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Interpenetrating polymeric hydrogels as favorable materials for hygienic applications

Ahmed M. Khalil [1, *]
[1]Photochemistry Department, National Research Centre, El-Buhouth St., Dokki - 12622, Giza, Egypt
*corresponding author e-mail address: ***akhalil75@yahoo.com*** | Scopus ID: 55605778944

ABSTRACT
Polymers can crosslink to produce intermingled materials with three-dimensional network structure known as interpenetrating polymeric network (IPN). They comprise elastic crosslinked polymeric chains. The chains of the hydrogels are either physically or chemically entangled together. Interpenetrating hydrogels can be tailored to provide enhanced materials. They can be classified according to methods of their synthesis as simultaneous or sequential IPNs and the structure to be homo or semi IPNs. The preparation factors play a role in controlling the properties of the produced IPNs. Moreover, the ambient conditions such as pH, temperature as well as the ionic strength may affect the performance of these hydrogels. The swelling capacity is an important feature that allows the prepared hydrogel to perform the required application. Some disadvantages may arise such as the low mechanical properties that are suggested to be overcome. IPNs can be used in various applications that serve the human requirements like drug delivery, tissue engineering, medical and packaging applications. Hydrogels present biocompatibility and nontoxicity when used in biomedical applications. Interpenetrating hydrogels can be prepared from natural or synthetic polymers. Polysaccharides as natural polymers can be used to produce efficient interpenetrating hydrogels. Polyacrylates, poly(ethylene glycol) and poly(vinyl alcohol) are designated as promising synthetic polymers capable of forming interpenetrating hydrogels.
Keywords: *Interpenetrating polymeric network; hydrogel; medical application; tissue engineering, food packaging.*

1. INTRODUCTION
Interpenetrating polymers are crosslinked materials composed of two or more polymers. They are intermingled partly without covalent bonds. Hydrogels are polymers with three-dimensional network structure. This structure detaches when the chemical bonds are cracked. Interpenetrating polymeric network (IPN) has the ability to swell in water. Upon swelling, these polymers are elastic and smooth like living tissue. They can be employed in controlled release applications. This can be supported by their low toxicity, biocompatibility and facile dispersion in the medium they are used in. Different natural or synthesized hydrogels are used in drug delivery and pharmaceutical products and heavy metal removal [1-4]. Chitosan is a natural polymer derived from chitin. It is a successful and common polymer used in such applications. Hydrogels can be formed chemically stable polymers known as physical gels. This kind is heterogeneous. They result from an interaction between two oppositely charged polyelectrolytes. These gels may degrade by altering the surrounding conditions including the temperature, pH and ionic strength of the solution as well. They can be employed in biomedical implementations such as wound dressing and drug delivery [5-7]. Meanwhile, chemical gels are produced from covalently crosslinked networks. These hydrogels can be categorized as single network hydrogels. Some disadvantages may arise such as their feeble mechanical properties which have to be overcome. Various hydrogels may face the problem of weak mechanical properties after prolonged use in aqueous media. Reinforcing agents are used to enhance the mechanical strengths of these gels [8,9]. Polymer hydrogels are composed of elastic crosslinked networks. They have liquid filling interspaces. They are able to alter their shape and volume and shape with respect to the surrounding conditions such as temperature and pH of their hosting media [10-12]. The response of IPNs may take place either by swelling, shrinking or bending features. Interpenetrating polymeric network (IPN) can be assorted as illustrated in Figure 1; referring to: i) Methods of their synthesis to be: a) Simultaneous IPN; where the parent components are polymerized at the same time. b) Sequential IPN; that takes place by swelling a hydrogel in a medium loaded with monomer, initiator in absence or in the presence of crosslinker as a polymeric network is formed followed by the formation of the other [13-15]. ii) The structure to be: a) Homo-IPN where two polymers have the same structure produce two different networks. b) Semi-IPN is composed of a crosslinked polymer with a linear one. The structures of IPN and semi-IPN are shown in Figure 2.

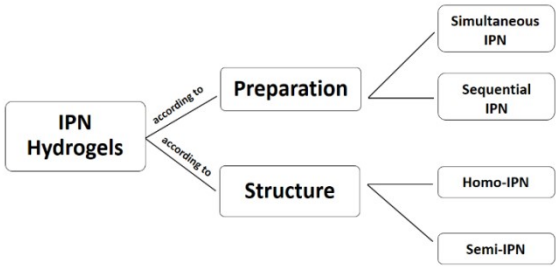

Figure 1. Schematic illustration for the classification of interpenetrating polymeric network hydrogels.

Cellulose, chitosan and chitin as well as their derivatives as natural polysaccharides are used widely in industrial and medical implications. They are safe, biodegradable with specific structures. Carboxymethyl cellulose and carboxymethyl chitosan are cellulose and chitosan derivatives; respectively [16,17]. They are used utilized in pharmaceutical, food, and metal ions removal [18,19]. These natural polymers are blended with natural and

synthetic polymers to show high adsorption abilities as metal adsorbents. The behavior of these hydrogel in metal ions adsorption was controlled by the composition of each blend. The pH-sensitive chitosan hydrogel sustains drug delivery in the stomach. It swells in acidic media. This results from protonating their free NH_2 groups [20-22]. Chitosan/alginate polymers as pH-sensitive hydrogels are used in biomedical implications [23,24]. These polymers were developed to produce a crosslinked semi-interpenetrating polymeric network (semi-IPN) hydrogel. Protecting peptide and protein drugs has to be considered as they have to be conserved from the acidic medium of the stomach before absorption in the intestine [25]. IPNs can contribute to delivering these drugs safely to the required site safely. Semi-interpenetrating network hydrogels (semi-IPN) of chitosan and polyacrylonitrile, crosslinked with glutaraldehyde were prepared in different compositions. These semi-IPNs as temperature and pH-sensitive gels showed comparatively high swelling capacity upon increasing the chitosan amount [26,27]. Interpenetrating polymeric network is known as a mixture of two polymers. One of them is synthesized or crosslinked in the presence of the other one [28]. This can be achieved by preparing monomers solution with an initiator. IPN is able to get control of thermodynamic incompatibility resulting from the interlocking of polymeric network. However, restricted phase separation may occur with maintaining the morphological features [29-31]. Producing IPNs has merit of having robust hydrogel network with stiff mechanical properties. The physical properties can be tailored to show higher loading efficiency when compared to conventional hydrogels [32]. Interpenetrating hydrogels demonstrate various degradation stages. They may differ in the swelling capacities as they are able to be employed in supplying variable swelling response of hydrogels in the drug release kinetics [33,34]. IPNs are capable of restraining the environmental changes that can affect their behavior including their swelling and elasticity. It was reported that crosslinked interpenetrating hydrogels show sensitivity, i.e. the swelling capacity may change at different pH values [35,36]. This response may reduce the burst release of drugs in oral implications. Crosslinked interpenetrating hydrogel based on chitosan and poly(N-isopropylacrylamide) network showed a significant increase in the loading capacity of diclofenac compared to sole poly(N-isopropylacrylamide) hydrogel. The thermal sensitivity of the polymer was maintained with regular release kinetics [37]. Modified polyethylene glycol diacrylate gels with β-chitosan showed enhanced biocompatibility. This hydrogel was prepared via mixing aqueous solution of polyethylene glycol diacrylate with a solution of chitosan in acetic acid. This was followed by induced ultraviolet (UV) crosslinking. IPN hydrogels of polyurethane and polyacrylamide are capable of monitoring water absorption [38,39]. These aforementioned polymers were mingled together, then crosslinked after exposure to UV radiation. The prepared interpenetrating hydrogels are commonly employed as wound dressing substrates, biosensors and artificial muscles as well.

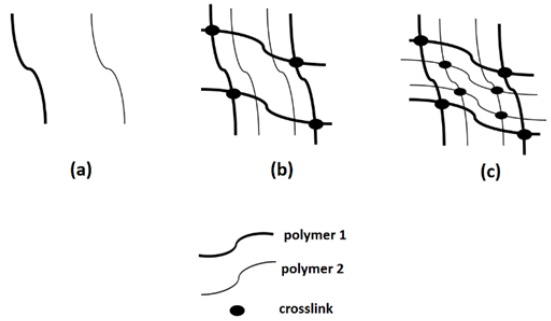

Figure 2. a) Two different polymers. b) Semi-interpenetrating polymer network. c) Interpenetrating polymer network.

Interpenetrating calcium alginate with dextran-hydroxy-ethyl methacrylate-derivative is considered as an *in-situ* formed polysaccharide hydrogel [40,41]. The prepared IPN hydrogel was designed for protein releasing and to monitor the behavior of embedded cells. The results proposed that these IPNs are promising candidates for pharmaceutical and biomedical applications. This originates from their convenient mechanical and degradation characteristics and biocompatibility. Polysaccharide hydrogel [42] based on calcium alginate and dextran methacrylate derivative reflected successful features for this hydrogel to be used in pharmaceutical applications. The distribution of dextran-acrylate chains inside the calcium alginate hydrogel evolved superior rheological properties than those of calcium alginate. This facilitates the way to inject this semi-IPN easily through hypodermic needle. UV Curing the semi-IPN [43,44] leads to crosslinking. Hence, this hydrogel is robust enough to deliver bioactive molecules such as proteins.

