American Journal of Medicine and Medical Sciences 2025, 15(3): 615-620
DOI: 10.5923/j.ajmms.20251503.27

Mechanisms of Local Hemostasis Using Hemostatic Implants Based on Chitosan

Xodjiyev Doniyor Shomuradovich*, Kadirov Marat Jalgasovich

Republican Medical Center named after U. Khalmuratov, Uzbekistan

Abstract The article discusses unresolved issues of local hemostasis in parenchymal bleeding and presents the latest research findings on the development of multifunctional polymers with hemostatic and anti-adhesive properties. It specifically describes the properties of chitosan and its various composite materials, highlighting existing challenges and outlining development pathways in experimental surgery to create a new multifunctional inert material with rapid hemostatic and delayed regenerative properties. Over the past decade, advancements in science have led to the creation of innovative materials and drugs for controlling internal and uncontrolled bleeding, which were previously unimaginable. Significant progress has been made in experimental surgery with the development of multifunctional hemostatic agents, including nano- and micro-materials. These materials exhibit superior biocompatibility, rapid hemostatic properties, and regenerative capabilities. Future research should focus on exploring and optimizing these materials to develop an inert multifunctional agent with enhanced performance in both hemostasis and tissue regeneration.

Keywords Hemostasis, Experimental surgery, Bleeding control, Tissue adhesives, Biocompatible materials

Bleeding and adhesion formation are common complications during liver and spleen surgeries. Intraoperative and postoperative bleeding result in mortality in 6-12% and 28-72% of cases, respectively [4]. The spleen parenchyma does not contract upon injury, leading to prolonged and intensive bleeding. According to Semichev E.V. (2015), significant efforts are often required to stop splenic bleeding. Splenic injuries occur in 7% of cases involving abdominal trauma and 26% of closed abdominal injuries. A distinct characteristic of spleen injuries is the development of profuse bleeding that persists for a long time [42]. The primary causes of such bleeding include the spleen's extensive vascular network, its blood-engorged state, and the low contractility of its parenchyma, which results in prolonged bleeding even from minor injuries.

In surgical practice, various hemostatic sponges are increasingly used to control internal bleeding [1,2]. However, within the abdominal cavity, the majority of these agents can lead to adhesion formation. Adhesive disease, which can cause intestinal obstruction and other pathological conditions, often necessitates repeat surgeries. This compels the search for new materials with high hemostatic activity, biological inertness, and anti-adhesive properties.

One of the multifunctional materials with excellent biocompatibility, absence of immunogenicity, and non-irritating properties is chitosan (CS), a natural polycationic polysaccharide derived from various sources such as shrimp, crabs, squid, and some fungi. In 2001, it was approved by the U.S. Food and Drug Administration (FDA) as a GRAS (Generally Recognized As Safe) substance [19,33]. Currently, several FDA-approved chitosan-based hemostatic products are available, including Celox® (MedTrade Products Ltd., Cheshire, UK), TraumaStat® (Ore-Medix, LLC, Lebanon, Oregon, USA), and HemCon® bandages (HemCon Medical Technologies Inc., Portland, Oregon, USA). However, enhancing their hemostatic potential remains a significant challenge. Composite hemostatic materials based on CS represent a new class of multifunctional hemostatic agents developed by combining physically and chemically modified CS and its derivatives with other functional materials. Composite materials have gained considerable attention due to their potential synergistic effects, which can significantly enhance performance. As a result, chitosan-based composite hemostatic materials are finding increasingly widespread application. To date, the efficacy of numerous novel composite hemostatic materials based on CS for rapid and functional hemostasis has been demonstrated.

In 1964, the cascade theory of blood coagulation was proposed, which marked the beginning of the study of endogenous pathways of blood clotting. Traditional hemostatic agents promote blood coagulation by activating specific components described in the cascade theory. However, numerous studies have shown that chitosan triggers coagulation without activating the intrinsic pathway, indicating that the hemostatic mechanism of CS is independent of the classical coagulation cascade [13]. Although not yet fully understood, the hemostatic

* Corresponding author:
sammi-xirurgiya@yandex.com (Xodjiyev Doniyor Shomuradovich)
Received: Jan. 9, 2025; Accepted: Feb. 2, 2025; Published: Mar. 10, 2025
Published online at http://journal.sapub.org/ajmms

mechanism of CS involves the following aspects.

