Hydrogel Drug Delivery Systems

Khushalini Ulman
S.Y.B.Tech. (Textiles)

Kaushik Mishra
S.Y.B.Tech. (Polymers)

Khushalini Ulman : I have a strong "never say die" attitude and like being independent and self-sufficient. I always put in my heart and soul to whatever I do and derive satisfaction from the same. I have a keen interest in extra-curricular activities. I have always found science intriguing and thus chose my career in the ever expanding field of chemistry. I aspire to be a postgraduate in organic chemistry. My vision is to educate rural India and not to make it merely literate. I want the Indian society to benefit from the scientific advances that India has achieved.

Kaushik Mishra : I have always looked forward to taking up responsibilities and giving my best to everything that I do irrespective of the field of work. My ambition is to have a double PhD (technical + management). Early Future plans would be to get an industrial summit done in my college, which would ensure to get UICT known amongst the masses. My vision contemporarily revolves around the industry-academic symbiosis for the betterment of the society that would bring about more practical knowledge transfer while also bringing about better productivity cum efficiency in both the fields.

Abstract

The article reviews the use of hydrogels as the new age drug delivery system. Hydrogels are three dimensional networks of hydrophilic polymers that have properties strikingly similar to that of a living tissue and thus, are exploited in delivering substrate specific controlled drug release in living beings. This article provides an elaborate description of the various properties and types of hydrogels. Emphasis has been given on the self-regulated insulin-release hydrogel (biodegradable) membrane system and on the non-toxicity of such drug delivery.

Keywords: Hydrogels, Drug Delivery System, Bio-Medical Applications, Polymer, Pharmacology.

1. Introduction

Hydrogels are three-dimensional networks of hydrophilic polymers, generally covalently or ionically cross-linked, which interact with aqueous solutions by swelling to an equilibrium value. They can be defined as polymeric materials which exhibit the ability to swell in water or biological fluids and retain a significant fraction (e.g. in case of super absorbent > 95%) of water within its structure but which will not dissolve in water. The hydrated matrix results in good compatibility with proteins as well as living cells and body fluids. Since the first report on the biomedical use of poly (2-hydroxyethyl methacrylate) hydrogels by Wichterle and Lim in 1960, various other hydrogels have been developed for biomedical and pharmaceutical applications, particularly for enzyme therapeutic systems, drug delivery systems and for producing artificial organs.

2. Properties of Hydrogels

2.1 Swelling

The bulk property of swelling is used for making "swelling implants" i.e., implants which can be implanted in a small dehydrated state via a small incision and which then swell to fill a body cavity and /or to exert a controlled pressure.

2.2 Permeability

Hydrogels are permeable to low molecular weight solutes. This property of solute diffusivity in gels is used in sustained drug release applications and in the transport of solutes to gel-entrapped

2.3 Classification of Hydrogels

Origin	Natural Synthetic
Water content or degree of swelling	Low swelling Medium Swelling High Swelling Superabsorbent
Porosity	Nonporous Microporous Macroporous Superporous
Cross-linking	Chemical (or covalent) Physical (or noncovalent)
Biodegradability	Biodegradable Nondegradable

Table 1: Various Criteria for the Classification of Hydro gels (Ref. No. 4)

macromolecules, particularly enzymes immobilized in the gel network.

2.4 Interface Tension

Hydrogels have low interfacial tension with water or biological fluids. The hydrogel/water interface can be compared to that of living cell/ physiological solution interface due to similar surface and interfacial properties. But these interfacial properties are difficult to study and interpret as many of the assumptions of classical surface chemistry cannot be applied. Some of the methods available for study of gel/ solution interfaces are as follows:

2.4.1 Rheological or Viscometric Analysis

Rheology is the study of the deformation and flow of matter under the influence of an applied stress. This method is used to study the mechanical properties of hydrogels, basically the flow of fluid into and out of the hydrogel-fluid interface. A graph of viscosity Vs shear stress rate is plotted and the nature of hydrogel is observed. This also helps in deciding the polymerisation method to be used for manufacture of the hydrogel. (See Ref. No.3 and 4)

2.4.2 Ellipsometry

Ellipsometry is a versatile and powerful optical technique for the investigation of the dielectric properties (complex refractive index or dielectric functions) of thin films. As an optical technique, spectroscopic ellipsometry is non-destructive and contactless. It is used to measure the thickness of films deposited on the hydrogel surface. It is also used to study stimuli dependent swelling of hydrogels. It gives a two-dimensional map of an ellipsometric parameter resulting in a 3D-profile.

