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Functional Wound Dressing Materials with Highly Tunable Drug Release Properties

Tina MAVER[a], MPharm, Silvo HRIBERNIK[a], PhD, Tamilselvan MOHAN[b,], PhD, prof. Dragica Maja SMRKE[c], MD, PhD, assist. prof. Uroš MAVER[d,⊕,*], MPharm, PhD and prof. Karin STANA-KLEINSCHEK[a*], PhD*

[a] University of Maribor, Faculty of Mechanical Engineering, Laboratory for Characterisation and Processing of Polymers, Smetanova 17, SI-2000 Maribor, Slovenia
[b] University of Graz, Institute for Chemistry, Heinrichstrasse 28, 8010 Graz, Austria
[c] University Medical Centre Ljubljana, Zaloška cesta 2, SI-1000, Ljubljana, Slovenia
[d] University of Maribor, Faculty of Medicine, Department of Pharmacology and Experimental Toxicology, Taborska ulica 8, SI-2000 Maribor, Slovenia

⊕ *Member of Institute of Palliative Medicine and Palliative Care, Faculty of Medicine, University of Maribor, 2000 Maribor, Slovenia*

*Corresponding authors
Prof. Dr. Karin Stana-Kleinschek
University of Maribor, Faculty of Mechanical Engineering
Laboratory for Characterisation and Processing of Polymers
Smetanova 17, SI-2000 Maribor, Slovenia
karin.stana@um.si
Phone: +386 2 220 7881
Fax: +386 2 220 7990

Dr. Tamilselvan Mohan
University of Graz
Institute for Chemistry
Heinrichstrasse 28, 8010 Graz, Austria
tamilselvan.mohan@uni-graz.at
Phone: +43 316 380 5413

Assist. prof. dr. Uroš Maver
University of Maribor, Faculty of Medicine
Department of pharmacology and experimental toxicology
Taborska ulica 8, SI-2000 Maribor, Slovenia
uros.maver@um.si
Phone: +386 2 234 5823
Fax: +386 2 234 5923

Abstract

Wound dressings, capable of local controlled delivery of non-steroid anti-inflammatory pain-killing drugs (NSAIDs) to the wound bed, offer great potential to accelerate wound healing, hence increase the quality of patient life. With local NSAID delivery, unwanted side effects encountered in their systemic delivery, are drastically diminished. In this study, four functional fibrous wound dressing materials, namely viscose, alginate, sodium carboxymethyl cellulose (Na-CMC) and polyethylene terephthalate (PET) loaded with a NSAID, diclofenac sodium (DCF) are prepared, and their suitability to tune the release rate of DCF is evaluated. Through careful examination of material-drug combinations, in terms of their physicochemical properties (air permeability, wettability and water retention) and structural/morphological properties (infrared spectroscopy, wide angle X-ray scattering and scanning electron microscopy), possible wound care applications are proposed. *In vitro* release studies using an automated Franz diffusion cell system, combined with UV-Vis absorption spectroscopy for drug release profile determination, are performed as the final pre-formulation test. Results showed significant differences in the release profiles between different material-drug combinations, making the examined materials highly applicable for several wound care applications. The present study presents a novel cost effective approach for preparation of drug loaded wound dressing materials without a sacrifice in patient safety. Additionally, novel methods and material-drug combinations are introduced, paving the way for possible future wound treatment options.

Keywords: wound dressing, NSAID, diclofenac sodium, release tuning, *in vitro* drug release investigation

1

1　**1. Introduction**

2　A wound is commonly referred to as a skin injury caused by trauma or surgery. Wound

3　healing generally follows a well-defined yet complex cascade of processes commonly divided

4　into four main stages; coagulation, inflammation, cell proliferation with repair of the matrix,

5　and epithelialization with remodeling of the scarred tissue[1]. Depending on the extent and

6　depth of skin damage, the entire healing process can last for several months[2]. Among the most

7　important conditions affecting wound healing start, are the wound cleanliness, a suitable

8　blood supply, and the absence of necrotic leftovers and fibrin plaques[3]. Once the healing is

9　underway, an appropriate moisture balance and prevention of infections, as well as exudate

10　management, are necessary to assure effective healing[4]. Although multi-layered and multi-

11　functional wound dressings are not a novelty in wound care/healing process[5], existing

12　products do not address the challenging issues in wound treatment, such as controlled

13　therapeutic action or wound type specific healing.

14　Different fiber forming polymers are often used as drug carriers, absorbents or as moisturizers

15　in wound dressings[6]. Their semi-crystalline structures, nano-, micro- and especially macro-

16　porosity allow them to incorporate, bind and release different amounts of active ingredients

17　according to their respective structural and physico-chemical properties[7]. The most commonly

18　used are PET, cellulose and its derivatives and regenerated cellulose such as viscose, as well

19　as other types of polysaccharides. PET is a hydrophobic polymer, which is often used as an

20　inert layer of the dressing, suitable for contact with the damaged skin[8]. Regenerated cellulose

21　(viscose) and cellulose derivatives (sodium salt of carboxymethyl cellulose, Na-CMC), as

22　well as alginate, are among the most common functional parts of different modern wound

23　dressings[9]. Their final formulation shapes range from fibers, non-woven materials and

24　hydrogels to foams[8].

