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Film wound dressing with local anesthetic based on insoluble carboxymethylcellulose 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/cm². 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.

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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
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 distorts the wound site (Eidelberg et al., 2005). Moreover, Eidelberg 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; Gaulberg 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-mediated 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 predetermines 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 (Gadjziok et al., 2015; Landová et al., 2013; Raju et al., 2011; Ramineni et al., 2013; Saha et al., 2013; Semalty et al., 2010; Vetchy 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-mediated 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 Zlíc (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
films with suitable properties. Thus the films were prepared as follows: The polymer dispersion was composed of 1% (w/w) NaCMC and 2% (w/w) macrogol 300 or glycerin in purified water. Non-woven sodium carboxymethylcellulose textile (Hcel NaT) was cut into small pieces and poured over with a solution of macrogol or glycerin in hot water (80 °C). This mixture was heated in a water bath to maintain a temperature of 80 °C for 3 h, then stirred using a Cito-UNGUATOR 2000 dispersing device (SMS Heiztechnik GmbH, Germany) at 70 °C until a pH value of 3 was achieved. Then 25 g of the resulting dispersion was casted on a glass Petri dish 10 cm in diameter and pre-dried in the oven (Heratherm, Germany) at 70 °C for 1 h followed by 24 h of drying at ambient conditions. The dry films were left in the Petri dishes, and acidification/washing was administered as follows: 20 ml of 5% solution of HCl for 20 min — straining — rinsing with purified water — 20 ml of purified water for 20 min — straining — 20 ml of purified water for 20 min — straining — 20 ml of 5% solution of macrogol or glycerin for 20 min — straining. Macrogol or glycerin was added into the final washing liquid to compensate for these plasticizers washed away from the film during the acidification/washing process. The final layer of film was created from a solution of lidocaine hydrochloride — to obtain the required concentration of the drug (5 mg/cm²) 5 g of 6.3% solution for one Petri dish were added. Once the final layer was applied, the films were left to dry under ambient conditions. The dried films were peeled from the Petri dishes, examined visually for morphological defects (e.g. cracks, shrinking, etc.) which can affect handling, testing and application as well as aesthetic appearance, and stored in a closed box to await testing. Films without active substance were made in the same manner for comparison of physical properties.

**Microscopic properties and thickness**

The microscopic properties of the prepared films were evaluated using an optical microscope (STM-902 ZOOM, Opting, Czech Republic) and a color digital camera (DFW ×700, Sony, Japan). The appearance of the films was observed at a magnification factor of 20 and 50. Illustrative digital images were taken at the same time.

At the measurement of film thickness, a rectangular sample of the film was vertically fixed in a holder, the microscope was focused on the edge of the film, and the sample thickness was measured at 10 different places along the film. This was repeated 5 times with each film sample.

**Swelling property**

The swelling properties of the prepared films were measured in a physiological buffer solution of pH 7.2 (PBS). For these purposes, an artificial wound model developed by us was used. This wound model consisted of a Petri dish and absorptive sponge soaked in a test liquid. The surface of the sponge was rough resembling the surface of wound. The amount of PBS was 20 ml, which was enough to fill the sponge and create a thin layer of a liquid on the surface imitating the wound exudate. 6.25 cm² (2.5 × 2.5 cm) samples of the film were cut and weighed (Wₐ). The sample was placed on the surface of the wound model, the Petri dish was covered with a lid to prevent water evaporation, and swollen films were then weighed at determined time intervals (Wₑ). The degree of swelling Sw in the film was calculated as

\[ Sw = \frac{(Wₑ - Wₐ)}{Wₐ} \]  

(1)

**Surface pH**

The surface pH of the prepared films was evaluated using a WTW pH 3210 SET pH-meter (WTW, Germany) with a flat glass electrode. Alterations of the surface pH in the conditions simulating the wound environment were assessed using an artificial wound model (as described above). 6.25 cm² (2.5 × 2.5 cm) samples of the film were cut and put on the surface of the wound model. The Petri dish was covered with a lid to prevent water evaporation, and surface pH was measured at determined time intervals in triplicate.

**Mechanical properties**

A modified method according to Shidhaye et al. (2008) was used to evaluate the mechanical properties of the prepared films in dry state and after swelling for 3 h on an artificial wound model. A CT3 Texture Analyzer (Brookfield, USA) equipped with a 4.5 kg load cell and TexturePro CT software was used to determine the tensile strength of the prepared films. Film samples (10 × 40 mm) were held between two clamps of a TA-DGA probe positioned at a distance of 2 cm. The lower clamp was held stationary and the strips of the film were stretched by the upper clamp moving at a rate of 0.5 mm/s until the strip broke. The work done during this process and the deformation (elongation) of the film at the moment of tearing were both measured. This process was repeated five times for each film sample.

