Hydrogels as Controlled Drug Delivery Systems: Synthesis, Crosslinking, Water and Drug Transport Mechanism

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Hydrogels are presently under investigation as a delivery system for bioactive molecules, because of their similar physical properties as that of living tissue, which is due to their high water content, soft and rubbery consistency, and low interfacial tension with water or biological fluids. Anionic hydrogels are used in the design of intelligent controlled release devices for site-specific drug delivery of therapeutic proteins to the large intestine, where the biological activity of the proteins are prolonged, and cationic hydrogels are studied for the development of self-regulated insulin delivery system, which releases the insulin in response to changing glucose concentration. The different methods of preparation of hydrogels, novel methods of crosslinking used in the preparation of hydrogels, the mechanism of water transport through the ionic hydrogels, and the release mechanism of the solute from the hydrogels, are discussed in the present article.

The hydrogels, since their discovery by Wichterle and Lim in 1960 of poly(2-hydroxyethyl methacrylate)[1], have been of great interest to biomedical scientists. Hydrogels are three dimensional hydrophilic polymer networks capable of swelling in water or biological fluids, and retaining a large amount of fluids in the swollen state[2]. Their ability to absorb water is due to the presence of hydrophilic groups such as –OH, –CONH–, $–CONH_2$, –COOH, and $–SO_3H$[3]. The water content in the hydrogels affect different properties like permeability, mechanical properties, surface properties, and biocompatibility. Hydrogels have similar physical properties as that of living tissue, and this similarity is due to the high water content, soft and rubbery consistency, and low interfacial tension with water or biological fluids[4]. The ability of molecules of different size to diffuse into (drug loading), and out (release drug) of hydrogels, permit the use of hydrogels as delivery systems. Since hydrogels have high permeability for water soluble drugs and proteins, the most common mechanism of drug release in the hydrogel system, is diffusion. Factors like polymer composition, water content, crosslinking density, and crystallinity, can be used to control the release rate and release mechanism from hydrogels[5].

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TYPES OF HYDROGELS

Hydrogels, based on their nature, can be classified as pH sensitive, temperature sensitive, enzyme sensitive, and electrical sensitive[6]. pH sensitive hydrogels can be neutral or ionic in nature. The anionic hydrogels contain negatively charged moieties, cationic networks contain positively charged moieties, and neutral networks contain both positive and negatively charged moieties. In neutral hydrogels, the driving force for swelling arises from the water-polymer thermodynamic mixing contributions, and elastic polymer contributions. In ionic hydrogels, the swelling is due to the previous two contributions, as well as ionic interactions between charged polymer and free ions[7]. The presence of ionizable functional groups like carboxylic acid, sulfonic acid or amine groups, renders the polymer more hydrophilic, and results in high water uptake.

In the case of anionic polymeric network containing carboxylic or sulphonic acid groups, ionization takes place, as the pH of the external swelling medium rises above the pK_a of that ionizable moiety. The dynamic swelling change of the anionic hydrogels can be used in the design of intelligent controlled release devices for site-specific drug delivery of therapeutic proteins to large intestine, where the biological activity of the proteins is