Erythrocytes, the main type of hematocytes in the blood, increase blood viscosity and enhance platelet transport to the vascular wall for physiological hemostasis. The cell membrane surfaces of erythrocytes contain various negatively charged proteins and glycolipids. Under physiological conditions, erythrocyte aggregation and adhesion are inhibited by electrostatic repulsion. Chitosan (CS), a natural cationic alkaline polysaccharide, carries a positive charge (-NH3+) on its chain, which interacts electrostatically with anions on the surface of erythrocytes. This interaction induces intensive erythrocyte aggregation at the wound site, forming clots that rapidly stop bleeding [38]. Studies have shown that the ability of chitosan to initiate coagulation is related to its degree of deacetylation and is highly dependent on the number of protonated amino groups [7,32].

Under normal physiological conditions, platelets do not attach to endothelial cells. However, in wounds, the activation of platelet adhesion and aggregation plays a vital role in the hemostatic process [41]. Biopolymers can initiate platelet adhesion and aggregation, a complex process influenced by various properties, including surface chain mobility, surface chemical composition, hydrogen bonding properties, charge density, hydrophobicity/hydrophilicity, and others [17]. Certain studies have demonstrated that CS can enhance platelet activation and accelerate platelet adhesion and aggregation [45].

Thanks to its excellent properties, such as hemostatic, antibacterial, anti-inflammatory, wound-healing, biocompatibility, biodegradability, and non-toxicity, CS is expected to become an outstanding hemostatic agent [6,8,37]. However, hemostatic materials containing only CS have a limited hemostatic effect. To improve the hemostatic properties, composite materials based on CS have been prepared by combining CS with other functional components that can act synergistically, ensuring rapid and effective hemostasis. Since chitosan can be easily processed into various forms, CS-based composite materials have been developed into different forms, including films, sponges, hydrogels, particles, and fibers.

Peng H. (2009) prepared composite chitosan/gelatin (CS/GE) films containing ibuprofen using a solvent casting method and demonstrated that the CS content in the composite films directly affects tensile strength and elongation at break. Cross-linking with glutaraldehyde likely increases vapor transmission rates and the swelling degree of composite films. As shown in antibacterial activity analyses against Escherichia coli and Staphylococcus aureus, CS/GE composite films containing ibuprofen exhibited better antibacterial activity compared to the latter.

For achieving a satisfactory hemostatic effect, selecting suitable components for the preparation of powdered hemostatic agents is crucial. Alginate (AG), a natural linear polysaccharide extracted from brown algae, is widely used in biological carriers and tissue engineering due to its biocompatibility, low toxicity, and cost-effectiveness. In the application of hemostatic materials, AG has gained increasing attention due to its excellent wound adhesion and high water absorption properties [10].

Yunnan Baiyao, a well-known herbal remedy used in Eastern countries for over 100 years, is an effective surgical sealant and hemostatic agent. However, it is unsuitable for direct intraluminal application due to the absence of an ideal substrate [11,25]. Lu B. and colleagues prepared composite hemostatic films of chitosan/sodium alginate-Yunnan Baiyao by mixing Yunnan Baiyao with CS and sodium alginate. A rat liver bleeding model was created, and the hemostatic effects of the films were analyzed using semi-quantitative evaluation. Compared to the chitosan/sodium alginate composite film group, the CS hemostatic film group, and the GE sponge group, the chitosan/sodium alginate-Yunnan Baiyao composite film group exhibited superior hemostatic effects.

Mesoporous Bioactive Glass (MBG) is a promising new family of biomaterials. Thanks to its uniform nanoscale mesoporous structure, high specific surface area, and excellent biological activity, MBG can serve as an effective hemostatic agent [11,35,45]. However, certain challenges remain in utilizing MBG in the hemostatic process. Jia T.B. and colleagues successfully prepared composite porous MBG/CS films using the freeze-drying method. The MBG/CS films exhibited high porosity with a continuous structure of well-connected pores and demonstrated excellent water absorption, which could be adjusted by altering the mass ratio of MBG to CS. In a rat liver bleeding model, composite films with varying MBG/CS ratios displayed different hemostatic effects. Increasing the MBG content reduced hemostasis time and bleeding volume. In vitro studies revealed that the composite films exhibited good degradability, biocompatibility, and non-cytotoxicity.

