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A REVIEW ON HYDROGEL AS DRUG DELIVERY SYSTEM

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ABSTRACT

Hydrogel is a network of polymer chains that are water-insoluble, sometimes found as a colloidal gel in which water is the dispersion medium. Hydrogels are cross linked polymer networks that absorb substantial amounts of aqueous solutions. Due to their high water content, these gels resemble natural living tissue more than any other type of synthetic biomaterial. Several techniques have been reported for the synthesis of hydrogels like co polymerization/cross linking of co-monomers using multifunctional co-monomer, which acts as cross linking agent. Chemical initiator initiates the polymerization reaction. Some applications are used of hydrogels in human body. 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. The aim of this article is to present a concise review on the applications of hydrogels in the pharmaceutical field, hydrogel properties, and method of preparation of hydrogel, advantages and disadvantages of hydrogel.

KEYWORDS: synthetic biomaterial, polymerization reaction.

INTRODUCTION[1-6]

Hydrogels are three-dimensional, cross linked networks of water-soluble polymers.Hydrogels can be made from virtually anywater-soluble polymer, encompassing a wide range of chemical compositions and bulk physical properties. Further- more, hydrogels can be formulated in a variety of physical forms, including slabs, microparticles, nanoparticles, coatings, and films. As a result, hydrogels are commonly used in clinical practice and

experimental medicine for a wide range of applications, including tissue engineering and regenerative medicine, diagnostics, cellular immobilization, separation of biomolecules or cells, and barrier materials to regulate biological adhesions. The unique physical properties of hydrogels have sparked particular interest in their use in drug delivery applications. Their highly porous structure can easily be tuned by controlling the density of cross links in the gel matrix and the affinity of the hydrogels for the aqueous environment in which they are swollen. Their porosity also permits loading of drugs into the gel matrix and subsequent drug release at a rate dependent on the diffusion coefficient of the small molecule or macromolecule through the gel network. Indeed, the benefits of hydrogels for drug delivery may be largely pharmacokinetic especifically that a depot formulation is created from which drugs slowly elute, maintaining a high local concentration of drug in the surrounding tissues over an extended period, although they can also be used for systemic delivery.

Hydrogels are also generally highly biocompatible, as reflected in their successful use in the peritoneum and other sites in vivo. Biocompatibility is promoted by the high water content of hydrogels and the physiochemical similarity of hydrogels to the native extracellular matrix, both compositionally (particularly in the case of carbohydrate-based hydrogels) and mechanically. Biodegradability or dissolution may be designed into hydrogels via enzymatic, hydrolytic, or environmental (e.g. pH, temperature, or electric field) pathways; however, degradation is not always desirable depending on the time scale and location of the drug delivery device. Hydrogels are also relatively deformable and can conform to the shape of the surface to which they are applied. In the latter context, the muco or bioadhesive properties of some hydrogels can be advantageous in immobilizing them at the site of application or in applying them on surfaces that are not horizontal. Despite these many advantageous properties, hydrogels also have several limitations. The low tensile strength of many hydrogels limits their use in loadbearing applications and can result in the premature dissolution or flow away of the hydrogel from a targeted local site. This limitation may not be important in many typical drug delivery applications (e.g. subcutaneous injection). More important, perhaps, are problems relating to the drug delivery properties of hydrogels. The quantity and homogeneity of drug loading into hydrogels may be limited, particularly in the case of hydrophobic drugs. The high water content and large pore sizes of most hydrogels often result in relatively rapid drug release, over a few hours to a few days. Ease of application can also be problematic; although some hydrogels are sufficiently deformable to

be injectable, many are not, necessitating surgical implantation. Each of these issues significantly restricts the practical use of hydrogel-based drug delivery therapies in the clinic.

In this review, we focus on recent developments addressing three key clinically relevant issues regarding the use of hydrogels for drug delivery: facilitating the in vivo application of drug-eluting hydrogels, extending their duration of drug release, and broadening the range of drugs which they effectively deliver.

CLASSIFICATION OF HYDROGELS

1. Based on the method of preparation, hydrogels are classified into:

A) Homopolymer hydrogels

B) Co-polymer hydrogels

C) Multi polymer hydrogels

2. Based on the ionic charges hydrogels can be classified into :

A) Neutral hydrogels

B) Anionic hydrogels

C) Cationic hydrogels

D) Ampholytic hydrogels

3. Based on the structure hydrogels can be classified into:

A) Amorphous hydrogels

B) Semi-crystalline hydrogels

C) Hydrogen bonded hydrogels

4. Based on the mechanism controlling the drug release they are classified into:

A) Diffusion controlled release systems

B) Swelling controlled release systems

C) Chemically controlled release systems

D) Environment responsive systems

MATERIALS USED IN THE PREPARATION OF HYDROGELS

Different polymers can be used for the development of hydrogel systems including cellulose derivatives, natural gums, polycrylates and gelatin.

