Chitosan-Based Materials and Devices

Subjects: Surgery

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Chitosan is one of the most studied polysaccharides in recent decades for its biomedical application. This polymer is derived from chitin, the main component in the exoskeleton of insects and crustaceans, a homopolymer consisting of β-(1→4)-N-acetyl-D-glucosamine. The degree of deacetylation of chitosan depends on the conditions applied during the deacetylation process—such as temperature or sodium hydroxide concentration—and determines various properties of the polymer, such as pKa, solubility, and viscosity. Chitosan has been used in a broad assortment of medical materials and devices. Each system benefits from the properties that chitosan can provide for surgical applications. The shape, porosity, consistency, and size of the fabricated systems can be precisely tuned for the intended application.

Keywords: bleeding control ; bone regeneration ; hemostasis ; hydrogels ; scaffolds ; soft tissue

1. Scaffolds

Scaffolds are porous solids with controlled geometry and microstructures. They provide extracellular support for cell proliferation and can also serve as a template, for example, to guide tissue regeneration [1]. Biocompatible polymers such as chitosan are considered for the manufacture of implantable scaffolds since they generally ensure absorption/degradability capacity and the absence of toxicity [2]. A described method for the fabrication of chitosan-based scaffolds is the lyophilization of chitosan gels and solutions [3]. This technique makes it possible to control the average pore diameter—which varies from 1 to 250 µm—by means of freezing conditions. An alternative is the manufacturing of chitosan scaffolds by 3D printing, a technique that allows to obtain systems with a tightly controlled shape and structure [4]. Finally, it is also possible to obtain self-assembled scaffolds. For this, it is necessary to use a second raw material that, when combined with chitosan, spontaneously forms a scaffold structure. An example is the manufacture of hybrid scaffolds of chitosan and sericin; the positive charges present in the chitosan structure react with the negative charges of aspartic and glutamic acids that are present in the serine structure [5]. This combination also improves cell adhesion and porosity, maintaining the biocompatibility of the system.

2. Sponges

Sponges are porous solid systems, similar to scaffolds, but with a different manufacturing process. For the manufacture of chitosan sponges, the polymer is dissolved in an acidic or saline aqueous solution. A surfactant, usually sodium dodecyl sulfate, is then added while stirring at high speed to obtain a foam. A pore-forming agent may be incorporated into the foam at this point in the process. Finally, the system is lyophilized to obtain the chitosan sponge [6]. The use of chitosan sponges in post-surgical procedures as hemostatic systems has been deeply studied [7]. These devices are valued for their biodegradability and antimicrobial activity and their ability to absorb large volumes of fluids. In addition, they can also be used as reservoirs for the release of antibiotics, such as doxycycline, thus improving their antibacterial activity [8]. Different modifications have been made to chitosan to improve the properties of these sponges. For example, hydrophobically modified chitosan sponges showed improved bleeding control compared to unmodified chitosan [9]; thiol-modified chitosan also showed excellent hemostatic performance [10], and alkylated chitosan sponges were able to rapidly absorb large volumes of water and blood [11]. It is also possible to develop mixed sponges, combining chitosan with other polymers, the combination of chitosan and gelatin being the most studied [12][13].

3. Meshes

Other devices widely used nowadays in surgery are meshes, replacing sutures in many cases, such as in hernia repair or pelvic floor construction. They are flexible networks formed by crosslinked fibers. Polypropylene meshes are the most common, being a resistant, economical, and non-resorbable material. However, there are still some cases of rejection due to foreign-body reactions and infections of the area [14]. These polypropylene-based meshes have been modified by including chitosan on their surface, which improves biocompatibility and antimicrobial properties, thus accelerating the

healing process [15]. This synergy needs to be explored more deeply; another study evaluated the coating of polypropylene meshes with different concentrations of chitosan, but when they were implanted in rats, the adhesion and histopathological parameters were not modified [16]. It is also possible to obtain meshes of other materials. For example, a poly(N-isopropylacrylamide)/chitosan hydrogel mesh was able to form a swelling-resistant structure with improved adhesive properties [17].

