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Chitosan based hydrogels: characteristics and pharmaceutical applications

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Abstract

Go to:

1. INTRODUCTION

There has been an increasing interest in developing medically relevant hydrogels. Such an interest is due to the wide range of suitable characteristics and preparation methods for hydrogels in medical and pharmaceutical industries.

Various natural and synthetic polymers have been studied in hydrogel researches. Chitosan is a natural cationic copolymer that presents well deal of interests for hydrogel structures. This polymer has hydrophilic nature with ability of degradation via human enzymes which result in biocompatibility and biodegradability, the two biological properties commonly needed for biological devices. Chitosan-based hydrogels are potentially engineering scaffolds to obtain tissue repair achievements.

Furthermore, they have been applied as delivery systems for the controlled release of therapeutic ingredients. Many polymers used in hydrogel lattices, like chitosan, exert their mucoadhesive characteri-stics via interactions between opposite charges. This specific feature can provide the ability of tissue binding for the aim of specific drug delivery (1,2). In order to improve feasibility of chitosan for medical and pharmaceutical applications, several derivatives of chitosan with different ligands such as 4-azidobenzoic acid, methyl acroloyl glycine and poly ethylene glycol have been synthesized and studied. In this review, hydrogel structure and characterization of the systems compromised from chitosan derivatives prepared using different ligands will be briefly explained. Then, specifically chitosan-based hydrogels with biomedical and biopharmaceutical applications will be discussed and their cons and pros in comparison with each other would be interpreted.

Go to:

2. Hydrogels

2.1. Definition and structure of hydrogels

Hydrogels are cross-linked networks of the same or different types of polymerswith high capacity for water absorption.

Hydrogel forming polymers have hydrophilic functional groups in their polymeric structure such as amine (NH2), hydroxyl [-OH], amide (-CONH-, -CONH2) and sulphate (-SO3 H)(3). The hydrophilic groups enable the hydrogel to absorb water and watery fluids that results in hydrogel expansion and occupation of larger volume, the process which is known as swelling. During swelling, the cross-linked structure of hydrogels prevents the dissolution and destruction of the hydrogel cross-links (4). A schematic representation of hydrogel swelling is shown in Fig. 1.

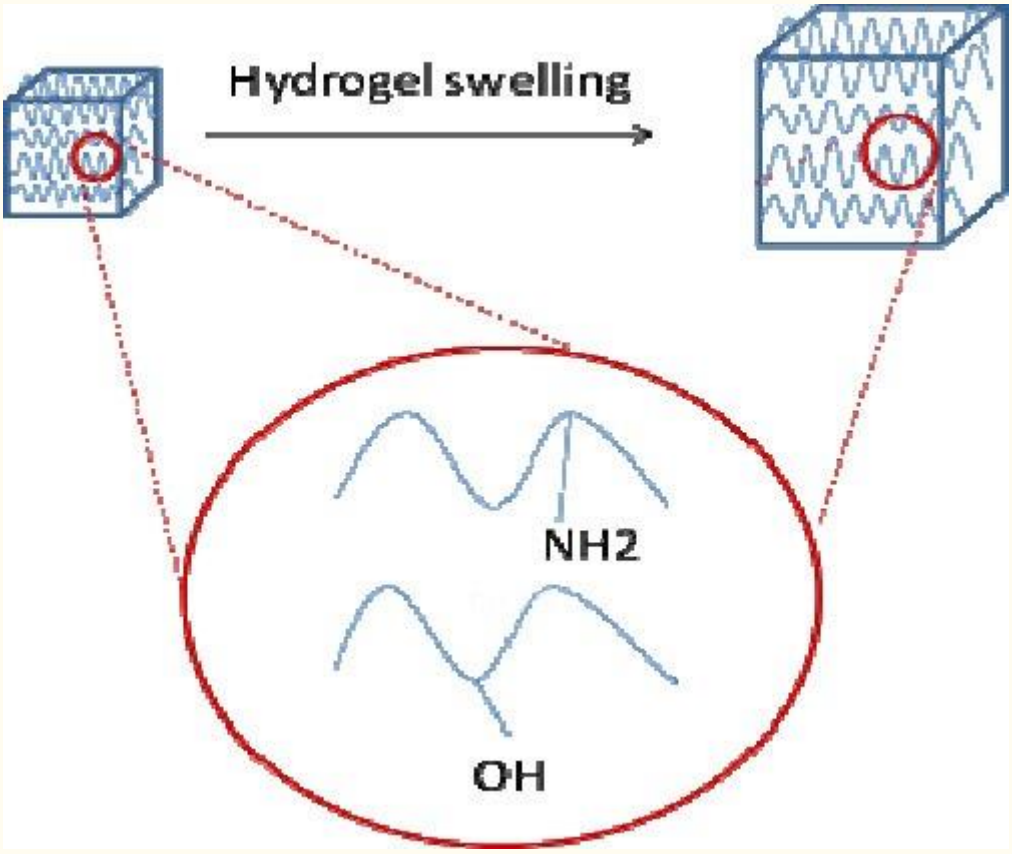


Fig. 1

A schematic representation of hydrogel construct and hydrogel swelling in water. Circle depicts some of the possible functionalities responsible for water absorption.

There are three states of water molecules in polymeric hydrogel, free, intermediate and bound water molecules. Free water molecules undergo freezing process at freezing points since no bond exists between free water and polymer functional groups. The amount of free water molecules is dependent on the hydrogel structure that ultimately influences the swelling ratio. Thereby, a compact hydrogel structure contains lower quantity of free water. Second state of water or intermediate water can form weak interactions with functional groups in polymeric chains. Hydrogen bonding between polymeric chains and water molecules forms bound water. These water molecules are nonfreezing (5).

The amount of water absorption in different types of hydrogel is varied from trivial to significant volumes. Quantity and speed of water absorption is dependent on the following factors: i) cross-linking density, ii) chemical structure of the polymers and iii) environmental conditions.

Cross-linking density, the amount of cross-linked chains, governs the hydrogel swelling ratio and is inversely proportional to water quantity. In addition, presence of hydrophilic or hydrophobic functional groups on the polymer chain determines the swelling ratio (6). Hydrogels have ability to swell in water or aqueous solutions. Because of high amount of water absorption, these structures can be similar to human body tissues.