25 Lately, novel advanced wound dressing formulations are explored in order to achieve

26 controlled release and delivery of drugs to wound sites[10, 11]. The release from such materials is

27 sparsely reported in literature with few clinical studies carried out to date[12, 13]. Especially little

28 or almost no literature is available regarding the controlled wound type specific drug delivery

29 using polymeric drug loaded materials as dressings. Despite the well-known fact that different

30 wounds exhibit significantly altered wound bed conditions[14], they provide different

31 physiological conditions for drug release. Polymer-based dressings employed for controlled

32 drug delivery to wounds include hydrogels such as poly(lactide-co-glycolide)[15], poly(vinyl

33 pyrrolidone)[16], poly(vinyl alcohol)[17] and poly(hydroxylalkyl-methacrylates)[18], polyurethane-

34 foam[19], hydrocolloid[20] and alginate dressings[21]. Other polymeric dressings reported in

35 literature for this purpose include novel hybrid formulations prepared from hyaluronic acid[22],

36 collagen[23] and chitosan[24,25].

37 Drug release from polymeric formulations is mostly controlled by one or more physical

38 processes including (a) hydration of the polymer, (b) swelling and gel formation, (c) diffusion

39 of the drug through the matrix and (d) eventual erosion of the matrix[26]. Since wounds exhibit

40 different extents of exudation, it is expected that wound specific healing can be achieved by

41 combining swelling, erosion and subsequent drug diffusion kinetics as part of the controlled

42 drug release mechanism. In fact, most of the recently researched materials intended for wound

43 dressings (either natural or synthetic) release incorporated drugs by a combined mechanism of

44 either two or three above mentioned principles[27, 28].

45 Non-steroid anti- inflammatory drugs (NSAIDs) are important drugs in relieving pain,

46 fighting fever and decreasing inflammation. However, both NSAIDs and their selective

47 cyclooxygenase-2 (COX-2) inhibitors inhibit PGE2 production, which might exacerbate

48 excessive scar formation, especially when used during the later proliferative phase.

49 Nevertheless, it was shown that pain reduction induced decrease in stress, can positively

2

50   affect wound healing, resulting in shortened healing times[29]. Based on scientific and clinical

51   evidence, pain can significantly slow down the healing process (mostly through stress induced

52   release of hormones like cortisol and norepinephrine), which results in decreased patient

53   quality of life as well as in exponentially increased personal and public expenditures[30-32].

54   Mostly NSAIDs are taken through systemic administration (i.e., in the form of pills), whereas

55   several approaches have been and are researched towards their integration into different

56   wound dressing formulations[33-36]. Although antibiotics are not the preferred type of drugs for

57   local treatment due to possible resistance acquisition of commensal bacteria, there are several

58   interesting studies available about preparation of dressing, combining NSAIDs and

59   antimicrobials[37-39].

60   The purpose of this study was therefore to prepare wound dressing materials with

61   incorporated NSAIDs and to study their efficiency related to material performance and drug

62   release. For this purpose, only commercially available and clinically approved materials were

63   used. Four wound dressing materials, widely differing in their ability to take up liquids,

64   namely sodium salt of carboxymethyl cellulose (Na-CMC), alginate (ALG), viscose and

65   polyethylene terephthalate (PET) were chosen and subsequently integrated or loaded with the

66   (NSAID), diclofenac (DCF). The structural and surface properties of the material-DCF

67   potential wound dressing combinations were analyzed in detail using contact angle, water

68   retention and air permeability measurements, wide angle X-ray diffraction (WAXS) and

69   scanning electron microscopy (SEM). The application potential of the chosen materials was

70   shown in the release of the NSAID DCF *in vitro* using Franz diffusion cell release studies

71   followed by quantification using UV-Vis absorption spectroscopy. Through preparation of

72   four different material-DCF combinations and their ability to release DCF, this study was

73   intended to assess the suitability of different wound dressing materials for effective and safe

74   pain reduction in relation to the treatment of different wound types. To our best knowledge,

3

75   WAXS was never before used in examination of novel wound dressing formulations. Our

76   study aimed at providing a novel approach towards preparation of cost effective drug loaded

77   wound dressing solutions without the sacrifice of patient safety. It also provides a possible

78   novel PET based wound dressing with potential for future wound care applications.

79

80   **2. Materials and methods**

81   **2.1. Materials**

82   Four commercially available materials differing in their surface properties (wettability and

83   composition) were used as wound dressings. Viscose nonwoven (specific surface area mass=

84   175 g/m^2) was purchased from KEMEX, Netherlands. Fibrous alginate (ALG) and

85   carboxymethyl cellulose (Na-CMC; commercial, clinically used, wound dressing Aquacel®)

86   nonwoven were purchased from Sigma-Aldrich, Slovenia and ConvaTec, USA, respectively.

87   Polyethylene terephthalate, PET (100%, specific surface area = 75 g/m^2) in the form of a

88   mesh (mesh size of 0.8 mm) was purchased from BETI, Slovenia. Diclofenac sodium (DCF)

89   was purchased from Sigma-Aldrich, Germany. All the materials were used as received

90   without any further modification prior to sample preparation or testing. Ultra-pure water (18.2

91   MΩ cm at 25 °C) from an ELGA PureLab water purification system (Veolia Water

92   Technologies, UK) was used for preparation of all solutions.

93   **2.2. Integration of drug molecules into wound dressing materials**

94   The wound dressing samples were cut into 1 x 1 cm squares and impregnated with DCF

95   (dissolved in ultra-pure water, 1 mg/ml) for 15 minutes. Afterwards, the samples were dried in

96   an oven at 50 °C for 5 minutes, cooled down to room temperature and finally flushed with

97   nitrogen gas. The as-prepared samples were immediately used for *in vitro* release testing and

98   characterization.

