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Molecular imprinting within hydrogels

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Abstract

Hydrogels have been used primarily in the pharmaceutical field as carriers for delivery of various drugs, peptides and proteins. These systems have included stimuli-responsive gels that exhibit reversible swelling behavior and hence can show modulated release in response to external stimuli such as pH, temperature, ionic strength, electric field, or specific analyte concentration gradients. The focus of this article is to review molecular imprinting within hydrogels and discuss recent efforts on analyte-responsive intelligent gels, specifically suggesting the possibility of utilizing molecular imprinting strategies to impart analyte specificity and responsiveness within these systems. Molecular imprinting is an emerging field that produces precise chemical architecture that can bind analytes and differentiate between similar molecules with enantiomeric resolution. On the forefront of imprinting gel systems are intelligent, stimuli-sensitive imprinted gels that modify their swelling behavior and in turn modulate their analyte binding abilities. We discuss the challenges creating an imprinting effect in hydrogels and the possibilities of using molecularly imprinted mechanisms within controlled release gels.

Keywords: Hydrogels; Imprinting; Molecular imprinting; MIP; Controlled release; Modulated release; Stimuli-responsive; Intelligent gels; Analyte sensitive gels; Intelligent imprinted gels; Biomimetic

Contents

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1. Introduction

Hydrogels are insoluble, crosslinked polymer network structures composed of hydrophilic homo- or hetero-co-polymers, which have the ability to absorb significant amounts of water. From a biological viewpoint, this is an essential property to achieve an immunotolerant surface and matrix (i.e., with respect to protein adsorption or cell adhesion). Due to their significant water content, hydrogels also possess a degree of flexibility very similar to natural tissue, which minimizes potential irritation to surrounding membranes and tissues.

The design of controlled release systems involving hydrogels has been well documented [1–4]. The hydrophilic and hydrophobic balance of a gel carrier can be altered to provide tunable contributions that present different solvent diffusion characteristics, which in turn influence the diffusive release of drug contained within the gel matrix.

On the forefront of controlled drug delivery are enviro-intelligent and stimuli-sensitive gel systems that exhibit oscillatory swelling and hence modulate release in response to pH, temperature, ionic strength, electric field, or specific analyte concentration differences. In these systems, release can be designed to occur within specific areas of the body (e.g., within a certain pH of the digestive tract) or also via specific sites (adhesive or cell-receptor specific gels via tethered chains from the hydrogel surface). This article reviews recent efforts on analyte-responsive intelligent gels and discusses the possibility of using molecular imprinting strategies to impart analyte specificity and responsiveness within hydrogels. Currently, most analyte-sensitive gels are not entirely artificial and require a protein within the polymer matrix as the sensing/activation mechanism. The inclusion of proteins, lectins, and other compounds introduces immunogenic targets within these gels as well as more constrained processing procedures. For analyte intelligent systems that are completely artificial, specific moieties are included for analyte binding which have significant cross reactivity of binding similar analytes; thus, they exhibit a higher degree of immunogenicity. Molecular imprinting is an emerging field that produces precise chemical architecture that can bind analytes and differentiate between closely established isomers. On the forefront of imprinting gel systems are intelligent, stimuli-sensitive gels that modify their swelling behavior and in turn modulate their analyte binding abilities.

2. Hydrogels as carriers for controlled release

In the context of this review, molecularly imprinted hydrogels will be examined as potential carriers for drug delivery or drug elimination. It is therefore instinctive to examine first how the gel molecular structure can influence the associated drug release.

The drug release behavior and associated swelling characteristics of hydrogels are the result of crosslinks (otherwise known as tie-points or junctions), permanent entanglements, ionic interactions, or microcrystalline regions incorporating various chains [1–4]. Hydrogels have been used as prime carriers for pharmaceutical applications, predominantly as carriers for delivery of drugs, peptides or proteins. They have been used to regulate drug release in reservoir-based, controlled release systems or as carriers in swellable and swelling-controlled release devices [5–7].

Hydrogels can be classified as neutral, anionic or cationic. From a thermodynamic point of view, their swelling behavior is governed by a delicate balance between the polymer-water Gibbs free energy of mixing and the Gibbs free energy associated with the elastic nature of the polymer network [1]. As equilibrium swelling is reached, the partial molar quantities of these free energies become equal. Hydrogels can be rendered sensitive to physiological conditions due to the presence of specific functional groups along their backbone polymer chains. The swelling behavior and associated release kinetics of these gels may be dependent on pH, temperature, ionic strength, or even drug concentration (Fig. 1).