**Uniformity of mass**

For this evaluation, the adapted test as described in European Pharmacopoeia (chapter 2.9.5. Uniformity of mass of single-dose preparations) was applied. 20 units of precisely cut samples from random sites of the prepared films (2.5 × 2.5 cm) were weighed individually, and the average mass ± SD was determined. The individual masses were then compared with the average mass and the percentage of deviation was calculated.

**Uniformity of drug content**

For this evaluation, the adapted test as described in European Pharmacopoeia (chapter 2.9.6. Uniformity of content of single-dose preparations) was applied. 10 units (5 × 5 cm) were precisely cut from random sites of the prepared films and dissolved separately in beakers containing 200 ml of PBS. Standard solutions of 0.15, 0.3, 0.45, 0.6 and 0.75% lidocaine hydrochloride (w/w) were prepared using a PBS, and calibration curves using HPLC were constructed. The HPLC system employed was a YL 9110 chromatograph (Young Lin Instrument, South Korea), using a variable wavelength UV detector set at 210 nm. Analysis was performed on a Polaris C18 column (250 × 4.6 mm; 5 μm) at temperature 30 °C. A mixture containing 0.2% (w/w) phosphoric acid in water and acetonitrile (75:25) was used as a mobile phase, at a flow rate of 1 ml/min and injection volume of 3 μl. The average concentration of lidocaine hydrochloride in each sample, percentage deviation and SD were then calculated.

**In vitro drug release**

A standard paddle dissolution apparatus Sotax AT7 Smart (Donau Lab, Zurich, Switzerland), as described in the European Pharmacopoeia, was employed to evaluate drug release. A portion of 25 cm² (5 × 5 cm) of film was used. A side of the film without the drug was attached using double adhesive tape to an inert glass plate as described by Okamoto et al. (2001), then the vessel was filled with 500 ml of PBS, and maintained at 32 °C (temperature of
skin surface) while stirring at 50 rpm. Two-milliliter samples were collected automatically at predetermined time intervals and replaced with an equal amount of PBS to maintain a constant volume. Lidocaine hydrochloride release was quantified by HPLC as described above and was expressed as a cumulative percent released versus time for the 3-h duration of the study.

**Statistical analysis**

All experiments were carried out at least in triplicate, and data was expressed as a mean ± standard deviation (SD). Comparison of the means was performed by analysis of variance (ANOVA) at a significance level of α = 0.05. p-values were used as a decisive criterion for indication of significance. The statistical significance of parameters was confirmed if the p-value was equal to or smaller than α. Statistical evaluation of data was performed by means of QC Expert software, version 3.2.

**Results and discussion**

Partially substituted microfibrous NaCMC (non-woven textile Hcel® NaT) was used in order to increase the mechanical resilience of the films after wetting. It was assumed that non-substituted fibers would act as fillers. According to Paunonen (2013), if the filler is well dispersed in the polymer matrix, an improvement in the mechanical properties is usually observed. Despite the excellent cohesiveness of the wetted films, thanks to the microfibrous NaCMC and proved in our previous study (Vinklárková et al., 2015), it was still necessary to reinforce them even more to enhance handling properties. For this reason, a technological procedure that enables the creation of an insoluble matrix of the acidic form of CMC (HCMC) was chosen. Macrogol 300 and glycerin were used as plasticizers. The solvent casting method was chosen for film preparation. It is a widely used manufacturing process for making films distinguished by its relative simplicity and the low cost that system setup incurs at a research laboratory scale (Morales and McConville, 2011).

In the case of medicated film, an active substance may be incorporated in different ways. Considering the fact that the assumed indication of the film was anesthesia before painful intervention on the wound, the onset of action must be rapid. For this reason, lidocaine hydrochloride was incorporated as the external layer on only one side of film in the form of fine crystallized, evenly distributed and firmly adhered particles on the surface (see microscopic appearance). The concentration of the drug in the film was expressed as mg/cm² of film. This expression facilitates dosage since wound dressings are applied to a certain surface area. Perumal et al. (2008) even postulate that determination by weight is erroneous because the final dosage form is determined by area instead of weight in the particular case of films. Moreover, expression related to area is independent of the weight of the film which may vary considerably, as films made from hydrophilic polymers tend to fluctuate in terms of moisture content (Paunonen, 2013). A concentration of 5 mg/cm² was chosen on the basis of doses for topical application of lidocaine proven in clinical practice (Cuomo et al., 2015; Pasero, 2013; Sussman and Bates-Jensen, 2012). Visual examination demonstrated that prepared films were homogenous with a smooth surface. Although the presence of insoluble HCMC did not allow the excellent transparency typical of films from NaCMC, the prepared films were translucent enough to facilitate observation of wound conditions, especially when wetted (Fig. 1). Dry films were firm and resilient, and films with glycerin were more flexible than macrogol ones. After wetting they both became soft and pliable, with good adherence to the skin. However, conversion of NaCMC to HCMC led to a loss of bioadhesive/mucoadhesive properties which are distinctive to films from NaCMC (Vetchý et al., 2014). Nevertheless, this change of properties would be positive when applied to wounds as a local anesthetic, as it enables very easy and quick removal without residues.

