



Diclofenac release from alginate/carboxymethyl cellulose mono and bilayer films for wound dressing applications

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Received: 4 November 2019 / Accepted: 5 May 2020 / Published online: 15 May 2020
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Abstract In this study, alginate and carboxymethyl cellulose (CMC) were used to create films to serve as materials for wound dressing applications. These films were obtained by casting as monolayer (ML) and bilayer (BL) structures with and without diclofenac (MLD and BLD, respectively). Morphological characteristics of the films, incorporation efficiency, mechanical properties, water behavior properties, and release kinetics in aqueous media were evaluated. In addition, the mass transfer mechanisms were determined by fitting mathematical models to the experimental data. Bilayer films showed higher diclofenac incorporation efficiency (77.3%) than the monolayer films (57.5%), and both morphological structures were homogeneous and cohesive. The incorporation of diclofenac lowered the mechanical properties of the films without modifying the water absorption capacity. The BLD film had a slower release time (600 min) than the MLD (420 min), thus demonstrating the drug-free layer acts as a barrier to mass transfer and reduces the burst effect. The release

from both films was influenced by diffusion; the apparent diffusion coefficients were in the order of $10^{-14} \text{ m}^2 \text{ s}^{-1}$. MLD had pseudo-Fickian diffusion while BLD had anomalous diffusion. This study demonstrated that the alginate and CMC-based matrices have potential to be used as drug-delivery systems for wound dressing applications.

Keywords Biopolymer · Drug-delivery · Membrane · Polysaccharides

Introduction

Wounds are common injuries that involve damage to the skin. These types of lesions may vary in their severities; therefore, different types of treatments are required for small scratches, deep cuts, ulcers, and burns. Wound healing, a complex biological process, is responsible for regenerating and repairing the injured area (Lazarus 1994). However, this process is not always efficient, and pharmacological treatments are often recommended to improve the healing and suppress pain associated with this process (Bechert and Abraham 2009; Frescos 2011). Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) and analgesic that is used worldwide (Acuña et al. 2015) as a pain-relief agent. Although diclofenac is most frequently administered orally, only 50% of the

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drug administered by this method reaches the circulatory system (Willis et al. 1979; Lamoudi et al. 2016). In addition, orally-administered diclofenac also may cause adverse gastrointestinal side effects (Ulubay et al. 2018).

Transdermal drug delivery systems have been studied for several years. This drug delivery system is easy to use, has better patient compliance, and enhances drug efficacy without the need for frequent dosing, avoiding adverse effects (Sim et al. 2003; Manosroi et al. 2013). Transdermal drug delivery systems can combine matrix properties such as water vapor permeability and fluid absorption capacity with an incorporated therapeutic agent such as an analgesic, to yield a desirable product for wound dressing (Boateng et al. 2013; Pawar et al. 2013; Maver et al. 2015, 2019). Hence, a wide range of wound-care products have been created to treat wounds of varying causes and severities (Boateng et al. 2008). The use of biopolymers in wound-care dressing has received increased attention over the years because they offer several advantages including biocompatibility and biodegradability (Mogoşanu and Grumezescu 2014).

Alginate is a polysaccharide that has been extensively studied as a candidate for wound-dressing products including hydrogels, films/membranes, and nanofibers. It demonstrates several unique properties such as non-toxicity, non-immunogenicity, affordability, hemostatic activity, and an ability to enhance wound healing (Aderibigbe and Buyana 2018). Carboxymethyl cellulose (CMC) is another polysaccharide that can also be used to improve wound healing due to its desirable characteristics such as the ability to absorb large amounts of exudates and maintain wound moisture, for example (Ramli and Wong 2011; Vinklářková et al. 2015). Alginate and CMC biopolymers can be blended to obtain a resultant material, such as a film, with a homogeneous structure and good mechanical strength, water permeability/transmission rate, and fluid-absorption capacity, as described in the literature (Oliveira et al. 2011; Sritweesinsub and Charuchinda 2015; Lan et al. 2018; Han et al. 2018; Ye et al. 2018), making it desirable for wound-dressing applications.

Despite these characteristics, the use of alginate- and CMC-based materials are limited due to their high water solubility. These blended biopolymer films can easily disintegrate in a moist wound area, thus rendering them inappropriate for use in wound

dressing (Boateng et al. 2008; Eskandarinia et al. 2020). This problem can be overcome by the alginate ability to physically cross-link with divalent ions, especially Ca^{2+} . This cross-linking step increases the resistance of films to aqueous media (Santana and Kieckbusch 2013) and improves tensile strength, thereby controlling the rate of release of active compounds through its matrix. In contrast, water transmission rate and capacity of fluid absorption usually decreases after cross-linking (Bierhalz et al. 2012; Jang et al. 2014; Bonilla et al. 2018). In our previous study (Trevisol et al. 2019), we demonstrated that blending Ca^{2+} -cross-linked alginate with CMC produced films possessing improved properties, where each biopolymer complemented the activity of the other. The optimal properties for wound-dressing films were achieved using a 1:1 ratio of alginate and CMC.

Owing to the hydrophilic characteristics of these biopolymers, polysaccharide-based controlled release formulations usually lead to a burst effect, which occurs during the first minutes of contact with the external medium. Multilayer systems can reduce this effect by confining the drug on the top layers and allowing it to diffuse gradually through drug-free bottom layers: the bottom layer acts as an additional barrier, thus delaying drug release (Thu et al. 2012; Ng and Tan 2015; Eskandarinia et al. 2020). In this study, we evaluated the *in vitro* release behavior of sodium diclofenac from monolayer and bilayer alginate- and CMC-based films using a Franz diffusion cell as well as the influence of drug loading on the properties of these films. To the best of our knowledge, this is the first time that the release behavior of a model drug incorporated in monolayer or bilayer alginate- and CMC-based films has been reported.

