders. A study conducted by Witschi and Mrsny (Witschi and Mrsny, 1999) found that protein transport across Calu-3 cells (a type of cell line derived from human respiratory tract epithelial cells) was increased by using Carbopol and chitosan microparticles.

Buccal

Buccal drug delivery is the administration of drugs through the mucosa lining the insides of the cheeks. The buccal mucosa is relatively thick and dense, with multiple layers of cells in the epithelium, which decrease the permeability of the mucosa considerably. It is also difficult to keep the formulation in place due to both the huge amount of saliva that is secreted and the reflex action of swallowing. What's more, we have to also take into consideration the abundance of enzymes present in the oral cavity, which can enzymatically degrade the drug particles.

Strategies to enhance the absorption of buccal-delivered drugs have been studied extensively in the past. In a promising study for buccal drug administration, Nagai

was able to formulate a small, double-layered tablet, with an upper layer of lactose and a lower layer of mucoadhesives containing HPC and Carbopol 934P (CP). There have been numerous other studies that explore the use of other mucoadhesives besides just HPC and CP. Robinson et al. (Robinson, Longer, et al., 1987) were able to design a buccal patch using polycarbophil (polycarbophil is a synthetic polymer of polyacrylic acid cross-linked with divinyl glycol). This patch was tested in dogs and found to remain in place while eating and drinking. More recently, buccal adhesive tablets of metronidazole were formulated using CP, hydroxypropylmethyl cellulose and sodium carboxymethyl cellulose as mucoadhesives (Ahuja, Khar, et al., 1998). These tablets were held in place in the buccal cavity for 6 h and released metronidazole continuously. Other materials that have also been experimented on for enhancing buccal delivery include hydroxyethyl cellulose (Anders and Merkle, 1989), polyvinylpyrrolidone, sodium alginate (Remunan-Lopez, Portero, et al., 1998) and gellan gum.

Ophthalmic

Any ocular administration of drugs is countered by the reflex tear and blinking action, which will quickly remove the drugs from the site of contact, resulting in poor bioavailability of the drugs and inadequate therapeutic effect. Therefore, the main challenge in ophthalmic drug delivery is to retain the drug for a sufficiently long period of time on the ocular mucosa. The appropriate strategy is to choose a vehicle for the drug that will retard ocular drug elimination and increase the amount of contact time. Examples of such vehicles are gels, nano- and microparticles and polymer matrices (Sintzel, Bernatchez, et al., 1996).

Gels or viscous solutions have been extensively investigated for their use in ophthalmic drug delivery. Most of these gels are prepared from hydrophilic polymers, which prolong the corneal residence time; consequently, drug bioavailability is improved. The most widely used hydrophilic polymers for gels or viscous solutions are semi-synthetic derivatives of cellulose and poly(vinyl alcohol). Other viscosifiers include many natural or semisynthetic polysaccharides such as dextran, xanthan and gellan gum, as well as synthetic polymers such as polyacrylates, especially poly(acrylic acid). Another mucoadhesive that is often used to increase vehicle contact time with the corneal surface is hyaluronic acid.

Since the administration of highly viscous drug formulations is an important issue that needs to be considered, in situ gelling systems have been developed that allow a solution with a relatively low viscosity at room temperature to become more viscous at temperatures approaching that of the eye. The polymers that have been successfully used in such systems are Pluronics® and Tetronics® (Vadnere, Amidon, et al., 1984). Other types of in situ gelling systems that depend on the change in chemical environment

when contacting the eye utilize polymers such as cellulose acetophthalate latex (Gurny, Boye, and Ibrahim, 1985) and the gellan derivative Gelrite.

Micro- and nanoparticles have demonstrated the ability to improve corneal contact time. The commonly used materials for microspheres are poly(lactic acid), poly(glycolic acid), their copolymers as well as natural polymers such as albumin or gelatin (Sintzel, Bernatchez, et al., 1996). The materials most often used for the formulation of nanospheres are polyalkylcyanoacrylates, polycaprolactones and copolymers of lactic and glycolic acids (Sintzel, Bernatchez, et al., 1996).

