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A SHORT DISCUSSION ON TOPICAL HYDROGEL

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ABSTRACT
Hydrogels are three-dimensional network structures able to imbibe large amount of water. Natural as well as synthetic hydrophilic polymers can be physically or chemically cross-linked in order to fabricate hydrogels. Their close similarity to living tissue opens up many prospects for applications in biomedical field. Topical hydrogel preparations are intended for skin application or to certain mucosal surface for local action or transdermal penetration. It is for the topical application so; it can avoid first pass metabolism and increase the local action. In view of adverse drug reaction associated with oral formulation are given by topical route.

KEYWORD: Introduction of Hydrogel, Classification, Advantages and Disadvantages, Applications and evaluations.

1. INTRODUCTION[1,2,3]

Hydrogels are swollen three-dimensional networks of hydrophilic polymers, held together by association bonds or cohesive forces and are suitable carriers for drug delivery. Proteins, peptides and other drugs can be made safely available in the colon using hydrogel as vehicle. They have high water content and rubbery nature similar to natural tissues, which make them desirable for biomedical applications. The polymeric biomaterials are employed in hydrogel formulations to delay the dissolution of drug depending upon the exposure of drug molecules to aqueous environment surrounding the drug delivery system. They are having various advantageous in safety, ease of manufacture, cost effectiveness, biocompatibility and biodegradability. They have been used for various biomedical, agricultural applications, for their absorbent properties, biodegradability and biocompatibility.[1] Hydrogels can either be chemically durable or they may eventually disintegrate and dissolve. Hydrogels are also known as 'reversible' or 'physical' gels if molecular entanglements and/or secondary forces such as ionic, hydrogen bonding or hydrophobic forces play the principal role in forming the linkage. Hydrogel can be manufactured practically from any water-soluble polymer, including a wide range of chemical compositions and bulk physical properties. Additionally, hydrogels can also be formulated in a number of physical forms such as slabs, microparticles, nanoparticles, coatings or films.[2] If water is removed from these swollen biomaterials, they are called xerogels, which are the dried hydrogels. The network structure can be macroporous, microporous or nonporous. Macroporous hydrogels are having large pores of dimension 0.1 to 1 µm. Microporous hydrogels having small pore size of the gel network, usually in the range of 100-1000 angstrom. Nonporous hydrogels are the mesh- like structures of macro- molecular dimension usually in the range of 10 - 100 angstrom.[13] Hydrogels can be formed from both natural and synthetic polymers. Hydrogels based on natural polymers can have insufficient mechanical properties, contain pathogens and evoke immune responses. On the other hand, they have numerous advantageous properties like inherent biocompatibility, biodegradability, bacteriostatic and wound healing properties, ex: collagen, gelatine and polysaccharides such as alginate and agarose. Synthetic hydrogels do not have these inherent bioactive properties and can be prepared by using chemical polymerization methods. There are many approaches based on genetic engineering and biosynthetic methods to also create the unique hydrogel materials.[3]

Preparation of Hydrogels[4,5]

In general, hydrogels can be prepared from either synthetic polymers or natural polymers. The synthetic polymers are hydrophobic in nature and chemically stronger compared to natural polymers. Their mechanical strength results in slow degradation rate, but on the other hand, mechanical strength provides the durability as well. These two opposite properties should be balanced through an optimal design. Also, it can be applied to the preparation of hydrogels based on natural polymers provided that these polymers have suitable functional groups or have been functionalized with radically polymerizable groups. In the most succinct sense, a hydrogel is simply a hydrophilic polymeric network

cross-linked in some fashion to produce an elastic structure. Thus, any technique which can be used to create a cross-linked polymer can be used to produce a hydrogel.[14] Copolymerization/cross-linking free-radical polymerizations are commonly used to produce hydrogels by reacting hydrophilic monomers with multifunctional cross-linkers. Water-soluble linear polymers of both natural and synthetic origin are cross-linked to form hydrogels in a number of ways:

1. Linking polymer chains via chemical reaction.
2. Using ionizing radiation to generate main-chain free radicals which can recombine as cross-link junctions.[14]
3. Physical interactions such as entanglements, electrostatics and crystallite formation.

