Hydrogel: Preparation, Characterization and Applications

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Abstract

This review article is intended to provide an overview of hydrogel as novel vesicular drug delivery system.For the treatment of many diseases large molecular weight proteins are required. These can be available with the availability of Hydrogels. Hydrogels are hydrophilic, three-dimensional networks, which are able to imbibe large amounts of water or biological fluids, and thus resemble, to a large extent, a biological tissue. They are insoluble due to the presence of chemical (tie-points, junctions) and/or physical crosslinks such as entanglements and crystallites. It has focused on to present a concise review on the applications of hydrogels in the pharmaceutical field, hydrogel properties, method of preparation of hydrogel, advantages and disadvantages of hydrogel, characterization of hydrogel.

Keywords: Hydrogel, homo-polymer, Co-polymer, Interpenetrating network, Novel drug delivery system.

Introduction

A hydrogel is a three-dimensional (3D) network of hydrophilic polymers that can swell in water and hold a large amount of water while maintaining the structure due to chemical or physical cross-linking of individual polymer chains. Hydrogels were first reported by Wichterle and Lím (1960) [1]. Owing to their high-water content, porosity and soft consistency, they intently simulate natural living tissue, more so than any other category of synthetic biomaterials. Hydrogels can either be chemically durable or they may eventually disintegrate and dissolve[2].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. Physical gels are often rescindable and it is achievable to dissolve them by altering the environmental conditions, such as pH and the ionic strength of solution or temperature. In 'permanent' or 'chemical' gels, the linkage of covalent bonds linking distinct macromolecular chains can be attained by crosslinking polymers in the dry state or in solution[3]. These gels may be either charged or non-charged dependent on the behaviour of functional groups existing in their structure. The charged hydrogels typically display changes in swelling upon variations in pH and it is wellknown that they can undergo changes in shape when subjected to an electric field[4].

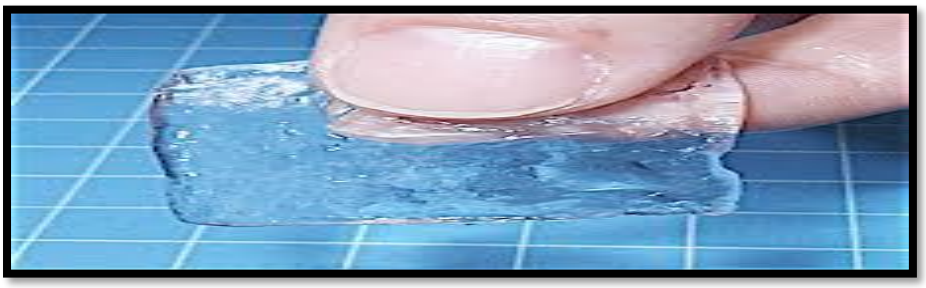

Fig.1: Hydrogel

Hydrogels 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[5]. Accordingly, hydrogels are universally being employed in clinical practices and investigational medicine for a wide variety of applications, counting the tissue engineering and regenerative medicine diagnostics, cellular immobilization, separation of biomolecules or cells and barrier materials to control biological adhesions[6].

Due to its simplicity in manufacturing and self-application hydrogels have been widely used as a drug carrier. Hydrogels may be synthesized in a many of ‘‘classical’’ chemical ways. These include one-step procedures like polymerization and parallel cross-linking of multifunctional monomers, by reacting polymers with suitable cross-linking agents and as well as multiple step procedures involving synthesis of polymer molecules having reactive groups and their subsequent cross-linking[7].

Properties of hydrogel

Hydrophilic gels called hydrogels receive considerable attention for their use in the field of pharmaceutical and biomedical engineering.

Swelling properties A small change in environmental condition may trigger fast and reversible changes in hydrogel. The alteration in environmental parameters like electric signal, pH, temperature, and presence of enzyme or other ionic species may lead to a change in physical texture of the hydrogel.

Mechanical properties The desired mechanical property of the hydrogel could be achieved by changing the degree of Crosslinking and by increasing the degree of crosslinking a stronger hydrogel could be achieved though the higher degree of crosslinking decreases the % elongation of the hydrogels creates a more brittle structure[8].

