SYNTHESIS POLY(VINYL FORMAL) SPONGES FOR HEMOSTATIC DRESSING

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The relevance of the development of hemostatic agents is related to the fact that severe blood loss due to hemorrhage continues to be the leading cause of preventable death of patients with military trauma and the second leading cause of death of civilian patients with injuries [1, 2]. Standard gauze field dressings and direct pressure by tourniquets in some situations can be inadequate in controlling hemorrhage [3]. Despite the number and variety of commercially available hemostatic materials, lots of them have a number of side effects and limitations. The main active ingredient of some hemostatic dressings is chitosan, a natural polysaccharide containing amino groups. At physiological pH, the positive charge of the protonated amino groups facilitates attraction of negatively charged erythrocytes and formation of a dense clot regardless of the physiological mechanism of blood coagulation. Due to this, the bleeding stops quickly. Chitosan also actively adsorbs water from blood, thus concentrating the natural factors of blood coagulation and thereby activating the natural coagulation mechanisms. However, chitosan is difficult to remove from the wound because of its high adhesion to the tissues of the damaged organ. One of the disadvantages of styptic bandages can be moreover the possibility of tissue damage due to their strong adhesive properties.

The accumulated knowledge in the field of the hemostasis mechanisms and development of hemostatic agents with different composition and structure allows us to define the main requirements for increasing the effectiveness of hemostatics: hydrophilicity, the presence of positively charged functional groups, spatial porous structure, and good adhesion. An important characteristic for improving effectiveness of hemostatics is their macroporous structure which can also contribute to the rupture of platelets with the release of thrombin and aggregation of erythrocytes due to structural and mechanical factors. Polyvinyl formal (polyvinyl acetal), as a biocompatible hydrophilic polymer, meets the aforementi.

Acetalization of PVA was performed by condensation of PVA with formaldehyde in the presence of sulfuric acid as described in our previous paper. The composition of solutions used to synthesize PVA acetals, also known as poly(vinyl formals) (PVFs), are listed in Table I.

Table I. Composition of solutions used to synthesize PVF sponges.

Component	PVF-CPA			PVF-FPA
	original	+ $mSiO_2$	+ $CaCO_3$	original
PVA	7.3 %	7.3 %	7.3 %	8.4 %
Triton X-100	0.3 %	0.3 %	0.3 %	0.3 %
Formaldehyde	3.5 %	3.5 %	3.5 %	3.5 %
Sulfuric acid	3.2 %	3.2 %	3.2 %	3.2 %
$mSiO_2$	—	0.5 %	—	—
$CaCO_3$	—	—	2.0 %	—
Distilled water	85.7 %	85.2 %	83.7 %	84.6 %

The estimated molar ratio of formaldehyde to hydroxyl groups in sponges was 0.5. Two PVF sponges with coarse and fine pore architecture (further denoted as PVF-CPA and PVF-FPA), and two hybrid sponges based on PVF-CPA and filled with modified, aminosilane grafted, fumed silica A-300 ($mSiO_2$) or calcium carbonate ($CaCO_3$) have been synthesized. The composite materials were denoted as PVF-CPA + $mSiO_2$ and PVF-CPA + $CaCO_3$. PVF-CPA and PVF-FPA sponges were also partially (50 %) filled with chitosan hydrogel (CH) composition using a previously described method. The chitosan-based samples were denoted as PVF-CPA + CH and PVF-FPA + CH, respectively. The weight fraction of glutaraldehyde in crosslinked chitosan hydrogel was 7 %, while the chitosan weight fraction in hydrogel composition used to partially fill PVF-CPA and PVF-CPA sponged was 7 and 3.5 %, respectively.

Since polyvinyl formal is synthesized by the acetalization reaction of polyvinyl alcohol with formaldehyde in the presence of inorganic acid as a catalyst, the carbonyl group of formaldehyde reacts with two adjacent hydroxyl groups of PVA units forming methylenedioxy group. Therefore, in the general formula of polyvinyl formal the methylenedioxy and hydroxyl groups of the side chain as well as of the aliphatic –CH and –CH_2 groups of the polymer backbone are present.

