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Continuous pH monitoring in wounds using a composite indicator dressing — A feasibility study

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ABSTRACT

Purpose: Modern burn care strives for new means to guarantee optimised wound healing. Several studies have shown a correlation between the pH value in a (burn) wound and successful wound healing. A multitude of devices to monitor pH is available, all requiring direct wound contact and removal of the dressing for pH monitoring. The aim of this feasibility study was to create a sterile and easy to handle method for pH monitoring while simultaneously using an advanced wound dressing.

Materials and methods: Dressing sheets of biotechnologically generated nanofibrillar cellulose (epicite^{hydro}) were chemically functionalised with the indicator dye GJM-534. pH-donors with increasing pH were subsequently applied to the created indicator dressing. To investigate temporal resolution and continuous monitoring we used circular pH-donors with different pH (7 and 10) and decreasing diameters that were placed on another dressing sheet. Clinically relevant spatial resolution was checked by a wound bed simulation with small areas (8 mm) of higher pH (10) on a field of lower pH (7) and vice versa.

Results: The indicator dressing showed a gradual colouring from yellow to dark orange with increasing pH in steps of 0.3. After conversion of digital pictures to greyscale values, a sigmoidal distribution with a pK_a-value of 8.4 was obtained. A ring-like pattern with alternating colour change corresponding to the pH was observed in the continuous monitoring experiment and the wound bed simulation delivered excellent local resolution.

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Conclusion: Since the pH of a (burn) wound can have a significant influence on wound healing, a pH indicator was successfully linked to an advanced, temporary, alloplastic wound dressing material. We were able to show the possibility of pH monitoring by the dressing itself. Additional testing, including studies with large case numbers for optimisation are necessary before clinical implementation.

1. Introduction

Despite remarkable developments in burn care, wound complications after burn injury still play a significant clinical and economic role [1–3]. Wound management is one of the key factors in clinical outcome; questions as how to best treat wounds and what constitutes an 'ideal' wound dressing have been repeatedly discussed [4–10]. The maintenance of a moist and 'healthy' wound milieu is well established [6,11], with different advanced alloplastic materials available, one of which is biotechnologically generated nanocellulose (BNC) with a water content of at least 95% [12]. BNC-based dressings can create a moist environment while still being able to absorb wound exudate. BNC also remains permeable for gases and is easily loadable with antiseptic substances, thus direct inhibition of microbial activity is possible [13,14]. The advantages of BNC are well summarised [12,13,15,16] and constitute major features of an "ideal" wound dressing.

Despite ideal settings some wounds still show a dysfunctional healing response. More research is thus required to better understand wound healing processes. The search for relevant biomarkers to predict wound healing responses is ongoing and pH has been identified as a relevant factor in the outcome of wound healing [17–21]. An increase in the pH of wound exudate was observed in burn wounds prior to a clinically discernible infection [22]. Therefore, routine monitoring of wound pH could be one promising approach to identify potentially deteriorating wounds at an early stage. But a very close monitoring of wounds at risk requires frequent consultations in an outpatient setting and regular dressing changes both of which are time-consuming and expensive. Since conventional dressings also lack diagnostic potential, recent developments in wound management have a trend towards so-called *smart dressings* [23–26]. Smart dressings are designed to overcome this key limitation of conventional dressings and achieve a new combination of therapeutic and diagnostic features. This can be accomplished by actively monitoring the wound environment and simultaneous measurement of (bio)markers that have shown a correlation to wound healing, as for example pH, temperature, oxygen or moisture [25].

We are currently developing novel smart dressings for burn wounds [27] and this study aimed to show the first proof-of-concept for an easy to use pH indicator dressing. This new dressing was designed to not interfere with physiological wound healing, to be non-invasive, highly sensitive and to have a high spatial and temporal resolution.

2. Materials and methods

2.1. *Wound dressings*

For the experiments we used the primary wound dressing epicite^{hydro} (QRSKIN GmbH, Germany). epicite^{hydro} is a semitransparent biomaterial made of BNC synthesized by *Komagataeibacter xylinus* DSM 14,666 (culture collection of the Friedrich-Schiller-University, Jena, deposited at the DSMZ, German Collection of Microorganisms and Cell Cultures, Braunschweig, Germany). epicite^{hydro} is primarily used as a temporary, alloplastic epidermis substitute.