Pulmonary

The primary site of pulmonary drug absorption is within the alveoli. The delivery of drugs via the pulmonary mucosal route is often met with a variety of difficulties. The major barriers are represented by the geometry of the pulmonary tract, mucociliary clearance, pulmonary enzymes as well as macrophage activities (Worakul and Robinson, 2002). The geometry of the pulmonary tract presents a problem for the targeting of drug molecules to site of absorption and could cause particles to impact or deposit prematurely on the upper respiratory tract, where they are likely to be engulfed by mucus and removed. Within the lung, there is a diverse population of enzymes such as amine oxidase, reductases and esterases, which can metabolize the drugs (Cohen, 1990). Although cilia and mucus are absent in the alveoli, there are numerous macrophages that are capable of engulfing insoluble foreign substances and transporting them to the ciliated epithelium for clearance (Florence and Attwood, 1998).

One general approach to solve these problems is to design particles with low mass density (porous) and large diameters (10–15 μm), using biodegradable polymers or lipophilic carriers to prevent enzymatic metabolism of the drug or carrier system (Edwards, Hanes, et al., 1997). Grenha et al. produced a new pulmonary drug delivery system through the complexation of chitosan-tripolyphosphate nanoparticles with phospholipids and microencapsulating these complexes by spray-drying with mannitol (Grenha, Remunan-Lopez, et al., 2008). The resulting microspheres had adequate characteristics for delivery to the deep lung. Kawashima modified the surface of powders by using (hydroxypropyl-methylcellulose)phthalate, which dramatically improved the inhalation properties of the powders compared with the original unaltered formulation (Kawashima, Serigano, et al., 1998). Ben-Jebria et al. (Ben-Jebria, Chen, et al., 1999) utilized dipalmitoylphosphatidylcholine as lipophilic carrier to sustain bronchodilation in the lungs. They found that the inhalation of large porous particles inhibited bronchoconstriction more than three times longer than small porous particles.

Another approach is to enhance the retention time within the lungs. One method that has been extensively

studied is the entrapment of drug particles in liposomes. Taylor et al. (Taylor, Taylor, et al., 1989) studied the effect of sodium cromoglycate inhaled as a solution or encapsulated in dipalmitoylphosphatidylcholine-cholesterol liposomes and found that the encapsulated drug displayed longer retention times within the lung. In another experiment, cytosine arabinoside in free or liposome-encapsulated form was given to rats via intratracheal instillation (Juliano and McCullough, 1980). The encapsulated form prolonged the effect of the drug in the lung. Mucoadhesives have also been used. Tahara et al. successfully prepared poly(lactide-co-glycolide) nanospheres and modified the nanosurface with chitosan to improve mucosal peptide administration (Tahara, Yamamoto, et al., 2007).

Gastrointestinal

The oral route of drug administration is still by far the most popular delivery route due to its relative ease of administration and high patient compliance. However, oral dosage forms commonly encounter several problems that can influence their absorption from the GI tract. These problems include (1) the variations in pH as drug particles travel through the GI tract; (2) the profusion and huge variety of enzymes that are present in the GI tract; and (3) the complex and diverse absorptive surfaces throughout the GI tract.

Due to the limited absorption surface area and blood supply in surrounding tissues of the stomach, most of the drugs delivered via the gastric route have been for local effects within the stomach. The acidic environment in the stomach and the presence of enzymes such as pepsin can be detrimental to the stability of the drug particles delivered to the stomach. In addition, peristaltic contractions within the stomach greatly affect the ability of the drug to adhere to the mucosa lining for efficient drug delivery. However, despite these difficulties, progress has been made toward stabilizing the formulation at acidic pH values and prolonging the gastric residence time using a variety of methods.

