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(REVIEW ARTICLE)

Dynamicity of hydrogels and their diverse biological applications

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Abstract

Ever increasing use of hydrogels in various sectors of biology imposes the need of rigorous study of various aspects related to it. Its compatibility with the biological system makes it suitable candidate to achieve any complex application of such hydrogels in living systems. Depending upon the need, it can be modified chemically which in turn gives it desired physical properties. These modifications enable us the wide spectrum use of hydrogels for various purposes. Nature of response given by prepared hydrogels greatly varies according to the protocol followed while preparing such hydrogels. Slight change in the composition of hydrogels changes its properties and forms entirely new features bearing form. The overall architecture of hydrogel is designed in such a manner that it can be applicable in various regenerative and biomedical applications and still further modified to be used in novel different application fields. This review highlights preparation techniques being followed to fabricate hydrogels which are having major applications in biological fields. Properties of various hydrogels depending upon their compositions and material which give them new face and can be extrapolated to the new research area have also discussed further

Keywords: Hydrogel; Smart Hydrogel; Scaffold; Alginate; Chitosan; Wound Exudates.

1. Introduction

Hydrogel is hydrophilic, semi solid, 3-dimensional network of polymer which maintains structure by its physical and chemical cross-linking property. It consists of water which constitutes for about 10% of its total weight. It was first reportedby Whichterte and Lim (1960). Hydrogel possess degree of flexibility very similar to natural tissue due to water content in it [45]. The hydrophilicity of hydrogel is because of the hydrophilic group like $-NH_2$, -COOH,

$-CONH_2$ and $-SO_3H$ present in it. Hydrogel may degrade and after a period of time disintegrate and dissolve. In hydrogel that are cross linked chemically, the networks formed are interconnected by covalent bonding. The overall architecture of hydrogel is designed in such a manner that it can be applicable in various application taking in account its mechanical property and flexible behavior [46]. Designing of hydrogel in combination with nanoparticles of metal have developed new prospective of application in regenerative medicines and other biomedical applications [36].

2. History

The primarily produced hydrogel has a variety of cross-linking properties with certain chemical modifications. The basic goal was to develop material having high swelling, more durable and good mechanical properties. Later the concept of hydrogel bloomed into next degree of hydrogel which had a tendency to respond to specific stimuli that

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triggered specific events. Finally, a modified hydrogel was developed which stressed on cross-linking property [10]. These progress in hydrogel's science led to interesting innovation of so called 'smart hydrogel' [47]

2.1. Properties

Hydrogel is used in various application in field of biomedical and pharmaceutics. It is used as drug delivery system as it has biodegradable and biocompatible property [6]. Therefore, while production of such material it is necessary to known its characteristic behavior like swelling, mechanical and toxicity behavior. Thus, it can be used in precise biomedical application [27].

2.1.1. Swelling property

Hydrogel has exclusive potential to swell in liquid medium and absorbs around 10-20% up to thousand the times of dry weight in water. Content of water in hydrogel decides the complete infiltration of nutrients inside and cellular product out of the hydrogel. During absorption of water in dry hydrogel the foremost molecule entering the matrix, hydrates the hydrophilic and polar groups forming primary water in bound state. When these polar groups are hydrated, hydrogel network starts swelling, resulting in hydrophobic groups that interact with molecules of water, known as secondary water in bound state [13]. Primary and secondary bound water mixture together is known as total bound water. After the bound water molecules are interacted with hydrophobic and polar sites, the network of hydrogel will absorb excess water as it has osmotic driving force. This excess of water will undergo swelling which is resisted by covalent or physical crosslink resulting in retraction force. Variation in parameters like temperature,pH and presence of enzyme may alter the texture of hydrogel. The concentrationof aqueous medium present in hydrogel is established and is given by swelling ratio [27]

2.1.2. Mechanical property

From pharmaceutical and biomedical prospective, the mechanical properties of hydrogel are very important. This property should be such that it sustains the physical texture during the release of specific target molecules are for the desired period of time. Mechanical property of hydrogel is obtained only by change in the degree of cross linking [45]