2.2. *Chemicals*

The pH indicator dye GJM-534 (4-[4-(2-hydroxyethanesulfonyl)-phenylazo]-2,6-dimethoxyphenol) was kindly provided by MATERIALS - Institute for Surface Technologies and Photonics, Joanneum Research Forschungsgesellschaft mbH (Austria). The indicator chemistry is certified for contact with babies according to the OekoTex100 classification, and has been shown not to be cytotoxic [28]. The chemicals for colouring the epicite^{hydro} dressing (concentrated sulfuric acid, sodium hydroxide, sodium carbonate) and the buffers for optical evaluation (Tris/HCl) were obtained from Sigma-Aldrich (Austria, Germany). Furthermore, we used a 1% agarose gel (Biozym Scientific GmbH, Germany) for wound bed simulations.

2.3. *Linking of the pH indicator dye to BNC*

The general immobilisation procedure of binding the indicator dye to the BNC in a reliable, highly stable and safe way was performed as described before [29]. In short, the pH indicator dye (GJM-534) was treated with concentrated sulfuric acid for 30 min at room temperature, before pouring the viscous mixture into 400 ml of distilled water under stirring, and neutralising with 2.0 ml of a 30% sodium hydroxide solution. Finally, 25.0 g of sodium carbonate in 100 ml of water and 5.0 ml of a 30% sodium hydroxide solution were added. epicite^{hydro} sheets were placed in the solution and after 45 min of gentle stirring at room temperature, they were washed with copious amounts of distilled water until no more leaching of unbound dye was observed. This resulted in *BNC-SENS*, a readily modified product based on a BNC matrix and modified for pH sensing.

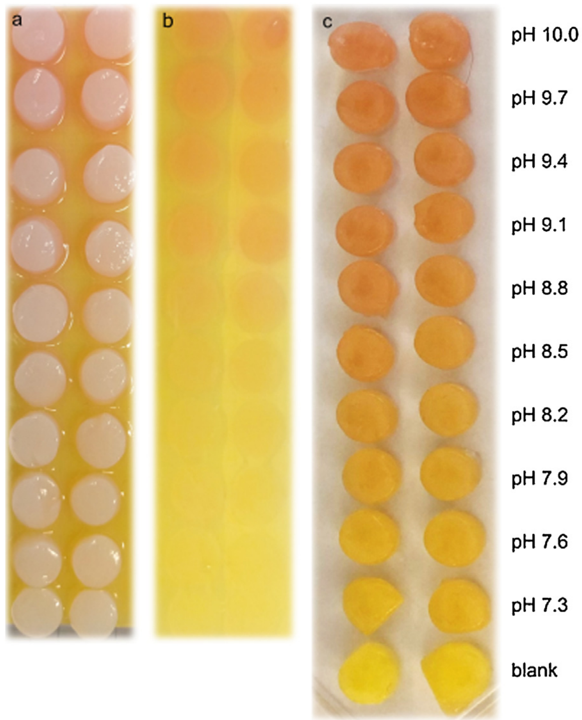

Fig. 1 – (*a*) Pictures of the applied pH-donor of pH 7.3–10.0 on *BNC-SENS*. In (*b*) the bottom of *BNC-SENS* after 15 min contact with the pH-donor is shown from the perspective of a potential examiner in a clinical setting. The excised punch samples of *BNC-SENS* are shown in (*c*); a clear shift from yellow to red is visible with increasing pH in (*b*) and (*c*). A blank sample without pH application is shown in (*c*) for reference.