There are typically three types of methods to prolong gastric retention (Conway, 2005). The first is through the design of a floating system, which utilizes the floating behavior of substances in the gastric fluid. Multiple-unit divided systems such as microspheres have been extensively studied. Polymers often used in this type of formulation include casein-gelatin (Bulgarelli, Forni, et al., 2000), acrylic polymers such as Eudragits (Lee, Park, et al., 1999) and alginates (Murata, Sasaki, et al., 2000). A second approach is the use of mucoadhesive systems. Akiyama et al. (Akiyama, Nagahara, et al., 1995) prepared microspheres of CP dispersion in polyglycerol esters of fatty acid (PGEF) that prolonged GI transit time by adhering to the gastric or upper intestinal mucosa. Nagahara et al. (Nagahara, Akiyama, et al., 1998) tested this system for the anti-*Helicobacter pylori* effect of amoxicillin and found that the amount of the drug left in the

stomach of Mongolian gerbils was approximately three times higher than that of the drug in 0.5% methylcellulose suspension. This effect was attributed to the increase in adhesion due to the CP-PGEF system. Chitosan, one of the most widely investigated mucoadhesives for gastric delivery, has produced results that show improved adhesion and sustained release of drugs in the stomach (Sugimoto, Yoshida, et al., 1998) and so have studies involving microencapsulation with combinations of polycarbophil and Carbopol. Finally, the third approach to prolong gastric mucosal retention time is the employment of swelling systems, which mainly include the family of polymeric hydrogels. Some examples of these hydrogels are chitosan-poly(acrylic acid) hydrogel, chitosan-poly(*N*-isopropylacrylamide) stimuli-responsive hydrogel and (acrylamide-co-acrylic acid) hydrogel (Chen, Blevins, et al., 1998; de la Torre, Enobakhare, et al., 2003).

It is important to point out that these bioadhesive systems for intestinal mucosal delivery are nonspecific. Targeting a particular area on a mucosal surface is very difficult, but recent advances have been made using lectin. Lectins are proteins capable of interacting specifically with epithelial cells by binding with sugar residues on the surface of the cells (Pusztai, Bardocz, and Ewen, 1999). In two separate studies, Lehr, Bouwstra, et al. (1992) and Naisbett and Woodley (1994) found that tomato lectin binds specifically to the small intestine *in vitro*. Thus, bioadhesive systems are sometimes formulated by grafting lectins onto the surface of microspheres, nanospheres and liposomes.

Vaginal

One of the key features of the vaginal mucosa is that its thickness varies with the menstrual cycle, which is regulated by fluctuations in hormonal levels. Estrogen increases the mucosal thickness and the amount of endocervical fluid while decreasing the viscosity of the fluid. Progesterone increases the amount of glycogen and fluid secretion from the epithelium as well as the viscosity of the fluid. These cyclic changes affect the absorption of drug particles in different ways. For example, Okada et al. investigated the effect of the estrus cycle on vaginal absorption of insulin, phenolsulfonaphthalein and salicylic acid in rats (Okada, Yashiki, et al., 1983). They concluded that the estrus cycle has more effect on hydrophilic compounds than on hydrophobic compounds. This must be taken into consideration when formulating drugs for vaginal mucosal delivery. Another factor is the presence of enzymes such as β -glucuronidase, acid phosphatase, phosphoamidase and various proteases in the vaginal mucosa. These enzymes could potentially degrade the drugs designed for vaginal mucosal delivery.

