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Hydrogel: Preparation, Characterization and Applications

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Abstract
Hydrogel products constitute three-dimensional networks which contains a group of polymeric materials, the hydrophilic structure of which renders them capable of holding large amounts of water. These biomaterials can integrate large quantum of biological fluids and swell. When swelled, they are soft & rubbery and resemble the living tissue, exhibiting excellent biocompatibility. Broad use of these products in a number of industrial and environmental areas of application is considered to be of prime importance. Today, drug delivery experience several challenges where hydrogel could be one potential answer to those. Due to the vast properties of hydrogel they are widely exposed to different biomedical fields. The primary objective of this article is to concerning classification of hydrogels on different bases, properties of hydrogels and its methods of preparations, physical and chemical characteristics of these products, and technical feasibility of their utilization.

Keywords: Hydrogel, homo-polymer, Co-polymer, Interpenetrating network, Swelling, Mechanical, Biocompatible

Introduction
Recently considerable attention has been gained about hydrogels. Hydrogels are three-dimensional cross-linked polymer network that are smart enough to respond the fluctuations of environmental stimuli (ionic strength, pH, temp, presence of enzyme, electric field etc.) and swell or shrink accordingly. In the swollen state, they are soft and rubbery, resembling the living tissue exhibiting excellent biocompatibility [1].
For their delivery of drugs into specific sites of the body new therapeutic moieties are discovered with specialized carrier by the use of medical science. By the help of conventional methods hydrogels are capable of delivering genetically engineered pharmaceuticals, *viz.* protein and peptides and improve the therapeutic efficacy of drugs. Depending on the preparation methods the hydrogels could be homo-polymeric, co-polymeric, semi-interpenetrating and interpenetrating polymer networks. Recently, for biomedical applications thermoplastic co-polymeric biodegradable hydrogels with optimum mechanical strength have been designed.
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 [2].

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

1. 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.

2) 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 [3].

3) Polymers used in hydrogels

Hydrogels are prepared from natural and synthetic polymers.

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

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

4) 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 [4].

Advantages of hydrogels

1. Due to their significant water content they possess a degree of flexibility very similar to natural tissue.
2. Release of medicines or nutrients timely.
3. They are biocompatible, biodegradable and can be injected.
4. Hydrogels have the ability to sense changes of pH, temperature, or the concentration of metabolite and release their load as result of such a change.
5. Hydrogels also possess good transport properties and easy to modification.

Disadvantages of hydrogels

1. High cost.
2. Can be hard to handle.
3. Low mechanical strength.
4. They are non-adherent and may need to be secured by secondary dressing and also cause sensation felt by movement of the maggots.
5. Difficult to load with drugs/nutrients [5].

Classification of hydrogel products

The hydrogel products can be classified on different bases as detailed below:

I. Classification based on source

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

a. **Natural hydrogels-** Natural hydrogels are biodegradable, biocompatible and good cell adhesion properties. There are two major types of natural polymers which are used to produce natural hydrogels are proteins such as collagen, gelatin and, lysozyme (LYZ) and polysaccharides such as hyaluronic acid (HA) and alginate and Chitosan (Cts)

b. **Synthetic hydrogels-** they are more useful 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. Polyethylene glycol (PEG) based hydrogels are one class of the widely used material in biomedical application due to their non-toxicity there compatibility and low immunogenicity.

c. **Hybrid hydrogels-** they are the combination of natural and synthetic polymer hydrogels. To combine the advantages of both synthetic and natural hydrogels many naturally occurring biopolymers such as dextran, collagen, Chitosan, have been combined with synthetic polymers such as poly (*N*-isopropylacrylamide) and polyvinyl alcohol [6].

II. Classification according to polymeric composition

a. Homopolymeric hydrogels- they are a basic structural unit comprising of any polymer network referred to polymer network derived from a single species of monomer. Depending on the nature of the monomer and polymerization technique homopolymers may have cross-linked skeletal structure. Homopolymers can be prepare by using polyethylene glycol dimethacrylate as cross-linking agent, poly (2-hydroxyethyl methacrylate) (poly HEMA) as a monomer and benzoin isobutyl ether as the UV-sensitive initiator. The film was prepared in de-ionised water and treated with UV radiation (λ = 253.7 nm, 11 mm distance from the source for 20 minutes). The film was then immersed for 24 h in water until it is fully saturated in order to remove toxic or unreacted substances that could damage a living tissue. Besides contact lenses, they can also be applied in artificial skin manufacturing and burn dressings, as it ensures good wound-healing conditions. It is also used for bone marrow and spinal cord cell regeneration, scaffolds for promoting cell adhesion and in artificial cartilage production [7].