Material and methods

Materials

Biopolymers sodium alginate of medium-viscosity (A-2033, Sigma-Aldrich, USA) from *Macrocystis pyrifera* (61% of mannuronic and 39% of guluronic acid) and medium-viscosity sodium carboxymethyl cellulose (degree of substitution 0.7, Synth, Brazil) were used to obtain the films. Calcium chloride dihydrate (Sigma-Aldrich, USA) was used as cross-

linking agent and glycerol (Sigma-Aldrich, USA) as plasticizer. Sodium diclofenac was obtained from Henan Dongtai Pharmacy Limited Company (CH). Conventional simulated body fluid (SBF) was prepared according to reported by Oyane et al. (2003) with potassium chloride, calcium chloride, and Tris (Sigma-Aldrich, USA), sodium bicarbonate, potassium phosphate dibasic trihydrate, and sodium sulfate (Nuclear, Brazil). All reagents were analytical-grade quality.

Film preparation

The alginate- and CMC-based films were prepared using two steps of cross-linking (Trevisol et al. 2019). Briefly, 1.5 g of alginate and 1.5 g of CMC were dissolved separately in 100 mL of aqueous solutions containing glycerol (3% w v⁻¹). To the alginate filmogenic solution, 1% (w v⁻¹) of CaCl₂ (0.05 g per g of alginate) was slowly added to perform the first cross-linking step. Both solutions were kept under stirring (900 rpm) and heating at 50 °C. Approximately 50 g of each filmogenic solution was mixed to obtain a 1:1 alginate:CMC ratio. After deaeration under vacuum, aliquots (100 g) of alginate- and CMC-blended dispersions were poured in Petri dishes (d = 15 cm) and dried for 20 h at 40 °C in a convective oven (model TE-349/2, Tecnal, Brazil). For the bilayer films, half of the filmogenic solution (50 g) was poured in the Petri dishes and, after 10 h the remaining dispersion (50 g) was poured over the material. All formulations contained 0.75 g of each polymer per film.

Then, the detached films were immersed during 20 min in 60 mL of an aqueous solution of chloride calcium (5% w v⁻¹) and glycerol (3% w v⁻¹) to perform the second cross-linking step. Residual calcium not cross-linked was removed by washing the films in an aqueous glycerol solution (3% w v⁻¹) for 1 min. A second drying step was carried out at room temperature for 24 h (fixing the border of the films with wooden rings to prevent shrinking).

The monolayer and bilayer films with diclofenac incorporation were prepared as described above, with 0.5 mg mL⁻¹ of the drug which was initially dissolved at room temperature in the first 3% (w v⁻¹) glycerol aqueous solution. In the case of bilayer structure, the diclofenac was incorporated only on the top layer. The following films were named as

monolayer without diclofenac (ML), monolayer incorporated with diclofenac (MLD), bilayer without diclofenac (BL), and bilayer incorporated with diclofenac (BLD).

Characterization of the films

Before any characterization test, the films were conditioned at 58 ± 2% relative humidity for at least 48 h. During the preparation of the films, some fraction of the drug initially added to the formulation may be released in the steps of cross-linking and washing, where the films remain immersed in water solutions for a certain period. The drug content in the final films was determined according to the method adapted from Ng and Tan (2015). The films were immersed in phosphate saline buffer (PBS, 1 M, pH 7.4) for 10 h to dissolve the polymers, Then, the samples were centrifuged at 2000 rpm for 2 min and the diclofenac present in the supernatant was quantified spectrophotometrically (model Cirrus 80, FEMTO, Brazil) at 276 nm. The standard curve was determinate in a range of diclofenac from 5 to 25 mg L⁻¹ ($y = 29.278x - 0.1326$, where y is the absorbance (u. a.) and x is the concentration of the drug (mg L⁻¹), $R^2 = 0.9998$). The diclofenac incorporation efficiency was calculated by Eq. (1), where D_{sample} is the diclofenac mass in the film samples and $D_{\text{theoretical}}$ is the mass of diclofenac initially added to the film formulation.

Diclofenac Incorporation Efficiency (%)

$$= \frac{D_{\text{sample}}}{D_{\text{theoretical}}} \times 100 \quad (1)$$

The visual macroscopic aspect was determined with a photographic camera (model DSLR D5500, Nikon, Japan). The film morphology was evaluated with a scanning electron microscope (model JSM-6390LV, JEOL, Japan) with an accelerating voltage of 10 kV. The samples were placed on a stub and coated with an ultrathin gold layer (model SCD500, Leica, Germany).

The thickness of the films ($n = 10$) was measured with a digital micrometer (MDC-25P, Mitutoyo, Japan) at 10 random positions. Specimens with any visible defects were discarded. Attenuated total reflectance Fourier Transform Infrared (ATR-FTIR) spectroscopy was performed in a spectrometer

(SENSOR 27, Bruker, United Kingdom) between 700 and 4000 cm^{-1} , with 32 scans at 4 cm^{-1} of resolution.

The tensile strength and elongation at break were determined at 25 °C using a uniaxial testing machine (model TA.HD.plus Texture Analyser, Stable Micro Systems, United Kingdom) according to ASTM D88-02 (2002), with a crosshead speed of 0.075 cm s^{-1} , initial grip spacing of 6 cm at room temperature. Samples of 9 cm \times 2.54 cm were tested with 10 replicates for each test group.

The water uptake capacity of the films was determined gravimetrically in triplicate by immersion of the samples (4.5 \times 2.5 cm^2) in 20 mL of distilled water during 24 h (37 °C). The Eq. (2) was used to calculate the results, where W_{initial} indicates the initial mass of the films and W_{wet} is the mass obtained after immersion. The excess of the liquid was removed previously by maintaining the films in a vertical position (90°) for 30 s (Rodrigues et al. 2008).