Vaginal delivery systems typically suffer from short residence times. Robinson and Bologna presented a possible solution to this problem by using a vaginal delivery system consisting of Polycarbophil® (Robinson and Bologna, 1993). This system was able to remain on the vaginal tissue

for 3–4 days. Lee and Chien (Lee and Chien, 1996) used CP as a gel base and combined nonoxynol 9 with a chelating agent (ethylenediaminetetraacetic acid). This vaginal drug delivery platform demonstrated a longer contact time with the vaginal mucosa. Another formula made from Nonoxynol 9 coprecipitated with polyvinylpyrrolidone with or without iodine was incorporated into bilayer tablets or hard gelatin capsules. These systems were able to release their contents rapidly and sustained drug levels for at least 4 h (Digenis, Nosek, et al., 1999). The longer residence time on the vaginal mucus is especially important for delivery of microbicides. Kiser et al. used hydroxyethylcellulose gel to deliver tenofovir and to block HIV from penetrating the vaginal mucus (Kiser et al. 2012). In a recent research by Albertini et al., the lipid-hydrophilic matrix Gelucire 53/10 was used as a carrier for the antifungal drug econazole nitrate along with several other mucoadhesive polymers such as chitosan, sodium carboxymethyl cellulose and poloxamers (Lutrol F68 and F127) (Albertini, Passerini, et al., 2009). It was found that the poloxamers-matrix combination best improved the bioavailability of the low-bioavailable drug and its mucoadhesive strength. Other formulations that were found capable of enhancing vaginal mucosal delivery include microspheres of hyaluronic acid esters (Richardson, Whetstone, et al., 1996) and liposomes incorporated into polyacrylamide gel (Jain, Singh, et al., 1997).

CONCLUSIONS

This chapter presents an overview of mucosal drug delivery and includes descriptions of the structure and composition of the mucosal membrane, the mechanisms of transport, the barriers drug particles may face, strategies to overcome these barriers, and some specific mucosal drug delivery systems. However, our current knowledge of this field is still far from being sufficient and many areas are yet to be understood. Although mucosal drug delivery offers a number of advantages over traditional routes of delivery (such as parenteral delivery), there are still many challenges facing us in designing an effective mucosal drug delivery system.

REFERENCES

- Ahuja, A., Khar, R. K., & Chaudhry, R. (1998). Evaluation of buccoadhesive metronidazole tablets: microbiological response. *Pharmazie*, 53(4), 264–267.
- Akiyama, Y., Nagahara, N., Kashihara, T., Hirai, S., & Toguchi, H. (1995). In-vitro and in-vivo evaluation of mucoadhesive microspheres prepared for the gastrointestinal-tract using polyglycerol esters of fatty-acids and a poly(acrylic acid) derivative. *Pharm. Res.*, 12(3), 397–405.
- Albertini, B., Passerini, N., Di Sabatino, M., Vitali, B., Brigidi, P., & Rodriguez, L. (2009). Polymer-lipid based mucoadhesive microspheres prepared by spray-congealing for the vaginal delivery of econazole nitrate. *Eur. J. Pharm. Sci.*, 36(4–5), 591–601.
- Amsden, B. (1999). An obstruction-scaling model for diffusion in homogeneous hydrogels. *Macromolecules*, 32(3), 874–879.

