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Review Article

Review on Hydrogel- A Novel Carrier

C. Mallikarjuna*[1], V. Hari Bhaskar[1], Junju Mohan Kumar[2], Rayaprolu Mounica[2], Sai Padmini Bolla[2]
[1]Department of Pharmaceutics, Vagdevi College of Pharmacy and Research Centre, SPSR Nellore, Andhra Pradesh, India.
[2]Department of Pharmaceutics, Rao's College of Pharmacy, SPSR Nellore, Andhra Pradesh, India.
Mallikarjuna2055@gmail.com

ABSTRACT

Hydrogels are three–dimensional cross-linked hydrophilic polymers that swell in water and aqueous solutions without dissolving in them. Softness, smartness, and the capacity to store water make hydrogels unique materials. Several techniques have been reported for the synthesis of hydrogels like co-polymerization/crosslinking of co-monomers using multifunctional co-monomer, which acts as crosslinking agent. They can be classified in different ways on the basis of their preparation, biodegradable properties, polymer, sensitivity to surrounding environment and also their application. Hydrogels being biocompatible materials have been recognized to function as drug protectors, especially for peptides and proteins, from in-vivo environment. Hydrogels that are responsive to specific molecules, such as glucose or antigens, can be used as biosensors as well as drug delivery systems. This review mainly deals with the advantages, properties, method of preparation and characterization of hydrogels.

Keywords: Hydrogels, Crosslinking polymers, Light scattering, Water vapour transmission rate, Poly methacrylic acid-alginate

INTRODUCTION

In recent years pharmaceutical companies are oriented towards designing new pharmaceutical dosage forms of existing drugs rather than discovering new drug products. Utilization of the existing resource of marketed and patented drug substances with known therapeutic effects, and modification of their pharmaco-therapeutic characteristics by incorporation in suitable drug delivery system, has been the target of recent pharmaceutical development. Hydrogels have been used extensively in the development of the smart drug delivery systems. Hydrophilic gels called hydrogels are cross-linked materials absorbing large quantities of water without dissolving. Their ability to absorb water is because of its crosslinking network structure which is formed by polymer bearing hydrophilic groups such as –OH, –CONH, –COOH, $–SO_3H$, and $–NH_2$ [1, 2]. Softness, smartness, and the capacity to store water make hydrogels unique materials [3, 4].

If water is removed from these swollen biomaterials, they are called xerogels, which are the dried hydrogels. The network structure can be macroporous, microporous or nonporous. Macroporous hydrogels are having large pores of dimension 0.1 to 1 µm. Microporous hydrogels having small pore size of the gel network, usually in the range of 100-1000 angstrom. Nonporous hydrogel are the mesh-

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like structures of macro- molecular dimension usually in the range of 10 - 100 angstrom.

Hydrogels can be formed from both natural and synthetic polymers [5, 6]. Hydrogels based on natural polymers can have insufficient mechanical properties, contain pathogens and evoke immune responses. On the other hand, they have numerous advantageous properties like inherent biocompatibility, biodegradability, bacteriostatic and wound healing properties, ex: collagen, gelatin and polysaccharides such as alginate and agarose. Synthetic hydrogels do not have these inherent bioactive properties and can be prepared by using chemical polymerization methods. There are many approaches based on genetic engineering and biosynthetic methods to also create the unique hydrogel materials [7].

CLASSIFICATION OF HYDROGEL

Hydrogels are classified into two categories

1. Chemical gel: They are called as permanent or chemical gels, when they are covalently cross-linked (replacing hydrogen bond by stronger and stable covalent bonds) networks [8]. They attain an equilibrium swelling state which depends on the polymer-water interaction parameter and the crosslink density.

2. Physical gel: They are called as reversible or physical gels, when the networks are held together by molecular entanglements, and / or secondary forces including ionic, hydrogen bonding or hydrophobic interactions. In physically cross-linked gels, dissolution is prevented by physical interactions, which exist between different polymer. All of these interactions are reversible, and can be disrupted by changes in physical conditions or application of stress [9].

