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Film wound dressing with local anesthetic based on insoluble carboxymethycellulose matrix

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ABSTRACT

The aim of the presented research was to formulate, prepare and evaluate novel film wound dressings containing lidocaine hydrochloride. The conversion of partially substituted fibrous sodium carboxymethylcellulose (CMC) to an acidic form of CMC enabled the formation of an insoluble matrix which consequently provided the prepared films with excellent handling properties in their wet state. The drug concentration which was incorporated into an external layer of the film was 5 mg/cm^2. The films demonstrated satisfactory mass and drug content uniformity as well as an acidic surface pH advantageous for wound application. An *in vitro* drug release test proved that the insoluble CMC matrix served as a reliable carrier without slowing down the release of lidocaine hydrochloride – more than 90% of the drug was released during the first 15 min, indicating a quick rate of anesthetic action. The prepared films could be potential wound dressings for comfortable and efficient topical anesthesia before/after procedures on the wound.

Introduction

Wound-related pain can be temporary (acute) or persistent (chronic) (Woo et al., 2008). Acute wound pain can be exacerbated whenever the wound is handled or manipulated: during dressing removal, wound cleansing or debridement (removing of necrotic tissues). In contrast, persistent (chronic) wound pain is a background symptom that exists at rest and between wound-related procedures. The level of pain depends on the causes of the pain – procedural pain (e.g. during dressing removal) and operative pain (e.g. wound debridement) are worse than pain at rest (Arroyo-Novoa et al., 2009). Unresolved pain predisposes individuals to stress and associated physiological responses that can impair wound healing (Boateng and Catanzano, 2015; Woo, 2011), often leading to the need for pharmacological interventions for pain prevention.

Separate analgesic strategies may be required for background pain and the pain arising from wound procedures (Orsted, 2010). Guidelines for pharmacological wound pain management based on the recommendations by the World Health Organization recommend the use of non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen for patients with mild to moderate pain (Briggs and Bou, 2002; Woo et al., 2008). NSAIDs provide good pain relief. Moreover, they can positively influence inflammatory processes in the wound, since there is a tendency in chronic wounds for the inflammatory response (an important element in the initial wounding response) to become exaggerated (Boateng and Catanzano, 2015). The treatment of wound infection, by reducing bacterial load and thereby reducing the inflammatory stimulus to the nervous system, should also result in a reduction in pain (Boateng and Catanzano, 2015; Sarheed et al., 2016). Unfortunately, oral use of NSAIDs as well as systemic administration of high antibiotic doses can lead to serious side effects such as gastrointestinal problems, risk of renal failure, prolonged bleeding time due to impaired coagulation, allergic reactions etc. (Meek et al., 2010; Sarheed et al., 2016; Wallace and Vong, 2008). For this reason, non-pharmacological strategies and topical agents to achieve optimal wound-related pain management are an attractive solution. Topical agents and correctly selected dressings play a

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critical role in alleviating wound-related pain (Boateng et al., 2008; Woo et al., 2008). Recently, an evaluation of the effect of ibuprofen in the form of a foam dressing (Biatain Ibu) on persistent and temporary wound pain underwent clinical trials (Fogh et al., 2012). The ibuprofen foam dressing was shown to consistently relieve wound pain in exuding wounds of various etiologies (Romanelli et al., 2009), thus, local pain relief by this dressing is possible in the most common, painful, exuding, chronic and acute/traumatic wounds and therefore is a safer alternative for systemic pain treatment (Arapoglou et al., 2011).

For the management of procedural or operative pain, local anesthesia, which includes infiltration or topical application of anesthetics, is usually used. Infiltration anesthesia (injection into the tissue in and around the wound) per se induces discomfort, may worsen "needle anxiety" in pediatric subjects, and distort the wound site (Eidelman et al., 2005). Moreover, Eidelman et al. (2005) found that the majority of clinical trials demonstrated equivalent or superior analgesic efficacy for topical formulations compared with conventional lidocaine infiltration.

Lidocaine is an essential drug on the World Health Organization's essential drug list, and is considered efficacious, safe and cost-effective for any health-care system (Weinberg et al., 2015). The efficacy of topical lidocaine alone or in combination with other anesthetic agents in the management of acute wound pain has been confirmed in clinical practice (Cuomo et al., 2015; Desai et al., 2014; Gaufberg et al., 2007; Little et al., 2009; Pasero, 2013). According to Sussman and Bates-Jensen (2012), lidocaine in the form of a soak may be recommended as a quick and efficient way to reduce local wound pain during debridement procedures. Another option is EMLA cream (containing a eutectic mixture of lidocaine and prilocaine), which is only intended for contact with intact adjacent skin. Nevertheless, Blanke and Hallern (2003) found that, on the basis of clinical experience, the topical application of EMLA cream directly to the wound before sharp debridement is efficient, economical, safe, and tolerable for the patient. One common disadvantage of topical analgesics is the amount of time needed before effect (usually 20–30 and up to 60 min prior to procedures (Sussman and Bates-Jensen, 2012)). For this reason they are more suitable for non-emergent procedures. Another deficiency of topical liquid or semisolid anesthetics is the messiness of application and removal (Little et al., 2009). Currently, if the anesthetic must be applied directly to the wound topically, there is no other choice than a liquid or semisolid preparation. Thus the development of new, more sophisticated forms is required. Film wound dressing is a pharmaceutical form without the drawback messy application and removal. Moreover, film application allows more precise dosing of active substances.