4. Membranes

Similar to meshes, membranes or films can be manufactured. They are also flexible polymeric layers, but with a continuous structure instead of a fiber network. The standardized manufacturing technique for chitosan membranes involves the preparation of an acid solution of chitosan, which is freeze-dried after being poured into a mold. After this process, the membrane is treated with alkali to displace the acid used to dissolve the polymer and facilitate the polymerization of chitosan. Finally, the system is dried to obtain chitosan membranes [18]. Some authors have replaced the lyophilization step with the immersion of the membrane in liquid nitrogen for 10 s [19]. Chitosan acetate films were developed for biomedical applications. The influence of the inclusion of glycerol, oleic acid, and a mixture of them as plasticizers was evaluated. All of them became biodegradable films suitable for skin recovery [20]. Membranes can also be manufactured as multilayer films, allowing different materials to be combined and providing different properties to the membrane. For example, multilayer chitosan/poly(L-lactic acid) membranes combine the biocompatibility and cell-growth promotion of chitosan with the mechanical strength of poly(L-lactic acid) [21]. HemCon® is a commercialized chitosan-based film that is recommended for preventing blood loss, thanks to its hemostatic properties, while providing an antibacterial barrier that avoids wound infection [22]. Similarly, CELOX™ is a chitosan hemostatic dressing that has shown equivalence to HemCon® in the control of bleeding [23]. Chitosan membranes can also be used in surgical procedures in combination with polypropylene mesh; they provide an antiadhesive barrier that prevents the adhesion of peritoneal tissue to the mesh [24]. There are also references to the use of chitosan membranes in guided tissue regeneration [25]. A collagen film impregnated with a layer of chitosan has been used as a barrier membrane for managing periodontal furcation, resulting in excellent biological acceptance and low gingival recession [26]. Chitosan membranes have also been developed for guided bone regeneration; these devices have antimicrobial properties and are capable of inducing angiogenesis, thus promoting bone regeneration in in vivo studies [27].

5. Hydrogels

Hydrogels have also been studied for surgical applications. These systems consist of a liquid phase, which generally comprises 90% of the formulation, trapped in a solid phase that gives the gel its structure [28]. This water content makes these systems highly biocompatible, and their soft consistency prevents damage to surrounding tissues. Chitosan hydrogels show similar mechanical properties to connective tissues, which favors tissue regeneration [29]. Three types of chitosan hydrogels for surgical applications are described in the literature: physically associated hydrogels based on the crosslinking of chitosan chains through hydrogen bonds or electrostatic interactions; coordination complex crosslinked hydrogels, which require metal ions to form covalent bonds with chitosan, making them less suitable for biomedical applications; and chemically crosslinked hydrogels that undergo irreversible gelation via covalent bonds but require modifications to the chitosan structure [30][31]. Chitosan hydrogels have been studied for different applications, such as hemorrhage control, dental and bone regeneration, and treatment of wound infections [32][33][34][35]. It is worth mentioning the possibility of developing thermosensitive hydrogels, which are capable of forming a gel after administration in response to increased temperature [36]. For example, a thermosensitive chitosan/gelatin hydrogel was developed for the sustained release of stem cells in therapeutic angiogenesis [37].

6. Nanofibers and Nanoparticles

Another formulation prepared from chitosan is nanofibers. The electrospinning technique allows the fabrication of chitosan nanofibers with a diameter of a few nanometers and, therefore, a large specific surface [29]. Porous meshes or scaffolds can be manufactured from the developed nanofibers [38][39].

Chitosan nanoparticles have also been developed for surgical applications. These formulations can be included in another system to enhance their activity. For example, melatonin-loaded lecithin–chitosan nanoparticles have been included in a hydrogel for topical administration as a wound-healing promoter. In vivo studies have shown the induction of angiogenic and fibroblast proliferation after the administration of nanoparticles [40]. Another example is the minocycline-loaded

nanoparticles developed by Ma et al., which were included in a collagen/chitosan membrane for guided bone regeneration [27].