99   **2.3. Methods**

4

100   *2.3.1. The Powder water contact angle measurement*

101   The wettability of the wound dressing materials (with and without incorporated DCF) was

102   measured using the powder contact angle measurement method (CA), which was performed

103   on a Krüss K12 processor Tensiometer (Hamburg, Germany). For the measurements, the

104   samples were cut into 2 cm × 5 cm rectangular pieces and placed into a special sample holder.

105   Prior to measurement, the container with the liquid (n-heptane or water) was raised until the

106   sample edge touched the liquid surface. The samples' mass (m) changes as a function of time

107   (t) during the water adsorption phase were monitored. The initial slope of the function $m^2 = f$

108   (t) is known as the capillary velocity, which can be used for determination of the contact angle

109   between the solid (polymer sample) and water using a modified Washburn equation:

$$\cos \theta = \frac{m^2}{t} \cdot \frac{\eta}{\rho^2 \cdot \gamma \cdot c} \qquad (1)$$

110   where θ is the contact angle between the solid and liquid phases, $\frac{m^2}{t}$ is the capillary velocity, η

111   is the liquid viscosity, ρ is the liquid density, γ is the surface tension of the liquid and c is a

112   material constant[4, 5, 40].

113   All measurements were performed on three independent samples at three different sample

114   regions. An average value was calculated and the standard error is reported.

115   *2.3.2. Water retention values*

116   The water retention value of the chosen materials was determined according to standard DIN

117   53 814. This method is based on determining the quantity of water that the sample can absorb

118   and retain under defined and strictly controlled conditions. The water retention value is

119   expressed as the ratio between the mass of water, retained in the sample after soaking (t = 2 h)

120   followed by centrifuging (20 minutes), and the mass of an absolutely dry sample (T = 105 °C,

121   t = 4 h). All measurements were performed in four parallels and an average value was

122   calculated.

5

123　　*2.3.3. Moisture content*

124　　The moisture content of the wound dressing materials was determined using a Halogen

125　　Moisture Analyser HB43 (Mettler Toledo, Giessen, Germany). This was done using the

126　　thermo-gravimetric principle: the samples' weight was measured before and after controlled

127　　heating.

128　　*2.3.4. Air permeability determination*

129　　Air permeability determination of all materials was performed according to standard DIN 53

130　　887 with the Karl Schröder apparatus (Karl Schröder KG, Germany). The pinned surface of

131　　the sample was 20 cm^2, while the three-level air-flow measurer operated at 20 °C in 1013

132　　mbar. During the measurement, the pressure at the surface of the sample and the temperature

133　　were fixed at 1 mbar 23 °C, respectively.

134　　The reference air permeability was calculated using the following equation (2):

$$V_N = f \cdot V_G \cdot \sqrt{\frac{P_U \cdot T_N}{P_N \cdot T_U}} \qquad\qquad (2)$$

135　　where V_N, P_N and T_N are the reference air permeability, pressure and temperature,

136　　respectively, while V_G is the air permeability and P_U and T_U are the ambient pressure and

137　　temperature and f is a factor for calculation, corresponding to a defined surface area.

138　　*2.3.5. Determination of surface thickness*

139　　The surface thicknesses of the samples was determined by the standard SIST ISO 5084, which

140　　is defined as the perpendicular distance between the upper and lower side of the sample.

141　　According to the measured thicknesses, the pore volumes and the heights of the air layers

142　　were determined, which serve as the perfect basis for prediction of the samples voluminosity.

143　　Measurements were performed using the Louis Schopper apparatus (Leipzig, Austria). The

144　　thickness of the pressure plate and its surface area were 4 mm and 1000 mm^2 (with a diameter

6

145   of 35.68 mm), respectively. For each sample five measurements were performed and an

146   average value was calculated with an added standard error.

147   *2.3.6. Attenuated total reflectance-infrared (ATR-IR) measurements*

148   ATR-IR spectra were recorded using an Agilent Cary 630 FTIR spectrometer with the

149   diamond ATR module at a scan range of 4000-650 cm^{-1}. The scans were performed on three

150   different places in 8 repetitions on each sample surface before and after impregnation with

151   DCF and after the DCF release.

152   *2.3.7. Wide angle X-ray scattering (WAXS) measurements*

153   The WAXS experiments were performed using the S3-MICROpix solution of Hecus (Graz,

154   Austria) with a 50 Watt microsource Genix 2009 from Xenocs (Sassenage, France). The tube

155   consists of a copper anode with an emission wavelength of 1.5418 Å for the Kα line. The

156   sample to detector distance was 291 mm with an angle of 4.2°. The optics are 3D for point

157   focus with a beam size of 50 x 200 μm^2 and a flux up to 4 x 108 photons s^{-1} mm^{-2}. The point

158   focus at the detector has a monochromatic WAXS resolution of q(min) ≥ 4*10^{-3} Å^{-1}. The

159   scattering vector (q) range is between 0.003 Å^{-1} and 1.9 Å^{-1}. As detection system, a 2D

160   Pilatus 100k Dectrics Detector (Baden, Switzerland) 34 x 84 mm^2, with a pixel size of 172 x

161   172 μm^2 was used. A Nickel filter was used as semi-transparent primary beam stop. X'Pert

162   Highscore Plus (PANalytical B.V., Almelo, Netherlands) was used for analysis of the

163   obtained diffractograms.