ADVANTAGES

* Environmentally sensitive hydrogels : These hydrogels have the ability to sense changes of pH, temperature, or the concentration of metabolite and release their load as result of such a change.
* Hydrogel is more elastic and stronger.
* Entrapment of microbial cells within polyurethane hydrogel beads bears the advantage of low toxicity.
* Natural hydrogel materials are being investigated for tissue engineering, these materials include agarose, methylcellulose, hyaluronan, and other naturally derived polymers [10, 11].
* Hydrogel-based microvalves have a number of advantages over conventional microvalves, including relatively simple fabrication, no external power requirement, no integrated electronics, large displacement and large force generation.

DISADVANTAGES

* The main disadvantages are the high cost and the sensation felt by movement of the maggots.
* Its disadvantage includes thrombosis at anastomosis sites and the surgical risk associated with the device implantation and retrieval.
* Hydrogels are nonadherent, they may need to be secured by a secondary dressing.
* Disadvantages of hydrogel in contact lenses are lens deposition, hypoxia, dehydration and red eye reactions.

PROPERTIES OF HYDROGEL

Hydrogels are water swollen polymer matrices, with a tendency to imbibe water when placed in aqueous environment. This ability to swell, under biological conditions, makes it an ideal material for use in drug delivery and immobilization of proteins, peptides, and other biological compounds. Due to their high water content, these gels resemble natural living tissue more than any other type of synthetic biomaterial. These networks have a three dimensional structure, crosslinked together either physically or chemically. This insoluble crosslinked structure allows immobilization of

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active agents, biomolecules effectively, and allows for its release in well-defined specific manner. Thus the hydrogels biocompatibility and crosslinked structure are responsible for its varied applications [12].

PREPARATION METHODS OF HYDROGELS

Hydrogels are polymeric networks. This implies that crosslinks have to be present in order to avoid dissolution of the hydrophilic polymer chain in aqueous solution. The various methods for crosslinking are as follows:

Crosslinking of Polymers: In this method chemically crosslinked gels are formed by radical polymerization of low molecular weight monomers, or branched homopolymers, or copolymers in the presence of crosslinking agent. This reaction is mostly carried out in solution for biomedical applications [13].

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

Crosslinking by High Energy Radiation: High energy radiation, such as gamma and electron beam radiation can be used to polymerize unsaturated compounds. Water soluble polymers derivatized with vinyl groups can be converted into hydrogels using high energy radiation [14].

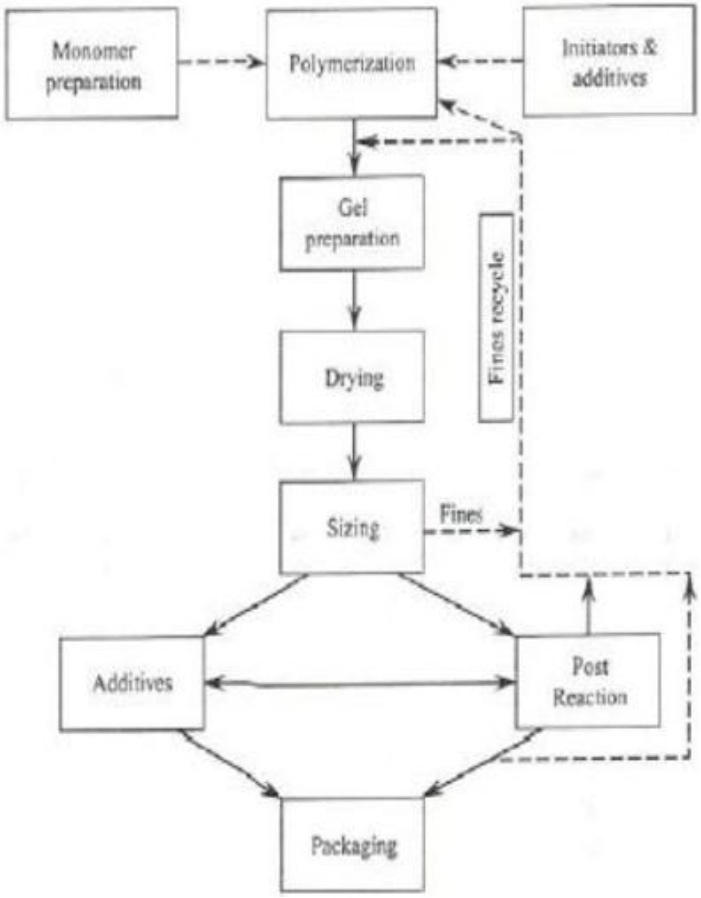

Fig 1: Hydrogel preparation block diagram

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Complex coacervation: Complex coacervate gels can be formed by mixing of a polyanion with a polycation. 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 2). One such example is coacervating polyanionic 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)

