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ARTICLE TYPE

Hemostatic polymers: concept, state of the art and perspectives

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This article presents a critical overview of the most significant developments in the use of polymers as hemostatic agents. The materials have been divided into two groups, that is, naturally occurring and synthetic. Remarkable examples include collagen, chitosan, bovine serum albumin/glutaraldehyde hydrogels, poly(cyano acrylate)s and poly(alkylene oxide)s. The different mechanisms for their modes of action as well as the structural features that are believed to induce hemostasis are discussed. Finally, an overview of the future challenges is given.

Introduction

The ancient Greeks were the first to give blood a scientific consideration. They found out that blood circulates uninterruptedly thoughtout the body, that it can be venous (which they termed "dark") and arterial (which they termed "red"), and that it is produced in the bone marrow.[1] Moreover, they conducted studies on blood coagulation[2] and discovered that the application of certain plant (e.g., turpentine) and mineral (e.g., alum) compounds on wounds favoured blood stagnation.[3] The process was termed *αμα* (=haíma=blood) *στάσις* (=stàsis=halting), that is, hemostasis. We now know that the hemostatic effect of such compounds is a consequence of the contraction, i.e., the stypsis, of tissue and blood vessels that they cause.

Many of the theories above were revised and refined by ancient Romans, in particular by Galen of Pergamon, arguably the greatest physician of the antiquity. Galen's views have dominated the European medicine until the XVII century, when his claims started to be questioned. It was, however, not until 1905, with the seminal work of Morawitz,[4] that the theory of hemostasis as we know it today (*vide infra*) began to take shape. Probably inspired by these studies, in 1909, Bergel described the topical use of fibrin powder to promote wound healing.[5] The next milestone in the history of hemostatic materials was placed in 1944 by Cronkite[6] and Tidrick[7], who independently reported on early forms of fibrin glues by mixing fibrinogen and thrombin. In a matter of seconds, thrombin catalyses the conversion of fibrinogen into fibrin units, which assemble in a three-dimensional network that seals the wound.[8] Increasingly more effective formulations of fibrin glues have followed in the subsequent years, resulting in the present generation of commercial sealants such as Tisseel®, Beriplast®, and Biocol®. Such glues, however, are costly and, despite various screening protocols, may transmit viral or prion agents because they are obtained from pooled blood products. Hemostats based on inorganic species, e.g., zeolites, have also been developed.[9] These are microporous aluminosilicates with a high surface area that are able to entrap large volumes of water into their pores. As a result, the coagulation factors and the platelets concentrate at the bleeding site accelerating the hemostasis. Materials of this type are commercially available with the name QuikClot®. Although cheaper than fibrin sealants, zeolite powders are not without drawbacks. For example, they may cause thermal injuries due to the strong exothermic reaction with blood, may remain as a foreign body in the wound, and they are toxic for the eyes and the lungs. Hemostats based on fibrin glues and inorganic materials, however, are out of the scope of this article and will not be discussed further.

In the sections below, after a discussion of the basic principles of hemostasis, the various polymer-based hemostatic agents are described. A thorough and critical overview of their modes of action as well as of the structural features that are believed to induce hemostasis is given. Yet, the major challenges in the field are discussed and the reasons why modern polymer chemistry can be helpful in facing them explained. Literature up to the beginning of 2013 is covered.

Fundamentals of hemostasis

Due to space limitation and the presence of excellent reviews in the literature,[10-13] this section will give only an overview of hemostasis. Hemostasis is a complex physiological process that takes place through the synergistic action of three phenomena: (i) vasoconstriction or stypsis; (ii) platelet plug formation; and (iii) blood coagulation or clotting. The three processes come in succession as described below. When a blood vessel ruptures, the body releases natural styptics like thromboxane and epinephrine that stimulate, respectively, a local and a general vasoconstriction. Vasoconstriction is the narrowing of blood vessels following the contraction of small muscles in their walls. This reduces the blood flow and thus the blood loss. At the same

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Table 1 Modes of action of polymer hemostats according to literature data.

	Vasoconstriction	Water absorption	Artificial clot formation/blood gelation	Tissue adhesion/barrier formation	Acceleration of coagulation cascade
Basic poly(amino acid)s					•
Collagen/gelatin				•	•
Chitin/chitosan	•		•	•	
Chitosan/polylysine gel	•		•	•	•
Hydrophobically modified chitosan			•		
Oxidized cellulose			•		
BSA[a]/glutaraldehyde gel			•	•	
Polyphosphates					•
Poly(cyano acrylate)s				•	
Poly(acrylic acid)		•	•		
Poloxamers[b]				•	
PEO[c]-b-PDHA[d]				•	
PEO[c]/chitosan gel	•		•	•	
SAP[e]/chitosan blends	•	•	•	•	
PLA[f]/PCL[g]/chitosan blends	•		•	•	
RADA16-I[h] peptide			•		
Acrylic cationic hydrogels				•	•
GRGDS[i]-tagged PLGA[l]-b-PLL[m]-b-			•		

PEO[c] nanoparticles					

[a] Bovine serum albumin. [b] Poly(ethylene oxide-*b*-propylene oxide-*b*-ethylene oxide). [c] Poly(ethylene oxide). [d] Poly(dihydroxyacetone). [e] Super absorbent polymer such as starch–poly(sodium acrylate-*co*-acrylamide). [f] Polylactic acid. [g] Poly-ε-caprolactone. [h] 16-residue synthetic peptide; see text for further information. [i] Gly-Arg-Gly-Asp-Ser sequence. [l] Poly(lactic-*co*-glycolic) acid. [m] Poly(*L*-lysine).