2. PROPERTIES OF HYDROGELS

Hydrogels are supposed to be favorable materials for use in pharmaceutical industry and biomedical applications. They can be functionalized as drug carriers because of their biocompatibility and nontoxicity. To estimate the efficiency of these materials, their characteristic properties have to be evaluated in order to rely upon these hydrogels upon application.

2.1. Swelling behavior.

The chains of the hydrogels are either physically or chemically entangled. Hence they are taken into consideration as one molecule; i.e. large molecules or super macromolecules. Some variations in the ambient conditions are able to cause rapid and reversible changes in hydrogels. The changes in the surrounding conditions as temperature, pH of the medium or the presence of ionic species may vary the physical structure and the volume of the hydrogel. The extent of ionization for the functional groups contributes to the swelling behavior and the generated changes in the volume. Polyacrylic acid is a pH sensitive hydrogel [45,46].

The swelling behavior varies according to the ionization of carboxyl groups in the polymeric chains. Some hydrogels based on poly(N-isopropylacrylamide) were investigated. The fluorescence of these hydrogels was influenced by the crosslinker and monomer concentrations. The thermal response these hydrogels was affected by copolymerization of N-Isopropylacrylamide with the hyrophilic N,N-dimethylacrylamide monomer and methyl methacrylate as a hydrophobic monomer [47].

2.2. Mechanical properties.

The mechanical properties of hydrogels are essential ones to be investigated from the biomedical perspective. This application comprises wound dressing, tendon repair, tissue

engineering and cartilage replacement. The mechanical properties of hydrogels have to preserve the physical texture of therapeutics. Raising the degree of crosslinking of a stronger hydrogel may lead to decreasing the percentage elongation with a brittle hydrogel. IPNs show a covalently crosslinked network. Ionically crosslinked gels were prepared to explore the efficient factors able to monitor the physical and mechanical properties interpenetrating hydrogels. The mechanical properties are highly affected by the blending ratio of the components. Some modifiers and compatibilizers can be used to improve the mechanical properties of interpenetrating gels. Physical crosslinking may restrict some mechanical properties. Covalently crosslinked gels, may supply many featured advantages, comprising controlled gel formation and degradation. Moreover, potent mechanical properties may arise permitting superior gel loading. Copolymerizing a hydrogel with monomer via hydrogen bonding can support in reaching optimum mechanical properties [48,49].

2.3. Biocompatibility of IPNs.

Hydrogels are supposed to show biocompatibility and nontoxicity to be employed in biomedical applications. For these materials to be biocompatible, they have to act as a suitable host for the enclosing tissues and biofunctional materials so as to be capable of carrying out certain functions. In tissue engineering application, it is important that tissues can be generated by continuous interaction with the body. This takes place upon healing and cellular regeneration step. Upon polymerizing synthetic hydrogels, some hazardous compounds may exist. They have to be totally removed to obtain a safe and biocompatible hydrogel. Among the troubles regarding the hydrogel toxicity, the unreacted monomers and initiators are mentioned. It is essential to estimate the toxicity of the hydrogel components such as monomers and initiators [50]. To get rid of the toxic chemicals, purification step has to be done with consecutive washing. Preparing hydrogels without initiators may reduce the risk of having toxic hydrogels. Poly(vinyl alcohol) hydrogels were prepared via freeze-thawing method in an attempt to reduce toxicity. The formed crystals presented physical crosslinks. They are able to resist the exerted load on the hydrogels. Poly(ethylene glycol)-poly(epsilon-caprolactone)-poly (ethylene glycol) copolymer was synthesized [51]. The toxicity of the hydrogel as an efficient material in drug delivery system was investigated. The biodegradation of the hydrogel was evaluated in ophthalmic uses.

The results showed promising biocompatibility and toxicity significance. Natural polymers have the privilege to be biocompatible when compared to synthetic ones. They can ensure possessing safe ingredients with high performance upon being used in specific applications. For investigating the compatibility of tissue after being implanted, *in-vitro* cell culture assays known as cytotoxicity tests have to be undertaken. These investigations are utilized to estimate the biocompatibility of the hydrogels comprising elution, direct contact and agar diffusion [52-54]. The alterations that may arise in cell morphology were monitored. Evaluating the tissue compatibility of a hydrogel is performed with perceiving the chemical composition of the biomaterial. Moreover, the criteria of exposing the tissue exposure such as nature, degree and duration of exposure have to be taken into consideration.

3. CHARACTERIZATION OF IPNs

3.1. IPN hydrogels based on natural polymers.

Polysaccharides as natural polymers are employed as successful materials for building up IPN hydrogels. Chitosan is a linear polysaccharide is formed from acetylated and deacetylated glucosamine units. By the high content of amino and hydroxyl functional groups, chitosan acts efficiently in adsorbing dyes and heavy metal ions [55-58], due to comprising NH_2 and OH groups. Chitosan drew the attention to be used in designing potent drug delivery materials [59-62]. The preparation of hydrogels composed of polyethylene glycol grafted on carboxymethyl chitosan and alginate has been investigated. An improvement in the protein release at a certain pH was monitored. This proposed that the prepared hydrogel is effective for protein intestinal drug delivery [63]. Chitosan and its derivatives were utilized to produce IPN composite hydrogels with different polymers possessing carboxylic groups such as poly(acrylic acid) [64-66], poly(N-acryloylglycine) and poly(methacrylic acid) [22,67-69]. Preparing semi-IPN was attained by selective crosslinking of chitosan in the presence of a polyelectrolyte [70-72] or by the synthesis of the crosslinked polyelectrolyte in the presence of chitosan [73,74]. Thermo- and pH-responsive semi-IPN polyampholyte hydrogels based on carboxymethyl chitosan and methacrylate derivative [75] drew attention. This hydrogel showed swelling as the pH departed from the isoelectric point and exhibited shrinking at the aforementioned point. Various IPN hydrogels were synthesized via crosslinking polymerization of nonionic monomers with chitosan. The commonly used monomers are acrylamide [76,77], N-isopropylacrylamide [78,79], N,N-dimethylacrylamide [80,81] and 2-hydroxyethyl methacrylate [82,83].

Cryogels are three dimensional flexible macroporous polymeric gels. Their preparation takes place below the freezing point of water (as a solvent) [84,85]. It is characteristic that cryogels comprise interconnected macropores (with sizes between 1 and 100 υm). This permits fast mass-transport of any solute beside microparticles as well. These gels possess capillary networks where the solvents flow by convective mass transport. The osmotic stability allows these substrates to be convenient in many materials for various biomedical applications and bioseparations [86,87]. A unique character of cryogels is their rapid swelling at equilibrium. They depend on the total monomer concentration, the crosslinking density and polymerization temperature. Both IPN and semi-IPN are pH responsive. Meanwhile, IPN shows higher swelling kinetics than semi-IPN cryogels. More time is important to attain the equilibrium swelling due to the presence of two networks. They respond independently with respect to surrounding variations. Sodium alginate is a linear polysaccharide. It is derived from sea algae. It can crosslinks easily. Sodium alginate is used excessively in foods, fabrics and drug delivery systems [88]. Alginate based IPN are employed in industrial applications as actuators. This results from their rapid electric response with high mechanical strength. pH and thermo responsive IPN hydrogels, consisting of sodium alginate and poly(diallyl dimethyl ammonium chloride) were prepared [89]. At pH range 2-6, the IPN hydrogels illustrated that the swelling rates

increased with elevating the pH reaching a maxima at pH 4. This resulted from an electrostatic repulsion upon ionizing the carboxylic groups of alginate. An IPN based on sodium alginate and poly(acrylamide) was prepared. It started with preparing ionically crosslinked sodium alginate beads. It was soaked in the solution of N-isopropyl acrylamide, crosslinker, and initiator. This was followed by crosslinking polymerization [90]. The resulting composite changed its transparency according to temperature variations.