Water Uptake Capacity (%)

$$= \frac{W_{\text{wet}} - W_{\text{initial}}}{W_{\text{initial}}} \times 100 \quad (2)$$

The water vapor transmission rate (WVTR) of the films were gravimetrically evaluated in accordance with ASTM E96/E96M-10 (2010). The samples, in triplicate, were sealed in an oval aluminum capsules (permeation area (A) of 0.0031 cm^2) containing silica gel, kept at 25 °C in a glass chamber with a controlled relative humidity of 75%. The capsules were weighted every 1 h during 24 h and the permeation rate (G, g day^{-1}) was obtained by the linear regression of weight gain versus time. The WVTR was calculated by the quotient of permeation rate and permeation area [Eq. (3)].

$$\text{WVTR} = \frac{G}{A} \quad (3)$$

The hydrolytic films degradation was performed by gravimetric method, as described by Rodrigues et al. (2008). Briefly, four samples (4.5 \times 2.5 cm^2) were weighed (W_0) and immersed in 20 mL of SBF for 7 days at 37 °C. Then, the film was dried at 105 °C for 24 h and weighed (W). The film weight loss (%) was calculated by Eq. (4).

$$\text{Weight Loss} = \frac{W_0 - W}{W_0} \times 100 \quad (4)$$

Diclofenac release studies and mathematical adjustment

A film with 2.5 cm^2 was sealed in Franz diffusion cell (14 cm^3) with SBF medium in the receptor compartment. For the BLD film, only the drug-free layer (bottom layer) was maintained in contact with the medium. The cell temperature was kept at 37 °C and magnetically stirred at 150 rpm to reduce the convective mass transfer resistance. To ensure the medium-film contact during the experiments, all cell gaps were sealed to prevent the evaporation and the medium was sporadically replaced, considering the dilution effect. Aliquots were withdrawn at pre-established times and replaced in the cell. The released diclofenac was quantified by spectrophotometry UV–Vis at 276 nm.

The diclofenac dermatological dosage released from the films was determined according to Souza et al. (2016). Briefly, the amount of ointment contained from the distal crease to the tip of the index finger, denominates “fingertip unit”, corresponds to 0.5 g of ointment (in mean) (Finlay et al. 1989). A “fingertip unit” must be able to cover 286 cm^2 of skin (Long and Finlay 1991). Based on the concept of “fingertip unit” and considering that the diclofenac ointments/gels contain 10 mg of diclofenac per g of vehicle, the application of 0.017 mg of diclofenac per cm^2 of skin is considered as a therapeutic dosage.

Diclofenac release mechanism determination

The models Korsmeyer–Peppas [Eq. (5)] (Korsmeyer et al. 1983), zero-order [Eq. (6)] (Costa and Lobo 2001), Higuchi (Eq. (7)) (Higuchi 1961), and Peppas–Sahlin [Eq. (8)] (Peppas and Sahlin 1989) were fitted to experimental data to determine the mass transfer release mechanism. The software ORIGIN 8.5 was used in the data adjustment.

$$\frac{M_t}{M_\infty} = k_{\text{KP}} t^n \quad (5)$$

$$\frac{M_t}{M_\infty} = k_0 t \quad (6)$$

$$\frac{M_t}{M_\infty} = k_H \sqrt{t} \quad (7)$$

$$\frac{M_t}{M_\infty} = k_d t^m + k_r t^{2m} \quad (8)$$

where M_t/M_∞ fractional diclofenac release from the film at time and at infinite time; k_{KP} Korsmeyer–Peppas kinetic constant; n exponent characteristic of the release mechanism; k_0 zero-order kinetic constant; k_H Higuchi kinetic constant; k_d diffusional contributions constants; k_r relaxation contributions constants; m purely Fickian diffusion exponent; and t time.

Effective diffusion coefficients (\mathcal{D}) were determined from the release data using a relationship from the solution of the Second Fick's Law (Crank 1975). Equation (9) was adapted for the fractional diclofenac release under the experimental conditions considering the film thickness (δ) constant during the assay. A simplified solution of Fick's Second Law [Eq. (10)] was also used for short contact times (when less than 60% of the drug was released). Both solutions and data adjustment were performed in the software MATLAB R2013a.

$$\frac{M_t}{M_\infty} = 1 - \frac{8}{\pi^2} \sum_{n=0}^{\infty} \left[\frac{1}{(2n+1)^2} \exp\left(-\frac{\mathcal{D}(2n+1)^2 \pi^2 t}{\left(\frac{\delta}{2}\right)^2}\right) \right] \quad (9)$$

$$\frac{M_t}{M_\infty} = 4 \sqrt{\frac{\mathcal{D}t}{\pi \left(\frac{\delta}{2}\right)^2}} \quad (10)$$

Statistical analysis

Analysis of variance (ANOVA) and Tukey Test was used to statistically determine the significant differences ($p < 0.05$) among averages using the software STATISTICA (version 7.0).

The Coefficient of Determination (R^2), Eq. (11), and Root Mean Square Error (RMSE), Eq. (12), statistical indexes were used to evaluate the performance of the models of diclofenac release. In these equations: p_{yre} are the values predicted by the model, y_{exp} , are the values obtained in the experiments, \bar{y} is the arithmetic mean of all values of each result, n is the number of experimental data, and p are the number of model parameters.

$$R^2 = \frac{\sum (y_{pred} - \bar{y})^2}{\sum (y_{exp} - \bar{y})^2} \quad (11)$$

$$RMSE = \sqrt{\frac{\sum (y_{pred} - y_{exp})^2}{n - p}} \quad (12)$$

Results and discussion

Incorporation efficiency

Despite the hydrophobic characteristic of diclofenac (Polo Fonseca et al. 2018), a loss of the drug content was observed for both formulations, predominantly during the initial immersion into the calcium aqueous solution. The incorporation efficiency of diclofenac was significantly different ($p > 0.05$) between the MLD ($57.5 \pm 6.7\%$) and BLD ($77.3 \pm 5.3\%$) films. When the calcium diffuses through the matrix to initiate alginate cross-linking, the hydrophilic film exhibits no resistance to the aqueous medium, which leads to swelling and rapid loss of the drug during this period. The drug-free layer of the BLD film seems to act as a barrier against diclofenac release after the immersion of the films in the solutions during cross-linking and washing. Ng and Tan (2015) also observed a higher Hidrox-6 content on the bilayer when comparing with monolayer alginate and gelatin-based films.

