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A REVIEW ON HYDROGEL AS A DRUG DELIVERY CARRIER

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ABSTRACT

A Hydrogel is a system of polymer chains that are hydrophilic, occasionally found as a colloidal gel in which water is the dispersion medium. Hydrogel have become very popular due to their exclusive properties such as high water content, softness, flexibility and biocompatibility. Natural and synthetic hydrophilic polymers can be physically or chemically cross-linked to facilitate produce hydrogels. Their similarity to living tissue opens up many opportunities for applications in biomedical areas. Presently, hydrogels are used for manufacturing contact lenses, hygiene products, tissue engineering scaffolds, drug delivery system and wound dressings.

KEYWORDS: Hydrogel, cross-linking, drug delivery, polymers.

INTRODUCTION

A Hydrogel is a system of polymer chains that are hydrophilic, occasionally found as a colloidal gel in which water is the dispersion medium. Hydrogels are three-dimensional, hydrophilic, polymeric networks able of absorbing large amounts of water or biological fluids. Due to their high water content, porosity and soft consistency, they closely stimulate natural living tissue, more so than any other class of synthetic bio-materials. Hydrogels may be chemically stable or they may degrade and ultimately disintegrate and dissolve.[1] Hydrogels are called ‘reversible’ or ‘physical’ gels if molecular entanglements or secondary forces for example ionic, H-bonding and hydrophobic forces play the major role in forming the network. Physical gels are frequently reversible and it is possible to dissolve them by altering environ-mental conditions, such as pH, and the ionic strength of solution or temperature. In ‘permanent’ or ‘chemical’ gels, the network of covalent bonds joining different macromolecular chains can be achieve by cross-linking polymers in the dry state or in solution.[2] These gels may be charged or non-charged depending on the nature of

functional group present in their structure. The charged hydrogels generally exhibit changes in swelling upon variations in pH, and it is known that they can undergo changes in shape when exposed to an electric field.[3] Chemical hydrogels are usually prepared in two different ways: 'three-dimensional polymerization' which a hydrophilic monomer is polymerized in the presence of a poly-functional cross-linking agent, or by direct cross-linking of water-soluble polymers. However, three-dimensional polymerization often results in materials containing significant levels of residual monomers and hence purification of these materials has to be performed thoroughly because the untreated monomers are may be toxic and may be leach out from the hydrogels continuously. The purification of hydrogels contain residual monomers is typically perform by extraction into excess water, and can take up to more than a few weeks to be completed.[4–7] There are several approaches that could be used to improve or avoid the purification process. One possibility is the use of further processes that lead to the highest possible degrees of monomer conversion, which could be achieve by conduct three-dimensional polymerization followed by subsequent post-polymerization curing (e.g. by thermal action or irradiation of the resulting products).[8,9] Alternatively, the selection of non-toxic monomers used for the three-dimensional polymerization, such as oligomers or macromonomers (e.g. polyethylene glycol dimethacrylate) may be a solution.[10] It may be possible to avoid the need for purification of hydrogels after their synthesis by cross-linking readymade water-soluble polymers.

Physical Forms of Hydrogels

Hydrogels are may be present in different dosage form like microparticles, pressed powder matrices, encapsulated solids & liquids etc.

Table-1: Different physical forms of hydrogel.

Physical forms	Examples
Solid molded forms	e .g., soft contact lenses
Pressed powder matrices	e.g.,pilles or capsules for oral ingestion
Micro particles	e.g., as bioadhesive carriers or wound treatments
Coatings	e.g., on implants or catheters; on pills or capsules; or coatings on the inside capillary wall in capillary electrophoresis
Membranes or sheets	e.g., It may be use as a reservoir in a transdermal drug delivery patch; or for 2D electrophoresis gels
Encapsulated solids	e.g., in osmotic pumps
Liquids	e.g., that form gels on heating or cooling.[40]

