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Electro sensitive Hydrogel Quick Drying Paint

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Abstract

Hydrogel products constitute a group of polymeric materials, the hydrophilic structure of which renders them capable of holding large amounts of water in their three-dimensional networks. Extensive employment of these products in a number of industrial and environmental areas of application is considered to be of prime importance. As expected, natural hydrogels were gradually replaced by synthetic types due to their higher water absorption capacity, long service life, and wide varieties of raw chemical resources. Literature on this subject was found to be expanding, especially in the scientific areas of research. However, a number of publications and technical reports dealing with hydrogel products from the engineering points of view were examined to overview technological aspects covering this growing multidisciplinary field of research. The primary objective of this article is to review the literature concerning classification of hydrogels on different bases, physical and chemical characteristics of these products, and technical feasibility of their utilization. It also involved technologies adopted for hydrogel production together with process design implications, block diagrams, and optimized conditions of the preparation process. An innovated category of recent generations of hydrogel materials

Key words: - Hydrogel, Electro Sensitve, Paint, Biodegrable, Solubility, Bulk polymerization and Suspension polymerization

1.1 Introduction

The terms hydrogels are used interchangeably by food and biomaterials scientists to describe polymeric cross-linked network structures. Gels are defined as a substantially dilute cross-linked system, and are categorised principally as weak or strong depending on their flow behaviour in steady-state (Ferry, 1980). Edible gels are used widely in the food industry and mainly refer to gelling polysaccharides (i.e. hydrocolloids) (Phillips & Williams, 2000). The term hydrogel describes three-dimensional network structures obtained from a class of synthetic and/or natural polymers which can absorb and retain significant amount of water (Rosiak & Yoshii, 1999). The hydrogel structure is created by the hydrophilic groups or domains present in a polymeric network upon the hydration in an aqueous environment.

This chapter reviews the preparation methods of hydrogels from hydrophilic polymers of synthetic and natural origin with emphasis on water soluble natural biopolymers (hydrocolloids). Recent advances in radiation cross-linking methods for the preparation of hydrogel are particularly addressed. Additionally, methods to characterise these

hydrogels and their proposed applications are also reviewed.

On the basis of nature of the network: homopolymer, copolymer, interpenetrating, or double networks; physical structure: (optically transparent), microporous, and macroporous hydrogels, and on their fate in the organism: degradable and non-degradable hydrogels. Due to their high water content, most hydrogel structures possess excellent biocompatibility.

There is a wide variety of the design options for the preparation of hydrogels of different structures and properties. The traditional methods of hydrogel synthesis were limited in the control of their detailed structure, but novel approaches based on genetic engineering and hybrid hydrogels, have considerably enhanced this research.

As a result, the application potential of hydrogels, in addition to traditional areas such as biomaterials and drug delivery systems, has expanded to other fields, such as microfluidics and nanotechnology.

DISCOVERY • In the early 1950s Otto and Lím from the Prague(Czechoslovakia) Institute of Chemical Technology initiated a research program to design polymers for medical use. Some merchandised polymers had been applied in humans use previously, but this was the first attempt to design polymers for human use with properties to fulfill the criteria of biocompatibility.

Electro-sensitive hydrogels, as the name indicates, undergo shrinking or swelling in the presence of an applied electric field. Like pH-sensitive hydrogels, they are usually composed of polyelectrolytes. Under the influence of an electric field, a force on counterions and immobile charged groups is produced in the network, which attracts mobile ions to the electrodes. As a result, the hydrogel can swell and shrink regionally at the cathode and anode, respectively. This phenomenon leads to bending of the hydrogel, which is caused by ion concentration difference inside the hydrogel network and culture medium and can be explained by Flory's theory of osmotic pressure [12–17]. The extent of bending depends on hydrogel structure and electrical field characteristics including strength, direction, and duration of the electrical stimulus. Electro-sensitive hydrogels can selectively be permeable for a specific molecular size and adjust the water permeability by expanding and contracting in micropore size under electrical stimulation [18]. Because electro-responsive hydrogels can transform electrical energy into mechanical energy and have promising applications in biomechanics, sensing, energy transduction, sound dampening, chemical separations, controlled drug delivery [33], and tissue engineering [20, 21], these polymers are an increasingly important class of smart materials. Hydrogels of acrylamide and carboxylic acid derivatives like PAA have been utilized as electro-sensitive and biocompatible smart muscle-based devices [22, 23].

1.2 Classification of Hydrogels

Classification based on their Natural or Synthetic Origins.

1.2.1. Natural Hydrogels Natural hydrogels are

biodegradable,
biocompatible and
good cell adhesion properties.

1.2.1.2 Biocompatible

Biocompatibility is the first, and perhaps the most critical, parameter when considering the application of hydrogels in the cellular microenvironment. Biocompatibility is defined as the ability of a biomaterial to perform its desired function without eliciting any undesirable local or systemic side effects.[12] The hydrogel must be immunocompatible and not elicit a significant inflammatory response for use within *in vivo* microenvironments. Various naturally derived polymers (*e.g.*, polysaccharides such as hyaluronic acid) and a few synthetic polymers (*e.g.*, polyethylene glycol) have demonstrated adequate biocompatibility. Removal of small molecules used or generated during hydrogel fabrication (such as unreacted monomer, initiator, and crosslinkers) is essential to consider during material design, as such molecules can be toxic to host cells both *in vivo* and *in vitro*. For example, unreacted maleimides, which are widely used in Michael-type addition reactions, are highly potent neurotoxins;[13] similarly, photoinitiators, such as 2,2-dimethoxy-2-phenyl-acetophenone used frequently in free-radical polymerization, can be cytotoxic.[14]

addition, no significant statistical differences were seen in postoperative infection and healing many natural polymers are inherently biodegradable and possess special properties, such as self-assembly, specific recognition of other molecules, and the formation of reversible bonds.

In addition, the hydrogel or its base components need to be simple to sterilize and should not undergo any significant functional changes during sterilization. Further, hydrogels for implantation also need to meet appropriate regulatory body (*i.e.*, FDA, EPA) guidelines. Synthetic polymers, such as PEG, PLGA, and PLA, and natural polymers, such as alginate, collagen and fibrin, have been approved for specific clinical applications by the FDA. Kim and Wright recently investigated use of FDA-approved DuraSeal™, a PEG based hydrogel used as a sealant for human spinal fluid leaks.[15] In a clinical trial with a total of 158 patients, it was found that DuraSeal™ spinal sealant had a significantly higher rate of intraoperative watertight dural closure (100%) compared to the control (*i.e.*, treated with traditional methods, 65%). In between the PEG hydrogel and the control group. Overall, the PEG hydrogel spinal sealant system

was found to be an efficient and safe adjunct to suturing for watertight dural repair. Such biocompatible and clinically tested hydrogels (*i.e.*, DuraSeal™, Evolence®, TachoSil™, Tisseel Artiss™, Tegagel™), which are commercially available, cost effective, easy to use and have a stable shelf life (ranging from 6 months to 36 months) along with well defined *in vivo* stability, hold potential for bioengineering applications, such as wound healing, tissue engineering, 3D cell culture and vascular surgeries.[16]

Biocompatibility is the third most important characteristic property required by the hydrogel. Biocompatibility calls for compatibility with the immune system of the they should be metabolised into harmless products or can be excreted by the renal filtration process. Generally, hydrogels possess a good biocompatibility since their hydrophilic surface has a low interfacial free energy when in contact with body fluids, which results in a low tendency for proteins and cells to adhere to these surfaces. Moreover, the soft and rubbery nature of hydrogels minimises irritation to surrounding tissue (Anderson & Langone, 1999; Smetana, 1993).

The cross-links between the different polymer chains results in viscoelastic and sometimes pure elastic behaviour and give a gel its structure (hardness), elasticity and contribute to stickiness. Hydrogels, due to their significant water content possess a degree of flexibility similar to natural tissue. It is possible to change the chemistry of the hydrogel by controlling their polarity, surface properties, mechanical properties, and swelling behaviour.

1.2.1.3 Good cell adhesion properties

The field of biomaterials continues to advance the introduction of such complexity into cell culture systems, providing ways to control mechanical, compositional, and structural cues and thus more accurately represent features of native tissues[2]. A range of biomaterial systems have been developed towards this goal, for example patterned glass substrates, elastomeric films, hydroxyapatite ceramics and fibrillar foams. However, hydrogels - water-swollen networks of polymers - have emerged as the most promising for cell culture (Fig. 2) since they mimic salient elements of native extracellular matrices (ECMs), have mechanics similar to many soft tissues, and can support cell adhesion and protein sequestration[3].

3D hydrogels for cell culture

(**a**) 3D hydrogels can be engineered to present a more realistic microenvironment to cells. Hydrogel design variables are indicated.

(**b**) Mouse MSCs cultured in 3D alginate hydrogels display rounded morphology regardless of substrate stiffness. Left panel: 5 kPa, right panel: 110 kPa. Images modified from [61] with permission.

(**c**) Bovine dermal fibroblasts encapsulated in 3D collagen hydrogels spread at low stiffness (< 1 kPa). Image modified from [96] with permission.

(**d**) Human MSCs cultured in a hyaluronic acid (HA) hydrogel are restricted from spreading regardless of substrate stiffness (shown here ~ 4 kPa). Image modified from [97] with permission.

(**e**) Human MSCs cultured within a HA hydrogel with equivalent stiffness to (d) but crosslinked with MMP-degradable crosslinkers permits cells to locally remodel their environment, generate tractions, and spread. Image modified from [97] with permission.

(**f**) Human foreskin fibroblast spreading and migration speed is influenced by collagen fibril size.

Image modified from [44] with permission. Scale bars: 10 μm.

There are two major types of natural polymers which are used to produce natural hydrogels are proteins such as collagen, gelatin and polysaccharides.

1.2.1.4 Permanent / chemical gel: they are called 'permanent' or 'chemical' gels when they are covalently cross-linked (replacing hydrogen bond by a stronger and stable covalent bonds) networks (Hennink & Nostrum, 2002). They attain an equilibrium swelling state which depends on the polymer-water interaction parameter and the crosslink density (Rosiak & Yoshii, 1999).

1.2.1.5 Reversible / physical gel: they are called '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 chains (Hennink & Nostrum, 2002). All of these interactions are reversible, and can be disrupted by changes in physical conditions or application of stress (Rosiak & Yoshii, 1999).

1.3 Hydrogels from natural polymers

3.1.1 Hyaluronic acid. Hyaluronate or HA is a non-sulfated GAG in the ECM that is distributed throughout connective, epithelial, and neural tissues. This GAG is composed of alternating disaccharide units of D-glucuronic acid and *N*-acetyl-D-glucosamine linked together with β-1,4 and β-1,3 glycosidic bonds (Fig. 3A).[55] HA is inherently biocompatible and non-immunogenic and degrades in the presence of hyaluronidase as well as in the presence of reactive oxygen species. HA is a critical component of the ECM and plays an important role in various biological processes, including wound healing, angiogenesis, and activation of various signaling pathways that direct cell adhesion, cytoskeletal rearrangement, migration, proliferation, and differentiation.[56–59] Although concerns over batch-to-batch variation and the possibility of contamination with endotoxins and pathogenic factors persist, recent developments in recombinant technology have significantly improved the quality of commercially-available HA.[60,61] However, the rapid degradation of HA in the presence of hyaluronidase can hinder its usefulness in certain applications. For example, approximately one-third of the typical fifteen grams of HA found in a human is degraded and re-synthesized daily.[62] Limited control over HA degradation kinetics (*i.e.*, rapid degradation) can lead to precipitate changes in mechanical properties, such as hydrogel stiffness, which may be undesirable in certain bioengineering applications.

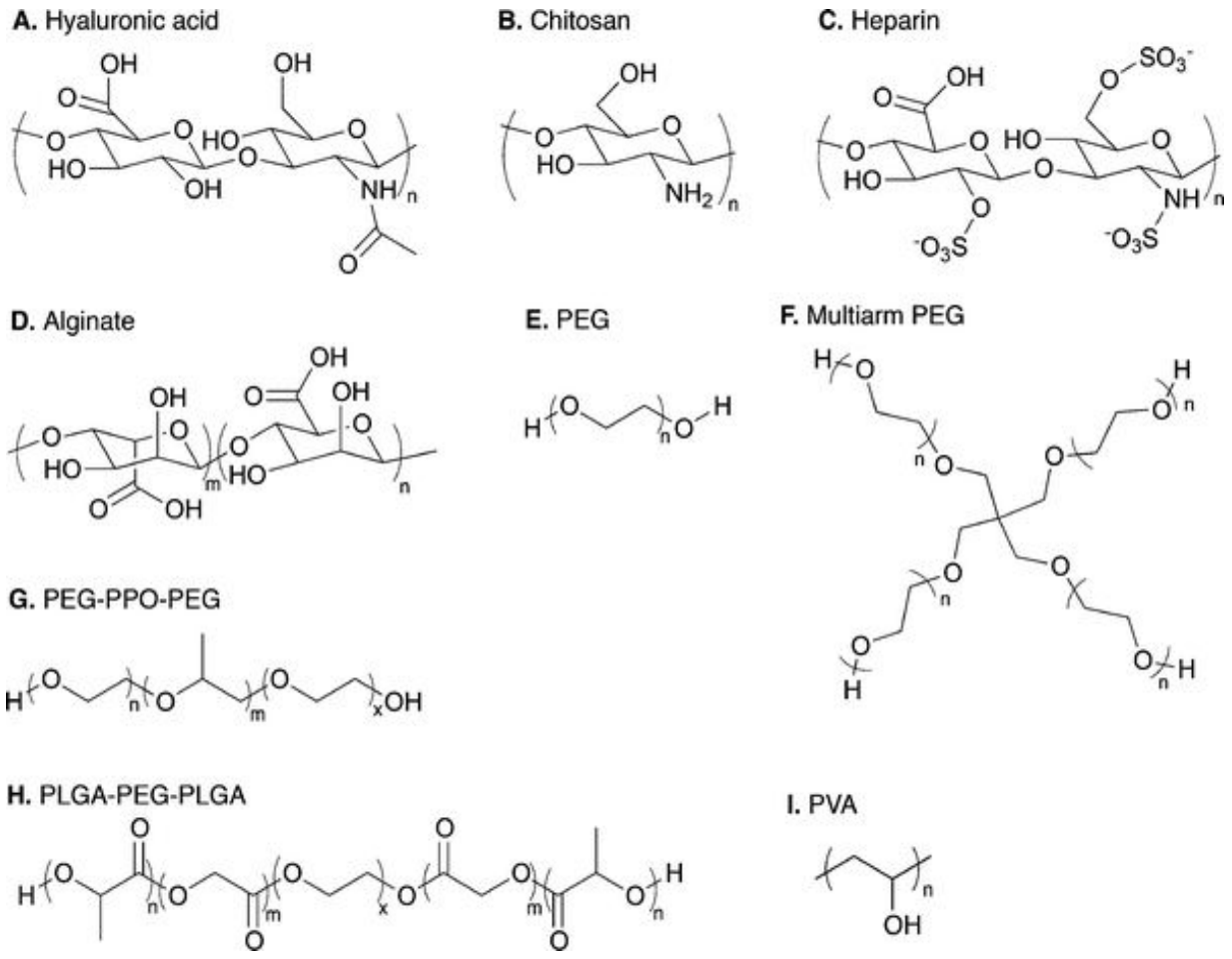


Fig. 1 Range of natural and synthetic polymer building bl
polymer repeat units used for preparation of cell compatib
(A) hyaluronic acid, (B) chitosan, (C) heparin, (D) alginat
(F) four-arm PEG, (G) poly(ethylene glycol)-*b*-poly(prop
(PEG-PPO-PEG), (H) poly(lactic acid-*co*-glycolic acid)-*b*
acid-*co*-glycolic acid) (PLGA-PEG-PLGA), and (I) poly(

HA can be modified with thiols, haloacetates, dihydrazides, aldehydes, or carbodiimide functional
- and heparin-based spherical hydrogel particles with an inverse emulsion polymerization, creating inherently bioactive delivery vehicles (due to

groups to allow crosslinking into hydrogels.[63] HA-based hydrogels have shown excellent potential for biomedical engineering applications, such as tissue engineering,[64–66] valve regeneration,[67,68] controlled delivery,[69–72] and controlling stem cell behavior.[73,74] For example, Jia and coworkers synthesized HA

inductive role of HA in chondrogenesis) for controlled growth factor (BMP-2) release (Fig. 4).[75] Additionally, Elia *et al.* used HA-based

degradable hydrogels embedded within electrospun silk for sustained release of encapsulated cargo molecules (anti-inflammatory steroid drugs and proteins) over 45 to 400 minutes.[72] Such approaches that utilize simple fabrication techniques and tuning of release kinetics make HA hydrogels attractive candidates for tissue regeneration and sustained therapeutic delivery. For a comprehensive overview of HA hydrogels, readers are referred to recent reviews by Burdick and Prestwich[63] and by Jia and coworkers.[46]

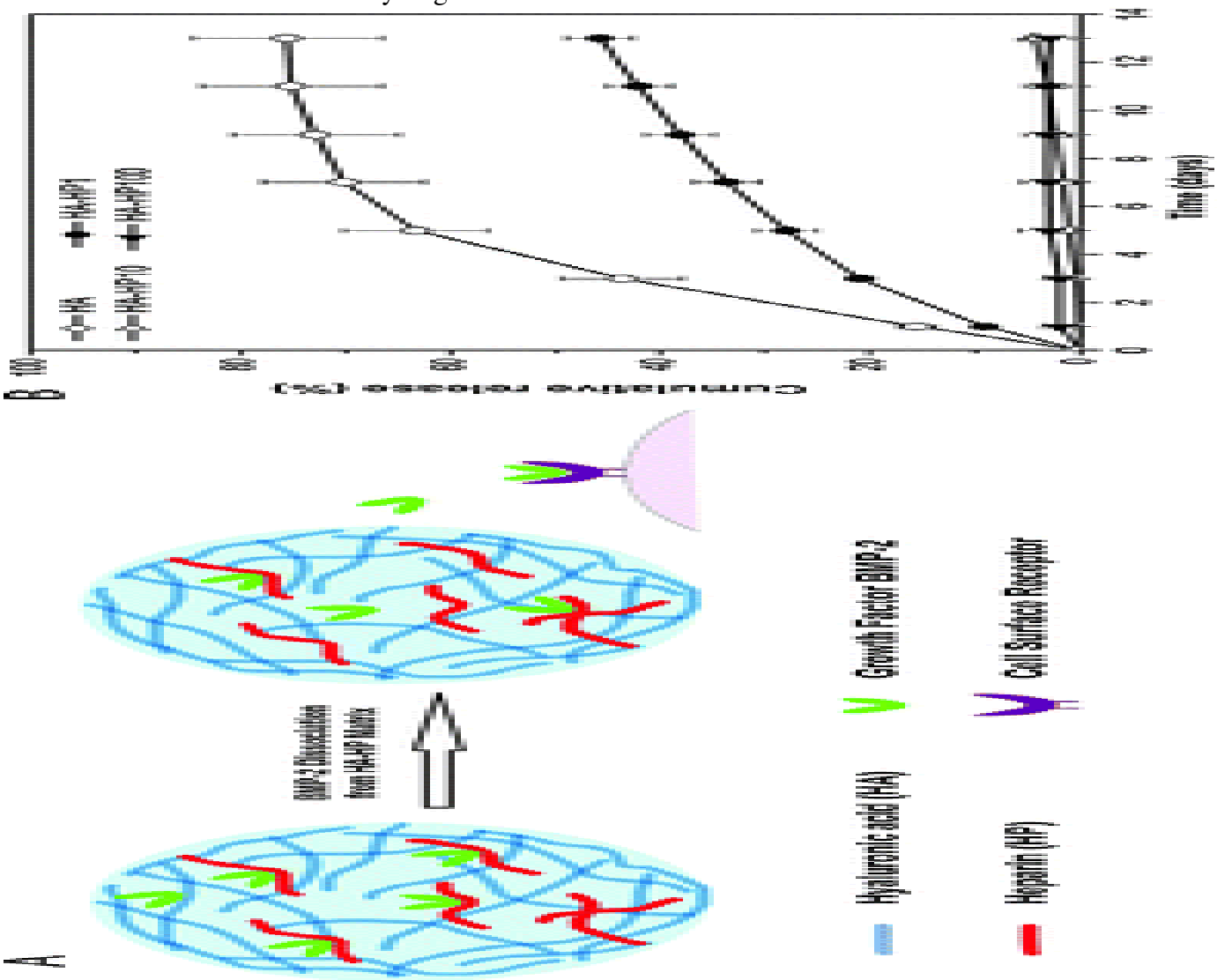


Fig. 2 Hyaluronic acid hydrogels for controlled release applications. (A) HA/heparin hydrogel particles were synthesised by inverse emulsion polymerization and amount of heparin in hydrogel particle was varied. BMP-2 was subsequently loaded. (B) The addition of heparin to HA hydrogel particles inflenced the *in vitro* release of BMP-2 from hydrogels with higher heparin conent, with less than 5% of loaded BMP-2 released over 13 days (HA-HP*x*, *x* = micrograms of heparin per milligram in hydrogel particles). Reprinted from Xu *et al.*[75] with permission from Elsevier. Copyright (2011).

1.3.1 Chitosan. Chitosan, the deacetylated derivative of chitin, is a linear polycationic polysaccharide composed of randomly distributed β-(1-4)-linked D-glucosamine and *N*-acetyl-D-glucosamine (Fig. B). The structural units of chitosan are similar to those of GAGs of the ECM.[76] It can be degraded by various mechanisms, including surface erosion, enzymatic degradation through chitosanase and lysozyme, and dissolution.[77] By using appropriate crosslinking chemistries and densities, the degradation kinetics can be tuned. The inherent properties of chitosan, such as excellent cytocompatibility, biodegradation, minimal foreign body response, and antimicrobial properties, make chitosan-based hydrogels attractive candidates for engineering applications, including wound-healing, bioactive molecule delivery and soft tissue engineering.

The large number of accessible hydroxyl and amine groups in chitosan provide numerous possibilities to create hydrogels *via* chemical crosslinking.[78] These functional groups can react with many bifunctional small molecule crosslinkers, such as glutaraldehyde, formaldehyde, genepin, diethyl squarate and diacrylate, to form chemically crosslinked hydrogels.[79] In addition, incorporation of new functionalities along the backbone chain (*i.e.*, those susceptible to the Schiff base reaction, disulfide bonding or Michael-type additions, Section 4) can be used for *in situ* gel formation. Chitosan-based hydrogels can be used for the controlled delivery of drugs,[79,80] proteins,[80] and growth factors[81] as well as the encapsulation of living cells,[81,82] the controlled differentiation of stem cells,[83,84] and applications in tissue engineering.[85–88] For example, Bellamkonda and coworkers recently reported chitosan-based photocrosslinkable, degradable hydrogels for neural tissue engineering application (Fig. 5).[88] Chitosan was functionalized with amino-ethyl methacrylate for network formation *via* photoinitiated radical

polymerization. The cytocompatible hydrogel enhanced differentiation of primary cortical neurons by ~30% and enhanced dorsal root ganglia neurite extension by about two-fold in 3D *in vitro* studies, as compared to an agarose-based hydrogel control. In principle, such hydrogels additionally can be used to control cell behavior and lineage specific differentiation by incorporation of growth factors since the gel formation chemistry does not alter the active end groups on chitosan, which allow bioactive molecule binding.

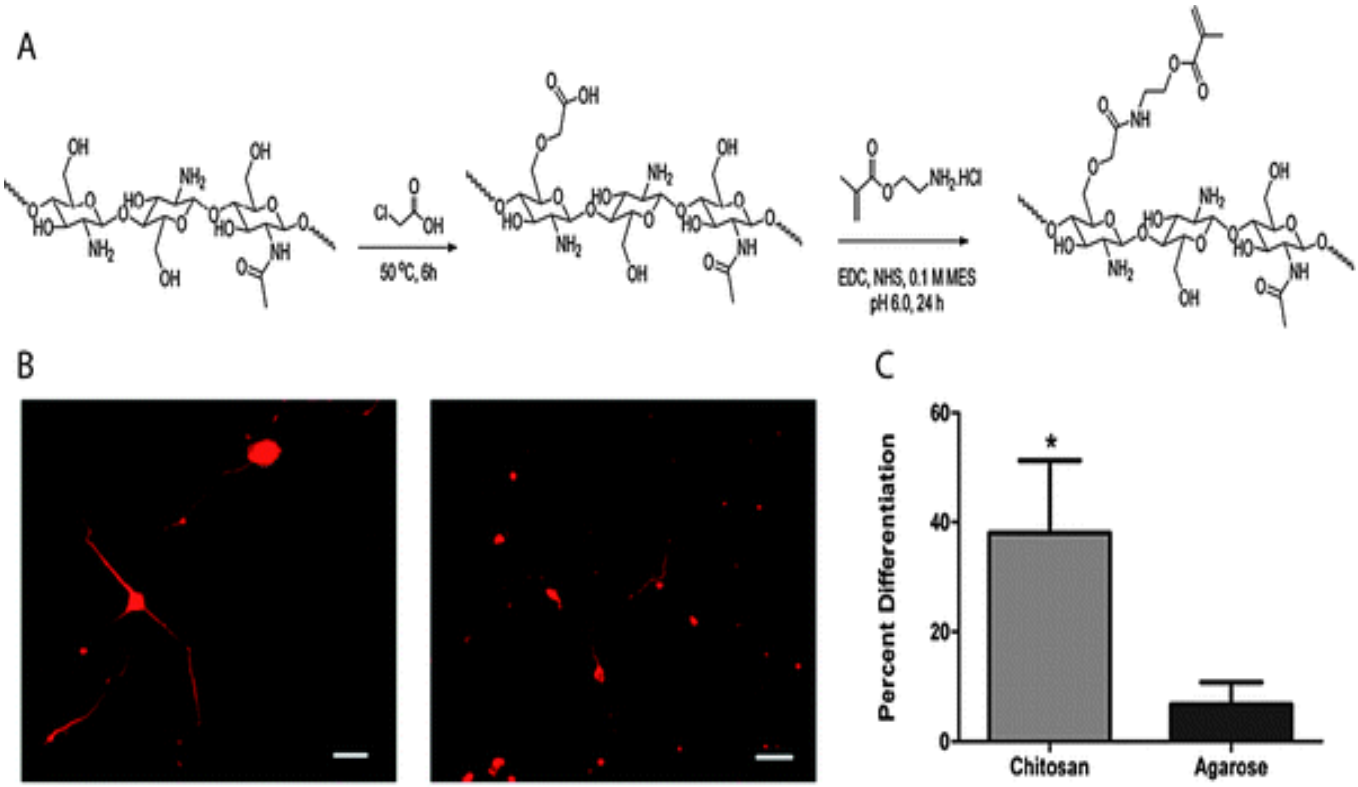


Fig. 3 Chitosan-based hydrogels for neural tissue enginee

(A) Schematic of synthesis of methacrylated chitosan. M hydrogels were crosslinked in the presence of cells b polymerization (Irgacure photoinitiator with 365 nm
(B) E-18 rat cortical neurons were immobilized within cl hydrogels for investigating neuronal survival and dif groups and displayed extensive neurite outgrowth in to agarose hydrogels (right), indicating enhanced neu matrices (scale bar, 50 μm).
(C) Neurite outgrowth quantification ($p < 0.05$). Reprinte permission from The Royal Society of Chemistry. C

1.3.2 Heparin. Heparin is a heterogeneous GAG, consisting of α-L-iduronic acid, β-D-glucuronic acid, and α-D-glucosamine residues (Fig. 3C). Heparin has the highest negative charge density of any known biological macromolecule giving rise to ionic interactions with bioactive molecules such as proteins, growth factors, and cytokines.[89,90] Such noncovalent interactions of heparin in many cases serve not only to sequester the proteins, but also to control their biological activity (*e.g.*, enhancing cell receptor affinity).[89] Heparin and heparan sulfate mediate a number of biological interactions, such as cell adhesion, cell proliferation, or cell surface binding of lipase and other proteins that are critical in developmental processes, blood coagulation, angiogenesis, viral invasion, and tumor metastasis.[91] Moreover, heparin and heparan sulfate protect proteins from degradation, regulate protein transport through basement membranes, and mediate internalization of proteins.[92] However, potential adverse effects of heparin, a potent anticoagulant include bleeding, thrombocytopenia, osteoporosis, alopecia, and priapism, and are related to this wide variety of biological activities.[93–95] Such undesirable effects may limit the use of heparin in certain *in vivo* applications.