Any of these various polymerization techniques can be used to form gels, including bulk, solution, and suspension polymerization. Hydrogels have been attractive to the pharmaceutical industry for several reasons including the controlled release of an active pharmaceutical ingredient, disintegration of dosage forms, protecting a drug substance and to increase the product life cycle.

2. Classification of Hydrogel

The hydrogel products can be categorized on different bases as described below:

2.1 Classification based on source

Hydrogels can be classified into two groups based on their natural or synthetic origins.

2.2 Classification according to polymeric composition: The technique of preparation leads to formations of principal classes of hydrogels. These can be represented as following:

(a) Homopolymeric Hydrogels

polymer network which are derived from a single species of monomer, which is the basic structural unit comprising of any polymer network. Homopolymers may have cross-linked skeletal structure dependent on the nature of the monomer and polymerization method.

b) Copolymeric Hydrogels

more distinct monomer species with at least one hydrophilic component, assembled in a random, block or alternating configuration along the chain of the polymer network.

(c) Multipolymer

These are also called as interpenetrating polymeric hydrogel (IPN), an important class of hydrogels, which is made of two independent cross-linked synthetic and/or natural polymer component, confined in a network form. In semi-IPN hydrogel, one component is a crosslinked polymer and other component is a non-cross-linked polymer.

2.3 Classification based on configuration: This classification of hydrogels relies on their physical structure and chemical composition which can be illustrated as follows:

(a) Amorphous (non-crystalline).
(b) Semicrystalline: A complex mixture of amorphous and crystalline phases.
(c) Crystalline.

2.4 Classification based on type of cross-linking

Hydrogels can be divided into two groups on the basis of their chemical or physical behaviour of the cross-link junctions. Chemically cross-linked networks have stable junctions, while physical networks have temporary junctions that results from either polymer chain entanglements or physical interactions such as ionic interactions, hydrogen bonds or hydrophobic interactions.

2.5 Classification based on physical appearance: Hydrogels appearance as matrix, film or microsphere is dependent on the procedure of polymerization employed in the formulation process. Hydrogels may be classified into four groups on the basis of presence or absence of electrical charge situated on the crosslinked chains:

(a) Non-ionic (neutral).
(b) Ionic (including anionic or cationic).
(c) Amphoteric electrolyte (ampholytic) comprising both acidic and basic groups.
(d) Zwitterionic (polybetaines) consisting of both anionic and cationic groups in each structural repeating unit.

3. Properties of Hydrogel[2]

3.1 Physical and chemical properties

In spite of so much advancement, a basic understanding of gel properties is not yet appropriate for a realistic design of novel gel systems. For such designs, it is imperative to know how solute molecules interact with the gel, particularly how they partition between the gel phase and the surrounding liquid phase. Partitioning majorly relies on two major effects i.e. size exclusion and molecular attraction/repulsion.

3.2 Swelling

Hydrogels are cross-linked polymer networks swollen in a liquid medium. The absorbed liquid performs as a selective filter to permit free diffusion of some solute molecules, while the polymer network acts as a matrix to hold the liquid together. Hydrogels may soak up from 10-20% (an arbitrary lower limit) up to thousands of times of their dry weight in water. The nature of the water in a hydrogel can ascertain the complete permeation of nutrients into and cellular products out of the gel. When a dry hydrogel starts to soak water, the initial water molecules moving into the matrix will hydrate the most polar, hydrophilic groups, leading to. As the polar groups are primary bound water hydrated, the hydrogel linkage swells and exposes hydrophobic groups, which also intermingle with water molecules,