**Fig. 1.** Appearance of wetted film after application to small lesion.

**Fig. 2.** Microscopic appearance of the film without drug: (A) surface of film, (B) edge of film with easily recognizable fibers (magnification 20×, bar 500 μm).

**Fig. 3.** Microscopic appearance of the film with lidocaine hydrochloride: (A) magnification 20×, bar 500 μm, (B) magnification 50×, bar 100 μm.
Observation of microscopic appearance of prepared films confirmed that partially substituted CMC maintained a fibrous nature (Fig. 2). Medicated films contained evenly distributed particles of crystallized lidocaine hydrochloride (Fig. 3).

Film thickness is an important parameter from a technological standpoint. Uniform thickness indicates a correct preparation method and a strong likelihood of drug content uniformity as well as a regular process of drug release. The thickness of prepared films was dependent on drug content – films with lidocaine hydrochloride were thicker ($p < 0.05$) than lidocaine-free ones (Table 1). The influence of type of plasticizer (macrogol or glycerin) was negligible ($p > 0.05$).

The swelling behavior of the films is an important property for their practical application. Liquid-uptake of the film prevents dry-out and creates conditions for moist wound healing (Pišlová et al., 2015). It may be affected by several factors such as pH or the presence and character of ions. A physiological buffer solution of pH 7.2 is similar to wound fluid with regard to ion content as well as pH value, thus determined swelling values of prepared films could adequately reflect those in a real wound.

The films exhibited a low degree of swelling (Fig. 4), indicating weak holding capacity for the exudate while still maintaining their excellent structural integrity for a reasonable time period. The degree of swelling (Sw) increased only slightly with time. The higher swelling values were obtained from medicated films ($p < 0.05$). Most likely, a lidocaine salt of CMC with a higher swelling responsiveness was formed during preparation. The influence of type of plasticizer on swelling properties was not confirmed.

Alterations to the surface pH of the films during 3 h in conditions simulating a wound environment are shown in Fig. 5. The figure demonstrates that surface pH increased with time ($p < 0.05$) probably due to an ion-exchange reaction resulting in the gradual formation of sodium or potassium salts of the CMC. Nevertheless, all prepared films retained acidic pH values (pH < 4.5). This evaluation is very important because it reflects

![Fig. 4. Swelling behavior of prepared films.](image)

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**Table 1**

<table>
<thead>
<tr>
<th>Thickness, mass, mechanical properties and uniformity of drug content of prepared films.</th>
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<tbody>
<tr>
<td><strong>Films with macrogol 300</strong></td>
</tr>
<tr>
<td>without drug</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Thickness ($\mu$m)$^b$</td>
</tr>
<tr>
<td>Mass of sample 2.5 × 2.5 cm (mg)$^b$</td>
</tr>
<tr>
<td>Mechanical properties$^c$</td>
</tr>
<tr>
<td>– dry film</td>
</tr>
<tr>
<td>• tensile strength (N)</td>
</tr>
<tr>
<td>• deformation/elongation (mm)</td>
</tr>
<tr>
<td>• – work done (mJ)</td>
</tr>
<tr>
<td>– swelled film after 3 h on the artificial wound model</td>
</tr>
<tr>
<td>• tensile strength (N)</td>
</tr>
<tr>
<td>• deformation/elongation (mm)</td>
</tr>
<tr>
<td>• – work done (mJ)</td>
</tr>
<tr>
<td>Uniformity of drug content (sample 5 × 5 cm)$^d$</td>
</tr>
<tr>
<td>– average content (mg)</td>
</tr>
<tr>
<td>– deviation from the stated content (125 mg/25 cm$^2$) (%)</td>
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<tr>
<td>– marginal deviation below average content (%)</td>
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<td>– marginal deviation above average content (%)</td>
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Mean ± SD ($^a n = 50$, $^b n = 20$, $^c n = 5$, $^d n = 10$).
soft, flexible, pliable and elastic in order to cope with the stresses exerted by different parts of the body (Boateng et al., 2008). These desirable characteristics can be achieved by investigating their tensile properties to ensure a balance between flexibility and rigidity. Fig. 6 demonstrates comparable mechanical properties of prepared films. Films with glycerin had slightly better mechanical properties than macrogol plasticized ones, but this difference was not statistically significant ($p > 0.05$), thus the influence of plasticizer was not proved. The greatest statistically significant differences ($p < 0.05$) were noticeable between films with and without lidocaine or dry and swelled ones. Not surprisingly, lower values of tensile strength, higher elongation and less work necessary to tear the film were all observed in swelled films. The lower tensile strength of medicated films was probably caused by the interaction of anionic HCMC and cationic lidocaine hydrochloride leading to the formation of a compound with worse mechanical properties. The fact that added active compounds, in general, affect mechanical properties of CMC films, is also stated by Paunonen (2013). Nevertheless, both medicated films and lidocaine-free ones manifested excellent handling properties after swelling (3 h on wound model), making them extremely beneficial in clinical applications. It would be interesting to compare the mechanical properties of prepared films with those described in the patent (Butler, 1962) which gave us this idea. Unfortunately, direct comparison was impossible due to differing units of measurement of tensile strength used in the patent which could not be converted. Nevertheless, a relative comparison of strength loss after wetting seemed to favor our films – wet films in the patent were ca. five times weaker than dry ones, whereas the weakening of films prepared by us was less than half of dry value after swelling on the wound model (Table 1). This finding confirms the correctness of the developed technology.