The development of ‘conventional’ controlled release devices based on hydrogels or hydrophilic carriers that can swell in the presence of a biological fluid has been described in several reviews [3,4]. Solvent-activated systems include osmotic-controlled and swelling-controlled release systems. The overall rate of drug release is controlled by the rate of water influx. In swelling-controlled systems, the drug,

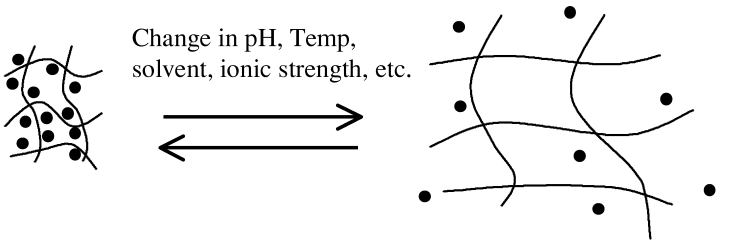

Fig. 1. Intelligent, Stimuli-Responsive Hydrogels. Modulated release of drug (circles).

which is dispersed in the polymer, diffuses out as water uptake occurs and the polymer swells. The drug release rate is dependent both on water diffusion and polymer chain relaxation. Continued swelling of this system results in the drug diffusing out at a faster rate with the rate of carrier swelling controlling the overall drug release rate. The time dependence of the rate of drug release can be determined depending on the rate of water diffusion and chain relaxation [5].

Recently there has been increased research in the preparation and characterization of materials responsive to changing environmental conditions. Some of the environmental conditions that can affect hydrogel swelling include pH, ionic strength, temperature, and drug concentration. In networks containing weakly acidic or basic pendent groups, water sorption can result in ionization of these pendent groups depending on the solution pH and ionic composition. The gels then act as semi-permeable membranes to the counterions influencing the osmotic balance between the hydrogel and the external solution through ion exchange, depending on ion-ion interactions. For ionic gels containing weakly acidic pendent groups, the equilibrium degree of swelling increases as the pH of the external solution increases. For gels containing weakly basic pendent groups, the equilibrium degree of swelling increases as the pH decreases.

Numerous physicochemical parameters contribute to the swelling of ionic hydrogels. Peppas and Khare [8] discussed the effect of these parameters including the ionic content, ionization equilibrium considerations, nature of counterions, and nature of the polymer. An increase in the ionic content of the gel increases the hydrophilicity leading to faster swelling and a higher equilibrium degree of swelling. Anionic hydrogels, which contain carboxylic groups, swell at a pH higher than the gel pK_a because of ionization within the network. The opposite behavior occurs for cationic gels that may contain amine groups. In an ampholyte, which contains both acidic and basic groups, the isoelectric pH determines the transitional pH of swelling of the gel. Ionization equilibrium considerations also affect the swelling behavior of ionic hydrogels. Fixed charges in the network lead to the formation of an electric double layer of fixed charges and counterions in the gel. Due to Donnan equilibrium [8], the chemical potential of the ions inside the gel is equal to that of the ions outside the gel in the swelling medium. Donnan exclusion prevents the sorption of co-ions because of electroneutrality resulting in a higher concentration of counterions in the gel phase than in the external swelling agent. The efficiency of co-ion exclusion, or an increase in the Donnan potential, increases with decreasing solution concentration. Increasing ionic content of the gel also increases the efficiency of co-ion exclusion.

Hydrogels have also been studied as potential carriers for controlled insulin release. An approach of using hydrogels that are sensitive to glucose is immobilization of glucose oxidase on a pH-sensitive hydrogel [9–11]. Glucose oxidase acts as a glucose sensor as it produces gluconic acid by an enzymatic reaction with glucose. The gluconic acid produced lowers the pH of the medium resulting in a release of insulin because of significant changes in swelling. An alternate route through phenyborate–poly(vinyl alcohol) polymers was discussed by Hisamitsu et al. [12].

Certain hydrogels may exhibit environmental sensitivity due to the formation of polymer complexes. Polymer complexes are insoluble, macromolecular

structures formed by the non-covalent association of polymers with an affinity for one another. The complexes form due to association of repeating units on different chains (interpolymer complexes) or on separate regions of the same chain (intrapolymer complexes). Polymer complexes can be stereocomplexes, polyelectrolyte complexes, and hydrogen bonded complexes. The stability of the associations is dependent on such factors as the nature of the swelling agent, temperature, type of dissolution medium, pH and ionic strength, network composition and structure, and length of the interacting polymer chains. In this type of gel, complex formation results in the formation of physical crosslinks in the gel. As the degree of effective crosslinking is increased, the network mesh size and degree of swelling is significantly reduced. As a result, the rate of drug release in these gels decreases dramatically upon the formation of interpolymer complexes [13].