2.4.3 Contact Angles

Contact angle methods are widely used for measuring surface tensions or free energies of liquids. The classical contact angle or Young-Dupree equation is

$$\gamma_{sv} = \gamma_{SL} + \gamma_{LV} \cos \theta_e$$

Where: γ_{sv} = solid/vapor interfacial tension

γ_{SL} = solid/liquid interfacial tension

γ_{LV} = liquid/vapor interfacial tension

θ_e = equilibrium contact angle

The water/fluid contact angles of hydrogels are measured to check the extent of surface polarity of the hydrogel and also to examine the mobility of the polymer chain. Also the contact angle made by the hydrogel with the substrate surface gives the extent of adhesiveness of the hydrogel. (See Ref.No.3)

2.4.4 Optical Microscopy

The optical microscope is a type of microscope which uses visible light and a system of lenses to magnify images of small samples. It is used to view the hydrogel surface topography. When higher magnification is required, one resorts to scanning electron microscope (SEM). The SEM is a type of electron microscopee that creates various images by focusing a high energy beam of electrons onto the surface of a sample and detects signals from the interaction of the incident electrons with the sample's surface. The hydrogel is first rapidly frozen in liquid Freon and fractured under liquid nitrogen. The fractured surface is then directly observed under SEM. (See Ref. No. 3)

2.4.5 Similarity to Living Tissue

The physical properties of hydrogels are similar to that of living tissue mainly because of the expanded nature of the hydrogel structure and its permeability to small molecules. Also due to the soft and rubbery consistency of most hydrogels, their biocompatibility increases minimizing mechanical (frictional) irritation to surrounding cells and tissue. (See Ref. No.8.1.3)

3. Types of Hydrogels

Hydrogels are mainly of the following four types:

- pH sensitive
- temperature sensitive
- enzyme sensitive
- electrical sensitive

(See Ref. No. 8)

3.1 pH Sensitive Hydrogels

pH-sensitive hydrogels have a high density of dissociable acidic or basic groups that can be ionized at a certain pH. The ionization of the groups ($CONH_2$, COOH etc.) causes a high concentration of ions inside the gel structure because of the fixed-charge groups and the migration of counter ions from the surrounding medium. The high ion concentration encourages the transfer of water molecules into the gel network to reduce the concentration difference between the inside and outside of the hydrogels induced by the fixed-charge groups. As a result, a substantial volume change occurs and it is known as the gel phase transition. This process is also described as the *Donnan equilibrium*, which regards swelling as the elimination of the osmotic pressure difference between the inside and outside of gels caused by the migration of charged ions. The swelling of ionic gels in water or another polar solvent will eventually reach an equilibrium state, in which the gel expansion is balanced by a contractive force generated by the expanding networks. E.g. Poly (acrylic acid) (PAA), poly (acrylic acid-co-2-hydroxyethyl methacrylate) [P (AA-co-HEMA)], poly (N-isopropyl acrylamide-co-methacrylic acid) etc. (See Ref. No. 8)

3.2 Temperature Sensitive Hydrogels

The thermo sensitive 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 lower critical solution temperature (LCST) of 32° in water and cross-linked gels of this material collapse around this temperature. (See Ref. No.5 and 8)

Temperature sensitive hydrogels are classified into the following three types:

a. positively thermo sensitive

b. negatively thermo sensitive
c. thermally reversible

(Type a and b are thermally irreversible)