Starch is a widely used polysaccharide. It exhibits advantageous features such as biodegradability, biocompatibility and bioactivity. Starch granules are insoluble in water. Many improvements were carried out with starch to enhance its hydrophilic character [91]. Pristine and improved starches were utilized as raw substrates to produce biodegradable hydrogels for biomedical applications [92]. Amphoteric semi-IPN hydrogels were synthesized via grafting acrylic acid on the surface of starch in the presence of poly(methacryloyl oxyethyl ammonium chloride) [93]. The swelling tests displayed a high swelling capacity in distilled water. In other studies, potato starch was modified with poly(acrylamide) [94]. The morphologies were affected by the composition of the gels in addition to hydrolysis. Hyaluronic acid; known as hyaluronan as it exists as polyanion, is a linear hydrophilic polysaccharide of high molecular weight consisting of glucuronic acid and glucosamine [95]. It is widely used in tissue engineering and implanting materials applications. It is able to adjust water balance to act as a lubricant by protecting the cartilage's surface [96]. Among the disadvantages of hyaluronic acid, its low stability is mentioned. This is due to its high solubility in water. Some studies were performed to obtain stable semi-IPN hydrogels based on hyaluronic acid with synthetic polymers [96] or modified dextran [97]. The preparation temperature has a role in determining the porous structure of the networks. Thus, the network structures of the prepared semi-IPNs showed a heterogeneous morphology consisting of interconnected pores of various sizes. Besides, the stability of the prepared hydrogels increased upon lowering the synthesis temperature by elevating the crosslinker content.

3.2. IPN hydrogels based on synthetic polymers.

IPN hydrogels may be prepared from synthetic polymers. They are designed and tailored with specific forms according to the application they are going to be used in. IPN hydrogels based on synthetic polymers can be classified into: a) IPN hydrogels derived from nonionic synthetic polymers. The synthesis of semi-IPN or IPN hydrogels depends mainly on poly(hydroxyl ethyl methacrylate), polyethylene glycol, poly(acrylamide) and poly(vinyl alcohol). These gels are employed mainly in separation and biomedical implementations [98-100]. b) IPN hydrogels derived from ionic synthetic polymers. These hydrogels include anionic [101-103], cationic [104,105] and anionic/cationic [106,107] polymers. The implicated linear polymer in semi-IPN may change the sensitivity of the gels. The swelling kinetics of the semi-IPN hydrogels is more rapid than that of the single-network hydrogels. An irreversible breakdown of semi-IPN is presented. The hydrogels did not retain their volume by reswelling after shrinking [101]. Thermo-sensitive semi-IPN hydrogels were developed by embedding poly(vinyl pyrrolidone) in poly(hydroxyl ethyl methacrylate [108]. For enhancing the drug delivery of hydrogels for hydrophobic drugs, semi-IPN hydrogels based on b-cyclodextrin-epichlorohydrin in poly(3-acrylamidophenylboronic acid-co-2-dimethyl aminoethyl methacrylate) were prepared [104]. The drug release was slower than in the corresponding conventional hydrogel. This was affected by pH, temperature, ionic strength and the glucose concentration. IPN hydrogels possessing anionic and cationic groups in their chains stabilize by ionic bonds beside covalent bonds. Polyion complexes may be formed as IPN comprise particular ratios of adversely charged groups. This leads to a promising category of functional substrates that can be utilized in manufacturing drug delivery systems and biomaterials. An IPN of poly(acrylic acid) and poly(vinyl amine) were prepared. The proportion between anionic and cationic groups was directed according to the amount of poly(acrylic acid).

3.3. IPN hydrogels based on proteins.

Different proteins were utilized to synthesize IPN hydrogels mixed with either gelatin or synthetic polymers. The aim of this process is to improve the blood biocompatibility of the semi- IPN hydrogels. Polyethylene glycol diacrylate was used as a crosslinker which goes through free radical crosslinking polymerization without interacting with the functional groups of gelatin. The resulting gel has improved structural stability in aqueous solutions. Silk sericin is a water soluble protein derived from silkworm. It was used to synthesized IPN hydrogels with poly(N-isopropylacrylamide) [78] and poly(methyl methacrylate); as a rapid pH-responsive hydrogel. Other protein based IPN hydrogels are composed of fibrin with poly(ethylene glycol) or hyaluronic acid [95] or soy protein [109]. Silk fibroin as a fibrous protein with chains of connected polypeptides via disulfide was utilized to prepare IPN hydrogels. The resulting fiber is a promising material to be involved in biomaterials. This is due to its reasonable mechanical strength in wet media. In addition, it is biocompatible for implanting cells and resistant against enzymatic disintegration. Poly(N-isopropylacrylamide) hydrogels show acceptable mechanical properties with a slow deswelling rate. Hence they can be used in tissue engineering and regenerative medicine. This results from composing a skin layer. It opposes releasing internal water molecules in the deswelling process which is known as skin effect.

4. SOME APPLICATIONS FOR IPNs

4.1. Drug delivery applications.

IPNs of polysaccharides are nominated as efficient materials for drug delivery implication. They possess high mechanical properties when compared to single drug delivery polymers. IPN based on methylcellulose and chitosan was employed for controlled release of theophylline with an acceptable antiasthmatic effect [110]. IPN gels were also synthesized from carboxymethyl cellulose and kappa-carrageenan. Genipin was used as a crosslinker to change the drug release process of beta-carotene [111]. Egg white showed a novel IPN hydrogel when blended with carboxymethyl cellulose coated with folic acid-egg white. Cyclophosphamide was introduced to this gel as an anticancer drug. This gel was utilized to treat breast cancer. Releasing cyclophosphamide from folic acid/egg white

cyclophosphamide (IPN-NPs) showed a fast release and pH sensitivity pH 5 and 6 [112]. Poly(vinyl alcohol) was blended with poly(acrylic acid) to produce IPN hydrogels. The swelling capacity, thermal stability and biodegradability were investigated. The prepared hydrogel demonstrated higher swelling at intestinal pH than that of the stomach. The existence of NaCl in the hydrophilic hydrogels boosted swelling behavior. The prepared nontoxic gels showed promising results for drug delivery applications referring to their swelling properties and biodegradability [113].

4.2. Medical applications.

Interpenetrating hydrogels were used in some medical applications mainly for neuronal applications. They were employed in supporting neural stem cells. Signals to stem cell can be reinforced by developing substrates able to coordinate these signals. Efficient biomimetic IPNs can act as synthetic and efficient stand for culturing adult neural stem cells. IPNs were adjusted with cell-binding ligands from bone protein and laminin. They were tested to regulate self-renewal and show the ability to differentiate in dose dependency [114]. Various human neural cells were cultured in different hydrogel 3D scaffolds. The results illustrated that no single hydrogel exceeds the other hydrogels. Collagen and hyaluronan with poly(vinyl alcohol) were mingled to form an interpenetrating network (IPN) hydrogel. This IPN gel merges cell supportiveness of the collagen gel with the stability of the prepared hydrogel. The adhesion of neurons varies from that of the fibroblasts. The results showed that the synthesized hydrogel acts as a proper scaffold for neuronal cells [115]. Many humans suffer from blindness as a result of corneal diseases. Treatment for this problem may arise in the form of artificial corneal transplantation. This can be obtained through tissue-engineered corneas or synthetic corneal prostheses. Poly(ethylene glycol) and poly(acrylic acid) IPNs were synthesized and molded. The produced transparent hydrogel was removed softly from the mold. It had a homogeneous and smooth texture. The prepared IPNs showed good swelling properties. Their water content extended up to 90% [116]. Artificial corneal scaffolds based on poly(vinyl alcohol), silk fibroin and hydroxyapatite in the presence of genipin as crosslinker were tailored to replace damaged cornea. This IPN gel was a successful medical material to act as an alternate for artificial cornea scaffold matrix. The physiological properties of hydrogel were explored. The prepared hydrogels showed promising physical features. The thermal stability and tensile properties showed progress [117].

4.3. Tissue engineering application.

It is essential to synthesize scaffolds able to repair or replace damaged tissues. Interpenetrating hydrogel networks can be selected as promising materials with their three-dimensional structure to be used as tissue engineering scaffolds for cell encapsulation. This results from their high water content in addition to being capable of imitating the native extracellular material. Gelatin methacrylate and silk fibroin based IPN hydrogels were synthesized and crosslinked to show structural and biological properties. This study presented promising photocrosslinkable IPN hydrogels. They have strong mechanical properties and able to be used in tissue engineering applications [118]. Biodegradable interpenetrating network hydrogels were prepared from the gelatin and hyaluronic acid to resemble an alternative for natural cartilage matrix. Poly(ethylene glycol) diacrylate was blended with agarose to form a novel IPN hydrogel with improved mechanical properties. The viability of these gels was tested to show successful results. Encapsulating cells in these hydrogels provided favorable alternatives to be used in repairing disordered cartilages. This process may be employed to produce different cell-based IPNs. This can be achieved by changing monomers and their concentrations. In addition, introducing functional groups may contribute to improving the properties of these hydrogels [119].