Hydrophobic hydrogels with hydrophobic chains such as poly (Lactic acid) (PLA) or poly (Lactide-co-glycolide) (PLGA) (7) or those prepared via polymeric modifications to enhance polymer hydrophobicity (8) have lower water capacity than hydrophilic lattices. Swelling ratio of hydrophilic hydrogels varies with polymer hydrophilic density. Environmental conditions such as pH, temperature, certain chemicals (9), light, pressure and electrical field (3) are influential on hydrogel swelling. The environmental factors control the swelling kinetics and could be modified to modulate the swelling properties of the hydrogels. For example protein-based systems are susceptible to acidic gastric environment. Therefore, pH sensitive swelling hydrogels that are swollen in intestinal pH are useful devices for the purpose of oral delivery.

2.2. Classification of hydrogels

Hydrogels are classified into natural or synthetic polymeric based networks.

Natural hydrogel constructs are often made of polysaccharide or protein chains. Polysaccharides have hydrophilic structure which is a favorable property of hydrogel preparation (10). Some examples of polysaccharide-based hydrogels are hydrogels made of alginate (11), cellulose (12), chitin, chitosan (13), dextran, hyaluronic acid (14), pectin (15), starch (16) and xanthan gum.

Collagen (17), silk, keratin, elastin, resilin (18) and gelatin (19) are protein chains that form natural hydrogel lattices.

Synthetic polymers such as poly (vinyl alcohol), polyacrylamide, poly (ethylene oxide) and poly (ethylene glycol) have been used for hydrogel formation (1). Natural polymers usually present higher biocompatibility compared to synthetic polymers, as they undergo enzyme controlled biodegradation by human enzymes like lysozyme and produce biocompatible byproducts (20). On the other hand, synthetic polymers are chemically stronger than natural ones, because of hydrolysable moieties with slower degradation rate. This feature provides more prolonged lifetime in human body (21).

2.3. Formation of hydrogels

Hydrogels are prepared via chemical (permanent bonds) or physical cross-linking. Methods for chemical cross-linking of hydrogels include i) radical polymerization (22), ii) photopolymerization (23), iii) enzymatic reactions, iv), and covalent cross-linking via linkers such as aldehydes (24). In contrast, physical cross-linking forms a nonpermanent network with physical interactions such as hydrogen or electrostatic bonds, physical entanglements (25,26) and crystal formation (27). So the physically cross-linked hydrogels can be formed via ion interactions, using graft copolymers (28), crystallization and stereocomplex formation (29).

2.4. Applications of hydrogels in pharmaceutical sciences

Hydrogels are widely used in agriculture (30), food industry (31) and pharmaceutical fields (32).

In pharmaceutical area, they are applied for systemic and localized drug delivery and tissue engineering.

2.4.1. Drug delivery

Hydrogels are used as platforms for both drugs and gene delivery (33). Hydrogels can encapsulate macromolecule drugs especially proteins (34) into their polymeric chains. Polymeric network of hydrogels protects drugs from fast dissolution (35) and control release rate from matrices (36).

Hydrogels can be administered via oral, ocular, nasal, vaginal and subcutaneous routes. Table 1summarizes some of studies on applying hydrogels for drug delivery.

Table 1

Examples of applying hydrogels as drug delivery systems.

Polymer based hydrogel	Drug loaded in system	Application
Sodium carboxymethyl cellulose and poly vinyl alcohol	Diclofenac sodium	Oral drug delivery
4-arm PEG-Mal and 4-arm PEG-SH	Bevacizumab	Ocular drug delivery
N-trimethyl chitosan chloride and poly (ethylene glycol)	-	Nasal drug delivery
Poloxamer	Flavonoid of Baicalein	Vaginal drug delivery
Pluronic® F127	Recombinant hirudin variant-2 (rHV2)	Subcutaneous drug deliv
Chitosan and dextran	Vancomycin	Topical drug delivery f wound healing

Hydrogels are also utilized extensively in tissue repairs (43,44). Some examples of this application of hydrogels are presented in Table 2.

Table 2

Hydrogel applications in tissue engineering.

Polymer based hydrogel	Drug/Cell loaded in system	Application
Photo-cross-linkable methacrylated glycol chitosan	Adipose-derived stem cells	Soft tissue engineeri
Gelatin methacrylamide (Gel-MA) polymerized within PEG	-	Internal cell encapsulatic surface cell adherenc
Oligo(poly(ethylene glycol) fumarate)	Growth factor 1 and bone morphogenic protein-2	Osteochondral tissue re
Oxidized alginate and gelatin	Murine chondrocytes	Cartilage regeneration treatment of osteoarthr
Gelatin and chitosan	Cardiomyocyte	Congenital heart disease cardiac tissue engineer

Hydrogels have also been developed as artificial cartilages (50), contact lenses, artificial corneas (5), biosensors (51) and surgical aids. Synthetic materials are also applied as alternative to extracellular matrix.

Table 3 lists some of the hydrogels marketed by different companies for their clinical applications.

Table 3

Current marketed hydrogels and their applications.

Product name	Usage
Bioglue® surgical adhesive	Adjunct to standard methods of cardiac and vascular repair such as sutures provide hemostasis
SurgiSeal®	Topical skin adhesive
Derma seal	Used for transtibial amputees
Gluetiss®	Tissue adhesive in otorhinolaryngology

Go to:

3. Chitosan-based hydrogels

3.1. Chitosan

Chitosan is obtained by partial deacetylation (56) of insoluble naturally available chitin, obtained from exoskeletons of crustaceans (57), fungi and insects (58). Chitin has rigid crystalline structure due to hydrogen interactions between acetamide groups and hydroxyl groups (59). Chitin is not readily applicable due to its high level of acetylated groups and rigid structure as well as poor solubility in aqueous solutions. When chitin is partially deacetylated and converted to chitosan (Fig. 2), the amount of amino groups and its aqueous solubility is enhanced. There is

a proportional increase in chitosan deacetylation, and enhancement of bio-compatibility and biodegradability.