resulting in hydrophobically-bound water or. secondary bound water Primary and secondary bound water are often merged and solely called as. After the polar and hydrophobic sites total bound water have interacted with bound water molecules, the network will suck up additional water, because of osmotic driving force of the network chains towards infinite dilution. This surplus swelling is resisted by the covalent or physical crosslink, producing an elastic network retraction force. Consequently, the hydrogel will attain an equilibrium swelling level. The additional swelling water that is imbibed after the ionic, polar and hydrophobic groups become saturated with bound water is termed as free water or bulk water and is presumed to fill the space between the network chains and/or the centre of larger pores, macropores or voids. Progressively as the network swells, if the network chains or crosslink are degradable, the gel will initiate to disintegrate and dissolve, at a rate depending on its composition. There are various methods employed by investigators to evaluate the relative amounts of free and bound water, as fractions of the total water content. All of them are contentious, since there is proton NMR evidence that the exchange of water molecules between the so-called bound and free states is very prompt, perhaps as fast as one H2O molecule every 10-9s. The three main procedures exercised to characterize water in hydrogels are reliant on the use of small molecular probes, DSC and NMR. When probe molecules are utilized, the labelled probe solution is equilibrated with the hydrogel, and the concentration of the probe molecule in the gel at equilibrium is determined. By presuming that only the free water in the gel can dissolve the probe solute, one can assess the free water content from the amount of the absorbed probe molecule and the known (measured) probe molecule concentration in the external solution. Then the bound water is determined by difference of the measured total water content of the hydrogel and the estimated free water content. The use of DSC is based on the postulation that only the free water may be frozen, so it is believed that the endotherm measured when warming the frozen gel corresponds to the melting of the free water and that value will yield the amount of free water in the HG sample being experimented. Then the bound water is achieved by difference of the measured total water content of the HG test specimen, and the calculated free water content. In another formulation, swelling is the property to absorb water and retain it for a relative long time. It can be estimated by measuring the dry weight and the swollen state weight and calculating either a ponderal variation (water uptake) or a volume of adsorbed solvent (both the quantities are considered as percentages).

W U swollen weight- dry weigh/dry weight = ×100

V A S swollen weight- dry weigh/ water density = ×100

3.3 Mechanical properties[15]

The mechanical properties can fluctuate and be altered depending on the nature of the material. It is achievable to acquire a gel with superior stiffness by increasing the crosslinking degree or lowering it by heating the material. The alterations in mechanical properties relate to a wide variety of variables. For instance, white gelatine shows a conspicuous increase in Young Modulus through crosslinking, silk fibroin has a very high Young Modulus, but after the regeneration it will decrease. These properties can be assessed by a Dynamic Mechanical Analysis (DMA) device or a rheometer, as stated by the thousands of techniques available on the market that will be no further. It's prominent to note that in a hydrogel, the Young Modulus is the outcome of the union between water and gel matrix. If we have to seeds osteoblast cells, we will require a more rigid material than if we culture adipocyte, the same logic is valid for the advancement of a heterogeneous prosthetic device, e.g. substitute for the intervertebral disc.

3.4 Porosity and permeation

Pores may be created in hydrogels by the process of phase separation in the course of synthesis or they may present as smaller pores within the network. The average pore size, the pore size distribution and the pore interconnections are essential factors of a hydrogel matrix that are often challenging to compute and are generally included together in the parameter called tortuosity. The effective diffusion path length across a HG film barrier is evaluated by the film thickness times the ratio of the pore volume fraction divided by the tortuosity. These aspects, in turn, are most affected by the composition and crosslink density of the hydrogel polymer network. Labelled molecular probes of a range of molecular weights (MWs) or molecular sizes are used to probe pore sizes in hydrogels. Pore-size distributions of hydrogels are effectively influenced by three factors:

1. Concentration of the chemical cross-links of the polymer strands. That concentration is calculated by the initial ratio of cross-linker to monomer.
2. Concentration of the physical entanglements of the polymer strands. That concentration is ascertained by the initial concentration of all polymerizable monomers in the aqueous solution
3. Net charge of the polyelectrolyte hydrogel. That charge is determined by the initial concentration of the cationic and/or anionic monomer.

These three factors can be calculated by using the composition of the hydrogel, that is, by the nominal concentrations of monomer and cross-linker.

%T =weight of monomer+ weight of x - crosslinker/total volume

%C weight of x- crosslinker /weight of monomer+ weight of x- crosslinker

The porous structure of a hydrogel is also influenced by the properties of the surrounding solution, principally by dissolved ionic solutes and by dissolved uncharged solutes which separate unevenly between the gel phase and the solution phase (Osmotic effects). For realistic design of hydrogels, it is advantageous to know the pore-

size distribution which depends on the hydrogel characterization usually expressed by %C and %T. Most procedures used to evaluate the porosity of hydrogels are restricted because they necessitate the pore solvent and/or temperature to be altered, which cause the gel to shrink, swell or require mathematical manipulation and postulation, which may set up unwanted artifacts. Porosity is a morphological characteristic of a material that can be illustrated as the presence of void cavity inside the bulk. It is worthwhile to control the porosity in many devices for a wide range of applications, such as optimal cell migration in hydrogel-based scaffolds or tunable lode/release of macromolecules.