164   *2.3.8. Scanning electron microscopy (SEM)*

165   The surface morphology of samples prior and after DCF impregnation was analyzed by SEM.

166   Prior to imaging, several single fibers were removed from all samples and pressed on a

167   double-sided adhesive carbon tape (SPI 116 Supplies, USA). Micrographs were taken using a

168   field emission scanning electron microscope (FE-SEM, Supra 35 VP, Carl Zeiss, Germany)

169   operated at 1 keV at room temperature.

170   *2.3.9. In vitro release studies*

171   *In vitro* drug release studies were performed using an Automated Transdermal Diffusion Cells

172   Sampling System (Logan System 912-6, Somerset, USA). The drug loaded samples were cut

173   into 1 x 1 cm squares and placed on the top of a cellulose acetate membrane. The receptor

174   compartment was filled with ultra-pure water and its temperature was maintained at 37 °C.

175   During the dissolution testing the medium was stirred continuously with a magnetic bar.

176   Samples were collected over a period of 24 h at different time intervals, while the

177   released/dissolved DCF concentration in the receptor medium was determined by UV-Vis

178   spectrophotometer (Cary 60 UV-Visible Spectrophotometer, Agilent, Germany) by

179   quantification of the absorption band at 276 nm.

180   The withdrawn sample volumes were replaced by fresh ultra-pure water. Due to sample

181   withdrawal, followed by sample dilution through media replacement, sink conditions were

182   assured. In calculation of concentrations using the Beer-Lambert Law, this dilution was

183   accounted for. All release studies were performed in three parallels. For the determination of

184   final incorporated DCF amount, pieces of the same size (1 x 1 cm squares) of each material

185   with incorporated drug were shredded and immersed into 20 ml absolute ethanol. After 48 h

186   of shaking, DCF concentration was determined by UV-Vis spectrophotometry. Furthermore,

187   to confirm the complete release of DCF the samples were dried in oven at 50 °C for 15

188   minutes and analyzed by ATR-IR.

189   To compare the differences in release rates of wound dressing materials loaded with DCF

190   drug, a regression analysis was performed using the GraphPad Prism Software Version 5.01.

191   A difference is considered to be significant, when the obtained p-value is lower than 0.05 ($p <$

192   0.05). The calculated p-values are given in the supporting information (Table S1).

193

194   **3. Results and discussion**

8

195   **3.1. Wettability, water retention and moisture content of unloaded samples**

196   Keeping the wound's surface moist is the fundamental principle of open wound treatment[41].

197   Several methods can be applied to evaluate a material capability to assure appropriate

198   moisture in the wound bed. The common denominator of such measurements is

199   hydrophilicity, which is connected with the water contact angle and is reflected in the water

200   retention value, as well as in the materials moisture content. The water contact angles

201   ($CA(H_2O)$) and water retention values of unloaded wound dressing samples are shown in

202   **Figure 1**.

203   It is expected that $CA(H_2O)$ are inversely proportional to the water retention values – the

204   larger the contact angle, the lower the water retention value, but while measuring the

205   mentioned on wound dressing materials, their 3D structure (often fibrous), in particular in the

206   case of PET and viscose materials, plays an important role in regulating their overall

207   hydrophilicity. The relation between $CA(H_2O)$ and water retention values is therefore not

208   straightforward, as shown also in case of our results. The $CA(H_2O)$ values demonstrate that

209   the most hydrophilic materials are clearly Na-CMC and alginate compared to other two

210   materials (viscose and PET). Alginate exhibits the lowest $CA(H_2O)$: $54 \pm 3°$, whereas the

211   measurement of the $CA(H_2O)$ is not possible for Na-CMC (Aquacel®) due to its extremely

212   high soaking ability and hydrophilic nature, which is facilitated by a higher content of

213   carboxylic groups. The latter prevented us to determine the capillary velocity, and hence the

214    $CA(H_2O)$ value for this sample. From literature it is clear that the contact angle of Na-CMC is

215   very dependent on the material type. A range of $CA(H_2O)$ values from low to high can be

216   found in the literature[42, 43]. Since we are not able to measure this value, probably due to Na-

217   CMC super-molecular structure that allows the material to form a gel-like structure, which

218   results in an extremely high water uptake, this value is missing in Figure 1. The PET sample,

219   as a known hydrophobic synthetic polymer, exhibited a $CA(H_2O)$ of $90 \pm 4°$[43]. Viscose

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220   (cellulose, regarded as a hydrophilic material) rather shows a higher $CA(H_2O)$: $88 \pm 4°$,

221   similar to PET. This increased $CA(H_2O)$ can be attributed to complex structural properties of

222   cellulose fibers, such as two-phase regime composed of disordered accessible regions and

223   ordered crystalline regions, porous system with voids and interfibrillar interstices, fiber

224   orientation, etc.[44, 45]

225   By far the highest water retention value was determined for the Na-CMC sample. Indeed, the

226   measured value is so high (1521%) that we have to present it in a separate diagram (Figure

227   2B) to allow for a clearer comparison of the other samples. The higher water retention values

228   of Na-CMC can be related to incorporation of a larger number of water molecules by its

229   ionisable carboxylic groups ($-COO^-$). PET samples, on the other hand, exhibit the lowest

230   values for water retention due to their high hydrophobic character. The water is repelled from

231   its surface, and consequently, the resulting value can almost not be seen in Figure 1 (0.3%).

232   Alginate and viscose exhibit water retention values of 81% and 61%, respectively. These

233   values are in agreement with the values reported in literature for alginate[46] and viscose[4]. The

234   differences in their water retention properties can be attributed to their functional groups and

235   structural properties (porosity, degree of crystallinity and fiber orientation)[45, 47].

