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Hydrogels: a smart drug delivery device

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ABSTRACT

Among various investigations hydrogels have attracted much attention Hydrogels are three-dimensional, hydrophilic, polymeric networks capable of imbibing large amounts of water or biological fluid and swell. When swelled, they are soft & rubbery and resemble the living tissue. The various preparation techniques adopted are physical cross-linking, chemical cross-linking, grafting polymerization, and radiation cross-linking for the preparation of hydrogels. These biomaterials have gained attention owing to their peculiar characteristics like swelling in aqueous medium, pH and temperature sensitivity or sensitivity towards other stimuli. Hydrogels being biocompatible materials have been recognized to function as drug protectors, especially for peptides and proteins, from in-vivo environment. Also, these swollen polymers are helpful as targetable carriers for bioactive drugs with tissue specificity. Generally hydrogels are characterized for their morphology, swelling property, chemical structure and rheology. Morphological studies performed by using scanning electron microscopy (SEM) give us information about porous structure of hydrogels. Swelling determines the release mechanisms of the drug from the swollen polymeric mass while rheology give information about hydrogels.The hydrogels have been used extensively in various biomedical applications, viz. drug delivery, cell carriers and/or entrapment, wound management and tissue engineering. This article has been devoted to study the common methods of preparation, characterization, and application of hydrogels.

Keywords: Hydrogels, Swelling, Polymerization, Drug delivery; Tissue engineering, Characterization

Introduction

Now a day ongoing research in advanced drug delivery formulations to provide stable and economical drug delivery systems, the focus is on hydrogels which are known to reduce the problems of both conventional dosage forms and novel drug delivery systems which require a biocompatible, convenient and stable drug delivery system for molecules as small as NSAIDs (Non-steroidal anti-inflammatory drugs) or as large as proteins and peptides [1-3]. Hydrogels have been widely used as a drug carrier due to its ease in manufacturing and self application. The production of a large and constant surface area is one of the major merits for them to be widely used for clinical and fundamental applications.

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Various combinations of polymers are made into hydrogels formulations to investigate their potential as a drug delivery system. The combination of natural and synthetic polymers may provide mechanical stability and biological acceptability, acquiring from synergistic properties of both materials. The hydrogels were found stable and resilient [4-5].Recently hydrogels have gained considerable attention. Hydrogels are enough to respond the fluctuations of environmental stimuli (pH, temp, ionic strength, electric field, presence of enzyme etc.) and swell or shrink accordingly. In the swollen state, they are soft and rubbery, resembling the living tissue exhibiting excellent biocompatibility [6-7]. Hence these biomaterials are widely used in different field of pharmaceutical and biomedical engineering[7-8].With the establishment of the first synthetic Hydrogels by Wichterle and Lim in 1954[9-10], the hydrogel technologies may be applied to food additives[11],pharmaceuticals[12],biomedicalimplants[13], tissue engineering and regenerative medicines[14],diagnostics[15], cellular immobility[16],

separation of biomolecules or cells[17]and barrier materials to regulate biological adhesions[18], Biosensor and Biomembrane devices and drug carriers[19].It was in 1955 that Professors Lim and Wichterle of Prague, Czech Republic, synthesized the first hydrogel with potential biomedical uses. That was synthetic poly-2-hydroxyethyl methacrylate, used soon after its discovery in contact lens production. Hydrogel can be defined as a three-dimensional, hydrophilic, cross-linked polymeric network which has the capacity to hold water within its porous structure. Hydrogels may be chemically stable or they may degrade and eventually disintegrate and dissolve. They are called 'reversible' or 'physical' gels when the networks are held together by molecular entanglements [20-21]. The water holding capacity of the hydrogels arise mainly due to the presence of hydrophilic groups, viz. amino, carboxyl and hydroxyl groups, in the polymer chains. According to Hoffmann, the amount of water present in a hydrogel may vary from 10% to thousands of times of the weight of the xerogel [10]. A xerogel may be defined as a polymeric network devoid of water. The water holding capacity of a xerogel is dependent on the number of the hydrophilic groups and cross linking density. Higher the number of the hydrophilic groups, higher is the water holding capacity while with an increase in the cross linking density there is a decrease in the equilibrium swelling due to the decrease in the hydrophilic groups [21].

Advantages of Hydrogels

- They possess a degree of flexibility very similar to natural tissue due to their significant water content.
- Timed release of medicines or nutrients.
- They are biocompatible, biodegradable and can be injected.
- Hydrogels also possess good transport properties and easy to modify.
- 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 [22, 23].

Disadvantages of Hydrogels

- High cost.
- Low mechanical strength.
- Can be hard to handle.
- Difficult to load with drugs/nutrients.
- They are non-adherent and may need to be secured by secondary dressing and also cause sensation felt by movement of the maggots [9, 27].

Hydrogels as compared to gels

One of the common misconceptions in polymer science is the use of the concept "gel" instead of "hydrogel" and vice versa. The gels are semi-solid materials made of hydrophilic polymeric systems comprising small amounts of solids, dispersed in relatively large amounts of liquid. However, gels may appear more solid-like than liquid-like [24] .The hydrogels are also made of hydrophilic polymer strands but they are cross linked and that enables them to swell while retaining their three-dimensional structure [25]. However, gels can also get a low level of virtual cross linking under the influence of shear forces, but this kind of cross linking is very weak and reversible [26] The distinct behavior of gels and hydrogels in aqueous environment are shown in fig 1.