References

1. Thein-Han, W.; Saikhun, J.; Pholpramoo, C.; Misra, R.; Kitiyanant, Y. Chitosan–gelatin scaffolds for tissue engineering: Physico-chemical properties and biological response of buffalo embryonic stem cells and transfectant of GFP–buffalo e mbryonic stem cells. Acta Biomater. 2009, 5, 3453–3466.
2. Rodríguez-Vázquez, M.; Vega-Ruiz, B.; Ramos-Zúñiga, R.; Saldaña-Koppel, D.A.; Quiñones-Olvera, L.F. Chitosan and Its Potential Use as a Scaffold for Tissue Engineering in Regenerative Medicine. BioMed Res. Int. 2015, 2015, 821279.
3. Madihally, S.; Matthew, H.W. Porous chitosan scaffolds for tissue engineering. Biomaterials 1999, 20, 1133–1142.
4. Sahai, N.; Gogoi, M.; Tewari, R.P. 3D Printed Chitosan Composite Scaffold for Chondrocytes Differentiation. Curr. Med. Imaging 2021, 17, 832–842.
5. Chollakup, R.; Uttayarat, P.; Chworos, A.; Smitthipong, W. Noncovalent Sericin-Chitosan Scaffold: Physical Properties and Low Cytotoxicity Effect. Int. J. Mol. Sci. 2020, 21, 775.
6. Fan, X.; Li, M.; Li, N.; Wan, G.; Li, Y.; Ali, M.A.; Tang, K. One-step fabrication of chitosan sponge and its potential for ra pid hemostasis in deep trauma. Biomed. Mater. 2020, 16, 015010.
7. Huang, X.; Sun, Y.; Nie, J.; Lu, W.; Yang, L.; Zhang, Z.; Yin, H.; Wang, Z.; Hu, Q. Using absorbable chitosan hemostatic sponges as a promising surgical dressing. Int. J. Biol. Macromol. 2015, 75, 322–329.
8. Phaechamud, T.; Charoenteeraboon, J. Antibacterial Activity and Drug Release of Chitosan Sponge Containing Doxycy cline Hyclate. AAPS PharmSciTech 2008, 9, 829–835.
9. De Castro, G.P.; Dowling, M.B.; Kilbourne, M.; Keledjian, K.; Driscoll, I.R.; Raghavan, S.R.; Hess, J.R.; Scalea, T.M.; B ochicchio, G.V. Determination of efficacy of novel modified chitosan sponge dressing in a lethal arterial injury model in s wine. J. Trauma Acute Care Surg. 2012, 72, 899–907.
10. Wu, Z.; Zhou, W.; Deng, W.; Xu, C.; Cai, Y.; Wang, X. Antibacterial and Hemostatic Thiol-Modified Chitosan-Immobilize d AgNPs Composite Sponges. ACS Appl. Mater. Interfaces 2020, 12, 20307–20320.
11. Du, X.; Wu, L.; Yan, H.; Jiang, Z.; Li, S.; Li, W.; Bai, Y.; Wang, H.; Cheng, Z.; Kong, D.; et al. Microchannelled alkylated chitosan sponge to treat noncompressible hemorrhages and facilitate wound healing. Nat. Commun. 2021, 12, 4733.