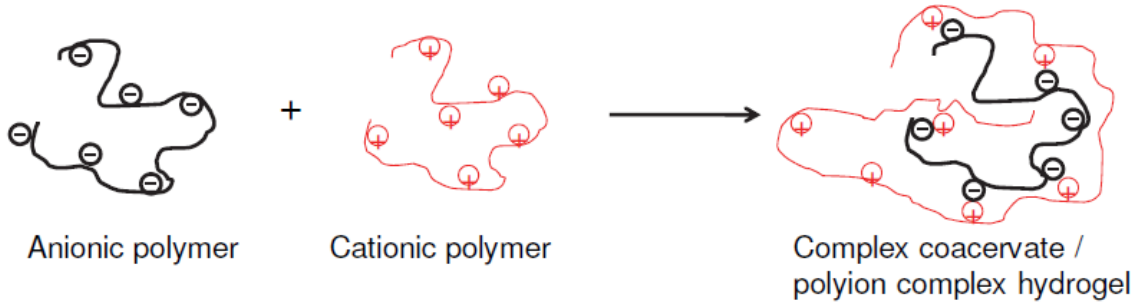

Fig 2: Complex coacervation between a polyanion and a polycation.

Crosslinking Using Enzymes: Recently a new method was published using an enzyme to synthesize PEG-based hydrogels. A tetrahydroxy PEG was functionalized with addition of glutaminyl groups and networks were formed by addition of transglutaminase into solution of PEG and poly (lysine-cophenylalanine).

Several techniques have been reported for the synthesis of hydrogels. A chromia alumina hydrogel was prepared as in the preceding example except that ammonium nitrate was substituted as ammonium sulfate as base exchange solution. A portion of washed hydrogel was impregnated in 13 liters of an aqueous solution maintaining 775 g of copper acetate and 223 g of potassium acetate. The impregnated hydrogel was dried in 100% steam at 260-270^{o} F and tempered 4 hours at 1100^{o} F in a hydrogen atmosphere.

* Polyvinyl Alcohol–Gelatin Hydrogel was prepared, In short, 2.5 g of gelatin was dissolved in 100 mL of a 10% aqueous solution of PVA. Concentrated hydrochloric acid (HCl, 0.05 mL) was added, and the resulting dispersion was stirred (using a overhead stirrer at 100 ± 5 rpm) at 70°C for a half-hour to carry out the esterification reaction between PVA and gelatin.

* Hydrogel sheets based on poly(vinyl alcohol) (PVA) and poly(vinyl acetate) (PVAc) have been prepared by the technique of acetalization of PVA using formaldehyde and grafting of acrylic acid onto PVAc by gamma irradiation. PVA hydrogel (PVAB) sheets have been prepared in geometrically stable shapes by compression moulding process.

* Semicrystalline crosslinked poly (vinyl alcohol) hydrogels in the form of films were prepared by electron beam irradiation and a subsequent slow dehydration process at 25 ± 1°, using various drying agents.1 As a result, hydrogels synthesized contain weakly acidic groups like carboxylic acids, or a weakly basic group like substituted amines, or a strong acidic and basic group like sulfonic acids, and quaternary ammonium compounds.

* The synthesis of hydrogel in industry is consist of solution and reversed suspension and reversed emulsion polymerizations.

DRUG RELEASE MECHANISM

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Diffusion controlled: Most common drug release mechanism for hydrogel is Diffusion-controlled. Fick's law of diffusion with either constant or variable diffusion coefficients is commonly used in modeling diffusion-controlled release. Drug diffusivities are generally determined empirically or estimated a prior using free volume, hydrodynamic, or obstruction-based theories.