time, as soon as the blood enters in contact with the collagen present in the outer shell of the vessel membrane, the platelets stick to collagen and become activated (contact pathway). Activated platelets release chemical messengers such as adenosine diphosphate and thromboxane, which cause the aggregation of more platelets at the site of injury and enhance the vascular contraction, respectively. As a result, a platelet plug is formed that physically prevents the blood from escaping the vessel. While all this is going on, the blood clotting mechanism enters into action. This involves a series of coagulation factors – mostly serine proteases – interacting with each other in a cascade reaction that results in the conversion of fibrinogen into fibrin strands, which reinforce the platelet plug. The coagulation factors exist in the blood in an inactive state and, following the damage of a blood vessel, are activated according to two pathways: the intrinsic pathway and the extrinsic pathway. The extrinsic pathway is a chemically concise process that starts 12-15 seconds after the vessel damage. It is triggered by thromboplastin (Factor III), a protein that is normally not present in the blood stream (hence, the term "extrinsic") and that is released by the damaged tissue cells. The intrinsic pathway, on the other hand, is a slower process that utilizes only molecules present in the blood stream (hence, the term "intrinsic"). It is triggered by Factor XII, an enzyme that, like the platelets in the contact pathway, becomes active as soon as it enters in contact with the collagen present in the outer shell of the vessel membrane. Ultimately, both pathways lead to the activation of Factor X, an enzyme that converts prothrombin to thrombin. Thrombin promotes the transformation of fibrinogen into fibrin monomers that, in the presence of Ca^{2+}, polymerize to form fibrin polymers. At the same time, thrombin activates Factor XIII, an enzyme that catalyzes the cross-linking of fibrin polymers, leading to a reinforced platelet plug.

As it will be shown in the next section, hemostatic agents perform their task by enhancing one or more of the processes above. In particular, they can:

i. induce vasoconstriction strengthening the natural stypsis;
ii. absorb water from blood concentrating the coagulation factors as well as the platelets at the bleeding site;
iii. denature the blood proteins and/or activate the platelets inducing aggregation and thus forming clots at the bleeding site;
iv. adhere to tissue strongly so that a mechanical barrier to bleeding is created.
v. accelerate the production of one or more coagulation factors.

Table 1 summarizes which of these phenomena is produced by each class of polymer hemostats described in the following section.

Current polymer-based hemostatic agents

Naturally occurring polymers

Basic poly(amino acid)s. In 1954, Katchalski and co-workers reported that basic poly-α-amino acids such as polylysine (**1**), polyornithine (**2**) and polyarginine (**3**) accelerate the conversion of fibrinogen into fibrin whereas polyaspartic, polyglutamic, and polycysteic acids retard this reaction.[14] In a follow-up study focused on polylysine, they proposed two possible mechanisms for this.[15] In one, polylysine, because of its cationic nature, forms a complex with fibrinogen which is then more readily attacked by the clotting agents. In the other, it acts as a link between fibrinogen and the clotting agents. Miller later demonstrated that polylysine influences the coagulation cascade by activating the coagulation factor X. As said above, this catalyzes the transformation of prothrombin into thrombin, which in turn catalyzes, together with other coagulation-related reactions, the conversion of fibrinogen into fibrin.[16] He also found that polylysines of smaller average molecular weights produce greater yields of thrombin, and that the optimum pH range for the polylysine-mediated activation of prothrombin is 8.0-8.5. No activation occurred at or below pH 6.0. Pedersen and coworkers proposed that blood-coagulation factor VII is auto-activated in the presence of polylysine as a result of the cationic nature of the latter.[17] Because of this behavior, polylysine has been employed to enhance the performance of chitosan-based hemostats (*vide infra*).

Collagen and gelatin. Collagen is the most abundant protein in mammals and makes up most of their connective tissue. It consists of elongated fibrils resulting from the aggregation of tropocollagen, which is composed of three left-handed α-helices assembled into a supramolecular, right-handed triple helix. In 1969, Hait and co-workers reported on the hemostatic properties of bovine collagen (BC).[18, 19] BC was found to be effective for mild to moderate bleeding and to adhere well to wet surfaces so that no suture fixation is required to maintain hemostasis.[20] Apart from this "sealing effect", it is likely that collagen, as in the contact and intrinsic pathways described above, promotes hemostasis also by activating the platelets and Factor XII. BC has been marketed with various names such as Avitene™ (sheets, flour, and foam sponges), Helistat™ (sponges), Helitene™ (fiber form, pads), and Instat MCH™ (microfibrillar form). Although biocompatible and biodegradable, BC may produce allergic/immune reactions to porcine proteins as well as a foreign body reaction.