PROPERTIES OF HYDROGEL[7]

Hydrogels are water swollen polymer matrices, with a tendency to imbibe water when placed in aqueous environment. This ability to swell, under biological conditions, makes it an 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. These networks, have a three dimensional structure, cross linked together either physically (entanglements, crystallites), or chemically (tie-points, junctions). This insoluble cross linked structure allows immobilization of active agents, biomolecules effectively, and allows for its release in well-defined specific manner. Thus the hydrogels biocompatibility and cross linked structure are responsible for its varied applications.

Physical, chemical and toxicological properties of hydrogels[8-14]

1. Factors affecting swelling of Hydrogels

The cross linking ratio is one of the most important factors that affect the swelling of hydrogels. It is defined as the ratio of moles of crosslinking agent to the moles of polymer repeating units. The higher the cross linking ratio, the more cross linking agent is incorporated in the hydrogel structure. Highly cross linked hydrogels have a tighter structure, and will swell less compared to the same hydrogels with lower cross linking ratios. Cross linking hinders the mobility of the polymer chain, hence lowering the swelling ratio. The chemical structure of the polymer may also affect the swelling ratio of the hydrogels. 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. Swelling of environmentally-sensitive hydrogels can be affected by specific stimuli. Swelling of temperature sensitive hydrogels can be affected by changes in the temperature of the swelling media. 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.

They may perform dramatic volume transition in response to a variety of physical and chemical stimuli, where the physical stimuli include temperature, electric or magnetic field,

light, pressure, and sound, while the chemical stimuli include pH, solvent composition, ionic strength, and molecular species

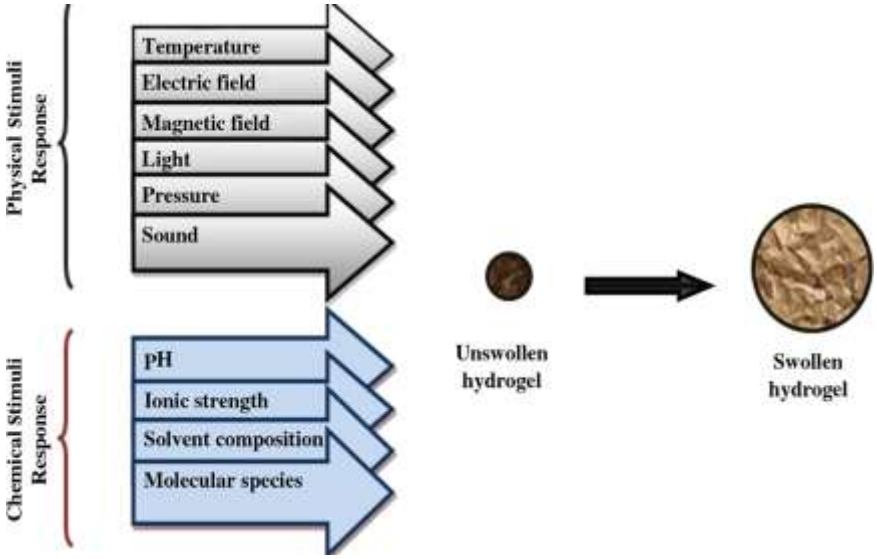

Fig. 1. Stimuli response swelling hydrogel.

Dynamics of swelling

The swelling kinetics of hydrogels can be classified as diffusion-controlled (Fickian) and relaxation-controlled (non-Fickian) swelling. When water diffusion into the hydrogel occurs much faster than the relaxation of the polymer chains, the swelling kinetics is diffusion-controlled.

Mechanical properties

Mechanical properties of hydrogels are very important for pharmaceutical applications. For example, the integrity of the drug delivery device during the lifetime of the application is very important to obtain FDA approval, unless the device is designed as a biodegradable system. A drug delivery system designed to protect a sensitive therapeutic agent, such as protein, must maintain its integrity to be able to protect the protein until it is released out of the system. Changing the degree of cross linking has been utilized to achieve the desired mechanical property of the hydrogel. Increasing the degree of cross linking of the system will result in a stronger gel. However, a higher degree of cross linking creates a more brittle structure. Hence, there is an optimum degree of cross linking to achieve a relatively strong and yet elastic hydrogel.

Copolymerization has also been utilized to achieve the desired mechanical properties of hydrogels. Incorporating a co monomer that will contribute to H-bonding can increase the strength of the hydrogel.