Chemically controlled: Chemically-controlled release is used to describe molecule release determined by reactions occurring within a delivery matrix. The most common reactions that occur within hydrogel delivery systems are cleavage of polymer chains via hydrolytic or enzymatic degradation or reversible or irreversible reactions occurring between the polymer network and releasable drug. Under certain conditions the surface or bulk erosion of hydrogels will control the rate of drug release. Alternatively, if drug-binding moieties are incorporated in the hydrogels, the binding equilibrium may determine the drug release rate. Chemically-controlled release can be further categorized according to the type of chemical reaction occurring during drug release. Generally, the liberation of encapsulated or tethered drugs can occur through the degradation of pendant chains or during surface erosion or bulk-degradation of the polymer backbone.

Swelling controlled: Swelling-controlled release occurs when diffusion of drug is faster than hydrogel swelling. The modeling of this mechanism usually involves moving boundary conditions where molecules are released at the interface of rubbery and glassy phases of swollen hydrogels.

CHARACTERIZATION OF HYDROGELS

Morphological Characterization: Hydrogels are characterized for morphology which is analysed by equipment like stereomicroscope. Also the texture of these biomaterials is analysed by scanning electron microscope to ensure that hydrogels, especially of starch, retain their granular structure [15].

Rheology: Hydrogels are evaluated for viscosity under constant temperature of usually 4^{o}c by using Cone Plate type viscometer. 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.

X-ray diffraction: Diffraction analysis is the estimation of crystalline or amorphous characteristics. The appearance of new peaks in powder pattern is characteristic of drug - excipient interaction. X-ray diffraction is particularly used for the determination of broad halos that is a characteristic of impurities in powder that determines the pattern of the arrangement in which the hydrogel layers are distributed.

Light scattering: Gel permeation chromatography coupled on line to a multi angle laser light scattering (GPCMALLS) is a widely used technique to determine the molecular distribution and parameters of a polymeric system. Hydrogel in a polymeric system can be quantified using this technique. This technique is widely used in quantifying the hydrogels of several hydrocolloids such as gum arabic, gelatin and pullulan. It can be demonstrated how mass recovery data obtained from GPC-MALLS correlate with actual amount of hydrogel obtained for dextran radiation in solid state[16].

In-Vitro Diffraction: The in-vitro diffraction study is quite popular for studying the release profile of hydrogel. 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

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equivalence between the drug solution is carried out. *In-vitro* diffraction of type-1 collagen hydrogel containing bioactive glass and silica sol-gel micromeritics particles are formulated and their *in-vitro* apatite forming ability have been simulated by body fluids that is assessed.

Fourier Transform Infrared Spectroscopy: Any change in the morphology of hydrogels changes their IR absorption spectra due to stretching and O-H vibration. Formation of coil or helix which is indicative of cross linking is evident by appearance of bonds near 1648cm-1. The stretching or bending vibrations are basically responsible for the changes in IR absorption spectra. FTIR is an easy way to identify the presence of certain functional groups in a molecule. Also one can use the unique collection of absorption bands to confirm the identity of a pure compound or to detect the presence of certain impurities.

Swelling measurement

The swelling measurement of hydrogel was carried out as follows. Pieces of xerogel were immersed into 250 ml distilled water. The samples of swollen hydrogel were weighed after removal of surface water using filter paper at designed time intervals. Data presented in this experiment were the mean values of triplicate measurements. Results were calculated according to the following equation:

Q= Ws/Wd

Where Ws is the mass of the hydrogel in the swollen state, Wd is the mass of the hydrogel in the dried state and Q is equilibrium swelling ratio.

Scanning Electron Microscopy : 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 [17, 18].

HYDROGELS TEST

Water Vapour Transmission Rate:

Water vapour transmission rate (WVTR) is defined as the quantity of the water vapour under specified temperature and humidity conditions, which passes through unit area of film material in fixed time. Water vapour transmission rate is measured in grams per square meter over a 25 hours period. It is inversely proportional to the moisture retentive nature of a wound dressing i.e the wound dressing with lower water vapour transmission rate will be able to retain wound surface moisture. Typically, a wound dressing material showing WVTR less than 35g/m2/hr is defined as moisture retentive and helps in a rapid healing.