12. Lan, G.; Lu, B.; Wang, T.; Wang, L.; Chen, J.; Yu, K.; Liu, J.; Dai, F.; Wu, D. Chitosan/gelatin composite sponge is an ab sorbable surgical hemostatic agent. Colloids Surf. B Biointerfaces 2015, 136, 1026–1034.
13. Lu, B.; Wang, T.; Li, Z.; Dai, F.; Lv, L.; Tang, F.; Yu, K.; Liu, J.; Lan, G. Healing of skin wounds with a chitosan–gelatin sp onge loaded with tannins and platelet-rich plasma. Int. J. Biol. Macromol. 2016, 82, 884–891.
14. Piasecka-Zelga, J.; Zelga, P.; Szulc, J.; Wietecha, J.; Ciechańska, D. An In Vivo biocompatibility study of surgical mesh es made from bacterial cellulose modified with chitosan. Int. J. Biol. Macromol. 2018, 116, 1119–1127.
15. Saha, T.; Houshyar, S.; Sarker, S.R.; Pyreddy, S.; Dekiwadia, C.; Nasa, Z.; Padhye, R.; Wang, X. Nanodiamond-chitosa n functionalized hernia mesh for biocompatibility and antimicrobial activity. J. Biomed. Mater. Res. Part A 2021, 109, 24 49–2461.
16. Altınel, Y.; Öztürk, E.; Özkaya, G.; Akyıldız, E.Ü.; Ulcay, Y.; Özgüç, H. The effect of a chitosan coating on the adhesive potential and tensile strength of polypropylene meshes. Hernia 2012, 16, 709–714.
17. Gao, Y.; Han, X.; Chen, J.; Pan, Y.; Yang, M.; Lu, L.; Yang, J.; Suo, Z.; Lu, T. Hydrogel–mesh composite for wound clos ure. Proc. Natl. Acad. Sci. USA 2021, 118, e2103457118.
18. Dooley, T.P.; Ellis, A.L.; Belousova, M.; Petersen, D.; Decarlo, A.A. Dense chitosan surgical membranes produced by a coincident compression-dehydration process. J. Biomater. Sci. Polym. Ed. 2012, 24, 621–643.
19. Ma, S.; Chen, Z.; Qiao, F.; Sun, Y.; Yang, X.; Deng, X.; Cen, L.; Cai, Q.; Wu, M.; Zhang, X.; et al. Guided bone regener ation with tripolyphosphate cross-linked asymmetric chitosan membrane. J. Dent. 2014, 42, 1603–1612.
20. Cárdenas, G.; Anaya, P.; von Plessing, C.; Rojas, C.; Sepúlveda, J. Chitosan composite films. Biomedical applications. J. Mater. Sci. Mater. Electron. 2007, 19, 2397–2405.
21. Ku, Y.; Shim, I.K.; Lee, J.Y.; Park, Y.J.; Rhee, S.-H.; Nam, S.H.; Park, J.B.; Chung, C.P.; Lee, S.J. Chitosan/poly(L-lactic acid) multilayered membrane for guided tissue regeneration. J. Biomed. Mater. Res. Part A 2008, 90, 766–772.