prolonged[12]. The change in the pH of the external environment will act as a stimulus, and the response to the stimulus is the change in swelling properties of the hydrogels, causing the release of the protein. Bettini *et al.*[8] prepared anionic copolymer of methyl methacrylate and 2-hydroxyethyl methacrylate by bulk polymerization, using ethylene glycol dimethacrylate as crosslinking agent. The prepared pH sensitive delivery system showed increased swelling above the pK_a (5.9) of methyl methacrylate. The drug release was relaxation controlled, since the swelling of glassy polymer was accompanied by chain relaxation process. Hydrogels of poly(acry1ic acid) (PAA), and poly(acry1ic acid-co-2-hydroxyethyl methacrylate) [P(AA-co-HEMA)] hydrogels, were synthesized by Ende and Peppas[9] with varying degree of hydrophilicity and crosslinking density, and were studied as potential bioadhesive controlled-release dosage forms. Equilibrium and dynamic swelling studies were carried out to determine the polymer mesh size and molecular weight between crosslinks of the hydrogels, in the ionized and nonionized states. The PAA hydrogel mesh sizes ranged from 100 to 400 Å, over pH values of 3-7, whereas the p(AA-co-HEMA) hydrogel mesh sizes were between 13 and 140 Å. These results demonstrated the significance of the swelling medium pH on the hydrated state of the polymers, related to crosslinking or copolymerization composition. Kim *et al.*[10] prepared pH sensitive anionic hydrogels based on poly(methacrylic acid-co-methacryloxyethyl glucoside) and poly(methacrylic acid-g-ethylene glycol). The hydrogels showed limited swelling in a pH 2.2 buffer, but rapid swelling was observed in the pH 7.0 buffer solution. The mechanism of water transport through the hydrogel was non-fickian at pH 2.2, and became relaxation controlled (case II) at pH 7.0 (higher than pK_a of hydrogel). Brazel and Peppas[11] studied hydrogels based on poly(N-isopropylacrylamide-co-methacrylic acid). Heparin and streptokinase were loaded to study the release pattern, under pulsatile conditions of varying temperature and pH. The hydrogels showed higher streptokinase release at pH 6.0 and 33°, and collapsed at pH 5.0 and 36°. But the same results were not observed in the case of heparin, which has smaller molecular diameter than streptokinase. It was concluded that the mesh size was too large to control the diffusion of heparin, even in the collapsed state.

The pH sensitivity of anionic hydrogels has been used to deliver proteins to the colon, where the activity of the proteolytic enzymes is comparatively lower. Calcitonin was loaded into hydrogels of poly(methacrylic acid-g-ethylene glycol)[12], and the release mechanism was found to be relaxation controlled, and calcitonin was released in 7 h. The hydrogels were prepared with different solvent volume fractions, ranging from 0.17 to 0.57. The calcitonin loading and the diffusion coefficient through the hydrogels decreased with increase in solvent volume fraction. Hydrogels of poly(methacrylic acid-co-methacryloxyethyl glucoside) and poly(methacrylic acid-g-ethylene glycol) was studied as a delivery system of insulin[13]. The hydrogels showed slow release of insulin in acidic medium, and in alkaline pH, the release was rapid. The hydrogels were able to provide protective effect of insulin when treated with simulated gastric fluid.

The cationic hydrogels show swelling at pH values below pK_a of the cationic group. The amine groups are protonated at pH lower than pK_a, and become hydrophilic and absorb water. At pH greater than pK_a, the polymer is hydrophobic, and exclude water. Hydrogels of poly(methyl methacrylate-co-dimethylaminoethyl methacrylate)[14] were studied for diffusion coefficients of different water soluble drugs. The diffusion of water-soluble drugs followed free volume theory, which suggests pore type mechanism, and water insoluble drugs, followed a partition or solution-diffusion mechanism. The water transport mechanism through these hydrogels was non-Fickian in acidic pH, and became Fickian in alkaline pH.

Cationic hydrogels are used in the preparation of self-regulated insulin delivery systems. The use of cationic hydrogels in the preparation of self-regulated insulin delivery systems, has been reviewed by Shivakumar and Satish[15]. The self-regulated insulin delivery system utilizes glucose oxidase (GOD) as the glucose sensor, and pH sensitive cationic hydrogel as the insulin release controller. In such a system, glucose is oxidized to gluconic acid, and catalyzed by GOD[36], as shown here. glucose + O_2 + H_2O → gluconic acid + H_2O_2. Because of the formation of gluconic acid, the pH inside the microenvironment decreases with the increase in glucose concentration. This causes swelling of pH sensitive hydrogel, which results in the release of entrapped insulin.

Klumb and Horbett[16] have studied systems containing immobilized glucose oxidase (GOD) in a pH responsive cationic polymeric hydrogel poly (2-hydroxyethyl methacrylate-co-N,N-dimethylaminoethyl methacrylate) poly(HEMA-co-DMAEMA) and Tetraethylene glycol dimethacrylate (TEGDMA) as cross-linking agent. Several parameters that affect the swelling and permeability of the

