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Hydrogels for Drug Delivery System: Colon-Specific Delivery

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히드로겔을 이용한 약물수송시스템

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A major problem with the peptide-based drugs is that these drugs must generally be administered by injection. Therefore, there is considerable research interest in alternative routes of delivery, such as buccal, nasal, gastrointestinal route and etc. Site-specific drug delivery to the colon, as an alternative to parenteral drug delivery, is of interest for the delivery of peptide-based drugs as well as the delivery of low molecular weight drugs for the treatment of colonic disease. This review describes some considerations of colon-specific drug delivery using hydrogels.

Keywords—Hydrogels; Colon-specific delivery; Biodegradable hydrogels; Stimuli-sensitive hydrogels.

Hydrogels are defined as infinite three-dimensional polymeric networks (cross-linked structures) containing considerable amounts of water, e. g., more than 20%.[1,2] Crosslinks can be formed by covalent or ionic bonds. Often, weaker forces (hydrogen bond, van der Waals forces) can serve as crosslinks. In addition, semicrystalline, uncrosslinked hydrophilic polymers may form hydrogels upon swelling since the crystallites act as physical crosslinks and do not dissolve in water.

Due to their high water content, hydrogels possess in general good biocompatibility.[3] Hydrogels have been extensively studied as potential candidates for replacement of soft tissue or for other medical applications.[4,5] Hydrogels have in general the following unique properties: (a) water insolubility in physiological environments; (b) swellability to an equilibrium value; and (c) good biocompatibility. Hydrogels have been widely investigated for use in controlled release systems. The primary advantages in using hydrogels are: first, it is easy to remove toxic residual monomers and initiators after polymerization by extraction with solvent. Second, the swelling kinetics of hydrogels is reproducible and the degree of swelling can be very high, which allows for high permeability to solutes and good prediction of release kinetics. The permeability of a specific drug can be controlled by varying structure and crosslinking density of the hydrogel. In addition to the ability of controlling the release of drug from the device, hydrogels can protect the drug from degradation in the body. They can release the drug after response to stimuli, by degradation of the device or after being targeted to a specific site in the body.[6]

This review will be divided into the following parts: general hydrogel systems, stimuli-sensitive hydrogel systems and degradable hydrogel system. Examples illustrating these gel systems will be focused on site-specific drug delivery to colon.

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General Hydrogel Systems

Design of Hydrogel Drug Delivery Devices

The hydrogel device can be designed in several ways which influence the release rate of drug from hydrogel. Depending on the polymer or copolymer composition, both hydrophobic and hydrophilic drugs, ions and macromolecules, diffuse through or out of hydrogel membrane. Typical hydrophilic monomers and the main polymerization methods used in the preparation of hydrogels are summarized in Table I and II, respectively. Hydrogels can generally be devided into two system: monolithic and reservoir system,[7] as shown in Figure 1.

In monolithic systems the drug is either dissolved or suspended uniformly within the hydrogel. The release rate from monolithic devices is not zero-order, but more likely first or mixed zero/first order due to the decrease in the concentration inside the gel. Drug release rate decreases with time. The rate will be controlled by the amount of drug loaded into the gel and by the properties of the hydrogel, such as surface area and permeability of drug through polymer.

Reservoir systems have a core containing the drug surrounded by a release rate-limiting barrier. The release rate is determined by the properties of the surrounding polymer, such as surface area, thickness and permeability of the drug through the polymer. Release from the reservoir devices is zero-order as the concentration of drug in the membrane is constant. When depletion of the reservoir occurs, the rate will decrease. The disadvantage of reservoir system can occur when a large amount of drug loaded inside the gel, if the device is defective, can become hazardous to the patients.[7]

Drug delivery devices can be fabricated as a combination of the two types of devices which could result in a mixed release profile depending on the properties of the devices. Release from biodegradable hydrogels can also result in a mixed release profile, depending on whether the re-

Table I—*Monomers for Preparation of Hydrogels*

Hydroxyethyl methacrylate (HEMA)	$CH_2=C(CH_3)COOCH_2CH_2OH$
Hydroxyethoxyethyl methacrylate (HEEMA)	$CH_2=C(CH_3)COOCH_2CH_2OCH_2CH_2OH$
Hydroxydiethoxyethyl methacrylate (HDEEMA)	$CH_2=C(CH_3)COOCH_2CH(2OCH_2CH_2OH)$
Methoxyethyl methacrylate (MEMA)	$CH_2=C(CH_3)COOCH_2CH_2OCH_3$
Methoxydiethoxyethyl methacrylate (MDEEMA)	$CH_2=C(CH_3)COOCH_2CH_2OCH_2CH_2OCH_3$
Ethylene glycol dimethacrylate (EGDMA)	$CH_2=C(CH_3)COOCH_2CH_2OOCC(CH_3)=CH_2$
Vinyl acetate	$CH_2=CHCOOCH_3$
N-vinyl-2-pyrrolidone (NVP)	$CH_2=CHNCOCH_2CH_2CH_2$
Methacrylic acid (MA)	$CH_2=C(CH_3)COOH$
Sodium styrene sufonate	$CH_2=CH(C_6H_4)\text{-}SO_3^-Na^+$

