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PRAGMATIC HYDROGELS

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ABSTRACT
Man has always been plagued with many ailments and diseases. The field of pharmaceutical science has today become more invaluable in helping to keep us healthy and prevent disease. The availability of large molecular weight protein and peptide-based drugs due to the recent advances has given us a new ways to treat a number of diseases. I wish to present new and promising techniques for the production of drug and protein delivery formulations that have been developed that is Hydrogel. These are presently under investigation as a delivery system for bioactive molecules as having 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 and biological fluids.
Hydrogels are three-dimensional, hydrophilic, polymeric networks capable of imbibing large amounts of water or biological fluids. The networks are composed of homopolymers or copolymers, and are insoluble due to the presence of chemical crosslink (tie-points, junctions) or physical crosslink, such as entanglements or crystallite. The latter provide the network structure and physical integrity. These hydrogels exhibit a thermodynamic compatibility with water which allows them to swell in aqueous media. The nature of the degradation product can be tailored by a rational and proper selection of building blocks. The soft and rubbery nature of hydrogels minimizes irritation to surrounding tissues. In general, hydrogels possess good biocompatibility and biodegradability.
KEYWORDS: Hydrogel, Crosslinking, Properties, Classification, Preparation.

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INTRODUCTION

The Hydrogel, since their discovery by Wichterle and Lim in 1960 of poly (2-hydroyethyl methacrylate) [1], have been of great interest to biomedical scientist[2]. The dedicated research from scientists all over the world has made it possible to treat, prevent and eradicate many of these diseases that plague man. The field of pharmaceutical science has been developing steadily over the years, and has today become invaluable in helping to keep us healthy and prevent disease. An avenue of research that has progressed a great deal in the past few decades is the treatment of diseases via biomolecules such as drugs, proteins etc. Initially these could only be administered in limited manner, due to limitations of drug delivery through harmful environments in the body. Thus limited mobility reduced the effectiveness of administered drugs[3]**.** Progress came with the development of biomaterial carriers which could be encapsulated, or immobilized with drugs, allowing the drug to safely reach the required site without harm. These carriers allowed for the release of drug in sites which were previously inaccessible. The nature of these carriers progressed over the years from ceramics, to natural, to synthetic materials[4]. Factors such as integrity, biocompatibility flexibility and biodegradability were considered, and lead to the use of hydrophilic three dimensional matrices as carrier materials[5].

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. Their ability to absorb water is due to the presence of hydrophilic groups such as –OH, -CONH-, $CONH_2$,-COOH, and SO_3H[2,6]. The water content in the hydrogels affect different properties like permeability, mechanical properties, surface properties and biocompatibility.

Hydrogels can be prepared from a wide variety of materials of natural origin obtained from plants and animals, as well as from materials prepared by the modification of the aforementioned natural structures

and from synthetic polymeric materials. Among the natural polymers, proteins such as collagen[7] and polysaccharides such as chitosan[8] or hyaluronic acid[9] are used. Regarding synthetic polymers, due to the singular properties that characterize them and as a consequence of their vast structural versatility, they are the materials that have experienced greater growth and development in terms of their practical applications[10]. Hydrogels, which in a dehydrated state have a crystalline aspect and are called xerogels, apart from their immediate definition of being gels containing water, are polymers or copolymers with particular characteristics. They are hydrophilic and insoluble in water, and they swell in its presence (or in the presence of any aqueous fluid), increasing in volume and becoming soft and elastic, but keeping their shape, until reaching a physical–chemical balance. Hydrogels have thus become a premier material used for drug delivery formulations and biomedical implants.[11]

POSSIBILITIS OF HYDROGELS TO BE USED AS DRUG DELIVERY SYSTEMS

Hydrogels has infinite possibilities in bio-nanotechnology, drug delivery, biological recognition, tissue engineering. Thus, in recent years we have seen an explosion in the field of novel micro-fabricated and nanofabricated devices using intelligent hydrogels. Such devices seek to develop a platform of well controlled functions in the micro- or nano-level. They include nano particulate systems, recognitive molecular systems, bio-sensing devices, and micro fabricated and microelectronic devices.