membrane; such as concentration of amine groups (DMAEMA), cross-linking agent (TEGDMA), and glucose oxidase were studied. The swelling increased with increase in amine concentration, and decreased in cross-linking agent concentration. Goldraich and Kost[17] have evaluated a matrix system, in which the drug and enzymes were uniformly distributed throughout the hydrogel poly(HEMA-co-DMAEMA). The results showed that the hydrogels with high amine content of DMAEMA (18.5 vol%) and low cross-linking agent concentration of TEGDMA (0.3 vol%), are the most sensitive to pH. Traitel and coworkers[18] studied the same hydrogel in simulated *in vivo* conditions. The polymer morphology was modified by changing the cross-linking agent (TEGDMA) concentration (0-0.95%). The swelling rates and swelling extent increased at a steady state, with decreasing cross-linking agent concentration. The matrices without cross-linking agent were stable in water, and did not dissolve in water for an extended period of few months. Also, it was observed that physically cross-linked hydrogel showed faster insulin release rates, than chemically cross-linked hydrogel. The *in vivo* experiment with physically cross-linked hydrogel showed significant reduction in blood glucose levels from 400 mg/dl to 100-200 mg/dl after 2.5 h and to 50-120 mg/dl after 6.5 h.

Electric current can also be used as an environmental signal to induce responses of hydrogels. Hydrogels, sensitive to electric current, are usually made of polyelectrolytes. An electric field as an external stimulus has advantages, such as the availability of equipment, which allows precise control with regards to the magnitude of current, duration of electric pulses, intervals between pulses, etc. It has been demonstrated that, four distinct electrochemical and electromechanical mechanisms exists for selective controlled transport of proteins and neutral solutes across hydrogel membranes: (1) electrically and chemically induced swelling of a membrane to alter the effective pore size and permeability; (2) electrophoretic augmentation of solute flux within a membrane; (3) electroosmotic augmentation of solute flux within the membrane; and (4) electrostatic partitioning of charged solutes into charged membranes[19].

Sahawata *et al.*[20] studied microparticles of sodium salt poly(acrylic acid) as an electroresponsive delivery system, using pilocarpine as model drug. The microparticles showed 96% volume change within 50 s of application of a d.c. of 0.3 mA cm^{-2}. The deswelling occurred due to diffusion of mobile cations away from the carboxylate ions, under the influence of an electric field gradient. The carboxylate anions remain undissociated under this condition, and leads to the constriction of gel. The pilocarpine release observed was, 9.8×10^{-7} mol dm^{-3} s^{-1} when d.c. was applied, and when switched off, the release decreased to 1.8×10^{-7} mol dm^{-3} s^{-1}.

The electrical behaviour of the interpenetrating polymer network (IPN) hydrogel composed of sodium alginate (SA) and poly(diallyldimethylammonium chloride) (PDADMAC) was studied by Kim *et al.*[21] The SA/PDADMAC IPN hydrogel exhibited pH and electrolyte concentration sensitive behavior. When an electric field is applied to a strip of the SA/PDADMAC IPN hydrogel in an aqueous HCl solution, the gel showed significant and quick bending toward the cathode. The bending angle measured was 90°, 82°, 52°, and 27° at 15, 10, 7 and 5 V respectively, at a constant HCl concentration. It was concluded that the deformation of a polymer hydrogel under an electric field was due to the voltage-induced motion of ions, and the concomitant expansion of one side of the polymer and the contraction of the other side of the polymer. Kim *et al.*[22] studied interpenetrating polymer networks (IPN) hydrogels of poly(vinyl alcohol) (PVA), and hyaluronic acid (HA). When swollen, IPN was placed between a pair of electrodes, and an electric field applied, it exhibited bending behavior. The equilibrium bending angle (EBA) of the PVA/HA IPN showed an apparent peak (74°) in a 0.25M aqueous NaCl solution. The bending degree increased with increasing NaCl solution concentration, with concentrations <0.25 M. However, the bending degree decreased with NaCl solution concentrations >0.25 M. The bending angle measured was 72°, 58°, 38°, and 22° at 15, 10, 7 and 5 V respectively, at a constant NaCl concentration.