Table II—*Polymerization Methods for Preparation of Hydrogels*

Polymerization	Important features
Bulk	Only initiators and monomer needed; crosslinker can be added.
Solution	Initiator, solvent and monomer needed; easy agitation: controlled heat transfer: polymer soluble or insoluble in solvent.
Suspension	Initiator, solvent, monomer and suspending agent needed, crosslinker can be added; polymer produced in spherical or irregular particles depending on monomer/suspending agent interfacial tension.
Emulsion	Initiator, solvent, monomer, suspending agent, and emulsifier needed.
Gaseous	Reaction in gaseous phase; high pressure: unknown kinetics.
Plasma	Glow discharge; unknown kinetics

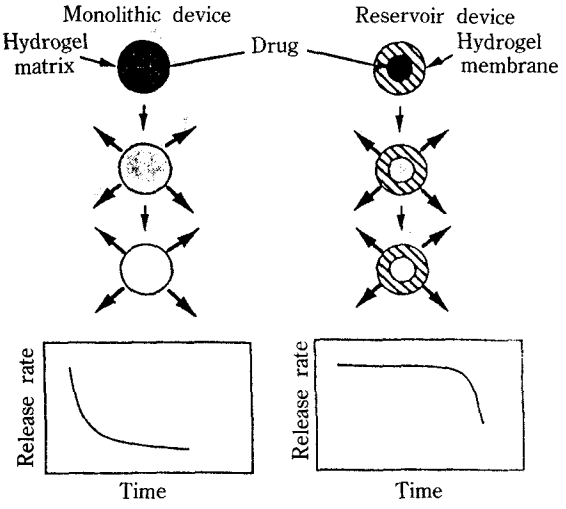

Figure 1—Schematics for delivery of drug from monolithic and reservoir type devices and typical release profile.

lease is diffusion or degradation controlled and whether it is a monolithic or reservoir type device.

Many factors influence the permeability of hydrogels as summarized in Table III. These include equilibrium degree of swelling, hydrophilicity/hydrophobicity of the polymer and crosslinking density.[8] Hydrophilic drugs are predominantly assumed to diffuse by a "pore" mechanism; permeation occurs through water-filled pores created by the interpenetration of the chains in the polymer network. This has been described by Yasuda *et al.*,[9,10] who developed the free volume theory. The theory describes the relationship between the diffusion coefficient of small solute and the swelling (hydration) of the membrane in which diffusion take place:

$$\ln\frac{Dm}{Do}\alpha-\frac{Bq^2}{Vf}\left[\frac{1}{H}-1\right]$$

where Dm is the solute diffusion coefficient in the membrane, Do is the self diffusion coefficient, Bq^2 is proportional to solute cross-sectional area (πr^2), Vf is the molar free volume and H is the equilibrium hydration of polymer. This demonstrates that natural logarithm of the diffusion coefficient is proportional to the inverse of hydration, where the hydration is the volume fraction of water in the membrane.[9,10] For highly swollen membranes, where the partition coefficient is close to unity, the natural logarithm of the permeability coefficient is also assumed to proportional to the inverse of the hydration. The permeability of high molecular weight molecules can also be approximated using this relationship.[11] The permeability or release of a drug loaded into the gel can be controlled by controlling the degree of swelling of the gel.

Table III—*Factors Influencing Permeability of Hydrogels*

—Crosslinking density
—Hydrophilicity/hydrophobicity of polymer backbone
—Equilibrium degree of swelling
—Solute size and hydrophilicity/hydrophobicity

Hydrophobic drugs can permeate via "partition" mechanism, where the drug (solute) interacts with and along the polymer matrix. The mechanism of diffusion is dependent on the pore size, degree of swelling, hydrophilicity/hydrophobicity of polymer, and size and hydrophilicity of solutes.[11]

General Drug Delivery Systems

Hydrogels have been widely investigated for use in controlled release systems as described earlier.

Polyacrylamide hydrogels containing insulin were prepared by Davis *et al.*[12]. These gels were implanted subcutaneously into diabetic rats. It was shown that the rats had normal urine and grew at normal rate for 20 days in contrast to untreated diabetic rats which had hyperglucosuria and slow weight gain. Implants based on polyacrylamide and polyvinylpyrolidone gels containing drug were implanted into hamsters.[13] It was concluded that an increase in polymer concentration in the gel or an increase in molecular weight of the solute resulted in a decrease in the diffusion coefficient of the solute through the gels. This was shown to be in accordance with the free volume theory.

Sorensen and Peppas[14] investigated the permeability of polyvinyl alcohol gels using proteins with varied molecular weight. It was observed that as the crosslinking density increased, the permea-

bility decreased due to the decrease in the mesh size of the gel and a decrease in equilibrium degree of swelling. This effect increased as the molecular weight of the solute increased.

Poly(hydroxyethy methacrylate) hydrogels were fabricated to enclose living pancreatic islet cells for implantation in diabetic rats.[15] ^{125}I-insulin was used for *in vitro* permeability studies. Diffusion coefficients were determined through hydrogels with varying crosslink density and water in the polymerization mixture. Diffusion through the gel was fast which was necessary in assuring good control of the blood glucose levels under physiological conditions.