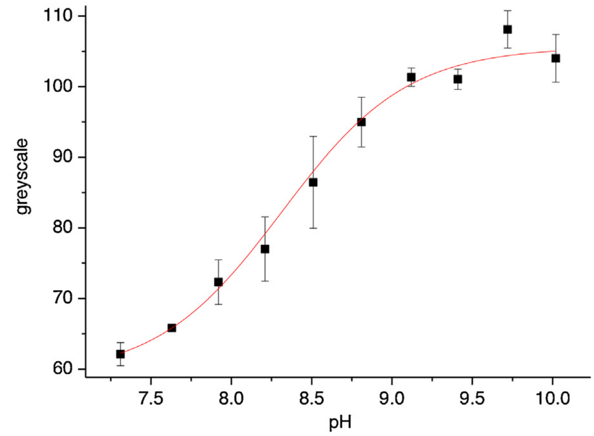

Fig. 2 – Greyscale values of the black and white version of the image of Fig. 1c plotted against the pH values of the applied pH-donor. A sensitivity range of the indicator system of approximately three pH units, i.e. pH 7–10, is covered.

2.4. *Sensitivity of BNC-SENS*

We tested the sensitivity of *BNC-SENS* by subjecting it to a pH-donor. epicite^{hydro} was identified as a suitable pH-donor based on its capacity to both load and deliver solutions. To obtain functional pH-donors, we equilibrated 20 samples (8 mm diameter each) of epicite^{hydro} at a pH between 7 and 10 in increments of 0.3 by incubation for 3 h with a 70 mM Tris/HCl buffer adjusted to the respective pH. Two "blank", unequilibrated, untreated epicite^{hydro} samples were used as negative control. The different pH-donors (2 for each pH value) were then placed on a sheet of *BNC-SENS* (10 × 3 cm) in a transparent dish (Fig. 1a) and incubated at room temperature for 30 min. Photographs of the setup were taken from the top and the bottom after 15 min (Fig. 1a and b). After 30 min the pH-donors were removed from the *BNC-SENS* sheet and punch samples of the *BNC-SENS* sheet were taken at the exact spots where the pH-donors had been placed. Pictures of these punch samples were taken to analyse the indicator colour intensity after 30 min of exposure to pH-donors (Fig. 1c). Pictures were converted into greyscale and the mean greyscale values were determined at the punch sample surface area using the ImageJ software (ImageJ 1.52 g Wayne Rasband, National Institute of Health, USA). The pK_a value (point of inflection of the sigmoidal calibration function) was calculated by taking those greyscale values and depicting them against pH fitting the corresponding data with the Boltzmann fit function in Origin (OriginPro 8.6 G, United States of America; Fig. 2).

2.5. *Continuous monitoring*

Reversibility and continuous pH sensing were analysed by successively placing 6 circular pH-donor samples with decreasing diameters and alternating pH values (36 mm — pH 10, 26 mm — pH 6, 20 mm — pH 10; 14 mm — pH 6; 8 mm — pH 10 and 4 mm — pH 6) onto a *BNC-SENS* sheet (5 × 5 cm) for three minutes each. After removal of the pH-donor samples, photographs were taken for visual analysis (Fig. 3).

2.6. *Wound bed simulation*

In order to mimic a wound bed composed of a larger alkaline (non-healing) area with islands of healing areas with 'normal' skin pH, circular agarose discs of pH 6 (8 mm diameter) were inserted into an agarose bed with pH 10 and *vice versa* to simulate islands of non-healing areas (pH 10) in an otherwise healing wound (pH 6). These agarose gel matrices, simulating a wound bed, were each covered with one sheet of *BNC-SENS* for 30 min. After removal, the *BNC-SENS* sheets were photo documented (Fig. 4).

3. Results

After having subjected the epicite^{hydro} sheets to the described procedure, an indicator-linked wound dressing (*BNC-SENS*) was produced, which showed a yellowish colour with maintained semitransparency.

The sensitivity experiment showed the arrangement of the pH-donors on *BNC-SENS* in Fig. 1a. After an incubation time of 15 min, a gradual colour change to dark orange with increasing pH was observed. This colour change was also (moderately)