Thermosensitive hydrogels are one of the widely studied responsive polymer systems. The thermosensitive polymers are characterized by the presence of hydrophobic groups, such as methyl, ethyl, and propyl groups. The most widely studied temperature sensitive polymer is poly(N-isopropylacrylamide) P(NIPAAm). P (NIPAAm) is a non-biodegradable polymer with a LCST ~32° in water, and cross-linked gels of this material collapse around this temperature[23]. Pluronics® or Poloxomers® are the commercially available copolymers of poly(ethylene oxide) (PEO) and poly(propylene oxide) (PPO). These copolymers show phase change from sol-gel around body temperature, and are used as injectable implants. Temperature sensitive hydrogels are classified

into negatively thermosensitive, positively thermosensitive, and thermally reversible gels[24]. Certain hydrogels formed by IPNs show swelling at high temperature, and shrinking at low temperature. IPNs of poly(acrylic acid) and polyacrylamide (PAAm) or poly poly(acrylamide–co-butyl methacrylate), have positive temperature dependence of swelling. Such types of hydrogels are called positively thermosensitive hydrogels. The negatively thermosensitive hydrogels include P(NIPAAm–co-BMA) hydrogels[25], and inter-penetrating polymer networks (IPNs) of P (NIPAAm) and poly(tetramethyleneether glycol) (PTMEG). These type of hydrogels swell when the temperature is decreased, and deswell when the temperature is increased. The on-off release profile of drugs from the matrices was explained by the formation of a dense, less permeable surface layer of gel, described as a skin-type barrier. The skin barrier was formed upon a sudden temperature change, due to the faster collapse of the gel surface than the interior. This surface shrinking process was found to be regulated by the length of the methacrylate alkyl side-chain, i.e. the hydrophobicity of the comonomers. As the surface shrinks, it represents an increasing resistance to transport out of the gel[26]. Thermoreversible gels that are widely studied, are copolymers of poly(ethylene oxide) (PEO) and poly (propylene oxide) (PPO). To make the hydrogels biodegradable, the PPO segment of PEO–PPO–PEO block copolymers can be replaced by a biodegradable poly (L-lactic acid) segment[27].

Temperature-modulated insulin release from pH/ temperature sensitive hydrogels of NIPAAm and the cationic monomer, *N*, *N*-dimethylaminopropylmethacrylamide (DMAPMAAm) has been studied by Park[28]. The former allows the gel to exhibit temperature sensitivity, and the latter gives the gel a pH-sensitivity. It was found that the crosslinked co-polymer gel of NIPAAm/ DMAPMAAm in the molar ratio of 97:3, demonstrated a pH-sensitivity around pH 7.4 as well as a temperature-sensitivity around 37°. The insulin release profile exhibited Fickian diffusion at 32°, and showed a near zero-order release at 42°, while a two-stage release profile was observed at 37°. Erbil *et al.*[29] have synthesized and characterised poly(dimethyl siloxane)/ poly(N-isopropyl acrylamide) PDMS/P(NIPAAm) semi-interpenetrating networks. The phase morphologies was characterized by FTIR, DSC, and SEM. Semi-IPNs exhibited phase transition temperatures higher than glass transition temperatures of their respective homopolymers, suggesting a heterophase morphology, and only physical entanglement between the P(NIPAAm) network and linear PDMS. Liu and Sheardown[30] have studied composite interpenetrating network (IPN) of PDMS and P (NIPAAm) to generate polymers with oxygen and glucose permeability, as well as improved wettability compared to PDMS homopolymers, and greater mechanical strength than P(NIPAAm) homopolymers. Transmission electron microscopy images verified the structure of the IPNs. Surface analysis suggested that P(NIPAAM) was present on the surface, as well as in the bulk material. PDMS-OH (hydroxyl terminated PDMS) IPNs generated had the highest glucose permeability at 10^{-7} cm^2/s, comparable to that of the native cornea. The results suggested that these materials can be developed as ophthalmic biomaterials, or for controlled drug-release applications.

The diffusional characteristics for P(NIPAAm) gel for glucose and insulin with changing temperature, have been investigated by Andersson and others[31]. The gel was a critical one which means that small changes in the environment influenced the gel volume considerably. The effective diffusion coefficients for the solutes glucose and insulin were determined below the critical temperature: 10, 20 and 30°. The effective diffusion coefficient for glucose increases from 2.7×10^{-10} to 4.7×10^{-10} m^2/s, and for insulin effective diffusion coefficient increased from 4.4×10^{-10} to 5.9×10^{-10} m^2/s, when the temperature was changed from 10 to 30°.