Biodegradable sponges, as promising hemostatic biomaterials, have been in clinical demand over the past decades. Gelatin (GE) has been extensively studied as a resorbable hemostatic material due to its excellent properties, including low antigenicity, good biocompatibility, and biodegradability [23,40,43]. GE dissolves in water and can be combined with various natural polymers to enhance the chemical stability and mechanical properties of composite materials. Numerous composite functional materials have been developed by cross-linking GE with CS [5,54]. Lan G. and colleagues prepared a composite porous CS/GE sponge using a modified gradual base extraction and freeze-drying method, with tannic acid as a cross-linking agent. In vitro blood coagulation experiments demonstrated that hemostatic efficiency was optimal at a CS/GE ratio of 5/5 (wt/wt).

Sepia ink has been used for centuries in traditional Chinese medicine due to its various bioactivities, such as anti-radiation, anti-tumor, immunomodulatory effects, and procoagulant functions [29]. Squid ink polysaccharide (SIP) can shorten blood coagulation time both in vitro and in vivo and activate the coagulation factor FXII, indicating a significant procoagulant effect. To address the limited hemostatic effects of chitosan, SIP-CS composite sponges were developed using a freeze-drying technique [21]. Compared to pure chitosan, the addition of SIP enhanced

the hemostatic efficiency of the composite sponges. In burned New Zealand rabbits, SIP-CS sponges also promoted wound healing, re-epithelialization, and the restoration of the epidermis and dermis. Thus, SIP-CS composite sponges represent innovative marine biomaterials for rapid hemostasis and wound healing.

Hydroxybutyl chitosan (HBC) is a chitosan derivative obtained by conjugating hydroxybutyl groups to chitosan chains. It possesses good water solubility and controllable thermosensitive properties, making the phase transition process of its hydrogel reversible [45]. To address the limitations of pure chitosan sponges, Hu S. et al. (2018) prepared a composite sponge by physically mixing HBC with CS through vacuum freeze-drying. The HBC/CS sponge exhibited high porosity (approximately 85%), significant water absorption (approximately 25 times its weight), good softness, non-cytotoxicity, and excellent antibacterial properties. In vitro blood coagulation studies demonstrated that the HBC/CS composite sponge could transform blood into viscous gels, facilitating blood clotting.

Proper blood clotting at the wound site is a critical requirement for wound healing, and the exceptional properties of surgical hemostatic agents play a vital role in this process. Oxidized nanofibrillar cellulose (ONFC), a derivative of cellulose-one of the most abundant natural linear polysaccharides-is biocompatible and bioabsorbable [24]. It absorbs water from the blood, forming hydrogels that activate platelets [43]. To develop a more effective hemostatic agent, Sukul M. et al. (2017) created a novel composite hemostatic sponge, ONFC-CS, by linking the carboxyl group (-COOH) of ONFC with the amino group (-NH2) of CS through peptide bonds to form a stable hydrogel network without the need for additional cross-linking agents. Hemostatic evaluation of the ONFC-CS sponge in a liver injury model demonstrated superior hemostatic effects compared to the ONFC sponge alone. The combination of ONFC and CS exhibited a synergistic hemostatic effect. Experiments involving implantation in rats with liver injuries showed that the ONFC-CS sponge had excellent biocompatibility and biodegradability.

Rapid dehydration of blood causes a concentration of blood cells and clotting factors, leading to clot formation. A new hemostatic system comprising covalently bonded chitosan, sodium polyacrylate (SPA), and polyethylene glycol (PEG) in a porous network was developed by Qian Z. et al. [39]. They fabricated a soft, elastic, porous xerogel sponge (SPA-co-CS) capable of achieving maximum water absorption within 200 seconds. In thromboelastography (TEG®) testing and a rabbit limb lethal arterial bleeding model, the SPA-co-CS sponge demonstrated superior hemostatic effects by concentrating platelets and enhancing dynamic thrombus formation. Compared to existing commercial products such as QuikClot zeolite granules (Z-Medica Corporation, Wallingford, Connecticut, USA), QuikClot Combat Gauze (Z-Medica Corporation), and Celox (MedTrade Products Ltd., Cheshire, UK), SPA-co-CS also exhibited significantly improved wound-sealing properties, external pressure application, and ease of removal after use.