Physically and chemically crosslinked heparin-based hydrogels have been employed for the investigation of cell function and fate,[96–99] cell encapsulation,[100–103] and controlled bioactive molecule delivery.[29,104–106] For instance, Kiick and coworkers used heparin-based hydrogels to modulate cell response in a 2D *in vitro* experiment.[96] To modulate cell adhesion and response, hydrogels with different moduli were prepared using the Michael addition reaction between combinations of maleimide-functionalized heparin, thiol functionalized PEG and maleimide functionalized PEG. Such systems, with the ability to tune biochemical and mechanical properties, make heparin based hydrogels promising candidates for controlling adventitial fibroblast remodeling of blood vessels. In another example, Tae and coworkers took advantage of heparin-based hydrogels to stably bind fibrinogen and collagen type I on a hydrogel surface using heparin binding affinity by physisorption.[98] The hydrogels were

prepared by a Michael-type addition reaction using thiolated heparin and PEG diacrylate. The significant physisorption of proteins on the heparin hydrogel, as compared to a control PEG hydrogel, led to enhanced fibroblast adhesion and proliferation. Such approaches can be used to adhere cells on selective heparin hydrogel surfaces for applications such as biosensors, cell culture, and tissue engineering. Additionally, Werner and coworkers recently reported use of heparin-based hydrogels for cell replacement therapies in the neurodegenerative diseases.[99] By tuning the mechanical and biological properties of the PEG-heparin hydrogels, neural stem cell differentiation and axo-dendritic outgrowth were modulated. *In vivo* stability and excellent histocompatibility make such hydrogel systems attractive candidates for neuronal cell replacement therapies. For a comprehensive overview of heparin hydrogels, readers are referred to a recent book chapter by McGann and Kiick.[89]

1.3.3 Alginate. Alginate is a hydrophilic, cationic polysaccharide consisting of (1–4)-linked β-D-mannuronate (M) and its C-5 epimer α-L-guluronate (G) residues (Fig. 3D). It is obtained from brown algae, and depending upon the algae source, it may consist of blocks of similar or strictly alternating residues. Alginate-based hydrogels are biocompatible and undergo physical gelation in the presence of divalent cations. Despite these advantages, the uncontrolled degradation of physically crosslinked alginate hydrogels upon the loss of divalent cations can hinder their stability. Covalent crosslinking with various crosslinkers, such as adipic acid dihydrazide and lysine, can be employed to overcome this uncontrolled degradation. A lack of cell-specific interactions, however, can limit the use of alginate hydrogels in bioengineering applications; an attractive approach to induce bioactivity for cell culture is by covalent incorporation of bioactive ligands such as RGD-containing peptides. An additional challenge for alginate hydrogels *in vivo* is that the alginate macromolecule itself is difficult to break down under physiological conditions, and the molecular weight of released alginate strands is typically above the renal clearance threshold.[107,108] However, partially oxidized alginate, which undergoes biodegradation, can be utilized to overcome these limitations.[109]

Alginate-based hydrogels have been used for in drug delivery,[110–112] tissue engineering,[113–115] wound healing,[116–118] cell encapsulation,[119,120] and as adhesion barriers.[121] For instance, recently Kim *et*

al. employed alginate-based hydrogels for delivering differentiated adipogenic cells for adipose tissue engineering.[115] Oxidized alginate (susceptible to hydrolysis) was coupled with an adhesion peptide and crosslinked with calcium sulfate to encapsulate cells *in vivo*. The injected cell-laden hydrogels led to the formation of soft, semitransparent adipose tissue after 10 weeks in male nude mice highlighting the ability of degradable alginate hydrogels to deliver cells and generate living tissue *via* a minimally invasive injection.

1.3.4 Fibrin. Fibrin is a fibrous, non-globular protein that is an important element of the provisional extracellular matrix. It forms hydrogels by the enzymatic polymerization of its precursor, fibrinogen, *via* thrombin-mediated cleavage of fibrinopeptide A in the presence of factor XIII.[122] Fibrinogen molecules are composed of two sets of disulfide-bridged Aα-, Bβ-, and γ-chains.[123] The proteinase inhibitor, apronitin, can control the degradation rate of these biocompatible and cell-adhesive hydrogels. Further, fibrin can promote cell migration, proliferation, and adhesion.[124,125] Although recent improvements in hydrogel formation have been reported with the use of additional salt during gelation,[126,127] the fast gelation time and restricted mechanical properties still limit the use of fibrin-based hydrogels. Nevertheless, fibrin-based hydrogels have been used for wound healing,[127,128] controlled delivery,[129,130] and tissue engineering.[127,131] For example, Scotti *et al.* reported enhanced synthetic activity of chondrocytes encapsulated in fibrin hydrogels.[131] It was found that DNA content remained stable, indicating limited cell death or proliferation, and indices of cartilage matrix production, such as GAG and collagen II content, increased.

1.3.5 Other natural polymers. Discussion of natural polymers for hydrogel preparation in this section mainly has been limited to HA, chitosan, heparin, alginate, and fibrin, owing to scope of the article. However, other natural polymers, such as collagen, gelatin, chondroitin sulfate, agarose, carrageenan, dextran, and silk, have been utilized for variety of bioengineering applications, including cartilage, neural, spinal cord, skin and vocal cord tissue engineering as well as therapeutic and controlled delivery. Readers are directed to recent reviews by Slaughter *et al.*[10] for collagen based hydrogels, Vlierberghe *et al.*[132] for collagen, gelatin, and chondroitin sulfate based hydrogels, Perale *et al.*[133] for alginate and collagen based hydrogels, and Kaplan and coworkers[134,135] for silk based hydrogels.

1.4 Mechanism of network formation

Gelation refers to the linking of macromolecular chains together which initially leads to progressively larger branched yet soluble polymers depending on the structure and conformation of the starting material. The mixture of such polydisperse soluble branched polymer is called 'sol'. Continuation of the linking process results in increasing the size of the branched polymer with decreasing solubility. This 'infinite polymer' is called the 'gel' or 'network' and is permeated with finite branched polymers. The transition from a system with finite branched polymer to infinite molecules is called 'sol-gel transition' (or 'gelation') and the critical point where gel first appears is called the 'gel point' (Rubinstein & Colby, 2003). Different types of gelation mechanism are summarised in Figure 1. Gelation

can take place either by physical linking (physical gelation) or by chemical linking (chemical gelation). Physical gels can be sub categorised as strong physical gels and weak gels. Strong physical gel has strong physical bonds between polymer chains and is effectively permanent at a given set of experimental conditions. Hence, strong physical gels are analogous to chemical gels. Examples of strong physical bonds are lamellar microcrystals, glassy nodules or double and triple helices. Weak physical gels have reversible links formed from temporary associations between chains. These associations have finite lifetimes, breaking and reforming continuously. Examples of weak physical bonds are hydrogen bond, block copolymer micelles, and ionic associations. On the other hand, chemical gelation involves formation of covalent bonds and always results in a strong gel. The three main chemical gelation processes include condensation, vulcanisation, and addition polymerisation.

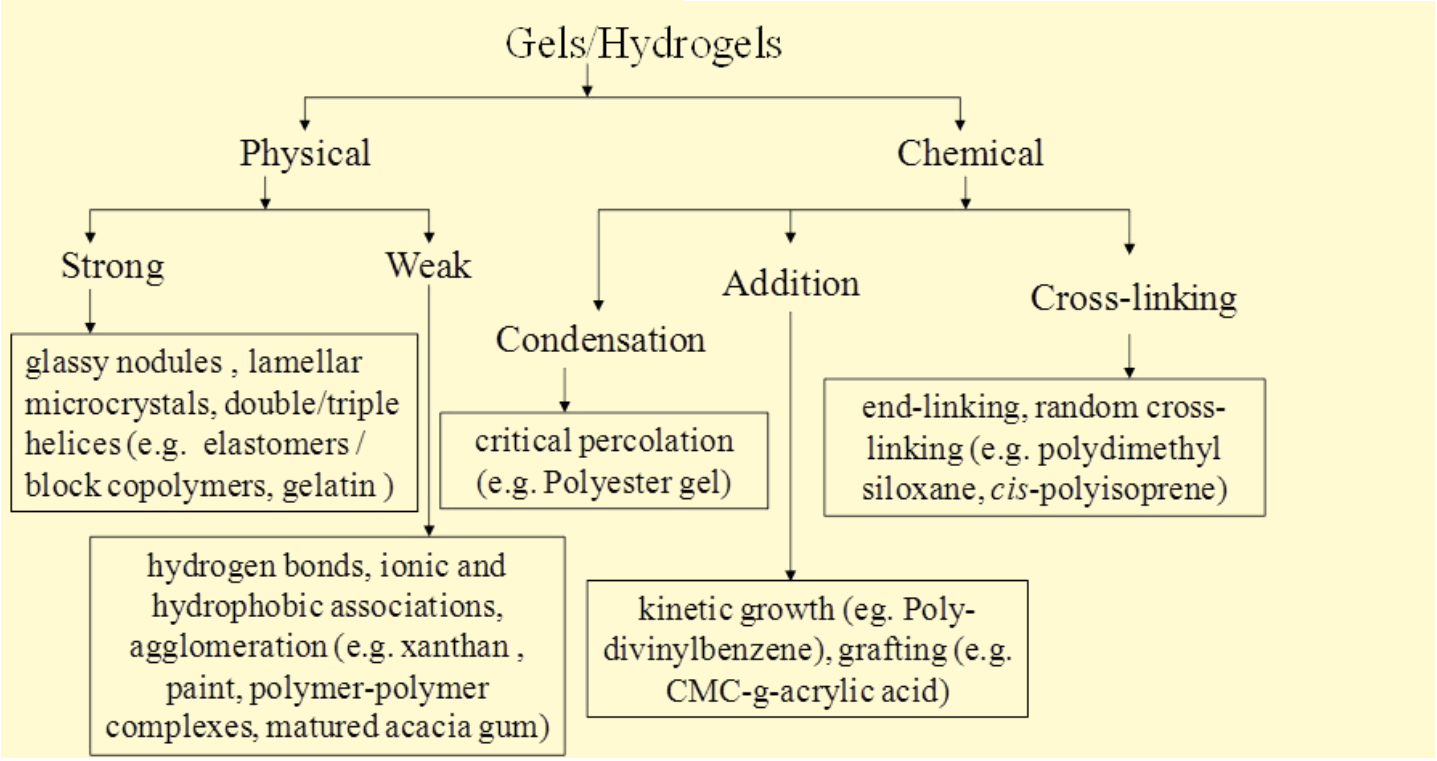


Figure 4.

Classification of gelation mechanism and relevant examples.

1.5 Characteristic of hydrogel

The water holding capacity and permeability are the most important characteristic features of a hydrogel. The polar hydrophilic groups are the first to be hydrated upon contact with water which leads to the formation of primary bound water. As a result the network swells and exposes the hydrophobic groups which are also capable of interacting with the water molecules. This leads to the formation of hydrophobically-bound 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 covalent or physical cross-links, leading to an elastic network retraction force. Thus, the hydrogel will reach an equilibrium swelling level. The additional absorbed water is called 'free water' or 'bulk water', and assumed to fill the space between the network chains, and/or the centre of larger pores, macropores, or voids. Depending on the nature and composition of the hydrogel the next step is the disintegration and/or dissolution if the network chain or cross-links are degradable. Biodegradable hydrogels, containing labile bonds, are therefore advantageous in applications such as tissue engineering, wound healing and drug delivery. These bonds can be present either in the polymer backbone or in the cross-links used to prepare the hydrogel. The labile bonds can be broken under physiological conditions either enzymatically or chemically, in most of the cases by hydrolysis (Hennink & Nostrum, 2002; Hoffman, 2002).

1.6 Stimuli responsive hydrogels

Hydrogels can also be stimuli sensitive and respond to surrounding environment liketemperature, pH and presence of electrolyte (Nho et al., 2005). These are similar to conventional hydrogels except these gels may exhibit significant volume changes in response to small changes in pH, temperature, electric field, and light. Temperature sensitive hydrogels are also called as thermogels (Jarry et al., 2002; Schuetz et al., 2008). These stimuli-sensitive hydrogels can display changes in their swelling behaviour of the network structure according to the external environments. They may exhibit positive thermo-sensitivity of swelling, in which polymers with upper critical solution temperature (UCST; temperature at which mixture of two liquids, immiscible at room temperature, ceases to separate into two phases) shrink by cooling below the UCST (Said et al., 2004). Some of the examples of stimuli sensitive hydrogels are poly (vinyl methyl ether) and poly (N-isopropyl acrylamide) gels, kappa-carrageenan-calcium based hydrogels, etc. (Bhardwaj et al., 2005; Sen, 2005). A summary of recent progress in biodegradable temperature sensitive polymers including polyesters, polyphosphazenes, polypeptides, and chitosan, and pH/temperature-sensitive polymers such as sulfamethazine-, poly(b-amino ester)-, poly(amino urethane)-, and poly(amidoamine)-based polymers is reviewed recently by Nguyen and Lee (2010). Recent progresses in the development and applications of smart polymeric gels have been reviewed extensively by Masteikova, Chalupova et al. (2003) and Chaterji, Kwon et al. (2007).

1.7 Xerogel & aerogel

A 'xerogel' is a solid formed from a gel by drying it slowly at about room temperature with unhindered shrinkage (Livage et al., 1988). Xerogels usually retain high porosity (25%) and enormous surface area (150–900 m^2/g), along with very small pore size (1-10 nm). One such example of xerogel is boehmite AlO(OH)-monolithic gels with proposed application in space exploration and electronics (Yoldas, 1975). 'Aerogel' is derived from a gel (essentially by supercritical drying technique) in which the liquid component of the gel has been replaced with a gas. The result is an extremely low-density solid with several remarkable properties, most notably its effectiveness as a thermal insulator and its extremely low density. It is also called frozen smoke, solid smoke or blue smoke due to its translucent nature and the way light scatters in the material. Some of the examples are carbon and silicon aerogels which can be used in buildings double window glazing as transparent thermal super-insulators (Kistler, 1931).

2 LITERATURE REVIEWS

In 2017, Experimental studied by Nishi Panchal, Dhruv Patel and Nimish Shah shows the effect of pH and ionic strength hydrogels respond to change in environment during swelling. The swelling ratio increases with increase in pH and with increase in ionic strength and the swelling decreases as electrostatic attraction increases between the chains. Decrease in concentration of cross linker leads to increased swelling in the polymer but its strength decreases. As the pH of the solution increases the amount of swelling increases. This is because the number of fixed charges on the gel increases as more carboxylic groups get converted to their basic salt form. This increases electrostatic repulsion between the polymer chains and allows more water to get absorbed. The ionic strength of the solution in which hydrogel is immersed also has an impact on absorption capacity. The electrostatic repulsion between crosslinked chains decreases with increasing NaCl concentration as it tends to partially neutralize the carboxylic acid attached to polymer chains. [4].

Mahdavinia et al. carried out graft copolymerization of mixtures of acrylic acid (AA) and acrylamide (AAm) onto chitosan by using potassium persulfate (KPS) as a free radical initiator in the presence of methylenebisacrylamide (MBA) as a crosslinker. The effects of reaction variables such as MBA concentration and AA/AAm ratio on the water absorbency capacity have been investigated. The polymer structures were confirmed by FTIR spectroscopy. Water absorbencies were compared for the hydrogels before and after alkaline hydrolysis. In the non-hydrolyzed hydrogel, enhanced water absorbency was obtained with increasing AA in monomer feed.[5].**Yiu and Hiu prepared a novel carboxymethylchitosan-gpoly (acrylic acid) superabsorbent polymer through graft polymerization of acrylic acid onto the chain of carboxymethyl chitosan and subsequent crosslinking.** It was demonstrated by FTIR spectroscopy that acrylic acid had been graft polymerized with carboxymethyl chitosan. By studying the swelling ratio of the polymer synthesized under different conditions, optimization conditions were found for a polymer with the highest swelling ratio. The rate of water absorption of the polymer was high, and the swelling of the polymer fitted the process of first dynamics. The swelling ratio of the polymer was pH-dependent superabsorbent.[5].

2.1 History of

- Electrosensitive hydrogels exhibit swelling or deswelling with applied currents
  - Ionizable groups sensitive to pH and electrical current
  - Applied electrical current causes matrix reconfiguration
- Hydrophilicity changes with applied current
  - Result: expulsion or absorption of water from gel matrix (syneresis)
- Hypothesis: syneresis can be used to quickly dry thin film of hydrogel polymer

based paint

2.2 History of Hydrogel Applications

- Electrosensitive hydrogels used in pharmaceuticals for drug delivery
  - Drugs loaded into an electrosensitive gel
  - Applied current to a particular location on patient,
    - Forces drug out of the gel matrix
- Hydrogel paints formulations are marketable
  - Anti-fouling paints use hydrogels to create lipid bilayers
  - Eliminates marine life growth on boat hulls
    - Reduces drag on boat
    - Reduced fuel consumption
  - Natural sound absorbent

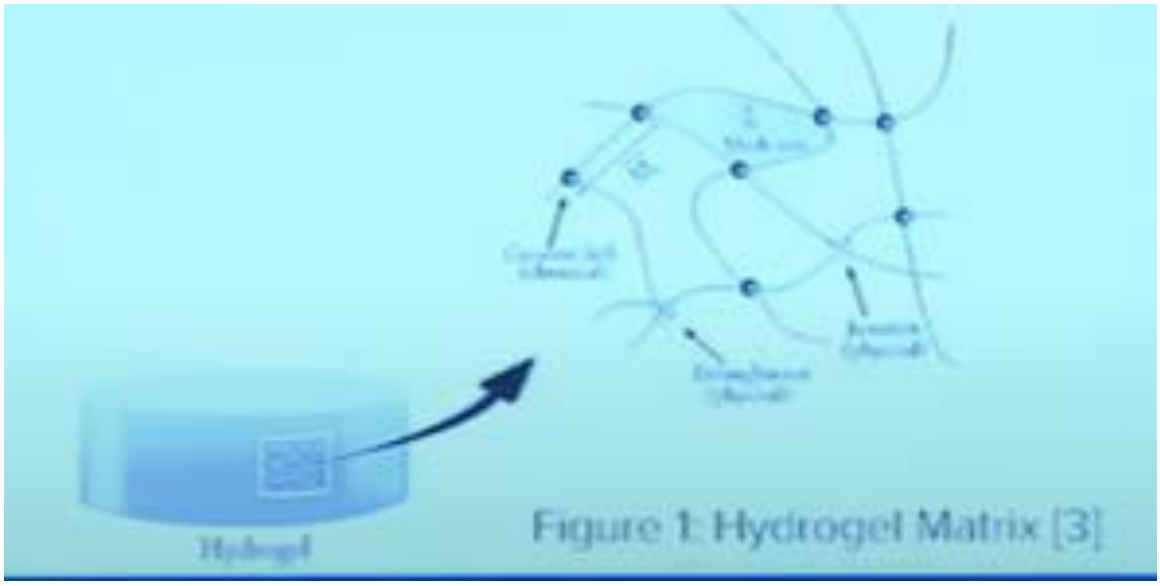
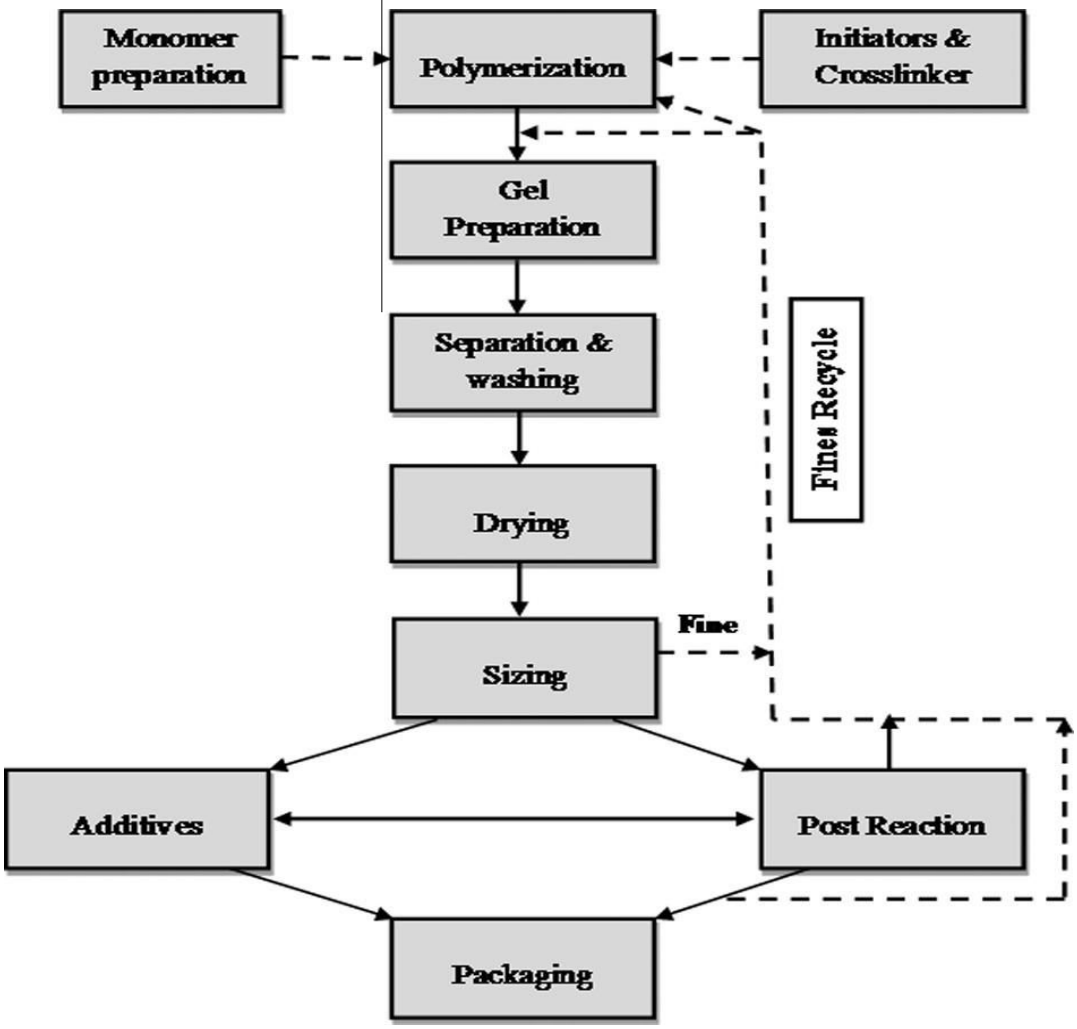


Figure 1: Hydrogel Matrix [3]

Fig 5 Hydrogel M



atrix

Fig production of hydrogels in industry consists of solution and reversed suspension and reversed emulsion polymerizations. Fig. 3 represents a block diagram of a generic solution polymerization process. This figure provides the major procedures for hydrogel manufacturing in the semi-pilot and industrial scales.

3 Materials and Methods

Hydrogel preparation

Cell-compatible hydrogels have been prepared using a variety of polymeric materials, which can be divided broadly into two categories according to their origin: natural or synthetic.[7] Natural polymers such as polysaccharides serve as ideal building blocks for preparing hydrogels that can mimic aspects of the structural and biological properties of the cellular microenvironment. For instance, proteoglycans are one of the vital components of articular cartilage, and use of glycosaminoglycan (GAG) hydrogels, such as those based on hyaluronic acid or chitosan, as a scaffold can be useful for cartilage tissue engineering.[52] Moreover, as shown in Table 1, the mechanical properties, water content, and inherent chain flexibility of polysaccharide-based hydrogels help to mimic the natural ECM. In addition, such polymers can be degraded by naturally occurring cell-secreted enzymes in the cellular microenvironment, mimicking the dynamic nature of the ECM.

Further, the specific cell–surface receptors for polysaccharides are known and have been extensively studied. For example, in the case of hyaluronic acid (HA), a non-sulfated glycosaminoglycan found in the ECM, both cluster of differentiation (CD) 44 and the receptor for hyaluronan-mediated motility (RHAMM) are known to enable cell adhesion and proliferation on HA.[53] However, limited tunability of degradation kinetics, relatively poor mechanical properties, batch-to-batch variations from manufacturers, or potential immunogenic reactions can restrict the application of natural polymer based limit their use in applications where targeted and specific biological activity is desired. Hence, many combinations of natural and synthetic polymers have been studied for developing hydrogels with orthogonal property control in the cellular microenvironment. In this section, we will limit the discussion to several widely used natural and synthetic polymer building blocks used in controlled microenvironments.

hydrogels.[54] Synthetic polymers afford tunable mechanical properties and a large scope of chemical modification, including the introduction of degradable or biochemical moieties. Commercial availability, coupled with great flexibility in the working range of pH, ionic strength, and chemical conditions, make synthetic polymers excellent candidates for hydrogel preparation. However, purely synthetic materials often exhibit inferior biocompatibility and biodegradability in comparison to naturally derived materials, which may

Table 1 Selecting materials for hydrogel preparation. Comparison of natural and synthetic polymers typically used for preparation of cell compatible hydrogels

Feature/function	Natural polymers	Synthetic polymer
Biocompatibility	Polymer dependent	Polymer dependent

Bioactivity (*i.e.* cell specific receptor)	Possible	Limited
Inherent biodegradability	✓✓	✓
Tunability of degradation kinetics	✓	✓✓
Degradation byproducts	Biocompatible	Potentially harmful
Flexibility for chemical modification	✓	✓✓
Flexibility of working range (*i.e.* pH and ionic strength)	✓	✓✓
Tuning of mechanical properties	✓	✓✓
Commercial availability	✓	✓✓
Batch to batch variatins	Likely	Controlled

3.1 Characterisation

An easy way to quantify the presence of hydrogel in a system is to disperse the polymer in water using a cylindrical vial and visually observe the formation of insoluble material. Visual monitoring of the solution viscosity by turning the universal up-side down can also provide quick measure of the bulk viscosity. reported in literature .