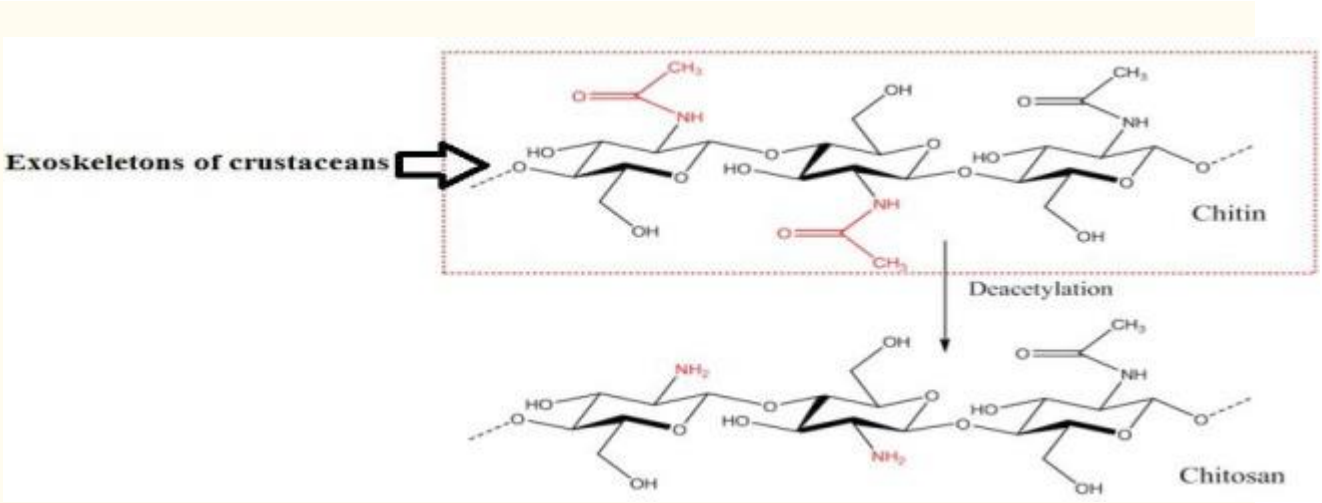


Fig. 2

Chitin is extracted from crab shell from which chitosan is made by N-deacetylation.

The polysaccharide structure of chitosan is made of glucosamine and N-acetylglucosamine. Glucosamine is generated from glucose in body and it can produce glucosaminoglycans (GAGs), which is a part of extracellular matrix and cartilage tissue (60).

The charge density of chitosan depends on degree of deacetylation which represents the amino group density. Indeed, pH of the chitosan solution represents the quantity of ionized amino groups (61).

Chitosan is a weak base with pk_a 6.5 which can be dissolved in dilute acidic medium. Because of the presence of amine and hydroxyl groups, chitosan molecules can form hydrogen bonds leading to the crystalline structure of the polymer (62).

Chitosan exists in different molecular weights and degree of acetylation. The average molecular weight of chitosan lies between 50-2000 KD. Hydrophilic polymers such as chitosan may undergo systemic absorption in human body, so the polymers should have proper molecular weight to eliminate by renal filtration. In vitro studies showed that chitosan can be degraded via several enzymes such as β-N-acetylhexosaminidase, chitosanase, chitinase and chitin deacetylase. In human body, chitosan can be biodegraded by lysozyme, acid, gastrointestinal enzymes and colon bacteria (63).

3.2. Hydrogel preparation via chitosan cross-linking

The intermolecular forces between polysaccharide chains of chitosan are hydrogen, hydrophobic and ionic interactions. These interactions are influenced by molecular weight and ionic strength (64).

Cross-linking of chitosan polymers is necessary to improve chitosan properties such as stability and durability for the aim of drug delivery. Chitosan based hydrogel networks are categorized based on the method of chitosan cross-linking and preparation.

3.2.1. Preparation of chitosan hydrogels via chemical cross-linking

Chemically cross-linked hydrogels are formed by covalent linking of the chitosan macromers, where the bond formation is irreversible. Chemical cross-linked hydrogels are found in four states of formation, a) chitosan cross-linked system, b) hybrid polymer networks (HPN), c) interpenetrating polymer networks (IPN), and d) semi interpenetrating polymer networks (SIPN). Fig. 3 shows schematic representation of these four states.

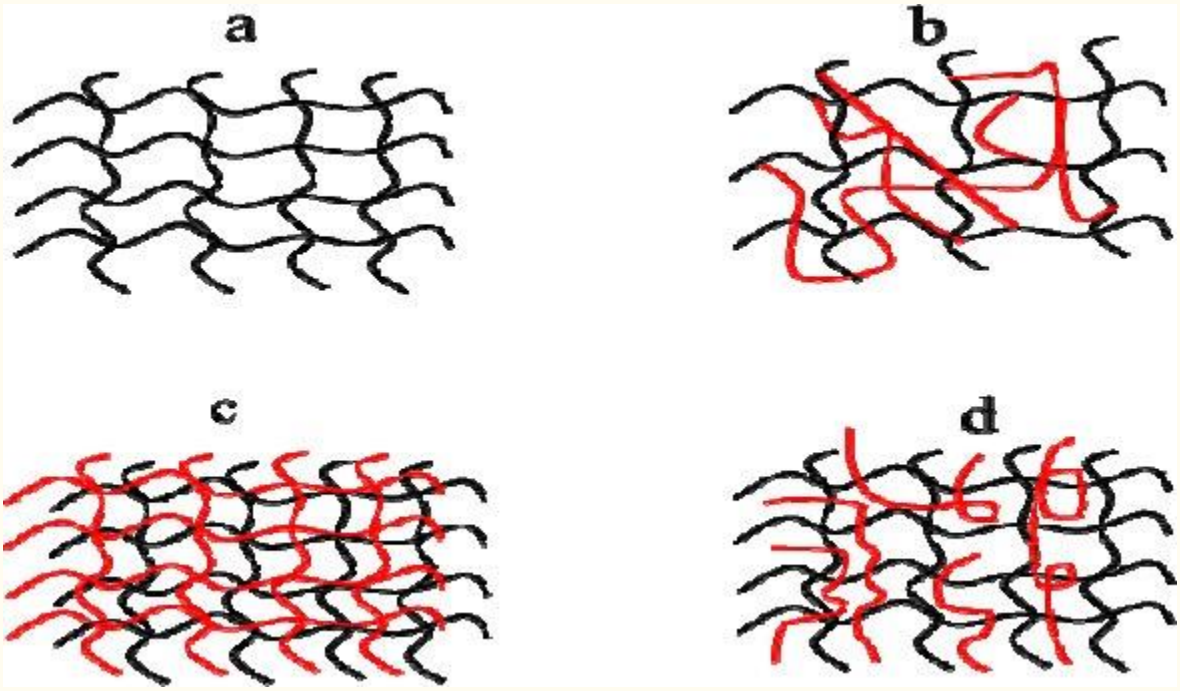


Fig. 3

Structure of chitosan-based hydrogel prepared by covalent cross-linking. Chitosan-based hydrogels include a; only chitosan chain cross links, b; chitosan is cross linked via a different polymer, c; chitosan and another polymer are entangled and each polymer type is cross-linked, d; another polymer entangles with chitosan, where chitosan macromers are crosslinking.