Porosity %=V /V +V ×100

3.5 Biocompatible properties

It is imperative for the hydrogels to be biocompatible and nontoxic so as to make it pertinent in biomedical field. Most polymers used for this purpose must pass cytotoxicity and in vivo toxicity tests. Biocompatibility is the capability of a material to function with an appropriate host response in a specific application. Biocompatibility analysis consists of two parameters namely biosafety and bio functionality:

(a) Biosafety i.e. adequate host response not only systemic but also local as well (i.e. surrounding tissue), the absence of cytotoxicity, mutagenesis, and/or carcinogenesis.
(b) Bio functionality i.e., the capacity of material to perform the specific task for which it is intended.

This explanation is exceptionally applicable in tissue engineering since the nature of tissue construct is to constantly interact with the body through the healing and cellular regeneration process as well as during scaffold degradation. Moreover, initiators, organic solvents, stabilizers, emulsifiers, unreacted monomers and crosslinkers utilized in polymerization and hydrogel synthesis may be toxic to host cells if they ooze out to tissues or encapsulated cells. To eradicate harmful chemicals from preformed gels, certain purification processes should be implemented such as solvent washing or dialysis.

3.6 Crosslinking[2]

Crosslinking cannot be suitably defined as a property of hydrogels, while it is more of a cause of all the other properties of the material itself. The extent of the crosslinking can differ a lot. Certainly, the hydrogel's network can be attained by many ways. The processes can be categorized into two big categories: first one is the physical crosslinking that occurs by hydrophobic interactions between chains, ionic interactions between a polyanion and a polycation (complex coacervation) or ionic interactions between a polyanion and multivalent cations (ionotropic hydrogel). The second category includes the chemical bound gels. The crosslinking can take place by ultraviolet irradiation, heating or chemical crosslinking via crosslinker with a huge collaborative reaction, such as Michael's reaction, Michaelis-Arbuzov reaction, nucleophile addition and so on. By regulating the degree of crosslinking, it is feasible to modify the property of the material and optimize it for many kinds of applications, in this way, a wide spectrum of applications starts from the same original polymer.

4. Ideal Characteristics of A Hydrogel Material

- The highest absorption capacity (maximum equilibrium swelling) in saline.
- Preferred rate of absorption (preferred particle size and porosity) depending on the application necessity.
- The topmost absorbency under load (AUL).
- The lowermost soluble content and residual monomer.
- The lowest price.
- The utmost robustness and steadiness in the swelling environment as well as during the storage.
- The highest biodegradability without formation of toxic species following the degradation.
- pH-neutrality after swelling in water
- Colourlessness, odorlessness and absolutely nontoxic
- Photo stability
- Re-wetting competency (if required) the hydrogel must be able to give back the imbibed solution or to maintain it; dependent on the application requisite (e.g., in agricultural or hygienic applications).

Practically, it is unachievable that a hydrogel sample would concurrently fulfil all the above described required features. The synthetic components for acquiring the maximum level of some of these features will lead to inadequacy of the rest. Thus, in practice the production reaction variables must be adjusted such that an applicable balance between the properties is can be attained. For instance, a hygienic product of hydrogels must retain the topmost absorption rate, the lowest re-wetting and the lowermost residual monomer and the hydrogels employed in drug delivery must be porous and be responsive to either pH or temperature.