Upon irreversible hydrolysis, collagen affords gelatin, which is a hemostat as well.[21-23] The first clues about the ability of gelatin to halt bleeding date back to the late XIX century.[24, 25] It was however not until the 1940s that gelatin found commercial application. It shares with collagen a similar mechanism of action and disadvantages. However, for reasons that are not entirely clear yet, its hemostatic abilities are less pronounced than those

of collagen. Hence, it is sometimes used in combination with

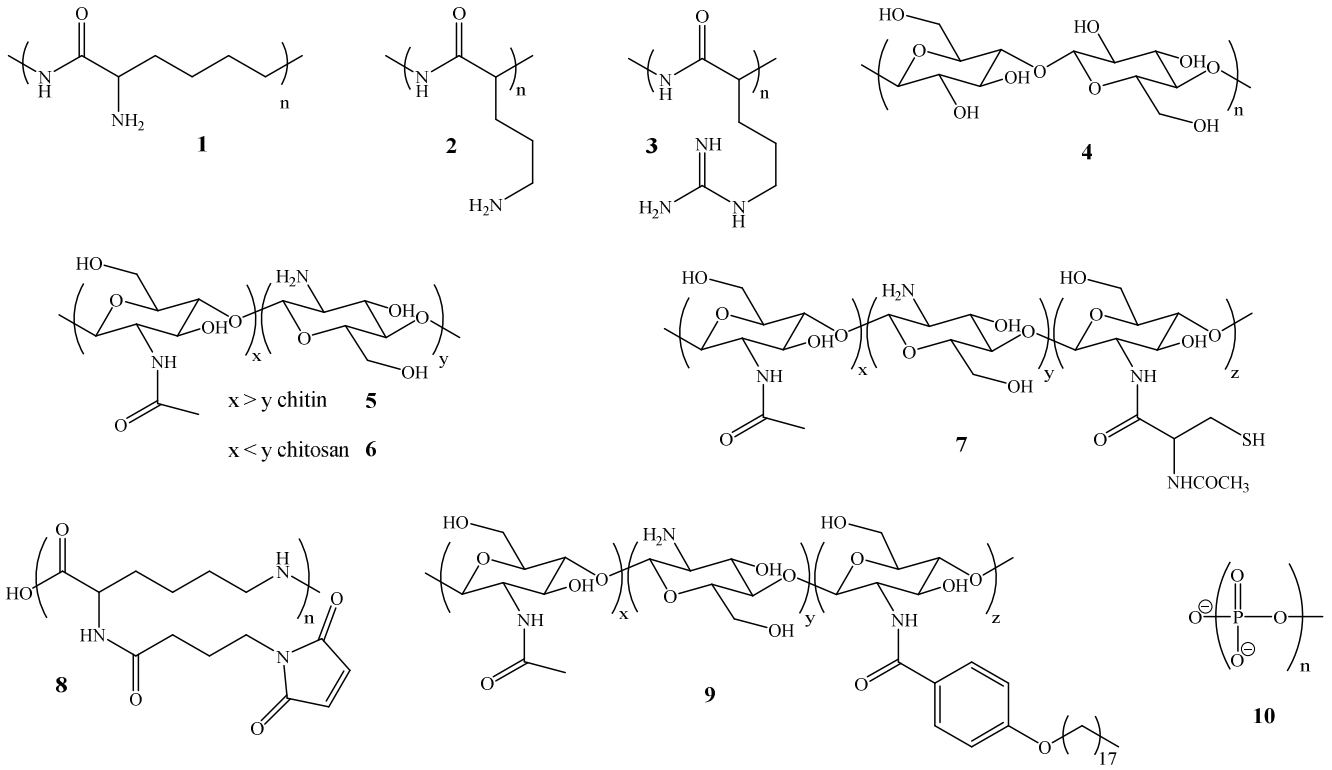

Chart 1 Naturally occurring polymer hemostats

thrombin as a performance enhancer. Gelatin hemostats have been marketed as Gelfoam® (sponge and powder) and Surgifoam® (sponge and powder), to name a few.

Oxidized cellulose. Under oxidative conditions, the primary and secondary alcohol moieties contained in cellulose (**4**) can be converted to aldehyde, ketone, and carboxyl groups.[26-28] The *β*-D-1,4 glucosidic bonds are also oxidized in the process, which results in the depolymerization of cellulose. The type and the extent of oxidation depend on the nature of the oxidizing agent as well as on the oxidation conditions. These structural modifications confer oxidized cellulose (OC) chemical, physical and mechanical properties that are significantly different from those of conventional cellulose.[29] For instance, OC is fully bioabsorbable in humans, the degradation occurring through both chemical and enzymatic routes. Yet, it is an efficient enterosorbent when used in the form of a gel,[30] and it has pronounced antibacterial[31, 32] and hemostatic properties.[29] The latter are probably related to the presence of the carboxyl groups, which decrease the pH, leading to the nonspecific aggregation of platelets and, consequently, to the formation of an artificial clot. This is then firmly supported by the OC structure. The lack of a suitable mechanical support for the clots may explain, at least in part, why other polyacids, e.g., polyaspartic and polycysteic acids, are not equally good antihemorrhagics. Although the reason is still unclear, OC is reported to be a less effective hemostat than collagen, especially when it comes to profuse bleeding and irregular cavities or lacerations.[20] On the other hand, similar to collagen and gelatin, oxidized cellulose may induce a foreign body reaction. OC is found in commerce with the names Surgicel™ (gauze and fleece), Oxycel™ (gauze and powder), Gelitacel™ (gauze, fleece and powder) and Interceed™ (gauze).