The simplest type of chemical hydrogel formation occurs when chitosan undergoes cross-linking reaction with another polymeric chain of its own. Second chain can be similar to or different from first structural unit in derivation.

Amines and hydroxyl groups situated on chitosan chains are responsible for chemical cross-linking. Chemical cross-linking can occur via cross-linkers or photopolymerization reaction.

3.2.1.1. Cross-linking via cross-linkers

Cross-linking can be formed between polymers themselves or between polymers and a cross-linker (65). Cross-linkers initiate cross-linking reaction between chitosan chains (4,26).

A few of customary cross-linkers include dialdehyde compounds such as glutaraldehyde (66) and other reagents like genipine (67), palladium cation (68), diisocyanate (69), and acrylic acid (70).

Glutaraldehyde has been extensively used for chemical cross-linking of chitosan. Glutaraldehyde is mainly used for cross-linking when a second polymer is added to chitosan for modification of its properties. In an attempt, Pluronic F127 has been used for modification of chitosan and this hybrid was cross-linked by glutaraldehyde for controlled delivery of 5-FU (71). Genipine is a natural, water soluble and bifunctional cross-linking agent made of a glucoside named geniposide by β-glucosidase enzyme. Genipine is isolated from gardenia fruits and as shown in Fig. 4, it could react with amines, proteins and amino groups of chitosan (72).

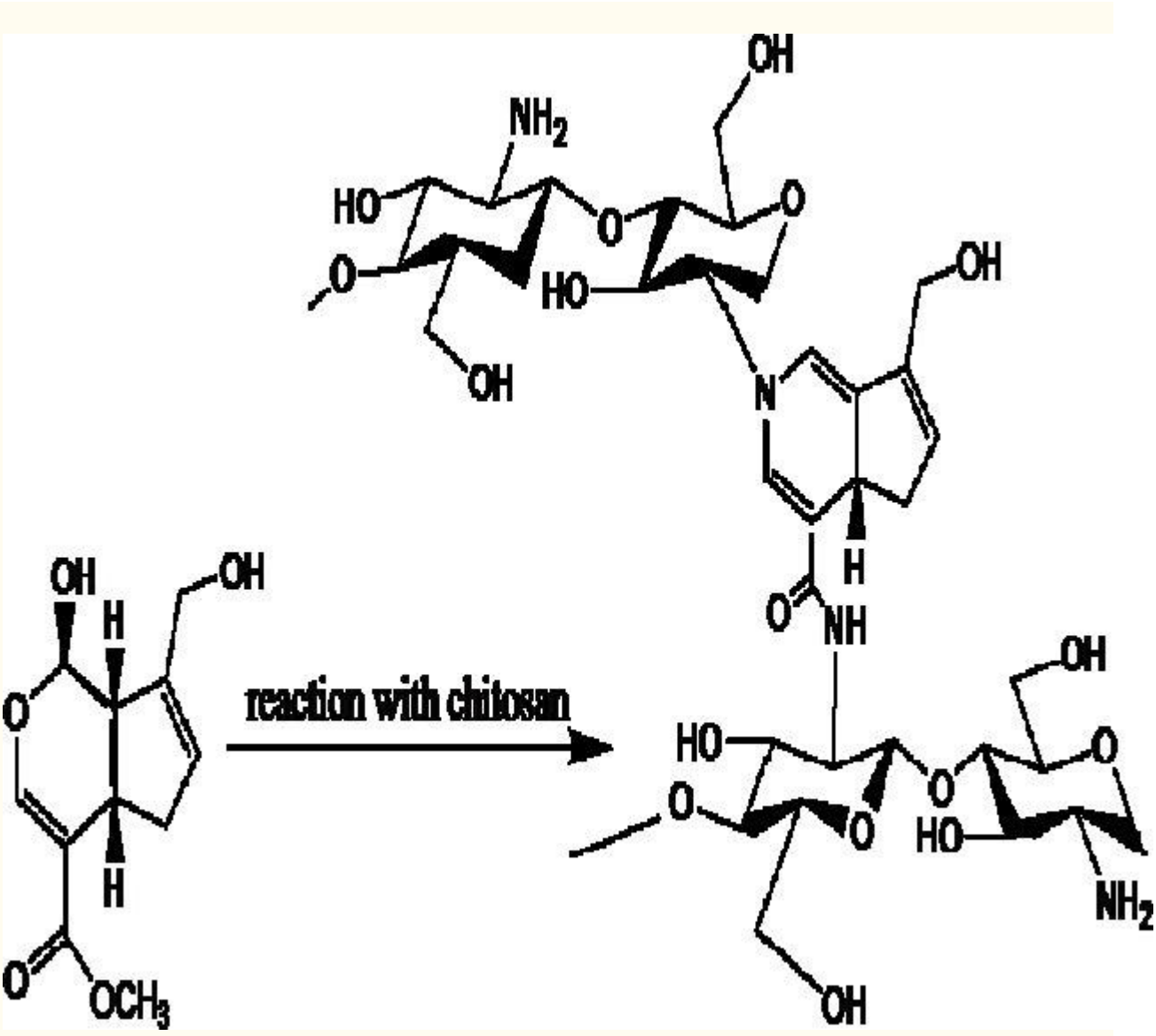


Fig. 4

Chemical cross-linking between chitosan chains in the presence of genipin.

Genipine is widely used as cross-linker in tissue fixation, food industries and drug delivery which is due to its, lower toxicity and higher biocompatibility versus other cross-linkers especially glutaraldehyde (73). There are a large number of studies on cross-linking of chitosan by genipine. Chitosan/gelatin networks cross-linked by genipine have been developed for articular cartilage tissue repair (71). Genipine-cross-linked chitosan hydrogels present slower degradation rate in comparison to glutaraldehyde-cross-linked hydrogels and higher biocompatibility, but there is the risk of incompatibility with the therapeutic agent loaded into the hydrogel (65).