3.2. Solubility

3.2.1. Method A

Normally the hydrogel content of a given material is estimated by measuring its insoluble part in dried sample after immersion in deionised water for 16 h (Katayama, Nakauma 2006) or 48 h at room temperature (Nagasawa et al., 2004). The sample should be prepared at a dilute concentration (typically ~ 1%) to ensure that hydrogel material is fully dispersed in water. The gel fraction is then measured as follows:

GelFraction(hydrogel%)=(WdWi)*100GelFraction(hydrogel%)=(WdWi)*100

E1

Where, W_i is the initial weight of dried sample and W_d is the weight of the dried insoluble part of sample after extraction with water.

3.2.2. Method B

A more accurate measure of the insoluble fraction (also termed as hydrogel can be determined by measuring the weight retained after vacuum filtration. This is essentially the method prescribed by JECFA (Joint Expert Committee on Food Additives) for hydrocolloids which we have modified by changing the solvent from mild alkaline to water (Al-Assaf et al., 2009). The weight (W_1) of a 70 mm glass fibre paper (pore size 1.2 micron) is determined following drying in an oven at 105°C for 1 hour and subsequently cooled in a desiccator containing silica gel. Depending on the test material, 1-2 wt% (S) dispersion can be prepared in distilled water followed by overnight hydration at room temperature. The hydrated dispersion is then centrifuged for 2-5 minutes at 2500 rpm prior to filtration. Drying of the filter

paper is carried out in an oven at 105°C followed by cooling to a constant weight (W_2). % Insoluble can then be calculated:

%Hydrogel=(W2−W1S)*100%Hydrogel=(W2−W1S)*100

E2

Depending on the test material different mesh size can be also used, e.g. the use of a 20-mesh steel screen (1041 µm) to determine the gel fraction (Yoshii & Kume, 2003).

3.3. Swelling measurement

3.3.1. Method A

The Japanese Industrial Standard K8150 method has been used to measure the swelling of hydrogels. According to this method the dry hydrogel is immersed in deionised water for 48 hours at room temperature on a roller mixer. After swelling, the hydrogel is filtered by a stainless steel net of 30 meshes (681 µm). The swelling is calculated as follows (Nagasawa et al., 2004):

Swelling=Ws−WdWdSwelling=Ws−WdWd

E3

Where, W_s is the weight of hydrogel in swollen state and W_d is the weight of hydrogel in dry state. The terms 'swelling ratio' (Liu et al., 2005), '

equilibrium degree of swelling' (EDS) (Valles et al., 2000) or 'degree of swelling' (Liu et al., 2002a) has been used for more or less similar measurements.

3.3.2. Method B

Alternatively, to measure the swelling of hydrogel, in a volumetric vial (Universal) the dry hydrogel (0.05-0.1g) was dispersed into sufficiently high quantity of water (25-30 ml) for 48 hrs at room temperature. The mixture is then centrifuged to obtain the layers of water-bound material and free unabsorbed water. The free water is removed and the swelling can be measured according to Method A above.

3.3.3. Method C

The swelling can also be measured according to the Japanese Industrial Standard (JIS) K7223. The dry gel is immersed in deionized water for 16 h at room temperature. After swelling, the hydrogel was filtered using a stainless-steel net of 100-mesh (149 µm). Swelling is calculated as follows (Katayama et al., 2006):

Swelling=CB*100Swelling=CB*100

E4

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

3.4 FTIR

FTIR (Fourier Transform Infrared Spectroscopy) is a useful technique for identifying chemical structure of a substance. It is based on the principle that the basic components of a substance, i.e. chemical bonds, usually can be excited and absorb infrared light at frequencies that are typical of the types of

the chemical bonds. The resulting IR absorption spectrum represents a fingerprint of measured sample. This technique is widely used to investigate the structural arrangement in hydrogel by comparison with the starting materials (2004; Mansur et al., 2004; Torres et al., 2003).

3.5. Scanning Electron Microscopy (SEM)

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 (Aikawa et al., 1998; Aouada et al., 2005; El Fray et al., 2007; 2004; Pourjavadi & Kurdtabar, 2007).

3.6. Light scattering

Gel permeation chromatography coupled on line to a multi angle laser light scattering (GPC-MALLS) 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 (Al-Assaf et al., 2007a). This technique is widely used in quantifying the hydrogels of several hydrocolloids such as gum arabic, gelatine and pullulan (Al-Assaf et al., 2006b; Al-Assaf et al., 2007b; 2006). 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 (Al-Assaf et al., 2006b) (Figure 2).

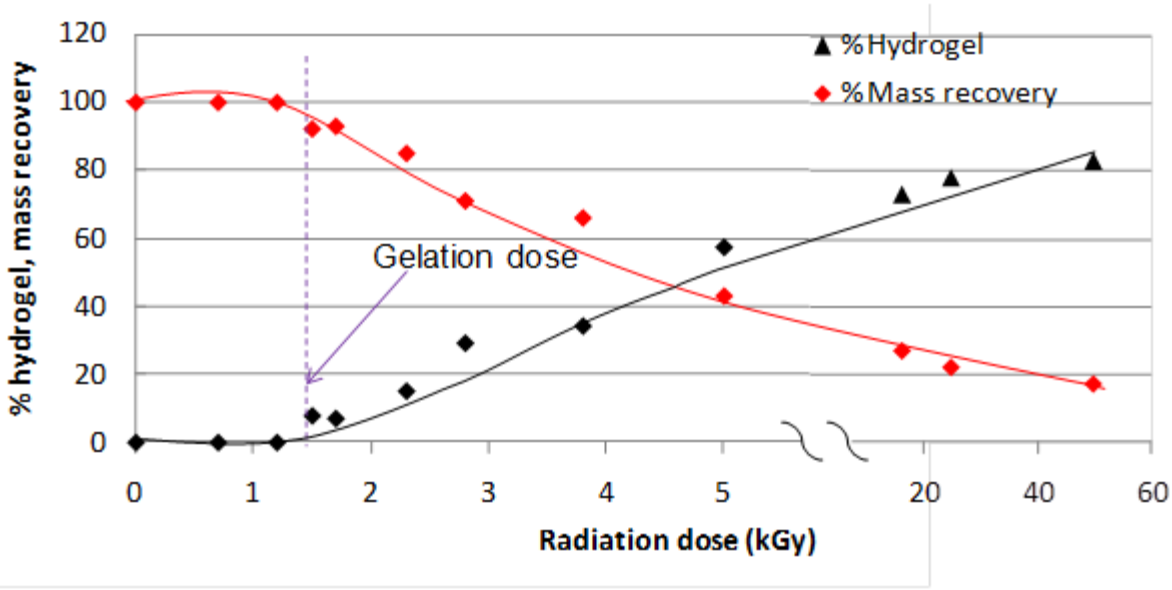


Figure 6

Correlation between mass recovery data obtained from GPC-MALLS for dextran and amount of hydrogel formed as a function of radiation dose.

2.6. Sol – gel analysis

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 5. This equation is widely reported for the linear polymers like carboxymethyl cellulose (Liu et al., 2002b).

s+s√=p0q0+2q0μ2,0Ds+s=p0q0+2q0μ2,0D

E5

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. μ2,0 is the initial weight average degree of polymerisation, and D is the radiation dose in Gy.

To avoid an inaccuracy resulting from unknown molecular weight distribution of used polymers, the Charlesby–Rosiak equation (Equation 6) is used. This equation allows for estimation of radiation parameters of linear polymers of any initial weight distribution as well as is applicable to systems when an initial material is monomer or branched polymer (Wach et al., 2003b).

s+s√=p0q0+(2−p0q0)Dv+DgDv+Ds+s=p0q0+(2−p0q0)Dv+DgDv+D

E6

Where, D is the absorbed dose in Gy. D_g is gelation dose – a dose when the first insoluble gel appears. D_v is the virtual dose – a dose required to change the distribution of molecular weight of the certain polymer in such a way that the relation between weight-average and number-average molecular weight would be equal to 2. However, there is limitation to Charlesby–Pinner equation that it does not allow the chain reaction that occurs during the event of ionising radiation into its consideration and, so most of the experimental data of radiation polymerisation do not obey this equation. It is recently shown that chain reactions, rather than polydispersity and structure, explain most of the deviation from ideal Charlesby-Pinner behaviour of irradiated polymers (Jones et al., 1996).

To obtain the gelation dose, yield of cross-linking and scission, following equations are used:

G(x)=4.8*105Mw,0*DgG(x)=4.8*105Mw,0*Dg

E7

G(s)/G(x)=2p0/q0G(s)/G(x)=2p0/q0

E8

Where, G(x) and G(s) are radiation yield of cross-linking and of scission in mol J-1, respectively. $M_{w,0}$ is weight average molecular weights of initial polymer before irradiation. The above equations are valid for polymers with initial most probable molecular weight distribution and degree of polydispersity $M_{w,0}$ / $M_{n,0}$ = 2 (Rosiak et al., 2003; Wach et al., 2003b). For the degradation process occurring in a polymer solution when it is subjected to irradiation, the yield of scission (mol/J) can be calculated as:

G(s)=2cDd(1Mw−1Mw,0)G(s)=2cDd(1Mw−1Mw,0)

E9

Where c is the concentration of polymer in solution (g/dm3); D is the absorbed dose (Gy); d is the solution density (kg/dm^3); $M_{w,0}$ and M_w are the weight-average molecular weight of polymer before and after irradiation, respectively. Degradation rate in irradiation is first-order reaction and the rate constants k can be evaluated from the following first order kinetic equation (Wasikiewicz et al., 2005):

1Mt=1M0+ktm1Mt=1M0+ktm

E10

Where, M_0 and M_t are weight-average molecular weights before and after the treatment for t hours, respectively, m is the molecular weight of polymer monomer unit and k (h^{-1}) is the rate constant.

2.7. Rheology

The rheological properties are very much dependant on the types of structure (i.e. association, entanglement, cross-links) present in the system. Polymer solutions are essentially viscous at low frequencies, tending to fit the scaling laws: G' ~ ω^2 and G" ~ ω. At high frequencies, elasticity dominates (G' > G"). This corresponds to Maxwell-type behaviour with a single relaxation time that may 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 (Omari et al., 2006; Rubinstein & Colby, 2003). This technique has been used to characterize the network structure in seroglucan/borax hydrogel (Coviello et al., 2003), chitosan based cationic hydrogels (Kempe et al., 2008; Sahiner et al., 2006) and a range of other hydrocolloids (Al-Assaf et al., 2006b).

2.8. Other techniques

The main 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 (Phillips et al., 2003). 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). Thermo-gravimetric analysis (Lazareva & Vashuk, 1995; Singh & Vashishth, 2008; Torres et al., 2003), X-ray diffraction (2008; Mansur et al., 2004), sol-gel analysis (Janik et al., 2008; Rosiak, 1998; Wach et al., 2003b; Xu et al., 2002) etc. are also used to confirm the formation of cross-linked network gel structures of hydrogel.

3.7 Chemically crosslinked hydrogels

3.7.1 Radical polymerization.

Radical polymerization involves the formation of free radicals *via* decomposition of an initiator by light, temperature, or redox reaction.[196] The successive reaction of multifunctional free radical building blocks leads to the formation of a polymer network. Free radicals can be used to initiate hydrogel formation by different polymerization mechanisms: chain growth, step growth, or mixed mode (a combination of chain and step) polymerization.[197] Hydrogel formation by free radical polymerization offers advantages such as

well-characterized reaction kinetics and facile *in situ* polymerization in presence of cells with spatiotemporal control.[198] However, free radicals can be transferred to proteins, affecting their bioactivity, or transferred to biomolecules present in the ECM, affecting cell viability.[19,199] These exothermic reactions also can cause a local increase in temperature,[200] where temperature rise must be minimized to maintain cell viability and function. Despite these challenges, free radical polymerization *via* chain growth mechanisms is a well-established method for cell encapsulation; however, the heterogeneous nature of the chain polymerization mechanism leads to a distribution of polymer chain molecular weights and thus molecular-level inhomogeneity within the network. Inhomogeneity in network can dramatically reduce the mechanical strength of hydrogels.[201] The widespread use of free radical chain polymerization for hydrogel formation partly arises from the availability of many hydrophilic meth(acrylate)-functionalized building blocks. Historically, radical polymerization of hydroxyethyl methacrylate (HEMA) using ethylene dimethacrylate (EDMA) as a crosslinker was extensively studied for commercial-scale manufacturing of flexible contact lenses.[181] A large number of macromolecules, such as HA,[67,202–204] chitosan,[193,205] and PEG,[205,206] are easily functionalized with vinyl end groups and can undergo radical polymerization to form hydrogels in presence of appropriate initiators. For example, Morelli and Chiellini functionalized Ulvan, a sulfated polysaccharide from green seaweed, with methacryloyl groups.[207] The biocompatible hydrogel network was formed *via* radical polymerization using UV irradiation in the presence of methacrylic anhydride or glycidyl methacrylate.

Radical polymerization

A significant advantage of radical polymerization methods is that, when used in conjunction with a photoinitiator, they can provide spatiotemporal control over hydrogel formation and *in situ* properties.[14,208] For instance, Guvendiren and Burdick demonstrated short and long-term cellular response to a dynamic microenvironment using methacrylated hyaluronic acid.[208] The methacrylated HA was crosslinked with a dithiol *via* the Michael-type addition, creating a low modulus hydrogel, and subsequently *via* free radical chain polymerization of the remaining methacrylates, increasing the crosslink density and modulus of the hydrogel at time points of interest. Human mesenchymal stem cells (hMSCs) that were cultured on these hydrogel substrates spread from

cell areas of ~500 to 3000 μm^2 and exhibited greater traction over a timescale of hours during stiffening (with *E* increasing from 3 to 30 kPa). The cell response to matrix stiffening was found to vary over 2 weeks in culture; an increased population of terminally differentiating hMSCs was present over time and was no longer responsive to variations in the mechanical properties of the hydrogel.

Alternatives such as controlled chain polymerization have been employed for hydrogel preparation to provide more control of hydrogel properties;[209–211] however, potential cytotoxicity of the unremoved metal catalysts employed during these methods can restrict their use in the cell microenvironment. Free radical step growth polymerization recently has emerged as an alternative hydrogel formation strategy that provides a more homogeneous network structure and enables spatiotemporal control of hydrogel formation;[212] recent developments in this area (*e.g.*, thiol–ene click reactions)

3.7.2 Click chemistry.

Click reactions, broadly defined, are a class of reactions that are fast, versatile, regiospecific, and highly efficient.[213] Click reactions usually yield a single product, leaving no reaction byproducts, and occur under mild conditions. After the introduction of click reactions by Sharpless,[213] the copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) has been widely used for the facile synthesis of new molecules, polymers, and hydrogels.[214] Over the past decade, several reactions have been observed to have 'click' reaction attributes while not requiring a metal catalyst, including the radical addition of thiols to select alkenes and alkynes, Michael-type addition of thiols to maleimides, Diels–Alder reactions between dienes and dienophiles, and oxime reactions between aminooxy groups and aldehydes or ketones (Table 2).[215] Click reactions are attractive tools for synthesizing cell-compatible hydrogels, which can be used for controlled cell culture, tissue engineering, and controlled release applications.[216–219] Advantages such as fast reaction kinetics, high regio- and chemo-selectivity, mild reaction conditions, and facile tuning of structural and mechanical properties using stoichiometry make click reactions highly useful for synthesizing cell-compatible hydrogels.[169,220,221]

Table 2 Click reactions for hydrogel for hydrogel formation. Comparison of important click reactions

typically used for formation of cell compatible hydrogels

Click reactions	Reacting functional groups	Reaction condition	Key features	Applications
CuAAC	Azide and alkyne	pH 4–12, reaction time <1 h, Cu catalyst required	– Bioorthogonal – Reversible – Difficulties with complete removal of cytotoxic Cu	Cell encapsulation and delivery,[217] drug delivery,[223,224] 2D cell culture[225]
SPAAC	Cyclooctyne and azide	pH 7.4, reaction time <1 h	No catalyst required	Cell encapsulation,[230,231] 3D cell culture[216,218]
Diels–Alder	Conjugated diene and substituted alkene	pH 5.5–6.5, reaction time <8 h	– No catalyst required Longer reaction time than most of the other click reactions	Cell encapsulation and release,[234] controlled cargo delivery[235]
Inverse electron demand Diels–Alder	Dienophile and diene	pH 7.4, reaction time <5 min	Faster rate of reaction than many other Cu-free click reactions	cell imaging,[238] drug targeting,[239] cell surface protein labeling[240]

Michael addition	Thiol and α,β-unsaturated carbonyl group	pH 6–8, reaction time <30 min	– No catalyst required	Cell encapsulation,[157,160,250] controlled cargo delivery[29,248]
Oxime	Aminooxy and aldehyde/ketone	pH 6–8, reaction time min	– Reversible	Cell encapsulation, protein immobilization

3.7.2.1 Azide–alkyne *cycloadditions.* Copper(I)-catalyzed azide–alkyne cycloadditions (CuAAC) unite two unsaturated reactants, azides and alkynes, to form triazoles.[222] CuAAC click reactions have been extensively used for crosslinking both natural[223–225] and synthetic[169,217,226] polymer-based hydrogels. One advantage of this class of reactions is that both azides and alkynes are almost completely unreactive toward biological molecules.[227] Their limitations include alkyne homocoupling, difficulties removing residual heavy metal catalyst, and the biocompatibility of the resulting 1,2,3-triazoles. In particular, use of toxic and unstable Cu catalysts can limit applicability in cellular microenvironments. Nevertheless, Piluso *et al.* recently reported the preparation of HA-based hydrogels *via* CuAAC click crosslinking of alkyne-functionalized HA.[225] The elastic modulus of the resulting HA hydrogels was tuned between 0.5 to 4 kPa by varying the stoichiometry, length, and rigidity of an azide-functionalized crosslinker. In this case, limited toxicity was observed with L292 cells encapsulated in these hydrogels, indicating their potential as biomaterials.

Copper-free strain-promoted azide–alkyne cycloaddition (SPAAC) reactions have emerged to address issues with copper toxicity in biological systems.[228] Ring strain, as well as electron-withdrawing fluorine substituents in some cases, promotes rapid reaction of cyclooctynes with azides in the absence of the Cu catalyst.[229] Owing to the absence of the catalyst, SPAAC click chemistry has been used to crosslink hydrogels in the presence of cells to form controlled cellular microenvironments.[216,218,230,231] For instance, Zheng *et al.* reported use of a SPAAC strategy to create hydrogels by functionalizing PEG with 4-dibenzocyclooctynol.[231] The versatility and biocompatibility of this strategy allowed hMSC encapsulation, maintaining their viability as

assessed using a live-dead imaging-based cytotoxicity assay (~90% viability after 24 h). In a broader context, such an approach can be useful for cell delivery, in which cells are hypersensitive to presence of Cu during crosslinking. In another example, DeForest *et al.* used SPAAC click chemistry for hydrogel formation followed by a thiol–ene reaction for photoaddition of three-dimensional biochemical patterns with micrometer scale resolution and in the presence of fibroblasts (>90% viability at post 24 h encapsulation).[218] Specifically, an enzymatically degradable peptide sequence was incorporated into the hydrogel *via* SPAAC reaction, and the adhesion ligand was incorporated in the hydrogel network *via* cytocompatible thiol–ene photolithographic patterning. The cells selectively adhered to regions in which the RGD motif was presented and subsequently degraded the hydrogel matrix through cleavage of the enzymatically degradable linker, leading to localized cell proliferation. In principle, such approaches can be used to study cell behavior in spatiotemporally controlled 3D microenvironments.

3.7.2.2 Diels–Alder *reactions.* The Diels–Alder (DA) reaction is a well-established solution-based reaction that has also been utilized for hydrogel formation. DA reactions involve addition of conjugated dienes to substituted alkenes to form substituted cyclohexenes.[215,232] The efficient and facile DA reaction occurs under mild reaction conditions and does not require an initiator, which is advantageous for crosslinking hydrogels in the presence of cells. However, the reactions are slow, which could be a limitation in certain applications. The DA reaction has been utilized for the preparation of various hydrogels for bioengineering applications.[233–235]

Shoichet and coworkers recently demonstrated the use of a Diels–Alder click reaction to create stable and biocompatible hyaluronic acid hydrogels (Fig. 7).[234] The carboxylic acid group of HA was reacted with furfurylamine to create furan-functionalized HA, and the modified HA was crosslinked with a maleimide PEG crosslinker to form a hydrogel. The mechanical and degradation properties of these hydrogels were modulated using the furan to maleimide molar ratio. *In vitro* studies with a cancer cell line, MDA-MB-231, demonstrated the cytocompatibility of these Diels–Alder HA-PEG hydrogels, and a high level of cell viability was maintained over 2 weeks (>98%, live-dead assay after 14 days). Using a similar approach,

Marra and coworkers prepared HA-based hydrogels for controlled release application.[235] HA was functionalized with either a maleimide or a furan group and crosslinked in PBS at 37 °C within ~40 minutes. Insulin (negatively charged) or lysozyme (positively charged) were encapsulated as model proteins within these HA-based hydrogels. The release profiles showed slight or no burst release depending upon the protein, owing to electrostatic interactions. In addition, the hydrogels were cytocompatible and maintained the viability of the entrapped cells. Taken together, these recent examples indicate that the Diels–Alder crosslinking for creating cell-compatible hydrogels is a promising strategy for soft tissue engineering, regenerative medicine and controlled release applications.

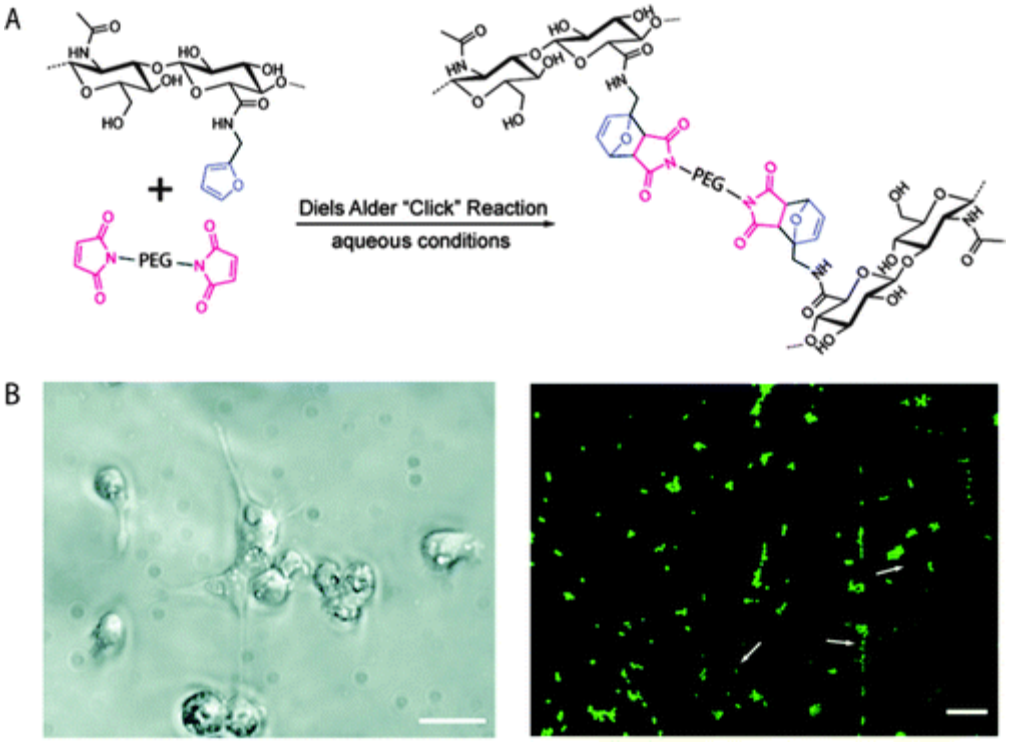


Fig. 7 Diels–Alder click reaction for forming degradable hydrogels. (A) Schematic of hydrogel formation using Diels–Alder reaction between furan groups of HA and maleimide groups present on a PEG macromer. (B) Brightfield image of MDA-MB-231 cells (left), which are known to interact with HA *via* CD 44 receptor. Cells were seeded on HA/PEG hydrogels and after 14 days adopted a flattened or elongated morphology, indicating cell adhesion (scale bar, 20 μm). Cell viability was assessed using a live/dead assay (right, live cells in green, dead cells indicated by arrows) signifying a high level of cell survival (>98%), after 14 days (scale bar, 60 μm). Reprinted from Nimmo *et al.*[234] with permission from

Fox and coworkers created an inverse-electron-demand Diels–Alder reaction, reacting a *trans*-cyclooctene with dipyridyltetrazine.[236] As compared to any other Cu-free click reaction, the rate of this reaction was an order of magnitude higher (k = 10^3 M^{-1} s^{-1}).[237] Using a similar approach, reactions of tetrazines with other alkenes such as norbornene[238] and cyclobutene[239] have also been reported. In principle, such reactions could be valuable for crosslinking cell-compatible hydrogels. Additionally, the inverse-electron-demand Diels–Alder reaction has been used for cell surface protein labeling indicating their bioorthogonality.[240]

3.7.2.3 Thiol–ene reactions. Thiol–ene reactions typically involve reaction of thiols with unsaturated functional groups, such as unactivated alkenes, maleimides, acrylates, and norbornenes. Thiol–ene reactions can proceed by free radical addition, Michael-type nucleophilic addition, or a combination of these mechanisms depending on the reaction conditions. Thiol–ene reactions share many attributes with classical click reactions: thiol–ene reactions proceed rapidly under mild conditions, have high orthogonality, yield a single regioselective product, and do not yield any byproducts. Hence, reactions that proceed by either mechanism are commonly referred as thiol–ene click reactions. For a comprehensive review of thiol–ene click reactions, readers are referred to recent reviews Hoyle *et al.*[241] and Kade *et al.*[242]

Gress *et al.* were the first to identify the radical-mediated thiol–ene reaction as a click reaction.[243] This radical-mediated thiol–ene coupling has since emerged as a highly attractive reaction for hydrogel formation and modification due to its high efficiency, ease of photoinitiation, and orthogonality with numerous functional groups.[241,244] The reaction offers advantages, such as spatiotemporal control over crosslinking and the possibility of conducting crosslinking in the presence of cells. Rydholm *et al.* reported the use of thiol–acrylate mixed mode free radical photopolymerization for the formation of hydrolytically degradable PEG hydrogels.[147] The mechanical properties and degradation profiles were modulated with thiol concentration. Use of photoinitiation enables controlled polymerization both spatially and temporally. In addition, thiols and acrylates also can photopolymerize in absence of a photoinitiator, which could prove useful for *in situ* crosslinking in the presence of cells.[241]

Fairbanks *et al.* have utilized a thiol–norbornene reaction to synthesize enzymatically degradable

PEG hydrogels.[245] Four-arm PEG was functionalized with norbornene end groups, and thiol-containing chymotrypsin- or MMP-degradable peptides were used for crosslinking. The step-growth mechanism ensured homogeneity in the resulting hydrogel network, and the crosslinking reaction did not significantly affect the viability of encapsulated hMSCs. Shih and Lin have recently shown the hydrolytic degradability of similar thiol–norbornene PEG hydrogels *via* ester hydrolysis under neutral or mildly basic conditions.[246] Taken together, degradation properties of these hydrogels can be modulated with the degree of crosslinking and the crosslinking peptide sequence, making them promising for tissue engineering applications in which fine control over degradation is desired.[247]

Nucleophilic Michael-type addition reactions between thiols and electron deficient 'ene's, such as maleimides, methacrylates, α,β-unsaturated ketones, acrylonitrile, and crotonates, are another type of thiol–ene click reaction. Due to the mild reaction conditions, numerous hydrogels have been prepared *via* Michael-type addition in the presence of cells without significantly altering cell viability.[157,160,248–250] For example, Phelps *et al.* used 4-arm PEG macromers functionalized with maleimide end groups and dithiol-containing protease-cleavable peptides to form hydrogels.[157] The mechanical properties of the hydrogels were modulated using appropriate polymer concentrations to mimic the modulus of the native ECM. Further, these PEG hydrogels maintained cell viability during gel formation and promoted the spreading of encapsulated C2C12 cells. Kiick and coworkers have employed Michael-type additions in the production of a variety of hydrogels. In one example, polypeptide-PEG hybrid hydrogels were produced *via* the reaction of the cysteine (CYS) residues of the polypeptide with vinyl sulfone (VS) functionalized PEG (Fig. 8).[250] Resilin-like polypeptides (RLP) were employed owing to the outstanding elastomeric properties of natural resilin for cardiovascular tissue engineering application and to provide bioactivity to inherently inert PEG hydrogels. Depending upon the molecular weight of the RLP and the stoichiometric ratio (CYS : VS), the storage modulus of the hydrogel was modulated from $G' \sim$ 2.6 kPa to 12 kPa. Encapsulated AoAFs adopted a spread morphology over 7 days and maintained their viability within *in vitro* culture in these hydrogels. These recent examples demonstrate the versatility of Michael-type addition reactions to

crosslink hydrogels in presence of cells for soft tissue and cardiovascular tissue engineering.