236   Moisture content measurement is an important feature, affecting our choice of drug host

237   materials in wound treatment, since it affects the final capacity to uptake fluids when applied

238   on the wound. On the other hand, the initial moisture content can seriously influence the

239   controlled release behavior due to porosity and changes in mechanical strength of the host

240   material. It also affects the release and distribution of drug molecules, especially considering

241   the drug molecules accessibility by the release media[48]. More related discussion will be

242   presented in the section explaining drug release studies. The results of materials' moisture

243   content evaluation show a similar order among tested samples as for the $CA(H_2O)$, except for

244   Na-CMC, for which $CA(H_2O)$ could not be obtained. Na-CMC was initially in a dry form

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245   than alginate, but exhibits in its pure form (out of the secondary packaging) a higher moisture

246   content than viscose and PET (**Table 1**). Based on the moisture content differences among the

247   used materials, extreme care is necessary during all other testing procedures in order to avoid

248   possible fluctuations in moisture during experimentation. Between measurements, all

249   materials were always placed into tightly sealed petri dishes and additionally sealed with

250   parafilm strips.

251   **3.2. Air permeability vs. thickness of samples**

252   A medical dressing must be permeable for gasses, but an excessive air permeability,

253   especially a higher moisture vapor transmission rate, could dry out the wound and have a

254   negative effect on healing. The latter is due to two mechanisms, either through direct impact

255   on newly formed cells (excessive drying of the wound bed causes cell death), or by resulting

256   in growing of the dressing into the wound[4]. The latter being a result of dressing interaction

257   with newly formed tissue, forming crusts and resulting in an unfavorable effect on the

258   wound's healing rate[49]. Given the conditions of the testing method, air permeability is mostly

259   affected by the manufacturing method of the material (knitting and preparation of non-

260   woven), yet sample structure, chemical nature, as well as the samples' thickness must be

261   taken into account. Air permeability of the chosen materials was evaluated against the sample

262   flat thickness. The results are shown in **Figure 2**.

263   The expected correlation between thickness and air permeability, namely the thicker the

264   material, the lower is the air permeability, is obtained for Na-CMC and alginate. One could

265   argue that also viscose exhibits the same correlation, especially with the error bars counted in.

266   Based on these results, it is clear that the demonstrated air permeability of Na-CMC, alginate

267   and viscose are satisfactory for ensuring and maintaining optimal wound healing conditions.

268   On contrary, the results also clearly show an extremely high air permeability for PET, not

269   suitable for desired maintenance of a moist wound environment. PET is therefore only

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270　applicable either in thicker layers or by preparation of multi-layered wound dressings

271　comprising additional materials.

272　**3.3. DCF incorporation and characterization: ATR-IR and WAXS spectroscopy of**

273　**samples**

274　ATR-IR spectroscopy is employed to access the chemical composition and structural

275　properties of the unloaded and DCF loaded wound dressing materials. A clear indication of

276　successful DCF incorporation in all samples (Na-CMC, alginate and viscose) except in the

277　case of PET can be seen from the IR spectra shown in **Figure 3**. For respective samples, these

278　are organized in a way allowing clear comparison of peaks that can be assigned to DCF. The

279　most important peaks are colored in green. A broad peak between 3700– 3000 cm^{-1} that

280　corresponds to OH vibration can be observed for all unloaded polysaccharide based materials

281　(Na-CMC, alginate and viscose). Pure PET, in contrast, can be characterized by –CH

282　vibrations at 2900 cm^{-1} and a typical finger print region (650-1700 cm^{-1})[50]. After DCF doping

283　the emergence of several new peaks can be observed. Peaks that can be assigned to C-Cl

284　stretching vibrations are visible in the region of 650 – 780 cm^{-1}, while a band corresponding

285　to CH–N–CH bending vibration can be observed at 1376 cm^{-1}. At 1577 cm^{-1}, R=C=O

286　stretching vibration can be observed. Additional peaks corresponding to R-C=O stretching

287　and CH$_2$ bending are visible at 1305 and 1462 cm^{-1}. All these peaks are clearly visible for all

288　DCF loaded polysaccharide-based samples. This is an evidence that DCF is successfully

289　loaded into the used wound dressing materials regardless of the difference in their chemical

290　functionality and structural properties. Even though no peaks corresponding to DCF are

291　observed in the IR spectra for the PET sample, the presence of DCF is clearly evident from

292　the *in vitro* release results (see section 3.4) from this sample. A plausible reason can be that

293　the concentration of loaded DCF is too low to be detected by IR.

294   WAXS measurements, as an additional tool to support the findings of ATR-IR, is performed

295   to determine the structure of wound dressing materials as well as to detect the presence of

296   DCF in the samples (**Figure 4**). From the obtained diffractograms a DCF corresponding peak

297   around 21°, could be identified for all samples, although the latter is not that evident for the

298   PET sample with the lowest amount of incorporated DCF. This data fits well with ATR-IR

299   results (see Figure 3d), where almost no peaks related to DCF presence were noted. Apart

300   from the mentioned peak an additional peak around 26° could be observed for the viscose and

301   alginate DCF loaded samples, while the peak around 23°, also assigned to DCF, could be

302   observed for Na-CMC. Although WAXS is not a very frequently used method for this

303   purpose, it still has a higher potential for identification purposes as turned out also in our case.