ADVANTAGES OF HYDROGELS AS DRUG DELIVERY SYSTEMS

- Environment can protect cells and other substances (i.e. drugs, proteins, and peptides)
- Good transport properties
- Biocompatible
- Biodegradable
- It has versatile routes of administrations like injection, topical, oral, rectal, nasal
- Easy to modify

DISADVANTAGES OF HYDROGELS AS DRUG DELIVERY SYSTEMS

- Low mechanical strength
- Hard to handle
- Difficult to load
- Sterilization

PROPERTIES OF HYDROGELS

Swelling

Hydrogels are characterized, first by their capacity to absorb water or aqueous solutions. The water content in the swelling equilibrium of a hydrogel is affected, fundamentally, by the nature of the monomer or monomers that make it up, by the type and density of the cross-link, and by other factors such as temperature, ionic strength, and pH of the hydration medium. Hydrogels containing hydrophilic groups swell to a higher degree compared to those containing hydrophobic groups. Hydrophobic groups collapse in the presence of water, thus minimizing their exposure to the water molecule and shows retarded release. Where hydrophilic group easily swell in water and thus maximizes exposure to the water molecule and thereby maximum drug entrapment and release observed. The amount of the aqueous medium incorporated in a hydrogel is determined, generally, gravimetrically and can be expressed in several ways. The fractional hydration (W)[12] can be obtained as follows:

$W= (w_1 - w_0)/w_1$

Where w_1 and w_0 are the weights of swollen and dry gels respectively

The swelling ratio (r) [13] is expressed as:

$R= (w_1 - w_0)/w_0$

At a particular temperature, the volume fraction of polymer (*f*2) within a hydrogel at swelling equilibrium is given by:

$Ø_2= (D_0/D)$ [3]

Factors affecting swelling of hydrogels

Crosslinking ratio

It is defined as the ratio of moles of crosslinking agent to the moles of polymer repeating units. The higher the crosslinking ratio, the more crosslinking agent is incorporated in the hydrogel structure. Highly crosslinked hydrogels have a tighter structure, and will swell less compared to the same hydrogels with lower crosslinking ratios. Crosslinking hinders the mobility of the polymer chain, hence lowering the swelling ratio. [3]

The chemical structure of the polymer

Hydrogels containing hydrophilic groups swell to a higher degree compared to those containing hydrophobic groups. Hydrophobic groups collapse in the presence of water, thus minimizing their exposure to the water molecule. As a result, the hydrogels will swell much less compared to hydrogels containing hydrophilic groups.

Temperature

Swelling of temperature-sensitive hydrogels can be affected by changes in the temperature of the swelling media.

Ionic strength and pH

Ionic strength and pH affect the swelling of ionic strength- and pH-sensitive hydrogels, respectively. There are many other specific stimuli that can affect the swelling of other environmentally-responsive hydrogels.

Dynamics of swelling

The swelling kinetics of hydrogels can be classified as:

- Diffusion-controlled (Fickian) swelling.
- Relaxation-controlled (non-Fickian) swelling.

In fickian diffusion, the rate of water absorption shows a linear increase as a function of 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 established a concentration profile in the polymer sample.

In non-fickian or anomalous transport, both diffusion as well as macromolecular relaxation time scale is similar, and both control rate of penetrant absorption.