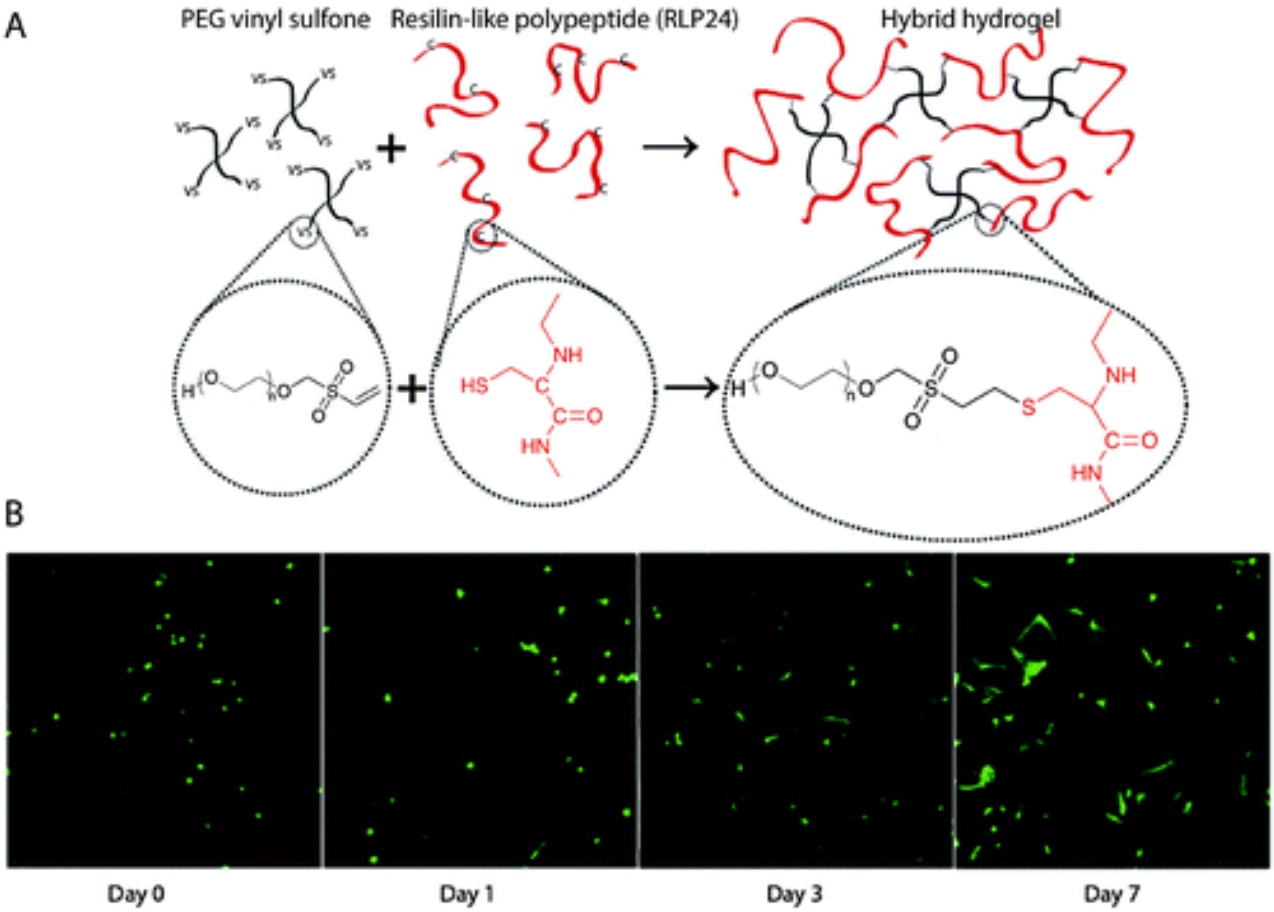


Fig. 8 Michael-type addition reaction for hydrogel format formation using the Michael-type addition reaction betwe PEG and cysteine residues present on the RLP. (B) Huma (AoAFs) were encapsulated during hydrogel formation an live/dead staining (fluorescent laser scanning confocal mi throughout the experiment, adopting a spread morphology from McGann *et al.*[250] with permission from John Wiley

3.7.2.4 Oxime reactions. Oxime reactions between aminooxy and aldehyde or ketone functional groups have recently been classified as click reactions owing to their fast reaction kinetics, orthogonality to various functional groups found in the cell microenvironment, and lack of catalyst. Recently, Grover *et al.* utilized oxime click reactions to synthesize cytocompatible PEG hydrogels.[251] Eight-arm PEG was functionalized with aminoxy groups and crosslinked with glutaraldehyde. By varying the polymer concentration and stoichiometric ratio of aminoxy to aldehyde, hydrogel mechanical properties and water content were modulated. This click reaction permitted encapsulation of murine MSCs, maintaining cell viability and metabolic

activity. However, glutaraldehyde has been observed to undergo various structural rearrangements in solution depending on the pH, influencing the reaction mechanisms and potentially influencing the 'click' nature of this reaction.[252] Maynard and coworkers used oxime click reaction and CuAAC to immobilize different proteins in PEG-hydrogel constructs.[253] PEG was functionalized with aminooxy and alkyne groups in order to conjugate ketoamide–myoglobin and azide-modified ubiquintin as model proteins for surface patterning. While the orthogonality of these two reactions is clear, many proteins and cells present free amines in solutions, such as hydrophilic lysines along the backbone of ECM proteins and growth factors; consequently, the specificity of the oxime reaction for orthogonal gel formation should be evaluated based on the protein and application of interest. In principle such an approach can be extended for numerous possible combinations of proteins in adjacent regions of a single plane or in multilayer constructs to modulate cell behavior.

3.7.3 Schiff base crosslinking reactions.

Schiff base crosslinking involves the reaction of macromolecules containing alcohol, amine, or hydrazide functionalities with aldehydes to form a hydrogel network. Due to the mild reaction conditions, this strategy has been utilized to prepare cell-compatible hydrogels for cell encapsulation and controlled drug delivery applications.[64,254] For example, Tan *et al.* synthesized *N*-succinyl-chitosan by introduction of succinyl groups at the *N*-position of the glucosamine units and also prepared hyaluronic acid with aldehyde functionality *via cis*-diol bond cleavage.[64] The chitosan-HA hydrogel was prepared with Schiff base linkages and exhibited a gelation time of ~1–4 minutes. The hydrogel supported cell adhesion, and encapsulated bovine articular chondrocytes were found to have regular spherical morphology, indicating the potential of this chemistry for tissue engineering applications. While a promising tool, many proteins present hydrophilic free amines (*e.g.*, lysines) or alcohols (*e.g.*, serine and tyrosine) in solution, as discussed with oxime reactions; the specificity of Schiff base crosslinking for orthogonal gel formation should be examined based on the desired application.

3.8 Application of hydrogel

Application of hydrogel

1. Hydrogel technologies may be applied to Hygienic Products.

2. Agriculture and Diaper Industries.

3. Drug delivery systems.

4. Sealing.

5. Coal Dewatering.

6. Artificial Snow

7. Food Additives

8. Pharmaceuticals.

9. Biomedical applications

• New researchers have demonstrated that a gel composed of small, woven protein fragments can successfully carry and release proteins of different sizes to different targets in the body.

• It is enabling the delivery of drugs such as insulin and trastuzumab (A monoclonal antibody (protein) often used to treat breast and ovarian cancer), hormones, growth factors as well as eye medications. 40

• Furthermore, one can control the rate of release of active ingredients from hydrogel by changing the

density of the gel, allowing for continuous drug delivery over a specific period of time.

• A newly introduced gel, known as a "nanofiber hydrogel scaffold," enables, over hours, days or even months, a gradual release of the proteins from the gel, and the gel itself is eventually broken down into harmless amino acids (the building blocks of proteins). 41

• Peptide hydrogels are ideally suited for drug delivery as they are pure, easy to design and use, non-toxic, bio-absorbable, and can be locally applied to a particular tissue.

• Depending on the size and density of the mesh, it can carry protein molecules between 14,000 and 150,000 daltons (a unit of molecular weight).

• Earlier work showed that the hydrogels could also carry smaller molecules, between 300 and 900 daltons. " So it can deliver both small molecules and big molecules,".

Hydrogel of many synthetic and natural polymers have been produced with their end use mainly in tissue engineering, pharmaceutical, and biomedical fields (Hoare & Kohane, 2008). Due to their high water absorption capacity and biocompatibility they have been used in wound dressing, drug delivery, agriculture, sanitary pads as well as trans-dermal systems, dental materials, implants, injectable polymeric systems, ophthalmic applications, hybrid-type organs (encapsulated living cells) (Benamer et al., 2006; Nho et al., 2005 ; Rosiak et al., 1995; Rosiak & Yoshii, 1999). A list of hydrogels with their proposed corresponding applications is shown in Table 1.

Application	Polymers	References
Wound care	polyurethane, poly(ethylene glycol), poly(propylene glycol),	(Rosiak & Yoshii, 1999)
	poly(vinylpyrrolidone), polyethylene glycol and agar	(Benamer et al., 2006; Lugao & Malmonge, 2001; Rosiak et al., 1995)
	Xanthan, methyl cellulose	(2006)
	carboxymethyl cellulose, alginate, hyaluronan and other hydrocolloids	(Kim et al., 2005; Rosiak et al., 1995; Rosiak & Yoshii, 1999; Walker et al., 2003)
Drug delivery, pharmaceutical	poly(vinylpyrrolidone)	(Benamer et al., 2006; Rosiak et al., 1995)
	starch, poly(vinylpyrrolidone), poly(acrylic acid)	(Kumar et al., 2008; Spinelli et al., 2008)
	carboxymethyl cellulose, hydroxypropyl methyl cellulose	(Barbucci et al., 2004; Porsch & Wittgren, 2005)
	polyvinyl alcohol, acrylic acid, methacrylic acid	(Nho et al., 2005)
	chitosan, αβ-glycerophosphate	(Zhou et al., 2008)
	κ-carrageenan, acrylic acid, 2-acrylamido-2-methylpropanesulfonic acid	(Campo et al., 2009; Pourjavadi & Zohuriaan-Mehr, 2002)

	acrylic acid, carboxymethyl cellulose	(El-Naggar et al., 2006; Said et al., 2004)
Dental Materials	Hydrocolloids (Ghatti, Karaya, Kerensis gum)	(Al-Assaf et al., 2009)
Tissue engineering, implants	poly(vinylalcohol), poly(acrylic acid)	(Rosiak et al., 1995)
	hyaluronan	(Kim et al., 2005; Shu et al., 2004)
	collagen	(Drury & Mooney, 2003)
Injectable polymeric system	polyesters, polyphosphazenes, polypeptides, chitosan	(2010)
	β-hairpin peptide	(Yan et al., 2010)
Technical products (cosmetic, pharmaceutical)	Starch	(Trksak & Ford, 2008)
	gum arabic	(Al-Assaf et al., 2006b; Al-Assaf et al., 2007b; 2006; Katayama et al., 2008)
	xanthan, pectin, carrageenan, gellan, welan, guar gum, locust bean gum, alginate, starch, heparin, chitin and chitosan	(Phillips et al., 2003; Phillips et al., 2005)
Others (agriculture, waste treatment, separation, etc.)	Starch	(Jeremic et al., 1999; Trksak & Ford, 2008; Yoshii & Kume, 2003; Zhao et al., 2003b)
	xanthan, polyvinyl alcohol	(2002)
	poly (vinyl methyl ether), poly (N-isopropyl acrylamide)	(Bhardwaj et al., 2005; Sen, 2005)

Table 3

3.9 Methods to produce hydrogel

3.9.1 Material functionalization for hydrogel formation

The stable crosslinking of hydrogels is essential to prevent uncontrolled dissolution of macromolecular chains in aqueous cellular microenvironments. Numerous chemical and physical crosslinking strategies have been utilized for the preparation of cell-compatible hydrogels (Fig. 6). Chemical crosslinking strategies covalently couple reactive functional groups for hydrogel formation using chain or step growth reactions, including free radical chain polymerization, click reactions, reactions of Schiff bases, and carbodiimide-mediated activation reactions. Physical crosslinking strategies utilize non-covalent interactions between functional groups, such as ionic interactions, electrostatic interactions, hydrogen bonding, crystallization, hydrophobic interactions, and protein interactions.

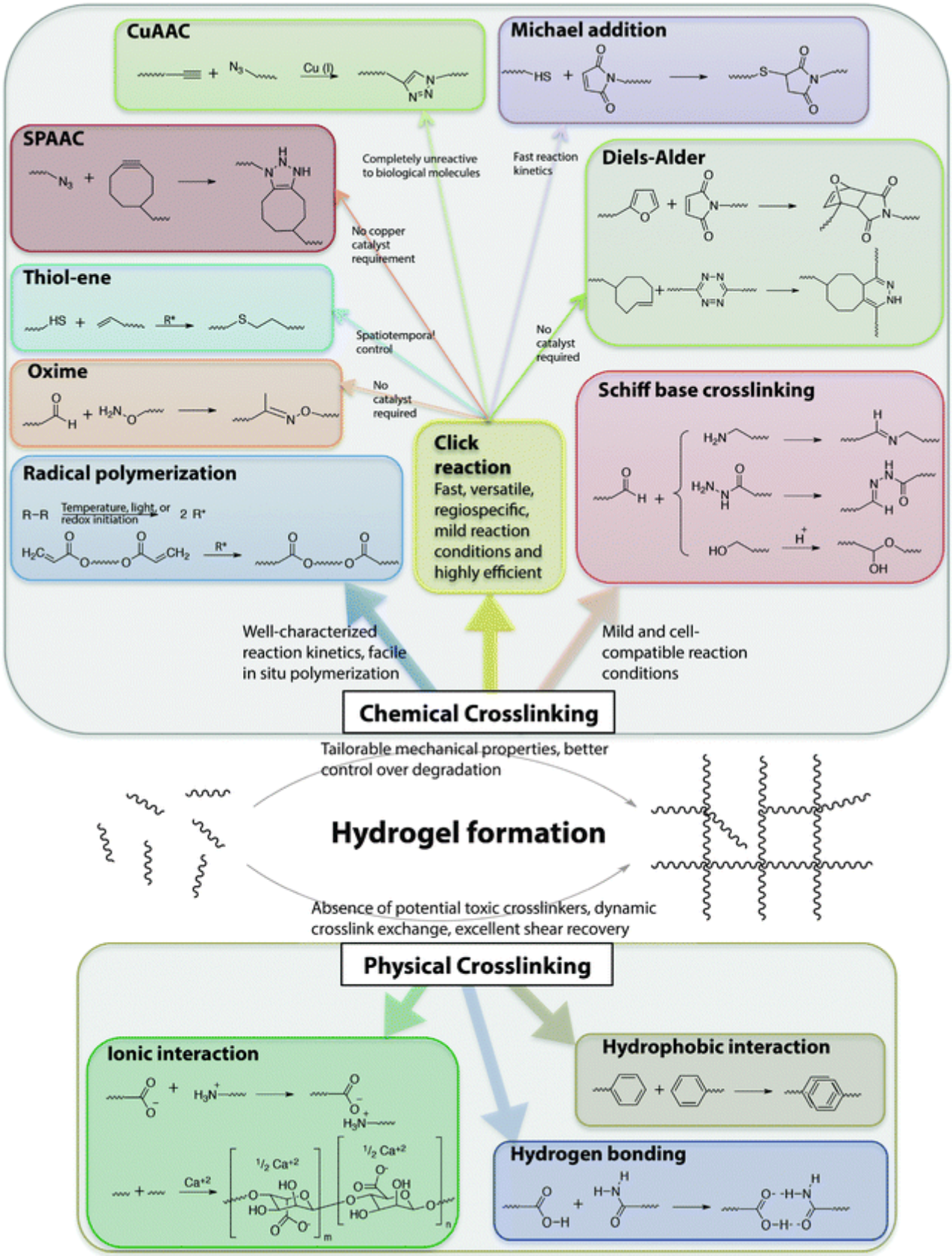

CuAAC
Michael addition
SPAAC
Diels-Alder
Thiol-ene
Oxime
Schiff base crosslinking
Radical polymerization
Completely unreactive to biological molecules
Fast reaction kinetics
No copper catalyst requirement
Spatiotemporal control
No catalyst required
No catalyst required
Click reaction
Fast, versatile, regiospecific, mild reaction conditions and highly efficient
Well-characterized reaction kinetics, facile in situ polymerization
Mild and cell-compatible reaction conditions
Chemical Crosslinking
Tailorable mechanical properties, better control over degradation
Hydrogel formation
Absence of potential toxic crosslinkers, dynamic crosslink exchange, excellent shear recovery
Physical Crosslinking
Ionic interaction
Hydrophobic interaction
Hydrogen bonding

Fig. 6 Chemical functional groups for hydrogel formation. A wide range of functional groups is available for either hydrogel formation or modification post-polymerization. Functional group selection depends on several factors related to the application of interest, including the desired initiation mechanism, the specificity and speed of the reaction, and the stability of the resulting bond under various solution conditions.

The crosslink concentration, or density, dictates various physical properties of hydrogels, including elasticity, diffusivity, water content, and mesh size. In addition, the degree of crosslinking influences the hydrogel degradation rate, and hence, precise control over hydrogel crosslinking is highly desirable. Further, for control of the properties of the cell microenvironment, hydrogel formation in the presence of cells or proteins is often required, and it is thus essential to choose a cytocompatible crosslinking method for preparing these applications.

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3.9.2 Synthetic Hydrogels They are more useful as compare to natural hydrogels because they can be engineered to have a much wider range of mechanical

The success of cell-compatible hydrogels in a given bioengineering application is usually coupled with achieving appropriate mechanical properties. For example, tissue formation can depend on the mechanical properties of the hydrogel scaffold (*e.g.*, load bearing capability until cells have produced their own functional ECM);[24,25] in cell-encapsulation applications, control of the mechanical properties of the hydrogel can determine the therapeutic efficacy of the transplanted cells.[26] It is well accepted that these effects are the result of the mechanical properties of the hydrogel substrate influencing cellular responses, including cell migration, proliferation, and differentiation; for example, the seminal work of Discher and coworkers demonstrated that stem cell lineage specification depends on optimal outside-in signaling of hydrogel matrix elasticity.[27,28] Polymer concentration, the stoichiometry of reactive groups, and crosslinking density are all commonly used to tune the mechanical properties of cell-compatible hydrogels and accordingly to control the cellular microenvironment.[29–31] The mechanism and design considerations associated with mechanotransduction were recently reviewed by Chen and coworkers,[32] and relevant examples within the context of degradable cell microenvironments will be presented in Sections 5 and 6. and chemical properties than their natural counterparts. Polyethylene glycol (PEG) based hydrogels are one class of the widely used material in biomedical application due to their nontoxicity there compatibility and low immunogenicity.

3.9.3. Hybrid hydrogels They are the combination of natural and synthetic polymer hydrogels. To combine the advantages of both synthetic and natural hydrogels many naturally occurring biopolymers such as dextran, collagen, Chitosan, have been combined with synthetic polymers such as polyvinyl alcohol. 1.2.2 Classification according to Polymeric Composition The method of

preparation leads to formations of some important classes of hydrogels. 1. Homopolymeric Hydrogels Homopolymeric hydrogels are 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. 2. Copolymeric Hydrogels Copolymeric hydrogels are comprised 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. 3. Multipolymer Interpenetrating Polymeric Hydrogel (IPN) Multipolymer Interpenetrating polymeric hydrogel an important class of hydrogels, is made of two independent cross-linked synthetic and/or natural polymer component, contained in a network form. In semi IPN hydrogel one component is a cross-linked polymer and other component is a non-cross-linked polymer 1.2.3 Classification based on Configuration

The classification of hydrogels depends on their physical structure and chemical composition

1. Amorphous (non-crystalline).

2. Semicrystalline: A complex mixture of amorphous and crystalline phases.

3. Crystalline.Synthesis (Preparation) of Electrosensitive Hydrogel (Polyacrylamide P. 1.2.4 Classification based on type of Cross-Linking Hydrogels can be divided into two categories based on the chemical or physical nature of the cross-link junctions. Chemically cross-linked networks have permanent junctions, while physical networks have transient junctions that arise from either polymer chain entanglements or physical interactions such as ionic interactions, hydrogen bonds or hydrophobic interactions.

1.2.5 Classification based on Physical Appearance Hydrogels appearance as matrix, film, or microsphere depends on the technique of polymerization involved in the preparation process.

1.2.6 Classification according to Network Electrical Charge Hydrogels may be categorized into four groups on the basis of presence or absence of electrical charge located on the crosslinked chains:

1. Nonionic (neutral).

2. Ionic (including anionic or cationic).

3. Amphoteric electrolyte (ampholytic) containing both acidic and basic groups.

4. Zwitterionic (polybetaines) containing both anionic and cationic groups in each structural repeating unit.

Cross-linked networks of synthetic polymers such as polyethylene oxide (PEO) (Khoylou & Naimian, 2009), polyvinyl pyrollidone (PVP) (Razzak et al., 2001), polylactic acid (PLA) (Palumbo et al., 2006),, polyacrylic acid (PAA) (Onuki et al., 2008), polymethacrylate (PMA) (Yang et al.), polyethylene glycol (PEG) (Singh et al.), or natural biopolymers (Coviello et al., 2007) such as alginate, chitosan, carrageenan, hyaluronan, and carboxymethyl cellulose (CMC) have been reported. The various preparation techniques adopted are physical cross-linking (Hennink & Nostrum, 2002), chemical cross-linking (Barbucci et al., 2004), grafting polymerisation (Said et al., 2004), and radiation cross-linking (Fei et al., 2000; Liu et al., 2002b). Such modifications can improve the mechanical properties and viscoelasticity for applications in biomedical and pharmaceutical fields (Barbucci et al., 2004; Nho & Lee, 2005; Rosiak et al., 1995; Rosiak & Yoshii, 1999). The general methods to produce physical and chemical gels are described below.

3.10 Physical cross-linking

There has been an increased interest in physical or reversible gels due to relative ease of production and the advantage of not using cross-linking agents. These agents affect the integrity of substances to be entrapped (e.g. cell, proteins, etc.) as well as the need for their removal before application. Careful selection of hydrocolloid type, concentration and pH can lead to the formation of a broad range of gel textures and is currently an area receiving considerable attention, particularly in the food industry. The various methods reported in literature to obtain physically cross-linked hydrogels are:

3.10.1 Heating/cooling a polymer solution

Physically cross-linked gels are formed when cooling hot solutions of gelatine or carrageenan. The gel formation is due to helix-formation, association of the helices, and forming junction zones (Funami et al., 2007). Carrageenan in hot solution above the melting transition temperature is present as random coil conformation. Upon cooling it transforms

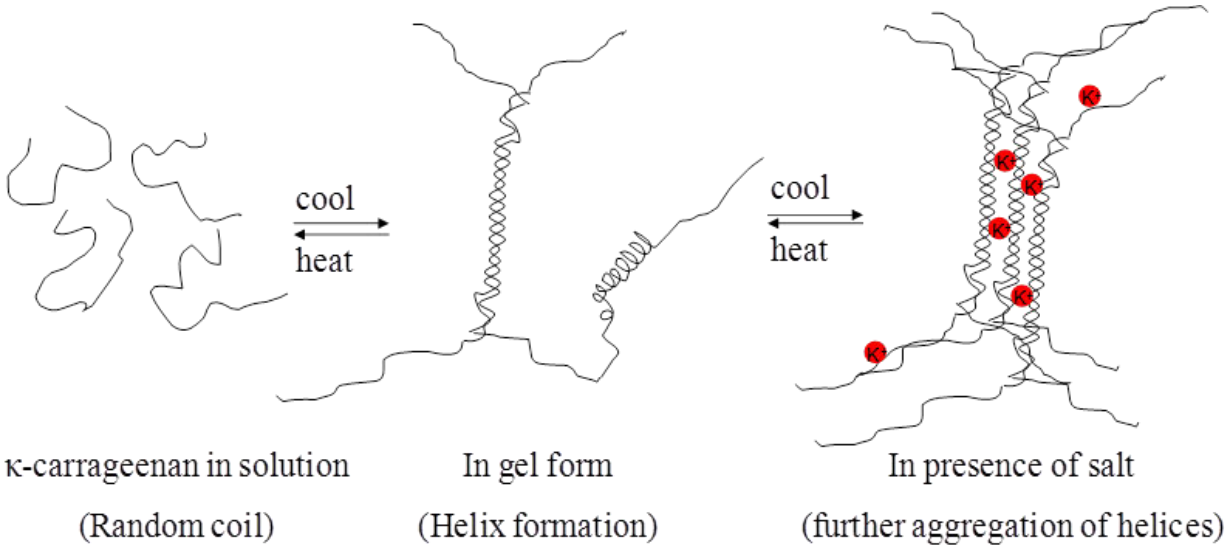


Figure 9

Gel formation due to aggregation of helix upon cooling a hot solution of carrageenan.

to rigid helical rods. In presence of salt (K^+, Na^+, etc.), due to screening of repulsion of sulphonic group (SO^-_3), double helices further aggregate to form stable gels (Figure 3). In some cases, hydrogel can also be obtained by simply warming the polymer solutions that causes the block copolymerisation. Some of the examples are polyethylene oxide-polypropylene oxide (Hoffman, 2002), polyethylene glycol-polylactic acid hydrogel (Hennink & Nostrum, 2002).