- Anders, R., & Merkle, H. P. (1989). Evaluation of laminated muco-adhesive patches for buccal drug delivery. *Int. J. Pharm.*, **49**(3), 231–240.
- Ben-Jebria, A., Chen, D. H., Eskew, M. L., Vanbever, R., Langer, R., & Edwards, D. A. (1999). Large porous particles for sustained protection from carbachol-induced bronchoconstriction in guinea pigs. *Pharm. Res.*, **16**(4), 555–561.
- Bulgarelli, E., Forni, F., & Bernabei, M. T. (2000). Effect of matrix composition and process conditions on casein-gelatin beads floating properties. *Int. J. Pharm.*, **198**(2), 157–165.
- Carlstedt, I., & Sheehan, J. K. (1984). Is the macromolecular architecture of cervical, respiratory and gastric mucins the same. *Biochem. Soc. Transact.*, **12**(4), 615–617.
- Chen, J., Blevins, W. E., Park, H., Park, K. (2000). Gastric retention properties of superporous hydrogel composites. In: *5th symposium on controlled drug delivery, Noordwijk Aan Zee, Netherlands*.
- Chien, Y. W. (1995). Biopharmaceutics basis for transmucosal delivery. *Stp Pharm. Sci.*, **5**(4), 257–275.
- Cohen, G. M. (1990). Pulmonary metabolism of foreign compounds – its role in metabolic-activation. *Environ. Health Perspect.*, **85**, 31–41.
- Cone, R. (2005). *Mucus*. Mucosal immunology. J. Mestecky, Elsevier. 49–72.
- Cone, R. A. (2009). Barrier properties of mucus. *Adv. Drug Deliv. Rev.*, **61**(2), 75–85.
- Conway, B. R. (2005). Drug delivery strategies for the treatment of *Helicobacter pylori* infections. *Curr. Pharm. Des.*, **11**(6), 775–790.
- Corthesy, B., & Kraehenbuhl, J. P. (1999). *Antibody-mediated protection of mucosal surfaces. Defense of mucosal surfaces: Pathogenesis, immunity and vaccines* (Vol. 236). Berlin: Springer-Verlag Berlin.
- Davis, S. S., Illum, L., Burgess, D., Ratcliffe, J., & Mills, S. N. (1987). Microspheres as controlled-release systems for parenteral and nasal administration. *ACS Symp. Ser.*, **348**, 201–213.
- Digenis, G. A., Nosek, D., Mohammadi, F., Darwazeh, N. B., Anwar, H. S., & Zavos, P. M. (1999). Novel vaginal controlled-delivery systems incorporating coprecipitates of non-oxynol-9. *Pharm. Dev. Technol.*, **4**(3), 421–430.
- Edwards, D. A., Hanes, J., Caponetti, G., Hrkach, J., Ben-Jebria, A., Eskew, M. L., et al. (1997). Large porous particles for pulmonary drug delivery. *Science*, **276**(5320), 1868–1871.
- Florence, A. T., & Attwood, D. (1998). Physicochemical principles of pharmacy. In Florence A. T., Attwood D. (Eds.), *Drug absorption and routes of administration* (pp. 372–447). Wales, Ebbw Vale, U.K.: Creative Print and Design.
- Grenha, A., Remunan-Lopez, C., Carvalho, E. L.S., & Seijo, B. (2008). Microspheres containing lipid/chitosan nanoparticles complexes for pulmonary delivery of therapeutic proteins. *Eur. J. Pharm. Biopharm.*, **69**(1), 83–93.
- Gurny, R., Boye, T., & Ibrahim, H. (1985). Ocular therapy with nanoparticulate systems for controlled drug delivery. *J. Control. Release*, **2**, 353–361.
- Hanes, J., & Demeester, J. (2009 Feb 27). Drug and gene delivery to mucosal tissues: the mucus barrier. Preface. *Adv. Drug Deliv. Rev.*, **61**(2), 73–74.
- Jain, S. K., Singh, R., & Sahu, B. (1997). Development of a liposome based contraceptive system for intravaginal administration of progesterone. *Drug Dev. Ind. Pharm.*, **23**(8), 827–830.
- Juhász, J., Lenaerts, V., & Ong, H. (1990). Poloxamer gels for peptide delivery: in vitro studies. *J. Control. Release*, **13**.
- Juliano, R. L., & McCullough, H. N. (1980). Controlled delivery of an anti-tumor drug – localized action of liposome encapsulated cytosine-arabinoside administered via the respiratory system. *J. Pharmacol. Exp. Ther.*, **214**(2), 381–387.