Macromolecular diffusion through collagen membrane was investigated by Gilbert *et al.*[16] Collagen membranes with different quarternary structure, crosslinking density, hydrophilicity of crosslinker and membrane porosity were evaluated. Diffusion of macromolecule was shown to take place by "pore" mechanism. An increase in crosslinking density or in hydrophobicity of crosslinker decreased permeability.

Colton *et al.*,[17] investigated the permeability of cellulose membranes for various molecular weight compounds, ranging from 58,000 to 68,000. The Permeability was related to water content and mechanical strength properties. It was found that permeability decreased as a molecular wegith (m. w.) of solute increased. This was most pronounced for membrane with low water content such as cellophane membrane. This supports the free volume theory, even for high m.w. compounds.

Sato and Kim[18] studied the permeability of porous and dense hydrogels, cellulose and biodegradable polymers to macromolecules. Depending on the size of the solute, membrane water content and pore size, it was concluded that macromolecules diffuse via bulklike water in the polymer, depending on the degree of swelling of the membrane and solute size and hydrophilicity. Similar results regarding peptide drug permeability in the hydrogels were reported by other groups.[19,20] Domb *et al.*,[19] investigated the permeability of four decapeptides (LHRH analogs) through various gels based on glycerol methacrylate, hydroxy methacrylate and methyl methacrylate. It was found that the permeability was related to swelling of the membrane and volume of the solute. Solutes with the same volume showed same permeability, regardless of chemical and physical properties of the solute. Sefton and Nishimura[20] showed that the permeability of the insulin through hydrogels was related to swelling of the membrane.

Lee[21] synthesized monolithic-type hydrogel beads with a nonuniform drug distribution. Release from these gels appeared to be zero-order, similar to release from reservoir devices. The potential in development of new drug delivery devices using this method is high, since, unlike reservoir device, it does not have the risk of leaking.

Stimuli Sensitive Hydrogels Systems

Some hydrogels exhibit changes in permeability to solute or release rate of drug incorporated into the device under different evnvironmental conditions. In general, swelling, conformational, or morphological changes in the polymer matrices are usually responsible for the altered diffusional properties. Typical examples would be the "stimuli sensitive hydrogels". These systems may be useful in adjusting drug release in response to physiological stimuli or in a pulsatile manner after external triggering (Fig. 2). Stimuli sensitive hydrogels systems can be divided into two systems: closed loop and open loop systems (Table IV). Closed loop systems are self-regulated systems where a physiological response provides feedback to the drug delivery system and a release of a drug is adjusted to these conditions. Examples are hydrogels responsive to pH,[22,23] ionic strength,[24] chemical species,[25] enzyme-substrate complexes[26,27] and competitive binding.[28] In open-loop systems, the release is insensitive to physiological changes and release is regulated from external source. As externally regulated or pulsed delivery systems, magnetic,[29] thermal,[30,31] electrical,[31] ultrasonic[32] and photochemical[33] systems can be mentioned. The advantage of closed-loop systems is, that no external triggering is needed to regulate release; physiological stimuli trigger release. Some

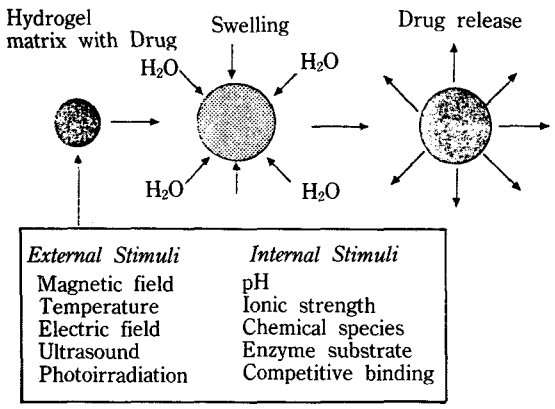

Figure 2—Stimuli sensitive hydrogel drug delivery system.

systems have demonstrated very good "on-off" control according to the body's need for the drug, e.g., insulin sensitive membranes which are regulated by glucose concentration in the blood. Important points regarding responsive polymers are problems concerning leaking from the reservoir and response kinetics. For self regulated devices, physiological variability and external source for triggering[34] are additional concerns.

pH Sensitive Hydrogels Systems

pH sensitive hydrogels usually contains pendent weakly acidic and basic groups, such as carboxylic acids and amines, or strong acids and bases, such as sulfonic acids and quarternary amonium salts. These groups change ionization in response to the change in pH, changing the properties of the gel.[35] Among the first hydrogels investigated were gels based on acrylic and methacrylic acid.[36,37] It was observed that the equilibrium degree of swelling of gels responded to changes in pH. When the pH of the swelling medium was increased, the gels showed an increase in swelling. The fact that polyelectrolyte gels change properties in response