b. Copolymeric hydrogels- they are comprised of two or more different monomer species with at least one hydrophilic component, arranged in block or alternating configuration, a random, along the chain of the polymer network. Synthesized by polymerization of BLG *N*-carboxyanhydride, initiated by diamine groups located at the ends of poly (ethylene oxide) chains of the poloxamer a thermoplastic co-polymeric hydrogel based on γ-benzyl L-glutamate (BLG) and poloxamer was formed. These hydrogel was pH and temperature sensitive and characterized for drug delivery application.

c. Multipolymer interpenetrating polymeric hydrogel (IPN), an important class of hydrogels, having network system which is made of two independent cross-linked synthetic and/or natural polymer component. In semi- IPN hydrogel, one component is a cross-linked polymer and other component is a non-cross-linked polymer. IPN method can overcome thermodynamic incompatibility occurs due to the permanent interlocking of network segments and limited phase separation can be obtained. The interlocked structure of the cross-linked IPN components is believed to ensure stability of the bulk and surface morphology.

Advantages

1. Dense hydrogel matrices can be produced which feature stiffer and tougher mechanical properties.
2. Controllable physical properties and more efficient drug loading compared to conventional hydrogels.
3. Drug loading is often performed in conjunction with the polymerization of the interpenetrating hydrogel phase[8].

III. According to the biodegradability

a. Biodegradable hydrogels

Hydrogels are biodegradable many polymers created by nature are biodegradable, such as Chitosan, fibrin and agar. Poly (aldehyde guluronate), Polyanhydrides and poly (*N*-isopropyl acrylamide) are examples of synthetic biodegradable polymers.

b. Non-biodegradable hydrogels

Various vinylated monomers or macromers such as 2-hydroxyethylmethacrylate (HEMA), methoxyl poly (ethylene glycol) (MPEG), 2- hydroxypropyl methacrylate (HPMA) and acryl amide (AAm) are widely applied in the preparation of non-biodegradable hydrogels [9].

IV. Classification based on configuration

The classification of hydrogels depends on their physical structure and chemical composition can be classified as follows:

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

V. Classification based on type of cross-linking:

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

a. Chemically cross-linked networks have permanent junctions.
b. Physical networks have transient junctions that arise from either polymer chain entanglements or physical interactions as hydrogen bonds, or hydrophobic interactions [10].

VI. Classification based on physical appearance

Hydrogels appearance as matrix, film, or microsphere depends on the technique of polymerization involved in the preparation process.

VII. Classification according to network electrical charge

Hydrogels may be categorized into four groups on the basis of presence or absence of electrical charge located on the crosslinked chains:

a) Nonionic (neutral).
b) Ionic (including anionic or cationic).
c) Amphoteric electrolyte (ampholytic) containing both acidic and basic groups.
d) Zwitter ionic (polybetaines) containing both anionic and cationic groups [11].

Technologies adopted in hydrogel preparation

Hydrogels are polymer networks having hydrophilic properties. Hydrophilic monomers, hydrophobic monomers are sometimes used in hydrogel preparation to regulate the properties for specific applications. Hydrogels can be produced by reacting hydrophilic monomers with multifunctional cross-linkers by using Copolymerization/ cross-linking free-radical polymerizations. Water-soluble linear polymers of both natural and synthetic origin are cross-linked to form hydrogels in a number of ways:

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

In general, the three integral parts of the hydrogels preparation are monomer, initiator, and cross-linker.

a. Bulk polymerization

Bulk hydrogels can be formed with one or more types of monomers mainly include vinyl monomers for the productions of hydrogels. Usually, a small amount of cross-linking agent is added in any hydrogel formulation. Radiation, ultraviolet, or chemical catalysts is used for the initiation of the polymerization reaction. The initiator is chosen which depends upon the type of monomers and solvents being used. The polymerized hydrogel may be produced in a wide variety of forms including rods, particles, films and membranes, and emulsions [12].

