International Journal of Pharmaceutics 529 (2017) 576–588

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Layering of different materials to achieve optimal conditions for treatment of painful wounds

T. Maver[a,*], L. Gradišnik[b], M. Kurečič[a,c], S. Hribernik[a], D.M. Smrke[d], U. Maver[b,e,**], K. Stana Kleinschek[a]

[a] University of Maribor, Faculty of Mechanical Engineering, Laboratory for Characterisation and Processing of Polymers, Smetanova 17, SI-2000 Maribor, Slovenia
[b] University of Maribor, Faculty of Medicine, Institute of Biomedical Sciences, Taborska ulica 8, SI-2000 Maribor, Slovenia
[c] Centre of Excellence PoliMaT, Tehnološki park 24, SI-1000 Ljubljana, Slovenia
[d] University Medical Centre Ljubljana, Zaloška cesta 2, SI-1000 Ljubljana, Slovenia
[e] University of Maribor, Faculty of Medicine, Department of Pharmacology, Taborska ulica 8, SI-2000 Maribor, Slovenia

ARTICLE INFO

Article history:
Received 28 March 2017
Received in revised form 8 July 2017
Accepted 12 July 2017
Available online 16 July 2017

Keywords:
Painful wounds
Multilayered wound dressing
Alginate
Viscose
Polyethylene terephthalate
Diclofenac
Lidocaine

ABSTRACT

Despite a range of advanced wound dressings that can facilitate wound healing, there are still no clinically used dressings for effective local pain management. The latter was the main motivation of the present study. We designed a novel wound dressing with three layers. A macro-porous polyethylene terephthalate (PET) mesh with incorporated lidocaine, a fast-acting local anesthetic, was chosen as the layer in direct contact with the skin. Fast release from this layer enables an immediate pain relieving effect, caused by dressing changes. For the second and third layer, alginate and viscose were chosen respectively. A potential long-lasting pain relieving effect was achieved through incorporation of a nonsteroidal anti-inflammatory drug diclofenac into both layers. The chosen dressing structure enables also an unhindered absorption of the wound exudate, which is possible through the macro-porous PET into the alginate layer. Alginate additionally maintains a moist wound environment. Our novel wound dressing was systematically tested in regard of the structural (contact angle measurements, IR spectroscopy, SEM), functional (water retention, air permeability) properties and its biocompatibility (Live/Dead and MTT assays) towards human skin fibroblasts. Combined results confirmed the suitability of the chosen wound dressing composition for a faster and painless wound treatment.

1. Introduction

Wound healing is one of the most complex physiological processes that occur during human life. After injury, several biological pathways are activated and contribute to the overall healing efficiency (Gurtner et al., 2008). Effective wound healing is not possible without a clean, adequately perfused wound environment that is free from infection, necrotic tissue and foreign material (Gantwerker and Hom, 2012; Maver et al., 2015c). If this is the case, epithelial cells are able to move unimpeded, and the wound healing follows an optimal physiological path (Powers et al., 2016).

Among the most desired properties of wound dressings are the control of hydrophilicity (ensuring an appropriately moist environment), an effective oxygen circulation to aid regenerating cells/tissues, and a low bacterial load (Frykberg and Banks, 2015; Häkkinen et al., 2015). Other, as much important factors affecting wound healing, are strongly connected with the respective wound etiology (e.g. acute, chronic, exudating and dry wounds, etc.).

Wound healing is often divided into three sequential phases (Maver et al., 2015c). The inflammatory phase begins right after the clotting cascade (sometimes the latter is referred to as the hemostasis phase, preceding the inflammatory phase). Twelve to twenty-four hours after injury, begins the proliferative phase with extensive formation of granulation tissue. The healing is concluded with the remodeling phase (with collagen degradation and deposition, as well as wound contraction), which can persist for several months (Reinke and Sorg, 2012). Wounds that do not heal in these orderly set of phases within six to eight weeks, are considered as chronic (Powers et al., 2016). Chronic wounds often

* Corresponding author.
** Corresponding author at: University of Maribor, Faculty of Medicine, Institute of Biomedical Sciences, Taborska ulica 8, SI-2000 Maribor, Slovenia.
E-mail addresses: tina.maver@um.si (T. Maver), uros.maver@um.si (U. Maver).

http://dx.doi.org/10.1016/j.ijpharm.2017.07.043
0378-5173/

remain in the inflammatory phase and are most common in patients with an underlying not successfully treated disease (Ortenzio et al., 2014). Characteristic for chronic wounds is also an imbalance between the production and degradation of tissue components, which is heavily inclined towards degradation (Powers et al., 2016). There are more than 6.5 million chronic skin ulcers caused by pressure (pressure sores), venous stasis or diabetes mellitus annually in the United States only (Kahn et al., 2015). Therefore, it is no wonder why wound healing has become a topic of ongoing research worldwide and is calling for development of cost-effective therapies.

Lately, studies of multilayered dressings, composed from different material combinations, have become increasingly interesting (Maver et al., 2016; Tan et al., 2015). This is evident also from the number of related patents in the last two decades (Arnold, 1998; Becker et al., 2006; Gladman and Griffiths, 2016; Patel et al., 2007). Clinically used are only a few dressings from this range. Among these are the so called absorptive dressings, composed of a semi-adherent or a non-adherent layer and a highly absorptive layer of fibers such as cotton, rayon fabrics, and others. Such dressings are generally used to treat burns, abrasions, surgical incisions, lacerations or other similarly demanding wound types (Sood et al., 2014). Many more multilayered dressings are the subject of different research studies (Gunavathi, 2015; Zhao et al., 2015; Thu et al., 2012; Sussman and Bates-Jensen, 2007).