Table IV—*Responsive Hydrogel Systems*

Stimulus	Hydrogel	Mechanism
pH	Acidic or basic	Change in pH→change in ionization→change in swelling→change in release of drug
Ionic strength	Ionioc hydrogel	Change in ionic strength→change in concentration of ions inside gel →change in swelling→change in release of drug
Chemical species	Gel containing electron accepting groups	Electron donating compounds→formation of charge transfer complex →change in swelling→change in release of drug
Enzyme-substrate	Gel containing immobilized enzyme	Substrate present→enzymatic conversion→product changes swelling of gel→change in release of drug
Competitive	Concanavalin A gel containing glycosyl -ated insulin	Increase in glucose concentration→displacement of glycosylated insulin by competetive binding→release of glycosylated insulin
Magnetic	Magnetic particles dispersed in alginate microspere	Applied magnetic field→change in pores in gel→change in swelling →change in drug release
Thermal	Thermo sensitive hydrogel, (poly(N-isopropylacrylamide))	Change in T→change in polymer-polymer and water-polymer interactions→change in swelling→change in drug release
Electrical	Polyelectrolyte gel	Applied electric field→change in membrane charge and electrophoresis of charged drug→change in swelling→change in drug release
Ultrasound irradiation	Ethylene-vinyl alcohol gel	Ultrasound irradiation→temperature increase→release of drug
Photochemical	2-Hydroxyethyl methacrylate gel	Photoirradiation→photoisomerization of azobenzene moiety→change in swelling→change in drug release

to pH can be exploited in the development of new drug delivery systems. Not many such systems have yet been described, even though the swelling properties and permeability of pH sensitive hydrogels have been studied. As described earlier, the permeability of gels is dependent on the equilibrium degree of swelling. The swelling of pH sensitive gels is more complex than that of neutral gels.

Factors Influencing the Degree of Swelling

The equilibrium degree of swelling of pH sensitive gels depends on the change of the ionic monomer, pKa of the ionizable group, degree of ionization, concentration of ionizable monomer in the network and pH, ionic strength and composition of the swelling solution. Factors such as crosslinking density and hydrophilicity/hydrophobicity of the polymer (as for uncharged gels) influence the degree of swelling and pH sensitivity, that is, the magnitude of the response to changes in pH. The effects of these factors on the equilibrium degree of swelling are summarized in Table V.

The charge of the ionic monomer affects the pH sensitivity of the gel. An acidic hydrogel will be ionized at high pH but unionized at low pH. Thus, the equilibrium degree of swelling will increase at high pH where the gel will be ionized.[22] A basic hydrogel has opposite pH dependence of swelling.[23] This was illustrated by relating the specific resistance of hydrogel membrane containing ionogenic groups to pH.[38-40] The hydrogels were based on 2-hydroxy methacrylate and methacrylic acid and N,N-(dimethylaminoethyl) methacrylate were used in order to obtain acidic, and ampholytic gels. The dependence of the specific resistance on pH as a function of content of ionogenic groups, crosslinking density and degree of neutralization were evaluated. It was found that the acidic membrane showed maximum specific resistance at pH around 3.5, the basic membrane at pH 10 and the ampholytic membrane around pH 6. Maximum specific resistance was obtained at a pH close to pKa of the membrane, where the membrane became neutral or at the isoelectic point of the ampholytic membrane.[38]

pKa was shown to influence the pH-swelling curve. An increase in the pKa of an acidic monomer shifted the curve to a higher pH.[41] It was shown that the swelling response was very sensitive at pH close to the pKa of the hydrogels. Strong acid membranes containing sulfoxyethyl methacrylate as the ionogenic monomer were found

Table V—*Factors Influencing Swelling of pH-Sensitive Hydrogels*

	Factors	Effects
Gel properties	pKa of ionic monomer	As pKa ↑, pH-ionization profile shifts to ↑ pH.
	Degree of ionization	As ionization ↑, swelling ↑.
	Charge of ionizable monomer	Acidic: as pH ↑, ionization ↑.
		Basic: as pH ↑, ionization ↓.
	Concentration of ionizable monomer	As concentration ↑, swelling in ionized state ↑.
	Crosslinking density	As density ↑, swelling ↓.
	Hydrophilicity/Hydrophopbicity of polymer backbone	As hydrophilicity ↑, swelling ↑.
Swelling solution	pH	As pH ↑, swelling ↑. (acidic)
		As pH ↑, swelling ↓. (basic)
	Ionic strength	As ionic strength ↑, osmotic pressure inside gel ↓, swelling ↓ (exception: polyelectrolyte complexes).
	Coion	Usually no charge
	Counterion	Effect depends on species (salting-in/salting-out and effect on water structure).
	Valency of counterion	Valency ↑, swelling ↓.

only to have a small dependence on pH.[42]

The concentration of ionizable monomer in the hydrogel has shown to be important for the swelling and pH sensitivity of the gel. This effect depends on the relative hydrophilicity of the ionizable monomer to neutral comonomer. It was found that as the amount of methacrylic acid in poly (methacrylic acid-co-2-hydroxyethyl methacrylate) hydrogel increases, dependence of the specific resistance on pH increases. The specific resistance increases at low pH and decreases at high pH with increased amount of methacrylic acid increases, both at low and high pH.[43]

Crosslinking density influences pH dependent swelling. An increase in crosslinking density restricts the equilibrium degree of swelling. Investigating the swelling of poly(methacrylic acid-co-2-hydroxyethyl methacrylate) hydrogels with different crosslinking density, it was found that this effect was more pronounced at high pH than at low pH. At high pH the gel was ionized and hydrophobic interactions and hydrogen bonding inside the gel present at low pH were interrupted.[22]

The effect of the structure of the polymer backbone on swelling was investigated using copolymers of methacrylic acid, butyl methacrylate and hydroxyethyl methacrylate.[44] It was found that, the more hydrophilic the polymer backbone, the lower the pH sensitivity. Siegel[23] found that increasing the hydrophobicity of the more hydrophobic n-alkyl methacrylates would decrease the pH sensitivity of the poly(n-alkyl methacrylate-co-N,N-dimethylaminoethyl methacrylate) hydrogels. In this case, the swelling at low pH where the gel is ionized is highly dependent on the hydrophobicity of the neutral monomer.

