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;

TABLE II.5.16.1 Environment-Sensitive Polymers to Make Smart Hydrogels for Drug Delivery

Stimulus	Polymer	References
	Physical Stimuli	
Temperature	Polyphosphazene	(Al-Abd, Hong, Song, and Kuh, 2010)
	Chitosan neutralized with dibasic salts (e.g. β-glycerophosphate, DHO)	(Ruel-Gariepy et al., 2004; Ta, Han, Larson, Dass, and Dunstan, 2009)
	PEG-modified chitosan/α-CD complex	(Huh et al., 2004)
	Poly(γ-CD-NMA-*co*-HMAAm)	(Siemoneit et al., 2006)
	Genetically engineered silk-elastin-like protein (SELP)	(Banta, Wheeldon, and Blenner, 2010; Dinerman, Cappello, El-Sayed, Hoag, and Ghandehari, 2010; Dinerman, Cappello, Ghandehari, and Hoag, 2002)
	NIPAAM copolymers	(Park and Hoffman, 1994; Jeong, Kim, and Bae, 2002)
	PEO-*b*-PPO-*b*-PEO	(Jeong et al., 2002)
	Block copolymers of PEG and polyesters	(Jeong et al., 2002; Nguyen and Lee, 2010)
Electric fields	Poly(AMPS-*co*-BMA)	(Kwon, Bae, Okano, et al., 1991)
	Complex of PEOx/PMAA or PEOx/PAA	(Kwon, Bae, and Kim, 1991)
	Acetylated chitosan	(Ramanathan and Block, 2001)
	Cross-linked chondroitin 4-sulfate	(Jensen, Hansen, Murdan, Frokjaer, and Florence, 2002; Murdan, 2003)
Magnetic fields	Nanocomposite of iron oxide in poly(PEGMMA-*co*-PEGDMA), PVA, κ-carrageenan hydrogels*	(Daniel-da-Silva et al., 2009; Meenach, Hilt, and Anderson, 2010; Lao and Ramanujan, 2004; Liu, Hu, Liu, Liu, and Chen, 2008)
	Nanocomposite of poly(3-morpholinopropylamine-*co*-DEGDA)/iron oxide nanoparticle	(Hawkins, Satarkar, and Hilt, 2009; Liu, Hu, Liu, and Chen, 2006)
Ultrasound	Microcomposite of Dex-CHO/CMC-ADH containing liposome and microbubble	(Epstein-Barash et al., 2010)
Pressure	PMMA/PVP or PMMA/CE complex	(Minghetti, Cilurzo, Tosi, Casiraghi, and Montanari, 2003)
	Chemical Stimuli	
pH	PHEA	(Casadei, Pitarresi, Calabrese, Paolicelli, and Giammona, 2008)
	β-CD hydrogel cross-linked by EPI	(Rodriguez-Tenreiro, Diez-Bueno, Concheiro, Torres-Labandeira, and Alvarez-Lorenzo, 2007)
	HP-β-CD/Carbopol ms-IPN	(Yang and Kim, 2010)
Ion species	PAAm with CaM and phenothiazine peptide—Ca^{2+} sensitivity	(Banta et al., 2010; Ehrick et al., 2005)
	PEG tetraacrylate hydrogel with CaM—Ca^{2+}-sensitivity	(Banta et al., 2010; Murphy, Dillmore, Modica, and Mrksich, 2007)
	Poly(NIPAAm-*co*-BCAm)—Ba^{2+} and Cs^{+} sensitivity	(Ju, Chu, Liu, Mi, and Lee, 2008; Pi, Ju, Wu, Xie, and Chu, 2010)
	Melamine hydrogel—oxoanion (e.g. NO^{3-}, PO_4^{3-}, ATP, SO_4^{2-}) sensitivity	(Shen, Cai, Jiang, and Zhang, 2010)
Ionic strength	Genetically engineered SELP	(Banta et al., 2010)
	Pullulan acetate nanogel	(Park et al., 2007)
Drug	PAAm/genetically engineered GyrB conjugate responding to coumermycin and novobiocin	(Ehrbar, Schoenmakers, Christen, Fussenegger, and Weber, 2008)
	Biological Stimuli	
Glucose	Copolymer of acrylated GBP and AAm	(Ehrick et al., 2009)
	Poly(NIPAAm)/poly(NIPAAm-*co*-MPBA) core/shell microgel	(Zhang, Guan, and Zhou, 2007)
	Poly(AAm-co-MPBA) microdevices	(Siegel et al., 2010)
	Poly(AG-*co*-SPAK), poly(AG-*co*-VP), and poly(AG-*co*-AAm) loading PEGylated Con A	(Kim and Park, 2001)
	Copolymer of SMD, DMAAm, MBAAm, methacryloyl enzymes (GOD and/or catalase)	(Kang and Bae, 2003)
Antigen	Copolymer of acrylated GAR IgG and acrylated rabbit IgG	(Miyata, Asami, and Uragami, 1999)
Enzyme	IPN structure of gelatin and dextran degraded in the presence of α-chymotrypsin and dextranase	(Kurisawa and Yui, 1998)
	Ionic complex of NAH-Dex and CMD degraded by dextranase	(Kamimura, Ooya, and Yui, 2001)
	Cross-linking PEG with enzyme-degradable peptide (e.g. HNE, MMP)	(Aimetti, Machen, and Anseth, 2009; Lei and Segura, 2009)
	Methacrylated gelatin degraded by MMP-1	(Sutter, Siepmann, Hennink, and Jiskoot, 2007)