When water diffusion into the hydrogel occurs much faster than the relaxation of the polymer chains, the swelling kinetics is diffusion-controlled. A nice mathematical analysis of the dynamics of swelling is presented by Peppas and Colombo.[14]

Mesh size

Theoretically, no solute diffusion is possible within the hydrogel matrix when mesh size approaches the size of the solute. Mesh size is affected by several factors including:

- Degree of crosslinking of the gel
- Chemical structure of the composing monomers
- External stimuli such as temperature, pH and ionic strength

Mesh size is important in determining the physical properties of the hydrogels including mechanical strength, degradability, and diffusivity of the releasing molecule [15,16]. Typical mesh sizes reported for biomedical hydrogels range from 5 to 100 nm in their swollen state [10,17]. These size scales are much larger than most small-molecule drugs and therefore diffusion of these drugs are not significantly retarded in swollen hydrogel matrices. However, the release of macromolecules such as peptides, proteins, and oligo-nucleotides can be sustained from swollen hydrogels due to their significant hydrodynamic radii as shown in figure no.1. When designed appropriately, the structure and mesh size of swollen hydrogels can be tailored to obtain desired rates of macromolecule diffusion[18]. Alternatively, the rate and degree of gel swelling or degradation can also be tailored to control the release of molecules much smaller than the gel mesh size.

Thermodynamics

Stimuli-responsive polymers are plastic materials with molecule chains cross-linked to a three dimensional network. They are synthesized by a cross-linking reaction between polymer molecules[19] or by a cross-linking polymerization, which is simultaneously synthesizing polymer chains and linking them concomitantly[20]. Polymer molecules consist of small molecular units, the so-called monomers, which can be arranged in a sequence to form a long polymer chain or to form branched polymer molecules with side chains. Generally, all polymers are solvophilic to certain solvents. Not cross-linked polymers are soluble in presence of these solvents. Due to the interconnections between the polymer chains cross-linked polymers are insoluble but swell by solvent absorption. If they can swell in water they are called hydrogels.

Hydrogel behavior in solvents

Unlike normal solvophilic polymers stimuli-responsive hydrogels exhibit a first-order- or a continuous (also called second-order) phase transition behaviour. As illustrated in figure they exhibit two phases. A separated phase of the gel is dominated by polymer-polymer interactions. In this case the gel reaches its maximal value of hydrophobicity and shrinks. The second phase, a mixed phase, is characterised by solvent-polymer-interactions, which aspire the best mixing of polymer and aqueous solution. Therefore, the polymer-solvent-interactions of the mixing phase generate osmotic pressures acting expansively. Due to the polymer-polymer-interactions the polymer network counteracts this expansion by an elastic force respected by. The hydrogel obtains its swelling equilibrium at the balance of the pressures, which can be described by;

$$\pi\Delta = \pi\Delta_{elast} + \Delta\pi_{mix}$$

The Flory-Rehner theory[21, 22] and the Flory-Huggins theory[23, 24] describe these processes in detail.

Physical properties

- These are water swollen polymer matrices. [25]
- They have tendency to imbibe water when placed in aqueous environment.
- These are ideal material for use in drug delivery and immobilization of proteins, peptides, and other biological compounds.
- Due to their high water content, these gels resemble natural living tissue more than any other type of synthetic biomaterial.
- They have a three dimensional structure.
- They crosslinked together either physically (entanglements, crystallites), or chemically (tie-points, junctions).
- Insoluble crosslinked structure allows immobilization of active agents, biomolecules effectively, and allows for its release in well-defined specific 3 manners.

Mechanical properties

- Drugs and other biomolecules must be protected from the harmful environments in the body such as, extreme pH environment before it is released at the required site.
- The carrier gel must be able to maintain its physical integrity and mechanical strength in order to prove an effective biomaterial.
- The strength of the material can be increased by incorporating crosslinking agents, co monomers, and increasing degree of crosslinking.
- Elasticity of the gel is important to give flexibility to the crosslinked chains, to facilitate movement of incorporated bioactive agent.

Biological properties

Most toxicity problems associated with hydrogels arise due to unreacted monomers, oligomers and initiators that leach out during application. Thus an assessment of the potential toxicity of all materials used for fabrication of gel is an integral part of determining suitability of the gel for biological applications. To lower chances of toxic effects, the use of initiators is being eliminated, with the advent of gamma irradiation as polymerization technique. Steps are also taken to eliminate contaminants from hydrogels, by repeated washing and treatment.