2.1.3. Biocompatible property

In order to use in various application, it is important that the material should be biocompatible with the system and should not cause any toxic response. Biocompatibility consists of parameters like a) Biosafety and b) bio functionality. Biosafety is concern not only to specific tissue but also the surrounding tissue is taken into consideration such as there is no toxicity or mutagenesis. bio functionality is the potential to carry out the particular task for which it is targeted [45]

2.2. Porosity and permeation

Pores are formed in hydrogel due to separation of phase during synthesis or present as small pores in networks. The important factors of this matrix such as pore size distribution, pore size and interconnection within pores are generally difficult to quantify [13]. Distribution of pore size of hydrogel is depended on certain factors like: a) Concentration of chemically crosslinked polymer of hydrogel which is derived from initial ratio of monomer to cross-linker. b) Concentration of entanglements of strand of polymer which are derived through the very first concentration of monomers that are polymerized in solution which is aqueous. c) Overall charge of hydrogel that are polyelectrolyte which is derived from primary concentration of anionic and cationic monomers. Structure of hydrogel which is porous is influenced by properties that are present in surrounding solution. To design a hydrogel, it is important to known the distribution of pore size. To evaluate to porosity of hydrogel many techniques; porosity is basically a visually observed phenomenon that is illustrated by void cavity present in bulk [28].

2.3. Advantage

- It has high degree of flexibility.
- It is easy to modify.
- It can be injected.
- It is biocompatible.
- It has good transport property.
- It has ability to sense changes in pH and temperature.
- Disadvantage:
- It is expensive.

- It has low mechanical strength.
- It is difficult in handling.
- It is difficult in loading.
- It is difficult to sterilize.

3. Preparation method of hydrogel

Depending upon the method of preparation, hydrogels are classified into: a) Homopolymer, b) Copolymer, c) Semi interpenetrating network, d) Interpenetrating network. [1].

3.1. Homopolymer

Homopolymer, a fundamental unit, is a network of polymer of single species of monomer. It has a cross-linked skeletal structure which relies upon monomer and polymerization technique. It is used in drug delivery and in contact lenses, also used for bone marrow and spinal cord regeneration [1]. The mechanical properties of the hydrogel can be optimized if its application could further be extended. Hydrogel based on Polyetheleneglycol (PEG) responds to external stimuli and therefore these smart hydrogels are used in drug delivery system. And so, it is an appropriate biomarker for proficient and restricted release

of drugs, proteins and some biomolecules. Chemically crossed-linked PEG hydrogel are used in functional tissue production and protein recombination as scaffolds. Polyvinyl alcohol (PVA) hydrogel can be synthesized by interchanging cycles of freezing and thawing; material of PVA obtain from this method has mechanical strength higher than UV radiation. The functional group of PVA has broad range of application as it has higher accessibility. [45].

3.2. Copolymer

Copolymer hydrogel comprises two types monomer among which at least one has hydrophilic behavior. These are biodegradable and biocompatible, and are potential for release of hydrophobic and hydrophilic drugs including protein.

3.2.1. Semi interpenetrating network

Semi interpenetrating hydrogel network are those in which one polymer is linear, penetrates another cross-linked network without chemical bond between them. These types of hydrogels were synthesized and assessed as a nanoreactor for producing silver nanoparticle. Here, PVP chains were discrete throughout Polyacrylic acid (PAA) hydrogel network. [45].

3.3. Interpenetrating network

Conventionally, interpenetrating network of hydrogel are known as mixture oftwo polymers where one of it is cross-linked and synthesized in instant presenceof other. This is usually done by immersing a pre-polymerized hydrogel in polymerization initiator and solution of monomers. The main advantage is that comparatively dense hydrogel matrices are be produced and so it has strongmechanical properties, convenient physical properties and high potential drugloading compared to conventional hydrogels.

4. Classification of hydrogel

Depending upon various parameters hydrogel are categorized into different types. [39].

4.1. Crosslinking in hydrogel

When the crosslinking between the polymers is initiated, the purely elastic and visco-elastic nature is achieved. It has been reported that the physically crosslinked nature in polymer shown greater interest. To produce such crosslinked gels many different methods are studied. [39].

4.2. Crosslinking occurred by radical polymerization

Amount of crosslinker control the swelling behavior of hydrogel. In addition, the materials that are stimuli sensitive can be produced by crosslinker with required property. Using radical polymerization method, not only radically polymerized molecules are obtained but also chemically linked hydrogel are produced. So, for developing hydrogel using the method, different polymers that are water-soluble are been used.