4.4. Food packaging application.

Plastics are commonly used as convenient materials for packaging purposes. This results from their availability at a low cost. Moreover, they resist water and dirts with acceptable mechanical, optical, thermal and barrier properties. The disadvantages of using plastics are the difficulty in recycling them besides being non-biodegradable materials. Interpenetrating hydrogels can act as suitable alternatives for conventional plastics in packaging implementations. Using interpenetrating hydrogels in packaging applications allows the opportunity to generate hydrogels from bio-based materials. This provides a favorable approach to develop new biodegradable packaging materials. They can be used in food packaging, as there is augmenting needs towards having natural and environmentally compatible packaging materials. Cellulose interpenetrating hydrogels show considerable significance in biodegradable food packaging. Cellulose-based hydrogels consist of cellulose and its derivatives. The aforementioned materials can blend with gelatin, polyvinyl pyrrolidone or polyvinyl alcohol to offer convenient packaging food materials. Introducing bioactive substrates like silver nanoparticles and antioxidants are able to improve the properties of these hydrogel sheets [120]. Composites based on poly(vinyl alcohol) and micro- and nano-fibrillated cellulose were prepared. Inserting hydroxyethyl methacrylate with photo-initiator assisted in producing an interpenetrated polymer network with improved distribution and interfacial adhesion. The prepared IPN composites presented enhanced materials for packaging applications [121].

5. CONCLUSIONS

Interpenetrating polymeric network (IPN) hydrogels as three-dimensional network polymers are either physically or chemically entangled together. According to their classifications either as simultaneous or sequential IPNs and the structure to be homo or semi IPNs, they can be favored as promising materials for hygienic applications. The preparation procedures influence the properties of the produced IPNs. Hydrogels show biocompatibility and nontoxicity when used in biomedical applications. The swelling capacity is an important feature that allows the prepared hydrogel to perform the required application. Some disadvantages may arise such as the low mechanical properties that are suggested to be overcome. IPNs can be used in various applications that serve the human requirements like drug delivery, tissue engineering, medical and packaging applications.

Interpenetrating hydrogels can be prepared from natural or synthetic polymers. For many years, interpenetrating hydrogels invaded the medical and pharmaceutical fields. Nowadays many drug dosages are delivered and working efficiently with the aid of using IPNs. These hydrogels are based on natural polymers that are favored as biocompatible and degradable materials. Some IPNs and semi-IPNs are created by mixing natural with synthetic polymers to generate novel hydrogels. The aforementioned materials have superior mechanical and biomaterials with enhanced rheological properties. This allows these gels to mimic natural tissues with favorable performance to be used in tissue engineering implications. Besides, IPNs act as successful materials used in packaging applications.

6. REFERENCES

1. Mi, F.L.; Tan, Y.C.; Liang, H.F.; Sung, H.W. In vivo biocompatibility and degradability of a novel injectable-chitosan-based implant. *Biomaterials* **2002**, *23*, 181-191, https://doi.org/10.1016/S0142-9612(01)00094-1.
2. Das, S.; Subuddhi, U. Controlled delivery of ibuprofen from poly (vinyl alcohol)− poly (ethylene glycol) interpenetrating polymeric network hydrogels. *Journal of pharmaceutical analysis* **2019**, *9*, 108-116, https://doi.org/10.1016/j.jpha.2018.11.007.
3. Karbarz, M.; Khalil, A.M.; Wolowicz, K.; Kaniewska, K.; Romanski, J.; Stojek, Z. Efficient removal of cadmium and lead ions from water by hydrogels modified with cystine. *Journal of environmental chemical engineering* **2018**, *6*, 3962-3970, https://doi.org/10.1016/j.jece.2018.05.054.
4. Jana, S.; Sharma, R.; Maiti, S.; Sen, K.K. Interpenetrating hydrogels of O-carboxymethyl Tamarind gum and alginate for monitoring delivery of acyclovir. *International journal of biological macromolecules* **2016**, *92*, 1034-1039, https://doi.org/10.1016/j.ijbiomac.2016.08.017.
5. Martinez-Martinez, M.; Rodriguez-Berna, G.; Gonzalez-Alvarez, I.; Hernandez, M.A.J.; Corma, A.; Bermejo, M.; Merino, V.; Gonzalez-Alvarez, M. Ionic hydrogel based on chitosan cross-linked with 6-phosphogluconic trisodium salt as a drug delivery system. *Biomacromolecules* **2018**, *19*, 1294-1304, https://doi.org/10.1021/acs.biomac.8b00108.
6. Hoffman, A.S. Hydrogels for biomedical applications. *Advanced drug delivery reviews* **2012**, *64*, 18-23, https://doi.org/10.1016/j.addr.2012.09.010.
7. Yu, S.; Zhang, X.; Tan, G.; Tian, L.; Liu, D.; Liu, Y.; Yang, X.; Pan, W. A novel pH-induced thermosensitive hydrogel composed of carboxymethyl chitosan and poloxamer cross-linked by glutaraldehyde for ophthalmic drug delivery. *Carbohydrate polymers* **2017**, *155*, 208-217, https://doi.org/10.1016/j.carbpol.2016.08.073.
8. Chen, J.; Shi, X.; Ren, L.; Wang, Y. Graphene oxide/PVA inorganic/organic interpenetrating hydrogels with excellent mechanical properties and biocompatibility. *Carbon* **2017**, *111*, 18-27, https://doi.org/10.1016/j.carbon.2016.07.038.
9. Feig, V.R.; Tran, H.; Lee, M.; Bao, Z. Mechanically tunable conductive interpenetrating network hydrogels that mimic the elastic moduli of biological tissue. *Nature communications* **2018**, *9*, 2740, https://doi.org/10.1038/s41467-018-05222-4.
10. Jayaramudu, T.; Ko, H.U.; Kim, H.C.; Kim, J.W.; Li, Y.; Kim, J. Transparent and semi-interpenetrating network P (vinyl alcohol)-P (Acrylic acid) hydrogels: pH responsive and electroactive application. *International Journal of Smart and Nano Materials* **2017**, *8*, 80-94, https://doi.org/10.1080/19475411.2017.1335247.
11. Kaniewska, K.; Karbarz, M.; Stojek, Z. Electrochemical attachment of thermo-and pH sensitive interpenetrating-polymers-network hydrogel to conducting surface. *Electrochimica Acta* **2015**, *179*, 372-378, https://doi.org/10.1016/j.electacta.2015.02.196.
12. Kim, A.R.; Lee, S.L.; Park, S.N. Properties and in vitro drug release of pH-and temperature-sensitive double cross-linked interpenetrating polymer network hydrogels based on hyaluronic acid/poly (N-isopropylacrylamide) for transdermal delivery of luteolin. *International journal of biological macromolecules* **2018**, *118*, 731-740, https://doi.org/10.1016/j.ijbiomac.2018.06.061.
13. Puchot, L.; Verge, P.; Peralta, S.; Habibi, Y.; Vancaeyzeele, C.; Vidal, F. Elaboration of bio-epoxy/benzoxazine interpenetrating polymer networks: a composition-to-morphology mapping. *Polymer Chemistry* **2018**, *9*, 472-481, https://doi.org/10.1039/C7PY01755C.
14. Wang, J.J.; Liu, F. Enhanced adsorption of heavy metal ions onto simultaneous interpenetrating polymer network hydrogels synthesized by UV irradiation. *Polymer bulletin* **2013**, *70*, 1415-1430, https://doi.org/10.1007/s00289-013-0934-z .
15. Myung, D.; Waters, D.; Wiseman, M.; Duhamel, P.E.; Noolandi, J.; Ta, C.N.; Frank, C.W. Progress in the development of interpenetrating polymer network hydrogels. *Polymers for advanced technologies* **2008**, *19*, 647-657, https://doi.org/10.1002/pat.1134.
16. Cao, J.; Tan, Y.; Che, Y.; Xin, H. Novel complex gel beads composed of hydrolyzed polyacrylamide and chitosan: An effective adsorbent for the removal of heavy metal from aqueous solution. *Bioresource technology* **2010**, *101*, 2558-2561, https://doi.org/10.1016/j.biortech.2009.10.069.
17. Fakhre, N.A.; Ibrahim, B.M. The use of new chemically modified cellulose for heavy metal ion adsorption. *Journal of hazardous materials* **2018**, *343*, 324-331, https://doi.org/10.1016/j.jhazmat.2017.08.043.
18. Butnaru, E.; Cheaburu, C.N.; Yilmaz, O.; Pricope, G.M.; Vasile, C. Poly (vinyl alcohol)/chitosan/montmorillonite nanocomposites for food packaging applications: Influence of montmorillonite content. *High Performance Polymers* **2016**, *28*, 1124-1138, https://doi.org/10.1177/0954008315617231.
19. Perumal, S.; Atchudan, R.; Yoon, D.H.; Joo, J.; Cheong, I.W. Spherical Chitosan/Gelatin Hydrogel Particles for Removal of Multiple Heavy Metal Ions from Wastewater. *Industrial & Engineering Chemistry Research* **2019**, *58*, 9900-9907, https://doi.org/10.1021/acs.iecr.9b01298.
20. Udeni Gunathilake, T.; Ching, Y.; Chuah, C. Enhancement of curcumin bioavailability using nanocellulose reinforced chitosan hydrogel. *Polymers* **2017**, *9*, 64, https://doi.org/10.3390/polym9020064.
21. Soni, S.R.; Ghosh, A. Exploring pullulan-poly (vinyl alcohol) interpenetrating network microspheres as controlled release drug delivery device. *Carbohydrate polymers* **2017**, *174*, 812-822, https://doi.org/10.1016/j.carbpol.2017.07.016.
22. Pal, D.; Nayak, A.K.; Saha, S. Interpenetrating polymer network hydrogels of chitosan: applications in controlling drug release. *Cellulose-Based Superabsorbent Hydrogels* **2018**, 1-41, https://doi.org/10.1007/978-3-319-76573-0_57-1.
23. Jabeen, S.; Islam, A.; Ghaffar, A.; Gull, N.; Hameed, A.; Bashir, A.; Jamil, T.; Hussain, T. Development of a novel pH sensitive silane crosslinked injectable hydrogel for controlled release of neomycin sulfate. *International journal of biological macromolecules* **2017**, *97*, 218-227, https://doi.org/10.1016/j.ijbiomac.2017.01.014.