In the past five years, there have been numerous new or improved pharmaceutical applications of hydrogels. Of particular interest have been the applications of poly(ethylene glycol) (PEG) in such applications [14]. PEG has many properties that make it an excellent candidate as a biomaterial. PEG is soluble in water and many organic solvents including toluene, methylene chloride, ethanol, and acetone. PEG is non-toxic and has a rapid clearance from the body, and has been approved for internal consumption by the Food and Drug Administration. One of the most important properties is that PEG resists recognition from the immune system. It also resists protein and cell adsorption. For example, Okano, Kataoka [15–17] and their collaborators developed PEG-based gels forming micellar structures, which have shown promising results for in vivo release of adriamycin and related cancer therapy drugs.

In addition, an exciting new technology of hydrogels was developed and reported by Park and collaborators [18]. They reported the preparation of superporous hydrogels and composites from a wide range of polymers including poly(acrylic acid) (PAA), PNIPAAm, and numerous others. The highly porous and well-structured porous network can be used for the relatively fast release of a wide range of drugs or proteins. Such developments can lead to improved drug delivery systems.

3. Molecular imprinting

The design of a precise macromolecular chemical architecture that can recognize target molecules from an ensemble of closely related molecules has a large number of potential applications. The main thrust of research in this field has included separation processes (chromatography, capillary electrophoresis, solid-phase extraction, membrane separations), immunoassays and antibody mimics, biosensor recognition elements, and catalysis and artificial enzymes [19,20]. However, currently there are no commercialized applications of imprinting technology [20] and relatively little attention has been paid to hydrogels. Recently, intelligent-imprinted gels have been prepared that memorize their binding conformation and can be switched on and off by external stimuli which modify their swelling behavior [21–25]. We believe that the field of molecularly imprinted polymers (MIPs) will evolve further to include new applications such as recognition elements in intelligent drug delivery devices, in targeted drug delivery applications [26], and in microfluidics devices with applications as analyte sensing micro-valves and micro-actuators [27] (Fig. 2).

Molecular imprinting involves forming a pre-polymerization complex between the template molecule and functional monomers or functional oligomers (or polymers) [28] with specific chemical structures designed to interact with the template either by covalent [29], non-covalent chemistry (self-assembly) [30,31], or both [32,33]. Once the pre-polymerization complex is formed (Fig. 3), the polymerization reaction occurs in the presence of a crosslinking monomer and an appropriate solvent, which controls the overall polymer morphology and macroporous structure. Once the template is removed, the product is a heteropolymer matrix with specific recognition elements for the template molecule. Several reviews exist describing the evolving field of molecular imprinting and designed molecular recognition [19,29–31,34–37].

The MIP network structure depends upon the type of monomer chemistry (anionic, cationic, neutral, amphiphilic), the association interactions between monomers and pendent groups, the solvent, and the relative amounts of co-monomers in the feed from which the structure is formed. Since recognition