Rheological properties

Hydrogels can also be described in a rheological way. Aqueous solutions of hydrophilic polymer at low concentration, where no substantial entanglement of chains occurs, normally show Newtonian behavior. On the other hand, once crosslinked between the different polymer chains are introduced, the so obtained networks show visco-elestic and sometimes pure elastic behavior.[26-32]

CLASSIFICATION OF HYDROGELS

Currently, two groups of hydrogels are broadly distinguished namely preformed and *in situ* forming gels and depending upon the various characteristics as shown in table no.1. Preformed hydrogels can be defined as simple viscous solutions, which do not undergo any modifications after administration, while *in situ* forming gels are formulations, applied as a solution, which undergoes gelation after instillation due to physico-chemical changes inherent to the eye. [33]

DESIGN CRITERIA FOR HYDROGELS IN DRUG DELIVERY FORMULATIONS

Several design criteria are crucial for drug delivery formulations and have to be evaluated prior to hydrogel fabrication and drug loading. These criteria are also important in mathematical modeling of drug release. Following table no.2 lists these important criteria and variables for designing hydrogel-based drug carriers.[34]

PREPARATION OF HYDROGELS

As these hydrogels are polymeric networks. This implies that crosslinks have to be present in order to avoid dissolution of the hydrophilic polymer chain in aqueous solution. The nature of the degradation products can be tailored by a proper selection of the hydrogel building blocks. Keeping this consideration in mind, various chemical and physical crosslinking methods are used today for the design of biocompatible hydrogels.[35]

Physical cross linking

The main reason is that use of crosslinking agents is avoided. In physical crosslinking, polysaccharides forms crosslinked network with counter ion at the surface. High counter ion concentration would require longer exposure times to achieve complete crosslinking of the polysaccharides. For physical crosslinking different methods have been investigated.[36]

- Crosslinking by ionic interaction
- Crosslinking by crystallization
- Hydrophobised polysaccharides
- Crosslinking by Hydrogen Bonds
- By Protein Interaction

Crosslinking by ionic interaction

Alginate is a polysaccharide with mannuronic and glucuronic acid residues can be crosslinked by calcium ions.[37] Crosslinking can be carried out at room temperature and physiological pH. Therefore alginates gels can be frequently used as matrix for the encapsulation of living cells[38] and for the release of proteins.[39]

Chitosan based hydrogels were obtained by crosslinking with glycerol-phosphate disodium salt.[40]Interestingly, in presence of this salt, chitosan solution remains liquid below room temperature, but quickly gel when heated.

Carrageenan a polysaccharide composed of 1,4-linked-α-D-galactose and 1, 3 linked-β-D-galactose with a variable portion of sulfate groups, forms a gel with potassium ions, but also shows gelation under salt-free conditions.

Likewise hydrogels of Acetaminophen, Doxorubicine, Diclofenac Na, and Propronolol can also be formed by ionic interactions.

Crosslinking by crystallization

When aqueous solutions of PVA are stored at room temperature they gradually form a gel with, however, a low mechanical strength. Interestingly, once aqueous solution of this polymer undergoes freeze-thawing process a strong and highly elastic gel is formed. Addition of alginate to the PVA solution before freeze-

thawing, the gel properties could be modulated. With increase in concentration of alginate, the mechanical strength of gel increased which was associated with a decrease in release of model drug.

Hydrophobised polysaccharides

Examples of polysaccharides reported in literature used for preparation of physically crosslinked hydrogels by hydrophobic modification are chitosan, dextran, and pullulan and carboxy methyl curdlan. As example, the hydrophobic antitumor drug adriamicin (ADR) was taken up inside the particles by simply mixing the pullulan suspension with ADR. Slow release was observed at pH 7.4, which increases at lower pH of the medium due to increased solubility of drug.