24. Mukhopadhyay, P.; Maity, S.; Mandal, S.; Chakraborti, A.S.; Prajapati, A.K.; Kundu, P.P. Preparation, characterization and in vivo evaluation of pH sensitive, safe quercetin-succinylated chitosan-alginate core-shell-corona nanoparticle for diabetes treatment. *Carbohydrate polymers* **2018**, *182*, 42-51, https://doi.org/10.1016/j.carbpol.2017.10.098.
25. Chen, S.C.; Wu, Y.C.; Mi, F.L.; Lin, Y.H.; Yu, L.C.; Sung, H.W. A novel pH-sensitive hydrogel composed of N, O-carboxymethyl chitosan and alginate cross-linked by genipin for protein drug delivery. *Journal of Controlled Release* **2004**, *96*, 285-300, https://doi.org/10.1016/j.jconrel.2004.02.002.
26. Sampath, U.T.M.; Ching, Y.C.; Chuah, C.H.; Singh, R.; Lin, P.C. Preparation and characterization of nanocellulose reinforced semi-interpenetrating polymer network of chitosan hydrogel. *Cellulose* **2017**, *24*, 2215-2228, https://doi.org/10.1007/s10570-017-1251-8.
27. Kim, S.J.; Shin, S.R.; Lee, Y.M.; Kim, S.I. Swelling characterizations of chitosan and polyacrylonitrile semi-interpenetrating polymer network hydrogels. *Journal of applied polymer science* **2003**, *87*, 2011-2015, https://doi.org/10.1002/app.11699.
28. Lu, S.; Liu, M.; Ni, B.; Gao, C. A novel pH-and thermo-sensitive PVP/CMC semi-IPN hydrogel: Swelling, phase behavior, and drug release study. *Journal of Polymer Science Part B: Polymer Physics* **2010**, *48*, 1749-1756, https://doi.org/10.1002/polb.22040.
29. Yang, H.; Lopina, S.T. Extended release of a novel antidepressant, venlafaxine, based on anionic polyamidoamine dendrimers and poly (ethylene glycol)-containing semi-interpenetrating networks. *Journal of Biomedical Materials Research Part A* **2005**, *72*, 107-114, https://doi.org/10.1002/jbm.a.30220.
30. Sun, X.F.; Zeng, Q.; Wang, H.; Hao, Y. Preparation and swelling behavior of pH/temperature responsive semi-IPN hydrogel based on carboxymethyl xylan and poly (N-isopropyl acrylamide). *Cellulose* **2019**, *26*, 1909-1922, https://doi.org/10.1007/s10570-018-2180-x.
31. Li, B.; Zhong, Q.; Li, D.; Xu, K.; Zhang, L.; Wang, J. Influence of Ethylene Glycol Methacrylate to the Hydration and Transition Behaviors of Thermo-Responsive Interpenetrating Polymeric Network Hydrogels. *Polymers* **2018**, *10*, 128, https://doi.org/10.3390/polym10020128.
32. Mohamadnia, Z.; Zohuriaan-Mehr, M.J.; Kabiri, K.; Jamshidi, A.; Mobedi, H. pH-sensitive IPN hydrogel beads of carrageenan-alginate for controlled drug delivery. *Journal of Bioactive and Compatible Polymers* **2007**, *22*, 342-356, https://doi.org/10.1177/0883911507078519.
33. Ghosh, S.K.; Das, A.; Basu, A.; Halder, A.; Das, S.; Basu, S.; Abdullah, M.F.; Mukherjee, A.; Kundu, S. Semi-interpenetrating hydrogels from carboxymethyl guar gum and gelatin for ciprofloxacin sustained release. *International journal of biological macromolecules* **2018**, *120*, 1823-1833, https://doi.org/10.1016/j.ijbiomac.2018.09.212.
34. Mandal, B.B.; Kapoor, S.; Kundu, S.C. Silk fibroin/polyacrylamide semi-interpenetrating network hydrogels for controlled drug release. *Biomaterials* **2009**, *30*, 2826-2836, https://doi.org/10.1016/j.biomaterials.2009.01.040.
35. Slaughter, B.V.; Blanchard, A.T.; Maass, K.F.; Peppas, N.A. Dynamic swelling behavior of interpenetrating polymer networks in response to temperature and pH. *Journal of applied polymer science* **2015**, *132*, https://doi.org/10.1002/app.42076.
36. Bukhari, S.M.H.; Khan, S.; Rehanullah, M.; Ranjha, N.M. Synthesis and characterization of chemically cross-linked acrylic acid/gelatin hydrogels: effect of pH and composition on swelling and drug release. *International Journal of Polymer Science* **2015**, *2015*, http://dx.doi.org/10.1155/2015/187961.
37. Brahima, S.; Boztepe, C.; Kunkul, A.; Yuceer, M. Modeling of drug release behavior of pH and temperature sensitive poly (NIPAAm-co-AAc) IPN hydrogels using response surface methodology and artificial neural networks. *Materials Science and Engineering: C* **2017**, *75*, 425-432, https://doi.org/10.1016/j.msec.2017.02.081.
38. Wei, J.; Low, Z.X.; Ou, R.; Simon, G.P.; Wang, H. Hydrogel-polyurethane interpenetrating network material as an advanced draw agent for forward osmosis process. *Water research* **2016**, *96*, 292-298, https://doi.org/10.1016/j.watres.2016.03.072.
39. Shahrousvand, M.; Ghollasi, M.; Zarchi, A.A.K.; Salimi, A. Osteogenic differentiation of hMSCs on semi-interpenetrating polymer networks of polyurethane/poly (2-hydroxyethyl methacrylate)/cellulose nanowhisker scaffolds. *International journal of biological macromolecules* **2019**, *138*, 262-271, https://doi.org/10.1016/j.ijbiomac.2019.07.080.
40. Nair, A.V.; Raman, M.; Doble, M. Polysaccharide-based hydrogels for targeted drug delivery. In: *Materials for Biomedical Engineering* **2019**, 343-382, https://doi.org/10.1016/B978-0-12-818435-6.00013-X.
41. Gyles, D.A.; Castro, L.D.; Silva Jr, J.O.C.; Ribeiro-Costa, R.M. A review of the designs and prominent biomedical advances of natural and synthetic hydrogel formulations. *European Polymer Journal* **2017**, *88*, 373-392, https://doi.org/10.1016/j.eurpolymj.2017.01.027.
42. Matricardi, P.; Pontoriero, M.; Coviello, T.; Casadei, M.A.; Alhaique, F. In situ cross-linkable novel alginate-dextran methacrylate IPN hydrogels for biomedical applications: mechanical characterization and drug delivery properties. *Biomacromolecules* **2008**, *9*, 2014-2020, https://doi.org/10.1021/bm800252c.
43. Vitale, A.; Cominotti, M.; Ameduri, B.; Bongiovanni, R. Semi-interpenetrating polymer networks by cationic photopolymerization: Fluorinated vinyl ether chains in a hydrogenated vinyl ether network. *European Polymer Journal* **2016**, *82*, 122-131, https://doi.org/10.1016/j.eurpolymj.2016.07.009.
44. Hao, P.; Zhao, T.; Wang, L.; Liu, S.; Tang, E.; Xu, X. IPN structured UV-induced peelable adhesive tape prepared by isocyanate terminated urethane oligomer crosslinked acrylic copolymer and photo-crosslinkable trifunctional acrylic monomer. *Progress in Organic Coatings* **2019**, *137*, 105281, https://doi.org/10.1016/j.porgcoat.2019.105281.
45. Lim, L.; Rosli, N.; Ahmad, I.; Mat Lazim, A.; Mohd Amin, M. Synthesis and swelling behavior of pH-sensitive semi-IPN superabsorbent hydrogels based on poly (acrylic acid) reinforced with cellulose nanocrystals. *Nanomaterials* **2017**, *7*, 399, https://doi.org/10.3390/nano7110399.
46. Li, G.; Zhang, G.; Sun, R.; Wong, C.P. Dually pH-responsive polyelectrolyte complex hydrogel composed of polyacrylic acid and poly (2-(dimthylamino) ethyl methacrylate). *Polymer* **2016**, *107*, 332-340, https://doi.org/10.1016/j.polymer.2016.11.037.
47. Orakdogen, N.; Sanay, B. Poly (Hydroxypropyl methacrylate-co-glycidyl methacrylate): Facile synthesis of well-defined hydrophobic gels containing hydroxy-functional methacrylates. *Polymer Degradation and Stability* **2017**, *144*, 251-263, https://doi.org/10.1016/j.polymdegradstab.2017.08.020.
48. Feng, Z.; Zuo, H.; Gao, W.; Ning, N.; Tian, M.; Zhang, L. A Robust, Self-Healable, and Shape Memory Supramolecular Hydrogel by Multiple Hydrogen Bonding Interactions. *Macromolecular rapid communications* **2018**, *39*, 1800138, https://doi.org/10.1002/marc.201800138.
49. El-Sherbiny, I.M.; Lins, R.J.; Abdel-Bary, E.M.; Harding, D.R.K. Preparation, characterization, swelling and in vitro drug