Structural, compositional, mechanical, and water behavior properties of the films

The macroscopic aspect of the films in the absence (ML and BL) and presence of diclofenac (MLD and BLD) (Fig. 1) was compared, and it was possible to verify that all films were homogeneous and cohesive. MLD and BLD films were opaquer and had a whitish hue, which may be attributed to the low water solubility of diclofenac. In fact, this effect was more pronounced for the BLD film probably due to the higher diclofenac content in the top layer. Uz and Altunkaya (2011) also observed similar results when observing cellulose and acetate films containing potassium sorbate. The authors attributed the whitish hue to the drying process of the films, which causes

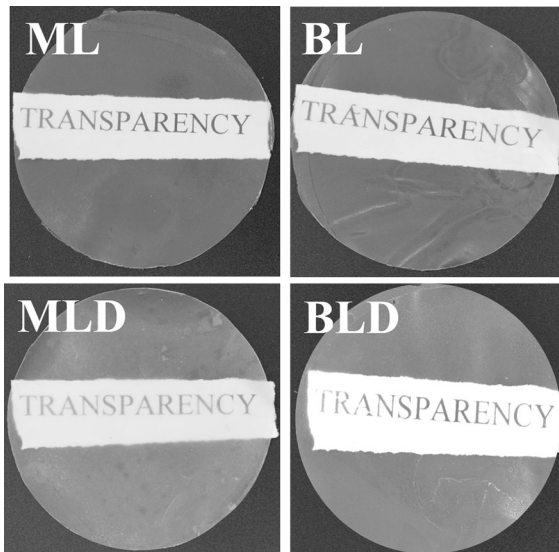


Fig. 1 Visual aspect of mono (ML), bilayer (BL), monolayer with diclofenac (MLD) and bilayer with diclofenac (BLD) films

supersaturation of the drug. This phenomenon may have occurred in the present study.

In addition to the visual aspect, SEM images of the films are shown in Fig. 2. Whitish particles, which are

probably related to Ca^{2+} , were observed for all formulations. The surface of the ML (Fig. 2a) and BL (Fig. 2c) films showed high homogeneity and pore-less and regular microstructures without visual disruption or phase separation. On the other hand, the surface of the MLD and BLD films showed small striae-like structures, which could be attributed due to the presence of diclofenac (Fig. 2e, g). Similar results have been reported in the literature for the incorporation of diclofenac (Boateng et al. 2013; Pawar et al. 2013) and ibuprofen (Vinklárková et al. 2015) into the polymeric film matrix. These results corroborate the opaque aspect of the films that were visually observed in this work.

Cross-sections of the ML (Fig. 2b) and BL (Fig. 2d) films showed homogenous structures with no phase separation. The striae-like structures present on the surface of the MLD and BLD films were also observed in the images of the cross-sections (Fig. 2f, h). By comparing the BL and BLD formulations, the bilayer structure was highlighted in Fig. 2d, h (with only diclofenac lying within the top layer of the BLD film). Studies with drugs incorporated into bilayer

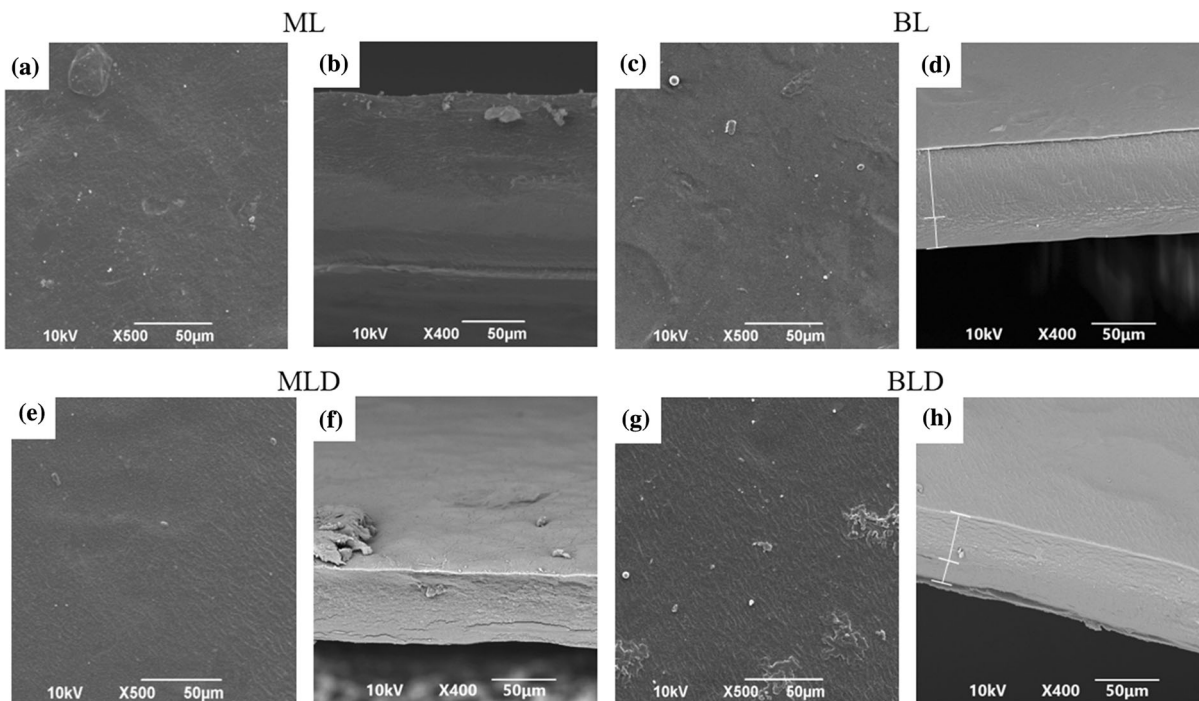


Fig. 2 Scanning electron micrographs of the surface and cross-section of mono (ML), bilayer (BL), monolayer with diclofenac (MLD) and bilayer with diclofenac (BLD) films. The white forms indicate the bilayer structure

films showed similar results of SEM analysis (Thu et al. 2012; Thu and Ng 2013; Muller et al. 2017).