3.2.1.2.Cross-linking via photopolymerization

The other method of forming covalently cross-linked chitosan hydrogels is photopolymerization(74). Photopolymerization is the process of changing liquid precursor solution to gel with the help of photoinitiators and visible or UV irradiation. This technique is used *in vivo* and *in vitro* (75,77). The polymeric reaction is controlled by adjusting the distance and duration of exposure. UV or visible light in reaction with molecules called photoinitiators, produce free radicals which initiates radical polymerization and forms cross-linked hydrogel. Photopolymerization has a distinct advantage over general methods of polymerization and that is in situ formation of hydrogels which can be used *in vivo* for several applications like in laparoscopic devices, following subcutaneous injection or in different surgeries (75).

By introducing azide and lactose moieties to chitosan, a photocrosslinkable derivative of this polymer has been synthesized. This modified chitosan can be used as a tissue adhesive in punctures.

Azide modified chitosan and vinyl benzoic acid derivatives of chitosan can also provide photo cross-linked networks for different applications (78).

3.2.2. Physical cross-linking

Physical cross-linking to form chitosan-based hydrogel networks is another class of crosslinking. Physical interactions can be ionic interactions, as in ionically cross-linked chitosan hydrogels and polyelectrolyte complexes, or can be secondary interactions such as networks named grafted chitosan hydrogels and entangled chitosan hydrogels (26).

3.2.2.1. Ionically cross-linked chitosan hydrogel

Since chitosan is a cationic polyelectrolyte polymer with ionizable amine groups (56), anions are often employed as ionic cross-linkers to engineer ionically cross-linked chitosan hydrogels (Fig. 5). One of the examples is the multivalent counter ions such as phosphate bearing molecules like tripolyphosphate (TPP). This ionic cross-linking process which is also called ionic gelation of chitosan is mostly used for loading of low molecular weight drugs, but recently has been used for macromolecules as well (79).

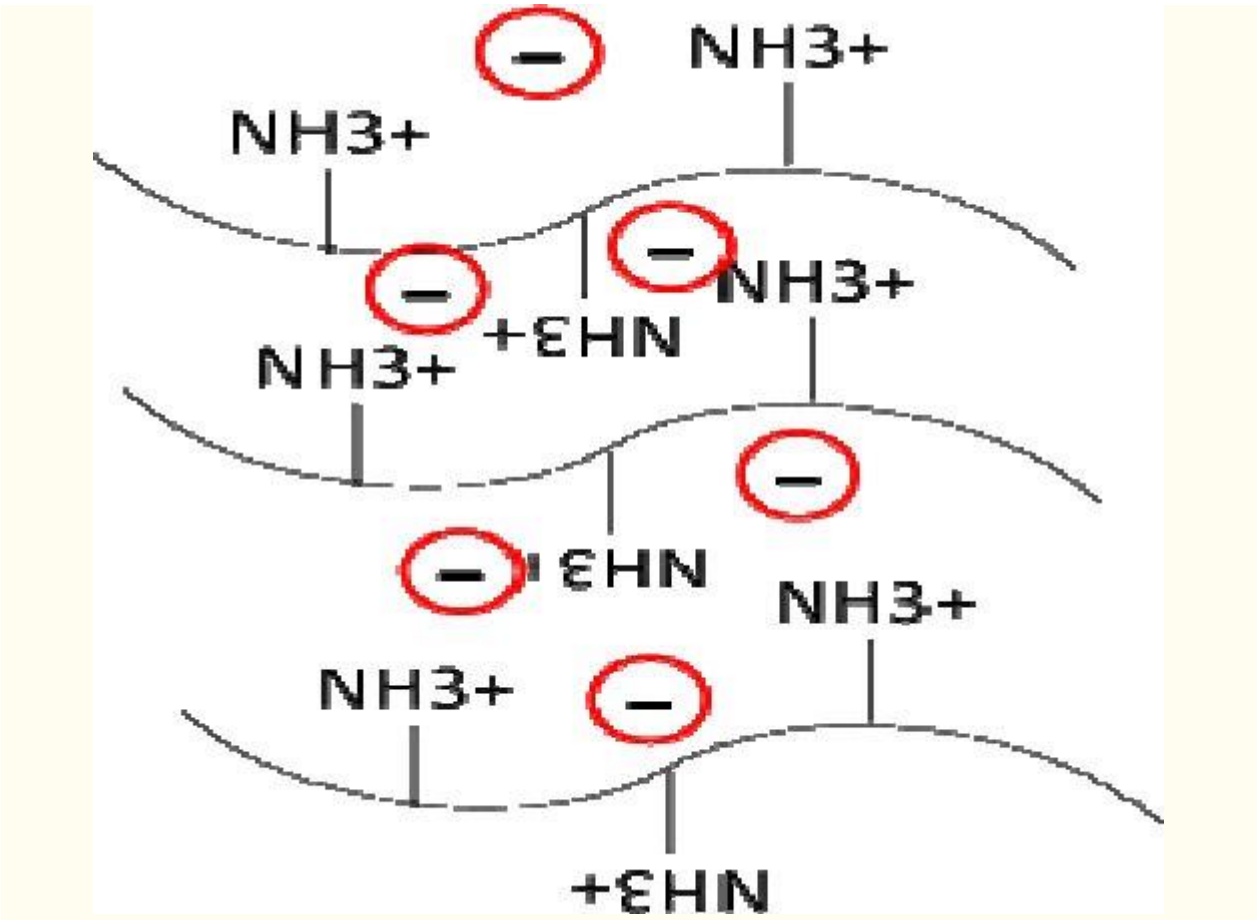


Fig. 5

Structure of chitosan-based hydrogel prepared by ionic interactions.

3.2.2.2. Polyelectrolyte complexed chitosan hydrogel

Polyelectrolyte complex networks are formed via ionic interactions between two opposite charged polymers. Polysaccharides are good choices for preparing polyelectrolyte complex because of biocompatibility and biodegradability (61).

Oppositely charged polysaccharides interact with each other in the solution spontaneously and form polyelectrolyte complexes. Chitosan is positively charged, thereby, a negatively charged natural polymer like alginate, pectin, carrageenan, xanthan gum, chondroitin sulfate, dextran sulfate or hyaluronic acid or a synthetic one like polylactic acid, polyacrylic acid or polyphosphoric acid are suitable candidates for such interactions (80,81).

Formation of these polyelectrolyte complexes depends on a number of variables including the charge density of the polymers, mixing ratio, amount of each polymer, etc. Solubility of the resulting complex also depends on the net charge. If the net charge is zero then the complex will usually be insoluble and precipitates (80).

3.2.3. Chemical versus physical cross-linking

Type of cross-linking determines the stability of hydrogels. Covalently cross-linked hydrogels with covalent cross-linkers have permanent feature that show resistance to environmental variables. However these systems need extra process of purification to remove toxic unreacted cross-linkers.