3.2.2. Ionic interaction

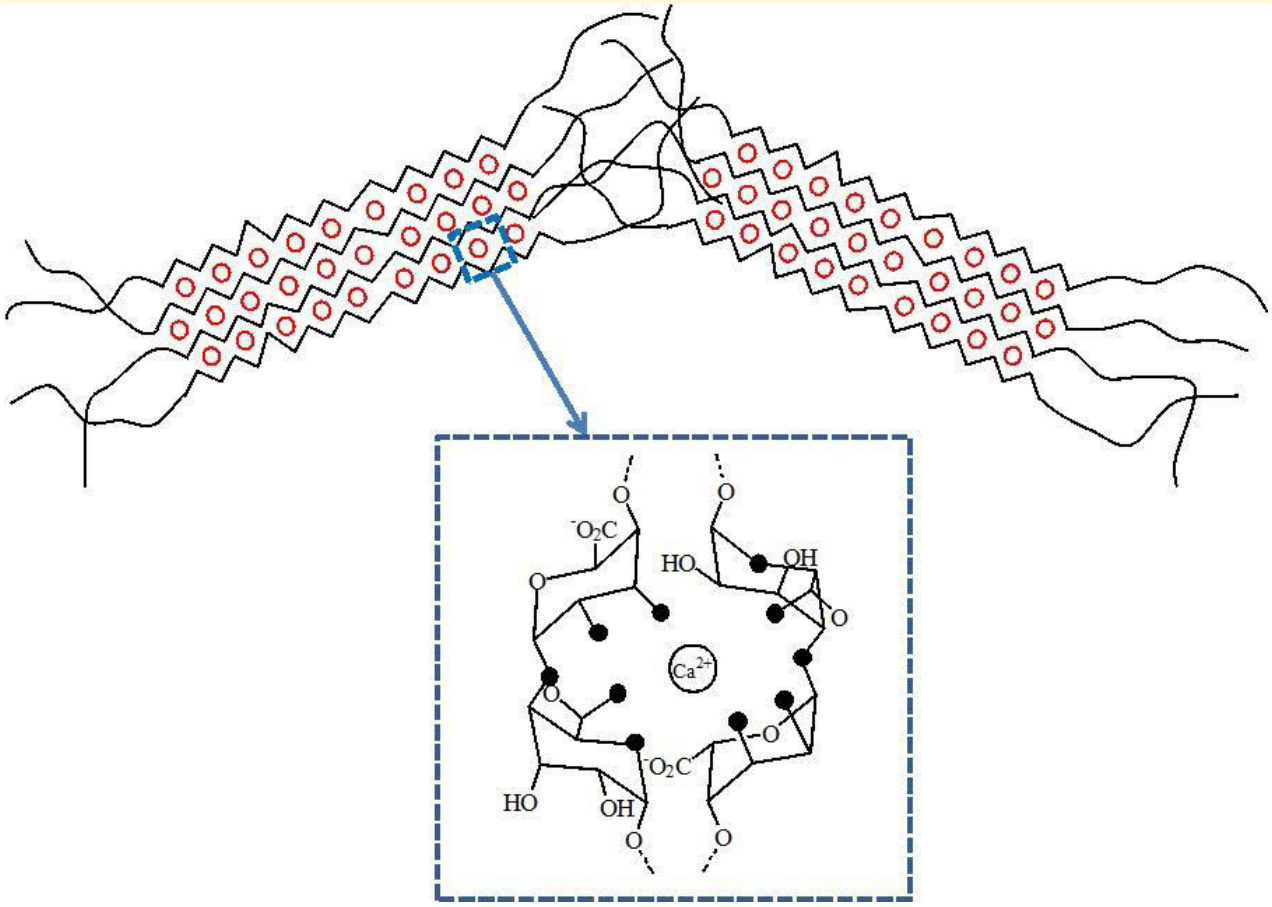


Figure 10

Ionotropic gelation by interaction between anionic groups on alginate (COO^-) with divalent metal ions (Ca^{2+}).

Bajpai et al., 2008), chitosan-glycerol phosphate salt (Zhao et al., 2009), chitosan-dextran hydrogels (Hennink & Nostrum, 2002).

3.10.2. Complex coacervation

Complex coacervate gels can be formed by mixing of a polyanion with a polycation. The underlying polyanionic xanthan with polycationic chitosan (Esteban & Severian, 2000; 2001; 1999). Proteins below its isoelectric point are positively charged

Ionic polymers can be cross-linked by the addition of di- or tri-valent counterions. This method underlies the principle of gelling a polyelectrolyte solution (e.g. Na^+ alginate$^-$) with a multivalent ion of opposite charges (e.g. Ca^{2+} + $2Cl^-$) (Figure 4). Some other examples are chitosan-polylysine (

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 5). One such example is coacervating

and likely to associate with anionic hydrocolloids and form polyion complex hydrogel (complex coacervate) (Magnin et al., 2004).

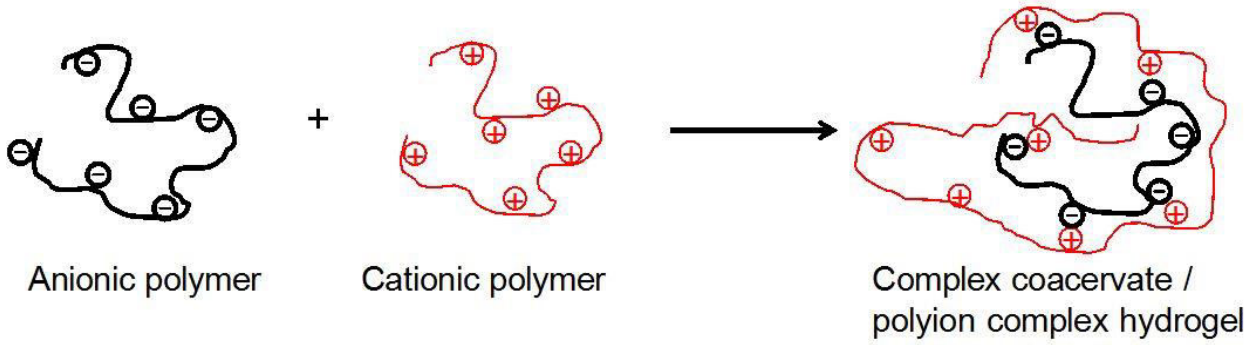
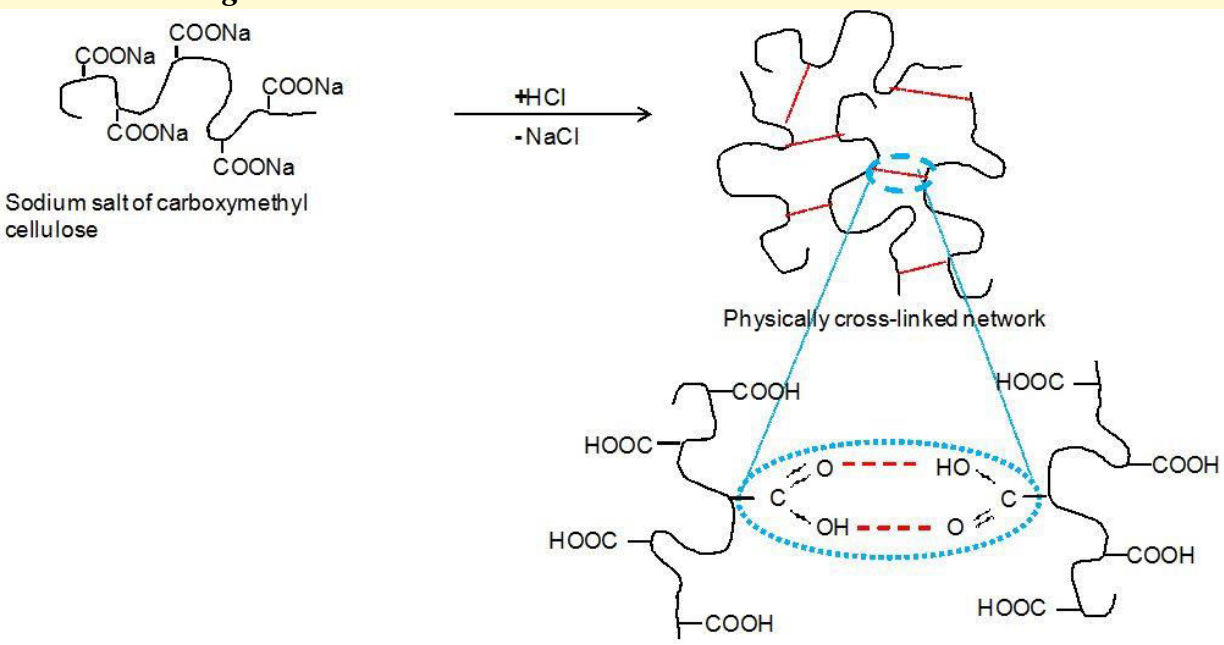


Figure 11

Complex coacervation between a polyanion and a polycation.

3.10.3 H-bonding



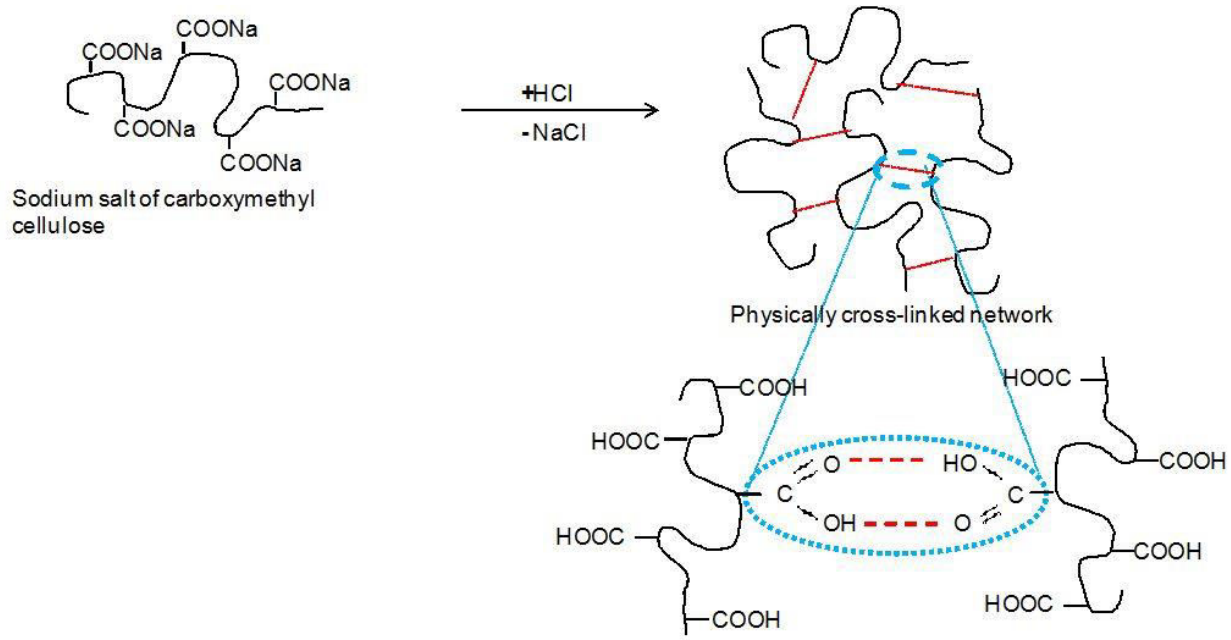


Figure 12

Hydrogel network formation due to intermolecular H-bonding in CMC at low pH.

H-bonded hydrogel can be obtained by lowering the pH of aqueous solution of polymers carrying carboxyl groups. Examples of such hydrogel is a hydrogen-bound CMC (carboxymethyl cellulose) network formed by dispersing CMC into 0.1M HCl (Takigami et al., 2007). The mechanism involves replacing the sodium in CMC with hydrogen in the acid solution to promote hydrogen bonding (Figure 6). The hydrogen bonds induce a decrease of CMC solubility in water and result in the formation of an elastic hydrogel. Carboxymethylated chitosan (CM-chitosan) hydrogels can also prepared by cross-linking in the presence of acids or polyfunctional monomers (2008). Another example is polyacrylic acid and polyethylene oxide (PEO-PAAc) based hydrogel prepared by lowering the pH to form H-bonded gel in their aqueous solution (Hoffman, 2002). In case of xanthan-alginate mixed system molecular interaction of xanthan and alginate causes the change in matrix structure due to intermolecular hydrogen bonding between them resulting in formation of insoluble hydrogel network (2007).

3.10.4 Maturation (heat induced aggregation)

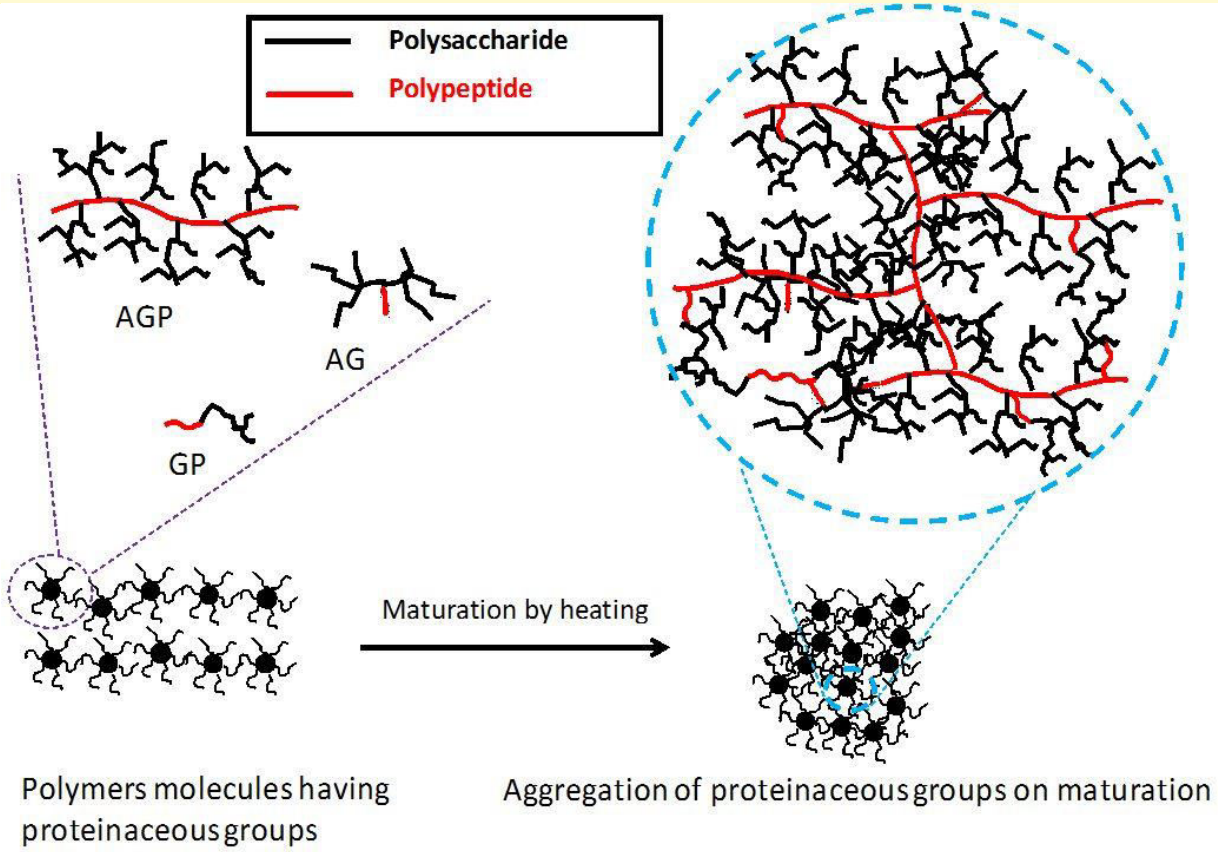


Figure 13

Maturation of gum arabic causing the aggregation of proteinaceous part of molecules leading to cross-linked hydrogel network.

Gum arabic (Acacia gums) is predominately carbohydrate but contain 2-3% protein as an integral part of its structure (Williams & Phillips, 2006). Three major fractions with different molecular weights and protein content have been identified following fractionation by hydrophobic interaction chromatography with different molecular weights and protein content (Islam et al., 1997). These are arabinogalactan protein (AGP), arabinogalactan (AG) and glycoprotein (GP). Aggregation of the proteinaceous components, induced by heat treatment, increases the molecular weight and subsequently produces a hydrogel form with enhanced mechanical properties and water binding capability (Aoki et al., 2007a; Aoki et al., 2007b). The molecular changes which accompany the maturation process demonstrate that a hydrogel can be produced with precisely structured molecular dimensions. The controlling feature is the 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 (AGP) (Figure 7). The method has also been applied on to other gums such as gum ghatti and Acacia kerensis for application in denture care (Al-Assaf et al., 2009).

3.10.5. Freeze-thawing

Physical cross-linking of a polymer to form its hydrogel can also be achieved by using freeze-thaw cycles. The mechanism involves the formation of microcrystals in the structure due to freeze-thawing. Examples of this type of gelation are freeze-thawed gels of polyvinyl alcohol and xanthan (Giannouli & Morris, 2003; Hoffman, 2002; 2004).

4.2. Chemical cross-linking

Chemical cross-linking covered here involves grafting of monomers 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 NH_2) with cross-linkers such as aldehyde (e.g. glutaraldehyde, adipic acid dihydrazide). There are a number of methods reported in literature to obtain chemically cross-linked permanent hydrogels. Among other chemical cross-linking methods, IPN (polymerise a monomer within another solid polymer to form interpenetrating network structure) (2003) and hydrophobic interactions (Hennink & Nostrum, 2002) (incorporating a polar hydrophilic group by hydrolysis or oxidation followed by covalent cross-linking) are also used to obtain chemically cross-linked permanent hydrogels. The following section reviews the major chemical methods (i.e. cross-linker, grafting, and radiation in solid and/or aqueous state) used to produce hydrogels from a range of natural polymers.

3.10.6 Chemical cross-linkers

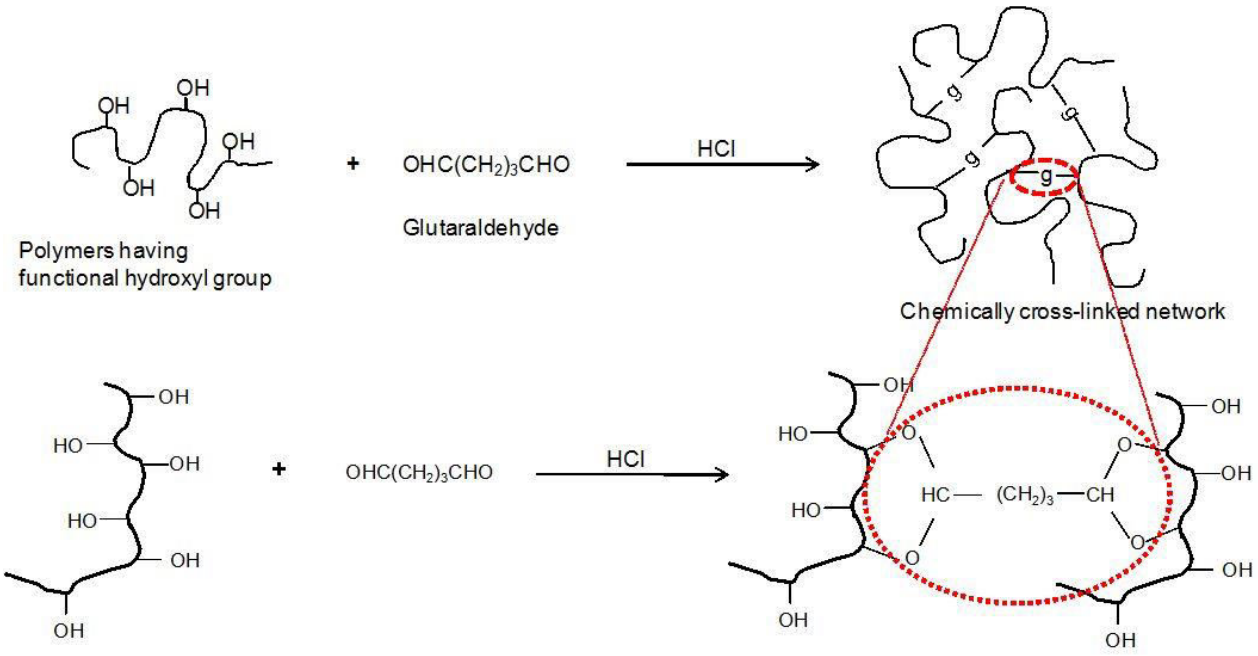


Figure 14

Schematic illustration of using chemical cross-linker to obtain cross-linked hydrogel network.

Cross-linkers such as glutaraldehyde (2008), epichlorohydrin (2002), etc have been widely used to obtain the cross-linked hydrogel network of various synthetic and natural polymers. The

technique mainly involves the introduction of new molecules between the polymeric chains to produce cross-linked chains (Figure 8). One such example is hydrogel prepared by cross-linking of corn starch and polyvinyl alcohol using glutaraldehyde as a cross-linker (2008). The prepared hydrogel membrane could be used as artificial skin and at the same time various nutrients/healing factors and medicaments can be delivered to the site of action.CMC chains can also be cross-linked by incorporating 1, 3-diaminopropane to produce CMC-hydrogel suitable for drug delivery through the pores (2004). Hydrogel composites based on xanthan and polyvinyl alcohol cross-linked with epichlorohydrin in another example (2002). κ-carrageenan and acrylic acid can be cross-linked using 2-acrylamido-2-methylpropanesulfonic acid leading to the development of biodegradable hydrogels with proposed use for novel drug delivery systems (Pourjavadi & Zohuriaan-Mehr, 2002). Carrageenan hydrogels are also promising for industrial immobilisation of enzymes (Campo et al., 2009). Hydrogels can also be synthesized from cellulose in NaOH/urea aqueous solutions by using epichlorohydrin as cross-linker and by heating and freezing methods (Chang et al., 2010; Chang & Zhang, 2011).

3.10.7 Grafting

Grafting involves the polymerisation of a monomer on the backbone of a preformed polymer. The polymer chains are activated by the action of chemical reagents, or high energy radiation treatment. The growth of functional monomers on activated macroradicals leads to branching and further to cross-linking (Figure 9).

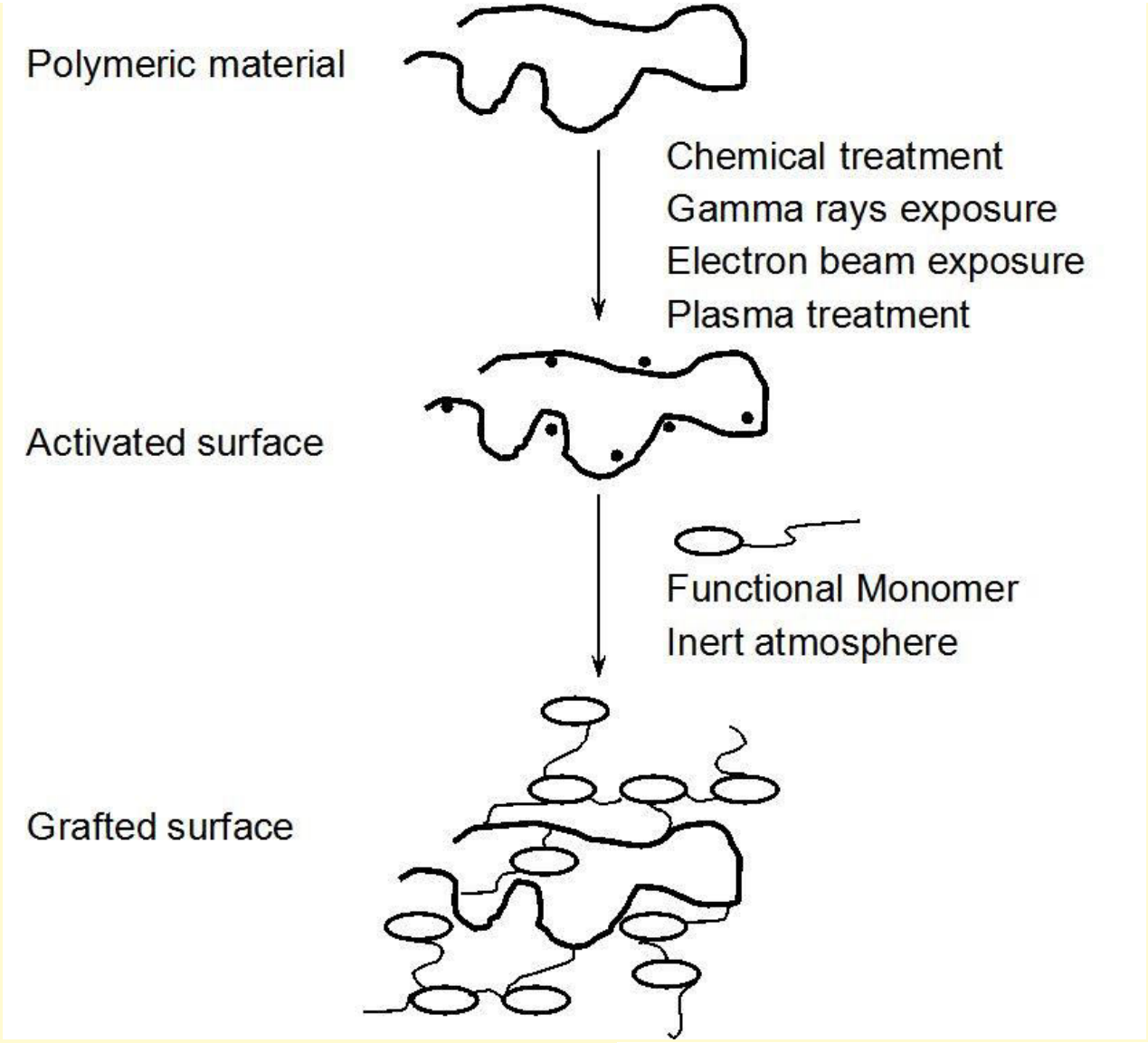


Figure 15

Grafting of a monomer on preformed polymeric backbone leading to infinite branching and cross-linking.