release behaviour of poly [N-acryloylglycine-chitosan] interpolymeric pH and thermally-responsive hydrogels. *European Polymer Journal* **2005**, *41*, 2584-2591, https://doi.org/10.1016/j.eurpolymj.2005.05.035.
50. Mao, Y.; Li, X.; Chen, G.; Wang, S. Thermosensitive hydrogel system with paclitaxel liposomes used in localized drug delivery system for in situ treatment of tumor: better antitumor efficacy and lower toxicity. *Journal of pharmaceutical sciences* **2016**, *105*, 194-204, https://doi.org/10.1002/jps.24693.
51. Zhu, W.; Song, Z.; Wei, P.; Meng, N.; Teng, F.; Yang, F.; Liu, N.; Feng, R. Y-shaped biotin-conjugated poly (ethylene glycol)–poly (epsilon-caprolactone) copolymer for the targeted delivery of curcumin. *Journal of colloid and interface science* **2015**, *443*, 1-7, https://doi.org/10.1016/j.jcis.2014.11.073.
52. Pelegrino, M.; de Araujo Lima, B.; do Nascimento, M.; Lombello, C.; Brocchi, M.; Seabra, A. Biocompatible and Antibacterial Nitric Oxide-Releasing Pluronic F-127/Chitosan Hydrogel for Topical Applications. *Polymers* **2018**, *10*, 452, https://doi.org/10.3390/polym10040452.
53. Su, F.; Wang, Y.; Liu, X.; Shen, X.; Zhang, X.; Xing, Q.; Wang, L.; Chen, Y. Biocompatibility and in vivo degradation of chitosan based hydrogels as potential drug carrier. *Journal of Biomaterials Science, Polymer Edition* **2018**, *29*, 1515-1528, https://doi.org/10.1080/09205063.2017.1412244.
54. Hu, C.; Wang, M.X.; Sun, L.; Yang, J.H.; Zrinyi, M.; Chen, Y.M. Dual-Physical Cross-Linked Tough and Photoluminescent Hydrogels with Good Biocompatibility and Antibacterial Activity. *Macromolecular rapid communications* **2017**, *38*, 1600788, https://doi.org/10.1002/marc.201600788.
55. Zarghami, Z.; Akbari, A.; Latifi, A.M.; Amani, M.A. Design of a new integrated chitosan-PAMAM dendrimer biosorbent for heavy metals removing and study of its adsorption kinetics and thermodynamics. *Bioresource technology* **2016**, *205*, 230-238, https://doi.org/10.1016/j.biortech.2016.01.052.
56. Habiba, U.; Siddique, T.A.; Joo, T.C.; Salleh, A.; Ang, B.C.; Afifi, A.M. Synthesis of chitosan/polyvinyl alcohol/zeolite composite for removal of methyl orange, Congo red and chromium (VI) by flocculation/adsorption. *Carbohydrate polymers* **2017**, *157*, 1568-1576, https://doi.org/10.1016/j.carbpol.2016.11.037.
57. Shariful, M.I.; Sharif, S.B.; Lee, J.J.L.; Habiba, U.; Ang, B.C.; Amalina, M.A. Adsorption of divalent heavy metal ion by mesoporous-high surface area chitosan/poly (ethylene oxide) nanofibrous membrane. *Carbohydrate polymers* **2017**, *157*, 57-64, https://doi.org/10.1016/j.carbpol.2016.09.063.
58. Li, Z.; Li, L.; Hu, D., Gao, C., Xiong, J., Jiang, H., & Li, W. Efficient removal of heavy metal ions and organic dyes with cucurbit [8] uril-functionalized chitosan. *Journal of colloid and interface science* **2019**, *539*, 400-413, https://doi.org/10.1016/j.jcis.2018.12.078.
59. Yadollahi, M.; Farhoudian, S.; Namazi, H. One-pot synthesis of antibacterial chitosan/silver bio-nanocomposite hydrogel beads as drug delivery systems. *International journal of biological macromolecules* **2015**, *79*, 37-43, https://doi.org/10.1016/j.ijbiomac.2015.04.032.
60. Ishihara, M.; Obara, K.; Nakamura, S.; Fujita, M.; Masuoka, K.; Kanatani, Y.; Maehara, T. Chitosan hydrogel as a drug delivery carrier to control angiogenesis. *Journal of Artificial Organs* **2006**, *9*, 8-16, https://doi.org/10.1007/s10047-005-0313-0.
61. Li, J.; Mooney, D. J. Designing hydrogels for controlled drug delivery. *Nature Reviews Materials* **2016**, *1*, 16071, https://doi.org/10.1038/natrevmats.2016.71.
62. Xu, J.; Strandman, S.; Zhu, J.X.; Barralet, J.; Cerruti, M. Genipin-crosslinked catechol-chitosan mucoadhesive hydrogels for buccal drug delivery. *Biomaterials* **2015**, *37*, 395-404, https://doi.org/10.1016/j.biomaterials.2014.10.024.
63. Yang, J.; Chen, J.; Pan, D.; Wan, Y.; Wang, Z. pH-sensitive interpenetrating network hydrogels based on chitosan derivatives and alginate for oral drug delivery. *Carbohydrate polymers* **2013**, *92*, 719-725, https://doi.org/10.1016/j.carbpol.2012.09.036.
64. He, J.; Sun, F.; Han, F.; Gu, J.; Ou, M.; Xu, W.; Xu, X. Preparation of a novel polyacrylic acid and chitosan interpenetrating network hydrogel for removal of U (vi) from aqueous solutions. *RSC advances* **2018**, *8*, 12684-12691, https://doi.org/10.1039/C7RA13065A.
65. Wu, Y.; Liang, J.; Horkay, F.; Libera, M. Antimicrobial loading into and release from poly (ethylene glycol)/poly (acrylic acid) semi-interpenetrating hydrogels. *Journal of Polymer Science Part B: Polymer Physics* **2016**, *54*, 64-72, https://doi.org/10.1002/polb.23924.
66. Toledo, P.V.; Limeira, D.P.; Siqueira, N.C.; Petri, D.F. Carboxymethyl cellulose/poly (acrylic acid) interpenetrating polymer network hydrogels as multifunctional adsorbents. *Cellulose* **2019**, *26*, 597-615, https://doi.org/10.1007/s10570-018-02232-9.
67. Nayak, A.K.; Pal, D. Chitosan-based interpenetrating polymeric network systems for sustained drug release. In: *Advanced Theranostics Materials* 2015; pp. 183-208, WILEY-Scrivener USA, https://doi.org/10.1002/9781118998922.ch7.
68. Qi, X.; Li, J.; Wei, W.; Zuo, G.; Su, T.; Pan, X., Zhang. J.; Dong, W. Cationic Salecan-based hydrogels for release of 5-fluorouracil. *RSC advances* **2017**, *7*, 14337-14347, https://doi.org/10.1039/C7RA01052D.
69. Qi, X.; Wei, W.; Li, J.; Liu, Y.; Hu, X.; Zhang, J.; Bi, L.; Dong, W. Fabrication and characterization of a novel anticancer drug delivery system: salecan/poly (methacrylic acid) semi-interpenetrating polymer network hydrogel. *ACS Biomaterials Science & Engineering* **2015**, *1*, 1287-1299, https://doi.org/10.1021/acsbiomaterials.5b00346.
70. Chen, S.; Liu, M.; Jin, S.; Chen, Y. Synthesis and swelling properties of pH-sensitive hydrogels based on chitosan and poly (methacrylic acid) semi-interpenetrating polymer network. *Journal of applied polymer science* **2005**, *98*, 1720-1726, https://doi.org/10.1002/app.22348.
71. Ng, W.L.; Yeong, W.Y.; Naing, M.W. Development of polyelectrolyte chitosan-gelatin hydrogels for skin bioprinting. *Procedia CIRP* **2016**, *49*, 105-112, https://doi.org/10.1016/j.procir.2015.09.002.
72. Kim, S.J.; Shin, S.R.; Spinks, G.M.; Kim, I.Y.; Kim, S.I. Synthesis and characteristics of a semi-interpenetrating polymer network based on chitosan/polyaniline under different pH conditions. *Journal of Applied Polymer Science* **2005**, *96*, 867-873, https://doi.org/10.1002/app.21524.
73. Kim, S.J.; Yoon, S.G.; Kim, I.Y.; Kim, S.I. Swelling characterization of the semiinterpenetrating polymer network hydrogels composed of chitosan and poly (diallyldimethylammonium chloride). *Journal of applied polymer science* **2004**, *91*, 2876-2880, https://doi.org/10.1002/app.13516.
74. Dragan, E.S. Design and applications of interpenetrating polymer network hydrogels. A review. *Chemical Engineering Journal* **2014**, *243*, 572-590, https://doi.org/10.1016/j.cej.2014.01.065.
75. Guo, B.; Yuan, J.; Yao, L.; Gao, Q. Preparation and release profiles of pH/temperature-responsive carboxymethyl chitosan/P (2-(dimethylamino) ethyl methacrylate) semi-IPN amphoteric hydrogel. *Colloid and Polymer Science* **2007**, *285*, 665-671, https://doi.org/10.1007/s00396-006-1611-7.
76. Varaprasad, K.; Reddy, N.N.; Kumar, N.M.; Vimala, K.; Ravindra, S.; Raju, K.M. Poly (acrylamide-chitosan) hydrogels: Interaction with surfactants. *International Journal of*