Polyvinyl formal (PVF) sponges with open system of macropores and PVF sponges modified with pH- and thermosensitive hydrogels were synthesized and characterized in our previous study Because of the open-pore structure, fast swelling of PVF, and their mechanical properties, we used PVF sponges with fine and coarse pore architecture in this study to investigate their potential application as hemostatic dressing. Unmodified sponges (PVF-FPA and PVF-CPA) and sponges with incorporated nanosilica, calcium carbonate, and chitosan hydrogel were developed and tested. Fig. 1. Particles of $CaCO_3$ have a cubic shape and a size of 2–5 μm. The distribution of Ca in the composite matrix is uniform, while nanosilica is distributed in the form aggregates of particles

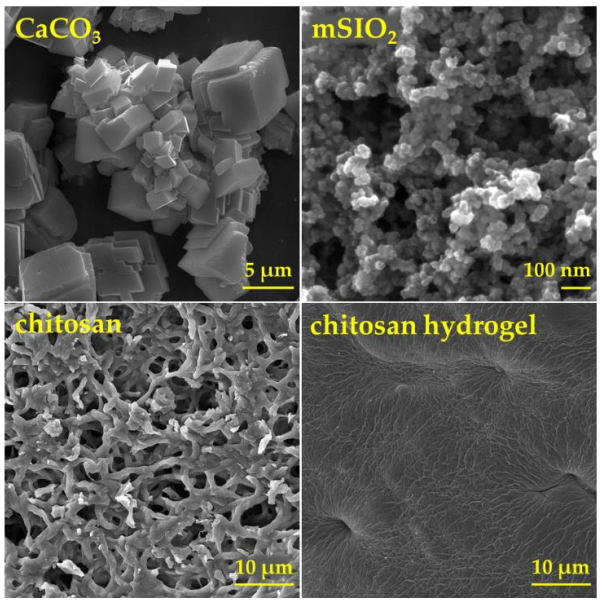

Fig. 1. Microphotographs (SEM) of $CaCO_3$, modified SiO_2, chitosan, and chitosan hydrogel (dried at critical point of CO_2).

The effect of the hydrophilic properties of hemostatic materials on the factor concentrating is based on fast adsorption of water. To estimate the concentrating effect of PVF materials towards natural factors of blood coagulation, we studied water sorption by PVF-based samples in distilled water and in three buffer solutions with pH 1.68, 6.86, and 9.18 at 25 °C. The swelling degree for chitosan-modified PVF with fine pore architecture was significantly higher compared to PVF with coarse pore architecture (Fig. 2). This can be attributed to more intense action of capillary forces within the fine pores. When diameter of the capillaries is sufficiently small, the combination of surface tension and adhesive forces between the liquid and pore act to propel the liquid inside the porous material.

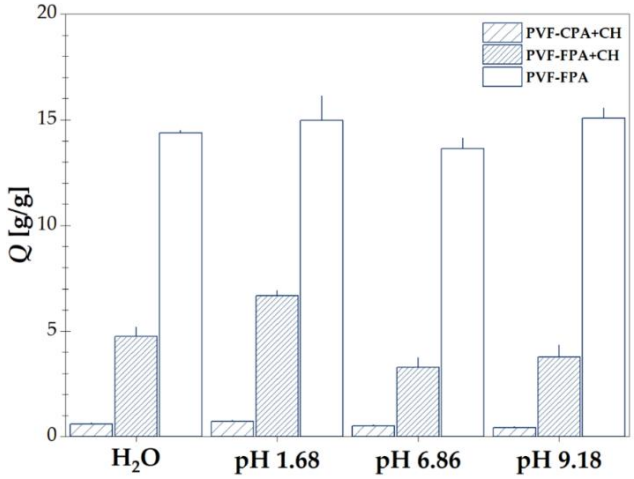

Fig. 2. Equilibrium swelling degree (after 72 h) of PVF-CPA and PVF-FPA modified with chitosan hydrogel (CH) and original PVF-FPA.

Filling sponges with chitosan hydrogel resulted in decrease of equilibrium swelling degree ((Fig. 1). For PVF-FPA the swelling degree at pH 6.86 decreased approximately fourfold: from 13.6±0.5 g/g to 3.3±0.5 g/g upon introducing chitosan hydrogel into PVF-PVF composition. Due to the absence of charged functional groups, the swelling degree of unmodified PVFs was independent of pH, while PVF samples filled with chitosan hydrogels had higher equilibrium swelling degree at acidic pH due to osmotic swelling. For PVF-FPA and PVF-FPA + CH the difference in the equilibrium swelling degrees between pH 1.68 and 6.86 were 1.3±1.6 g/g (no difference) and 3.4±0.7 g/g, respectively.

Currently, the hemostatic properties of the developed hybrid hydrogel materials are being tested in vivo experiments. The results will be reported in subsequent publications.

Thus, from the studies we carried out, it can be concluded that in order to further improve the hemostatic properties of composite hemostatics based on PVF-sponges, special attention should be paid to increasing their hydrophilic properties and overall porosity.

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