Composite sponges composed of CS and poly(methyl vinyl ether-co-maleic anhydride) (PVM/MA) were successfully prepared using ammonium bicarbonate particles as a porogen in a supercritical CO_2 process [43]. The CS-PVM/MA sponges featured a porous structure (approximately 80% porosity), which facilitated the formation of erythrocyte clots or plugs. In vitro and in vivo experiments showed that CS-PVM/MA sponges exhibited high blood coagulation capability, comparable to Avitene, a commercially available collagen-based hemostatic agent.

Hydrogels derived from polysaccharides offer unique advantages, such as excellent biodegradability and biocompatibility, high swelling capacity, rapid hemostasis, and the ability to create a moist environment, which has garnered increasing interest. Nie W. et al. (2013) developed a novel polysaccharide/polypeptide hydrogel as an adhesive sealant and hemostatic material. This hydrogel was formed via rapid in situ cross-linking of thiol-functionalized chitosan (CSS) with ε-polylysine modified with maleimide groups (EPLM) through Michael addition under mild conditions. Due to its resemblance to the natural extracellular matrix, the CSS/EPLM hydrogel exhibited no cytotoxicity. In vivo hemostatic tests demonstrated that the CSS/EPLM hydrogel possessed excellent hemostatic properties.

Tissue adhesive materials are widely used in wound healing, surgical tissue adhesives, wrinkle fillers, and hemostasis during surgical procedures [22]. Inspired by the adhesive properties of mussels, it was discovered that mussel adhesive proteins play a crucial role in forming hydrogel-like adhesive pads on substrates. Ryu J.H. et al. (2011) synthesized injectable and thermosensitive hydrogels composed of chitosan/ pluronic (CS-C/Plu-SH) for tissue adhesives and hemostatic materials. These hydrogels were created through in situ cross-linking between catechin-functionalized chitosan and thiol-terminated pluronic. Both in vitro and in vivo evaluations demonstrated that CS-C/Plu-SH hydrogels exhibit excellent mechanical properties, strong adhesion to soft tissues and mucosal layers, as well as superior hemostatic performance.

Human-like collagen (HLC) is a novel genetically engineered protein expressed by recombinant Escherichia coli BL21 (a molecular biology strain expressing T7 polymerase for the pET system) containing a partial cDNA clone derived from human mRNA through reverse transcription. In addition to collagen's characteristics, HLC offers numerous advantages, including excellent water solubility, low immunogenicity, good stability, and non-toxicity. Therefore, HLC is considered a promising biomaterial [44]. Pan H. et al. developed a series of soft, flexible, porous, translucent, breathable, and non-adherent hydrogel dressings using a simple repetitive freeze-thaw process [36]. Hydrogels composed of polyvinyl alcohol (PVA), HLC, and carboxymethyl chitosan (CMCS) with Tween 80 as a porogen were successfully fabricated. The hydrogels, designated as PVA-HLC-CS-T80, demonstrated outstanding swelling ratios, bacterial barrier activity, vapor permeability, hemostatic activity, and biocompatibility. Furthermore, in vivo evaluation revealed that PVA-HLC-CS-T80 hydrogels significantly improved wound healing by reducing inflammation,

stimulating granulation tissue formation, promoting collagen deposition, and accelerating re-epithelialization.

To enhance the hemostatic effects of CS-based materials, many researchers have developed hemostatic agents by mixing CS with other materials [26,30] and modifying the physical or chemical structure of CS [16,29]. For powdered hemostatic agents, composition is critical, as these particles can be applied to wounds of any shape and depth, where traditional hemostatic materials like sponges and films often fall short.

