Novel Biomaterial for Suppression of MMPs: Synthesis and Evaluations

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Statement of Purpose: Delayed wound healing is normally characterized by insufficient new tissue formation at the site of wound bed. It is thought that over excess, high levels of proteinases especially matrix metalloproteinases (MMPs) within the chronic wound environment stalled the healing process. MMPs normally degrade and remove dead cell and tissue on the surface, however, with high level of protease like MMP9, not only damaged tissue will be eliminated, but also newly regenerated tissue will be degraded. Therefore, there's a need to develop functional dressing materials to regulate and inhibit MMPs for chronic wound management. In this study, we first synthesized the novel biomaterials and further evaluated the effectiveness of materials to reduce the activities of metalloproteinases via in vitro assays.

Methods: Polymers immobilized with histidine as active binding sites which can attract excess MMPs were developed. The polymer-g-histidine series of materials including hyaluronic acid-g-Histidine (HA-g-His) and polyethylene vinyl alcohol-g-Histidine (EVOH-g-His) were first synthesized and characterized using nuclear magnetic resonance spectroscopy. The inhibitory effect of grafting materials on MMP-9 was incubated with activated pro-MMP9 and evaluated.

Results: Synthesis steps and structure of the histidine grafted-poly(ethylene vinyl-co-alcohol) derivative, "EVOH-g-BocHis" are as shown in Figure 1. The grafting polymers containing various grafting ratio of histidine ranging from 10 ~20% were determined by NMR (Data not shown).

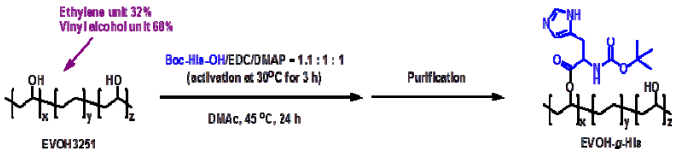


Figure 1. Synthesis of EVOH-g-BocHis

HA-g-BocHistidine was also synthesized and characterized. In vitro studies show that HA-g-His and significantly reduce MMP-9 activities (Figure 2).

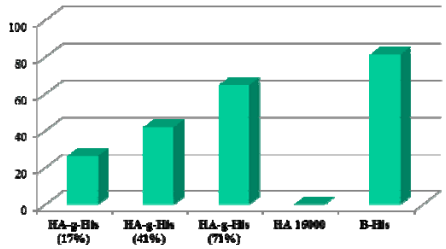
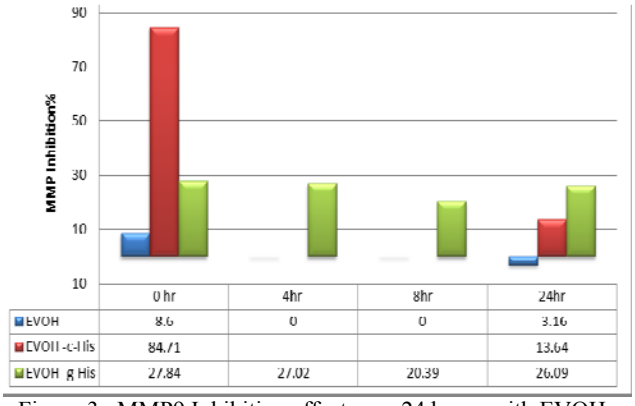


Figure 2. Change in MMP9 Activity inhibition with HA-g-Histidine

Long-term inhibiting effect of both histidine coated (EVOH-c-BocHis) and histidine grafted (EVOH-g-BocHis) film sample were evaluated. The results presented in Figure 3 revealed that though hitidine containing samples exhibit MMP inhibition at first, only EVOH-g-BocHis is able to supppress the activity of MMP9 over 24 hours.



	0 hr	4hr	8hr	24hr
EVOH	8.6	0	0	3.16
EVOH -c-His	84.71			13.64
EVOH g His	27.84	27.02	20.39	26.09

Figure 3. MMP9 Inhibition effect over 24 hours with EVOH, histidine coated EVOH film, and EVOH-grafting-histidine.

From the results above, it was suggested that the ability of polymer-g-Histidine to reduce MMPs level was attributed to the histidine component. In addition, the grafting materials demonstrated long term inhibitory effects to the MMP9 up to 24 hour.

Conclusions: This materials development and studies have allowed us to inhibit the activities of MMPs by introduction of this new polymer-g-histidine. The inhibitory effect of this new material can be further combined with dressing and work as surface coating in the treatment of chronic wound management.

References:

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