MERITS OF HYDROGELS

1. Biocompatible in nature
2. It can be injected in-Vivo as liquids.
3. May be easily modified with cell adhesion ligands.
4. Aqueous environment can protect cells and fragile drugs like peptides, proteins, oligo nucleotides, DNA.
5. Easy transport of nutrient to cells and products from cells to make sure proper tissue growth.
6. Entrapment of microbial cells within polyurethane
7. Hydrogel beads with the advantage of low toxicity
8. Environmentally sensitive hydrogels have the ability to sense changes of pH, temperature or the Concentration of metabolite.
9. Natural hydrogel may be use for tissue engineering, like agarose, methylcellulose etc.

Demerits of Hydrogels

1. High cost.
2. Low mechanical strength or mechanically weak
3. Difficult to load
4. Difficult to sterilize
5. Nonadherent
6. lens deposition, hypoxia, dehydration and red eye reactions in contact lenses [11,12] .

Strategy for the delivery of hydrogels

Hydrogels used in drug delivery are generally formed outside of the body and impregnated with drugs before placement of the hydrogel drug complex in the body. A wide range of cross-linking strategy can be used, Together with UV photo polymerization and various chemical cross-linking techniques. Such cross-linking methods are helpful only if toxic reagents can be completely removed prior to hydrogel implantation, which may be difficult to achieve without leaching loaded drug out of the hydrogel. The main disadvantage of such approach is that the preformed material must be implanted, since bulk hydrogels have a defined dimensionality and often high elasticity which generally excludes their extrusion through a needle.

Physically cross-linked hydrogels

Physical cross-linking of polymer chains can be achieve by using a different type of environmental triggers (pH, temperature, ionic strength) and a variety of physicochemical interactions.

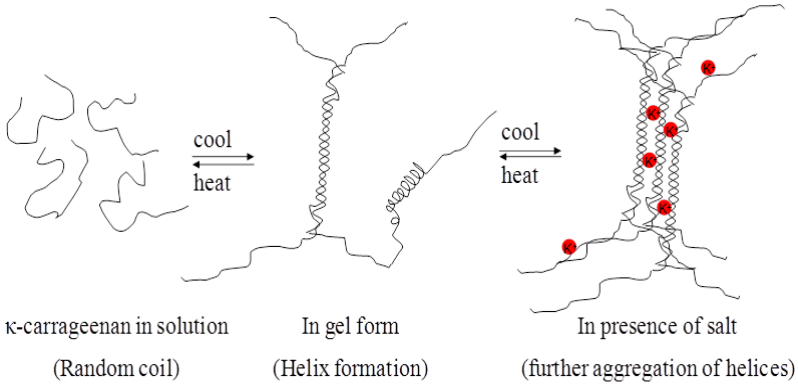

Fig. 1: Physically cross-linked hydrogels.

a) Hydrophobic interactions

Polymers with hydrophobic domains can cross-link in aqueous environments via reverse thermal gelation, also known as 'solegel' chemistry. Polymers (or oligomers) with such gelation property are referred to as gelators and are characteristically moderately hydrophobic. Hydrophobicity-driven gelation frequently occurs via the mechanism. A gelator or the hydrophobic segment is attached to a hydrophilic polymer segment by post-polymerization grafting or by directly synthesizing a block copolymer to create a polymer amphiphile. Such amphiphiles are water soluble at low temperature. However, as the temperature is increased, hydrophobic domains collective to minimize the hydrophobic surface area contacting the bulk water, reducing the amount of structured water surrounding the hydrophobic domains and maximize the solvent entropy. The temperature at which gelation occurs depends on the concentration of the polymer, the length of the hydrophobic block, and the chemical structure of the polymer: the additional hydrophobic the segment, the larger the entropic cost of water structuring, the larger the driving force for hydrophobic aggregation, and the lower the gelation temperature. The chemical structures of a number of common hydrophobic blocks which can undergo reverse thermal gelation at or near physiological temperature Triblock copolymers of poly(ethylene oxide)epoly(propylene oxide)e poly(ethylene oxide) (PEOePPOePEO, the poloxamers/Pluronics) are the most widely used reverse thermal gelation polymers.[13]