(Continued)

TABLE II.5.16.1 Environment-Sensitive Polymers to Make Smart Hydrogels for Drug Delivery *(Continued)*

Stimulus	Polymer	References
	Multiple Stimuli	
pH/temperature	OSM-PCLA-*b*-PEG-*b*-PCLA-OSM; PAE-*b*-PCL-*b*-PEG-*b*-PCL-*b*-PAE, PAA-*b*-PEG-*b*-PAA; PAE-*b*-PEG-*b*-PAE; $(PCL\text{-}b\text{-}PEG\text{-}b\text{-}PCL\text{-}b\text{-}PAU)_n$; $(PEG\text{-}b\text{-}PAU)_m$	(Nguyen and Lee, 2010)
	Poly(NIPAAm-*co*-PrAA)	(Garbern, Hoffman, and Stayton, 2010)
	Poly(PEGMMA-*co*-DMA)/α-CD complex	(Ren et al., 2009)
	PL-Dex/α-CD complex	(Choi, Yamamoto, Ooya, and Yui, 2005)
	Coiled coil peptides	(Banta et al., 2010; Woolfson, 2010)
	Genetically engineered silk-elastin-like protein	(Banta et al., 2010)
pH/enzyme	Poly(GMD-*co*-AA) degraded by dextranase	(Kim and Oh, 2005)
Temperature/enzyme	Copolymer of NIPAAm, AA, MMP-degradable peptide	(Kim and Healy, 2003)
pH/ionic strength	CMD	(Zhang, Tang, Bowyer, Eisenthal, and Hubble, 2005)
Temperature/pH/Ca^{2+}/light	Phosphate-type hydrogelators—molecular logical gate	(Komatsu et al., 2009)

Review articles are marked as underlined references.
Abbreviations: AA, acrylic acid; AAm, acrylamide; AG, allyl glucose; AMPS, 2-acrylamido-2-methylpropane sulfonic acid; BCAm, benzo-18-crown-6-acrylamide; BMA, *n*-butylmethacrylate; α-CD, α-cyclodextrin; β-CD, β-cyclodextrin; γ-CD-NMA, acrylamidomethyl-γ-cyclodextrin; CaM, calmodulin; CE, cellulose acetate; CMC-ADH, carboxymethyl cellulose-adipic dihydrazide conjugate; CMD, carboxymethyl dextran; Con A, concanavalin A; DEGDA, diethylene glycol diacrylate; DEX-CHO, dextran aldehyde; DHO, dipotassium hydrogen orthophosphate; DMAAm, *N,N*-dimethylacrylamide; EPI, epichlorohydrin; GAR, goat antirabbit; GBP, glucose/galactose binding protein; GMD, glycidyl methacrylate dextran; GOD, glucose oxidase; GyrB, gyrase subunit B; HMAAm, *N*-(hydroxymethyl) acrylamide; HNE, human neutrophil elastase; HP-β-CD, hydroxypropyl-β-cyclodextrin; IgG, immunoglobulin G; MBAAm, *N,N′*-methylene-*bis*-acrylamide; MMP, matrixmetalloproteinase; MPBA, methacrylamidophenylboronic acid; ms-IPN, microscale interpenetrating network; NAH-Dex, 1,4-dihydronicotinamide-modified dextran; NIPAAm, *N*-isopropylacrylamide; OSM, sulfamethazine oligomer; PAA, poly(acrylic acid); PAE, poly(β-aminoester); PAU, poly(aminourethane); PCL, poly(ε-caprolactone); PCLA, poly(ε-caprolactone-*co*-lactide); PEG, poly(ethylene glycol); PEGMMA, poly(ethylene glycol) methylether methacrylate; PEO, poly(ethylene oxide); PHE, *N*-acryloyl-L-phenylalanine; PHEA, α,β-poly(*N*-2-hydroxyethyl)-D,L-aspartamide; PL-Dex, poly(ε-lysine)-*g*-dextran; PLGA, poly(lactic-*co*-glycolic acid); PLLA, poly(L-lactic acid); PMAA, poly(methacrylic acid); PMMA, poly(methylmethacrylate); PPO, poly(propylene oxide); PrAA, propylacrylic acid; PVA, poly(vinyl alcohol); SDM, methacrylated sulfadimethoxine monomer; SPAK, 3-sulfopropylacrylate potassium salt; VP, *N*-vinyl pyrrolidone.
*The nanogel converts magnetic energy to heat energy, rather than inducing a structural change.