3.10.7.1 Chemical grafting

In this type of grafting, macromolecular backbones are activated by the action of a chemical reagent. Starch grafted with acrylic acid by using N-vinyl-2-pyrrolidone is an example of this kind of process (Spinelli et al., 2008). Such hydrogels show an excellent pH-dependent swelling behaviour and possess ideal characteristic to be used as drug and vitamin delivery device in the small intestine.

3.10.7.2 Radiation grafting

Grafting can also be initiated by the use of high energy radiation such as gamma and electron

beam. Said, Alla et al. (2004) reported the preparation of hydrogel of CMC by grafting CMC with acrylic acid in presence of electron beam irradiation, in aqueous solution. Electron beam was used to initiate the free radical polymerisation of acrylic acid on the backbone of CMC. Water radiolysis product will also be helpful to abstract proton form macromolecular backbones. Irradiation of both (CMC and monomer) will produce free radicals that can combine to produce hydrogel. They proposed the application of such acrylic acid based hydrogel for the recovery of metal ions like copper, nickel, cobalt, and lead. Also, they reported the application of hydrogels in dressings for temporary skin covers.

Zhai, Yoshii et al. (2002) also reported the preparation of starch based hydrogel by grafting polyvinyl alcohol PVA. Starch was first dissolved into water to form gel-like solution and then added to PVA solution, continuously stirred to form homogeneous mixture after heating at 90°C for 30 mins. The result showed there was a grafting reaction between PVA and starch molecule besides the cross-linking of PVA molecule under irradiation. Amylose of starch was found to be a key reactive component. The properties of starch/PVA blend hydrogel too were governed by amylose component of starch.

Cai, Zhang et al. (2005) have reported the preparation of thermo- and pH-sensitive hydrogels by graft copolymerisation of chitosan (CS) and N-isopropylacrylamide (NIPA). The results showed that the grafting percentage and grafting efficiency increased with the increase of monomer concentration and total irradiation dose. The CS-g-NIPA hydrogels showed good thermo- and pH-sensitivity and swelling property.

3.11 Physically crosslinked hydrogels

Noncovalent interactions, such as ionic interactions, crystallization, hydrophobic interactions, electrostatic interactions, hydrogen bonding, or combinations of these, can be used for physically crosslinking of macromolecules to obtain cell-compatible

hydrogels.[255–262] Self-assembled amphiphilic block copolymers, proteins, peptides, and polypeptides typically form hydrogels *via* physical crosslinking.[121,263–266] Physically crosslinked hydrogels afford simple network formation, without the use of any potentially toxic chemical crosslinkers or initiators. In addition, their dynamic crosslink exchange, shear-thinning flow, and excellent shear recovery can be attractive for use as injectable hydrogels for therapeutic delivery.[121,261] However, potential limitations include insufficient mechanical strength for some applications due to the weakness of the physical interactions and limited control over their degradation rates, presenting possible challenges for controlled cell culture. Here, physical crosslinking methods used to design cell-compatible hydrogels from ‘off the shelf’ polymers (*e.g.*, alginate, PVA), block copolymers, and peptide–proteins are discussed along with potential applications for orthogonal property control in cellular microenvironments.

Ionic interactions have been extensively used to physically crosslink commercially available polysaccharides, such as alginate and chitosan, to form hydrogels.[258–260] The use of ionic interactions offers the possibility of biodegradation since ionic species present in cellular microenvironments can competitively bind, leading to dissociation of the hydrogel network. Matyash *et al.* used physical

crosslinking with divalent cations such as Ca^{2+} to prepare alginate-based hydrogels that were biocompatible and facilitated neurite outgrowth.[260] Hydrogels can also be created by the formation of crystallites, which act as physical crosslinks for network formation. As in the example above (Section 3.2.2), PVA can form a highly elastic hydrogel when subjected to a freeze-thawing process to form crystallites, and such hydrogels have been used for various bioengineering applications, such as controlled drug delivery.[175,255,262] For example, Abdel-Mottaleb *et al.* used three cycles of freeze-thawing to prepare PVA hydrogels for topical delivery of Fluconazole within the dermal microenvironment.[255] The hydrogels were stable up to 6 months and effective in the topical treatment of skin infections.

Multiblock copolymers or graft copolymers can also be physically crosslinked for hydrogel formation. For example, Hunt *et al.* developed hydrogels with tunable physical and chemical properties using ionic coacervation upon mixing of two ABA triblock polymers, poly(allyl glycidyl ether-*b*-ethylene glycol-*b*-allyl glycidyl ether) with an oppositely charged poly(allyl glycidyl ether)-*block*, as shown in Fig. 9.[257] Non-covalent interactions of the positively charged (ammonium and guanidinium) and negatively charged (sulfonate, carboxylate) ABA triblock copolymers resulted in the formation of polymer-dense coacervate domains leading to network formation. The ionic interactions were efficient, specific, and sensitive to polymer concentration, pH and presence of salt. Such an approach highlights the use of ionic interactions for preparing highly tunable and dynamic physically crosslinked hydrogels with superior mechanical properties and ease of synthesis, which can be potentially used as 3D cell scaffolds.

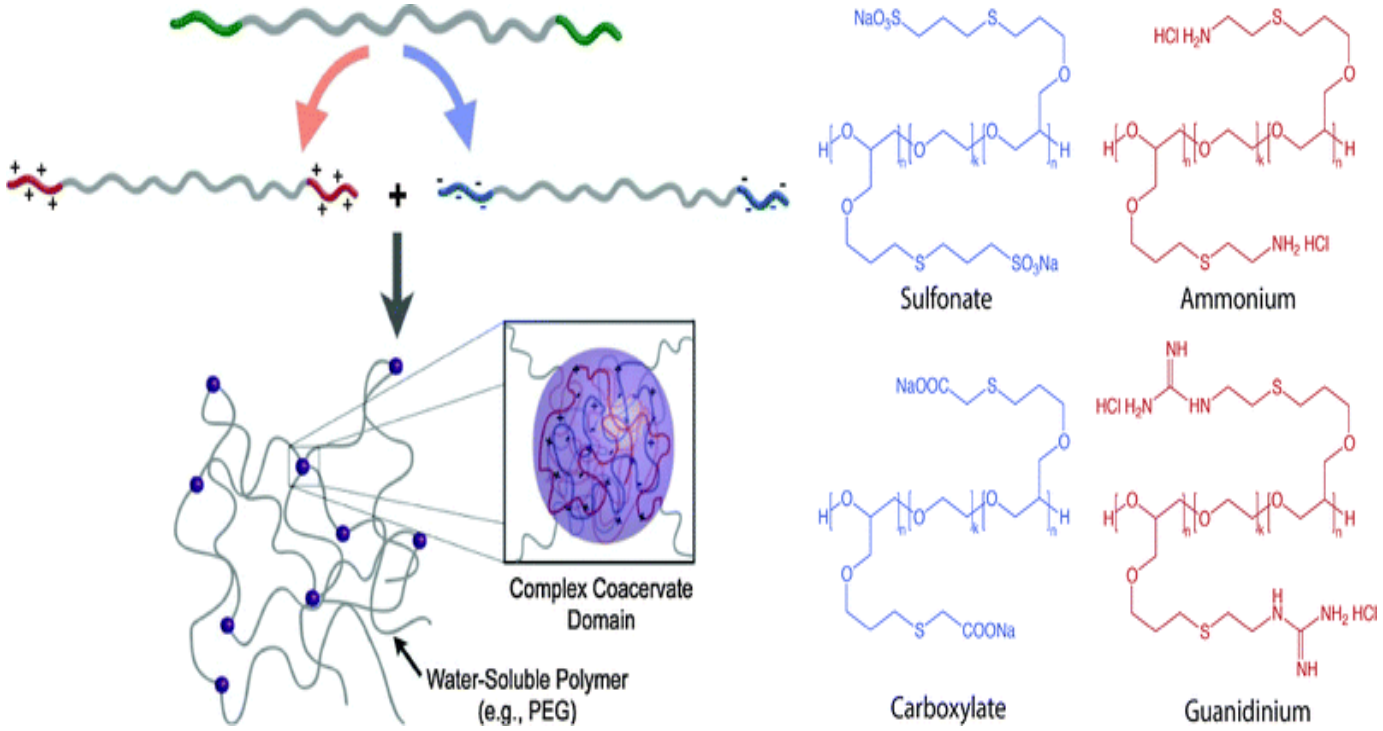


Fig. 16 Block copolymer assembly for hydrogel formatio hydrogels have been prepared with coacervate crosslinki solution of negatively charged (sulfonate, carboxylate) an guanidinium) ionic ABA triblocks. Image reprinted from from John Wiley and Sons publishing. Copyright (2011).

Polypeptides and proteins represent another important class of biocompatible polymers that can be physically crosslinked upon the formation of secondary structures (*i.e.*, α-helix and β-sheet) that drive intermolecular association. Peptide based hydrogels have been synthesized for potential applications in controlled release, 3D cell culture, and tissue regeneration.[121,264,267–270] For example, Yan *et al.* recently prepared β-hairpin peptide-based hydrogels *via* self-assembly for osteoblast encapsulation.[121] The effect of shear flow on the preformed, injectable β-hairpin hydrogel was investigated. The gel that was directly in contact with the syringe wall experienced a velocity gradient, while the central, plug-flow region experienced little to no shear. The study demonstrated that the shear thinning of preformed hydrogels did not significantly affect encapsulated cell viability. Further, Heilshorn and coworkers used tryptophan and proline-rich peptide domains for preparing mixing-induced, two component hydrogels (MITCH) for effective encapsulation of cells within 3D hydrogels.[269] In addition to peptide–peptide interactions, specific peptide–

polysaccharide interactions also can be utilized for physically crosslinking hydrogels.[271]

Kiick and coworkers employed noncovalent interactions between heparin-modified PEG polymers and a heparin-binding growth factor (VEGF) to create bioresponsive hydrogels.[272] The VEGF–LMWH interactions were confirmed by the increase in hydrogel modulus by addition of VEGF to PEG–LMWH ($G'(\omega)$ > 10 Pa in presence of VEGF, ~1 Pa in absence of VEGF) measured using optical tweezer microrheology. The hydrogels significantly eroded after day 4, and released approximately 80% of VEGF by day 10 in presence of VEGFR-2 (a VEGF receptor), as compared to PBS (~30% release over same time period). The released VEGF was bioactive, and the hydrogels were biocompatible, as confirmed by *in vitro* experiments (cell proliferation assay and live-dead staining, respectively). VEGF–LMWH interactions were further studied for their cell-responsive nature employing two different cell types: porcine aortic endothelial (PAE) cells overexpressing VEGFR-2 and PAE cells that were not equipped with VEGFR-2 transcript.[273] The hydrogels were eroded by day 4, and VEGF release was greater in presence of VEGFR-2 expressing cells. Such physically crosslinked hydrogels offer novel targeting strategies depending upon cell surface receptor–ligand interactions and could be used for sustained and targeted delivery of VEGF to promote angiogenesis.

3.12 Radiation cross-linking

Radiation cross-linking is widely used technique since it does not involve the use of chemical additives and therefore retaining the biocompatibility of the biopolymer. Also, the modification and sterilisation can be achieved in single step and hence it is a cost effective process to modify biopolymers having their end-use specifically in biomedical application (Lugao & Malmonge, 2001). The technique mainly relies on producing free radicals in the polymer following the exposure to the high energy source such as gamma ray, x-ray or electron beam. The action of radiation (direct or indirect) will depend on the polymer environment (i.e. dilute solution, concentrated solution, solid state).

3.12.1 Aqueous state radiation

Irradiation of polymers in diluted solution will lead to chemical changes as a result of 'indirect action' of radiation. Equation 11 shows that the radiation is mainly absorbed by water. The water radiolysis generates reactive free radicals which can interact with the polymer solute:

Radiation chemical yield (G value) is defined as the number of a particular species produced per 100 eV of energy absorbed by the system from ionising radiation (Clark, 1963). This unit has been redefined in SI mode units by multiplying the old values by 1.036×10^{-7} in order to convert the yield to mol J^{-1}. The radiation chemical yield of these species are now well established as being 2.8, 0.6, 2.7, 0.7, 0.5 and 2.7×10^{-7} mol J^{-1} for $^{\bullet}OH$, $^{\bullet}H$, e^-_{aq}, H_2O_2, H_2 and H^+ respectively (Sonntag, 1987).

A frequently used technique is to irradiate in nitrous oxide saturated solutions when the hydrated electrons (e^-_{aq}) are converted into $^{\bullet}OH$ radicals:

eaq−+N2O→●OH+N2+−OHeaq−+N2O→●OH+N2+−OH

E11

Under the above conditions the $^{\bullet}OH$ radical yield is 5.6×10^{-7} mol J^{-1} whereas the H atoms are formed with yield of ~ 0.6×10^{-7} mol J^{-1}.

Therefore radiation chemical techniques can be used for the quantitative generation of free radicals in aqueous solution. Table 2 gives details of natural polymers and monomers which have been irradiated in diluted solutions and solid state. Changes in molecular weight, rheology, viscometry, UV spectroscopy, and FT-IR have been used to follow the radiolysis reactions.

All the materials given in Table 2, irrespective of their structure and conformation degrade when irradiated in diluted aqueous solution. This is because at a low polymer concentration (i.e. below critical overlap concentration) the chain density of the polymer is not sufficient enough for the chain to recombine and form cross-link network. The two main radicals present in saturated aqueous system react with carbohydrates (RH) by abstracting carbon-bound H-atoms (Equation 13). The hydroxyl radical is not specific in its action and so there are radical sites formed at many position in a carbohydrate solute (Figure 10). In such systems it is the hydroxyl radical which is the main H-abstracting entity. The hydroxyl radicals react with hyaluronan with a rate constant $k_2 = 0.9 \times 10^9$ mol^{-1} dm^3 s^{-1}, whereas H atoms rate is a lower order of magnitude $k_2 = 7 \times 10^7$ mol^{-1} dm^3 s^{-1} (Myint et al., 1987). Figure 11 shows the various hydrolysis, rearrangement, and fragmentation reactions during aqueous radiolysis of cellobiose to gives possible chain break (Sonntag, 1987).

RH+●OH(H●) → R●+H2O(H2)RH+●OH(H●) → R●+H2O(H2)

E12

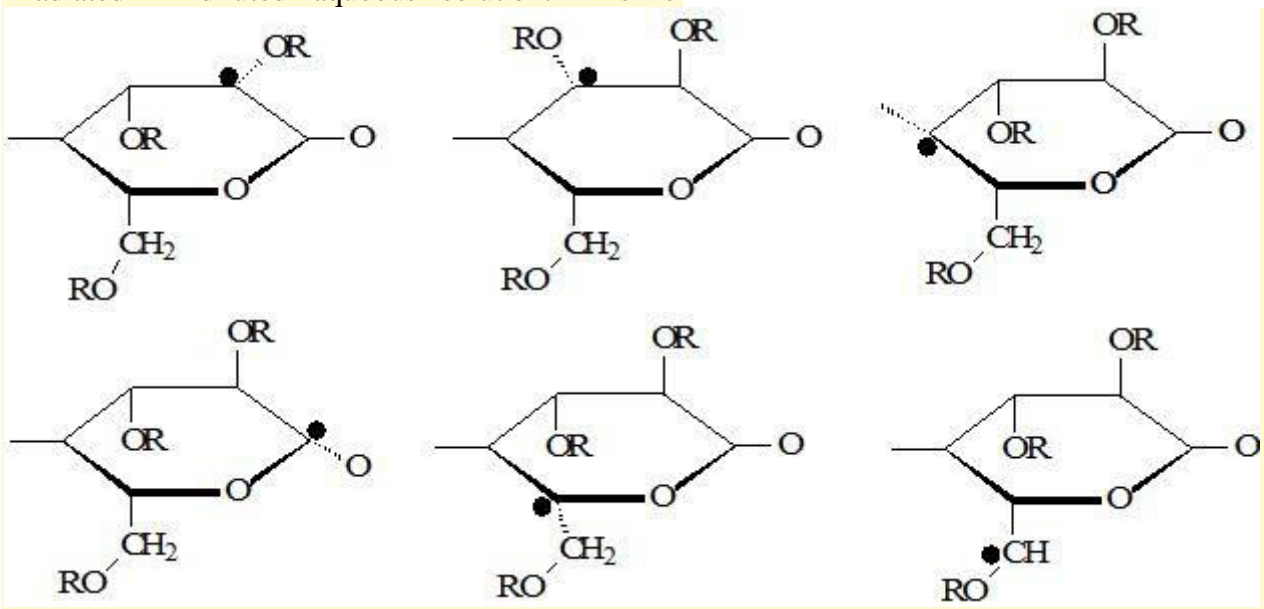


Figure 17

Primary radicals formed on C1–C6 atoms of anhydroglucose unit upon radiolysis in absence of oxygen.

Material	References for degradation	
	In aqueous state	In solid state
Carboxymethyl cellulose (CMC)	(Choi et al., 2008; Fei et al., 2000; Liu et al., 2002b; Wach et al., 2003a; Yoshii et al., 2003)	(Fei et al., 2000; Liu et al., 2002b; Wach et al., 2001; Wach et al., 2003a; Yoshii et al., 2003)
Hydroxy ethyl cellulose	(Fei et al., 2000; Wach et al., 2003a)	(Fei et al., 2000; Wach et al., 2001)
chitin, chitosan & derivatives	(Ershov et al., 1993; Ershov, 1998; Jarry et al., 2001; Jarry et al., 2002; Yoshii et al., 2003)	(Wasikiewicz et al., 2005)
Cellulose & derivatives	(Ershov, 1998; Nakamura et al., 1985; Phillips, 1961; Phillips, 1963; Wach et al., 2002)	(Phillips & Moody, 1959; Wach et al., 2002)
Starch and derivatives	(Ershov, 1998; Nagasawa et al., 2004; Phillips, 1961; Yoshii & Kume, 2003; Yoshii et al., 2003; Zhai et al., 2003)	(Yoshii & Kume, 2003)
D-glucose	(Phillips, 1963; Schiller et al., 1998)	(Sharpatyi, 2003)
Hyaluronan & hyaluronic acid	(Al-Assaf et al., 1995; Al-Assaf et al., 2006a; Ershov, 1998; Phillips, 1961; Reháková et al., 1994; Stern et al.)	(Choi et al.; Reháková et al., 1994; Stern et al.)
Glucomannan, galactomannan	(Jumel et al., 1996)	(Sen et al., 2007)
Alginate	(Phillips, 1961)	(Wasikiewicz et al., 2005)
Carrageenan	(Abad et al., 2008; Abad et al., 2009)	(Abad et al., 2009; Relleve et al., 2005)
Dextran	(Phillips, 1961)	(Phillips & Moody, 1959)
Pectin	(Phillips, 1961; Zegota, 1999)	(Phillips & Moody, 1959)
Agar	(Abad et al., 2008; Phillips, 1961)	
Gum arabic	(Al-Assaf et al., 2006b; Katayama et al., 2006)	(Blake et al., 1988)
Xanthan, β-glucan	(Byun et al., 2008; Parsons et al., 1985)	

Table 4
List of references showing degradation of polysaccharide upon irradiation in dilute aqueous solution and in solid state.

Hydrated electrons (e^-_{aq}) formed upon water radiolysis react with the hydrocolloids only if the system contains no oxygen. They do not have the ability to abstract electrons from carbohydrate polymers, as for example carrageennan (Abad et al., 2007), hyaluronan (Myint et al., 1987) and CMC where the rate constant for the disappearance of the hydrated electron was measured as 4–5.2 x 10^6 $mol^{-1}dm^3s^{-1}$ (Wach et al., 2005). This rate constant approaches the normal disappearance rate of hydrated electrons in water alone in the absence of CMC, demonstrating that its reactivity with CMC is negligible.

In oxygenated solution the hydrated electron react with oxygen to produce superoxide radical ($O^{\cdot-}_2$), (Equation 14).

e−aq+O2→O2.− (k2=1.9x1010mol−1dm3s−1)e−aq+O2→O2.− (k2=1.9x1010mol−1dm3s−1)

●H+O2→HO2.−−− (k2=1.9x1010mol−1dm3s−1)●H+O2→HO2.−−− (k2=1.9x1010mol−1dm3s−1)

E14

The role of superoxide radicals have been considered to be important in arthritis diseased conditions due to their interaction with the body biopolymers. Two possible mechanisms for the generation of hydroxyl radicals through the reaction

E13

Additionally, in oxygenated solutions the hydrogen atoms form peroxyl radicals (Equation 15) which is unreactive with most organic compounds unless they contain weekly bonded hydrogen (Bielski & Gebicki, 1970).

of superoxide radicals via metal catalysed processes and its dismutation and subsequent reaction with hydrogen peroxide were reviewed (Al-Assaf et al., 1995).

In case of radiolysis of oxygenated solution of D-glucose, six primary peroxyl radicals are formed which rapidly undergo $HO_2^{\cdot}$. elimination and subsequently lead to chain break (Sonntag, 1987).

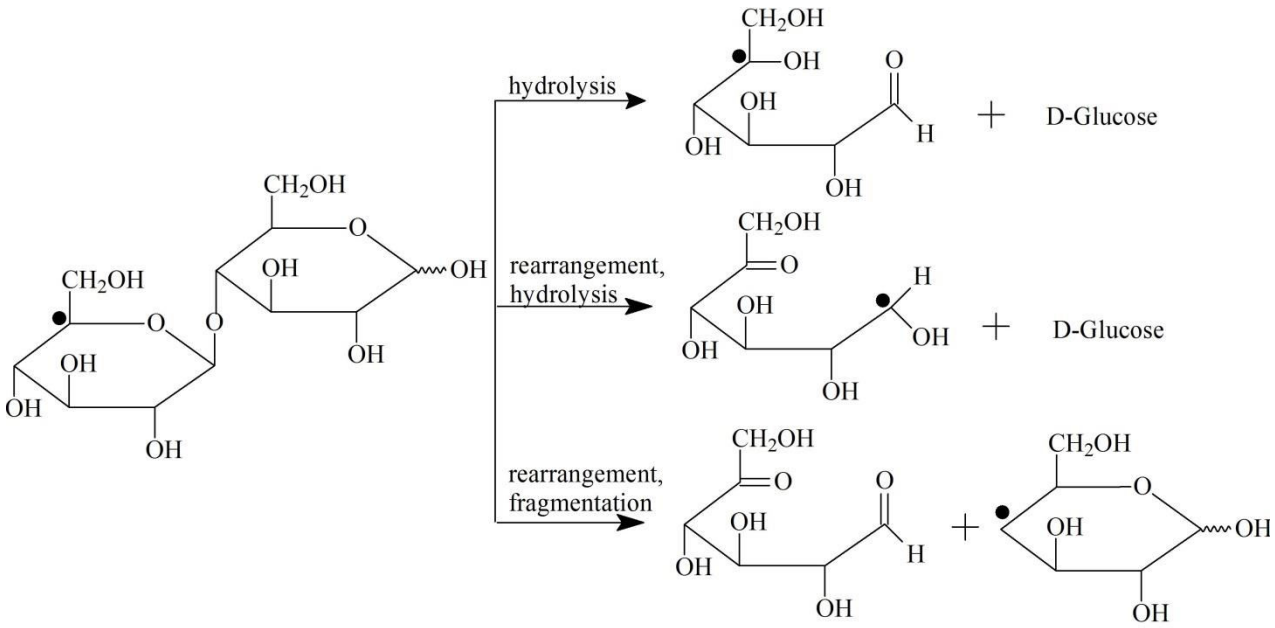


Figure 18

Various hydrolysis, rearrangement, and fragmentation reactions during aqueous radiolysis of cellobiose.

3.12.2 Radiation in paste

The cross-linking of hydrocolloids in aqueous paste-like conditions state has received considerable attention recently. Under these conditions the concentration of the polymer is high such that both direct action of the radiation can form free radicals

and also there is also sufficient water present to be radiolysed to form •OH and related radicals. There is thus a high concentration of radicals in close association with the original polymer and other secondary formed polymer radicals. Thus cross-linking to form new polymers can form by way of radical-radical reaction and polymer - polymer radical reactions. If the original polymer concentration is not sufficient to network. Also, the radiolysis of water generate free radicals (hydrogen atoms and hydroxyl radicals), which increase the yield of macroradicals by abstracting H-atoms from the polymer chain. The concentration at which the modification can be achieved varies according to the structure, degree of substitution, distribution of substitution group and initial molecular weight. For example, a higher DS is effective for cross-linking of CMC due to the fact that intermolecular linkages are result of ether function (Shen et al., 2006; Wach et al., 2003a).

Similar results have been reported on aqueous state irradiation of methylcellulose and hydroxypropyl cellulose (Horikawa et al., 2004; Wach et al., 2003b), carboxymethyl starch (Yoshii & Kume, 2003; Yoshii et al., 2003), gum arabic (Katayama et al., 2006), carboxymethylated chitin and chitosan (Wasikiewicz et al., 2006; Zhao et al., 2003a). The % hydrogel produced together with the proposed application from various investigations are summarised in Table 3.

Polymer	Maximum hydrogel (%)	Proposed application	Reference
Carboxymethyl cellulose	55% at 30 kGy	Wound care	(Fei et al., 2000; 2006).
	50% at 80 kGy		(Wach et al., 2001)
	40% at 100 kGy		(Xu et al., 2002)
	60% at 80 kGy		(Yoshii et al., 2003)
Carboxymethyl starch	70% at 10 kGy	Food and cosmetics	(Yoshii & Kume, 2003)
	40% at 2 kGy		(Nagasawa et al., 2004)
Carboxymethl chitosan	70% at 80kGy	Biomedical field	(Zhao et al., 2003a)
Gum Arabic	50-60% at 49.8 kGy	Food, cosmetic, agricultural, and hygienic materials	(Katayama et al., 2006)

Table 5

Radiation of different polymers in paste like condition with maximum amount of hydrogel obtained and their proposed applications.