- Kawashima, Y., Serigano, T., Hino, T., Yamamoto, H., & Takeuchi, H. (1998). A new powder design method to improve inhalation efficiency of pranlukast hydrate dry powder aerosols by surface modification with hydroxypropylmethylcellulose phthalate nanospheres. *Pharm. Res.*, **15**(11), 1748–1752.
- Kerss, S., Allen, A., & Garner, A. (1982). A simple method for measuring thickness of the mucus gel layer adherent to rat, frog and human gastric mucosa – influence of feeding, prostaglandin, N-acetylcysteine and other agents. *Clin. Sci.*, **63**(2), 187–195.
- Kiser, P. F., Mahalingam, A., Fabian, J., Smith, E., Damian, F. R., Peters, J. J., et al. (2012). Design of tenofovir-UC781 combination microbicide vaginal gels. *J. Pharm. Sci.*, **101**(5), 1852–1864.
- Lai, S. K., O'Hanlon, D. E., Harrold, S., Man, S. T., Wang, Y. Y., Cone, R., et al. (2007). Rapid transport of large polymeric nanoparticles in fresh undiluted human mucus. *Proc. Natl. Acad. Sci. U. S. A.*, **104**, 1482–1487.
- Lai, S. K., Wang, Y. Y., & Hanes, J. (2009). Mucus-penetrating nanoparticles for drug and gene delivery to mucosal tissues. *Adv. Drug Deliv. Rev.*, **61**(2), 158–171.
- Lee, C. H.C., & Chien, Y. W. (1996). Development and evaluation of a mucoadhesive drug delivery system for dual-controlled delivery of Nonoxynol-9. *J. Control. Release*, **39**, 93–103.
- Lee, J. H., Park, T. G., & Choi, H. K. (1999). Development of oral drug delivery system using floating microspheres. *J. Microencapsul.*, **16**(6), 715–729.
- Lehr, C. M., Bouwstra, J. A., Kok, W., Noach, A. B. J., Deboer, A. G., & Junginger, H. E. (1992). Bioadhesion by means of specific binding of tomato lectin. *Pharm. Res.*, **9**(4), 547–553.
- Makhlof, A., Werle, M., & Takeuchi, H. (2008). Mucoadhesive drug carriers and polymers for effective drug delivery. *J. Drug Deliv. Sci. Technol.*, **18**(6), 375–386.
- Marriott, C., & Gregory, N. P. (1990). *Mucus physiology and pathology*. Bioadhesive drug delivery systems. V. Lanaerts, R. Gurny, Florida: CRC Press.
- Morimoto, K., Tabata, H., & Morisaka, K. (1987). Nasal absorption of nifedipine from gel preparations in rats. *Chem. Pharm. Bull.*, **35**(7), 3041–3044.
- Murata, Y., Sasaki, N., Miyamoto, E., & Kawashima, S. (2000). Use of floating alginate gel beads for stomach-specific drug delivery. *Eur. J. Pharm. Biopharm.*, **50**(2), 221–226.
- Nagahara, N., Akiyama, Y., Nakao, M., Tada, M., Kitano, M., & Ogawa, Y. (1998). Mucoadhesive microspheres containing amoxicillin for clearance of *Helicobacter pylori*. *Antimicrob. Agents Chemother.*, **42**(10), 2492–2494.
- Nagai, T., Nishimoto, Y., Nambu, N., Sozuki, Y., & Sekine, K. (1984). Powder dosage form of insulin for nasal administration. *J. Control. Release*, **1**, 15–22.
- Naisbett, B., & Woodley, J. (1994). The potential use of tomato lectin for oral-drug delivery. 1. Lectin-binding to rat small-intestine in-vitro. *Int. J. Pharm.*, **107**(3), 223–230.
- Nakamura, F., Ohta, R., Machida, Y., & Nagai, T. (1996). In vitro and in vivo nasal mucoadhesion of some water-soluble polymers. *Int. J. Pharm.*, **134**(1–2), 173–181.
- Okada, H., Yashiki, T., & Mima, H. (1983). Vaginal absorption of a potent luteinizing-hormone releasing hormone analog (leuprolide) in rats. 3. Effect of estrous-cycle on vaginal absorption of hydrophilic model compounds. *J. Pharm. Sci.*, **72**(2), 173–176.
- Olmsted, S. S., Padgett, J. L., Yudin, A. I., Whaley, K. J., Moench, T. R., & Cone, R. A. (2001). Diffusion of macromolecules and virus-like particles in human cervical mucus. *Biophys. J.*, **81**(4), 1930–1937.
- Pereswetoff-Morath, L. (1998). Microspheres as nasal drug delivery systems. *Adv. Drug Deliv. Rev.*, **29**(1–2), 185–194.
- Pereswetoff-Morath, L., Bjurstrom, S., Khan, R., Dahlin, M., & Edman, P. (1996). Toxicological aspects of the use of dextran microspheres and thermogelling ethyl(hydroxyethyl) cellulose (EHEC) as nasal drug delivery systems. *Int. J. Pharm.*, **128** (1–2), 9–21.