Crosslinking occurred by chemical reaction of complementary groups Water-soluble polymers have their property of solubility for functional groups thatare used in hydrogel formation. Covalent linking within the polymer chains is formed by reaction of functionally present groups such as amine-carboxylic acidor by formation of Schiff base. [39].

4.3. Crosslinking occurred by ionic interaction

Various different polymers are used in hydrogel. Alginate is one of the polymers used that is crosslinked by ionic interaction; having mannuronic acid and glucuronic acid residues which are crosslinked are by calcium ions. This crosslinking mainly occurs at room temperature and specific pH. Thus, alginate is usually preferred for cell encapsulation and in protein release mechanism.

4.4. Stimuli responsive hydrogel

The type of stimuli responsive hydrogel responds to external stimuli like environment stimuli and changes in growth actions, permeability and mechanical strength are experienced. And physical stimuli such as light, pressure, temperatureand mechanical stress can change the interaction at molecular level. Also, chemicalstimulus such as pH, ionic factors and chemical mediators alters the interaction within solvent and chain of polymer [48]. The other category of hydrogel known as 'dual responsive hydrogel' is formed from mixtureof two stimuli responsive mechanism present in one of the hydrogels. A stimulus which is biochemical comprises response towards ligands, biochemical molecules and enzymes. Therefore, these types of hydrogels are captivating biomaterial used in biomedical and pharmaceutical applications [38].

4.5. pH responsive hydrogel

In this hydrogel at specific pH, the degree of ionization is considerably changed; this change in total charge creates steady volume transition by producing forces which are electro statically repulsive within ionized groups that eventually generates greater osmotic force. The classification is done into two categories like cationic and anionic hydrogels. The first group contain hydrogel that are cationic which has groups like amine groups where ionization occurs leading to high swelling. And the other group is hydrogel that are anionic which has groups like sulfonic and carboxylic acid [38].

4.6. Temperature responsive hydrogel

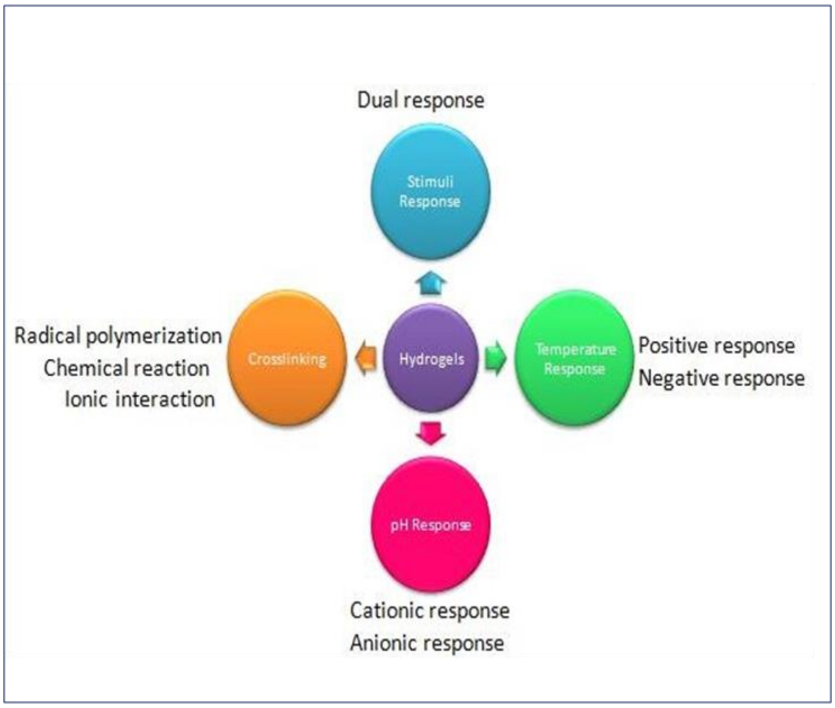

Figure 1 Classification of hydrogel depending into different properties

The hydrogel those have potential to shrink and swell when there is changes in surrounding medium are called as hydrogel that are temperature responsive. So, the swelling behavior is depended on temperature in nearby area. These hydrogels are grouped such as positive or negative temperature responsive hydrogels. These positive responsive hydrogels are renowned by upper critical solution temperature (UCST), when temperature drops than UCST, the contraction in hydrogel occurs and discharge of liquid or solvent from matrix takes place. Thus, the dehydration occurs. And when temperature is above UCST, the phenomenon of swelling takes place. [39].