Cytotoxicity and in-vivo toxicity[8-14]

Cell culture methods, also known as cytotoxicity tests can be used to evaluate the toxicity of hydrogels. Three common assays to evaluate the toxicity of hydrogels include extract dilution, direct contact and agar diffusion. Most of the problems with toxicity associated with hydrogel carriers are the unreacted monomers, oligomers and initiators that leach out during application. Therefore, an understanding the toxicity of the various monomers used as the building blocks of the hydrogels is very important. The relationship between chemical structures and the cytotoxicity of acrylate and methacrylate monomers has been studied extensively. Several measures have been taken to solve this problem, including modifying the kinetics of polymerization in order to achieve a higher conversion, and extensive washing of the resulting hydrogel.

The formation of hydrogels without any initiators has been explored to eliminate the problem of the residual initiator. The most commonly used technique has been gamma irradiation. Hydrogels of PVA have been also made without the presence of initiators by using thermal cycle to induce crystallization. The crystals formed act as physical cross links. These crystals will be able to absorb the load applied to the hydrogels .

Preparation Methods of Hydrogels-

Hydrogels are polymeric networks. This implies that cross links have to be present in order to avoid dissolution of the hydrophilic polymer chain in aqueous solution. The various methods for cross linking are as follows: In general, the three integral parts of the hydrogels preparation are monomer, initiator, and cross-linker. To control the heat of polymerization and the final hydrogels properties, diluents can be used, such as water or other aqueous solutions. Then, the hydrogel mass needs to be washed to remove impurities left from the preparation process. These include nonreacted monomer, initiators, cross-linkers, and unwanted products produced via side reactions (Fig. 2). Preparation of hydrogel based on acrylamide, acrylic acid, and its salts by inverse-suspension polymerization and diluted solution polymerization have been investigated elsewhere. Fewer studies have been done on highly concentrated solution polymerization of acrylic monomers, which are mostly patented.

Chen [produced acrylic acid-sodium acrylate superabsorbent through concentrated (43.6 wt %) solution polymerization.

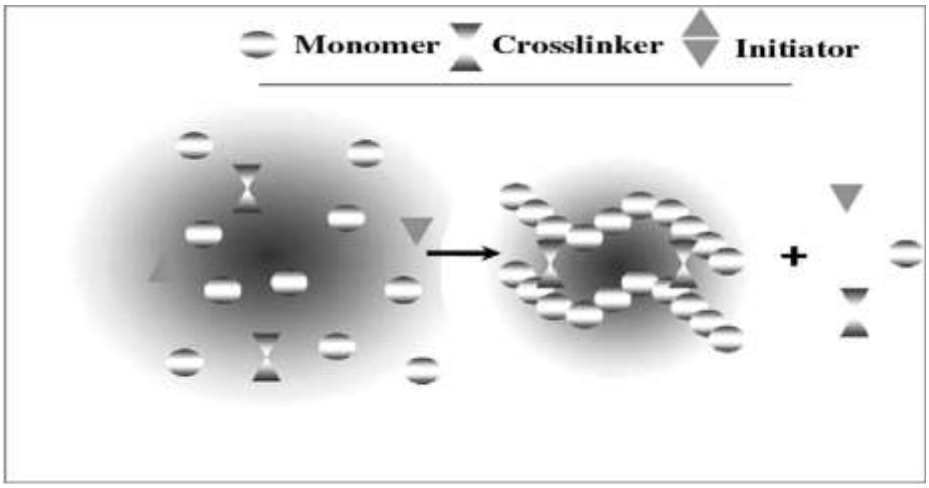

Fig. 2. Schematic diagram of hydrogel preparation

Cross linking of Polymers

In this method chemically cross linked gels are formed by radical polymerization of low molecular weight monomers, or branched homopolymers, or copolymers in the presence of cross linking agent. This reaction is mostly carried out in solution for biomedical applications.

Copolymerization/Cross linking Reactions

Copolymerization reactions are used to produce **polymer** gels, many hydrogels are produced in this **fashion**, for example poly (hydroxyalkyl methylacrylates).

Cross linking by High Energy Radiation

High energy radiation, such as gamma and electron beam radiation can be used to polymerize unsaturated compounds. Water soluble polymers derivatized with vinyl groups can be converted into hydrogels using high energy radiation.