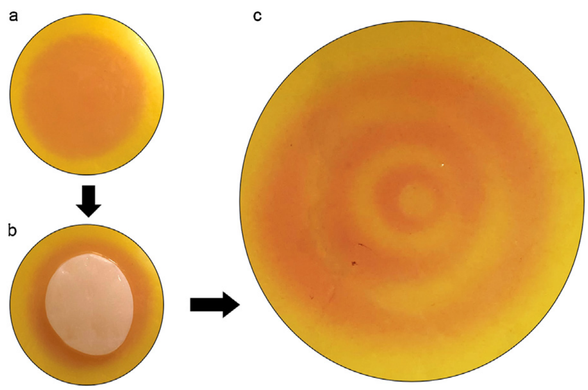

Fig. 3 – Visualisation of the continuous monitoring experiment: successive placement of pH-donor samples with decreasing diameters and alternating pH values of pH 6 and 10. (*a*) displays *BNC-SENS* after the first application of a pH-donor of pH 10.0. In (*b*) the applied smaller pH-donor of pH 6.0 is shown. (*c*) presents an image of *BNC-SENS* after 6 successive applications. It illustrates a distinct ring-like colouration pattern, reflecting the intended pH value of the applied circular pH-donor.

visible from the other side of the *BNC-SENS* sheet, which would be the one facing the observer (Fig. 1b). After excision of the areas beneath the pH-donors, they showed a gradual colour shift from yellow to dark orange according to the increasing pH from 7.3 to 10.0. A blank sample was used for non pH-treated *BNC-SENS*. The greyscale values of the correspondent *BNC-SENS* punch samples in Fig. 1c were plotted against the expected pH values of the buffers used for incubation (Fig. 2). A regression analysis revealed a sigmoidal shape of the curve with pH-dependant means and interpolated values, and a pK_a of 8.38.

The continuous monitoring experiment revealed a distinct pattern with pH-dependent ring-like colouration (Fig. 3), reflecting the fields on which the respective circular pH-donors had been placed.

The wound bed simulation experiments' results are displayed in Fig. 4a and b, respectively. *BNC-SENS* showed yellow circles of 8 mm diameter (pH 6) in an otherwise red field (pH 10), and *vice versa*. Furthermore, the semitransparency of *BNC-SENS* persisted.

4. Discussion

We successfully produced a prototypic, BNC-based, smart wound dressing by covalent immobilisation of a reactive indicator dye with vinylsulfonyl groups to BNC, which exhibits functional hydroxyl groups similar to cellulose where this procedure is well established [30]. In this previous study the reactive indicator dye GJM-534 ($pK_a = 7.6$) was immobilised to thin layers of transparent regenerated cellulose, and with increasing the pH from 6 to 9, a colour change from yellow to purple-red was observed [29]. We thus expected a similar colour change for the BNC-based smart dressing. Indeed, we were able to observe a colour change from yellow to dark orange in our feasibility experiment, as increasing pH resulted in distinct colour pattern on the composite BNC-based dressing. The subsequent analysis of the greyscale values, obtained from the black and white images, allowed a quantification of the resulting colours and a graphical representation of the changes corresponding to the pH shift. The sigmoidal shape of the curve indicated a pH range coverage of *BNC-SENS* of about three pH units with lower resolution towards both ends of the scale. We also observed a shift of the pK_a value towards more alkaline values, namely 8.4, when compared to the uncoupled dye (pK_a 7.6). This indicated a slight influence of BNC on the dissociation of the dye, which has been described in earlier studies for other cellulose materials [29], and should be investigated in further studies for BNC-based dressings. While healthy skin pH is supposed to range between 4.0 and 6.0 [31], pH in wounds was reported to be increased up to 8.9 [18]. A pH higher than 8 approximately one week after injury results in an increased probability of healing failure [18]; thus, the critically relevant range in wounds is sufficiently covered by our present *BNC-SENS*, so

