Available Online at http://www.journalajst.com

ASIAN JOURNAL OF SCIENCE AND TECHNOLOGY

ISSN: 0976-3376

Asian Journal of Science and Technology
Vol. 09, Issue, 05, pp.8117-8125, May, 2018

RESEARCH ARTICLE

HYDROGELS AS ADVANCED BIO-MATERIALS FOR DRUG DELIVERY SYSTEM

[1,*]Shanti Sagar, [1]Srivani, M., [1]Lavanya, S., [2]Basavaraj K. Nanjwade and [3]Sunitha Reddy, M.

[1]Bojjam Narasimhulu Pharmacy College for Women, Saidabad, Hyderabad-500059, India
[2]Trroy Life Sciences Pvt Ltd, C-14, KSSIDC Industrial Area, New Town Yelahanka, Bangalore-560064, Karnataka, India
[3]Jawaharlal Nehru Technological University Kukatpally Hyderabad, India

ARTICLE INFO

Article History:
Received 19th February, 2018
Received in revised form
20th March, 2018
Accepted 16th April, 2018
Published online 30th May, 2018

Key words:
Hydrogels, Polymer,
Hydrophilic,
Cross linking,
Swelling,
Biocompatibility.

ABSTRACT

Soft and jelly like structure, physical properties, higher permeability and release of entrapped drug in controlled and lower interfacial tension, manner have made hydrogels to focus on exploration in different biomedical fields in particular hydrogels have been used extensively in the development of drug delivery system. These unique physico-chemical properties of hydrogels have emerged their particular interest in their use in drug delivery system. These are three-dimensional, hydrophilic, polymeric networks capable of absorbing and retaining large amounts of water or biological fluids. Their affinity to absorb and retain a large amount of water is attributed to the presence of hydrophilic groups such as –OH, CONH–, –CONH2–, and –SO3H in polymers forming hydrogel structures. Due to the contribution of these hydrophilic groups in the network make the polymer hydrated to different degrees (sometimes, more than 90% wt.), their high water content, porosity and soft texture and consistency, they closely resemble to natural living tissues. Hydrogels may be chemically stable or they may degrade and eventually disintegrate and dissolve. The purpose of this present review is to describe some advances in hydrogels, in its preparation methods, their application in biomedical and pharmaceutical fields.

INTRODUCTION

According to an article published in 1894 Lee, Kwon and Park was first used the term hydrogels, anyway, these materials are now not considered as hydrogels. Hydrogels are in fact the first materials prepared to be used inside the patient body. After that a number of studies on hydrogels for many biomedical applications began to rise, especially from the year of 70's. The aims and goals and the number of materials changed and enlarged constantly over the years. Wichterlie and Lim was the first to report these synthetic hydrogels with controlled properties such as absorbing swelling and shrinking over several orders of magnitude. This initial discovery provided the foundation for stimuli-responsive systems. The cross-linked polymer network was highly sensitivity to many stimuli such as solvent composition, solutes, pH, temperature, electric field, and light. [1] Hydrogels are the three dimensional network of hydrophilic co-polymers or homo-polymers. These gels are also named as Hydrophilic gels, in which the dispersion medium is a biological fluid or water. The important properties of hydrogels like softness, elasticity, swelling, absorbent nature, flexibility and the capacity to store water made very interesting polymers.

Corresponding author: **Shanti Sagar,**
Bojjam Narasimhulu Pharmacy College for Women, Saidabad, Hyderabad-500059, India

Compared with other types of biomaterials, hydrogels have distinct properties such as high water content, controllable swelling behavior, ease of handing, as well as biocompatibility, which makes them attractive for biomedical applications. Based on their chemical structure and crosslink network, hydrogels can respond to different types of stimuli including thermal, pH, light, and chemical stimuli, which can meet various application requirements. [2] These gels are intelligently responding to any variations of environmental stimuli such as ionic strength, pH, electric field, temperature, enzyme etc. Hydrogels resembles with the living tissue (in swollen state) due to their soft, flexible and biocompatible nature. Hence, these are used as biomaterials that find application in several fields of biomedical or pharmaceutical industry. [3]

Types of hydrogels

The polymer chains of a hydrogel are cross-linked. The nature of the connections is different for two general classes, physical and chemical. For the former, the connections are weaker and more reversible; for example, heat may break the chain-chain link. Physical hydrogels which contain polymer chains are combined together by hydrogen bonds, electrostatic forces, hydrophobic interactions or chain entanglements. The polymer chains of chemical hydrogels are connected by permanent covalent bonds. A covalent bond is characterized by the

sharing of pairs of electrons between atoms. [4] The hydrogel products can be classified on different bases as detailed below: [5,6,7]

a) Classification based on source **[5]:** Hydrogels can be classified into two groups based on their source

- natural origin
- synthetic origin

b) Classification according to polymeric composition **[5]**

A) **Homopolymeric hydrogels:** 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.
B) **Copolymeric hydrogels:** It comprises 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.
C) Multipolymer Interpenetrating polymeric hydrogel (IPN)

An essential class of hydrogels is made of two independent components which exist in network form known as cross-linked synthetic and/or natural polymer components. In semi-IPN hydrogel, one component is a cross-linked polymer and other component is a non-cross-linked polymer

c) Classification of hydrogels depends on their physical structure **[6]**

(a) Amorphous (non-crystalline).
(b) Semi-crystalline: A complex mixture of amorphous and crystalline phases.
(c) Crystalline.
(a) d) Classification based on physical appearance

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

e) Classification according to network electrical charge **[7]**

(a) Nonionic (neutral).
(b) Ionic (including anionic or cationic).
(c) Both acidic and basic groups are present in amphoteric electrolyte (ampholytic)
(d) Zwitter ionic (polybetaines) containing both anionic and cationic groups in each structural repeating unit.