b) Charge interactions

Charge interactions have been generally investigated for cross-linking in situ gelling polymers. One benefit of this approach is that biodegradation can occur as ionic species in extracellular fluid bind competitively with the gel components, breaking down the cross-linked network. Cross-linking (or decross-linking) can also be triggered by pH changes which ionize or protonate the ionic functional groups that reason gelation, in some cases enabling the delivery of the liquid-like gel precursors in a single syringe. Charge interactions may occur between a polymer and a small molecule or between two polymers of opposite charge to variety a hydrogel, as illustrated As an example of small-molecule cross-linking, elastin-like polypeptides have been cross-linked via electrostatic interactions between their cationic lysine residues and anionic organophosphorus crosslinkers under physiological conditions.[14]

c) Hydrogen bonding interactions

Hydrogen bonding interactions may be used for hydrogels formulations in vitro by freeze-thawing method, e.g. in the formulation of poly (vinyl alcohol)-based hydrogels.[15] Hydrogen bonding may also useful for the injectable hydrogels. Mixtures of natural polymers can show rheological synergism, meaning that the viscoelastic properties of the polymer blend are more gel-like than those of the constituent polymers measured individually.[16]

d) Stereocomplexation

Stereocomplexation refers to synergistic interactions which can occur between polymer chains or small molecules of the similar chemical composition but different stereochemistry of particular relevance, in situ forming hydrogels with high storage moduli (up to 14 kPa) can be prepared by exploiting the strong interaction between polylactide blocks with L- and D stereochemistry.[17,18] As illustrated schematically Multi-arm PEGePLAdendrimers or star diblock copolymers can be cross-linked using this stereospecific interaction to form hydrogels with transition temperatures ranging from 10 to 70 _C depending on the polymer concentration and PLA block length .

e) Supramolecular chemistry

A newer approach to form hydrogels in situ involves using specific molecular recognition motis and/or supramolecular chemistry (i.e. the ordered arrangement of molecules into defined structures). The most common type of cross-linking interaction in this category is the formation of inclusion complexes between poly(alkylene oxide) polymers and cyclodextrins.

Covalently cross-linked hydrogels

While physically cross-linked hydrogels have the general advantage of forming gels without the need for chemical modification or the addition of cross-linking entities in vivo, they have limitations. Because the strength of a physically crosslinked hydrogel is directly related to the chemical properties of the constituent gelators, it is difficult to decouple variables such as gelation time, network pore size, chemical functionalization, and degradation time, restricting the design flexibility of such hydrogels. In contrast, covalent cross-linking prevent both dilution of the hydrogel matrix and diffusion of the polymer away from the site of injection.

a) Small-molecule cross-linking

Small-molecule cross-linkers can be used to fabricate in situ cross-linked hydrogels, as illustrated by several recent examples as Dextranetyramine.

b) Polymer polymer cross-linking

Polymers pre-functionalized with reactive functional groups avoid the use of potentially toxic small-molecule cross-linking agents. The main restriction of this approach is that significant polymer modification chemistry may be required to prepare the functionalized pre-polymer. Additionally, the pre-gel polymers are often themselves to some extent cytotoxic, even when prepared from highly biocompatible polymer precursors. Although this problem is largely mitigated during gel formation due to the rapidity of cross-linking and the several functional groups attached to each polymer precursor (reducing the probability of unreacted residual polymers), As toxicity could become problematic as the polymer degrade to form potentially tissue-reactive oligomers. Multiple types of linkages can be made depending on the preferred speed of cross-linking and biodegradability of the resulting conjugate. The formation of a hydrogen bond an asymmetric Schiff base via the reaction of an aldehyde and a hydrazide facilitate rapid cross-linking of gel precursors.[19,20]