- Pusztai, A., Bardocz, S., & Ewen, S. W. B. (1999). Bioadhesive drug delivery systems: Fundamentals, novel approaches and development. In E. Mathiowitz, D. E. Chickering Lehr, C. M. (Eds.), *Plant lectins for oral drug delivery to different parts of the gastrointestinal tract* (pp. 387–407). New York: Marcel Dekker.
- Rathbone, M. J., & Tucker, I. G. (1993). Mechanisms, barriers and pathways of oral mucosal drug permeation. *Adv. Drug Deliv. Rev.*, **12**(1–2), 41–60.
- Remunan-Lopez, C., Portero, A., Vila-Jato, J. L., & Alonso, M. J. (1998). Design and evaluation of chitosan/ethylcellulose mucoadhesive bilayered devices for buccal drug delivery. *J. Control. Release*, **55**(2–3), 143–152.
- Richardson, J. L., Whetstone, J., Fisher, A. N., Watts, P., Farraj, N. F., Hinchcliffe, M., et al. (1996). Gamma-scintigraphy as a novel method to study the distribution and retention of a bioadhesive vaginal delivery system in sheep. *J. Control. Release*, **42**(2), 133–142.
- Robinson J. R. & Bologna W. J. (1993). Vaginal and reproductive system treatments using a bioadhesive polymer. In *6th International symposium on recent advances in drug delivery systems, Salt Lake City, UT*.
- Robinson, J. R., Longer, M. A., & Veillard, M. (1987). Bioadhesive polymers for controlled drug delivery. *Ann. N. Y. Acad. Sci.*, **507**, 307–314.
- Robinson, J. R., & Yang, X. (1999). Absorption enhancers *Encyclopedia of pharmaceutical technology. J. Swarbrick, J.C. Boylon* (Vol. 18) (pp. 1–27). New York: Marcel Dekker.
- Ross, M. H., Romrell, L. J., & Kaye, G. I. (1995). Histology: A text and atlas. In M. H. Ross Romrell L.J. Kaye, G.I. (Eds.), *Epithelial tissue*(pp. 58–93). Baltimore: Williams and Wilkins.
- Saltzman, W. M., Radomsky, M. L., Whaley, K. J., & Cone, R. A. (1994). Antibody diffusion in human cervical-mucus. *Biophys. J.*, **66**(2), 508–515.
- Sarkar, M. A. (1992). Drug-metabolism in the nasal-mucosa. *Pharm. Res.*, **9**(1), 1–9.
- Shen, W. C., & Lin, Y. J. (1994). Drug permeation enhancement: Theory and application. In D. S. Hsieh (Ed.), *Basic mechanisms in transepithelial transport enhancement* (pp. 25–40). New York: Marcel Dekker.
- Sintzel, M. B., Bernatchez, S. F., Tabatabay, C., & Gurny, R. (1996). Biomaterials in ophthalmic drug delivery. *Eur. J. Pharm. Biopharm.*, **42**(6), 358–374.
- Smart, J. D. (2005). The basics and underlying mechanisms of mucoadhesion. *Adv. Drug Deliv. Rev.*, **57**(11), 1556–1568.
- Sonju, T., Christen, T. B., Kornstad, L., & Rolla, G. (1974). Electron-microscopy, carbohydrate analyses and biological-activities of proteins adsorbed in 2 hours to tooth surfaces in vivo. *Caries Res.*, **8**(2), 113–122.
- Sugimoto, K., Yoshida, M., Yata, T., Higaki, K., Kimura, T. (1998). Evaluation of poly(vinyl alcohol) gel spheres containing chitosan as dosage form to control gastrointestinal transit time of drugs. *Biol. Pharm. Bull.*, **21**(11), 1202–1206.
- Tahara, K., Yamamoto, H., Takeuchi, H., & Kawashima, Y. (2007). Development of gene delivery system using PLGA nanospheres. *Yakugaku Zasshi – J. Pharm. Soc. Japan*, **127**(10), 1541–1548.
- Taylor, K. M. G., Taylor, G., Kellaway, I. W., & Stevens, J. (1989). The influence of liposomal encapsulation on sodium cromoglycate pharmacokinetics in man. *Pharm. Res.*, **6**(7), 633–636.
- de la Torre, P. M., Enobakhare, Y., Torrado, G., & Torrado, S. (2003). Release of amoxicillin from polyionic complexes of chitosan and poly(acrylic acid). Study of polymer/polymer and polymer/drug interactions within the network structure. *Biomaterials*, **24**(8), 1499–1506.
- Vadnere, M., Amidon, G., Lindenbaum, S., & Haslam, J. L. (1984). Thermodynamic studies on the gel sol transition of some pluronic polyols. *Int. J. Pharm.*, **22**(2–3), 207–218.
- Witschi, C., & Mrsny, R. J. (1999). In vitro evaluation of microparticles and polymer gels for use as nasal platforms for protein delivery. *Pharm. Res.*, **16**(3), 382–390.
- Worakul, N., & Robinson, J. R. (2002). Polymeric biomaterials. *Drug delivery via mucosal routes* (pp. 1031–1062). New York: Marcel Dekker.
- Wu, S. (1982). *Formation of adhesive bond, polymer interface and adhesion*. New York: Marcel Dekker.
- Yamamoto, A., Hayakawa, E., & Lee, V. H. L. (1990). Insulin and proinsulin proteolysis in mucosal homogenates of the albino rabbit – implications in peptide delivery from nonoral routes. *Life Sci.*, **47**(26), 2465–2474.