Polymers used in hydrogels Hydrogel are prepared from natural and synthetic polymers(Table 1):

Table 1: Natural polymers and synthetic monomers used in hydrogel fabrication

Natural polymers	Synthetic monomers/polymers
Chitosan	Hydroxy ethylmethacryate (HEMA) Gelatin
Gelatin	Vinyl acetate (VAc)
Alginate	Acryolic acid (AA)
Hyaluronic acid	N-(2-Hydroxy propyl) methacrylate (HPMA)
Fibrin	N-Vinyl-2-pyrrolidone (NVP)
Chitosan	N-Isopropylacrylamide (NIPAMM)

Biocompatible properties Biocompatibility is the ability of a material to perform with an appropriate host response in a specific application. Biocompatibility consists basically of two elements:

(a) bio functionality i.e. the ability of material to perform the specific task for which it is intended.

(b) bio-safety i.e. appropriate host response not only systemic but also local (the surrounding tissue), the absence of mutagenesis, cytotoxicity, and/or carcinogenesis[9].

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[10].

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 [11]

Classification of hydrogels

The literature reports a number of classifications of hydrogels and presents several views. Hydrogels are mainly formed from biopolymers and/or polyelectrolytes. Concerning definitions of hydrogel types, according to the source, hydrogels can be divided into those formed from natural polymers and those formed from synthetic polymers [12]. Depending on the ionic charges on the bound groups, hydrogels may be cationic, anionic, or neutral. The types of cross-linking agents also can be the criteria for classification. Hydrogels can be physical, chemical, or biochemical. Physical gels can undergo a transition from liquid to a gel in response to a change in environmental conditions such as temperature, ionic concentration, pH, or other conditions such as mixing of two components. Chemical gels use covalent bonding that introduces mechanical integrity and degradation resistance compared to other weak materials. In biochemical hydrogels, biological agents like enzymes or amino acids participate in the gelation process. It is also possible to divide hydrogels into groups based on their structure: amorphous, semi crystalline, crystalline, and hydrocolloid aggregates [13].Figures clearly represents the classification of hydrogels based on their source and properties, along with detailed classifications based on their response, that is, physically, chemically, and biochemically responsive hydrogels **(Fig.2 and 3)**