Properties of hydrogels

Hydrogels receive considerable attention today because of their use in the field of pharmaceutical and bio-medicals. These materials have their unique properties such as swelling, bio-compatible; providing mechanical support, one must evaluate hydrogels for these properties before use them in any concerned applications.

a) ***Swelling properties:*** A small change in surrounding condition may cause fast and reversible changes in hydrogel. The changes in some parameters like pH, temperature, electric signal, presence of enzyme or other ionic species may lead to a change in physical nature of the hydrogel. These change results in change in size as well as water content of hydrogels. Degree of ionization of the functional groups indicates its swelling profile and hence resulting in the volume change. First the polar hydrophilic groups get hydrated upon contact with water which leads to the formation of primary bounded water. As a result the network swells and expels the hydrophobic groups which are also capable of interacting with the water molecules. This results to the formation of hydrophobically bounded water, also called 'secondary bound water'. Primary and secondary bound water are often combined and called 'total bound water'. The network will absorb additional water, due to the osmotic driving force of the network chains towards infinite dilution. This additional swelling is opposed by the physical cross-links, leading to an elastic network retraction force. [8]

b) ***Mechanical properties:*** A mechanical property is one of the important aspects from the pharmaceutical as well as biomedical point of view. The evaluation of this property is essential in various biomedical applications viz. ligament and tendon repair, tissue generation, wound dressing material, matrix for drug delivery, tissue engineering and as cartilage replacement material etc. The mechanical properties of prepared hydrogels should be such that it should maintain its physical structure during the delivery of therapeutic moieties at the predetermined period of time. By changing its degree of cross-linking the desired mechanical property of the hydrogel can be achieved. A desired hydrogel can be obtained by cross linking, increasing the degree of cross-linking resulting in stronger hydrogel could be achieved, though the higher degree of cross-linking decreases the % elongation of the hydrogels creates a more harder and brittle structure. Hence there is an optimum degree of cross-linking required to achieve a relatively strong hydrogel and yet maintaining its elastic nature.

c) ***Biocompatibility [10]:*** The other most important characteristic property of the hydrogel is its biocompatibility. Biocompatibility is the compatibility of the hydrogels as well as its degradation product with the immune system which should not be toxic. Ideally they should be metabolized into harmless products in the body so that they can be used as biological products or can be clearly excreted by the renal filtration. Generally, their hydrophilic surface which has a low interfacial free energy when it come in contact with body fluids, which also results in a low tendency for proteins and cells to adhere to these surfaces and enhances the biocompatibility. Moreover, the soft and rubbery and elastic nature of hydrogels also minimizes irritation to the surrounding tissues.

Polymers used to design hydrogels

Methods [11]

Hydrogels are nothing but the polymeric networks having hydrophilic properties. Either hydrophilic monomers or hydrophobic monomers are sometimes used in hydrogel

preparation to regulate the desired properties for specific applications. Hydrogels can be produced by reacting hydrophilic monomers with multifunctional cross-linkers like copolymerization or cross-linking and free-radical polymerizations etc.

These cross linked networks can be produced many methods. General methods are described below:

a) Physical cross-linking [12]:

These are also called as reversible gels, due to relative ease of production and the advantage of not using any chemical cross-linking agents made this physical cross linking as one of the interesting method to prepare hydrogels. Physically cross-linked hydrogels are of huge interest for the labile bioactive substances and living cells encapsulation and entrapment, especially when hydrogel development does in the absence of organic solvents and under mild conditions

- Heating/cooling a polymer solution: In this method a hydrogel is prepared by cooling hot solutions of polymer such as gelatin or carrageen an to form physically cross-linked gels. The gel formation is due to helix-formation, association of the helices and thus forming junction zones. Examples of such hydrogels are polyethylene glycol-polylactic acid hydrogel and polyethylene oxide-polypropylene oxide.
- Ionic interaction: in this method a hydrogel is prepared by Addition of multivalent ion such as di- or trivalent counter ions in ionic polymer leads to formation of cross linking between polymers. This method based on the principle of gelling polyelectrolyte solution (e.g. Na+alginate-) with a multivalent ion of opposite charges (e.g. Ca2+ + 2Cl). Examples of such hydrogels are chitosan-polylysine, chitosan-glycerol phosphate salt, and chitosan dextran hydrogels.

b) Complex Coacervation [13]

In this method a hydrogel can be prepared by allowing polymers of opposite charge to react. Formation of complex co-acervate gels by mixing of polyanions with a polycations. The underlying principle of this method is that polymers with opposite charges attract and stick together resulting in formation of insoluble complexes depending on the concentration and pH of the respective solutions. One such example is coacervating polyanionic xanthan with polycationic chitosan

H-bonding: This method is based on principle that a hydrogen bond is formed when electron deficient hydrogen atom has association with 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

c) Maturation -heat induced aggregation [14]