The FTIR–ATR spectra obtained for the different films' formulations (Fig. 3) showed the presence of coexisted peaks in all formulations. COO[−] group antisymmetric and symmetric vibrations peaks were observed at 1595 and 1420 cm^{−1} (Swamy and Yun 2015). These peaks can be related to a carboxylic group interacting with a salt ion, as Ca²⁺, indicating that a binding and, consequently, the cross-linking occurs between the alginate and calcium ion, as observed by Peretiakko et al. (2018). The –OH bending vibrations peak was determined at 1325 cm^{−1} (Tong et al. 2008). C–O–C stretching vibration, attributed to saccharide structure, and skeletal mode vibration, related to the glycosidic linkage, were recognized around 1032 and 925 cm^{−1} (Huang et al. 1999; Juneja et al. 2014), respectively. Both alginate and CMC used in the study were salt sodium, being the Na–O characteristic seen at 819 cm^{−1} (AL-Kahtani and Sherigara 2014). Absorptions at 2850, 2930 and 3000 cm^{−1} were related to C–H stretching vibrations (Tong et al. 2008).

From Fig. 3, it was observed that the peak located at 2890 cm^{−1} slightly shifted to 2850 cm^{−1} for films containing diclofenac (MLD and BLD). Similarly, the –OH peak (3300 cm^{−1}) shifted to 3235 cm^{−1} in the MLD and BLD films. These results may indicate a

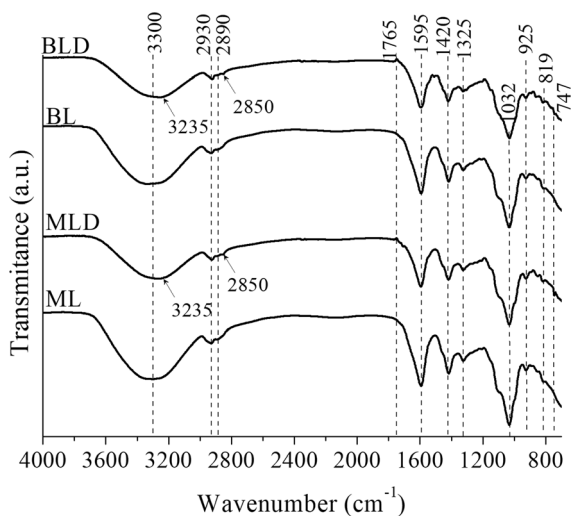


Fig. 3 Attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectra of the monolayer (ML), bilayer (BL), monolayer and bilayer incorporated with diclofenac (MLD and BLD, respectively) films

possible hydrogen bond between polymer-drug occurred in the present work. Another indicatives of possible electrostatic interactions between the films and diclofenac are related to the appearance of a small peak located at 1765 cm^{−1} (–C=O peak) and at 747 cm^{−1} (C–Cl stretching vibration) (Shivakumar et al. 2008). This last peak can be associated to diclofenac and can demonstrates that the drug kept its chemical structure intact (Thu and Ng 2013).

In relation to the use of the film as a dressing, it is desirable a device with a thin thickness lower than the human skin, with an average size from 0.5 to 2 mm (Ma et al. 2001). In this work, no significant difference ($p < 0.05$) film thickness was observed for all evaluated formulations (Table 1) This was expected, because the same amount of the polymers was used in the preparation of the film by casting. This experimental result confirms the structural similarity and homogeneity of the films. Furthermore, the incorporation of diclofenac did not change the film thickness, possibly due to low concentration of the drug and its even distribution throughout the matrix, as observed by SEM analysis results (Fig. 2).

The addition of diclofenac to the polymeric matrices reduced the tensile strength and the elongation at break properties of the monolayer and bilayer films (Table 1). The formation of fragile and poorly flexible films can be attributed to a modifications of the polymeric microstructure and lack of polymer-drug interactions (Norajit et al. 2010). Some studies demonstrated a similar reduction in the mechanical properties of alginate- and CMC-based films when incorporating compounds into the polymeric matrix. For example, Ye et al. (2018) synthesized alginate- and CMC-based film with obtained values of 27.23 MPa and 24.86% for tensile strength and elongation at break properties, respectively. However, these values decreased when *Lactococcus lactis* was incorporated into the films. The highest concentration of *L. lactis* used in the study reduced the tensile strength to 7.50 MPa and the elongation at break value to 9.19%. Similarly, Han et al. (2018) observed approximately 50% decrease in the tensile strength of alginate- and CMC-based films when higher levels of cinnamon essential oil and Tween 80 were incorporated. No significant differences ($p < 0.05$) were observed, when the mechanical properties of ML film were compared to those of BL film (or MLD with BLD), as shown in Table 1. This similarity in

Table 1 Characterization of mono (ML), bilayer (BL), monolayer with diclofenac (MLD) and bilayer with diclofenac (BLD) incorporated into the films

Characterization	Film			
	ML	BL	MLD	BLD
Thickness (mm)	0.112 ± 0.009 ^a	0.122 ± 0.021 ^a	0.112 ± 0.012 ^a	0.126 ± 0.019 ^a
Tensile strength (MPa)	25.89 ± 2.55 ^a	21.74 ± 4.45 ^a	15.54 ± 3.40 ^b	15.87 ± 4.86 ^b
Elongation at break (%)	41.60 ± 4.21 ^a	36.84 ± 4.38 ^a	28.85 ± 6.16 ^b	24.38 ± 3.87 ^b
Water uptake capacity (%)	619 ± 15 ^a	630 ± 33 ^a	629 ± 56 ^a	650 ± 73 ^a
WVTR (g m ⁻² d ⁻¹)	145.57 ± 5.90 ^b	301.41 ± 6.38 ^a	140.34 ± 5.06 ^b	299.05 ± 10.39 ^a
Weight loss (%)	44.3 ± 3.3 ^b	56.8 ± 2.1 ^a	39.6 ± 4.2 ^b	55.5 ± 3.5 ^a

WVTR water vapor transmission rate. Average ± standard deviation of experimental determinations. Averages with the same letter, in the same line, indicate no significant differences ($p < 0.05$) by the Tukey test

properties of the different films can be attributed to the formulation process, which yielded films that were uniform in thickness, structure, and composition (Trevisol et al. 2019).