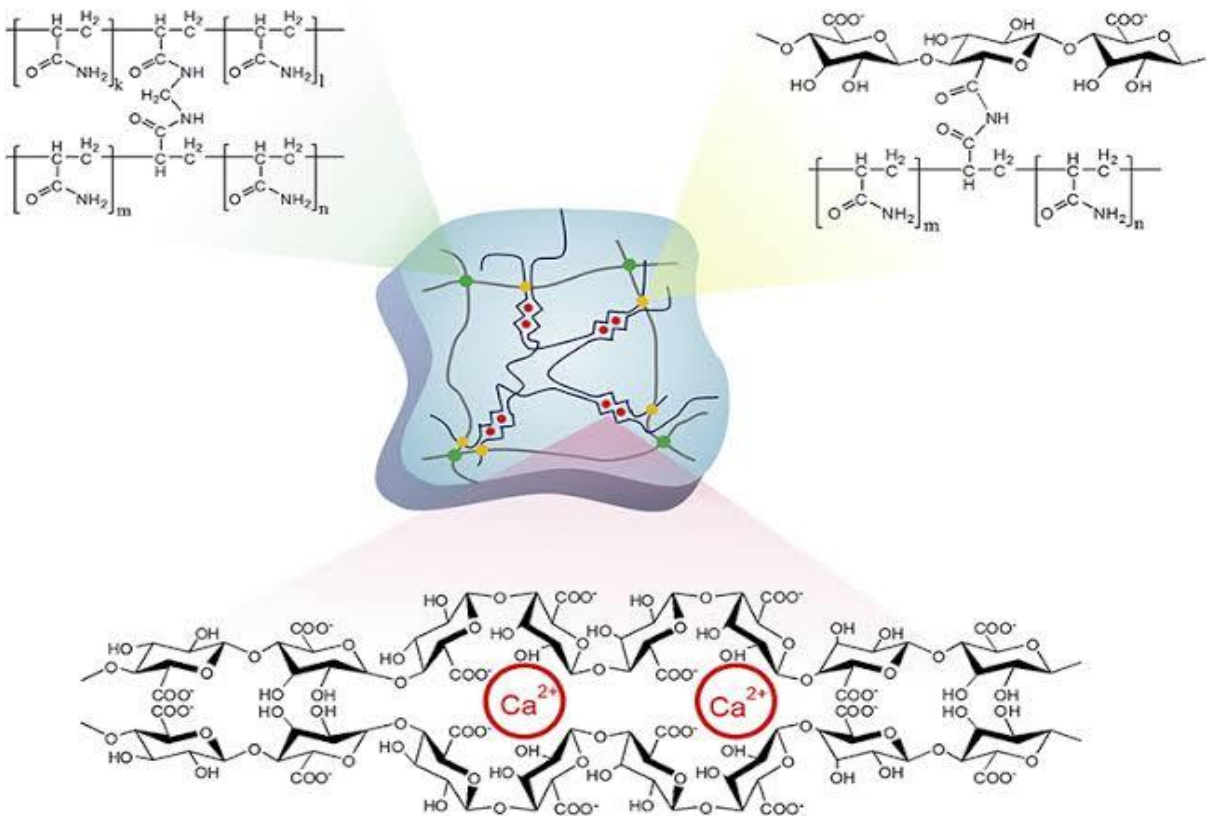

FIG 2:In situ hydrogel formation using chemical cross-linking and ionic interaction between alginate and calcium ions[14]

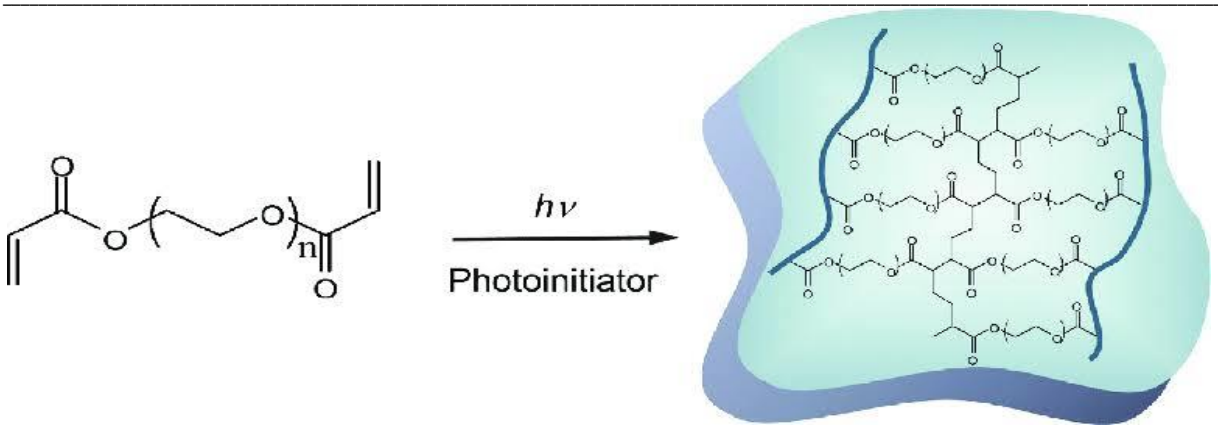

Fig 3: In situ hydrogel formation using an enzymatic cross-linking reaction with horseradish peroxidase (HRP) and H_2O_2. [15]

Classification of hydrogel products

The hydrogel products can be categorized on different bases as described below: Classification based on source Hydrogels can be classified into two groups based on their natural or synthetic origins [16].

Classification according to polymeric composition

The technique of preparation leads to formations of principal classes of hydrogels. These can be represented as following: These are referred to: -

(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 [17]. Homopolymers may have cross-linked skeletal structure dependent on the nature of the monomer and polymerization method.

(b) ***Copolymeric hydrogels:*** These are consisted of two or 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 [18]

(c) ***Multipolymer hydrogels:*** 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 [19].

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) Semi crystalline: A complex mixture of amorphous and crystalline phases.

(c) Crystalline.

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 from either polymer chain entanglements or physical interactions such as ionic interactions, hydrogen bonds or hydrophobic interactions. [20]

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) Nonionic (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[21].