3.2.1 Positively Thermo sensitive Hydrogels

These hydrogels swell at high temperature and shrink at low temperature. Examples are interpenetrating polymer networks (IPN) of poly (acrylic acid), polyacrylamide (PAAm) or poly (acryl amide-co-butyl methacrylate). (See Ref. No. 8.2.4)

3.2.2 Negatively Thermo sensitive Hydrogels

These hydrogels swell at low temperature and shrink at high temperature. Examples are IPNs of poly (tetramethyleneether glycol) (PTMEG), poly (N-isopropylacrylamide) P (NIPAAm). (See Ref.No.8)

3.2.3 Thermally Reversible Hydrogels

Such hydrogels exhibit an LCST wherein the gel shrinks and deswells when it is warmed through its LCST and then reversibly expands and reswells when it is cooled below the LCST. The immobilized cell-hydrogel system has been thermally cycled between two temperatures, each below the LCST. The upper temperature was selected to be just below the LCST, where the gel deswells but does not collapse, as it does at the LCST. The thermal cycling acts like a hydraulic pump which enhances mass transfer of the substrate (hydrocortisone) in and the product (prednisolone) out of the gel, thereby increasing steroid conversion dramatically relative to isothermal operation at either the upper or lower temperature. The increased conversion can also be due to reduced product inhibition. Mass transfer resistance and product inhibition are among the most serious problems in immobilized biocatalyst technology and thermal cycling of LCST. Hydrogels is both a novel and useful approach to minimizing these problems. Thermo reversible gels 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. (See Ref. No. 5 and 8)

3.3 Enzyme Sensitive Hydrogels (Biodegradable)

Biodegradable hydrogels can be broken down into biologically acceptable low-molecular-weight molecules in the body by enzymatic catalysis. Enzyme sensitive hydrogels eliminates the need of removing a drug delivery device after release of the drug has been completed. Biodegradable hydrogels can have many advantages in drug delivery, such as improved biocompatibility and flexibility in controlling the release of drugs. Colon-specific hydrogels have been developed by using polymers that can be degraded by microbial enzymes in the colon. (See Ref. No. 8.)

3.4 Electro Sensitive Hydrogels

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. The principle of electro sensitivity is an electrophoresis phenomenon: when an electro sensitive gel is sandwiched between two electrodes and placed in an electric field, the polyelectrolyte molecule dissociates into ionic species, which are attracted to the charge electrode. For e.g. polyacrylic sodium salt dissociates into a polymeric anion and a sodium cation under an electric field. Then NaOH forms in the cathode and the solution around the cathode turns alkaline. As the polymeric anion is attracted to the anode, but cannot diffuse, the polymeric gel is strained and transformed to the anode. At the same time, water in the gel is diffused out by a squeezing effect from the gel takes place and shrinkage of gel occurs. On switching off the electric field, the shrunken gel again recovers volume by a relaxation of polymer network. This is the principle of reversible volume change in response to electrical stimulation. (See Ref. No. 7 and 10)

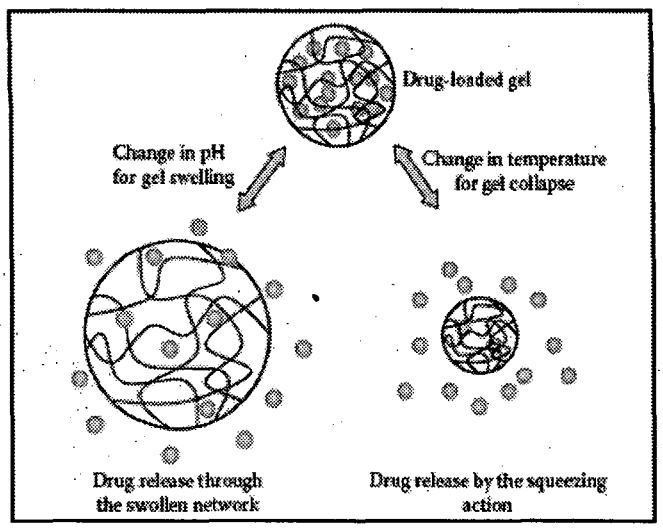

Fig 1: Molecular structures of selected environment-sensitive hydrogels. (See Ref. No. 4).