This method is based on principle that heat induced Aggregation of the proteinaceous material will usually resulting in increased molecular weight and subsequently produces a hydrogel form with enhanced mechanical properties and water binding and absorbing capability. The molecular changes occur due the maturation process demonstrates that a hydrogel can be produced with precisely structured molecular dimensions. The controlling step is that agglomeration of the proteinaceous components within the molecularly disperse system that is present in of the naturally occurring gum. Maturing of the gum leads to transfer of the protein associated with the lower molecular weight components to give larger concentrations of high molecular weight fraction. The method has also been applied on to other gums such as gum ghatti and Acacia

d) Freeze-thawing [15]

A cross linked hydrogel can also be prepared using repeating cycles of freeze thawing method as one of the physical cross linking method. The mechanism involves the formation of micro structures of crystals within the structure during freeze-thawing cycle. Examples of this type of hydrogels are freeze-thawed gels of polyvinyl alcohol and xanthan gum

e) Chemical cross-linking [16]

Chemical cross-linking here involves grafting of two monomers units on the backbone of the polymers or the use of a cross-linking agent to link two polymer chains. 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, formaldehyde etc). These methods are used to produce hydrogels from a range of natural polymers.

f) Chemical cross-linkers [17]

Hydrogels based on PHEA and commercial chitosan were prepared by crosslinking reaction in aqueous system using glutaraldehyde as the crosslinking reagent. In this methos 10 or 20 wt% aqueous solution with different composition of polymer was prepared and degassed by repeated vacuum and nitrogen purges. Next into the solution polymer a solution as added glutalaldehyde (10%) and catalytic HCl, was added, and the reaction mixture was placed at 40^0C for 5 h. The gel sheets could be formed in a glass mold and washed in excess water before being freeze-dried.

g) Grafting: [18]

Usually, hydrogels formulated by bulk polymerization have weak structure. To enhance the mechanical properties of a hydrogel and to increase this characteristic property, it can be attached on surface which is coated onto a sturdy solid 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

h) Radiation cross-linking [19]

Ionizing radiation, such as gamma rays and electron beams, can be used to initiate the polymerization for preparing the hydrogels of unsaturated compounds. The irradiation of

aqueous polymer solution results in the formation of radicals on the polymer chains. Also, radiolysis of water molecules results in the formation of hydroxyl radicals, which also attack the polymer chains resulting in the formation of macro-radicals. Recombination of the macro-radicals on different chains leads to forming of covalent bonds and finally a cross-linked structure. Examples of polymers cross-linked by this method are poly(vinyl alcohol), poly (ethylene glycol) and poly (acrylic acid).

Mechanism of water absorption

A hydrogel formation always refers to formation of gel by diffusion of water into this glassy polymer which often deviates from the predictions of Fick's law, leading to anomalous or non-Fickian diffusional behavior. According to fickian law there is no deformation of polymer during diffusion of water. The deviation from Fickian behavior has been associated with the finite rate at which the polymer structure deforms and rearranges, to accommodate more water molecules, and this has been observed situation for many hydrophilic polymeric systems. Depending upon the dynamics of polymer swelling and the penetration of drug and water, Fickian or non-Fickian drug transport may be observed. The relative importance of water diffusion and polymer relaxation can be described by the Deborah number (De), This viscoelastic nature of the polymer introduces relaxation times in the response, which affects the transport process defined as the ratio of a characteristic relaxation time (τ) to a characteristic diffusion time (θ). [20]

$De=\tau/\theta$
$\theta=L2/ Dwp$

Where, L is the characteristic length of the controlled release device and Dwp is the water diffusion coefficient.

When $De<<1$, relaxation is much faster than diffusion, and Fickian transport is observed. When $De\sim1$, relaxation and diffusion are coupled leading to a complex transport behavior, known as anomalous or non-Fickian transport. In Fickian diffusion, the rate of water absorption shows a linear increase as a function of the square root of time. Fickian diffusion is observed when the time scale of the macromolecular relaxation is either effectively infinite or zero, compared to the time required to establish a concentration profile in the polymer sample relative.

Characterization of hydrogels

Generally Hydrogels are characterized for their swelling, pH, network pore size, Rheology studies. Some of the characterization studies are discussed below.

a) Viscosity and pH [21]

The viscosity of hydrogel was determined by using Brookfield viscometer. The spindle number 2 was dipped in hydrogel preparation and rotated at 5, 10, 20, and 50 rpm at room temperature to determine viscosity pH of hydrogels is measured by using digital pH meter. In this method first the hydrogel preparation is wetted in saline phosphate buffer, then allowed to swell and then directly the pH measured by placing the electrode over the hydrogel provided the pH meter must be calibrated before its use.

b) Swelling properties [22]

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

Method A

In this method the dry hydrogel is placed in beaker in some amount deionized water for 48 hours at room temperature on a roller mixer. After complete swelling, the hydrogel is filtered through a stainless steel filer of 30 meshes size 681μm. The swelling is calculated as follows.

Swelling = WS-Wd/Wd

Where, Ws is the weight of hydrogels after swelling.
Wd is the weight of hydrogel in dry state.

Method B

In this method a dry hydrogel is placed in a volumetric vial and was dispersed in sufficient quantity of deionized water for 48 hrs at room temperature. The swollen hydrogel is then centrifuged to get the layers of water bound material and free unabsorbed water. The free water is separated and the swelling can be measured according to the Method A above.