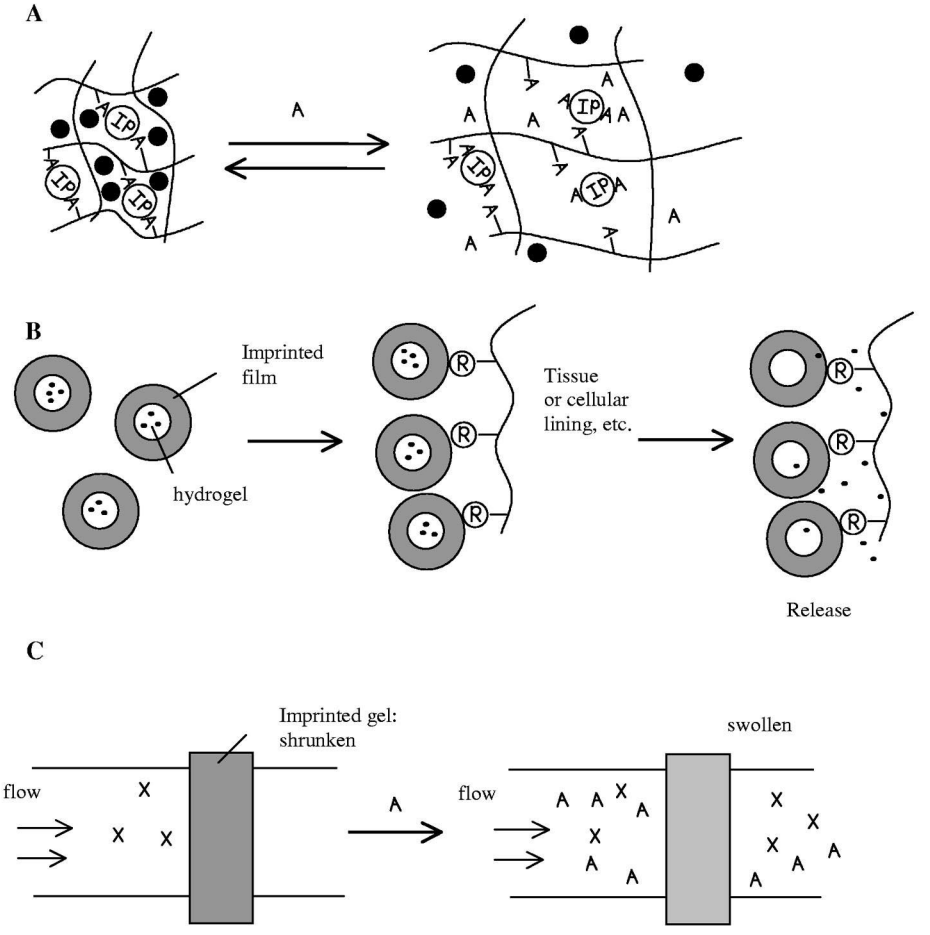

Fig. 2. Applications of Imprinted Gels. A: Intelligent release — Imprinted polymer (IP) binds analyte covalently attached to macromolecular chains. As free analyte (A) competes for binding sites, the network opens, and release occurs (the imprinted polymer is covalently attached or bigger than network mesh). (B) Targeted Drug Delivery — Imprinted film binds to specific cellular receptor (R), then release occurs by other stimuli-release mechanism (pH, temp, etc.). (C) Microfluidic Devices — Imprinted gel binds analyte causing the network to swell thereby opening the mesh size and allowing analyte X to diffuse through matrix. Sensing the concentration of X (fluorescence, etc.) would yield analyte concentration.

requires three-dimensional orientation, most techniques limit the movement of the memory site via macromolecular chain relaxation, swelling phenomena, and other processes, by using high ratios of crosslinking agent to functional monomers. As an increase in crosslinking monomer content leads to a decrease of the average molecular mass between crosslinks, the macromolecular chains become more rigid. In less crosslinked systems, movement of the macromolecular chains or, more specifically, of the spacing of functional groups will change as the network expands or contracts depending on the chosen rebinding solvent (thermodynamic interaction parameters characterizing the segment–solvent interaction) or application solution environment (Fig. 3). This process is reversible and transiently affects the binding behavior [21] and leads to sites with varying affinity and decreased selectivity [38,39].

Within biological applications, non-covalent techniques are the preferred synthesis route since an easy binding/non-binding template switching method is needed (i.e., no harsh conditions to remove tem-