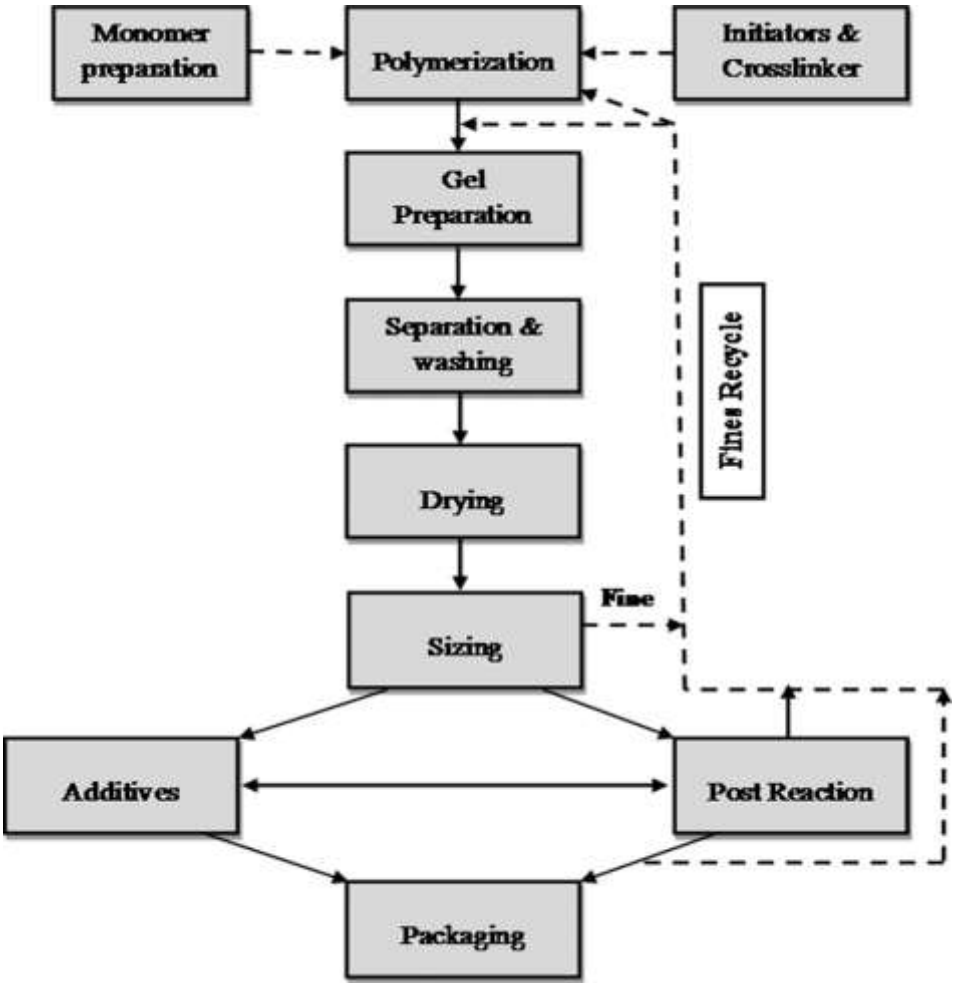

Fig. 2. Hydrogel preparation block diagram (solution polymerization/ Cross-linking procedure).

Cross linking Using Enzymes[15-18]

Recently a new method was published using an enzyme to synthesize PEG based hydrogels. A tetrahydroxy PEG was functionalized with addition of glutaminyl groups and networks were formed by addition of transglutaminase into solution of PEG and poly (lysinecophenylalanine). The synthesis of hydrogel in industry is Consist of solution and reversed suspension and reversed emulsion polymerizations.

Figure:2 shows a block diagram of a generic solution polymerization process. This figure represents the major procedure of super absorbent polymer manufacturing in the laboratory and industrial scales.

Characterization of Hydrogels[11-16]

Hydrogels are characterized by following methods/tests

Atomic Force Microscopy (AFM): The surface morphology of the hydrogels is studied by a Multimode Atomic Force Microscope.

X-ray Diffraction: X-ray diffraction is used to understand whether the polymers retain their crystalline nature or they get deformed during the pressurization process.[11]

Network pore size*:* Network pore size is measured by a number of techniques like Quasi-elastic laser light scattering, electron microscopy, mercury porosimetry, rubber elasticity measurements, and equilibrium swelling experiments.[11]

Fourier Transform Infrared Spectroscopy: Formation of coil or helix which is indicative of cross linking is evident by appearance of bands near 1648 cm-1 FTIR. Any change in the morphology of hydrogels changes their IR absorption spectra.[12]

Rheology: Hydrogels are evaluated for viscosity under constant temperature (4°C) by using Cone Plate viscometer.

Swelling Behavior: Hydrogels are allowed to immerse in aqueous medium or medium of specific pH to know their swellability. These polymers show increase in dimensions related to swelling.[13, 14]

Cross-linking and mechanical strength is measured by Ultimate compressive strength, change in polymer solubility with time.[15, 16]

Hydrogel technical features[48]

The functional features of an ideal hydrogel material can be listed as follows:

_ The highest absorption capacity (maximum equilibrium swelling) in saline.

_ Desired rate of absorption (preferred particle size and porosity) depending on the application requirement.