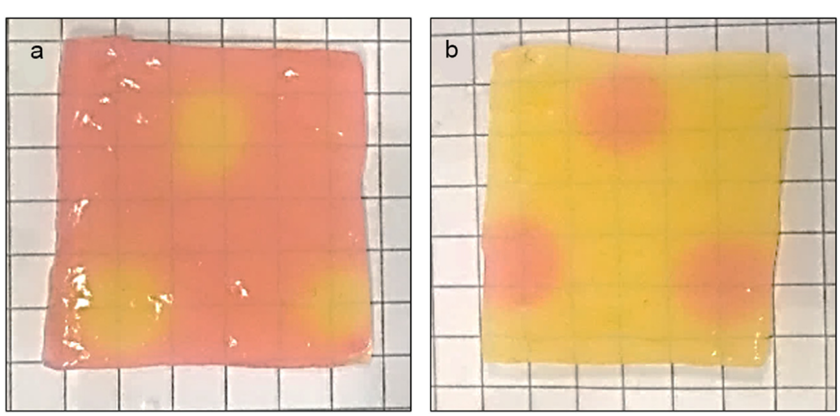

Fig. 4 – Photographs of *BNC-SENS* after the wound bed simulation, where it had been placed on a alkaline agarose gel (pH 10) with discs of acidic pH (pH 6) (*a*) and on an acidic agarose gel (pH 6) with alkaline discs (pH 10) for 30 min (*b*). The simulations show an excellent spatial resolution being only coloured in the respective areas. Furthermore, the semitransparency of the product is demonstrated.

that it could be utilised as an indicator dressing for wound healing progress, respective dysfunctional healing response.

The repeated application and monitoring of acidic and alkaline pH-donors in decreasing sizes suggests a reusability of the indicator. The obtained pattern, reflecting the different pH values after temporary application of a pH-donor implies a good temporal resolution and possible continuous monitoring of the wound without having to change the dressing, as BNC-SENS is capable of multiple, consecutive colour changes.

Results of the two wound bed simulation experiments indicate a good spatial resolution of the tested *BNC-SENS* as the indicator dressing showed a pH dependant colour change only in those areas where the pH-donor was applied without any significant gradual change around the 8 mm punches. Clinical experience indicates that wounds usually show a heterogenic wound bed with interdispersed areas of different healing and non-healing stages. Hence, a smart wound dressing which is able to indicate such different areas could greatly improve daily clinical practice.

Previous studies investigating the pH in wounds have mostly used non-sterile indicator strips or laboriously cleaned electrodes that needed to be in direct contact with the wound [20,22,32], which involves a considerable risk of contamination. On the other hand, studies have shown that chemical indicators, with a similar stucture to GJM-534 which we used in our study, can withstand a sterilization process with gamma irradiation [33]. Thus, a sterile application of an indicator wound dressing based on a linked chemical dye seems highly likely. Furthermore, the indicator chemistry for GJM-534 has already been certified for contact with babies according to the OekoTex100 classification and has been shown not to be cytotoxic [28].

Different approaches have been used so far to address the pH measurement in smart dressings. Predominantly several types of electrochemical sensors have been developed and tested (summarised by [25]). However, these methods include high-end electronic devices, which require costly equipment and technical know-how– and are therefore not easily suitable for clinical implementation. Colorimetric indicators, in contrast, are more robust and easy to use.

Our results also show that by using *BNC-SENS* a change in a wound's pH is easily observable with the naked eye while the indicator-linked dressing stays on the wound. Its easy applicability without further instruments, knowledge or waiting time might even make it usable by patients to primarily evaluate the wound situation and seek medical advice if a change of the wound dressing's colour appears.

We showed that it is possible to integrate a dye indicator in a wound dressing, which allows a continuous assessment of the wound milieu pH (increasing and decreasing). The colour changes in the conducted feasibility experiment are only moderately visible resulting in lower greyscale variation towards the end of the scale. This limitation can be solved in future developments by choosing more vibrant colours richer in contrast, which is influenceable in the synthesis process of the indicator dye as described in Ref. [34].

Future investigations should focus on further optimization of the product considering colour-choice, its accuracy and the exact determination of the resolution. Furthermore, its clinical usability should be analysed in large case number studies.

5. Conclusion

Since changes in pH have shown a considerable connection with the development of chronic wounds and their healing process, we tested the feasibility of a pH indicator linked to an advanced wound dressing. The developed, composite pH indicator dressing was able to continuously indicate pH changes in the simulated wound milieu without the use of any further sensing technology in promising spatial and temporal resolution. A refinement of the indicator dressing in combination with larger clinical studies are the next steps to investigate possible clinical implementation and added clinical value.

Conflict of interest statement

Martin Funk is the COO of QRSKIN GmbH. We report a project-related co-operation; however, no funding for this project occurred. Furthermore, there is no conflict of interest to declare.

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