304   Another useful information we could obtain from the measurements is an indication about

305   crystallinity of the sample. To confirm the overall sample crystallinity a more thorough

306   WAXS analysis would be necessary, but nevertheless, these results suggest that fractions of

307   all samples are amorphous and since the DCF assigned peak around 21° is evident even after

308   incorporation, the drug seems to remain in its crystal form. Most of the diffractograms exhibit

309   broad peaks, a characteristic contribution of the, structural components, lacking order. At this

310   point, we have to stress that the characterization was done at a limited range of angles,

311   therefore an explicit judgement is not possible. Since the crystal structure can significantly

312   affect the materials wetting properties[51], WAXS results will be integrated also in the

313   explanation of the drug release later in the article.

314   **3.4. *In vitro* release studies**

315   In this study the targeted application is wound healing, where the drug release rates have to

316   efficiently follow the pharmacological specifics of different wound types. *In vitro* drug release

317   testing is therefore a very important evaluation method in order to evaluate the prepared

318   materials applicability in treatment of different wounds.

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319 Results from the *in vitro* release testing, performed using an automated Franz diffusion cell

320 system, are depicted in **Figure 5**. Only the first 360 minutes of release are presented, since

321 this region exhibits the biggest differences between the used materials. The full release

322 profiles are given in the supporting information (Figure S1). The top figure (a) shows the

323 mass of the released drug (g/cm^2) for each DCF incorporated wound dressing material. The

324 reason for using such units lies in the suitability of such representation for possible clinical

325 application, where the dose can be easily calculated, based on the size of the dressing to be

326 applied. The bottom figure (b) exhibits the percentage of the released drug as a function of

327 time, which is important to immediately deduce the information about the release timeframe

328 of the incorporated dose. Since, acutely released higher doses could possibly lead to unwanted

329 side effects, such representation enables the planning of a safe and efficient treatment. In

330 general, both types of representation of the *in vitro* release results are highly useful, and

331 necessary to understand the release of the incorporated drug. Their combination renders

332 planning of treatments for specific wound types possible. The total amounts of the

333 incorporated DCF in the dressing after complete release (after 2880 minutes – 48h) are

334 presented in **Figure 6**. Significant differences in release profiles can be observed in both

335 representation types (Figure 5a and b). This is also reflected in p-value (significant difference,

336 see Table S1), which was calculated using a stepwise regression analysis. A p-value of 0.05 is

337 generally considered on the borderline of statistical significant difference. Thus, any p-value

338 that is below 0.05 is usually regarded as statistically significant. Obviously, in our case,

339 significant differences in release rates are observed for all wound dressing materials with

340 incorporated DCF (Table S1). Both alginate and Na-CMC samples, which are hydrophilic as

341 proven by $CA(H_2O)$, showed a superior statistical significant differences ($p < 0.001$)

342 compared to those of hydrophobic PET and viscose samples, where a p-value below 0.05 is

343 obtained. The high p-values of viscose and PET samples indicates that their release profiles

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344   are certainly different as compared to that of other two materials such as alginate and Na-

345   CMC, which can be clearly seen in Figure 5a. Despite following the same DCF incorporation

346   procedure, large differences were already observed in the amount of the incorporated drug per

347   surface area of the material (Figure 6). As mentioned above, these values are determined as

348   the released amount after the drug concentration did not change anymore.

349   Although the used drug in this study was not applied yet in a topical formulation clinically,

350   the desired dose can be calculated based on the presently commercially available and

351   clinically used DCF containing medicines for systemic use. The maximal dose in the latter is

352   75 mg per tablet. Since the bioavailability of the latter is in the range 30% locally, the desired

353   dose in the wound would be approximately 23 mg. Considering the *in vitro* release results, an

354   incorporation of DCF into a 10 x 10 cm squares alginate based dressing (alginate can

355   incorporate, and hence release the maximal DCF amount), would lead to a maximum possible

356   local concentration of around 20 mg. Considering the latter, we could claim that our

357   formulations could be efficient, as well as safe. But only further clinical studies can confirm

358   this assumption absolutely. As indicated in the introduction section, the literature only

359   sparsely reports the release from similar, whereas clinical studies are even more rare[12, 13].

360   There have been some reports about inclusion of ibuprofen, another NSAID into candidate

361   wound dressing materials[34, 36, 52], not to forget about Biatain® IBU, the commercial, clinically

362   used dressing with an incorporated NSAID[19, 53]. The latter served as a starting consideration

363   point in our assumptions in regard of the dose.

364   While only a small drug amount (0.0282 mg/cm^2) could be attached to PET, viscose (0.1289

365   mg/cm^2), Na-CMC (0.2084 mg/cm^2) and alginate (0.2426 mg/cm^2) exhibited higher amounts

366   of incorporated DCF (Figure 6). Based on these results we are also able to judge the

367   efficiency of the initial impregnation process, where the samples are able to soak the

368   following percentages of DCF from solution, PET 2.8%, viscose 12.9%, Na-CMC 21%, and

369 alginate 24.3%. Na-CMC and alginate can for example host almost an eight-fold larger

370 amount of incorporated DCF compared to PET, which makes them more suitable for

371 applications on chronic wounds, where the dressing change frequency is lower. On contrary,

372 PET based dressings are probably not applicable in a single-layered form, since the

373 incorporated amount of the drug does not cover the desired drug dose. Instead, considering

374 figure 5b, PET could be very interesting for application on wounds with acute pain, where an

375 immediate effect is necessary. The release profile shows a release of 60% of the incorporated

376 drug in the first 5 minutes and reaches a plateau after 30 minutes. In the form of multi-layered

377 dressings with PET as the bottom layer (in touch with skin/wound) could significantly add to

378 the quality of patient treatment, since the pain would diminish immediately. Additionally, in

379 such multi-layered dressings a PET based first layer would be interesting for treatment of

380 wounds, where the dressing change frequency is high and is accompanied with pain, mainly

381 caused by the removal of freshly epithelized skin or due to over-sensitization of the

382 surrounding tissue as a consequence of inflammation[54].