_ The highest absorbency under load (AUL).

_ The lowest soluble content and residual monomer.

_ The lowest price.

_ The highest durability and stability in the swelling environment and during the storage.

_ The highest biodegradability without formation of toxic species following the degradation.

_ pH-neutrality after swelling in water.

_ Colourlessness, odorlessness, and absolute non-toxic.

_ Photo stability.

_ Re-wetting capability (if required) the hydrogel has to be able to give back the imbibed solution or to maintain it; depending on the application requirement (e.g., in agricultural or hygienic applications).

COMMON USES FOR HYDROGELS[19-25]

1. Currently used as scaffolds in tissue engineering. When used as scaffolds, hydrogels may contain human cells in order to repair tissue.
2. Environmentally sensitive hydrogels. These hydrogels have the ability to sense changes of pH, temperature, or the concentration of metabolite and release their load as result of such a change.
3. As control-release delivery systems.
4. Provide absorption, desloughing and debriding capacities of necrotic and fibrotic tissue.
5. Hydrogels that are responsive to specific molecules, such as glucose or antigens can be used as biosensors as well as in DDS.
6. Used in disposable diapers where they "capture" urine, or in sanitary napkins.
7. Contact lenses (silicone hydrogels, polyacrylamides). Common ingredients are e.g. polyvinyl alcohol, sodium polyacrylate, acrylate polymers and copolymers with an abundance of hydrophilic groups. Natural hydrogel materials are being investigated for tissue engineering these materials include agarose, methylcellulose, hylaronan, and other naturally derived polymers.

RECENT ADVANCES IN HYDROGELS

1. Opthalmic in-situ gelling system

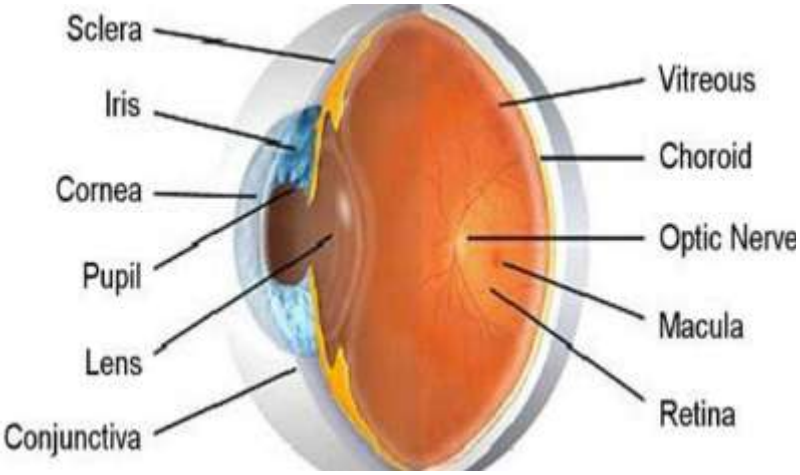

Fig. 3: Anatomy of human eye

Hydrogels are polymeric networks that absorb large quantities of water while remaining insoluble in aqueous solutions due to chemical or physical cross linking of individual polymer chains. They resemble natural living tissue more than any other class of synthetic biomaterials due to their high water content; furthermore, the high water content of the materials contributes to their biocompatibility. Hydrogels show minimal tendency to adsorb proteins from body fluids because of their low interfacial tension. Further, the ability of molecules of different sizes to diffuse into (drug loading) and out of (drug release) hydrogels allows the possible use of dry or swollen polymeric networks as drug delivery systems for oral, nasal, buccal, rectal, vaginal, ocular and parenteral routes of administration. These are polymers endowed with an ability to swell in water or aqueous solvents and induce a liquid–gel transition. Currently; two groups of hydrogels are distinguished, namely preformed and in situ forming gels. Preformed hydrogels can be defined as simple viscous solutions which do not undergo any modifications after administration. The use of preformed hydrogels still has drawbacks that can limit their interest for ophthalmic drug delivery or as tear substitutes. They do not allow accurate and reproducible administration of quantities of drugs and, after administration; they often produce blurred vision, crusting of eyelids, and lachrymation.

Thus in situ hydrogels can be instilled as eye drops and undergo an immediate gelation when in contact with the eye. In situ-forming hydrogels are liquid upon instillation and undergo phase transition in the ocular cul-de-sac to form viscoelastic gel and this provides a response to environmental changes. Three methods transition on the surface: change in temperature, pH, and electrolyte composition. Increase in solution viscosity by using polymers improves retention of product on the corneal surface. More recently, the approach to improve precorneal retention is based on the use of mucoadhesive polymers. The principle for use of bioadhesive vehicles relies on their ability to interact with the mucincoating layer present at the eye surface. The polymers chosen to prepare ophthalmic hydrogels should meet some specific rheological characteristics. It is generally well accepted that the instillation of a formulation should influence tear behaviour as little as possible. Because tears gave a pseudoplastic behaviour, pseudoplastic vehicles would be more suitable as compare to Newtonian formulations, which have a constant viscosity independent of the shear rate, whereas pseudoplastic solution exhibit decreased viscosity with increasing shear rate, thereby offering lowered viscosity during blinking and stability of the tear film during fixation.