Method C

In method C the dry hydrogel is placed in de-ionized water for 16 h at room temperature. After swelling, the hydrogel was filtered using a stainless-steel filter of 100 of mesh size 149μm. 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.

c) Rheology [23]

The rheological properties are very much important from the flow property point of view and it depends on the type and nature of polymer such as structure i.e. molecular weight, association, entanglement, cross-links present in the hydrogel system. A polymer solution is usually viscous at low frequencies, tending to fit the scaling laws: $G' \sim \omega 2$ and $G'' \sim \omega$. But at high frequencies, elasticity dominates ($G' > G''$). This type of behavior corresponds to Maxwell-type behaviour with a single relaxation time that can be determined from the crossover point and, this relaxation time increases with concentration. For cross-linked microgel dispersions, it exhibits G' and G" being almost independent of oscillation frequency.

d) Spreadability [24]

A specialized apparatus is used to check spread ability of hydrogels, it consist of wooden block with scale and two glass slides having a pan mounted on a pulley. A excess amount of

formulation of hydrogel was placed between these two glass slides and a weight 100 gm was placed on upper glass slide for 5 minutes to for uniform spreading of formuation. Weight can be added and the time to separate the two slides was taken as Spreadability time.

$S = (m \times l) / t$

Where S is Spreadability, m is weight tied on upper slide, l is length of glass slide and t is time taken in seconds.

e) Skin irritation test [21]

The most important test of hydrogel is skin irritancy test which is conducted on rabbits. In this method the preparation was applied on two rabbits and the applied area was protected with gauze or bandage and allowed to remain for 24 hours. After 24 hours the formulation was removed and the area was checked for any signs of edema and erythema. The average irritancy score was calculated using below formula.

Average irritation scores= (erythema reaction scores + edema reaction scores) / time interval.

f) Network pore size [25]

Pore-size distributions of hydrogels are effectively influenced by three factors:

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

Porosity is a morphological characteristic of a material that can be illustrated as the presence of void cavity inside the bulk. It is worthwhile to control the porosity in many devices for a wide range of applications, such as optimal cell migration in hydrogel-based scaffolds or tunable lode/release of macromolecules. One ultimate goal of microengineering techniques for tissue fabrication is the precise control of not only porous structures, but of the microarchitectural features within the construct as well. By recreating specific microarchitectural motifs, tissue engineers aim to optimize cell viability, morphology, and function.

g) Biocompatibility [26]

Drug Solubility: Solubility studies of these micro particulate systems were carried out at required pH range 1.2- 6.8 in the deionized water. Hydrogel microparticles were enclosed into screw-capped vials having 1 mL of buffer media, and then a thermo shaker incubator was used for shaking these vials at 37°C±0.5°C at 150 rpm for 72 h. All samples were filtered through 0.45 µm membrane filters, diluted with buffer and analyzed for solubility on a UV–visible spectrophotometer.

h) In-vitro release studies [27]

The in vitro drug release rate of from hydrogel Can be carried out using USP type 2 (Paddle) apparatus in 900 mL of 0.1 N HCl, at 370c ±0.50c at 50 rpm for the first 2 hours and then replaced by phosphate buffer of pH 7.4. Aliquots of 5 mL sample were withdrawn from the dissolution apparatus at the appropriate time interval for 24 hrs, and the samples were replaced with fresh dissolution medium after every withdrawal. The samples were filtered and absorbance of these solutions was measured using UV/Visible double-beam spectrophotometer. The percentage drug release was calculated.

i) Amount of free and bound water [28, 29]

The methods used to characterise and quantify the amount of free and bound water in hydrogels are differential scanning calorimetry (DSC) and nuclear magnetic resonance (NMR). The proton NMR gives information about the interchange of water molecules between the so-called free and bound states. 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 (Hoffman, 2002).

j) Solution-Gel analysis [30]

For radiation cross-linking, the sol-gel analysis is an important characterisation tool as it allows to estimate the parameters such as yield of cross-linking and degradation, gelation dose, etc. and to correlate these with some physico-chemical properties. The relation of sol fraction and absorbed dose according to the Charlesby–Pinner equation (Rosiak, 1998) is given in equation

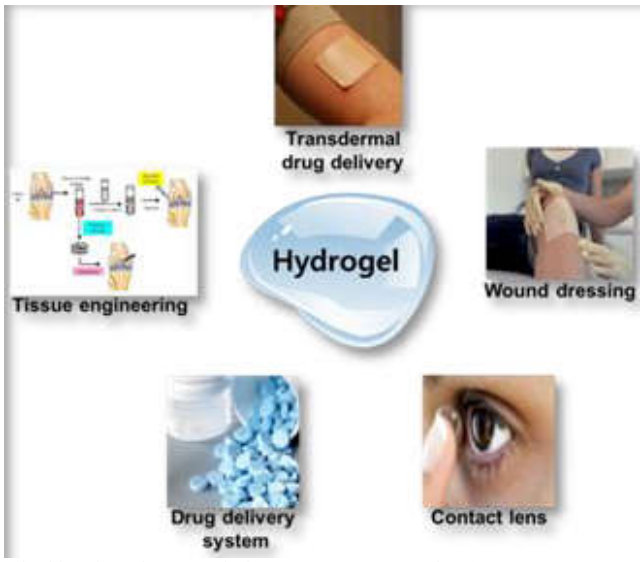
$$s + \sqrt{s} = \frac{p_0}{q_0} + \frac{2}{q_0 \mu_{2,0} D}$$

This equation is widely reported for the linear polymers like carboxymethyl cellulose.