Siegel et al., 2010). Most of the smart hydrogels that have been used for developing stimuli-responsive DDS are summarized in a book published recently (Bajpai, Shukla, Saini, and Tiwari, 2010). Of the various smart hydrogels, the temperature- and pH-responsive hydrogels have been most widely studied for the development of DDS (Ganta, Iyer, and Amiji, 2010, pp. 555–585; Kim, Kim, Min, Park, and Lee, 2010, pp. 293–308). Successful utilization of smart hydrogels for controlled drug delivery requires understanding of both the properties of smart hydrogels and the biological requirements that are necessary for drug delivery.

SMART HYDROGELS FOR DRUG DELIVERY

Smart hydrogels have been used to deliver various drugs for time periods ranging from hours to weeks. For oral delivery formulations, the drug delivery to the body is supposed to be completed within 24 h. Transdermal formulations are usually used to deliver a drug on the time-scale of a day to a week. On the other hand, other drug delivery routes, such as implanted depot systems, or localized DDS such as pumps, take from days to months to deliver drugs. Thus, when smart hydrogels are used for delivering drugs, the delivery routes as well as the drug release duration both need to be considered.

When smart hydrogels are used for delivering drugs, the delivery routes as well as the drug release duration need to be considered. For oral delivery formulations, the delivery is supposed to be completed within 24 h. Transdermal formulations usually deliver the drug from between a day to a week, while implanted depot systems and pumps deliver the drug in months.

The composition of the smart hydrogel and the design of the system are both very important. For example, oral formulations of smart hydrogels should be designed to control the drug release rate (1) as pH changes from stomach (gastric) to intestine (enteric) or (2) as the location along the gastrointestinal tract changes, e.g. upper small intestine vs. the colon (Hejazi and Amiji, 2003). If a smart hydrogel system is to deliver a drug with a release duration of weeks or longer, they will usually need to be implanted into the body. Such implantable systems must satisfy the important issues of safety and efficacy. Unless these considerations are considered, smart hydrogels cannot be used clinically no matter how smart they are.

It is important to examine the particular requirements of each application of a smart hydrogel system. Quite often, smart hydrogel DDS are proposed without a clear understanding of the clinical necessities that each drug delivery route will demand. Temperature-responsive hydrogels have been the most widely studied among

the smart hydrogels for development of DDS (Yoshida et al., 1995), especially poly(*N*-isopropylacrylamide) or PNIPAAm. In this case, a PNIPAAm/drug solution at ambient temperature will become a gel when it is injected into the body at 37°C due to the "smart polymer" temperature-dependent sol–gel phase transition. Because most thermosensitive polymers are based on acrylic monomers, they are not biodegradable, and thus the PNIPAAm gel residue may require surgical removal after the drug release is completed. This problem is often overlooked in publications proposing such thermally sensitive polymers and hydrogels as clinically useful DDS.

Recent research efforts have been focused on the development of smart hydrogels for *in vivo* use. These have special properties due to the use of new monomers and/or new combinations of existing systems. Such new smart hydrogels, or "smarter hydrogels", are discussed in the next section.

NEW SMART HYDROGELS FOR *IN VIVO* APPLICATIONS

Despite advances in drug delivery technologies over the last three decades, controlled delivery of protein drugs is still a major challenge (Jorgensen and Nielsen, 2009, p. 442). Due to its hydrophilic nature, a hydrogel DDS should be an excellent carrier for delivering hydrophilic drugs such as peptide or protein drugs. Many different environmentally sensitive polymeric compositions have been synthesized over the past 30 years. Some good examples of the newer smart hydrogels include (1) enzyme-responsive hydrogels that deliver proteins, such as albumin; (2) drug molecule-sensitive hydrogels for delivery of a protein; (3) hydrogels designed to deliver two proteins; and (4) magnetically controlled hydrogels (Ehrbar et al., 2008; Satarkar and Hilt, 2008). It is also important to remember that depot-type hydrogel systems should be biodegradable and biocompatible after the drug has been delivered (He, Kim, and Lee, 2008). Sometimes smart hydrogel DDS exhibit drug release duration of no more than a day or two, limiting their useful delivery route to oral administration.

Among the polymers incorporated in recent smart hydrogel DDS, natural biomacromolecules, such as nucleic acids (e.g. DNA), peptides and proteins (e.g. collagen, spider silk and albumin) and polysaccharides (e.g. hyaluronic acid and pullulan), have been utilized for their potential biocompatibility and degradability. It should be noted that the body's immunological response to such natural biomolecules is a major consideration for any *in vivo* application of such materials. Some may also have significant bioactivity, such as DNA and hyaluronic acid. One noteworthy development in smart natural hydrogels is the use of DNA as the backbone of a hydrogel network (Um et al., 2006). Branched DNA was used to construct three-dimensional hydrogels that were biocompatible and biodegradable. These two properties are ideally suited for making implantable long-term DDS. Insulin was used as a model protein to demonstrate the long-term release from the DNA hydrogels, which subsequently degrade into harmless materials in the body.