5. Advantages of Hydrogel

- Hydrogel possess a degree of flexibility very similar to natural tissue, due their significant water content
- Entrapment of microbial cells within hydrogel beads has the advantage of low toxicity
- Environmentally sensitive 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
- Timed release of growth factor and other nutrients to ensure proper tissue growth
- Hydrogel have good transport properties
- Hydrogel is biocompatible
- Hydrogel can be injected
- Hydrogel are easy to modify

6. Disadvantages of Hydrogel

- Hydrogels are expensive
- Hydrogel causes sensation felt by movement of the maggots
- The surgical risk associated with the device implantation and retrieval
- Hydrogels are non-adherent; they may need to be secured by a secondary dressing
- Hydrogels used as contact lenses causes lens deposition, hypoxia, dehydration and red eye reaction
- Hydrogels have low mechanical strength
- Difficulty in handling
- Difficulty in loading

7. Application of Hydrogel[16]

7.1 Drug delivery

Controlled drug delivery systems (DDS), which are used to deliver drugs at certain rates for predefined periods of time, have been used to overcome the limitations of regular drug formulations. The marvelous properties of hydrogels make them a great choice in drug delivery applications. The hydrogel structures with high porosity can be obtained by control- ling two factors: the degree of cross-linking in the matrix and the affinity of hydrogel to the aqueous environment in which swelling occurs. Due to the porous structures, hydrogels are highly permeable to different kinds of drugs and thus drugs can be loaded and, in proper conditions, released.[7] The possibility of releasing pharmaceuticals for long periods of time (sustained release) is the main advantage obtained from hydrogels in drug delivery investigations, which results in supplying a high concentration of an active pharmaceutical substance to a specific location over a long period of time. Both physical (electrostatic interactions) and chemical (covalent bonding) strategies can be employed to enhance the binding between a loaded drug and the hydrogel matrix to extend the duration of drug release. Hydrogels can store and protect various drugs from hostile environments and release them at a desired kinetics of the release. Drug release can be 20 Emerging Concepts in Analysis and Applications of Hydrogels activated on demand by local changes in pH, temperature, the presence of specific enzymes, or by remote physical stimuli.

7.2 pH-sensitive Hydrogels in DDS

Since the pH change occurs at many specific or pathological body sites, it is one of the important environmental parameters for DDS. The human body exhibits variations of pH along the gastrointestinal tract and also in some specific areas such as certain tissues (and tumoral areas) and subcellular compartments. Both acidic and basic polymers are employed in pH-sensitive DDS. PAA, PMAA, poly (L-glutamic acid), and polymers containing sulfonamide are the most commonly used acidic polymers for drug delivery. Typical examples of the basic polyelectrolytes include poly(2-(dimethylamino) ethyl methacrylate) and poly(2-(diethylamino) ethyl methacrylate), poly(2-vinylpyridine), and biodegradable poly (β-amino ester). pH-sensitive hydrogels were also used for extraction and determination purposes by different methodologies.[7,8]

7.3 **Temperature-sensitive Hydrogels in DDS**

Thermosensitive polymers, like pH-responsive systems, offer many possibilities in biomedicine. Among many temperature-sensitive polymers, poly(N-isopropylacrylamide) (PNIPAAm) and poly (N, N-diethylacrylamide) (PDEAAm) find many applications. PDEAAm has a low value of LCST (a critical temperature below which the components of a solution with any composition are miscible) in the range of 25–32°C, which is near to normal body temperature.

7.4 Dyes and heavy metal ions removal

Heavy metal pollution is commonly found in wastewater of many industrial processes and has been known to cause severe threats to the public health and ecological systems. The removal of heavy metal ions from various water resources is of great scientific and practical interest. Synthetic cross-linked polyacrylate hydrogels have been used to remove heavy metal toxicity from aqueous media. However, application of these synthetic materials on large scales may not be a practical solution because they are very costly. The pollution caused by heavy metal ions can be removed by well-known adsorption processes which, alongside flexibility in design and operation, offer the advantage of reusing the treated effluent. Also because of general reversibility of adsorption process, it is usually possible to regenerate the adsorbent to make the process most cost-effective. The use of hydrogels as adsorbents for the removal of heavy metals, recovery of dyes, and removal of toxic components from various effluents has been studied. Adsorbents with carboxyl, sulfonic, phosphonic, and nitrogen groups on their surface favour metal ion adsorption.