5. Applications

5.1. Injectable hydrogel for cartilage and bone tissue engineering

Tissue engineering has become an upcoming method for repairing the injuredtissue. Bone tissue engineering has created curiosity for investigators as a promising approach for overcoming the bone defects. Variety offilms, matrixes are known to be used, where injectable hydrogels are known to have great potential in 3D cell culture scaffolds due its excellent swelling ability similar to natural tissue [25]. Alginate is amid the widely searched biomaterial used in tissue engineering. It is described that an inventive 3D hydrogel that is injectable is used for bone engineering that uses β-tricalcium phosphate beads and alginate the same as scaffold [24]. Mesenchymal stem cells 3D cultured present in hydrogel were subcutaneously implanted in vivo experimentation which indicated the favorable support of scaffold for osteogenic differentiation. Also, mesenchymal stem cell co-culture in hydrogel have been demonstrated to be capable of supporting neovascularization and osteogenic lineage differentiation. Injectable calcium silicate/sodium alginate hybrid hydrogel are prepared by integrating calcium silicate into an alginate solution. Around 10 minutes, hydrogel starts gelling internally when calcium ions are formed from calcium silicate when exposed to D-gluconic acid δ-lactone. In addition, efficiency of hydrogel endorses the adhesion, proliferation and differentiation of osteogenic cells. Recently, synthetic biomaterial-based injectable hydrogel has fascinated interest for bone engineering. [40].

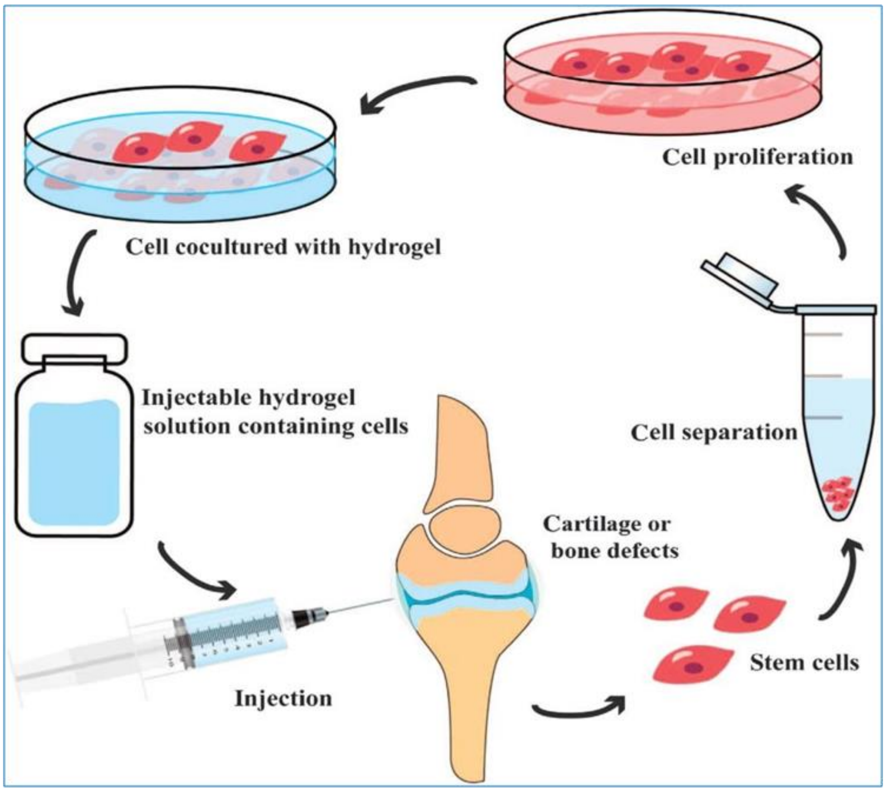

Figure 2 Schematic illustration of approaches to make injectable hydrogel for cartilage and bone tissue-engineering applications. Figure adapted from [24]