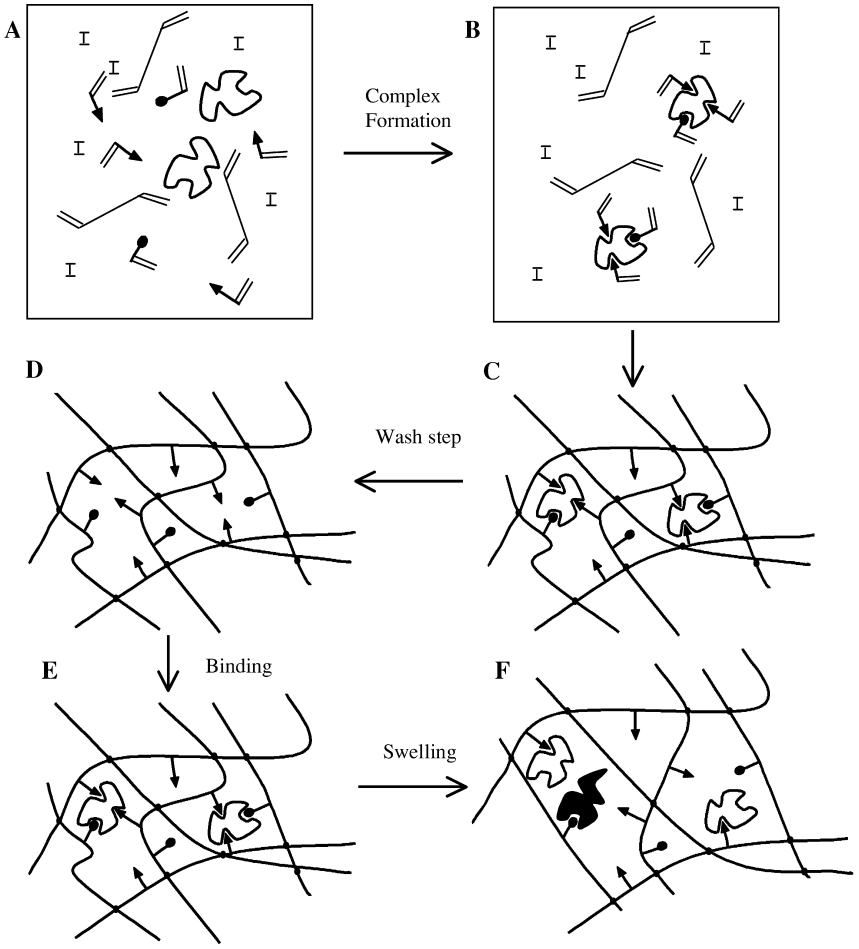

Fig. 3. Imprinting Process. (A) Solution mixture of template, functional monomer(s) (triangles and circles), crosslinking monomer, solvent, and initiator (I). (B) The pre-polymerization complex is formed via covalent or non-covalent chemistry. (C) The formation of the network. (D) Wash step where original template is removed. (E) Rebinding of template. (F) In less crosslinked systems, movement of the macromolecular chains will produce areas of differing affinity and specificity (filled molecule is isomer of template).

plate). Imprinting success, i.e., the ability to correlate high binding affinity and specificity, depends on the relative amount of cross interaction between the solvent and the intended non-covalent interactions (hydrogen bonding, hydrophobic interactions, $\pi-\pi$ orbital interactions, ionic interactions, and van der Waals forces) employed during template–monomer complex formation. If the solvent interferes or competes with any of these interactions, less effective recognition occurs. Naturally, these constraints have led to less polar organic synthesis routes for non-covalent aqueous recognition systems, which demonstrate orders of magnitude weaker binding affinity and decreased selectivity in polar, aqueous solvents [37,40].

However, proper tuning of non-covalent interactions such as increasing macromolecular chain hydrophobicity [41], including strong ionic directed recognition sites with hydrophobic domains [42], or including stronger hydrogen bond donors and acceptors [43], has been shown to enhance binding and achieve selective recognition in aqueous solutions. Thermodynamic analysis regarding energy contributions of ligand–receptor binding outlines the importance of directed tuning of these parameters in non-covalent recognition [38,39].

4. Imprinting within hydrogels

Since hydrogels swell significantly and contain large amounts of a hydrophilic solvent (within a thermodynamically favorable solvent the macromolecular network will solvate and the network will expand), imprinting in hydrogels requires a different methodology. However, there are numerous examples of such systems in nature. Proteins are heteropolymers that contain both flexible and rigid areas, which have diverse dynamic binding functions. A protein can have side chain flexibility, amino acid segment mobility, and domain flexibility between various amino acid chain domains [44]. Since proteins are composed of a linear sequence (or sequences) of amino acids with each amino acid having a unique residue group (hydrophilic or hydrophobic, varying electrostatic properties, hydrogen bond donor or acceptor, etc.), it is this sequence that dictates the conformation of the final protein. The direct interactions of these groups with the water, with each other, and with other molecules (e.g., cofactors, chaperones, etc.) influence the folding of a protein into a stable three-dimensional arrangement. Theoretical analysis of protein folding and recognition by heteropolymers is the subject of a number of reviews [45–48].

Based on a biomimetic approach, our group has outlined a few alternatives for successfully imprinting within hydrogels. The macromolecular architecture must be designed differently than more traditional dense networks and must include a spatially varying crosslinking density (micro and macroporous regions). Density fluctuations in the polymer network create regions or microgels of localized higher crosslinking, which contain an effective imprinting structure and proper rigidity to produce adequate specificity (areas or patches of recognition). The binding kinetics and mass transfer of this design can be enhanced compared to known dense gels (mass transfer is slow and rebinding percentage is low as templates inherently are trapped within the matrix). However, analyte binding capacity is reduced on a per gel mass or volume basis. Similarly, it is in this respect that liquid crystalline networks [49] and semi-crystalline hydrogels, which have dense regions of ordered macromolecular chains (physical entanglements), are thought to also produce an imprinting effect. It is this dense ordering of macromolecular chains that provides network stiffness which stabilize recognition sites.

One of the most promising alternatives includes a post-crosslinking reaction, either between excess functional monomers on opposite macromolecular chains or via other monomers introduced into the network, after the gel is formed and imprint is rebound. Tanaka and collaborators [21–25] have described how loosely crosslinked intelligent gels memorize their macromolecular conformation (reversibly self-organize upon gel swelling and shrinking). Since these systems display stimuli-sensitive binding behavior (e.g., recognition occurs as the gels attain their collapsed state), they will be highlighted within the next section on intelligently imprinted gels. Nonetheless, these systems provide convincing proof that recognition and memorization of binding sites can occur in low crosslinked systems.