All films presented excellent water-uptake capacity with no significant differences ($p < 0.05$) among formulations (Table 1). Although diclofenac is hydrophobic (Polo Fonseca et al. 2018), the small quantity of this drug was unable to alter the absorption capacity of the films. Similar to our findings, studies report that the incorporation of natamycin (Bierhalz et al. 2012) or ibuprofen (Vinklárková et al. 2015) did not influence the fluid-absorption capacity of alginate- or CMC-based films, respectively. Further, no significant differences were observed between monolayer and bilayer structures (Table 1). The water vapor transmission rate (WVTR) was significantly different ($p > 0.05$) between the monolayer (ML and MLD) and bilayer films (BL and BLD), as shown in Table 1. This difference can be attributed to a slight reduction in the degree of alginate cross-linking in the bilayer films (Trevisol et al. 2019). This hypothesis is corroborated by the results of weight loss (Table 1), which the film solubility values were lower for the monolayer films (ML and MLD films), indicating a greater compaction of matrices due to cross-linking. Results also indicate that the incorporation of diclofenac did not influence weight loss and the WVTR of films. However, it is important to highlight that higher concentrations of the drug could decrease the WVTR characteristic due to its hydrophobicity, as reported in

published literature (Rezvanian et al. 2016; Bierhalz and Moraes 2016). The low weight loss values of the films demonstrated their ability to maintain integrity during wound dressing, thereby preventing release of its compounds directly to the wound site. The results of weight loss are intermediate to the results obtained for films composed only of alginate or CMC. The values of weight loss of the blended films are intermediate to those of the pure polymers (100% for alginate and 25% for CMC) (Trevisol et al. 2019).

In vitro release kinetics of diclofenac

Our results demonstrated that the diclofenac incorporated in the films was released over a period of 420 min for the MLD film and 600 min for the BLD film (Fig. 4). To ensure that all drug was released, all assays were carried out up to a 1440 min time point (data not shown). The slower release behavior from the BLD compared to the MLD film may be related to the additional drug-free layer; this layer created a barrier to mass transfer (corroborating to the drug incorporation efficiency result), thus reducing the release rate. Other studies that compared the release of active agents from mono- or bilayer structures also observed this behavior (Mi et al. 2002; Thu et al. 2012; Ng and Tan 2015). In addition, the MLD film showed a burst release up to 60 min with 59% of the diclofenac released, differently for the BLD films, when only 26% of the diclofenac was released over this same time.

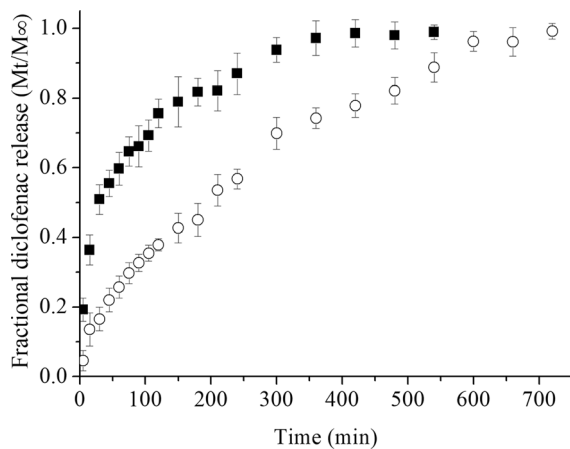


Fig. 4 Diclofenac kinetic release from monolayer (MLD, filled square) and bilayer (BLD, open circle) films

Considering the application of the film as a dressing material, the wound exudate or blood would cause it to swelling and increase the rate of drug release rate. Thus, the extra drug-free layer within the BLD film acted as a mass transfer barrier that delayed the drug release. It is important to mention that the MLD film may be preferred for rapid pain relief since it favors the rapid release of a drug. However, the slower release of diclofenac from the BLD may prolong its activity, avoid toxic side effects, prevent sub-therapeutic levels of the drug, and reduce the need for subsequent dressing changes (Boateng et al. 2008; Thu et al. 2012).

After 360 min of contact between the films and the liquid media, the release of diclofenac reached values of $0.147 \pm 0.021 \text{ mg cm}^{-2}$ for the MLD film and $0.166 \pm 0.016 \text{ mg cm}^{-2}$ for the BLD film. No statistically significant difference between these films was observed, and the amount of diclofenac released was higher than the recommended dosage (0.017 mg cm^{-2} , as defined in “Diclofenac release studies and mathematical adjustment” section). It is important to highlight that the rate of release rate for substances in liquid media is faster compared to that of solid media, as skin tissue (Ruela et al. 2016). Therefore, the dosage of 50 mg of diclofenac used in the films could reflect in the reduction of wound dressing changes, but a more in-depth study on solid media is needed.

Mechanism of drug release

To determinate the mechanism governing the release of the drug from the films, different models were fitted to the experimental data. These results are displayed in Table 2. By comparing the correlation coefficients, the evaluated models better fit the BLD experimental data compared to the MLD, which is probably associated with the effects of the burst release. The best correlation coefficient for both films was obtained by fitting the Korsmeyer–Peppas model to the experimental data. This model is used to evaluate which mechanism of mass transfer governs the release by the n constant value. For a value of 0.5, the mechanism is considered pure Fickian diffusion, while a value lower than 0.5 indicates a pseudo-Fickian mechanism. Values between 0.5 and 1 indicate an anomalous mechanism, and values above 1 indicate a super Case II mechanism (Korsmeyer et al. 1983). The MLD film

Table 2 Fitting of release kinetic models to diclofenac in simulated body fluid medium