Where, s is the sol fraction (s = 1-gel fraction). P_0 is the degradation density, average number of main chain scissions per monomer unit and per unit dose. q_0 is the cross-linking density, proportion of monomer units cross-linked per unit dose. $\mu_{2,0}$ is the initial weight average degree of polymerization, and D is the radiation dose in Gy.

Applications

Many synthetic and natural polymers have been produced as hydrogels with their main use in tissue engineering, pharmaceutical, and biomedical fields. Because of the high water absorption capacity and biocompatibility have made them to be used in many wound dressing, drug delivery, agriculture, sanitary pads as well as trans-dermal systems, dental materials, implants, Injectable polymeric systems, and ophthalmic applications.



Ref: Shivani P. Shetye et al. Ijrm.Human, 2015; Vol. 1 (1): 47-71.

Fig. 1. Various applications of hydrogels

Wound Dressing and Wound Healing

As Hydrogels are available in several forms such as fibre, membrane, emulsion, matrix, film, or microsphere scaffolds, including amorphous hydrogels (that can take up the shape of the wound), saturated gauzes or hydrogel sheets. Hydrogels that are shapeless are composed of insoluble non-crosslinked hydrophilic polymers can form of a gel containing water. These amorphous hydrogels can be packaged in tubes, spray bottles or foil packs and applied directly to the wound and which is usually covered with a secondary dressing (for example foam or gauze). Exudate is directly absorbed into the gel while moisture evaporates through the secondary dressing. [31]

Ref: www.carepathway.com

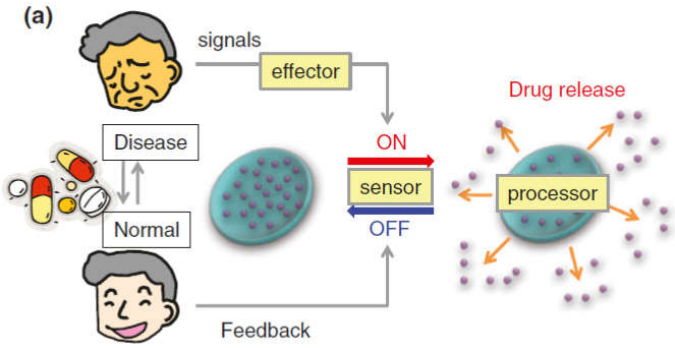
Fig. 2. A typical hydrocolloid dressing

Contact Lenses and Ocular Implants

One of important hydrogel application is medicated contact lenses which are attracting keen interest for ophthalmic drug delivery, as they significantly increase residence time of the drug in the precorneal area because of the geometric barrier provided by the contact lenses to the drug when it diffuses out from the gel matrix into the tear film. [32]

ON-OFF Controlled Drug Delivery in GIT

Well-designed drug delivery systems must control solute release over time 'on–off' drug release control is achieved by using sugar responsive gels for the possible treatment of diabetes mellitus. Pancreatic islets release insulin to lower the blood glucose level and regulate the glucose level within the range from 70 to 110 mg/dl by an auto feedback mechanism under healthy physiological conditions. [33]



Ref: M. Ebara et al., Smart Biomaterials, NIMS Monographs.

Fig. 3. on-off controlled drug release

Tissue Engineering and Tissue Regeneration

Tissue engineering has emerged as a promising technology for the design of an ideal, responsive, living substitute with properties similar to those of the native tissue Scaffolds play an important role in scaffold-guided in vitro tissue engineering. Scaffolds are basically 3D structural templates that support cell adhesion, migration, differentiation, and proliferation and provide guidance for neotissue formation. Hydrogels in particular have emerged as useful scaffolding biomaterials as they most closely resemble the natural tissues. Hydrogels are emergent candidates for applications in cartilage regeneration. Hydrogels are three-dimensional hydrophilic polymer networks made up of water-soluble polymers, cross-linked by either covalent or physical methods. Cell matrix adhesion to hydrogel is an important interaction which regulates stem cell survival, self-renewal, and differentiation. Depending on their physical structure and chemical composition, hydrogels can preserve a compositional and mechanical similarity with the native extracellular matrix of cartilage. These properties are necessary for controlling cell response, differentiation and functional tissue regeneration. [34]

Biosensors

A common aspect in all biosensors is the presence of a biological recognition part that makes it possible to analyze biological information. Biosensors are becoming increasingly important as practical tools to cover a wide variety of application areas including point-of-care testing, home diagnostics, and environmental monitoring. Biological recognition part known as bioelement consists of different structures like enzymes, antibodies, living cells, or tissues but

the point is its specificity toward one analyte and zero response to other interferents. There are various methods for coupling biomolecules with sensors including entrapment into membranes, physical adsorption, entrapment into a matrix, or covalent bonding. [35]

Dental Applications

Pulp regeneration therapy is important to overcome the limitations of conventional therapy to induce reparative dentinogenesis. Presently, dentists have no choice but to remove the whole dental pulp with an endodontic procedure when a dentin defect with pulp exposure reaches a critical size resulting in an irreversible pulp condition. To overcome this limitation, it is considered important to develop pulp regeneration therapy as well as clarify the mechanisms of pulp wound healing. Pulp wound healing and regeneration have common processes, and results of a number of studies have indicated that pulp wound healing consists of initial inductions of apoptosis of damaged pulp cells, followed by reactionary dentinogenesis by surviving odontoblasts and reparative dentinogenesis by odontoblast-like cells. [36, 37]