Chitin and chitosan.[33-38] Chitin (**5**) and chitosan (**6**) are closely related materials. Chitin is a polysaccharide with a structure similar to that of cellulose, the only difference being the presence of an amine or an acetyl amine group in place of the hydroxyl groups on the 2 and 2′ carbons. When the degree of deacetylation exceeds 50%, chitin is referred to as chitosan. Due to the higher amount of "free" amine moieties, chitosan is soluble in aqueous acidic solution, which makes it a more convenient material and explains why it is preferred to chitin. The discovery of chitosan's hemostatic properties dates back to the early 1980s.[39, 40] After some 30 years of research, chitosan's antihemorrhagic mode of action is still not fully understood. Since amino groups are key functional groups in both chitosan and polylysine, one would expect the two materials to have similar hemostatic modes of action. However, this is not what it is found in the literature. Independent studies suggest that, like collagen, gelatin and oxidized cellulose, chitosan does not interfere directly with the coagulation cascade.[40] Through its positively charged, protonated amino groups, chitosan seems to interact strongly with the negatively charged platelets membrane, leading to their activation and consequent thrombus formation. The fact that blending chitosan with organic acids, which increases the degree of protonation, enhances its hemostatic performance supports this claim. Yet, the process seems to be favored by the ability of chitosan to attract various circulating plasma proteins, which adsorb to the material surface, thus promoting the adhesion of platelets.[41] A local vasoconstriction has also been reported in the presence of chitosan. Moreover, like collagen, chitosan has demonstrated pronounced mucoadhesive properties, which are

likely to contribute to its overall antihemorrhagic effect. Last but not least, chitosan seems also to have a role in the wound healing process *via* macrophage activation, stimulation of cell proliferation and histo-architectural tissue organization.[42] Whether the different behavior of chitosan and polylysine is ascribable to the lack or the presence of certain functional groups or to the fact that rather different approaches have been used to investigate the two materials, further studies are required to elucidate their different modes of action. Marketed chitosan-based hemostats include HemCon® (patches and pads), QuikClot® (gauze, pads and sponge), and Clo-Sur® (pads). Up to date, no harmful effects have been associated with the use of these dressing. Notably, a recent study demonstrated that the HemCon® bandage is safe also for shellfish allergic patients.[43]

Recently, Zhao and co-workers described the facile preparation of chitosan/polylysine hydrogels exhibiting excellent hemostatic properties and no toxicity to L929 cells.[44] The materials were obtained by reacting, *via* an *in situ* Michael addition, thiol-modified chitosan (**7**) and ε-polylysine modified with maleimide groups (**8**). The authors ascribed the materials' antihemorrhagic action to a synergistic effect of the intrinsic hemostatic property of chitosan and the good adhesiveness (4 times higher than that of commercial fibrin sealants) of the hydrogels. However, in light of what is said above, one cannot exclude a possible contribution of polylysine to the overall performance of the hydrogel. In another recent study, Dowling and co-workers showed that hydrophobically modified chitosan (**9**) is capable of a reversible hemostatic action.[45] The material was prepared by reacting 4-octadecyl benzaldehyde with the amine groups of chitosan, which resulted in a bottle brush-like copolymer. The authors claim that, as fibrin self-assembles into a network that transforms liquid blood into a gelled clot, the hydrophobic segments of their modified chitosan insert into the membrane of blood cells, forming a tridimensional network that gels the blood. The network is disrupted, and the blood re-liquefied, upon the addition of α-cyclodextrin. This competes with the cell membranes and, probably due to a higher binding affinity, sequesters most of the chitosan's hydrophobic moieties, hindering the gel formation. Preliminary tests with animal injury models have shown that the antihemorrhagic effect of hydrophobically modified chitosan is comparable to that of fibrin glues.

Bovine serum albumin/glutaraldehyde gels. Astride the second and third millennium, Gundry and co-workers developed an effective surgical adhesive based on bovine serum albumin (BSA) and glutaraldehyde.[46] The product is marketed with the name BioGlue®. Glutaraldehyde is a known protein cross-linker and, as such, when it enters in contact with BSA, forms a 3D network that adheres tightly to the surrounding tissues as well as to synthetic graft materials, creating a mechanical seal. The polymerization starts within 20-30 seconds from mixing and takes around 2 minutes to complete. A hemostatic matrix based on a similar cross-linking reaction has also been developed and commercialized as BioFoam®. In this case, the reaction between BSA and glutaraldehyde produces a flexible hydrogel that provides a mechanical barrier to bleeding. The materials are FDA approved.

Inorganic polyphosphates. Inorganic polyphosphates (IPs, **10**) are a class of biopolymers found in every cell of any living organism. These linear macromolecules are composed of orthophosphate residues kept together by high-energy phosphoanhydride bonds. IPs are able to chelate metal ions, are components of cell capsules, and can act as reservoirs of orthophosphate.[47] In 2006, Morrissey and co-workers showed that IPs with a degree of polymerization ≥45 accelerate blood clotting by acting directly on the coagulation cascade.[48] In particular, a series of *in vitro* experiments demonstrated that IPs (i) activates the contact pathway of blood coagulation as well as the conversion of Factor V to Va, and (ii) delays fibrinolysis, probably by enhancing the function of natural antifibrinolytic proteins. As a result, an earlier peak of thrombin is generated during the clotting, which leads to an earlier and more robust coagulation. Notably, no change was observed in the total amount of thrombin generated. The reason why the average molecular weight of IPs needs to be greater than a certain value for the phenomenon to manifest itself is unclear. Another study showed that IPs are able to activate also the coagulation Factor XII.[49] In another investigation, the same research group reported that polyP has an impact on the fibrin clot structure.[48] They showed that polyP is incorporated into clots, which exhibited an increased turbidity and contained thicker fibrils. Yet, the clots looked firmer and more resistant to fibrinolysis. A drawback on the use of IPs as a hemostat is its instability in the blood or plasma due to the presence of phosphatases.