CLASSIFICATIONS OF HYDROGELS

Various classifications have been employed to hydrogels as depicted in Fig. 2. Some of these classifications[23] are given below & Fig-1;

i. According to origin:

Hydrogels can be classifying into natural, synthetic and semi-synthetic on the base of their origin. the majority of the synthetic hydrogels are synthesized by conventional polymerization of vinyl or vinyl-activated monomers. The balance swelling values of these

synthetic hydrogels vary broadly due to their hydrophilicity of the monomers and the crosslinking density.

ii. According to hydrogel durability

Hydrogels can be durable (such as most polyacrylate-based hydrogels) or biodegradable (such as polysaccharides -based hydrogels), due to their stability in a physiological environment. Biodegradation of polymeric biomaterials include the breakdown of hydrolytically or enzymatically sensitive bonds leading to polymer erosion.

iii. According to hydrogel response to environmental stimuli

Hydrogels can control drug release by change the gel structure in response to environmental stimuli. Hydrogels containing as 'sensor' features can undergo reversible volume phase transitions or gel–sol phase transitions upon only very small changes in the environmental condition. This type of environment sensitive hydrogels is called 'Intelligent' or 'smart' hydrogels. Many physical and chemical stimuli have been employed to induce a variety of response in the smart hydrogel systems.

The physical stimuli consist of temperature, electric fields, solvent composition, light, pressure, sound and magnetic fields, while the chemical or biochemical stimuli consist of pH, ions and particular molecular recognition events.

Table 2: Classification of Hydrogel.

S.N	Based on	Type
1	**Origin**	Natural Synthetic Semisynthetic
2	**Water Content**	Low swelling Medium Swelling High swelling Superabsorbent
3	**Porosity**	Nonporous Microporous Macroporous Superporous
4	**Cross-linking**	Chemical(Covalent Bonding) Physical (Non-covalent Bonding)
5	**Biodegradability**	Biodegrable Non-biodegradable
6	**Response to stimuli**	Smart Conventional
7	**Charge**	Cationic

		Anionic Neutral Ampholytics
8	**Structure**	Amorphous Semi-crystalline
9	**Composition**	Homo-polymer Co-polymer Semi interpenetrating network
10	**Based on Synthetic route**	Homopolymer Co-polymer Multipolymers

iv. According to type of ionic charges present on polymer networks

a) Ionic hydrogels: Ionic hydrogels contain charged anionic or cationic monomeric species. These may be homopolymeric involve only ionic polymer network or copolymer of ionic and neutral polymer network. For e g. Anionic hydrogels (anionicthermo-associative carboxymethylpullulan hydrogels) and Cationic hydrogels (new thermosensitive, cationic hydrogels of N-isopropylacrylamide (NIPAM) and (3-acrylamidopropyl) trimethylammonium chloride (AAPTAC).[21]

b) Neutral hydrogels: These hydrogels are temperature sensitive resulting in swelling–deswelling behavior with convert in temperature having permanent polymer networks as linkages formed are irreversible. This kind of linkage allows absorption of water without dissolution and therefore allows drug release by diffusion. Neutral hydrogels (miscible blends from water-insoluble polymers like poly(2,4,4-trimethylhexamethyleneterephthalamide).

c) Ampholytic hydrogels: Ampholytic hydrogels have polymeric network having both positive and negative charged monomeric species. The property of ampholytic hydrogels depend upon ionic species present beside the polymer chain. Oppositely charged solutions have coulombic attraction between them due to which ampholytic hydrogels have interionic as well as intra-ionic attractions for eg. acrylamide based ampholytic hydrogels.[22,23]

Drug Release Mechanisms From Hydrogel Devices

Hydrogels absorb more water than 90% of their weight due to hydrophilicity, thus differing in their release mechanisms from hydrophobic polymers. Various models have been developed to expect the release of an active agent from a hydrogel device as a function of time. These models are depends upon the rate limiting step for controlled release and are divided into three categories viz.

