Wound healing action of topical nitric oxide releasing poly(acrylic acid)/pluronic F127 hydrogel membranes

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Abstract

Nitric oxide (NO) plays fundamental roles in wound healing and is endogenously transported by S-nitrosoglutathione (GSNO). In the present work, we incorporated GSNO in hydrogel membranes comprised of poly(acrylic acid)/Pluronic F127 (PAAc/F127/GSNO), with the purpose of delivering NO topically to accelerate wound healing. Chemiluminescence measurements showed that dry PAAc/F127/GSNO membranes undergo slow hydration with concomitant NO release over more than 9 days. Topical application of the GSNO/PAAc/F127 membranes in an animal wound healing model led to decreased inflammation and increased collagen deposition and organization in the cicatricial tissue, after 21 days. These results point to a potential medical application of these membranes for accelerating wound healing.

Key words:

Nitric Oxide, Hydrogels, Wound healing

Introduction

Nitric oxide (NO) is an endogenous molecule with several physiological and pathophysiological actions. It has been demonstrated that NO is involved in both early and proliferative phases of wound healing and regulates collagen formation, cell proliferation and wound contraction^[1]. S-nitrosoglutathione (GSNO) is an endogenous NO carrier and has been used as an exogenous NO donor in experimental medical applications^[2]. As a water-soluble molecule, topical, localized applications of GSNO demand the use of hydrophilic matrices, such as hydrogels.

In the present work, we synthesized a hydrogel comprised of a chemically cross linked network of poly(acrylic acid) (PAAc), interpenetrated with a network of micelles of poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO, Pluronic F127). GSNO was incorporated into this membrane by solution absorption technique and the membranes were characterized regarding their morphology, water absorption, GSNO content and spontaneous NO release profile. For a preliminary evaluation of their wound healing action, the PAAc/F127/GSNO membranes were topically applied on lesions in an animal model, using Swiss mice.

Results and Discussion

Although the PAAc/F127 membranes displayed a dense morphology with the absence of pores, their water absorption capacity ranged from 84wt% in water to 210wt% in phosphate buffer saline solution at pH 7.4, at 37°C. This property was used to charge the membranes with aqueous GSNO solution and allowed preparing PAAc/F127 membranes containing up to $4.5 \pm 0.5 \mu\text{mol}_{\text{GSNO}}/\text{cm}^3$.

The NO release profile from the PAAc/F127/GSNO membranes due to the spontaneous NO release from GSNO, forming oxidized glutathione, was characterized by chemiluminescence. The membranes were shown to be capable of releasing NO continuously in a nmo/min range, over more than 9 days, under a slow hydration condition. Topical application of the membranes on the

wounds of the animals during 21 days led to a reduction in the inflammatory infiltrate and an increase in the collagen deposition and collagen fibers organization in the cicatricial tissue, compared to the control group (Fig. 1).

Fig. 1. Representative picro-sirius red-stained sections of the wound tissue of animals under polarized light 21 after wounding. Left: control animals; right: animals topically treated with NO-releasing PAAc/F127/GSNO hydrogel membranes.

Conclusions

PAAc/F127/GSNO are capable of prolonged spontaneous NO release during hydration. Topical application of the PAAc/F127/GSNO on wounds reduces inflammation and increases collagen deposition and orientation and has potential to accelerate wound healing.

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¹ Witte MB, Barbul A. Role of nitric oxide in wound repair. Am J Surg. 2002, 183:406-12.

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