The advantages and disadvantages of relevant, naturally occurring polymer hemostats are summarized in Table 2.

Synthetic polymers

Poly(cyano acrylate)s. Fischl[50] and Ashley[51] were among the firsts to investigate the use of cyano acrylates as adhesives for the sutureless closure of skin incisions. Due to the highly electron-deficient nature of the C=C bond, cyano acrylates polymerize very rapidly in the presence of nucleophiles such as the water contained in the blood and other body fluids. The resulting polymers (**11**) are colorless and amorphous, have high molecular weights and, because of their high polarity, stick well to the body tissues, keeping the wound edges tightly together and halting the bleeding.[52-55] While short-chain derivatives (methyl- and ethyl-cyano acrylate) have proved to be histotoxic, longer chain derivatives (e.g., octyl and decyl-cyano acrylate) are considered relatively non-toxic, although they may induce tissue inflammation followed by a foreign-body granuloma response.[56, 57] HistoAcryl®, LiquiBand®, PeriAcryl®, and GLUture® are some of the cyano acrylate tissue adhesives that have hit the market.

Poly(acrylic acid). In the early 1980s, Russian scientists developed Feracryl®, a poly(acrylic acid) (**12**) containing up to 2.5% of iron(III) salt coordinated to it.[58, 59] The material showed

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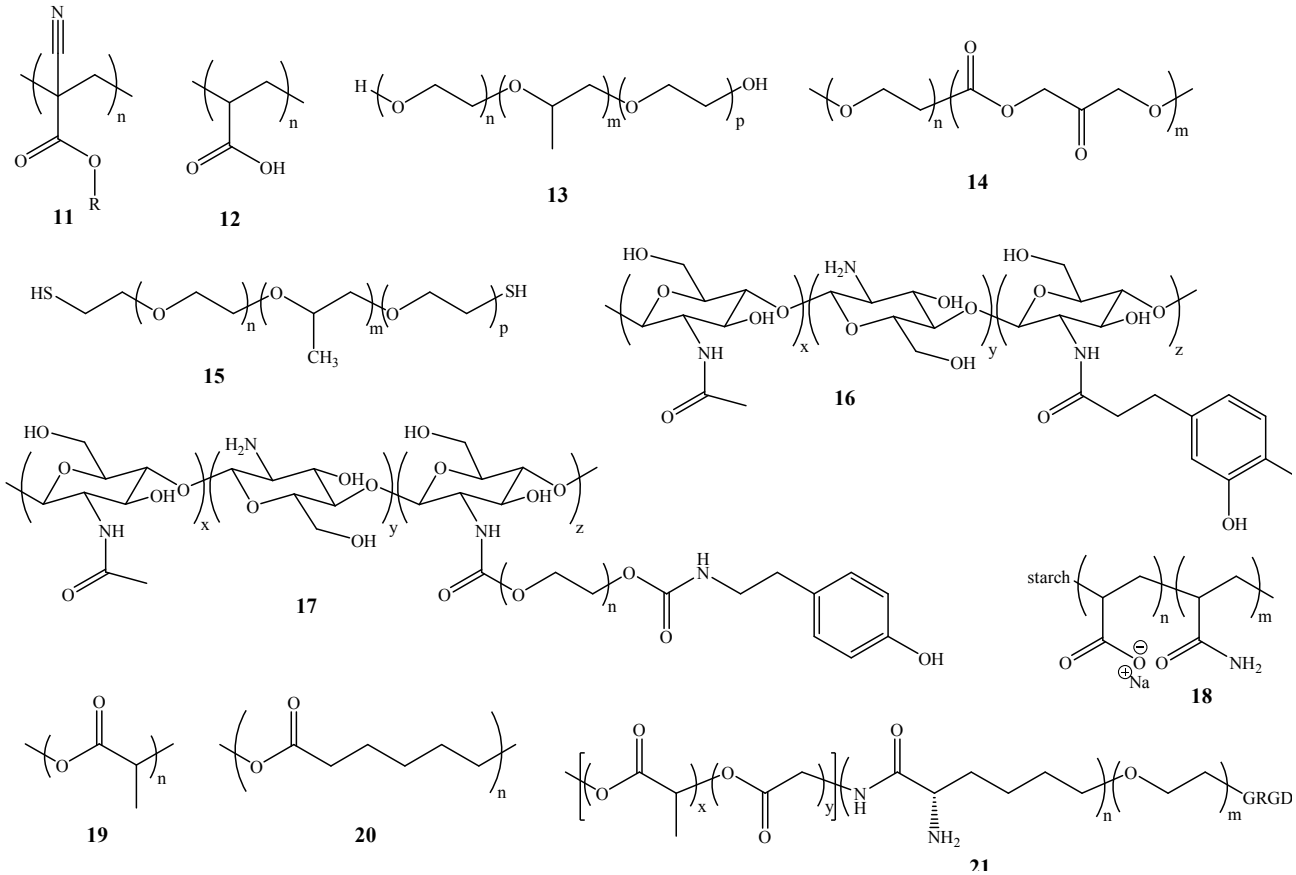