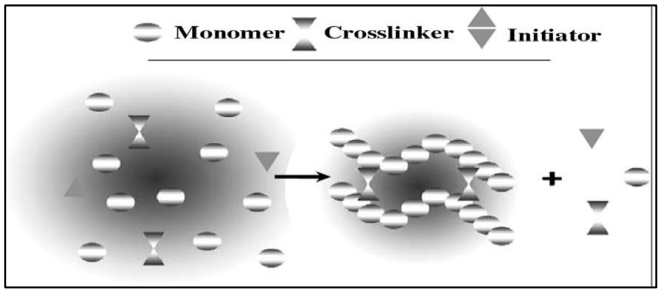

Fig 1: Schematic diagram of hydrogel preparation[12]

b. Free radical polymerization

The main monomers which are used in this method for the preparation of hydrogels are such as acrylates, vinyl lactams and amides. These polymers have suitable functional groups or have been functionalized with radically polymerizable groups. This method involves the chemistry of typical free-radical polymerizations, which includes propagation, chain transfer, initiation, and termination steps. For the radical generation in the initiation step a wide variety of thermal, ultraviolet, visible, and redox initiators can be utilized, the radicals react with the monomers which convert them into active forms [13].

c. Solution polymerization/cross-linking

In these ionic or neutral monomers are mixed with the multifunctional crosslinking agent. The polymerization is initiated thermally by UV-irradiation or by a redox initiator system. The major advantage of the solution polymerization over the bulk polymerization is the presence of solvent serving as a heat sink. The prepared hydrogels is washed with distilled water to remove the initiator, the soluble monomers, oligomers, cross-linking agent, and extractable polymer, and other impurities. Solvents used water–ethanol mixtures, water, ethanol, and benzyl alcohol.

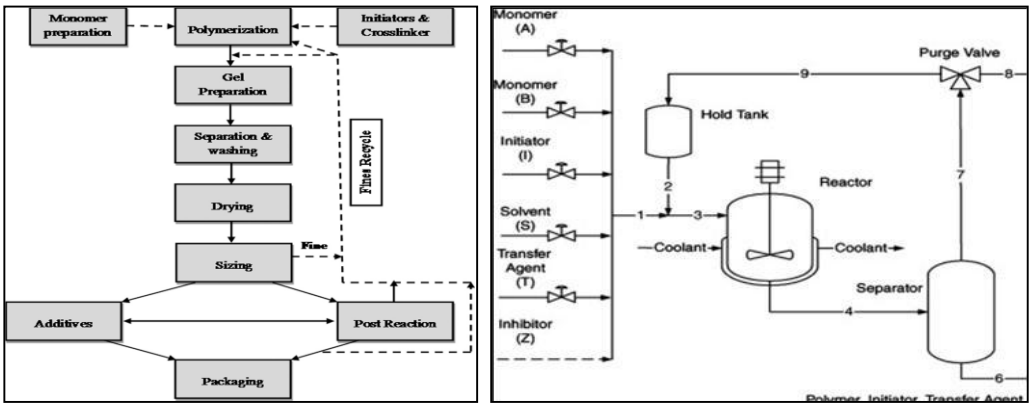

Fig. 2: A. Hydrogel preparation block diagram (solution polymerization/cross-linking procedure) B. solution polymerization with recycle loop [14]

d. Suspension polymerization or inverse-suspension polymerization

The advantageous of this method is that the products obtained as powder or microspheres (beads), and thus, grinding is not required. Since water-in-oil (W/O) process is chosen instead of the more common oil-in-water (O/W), the polymerization is referred to as ‘‘inverse suspension’’. In this technique, the monomers and initiator are dispersed in the hydrocarbon phase as a homogenous mixture. The resin particle size and shape is used to govern the viscosity of the monomer solution, rotor design, agitation speed, and dispersant type. The dispersion is thermodynamically unstable and requires both continuous agitation and addition of a low hydrophilic–lipophilic- balance (HLB) suspending agent.