Since polymerization occurs within a solvent (as crosslinking in dilute polymer solutions minimizes physical entanglements and heterogeneity within the polymer network (50)), matching polymerization and rebinding solvents in terms of dielectric constant, polarity, protic nature, etc. (or keeping the original solvent when rebinding) will reduce differences in swelling behavior (Gibbs free energies associated with the elastic nature of the network and the energy of mixing). In these cases, the network could be designed in a less dense manner with recognition occurring between flexible functionalized chains (i.e., longer and higher molecular weight) stabilized by additional post-crosslinking and post-stabilizing reactions either via opposite chains or within the functional monomer chain itself and a macromolecular chain.

To date little work has been completed on low crosslinked imprinted systems. Recently, Wizeman and Kofinas [28] produced a low crosslinked gel (13% mole per mole total monomers) with specific recognition properties for glucose by imprinting with a functional polymer chain rather than individual monomers. Of importance in the success of this network was crosslinking a portion of additional amine site on the functional polymer not involved in imprint site formation.

Other investigators employing more traditional and well-established imprinting techniques

(pioneered by Wulff [29,51] and Mosbach [30,52]) have also lowered the crosslinking percentage (19% [53], 22% [54]) while still retaining specific recognition. Typically, molecularly imprinted gels were highly crosslinked for greater affinity, capacity, and selectivity since early attempts involved separation processes and began with a rigid approach rather than flexible recognition. While these percentages are still large in proportion to normal hydrogel crosslinking amounts (0.1–3% mole per mole monomers), the results provide evidence that with various imprinting methods and revised techniques crosslinking percentages can be lowered and impart significant recognition capabilities within flexible low crosslinked systems. As these low crosslinked systems and hydrogels are examined, there is no doubt that new and interesting applications (intelligent controlled release imprinted gels, imprinted films, membranes, etc.) will be discovered.

Designing the network architecture for hydrogels has also shifted focus towards more traditional rigid body approaches to imprinting in regards to the crosslinking and functional monomer ratio. In designing the macromolecular architecture with respect to monomer type and composition, as the molecular mass of the crosslinking monomer is increased, the length of the functional monomer or monomers should increase accordingly to avoid loss of possible binding regimes irrespective of swelling or shrinking phenomena (Fig. 4). This mainly deals with polymerization kinetics and the nature of the chains formed during polymerization, which influence the network morphology on a molecular level. With high crosslinking monomer ratios, the types of chains formed consist of primary copolymer chains of crosslinker and functional monomer and other secondary chains of crosslinking monomer that connect each macromer unit [50]. This is a possible reason why investigators have seen marginal success in imprinting a given analyte by increasing the molecular mass of crosslinker without a corresponding increase in functional monomer molecular mass (linear size). Similarly, decreasing the crosslinker molecular size below a certain limit would produce a very restricted network for template diffusion and rebinding.

Therefore, there is an optimum crosslinking to functional monomer molecular mass ratio, which directly depends on the size of the template. For the types of small molecular mass molecules imprinted to date, ethylene glycol dimethacrylate has been the most favored and successful choice with currently available functional monomers [55]. For multi-functional crosslinking agents, the corresponding linear portions of the vinyl chains are expected to follow the same reasoning, albeit on a different length scale depending on the physical molecular nature of the crosslinker. Although, it is important to consider that as the macromolecular chains increase in size the flexibility of the chains will also increase. These may or may not need to be stabilized. Natural processes invariably have flexibility in recognition and Demchenko [56] reviews molecular recognition between flexible molecular structures and highlights the sequential steps of mutual conformation adaptation in the recognition of biological macromolecules.

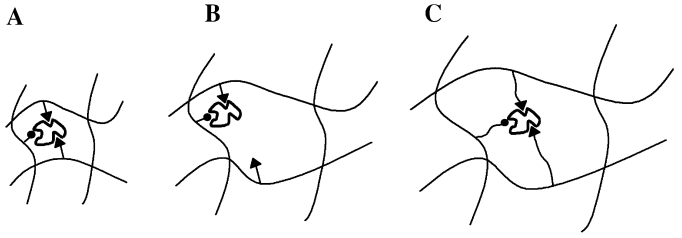

Fig. 4. Crosslinking to Functional Monomer Ratio. (A) Appropriate crosslinking to functional monomer size. (B) An increase in crosslinker molecular mass (linear size) without a change in functional monomer size. Note possible loss of effective recognition in some areas. (C) A corresponding increase in functional monomer molecular mass (linear size) compared to crosslinking monomer. Post stabilization of these more flexible functional monomer chains might be needed for binding specificity.