Crosslinking by Hydrogen Bonds

Poly (acrylic acid) and poly(methacrylic acid) form complexes with poly(ethylene glycol) by hydrogen bonding between the oxygen of the poly(ethylene glycol) and the carboxylic acid group of poly((meth)acrylic acid). Also hydrogen bonding has been observed in poly (methacrylic acid-g-ethylene glycol). The hydrogen bonds are only formed when the carboxylic acid groups are protonated. This also implies that the swelling of gels is pH dependent. Recently a hydrogel system was developed using the principle of DNA hybridization via hydrogen bonding.

By Protein Interaction

Genetic Engineering has also been used for the preparation of hydrogels. The major advantage is that the sequence of peptides and, therefore its physical and chemical properties can be precisely controlled by the proper design of the genetic code in synthetic DNA sequences Cappello and colleagues prepared sequential block copolymers containing a repetition of silk-like and elastine –like blocks, in which the insoluble silk like segments are associated in the form of aligned hydrogen bonded beta strands or sheets. These hydrogels can also be used for drug delivery with drug release influenced by concentration, polymer composition, and temperature. Crosslinking by antigen-antibody interaction was also performed.

Chemical cross linking

Chemical crosslinking of polysaccharide is highly versatile method with good mechanical stability. During crosslinking counter ions diffused into the polymeric and crosslinking agent reacts with polysaccharides forming either intermolecular or intramolecular linkages. Factors which affect chemical crosslinking are concentration of crosslinking agent and crosslinking time. The high concentration of crosslinking agent induces rapid crosslinking. Like physical crosslinking high counter ion concentration would require longer exposure times to achieve complete crosslinking of the polysaccharides. however the addition of crosslinking agent leads to adverse effects if the compound is toxic, which on liberation in the body becomes quite harmful. The various methods for chemical crosslinking are as follows:

- Crosslinking by radical polymerization
- Crosslinking by aldehyde
- Crosslinking by addition reaction
- Crosslinking by condensation reaction

Crosslinking by radical polymerization

Chemical crosslinking can be carried out by radical polymerization in presence of crosslinking agent. In particular dextran is used as building block for (degradable) hydrogels. Dextran is a bacterial polysaccharide, consists essentially of -1,6 linked D-glucopyranose residues. The low molecular weight fractions of dextran (Mw between 40 and 100 kDa) have been used as plasma expander which has resulted in a good documentation of pharmacological activities and side effects of dextran. Dextran has therefore been investigated for the delivery of drugs, proteins and imaging agents. Moreover, due to presence of dextranase in colon, dextran based gels are under investigation as a colon delivery system. Research on polymerizable dextran was pioneered by Edman et al. who has reacted dextran dissolved in water with glycidylacrylate.

Chitosan crosslinking leads to formation of permanently covalent network, which may allow the free diffusion of water/bioactive material and also enhance the mechanical properties. Chemical crosslinks are formed by irreversible covalent links as in covalently crosslinked chitosan. Thus allow drug delivery to be efficiently controlled.

Crosslinking by aldehyde

In order to establish crosslinking, rather drastic conditions have to be applied (low pH, high temperature etc.). This has especially been investigated for the preparation of crosslinked amine containing polysaccharides. Because glutaraldehyde is a toxic compound that even at low concentration shows cell growth inhibition, alternatives has been developed. Crosslinking of gelatin using polyaldehydes obtained by partial oxidation of dextran has been reported. The swelling and degradation of the gel could be controlled by the amount of adipic acid dihydrazide. These hydrogel films have therefore potential to act as a delivery matrix for sustained release of drug at wound sites.