Films, as pharmaceutical dosage forms, are currently used for oral, buccal or ophthalmic application with a variety of medicated or non-medicated preparations on the market. The film wound dressings on the market are non-medicated ones intended only for protection of the wound against the effects of the surrounding environment or mechanical injury (Sussman, 2010). For this reason, there have been many studies into how to prepare film wound dressings with an active substance (Boateng et al., 2013; Jridi et al., 2017; Liakos et al., 2013; Pereira et al., 2013; Thu et al., 2012; Wang et al., 2012). None of these, however, were dedicated to the development of a wound dressing with the rapid release of a local anesthetic.

Different polymers may be used to prepare the film. Natural materials are more friendly on bodily tissues than synthetic ones, and are therefore often studied for wound care applications (Juncu et al., 2016; Maver et al., 2015; Ramli and Wong, 2011; Xu et al., 2007). An ideal film dressing must be supple and possess homogenous and smooth surfaces (Ramli and Wong, 2011). Transparency is another important property allowing for the wound's assessment without removing the dressing (Sussman, 2010). Films prepared from sodium carboxymethylcellulose (NaCMC) possess all these characteristics. Moreover, carboxymethylcellulose (CMC) is generally regarded as a nontoxic, nonirritant, and biocompatible material which predestines it for use in food, cosmetic, pharmaceutical, and biomedical applications, including materials for wound care (Rowe et al., 2015). All of these factors make it a suitable candidate in the preparation of medicated film. A whole range of scientific works deals with the preparation and evaluation of medicated CMC films. However, these films are mainly intended for buccal/oral drug delivery (Gajdziok et al., 2015; Landová et al., 2013; Raju et al., 2011; Ramineni et al., 2013; Saha et al., 2013; Semalty et al., 2010; Vetchý et al., 2014), and much less for wound therapy (Donnadio et al., 2016; Vinklárková et al., 2015). The application properties of film wound dressings differ quite significantly from those intended for buccal/oral applications. Wound dressings are applied on a much larger surface area than buccal preparations. For this reason, good mechanical properties of medicated CMC films are required. Especially once wetted, they must maintain the cohesiveness that enables them to be easily manipulated and removed without residues. One option is to reinforce the film with a supporting material as was done in our previous study (Vinklárková et al., 2015). The other option is to prepare film containing an acidic form of CMC (HCMC), which is insoluble in water, thus more wet resistant. The idea that film containing HCMC would be of increased strength was described for the first time by Butler (1962) in his US patent. However, the patent contains only the general preparation conditions, and lacked precise description of the technology and evaluations methods necessary for the preparation of films with suitable properties for wound application. Moreover, the technique described in patent was for non-medicated films only. Films based on insoluble CMC with an active substance have not yet to be prepared and evaluated.

The aim of the presented research was to prepare a novel film wound dressings based on an insoluble carboxymethylcellulose matrix with lidocaine hydrochloride as an active compound, and evaluate their physicochemical properties as well as *in vitro* drug release.

Material and methods

The partially substituted (degree of substitution 0.34) sodium carboxymethylcellulose (NaCMC) in the form of non-woven textile (Hcel® NaT) was supplied by Holzbecher, spol. s r.o., Bleaching & Dyeing Plant in Zlíč (Czech Republic), lidocaine hydrochloride, macrogol 300, glycerin and hydrochloric acid (all Ph. Eur. grade) were purchased from Fagron (Czech Republic). All other chemicals and reagents used in the study were of analytical grade.

Preparation of films

Films based on an insoluble carboxymethylcellulose (CMC) matrix were prepared using an sequential solvent casting method. A modified technique according to the US patent (Butler, 1962) was used. In order to create the insoluble CMC (HCMC) matrix, the acidification of both polymer dispersion and casted film was necessary. Both the acidification of the polymer dispersion without any further treatment of the film and the acidification of casted NaCMC film itself without previously acidifying the dispersion proved insufficient. The acidification of NaCMC film itself did not achieve required mechanical properties. It is likely that the HCMC matrix was not completely formed. Similarly, films prepared from a dispersion acidified to a pH value of 3 or higher without additional treatment of casted films were low in quality. Acidification to pH values lower than 3 resulted in precipitation and loss of film-forming properties. The double acidification led to the creation of

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