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Exploiting stimuli-responsiveness to patient-personalized smart patches for the advanced treatment of hard-to-heal skin wounds / Laurano, R., Boffito, M., Pinto Ribeiro, V., Leite Oliveira, A., Ciardelli, G.. - ELETTRONICO. - (In corso di stampa). (34th annual conference of the European Society for Biomaterials Torino 7-11 Settembre 2025).

Availability:
This version is available at: 11583/3004122 since: 2025-10-16T13:21:11Z

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05 November 2026

Exploiting stimuli-responsiveness to patient-personalized smart patches for the advanced treatment of hard-to-heal skin wounds

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Introduction

Chronic skin wounds are a public health concern due to the huge economic and societal burden associated to their management. This critical condition is further exacerbated by the strongly rising number of new patients every year worldwide. Despite the engineering of advanced wound dressings, the lack of patient-personalization in patch shape and payload releasing mechanism strongly limits their effectiveness. The development of multi-stimuli-responsive biomaterial inks could simultaneously overcome both limitations paving the way to the fabrication of patient-personalized patches able to control payload release in response to a triggering stimulus directly coming from the wound bed. This work aimed at answering this clinical need by developing a smart polyurethane (PU)-based drug delivering biomaterial ink responsive to temperature and alkaline pH to: (i) allow a temperature-driven drug encapsulation and easy ink extrusion, (ii) provide patch stability and shape fidelity over time and, (iii) tune payload release in response to the alkalinity of infected wound exudate.

Materials and Methods

An amphiphilic PU was synthesized by reacting Poloxamer® 407, 1,6-diisocyanatohexane and 1,4-cyclohexane dimethanol and plasma-treated (P-CHP407) to expose -COOH groups [1,2]. Chemical characterization were performed to assess the success of the synthesis. Human Lactoferrin (hLF)-loaded P-CHP407 hydrogels (P-CHP407_hLF) were prepared at 15% w/V followed by protein addition at 2 mg/mL. Thermo- and pH-responsiveness were studied through rheology and swelling test in contact with buffers, respectively. The pH-controlled drug release was colorimetrically quantified, while RT-PCR was exploited to study the effectiveness of released hLF in reducing inflammation in an in vitro fibroblast wound model. Lastly, shape-personalization was investigated through the extrusion of different 3D constructs.

Results

The synthesized P-CHP407 was characterized by a Mn of 30 kDa, the presence of IR bands at 1720 cm-1 and 1540 cm-1 ascribed to the vibration of C=O and -NH and C-N bonds, respectively, and 4.7×10E18±5.6×10E17 -COOH groups/g of PU. P-CHP407 formulations showed temperature-dependent viscosity changes (0.6 vs. 14300 Pa×s at 4 and 37 °C, respectively), fast sol-gel transition (i.e., 6 min at 37 °C), quick internal pH changes when in contact with buffers at different pH values (i.e., ΔpH@5minutes=1.61 vs. 3.76 against pH5 and pH8, respectively) and, stability in a watery environment up to 14 days, with no alteration upon hLF encapsulation. Moreover, a pH-controlled hLF release was obtained by putting the systems in contact with buffers at different pHs (e.g., 29.5±1.5, 33.9±2.5, 47.4±5.2 and 75.1±7.5 µg of released hLF after 1h of incubation against pH 5, 7, 9 and 11, respectively). The DNA quantification showed hLF capability to promote human dermal fibroblast proliferation in normal conditions, while the RT-PCR quantified inflammation-related markers proved its capability to exert anti-inflammatory activity in an in vitro wound model. Lastly, engineered formulations were easily extrudable under mild processing conditions and able to keep the shape over time as proved through the fabrication of different constructs mimicking the irregular wound bed morphology.

Discussion

The adopted synthesis procedure effectively allowed the engineering of PU answering to intended requisites: fast sol-gel transition at physiological temperature and capability to release the therapeutic agent in response to wound clinical needs. Such an approach ensured a pH-controlled anti-inflammatory activity, opening the way to dressing personalization, further enhanced by the possibility to fabricate patient-specific patches.

Conclusions

The combination of ad hoc engineered multi-stimuli-responsive polymers for smart drug delivery biomaterial inks and additive manufacturing technologies could be considered a cutting-edge strategy to design patient-personalized patches to more effectively treat chronic skin wounds and overcome the main issues responsible for delayed wound closure.

Acknowledgments. Study carried out within the HERO project (CUP E53D23003120006) – funded by European Union – Next Generation EU Mission 4, Component 1 within PRIN 2022 program (D.D. 104 - 02/02/2022 MUR). Project UIDB/50016/2020,FCT - Fundação para a Ciência e a Tecnologia (FCT) and project IBEROS+ (0072_IBEROS_MAIS_1_E, Interreg-POCTEP2021-2027). FCT - individual funding 2023.07374.CEECIND.

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