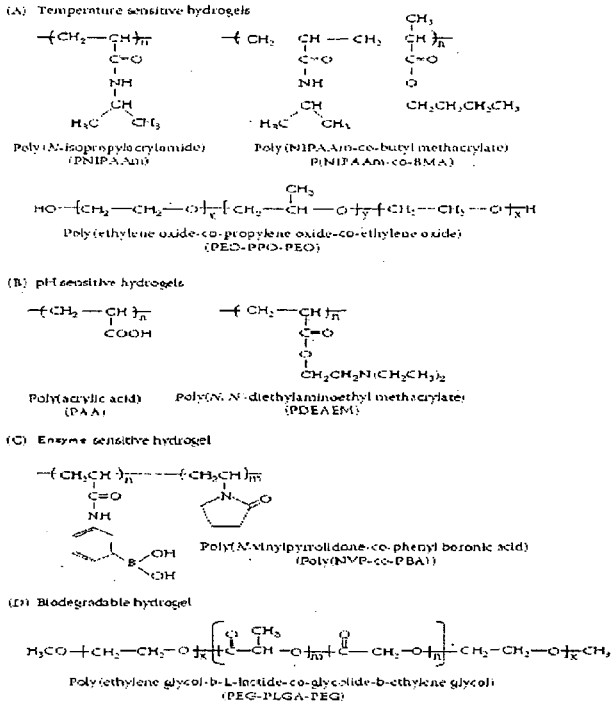

Fig 2: Mechanism of drug release from pH and temperature sensitive hydrogels. (See Ref. No. 4)

4. Hydrogel Fabrications

The techniques used for the production of hydrogels include bulk, solution, suspension and emulsion polymerizations. The monomers used in the preparation of the ionic polymer network contain an ionizable group, 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 sulphonic acids and quaternary ammonium compounds. Some of the commonly used cross linking agents include N, N'-methylene bis acryl amide, divinyl benzene and ethylene glycol dimethacrylate.

Polymerisation methods	Important features	Problems related to polymer preparation and purity
Bulk (mass)	Initiator and monomer needed, cross-linking agent can be added	High viscosity, difficult agitation lead to non-uniformity of products; residual monomers
Solution	Initiator, solvent and monomer needed; easy agitation; controlled heat transfer; polymer soluble or insoluble in solvent	Chain transfer frequently gives broad molecular weight distribution products; difficulty in removing solvent
Suspension	Initiator, solvent, monomer and suspending agent needed; cross-linking agent can be added; polymer production in spherical or irregular particles depending on monomer-suspending agent interfacial tension	---
Emulsion	Initiator, solvent, monomer, suspending agent and emulsifier needed	Residual emulsifier, etc.
Gaseous	Reaction in gaseous phase; high pressure	Pure polymers; technique not applied to many systems
Plasma	Glow discharge	New technique; ultrapure polymers, high cost of manufacture

Table 2: Various Polymerization Techniques (See Ref. No. 2)

5. Applications of Hydrogels in Drug Delivery

5.1 Self-regulated Insulin-release Hydrogel Membrane System

Glucose-sensitive hydrogels have been developed as self-regulated insulin delivery systems. The most common method involves adding glucose oxidase to pH-sensitive hydrogels. Glucose is converted to gluconic acid by glucose oxidase in the hydrogels and the resulting pH decrease can induce the swelling of the pH sensitive hydrogels to release more insulin. Concanavalin A (ConA) is also frequently used for modulated insulin delivery. ConA is a glucose-binding protein obtained from a plant. In ConA-based systems, insulin can be modified with glucose for interaction with ConA for modulated release in the presence of free glucose. Alternatively, ConA is used as a physical cross-linker of glucose-attached polymer chains. In the absence of free glucose, the system forms a gel to retard the release of insulin. In the presence of free glucose, however, the gel becomes sol for faster release of insulin. Phenylboronic acid and its derivatives (Figure 3) have also been used to form complexes with glucose for controlling the insulin release. (See Ref. No.12)