Physically cross-linked hydrogels are more biocompatible due to the lack of chemical cross-linkers and well tolerated compared to covalently systems.

However they may have not high mechanical stability and they may react to environmental changes such as pH, temperature or ionic strength (26). This especial feature of physically cross-linked hydrogels is very useful for preparation of stimuli responsive systems that are sensitive to environmental conditions and can be used for drug delivery in specific conditions (9).

3.3. Molecules used for modification of chitosan properties

In order to improve chitosan based hydrogel properties, chitosan derivatives have been synthesized and evaluated. The functional amino groups on chitosan chains help the polymer to enter chemical reactions which generate derivatives with improved properties such as muco-adhesion, high drug loading and ability for gene transfer (82). Some other chemical modifications have gained interest to prepare photopolymerizable chitosan derivatives or to improve water solubility of chitosan.

3.3.1. Chitosan and 4-azido-benzoic acid (Az-CS)

Azido-benzoic acid is one of the cross-linking agents and photoinitiators with two functional groups, azide and carboxylic acid.

The carboxylic acid group of benzoic acid enters in the reaction with amino group of chitosan which results in preparation of photosensitive chitosan derivative. Upon UV irradiation, the azide functional group is changed into nitrene and further process causes cross-linking for gel formation. Fig. 6 shows the reaction of chitosan with 4-azido-benzoic acid and resulting photo-cross-linking. Study on Az-CS derivatives showed that the solution made gel in less than a minute under UV light and the resulting gel was very adhesive similar to fibrin glue. The resulting gel was also non-toxic in acute and chronic exposures (83).

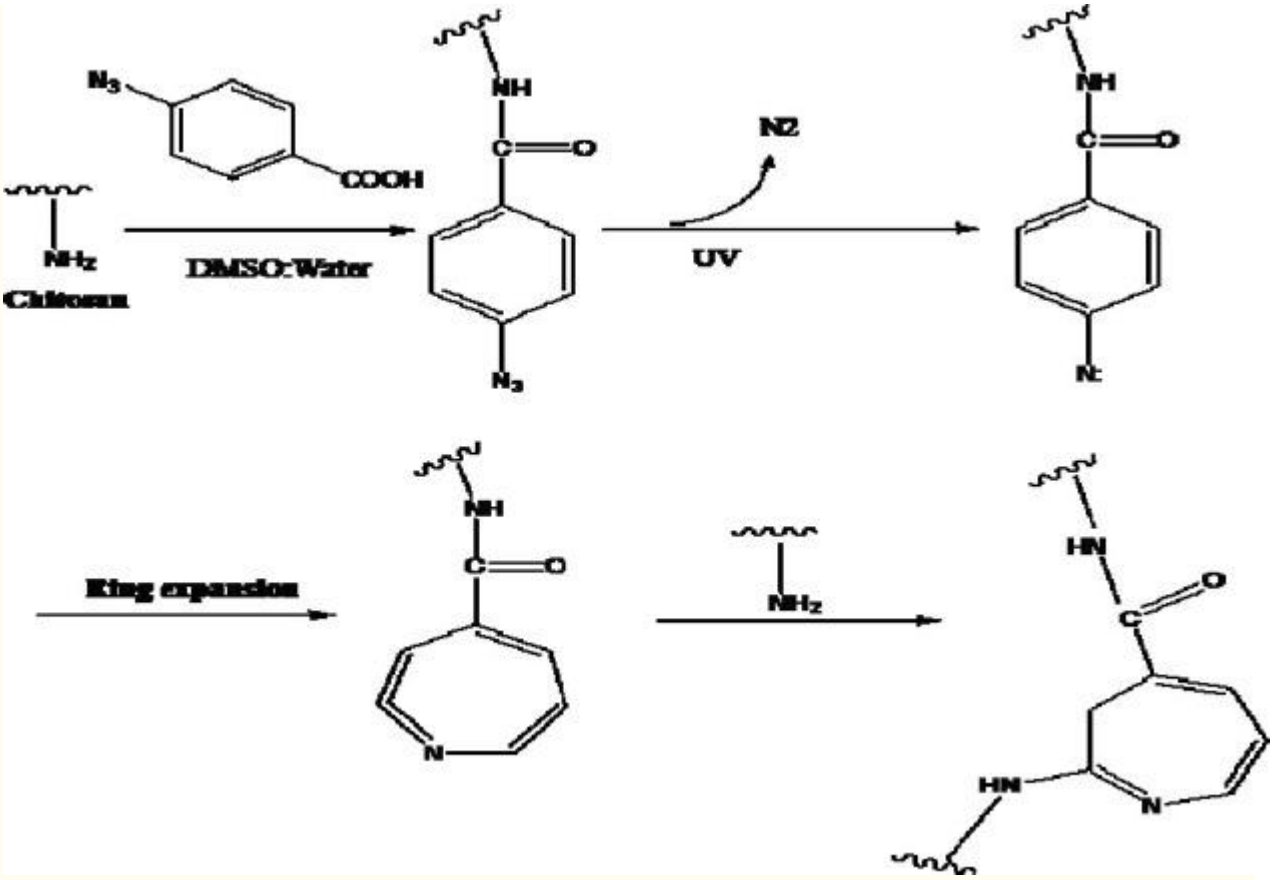


Fig. 6

Conjugation of chitosan and 4-azidobenzoic acid and photo-cross-linking of chitosan-4-azidobenzoic acid chains (ref. 75).

3.3.2. Chitosan and methyl acroloyl glycine

The conjugation of chitosan and methyl acroloyl glycin (CS-MAG) is obtained by reaction of amino group in chitosan with carboxyl group of methyl acroloyl glycine. Compared with crystallized form of chitosan, CS-MAG is an amorphous compound with lower intermolecular forces and thermal stability. The precursor can be gelled via photopolymerization in presence of photoinitiator (84).

3.3.3. Carboxylation of chitosan

As biodegradability is one of the essential features of biocompatible polymers such as chitosan, the extent of degradability is of importance. Dependent on chitosan chain length and its application, sometimes it is needed to enhance the degradation rate of chitosan.

One of the approaches is to synthesize carboxyl methyl chitosan with higher dissolution rate in aqueous environments and faster degradation in the presence of enzymes such as lysozyme (85,86). Fig. 7 depicts the chemical structure of carboxy methyl chitosan. Carboxy methyl chitosan is water soluble in a wide range of pH along with high viscosity, gel forming ability,

low toxicity and acceptable biodegradability which makes it a good option for use in food and cosmetic products (87).