22. Wedmore, I.; McManus, J.G.; Pusateri, A.E.; Holcomb, J.B. A Special Report on the Chitosan-based Hemostatic Dressing: Experience in Current Combat Operations. J. Trauma Inj. Infect. Crit. Care 2006, 60, 655–658.
23. Devlin, J.J.; Kircher, S.; Kozen, B.G.; Littlejohn, L.F.; Johnson, A.S. Comparison of ChitoFlex®, CELOX™, and QuikClot® in Control of Hemorrhage. J. Emerg. Med. 2009, 41, 237–245.
24. Paulo, N.M.; de Brito e Silva, M.S.; Moraes, A.M.; Rodrigues, A.P.; De Menezes, L.B.; Miguel, M.P.; De Lima, F.G.; Faria, A.D.M.; Lima, L.M.L. Use of chitosan membrane associated with polypropylene mesh to prevent peritoneal adhesion in rats. J. Biomed. Mater. Res. Part B Appl. Biomater. 2009, 91, 221–227.
25. Xu, C.; Lei, C.; Meng, L.; Wang, C.; Song, Y. Chitosan as a barrier membrane material in periodontal tissue regeneration. J. Biomed. Mater. Res. Part B Appl. Biomater. 2012, 100, 1435–1443.
26. Harikumar, K.; Nandakumar, K. Management of periodontal furcation defects by guided tissue regeneration using collagen—Chitosan as a barrier membrane. Int. J. Oral Health Dent. 2017, 3, 210–213.
27. Ma, S.; Adayi, A.; Liu, Z.; Li, M.; Wu, M.; Xiao, L.; Sun, Y.; Cai, Q.; Yang, X.; Zhang, X.; et al. Asymmetric Collagen/chitosan Membrane Containing Minocycline-loaded Chitosan Nanoparticles for Guided Bone Regeneration. Sci. Rep. 2016, 6, 31822.
28. Croisier, F.; Jérôme, C. Chitosan-based biomaterials for tissue engineering. Eur. Polym. J. 2013, 49, 780–792.
29. Oryan, A.; Sahvieh, S. Effectiveness of chitosan scaffold in skin, bone and cartilage healing. Int. J. Biol. Macromol. 2017, 104 Pt A, 1003–1011.
30. Berger, J.; Reist, M.; Mayer, J.; Felt, O.; Gurny, R. Structure and interactions in chitosan hydrogels formed by complexation or aggregation for biomedical applications. Eur. J. Pharm. Biopharm. 2003, 57, 35–52.
31. Dambies, L.; Vincent, T.; Domard, A.A.; Guibal, E. Preparation of Chitosan Gel Beads by Ionotropic Molybdate Gelation. Biomacromolecules 2001, 2, 1198–1205.
32. Zhao, Y.; Xiao, A.; Wu, P.; Chen, F.; Zhang, Q.; Liang, M.X.; Han, X.; Shi, X.; Li, Y.; Chen, Y. Fabrication of Hydroxypropyl Chitosan/Soy Protein Isolate Hydrogel for Effective Hemorrhage Control. Tissue Eng. Part A 2021, 27, 788–795.
33. Muşat, V.; Anghel, E.M.; Zaharia, A.; Atkinson, I.; Mocioiu, O.C.; Buşilă, M.; Alexandru, P. A Chitosan–Agarose Polysaccharide-Based Hydrogel for Biomimetic Remineralization of Dental Enamel. Biomolecules 2021, 11, 1137.
34. Cui, Z.-K.; Kim, S.; Baljon, J.J.; Wu, B.M.; Aghaloo, T.; Lee, M. Microporous methacrylated glycol chitosan-montmorillonite nanocomposite hydrogel for bone tissue engineering. Nat. Commun. 2019, 10, 3523.
35. Pawar, V.; Dhanka, M.; Srivastava, R. Cefuroxime conjugated chitosan hydrogel for treatment of wound infections. Colloids Surf. B Biointerfaces 2019, 173, 776–787.
36. Zhou, H.Y.; Jiang, L.J.; Cao, P.P.; Li, J.B.; Chen, X.G. Glycerophosphate-based chitosan thermosensitive hydrogels and their biomedical applications. Carbohydr. Polym. 2015, 117, 524–536.
37. Cheng, N.-C.; Lin, W.-J.; Ling, T.-Y.; Young, T.-H. Sustained release of adipose-derived stem cells by thermosensitive chitosan/gelatin hydrogel for therapeutic angiogenesis. Acta Biomater. 2017, 51, 258–267.
38. Ho, M.-H.; Yao, C.-J.; Liao, M.-H.; Lin, P.-I.; Liu, S.-H.; Chen, R.-M. Chitosan nanofiber scaffold improves bone healing via stimulating trabecular bone production due to upregulation of the Runx2/osteocalcin/alkaline phosphatase signaling pathway. Int. J. Nanomed. 2015, 10, 5941–5954.
39. Guo, S.; He, L.; Yang, R.; Chen, B.; Xie, X.; Jiang, B.; Weidong, T.; Ding, Y. Enhanced effects of electrospun collagen-chitosan nanofiber membranes on guided bone regeneration. J. Biomater. Sci. Polym. Ed. 2019, 31, 155–168.
40. Correa, V.L.R.; Martins, J.A.; de Souza, T.R.; Rincon, G.D.C.N.; Miguel, M.P.; de Menezes, L.B.; Amaral, A.C. Melatonin loaded lecithin-chitosan nanoparticles improved the wound healing in diabetic rats. Int. J. Biol. Macromol. 2020, 162, 1465–1475.