5.2. In drug delivery

The distinctive physical characteristics of hydrogel had gained attention to their use in drug delivery application. Property of porosity also permits the drug to get loaded into gel matrix and therefore the rate of release of drug is reliable on the coefficient of diffusion of molecules contained by the network. In drug delivery, hydrogels are usually preferred to form outside the body and injected along the drug prior assigning the hydrogel complex to the body. When the drug with hydrogel interrelate the aqueous medium, the water transmits into the system resulting in dissolving of drug [15]. The restricted discharge ofdrug through hydrogel is classified into reservoir and matrix devices. In the reservoir-based method, the reservoir is encapsulated inside the hydrogel allowing the drug diffusion. As water comes in contact in this system which gradually diffuses and drug dissolves providing concentration of saturation solubility of drug (Cs). Through the membrane the drug diffuses to outside environment leading to decrease in concentration below Cs. Wherein, the solid drug in reservoir dissolves and brings back the concentration to Cs. Thus, drug released from reservoir system remains invariable. Such drug delivery systems are highly used in delivery of agents by transdermal, oral and uterine routes[42]. In matrix system, the active agent is dispersed homogenously into hydrogel matrix as a solid. Depending upon the property of matrix, the release of drug occurs. Water diffuses in matrix by hydrated it when the matrix is present in aqueous medium. Hydration of matrix begins at surface, continuing till the core center. Drug release depends on diffusion of water in matrix after which dissolution of drug occurs andhence drug is released. Usually, matrixes made of inert polymer are regarded to use in this type of system. Interaction of drug and polymer act as key feature in drug release mechanism. Also, different strategies are investigated to build up the delivery system so as the drug delivery takes place in desired manner.

5.3. In wound healing

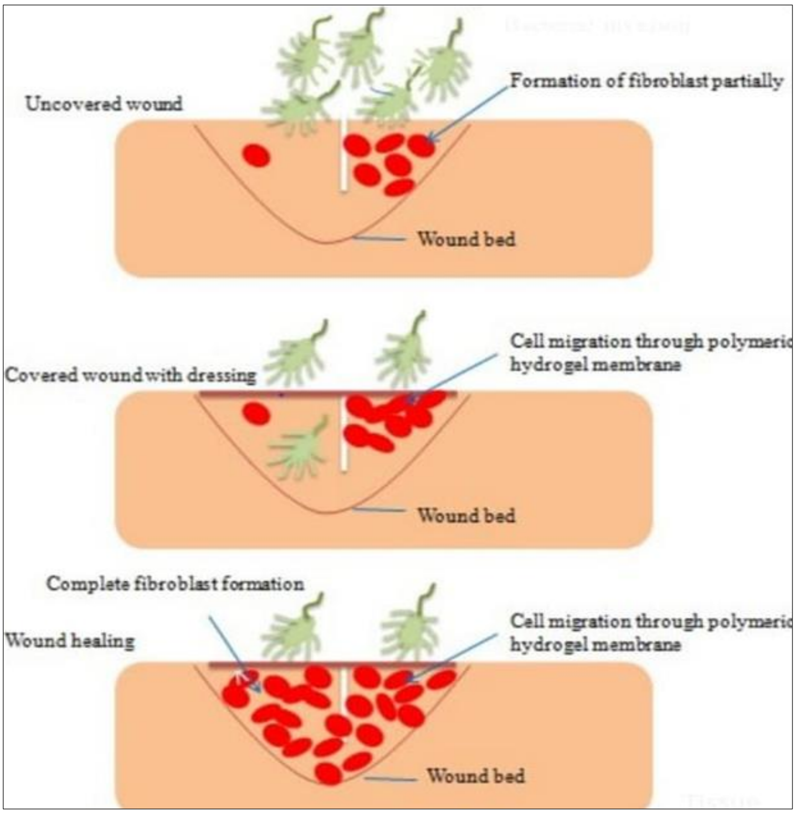

Figure 3 Representation of the role of hydrogel membrane materials for enhancing and accelerating the wound healing phases. Referred from: [49]