Model	MLD	BLD
<i>Korsmeyer–Peppas</i>		
R^2	0.98	0.99
RMSE	0.023	0.008
k_{KP} (min^{-n})	0.1167	0.0249
n	0.41	0.57
<i>Zero order</i>		
R^2	0.78	0.94
RMSE	0.335	0.142
k_0 (min^{-1})	0.0027	0.0017
<i>Higuchi</i>		
R^2	0.71	0.99
RMSE	0.123	0.030
k_H ($\text{min}^{-0.5}$)	0.0542	0.0374
<i>Peppas–Sahlin</i>		
R^2	0.99	0.99
RMSE	0.021	0.008
k_d (min^{-m})	0.1086	0.0294
k_r ($\text{min}^{-2 m}$)	< 0.0001	0.0004

m , equal to 0.5 for films (Peppas and Sahlin 1989); k_{KP} , Korsmeyer–Peppas kinetic constant; n , exponent characteristic of the release mechanism; k_0 , zero-order kinetic constant; k_H , Higuchi kinetic constant; k_d and k_r diffusional and relaxation contributions constants, respectively; R^2 , correlation coefficient; RMSE: Root mean squared error

presented a pseudo-Fickian mechanism of release, while the BLD film showed an anomalous mechanism of release (superposition of matrix swelling and pure Fickian diffusion effects).

Since the MLD film was formed by a single layer and the CMC is not cross-linked by calcium ions, a more dissolution of this polymer in the receptor medium probably occurred. This phenomenon may be related to the pseudo-Fickian mechanism of the diclofenac release. In the case of BLD, the anomalous mechanism may be related to the swelling of the polymeric matrix that primarily occurs in the bottom layer (drug-free) and subsequently in the top layer containing the active compound (Fig. 5). Vinklárková et al. (2015) observed the same difference in the release mechanisms for monolayer and bilayer CMC-based films containing ibuprofen. Other studies with alginate-based films obtained similar results. For instance, Bierhalz et al. (2012) and Jin et al. (2016) demonstrated the anomalous release of natamycin and fusidic acid from alginate-based films, respectively. On the other hand, Momoh et al. (2015) showed that the release of proteins from an alginate-based film occurred via a pseudo-Fickian mechanism.

The analysis shown in Fig. 4 indicates that the rate of drug release remains constant at some intervals. To investigate these results, the zero-order model was used. According to the results (Table 2), the BLD data

fitted the model better than the MLD data, which is probably due to the observed burst release. By comparing the correlation coefficients, the zero-order model had lower results, indicating that one more release mechanism can be associated to the diclofenac mass transfer. This observation corroborates the results of fitting the data using the Korsmeyer–Peppas model.

The Higuchi model was used to evaluate the pure Fickian release. A predominance of pseudo-Fickian release can be seen for the MLD film, once the Higuchi model did not well fit the experimental data (RMSE = 0.123). On the other hand, the model well fitted the BLD experimental data (RMSE = 0.030), demonstrating that the Fickian diffusion release is probably the major mechanism in the diclofenac release of this film.

From the last hypothesis of high influence of Fickian diffusion release, the Peppas–Sahlin model, which evaluated the effects of Fickian diffusion and polymer relaxation, was also studied. As expected by the anomalous release obtained by the Korsmeyer–Peppas model ($n \cong 0.5$) and by Higuchi model (Table 2), the diclofenac release from the BLD film is dominated by diffusion, however presents a little influence of the polymer relaxation, since k_r was higher than k_d (Table 2). The pseudo-Fickian release demonstrated by the Korsmeyer–Peppas model was also highlighted by the Peppas–Sahlin model using the

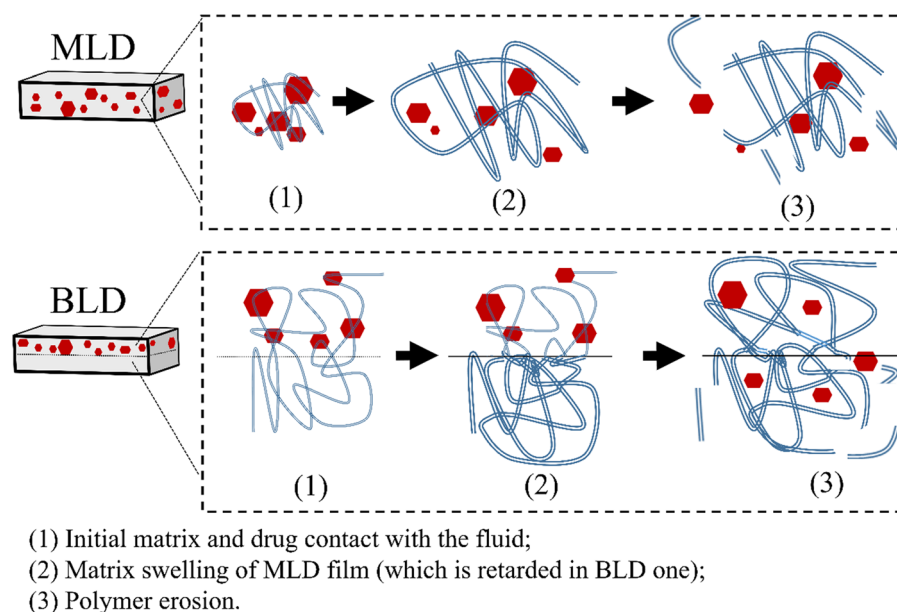


Fig. 5 Mechanisms of diclofenac release from monolayer (MLD) and bilayer (BLD) films incorporated with diclofenac

data from the MLD film; compared to the k_d constant, the k_r was insignificant (Table 2).

Despite the differences in release mechanisms from the MLD and BLD films, the Fickian diffusion mechanism acts strongly during the mass transfer. For this reason, the diffusion coefficient (D) was determined. Fick's Second Law for a flat plate and a simplified solution of Fick's Second Law for short contact time models were fitted to experimental data. The results from these analyses are shown in Fig. 6 and Table 3. From the adjustments, no significant differences ($p < 0.05$) for D calculated using the Eqs. (9) and (10) were observed, thus indicating that the swelling effect only occurs in during the earliest moment of contact between the film and the fluid, and is not influenced by a release mechanism.