5. Intelligent imprinted gels

Tanaka and collaborators [21–25] described sensitive gels with stimuli-sensitive recognition very similar to recognition in proteins. By outlining the principles developed by analyzing theoretical mechanics of heteropolymers, the underlying memory of macromolecule conformation is discovered and experimentally verified. Essentially, their design includes polymerizing in the presence of target molecule, functional monomer, thermo-sensitive monomer, and end shielded post-crosslinking monomer. After washing, the post-crosslinker caps were removed and the gels were post-crosslinked (total crosslinking 0.1–3 mole% per mole monomers) in the presence and absence of template molecules. The presence of additional post-crosslinking resulted in 3–5 times higher affinity compared to random post crosslinking and a reduction of 'frustration' within the gels (adsorbing monomers within the polymer chains are limited in coming closer to capture target molecules).

Furthermore, these adsorption sites were destroyed upon gel swelling and reformed upon shrinking. While these systems show multiple-point adsorption, they have yet to recognize other molecules than charged species. However, important contributions have been made describing the nature of recognition in low cross-linked systems, and it is only a matter of time when intelligent gels can recognize other types of molecules. It is important to note that their goal was not to accomplish better affinity and selectivity compared to traditional dense networks, but to form self-organizing active sites that can be memorized upon gel shrinking and swelling. It is also important to note that the observed imprinting effect is not a result of patches of recognition (heterogeneous gels as suggested previously).

6. Controlled release from imprinted gels

It is easy to speculate that imprinted gels or chains possessing certain macromolecular architecture with binding abilities could be used as the sensing elements within analyte sensitive controlled release systems. Analyte sensitive polymer networks have been the focus of much research (mostly saccharide recognition) and have been designed in a number of ways (Fig. 5). They have included enzymes, which as a result of reaction invoke a local pH change, modulating the swelling of the network and thus release [9–11,57–59]. They have included cross-link dependent systems where pendent (attached to the copolymer chains) and free analyte compete for binding positions within protein sites. As analyte replaces pendent analyte groups within the protein, the network loses effective crosslinks, opens the network mesh size, and regulates release [60–66]. As the analyte decreases in concentration within the bulk phase, the protein binds again with the pendent analyte groups closing the network structure. Similarly, systems have been designed that have a specific antigen and corresponding antibody grafted to a semi-interpenetrating network, which swells in response to binding of the antigen due to a loss of effective crosslinks [67]. Work of this type has also included artificial systems, which do not utilize proteins in the design (e.g., loss of complexation networks [12]). Incorporating analyte binding groups randomly into the polymer network and chemically modifying the released drug or protein [68] to have attached analyte produces a gel that will release in a competitive binding response to free analyte in solution.

The design and implementation of imprinted recognition release systems would not be easy, but certainly one can envision imprinted gel particles or particles with thin coatings of imprinted films taking the place of the proteins within the above-mentioned gels (Fig. 2a). In particular, low crosslinked gels could be formed consisting of a functionalized network (with template not bound) and then an interpenetrating procedure where another network is formed in presence of template (with additional crosslinks imposed by pendent analyte group interaction). When free analyte is in solution, the gel would lose effective imprints (or complexation) and release could occur. The releasable drug loading scheme would involve imbibition (equilibrium partitioning) or entrapment during polymerization (if the drug does not interfere with the network formation and the template complex itself).

To some degree the binding of molecules to active sites or specific chemical groups can indeed change the overall ionic character or hydrophilicity or