3.12.3 Solid state radiation

Irradiation of hydrocolloids in solid state induces the radical formation in molecular chains as a result of the direct action of radiation. Here mainly two events take place (i) direct energy transfers to the

macromolecule to produce macroradicals and (ii) generation of primary radicals due to the presence of water (moisture). During the solid state radiolysis reaction which eventually leads to decrease the molecular weight of macromolecules (Wach et al., 2003a). Generally, the degradation rates depend on the concentrations of reactants and temperature, like other chemical reactions. In addition, the rates depend on the purity, presence of substituted group and molecular weight of hydrocolloid (Makuuchi, 2010). The course of the degradation of carbohydrates in the solid state is illustrated in Figure 12. The main effects are fragmentation, hydrolysis (due to presence of moisture) or and rearrangement leading to low molecular weight products.

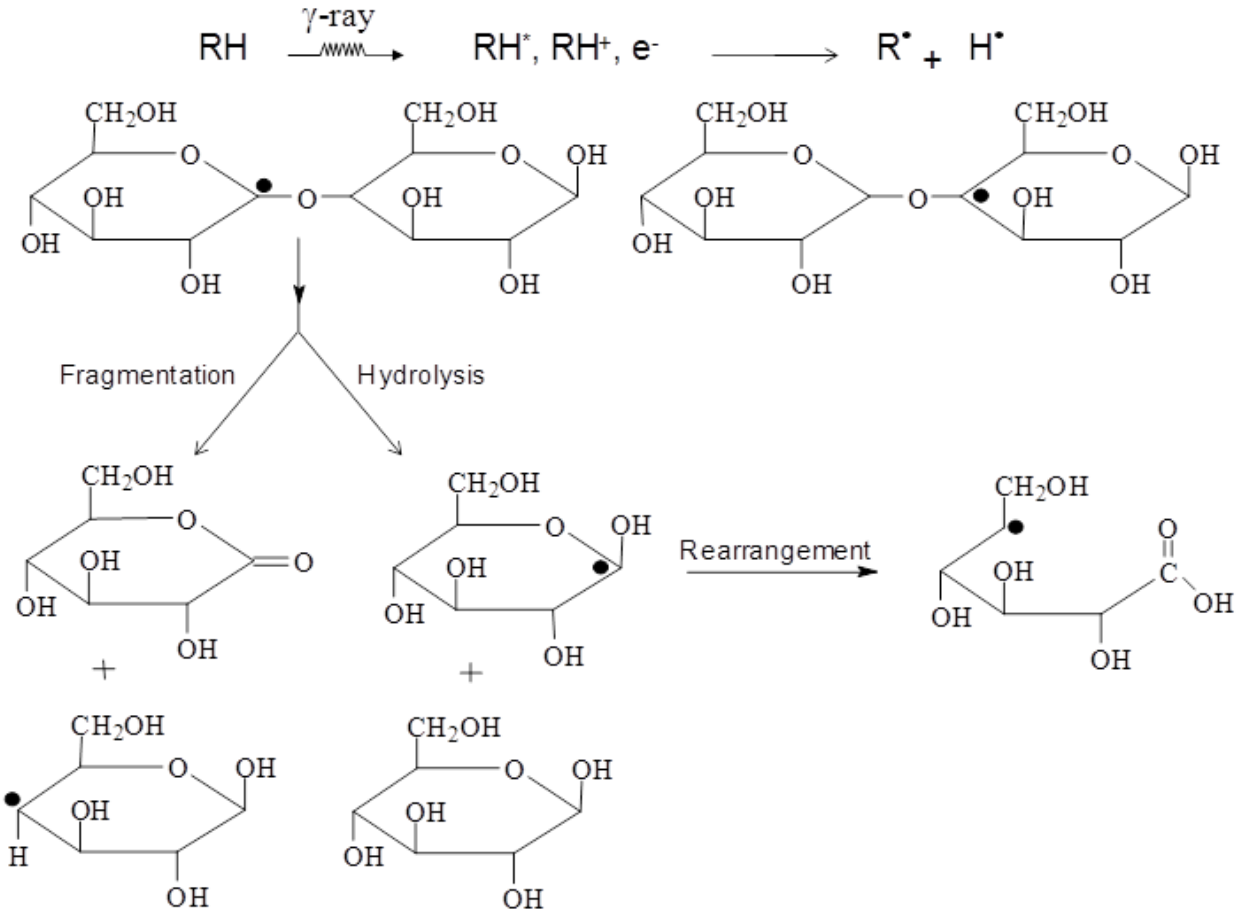


Figure 19

Events in solid state radiation of hydrocolloids; the glycosidic bond cleavage and chain scission of cellobiose upon solid state radiation of hydrocolloids.

The reported radiation degradation yield (G_d) of κ-, ι-, and λ-carrageenans irradiated in solid and at 1% aqueous solution at atmospheric conditions were almost the same for all types of carrageenan. G_d was in the range of 2.3–2.7 x 10^{-7} mol J^{-1} and 1.0–1.2 x 10^{-7} mol J^{-1} for solid and aqueous state irradiation, respectively which shows the solid state radiation of carrageenan more susceptible to degradation. However, G_d was

of hydrocolloids, scission of glycosidic bond is the dominant

relatively low (0.3 x 10^{-7} mol J^{-1}) for paste-like state (4% concentration) probably due to simultaneous cross-linking place in such system (Abad et al., 2009). Similarly, the G_d in aqueous form was also affected by the conformational state of κ-carrageenan. The helical conformation gave a lower G_d (0.7 x 10^{-7} mol J^{-1}) than the coiled conformation (G_d = 1.2 x 10^{-7} mol J^{-1}). A helical structure has some interchain stabilisation effects which increases the possibility of free radical interchain cross-linking (Abad et al., 2010). For galactomannans the values are found relatively lower (0.85–1.07 x 10^{-7} mol J^{-1}) suggesting these hydrocolloids are less susceptible to degradation. Several hydrocolloids such as α-D-glucose (Moore & Phillips, 1971; Phillips, 1963; Phillips et al., 1966; Phillips, 1968), cellulose and derivatives (Fei et al., 2000; Horikawa et al., 2004), amylose and starch (Phillips & Young, 1966; Phillips, 1968; Yoshii & Kume, 2003), chitin and chitosan (Kuang et al., 2008; Wasikiewicz et al., 2005) have reportedly undergone degradation when subjected to solid state radiation. The results for a range of polysaccharides are shown in Table.

3.12.4. Cross-linking in solid state

The application of radiation processing of synthetic polymers to introduce structural changes by cross-linking and special performance characteristics is now a thriving industry. In contrast treatment of polysaccharides and other natural polymers with ionizing radiation either in the solid state or in aqueous solution leads to degradation as described above. Therefore, a method to modify structure, without introducing new chemical groupings, could prove of advantage, particularly if the process could be achieved in the solid state. This has been possible in synthetic polymers by exposure to high energy ionizing radiation, arising mainly through the pioneering work of Charlesby (Rosiak & Yoshii, 1999). The method is now routinely used for the cross-linking of polymers. Polymer chains can be joined and a network formed. The method is used for crystal lattice modification for semiconductors and gemstones, etc., by which the crystalline structure of a material is modified. The sheathing on wire and cable is routinely cross-linked with radiation to improve a number of important properties and radiation cross-linked polymers are commonly used to make heat-shrinkable tubing, connectors, and films.

3.12.4.1 Natural polymers

Recently a process has been reported to modify natural polymers (e.g. hydrocolloids such as CMC, gum arabic, dextran, gelatine, etc) in solid state by high energy radiation (Al-Assaf et al., 2006b; Al-Assaf et al., 2007b) to obtain their hydrogel (Figure 13).

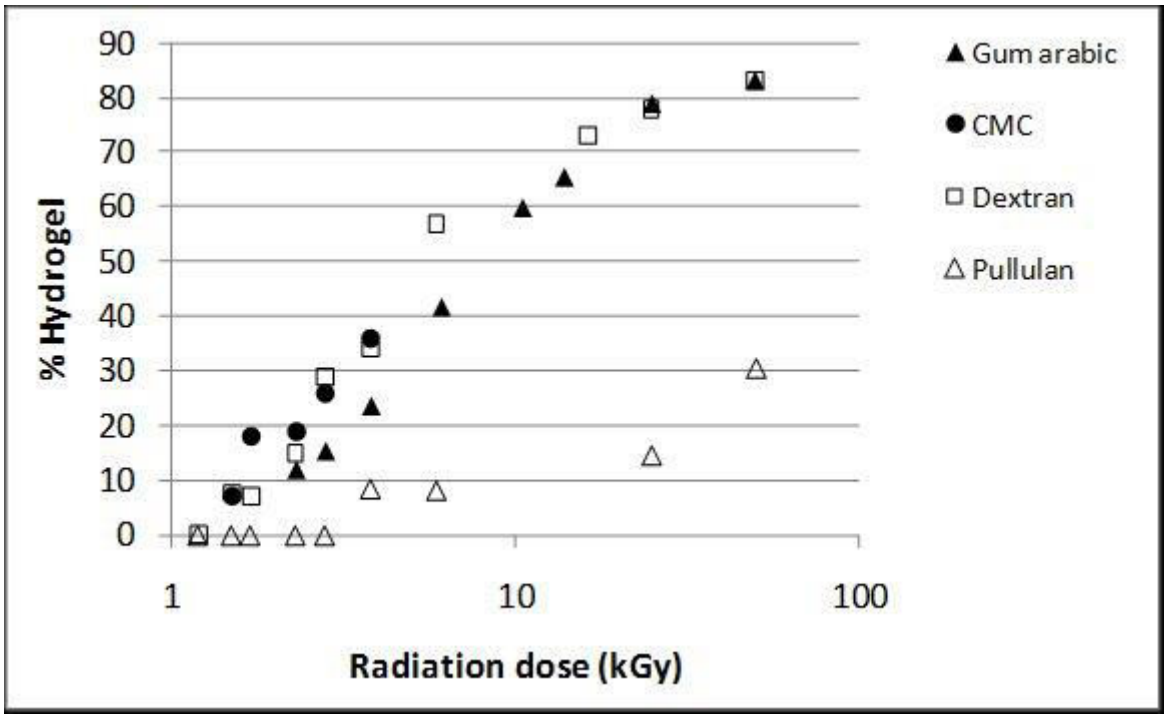


Figure 20.
Formation of hydrogel as a function of radiation dose for hydrocolloids irradiated in solid state in the presence of alkyne gas.

The new method allows the controlled modification of the structure of polysaccharide and other related materials in the solid state using ionizing radiation in the presence of a mediating alkyne gas. The method has been applied to a range of polysaccharides of differing origin and structure, to proteins either directly derived from animal connective tissue sources such as collagen, gelatin, and from human and animal products, such as casein, combinations of one or more such polysaccharides with proteins of plant origin. These polymers when irradiated in presence of acetylene gas, it leads to the cross-linking and hence formation of macromolecules with increased molecular weight and functionalities. Highly branched polysaccharide structures could produce a 4-fold increase in molecular weight with doses up to 10 kGy and hydrogels with doses up to 50 kGy, whereas straight chain structures can yield a similar change with doses as low as 1–3 kGy. Proteins require doses up to 25 kGy to achieve a similar result. The proposed cross-linking mechanism for solid state radiation is illustrated in Figure 14. For ease of presentation the two macromolecular chains are represented as R_1H and R_2H. The direct radiation action forms a free radical ($^{\bullet}R_1$) which then adds to the acetylene to give a radical with a double bond. This addition to the acetylene is slow and the reactive radical with a double bond abstracts hydrogen atom form a nearby polysaccharide chain to give two radicals, one on the original acetylene adduct and one on a nearby polysaccharide chain ($^{\bullet}R_2$). These

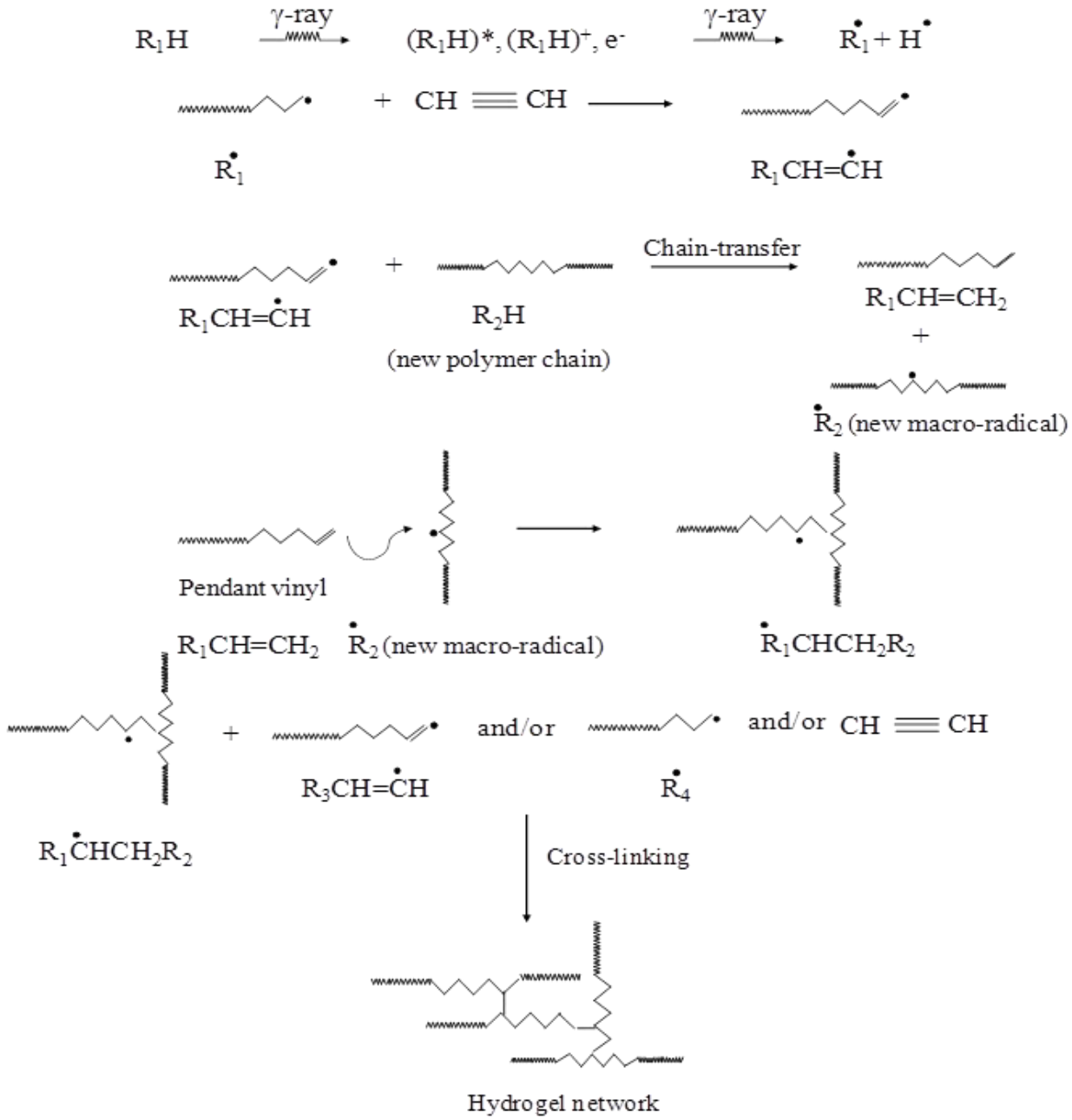


Figure 21.

Schematic representation of radiation cross-linking in solid state of polymers when irradiated in the atmosphere of acetylene.

ionizing radiation or another similar radical to form a cross-linked network (Al-Assaf et al., 2007b).

recombine to give a cross-linked stable radical. This radical has fair degree of mobility and either recombines with acetylene, radical generated as a result of the action of

Irradiation of carboxymethyl cellulose in solid state showed that the structural changes can again be achieved using the radiation processing. Result

showed that initial mean M_w of 1.55 x 10^5, is increased three-fold to 4.44 x 10^5 Da. Moreover the polydispersity is increased from 2 to 2.8 with an increase in R_g from 36 to 52 nm. Hydrogel is formed at the higher doses and is visible in solution. Gelation of CMC solution can be controlled to give stable gels ranging in consistency from soft pourable to very firm. At a frequency of 0.1 Hz there is a 10-fold increase in G' and G". The method allows controlled increase in molecular weight and gel formation which are increased linearly with the radiation dose. Result on solid state radiation of dextran showed 83% of hydrogel formation at a dose of around 50 kGy. An increase in M_w from initial value of 2.34 x 10^6 Da to a maximum of 4.58 x 10^6 Da was observed. The modified dextran showed a marked increase in viscoelastic properties compared to it control. Radiation of another slightly blanched hydrocolloid, pullulan showed that on radiation processing the average Mw doubles from 3.17 x 10^5 to 6.81 x 10^5 Da and moreover, there is conversion of the original material to form hydrogel to an extent of 30% of the original material. Measurements of G' shows the enhancement of the rheological properties in manner expected for the higher molecular weight polysaccharide. Result on a protein (gelatine) showed that using the solid state process, the molecular weight of gelatine can be increased in a controlled manner to produce a range of products with varying molecular weights and solution/gelling properties. The same behaviour has been achieved with casein in the form of its sodium salt. The modifications already demonstrated can be applied also to the widest range of commercial polysaccharides, including xanthan, pectin, carrageenan, gellan, welan, guar gum, locust bean gum, alginate, starch, heparin, chitin and chitosan (Phillips et al., 2003; Phillips et al., 2005).

A recent study on carrageenan modification in the solid state demonstrated that the hydrogel formation and the increase in viscoelasticity upon irradiation of κ-carrageenan are achieved without using a gelling agent (Gulrez et al., 2010). The optimum dose range to achieve modification is 5-10 kGy since at high dose degradation results in reduction of gel fraction. Irradiation of carrageenan led to production of nearly 78% hydrogel with an improvement in viscosity nearly four-fold to that of control material. The results showed improvement in viscoelasticity at moderate doses which can be defined as a result of increase in hydrodynamic radius of carrageenan gel solution. The results showed that radiation modified κ-carrageenan hydrogels are stronger than control sample. The strength of κ-carrageenan gels increased with increased radiation dose and reached to maximum at 5 kGy. The superior mechanical properties of the irradiated sample compared with the control can be explained as the aggregation of relatively longer superhelical rods in case of modified sample (Figure 15).

3.12.4.2 Synthetic/natural polymer blends

The same technique was applied on various mix systems of water soluble polymers of synthetic and natural origin and the result showed the synergistic effect on the functionalities of these mix systems. One such example is the radiation of mixture (1:1) of polyvinyl pyrrolidone (PVP) and gum arabic (GA) in solid state. The reheology measurement carried out for 10% aqueous solution of this system showed significant improvement in viscoelasticity of mixed polymers (synergy) compared to either of its constituents (Figure 16).

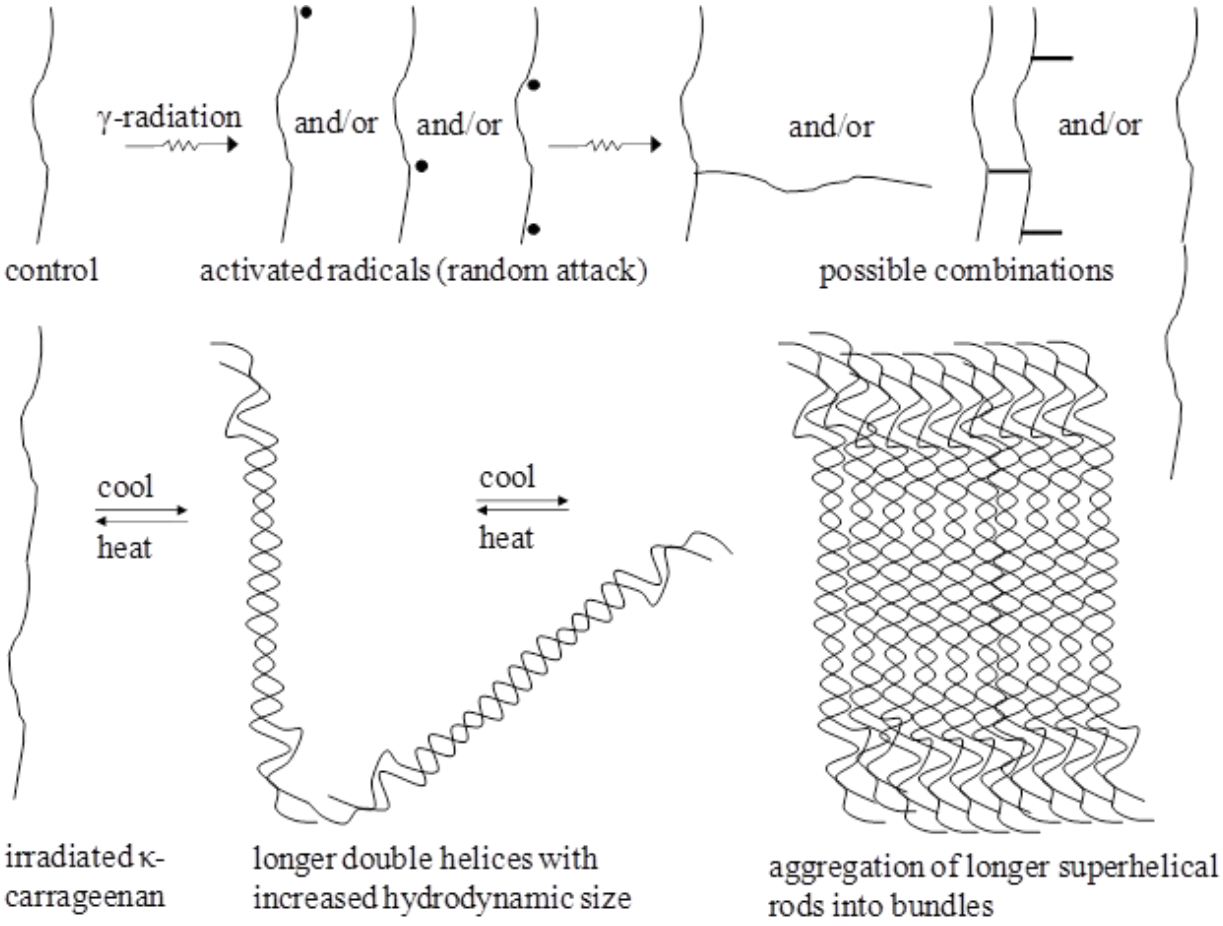


Figure 22

Proposed mechanism for aggregation of superhelical rods into bundles on cooling the hot solution of modified κ-carrageenan hydrogels.

Fig. 16.) Dynamic viscosity plotted as a function of oscillation frequency for 10% aqueous solution of PVP-GA blend system modified in solid state (Phillips et al., 2003).

3.12.5 Advantages and Disadvantages of Hydrogels

1.5.1 Advantages of Hydrogels

1 . Due to their significant water content they possess a degree of flexibility.

2. Release of medicines or nutrients timely.

3. They are biocompatible, biodegradable and can be injected.

4. Hydrogels have ability to sense changes of pH, temp. and concentration of metabolite

5. Hydrogels also possess good transport properties and easy to modification.

3.12.6 Disadvantages of Hydrogels

1. High cost.
2. Can be hard to handle.
3. Low mechanical strength.
4. They are non-adherent and may need to be secured by secondary dressing.
5. Difficult to load with drugs/nutrient

3.13 Hydrogel product sensitive to environmental conditions

As mentioned above, hydrogels as three-dimensional cross-linked hydrophilic polymer networks are capable of swelling or de-swelling reversibly in water and retaining large volume of liquid in swollen state. Hydrogels can be designed with controllable responses as to shrink or expand with changes in external environmental conditions. They may perform dramatic volume transition in response to a variety of physical and chemical stimuli, where the physical stimuli include temperature, electric or magnetic field, light, pressure, and sound, while the chemical stimuli include pH, solvent composition, ionic strength, and molecular species (Fig. 1).

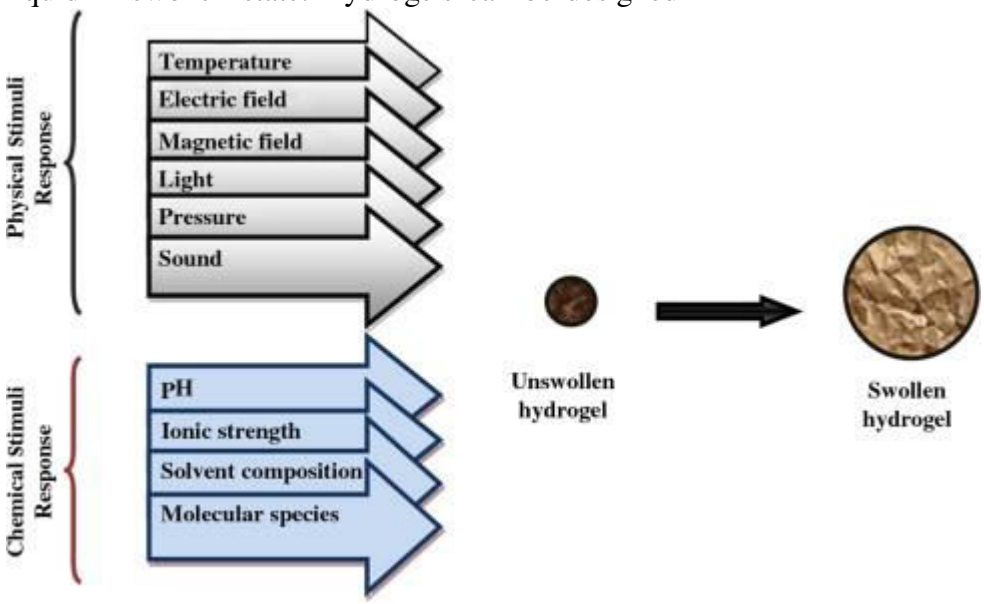


Fig. 23. Stimuli response swelling hydrogel.

The extent of swelling or de-swelling in response to the changes in the external environment of the hydrogel could be so drastic that the phenomenon is referred to as volume collapse or phase transition [12]. Synthetic hydrogels have been a field of extensive research for the past four decades, and it still remains a very active area of research today.

3.14 Utilization of hydrogel products

With the establishment of the first synthetic hydrogels by Wichterle and Lim in 1954 [13], the hydrogel technologies may be applied to hygienic products [14], agriculture [15], drug delivery systems [14], [16], sealing [14], coal dewatering [17], artificial snow [14], food additives [18], pharmaceuticals [19], biomedical applications [20], [21] tissue engineering and regenerative medicines [22], [23],

diagnostics [24], wound dressing [25], separation of biomolecules or cells [26] and barrier materials to regulate biological adhesions [27], and Biosensor [28].

In addition, the ever growing spectrum of functional monomers and macromeres widen their applicability. They were used in early agricultural water absorbents based on biopolymers through grafting of hydrophilic monomers onto starch and other polysaccharides [29], [30]. Hydrogel products for hygienic applications are mainly based on acrylic acid and its salts. Acrylamide is a main component employed for preparation of agricultural hydrogel products [14].

utilizations [34]. Dimitrios et al. [21] discussed the tailoring of hydrogels for various applications of medical interest.