Among the molecules incorporated in recent smart hydrogel DDS, natural biomolecules, such as nucleic acids (e.g. DNA), peptides and proteins (e.g. spider silk and collagen), and polysaccharides (e.g. hyaluronic acid), have been utilized for their biocompatibility and degradability. It should be noted that the body's immunological response to such natural biomolecules is a major consideration for any in vivo application of such materials.

A recently developed DNA hydrogel for cell-free synthesis of functional proteins is an excellent example of a biomimetic hydrogel (Bayer and Peppas, 2008; Park, Um, Funabashi, Xu, and Luo, 2009). These hydrogels produce proteins with compositions derived from the genes incorporated as a part of the gel scaffolding. The improved gene stability, higher local concentration and faster enzyme turnover resulted in high efficiency and the yield of more than a dozen proteins. These protein-producing gels can be expected to deliver therapeutic proteins continuously over a long period of time.

In addition to the versatility of materials and the innovative function of smart hydrogel systems, the definition of the hydrogel has also broadened. Recent advances in nanotechnology have resulted in a new form of hydrogels, i.e. a colloidal solution of hydrogel nanoparticles called "nanogels". In the conventional definition, a hydrogel is a physically or chemically cross-linked polymer network, which absorbs a large quantity of water without dissolution (Lin and Metters, 2006). Nanogels are also stabilized by chemical bonds or physical cross-linking including hydrophobic interactions, affinity interactions, H-bonding and ionic bonding. Their hydrodynamic volume is larger than that of the dried nanogel due to the absorption of water (hydration) by the nanogel particles. The drug release mechanisms of nanogels are similar to those of microscopic and macroscopic smart hydrogels, such as sol–gel phase transition, degradation, and swelling/deswelling. An example of a biologically inspired design is a virus-mimetic nanogel vehicle (Lee, Kim, Youn, Oh, and Bae, 2008). This nanogel was made of a hydrophobic core of poly(L-histidine-*co*-phenylalanine) poly(His-*co*-Phe) covered by a poly(ethylene glycol) inner shell and an albumin outer shell. Poly(His-*co*-Phe) is pH sensitive and undergoes reversible swelling and deswelling as the pH changes between 7.4 (normal physiological pH) and 6.4 (endosomal pH), thus stimulating the endosomal release of the loaded doxorubicin.

IDEAL SMART HYDROGELS FOR SELF-REGULATED INSULIN DELIVERY

In demonstrating protein release from smart hydrogels, insulin has been frequently used as a model protein. But delivery of insulin, as a representative of peptide

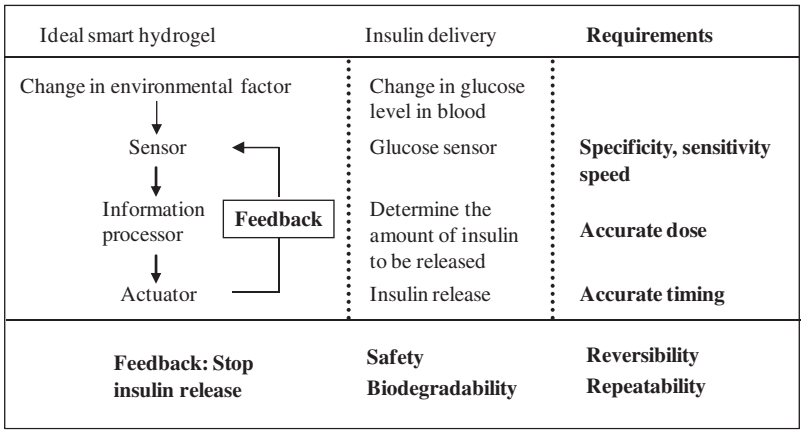

Figure II.5.16.1 This figure shows many of the design considerations for an ideal, implantable smart hydrogel system that will deliver just the right amount of insulin in response to a specific change in the blood glucose level. The system needs to have high specificity to glucose only, and high sensitivity to small changes in glucose concentration. The system also has to be biocompatible and it should biodegrade when the insulin delivery is completed, avoiding the need to retrieve it. The smart hydrogel must have rapid response, be reliable and reproducible over the term of use, and not induce any immunogenic responses.

hormones, is significantly different from delivery of other therapeutic protein drugs. Most protein drugs are released at a predetermined dose at a predetermined rate for a predetermined time period. Delivery of peptide hormones, however, requires a different mode from a predetermined release profile. The human body has multiple oscillation mechanisms to maintain metabolic homeostasis, and it is the hormone that tightly regulates each body function. An optimum amount of hormone results in a harmony between many functions of the body. Because of this, a lack of fine control in a DDS designed to deliver a hormonal peptide or protein drug could induce significant side effects, which could alter the desired clinical outcome. For instance, insulin should be delivered only when the blood glucose level is increased, and an accurate dose of insulin has to be delivered in a matter of minutes. Otherwise, either hyperglycemia or continued hypoglycemia will result in the body. Figure II.5.16.1 shows an example of how an ideal smart hydrogel insulin sensor with feedback delivery would be specifically designed to meet all the requirements for accurate and reproducible insulin delivery on demand.