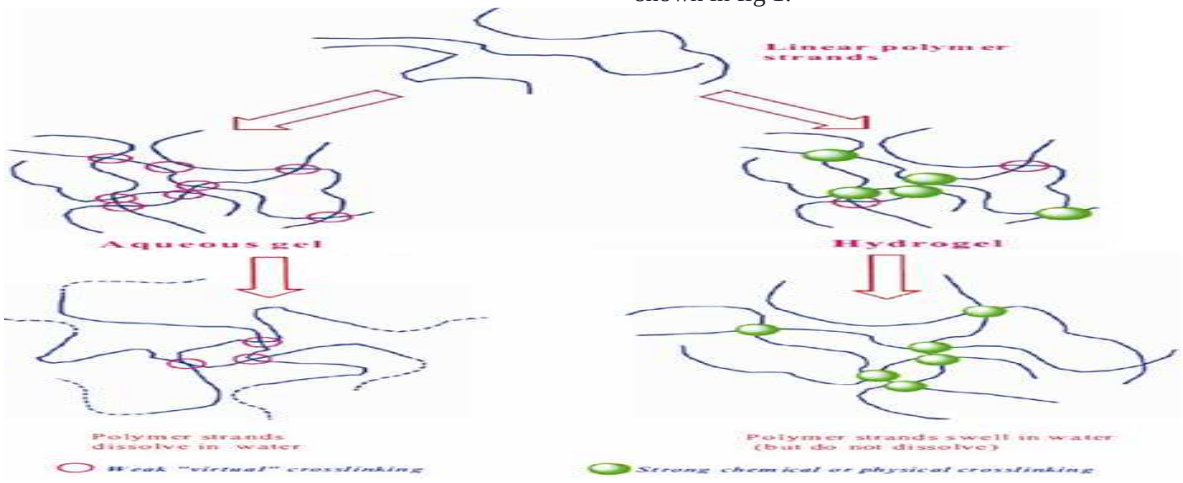

Fig.1: The distinct behaviors of gels and hydrogels in aqueous environment [26]

Mechanism of network formation

In gelation linking of macromolecular chains together this initially leads to progressively larger branched yet soluble polymers depending on the structure and conformation of the starting material. The mixture of such polydisperse soluble branched polymer is called 'sol'. Continuation of the linking process results in increasing the size of the branched polymer with decreasing solubility. This 'infinite polymer' is called the 'gel' or 'network' and is permeated with finite branched polymers. The transition from a system with finite branched polymer to infinite molecules is called 'sol-gel transition' (or 'gelation') and the critical point where gel first appears is called the 'gel point'. Different types of gelation mechanism are summarized in Figure 2. Gelation can take place either by physical linking (physical gelation) or by chemical linking (chemical gelation). Physical gels can be sub categorized as strong physical gels and weak gels. Strong physical gel has strong physical bonds between polymer chains and is effectively permanent at a given set of experimental conditions. Hence, strong physical gels are analogous to Chemical gels. Examples of strong physical bonds are lamellar microcrystals, glassy nodules or double and triple helices. Weak physical gels have reversible links formed from temporary associations between chains. These associations have finite lifetimes, breaking and reforming continuously. Examples of weak physical bonds are hydrogen bond, block copolymer micelles, and ionic associations. On the other hand, chemical gelation involves formation of covalent bonds and always results in a strong gel. The three main chemical gelation processes include condensation, vulcanization, and addition polymerization [27, 28].