Crosslinking by addition reaction

Polysaccharides can be crosslinked with 1,6-hexa-methylenediisocyanate or 1,6-hexanedibromide and many other reagents. The network properties can be easily tailored by the concentration of the dissolved polysaccharide and the amount of crosslinking agent. The crosslinking reactions are preferably carried out in organic solvents, because water can also react with the crosslinking agent. Further, since the crosslinking agents are generally speaking very toxic, the gels have to be extracted extensively to remove traces of unreacted agents. Once these matrices are aimed for the release of pharmaceutically active agent, they have to be loaded after the gel formation and extraction process. This means that protein molecules can be loaded in meshes of the gels which are larger than the protein and these systems therefore show typically first-order release. This often results in a limited duration of the release. Finally, between the polymer chains, linkages are established which are stable. This means that degradation only occurs once the polymer backbone is degraded by enzymes.

Crosslinking by condensation reaction

A very efficient reagent to crosslink polysaccharides with amide bonds is *NN*-(3-dimethylaminopropyl)-*N*-ethyl carbodiimide. In order to obtain alginate gels with better mechanical properties than the ionically crosslinked gels, Mooney et al. developed a method to a covalently crosslink this polymer. Alginate and PEG-diamines were crosslinked using *N*-ethyl carbodiimide. The mechanical properties could be controlled by the amount of PEG-diamine in the gel and molecular weight of PEG.

MONOMERS USED FOR FABRICATION OF HYDROGELS

Depending upon the application, hydrogel monomers are chosen according to their properties, ease of delivery or encapsulations, as well as cost and availability. Following table no.3 provides a list of popular monomers used for biomaterial synthesis.

Hydrogels may also show a swelling behavior dependent on the external environment. These polymers are physiologically- responsive hydrogels, where polymer complexes can be broken or the network can be swollen as a result of the changing external environment. Following table no.4 summarizes the mechanisms of hydrogel preparation with the corresponding stimulus[33].

The selection of monomers and cross-linking agent determines hydrogel properties. On the other hand, a hydrogel with specific properties must be synthesized using specific monomers and crosslinking agent. Following figure no.4 shows relationship between structure and properties of hydrogels.

APPLICATIONS OF HYDROGEL

Drug Delivery in the GI Tract

The ease of administration of drugs and the large surface area for absorption makes the GI tract most popular route for drug delivery. Patel and Amiji proposed stomach – specific antibiotic drug delivery systems for the treatment of *Helicobacter pylori* infection in peptic ulcer disease. They developed cationic hydrogels with pH sensitive swelling and drug release properties for antibiotic delivery in the acidic environment of the stomach. Akiyam reported novel peroral dosage forms of hydrogel formulations with protease inhibitory activities. Recently oral insulin delivery using pH responsive complexation hydrogels was reported. The hydrogels used were crosslinked copolymers of PMMA with graft chains of polyethylene glycol. These hydrogels protect the insulin in the harsh, acidic environment of the stomach.

Rectal Delivery

Hydrogels offer a way in which to overcome limitations of this route, provided that the hydrogels show bioadhesive properties. It was reported that increased bioavailability of propanol subject to extensive first-pass metabolism was observed by adding certain mucoadhesive polymeric compounds to poloxamer – based thermally gelling suppositories. The polymeric compounds tested were polycarbophil and sodium alginate. Miyazaki et al. investigated the potential application of xyloglucan gels with a thermal gelling property as matrices for drug delivery. Another important issue in rectal drug delivery is to avoid rectal irritation. The products discussed above, indicated no such mucosal irritation after drug administration.

Ocular Delivery

Hydrogels, because of their elastic properties can represent an ocular drainage-resistant device. In-situ forming hydrogels are attractive as an ocular drug delivery system because of their facility in dosing as a liquid, and long term retention property as a gel after dosing.

Cohen et al developed an in-situ gelling system of alginate with high gluronic acid contents for the ophthalmic delivery of pilocarpine. This system extended the duration of the pilocarpine to 10 hr, compared to 3 hr when pilocarpine nitrate was dosed as a solution.

Chetoni et al. reported silicone rubber hydrogel composite ophthalmic inserts. An in-vivo study using rabbits showed a prolonged release of oxytetracycline from the inserts for several days.