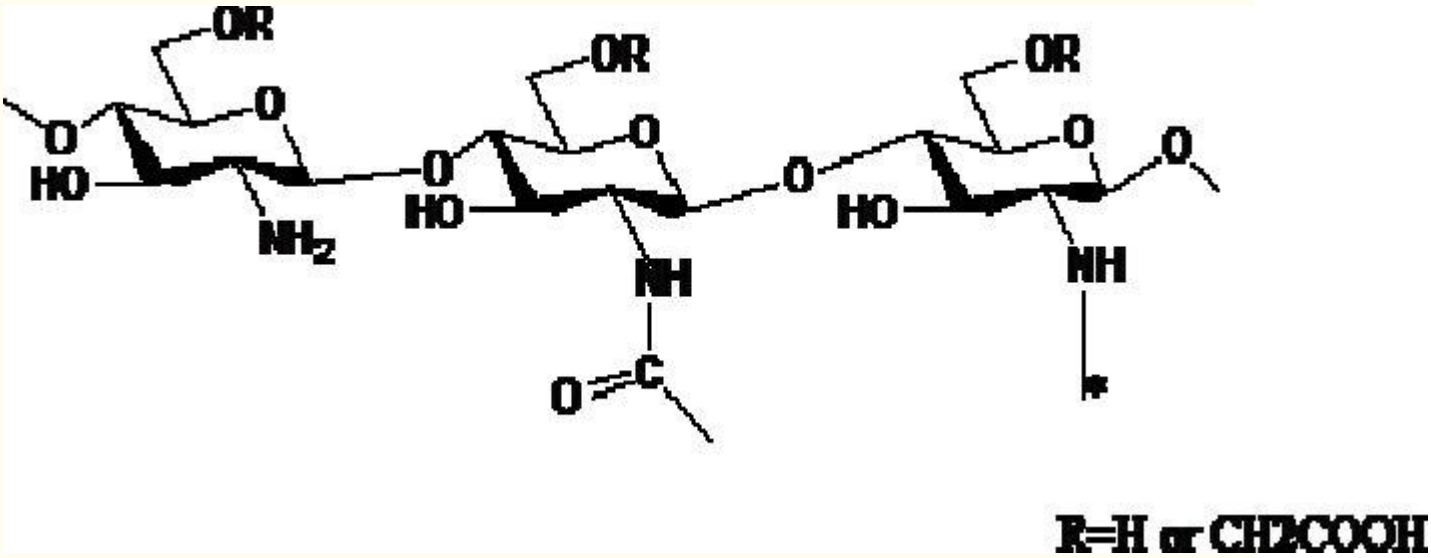


Fig. 7

Structure of carboxymethyl chitosan.

The carboxy methyl derivative of chitosan can also be modified by photoinitiators and provide photopolymerizabale derivatives. Low molecular weight carboxy methyl chitosan modified by photoreactive 4-azido benzoyloxy succinimide has been synthesized as antiadhesive agent in surgeries and tissue regeneration (88).

3.3.4. Chitosan and poly (ethylene glycol)

Poly (ethylene glycol) (PEG) is a polymer that is dissolved in aqueous and oily phases (89). This polymer is biocompatible, non-toxic and non-immunogenic material and has FDA approval for biomedical applications.

Chitosan conjugated with PEG has been used for sustained drug release in several drug delivery applications (90) like gastro-intestinal drug delivery (91). Results indicate that, the rate of drug release form PEG-chitosan carriers is greatly slower than that of chitosan based systems (92). PEG could improve the solubility of chitosan. Investigations have shown that pegylated chitosan has significantly higher solubility than unmodified chitosan (93). One of the benefits of increasing water solubility of chitosan via pegylation is increasing its transfection efficiency as a gene carrier (94).

The use of PEG can also reduce the elimination of carrier by reticulo-endothelial system as proved for pegylated derivatives of other polymers (95).

3.3.5. Chitosan and sugar

Sugar bearing chitosan derivatives have been synthesized to increase its water solubility in a wide range of pH. These derivatives are formed through an amide bond between chitosan and hydrophilic sugar moieties (96). Modification of chitosan with monosaccharides and disaccharides can occur via chitosan N-alkylation. One important application of this kind of chitosan derivative is recognition of specific cells, viruses or bacteria. Sugar moieties can recognize specific cells and bind to the specific receptors on cell surface. This interesting characteristic is very applicable for designing targeted drug delivery systems. For example fucosylated chitosan was synthesized for its specific interaction with lectins on the cells or galactosylated chitosan was used for targeting the delivery system to the hepatocytes (97).

3.3.6. Thiolated chitosan

One of important modifications on chitosan to increase its mucoadhesiveness is thilation of chitosa. By thiolation, -SH groups are introduced to the chitosan chain which readily can form disulfide bond with cystein-rich parts in the mucus glycoproteins. Besides increasing of mucoadhesion, thilation could also increase the solubility and permeation properties of chitosan. All these changes together would have positive effect on bioavailability of drugs encapsulated in thiolated chitosan systems (98,99).

3.3.7. Chitosan and alkyltrimethylammonium

Chtiosan is a natural polymer with activity against fungi and bacteria. Antifungal activity of chitosan is mostly related to the interaction of positively charged polysaccharide with the negatively charged residues on the fungi cell wall. Substitution of alkyltrimethyl-ammonium groups such as propyl and pentyltrimethylammonium improves the antifungal activity of chitosan. Antifungal activity and interactions between derivate chitosan and cells are related to hydrocarbon chain length. As a result the activity of chitosan-pentyl derivative is higher than chitosan-propyl activity (100).

Go to:

4. Chitosan-based hydrogel applications

Chitosan is known to be biocompatible and biodegradable (89,101) and its degradation products are non-toxic and non-immunogenic. Chitosan is bioadhesive and bacteriostatic (102), acts as chelating agent (103), hemostatic agent and antioxidant (104). This polymer can control bleeding via incorporating a procoagulant that helps accelerated clotting (105). Chitosan has found attention in many different fields including pharmaceutical, medical, cosmetics, agricultural and food industries (106). The pharmaceutical applications of chitosan include drug and gene delivery (107,108), wound dressing (109), tissue repair (77,110), and tissue engineering (111).

4.1. Drug delivery

Hydrogels based on chitosan and its chemical modified forms are investigated in several drug delivery applications (71).