Technologies implemented in the preparation of hydrogels

On the whole, hydrogels can be formulated from either synthetic polymers or natural polymers. The synthetic polymers are hydrophobic in nature and chemically stronger in comparison to natural polymers. Their mechanical strength brings about slow degradation rate, but on the other hand, mechanical strength offers the sturdiness as well. These two opposite properties should be balanced through optimum design. Water-soluble linear polymers of both natural and synthetic origin are cross-linked to form hydrogels in various ways: -

1. Linking polymer chains via chemical reaction

2.Using ionizing radiation
3.Physical interactions such as entanglements, electrostatics and crystallite formation.

Generally, the three integral parts of the hydrogel's preparation are monomer, initiator and crosslinker. To regulate the heat of polymerization and the final hydrogels properties, diluents can be employed in the formulation, such as water or other aqueous solutions. Hydrogels are normally prepared from polar monomers. According to their starting materials, they can be categorized into natural polymer, synthetic polymer and combinations of the two [22].

Many vinyl monomers can possibly be employed for the fabrication of hydrogels. Bulk hydrogels can be obtained with one or more types of monomers. Ordinarily, a small amount of cross-linking agent is supplemented for hydrogel formulation. The polymerization reaction is typically initiated with radiation, ultraviolet or chemical catalysts. The selection of a n appropriate initiator relies upon the type of monomers and solvents being used. The polymerized hydrogel may be yielded in a wide range of forms counting the films and membranes, rods, particles and emulsions. (Fig 4)

Bulk polymerization

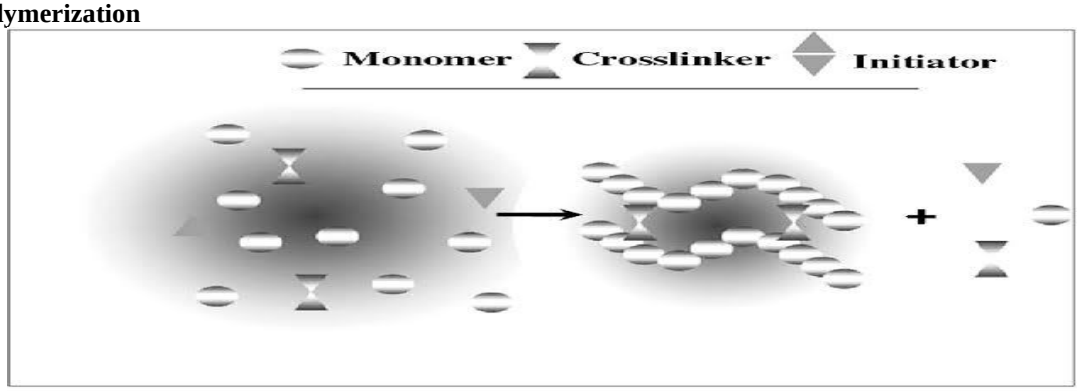

Fig.4: - Schematic Diagram of Hydrogel Preparation [23]

Bulk polymerization is the straightforward technique, which includes only monomer and monomer soluble initiators. The viscosity of reaction enhances significantly with the conversion which generates the heat during polymerization. These problems can be prevented by regulating the reaction. The bulk polymerization of monomers to make a homogeneous hydrogel yields a glassy, transparent polymer matrix which is very tough. When placed in water, the glassy matrix swells to become soft and flexible [24].

Solution polymerization/cross-linking

In solution copolymerization/cross-linking reactions, the ionic or neutral monomers are blended with the multifunctional cross-linking agent. The polymerization is instigated thermally by UV/IR radiation or by a redox initiator system. The prepared hydrogels require washing with distilled water to eliminate the monomers, oligomers, cross-linking agent, the initiator, the soluble and extractable polymer and other impurities. Phase separation takes place and the heterogeneous hydrogel is formed when the quantity of water during polymerization is more than the water content in proportion to the equilibrium swelling. Usual solvents utilized for solution polymerization of hydrogels include water, ethanol, water–ethanol mixtures and benzyl alcohol [25].