Numerous smart hydrogels have been prepared for the self-regulated delivery of insulin in response to changes in glucose level in the blood. While such smart hydrogels can recognize the change in the glucose level in the environment and alter the rate of insulin release accordingly, one of the main problems of such systems is their gradual decrease in reproducibility.

Numerous smart hydrogels have been prepared for the self-regulated delivery of insulin in response to changes in glucose level in the blood (Kataoka, Miyazaki, Bunya, Okano, and Sakurai, 1998; Kim and Park, 2001). While such smart hydrogels can recognize the change in the glucose level in the environment and alter the rate of insulin release accordingly, one of the main problems of such systems is their gradual decrease in reproducibility. The ability of the hydrogels to respond to glucose changes decreases gradually, and thus, maintaining the original property for an extended period of time is critical for the successful development of clinically useful smart hydrogel systems.

The lack of truly smart hydrogels that can be used for self-regulated insulin delivery indicates that our current approach needs reevaluation. It is all too common to develop new materials first and then to look for applications. Quite often, finding the right application from the known properties of the new material is not easy. A more effective way to develop clinically useful smart hydrogels may be to understand the physiological requirements for a specific application and then design the new smart hydrogels. Smart hydrogels that need to be used for self-regulated insulin delivery need to take into consideration the requirements first, instead of making the hydrogels first, without understanding the physiological needs. Smart hydrogels can be translated into clinical products much faster and more efficiently if the physiological requirements are understood first before developing any new smart hydrogels. One of the best ways to make ideal smart hydrogels is to make biomimetic systems, e.g. smart hydrogels that function as islet cells. Making such islet cell biomimetic systems requires much more complexity than is currently available in smart hydrogels.

SMART HYDROGELS AS BIOMIMETIC SYSTEMS

Recent progress on smart hydrogels has been indeed remarkable, and this improved technology should be used effectively in developing better DDS. While there is no doubt that the future of smart hydrogels is bright (Kopecek, 2007), the future development of smart hydrogels may have to consider many fundamental differences between artificial and natural nanomaterials.

Natural systems are made by association of molecules (i.e. the bottom–up approach) resulting in the simplest and

yet most efficacious systems for survival (Park, Yui, and Mrsny, 2004, pp. 427–437). On the other hand, synthetic systems are usually prepared by the top–down approach. Although self-assembly and layer-by-layer composition are common in synthetic systems, their microscopic structures and biological functions are worlds apart from natural systems. The truly biomimetic smart hydrogels will be those that can act like a natural system in its speed, function, and repeatability. Developing such smart hydrogels is the key to the successful formulation of self-regulated DDS, especially feedback insulin delivery systems. Another important point to consider in developing smart hydrogels for pharmaceutical and biomedical applications is their ultimate use in humans. The smart hydrogels must be made of materials that can be proven to be safe. For this reason, the GRAS (generally regarded as safe) materials are preferred, but new materials can be used, especially when they provide unique and useful properties, through proper testing of the safety.

REFERENCES

Aimetti, A. A., Machen, A. J., & Anseth, K. S. (2009). Poly(ethylene glycol) hydrogels formed by thiolene photopolymerization for enzyme-responsive protein delivery. *Biomaterials*, **30**(30), 6048–6054.

Al-Abd, A. M., Hong, K. Y., Song, S. C., & Kuh, H. J. (2010). Pharmacokinetics of doxorubicin after intratumoral injection using a thermosensitive hydrogel in tumor-bearing mice. *J. Control. Release*, **142**(1), 101–107.

Bajpai, A., Shukla, S., Saini, R., & Tiwari, A. (2010). *Stimuli responsive drug delivery systems: From introduction to application*. United Kingdom: iSmithers.

Banta, S., Wheeldon, I. R., & Blenner, M. (2010). Protein engineering in the development of functional hydrogels. *Annu. Rev. Biomed. Eng.*, **12**, 167–186.

Bayer, C. L., & Peppas, N. A. (2008). Advances in recognitive, conductive and responsive delivery systems. *J. Control. Release*, **132**(3), 216–221.

Casadei, M. A., Pitarresi, G., Calabrese, R., Paolicelli, P., & Giammona, G. (2008). Biodegradable and pH-sensitive hydrogels for potential colon-specific drug delivery: characterization and in vitro release studies. *Biomacromolecules*, **9**(1), 43–49.

Choi, H. S., Yamamoto, K., Ooya, T., & Yui, N. (2005). Synthesis of poly(epsilon-lysine)-grafted dextrans and their pH- and thermosensitive hydrogelation with cyclodextrins. *ChemPhysChem*, **6**(6), 1081–1086.

Daniel-da-Silva, A. L., Fateixa, S., Guiomar, A. J., Costa, B. F., Silva, N. J., Trindade, T., et al. (2009). Biofunctionalized magnetic hydrogel nanospheres of magnetite and kappa-carrageenan. *Nanotechnology*, **20**(35), 355602.