Enzyme sensitive hydrogels are mainly used in the targeting of drugs to colon. The colon-specificity is achieved due to the presence of pH-sensitive monomers and azo cross-linking agents in the hydrogel structure. When the hydrogels pass through the GI tract, the swelling capacity of the hydrogels increases as the pH increases, due to presence of pH sensitive polymers, with the swelling being highest around pH 7.4. Upon arrival in the colon, the hydrogels have reached a degree of swelling, that makes the cross-links accessible to the enzymes (azoreductase) or mediators. Subsequently, the hydrogel network is progressively degraded via the cleavage of the cross-links, and the drug entrapped is thus released[32]. The hydrogels can be obtained by cross-linking polymerization of *N*-substituted (meth) acrylamides, *N-tert*-butylacrylamide and acrylic acid, with 4, 42-di (methacryloylamino) azobenzene, 4, 42-di (*N*-methacryloyl -6-aminohexanoylamino) or 3, 32, 5, 52-tetrabromo-4, 4, 42, 42-tetrakis (methacryloylamino) azobenzene as the cross-linking agents[33].

PREPARATION OF HYDROGELS

Several techniques have been reported for the synthesis of hydrogels. The first approach involves copolymerization/crosslinking of co-monomers using multifunctional co-monomer, which acts as crosslinking agent. The polymerization reaction is initiated by chemical initiator. The polymerization reaction can be carried out in bulk, in solution, or in suspension. The second method involves crosslinking of linear polymers by irradiation, or by chemical compounds[3]. The monomers used in the preparation of the ionic polymer network contain an ionizable group, a group that can be ionized, or a group that can undergo a substitution reaction after the polymerization is completed. As a result, hydrogels synthesized contain weakly acidic groups like carboxylic acids, or a weakly basic group like substituted amines, or a strong acidic and basic group like sulfonic acids, and quaternary ammonium compounds. Some of the commonly used crosslinking agents include N, N'-methylenebisacrylamide, divinyl benzene, and ethylene glycol dimethacrylate. The monomers and the crosslinking agents used in the preparation of hydrogels are given in Table 1.

Solution polymerization/crosslinking:

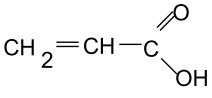
In solution, co-polymerization/crosslinking reactions, and ionic or neutral monomers are mixed with the multifunctional crosslinking agent. The polymerization is initiated thermally, by UV-light, or by redox initiator system. The presence of solvent serves as heat sink, and minimizes temperature control problems. The prepared hydrogels need to be washed with distilled water to remove the unreacted monomers, crosslinking agent, and the initiator. The best example is preparation of poly(2-hydroxyethyl methacrylate)[1] hydrogels from hydroxyethyl methacrylate, using ethylene glycol dimethacrylate as crosslinking agent. Using the above method, a great variety of hydrogels have been synthesized[34]. The hydrogels can be made pH- sensitive or temperature-sensitive, by incorporating methacrylic acid[35], or N-isopropylacrylamide[36], as monomers.

TABLE 1: STRUCTURE OF MONOMERS USED IN THE PREPARATION OF HYDROGELS

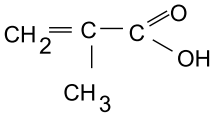
Ionic monomers used for Hydrogel synthesis