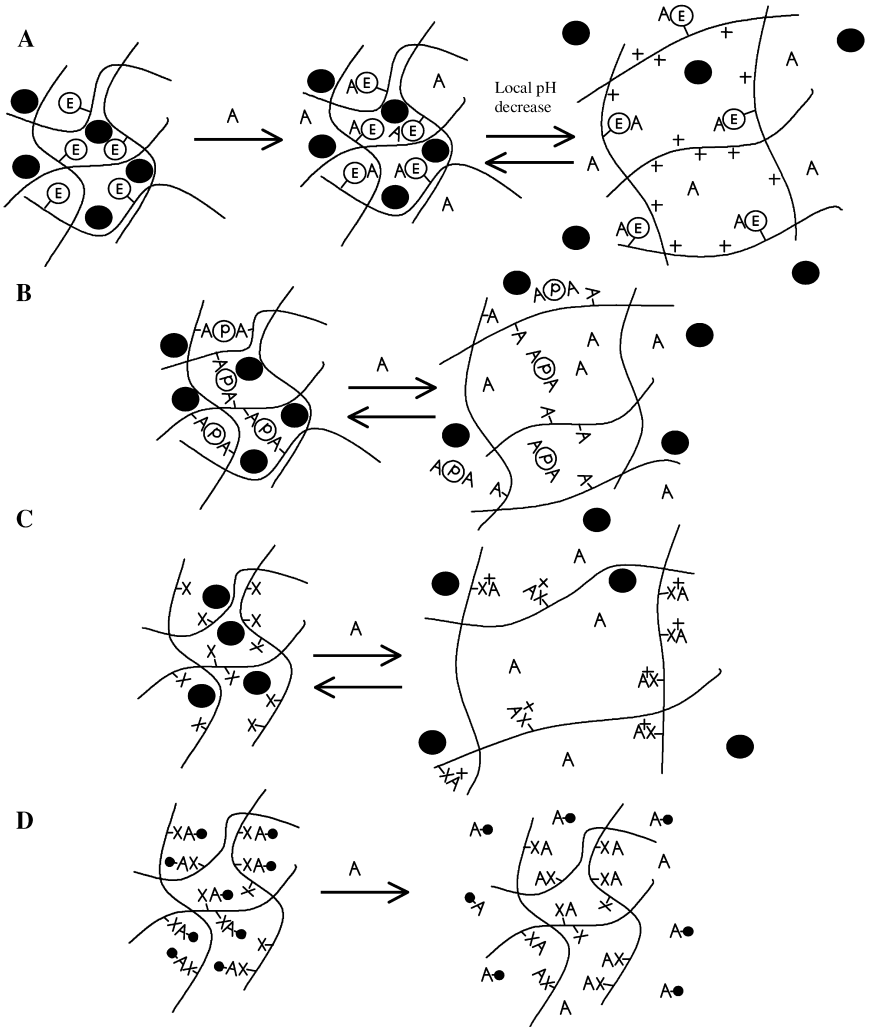

Fig. 5. Intelligent Analyte-Sensitive Hydrogel Networks. (A) Induced Swelling — As analyte (A) binds, the enzymatic reaction (E denotes covalently attached enzyme) produces a local pH decrease. For the cationic hydrogel, which is weakly basic, the result is ionization, swelling, and release of drug, peptide, or protein (filled circle). When A decreases in the bulk concentration, the gel shrinks (adapted from Ref. [9–11,57–59]). (B) Loss of Effective Crosslinks — Analyte competes for binding positions with the protein (P). As free analyte binds to the protein, effective crosslinks are reversibly lost and release occurs. Picture not to scale, binding protein is much larger than released drug, peptide, or protein (adapted from Ref. [60–63]). (C) Artificial System: Bound Analyte Induced Swelling — When analyte binds to a pendent functional group, an ionized complex forms which swells the network and release occurs (adapted from Ref. [69]). (D) Artificial System: Analyte Binding Switch — Analyte binding groups are randomly introduced into the network during polymerization. Then chemically modified (analyte (A) attached) drug, peptide, or protein is bound. As analyte from solution competes for binding sites, release occurs (adapted from Ref. [68]).

hydrophobicity and thus swelling of a polymer gel. Kataoka and coworkers [69] have shown this effect (borate–glucose complex) with a sharp transition in swelling degree with respect to glucose concentration. As glucose binds, the network becomes more hydrophilic due to the formation of a charged

template-binding group complex (Fig. 5c). Thus, as the authors speculate, this type of polymer gel can be used as a chemical valve to regulate solute permeation responding to glucose. Kataoka [70] has recently described the immunogenicity of the phenylboronate moiety, which may recognize *N*-acetylneuraminic acid residues on the plasma membrane of lymphocytes. Imprinting structures could be used in these circumstances to greatly decrease cross reactivity and non-specific binding. Certainly, one must recognize that imprinting techniques to date result in non-specific binding regions but to a lesser degree than randomly functionalized polymers. However, more work must be done to impart greater degrees of specificity in these systems, especially in flexible low crosslinked systems.

It is also important to discuss release similar to that shown in Fig. 5d, the analyte binding switch. Due to the possibility of tailoring unique receptors for molecules, imprinted polymers have been considered for separation of racemic drugs (intended from non-intended chiral twin) [71]. In cases where the non-intended twin molecule imposes side effects, imprinted polymers could be used to separate and purify drug mixtures. However, in controlled release applications loading and separation of intended drug would occur simultaneously and release could be tailored by the properties of the hydrogel. In these cases loading occurs via chemical means by the non-covalent forces during imprint/functional group formation.

7. Conclusions

The future of intelligent, controlled release, analyte-sensitive hydrogels will include molecularly imprinted contributions toward design. Better control of binding site structure and specificity will lead to replacement of protein within these devices and less specific, randomly introduced binding groups. As a result, new and interesting solutions to successful polymer network design and hence controlled release strategies will become available. This technology will also have direct impact in a number of areas including microfluidic devices, biomimetic sensors, and membrane separation technology.

Acknowledgements

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