

Novel Biodegradable Devices Forming Bioadhesive Hydrogels for Hemostatics and Adhesion Barriers (1): Preparation of Transparent Water-Swellable Film and Clinical Applications

Tomoko Ito¹, Keisuke Ueda¹, Masazumi Eriguchi¹, Yoshiyuki Koyama^{1,2}.

¹Japan Anti-tuberculosis Association, Shin-Yamanote Hospital. ²Otsu Women's University

Statement of Purpose: A bioadhesive hydro gel has been explored for medical devices such as an adhesion barrier, hemostat, wound dressing or drug release device. A film or sponge which forms an adhesive hydrogel absorbing body fluid on the wet tissue is useful as an adhesion barrier or hemostatic device, and some were already practicalized. Most of them are made of animal proteins such as gelatin (collagen) or fibrinogen, and risk of viral infection, bovine spongiform encephalopathy, or immunogenicity is not completely eliminated. Natural polysaccharides such as cellulose or hyaluronic acid and their derivatives have also been utilized as adhesion barriers or hemostasis devices. However, the adhesion strength is not high, and the efficacy is limited because of their inflammatory and wound healing retardation properties. Low flexibility in a dry state of the polysaccharides-derived materials also makes it difficult to be applied on a tissue of a complicated shape.

We focused on a hydrogen bonding gel consisting of poly(acrylic acid) (PAA) and poly(vinylpyrrolidone) (PVP), which are highly safe synthetic polymers approved as pharmaceutical excipients. When PAA and PVP are mixed in water, soft hydrogel is immediately formed, but soon precipitated as an insoluble solid. Resulting rigid gel does not swell, nor dissolve in water.

Recently, we found that under certain particular conditions, water-swellable film of PAA/PVP complex could be obtained. In this study, the application of the water-swellable PAA/PVP film as an adhesion barrier and a hemostatic device was examined.

Methods: Preparation of film: PAA solution was dried up to a clear film. PVP solution was then poured upon the PAA film to form the swelled gel. It was again dried to a transparent PAA/PVP complex film. Poly(vinyl Alcohol) (PVA)-containing film was similarly prepared by adding PVA to the PAA or PVP solution, previously.

Adhesion-preventing effect: Under pentobarbital anesthesia, the abdomen of mouse was incised, and the cecum was exposed. It was burned with a heated spatula, and PAA/PVP/PVA film was put on the burned site. The organ was replaced, and the abdomen was closed. After a given period, abdomen was again incised, and observed. The degradation behavior of the film was examined similarly with fluorescence-labeled PAA/PVP/PVA film.

Hemostatic effect: Mice were injected with Low-molecular-weight heparin (dalteparin sodium, 30 IU) from the tail vein. After 30 min, they were anesthetized, and the femoral vein was cut. PAA/PVP/PVA film was put on the hemorrhaging site, and hemostatic behavior was observed for an hour.

Clinical study: Film was prepared on cotton gauze. After blood collection from the patients taking warfarin, the film was put on the pricked site, and hemostasis was observed.

Results: When aqueous PAA- and PVP-solutions were mixed, the complex was precipitated as a white water-non-swellable hard solid. On the other hand, when the complex was prepared by pouring PVP solution onto a dried PAA film, a transparent water-swellable film was obtained (Fig. 1). Movement of the PAA molecule is limited in the film, and a partially complexed gel would be formed. The film including PVA was more flexible and tough. The film immediately swelled on a wet tissue, and firmly stuck to it (Fig. 2).

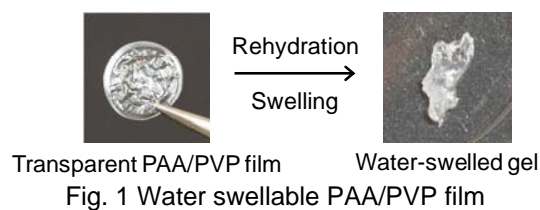


Fig. 1 Water swellable PAA/PVP film



Fig. 2 Adhesion of the PAA/PVP gel to the tissue

When the cecum was injured, and replaced in the peritoneal cavity, the organ strongly adhered to other intestines or peritoneum in days. The PAA/PVP film stuck to the burned site could effectively prevent the adhesion formation. The PAA/PVP gels are slowly dissolved at pH 7.4, and those left in the peritoneal cavity completely disappeared in several days.

The PAA/PVP/PVA film put on the bleeding femoral vein of mice, it quickly absorbed blood to form a hydrogel, and adhered to the tissue. It effectively arrested the bleeding, even on the mice which were treated with heparin. Also in the clinical study, the film could successfully stop bleeding after collecting blood from the patients taking high dose of warfarin.

Conclusions: Water-swellable film was prepared from poly(acrylic acid) and poly(vinylpyrrolidone). They form an adhesive hydrogels on a wet skin or tissues. They could effectively prevent abdominal adhesions. The gels are slowly dissolved at pH 7.4, and, after implanting intraperitoneally, they completely disappeared in several days. They could also effectively stop bleeding, and no adverse side effect was observed in the clinical study.

Acknowledgments: We acknowledge CBC Co., Ltd, BASF Japan Ltd, and JAPAN VAM & POVAL Co., Ltd. for providing PAA, PVP, and PVA, respectively. This work was partly supported by Izumi Science and Technology Foundation. This work was partly supported by Izumi Science and Technology Foundation.