Anionic acidic monomers

1. Acrylic acid

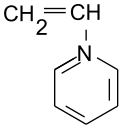


2. Methacrylic acid

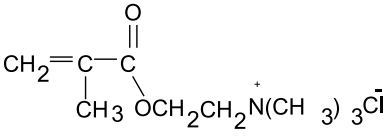


Cationic basic monomers

1. Vinyl pyridine

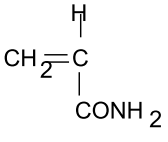


2. 2-methacryloyloxy-trimethylammonium chloride

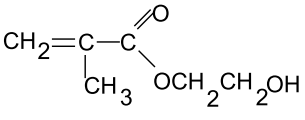


Neutral monomers for hydrogel synthesis

1. Acrylamide

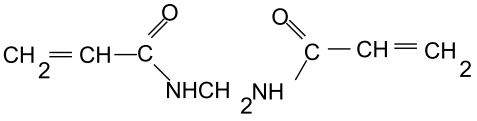


2. 2-Hydroxyethyl methacrylate

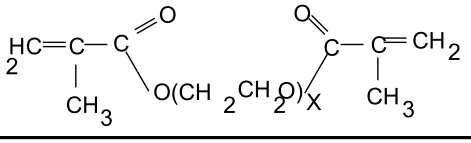


Poly functional crosslinking monomers for hydrogel synthesis

1. N, N-Methylenebisacrylamide



2. Ethylene glycol dimethacrylate



Suspension polymerization:
This method is employed to prepare spherical hydrogel microparticles with size range of 1 µm to 1mm. In suspension polymerization, the monomer solution is dispersed in the non-solvent forming fine droplets, which are stabilized by the addition of stabilizer. The polymerization is initiated by thermal decomposition of free radicals. The prepared microparticles then washed to remove unreacted monomers, crosslinking agent, and initiator. Hydrogel microparticles of poly(vinyl alcohol) and poly(hydroxy ethyl methacrylate) have been prepared by this method.

Polymerization by irradiation:
High energy radiation like gamma and electron beam, have been used to prepare the hydrogels of unsaturated compounds. The irradiation of aqueous polymer solution results in the formation of radicals on the polymer chains. Also, radiolysis of water molecules results in the formation hydroxyl radicals, which also attack the polymer chains, resulting in the formation of macroradicals. Recombination of the macroradicals on different chains results in the formation of covalent bonds, and finally a crosslinked structure is formed[37]. During radiation, polymerization macroradicals can interact with oxygen, and as a result, radiation is performed in an inert atmosphere using nitrogen or argon gas. Examples of polymers crosslinked by radiation method include poly(vinyl alcohol)[38], poly (ethylene glycol)[39-41], poly(acrylic acid)[42]. The major advantage over chemical initiation is the production of relatively pure, residue-free hydrogels.

Chemically crosslinked hydrogels:
Polymers containing functional groups like –OH, –COOH, $–NH_2$, are soluble in water. The presence of these functional groups on the polymer chain, can be used to prepare hydrogels by forming covalent linkages between the polymer chains and complementary reactivity, such as amine-carboxylic acid, isocyanate-OH/NH_2 or by Schiff base formation[43].

Gluteraldehyde can be used as a crosslinking agent to prepare hydrogels of polymers containing –OH groups like poly(vinyl alcohol)[44]. Also, polymers containing amine groups (albumin, gelatin, polysaccharides)[45-48], can be crosslinked using gluteraldehyde.

Polymers that are water soluble, can be converted to hydrogels, using bis or higher functional crosslinking agents like divinylsulfone[49], and 1,6-hexanedibromide[50]. The crosslinking agents react with the functional groups present on the polymer, via addition reaction. These crosslinking agents are highly toxic, and hence unreacted agents have to be extracted. Moreover the reaction has to be carried out in organic solvent, as water can react with the crosslinking agent. The drugs have to be loaded after the hydrogels are formed, as a result the release will be typically first order.

Crosslinking between polymers through hydrogen bond formation occur as in the case of poly(methacrylic acid) and poly(ethylene glycol). The hydrogen bond formation takes place between the oxygen of poly(ethylene glycol) and carboxylic acid group of poly(methacrylic acid)[51]. Carriers consisting of networks of poly(methacrylic acid-g-ethylene glycol) showed pH dependent swelling due to the reversible formation of interpolymer complex, stabilized by hydrogen bonding between the etheric groups of the grafted poly(ethylene glycol), and the carboxylic acid protons of the poly(methacrylic acid)[52].

Physically crosslinked hydrogels:
Most of the covalent crosslinking agents are known to be toxic, even in small traces. A method to overcome this problem and to avoid a purification step, is to prepare hydrogels by reversible ionic crosslinking. Chitosan, a polycationic polymer can react with positively charged components, either ions or molecules, forming a network through ionic bridges between the polymeric chains. Among anionic molecules, phosphate bearing groups, particularly sodium tripolyphosphate is widely studied[53,54]. Ionic crosslinking is a simple and mild procedure. In contrast to covalent crosslinking, no auxiliary molecules such as catalysts are required[55]. Chitosan is also known to form polyelectrolyte complex with poly(acrylic acid). The polyelectrolyte complex undergoes slow erosion, which gives a more biodegradable material than covalently crosslinked hydrogels[56,57].