According to European Pharmacopoeia, not more than 2 of the individual masses may deviate from the average mass by more than 10% if a pharmaceutical form has an average mass 80 mg or less, and none deviates by more than twice that percentage. All prepared films met these requirements. Films prepared with glycerin were slightly lighter than those with macrogol ($p < 0.05$), regardless of lidocaine content (Table 1).

European Pharmacopoeia does not state the requirements for medicated films regarding drug content. Thus, requirements for transdermal patches or ophthalmic inserts, as the most similar

Fig. 5. Alterations of surface pH in the conditions simulating wound environment.

The mechanical properties of the prepared films are shown in Table 1. Characterization of mechanical properties is important because film dressings are required to be durable, stress resistant,
pharmaceutical forms to film wound dressings, should be applied. In the case of transdermal patches, the preparation complies with the test of if the average content of 10 dosage units is between 90% and 110% of stated content and if the individual content of each dosage unit is between 75% and 125% of the average content. In the case of ophthalmic inserts, the preparation complies with the test of if each individual content is between 85% and 115% of the average content. The values shown in Table 1 confirm that the prepared films met the requirements for both transdermal patches and ophthalmic inserts.

Not surprisingly, drug release from prepared films was very rapid, because lidocaine hydrochloride is highly water-soluble and was incorporated as the external layer of the film. More than 90% of the drug released during the first 15 min, and the remaining content of lidocaine was released within an hour (Fig. 7). The data shows almost identical release profiles both for films containing macrogol and those containing glycerin. Drug release from the prepared films was similar to the observations made by Murata et al. (2010), who investigated fast dissolving films expected to be applied in the oral cavity or Vakili et al. (2012), who studied lidocaine hydrochloride release from porous cellulose film matrices. Sustained/extended release may be achieved if lidocaine is dispersed in a polymer matrix, as done by Repka et al. (2005) or Okamoto et al. (2001). However, extended release was not the aim of our study. We assumed that the drug-containing layer would dissolve within a short time period and release the drug toward the wound surface where the local anesthetic action of lidocaine hydrochloride could take effect. The dissolution test proved that the insoluble carboxymethylcellulose matrix served as a reliable carrier, without slowing down the release of lidocaine hydrochloride. The result was a dosage form that can be expected to provide a quick and satisfactory rate of anesthetic action as a prepared film wound dressing.

Conclusion

Film wound dressings based on an insoluble carboxymethylcellulose matrix were successfully prepared using a sequential solvent casting method. Films containing lidocaine hydrochloride possess properties making them suitable for use as comfortable and efficient topical anesthetics. This is due to their firmness and resiliency in dry state and excellent handling properties, softness, pliability, good transparency, and adherence to the skin after swelling. The high flexibility of wetted films provides good adaptability to the wound or other treated surfaces with disrupted skin integrity. The prepared films showed an acidic surface pH advantageous for wound application, as well as satisfactory mass and drug content uniformity. The films exhibited a low degree of swelling, indicating weak holding capacity for the exudate, which is typical of the most polymeric films. An in vitro drug release study confirmed rapid lidocaine hydrochloride release. The principal implication of the developed technology is that it is suitable for the preparation of both drug-containing film wound dressings and non-medicated ones. Films without an active substance could be used to protect slightly exuding or non-exuding wounds (such as epithelizing wounds) against injury and the growth of microorganisms, thanks to its good mechanical properties and low surface pH values. The described technology for drug incorporation, when a highly soluble active substance or combination of such substances form a layer on only one side of the film, is particularly beneficial for preparations with rapid drug release – in the case of local anesthesia the combination of several actives should result in major improvement of effect. These attributes, as well as evaluation of long-term stability or in vivo effects, will however, require further investigations.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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