Injectable Hydrogel Polymeric System

A novel biodegradable, fast in situ forming hydrogel based on oxidized dextran and amino gelatin. Dextran is oxidized to generate aldehyde functional groups to react with free amino groups of modified gelatin for formulating nontoxic hydrogels with highly porous structures. According to the results, adjustable physicochemical properties can be obtained through simply altering the ratio of Odex and gelatin. Moreover, with the increase of incorporated gelatin, better biocompatibility was shown in the composite hydrogels, which exhibited its potentially high application prospect in the field of cartilage tissue engineering. [38]

Ref: Pan J, Guo C, Fei T, Fan W, Liu J, *et al.* (2013)

Fig. 4. A Novel Injectable Hydrogel

Pharmaceutical and Technical Products

Based on the understanding of the structural and chemical characteristics, hydrogels have been widely used for numerous biological, medical and technological applications.such as molecular imprinting, configurational , biomimensis, cholesterol cage, tethered polymers, hydrogels and nanogels. [39]

Super Absorbents

Biodegradable superabsorbent hydrogels ameliorate water availability for plants by increasing water holding properties by growing media. Due to increasing attention for environmental protection issues, these hydrogels arise lively interest for potential application in agriculture in particular for short growing cycle crops. [40]

Watering Beads for Plants

Another simple application of hydrogels consists in rough powders of polyacrylamide or potassium polyacrylate matrix sold with a huge range of names (Plant-Gel, Super Crystals, Water -Gel Crystals) and used as long term reservoir of water for plant growth in gardening, domestic and sometimes industrial horticulture. hydrogel, these materials are optimized for their ability of releasing water, instead of the ability of retaining it. The sustained release of many diverse species is, indeed, one of the main strength of hydrogels on the market. [41, 42]

REFERENCES

1. Praveen Thoniyot, Mein Jin Tan, Anis Abdul Karim, Xian Jun Loh* et.al**.** Nanoparticle–Hydrogel Composites: Concept, Design, and Applications of These Promising, Multi-Functional Materials. https://www.ncbi.nlm.nih.gov/ pubmed/27980900
2. Qinyuan Chai, Yang Jiao and Xinjun Yu *. Hydrogels for Biomedical Applications: Their Characteristics and the Mechanisms behind Them. Gels 2017, 3, 6; doi: 10.3390/gels3010006 www.mdpi.com/journal/gels. www. mdpi. zcom/2310-2861/3/1/6/pdf
3. Anamica P. P. Pande. Polymer Hydrogels and Their Applications. *International Journal of Materials Science* ,ISSN 0973-4589 Volume 12, Number 1 (2017) © Research India Publications. http://www.ripublication.com. https:// www.ripublication.com/ijoms17spl/ijomsv12n1spl_ 03.pdf
4. George A. Paleos. What are Hydrogels? Pittsburgh Plastics Manufacturing, Butler, PA Copyright © Pittsburgh Plastics Manufacturing Inc. 2012. www.pittsburghplastics.com/ assets/files/What%20Are%20Hydrogels.pdf
5. Enas M. Ahmed. Hydrogel: Preparation, characterization, and applications: A review. *Journal of Advanced Research,* (2015) 6, 105-121. http://dx.doi.org/10.1016/ j.jare. 2013.07.006. sites.acca.org/sites/.../hydrogel_preparation_ characterization_and_applications.pdf
6. Waham Ashaier Laftaha , Shahrir Hashim a & Akos N. Polymer Hydrogels: A Review. Ibrahim a Polymer-Plastics Technology and Engineering, 50: 1475–1486, 2011 http://dx.doi.org/10.1080/03602559.2011.593082 https:// www.researchgate.net/publication/233211485_Polymer_H ydrogels_A_Review
7. Sweta Garg, Ashish Garg. Hydrogel: Classification, Properties, Preparation and Technical Features. Asian Journal of Biomaterial Research 2016; 2(6): 163-170 www.ajbr.in researchgate.net/publication/316075989_ Hydrogel_Classification_Properties_Preparation_and_Tech nical_Features
8. Shailesh Kumar Singh, Archana Dhyani and Divya Juyal. Hydrogel: Preparation, Characterization and Applications *The Pharma Innovation Journal,* 2017; 6(6): 25-32.