Pain has been often described as one of the most distressing complaints in patients with chronic wounds, significantly affecting their quality of life (Solowiej and Upton, 2010). Beside the physical discomfort, pain can cause general stress, fear, anxiety, depression and through all that causes delays in wound healing (Fogh et al., 2012; Hua et al., 2015). It has been demonstrated that patients with wounds experience one of the highest sensations of pain during wound dressing changes (Upton et al., 2012). The latter may even lead to serious complications, e.g. neurogenic shock (Freedman et al., 2004). Therefore, ensuring a painless wound healing through wound care, has become an increasingly important topic (Maver et al., 2015a, 2016, 2014). The materials used on their own can limit the sensation of pain only in a limited manner, and hence cannot provide a sufficient pain relief to aid the healing (Fogh et al., 2012).

Non-steroid anti-inflammatory drugs (NSAIDs) are important drugs in pain treatment, fighting fever and decreasing inflammation (Gotzsche, 2002). Mostly NSAIDs are taken in the form of pills (systemic administration) and as such lead to desired, as well as unwanted effects, the latter especially in the gastrointestinal tract (Jarupongprapa et al., 2013; Laine et al., 2006). In wound care, these unwanted effects can be almost completely diminished through local administration directly to the wound (Fogh et al., 2012; Maver et al., 2015d; Vinklarkova et al., 2015). Although, this for itself is an important step towards a painless wound care, there are still some important issues about this type of administration that have to be resolved. One of these is related to the very nature of the NSAIDs mechanism of action, where the drug molecule has to reach their target molecule in the brain (Vane and Botting, 1998), whereas the local activity of NSAIDs, is also known, but has a rather limited effect (Kyuki, 1982). Due to the latter, the pain reducing effect of NSAIDs starts only after 30 min, making them not the drug of choice for an immediate pain relief (e.g. caused by dressing changes). On the other hand, considering their relatively long effect (in the case of diclofenac (DCS), up to 24 h), NSAIDs are interesting as part of pain relieving wound dressings, where the dressing change frequency is one or two days (most of wounds) (Dreifke et al., 2015; Wright and Shirey, 2003).

For fast elevation of pain, caused through wound care, the fastest-acting amide local anesthetic lidocaine (LID) would be the best choice. Due to blocking of fast voltage-gated sodium channels in the cell membrane of postsynaptic neurons, amide local anesthetics prevent depolarization and inhibit the generation and propagation of nerve impulses. At higher concentrations, many of them possess some serious unwanted effects (bradycardia, hypotension, etc.), however LID is one of the safest among the amide group of local anesthetics (Chestnut, 2004; Polley et al., 2003).

Considering all mentioned above, the purpose of this study was to find optimal composition and positioning of the layers with incorporated drugs to achieve the best possible healing performance for potential use in chronic wound care. For direct contact with the damaged skin an inert, hydrophobic layer (often composed of polyethylene terephthalate – PET), is commonly used (Maver et al., 2015a; Mogoşanu and Grumezescu, 2014). Since it does not directly interact with the wound bed, PET does not damage the newly formed granulation tissue during dressing changes, and hence contributes to a faster wound healing (Mogoşanu and Grumezescu, 2014). LID, a fast-acting local anesthetic (time of onset is measured in seconds) was incorporated into the first, PET-based prototype dressing layer, to achieve an immediate release (direct contact with the wound environment and therefore fast release) and fast pain relief (Christensen et al., 2012; Desai et al., 2014; Kintzel and Mulder, 2012).

Due to its effective wound exudate absorption and possible maintenance of a moist wound environment, alginate (ALG) is among the most common functional parts of different modern wound dressings (Mayet et al., 2014). Different formulations of regenerated cellulose (VIS) (e.g. fibers, non-woven materials) are still often used either as part of different wound dressings or alone (Maver et al., 2015a). Combining both, ALG and VIS with DCS, a long-acting NSAID, makes sense, since it can provide an effective, as well as long-lasting pain relief (e.g. relievieng pain related to the wound itself).

In this study, three commonly used materials were drug loaded and combined into a multilayered wound dressing. By this, a fast pain relieve and protection of the newly grown tissue is ensured through the use of PET with included LID as the first layer in contact with the skin. A suitable maintenance of a moist wound environment and removal of debris is provided by ALG as the second layer, while the dressing is completed with a VIS layer on top, which provides a reservoir for possible drug inclusions and at

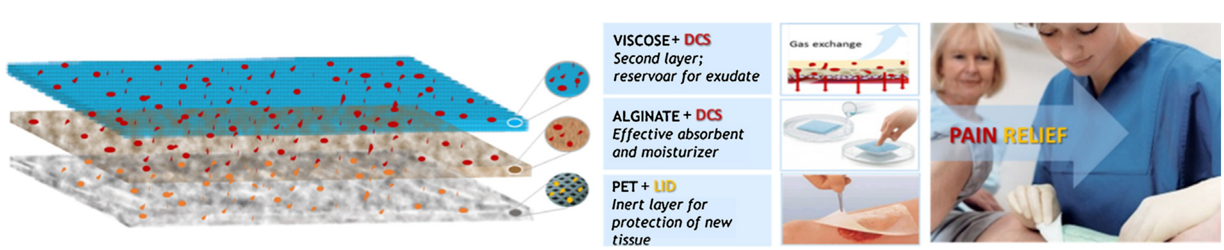

Fig. 1. The composition of developed multilayered material.