Chart 2 Synthetic polymer hemostats.

good hemostatic properties, which the authors ascribed to the formation of "artificial" clots consisting of Feracryl®/plasma proteins adducts.[58, 60] Since the hemostatic activity and the polymer solubility were found to be dependent on the iron content, the authors surmised that the latter might have an active role in the adduct formation.[61] However, being poly(acrylic acid) highly hygroscopic, one cannot exclude that the absorption of water from blood with the subsequent concentration of coagulation factors and platelets at the bleeding site might play a role in the overall antihemorrhagic effect. *In vivo* experiments demonstrated that Feracryl® is nontoxic when applied locally, nor caused it complications when used externally as well as on internal organs during surgery.[62] Moreover, the material showed to have strong antibacterial and antifungal activities.[63] Poly(acrylic acid)s containing other metals have also been developed.[64, 65]

Poly(alkylene oxide)s. Poly(ethylene oxide) (PEO) and poly(propylene oxide) (PPO) are the two most prominent members of the poly(alkylene oxide) family. Although the former is hydrophilic and the latter hydrophobic, they both are not biodegradable, but biocompatible, chemically inert, and eliminated from the body primarily *via* renal excretion. In 2001, Wang and co-workers demonstrated that blends of poloxamers, i.e., PEO-*b*-PPO-*b*-PEO amphiphilic triblock copolymers (**13**), are effective bone hemostasis materials.[66] Marketed as Ostene®,[67] this waxy compound sticks firmly onto the bone surface creating a mechanical barrier that rapidly halts the bleeding. Notably, it does not increase infection rate nor interferes with bone healing nor cause chronic inflammation. Recently, Spector and co-workers reported on a rapidly acting hemostatic hydrogel based on a poly(ethylene glycol)-*b*-poly(dihydroxyacetone) diblock copolymer (**14**).[68] The material proved to be resorbable and non-toxic. Yet, like Ostene® and other agents described above, the hemostatic action seems to be purely mechanical rather than due to an activation of the coagulation cascade.

Chitosan/synthetic polymer materials. In 2011, Lee and coworkers showed that, at body temperature and physiological pH, thiol-terminated poloxamers (**15**) react instantaneously with catechol-conjugated chitosan (**16**) to form hydrogels with effective antihemorrhagic properties.[69] The materials showed excellent stability and mechanical properties both *in vitro* and *in vivo*. Park and coworkers used a mixture of horseradish

peroxidase and hydrogen peroxide to cross-link, *in situ*, chitosan containing tyramine-modified poly(ethylene glycol) (**17**).[70] The resulting hydrogel showed tissue adhesiveness up to 20 times higher than that of fibrin glue and functioned as an effective hemostat. The antihemorrhagic activity of both materials is ascribed to the combined effect of the marked hydrogel adhesiveness and the intrinsic hemostatic property of chitosan.

Hudson and coworkers used a superabsorbant polymer (SAP) such as starch–poly(sodium acrylate-*co*-acrylamide) (**18**) to enhance the blood coagulation properties of chitosan.[71] Like zeolites, SAP entraps large volumes of water, concentrating the coagulation factors and the platelets at the bleeding site, which accelerates the hemostasis. The material also demonstrated a strong antibacterial activity against *Pseudomonas aeruginosa* as well as no cytotoxicity. Petsom and coworkers used chitosan/polylactic acid (PLA, **19**)/polycaprolactone (PCL, **20**) blends to prepare hemostatic wound dressing devices.[72] Since PLA and PCL do not mix well with chitosan, glycerin and polyethylene glycol had to be added as compatibilizers. According to the authors, only chitosan was responsible for the hemostasis whereas PLA improved the film strength and PCL the flexibility.

Oligopeptides. In 2006, Ellis-Behnke and coworkers reported on the high hemostatic efficacy of a 16-residue synthetic peptide (RADA16-I) applied directly to wounds in the brain, spinal cord, femoral artery, liver, or skin of mammals.[73] As soon as it enters in contact with the alkaline metal cations (e.g., Na^+) present in the blood, RADA16-I rapidly self-assembles into interwoven nanofibers, forming a hydrogel with pores of ca. 100-mesh and a water content of over 99.5%.[74, 75] As for other hydrogels described above, this results in the formation of a plug of clotted blood that seals the wound. When compared with Gelfoam® in a rat kidney injury model, the hydrogel based on RADA16-I afforded a reduced tissue inflammatory reaction as well as an improved biological tissue compatibility.[76]

Acrylic cationic hydrogels. In 2010, Kofinas and coworkers prepared, by means of traditional radical polymerization, a series of cationic hydrogels of the type poly[(acrylamide)-*co*-(*N*-(3-aminopropyl)methacrylamide)-*co*-(*N*,*N*′-methylenebisacrylamide)] capable of activating, *in vitro*, the blood-coagulation factor VII and thus accelerates fibrin formation.[77] As in the case of polylysine, the presence of positive charges plays certainly an important role in the activation process. However, the experimental data indicate that the cross-link density, and thus the stiffness of the material, as well as the water content of the hydrogel are likely to contribute significantly to the activation reaction.