Biocompatibility Test: Generally hydrogels are biocompatible and non-irritant in nature. In this method, the material whose biocompatibility has to be determined is placed in direct contact with the host environmental cells and is subsequently incubated for a specific period of time at 37^{o}c. In the second method, the material is placed in a suitable physiological solution and is incubated for a specific period of time at 37^{o}c to allow any leaching from the material. The leachates, so obtained, are used to carry out the biocompatibility tests in the presence of cells.

APPLICATIONS

· **Colon Specific Hydrogels:** Colon specific hydrogels of polysaccharide have been specifically designed because of presence of high concentration of polysaccharide enzymes in the colon region of GI. Dextran hydrogel is formulated for colon- specific drug delivery. The

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diisocyanate that is proposed for the equilibrium degree of mechanical strength[19].

· **Drug delivery in GI tract** - hydrogels delivers drugs to specific site in the GIT. In presence of micro flora drug loaded with colon specific hydrogels show tissue specificity and change in the pH or enzymatic action which causes degradation of drug.

· **Modified Dosage Forms:** An interesting research in the field of drug delivery is of bio-macromolecules like insulin delivered to the site of absorption with hydrogels of poly (methacrylamide co - itaconic acid)[20] .

· **Rectal Delivery** – hydrogels showing bioadhesive properties are used for recatal drug delivery.

· **Potein drug delivery –** hydrogels which show better compliance and form in situ polymeric network and release protein slowly.

· **Transdermal delivery –** hydrogels can be used as controlled release devices in the filed of wound dressing due to it swelling properties. Hydrogel based formulations are being explored for transdermal iontophoresis to obtain enhanced permeation of products.

· **Subcutaneous delivery –** anticancer drugs are mainly used for the subcutaneous delivery. Implantable vegetable are now leading towards the development of biodegradable system which don't require surgical removal once the drug administered.

· **Cosmetology –** hydrogels when implanted into breast accentuate them for aesthetic reason. These implants has silicon elastomer shell and are filled with hydroxyl propyl cellulose polysaccharide gels.

· **Gene delivery –** change in composition of hydrogels leads to effective targeting and delivery of nuclei acids to specific cells for gene therapy. Hydrogels has more potential application in the treatment of many genetic or acquired diseases.

· **Wound healing –** modified polysaccharide found in cartilage is used in formation of hydrogels to treat cartilage defects. For example, the hydrogel of gelatin and polyvinyl alcohol together with blood coagulants are formulated.

· **Tissue Engineering –** micronized hydrogels are used to deliver macromolecules into cytoplasm of antigen presenting cells. Natural hydrogels material is used for tissue engineering include agarose, methylcellulose and other naturally derived products.

· **Tropical drug delivery –** instead of conventional creams, hydrogels formulation are employed to deliver active components like desonide, a synthetic corticosteroids used as an anti – inflammatory for better patient compliance.

RECENT TRENDS OF HYDROGEL

Microparticles of Poly methacrylic acid and novel semi-interpenetrating network composed of Poly methacrylic acid-alginate (PMAA) were prepared and their application in oral insulin delivery was evaluated. The release kinetics at pH 7.4 exhibited sustained release of insulin for more than 5 hrs in case of PMAA microparticles whereas burst release of insulin (90% of total insulin loaded) within 1 hr of study was observed in the case of PMAA alginate microparticles.

The new type of hydrogel system HYPAN: A physical network of crystalline clusters, which fully replace the covalent network typical of other hydrogels, distinguishes HYPAN hydrogels. As a result, HYPAN hydrogels can be processed by a number of methods unusual for hydrogels, such as extrusion and injection

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molding. Recent developments in the field of polymer science and technology has led to the development of various stimuli sensitive hydrogels like pH, temperature sensitive, which are used for the targeted delivery of proteins to colon, and chemotherapeutic agents to tumors. Some environmental variables, such as low pH and elevated temperatures, are found in the body. For this reason, either pH-sensitive and/or temperature sensitive hydrogels can be used for site-specific controlled drug delivery. Hydrogels that are responsive to specific molecules, such as glucose or antigens, can be used as biosensors as well as drug delivery systems. The liposomal drug delivery system developed here enables controlled release of vasodilator and would allow an appropriate time for beginning irradiation treatment to be defined.