Buffer composition and ionic strength affect the swelling of polyelectrolyte hydrogels.[23,24] As ionic strength increases, the swelling decreases due to the increased counterion concentration, shielding of charges on the polymer chain and high ion concentration outside the gel. As the concentration of ions outside the gel increases, the concentration of ions inside and outside of the gel will become equal and osmotic pressure inside the gel decreases. A buffer containing the multivalent counterions decreases the degree of swelling. One multivalent ion is able to neutralize several charges inside the gel. The concentration of multivalent counterions inside the gel will be less than monovalent ions; the osmotic pressure and the degree of the swelling will be decreased. Swelling in phosphate buffer was greater than the swelling in citrate buffer. The buffer species is not important at high ionic strength; in that region, the ionic strength is the only determinant of swelling.[24] It was also found that the type of coion did not influence the equilibrium degree of swelling, since coions do not very easily permeate a swollen gel of the same charge. On the other hand, the counterion species was very important for swelling equilibrium, even if the valency was the same.[24]

With respect to applications in drug delivery, the kinetics and reversibility of swelling also have to be evaluated. It is often desirable that swelling changes rapidly in respond to pH. For "on-off" type delivery systems, it is necessary that the swelling is reversible.

pH Sensitive Drug Delivery Systems

It is necessary to investigate permeability as a function of gel charge, pH of medium and charge of the drug molecules. A drug with a charge opposite to the hydrogel could act as a counterion and the release of such a drug from the hydrogel would be by ion exchange.[45] A negatively charged drug molecule have decreased permeability through a negatively charged hydrogel membrane due to repulsion between like charges. Kopecek *et al.*[40] investigated the permeability of NaCl and $MgSO_4$ through hydrogel membranes. Four different kinds of membranes were investigated: neutral, acidic containing methacrylic acid, basic containing 2-(diethylamino)ethyl methacrylate and ampholytic containing equal amounts of the acidic and basic monomers. The dependence of permeability on the content of ionogenic groups, crosslinking density and pH were evaluated. It was found that permeability was lowest for solely acidic and basic membranes. Total diffusion of the salts were slowed due to the repulsion of coion from the membrane. The diffusion was fastest through the ampholytic membrane, since these membranes

enhance the permeability of both salts. The permeability of neutral membranes fell between that of ampholytic and acidic or basic membranes. The dependence on crosslinking density was found to be strongest in the case of neutral membranes where only pore size and swelling of the membrane were important. For ionized membrane, charge interactions were dominant and crosslinking density was not as important. As charge density increased, the permeability of ampholytic membranes increased, but was decreased in the case of acidic and basic membranes due to higher repulsion. The permeability of $MgSO_4$ was found to be lower than that of NaCl. For the ampholytic membranes, a high dependence of crosslinking density was observed. This was attributed to the higher radius of the hydrated Mg^{2+} and SO_4^{-2} ions as compared to Na^+ and Cl^- ions. As the radius of the solute increases, the permeability becomes more dependent on the pore size.[17]

Vacik *et al.*[46] reported that, as for salts, the permeability of organic compound such as urea and creatinine decreased as the crosslinking density of the membrane decreased. The permeability of these compounds through ampholytic membranes were increased; it was suggested that only molecules which interacts with charges on the hydrogel will have increased permeability in ampholytic membranes when compared to neutral membranes.

The permeability of various compounds, up to a molecular weight of 70,000, through hydrolyzed polyacrylonitrile membranes were investigated.[47] These gels have blocks of negative charges after partial hydrolysis. A linear relationship between the logarithm of the permeability coefficient and the logarithm of the molecular weight of about 70,000 was observed. Solutes with a higher molecular weight did not permeate at all in 72 hrs.

The influence of hydrophobicity of the polymer backbone on permeability of poly(2-hydroxyethyl methacrylate-co-methacrylic acid) hydrogels was studied.[44] The hydrophobicity was increased by copolymerization with butyl methacrylate. As the hydrophobicity increased, the dependence of permeability on pH increased, even though the rate of diffusion decreased.

Crosslinking density of the gel is important for pH-dependent permeability.[44,48] Weiss *et al.*[48] synthesized poly(methacrylic acid) membranes with different degree of crosslinking. Dextran coupled to lisasamine-rhodamine B (molecular weight 6,000) was used as the permeant. At high pH, the permeability was approximately the same for membranes containing different degree of crosslinking. At low pH, a membrane with a lower degree of crosslinking had a much higher permeability than a highly crosslinked membranes. The permeability correlated with the degree of swelling of membrane. When solutes of different molecular weight and charge were investigated, it was determined that the permeability of high molecular weight compounds were more dependent on pH than low molecular weight compounds. As pH increased and the gel became ionized, the degree of swelling increased. The permeability of high molecular weight solutes was more dependent on the degree of swelling, in accordance with the free volume theory.[48] A molecule possessing a negative charge also had increased permeability through acidic membranes as pH increased.[48,49] This shows that diffusion was mainly dependent on swelling and not on the charge density, because repulsion of the molecule from the membrane would then be expected.