Polymer nanoparticles. While hemostatic powders, sponges, gauzes, gels etc. are of great help for controlling the bleeding from external and compressible wounds, they can do little for internal hemorrhage. Recently, Lavik and coworkers developed biodegradable polymeric nanoparticles that, when intravenously administered, are able to reduce significantly internal bleeding in animal models.[78-80] The particles were based on poly(lactic-*co*-glycolic) acid-*b*-poly(L-lysine)-*b*-poly(ethylene glycol) triblock copolymers tagged at the ω-chain end with peptide sequences such as Gly-Arg-Gly-Asp-Ser (GRGDS) (**21**). Yet, they had an average hydrodynamic diameter of ca. 400 nm. In a rat femoral artery injury model, the nanoparticles halved the bleeding time.[78] Moreover, in a lethal liver resection injury in rats, they increased the 1 h survival from 40-47% in controls to 80%.[79] The overall performance of the nanoparticles was subsequently improved by increasing the GRGDS surface density.[80] A series of control experiments suggested that the nanoparticles interact specifically with platelets inducing their aggregation and thus enhancing the blood clotting. Furthermore, the interaction seems to be due to the GRGDS moiety with only a negligible contribution of the polymer matrix.

Table 3 summarizes the advantages and disadvantages of relevant synthetic polymer hemostats.

Challenges and perspectives

Although several hemostats have been developed and marketed in the last decades, hemorrhage is still a major cause of morbidity and mortality. It is estimated that almost half of combat fatalities as well as the vast majority of civilian trauma fatalities are due to uncontrolled bleeding. Moreover, hemorrhage is a potential complication of any surgical procedure. The reason for the partial success of the present generation of hemostats lies mainly in the fact that none of them is free of drawbacks (Tables 2 and 3). For instance, fibrin glues are costly and may transmit viral or prion agents. Zeolites may cause thermal injuries and are toxic for the eyes and the lungs. Collagen and gelatin may produce allergic/immune reactions. Oxidized cellulose is not very effective against profuse bleeding and on irregular lacerations. Poly(cyano acrylate)s may be toxic and induce tissue inflammation. In addition, all the materials above may induce a foreign body reaction. Last but not least, inorganic polyphosphates are instable in the blood due to the presence of phosphatases. The challenge for the coming years is therefore to design and prepare hemostats that are increasingly more effective, safer, and cheaper.

Polymers are very promising materials for facing these challenges. Polymer-based materials exhibit better mechanical properties (strength, deformability, elasticity, etc.) and processability than those based on low molecular weight compounds. Yet, compared to inorganic materials and biological polymers, synthetic polymers provide a more versatile synthetic platform for the preparation of functional materials. Nowadays, a great variety of powerful synthetic techniques have become available to the polymer chemist which allows fine-tuning of the final properties of a material. Processes such as atom transfer radical polymerization,[81-83] reversible addition-fragmentation and transfer radical polymerization,[84, 85] organocatalytic living ring-opening polymerization,[86-88] just to mention a few, have enabled the facile preparation of polymers with predetermined molecular weights, composition, functionality and molecular architecture. Techniques for mechanistic transformation[89] as well as click chemistry[90-92] have further expanded the scope of polymeric materials. The former enable the blocky enchainment of monomers that cannot be polymerized *via* the same polymerization mechanism, whereas the latter is a post-polymerization process that allows for the highly efficient "welding" of two or more preformed polymer segments. It is hence surprising that only a few examples of synthetic polymers with hemostatic properties have been reported to date.

Although the mode of action of each class of polymers described above should be investigated further, some general structure-property relationships can be identified in the discussion made in the previous sections. These may serve as guidelines for designing the next generation of polymer hemostats. For example, the presence of electrical charges in the polymer chain appears to be important in promoting hemostasis. In particular, both positive and negative charges seem able to activate, in one way or another, one or more coagulation factors and thus to accelerate the coagulation cascade. Also, they can activate the platelets and form insoluble adducts with various blood proteins with the consequent formation of "artificial" clots that help plugging the wound. Last but not least, the charges, together with those functional groups capable of forming hydrogen bonds like the hydroxyl and amine moieties, make polymers more hydrophilic and (muco)adhesive. On the one hand, a high hydrophilicity allows for the absorption of a high amount of water from the blood, which concentrates both the coagulation factors and the platelets at the bleeding site and thus accelerates hemostasis. Hydrogels are particularly appealing materials in this respect. On the other hand, a high (muco)adhesiveness enables the polymer to adhere firmly to the surrounding tissues, creating a physical barrier that prevents the blood from escaping the vessels. High molecular weights and chain flexibility as well as the presence of thiol-bearing functional groups are also known to enhance the mucoadhesiveness of polymers.[93] The flexibility of polymer chains is inversely proportional to the degree of cross-linking, that is, the higher the cross-linking density, the lower the flexibility of the chains. On the other hand, thiols are able to form covalent bonds with the cysteine-rich sub-domains of mucus glycoproteins, which strengthen the adhesion.