Diffusion controlled

It is most extensively applicable mechanism relating to drug release. Fick's law of diffusion is commonly used in modeling this release [24].The Types of diffusion Controlled hydrogel delivery systems are as follows:-

a) **Reservoir system:** For reservoir system, drug depot is surrounded by a polymeric hydrogel membrane. Fick's first law describe drug release through the membrane.

$$I_A = -D dc_A/dx$$

Where,

I_A =Flux of the drug/ drug corresponding to the mass average velocity of the system

D = Drug diffusion coefficient (assumed constant)

C_A = Drug concentration

b) **Matrix system:** For matrix system (drug uniformly dispersed throughout the matrix), unsteady state drug diffusion in a one dimensional slap- shaped matrix may be described using Fick's second law of diffusion.

$$dc_A/dt = d^2c_A/dx^2$$

Coefficient of drug diffusion is assumed to be constant. additional assumptions are sink condition and a thin planar geometry where the release through the edges is neglected. coefficient of drug diffusion is a function of drug concentration except in very dilute solutions. Diffusivities of encapsulated molecules depend on the degree of swelling and cross linking density of the gels for hydrogel device. Diffusion coefficient used to describe drug release is sensitive to environmental changes or degradation of the polymer network and varies over the time scale of release.[25]

Swelling controlled

It occurs when diffusion of drug is more rapidly than hydrogel swelling. In this condition the modeling of drug involve moving boundary, where molecules are released at the interface of the rubbery and glassy phases of swollen hydrogels. Transition occurs from a glassy state where entrapped molecules remain immobile to a rubbery state where molecules quickly diffuse. Release of drugs from HPMC hydrogel tablets are based on that type of mechanism. For example, Methocel matrices (a combination of methylcellulose and HPMC).[26,28]

Chemically controlled

It characterizes molecule release based on reaction occurring within a delivery matrix. Most commonly occurring reactions are Cleavage of polymer chains through hydrolytic or

enzymatic degradation. Reversible or irreversible reactions occur between the polymer network and releasable drug. It can be categorized on the basis of reaction occurring during drug release.[29]

a) **Purely–kinetic:** Controlled release Polymer degradation (bond cleavage) is the rate determining step although diffusion contributes almost negligible to the drug release.[30-31] It is two types Pendant Chain (prodrugs) and Surface Eroding Systems.

i. **Pendent chain systems:** In pendent chain systems, drugs are covalently linked to the hydrogel network device through cleavable spacer and drug release is controlled by the rate with which spacer bond cleavage occurs.[32,33] In specific applications where a more targeted delivery approach is desired, it is useful to design enzyme cleavable spacer bonds.

ii. **Surface eroding systems:** In surface eroding systems, drug release is mediated by the rate of surface erosion of the polymer matrix. In hydrophobic polymer networks, surface erosion occurs when the rate of water transport into the polymer is much slower than the rate of bond hydrolysis in hydrophobic polymer network. However, due to the inherently high amount of water content of hydrogels, surface erosion may occurs slowly in enzymatic degradation systems where the move of enzyme into the gel is slower than the rate of enzymatic degradation.[34] Models focusing on the release mechanisms are based on hydrolytic degrading polymers.

b) **Reaction based:** diffusion-controlled release reaction (polymer degradation, protein – drug interaction) and diffusion equally contribute to the drug release.

APPLICATION OF HYDROGELS

1. **Wound Healing by hydrogel–**Polysaccharide found in cartilage is useful for the formulation of hydrogels to treat cartilage defect. For example, the hydrogel of gelatin and polyvinyl alcohol (PVA) together with blood coagulants are used for the wound healing.
2. **Silicon hydrogels and polyacrylamides for Soft Contact Lenses –** The first commercially available silicon hydrogels adopted two different approaches. First was a logical extension of its development of silicon monomers with improved compatibility in hydrogel forming monomers. The second was the development of siloxy monomers contains hydrophilic polyethylene oxide segment and oxygen permeable polysiloxane units.