Transdermal Delivery

In recent years, however a transdermal route for the delivery of drugs has been investigated. Swollen hydrogels can be delivered for long duration and can be easily removed. These hydrogels can also bypass hepatic first-class metabolism making comfortable for the patient.

Current research in this field is now focused on electrically-assisted delivery using iontophoresis and electroporation. Hydrogel-based formulations are being looked at for transdermal iontophoresis to obtain enhanced permeation of products in question such as, hormones and nicotine.

Subcutaneous Delivery

Implantable devices that are subcutaneously inserted tend to illicit immune response of the body, leading to inflammation, carcinogenicity and immunogenicity. Thus biocompatibility becomes a major issue, and all 21 implantable materials must be compatible with the body. Hydrogels are an ideal candidate for implantable materials. They have high water content, environment similar to biological tissue, making them relatively biocompatible.

Proteins and peptides drug delivery

Hydrogel formulations for subcutaneous delivery of anticancer drugs have been proposed. For example, crosslinked PHEMA was applied to cyratabine (Ara-C). Current studies on implantable hydrogels are leading towards the development of biodegradable systems, which do not require surgical removal once the drug has been administered.

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Table 1: Classification of Hydrogel on The Basis of Various Characteristics

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

Table 2: Design criteria for hydrogels in drug delivery formulations

Design criteria	Design variables
Transport properties	Molecular weight and size of protein
	Molecular weight of polymer
	Crosslinking density
	Polymer–protein interactions
	Hydrogel degradation rate
	Additional functionalities
Physical properties	Polymer/crosslinker/initiator Concentrations
Gelling mechanisms / Conditions	Temperature, pH, ionic strength
Structural properties	Molecular weight of polymer
Biodegradability	Mechanical strength
Stimuli-responsiveness	Concentration of degradable groups
	Concentration of responsive groups
Biological properties	Cytotoxicity of the hydrogel
Biocompatibility	Capsule formation

Table 3: Monomers Used for Synthesis of Hydrogels

Monomer abbreviation	Monomer
HEMA	Hydroxyethyl methacrylate
HEEMA	Hydroxyethoxyethyl methacrylate
HDEEMA	Hydroxydiethoxyethyl Methacrylate
MEMA	Methoxyethyl methacrylate
MEEMA	Methoxyethoxyethyl Methacrylate
MDEEMA	Methoxydiethoxyethyl methacrylate
EGDMA	Ethylene glycol dimethacrylate
NVP	N-vinyl-2-pyrrolidone
NIPAAm	N-isopropyl AAm
VAc	Vinyl acetate
AA	Acrylic acid
MAA	MAA
HPMA	N-(2-hydroxypropyl) Methacrylamide
EG	Ethylene glycol

Table 4: Mechanisms of Hydrogel Preparation with the Corresponding Stimulus

Stimulus	Hydrogel	Mechanism
Light	Gelatin hydrogel	Photocrosslinkable/photo polymerization
Chemical species	Hydrogel containing electron-accepting groups	Electron-donating compounds - formation of charge/transfer complex - change in swelling – release of drug
Enzyme-substrate	Glucose-sensitive hydrogels containing immobilized enzymes	Substrate present - enzymatic conversion – product changes swelling of gel- release of drug
Magnetic	Magnetic particles dispersed in alginate microspheres	Applied magnetic field - change in pores in gel - change in swelling - release of drug
Applied magnetic field - change in pores in gel - change in swelling - release of drug	Chondroitin 4-sulphate hydrogels /Polyelectrolyte hydrogel	Applied electric field - membrane charging – electrophoresis of charged drug - change in swelling – release of drug
Ultrasound irradiation	Ethylene-vinyl alcohol hydrogel	Ultrasound irradiation - temperature increase – release of drug

Table 5: List of Marketed Formulations of Drug Delivery Systems Using Hydrogels

Product	Manufacturer
Tegagel	3M
Amerigel Topical Ointment	Amerx Health Care
Bard Absorption Dressing Biolex Iamin	Bard Medical
CarraSorb Carrasyn DIAB GEL	Carrington Laboratories
Woun'Dres Purilon	Coloplast
DuoDERM SAF-Gel	ConvaTec
Repair Hydrogel	Darja Laboratories Inc.
DermaSyn	DermaRite
Dermagran	Derma Sciences, Inc.
CURASOL	HEALTHPOINT
Restore	Hollister Inc.