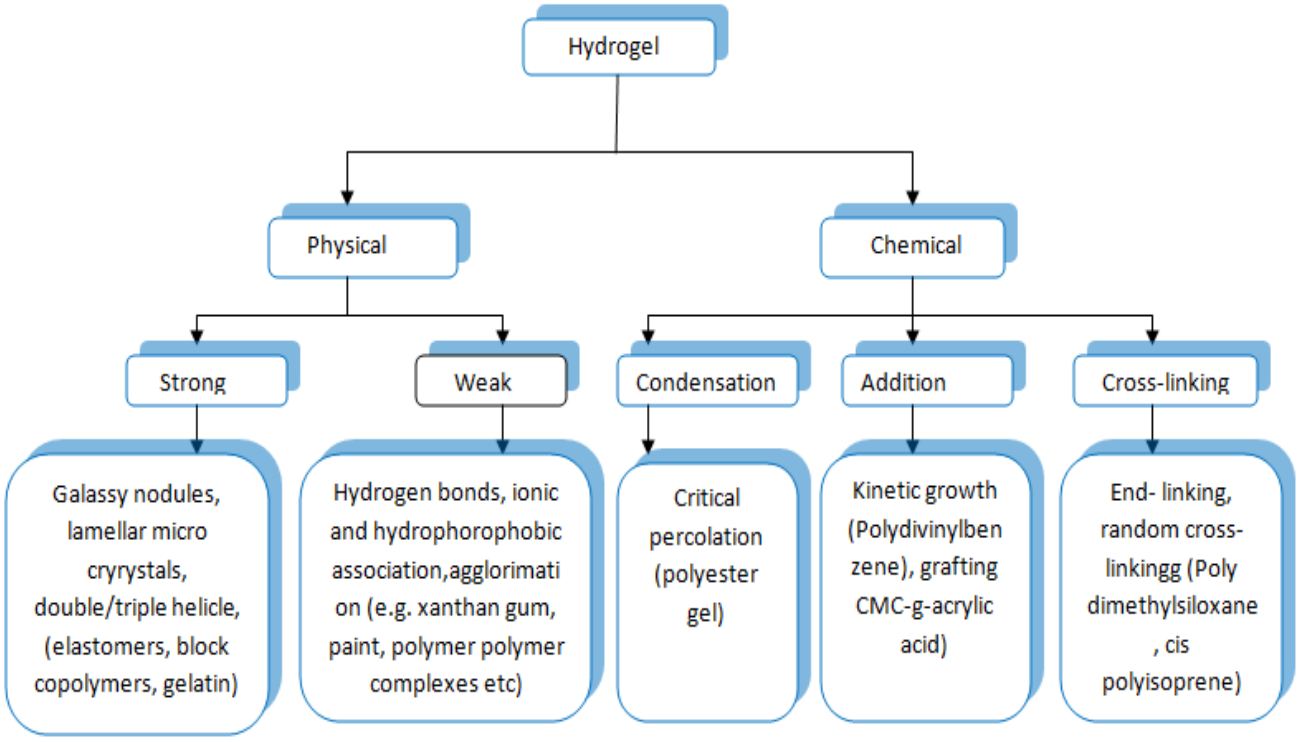

Fig.2: Classification of gelation mechanism and relevant examples

Classification of hydrogels

Hydrogels can be classified in six categories:

- According to origin
- According to the method of preparation
- According to ionic charge
- According to the biodegradability
- According to the method of crosslinking
- According to physical properties.

According to origin

Based on the polymer origin, hydrogels can be classified into three major types:

Natural hydrogels

Natural hydrogels are biocompatibility, biodegradability, and good cell adhesion properties. Proteins such as collagen, gelatin and, lysozyme (LYZ) and polysaccharides such as hyaluronic acid (HA), alginate and Chitosan (Cts) are two major types of natural polymers which are used to produce natural hydrogels, However, the use of natural hydrogels is often restricted because their mechanical and degradation properties are less controllable [29].

Synthetic hydrogels

Synthetic hydrogels get more attention as compare to natural hydrogels because they can be engineered to have a much wider range of mechanical and chemical properties than their natural counterparts. As an example, poly (ethylene glycol) (PEG) based hydrogels are oneclass of the widely used material in biomedical application due to their non-toxicity there compatibility and low immunogenicity [30].

Hybrid hydrogels

Hybrid hydrogels are usually referred to as combination of natural and synthetic polymer hydrogels.An extreme example might be synthetic polymers and biological macromolecules, although many totally synthetic and natural hybrid gels exist. To combine the advantages of both synthetic and natural hydrogels many naturally occurring biopolymers such as Chitosan, dextran, collagen, have been combined with synthetic polymers such as poly (*N*-isopropyl acrylamide) and polyvinyl alcohol[31]. Zhang *et al*.prepared a biodegradable hybrid hydrogel with a combination of a hydrophilic dextran derivative of allylisocyanate and hydrophobic polylactidediacrylatemacromer. Temperature sensitive hybrid hydrogels can be obtained by combining natural polymers with PNIPAm [29, 32] Combinations of polyacrylic acid with natural polymers led to pH sensitive hydrogels [33].

According to the method of preparation

Homopolymers

Homopolymeric hydrogels are referred to polymer network derived from a single species of monomer, which is a basic structural unit comprising of any polymer network.Homopolymers may have cross-linked skeletal structure depending on the nature of the monomer and polymerization technique[34].

Copolymers

Copolymeric hydrogels are comprised of two or more different monomer species with at least one hydrophilic component, arranged in a random, block or alternating configuration along the chain of the polymer network. The properties of copolymer hydrogels depend upon the varied combination of polymeric units and respective arrangements of these polymeric networks [35].

Interpenetrating polymer network hydrogels

Interpenetrating polymeric hydrogels are produced when one polymeric network swells in the network of another polymer and cannot separate due to physical entanglements[36,37]. IPNs are defined as intimate combination of two polymers, in which at least one is synthesized or cross linkedin the immediate presence of the other [38]. This is prepared by immersing a pre-polymerized hydrogel into a solution of monomers and a polymerization initiator. IPN method has advantage becauseit can overcome thermodynamic incompatibility occurs due to the permanent interlocking of network segments and limited phase separation can be obtained with it. The interlocked structure of the cross linked IPN components are believed to ensure stability of the bulk and surface morphology [39].The main advantages of IPNs is that relatively dense hydrogel matrices can be produced which has tougher mechanical properties, controllable physical properties and more efficient drug loading compared to conventional hydrogels. IPN pore sizes can also be controlled to tune the drug release kinetics, interaction between the hydrogel and the surrounding tissues along with its mechanical properties [40].

According to ionic charge

Hydrogels may be categorized into four groups on the basis of the presence or absenceof electrical charge located on the cross linked chains.

Non-ionic hydrogels

Non-ionic hydrogels such as agarose and dextran which have neutral monomeric units which cross linked to form three dimensional networks [41, 42].

Ionic hydrogels

Ionic hydrogel swelling is dependent on the pH of the aqueous medium, which determines the degree of dissociation of the ionic chains [43].Cationic hydrogels, such as. Chitosan, display superior swelling in acidic media and anionic hydrogels such as pectin andalginicacid swell more at higher pH [44].