sites.acca.org/sites/.../hydrogel_preparation_characterization_and_applications.pdf
9. Preparation Methods And Properties Of Hydrogel: A Review International Journal of Pharmacy and Pharmaceutical Sciences ISSN- 0975-1491 Vol 5, Issue 3, 2013. *Int J Pharm Pharm Sci.,* Vol 5, Issue 3, 112-117. http://www.ijppsjournal.com/Vol5Issue3/7124.pdf
10. Syed K. H. Gulrez, Saphwan Al-Assaf and Glyn O Phillips. Hydrogels: Methods of Preparation, Characterisation and Applications. Progress in Molecular and Environmental Bioengineering 118 – 150From Analysis and Modeling to Technology Applications. https://www.intechopen.com/books/howtoreference/progress-in-molecular-and-environmental-bioengineering-from-analysis-and-modeling-to-technology-applications/ hydrogels-methods-of-preparation-characterisation-and-applications
11. Muhammad Faheem Akhtar, Muhammad Hanif, Nazar Muhammad Ranjha. Methods of synthesis of hydrogels. A review. *Saudi Pharmaceutical Journal,* 2015. http://dx.doi.org/10.1016/j.jsps.2015.03.022. https://www.researchgate.net/publication/273889400_Methods_of_synthesis_of_hydrogels_A_Review
12. Shailesh Kumar Singh, Archana Dhyani and Divya Juyal. Hydrogel: Preparation, Characterization and Applications. *The Pharma Innovation Journal,* 2017; 6(6): 25-32 www.thepharmajournal.com/archives/2017/vol6issue6/PartA/6-5-33-916.pdf
13. Madolia H, Sheo DM. Preparation and Evaluation of Stomach Specific IPN Hydrogels for Oral Drug Delivery: A Review. Journal of Drug Delivery & Therapeutics. 2013; 3(2):131-140. http://jddtonline.info/index.php/jddt/article/view File/400/263
14. Aoki, H., Al-Assaf, S., Katayama, T. and Phillips, G. O. 2007a. Characterization and properties of Acacia senegal (L.) Willd. var. senegal with enhanced properties (Acacia (sen) SUPER GUM(TM)): Part 2--Mechanism of the maturation process. Food Hydrocolloids 21, 329-337. Hydrogels for biomedical applications. Advanced Drug Delivery Reviews 43, 3–12.
15. Giannouli, P. and Morris, E. R. 2003. Hydrogels for biomedical applications. Cryogelation of xanthan. Food Hydrocolloids 17, 495-501. Hoffman, A. S. 2002. Advanced Drug Delivery Reviews 43, 3–12. www.ijrpc.com/files/08-294.pdf
16. Chauhan S, Harikumar SL, Kanupriya. Hydrogels, A Smart Drug Delivery System, International Journal of Research in Pharmacy and Chemistry. 2012; 2(3):604-615.
17. Jeong Hoon KIM, Sang Jun SIM, Dong Hyun LEE, Dukjoon KIM, Young Kwan LEE, Dong June CHUNG, and Ji-Heung KIM. Preparation and Properties of PHEA/Chitosan Composite Hydrogel. *Polymer Journal,* Vol. 36, No. 12, pp. 943—948. (2004. https://www.researchgate.net/publication/260207166_Preparation_and_Properties_of_PHEAChitosan_Composite_Hydrogel
18. Talaat HA, Sorour MH, Aboulnour AGet.al. 2008. Development of a multi component fertilizing hydrogel with relevant techno economic indicators. *American-Eurasian Journal of Agricultural & Environmental Sciences,* 3(5):764–70. https://www.idosi.org/aejaes/jaes3(5)/16.pdf
19. Waham Ashaier Laftah, Shahrir Hashim & Akos N. Ibrahim (2011. Polymer Hydrogels: A Review, *Polymer-Plastics Technology and Engineering,* 50:14, 1475-1486 http://dx.doi.org/10.1080/03602559.2011.593082. www.academia.edu/2906773/Polymer_Hydrogel-_a_review
20. C. S. Satish, K. P. Satish And H. G. Shivakumar*. Hydrogels as controlled drug delivery systems, synthesis, crosslinking, water and drug transport mechanism. March - April 2006 *Indian Journal of Pharmaceutical Sciences*, 113-140.
https://www.researchgate.net/publication/26433391_Hydrogel_as_controlled_drug_delivery_systems_Synthesis_crosslinking_water_and_drug_transport_mechanism
21. Sabale, V., & Vora, S. 2012. Formulation and evaluation of microemulsion-based hydrogel for topical delivery. *International Journal of Pharmaceutical Investigation,* 2(3. 140–149. http://doi.org/10.4103/2230-973X.104397. http://www.jpionline.org/article.asp?issn=2230973X;year=2012;volume=2;issue=3;spage=140;epage=149;aulast=Sabale
22. Qavia S, Pourmahdiana S, Eslamia H. Acrylamide Hydrogels Preparation via Free Radical Crosslinking Copolymerization: Kinetic Study and Morphological Investigation. Journal of Macromolecular Science, Part A: Pure and Applied Chemistry. 2014; 51:842-848. www.thepharmajournal.com/archives/2017/vol6issue6/PartA/6-5-33-916.pdf
23. Syed K. H. Gulrez, Saphwan Al-Assaf and Glyn O Phillips. Hydrogels: Methods of Preparation Characterisation and Applications. Hydrocolloids Research Centre Glyndwr University, Wrexham United Kingdom www.intechopen.com Progress in Molecular and Environmental Bioengineering – From Analysis and Modeling to Technology Applications. https://www.researchgate.net/publication/241808349_Hydrogels_Methods_of_Preparation_Characterisation_and_Applications_in_Molecular_and_Environmental_Bioengineering
24. Amin S, Rajabnezhad S, Kohli K. Hydrogels as potential drug delivery systems, Scientific Research and Essay. 2009; 3(11):1175-1183. http://www.scirp.org/(S(351jmbntvnsjt1aadkposzje))/reference/ReferencesPapers.aspx?ReferenceID=438721
25. Nasim Annabi1, Jason W. Nichol, Xia Zhong, et.al. Controlling the Porosity and Microarchitecture of Hydrogels for Tissue Engineering. TISSUE ENGINEERING: Part B Volume 16, Number 4, 2010 Mary Ann Liebert, Inc. DOI: 10.1089=ten.teb.2009.0639 https://www.ncbi.nlm.nih.gov/pubmed/20121414
26. Rai Muhammad Sarfraz1 Mahmood Ahmad2 Asif Mahmood3 Muhammad Rouf Akram1 Asad Abrar2. Development of β-cyclodextrin-based hydrogel microparticles for solubility enhancement of rosuvastatin: an in vitro and in vivo evaluation. Drug Design, Development and Therapy 2017:11 3083–3096 http://dx.doi.org/10.2147/DDDT.S143712
27. Rajeswari K. R., Reddy R. R., Himabindu a., sudhakar m. and Ramesh. Design, Development and in vitro Evaluation of modified release Hydrogel based drug delivery systems of Oseltamivir Phosphate. Indian Drugs 52 (10) October 2015 https://www.researchgate.net/publication/284180968
28. Phillips, G. O., Plessis, T. A. D, Saphwan Al-Assaf & Williams, P. A. 2003. Vol. Biopolymers obtained by solid state irradiation in an unsaturated gaseous atmosphere. 6,610,810, (ed. U. S. Patent. Phillips Hydrocolloid Research limited, UK https://books.google.co.in/books?isbn=0128090871