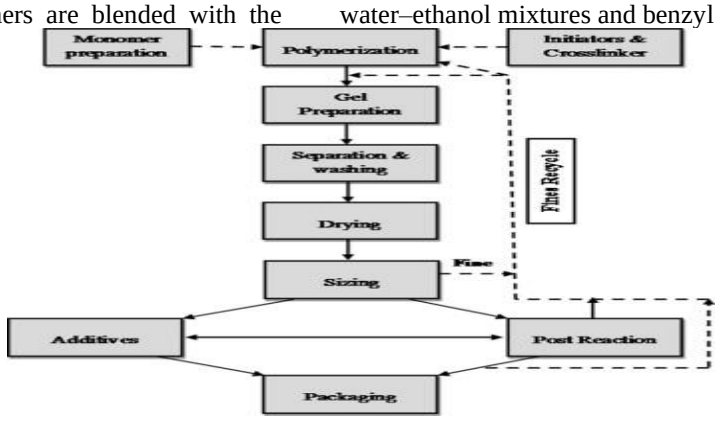

Fig 5: Hydrogel preparation block diagram (solution polymerization/cross-linking procedure) [26]

Suspension polymerization or inverse-suspension polymerization

Dispersion polymerization is a worthwhile technique since the products are acquired as powder or microspheres (beads) and thus, grinding is not needed. Since water-in-oil (W/O) process is selected in preference to the more common oil-in-water (O/W), the polymerization is denoted as "inverse suspension". In this method, the monomers and initiator are distributed in the hydrocarbon phase as a homogenous mixture. The viscosity of the monomer solution, agitation speed, rotor design and dispersant type chiefly regulates the resin particle size and shape [27]. Several comprehensive discussions on hetero-phase polymerizations have been published previously [28,29]. The dispersion is thermodynamically unsteady and necessitates both continuous agitation and addition of a low hydrophilic–lipophilic- balance (HLB) suspending agent.

Grafting to a support

Usually, hydrogels formulated by bulk polymerization have characteristic weak structure. To enhance the mechanical properties of a hydrogel, it can be attached on surface which is coated onto a sturdy support. This method that comprises the generation of free radicals onto a stronger support surface and then polymerizing monomers directly onto it, as a result of which, a chain of monomers are covalently bonded to the support. An assortment of polymeric supports have been employed for the synthesis of hydrogel by grafting techniques[30] Ionizing high energy radiation, like gamma rays and electron beams has been employed as an initiator to formulate the hydrogels of unsaturated compounds. The irradiation of aqueous polymer solution leads to the formation of radicals on the polymer chains. Also, radiolysis of water molecules brings about the formation of hydroxyl radicals, which also attack the polymer chains, leading to the formation of macro-radicals. Recombination of the macroradicals on different chains results in the formation of covalent bonds, so ultimately, a cross-linked structure is obtained [31]. Examples of polymers crosslinked by the radiation method are poly (vinyl alcohol), poly(ethylene glycol), and poly(acrylic acid). The foremost benefit of the radiation initiation over the chemical initiation is the fabrication of relatively pure and initiator-free hydrogels.

Fig.6: Block diagram for the preparation of the high swelling hydrogel[32]

Polymerization by irradiation

For the preparation of hydrogels of unsaturated compounds, the initiators such as the ionizing high energy radiation, like gamma rays and electron beams, has been used. The irradiation of aqueous polymer solution results in the formation of radicals on the polymer chains. Recombination of the macro-radicals on different chains results in the formation of covalent bonds, so finally, a cross-linked structure is formed. Poly (vinyl alcohol), poly (ethylene glycol), and poly (acrylic acid) is used for polymerization by irradiation. Relatively pure and initiator-free hydrogels is produced by this method[33].

Physical cross-linking

It is the most common and easy routes for hydrogel formation by cross linking of polymers through physical interactions.This physical cross linking includes interaction of ions such as hydrogen bonding, polyelectrolyte complexation and hydrophobic association. The various methods used in physically cross-linked hydrogels preparation are: -

- ***Heating/cooling a polymer solution*-**It is prepared by cooling hot solutions of gelatin or carrageenan to form physically cross-linked gels. The gel formation is due to association of the helices, helix-formation, and forming junction zones. Some of the examples are polyethylene glycol-polylactic acid hydrogel and polyethylene oxide-polypropylene oxide.