Drug release from hydrogels

As discussed in the previous sections, hydrogels have a unique combination of characteristics that make them useful in drug delivery applications. Due to their hydrophilicity, hydrogels can imbibe large amounts of water. Therefore, the molecule release mechanisms from hydrogels are very different from hydrophobic polymers. Both simple and sophisticated models have been previously developed to predict the release of an active agent from a hydrogel device as a function of time. These models are based on the rate limiting step for controlled release and are therefore categorized as diffusion, swelling & chemically controlled mechanism.

Smart hydrogels

"Smart" hydrogels, or stimuli-sensitive hydrogels, are very different from inert hydrogels in that they can "sense" changes in environmental properties such as pH and temperature and respond by increasing or decreasing their degree of swelling. The volume-changing behaviour of "smart" hydrogels is particularly useful in drug delivery applications as drug release can be triggered upon environmental changes. These are intelligent or smart polymers play important role in drug delivery since they may dictate not only where a drug is delivered, but also when and with which interval it is released. The stimuli that induce various responses of the hydrogel systems include physical (temperature) or chemical (pH, ions) ones. In this, polymers may undergo phase transition in presence of various ions. Gellan gum commercially available as Gelrite® is an anionic polysaccharide that undergoes *in situ* gelling in the presence of mono- and divalent cations, including Ca2+, Mg2+, K+ and Na+. Gelation of the low-methoxy pectins can be caused by divalent cations, especially Ca2+.

Mechanism and examples of stimuli sensitive hydrogels

External Stimuli-

A) Temperature

Formulation is liquid at room temperature (20°-25° C) which undergoes gelation with contact to body fluids (35° – 37°C) Temperature increases the degradation of polymer chain which leads to formation of hydrophobic domains and transition of an aqueous liquid to hydrogel network.

e.g Poloxamer/pluronics

Co-polymers of poly ethylene oxide

PEO

Co-polymers of polypropylene oxide

PPO

Polyester

Xyloglucan

Cellulose derivatives

B) Ionic interactions

Formulation undergoes liquid-gel transition under influence of an increase in ionic strength

Gel formulation takes place because of complexation with polyvalent cations (like Ca+2) in lacrimal fluid.

e.g Chitosan

Gallen gum

Alginates

C)PH change

Sol to gel transition when PH raised from 4.2-7.4 (eye PH). At higher PH polymer forms hydrogen bonds with mucin which leads to formation of hydrogel networks.

e.g Pseudolatexes

Acrylates (carbopols)

Cellulose acetate phthalate

(CAP)

2. Oral mucoadhesive drug delivery systems[92]

Mucoadhesion can be defined as a state in which two components, of which one is of biological origin are held together for extended periods of time by the help of interfacial forces. Generally, bioadhesion is an term which broadly includes adhesive interactions with any biological or biologically derived substance, and mucoadhesion is used when the bond is formed with a mucosal surface.

Polymers used for oral mucoadhesive drug delivery[93-96]

1. Hydrogels

These swell when in contact with water and adhere to tne mucus membrane.

These are further classified according to their charge

 Anionic polymers-
Carbopol,
Polyacrylates

 Cationic polymers-
Chitosan

 Neural/ non-ionic polymers-
Eudragit analogues.

1.1. Chitosan[97- 98]

It is an cationic polymer (polysaccharide),it is produced by the deacetylation of chitin. Chitosan is gaining importance in the development of mucoadhesive drug delivery system because of its good biocompatibility, biodegradability and non toxic nature. It binds to the mucosa via ionic bonds between the amino group and sialic acid residues. Chitosan being linear provides greater polymer chain flexibility. chitosan and its metaboloized derivatives are quickly eliminated by the kidney.

Mechanism of mucoadhesion[99-102]

As stated, mucoadhesion is the attachment of the drug along with a suitable carrier to the mucous membrane. Mucoadhesion is a complex phenomenon which involves wetting, adsorption and interpenetration of polymer chains.