Siegal *et al.* reported the system based on a basic poly(methyl methacrylate-co-N,N-diethylaminoethyl methacrylate) gel for oral delivery of foul trasting drugs.[50,51] At the neutral pH of the mouth the gel has a low degree of swelling and drug loaded into the gel will not be released. An acidic gel would have a potential in the delivery of acid labile drugs to the small intestine.[26]

Touitou and Robinson formulated capsules coated with a poly(acrylic acid) polymer containing insulin and surfactant, sodium laurate and cetyl alcohol, in arches oil.[52] This capsule protected the drug in the upper part of small intestine. As pH increased to 7.5, the release of drug increased. It was proposed that this resulted in release in colon. Insulin levels were monitored by glucose level depression and a reduction of 45% was mea-

sured.

Dong and Hoffman prepared the gels, based on N-isopropylacrylamide, acrylic acid and vinyl terminated polydimethylsiloxane for enteric drug delivery.[53] The gels exhibited both temperature and pH sensitive swelling. *In vitro* release studies were performed using indomethacine, which can cause severe gastric irritation. In 24 hrs almost no drug was released at pH 1.4, whereas at pH 7.4, more than 90% was released during 5 hrs. Ishihara *et al.*[54] and Albin *et al.*[55] reported glucose sensitive membrane systems which composed of a basic polyamine hydrogel membrane and glucose-oxidase immobilized membrane. The basic membrane was based on crosslinked N,N-diethylaminopentyl methacrylate, which is a cationic monomer and 2-hydroxypropyl methacrylate. As the glucose concentration in contact with the glucose-oxidase immobilized membrane increases, glucose will be diffuse into the membrane. There will be converted to gluconic acid by the action of glucose oxidase, and the pH will decrease. This results in an increase in the decrease of swelling of the polyamine gel due to ionization of the basic groups in the gel. Insulin loaded into the gel will theb be released. It was shown that the swelling of the membrane was reversible and very sensitive to changes in pH. Insulin release from the polyamine membrane was shown to be controlled by the degree of swelling of the membrane, which was dependent on the pH of the surrounding solution. The release of insulin could be controlled in response to changes in glucose concentration; as the glucose concentration increased the insulin release was increased. Since it has been shown that the swelling of the ionizable hydrogels is very dependent on the pH, composition and ionic strength of the surrounding solution, it is necessary to mimic physiological conditions as close as possible to be able to predict insulin release from this device.[55]

In drug delivery to the gastrointestinal(GI) tract, it can be desirable to use mucoadhesives to retain the drug delivery device at the site of action (for a drug with local action) or at the site of adsorption (for a drug with certain requirements for systemic action). This will prolong the residence time of the device and assure sufficient time for all of the drug to be released. For this purpose, bioadhesive polymers have been developed which adhere to the mucin of the GI-tract and increase residence time. Prolonged release would result in fewer daily administration of the drug and more convenience for the patient. The use of bioadhesives in drug delivery has been reviewed by Gupta *et al.*[56] The bioadhesive properties of neutral, acidic and basic polymers were evaluated by Park *et al.*[57] It was found that anionic polymers were the only type providing useful mucoadhesion.

The use of anionic gels as a mucoadhesives have been proposed for the use of prolonging gastric retention time.[58,59] Anionic materials with high charge density has shown to be a good mucoadhesive. A mucoadhesive, polycarbophil, based on acrylic acid, decreased mucoadhesion with increased crosslinking density due to reduced interpenetration of the mucus. Poly(acrylic acid-co-acrylamide) gels were prepared and mucoadhesion in relation to pH, crosslinking density, charge density and degree of swelling was determined. The results suggested that mucoadhesion was favored with high charge density and flexibility of the polymer chains. An increase in crosslinking density decreased mucoadhesion. The effect of mucus turnover still remains to be investigated. Prolonged release would result in fewer daily administrations of the drug and more convenience for the patient.

Degradable Hydrogel Systems

Biodegradable hydrogels have been proposed for use in parenteral drug delivery since surgical removal of the polymer after release of all drug is not necessary. The hydrogel slowly erodes and will eventually disappear. Drug release from degradable hydrogels will be influenced by either surface erosion or bulk degradation.[60] In surface erosion the polymer surrounding the drug erodes away and releases entrapped drug. Drug release by surface erosion can only be modelled if the kinetics of degradation are known. Zero-order

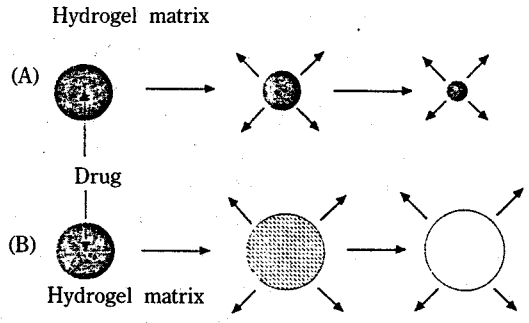

Figure 3—Drug delivery from degradable monolithic devices by surface erosion (A) and bulk degradation (B).