QuikClot® zeolite powder (Z-Medica Corporation, Connecticut, USA) has been FDA-approved and is widely used for bleeding control. However, this zeolite-based hemostatic agent is associated with challenges, including thermal damage from its exothermic reaction and poor biodegradability [45]. Mesoporous silica xerogels (MSX) with a large surface area and high porosity, developed by Li X.S. et al. (2008), exhibited excellent water absorption capacity with minimal thermal effects upon contact with blood, making them effective for hemostasis [31]. Building on this, Dai C. et al. (2010) developed a series of chitosan-silica xerogel granules (CSSX) with good biocompatibility. These granules combined a liquid-absorbing core of mesoporous silica xerogel with a macroporous chitosan coating layer, using a modified sol-gel process and polyethylene glycol (PEG) molecular imprinting technology. In vivo and in vitro coagulation assessments demonstrated that CSSX granules could significantly accelerate the contact activation pathway of the coagulation cascade, achieving desirable hemostatic effects. Moreover, CSSX granules promoted mouse myoblast proliferation with high cell viability and no cytotoxicity, indicating their safety and efficacy.

Microspheres have several advantages for biomedical applications compared to particles of other geometries, including individual porosity, a larger surface area, low bulk density, and superior cell attachment properties [20]. Collagen has been found to offer benefits such as facilitating platelet aggregation, initiating the intrinsic blood coagulation pathway, accelerating wound healing, boosting immunity, and reducing wound infections [14,15,27]. However, the effectiveness of hemostatic materials composed of a single component is often limited. Compared to chitosan (CS), carboxymethyl chitosan (CMCS) has better water solubility and lower toxicity. Shi X. et al. (2016) developed novel composite hemostatic microspheres (CSCM) using CMCS, sodium alginate, and collagen as raw materials [44]. Surface morphology characterization via scanning electron microscopy revealed numerous small protrusions on the CSCM surface, which increased contact with blood and promoted platelet adhesion. In vitro hemostasis tests showed that CSCM enhanced platelet adhesion, aggregation, and activation. Upon contact with blood, activated plasma proteins on the CSCM surface initiated the endogenous coagulation cascade, ultimately leading to thrombin formation. Thrombin converts fibrinogen into fibrin monomers, which polymerize to form a fibrous network, causing CMCS to swell and inducing blood clotting.

Nanofibers resemble the morphology of the natural extracellular matrix of the skin and offer advantages such as high porosity, variable pore size distribution, and a high surface area-to-volume ratio. Currently, various methods exist to produce nanofibers with controlled structures, such as self-assembly, phase separation, electroforming, and more. Among these, electrospinning is a simple, rapid, efficient, and cost-effective method widely used to produce polymeric nanofibers by applying high voltage to an electrically charged liquid [9]. Gu B.K. et al. (2015) fabricated CS-GE nanofiber mats using electrospinning [18]. In vitro blood coagulation studies showed that the hydrophilic gelatin and ultrasonic treatment synergistically enhanced hemostatic functions, including rapid blood absorption and effective coagulation. Additionally, ultrasonic-treated CS-GE nanofiber mats with high porosity supported active cell proliferation, migration, and infiltration.

With advancements in medical services, the demand for improved performance in hemostatic materials has increased. Developing new hemostatic materials that are fast, effective, safe, and ready-to-use is of great importance. Systematic study of hemostatic mechanisms and the synergistic effects of hemostatic materials is essential. Combining various hemostatic materials with different mechanisms can maximize their advantages, expand coagulation pathways, accelerate the rate of hemostasis, and ultimately achieve rapid clotting. Moreover, the hemostatic effects of these agents vary depending on their form.

Polymeric nanoparticles represent a class of nanoparticles synthesized from natural, synthetic, biodegradable, or non-biodegradable polymers at nanometer-scale dimensions. Due to the highly modifiable surface of these nanoparticles, they are used to minimize side effects in drug delivery and enhance biocompatibility for various applications. These nanoparticles are typically biodegradable and fall into two main categories based on their properties: (1) agro-polymers (e.g., polysaccharides and proteins) and (2) biopolystyrenes (e.g., microorganisms and synthetic polymers). Biodegradable synthetic nanopolymers are further divided into two groups: (1) synthetic (e.g., polylactic acid [PLA], poly(lactic-co-glycolic acid) [PLGA], polyanhydrides, polycaprolactone [PCL], and polyalkyl cyanoacrylate [PACA]) and (2) natural (e.g., alginate, chitosan, gelatin cellulose, and pullulan). However, there are also non-biodegradable types of synthetic nanopolymers, such as polymethyl methacrylate (PMMA) and polyamidoamine (PAMAM) [21].