383 Interestingly, the viscose dressing shows a release profile similar to PET. However in the case

384 of viscose 80% of the incorporated drug are released in the first 30 min, while the remaining

385 20% are released within 360 minutes. PET and viscose are very different chemically and

386 structurally, as well as exhibit different wettabilities. These leads to a huge difference in drug

387 uptake and importantly affects their possible usage in different applications. In addition, one

388 must account for a rather complex structure of the material as a whole. Namely, viscose fibers

389 are used in the form of a voluminous non-woven with plenty of space in-between individual

390 fibers, enabling significant drug incorporation. This is not the case with the thin PET mesh,

391 where only the actually exposed surface is capable to attach drug molecules. Its inert

392 structure, as well as nonporous form with a low surface area, allow for attachment or

393 incorporation of only small drug amounts (see Figure 6). Nevertheless, PET is still an

16

394   interesting material in wound care, since its inert surface prevents sticking to the wound. The

395   most suitable application of a PET dressing is therefore as the initial layer in contact with the

396   skin of multi-layered dressings. On the contrary, viscose in its non-woven form, allows on one

397   hand the incorporation of a larger amount of DCF (in the range of 450% more, when

398   compared to PET), and on the other, serves also a good absorbent for exudating wounds. The

399   exudate can often lead to infections, significantly slowing wound healing. Viscose has

400   therefore more options in regard of applicability. In can be used either as a lone dressing on

401   highly exudating painful wounds or as the second layer of multi-layered dressings, serving as

402   a drug reservoir in aid of the initial very fast release by the first PET layer.

403   Significantly higher doses of DCF could be incorporated into Na-CMC and alginate, also their

404   release profiles and p-values (see Table S1, supporting information) are quite different from

405   the other two materials (as discussed above), as well as differ also one from another. The

406   latter is especially evident in the drug release rate differences. Na-CMC releases

407   approximately 16% of DCF in 30 minutes, where the profile shows a turn and the release rate

408   decreases. After the first 30 minutes, DCF is released at a constant rate. Making a linear fit of

409   the curve from 30 minutes to the end, R^2 value of 0.96 is obtained (not shown). These results

410   suggest that incorporation of DCF into Na-CMC could assure a relatively constant DCF

411   supply for at least 24 h. Such prolonged release characteristics of Na-CMC together with the

412   highest capacity for binding and retaining water (see Figure 1), is highly desired in case of

413   chronic wound treatment, where pain is uninterruptedly present, the change of dressing is

414   infrequent and an extensive exudation is present. A high amount of exudate is already known

415   to limit the healing efficiency and therefore needs to be removed[41, 55]. Alginate on the other

416   hand shows a 45% DCF release in the first two hours of release. After 240 minutes a sudden

417   change in the release pattern is observed. In the next 60 minutes nearly 25% of DCF is

418   released. An explanation for this sudden burst release can be that Na^+ and Ca^{2+} in alginate

17

419 structure are exchanged, leading to the breakdown of the base material mesh[56]. This material

420 degradation exposes an additional portion of the drug, which is then readily dissolved. The

421 last 20% of the drug are then released in 24 h. Such materials and release performance could

422 be interesting for wounds that are not moist enough on their own. Since alginate can hold a

423 significant amount of water (see Figure 1), the degradation of the material can lead to

424 moisturizing of the wound bed. Release from alginate could be described as a combination of

425 all the other observed profiles. Initial fast release during the first 2 h, followed by a diffusion

426 controlled release with another burst of DCF release from 240 to 300 minutes. Using such

427 host materials would be suitable for applications on wounds, where the pain caused by

428 dressing change could be alleviated with a bolus dose and maintained through the following

429 diffusion drug release, which would additionally reduce the injury induced pain sensation.

430 The results of the *in vitro* release are in accordance with other material properties, especially

431 with the materials wettability. Viscose and especially PET exhibit high contact angles. And

432 since DCF has a higher solubility in the used media, its fast release/dissolution in the media

433 comes not as a surprise. Contrary, alginate with an intermediate hydrophilicity and a contact

434 angle of 50°, which already incorporates a certain amount of water, releases the water soluble

435 DCF with a smaller release rate. Na-CMC with its very high water retention value and an

436 immeasurable contact angle, retains the drug even longer, since DCF has first to diffuse

437 through the material and then only to the media. Both, alginate and Na-CMC form also gels

438 (Na-CMC swells significantly), which also contributes to the smaller release rate than

439 compared to the other two materials. Finally, all materials seem appropriate candidates for

440 wound care, although for different wound types and PET only in combination with other

441 materials. A schematic representation of the material-drug combinations in relation to the

442 respective material *in vitro* release performance for wound care applications is shown in

443 Figure 7. To further verify the complete release of DCF, the samples collected after 24 h

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444   release are analyzed by ATR-IR and WAXS (see the supporting material, Figure S2 and S3)

445   measurements.

446   The ATR-IR and WAXS spectra showed no characteristic peaks that can be assigned to DCF

447   in none of the used wound dressing materials collected after the *in vitro* release studies. The

448   latter is a clear indication that all the incorporated drug was released.