Dinerman, A. A., Cappello, J., El-Sayed, M., Hoag, S. W., & Ghandehari, H. (2010). Influence of solute charge and hydrophobicity on partitioning and diffusion in a genetically engineered silk-elastin-like protein polymer hydrogel. *Macromol. Biosci.*, **10**(10), 1235–1247.

Dinerman, A. A., Cappello, J., Ghandehari, H., & Hoag, S. W. (2002). Solute diffusion in genetically engineered silk-elastinlike protein polymer hydrogels. *J. Control. Release*, **82**(2–3), 277–287.

Ehrbar, M., Schoenmakers, R., Christen, E. H., Fussenegger, M., & Weber, W. (2008). Drug-sensing hydrogels for the inducible release of biopharmaceuticals. *Nat. Mater.*, **7**(10), 800–804.

Ehrick, J. D., Deo, S. K., Browning, T. W., Bachas, L. G., Madou, M. J., & Daunert, S. (2005). Genetically engineered protein in hydrogels tailors stimuli-responsive characteristics. *Nat. Mater.*, **4**(4), 298–302.

Ehrick, J. D., Luckett, M. R., Khatwani, S., Wei, Y., Deo, S. K., Bachas, L. G., et al. (2009). Glucose responsive hydrogel networks based on protein recognition. *Macromol. Biosci.*, **9**(9), 864–868.

Epstein-Barash, H., Orbey, G., Polat, B. E., Ewoldt, R. H., Feshitan, J., Langer, R., et al. (2010). A microcomposite hydrogel for repeated on-demand ultrasound-triggered drug delivery. *Biomaterials*, **31**(19), 5208–5217.

Ganta, S., Iyer, A., & Amiji, M. (2010). Multifunctional stimuli-responsive nanoparticles for targeted delivery of small and macromolecular therapeutics. In A. S. Narang, & R. I. Mahato (Eds.), *Targeted delivery of small and macromolecular drugs* (pp. 555–585). Baca Raton, FL: CRC Press.

Garbern, J. C., Hoffman, A. S., & Stayton, P. S. (2010). Injectable pH- and temperature-responsive poly(N-isopropylacrylamide-co-propylacrylic acid) copolymers for delivery of angiogenic growth factors. *Biomacromolecules*, **11**(7), 1833–1839.

Hawkins, A. M., Satarkar, N. S., & Hilt, J. Z. (2009). Nanocomposite degradable hydrogels: demonstration of remote controlled degradation and drug release. *Pharm. Res.*, **26**(3), 667–673.

Hejazi, R., & Amiji, M. (2003). Chitosan-based gastrointestinal delivery systems. *J. Control. Release*, **89**(2), 151–165.

He, C., Kim, S. W., & Lee, D. S. (2008). In situ gelling stimuli-sensitive block copolymer hydrogels for drug delivery. *J. Control. Release*, **127**(3), 189–207.

Huh, K. M., Cho, Y. W., Chung, H., Kwon, I. C., Jeong, S. Y., Ooya, T., et al. (2004). Supramolecular hydrogel formation based on inclusion complexation between poly(ethylene glycol)-modified chitosan and alpha-cyclodextrin. *Macromol. Biosci.*, **4**(2), 92–99.

Jensen, M., Hansen, P. B., Murdan, S., Frokjaer, S., & Florence, A. T. (2002). Loading into and electro-stimulated release of peptides and proteins from chondroitin 4-sulphate hydrogels. *Eur. J. Pharm. Sci.*, **15**(2), 139–148.

Jeong, B., Kim, S. W., & Bae, Y. H. (2002). Thermosensitive sol-gel reversible hydrogels. *Adv. Drug Deliv. Rev.*, **54**(1), 37–51.

Jorgensen, L., & Nielsen, H. M. (Eds.), (2009). *Delivery technologies for biopharmaceuticals: Peptides, proteins, nucleic acids and vaccines*. Hoboken, NJ: Wiley.

Ju, X. J., Chu, L. Y., Liu, L., Mi, P., & Lee, Y. M. (2008). A novel thermoresponsive hydrogel with ion-recognition property through supramolecular host-guest complexation. *J. Phys. Chem. B*, **112**(4), 1112–1118.

Kamimura, W., Ooya, T., & Yui, N. (2001). Transience in polyion complexation between nicotinamide-modified dextran and carboxymethyl dextran during enzymatic degradation of dextran. *J. Biomater. Sci. Polym. Ed.*, **12**(10). 1109–1022.

Kang, S. I., & Bae, Y. H. (2003). A sulfonamide based glucose-responsive hydrogel with covalently immobilized glucose oxidase and catalase. *J. Control. Release*, **86**(1), 115–121.

Kataoka, K., Miyazaki, H., Bunya, M., Okano, T., & Sakurai, Y. (1998). Totally synthetic polymer gels responding to external glucose concentration: their preparation and application to on-off regulation of insulin release. *J. Am. Chem. Soc.*, **120**(48), 12694–12695.