In summary, over the past 10–15 years, advances in science have enabled the development of numerous new materials and drugs, whose existence would have been inconceivable not so long ago. Promising results have been achieved, and pathways for the development of experimental surgery have been identified. In particular, future research should focus on nano- and micromaterials that have already been developed for the treatment of internal and uncontrolled bleeding. The search for a new multifunctional inert material with rapid hemostatic and delayed regenerative properties must continue.

REFERENCES

[1] Babaei Z., Jahanshahi M., Rabiee S.M. The fabrication of nanocomposites via calcium phosphate formation on gelatin-chitosan network and the gelatin influence on the properties of biphasic composites. Mat. Sci. Eng. C. 2013; 33: 370-375. doi:10.1016/j.msec.2012.08.053.

[2] Baylis JR, Chan KYT, Kastrup CJ. Halting hemorrhage with self-propelling particles and local drug delivery. Thromb Res. 2016; 141 (Suppl 2): 36-39. doi:10.1016/S0049-3848(16)303 62-0.

[3] Chang R, Eastridge BJ, Holcomb JB. Remote damage control resuscitation in austere environments. Wilderness Environ Med. 2017; 28(2): S124-S134. doi:10.1016/j.wem.2017.02.002.

[4] Chaturvedi A, Dowling MB, Gustin JP, Scalea TM, Raghavan SR, Pasley JD, et al. Hydrophobically modified chitosan gauze: a novel topical hemostat. J Surg Res. 2017; 207: 45-52. doi:10.1016/j.jss.2016.04.052.

[5] Curry NS, Davenport R. Transfusion strategies for major haemorrhage in trauma. Br J Haematol. 2019; 184(4): 508-523. doi:10.1111/bjh.15737.

[6] Dai C., Liu C., Wei J., Hong H., Zhao Q. Molecular imprinted macroporous chitosan coated mesoporous silica xerogels for hemorrhage control. Biomaterials. 2010; 31: 7620-7630. doi:10.1016/j.biomaterials.2010.06.049.

[7] Dai C., Yuan Y., Liu C., Wei J., Hong H., Li X., Pan X. Degradable, antibacterial silver exchanged mesoporous silica spheres for hemorrhage control. Biomaterials. 2009; 30: 5364-5375. doi:10.1016/j.biomaterials.2009.06.052.

[8] Davenport RA, Brohi K. Cause of trauma-induced coagulopathy. Curr Opin Anesthesiol. 2015; 29(2): 212-219. doi:10.1097/ACO.0000000000000295.

[9] Davlatov S. et al. Intraoperative determination of the level of amputation in patients with diabetic foot syndrome // Solution of social problems in management and economy. – 2023. – T. 2. – №. 13. – С. 140-151.

[10] Davlatov S. S. The review of the form of neuropathic diabetic foot // Science and education issues. – 2021. – №. 24 (149). – С. 28-42.

[11] DeFrates K.G., Moore R., Borgesi J., Lin G., Mulderig T., Beachley V., Hu X. Protein-based fiber materials in medicine: A review. Nanomaterials. 2018; 8: 457. doi:10.3390/nano 8070457.

[12] Dong C., Lv Y. Application of collagen scaffold in tissue engineering: Recent advances and new perspectives. Polymers. 2016; 8: 42. doi:10.3390/polym8020042.

[13] Fenger-Eriksen C, Fries D, David J-S, Bouzat P, Lance MD, Grottke O, et al. Pre-hospital plasma transfusion: a valuable coagulation support or an expensive fluid therapy? Crit Care. 2019; 23(1): 238. doi:10.1186/s13054-019-2524-4.

[14] Gu B.K., Park S.J., Kim M.S., Kim C.H. Gelatin blending and sonication of chitosan nanofiber mats produce synergistic effects on hemostatic functions. Int. J. Biol. Macromol. 2016; 82: 89-96. doi:10.1016/j.ijbiomac.2015.10.009.

[15] Hess JR, Brohi K, Dutton RP, Hauser CJ, Holcomb JB, Kluger Y, et al. The coagulopathy of trauma: a review of mechanisms. J Trauma Acute Care Surg. 2008; 65(4): 748-754. doi:10.1097/TA.0b013e3181877a9c.