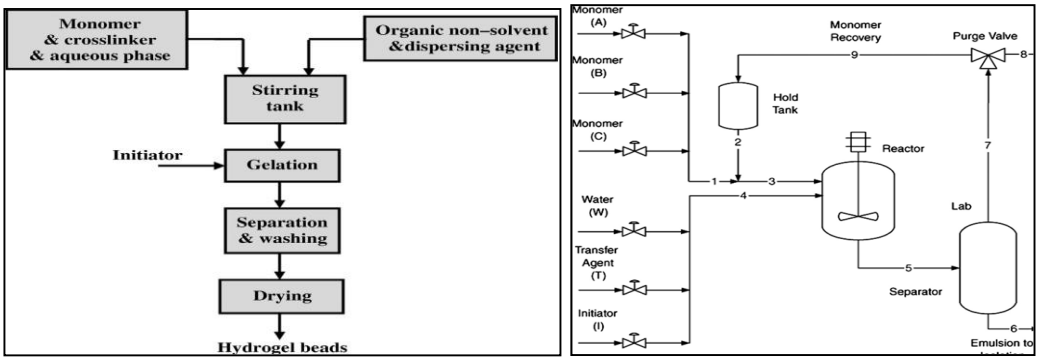

Fig. 3: Suspension polymerization with recycle loop [15]

e. Grafting to a support

Due to the weak structure of hydrogels prepared by bulk polymerization it is necessary to improve the mechanical properties of a hydrogel, so it can be grafted on surface coated onto a stronger support. This involves the generation of free radicals onto a stronger support surface and then polymerizing monomers directly onto it to form chain of monomers which are covalently bonded to the support [2].

f. 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 [3].

g. 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 [16].

- **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. Ca2+ + 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 [17].

Hydrogels and their application in controlled drug release

Table 1: 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 [18]
Drug delivery, pharmaceutical	poly(vinyl pyrrolidone) [76] starch, poly(vinyl pyrrolidone),poly(acrylic acid)
Dental Materials	Hydrocolloids (Ghatti, Karaya,Kerensis gum) [19]
Tissue engineering, implants	Hyaluronan
Injectable polymeric system	hairpin peptide
Technical products (cosmetic, pharmaceutical)	poly (vinyl methyl ether), poly(N-isopropyl acryl amide) [20]

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.

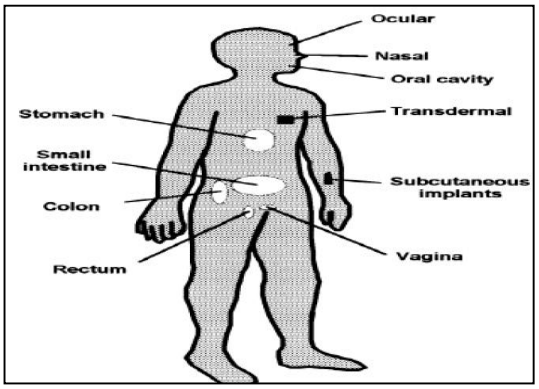

Fig 4: Tissue locations applicable for hydrogel-based drug delivery systems[4]

- **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-specific antibiotic drug delivery systems for the treatment of Helicobacter pylori infection in peptic ulcer disease [21].

- **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 [22].

- **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 for the drug administration having first pass metabolism. Its primary applications have been for local treatment of diseases associated with the rectum, such as hemorrhoids.

- **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 [23].

- **Subcutaneous Delivery**

Hydrogels are biodegradable in nature by utilization of this property we can form biodegradable implantable hydrogels**.** Used in subcutaneous delivery of anticancer drugs is being

prepared viz. cross linked PHEMA which is applied to cytarabine.

- **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[24].

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 [25].
- 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 [26].

Characterization of hydrogels

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

- **pH**

pH of hydrogels is measured by using digital pH meter. pH meter must be calibrated before its use.

- **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 [27].

- **Fourier Transform Infrared Spectroscopy**

It 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, can be excited and absorb infrared light at frequencies that are typical based on chemical bonds.

- **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 = W_S-W_d/W_d

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

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= 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 [28].

- **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.

- ***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 [29].

- **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 the angle of repose through that height and length is determined.

- **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 [30].

- **Skin irritancy test studies**

Skin irritancy tests are conducted on rabbits. The preparation was applied on two rabbits and the area was protected with gauze or bandage. After 24 hours the formulation was removed and the area was checked for any signs of edema and erythema. Average irritation scores= (erythema reaction

scores + edema reaction scores) / time interval.

- **X-ray diffraction**

X-ray diffraction is used to understand whether polymers retain their crystalline nature or they get deform during pressurization process.

- **Network pore size**

Pore size is measured by a number of technologies like electron microscopy, mercury porosimetry and others [31].

Conclusions

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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