449   **3.5. SEM microscopy of sample surfaces prior and after *in vitro* release studies**

450   **Figure 8** shows the SEM morphology of all materials prior and after drug incorporation, as

451   well as after the *in vitro* release testing. SEM micrographs of pure drug particles are given in

452   the supporting document (Figure S5). All four chosen materials possess a fibrous form in their

453   unloaded state (Figure 8 – (U) left column). Some differences between materials are already

454   evident after DCF incorporation (Figure 8 – middle column). Na-CMC fibers seem to have

455   been partially broken apart into block like parts and the presence of drug particles cannot be

456   clearly observed. Another possibility is that this micrograph shows a broken part of the Na-

457   CMC polymer film that formed after drug incorporation. All other materials retained their

458   fibrous structure, while additional surface features can be observed that can be attributed to

459   the loading of DCF. On the PET-based samples, only a small amount of drug particles could

460   be observed on the surface, which is in agreement with the calculated (and measured) small

461   amount of the incorporated drug. On the contrary, alginate and viscose samples exhibit clearly

462   observable morphological changes on their respective surfaces. These corresponds well to the

463   measured larger amounts of incorporated DCF during *in vitro* dissolution testing. While it

464   seems that DCF is still in the form of crystals on the viscose fibers, a thin coating of DCF is

465   visible on alginate samples. This is also in agreement with the results of *in vitro* release

466   testing, where alginate clearly outperforms other materials in terms of the amount of the

467   incorporated drug and release performance. Additional drug particles on the surface are

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468 smaller than crystals in the case of viscose (and PET), and as such, can improve the release

469 rate also by increasing the effective surface area.

470 Finally, SEM micrographs, taken after the *in vitro* drug release testing, are shown in Figure 8

471 – right. While the morphology of viscose and PET based samples retained their initial fibirilar

472 structure, there are significant differences evident for Na-CMC and alginate based samples.

473 Alginate fibers are probably partially deformed through degradation as a result of cation (Na^+

474 and Ca^{2+}) exchange in its structure. This did not lead to severe material disintegration, but to

475 an etching-like effect of the fiber surface as observed in Figure 8 - right. The most notable

476 changes after release are seen for Na-CMC, where the fibrous shape (and even the block-like

477 structure, present after DCF incorporation) disappeared completely. Through exposure of Na-

478 CMC to the dissolution media, Na-CMC swelled and formed a gel-like structure that

479 rigorously differs from the initial fibered structure. All mentioned observations seem to

480 correspond to the findings of other methods, especially with the results of *in vitro* drug release

481 testing.

482

483 **4. Conclusion**

484 Recent economic trends, as well as ongoing rationalizations in health care, dictate the

485 development of novel therapeutic approaches with lower overall costs without the sacrifice of

486 patient safety. This can be achieved through optimized treatment efficiency and lowered

487 hospitalization times. Wound care is no different from other health care sectors. We found

488 that a combination of optimal materials and potent drugs could lead to great improvement in

489 therapeutic efficiency of novel wound dressing materials, especially considering the different

490 treatment approaches for specific wounds. Our results not only show that significant

491 differences in the release profiles can be achieved by incorporating a NSAID, DCF into

20

492   different materials, but also indicate the importance of a careful drug host material

493   characterization in choosing the right material for the treatment of specific wounds.

21

Supporting Information

Acknowledgements

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FIGURE CAPTIONS

Figure 1. A: The water contact angle and water retention properties of the wound dressing materials prior to drug incorporation. PET water retention value is not missing, but almost zero (0.3%), and therefore cannot be seen in the diagram. **B:** Na-CMC water retention value is shown in a separate diagram due to its much higher value, when compared to the other samples, shown in part A of the diagram. Water contact angle for Na-CMC (Aquacel®) could not be obtained.

Figure 2. Air permeability and thickness of the unloaded samples.

Figure 3. ATR − IR spectra of A) unloaded Na-CMC, DCF and Na-CMC with incorporated DCF, B) unloaded alginate, DCF and alginate with incorporated DCF, C) unloaded viscose, DCF, viscose with incorporated DCF and D) unloaded PET, DCF and PET with incorporated DCF.

Figure 4. WAXS diffractograms of samples prior and after DCF incorporation, as well as the reference diffractograms of DCF.

Figure 5. (a) amount of DCF released from a 1 x 1 cm squares model wound dressing and (b) percentage of released DCF, whereas the incorporated DCF amounts differ between the samples. Full release profiles are available as Figure S1 in the supporting information.

Figure 6. Total amounts of incorporated DCF in different wound dressing materials.

Figure 7. Schematic depiction of the material-drug combinations *in vitro* release performance and possible wound care applications. a) Na-CMC with incorporated DCF suitable in treatment of chronic wounds, b) Alginate with incorporated DCF for treatment of chronic wounds with

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an even lower frequency of dressing change, c) Viscose with incorporated DCF for acute pain reduction and d) PET with incorporated DCF as an initial layer in contact with the skin for wounds, requiring frequent dressing change. The drug DCF is depicted in red, while the materials are shown in different colors and morphologies, according to their macroscopic nature. Shorter arrows exhibit a prolonged release, while longer arrows correspond to a faster release.

Figure 8. SEM micrographs of: LEFT - the unloaded (U) materials, MIDDLE - alginate, Na-CMC, viscose and PET impregnated with DCF (+DCF), RIGHT - alginate, Na-CMC, viscose and PET after the release studies (after). The used magnification was 10,000x.

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