APPENDIX G: CHAPTER II.5.16 — DRUG DELIVERY SYSTEMS: I, SMART HYDROGELS AS IN VIVO DRUG DELIVERY SYSTEMS

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INTRODUCTION

Hydrogels have been studied for more than a 100 years, initially as colloidal systems; however, systematic studies on the biological use of hydrogels began in 1960 with the introduction of poly(hydroxyethyl methacrylate) gels by Wichterle and Lim (Wichterle and Lim, 1960). Since then, the number of publications on hydrogels per year increased gradually until 1990, when the number began to grow exponentially. Currently, the number of

publications on hydrogels per year is close to 4000. This is partly due to the introduction of smart hydrogels (also called intelligent hydrogels) that have been an essential tool in the development of advanced biomaterials and drug delivery systems (DDS).

Ordinary hydrogels are those that swell by absorbing a large amount of water and shrink (or deswell) as the water is removed. “Smart” hydrogels are those that have the ability to undergo sharp structural changes in response to small changes in environmental stimuli, such as temperature and pH. The structural changes include not only swelling/deswelling, but also sol–gel phase transition, degradation, and shape transformation. The environmental stimuli can be divided into three categories: physical, chemical, and biological. Individual stimuli and polymers that react to the stimuli are listed in Table II.5.16.1. The four major areas of applications of smart hydrogels are controlled drug delivery, tissue engineering, bioseparations, and biosensor/bioimaging (Bayer and Peppas, 2008; Qiu and Park, 2001;