When developing the next generation of polymer hemostats, apart from taking these general guidelines into consideration, the polymer chemist will have to design macromolecular architectures that (i) are biocompatible and biodegradable, (ii) can be made up of renewable building blocks via "green" chemical routes, (iii) are easily recyclable, and (iv) can be produced in an economical and industrially friendly manner. Given the complexity of the challenge, it is unlikely that the conventional trial-and-error and one-variable-at-time approaches alone might provide the sought materials in a reasonable time and with an acceptable economic effort. Chemoinformatics offers unique opportunities in this respect, providing equations of the type $P=f(d_1, d_2, \ldots, d_n)$, where P is the property of interest (e.g., the clotting time of an hemostatic agent, the (muco)adhesiveness of a polymer etc.) and $d_1, \ldots, d_n$ are the molecular descriptors.[94, 95] According to Todeschini and Consonni, a *molecular descriptor is the final result of a logic and mathematical procedure which transforms chemical information encoded within a symbolic representation of a molecule into a useful number*.[96] The performance of a polymer hemostat can then be assessed simply by calculating, by means of specific software, the descriptors $d_1, \ldots, d_n$ prior to any synthesis or experimental assay. Hence, only the most promising candidates are prepared in the lab, saving time and money.

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Notes and references

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Table 2 Advantages and disadvantages of relevant, naturally occurring polymer hemostats.

	Advantages	Disadvantages
Collagen/gelatin	• Biocompatible and biodegradable • No suture fixation required for mild to moderate bleeding • Collagen more effective than oxidized cellulose • Approved and commercially available in various forms	• Limited efficacy in cases of profuse bleeding • May produce allergy and/or foreign body reaction • May transmit viral or prion agents
Chitin/chitosan	• Biocompatible and biodegradable • Effective hemostatic action • Approved and commercially available in various forms	• May produce allergy and/or foreign body reaction
Chitosan/polylysine gel	• Improved hemostatic action over pristine chitosan	• Still in preclinical phase: - Neither commercially available nor approved - Adverse effects on humans unknown
Hydrophobically modified chitosan	• As effective as fibrin glue • Reversible hemostatic action	• Still in preclinical phase: - Neither commercially available nor approved - Adverse effects on humans unknown
Oxidized cellulose	• Biocompatible and biodegradable • Approved and commercially available in various forms • Pronounced antibacterial activity	• Not as effective as collagen • Limited efficacy in cases of profuse bleeding • Limited efficacy in cases of irregular cuts • May produce foreign body reaction
BSA[a]/glutaraldehyde gel	• Biocompatible and biodegradable • Effective hemostatic action • Approved and commercially available in various forms	• May produce allergy and/or foreign body reaction • May transmit viral or prion agents
Polyphosphates	• Biocompatible and biodegradable • Effective blood clotting *in vitro*	• Still in preclinical phase: - Neither commercially available nor approved - Adverse effects on humans unknown - *In vivo* effectiveness unknown • Unstable in the blood or plasma

[a] Bovine serum albumin.

Table 3 Advantages and disadvantages of relevant, synthetic polymer hemostats.

	Advantages	Disadvantages
Poly(cyano acrylate)s	• Biocompatible and biodegradable • Effective hemostatic action • Long-chain derivatives are approved and commercially available	• Short-chain derivatives are histotoxic • May produce foreign body reaction and tissue inflammation

Poly(acrylic acid)	• Biocompatible and biodegradable • Effective hemostatic action • Pronounced antibacterial and antifungal activities • Approved and commercially available	• May produce foreign body reaction and tissue inflammation
Poloxamers[a]	• Biocompatible • Effective bone hemostasis • No inflammatory response • No increased risk of infection • Approved and commercially available	• Not biodegradable
PEO[b]-*b*-PDHA[c]	• Biocompatible and resorbable • Effective hemostatic action	• Still in preclinical phase: - Neither commercially available nor approved - Adverse effects on humans unknown
PEO[b]/chitosan gel	• Biocompatible and resorbable • Effective hemostatic action • Excellent stability and mechanical properties	• Still in preclinical phase: - Neither commercially available nor approved - Adverse effects on humans unknown
SAP[d]/chitosan blends	• Biocompatible • Effective hemostatic action • Antibacterial activity against *Pseudomonas Aeruginosa*	• Still in preclinical phase: - Neither commercially available nor approved - Adverse effects on humans unknown
PLA[e]/PCL[f]/chitosan blends	• Biocompatible and biodegradable • Effective hemostatic action	• Still in preclinical phase: - Neither commercially available nor approved - Adverse effects on humans unknown
RADA16-I[g] peptide	• Biocompatible and biodegradable • More effective than gelatin • Reduced tissue inflammatory reaction	• Still in preclinical phase: - Neither commercially available nor approved - Adverse effects on humans unknown
Acrylic cationic hydrogels	• Effective blood clotting *in vitro*	• Still in preclinical phase: - Neither commercially available nor approved - *In vivo* effectiveness unknown - Adverse effects on humans unknown
GRGDS[h]-tagged PLGA[i]-*b*-PLL[l]-*b*-PEO[b] nanoparticles	• Biocompatible • Effective hemostatic action in case of internal bleeding	• Still in preclinical phase: - Neither commercially available nor approved - Adverse effects on humans unknown

[a] Poly(ethylene oxide-*b*-propylene oxide-*b*-ethylene oxide). [b] Poly(ethylene oxide). [c] Poly(dihydroxyacetone). [d] Super absorbent polymer such as starch–poly(sodium acrylate-*co*-acrylamide). [e] Polylactic acid. [f] Poly-ε-caprolactone. [g] 16-residue synthetic peptide; see text for further information. [h] Gly-Arg-Gly-Asp-Ser sequence. [i] Poly(lactic-*co*-glycolic) acid. [l] Poly(*L*-lysine).