As it is known that hydrogel has versatile property to absorb water that retains the water in network, it is used in much different application. In it studied thathydrogel promotes proliferation of fibroblast by loss of fluid through the surface of wound and thus protecting the wound from infection essential for healing of wound [49]. This proliferation is important for the whole epithelialization of wound. Depending on nature of polymer, thetransparency of hydrogel is present. And so, the most important advantage of transparent hydrogel is that the wound healing can be under observe without removing the dressing of wound [49]. The sheets of hydrogel are impregnated on the surface of wound with support of polymer film and using some bandages are acquired on wound surface. In addition, the network of hydrogel prevents the wound from being infected and also protects from any microorganism that may infect the wounded area. During the gelling process, the desired drug molecules are capture in hydrogel network. These molecules are replaced with absorbing the wound infection for the duration of release process when hydrogel come in contact with wound surface. Thus, tissue like hydrogel provides adaptively and flexibility to wound at different locations of body. By providing the moist environment to wound, dressing using hydrogel guarantees that there is no infection caused and endorses the quick healing [42]. Due to this dead tissue getdetached and healing is ensured [7]. Hydrogel in general can be used in treatment of different wound injuries and also in second-degree burn cases. They have potential to absorb exudate wound. It is reported that one of the natural hydrogels like Chitosan shows good healing behavior and also alginate fibers can be altered into wound dressing by various textile methods. Due to its ease and absorbable nature, it is used in various applications [5].

5.4. In heart valve tissue engineering

Many different advancement studies have been performed in heart valve tissue engineering (HVTE) using scaffolds and different polymers. Research have been carried out predominantly that concentrates on use of hydrogel in HVTE. It allows the exchange of nutrients and oxygen to the tissue and provides analogous hydrated environment native to natural tissue [41]. Natural hydrogel like collagen, fibrin known to show excellent effects in various tissue engineering applications. Heart valve scaffold based on fibrin are prepared using injection molding method. Here, cells like myofibroblasts are mixed with calcium and thrombin in particular buffer are injected into the mold prepared by negative and positive stamp with shape of heart valve. Using dual syringe system, addition of fibrinogen is done simultaneously which initiated the fibrin polymerization process. Then, the recently formed polymerized heart valve is removed and kept in bioreactor under appropriate condition prior the implantation. This method can be used to fabricate the heart valves form different biomaterials. Contrasting collagen-gel, fibrin scaffolds show low mechanical strength and so cannot be used in direct implantation. As known that other chemical fixation with strong biomaterial like poly-L-lysine shown challenging effect in strengthening the fibrin gel which decreased the shrinkage of tissue [41] [42].

5.5. In cardiac tissue regeneration

Re-developing or reforming of any injured or damage tissue is very exigent task for overcoming. So, material that are conductive are been added to scaffolds to create the property similar to tissue. Conductive metals like gold, silver, arsenic etc are used in combination with nanoparticles. These metals are used while designing hydrogel in cardiac tissue regeneration [49]. Report suggests that electroactive gold nanoparticle (Au NP) infused in composite hydrogel of thiol 2- hydroxyethyl methacrylate (HEMA) knowing its mechanical property. The cardiomyocytes of juvenile rats were grown on scaffolds which were conductive. Results suggested that without any electrical stimulation, the expression of connexin-43 was improved. As this stimulation is usually required in absence of any conductive metal. Therefore, conductive metals are known to be essential in supporting the cardiac tissue applications. Other studies suggested, not only cardiomyocytes but also using stem cells effect of Au NP infused in composite hydrogel is explored. The integration of Au NP has endorsed the delineation of mesenchymal stem cell into cardiac form. Thus, composite hydrogel with nanoparticle combined with conductive metal helps to mimic the electroconductive property similar to natural tissue [44].

6. Conclusion

The enormous improvement made in different properties of hydrogel leading to progress in many biomedical applications. Successful improvement in biomedical and pharmaceutical aspects has made hydrogel a smart biomaterial. Hydrogels are widely found in many applications like wound healing, tissue engineering, bone regeneration, etc. Particular stimuli responsive hydrogels can be designed and properties such as biocompatibility and porosity make hydrogel highly potential smart biomaterial to use in diverse applications. Still further modifications are being carried out in order to use hydrogel in novel different application sectors.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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