CONCLUSION

Hydrogel based delivery devices can be used for oral, ocular, epidermal and subcutaneous application. Due to their high water contents and soft consistency hydrogels resemble natural living tissue more than any other class of synthetic biomaterials. Recent developments in the field of polymer science and technology has led to the development of hydrogel for the targeted delivery of proteins to colon, and chemotherapeutic agents to tumors. Synthesis of new polymers and crosslinkers with more biocompatibility and better biodegradability would be essential for successful applications. Modified dosage forms of hydrogels have paved the way for a large number of formulations and thus have gained tremendous approach in the field of science. These hydrogels being biocompatible and biodegradable in nature have been used in the development of nano biotechnology products and have marvelous applications in the field of controlled drug delivery as well. That is why these turn-able biomedical drug delivery devices are gaining attention as intelligent drug carriers.

TABLE 1 : EXAMPLE OF HYDROGEL PREPARED BY DIFFERENT METHODS

S. no	Preparation method	Type	Polymer system
1.	Solution polymerization/ cross-linking by radox initiator	pH	Poly(methacrylic acid-co-methyl methacrylate)
2.	Solution polymerization/ cross-linking by radox initiator	Thermo	Poly(N-t butyl acryl amide-co acrylamide)
3.	By physical cross-linking	pH	Chitosanalginate, chitosan CMC sodium and chitosancarbopol
4.	Solution polymerization/ cross-linking by radox initiator	Thermo	Poly(N-isopropylacrylamide) (PNIPAAm)-poly(ethylene glycol) diacrylate
5.	Polymerization by radiation	pH	Agarose and carbomer 974P macromers
6.	Solution polymerization/ cross-linking by radox initiator	pH	Poly (acrlyamide-co- acrylic acid)
7.	Solution polymerization/ cross-linking by radox initiator	Thermo	N-allyl maleamic acid (AMA) with acrylamide and acrylic acid
8.	Solution polymerization/ cross-linking by thermal initiator	Thermo	N-allyl maleamic acid (AMA) with acrylamide and acrylic acid
9.	Solution polymerization/ cross-linking by UV-induced initiation	pH	Poly(ethylene glycol) methacrylate-graft-poly(glutamic acid)
10.	Gamma radiation	Ion	Acrylamide/2-hydroxyethyl methacrylate

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TABLE 2: SUMMARY OF SELECTED HYDROGEL APPLICATIONS IN TISSUE ENGINEERING.

Intended tissue	Cell type(s) studied	Hydrogel type(s)	Hydrogel functioning
Bone	Osteoblast	PEG–PLA [a]	Drug delivery, Encapsulation
Bone	Fibroblast	PEG	Scaffold
Cardiovascular	Bone marrow cells	Fibrin	Cell delivery
Cardiovascular	Embryonic carcinoma	PEG	Encapsulation
Cardiovascular	Hepatocytes HA	HA, Alginate, Carboxymethylcellulose	Scaffold
Cartilage	Chondrocytes	Fibrin	Cell delivery, Scaffold
Cartilage	Chondrocytes	PEO Semi-IPN	Drug delivery, Encapsulation
Cartilage	Chondrocytes	PEG	Drug delivery, Encapsulation
Connective Tissue	Fibroblast	HA	Encapsulation, Scaffold
ECM	Fibroblast	HA, Chondroitin Sulfate, Gelatin	Encapsulation, Scaffold
Facial	Chondrocytes	Alginates	Encapsulation, Implant
Neural	Neuroprogenitors	SAP	Scaffold
Pancreatic	Islet of Langerhans	PEG	Encapsulation
Skin	Fibroblast	HA	Scaffold
Spinal cord	Astroglial cells	Collagen	Encapsulation
Vascular	HESCs	Dextran	Drug delivery, Encapsulation

TABLE 3: MARKETED FORMULATIONS OF HYDROGELS

Sr. No	Name of the Hydrogel Drug	Application
1	Aquatrix II (Skin adhesive hydrogel)	Wound, Burn, Adhesive
2	Medicell	Medicated foam for burns
3	Hydromer	Antithrombic DNA immobilisation
4	Aquamere(Coating hydrogel)	Cosmetics
5	Dermaseal	Allergen blocker
6	Aquatrix	Super absorbent

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