- ***Complex coacervation:*** Formation of complex coacervate gels by mixing of polyanions with a polycations. 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. One such example is coacervating polyanionic xanthan with polycationic chitosan [34].
- ***Ionic interaction-***Addition of di- or trivalent counter ions in ionic polymer leads to cross linking between polymers. This method underlies the principle of gelling polyelectrolyte solution (e.g. Na+alginate-) with a multivalent ion of opposite charges (e.g. Ca^{2+} + $2Cl^{-}$). Some other examples are chitosan-polylysine, chitosan-glycerol phosphate salt, and chitosan dextran hydrogels.
- ***Hydrogen Bonding-*** A hydrogen bond is formed through the association of electron deficient hydrogen atom and a functional group of high electron density. Example, a hydrogel can result from hydrogen bond formation between PA and PNVP. The factors which affect the hydrogels are the molar ratio of each polymer, polymer concentration, the type of solvent, the solution temperature, and the polymer structure.
- ***Chemical cross-linking-***In this process the use of a crosslinking 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). IPN is a polymerize monomer within another solid polymer to form interpenetrating network structure [35].

Hydrogels and their application in controlled drug release

Table.2: Pharmaceutical Applications of hydrogels types of polymers

Applications	**Polymers**
Wound care	polyurethane, poly (ethylene glycol), poly (propylene glycol) poly (vinyl pyrrolidone), polyethylene glycol and agar [36]
Drug delivery, pharmaceuticals	poly (vinyl pyrrolidone) starch, poly (vinyl pyrrolidone), poly (acrylic acid)
Dental materials	Hydrocolloids (Ghatti, Karaya,Kerensis gum)[37]
Tissue engineering, implants	Hyaluronan
Injectable polymeric system	hairpin peptide
Technical products	poly (vinyl methyl ether), poly (N-isopropyl acryl amide) [38]

Hydrogel technical features

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

- The highest absorbency under load (AUL).
- The lowest price and highest absorption capacity in saline.
- The lowest soluble content and residual monomer [39].
- The highest durability and stability in the swelling environment and during the storage.
- The highest biodegradability without formation of toxic species following the degradation.
- Colorlessness, odorlessness, absolute non-toxic and photostable [40].

Applications of hydrogels in drug delivery

Hydrogels have attracted considerable attention as excellent candidates for Bioadhesive devices, controlled release devices and targetable devices of therapeutic agents. Hydrogel-based delivery devices can be used for oral, rectal, ocular, epidermal and subcutaneous application. Various sites that is available for the application of hydrogels for drug delivery.

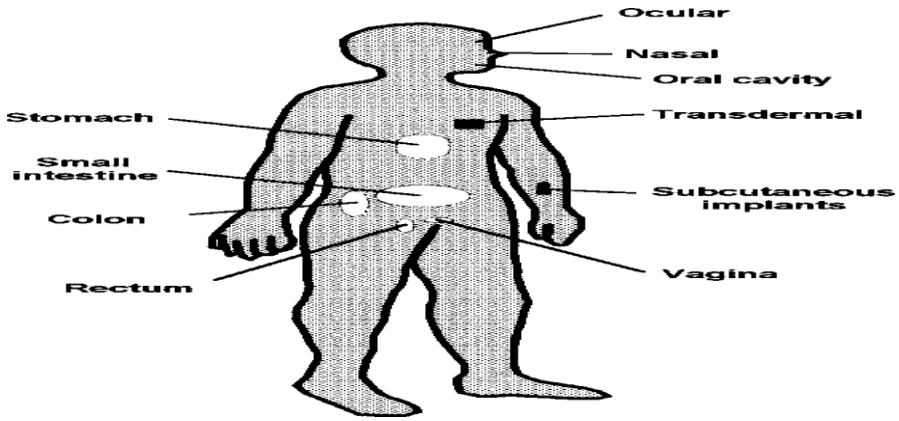

Fig.7: Tissue locations applicable for hydrogel-based drug delivery systems [41]

Drug delivery in the oral cavity

Drug is incorporated into hydrogels and delivers to oral cavity for local treatment of diseases of the mouth, such as stomatitis, fungal diseases, periodontal disease, viral infections, and oral cavity cancers.

Drug delivery in the GI tract

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. Like buccal delivery, hydrogel-based devices can be designed to deliver drugs locally to the specific sites in the GI tract. For example, stomach-specificantibiotic drug delivery systems for the treatment of Helicobacter pylori infection in peptic ulcer disease [42].