Ampholytic Hydrogels

Ampholytic hydrogels such as collagen, gelatin and carboxymethyl chitin possess both positive and negative charges, thus they allow a considerable spectrum for manipulating the swelling of their hydrogels[45-46].

According to the biodegradability

Biodegradable hydrogels

Most important property of Hydrogels is its biodegradability.Many polymers created by nature are biodegradable, such as Chitosan, fibrin and agar [47].Polyanhydrides, poly (aldehyde guluronate) and poly (*N*-isopropyl acrylamide) are examples of synthetic biodegradable polymers [48].

Non-biodegradable hydrogels

Non-biodegradable hydrogels have been extensively used for engineering bone and cartilage [49]. Variousvinylated monomers or macromerssuch as methoxyl poly (ethylene glycol) (MPEG), 2-hydroxyethylmethacrylate (HEMA), 2-hydroxypropylmethacrylate (HPMA) and acryl amide (AAm) are widely applied in the preparation of non-biodegradable hydrogels [50].

According to method of crosslinking

Hydrogels can be divided into two categories based on the chemical or physical nature of the cross-linked junctions.

Physically cross linked hydrogels

Physically cross linked hydrogels are held together by molecular entanglements, and/or secondary forces including ionic interactions, hydrogen bonding or hydrophobic interactions [51]. Many of the reconstituted biological proteins and polysaccharide hydrogels are assembled in this way [52].

Chemically cross linked hydrogels

In chemically cross linked hydrogels a cross linking agent is use to cross link the polymer. E.g. glutaraldehyde. The mechanical strength of physically cross linked hydrogels is generally low Traditional methods for the synthesis of covalently cross linked hydrogels include cross linking copolymerization, cross linking of reactive polymer precursors, and cross linkingvia polymer-polymer reactions [53].

According to physical properties

Conventional hydrogels

Conventional hydrogels are defined as hydrogels that do not show significant sensitivity to environmental changes.Examples of conventional hydrogels include HEMA and polyethyleneglycol methacrylate (PEGMA) based gels.

Stimuli responsive hydrogels "Smart hydrogels"

Stimuli responsive hydrogels are defined as polymer networks able to respond to small environmental changes resulting in abrupt changes in their swelling behavior, network structure, permeability and/or mechanical strength, [33, 54].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[55].

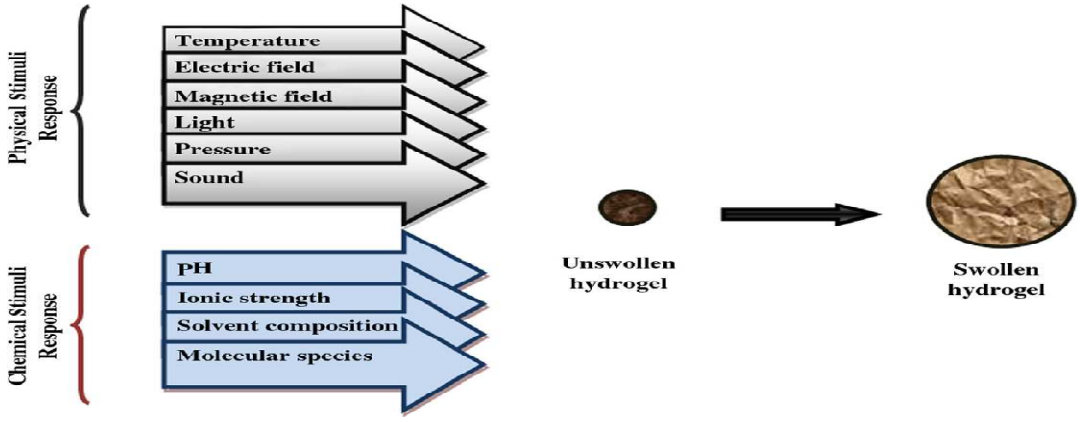

Fig.3:Stimuli response swelling hydrogels [55]

Method for preparation of hydrogels

Cross-linked networks of natural biopolymers such as alginate, chitosan, carrageenan, hyaluronan and carboxymethyl cellulose (CMC) and synthetic polymers such as polyethylene oxide (PEO), polyvinyl pyrollidone (PVP), polylactic acid (PLA), polyacrylic acid (PAA), polymethacrylate (PMA) and polyethylene glycol (PEG) have been reported. The various preparation techniques adopted are free radical polymerization physical cross-linking, chemical cross-linking, grafting polymerization and radiation cross-linking for the preparation of hydrogels.

Free radical polymerization

Free radical polymerization is the preferred method for the preparation of hydrogels based on some monomers such as acrylates, vinyl lactams and amides [56, 57]. 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 [58,59].This method involves the chemistry of typical free-radical polymerizations, which includes initiation, propagation, chain transfer, and termination steps. In the initiation step a wide variety of thermal, visible, ultraviolet, and redox initiators can be utilized for the radical generation. Then the radicals react with the monomers converting them into active forms. These active monomers react with more monomers and so on in the propagation step. The resulting long chain radicals undergo termination either through chain transfer or through radical combination forming a polymeric matrix. Free radical polymerization reactions can take place neither in solution or bulk. Solution polymerizations are favored during the synthesis of large quantities of hydrogels. In this method, water is the most common solvent. However, a wide variety of other polar solvents can be used provided that they can be exchanged by water in the hydration step. Bulk polymerizations are very fast and have the advantage over solution polymerizations, as there is no need for solvent removal. This removal of solvent is time-consuming in many cases. Hydrogels can be prepared also via free radical emulsion and suspension polymerizations. Free radical polymerization method is the superior one for the preparation of the hydrogels in the form of beads and microspheres. Thereby, this way is extremely good for developing hydrogels used as matrices for drug delivery purposes. In this method, a predetermined amount of a suspension agent and/or emulsifier is placed together with the monomer, the solvent, and the initiator. The procedure of the free radical emulsion and suspension polymerization is quite simple [60].