[16] Hossain K.M.Z., Patel U., Ahmed I. Development of microspheres for biomedical applications: A review. Prog. Biomater. 2015; 4: 1-19. doi:10.1007/s40204-014-0033-8.

[17] Huang Y., Feng L., Zhang Y., He L., Wang C., Xu J., Wu J., Kirk T.B., Guo R., Xue W. Hemostasis mechanism and applications of N-alkylated chitosan sponge. Polym. Adv. Technol. 2017; 28: 1107-1114. doi:10.1002/pat.4003.

[18] Ishihara M., Nakanishi K., Ono K., Sato M., Kikuchi M., Saito Y., Yura H., Matsui T., Hattori H., Uenoyama M., et al. Photocrosslinkable chitosan as a dressing for wound occlusion and accelerator in healing process. Biomaterials. 2002; 23: 833-840. doi:10.1016/S0142-9612(01)00189-2.

[19] Jiang X., Wang Y., Fan D., Zhu C., Liu L., Duan Z. A novel human-like collagen hemostatic sponge with uniform morphology, good biodegradability and biocompatibility. J. Biomater. Appl. 2017; 31: 1099-1107. doi:10.1177/0885328216687663.

[20] Kalia S., Dufresne A., Cherian B.M., Kaith B.S., Averous L., Njuguna J., Nassiopoulos E. Cellulose-based bio- and nanocomposites: A. Review. Int. J. Polym. Sci. 2011; 2011: 2341-2348. doi:10.1155/2011/837875.

[21] Lan G., Lu B., Wang T., Wang L., Chen J., Yu K., Liu J., Dai F., Wu D. Chitosan/gelatin composite sponge is an absorbable surgical hemostatic agent. Colloid. Surface. B. 2015; 136: 1026-1034. doi:10.1016/j.colsurfb.2015.10.039.

[22] Li F., Luo P., Liu H. A potential adjuvant agent of chemotherapy: Sepia ink polysaccharides. Mar. Drugs. 2018; 16: 106.

[23] Li J., Wu X., Wu Y., Tang Z., Sun X., Pan M., Chen Y., Li J., Xiao R., Wang Z., et al. Porous chitosan microspheres for application as quick in vitro and in vivo hemostat. Mat. Sci. Eng. C. 2017; 77: 411-419. doi:10.1016/j.msec.2017.03.276.

[24] Lih E., Lee J.S., Park K.M., Park K.D. Rapidly curable chitosan-PEG hydrogels as tissue adhesives for hemostasis and wound healing. Acta Biomater. 2012; 8: 3261-3269. doi:10.1016/j.actbio.2012.05.001.

[25] MacGoey P, Lamb CM, Brooks AJ. Damage control: the modern paradigm. Trauma. 2016; 18(3): 165-177. doi: 10.1177/1460408616629507.

[26] National Academies of Sciences Engineering and Medicine. A national trauma care system: integrating military and civilian trauma systems to achieve zero preventable deaths after injury. Washington, DC: The National Academies Press; 2016. p. 530.

[27] Nie W., Yuan X., Zhao J., Zhou Y., Bao H. Rapidly in situ forming chitosan/epsilon-polylysine hydrogels for adhesive sealants and hemostatic materials. Carbohydr. Polym. 2013; 96: 342-348. doi:10.1016/j.carbpol.2013.04.008.

[28] Obidovna, D. Z., & Sulaimonovich, D. S. (2023). Influence of the Mode of Work and Recreation of the Student's Health. International journal of health systems and medical sciences, 2(3), - С. 3-5.

[29] Obidovna, D. Z., & Sulaymonovich, D. S. (2022). The

concept of" healthy lifestyle" in psychological research. ResearchJet Journal of Analysis and Inventions, 3(06), - C. 53-64.

[30] Obidovna, D. Z., & Sulaymonovich, D. S. (2023). Forming a Healthy Lifestyle for Students on the Example of the Volleyball Section in Universities. European journal of innovation in nonformal education, 3(3), - C. 22-25.

[31] Ostomel T.A., Shi Q., Tsung C.K., Liang H., Stucky G.D. Spherical bioactive glass with enhanced rates of hydroxyapatite deposition and hemostatic activity. Small. 2006; 2: 1261-1265. doi:10.1002/smll.200600177.