29. Hoffman, A. S. 2002. Hydrogels for biomedical applications. Advanced Drug Delivery Reviews 43 3–12. yunus.hacettepe.edu.tr/~damlacetin/kmu407/index_dosyalar/Hoffman,%202012.pdf
30. Liu, P., Zhai, M., Li, J., Peng, J. and Wu, J. 2002b. Radiation preparation and swelling behavior of sodium carboxymethyl cellulose hydrogels. Radiation Physics and Chemistry 63 525–528. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5459021/
31. Shivani P. Shetye, Dr. Ajeet Godbole et.al., Hydrogels: Introduction, Preparation, Characterization and Applications. *International journal of research and methodology*. www.ijrm.humanjournals.com http://ijrm.humanjournals.com/wp-content/uploads/2015/10/3.Shivani-P.-Shetye-Dr.-Ajeet-Godbole-Dr.-Shilpa-Bhilegaokar-Pankaj-Gajare.pdf
32. Swarbrick J., Encyclopedia of Pharmaceutics, 4thedition,Vol III, F-O, 6000 Broken Sound Parkway NW, Suite 300, Boca Raton, FL 33487-2742, Taylor & Francis Group,, 2013
33. Gels and hydrogels Introduction Structure and properties of hydrogels. Types of hydrogels Applications Drug delivery systems Reference: Gels, pages 490-, Encyclopedia of Smart Materials. www.ing.unitn.it/~luttero/materiali funzionali/hydrogels.pdf
34. Daniela Anahí Sánchez-Téllez, 2017. Hydrogels for Cartilage Regeneration, from Polysaccharides to Hybrids. ID et.al. Polymers 2017, 9, 671; doi:10.3390/polym9120671 www.mdpi.com/journal/polymers
35. Morteza Bahram, Naimeh Mohseni and Mehdi Moghtader. An Introduction to Hydrogels and Some Recent Applications. http://dx.doi.org/10.5772/64301 Chapter 2 Emerging Concepts in Analysis and Applications of Hydrogels
36. Munarin F, Guerreiro SG, Grellier MA, Tanzi MC, Barbosa MA, et al. 2011. Pectin-based injectable biomaterials for bone tissue engineering. Biomacro molecules 12: 568-577. https://www.ncbi.nlm.nih.gov/pubmed/21302960
37. Bae MS, Ohe JY, Lee JB, Heo DN, Byun W, et al. 2014. Photocured hyaluronic acid-based hydrogels containing growth and differentiation factor 5 (GDF-5) for bone tissue regeneration. Bone 59: 189-198. www.springer.com/cda/content/document/cda.../9783319612874-c1.pdf?SGWID.
38. Jian-feng Pan, Chang-an Guo, Teng Fei et.al. Preparation and Characterization of a Novel Injectable Hydrogel. Advancements in Genetic Engineering 2013, 2:1 http://dx.doi.org/10.4172/2169-0111.1000105
39. N. Kashyap, N. Kumar, and M. N. V. Ravi Kumar. Hydrogels for pharmaceutical and biomedical applications. Critical Review in Therapeutic Drug Carrier Syst em 22(2):107–150 (2005) https://www.ncbi.nlm.nih.gov/pubmed/15862110
40. Francesco F. Montesano, angelo parente, pietro santamaria et.al. Biodegradable superabsorbent hydrogel increases water retention properties of growing media and plant growth. Published by elseiver B.V. 2210-7843, 2015 www.sciencedirect.com https://www.researchgate.net/publication/276139519_Biodegradable_Superabsorbent_Hydrogel_IncreasesWater_Retention_Properties_of_Growing_Media_and_Plant_Growth
41. Hydrogels – smart materials,Inspirational chemistry RSC advancing the chemical sciences pg.no:115-120
42. Naziha Chirani1, L'Hocine Yahia1, Lukas Gritsch1,2, Federico Leonardo Motta1, 2, Soumia Chirani3 and Silvia Faré2. History and Applications of Hydrogels. *Journal of Biomedical Sciences*, ISSN 2254-609X 2015 http://www.imedpub.com Vol. 4 No. 2:13

****