Physical cross-linking

Cross linking of polymers through physical interactions is one of the most common and easy routes for hydrogel formation. This physical cross linking includes interact ions such as polyelectrolytecomplexation, hydrogen bonding and hydrophobic association. There has been an increased interest in physical or reversible gels due to relative ease of production and the advantage of not using cross-linking agents [61]. The various methods reported in literature to obtain physically cross-linked hydrogels are:-

Heating/cooling a polymer solution

Physically cross-linked gels are formed when cooling hot solutions of gelatin or carrageenan. The gel formation is due to helix-formation, association of the helices, and forming junction zones. Carrageenan in hot solution above the melting transition temperature is present as random coil conformation. Upon cooling it transforms to rigid helical rods. In some cases, hydrogel can also be obtained by simply warming the polymer solutions that causes the block copolymerization. Some of the examples are polyethylene oxide-polypropylene oxide, polyethylene glycol-polylactic acid hydrogel[5].

Ionic interaction

Additionof di- or tri-valentcounterions in ionic polymer leads to cross linking between polymers. This method underlies the principle of gellingpolyelectrolyte solution (e.g. Na+ alginate-) with a multivalent ion of opposite charges (e.g. Ca2+ + 2Cl-). Some other examples are chitosan-polylysine, chitosan-glycerol phosphate salt, chitosan-dextran hydrogels [5,61].

Complex coacervation

In this method mixing ofpolyanion with a polycation polymer takes place which lead to formation of complex coacervate gels. The underlying principle of this method is that polymers with opposite charges stick together and form soluble and insoluble complexes depending on the concentration and pH of the respective solutions (Figure 4). One such example is coacervatingpolyanionic xanthan with polycationic chitosan. Proteins below its isoelectric point are positively charged and likely to associate with anionic

hydrocolloids and form polyion complex hydrogel (complex coacervate) [5].

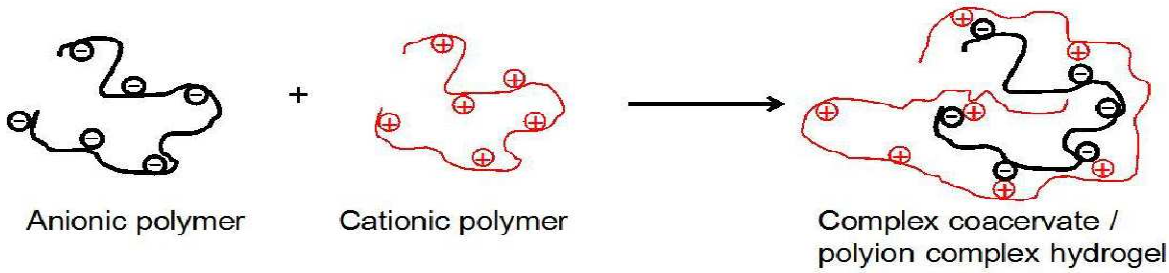

Fig.4:Complex coacervation between a polyanion and a polycation

Hydrogen Bonding

Hydrogen bonding between macromolecular chains can also participate in the hydrogel formations. A hydrogen bond is formed through the association of electron deficient hydrogen atom and a functional group of high electron density. Simillar to the polyelectrolyte complexes described earlier, hydrogen-bonded polymeric hydrogels occur in many biological systems. Example, a hydrogel can result from hydrogen bond formation between PA and PNVP. This hydrogel is affected by a variety of factors, such as polymer concentration, the molar ratio of each polymer, the type of solvent, the solution temperature, and the polymer structure (degree of ass[62].

Freeze-thawing

Freeze thawing cycle can be used to form hydrogels by physically cross linking of polymer.
Microcrystals are form at the end of the cycle. With freeze thawing method, the hydrogels so formed have sufficient mechanical strength and stability a little swelling capacity[3].

Chemical cross-linking

In Chemical cross-linking process use of a cross-linking agent to link two polymer chains and grafting of monomers on the backbone of the polymers takes place.The cross-linking of natural and synthetic polymers can be achieved through the reaction of their functional groups (such as OH, COOH, and NH2) with cross-linkers such as aldehyde (e.g. glutaraldehyde, adipic acid dihydrazide). There are a number of methods reported in literature to obtain chemically cross-linked permanent hydrogels. Among other chemical cross-linking methods, IPN (polymerize a monomer within another solid polymer to form interpenetrating network structure) and hydrophobic interactions (incorporating a polar hydrophilic group by hydrolysis or oxidation followed by covalent cross-linking) are also used to obtain chemically cross-linked permanent hydrogels. The following section reviews the major chemical methods (i.e. cross-linker, grafting, and radiation in solid and/or aqueous state) used to produce hydrogels from a range of natural polymers [63].