Although the concept of these environment-sensitive hydrogels is quite promising, significant improvements of the hydrogel properties are still required for practical applications. Response of the hydrogels to environmental changes should be fast for the timely release of insulin. One of the ways to accomplish this is to make thinner or smaller hydrogels, such as films and microparticles. This often results in dimensional limitations and mechanical failures in their practical uses.

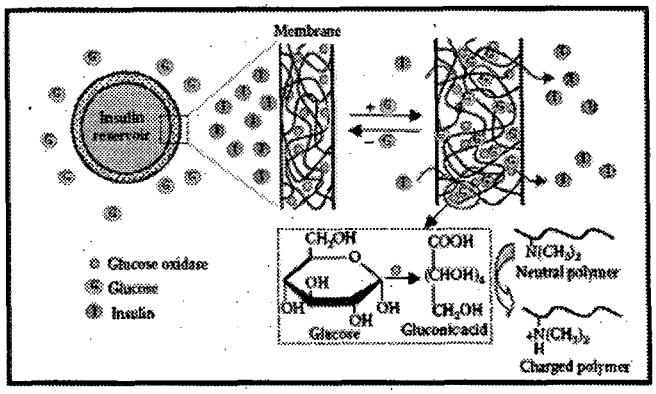

Fig.3 Mechanism of self-regulated insulin-release hydrogel membrane system (See Ref. No. 12)

Figure 3 shows an example of self –regulated insulin-release hydrogel membrane system. As glucose molecules go into the membrane, they are converted into gluconic acid by glucose oxidase, resulting in decrease of pH in the hydrogel. This results in ionization of the polymer, poly (N, N-dimethlyaminoethyl methacrylateco-ethylacrylamide), which in turn increases the LCST. This causes swelling of the membrane and insulin can be released to the surroundings through the swollen membrane.

5.2 Hydrotropic Hydrogels for Delivery of Poorly Soluble Drugs

A hydrotrope is a compound that solubilises hydrophobic compounds in aqueous solutions. Typically, hydrotropes consist of a hydrophilic part and a hydrophobic part (like surfactants) but the hydrophobic part is generally too small to cause spontaneous self-aggregation. For absorption of drugs into the body, drug molecules have to be first dissolved in the body fluid. Unfortunately, many drugs have been found to be poorly soluble in water, resulting in low absorption and low bioavailability. Designing clinically effective formulations for poorly soluble drugs has been one of the biggest

challenges. Recently, hydrogels with hydrotropic properties have been developed. Low-molecular-weight hydrotropes have been used to increase the aqueous solubility of poorly soluble drugs. As the concentrations of hydrotropes used in the delivery of poorly soluble drugs are very high, there is an unfavorable absorption of significant amounts of hydrotropes by the body. To prevent these polymeric forms of hydrotropes were developed. The study (See Ref. No.8) showed that the cross-linked hydrotropic polymers maintained the hydrotropic property. The solubility of drug named paclitaxel in hydrotropic hydrogels (e.g., hydrogels of poly (2-(4-vinylbenzyloxy) - *N*-picolylnicotinamide) was 5000 times higher than in pure water.

6. Summary

Hydrogels have played a pivotal role in the development of various controlled-release formulations. Hydrogels are known to be highly biocompatible owing to their ability to absorb water into their structures. Recent advances in the synthesis of smart hydrogels have resulted in the development of modulated drug delivery systems. In addition, hydrogels with new properties, such as increasing the solubility of poorly soluble drugs, can be exploited to develop new controlled-release formulations. Hydrogels with novel properties will continue to play important roles in drug delivery applications.

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