Polymeric Materials **2010**, *59*, 981-993, https://doi.org/10.1080/00914037.2010.504147.
77. Zhou, C.; Wu, Q. A novel polyacrylamide nanocomposite hydrogel reinforced with natural chitosan nanofibers. *Colloids and Surfaces B: Biointerfaces* **2011**, *84*, 155-162, https://doi.org/10.1016/j.colsurfb.2010.12.030.
78. Fernandez-Gutierrez, M.; Fusco, S.; Mayol, L.; San Roman, J.; Borzacchiello, A.; Ambrosio, L. Stimuli-responsive chitosan/poly (N-isopropylacrylamide) semi-interpenetrating polymer networks: effect of pH and temperature on their rheological and swelling properties. *Journal of Materials Science: Materials in Medicine* **2016**, *27*, 109, https://doi.org/10.1007/s10856-016-5719-0.
79. Alvarez-Lorenzo, C.; Concheiro, A.; Dubovik, A.S.; Grinberg, N.V.; Burova, T.V.; Grinberg, V.Y. Temperature-sensitive chitosan-poly (N-isopropylacrylamide) interpenetrated networks with enhanced loading capacity and controlled release properties. *Journal of Controlled Release* **2005**, *102*, 629-641, https://doi.org/10.1016/j.jconrel.2004.10.021.
80. Ma, G.; Yang, D.; Li, Q.; Wang, K.; Chen, B.; Kennedy, J.F.; Nie, J. Injectable hydrogels based on chitosan derivative/polyethylene glycol dimethacrylate/N, N-dimethylacrylamide as bone tissue engineering matrix. *Carbohydrate Polymers* **2010**, *79*, 620-627, https://doi.org/10.1016/j.carbpol.2009.09.015.
81. Babu, V.R.; Hosamani, K.M., Aminabhavi, T.M. Preparation and in-vitro release of chlorothiazide novel pH-sensitive chitosan-N, N′-dimethylacrylamide semi-interpenetrating network microspheres. *Carbohydrate Polymers* **2008**, *71*, 208-217, https://doi.org/10.1016/j.carbpol.2007.05.039.
82. Babu, V.R.; Kim, C.; Kim, S.; Ahn, C.; Lee, Y.I. Development of semi-interpenetrating carbohydrate polymeric hydrogels embedded silver nanoparticles and its facile studies on E. coli. *Carbohydrate Polymers* **2010**, *81*, 196-202, https://doi.org/10.1016/j.carbpol.2010.02.050.
83. Garcia, J.; Ruiz-Durantez, E.; Valderruten, N.E. Interpenetrating polymer networks hydrogels of chitosan and poly (2-hydroxyethyl methacrylate) for controlled release of quetiapine. *Reactive and Functional Polymers* **2017**, *117*, 52-59, https://doi.org/10.1016/j.reactfunctpolym.2017.06.002.
84. Tripathi, A.; Kumar, A. Multi-Featured Macroporous Agarose–Alginate Cryogel: Synthesis and Characterization for Bioengineering Applications. *Macromolecular bioscience* **2011**, *11*, 22-35, https://doi.org/10.1002/mabi.201000286.
85. Plieva, F.M.; Karlsson, M.; Aguilar, M.R.; Gomez, D.; Mikhalovsky, S.; Galaev, I.Y. Pore structure in supermacroporous polyacrylamide based cryogels. *Soft Matter* **2005**, *1*, 303-309, https://doi.org/10.1039/B510010K .
86. Li, J.; Wang, Y.; Zhang, L.; Xu, Z.; Dai, H.; Wu, W. Nanocellulose/gelatin composite cryogels for controlled drug release. *ACS Sustainable Chemistry & Engineering* **2019**, *7*, 6381-6389, https://doi.org/10.1021/acssuschemeng.9b00161.
87. Jain, E.; Kumar, A. Designing supermacroporous cryogels based on polyacrylonitrile and a polyacrylamide–chitosan semi-interpenetrating network. *Journal of Biomaterials Science, Polymer Edition* **2009**, *20*, 877-902, https://doi.org/10.1163/156856209X444321.
88. Samanta, H.S.; Ray, S.K. Synthesis, characterization, swelling and drug release behavior of semi-interpenetrating network hydrogels of sodium alginate and polyacrylamide. *Carbohydrate polymers* **2014**, *99*, 666-678, https://doi.org/10.1016/j.carbpol.2013.09.004.
89. Kim, S.J.; Yoon, S.G.; Kim, S.I. Synthesis and characteristics of interpenetrating polymer network hydrogels composed of alginate and poly (diallydimethylammonium chloride). *Journal of Applied Polymer Science* **2004**, *91*, 3705-3709, https://doi.org/10.1002/app.13615.
90. Lee, S.B.; Park, E.K.; Lim, Y.M.; Cho, S.K.; Kim, S.Y.; Lee, Y.M.; Nho, Y.C. Preparation of alginate/poly (N-isopropylacrylamide) semi-interpenetrating and fully interpenetrating polymer network hydrogels with γ-ray irradiation and their swelling behaviors. *Journal of applied polymer science* **2006**, *100*, 4439-4446, https://doi.org/10.1002/app.23726.
91. Reis, A.V.; Guilherme, M.R.; Moia, T.A.; Mattoso, L.H.; Muniz, E.C.; Tambourgi, E.B. Synthesis and characterization of a starch-modified hydrogel as potential carrier for drug delivery system. *Journal of Polymer Science Part A: Polymer Chemistry* **2008**, *46*, 2567-2574, https://doi.org/10.1002/pola.22588.
92. Kamoun, E.A. N-succinyl chitosan-dialdehyde starch hybrid hydrogels for biomedical applications. *Journal of Advanced research* **2016**, *7*, 69-77, https://doi.org/10.1016/j.jare.2015.02.002.
93. Li, X.; Xu, S.; Wang, J.; Chen, X.; Feng, S. Structure and characterization of amphoteric semi-IPN hydrogel based on cationic starch. *Carbohydrate Polymers* **2009**, *75*, 688-693, https://doi.org/10.1016/j.carbpol.2008.09.009.
94. Apopei, D.F.; Dinu, M.V.; Trochimczuk, A.W.; Dragan, E.S. Sorption isotherms of heavy metal ions onto semi-interpenetrating polymer network cryogels based on polyacrylamide and anionically modified potato starch. *Industrial & Engineering Chemistry Research* **2012**, *51*, 10462-10471, https://doi.org/10.1021/ie301254z.
95. Kim, S.J.; Lee, C.K.; Kim, S.I. Characterization of the water state of hyaluronic acid and poly (vinyl alcohol) interpenetrating polymer networks. *Journal of applied polymer science* **2004**, *92*, 1467-1472, https://doi.org/10.1002/app.13717.
96. Oh, S.H.; An, D.B.; Kim, T.H.; Lee, J.H. Wide-range stiffness gradient PVA/HA hydrogel to investigate stem cell differentiation behavior. *Acta biomaterialia* **2016**, *35*, 23-31, https://doi.org/10.1016/j.actbio.2016.02.016.
97. Pescosolido, L.; Schuurman, W.; Malda, J.; Matricardi, P.; Alhaique, F.; Coviello, T.; Vermonden, T. Hyaluronic acid and dextran-based semi-IPN hydrogels as biomaterials for bioprinting. *Biomacromolecules* **2011**, *12*, 1831-1838, https://doi.org/10.1021/bm200178w.
98. Chirila, T.V.; George, K.A.; Abdul Ghafor, W.A.; Pas, S.J.; Hill, A.J. Sequential homo-interpenetrating polymer networks of poly (2-hydroxyethyl methacrylate): Synthesis, characterization, and calcium uptake. *Journal of Applied Polymer Science* **2012**, *126*, E455-E466, https://doi.org/10.1002/app.36824.
99. Tang, Q.; Yu, J.R.; Chen, L.; Zhu, J.; Hu, Z.M. Porous silicone hydrogel interpenetrating polymer networks prepared using a template method for biomedical use. *Polymer International* **2011**, *60*, 1136-1141, https://doi.org/10.1002/pi.3053.
100. Varaprasad, K.; Mohan, Y.M.; Ravindra, S.; Reddy, N.N.; Vimala, K.; Monika, K.; Raju, K.M. Hydrogel–silver nanoparticle composites: a new generation of antimicrobials. *Journal of Applied Polymer Science* **2010**, *115*, 1199-1207, https://doi.org/10.1002/app.31249.
101. Kozhunova, E.Y.; Makhaeva, E.E.; Khokhlov, A.R. Collapse of thermosensitive polyelectrolyte semi-interpenetrating networks. *Polymer* **2012,** *53*, 2379-2384, https://doi.org/10.1016/j.polymer.2012.04.001.
102. Zhao, Y.; Tan, T.; Kinoshita, T. Swelling kinetics of poly (aspartic acid)/poly (acrylic acid) semi-interpenetrating polymer network hydrogels in urea solutions. *Journal of Polymer Science Part B: Polymer Physics* **2010**, *48*, 666-671, https://doi.org/10.1002/polb.21936.
103. Liu, M.; Su, H.; Tan, T. Synthesis and properties of thermo- and pH-sensitive poly (N-isopropylacrylamide)/polyaspartic acid IPN hydrogels. *Carbohydrate polymers* **2012**, *87*, 2425-2431, https://doi.org/10.1016/j.carbpol.2011.11.010.