Chemical cross-linkers

Since hydrogels are the polymers which swell in presence of water and they entrap drug within their pores; therefore, to impart sufficient mechanical strength to these polymers, cross linkers are incorporated like glutaraldehyde, calcium chloride and oxidized konjac glucomannan (DAK). These cross linkers prevent burst release of the medicaments. The technique mainly involves the introduction of new molecules between the polymeric chains to produce cross-linked chains Hydrogels of gelatin has been prepared with DAK. Some researchers have *reported in situ* hydrogel formation by incorporating lactose along with sodium azide that results in formation of azide groups along with amino groups in polymers like chitosan and thus a photocross linkable chitosan is formed which has desired integrity [3].

Grafting

Grafting involves the polymerization of a monomer on the backbone of a preformed polymer. The polymer chains are activated by the action of chemical reagents, or high energy radiation treatment. The growth of functional monomers on activated macroradicals leads to branching and further to cross-linking.

Characterization of Hydrogels

Generally hydrogels are characterized for their morphology, swelling property,chemical structure and

elasticity. Morphological study gives us information about porous structure of hydrogels. Swelling determines the release mechanisms of the drug from the swollen polymeric mass while elasticity affects the mechanical strength of the network and determines the stability of these drug carriers[3]. Some of the important features for characterization of hydrogels are as follows.

Scanning Electron Microscopy (SEM)

SEM can be used to provide information about the sample's surface topography, composition, and other properties such as electrical conductivity. Magnification in SEM can be controlled over a range of up to 6 orders of magnitude from about 10 to 500,000 times. This is a powerful technique widely used to capture the characteristic 'network' structure in hydrogels [64, 65].SEM images of polyacrylamide and chitosan based Super porous hybrid hydrogels are shown below. The integrated pore structure with interconnected channels was observed in SEM images of ethanol dehydrated-oven dried batches. Non-uniformity in pores with distorted capillary network was observed freeze dried batches [66, 67].

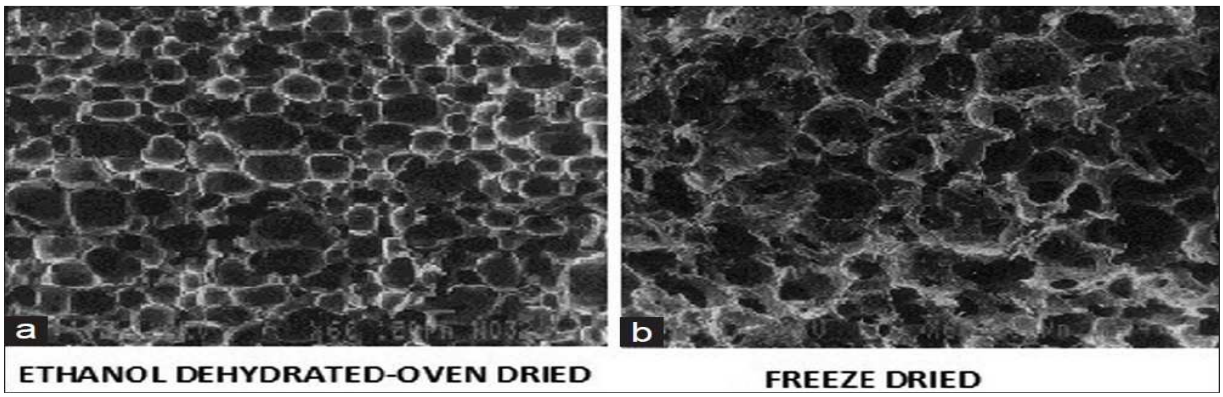

Fig.5:Scanning electron micrographs of (a) ethanol dehydrated-oven dried superporous hybrid hydrogels; (b) freeze dried SPHH [68]

Fourier Transform Infrared Spectroscopy

FTIR (Fourier Transform Infrared Spectroscopy) is a useful technique for identifying chemical structure of a substance. It is based on the principle that the basic components of a substance, i.e. chemical bonds, usually can be excited and absorb infrared light at frequencies that are typical of the types of the chemical bonds.Thoroughly ground IPN samples are mixed with dried KBr and discs are be prepared by compression under vacuum. Spectra are recorded with a resolution of 1 cm-1. It is an easy way to identify the presence of certain functional groups in a molecule [69].

Swelling measurement

There are present three different methodsby which we can measure swelling in hydrogels:-

Method A

In this method the dry hydrogel is immersed in deionised water for 48 hours at room temperature on a roller mixer. After swelling, the hydrogel is filtered by a stainless steel net of 30 meshes (681 μm). The swelling is calculated as follows.

$$\text{Swelling}=\frac{Ws-wd}{Wd}$$

Where, Ws is the weight of hydrogels in swollen state and Wdis the weight of hydrogel indry state.

Method B

Here are given another method to measure the swelling of hydrogel, in a volumetric vial (Universal) the dry hydrogel (0.05-0.1g) was dispersed into sufficiently high quantity of water (25-30 ml) for 48 hrs. at room temperature. The mixture is then centrifuged to obtain the layers of waterbound material and free unabsorbed water. The free water is removed and the swelling can be measured according to Method A above.