[32] Pan H., Fan D., Cao W., Zhu C., Duan Z., Fu R., Li X., Ma X. Preparation and characterization of breathable hemostatic hydrogel dressings and determination of their effects on full-thickness defects. Polymers. 2017; 9: 727. doi:10.3390/polym9120727.

[33] Pidcoke HF, Spinella PC. RDCR symposium fifth-year anniversary edition: global prehospital care rooted in a history of military innovation. Transfusion. 2016; 56 (Suppl 2): S107-S109. doi:10.1111/trf.13606.

[34] Qian Z., Wang H., Tuo X., Guo H., Xu P., Liu D., Wei Y., Liu H., Fan Y., Guo X. A porous sodium polyacrylate-grafted chitosan xerogel for severe hemorrhage control synthesized from one-pot reaction. J. Mater. Chem. B. 2017; 5: 4845-4851. doi:10.1039/C7TB00802C.

[35] Ramos M., Valdés A., Beltrán A., Garrigós M.C. Gelatin-based films and coatings for food packaging applications. Coatings. 2016; 6: 41. doi: 10.3390/coatings6040041.

[36] Rijnhout TWH, Wever KE, Marinus R, Hoogerwerf N, Geeraedts LMG, Jr, Tan E. Is prehospital blood transfusion effective and safe in haemorrhagic trauma patients? A systematic review and meta-analysis. Injury. 2019; 50(5): 1017-1027. doi:10.1016/j.injury.2019.03.033.

[37] Ritz J.P. Intraoperative complications of the lower gastrointestinal tract: Prevention, recognition and therapy // Chirurg. 2015. Feb. 18. German. PMID: 25687814.

[38] Rose J.B., Pacelli S., Haj A.J.E., Dua H.S., Hopkinson A., White L.J., Rose F.R.A.J. Gelatin-based materials in ocular tissue engineering. Materials. 2014; 7: 3106-3135. doi:10.3390/ma7043106.

[39] Shi X., Fang Q., Ding M., Wu J., Ye F., Lv Z., Jin J. Microspheres of carboxymethyl chitosan, sodium alginate and collagen for a novel hemostatic in vitro study. J. Biomater. Appl. 2016; 30: 1092-1102. doi:10.1177/0885328215618354.

[40] Shruti S., Salinas A.J., Lusvardi G., Malavasi G., Vallet-Regi M. Mesoporous bioactive scaffolds prepared with cerium-, gallium- and zinc-containing glasses. Acta Biomater. 2013; 9: 4836-4844. doi:10.1016/j.actbio.2012.09.024.

[41] Song H.F., Chen A.Z., Wang S.B., Kang Y.Q., Ye S.F., Liu Y.G., Wu W.G. Preparation of chitosan-based hemostatic sponges by supercritical fluid technology. Materials. 2014; 7: 2459-2473. doi:10.3390/ma7042459.

[42] Song X., Zhu C., Fan D., Mi Y., Li X., Fu R., Duan Z., Wang Y., Feng R. A novel human-like collagen hydrogel scaffold with porous structure and sponge-like properties. Polymers. 2017; 9: 638. doi:10.3390/polym9120638.

[43] Sukul M., Ventura R.D., Bae S.H., Choi H.J., Lee S.Y., Lee B.T. Plant-derived oxidized nanofibrillar cellulose-chitosan composite as an absorbable hemostat. Mater. Lett. 2017; 197: 150-155. doi:10.1016/j.matlet.2017.03.102.

[44] Wang Q.Q., Kong M., An Y., Liu Y., Li J.J., Zhou X., Feng C., Li J., Cheng X.J. Hydroxybutyl chitosan thermo-sensitive hydrogel: A potential drug delivery system. J. Mater. Sci. 2013; 48: 5614-5623. doi:10.1007/s10853-013-7356-z.

[45] Zhou H.Y., Wang C.W., Niu H.Y., Duan B., Ma X.Y., Hong H., Yuan Y., Liu C.S. A novel droplet-fabricated mesoporous silica-based nanohybrid granules for hemorrhage control. J. Biomed. Nanotechnol. 2018; 14: 649-661.