Kim, S., & Healy, K. E. (2003). Synthesis and characterization of injectable poly(*N*-isopropylacrylamide-*co*-acrylic acid) hydrogels with proteolytically degradable cross-links. *Biomacromolecules*, **4**(5), 1214–1223.

Kim, M. S., Kim, J. H., Min, B. H., Park, K., & Lee, H. B. (2010). Implantable delivery systems. In M. Morishita, & K. Park (Eds.), *Biodrug delivery systems. Fundamentals, applications, and clinical development*. New York, NY: Informa Healthcare.

Kim, I. S., & Oh, I. J. (2005). Drug release from the enzyme-degradable and pH-sensitive hydrogel composed of glycidyl methacrylate dextran and poly(acrylic acid). *Arch. Pharm. Res.*, **28**(8), 983–987.

Kim, J. J., & Park, K. (2001). Modulated insulin delivery from glucose-sensitive hydrogel dosage forms. *J. Control. Release*, **77**(1–2), 39–47.

Komatsu, H., Matsumoto, S., Tamaru, S., Kaneko, K., Ikeda, M., & Hamachi, I. (2009). Supramolecular hydrogel exhibiting four basic logic gate functions to fine-tune substance release. *J. Am. Chem. Soc.*, **131**(15), 5580–5585.

Kopecek, J. (2007). Hydrogel biomaterials: a smart future? *Biomaterials*, **28**, 5185–5192.

Kurisawa, M., & Yui, N. (1998). Dual-stimuli-responsive drug release from interpenetrating polymer network-structured hydrogels of gelatin and dextran. *J. Control. Release*, **54**(2), 191–200.

Kwon, I. C., Bae, Y. H., & Kim, S. W. (1991). Electrically Erodible polymer gel for controlled release of drugs. *Nature*, **354**(6351), 291–293.

Kwon, I. C., Bae, Y. H., Okano, T., & Kim, S. W. (1991). Drug release from Electric-current sensitive polymers. *J. Control. Release*, **17**(2), 149–156.

Lao, L. L., & Ramanujan, R. V. (2004). Magnetic and hydrogel composite materials for hyperthermia applications. *J. Mater. Sci. Mater. Med.*, **15**(10), 1061–1064.

Lee, E. S., Kim, D., Youn, Y. S., Oh, K. T., & Bae, Y. H. (2008). A virus-mimetic nanogel vehicle. *Angew. Chem. Int. Ed. Eng.*, **47**, 2418–2421.

Lei, Y., & Segura, T. (2009). DNA delivery from matrix metalloproteinase degradable poly(ethylene glycol) hydrogels to mouse cloned mesenchymal stem cells. *Biomaterials*, **30**(2), 254–265.

Lin, C. C., & Metters, A. T. (2006). Hydrogels in controlled release formulations: network design and mathematical modeling. *Adv. Drug Deliv. Rev.*, **58**(12–13), 1379–1408.

Liu, T. Y., Hu, S. H., Liu, D. M., & Chen, S. Y. (2006). Magnetic-sensitive behavior of intelligent ferrogels for controlled release of drug. *Langmuir*, **22**(14), 5974–5978.

Liu, T. Y., Hu, S. H., Liu, K. H., Liu, D. M., & Chen, S. Y. (2008). Study on controlled drug permeation of magnetic-sensitive ferrogels: effect of Fe_3O_4 and PVA. *J. Control. Release*, **126**(3), 228–236.

Meenach, S. A., Hilt, J. Z., & Anderson, K. W. (2010). Poly(ethylene glycol)-based magnetic hydrogel nanocomposites for hyperthermia cancer therapy. *Acta Biomater.*, **6**(3), 1039–1046.

Minghetti, Y., Cilurzo, F., Tosi, L., Casiraghi, A., & Montanari, L. (2003). Design of a new water-soluble pressure-sensitive adhesive for patch preparation. *AAPS PharmSciTech.*, **4**(1), E8.

Miyata, T., Asami, N., & Uragami, T. (1999). A reversibly antigen-responsive hydrogel. *Nature*, **399**(6738), 766–769.

Murdan, S. (2003). Electro-responsive drug delivery from hydrogels. *J. Control. Release*, **92**(1–2), 1–17.

Murphy, W. L., Dillmore, W. S., Modica, J., & Mrksich, M. (2007). Dynamic hydrogels: translating a protein conformational change into macroscopic motion. *Angew. Chem. Int. Ed. Eng.*, **46**(17), 3066–3069.

Nguyen, M. K., & Lee, D. S. (2010). Injectable biodegradable hydrogels. *Macromol. Biosci.*, **10**(6), 563–579.

Park, K. H., Song, H. C., Na, K., Bom, H. S., Lee, K. H., Kim, S., et al. (2007). Ionic strength-sensitive pullulan acetate nanoparticles (PAN) for intratumoral administration of radioisotope: ionic strength-dependent aggregation behavior and (99m) technetium retention property. *Colloids Surf. B Biointerfaces*, **59**(1), 16–23.