Chitosan has cationic nature due to the presence of amine group and mucosal glycoproteins are negatively charged (112,113).

Therefore, it can adhere to negatively charged biological surfaces as a bioadhesive material. The use of bioadhesive polymers like chitosan prolongs the residence time of drug-loaded system and provides localized drug delivery (114). Chitosan also mediates paracellular transportation of drugs that greatly influences efficiency of drug delivery systems (115). As chitosan is a biocompatible and biodegradable with a structure which could be modified easily, it has been used as drug carrier for different routes of administration. Some of the most important chitosan-based drug delivery routes are discussed in the next sections.

4.1.1. Oral drug delivery

Hydrogel scaffolds can be used for drug delivery to oral cavity, stomach, intestine and colon. Delivery of drugs to oral cavity can be used to alleviate mouth diseases without the risk of first pass effect. The pH sensitive hydrogels allocate drug delivery to specified sites such as stomach or intestine and increase drug bioavailability. Colon drug delivery systems of chitosan based hydrogels can be designed for relief of diseases such as irritable or inflammatory bowel diseases (116,117).

Mucoadhesion of chitosan is an important property for improving oral absorption of drugs. Buccal tablets of nifedipine and propranolol have been formulated with chitosan as the mucoadhesive layer to enhance the systemic bioavailability of the drugs (118).

Interpenetrating networks (IPN) of chitosan and polyethylene oxide has been developed as stomach-specific drug delivery system for treatment of *Helicobacter pylori*. This IPN network presents pH dependent swelling and drug release properties (119).

Chitosan-poly acrylic acid hydrogels have been tested for colon specific drug delivery. Biodegradability of chitosan by colonic normal flora along with pH sensitivity of the polyacrylic acid segment, provide a potential suitable carrier for release of drug in the colonic region (120).

4.1.2. Ocular drug delivery

The major drawback of conventional ocular formulations is their short retention in the affected area. Administration of drugs in hydrogel systems could increase the retention of drug in the site, thereby increasing the chance of higher bioavailability. Thermosensitive chitosan-gelatin based hydrogel loaded with latanoprost has been used for controlling ocular hypertension (121). In an attempt diclofenac micelles loaded into nano-composite hydrogel improved drug residual time compared to diclofenac eye drop (122). A thermosensitive chitosan-glycerophosphate hydrogel increased the permeation and corneal bioavailability of ofloxacin compared to the aqueous solution. In-situ thermosensitive hydrogel of chitosan and isopropyl acrylamide was used for ocular delivery of timolol and the system doubled the drug release (71).

4.1.3. Nasal drug delivery

Chitosan is capable of opening tight junctions between epithelial cells of mucosal membranes and improving drug molecules transportation (123). Furthermore, the high water absorption and mucoadhesive potential of chitosan facilitate nasal drug delivery (124). A thermo sensitive hydrogel was prepared with chitosan and PEG. After spraying of formulation into nasal cavity, the solution formed gel at body temperature. This hydrogel system presented lower mucosal clearance and sustained drug release in site (125). Nasal administration using chitosan hydrogels

was promising for delivery of vaccines and peptide drugs which oral drug delivery is not practically useful (126,127).

4.2. Wound healing

Chitosan in topical form is used for wound healing. The probable mechanism of healing is infiltration of inflammatory cells such as polymorphonuclear leukocytes, secretion of inflammatory mediators like tumor necrosis factor-α, migration of macrophages and increase in the amount of collagen. The binding of GlcNac (N-acetyl-D-glucoseamine), a part of chitosan, to specific receptors in body increases macrophage activation that results in further events such as release of biological mediators (128). Additionally, chitosan activates the complement system (129) and stimulates fibroblasts to release IL-(8) and other cytokines (130).

The major use of chitosan hydrogels for wound healing is using these systems as wound dressing and hemostatic agent to promote the process of wound healing. One of the commercially available chitosan based hemostatic products is HemCon bandage. HemCon can stop severe bleeding by attaching to negatively charged cells of tissue as well as attracting negatively charged red blood cells and forming a tight seal over the wound (131) A schematic representation of this interaction is presented in Fig. 8.

4.3. Tissue engineering

Chitosan hydrogels were used as scaffolds for tissue engineering in the past two decades. The foundation of these systems relies on two components, cells and polymeric chains of hydrogel. Biodegradability is amongst advantages of chitosan as a scaffold. Chitosan can be degraded with human enzymes like lysozyme (132). Additionally, chitosan can be modified via N-acetylation to optimize biodegradability and biocompatibility properties needed in tissue engineering applications. Chitosan with high deacetylation degree near to 100 is reported to have higher rate of degradation, cell biocompatibility and higher opportunity for cell adhesion (133). The biodegradation rate of scaffold should conform to the time that malfunction tissue requires to be repaired.

For scaffolds used in tissue engineering, porosity of chitosan-based hydrogels presents a huge impact on properties such as swelling, cell adhesion and cell proliferation rate that are of importance in tissue growth. There are methods of forming porous hydrogels for tissue regeneration including i) freeze drying, ii) gas foaming and iii) salt leaching. The method of high pressure CO_2 employs CO_2 gas as a foaming agent and reduces the need of organic solvents (134). As shown in Fig. 9, channels formed in the hydrogel allow host cells migration and proliferation into the injured tissue and finally replacing the malfunction organs (57).

Chitosan scaffolds can be used for regeneration of various tissues such as bone (135), cartilage (136), skin (137) and nerves (138). The treatment of central nervous system disorders is challengeable because neural cells have lower ability for regeneration. Nerve tissue engineering requires neural stem cells such as embryonic, fetal or adult stem cells (139).

Go to:

5. CONCLUSION

Numerous hydrogel structures have been prepared and characterized for biomedical and biopharmaceutical applications. The significant features of these networks for *in vivo* applications include swelling ability, similarity to host tissues and mechanical strength as well as biodegradability. In addition to owning biocompatibility and biodegradability, biopolymers like chitosan, has potential abilities for structural modifications, which results in formation of new applicable derivatives. In addition to inherent properties of chitosan like antibacterial and antifungal activities, biocompatibility and biodegradability, different strategies to prepare chitosan derivatives make it a good carrier for pharmaceuticals, cosmetics and food products. Hydrogel preparation, modified performance and cross-linking mechanism should be related to appointed aim, for example sustained release profile for drug delivery systems or porous structural appearance for tissue engineering applications.

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