Wound healing

Hydrogels have the ability to hold water and drug in them due to their cross-linked structure. Due to their water holding ability they can hold and retain wound exudates. Gelatin and sodium alginate-based hydrogels when applied have the ability to cover and protect the wound from bacterial infection.

Hydrogels for brain

Blood brain barrier is also a challenge for drug delivery like other barriers in human body, concerning 98 % of the newly synthesized drugs fail to cross this barrier. Due to that reason a low number of drugs are present for drug delivery for CNS. Camptothecin having long termed sustained release drug is loaded with PLGA microspheres which was observed in rats. These microspheres increase the survival period in rats against malignant gliomas [43].

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-situ forming hydrogels 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 [44].

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.

Topical drug delivery

Hydrogels have been used to deliver active component like Desonide which is a synthetic corticosteroid usually used as an anti-inflammatory. The hydrogels have been formulated for better patient compliance having moisturizing properties therefore scaling and dryness is not expected with this drug delivery system [45].

Characterization of hydrogel

Generally, hydrogels are characterized for their morphology, swelling property, chemical structure and elasticity. The important features for characterization of hydrogels are as follows:

Physical* Appearance *and pH Determination

Hydrogel were inspected visually for their colour, homogeneity, Consistency and pH. pH of hydrogels is measured by using digital pH meter. pH meter must be calibrated before its use [46]

Scanning Electron Microscopy (SEM)

SEM can be used to provide information about the sample's composition, surface topography, 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 [47].

Swelling measurement

There are present three different methods by which we can measure swelling in hydrogels:

Method A

In this method the dry hydrogel is immersed in deionized 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. Swelling = WS-Wd/Wd Where, Ws is the weight of hydrogels in swollen state and Wdis the weight of hydrogel in dry state.

Method B

In a volumetric vial 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 water bound material and free unabsorbed water. The free water is removed and the swelling can be measured according to Method A above.

Method C InMethod 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= C×100/B

Where C is the weight of hydrogel obtained after drying and B is the weight of the insoluble portion after extraction with water [48].

Network pore size: Pore size is measured by a number of technologies like electron microscopy, mercury porosimetry and others [49].

Spreadibility study: The apparatus was made of wooden block with scale and two glass slides having a pan mounted on a pulley. Excess formulation was placed between two glass slides and 100 gm weight was placed on upper glass slide for 5 minutes to compare the formulation to achieve uniform thickness. Weight can be added and the time to separate the two slides was taken as spreadibilty time. S= (m × l) / t Where S is spreadibilty, m is weight tied on upper slide, l is length of glass slide and t is time taken in seconds [50].

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. The parameters are matched with the standard plot so that the equivalence between the drug solutions is carried out [51]

Drug Content Determination: The drug content of Hydrogel was measured by dissolving a known weight of the hydrogel formulation (one gram) in 100 ml methanol, appropriate dilutions were made and the resulting solution was then filtering using millipore filter (0.45 μm). Absorbance was measured at 296 nm using UV- spectrophotometer (Shimadzu UV 1800). [52] Drug content was calculated using the slope and the intercept obtained by linear regression analysis of standard calibration curve.

Antifungal Activity Studies

The prepared hydrogel formulations were tested against candida albican strain using agar cup method. Cups of 10mm diameter were made aseptically in savoured dextrose agar after being inoculated with the tested fungal suspension strain (106cfu/ml) by spreading on the agar surface. The cups were filled with each prepared formulation by sterile syringe. The zone of inhibition of each cup was observed and the radius of the zone of inhibition was measured [53]

Stability Studies

The hydrogel were packed in aluminium tubes (5 grams) and subjected to stability studies at 25°C/60% relative humidity (RH) and 40°C/75% RH for period of 3 months. Samples were withdrawn at time intervals of 15 days and evaluated for physical appearance, pH, rheological properties, drug content and drug release [54].

Conclusion

Recently, many hydrogel-based networks have been designed and personalized to meet the needs of different applications. When putted in contact with an aqueous solution these hydrogels is either ability to swell. The present review demonstrates about the classification of hydrogels on different bases, physical and chemical characteristics and technical feasibility of their utilization, method of preparation and application.From the study we find that the hydrogels have fantastic properties that they will have abundant future applications as the next generation biomaterials. 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.

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