Since a slower rate of release was observed for the BLD films, this film presented a significantly lower D than that of the MLD film ($p < 0.05$). Similar results were observed by Uz and Altinkaya (2011). In this study, the authors evaluated the release of potassium sorbate from cellulose acetate-based films in water. The monolayer and bilayer films showed effective diffusion coefficients of 9.18×10^{-14} and $3.3 \times 10^{-12} \text{ m}^2 \text{ s}^{-1}$, respectively.

The calculated D values obtained in this study were smaller than those reported in the literature. For example, Siepmann et al. (1999), obtained values around $4.9 \times 10^{-11} \text{ m}^2 \text{ s}^{-1}$ for the release of diclofenac from hydroxypropyl methylcellulose tablets in PBS. Pimenta et al. (2016), showed that the release of diclofenac from 2-hydroxyethyl methacrylate and

Table 3 Effective diffusion coefficient (D), determination coefficient (R^2) and root mean squared error (RMSE) of diclofenac in mono (MLD) and bilayer (BLD) films with sodium diclofenac incorporation

Model	MLD	BLD
<i>Short contact times</i>		
R^2	0.96	0.99
RMSE	0.028	0.011
$\mathcal{D}(x \ 10^{-14}) \ (\text{m}^2 \ \text{s}^{-1})$	$7.00 \pm 0.53^{\text{Aa}}$	$1.47 \pm 0.19^{\text{Bb}}$
<i>Fick's second law</i>		
R^2	0.99	0.98
RMSE	0.048	0.049
$\mathcal{D}(x \ 10^{-14}) \ (\text{m}^2 \ \text{s}^{-1})$	$6.02 \pm 0.86^{\text{Aa}}$	$1.77 \pm 0.22^{\text{Bb}}$

Average \pm standard deviation of experimental determinations. Averages with the same uppercase (in the same column) and lowercase (in the same line) letter indicate no significant differences ($p < 0.05$) by the Tukey test

poly(vinylpyrrolidone)-based hydrogels in water and PBS buffer and yielded effective diffusion coefficients of 4.7×10^{-13} and $1.3 \times 10^{-13} \text{ m}^2 \text{ s}^{-1}$, respectively. These differences may be explained by the compositions of the polymeric matrix composition and for. Even though visually homogeneous films were obtained, improper blending of the alginate and CMC may produce a mass transfer barrier during diclofenac release. Oliveira et al. (2011) created alginate and CMC-based films using the same polymeric ratio (1:1) as that of the present study. The authors reported a D value of $0.51 \times 10^0 \text{ m}^2 \text{ s}^{-1}$ for

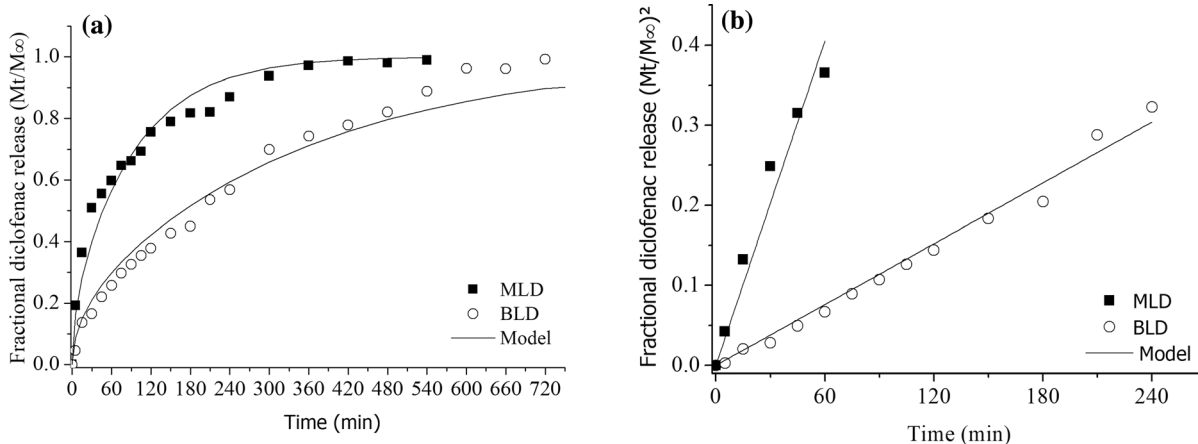


Fig. 6 Fractional diclofenac release from mono (MLD, filled square) and bilayer (BLD, open circle) films fitted by Eq. (9) (a) and Eq. (10) (b)

the release of sodium potassium in aqueous phase. By comparing the results to a study using the same polymeric matrix, it is evident that the lower effective diffusion coefficient value obtained in the present work may be attributed to the polymeric characteristics and alginate cross-linking. This may have created an additional barrier and thus improved the rate of drug release (Bonilla et al. 2018).

Conclusion

In this study, we evaluated the characteristics of wound dressing films prepared by blending alginate and CMC in monolayer and bilayer structures with and without the incorporation of diclofenac. In general, the films with diclofenac showed lower mechanical properties and physical properties similar to the films without the drug. The bilayer films were homogeneous and preserved major of monolayer properties, higher WVTR, and diclofenac incorporation efficiency. The release of diclofenac in liquid media was slower from the BLD film than the MLD film, indicating that the drug-free layer could act as an additional barrier to control the rate of release. The diclofenac was released over a period of 420 min and 600 min for the MLD and BLD films, respectively. The release mechanism was pseudo-Fickian for the MLD films and anomalous for the BLD films as calculated using the Korsmeyer–Peppas models. Regarding the applications for use as wound dressing, the MLD film would be optimal when fast pain relief is required while the BLD film would be best for controlled drug release. Controlled drug release would allow for a reduced frequency of wound dressing changes while maintaining the diclofenac activity at the wound site over a long period of time.

Disclosure statement

The authors declare that they have no conflict of interests.

Acknowledgments The authors thank the the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior—Brasil (CAPES)—Finance Code 001 and the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) for financial support, the Laboratório Central de Microscopia Eletrônica and Laboratório de Central de Análises of the Department of

Chemical and Food Engineering, of Federal University of Santa Catarina.

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