Park, K., Yui, N., & Mrsny, R. (2004). A perspective on current and future synthetic reflexive systems. In N. Yui, R. Mrsny, & K. Park (Eds.), *Reflexive polymers and hydrogels: Understanding and designing FAST-responsive polymeric systems* (pp. 427–437). Boca Raton: CRC Press.

Park, N., Um, S. H., Funabashi, H., Xu, J., & Luo, D. (2009). A cell-free protein-producing gel. *Nat. Mater.*, **8**, 432–437.

Park, T. G., & Hoffman, A. S. (1994). Estimation of temperature-dependent pore size in poly(N-isopropylacrylamide) hydrogel beads. *Biotechnology Progress*, **10**(1), 82–86.

Pi, S. W., Ju, X. J., Wu, H. G., Xie, R., & Chu, L. Y. (2010). Smart responsive microcapsules capable of recognizing heavy metal ions. *J. Colloid Interface Sci.*, **349**(2), 512–518.

Qiu, Y., & Park, K. (2001). Environment-sensitive hydrogels for drug delivery. *Adv. Drug Deliv. Rev.*, **53**(3), 321–339.

Ramanathan, S., & Block, L. H. (2001). The use of chitosan gels as matrices for electrically modulated drug delivery. *J. Control. Release*, **70**(1–2), 109–123.

Ren, L., He, L., Sun, T., Dong, X., Chen, Y., Huang, J., et al. (2009). Dual-responsive supramolecular hydrogels from water-soluble PEG-grafted copolymers and cyclodextrin. *Macromol. Biosci.*, **9**(9), 902–910.

Rodriguez-Tenreiro, C., Diez-Bueno, L., Concheiro, A., Torres-Labandeira, J. J., & Alvarez-Lorenzo, C. (2007). Cyclodextrin/carbopol micro-scale interpenetrating networks (ms-IPNs) for drug delivery. *J. Control. Release*, **123**(1), 56–66.

Ruel-Gariepy, E., Shive, M., Bichara, A., Berrada, M., Le Garrec, D., Chenite, A., et al. (2004). A thermosensitive chitosan-based hydrogel for the local delivery of paclitaxel. *Eur. J. Pharm. Biopharm.*, **57**(1), 53–63.

Satarkar, N. S., & Hilt, J. Z. (2008). Magnetic hydrogel nanocomposites for remote controlled pulsatile drug release. *J. Control. Release*, **130**(3), 246–251.

Shen, J. S., Cai, Q. G., Jiang, Y. B., & Zhang, H. W. (2010). Anion-triggered melamine based self-assembly and hydrogel. *Chem. Commun. (Camb)*.

Siegel, R. A., Gu, Y., Lei, M., Baldi, A., Nuxoll, E. E., & Ziaie, B. (2010). Hard and soft micro- and nanofabrication: an integrated approach to hydrogel-based biosensing and drug delivery. *J. Control. Release*, **141**(3), 303–313.

Siemoneit, U., Schmitt, C., Alvarez-Lorenzo, C., Luzardo, A., Otero-Espinar, F., Concheiro, A., et al. (2006). Acrylic/cyclodextrin hydrogels with enhanced drug loading and sustained release capability. *Int. J. Pharm.*, **312**(1–2), 66–74.

Sutter, M., Siepmann, J., Hennink, W. E., & Jiskoot, W. (2007). Recombinant gelatin hydrogels for the sustained release of proteins. *J. Control. Release*, **119**(3), 301–312.

Ta, H. T., Han, H., Larson, I., Dass, C. R., & Dunstan, D. E. (2009). Chitosan-dibasic orthophosphate hydrogel: a potential drug delivery system. *Int. J. Pharm.*, **371**(1–2), 134–141.

Um, S. H., Lee, J. B., Park, N., Kwon, S. Y., Umbach, C. C., & Luo, D. (2006). Enzyme-catalysed assembly of DNA hydrogel. *Nat. Mater.*, **5**, 797–801.

Wichterle, & Lim, D. (1960). Hydrophilic gels for biological use. *Nature*, **185**, 117–118.

Woolfson, D. N. (2010). Building fibrous biomaterials from alpha-helical and collagen-like coiled-coil peptides. *Biopolymers*, **94**(1), 118–127.

Yang, X., & Kim, J. C. (2010). beta-Cyclodextrin hydrogels containing naphthaleneacetic acid for pH-sensitive release. *Biotechnol. Bioeng.*, **106**(2), 295–302.

Yoshida, R., Uchida, K., Kaneko, Y., Sakai, K., Kikuchi, A., Sakurai, Y., et al. (1995). Comb-type grafted hydrogels with rapid de-swelling response to temperature-changes. *Nature*, **374**(6519), 240–242.

Zhang, Y., Guan, Y., & Zhou, S. (2007). Permeability control of glucose-sensitive nanoshells. *Biomacromolecules*, **8**(12), 3842–3847.

Zhang, R., Tang, M., Bowyer, A., Eisenthal, R., & Hubble, J. (2005). A novel pH- and ionic-strength-sensitive carboxy methyl dextran hydrogel. *Biomaterials*, **26**(22), 4677–4683.