Method C

In method C the dry gel is immersed in deionized water for 16 h at room temperature. After swelling, the hydrogel was filtered using a stainless-steel net of 100-mesh (149 μm). Swelling is calculated as follows:-

Swelling=$\frac{C}{B} \times 100$

Where C is the weight of hydrogel obtained after drying and B is the weight of the insoluble portion after extraction with water [70, 71].

X-ray diffraction

Diffraction analysis is the estimation of crystalline or amorphous characteristics. It is used to understand whether the polymers retain their crystalline structure or they get deformed during the processing pressurization process. The diffraction analysis is quite a popular study for the morphological characterization of hydrogels. The retention of crystalline structure or their deformation during pressurization has played a vital role. The appearance of new peaks in powder pattern is characteristic of drug - excipient interaction [1,3].

***In -Vitro* drug release study**

Since hydrogels are the swollen polymeric networks, interior of which is occupied by drug molecules, therefore, release studies are carried out to understand the mechanism of release over a period of application. One that basis the bioequivalence study is carried out to estimate the release of dosage forms. The parameters are matched with the standard plot so that the equivalence between the drug solutions is carried out. In - vitro diffraction of type-1 collagen hydrogels containing bioactive glass and silica sol-gel micromeritic particles are formulated and there *in vitro* apatite- forming ability have been simulated by body fluids that is assessed [1, 3].

Rheology

Viscosity of hydrogels is evaluated by using Cone plate type viscometer under constant temperature at 4ºC. This viscometer is highly specific for the evaluation of viscosity. The viscosity is determined by the simple equation of determining the angle of repose through that height and length is determined [1, 3].

Other techniques

Differential scanning calorimetry (DSC) and nuclear magnetic resonance (NMR)used to characterize and quantify the amount of free and bound water in hydrogels The proton NMR gives information about the interchange of water molecules between the so-called free and bound states [72]. The use of DSC is based on the assumption that only the free water may be frozen, so it is assumed that the endotherm measured when warming the frozen gel represents the melting of the free water, and that value will yield the amount of free water in the hydrogel sample being tested. The bound water is then obtained by difference of the measured total water content of the hydrogel test specimen, and the calculated free water content [20].

Application of hydrogels

Large numbers of hydrogel are reported to prepare by the combination of synthetic and natural polymers with their end use mainly in tissue engineering, pharmaceutical, and biomedical fields [73]. Due to their high water absorption capacity and biocompatibility they have been used in wound dressing, drug delivery, agriculture, sanitary pads as well as transdermal systems, dental materials, implants, injectable polymeric systems, ophthalmic applications, hybrid-type organs (encapsulated living cells) [75, 76]. A list of hydrogels with their proposed corresponding applications is shown in Table 1.

Table.1: Pharmaceutical Applications of hydrogels types of polymers

Applications	Polymers
Wound care	polyurethane, poly(ethyleneglycol), poly(propyleneglycol) [74] poly(vinyl pyrrolidone),polyethylene glycol and agar [75]
Drug delivery, pharmaceutical	poly(vinyl pyrrolidone) [76] starch, poly(vinyl pyrrolidone),poly(acrylic acid) [77]
Dental Materials	Hydrocolloids (Ghatti, Karaya,Kerensis gum) [78]
Tissue engineering, implants	Hyaluronan [79]
Injectable polymeric system	-hairpin peptide [80]
Technical products (cosmetic, pharmaceutical)	poly (vinyl methyl ether), poly(N-isopropyl acryl amide) [81]

Applications of hydrogels in drug delivery

A number of strategies have been proposed to achieve drug delivery systems for efficient therapy. Among them, hydrogels have attracted considerable attention as excellent candidates for controlled release devices, Bioadhesive devices, or targetable devices of therapeutic agents.Hydrogel-based delivery devices can be used for oral, rectal, ocular, epidermal and subcutaneous application. Fig. 6 illustrates various sites that are available for the application of hydrogels for drug delivery [82].