DYNAMICS OF SWELLING OF IONIC HYDROGELS

Water diffusion in glassy polymers often deviates from the predictions of Fick's law, leading to anomalous or non-Fickian diffusional behavior. The deviation from Fickian behavior has been associated with the finite rate at which the polymer structure rearranges, to accommodate water molecules, and has been observed for many hydrophilic polymer systems[59]. Depending upon the dynamics of polymer swelling and the relative

mobilities of drug and water, Fickian or non-Fickian drug transport may be observed. The relative importance of water diffusion and polymer relaxation can be described by the Deborah number (De), defined as the ratio of a characteristic relaxation time (τ) to a characteristic diffusion time (θ). $De=\tau/\theta$, $\theta=L^2/D_{wp}$ where L is the characteristic length of the controlled release device, and D_{wp} is the water diffusion coefficient. When $De<<1$, relaxation is much faster than diffusion, and Fickian transport is observed. When $De\sim1$, relaxation and diffusion are coupled leading to a complex transport behavior, known as anomalous or non-Fickian transport[58]. In Fickian diffusion, the rate of water absorption shows a linear increase as a function of the square root of time. Fickian diffusion is observed when the time scale of the macromolecular relaxation is either effectively infinite or zero, compared to the time required to establish a concentration profile in the polymer sample. In non-Fickian or anomalous transport, both diffusion as well as macromolecular relaxation time scales is similar, and both control the overall rate of penetrant absorption. Case II transport is the limit, when relaxation predominates. Zero-order, time-independent Case II kinetics are characterized by a linear mass uptake with time.

The amount of drug released from a thin slab at time t (M_t) with respect to the total amount of drug released (M_∞), can be expressed in terms of an exponential expression as follows:
$M_t/M_\infty=kt^n$, for $0<M_t/M_\infty<0.6$, where n is diffusional exponent. The value of n determines the dependence of the release rate on time[60]. The relationship between n and the drug transport mechanism through a polymer slab is shown in Table 2. Usually there is accumulation of drug on the surface of the hydrogel when the drug is loaded to preformed hydrogel, which leads to burst effect. This makes the release profile to have an intercept. To correct for this, the equation can also be written as $M_t/M_\infty=\alpha+kt^n$ for $0<M_t/M_\infty<0.6$, where α takes into account the burst release observed. The constant α is estimated as the intercept at time zero[12].

TABLE 2: TRANSPORT MECHANISMS OF A PENETRANT THROUGH A POLYMER SLAB

Exponent n	Type of transport	Time dependence
0.5	Fickian diffusion	$t^{-0.5}$
0.5<n<1.0	non-Fickian (anomalous)	t^{n-1}
1.0	Case II transport	Zero order (time-independent) release
n>1.0	Super Case II transport	t^{n-1}

n is diffusional exponent

Gumusderelioglu and kesgin[61] studied the release behaviour of bovine serum albumin from the copolymer of ethylene glycol vinyl ether, butyl vinyl ether, and acrylic acid, in the presence of crosslinking agent, diethylene glycol divinyl ether. Calculated *n*-values were ranging between 0.46 and 0.84, which indicated that the release deviates from the Fickian mode. It was concluded that the existence of some molecular relaxation process in addition to diffusion, was responsible for the observed non-Fickian behavior. García *et al.*[62] studied the Timolol maleate release from pH-sensitive poly(2-hydroxyethyl methacrylate-co-methacrylic acid) hydrogels. The n value was close to 0.50, which indicated a Fickian behavior. The diffusion coefficient calculated was in the range of 3.21×10^{-6} cm^2/sec to 11.52×10^{-6} cm^2/sec for pH 7.4, also the diffusion coefficient depended on the methacrylic acid content in the hydrogel.

CONCLUSION

Recent developments in the field of polymer science and technology has led to the development of various stimuli sensitive hydrogels like pH, temperature sensitive, which are used for the targeted delivery of proteins to colon, and chemotherapeutic agents to tumors. Some environmental variables, such as low pH and elevated temperatures, are found in the body. For this reason, either pH-sensitive and/or temperature sensitive hydrogels can be used for site-specific controlled drug delivery. Hydrogels that are responsive to specific molecules, such as glucose or antigens, can be used as biosensors as well as drug delivery systems. New synthetic methods have been used to prepare homo- and co-polymeric hydrogels for a wide range of drugs, peptides, and protein delivery applications. Random copolymers with balanced hydrophobicity/hydrophilicity, can offer desirable release rates and dissolution profiles, for the development of oral controlled drug delivery.

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