104. Huang, Y.; Liu, M.; Wang, L.; Gao, C.; Xi, S. A novel triple-responsive poly (3-acrylamidephenylboronic acid-co-2-(dimethylamino) ethyl methacrylate)/(β-cyclodextrin-epichlorohydrin) hydrogels: Synthesis and controlled drug delivery. *Reactive and Functional Polymers* **2011**, *71*, 666-673, https://doi.org/10.1016/j.reactfunctpolym.2011.03.007.
105. Zhang, N.; Liu, M.; Shen, Y.; Chen, J.; Dai, L.; Gao, C. Preparation, properties, and drug release of thermo-and pH-sensitive poly ((2-dimethylamino) ethyl methacrylate)/poly (N, N-diethylacrylamide) semi-IPN hydrogels. *Journal of materials science* **2011**, *46*, 1523-1534, https://doi.org/10.1007/s10853-010-4957-7.
106. Wei, J.; Xu, S.; Wu, R.; Wang, J.; Gao, Y. Synthesis and characteristics of an amphoteric semi-IPN hydrogel composed of acrylic acid and poly (diallydimethylammonium chloride). *Journal of applied polymer science* **2007**, *103*, 345-350, https://doi.org/10.1002/app.24375.
107. Higa, M.; Kobayashi, M.; Kakihana, Y.; Jikihara, A.; Fujiwara, N. Charge mosaic membranes with semi-interpenetrating network structures prepared from a polymer blend of poly (vinyl alcohol) and polyelectrolytes. *Journal of membrane science* **2013**, *428*, 267-274, https://doi.org/10.1016/j.memsci.2012.10.034.
108. Krezovic, B.D.; Dimitrijevic; S.I., Filipovic; J.M., Nikolic; R.R., Tomic; S.L. Antimicrobial P (HEMA/IA)/PVP semi-interpenetrating network hydrogels. *Polymer bulletin* **2013**, *70*, 809-819, https://doi.org/10.1007/s00289-012-0830-y.
109. Liu, Y.; Cui, Y. Thermosensitive soy protein/poly (n-isopropylacrylamide) interpenetrating polymer network hydrogels for drug controlled release. *Journal of Applied Polymer Science* **2011**, *120*, 3613-3620, https://doi.org/10.1002/app.33535.
110. Rokhade, A.P.; Shelke, N.B.; Patil, S.A.; Aminabhavi, T.M. Novel interpenetrating polymer network microspheres of chitosan and methylcellulose for controlled release of theophylline. *Carbohydrate Polymers* **2007**, *69*, 678-687, https://doi.org/10.1016/j.carbpol.2007.02.008.
111. Muhamad, I.I.; Fen, L.S.; Hui, N.H.; Mustapha, N.A. Genipin-cross-linked kappa-carrageenan/carboxymethyl cellulose beads and effects on beta-carotene release. *Carbohydrate Polymers* **2011**, *83*, 1207-1212, https://doi.org/10.1016/j.carbpol.2010.09.021.
112. Raj, V.; Priya, P.; Renji, R.; Suryamathi, M.; Kalaivani, S. Folic acid–egg white coated IPN network of carboxymethyl cellulose and egg white nanoparticles for treating breast cancer. *Iranian Polymer Journal* **2018**, *27*, 721-731, https://doi.org/10.1007/s13726-018-0647-0.
113. Kim, S.J.; Park, S.J.; Kim, I.Y.; Shin, M.S.; Kim, S.I. Electric stimuli responses to poly (vinyl alcohol)/chitosan interpenetrating polymer network hydrogel in NaCl solutions. *Journal of applied polymer science* **2002**, *86*, 2285-2289, https://doi.org/10.1002/app.11215.
114. Saha, K.; Irwin, E.F.; Kozhukh, J.; Schaffer, D.V.; Healy, K.E. Biomimetic interfacial interpenetrating polymer networks control neural stem cell behavior. *Journal of Biomedical Materials Research Part A* **2007**, *81*, 240-249, https://doi.org/10.1002/jbm.a.30986.
115. Yla-Outinen, L.; Harju, V.; Joki, T.; Koivisto, J.T.; Karvinen, J.; Kellomaki, M.; Narkilahti, S. Screening of Hydrogels for Human Pluripotent Stem Cell–Derived Neural Cells: Hyaluronan-Polyvinyl Alcohol-Collagen-Based Interpenetrating Polymer Network Provides an Improved Hydrogel Scaffold. *Macromolecular bioscience* **2019**, *1900096*, https://doi.org/10.1002/mabi.201900096.
116. Liu, L.; Sheardown, H. Glucose permeable poly (dimethyl siloxane) poly (N-isopropyl acrylamide) interpenetrating networks as ophthalmic biomaterials. *Biomaterials* **2005**, *26*, 233-244, https://doi.org/10.1016/j.biomaterials.2004.02.025.
117. Zhou, H.; Wang, Z.; Cao, H.; Hu, H.; Luo, Z.; Yang, X.; Zhou, L. Genipin-crosslinked polyvinyl alcohol/silk fibroin/nano-hydroxyapatite hydrogel for fabrication of artificial cornea scaffolds—a novel approach to corneal tissue engineering. *Journal of Biomaterials Science, Polymer Edition* **2019**, *30*, 1604-1619, https://doi.org/10.1080/09205063.2019.1652418.
118. Xiao, W.; He, J.; Nichol, J.W.; Wang, L.; Hutson, C.B.; Wang, B.; Dua, Y.; Fan, H.; Khademhosseini, A. Synthesis and characterization of photocrosslinkable gelatin and silk fibroin interpenetrating polymer network hydrogels. *Acta biomaterialia* **2011**, *7*, 2384-2393, https://doi.org/10.1016/j.actbio.2011.01.016.
119. Park, H.; Choi, B.; Hu, J.; Lee, M. Injectable chitosan hyaluronic acid hydrogels for cartilage tissue engineering. *Acta biomaterialia* **2013**, *9*, 4779-4786, https://doi.org/10.1016/j.actbio.2012.08.033.
120. Amini, E.; Azadfallah, M.; Layeghi, M.; Talaei-Hassanloui, R. Silver-nanoparticle-impregnated cellulose nanofiber coating for packaging paper. *Cellulose* **2016**, *23*, 557-570, https://doi.org/10.1007/s10570-015-0846-1.
121. Bai, H.; Li, Y.; Wang, W.; Chen, G.; Rojas, O.J.; Dong, W.; Liu, X. Interpenetrated polymer networks in composites with poly (vinyl alcohol), micro-and nano-fibrillated cellulose (M/NFC) and polyHEMA to develop packaging materials. *Cellulose* **2015**, *22*, 3877-3894, https://doi.org/10.1007/s10570-015-0748-2.