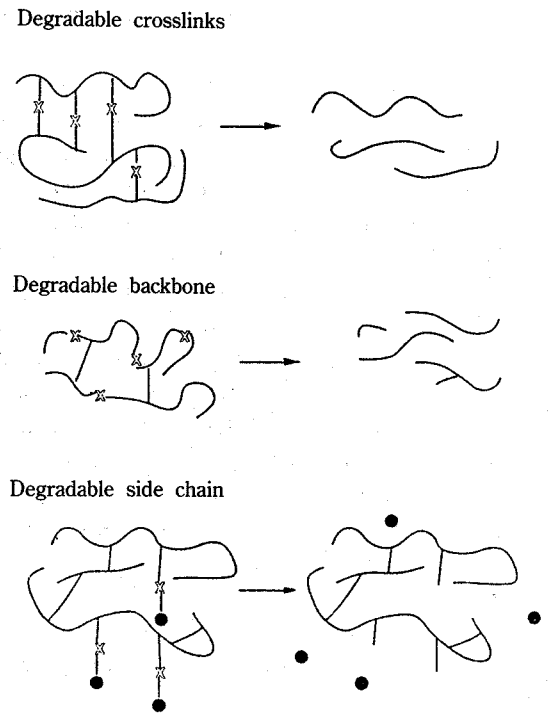

Figure 4—Schematic illustration of degradable hydrogel systems.

drug release, that is constant release with time, was obtained for slab, where the surface area did not change, as the gel degraded. For other shapes, such as spheres and cylinders, where the surface area decrease as the device degrades, the drug release would correspondingly decrease. Usually degradation take place not only by surface erosion but also bulk degradation. In bulk degradation the hydrogel matrix is degraded uniformly. Bulk degradation usually takes place in hydrophilic polymers with high water content, such as hydrogels. Release of drug can take place simultaneously by diffusion and erosion controlled release; this will complicate the prediction of the release. Drug release from a degradable hydrogel is shown schematically in Fig. 3.

Three different systems of degradable hydrogels can be suggested: hydrogel with degradable crosslinks, degradable backbone or drug connected to the polymer network by a degradable bond (Fig. 4).

Hydrogels with Degradable Crosslinks

Degradation of hydrogels containing enzymatically degradable or hydrolyzable crosslinks can be detected as an increase in swelling and release of polymer chains.[61,62]

Gels based on N-(2-hydroxypropyl) methacrylamide containing oligopeptide sequences in the crosslinks were prepared.[62] The degradation was investigated using chymotrypsin as model enzyme. The rate of degradation was dependent on structure and length of peptide sequence, network density and swelling. As the crosslinking density increased, steric hinderance prevented the enzyme-substrate complex from being formed and rate of degradation of macromolecules.[63] It was found that degradation of gels was dependent on crosslinking density, structure and length of oligopeptide sequence.

Hydrogels with Degradable Backbone

Dickinson and Hiltmer prepared hydrogels with degradable main chains from crosslinked poly(2-hydroxyethyl-L-glutamine) containing different amounts of crosslinker.[64] It was found that as degradation took place, the degree of swelling increased together with a decrease in dry weight. *In vitro* degradation study showed that degradation took place by bulk degradation, since there was an immediate increase in swelling, suggesting lower crosslinking density. Later, the gel dissolved and increase in lower molecular weight fragment was detected.

Heller *et al.*[65] prepared the polymeric precusors using poly(ethylene glycol), fumaric acid and N-vinylpyrolidone. Hydrogels with higher degradability were prepared containing electron withdra-

wing groups adjacent to the hydrolyzable ester groups. It was found that albumin was released from these gels in accordance with surface erosion of the gels. The degradability and release could be controlled by crosslinking density and structure of the hydrolytic ester group.

Hydrogels with Degradable Side Chains

Kopecek and coworkers[63] synthesized hydrogels containing drug connected via a degradable bond. Hydrogels were based on N-(2-hydroxypropyl) methacrylamide containing a pentapeptide in the crosslinks and drug bound to the polymer backbone via tetrapeptide side chains. After incubation with enzymes isolated from the liver, drug was released. However, it was found that the crosslinks were cleaved faster than the side chains, resulting in release of polymer containing side chains terminating in drugs.

Drug Delivery to the Colon

Peptide and protein drugs are commonly administered by the parenteral route of administration. The oral route of administration would be more attractive and convenient, but the bioavailability of orally administered peptide and protein drugs is very low with only a few percent absorbed.[66] In order to develop successful strategies to enhance the oral absorption of drug with absorption problems, it is important that the anatomy and physiology of the GI tract be thoroughly understood along with different uptake mechanism in the intestine. It is not the intent to cover these studies. These were well reviewed by Mrsny and Kararli.[67,68]

There are many obstacles to the oral delivery of peptide and protein drugs. First, peptides and proteins are digested by gastric and pancreatic enzymes present in the stomach and the small intestine, respectively. Second, the permeation of high molecular drugs through the GI mucosa is very low, further decreased by the fact the proteins are hydrophilic and charged.[69] Third, the residence time of the drug or delivery system at absorption site is frequently too short to allow therapeutic levels to be maintained for any length of time. Coadministration with enzyme inhibitors,[70] absorption enhancer,[71] and stabilizers[72] and the use of protective coatings[73,74] have been proposed to overcome obstacles to oral delivery.