7.5 Contact lenses

A key area in the use of synthetic hydrogels for bio applications is ophthalmology, especially contact lenses. A contact lens is a small optical device placed directly on the cornea to alter the corneal power. The first concept of using contact lenses was described by Leonardo da Vinci in 1508; this consisted of immersing the eye in a bowl of water. At the end of 1960, poly (2- hydroxyethyl methacrylate) (PHEMA) lenses were developed by Professor Otto Wichterle. This invention represents the most important step in contact lens development and the start of soft lenses' era. Direct placing of contact lenses on the surface of cornea prevents the exchange of atmospheric oxygen and thus disturbs the natural physiological metabolism of the cornea known as hypoxic stress, so a good contact lens must have maximum oxygen permeability. Mechanical stress to the cornea produces the same problems as the hypoxic stress, such as mitosis of the epithelial cells, elevated activity in protease and glycosidase, corneal sensitivity, and changes in corneal hydration and transparency. To

reduce these stresses, the proper choice of contact materials and their shape are necessary.

7.6 Injectable hydrogel for spinal cord regeneration

Spinal cord injury (SCI) is a complex regenerative problem because of the multiple facets of growth inhibition that occur following trauma to the cord tissue. Many of these injuries do not hurt the dura mater and some of the axons are yet alive in the injury site and can be recovered. In such conditions, inserting a preformed frame or DDS into the damaged spinal cord by surgical operations may cause subsequent lesion. One alternative for this method is the use of in situ-forming scaffolds. What happens after injection into the injured cord area is the fast conversion of viscoelastic hydrogel from liquid form to gel and adaptation to the tissue of injury site. The small spaces between spinal cord tissue and even transacted parts formed after SCI will be filled by in vivo conversion of liquid hydrogel to the gel form. The gel, which now serves as a scaffold, will eliminate vacant spaces and forms a template for regeneration of the injured cord tissue by helping cellular penetration and matrix. In this way, it is not necessary to create preformed scaffolds for each patient individually and disconnecting viable tissue at the injury site to implant the preformed scaffold, which can cause further damage and loss of functionality will be avoided.

8. Evaluation of Hydrogel[11,12]

The formulated gels were examined for their physical properties, rheological properties. Skin irritation test was carried out only on all formulations.

8.1 Physical appearance: The physical appearance and homogeneity of the prepared gels were tested by visual observations. The marketed formulation was considered as reference.

8.2 Grittiness Presence of any particulate matter in the formulations was observed microscopically.

8.3 pH measurement

The pH of gel formulation was determined by using digital pH meter. 1gram of gel was dissolved in 100 ml distilled water and stored for two hours. The measurement of pH of each formulation is done in triplicate and average values are calculated and reported.

8.4 Spredability

Concentric circles of different radius were drawn on graph paper and a glass plate were fixed onto it. 5gms of gel was placed on the centre of the lower plate. Another glass plate of 100±5 gm was placed gently on the gel and the spread diameter was recorded after 1 minute of each addition.

8.5 Extrudability

The gel formulations were filled in collapsible tubes. After being set in the containers, the extrudability of gel formulations was determined in terms of weight required in grams to extrude 0.5 cm ribbon of gel in 10 sec.

8.6 Drug content

1 g gel was dissolved in 100 ml of phosphate buffer pH 5.8. Suitable dilutions were made using phosphate buffer pH 5.8. Absorbance was measured at 282 λ max nm using UV spectrophotometer.

8.7 In-vitro drug diffusion study

In-vitro drug release studies were carried out using Franz diffusion cell. 0.5 g of gel was applied on cellophane membrane as donor compartment. Phosphate buffer pH 5.8 was placed in the receptor compartment as the dissolution medium. The whole assembly was place on magnetic stirrer with thermostat maintained at 37o c. samples were collected regular time interval and sink conditions were maintained by replacing with new buffer solution. Collected samples are analyzed at 282 λ max nm using UV spectrophotometer**.**

8.8 Skin irritation test

Skin irritation test was conducted on 10 healthy male and female volunteers. 100 mg of gel was applied on area of 2 cm and observed for any lesions or irritation/redness.

9. CONCLUSION

Recent development in the field of polymer science and technology has led to the development of various stimuli sensitive hydrogel like pH, temperature sensitive hydrogel. A new way to create hydrogels has been developed by immobilizing different proteins at the same time. Hydrogel with novel properties will continue to play important role in drug delivery. New synthetic methods have been used to prepare homo-and co-polymeric hydrogels for a wide range of drug, peptides, and protein delivery applications. Hydrogels are also used in regenerating human tissue cells.

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