3. **Industrial Applicability -** Hydrogels are used such absorbent for industrial effluents like methylene blue dye and as in adsorption of dioxins by hydrogel beads.
4. **Use of Hydrogels in tissue engineering –** Micronized hydrogels are use for delivery of macromolecules or phagosomes into cytoplasm of antigen-presenting cells. This property is also use for cartilage repairing. Natural hydrogel materials used for tissue engineering like agarose, methylcellulose and other naturally derived products.
5. **Drug Delivery in GI Tract by hydrogel –** Hydrogel deliver drug to specific sites in the GIT. Drugs load with colon specific hydrogels show tissue specificity and change in the pH or enzymatic actions reason liberation of drugs. They are designed to be extremely swollen or degraded in the presence of micro flora.
6. **Hydrogel for rectal Delivery–** Hydrogels show bioadhesive properties, which are useful for rectal drug delivery. Xyloglucan gel having thermal gelling property, use as matrices for drug delivery.
7. **Hydrogel for Ocular Delivery –** Silicon rubber hydrogel composite ophthalmic insert. It was developed by *in-situ* forming gelling system of alginate with high gluconic acid contents for the ophthalmic delivery of pilocarpine.
8. **Hydrogel for transdermal Delivery –** Swollen hydrogels can be used controlled release devices in the field of wound dressing. Hydrogel based formulations are also useful for transdermal iontophoresis to attain improved permeation of products viz. hormones and nicotine.
9. **Hydrogel for subcutaneous Delivery –** Hydrogel formulations for subcutaneous delivery of anticancer drugs are being prepared viz. crosslinked PHEMA was applied to cytarabine (Ara-c). Implantable hydrogels are now leading towards the development of biodegradable systems which don't require surgical removal once the drug has been administered.[35,36]
10. **Novel Hydrogel For Controlled Drug Delivery –** HYPAN is the novel hydrogel having properties useful controlled drug delivery. Physical network of crystalline clusters distinguishes HYPAN hydrogels from others.[37,38]
11. **Hydrogel For Gene Delivery –** Modification of hydrogel composition leads to effective targeting and delivery of nucleic acids to specific cells for gene therapy. Hydrogel may be useful for the treatment of many genetic and/or acquired diseases and conditions.
12. **Hydrogel use in cosmetology –** Hydrogels when implanted into breast emphasize them for aesthetic reason. These implants have made by silicon elastomer shell and are packed with hydroxyl propyl cellulose polysaccharide gel.

13. **Hydrogel for topical Drug Delivery –** Instead of conventional creams, hydrogel formulation are employed to deliver active components like Desonide, a synthetic corticosteroid used as an anti – inflammatory for better patient compliance.
14. **Hydrogel for protein Drug Delivery –** Interleukins conventionally administered as injection are now given as hydrogels which show better compliance and form *in-situ* polymeric network and release proteins slowly.[39]

CONCLUSION

These all hydrogels being biocompatible and biodegradable in nature have been used in the progress of nano biotechnology products and have wonderful applications in the field of controlled drug delivery as well. There have been new inventive methods of hydrophilic polymers preparation and hydrogels that may be employed in the future drug delivery applications. Production of new polymers and crosslinkers with large biocompatibility and better biodegradability would be necessary for victorious applications Hydrogels have played a important role in biomedical applications. Considerable progress has been made in improving the properties of hydrogels used for drug delivery and expanding the range of drugs and kinetics which can be achieved using a hydrogel based delivery vehicle. There is need for continuous improvement in the delivery of not only hydrophobic molecules, but also the delivery of extra sensitive molecules viz. proteins, antibodies or nucleic acids which get deactivated by interactions with the hydrogel delivery medium. Solution of as problems would greatly expand the potential of hydrogel based drug delivery to successfully deliver the next generation drug at the desired rate and location in the body.

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