Table VI—*Parameters Affecting Drug Absorption from Colon*

pH
Transit time
Motility
Water flux
Microbial enzymes
Microbial flora
Digestive enzymes
Food and liquid intake
Healthy/diseased state

For intravenously, intramuscularly and subcutaneously administered drug delivery system, release is usually followed almost instantaneously by absorption of drug action, In these cases, the absorption or drug action can be fairly accurately, predicted by taking into account relevant physicohemical parameters. These include drug solubility, molecular weight, pKa, partition coefficient and binding to blood components and tissues in the body. With oral delivery systems, release is not necessarily followed by absorption.[75] Several factors have to be considered; some drugs are only absorbed from specific parts of the GI tract.[67,76] Other physiological factors influencing drug absorption with oral drug delivery include GI transit time, food and liquid intake, intestinal motility and pH and enzymatic stability of the drug.[76] These parameters are summarized in Table VI. For oral drug delivery systems, it is not possible to prolong the release for as long as desired, since GI residence time determines the length of time the device will be at site of absorption. To prolong site-specific residence time, mucoadhesive drug delivery systems have been investigated.[77] Despite the problems involved in oral delivery, it is by far the most attractive route of administration. It is more convenient for the patient, resulting in high level of patient compliance and is less expensive to formulate than, for example, sterile produ-

cts for injection.

As described above, the stomach and small intestine contain digestive enzymes. To avoid the digestion of peptide and protein drugs by these enzymes, peptides can be delivered to the large intestine where the amount of digestive enzymes is drastically reduced.[78]

Drug delivery to the colon can be achieved in several ways: 1) a slow release dosage form can release the drug after 5 h when the carrier device can be assumed to arrive in colon, 2) a pH-sensitive coating can protect the drug until arrival in colon, 3) microbial enzymes present only in colon can be exploited in site-specific delivery to the colon.

Colon-specific drug delivery can be made by making low molecular weight[79,80] or polymeric[81,82] prodrugs which release the active component after the breakage by microbial enzymes predominantly present in colon, i.e., glycosidase or azoreductases. Saffaran *et al.*,[74] obtained the site-specific drug delivery of insulin and vasopressin by using polymeric coatings containing enzymatically degradable azobonds. Lancaster *et al.*,[83] investigated the degradation of polymers containing glycosidic bonds by colonic enzymes. Brown and coworkers reported the preparation of a polymeric prodrug that contains 5-aminosalicylic acid linked to a polymeric backbone via an azobond.[81] The active compound was released without releasing sulfapyridine. This principle was modified by Kopeckova and Kopecek by adding bioadhesive moieties attached to the polymer backbone to prolong the residence time of the prodrug in colon.[82]

Microbial glycosidase can also be exploited in formulation of prodrugs to the colon. Friend and Chang investigated steroid glycosides as a prodrugs for delivery of steroids to colon, which may be desirable in treatment of certain inflammatory diseases in colon.[80,83] Various galactoside and glucoside prodrugs with varying lipophilicity of the steroids were investigated. The glycosidase activity of various parts of the GI tract of rats was evaluated. It was found that the activity was much higher in cecum than in other parts of the GI tract.

Lancaster and Wheatley studied the degradation of polymers containing glycosidic bonds by microbial enzymes.[83] The microbial enzymes were isolated from colon and cecum of rats. These polymers have potential as drug coatings, but the system has to be optimized since the mechanical strength of these polymers were found to be too low.

Kopecêk and coworkers designed pH sensitive hydrogel for site-specific peptide and protein drug delivery to the colon.[78] The hydrogels contain acidic comonomers and enzymatically degradable azoaromatic crosslinks. In the low pH range of the stomach, the gel has a low equilibrium degree of swelling and the drug is protected against digestion by enzyme. The degree of swelling increases as the gel passes down the GI tract due to the increased pH. Upon arrival in colon, the gels have reached a degree of swelling that makes the crosslinks accessible to azoreductases and mediators. The rate of degradation depends on the structure of hydrogels. From the GI transit time, pH profile of the GI tract, diffusion of drug through the gel, rate of enzymatic degradation of the gel and the degree of swelling, it would be possible to design a device which gives a desired release profile. For protein drugs, it would be desirable to have no release occur in the small intestine with total amount loaded release in colon. A slow release rate in the small intestine with the major amount loaded released in colon would be useful for drug used in diseases both present in the small intestine and in the colon.

The potential for drug delivery to the colon is a very existing field with many possibilities. Drugs of interest are acid labile drugs, drugs sensitive to digestive enzymes, drugs with irritating effect in the upper GI tract and drugs for diseases present in colon. Exploitation of microbial enzymes for triggering site-specific drug release in colon appears to be suitable way of obtaining colon drug delivery.

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