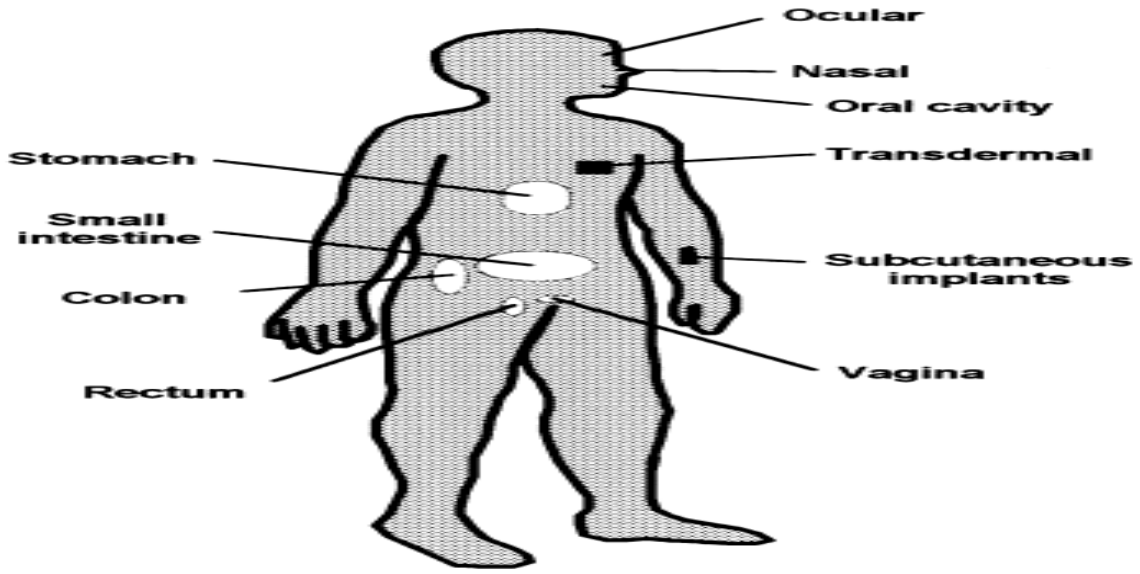

Fig.6: Tissue locations applicable for hydrogel-based drug delivery systems

Drug delivery in the oral cavity

Drug can be deliver to oral cavity through incorporating into hydrogels for local treatment of diseases of the mouth, such as periodontal disease, stomatitis, fungal and viral infections, and oral cavity cancers.Long-term adhesion of the drug containing hydrogel against copious salivary flow, which bathes the oral cavity mucosa, is required to achieve this local drug delivery. For this purpose, many types of bioadhesive hydrogel systems have been devised since the early 1980s. Some of these are already on the market. For example, a bioadhesive tablet developed by Nagai et al. is commercially available under the brand name Aftachw A hydrogel-based ointment can also be utilized for the topical treatment of certain diseases in the oral cavity [82,83].

Drug delivery in the GI tract

As we know that entire GI tract is the most popular route of drug delivery because of the facility of administration of drugs for compliant therapy, and its large surface area for systemic absorption. It is however, the most complex route, so that versatile approaches are needed to deliver drugs for effective therapy. Like buccal delivery, hydrogel-based devices can be designed to deliver drugs locally to the specific sites in the GI tract. For example, stomach-specific antibiotic drug delivery systems for the treatment of Helicobacter pylori infection in peptic ulcer disease. Recently, oral insulin delivery using pH-responsive complexation hydrogels was reported by Lowman et al. The hydrogels used to protect the insulin in the harsh, acidic environment of the stomach before releasing the drug in the small intestine [82, 83].

Rectal delivery

It is well known that drugs absorbed from the lower part of the rectum drain into the systemic circulation directly. Thus, the rectal route is a useful administration route for drugs suffering heavy first-pass metabolism. Its primary applications have been

for local treatment of diseases associated with the rectum, such as hemorrhoids.A problem associated with rectal administration using conventional suppositories is that drugs diffusing out of the suppositories in an uncontrolled manner hydrogels may offer a valuable way to overcome the problem in conventional suppositories, provided that they are designed to exhibit a sufficient bioadhesive property following their rectal administration [82].

Ocular drug delivery

Hydrogels are most widely used in ocular drug delivery system. Most of hard and soft contact lenses are formed of polymers in form of hydrogel films. In particular, in-situforminghydrogels are attractive as an ocular drug delivery system because of their facility in dosing as a liquid, and their long-term retention property as a gel after dosing. Cohen et al. developed an in-situgelling system of alginate with high guluronic acid contents for the ophthalmic delivery of pilocarpine [83].

Transdermal Delivery

Various hydrogel based drug delivery device are formed to deliver drug through transdermal route. 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.

Subcutaneous Delivery

Hydrogels are biodegradable in nature by utilization of this property we can form biodegradable implantable hydrogels**.** Hydrogel formulations for subcutaneous delivery of anticancer drugs are beingprepared viz. cross linked PHEMA was applied to cytarabine. Implantable hydrogels are nowleading towards the development of biodegradable systems which don't require surgical removal once the drug has been administered [9].

Topical drug delivery

To treat skin infection various hydrogels based formulations are prepare and apply topically for local action. 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 [1, 82].

Protein drug delivery

We can deliver the protein through incorporating into hydrogels. Interleukins which are conventionally given as injection are now given as hydrogels. These hydrogels have shown better patient compliance. The hydrogels form in situ polymeric network and release proteins slowly. These are biodegradable and biocompatible also [83].

Conclusion

From the above we find that the hydrogels have fantastic properties suggest that they will have numerous future applications as the next generation biomaterials. There are enough scientific evidences for the potentiality of hydrogels in delivery of drug molecules to a desired site by triggering the release through an external stimulus such as temperature, pH, glucose or light. That's why hydrogels also called a smart or intelligent biomaterial.There are present various methods by which hydrogels can be prepared. Some of them are discussed in this article. A novel method was introduced for delivery of chemotherapeutic agents using hydrogels. The characterization of hydrogels into morphological pattern demonstrate the scanning electron microscopy, x- ray diffraction, Fourier transform infra-red spectroscopy, rheology and the swelling behavior of hydrogels. The most important property of hydrogels is its biocompatibility, nontoxicity, biodegradability and swelling property due to which it is most widely used in biomedical application. Now a day hydrogels can be injected in - vivo as a liquid form that converted into gels form at body temperature. Swelling and mechanical features of hydrogel polymers have enabled them to find extensive applications in traditional, modern, and novel pharmaceutical area. They have gained wide applicability in the field of wound healing, colon specific drug devices, cosmetology, topical drug devices, oculardrug devices and modified dosage forms. 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. In future hydrogel and their properties, may give raise a novel approach for implementing the biomaterials in the pharmaceutical field in a better way.

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