3.15 Technologies adopted in hydrogel preparation

By definition, hydrogels are polymer networks having hydrophilic properties. While hydrogels are generally prepared based on hydrophilic monomers, hydrophobic monomers

, mechanical strength provides the durability as well. These two opposite properties should be balanced through optimal design [35]. Also, it can be applied to preparation of hydrogels based on natural polymers provided that these polymers have suitable functional groups or have been

hydrogel. Copolymerization/cross-linking free-radical polymerizations are commonly used to produce hydrogels by reacting hydrophilic monomers with multifunctional cross-linkers. Water-soluble linear polymers of both natural and synthetic origin are cross-linked to form hydrogels in a number of ways:

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

Various publications on this subject have discussed in detail synthetic methods and applications of hydrogels. For example, a comprehensive review of the chemistry and various synthetic schemes employed for hydrogel preparation can be found in various chapters of a compilation edited by Peppas [31]. More recently, hydrogels produced by radiation polymerization and grafting have been published by Khoylou [32]. Mi-Ran Park [33] described the preparation and chemical properties of hydrogels employed in agricultural applications. Vijayalakshmi and Kenichi have reviewed the potential of hydrogels in sensor

are sometimes used in hydrogel preparation to regulate the properties for specific applications.

In general, hydrogels can be prepared from either synthetic polymers or natural polymers. The synthetic polymers are hydrophobic in nature and chemically stronger compared to natural polymers. Their mechanical strength results in slow degradation rate, but on the other hand functionalized with radically polymerizable groups [36].

In the most succinct sense, a hydrogel is simply a hydrophilic polymeric network cross-linked in some fashion to produce an elastic structure. Thus, any technique which can be used to create a cross-linked polymer can be used to produce a

Any of the various polymerization techniques can be used to form gels, including bulk, solution, and suspension polymerization.

In general, the three integral parts of the hydrogels preparation are monomer, initiator, and cross-linker. To control the heat of polymerization and the final hydrogels properties, diluents can be used, such as

water or other aqueous solutions. Then, the hydrogel mass needs to be washed to remove impurities left from the preparation process. These include non-reacted monomer, initiators, cross-linkers, and unwanted products produced via side reactions (Fig. 2).

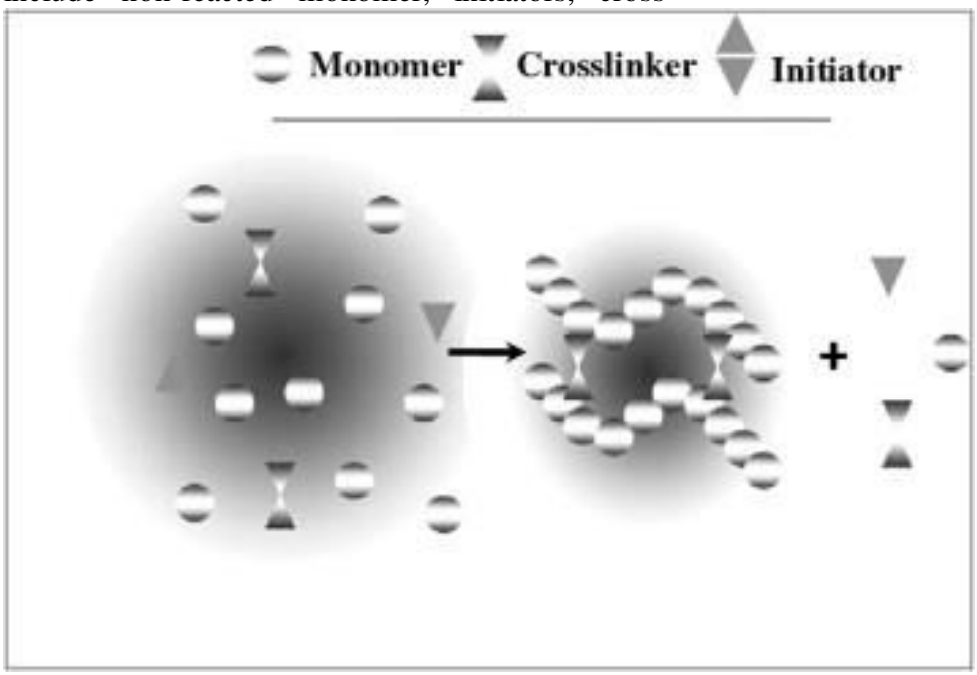


Fig. 24. Schematic diagram of hydrogel preparation.

Preparation of hydrogel based on acrylamide, acrylic acid, and its salts by inverse-suspension polymerization [37] and diluted solution polymerization have been investigated elsewhere. Fewer studies have been done on highly concentrated solution polymerization of acrylic monomers, which are mostly patented [38]. Chen [39] produced acrylic acid-sodium acrylate superabsorbent through concentrated (43.6 wt%) solution polymerization using potassium persulphate as a thermal initiator.
Hydrogels are usually prepared from polar monomers. According to their starting materials, they can be divided into natural polymer hydrogels, synthetic polymer hydrogels, and combinations of the two classes.

From a preparative point of view, they can be obtained by graft polymerization, cross-linking polymerization, networks formation of water-soluble polymer, and radiation cross-linking, etc. There are many types of hydrogels; mostly, they are lightly cross-linked copolymers of acrylate and acrylic acid, and grafted starch-acrylic acid polymers prepared by inverse-suspension, emulsion polymerization, and solution polymerization. The polymerization techniques have been described below.

3.16 Hydrogel technical features

The functional features of an ideal hydrogel material can be listed as follows [48]:
The highest absorption capacity (maximum equilibrium swelling) in saline.

Desired rate of absorption (preferred particle size and porosity) depending on the application requirement.

The highest absorbency under load (AUL).
The lowest soluble content and residual monomer.

The lowest price.

The highest durability and stability in the swelling environment and during the storage.

The highest biodegradability without formation of toxic species following the degradation.

pH-neutrality after swelling in water.

Colorlessness, odorlessness, and absolute non-toxic.

Photo stability.

Re-wetting capability (if required) the hydrogel has to be able to give back the imbibed solution or to maintain it; depending on the application requirement (e.g., in agricultural or hygienic applications).

Obviously, it is impossible that a hydrogel sample would simultaneously fulfill all the above mentioned required features. In fact, the synthetic components for achieving the maximum level of some of these features will lead to inefficiency of the rest. Therefore, in practice, the production reaction variables must be optimized such that an appropriate balance between the properties is achieved. For example, a hygienic products of hydrogels must possess the highest absorption rate, the lowest re-wetting, and the lowest residual monomer, and the hydrogels used in drug delivery must be porous and response to either pH or temperature.

4 Experiment analysis

Experimental analysis clear that the polymer with monomer ratio of acrylamide to acrylic acid 70:30 was taken and immersed in 500 mL solutions of pH ranging from 3.75 to 9.6. At lower pH, carboxylic acid in the copolymer structure turns into protonated form of carboxylic acid. Hence, the hydrogel in acidic environment gets less water to absorb and hence the swelling ratio decreases at lower pH. At higher pH, the carboxylic acid group gets transformed into its basic salt form. The copolymer with monomer ratio 70/30 of acrylamide and acrylic acid was synthesized by maintaining reaction temperatures of 50 °C, 60 °C and 70 °C. For preparing 70/30 monomer ratio, amount of MBA was increased to 0.06, 0.07 and 0.08 gm and swelling ratios are 300, 200 and 100 resp. A 70/30 sample of polymer was taken and put in different concentrations of salt solution from 0.1 to 0.9 gm of NaCl as salts strength of solution initially decrease and finally increase. Acrylamide (5 gm) is added to 100 mL distilled water to form a solution. 1 ml activator TEMED is added and solution is allowed to stir for 20 minutes. Maintain a temperature of 60 °C throughout the reaction. 0.5 gm of Acrylic acid and MBA which is the cross-linker are introduced while the contents of the beaker are constantly being stirred. 0.1 gm initiator KPS is added after 30 minutes. [4].

4.1 Marketing Strategy

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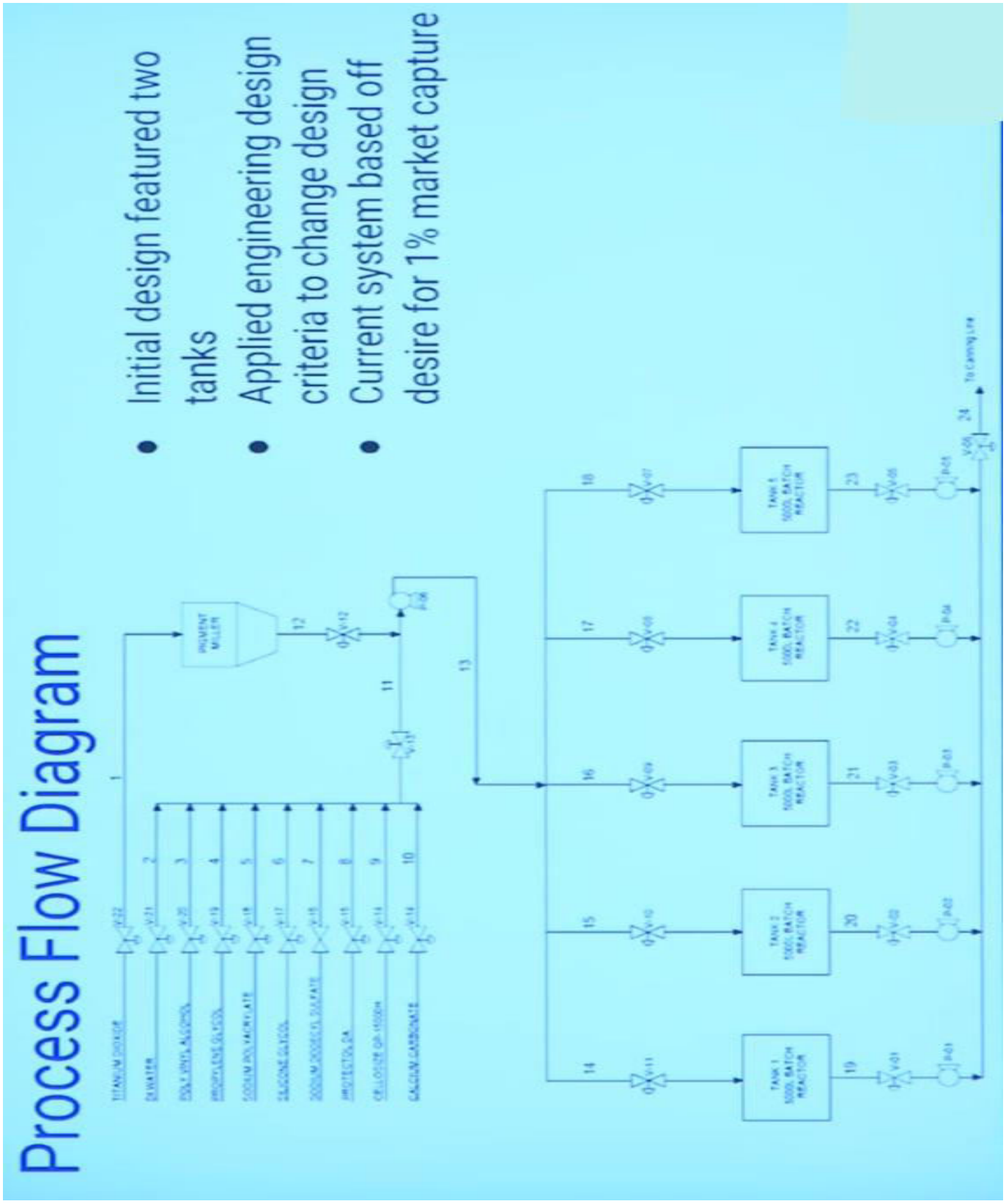
- Sold as part of a series
  - Primer and paint
  - Quick dry, electrosensitive series
- Sold through dual distribution model
  - Direct to consumer and through large retailers
- Electrical device will be included in package deal
  - Partnership for research and development
- Market brand as unique to eventually be acquired by a large corporation
  - Would reduce distribution costs

4.2 Design Criteria

- Paint
  - Fast drying
  - Affordable raw materials
  - Availability of hydrogel
  - Homogeneity of paint
  - Passes all quality control tests
- Current application method
  - Ease of use for painters
  - Longevity of application system


Process Flow Diagram
Initial design featured two tanks
Applied engineering design criteria to change design
Current system based off desire for 1% market capture

4.3 Product and Process Description

- Product: Electrically inducible quick-drying paint
    - Complete or partial replacement of binder with electro-sensitive

  hydrogels
- Manufacturing process:
  1. Mixing tank is filled with water

  2. Pigment is milled and mixed in with water in the tank

  3. Additives such as biocides, defoamers, and other surfactants are added and allowed to mix

  4. Binder is added and mixed

4.4 Safety Overview

- Tanks, valves, and pumps design:
    - Max Pressure: 5 atm
    - Max Temperature: 70°C
- Even with these limits the process should never exceed 30°C
- All valves are air to open (fail close)
    - Raw material inlet valves - prevent tank overfill
    - Product line valves - prevent accidental discharge to the production floor

4.5 Safety: Inherently Safer Design

- Minimize
    - One large tank replaced with five small tanks
        - Mitigates large spills
        - Ensures better dispersion
- Substitute
    - Substitute additives and binders with hydrogels
        - More een and less hazardous (VOC reduction)
- Moderate
    - Process pressures and temperatures are close to ambient
    - Control and pump rooms will be located far from the process floor

4.6 Experimental Design

- Paints provided:

  - One gallon standard semi-gloss paint
  - Four gallons standard semi-gloss paint without binder
  - Quality control inspection SOP's
- Polyacrylic acid hydrogel added at varying weight percentages
  - 0%, 0.10.4%
- Used California Paints standard operating procedures for
  - Mid and high shear viscosity
  - pH
  - Density
  - Drawdown
- Dry time was tested on drywall and sheet metal
  - Each parameter tested with and without current
  - Dry times were compared to find trends

4.6 Summary

- Final desired solution - white gloss paint 20% hydrogel by weight
  - Completely replace latex with hydrogel
- Poly acrylic acid hydrogel tests
  - Decreased dry time with applied current
    - Higher concentrations of hydrogel should continue trend
  - Increased viscosity and density
- Selected additional hydrogels for testing
- Possibly mill hydrogel to decrease particle size
  - Reduce agglomeration
- Investment of $12MM USD for initial start-up capital needed

5 Result and discussion

A schematic figure of hydrogel before swelling is shown inFigure 4a. The vectors exhibit the buffer diffusion into the gelzone. As shown in Figure 4b, the buffer diffusion flux wasincreased in the polymeric network during the time.
Figures 5ad shows the simulation result s for hydrogelswelling at various times. They were obtained from the simulatorsoftware. They clearly show the effect of buffer concentrationenhancement on buffer penetration inside the hydrogel.
These figures were extracted from the COMSOL simulator,and they simulate water diffusion in the hydrogel versus time.At $t = 0$ s (**Figure** 5a), there is no water diffusion (dark blue),while at $t = 5$ s (**Figure** 5b), water gradually diffuses in thehydrogel (yellow and greenish bands from outside, respectively).When water increases in hydrogel, the band gets dark red (forexample at $t = 10$ s (**Figure** 5c), the outset band becomes red,while at $t = 15$ s (**Figure** 5d), it becomes dark red howeverhydrogel cores still are blue (dry)).
According to the experiment, the swelling process was startedduring buffer diffusion. The gel diameter was then measured,and mathematical software was applied to calculate the deformation coefficient.

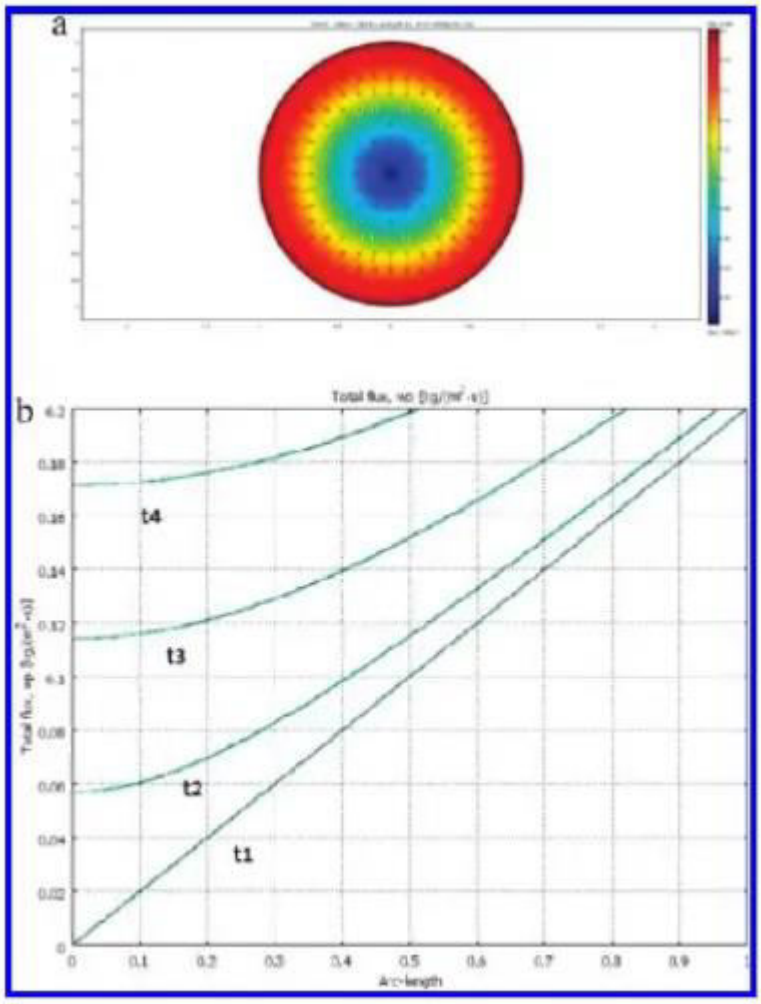


Figure 4. (a) Vectors of buffer diffusion at initial time. (b) Diffusion flux enhancement during the time ($t_1 < t_2 < t_3 < \ldots$).

Figure 25

Thetemperature effects were negligibleb ecause the experiments were carried out isothermally

The swelling percentages were calculated using eq 1. Theobtained data from model were plotted versus time and then compared with the experimental data. These result s are il-lustrated in Figure 6. As shown in this figure, the swellingpercentage was sharply increased with time up to time of 100(s) and then increased with time, slowly in both experimentand model. This phenomenon is legitimized by the chemicalpotential difference as shown in the following equation:where

μ
1

-
μ
1.0

$$\mu_1 - \mu_{1.0} = \Delta\mu_{elastic} + \Delta\mu_{mixing} + \Delta\mu_{ionic}$$

is chemical potential difference between solventand polymer,
Δ
μ
elastic
is chemical potential difference for elastic,which always is against the swelling,
Δ
μ
mixing
is chemicalpotential difference, which is defined in interactions betweenpolymer and solvent, and
Δ
μ
ionic
is ionic chemical potentialdifference.
Δ
μ
-
Stefanequation which is a basic equation for modeling of this work cannot produce the data which can be matched to the experi-mental data, completely.

ionic
and
Δ
μ
mixing
assist the swelling process.Initially, the ionic chemical potential difference is so much
andcontrols the swelling, after equilibrating between hydrogelinternal and external ions,
Δ
μ
mixing
controls the swelling processwhich its value is less than previous status. Therefore, theswelling trend initially increased and then decreased. This outputis supported by literature.
24
-
26
As shown in Figure 6, the modeled data are in goodagreement with the experimental data however there are somediscrepancies between them. It seems that Maxwell

The acrylamide (AAm) effect on the hydrogel swelling wasalso considered. For this purpose, the various amounts of AAmwere tested. As shown in Figure 7, an enhancement in acryl

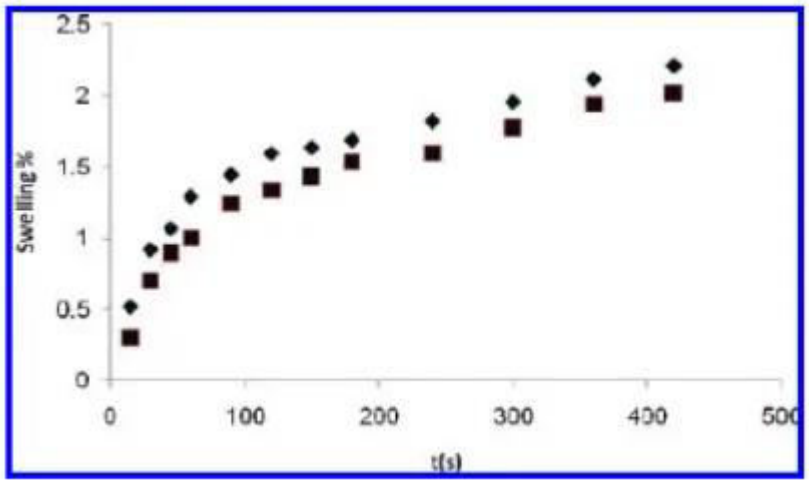


Figure 26.
Swelling percentage versus time. (
(
) Experimental data and (
0
)modeled data

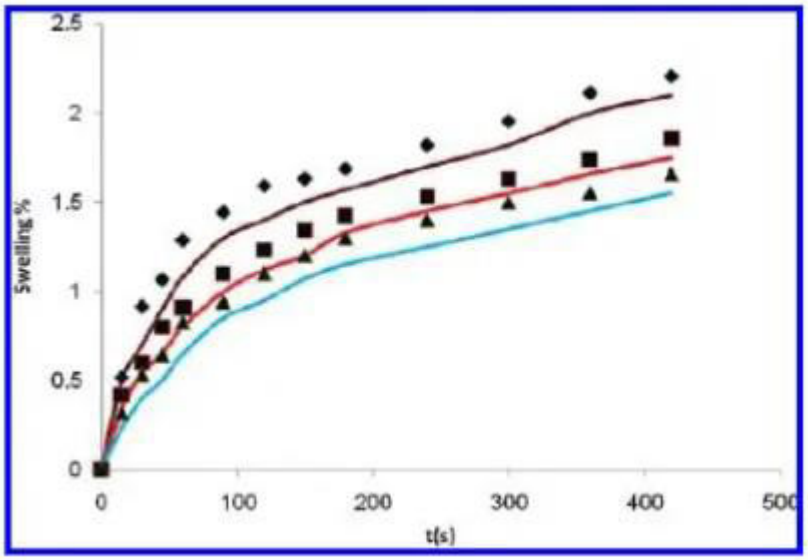


Figure 27
Effect of AAm amounts on the swelling percentage: (
2
) 1mol AAm based on experiment; (black line) 1 mol AAm based on simulation; (red line) 0.5 mol AAm based on simulation; (blue line) 0 molAAm based on simulation
) 0 molAAm based on experiment; (
0
) 0.5 mol AAm based on experiment; (
(

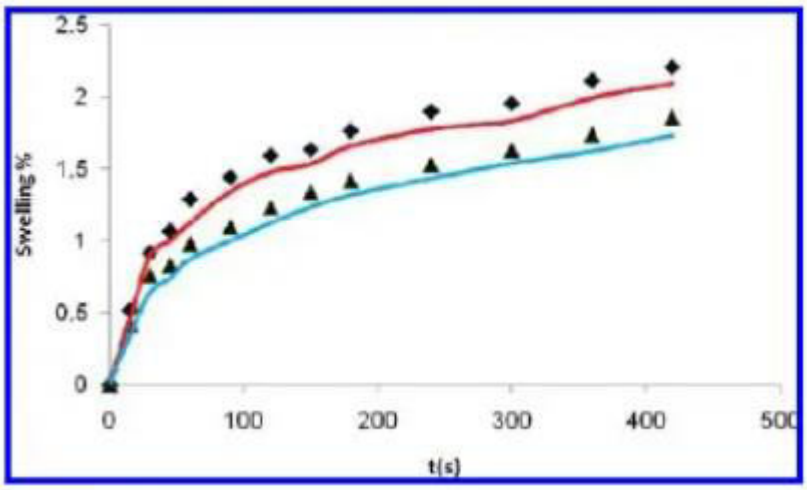


Figure 28
Effect of AAc amounts on the swelling percentage: (
(
) 0 molAAc based on experiment; (
2
) 1 mol AAc based on experiment; (red line):0 mol AAc based on simulation; (blue line) 1 mol AAc based on simulation

amide amount increased
the swelling percentage. According tothe hydrophilic properties of monomer, an increase in AAmamount caused
more swelling because average molecular mass(

M
j
c
) used in the calculations made this increment.
The polymers were prepared by varying the amount of acrylicacid (AAc) from 0 to 1 mol. The hydrogels swelling in theseconditions are presented in Figure 8. As shown in this figure,the polymers swelling increased w ith increasing monomerduring hydrogels synthesis process. A positive osmotic pressure inside the polymer matrix may be caused a further expansionin three-dimensional polymer network.

6 Conclusion

Recently, many hydrogel based networks have been designed and tailored to meet the needs of different applications. The favorable property of these hydrogels is either ability to swell when put in contact with an aqueous solution. The presented review demonstrates the literature concerning classification of hydrogels on different bases, physical and chemical characteristics of these products and technical feasibility of their utilization. It also involved technologies adopted for hydrogel production together with process design implications, block diagrams and optimized conditions of the preparation process. An innovated category of recent generations of hydrogel materials was also presented in some details. Super-porous hydrogels are new materials that, regardless of their original size, rapidly swell to a large size. Different generations of SPHs evolved to address the needs for certain applications. Based on the literature survey, it can be concluded that batch or semi-batch reactors are suitable reactors for polymerization processes. The variables for batch reactors include temperature, pressure, batch cycle time, the amount of reactants, and the feed addition strategy. Optimization variables such as batch cycle time and amount of reactant are continuous variables with fixed values for a certain batch reactor system depends mainly upon material and energy balance. Ribbon mixer with a screw around the axis, screw mixer with four baffles, and double ribbon mixer are three Impellers known to be effective in high viscosity ranges.

This chapter aims to introduce briefly the hydrogels: a class of natural or synthetic polymeric materials that have the ability to hold huge amounts of water because of their specific structures and subsequent swelling properties. Based on this ability, they found a wide variety of applications, and because of the possibility to modify the polymeric structure to obtain desired functionality, the areas of applications are rapidly expanding. They can be designed in such a way that they can respond to a specific stimulus including pH, temperature, light, etc. at a predefined level and thus be stimuli responsive. Among their amazing characteristics, the biocompatibility and biodegradability make them a powerful candidate to use in biological and environmental applications as implants or materials for removal of toxic pollutants. In addition, conducting hydrogels are often a good choice in designing and fabrication of supercapacitors, which promise the most rapid developments in electronics.

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