NU-GEL	Johnson & Johnson
CURAFIL	Kendall
SkinTegrity	Medline
Hypergel Normlgel	Molnlycke Health Care
MPM	MPM Medical, Inc.
Iamin	ProCyte
PanoPlex	Sage Laboratories
IntraSite SoloSite	Smith & Nephew
Elta Dermal	Swiss-American Products, Inc.

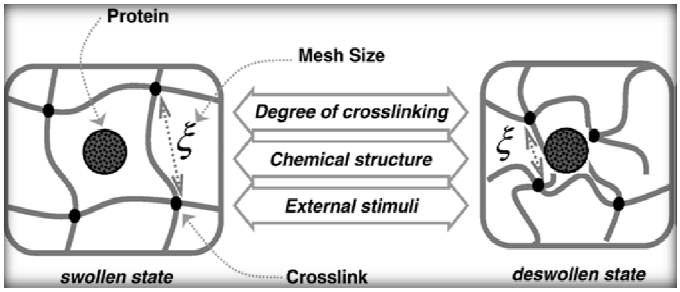

Fig. 1: Hydrogel State Affecting Mesh Size

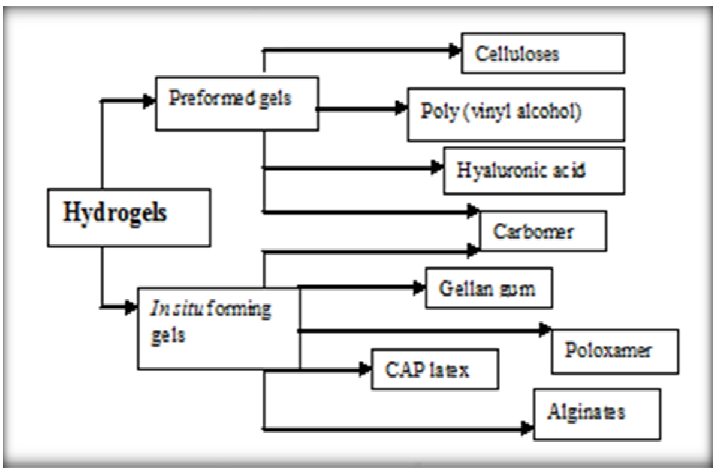

Fig. 2: General Classification of Hydrogels

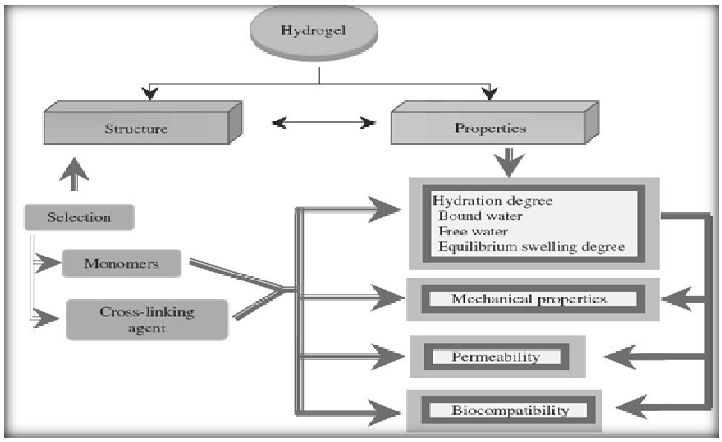

Fig. 3: Relationship between Structure and Properties of Hydrogels