Mucoadhesion has the following mechanism,

1. Intimate contact between a bioadhesive and a membrane (wetting or swelling phenomenon)
2. Penetration of the bioadhesive into the tissue or into the surface of the mucous membrane (interpenetration). Residence time for most mucosal routes is less than an hour and typically in minutes, it can be increased by the addition of an adhesive agent in the delivery system which is useful to localize the delivery system and increases the contact time at the site of absorption.[5] The exact mechanism of mucoadhesion is not known but an accepted theory states that a close contact between the mucoadhesive polymer and mucin occurs which is followed by the interpenetration of polymer And mucin. The adhesion is prolonged due to the formation of van der vaals forces, hydrogen bonds and electrostatic bonds.

ADVANTAGES[26-27]

1) Entrapment of microbial cells within polyurethane hydrogel beads with the advantage of low toxicity.

2) Hydrogel is more elastic and stronger than available hydrogels of similar softness. Poly (methyl acrylate-cohydroxyethyl acrylate) hydrogel implant material of strength and softness.

3) Hydrogel-based micro valves have a number of advantages over conventional microvalves, including relatively simple fabrication, no external power requirement, no integrated electronics, large displacement (185 μm), and large force generation.

4) Environmentally sensitive hydrogels. These hydrogels have the ability to sense changes of pH, temperature, or the concentration of metabolite and release their load as result of such a change.

5) Natural hydrogel materials are being investigated for tissue engineering, these materials include agarose, methylcellulose, hylaronan, and other naturally derived polymers.

DISADVANTAGES

1) The main disadvantages are the high cost and the sensation felt by movement of themaggots.

2) Its disadvantage includes thrombosis at anastomosis sites and the surgical risk associated with the device implantation and reterieval.

3) Hydrogels are nonadherent; they may need to be secured by a secondary dressing.

4) Disadvantages of hydrogel in contact lenses are lens deposition, hypoxia, dehydration and red eye reactions.

APPLICATIONS OF HYDROGELS[60, 65]

The main reason for wide applications of hydrogels are their unique properties such as absorption, swelling and de-swelling behaviour, hydrophilicity, and biocompatibility. Hydrogels have special application in pharmaceuticals field including diagnostic, therapeutic, and implantable devices such as catheters, biosensors, artificial skin, and tissue engineering. Natural polymers generally have better biocompatibility and less latent toxicity than other synthetic polymer, therefore, hydrogel of natural polymers have more attraction as excellent candidates for controlled release device, bio-adhesive device, and targetable therapeutic devices.

1. Wound Healing – Modified polysaccharide found in cartilage is used in formation of hydrogels to treat cartilage defects. For example, the hydrogel of gelatine and polyvinyl alcohol (PVA) together with blood coagulants are formulated.

2. Soft Contact Lenses (silicon hydrogels and polyacrylamides) – The first commercially available silicon hydrogels adopted two different approaches.

First approach by Bausch and Lomb was a logical extension of its development of silicon monomers with enhanced compatibility in hydrogel forming monomers. The second by Ciba vision was the development of siloxy monomers containing hydrophilic polyethylene oxide segments and oxygen permeable polysiloxane units

3. Industrial Applicability - Hydrogels are used as absorbents for industrial effluents like methylene blue dye. Another example is adsorption of dioxins by hydrogel beads.

4. Tissue Engineering – Micronized hydrogels are used to deliver macromolecules (phagosomes) into cytoplasm of antigen-presenting cells. This property is also utilized in cartilage repairing. Natural hydrogel materials used for tissue engineering include agarose, methylcellulose and other naturally derived products.

5. Drug Delivery in GI Tract – Hydrogel deliver drugs to specific sites in the GIT. Drugs loaded with colon specific hydrogels show tissue specificity and change in the pH or enzymatic actions cause liberation of drugs. They are designed to be highly swollen or degraded in the presence of micro flora.

6. Rectal Delivery – Hydrogels showing bioadhesive properties are used for rectal drug delivery. Miyazaki et al. explored the xyloglucan gel with a thermal gelling property as matrices for drug delivery.

7. Ocular Delivery – Chitosan is reported silicon rubber hydrogel composite ophthalmic inserts. Cohen et al. developed ***in-situ*** forming gelling system of alginate with high gluconic acid contents for the ophthalmic delivery of pilocarpine.

8. Transdermal Delivery – Swollen hydrogels can be used as controlled release devices in the field of wound dressing. Hydrogel based formulations are being explored for transdermal iontophoresis to obtain enhanced permeation of products viz. hormones and nicotine.

9. 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 administered5,6.

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 others15,16**.**

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 versatility has potential application in the treatment of many genetic and/or acquired diseases and conditions6.

12. Cosmetology – Hydrogels when implanted into breast accentuate them for aesthetic reasons. These implants have silicon elastomer shell and are filled with hydroxyl propyl cellulose polysaccharide gel.

13. Tropical 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. 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.

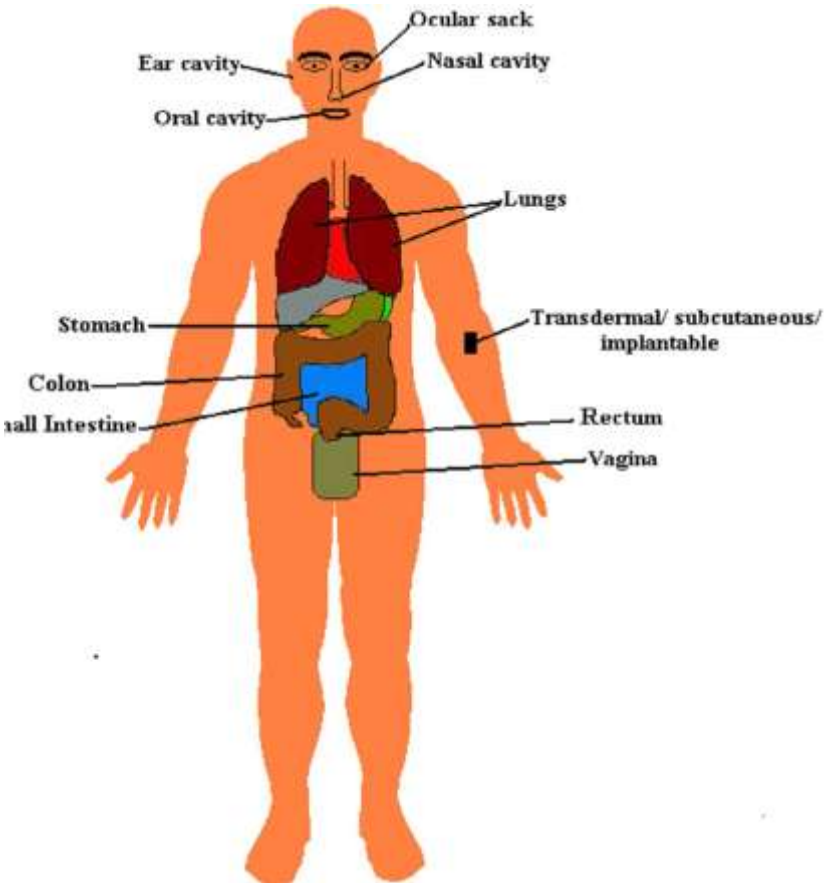

Fig. 4: Tissue locations applicable for hydrogel based drug delivery systems

15. Tissue engineering

The micronized hydrogels (microgels) have been used to deliver macromolecules like phagosomes into cytoplasm of antigen-presenting cells. The release is because of acidic conditions. Such hydrogels mold themselves to the pattern of membranes of the tissues and have sufficient mechanical strength. This property of hydrogels is also used in cartilage repairing.

16. Topical drug delivery

Hydrogels have been used to deliver active component like Desonide which is a synthetic corticosteroid usually used as an anti-inflammatory. Instead of conventional creams, the hydrogels have been formulated for better patient compliance. These hydrogels have moisturizing properties therefore scaling and dryness is not expected with this drug delivery system. An antifungal formulation like cotrimazole has been developed as hydrogel formuhydrlation for vaginitis. It has shown better absorption than conventional cream formulations**.**

17. Protein drug delivery[28-80]

Interleukins which are conventionally given as injection are now given as hydrogels. These hydrogels have shown better patient compliance. The hydrogels form insitu polymeric network and release proteins slowly. These are biodegradable and biocompatible also.

18. Application of Hydrogels to Fix Bone Replacements[81-83]

Provided are orthopedic fasteners and replacements such as nails, screws, pins, hip and knee replacements, etc., coated with hydrogels and other biocompatible/biodegradable materials which expand in the presence of liquids. Useful coating materials include methacrylate, hyaluronic acid esters, and cross linked esters of hyaluronic acid resulting from the esterification of hyaluronic acid with polyhydric alcohols Replacements can be thus coated, even those made of stainless steel, metal alloys, titanium, or cobaltchromium, treatment of the surfaces to improve metal-polymer adhesion.

CONCLUSION

Hydrogels are cross linked polymer networks that absorb substantial amounts of aqueous solutions. Due to their high water content, these gels resemble natural living tissue more than any other type of synthetic biomaterial. Hydrogels have a unique combination of characteristics that make them useful in drug delivery applications. Due to their hydrophilicity, hydrogels can imbibe large amounts of water. Therefore, the molecule release

mechanisms from hydrogels are very different from hydrophobic polymers. Hydrogels have been used to deliver active component like Desonide which is a synthetic corticosteroid usually used as an anti-inflammatory. Instead of conventional creams, the hydrogels have been formulated for better patient compliance. These hydrogels have moisturizing properties therefore scaling and dryness is not expected with this drug delivery system.

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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