PREPARATION AND CHARACTERIZATION OF COTTON FABRIC MODIFIED WITH CHITOSAN CONTAINING DICLOFENAC SODIUM FOR WOUND DRESSING

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ABSTRACT

Due to the different types of wounds and stages of their healing, the development of bioactive textile wound dressings is a challenge. In many cases, the dressing is expected to be multifunctional. It must actively support wound healing by absorbing excess exudate, but also provide a moist environment, inhibit microbial growth, and, if necessary, deliver bioactive substances in a controlled manner.

This study aims to modify cotton fabric with a layer of chitosan crosslinked with citric acid, involving diclofenac sodium. Different methods were applied to obtain two composite materials. The first treatment used the pad-dry technique at room temperature (CRTD), and the second applied pad-cure at 80°C for 180 min (CHTD). The new materials were characterised by optical microscopy and thermal analysis. The surface properties of the pristine cotton fabric were compared with the modified samples by determining the contact angle of a droplet of distilled water. The composites exhibit hydrophobic properties and antibacterial activity against model bacterial strains, Bacillus cereus and Pseudomonas Aeruginosa. The material CHTD inhibits approximately 78.0 % of the growth of P. Aeruginosa and approximately 31.6 % of B. Cereus. Using gravimetric and spectrophotometric analysis, the swelling of the obtained layers on the fabric surface and the release of diclofenac sodium in phosphate buffer with pH = 7.4 at 37°C were investigated. Therefore, the composite materials combine antibacterial efficacy with continued release of bioactive substances, making them promising for use as wound dressings.

Keywords: cotton, chitosan, diclofenac, drug release, antibacterial properties.

INTRODUCTION

Mammalian skin covers the entire surface of the body and plays a vital role in its external protection from physical injury, chemicals, and pathogens (bacteria, fungi, and viruses). Different reasons can disrupt its integrity and lead to the appearance of a wound. One of the classifications for wounds, depending on the duration and nature of the healing process, is acute or chronic. They can appear because of accidents (burns, cuts), after surgical intervention, or as a result of some disease (diabetes, malignant diseases, infected wounds, etc.) [1 - 3]. Their recovery is a dynamic process consisting mainly of four stages (coagulation and hemostasis, inflammation, proliferation, and maturation), some of which may overlap [4]. The first two stages occur immediately after injury as a primary response to skin damage, which lasts approximately three days. During the second phase, various cellular and vascular processes stop further damage by removing pathogens and cleaning the wound [5]. The last two stages, proliferation and maturation, involve collagen synthesis, which repairs the wound damage [4, 5]. Due to various factors, such as infections and inflammation, skin wounds do not heal

as planned, which prolongs their recovery time [6]. The leading cause of chronic healing is bacterial imbalance, which creates a barrier to the formation of necrotic tissue and changes in the composition of exudate. The authors report that the healing of such wounds can be influenced by the pH of the surface, which changes from alkaline to neutral pH, and upon complete healing reaches an acidic pH [7].

The role of wound dressings is to temporarily replace the functions of healthy skin, providing a physical barrier to the external environment and protecting against further injury and infection, reducing pain, promoting the formation of fibroblasts, and ultimately promoting the formation of healthy skin [8, 9]. Since ancient times, traditional wound dressings (cotton, gauze, plasters, and various types of bandages made from natural or synthetic textile materials) have been used, which have different absorption capacities. Their main function is to keep the wound clean and dry by evaporating exudate (fluid) and protecting it from contamination. These dressings require frequent changing, which limits their use, as they stick to the wound and damage the healing tissue when removed [10].

In the 20th century, scientists established through their research that the healing process is aided in a moist and warm environment, which led to the development of a new type of wound dressings that must meet the following requirements: not only cover the wound, but also actively support the healing process [11 - 13]. They can be divided into two types: passive and bioactive. The former can be absorbent, non-absorbent, and moist, while the latter come in six types (film, foam, hydrogel, hydrocolloid, alginate, and hydroactive) [14].

Hydrogels are a 3D structure that can retain a large amount of water and are considered ideal dressings as they absorb the fluid secreted from the wound and hydrate its surface. Their structure can also include a biologically active substance that provides pain relief, regulates temperature, ensures oxygen transfer, and creates comfort for the patient [15]. They can be synthesized from natural or artificial materials, with biopolymers such as chitosan, collagen, hyaluronic acid, and alginate being preferred for medical applications [16, 17]. Among these polymers, chitosan is a potential candidate for the development of a new type of dressing, as it keeps the wound moist, promotes cell migration, and reduces inflammation. It is an antimicrobial, biodegradable, and biocompatible polymer that is hydrophobic and economically accessible, which is why it is used in various biomedical applications [18]. The specific properties of chitosan are due to the functional groups in its structure ($-NH_2$) and (-OH), which are susceptible to modification and could improve its characteristics. Its solubility in weak acids is due to its polycationic nature [19]. In practical applications, its low porosity, small surface area, and poor mechanical properties limit its use [20]. The application of chitosan for the textile modification improves its mechanical strength and allows for easy removal of the obtained dressing without additional damage. This fabric can acquire antimicrobial properties and be used as a bioactive wound dressing by incorporating an anti-inflammatory biological substance (diclofenac sodium) into the chitosan structure. This type of wound dressing can be obtained by chemical or physical treatment, but since no strong bonds are formed between chitosan and cotton fabric, citric acid must be used as a cross-linking agent. This acid is organic and shows good biocompatibility with chitosan. It can form electrostatic bonds with the chitosan and the hydroxyl groups of the cotton fabric, and with heat treatment and in the presence of a catalyst, it can form a covalent bond. Citric acid has antimicrobial activity and can be used to treat wounds, including those caused by bacteria, by controlling infection and promoting granulation tissue formation [3]. Malu et al. report that most types of bacteria multiply at a pH above 6, so this acid is used to reduce the pH of the wound and inhibit bacterial growth by increasing oxygen flow and aiding the healing process in chronic and infected wounds [3, 21]. Diclofenac sodium is an insoluble compound in acidic solution (pKa = 4.0) but is soluble in ethanol and at pH = 5.0 - 8.0. It belongs to the group of nonsteroidal anti-inflammatory agents, has analgesic effects, and reduces inflammation in chronic and acute injuries. Authors report that the analgesic effect of diclofenac is twice that of indomethacin [22].

This work aims to develop new composite materials from cotton fabric coated with chitosan crosslinked with citric acid and containing a bioactive agent (diclofenac sodium) under different conditions, as well as to investigate their influence on the antibacterial properties and controlled release of diclofenac sodium from the resulting materials.

EXPERIMENTAL

Materials

100 % cotton fabric with a surface mass of 135 ± 5 g m^{-2} (Vratciza-Vratza, JSC, Vratza, Bulgaria); chitosan with Mw = 600.000 - 800.000 g mol^{-1} (Acros Organics, Geel, Belgium); glacial acetic acid 100 % with Mw = 60.05 g mol^{-1} (Merck, Darmstadt, Germany); Diclofenac sodium, 98 % with Mw = 357. 80 g mol^{-1}, (Thermo Scientific Chemicals, China); Ethyl alcohol 96 % pure with Mw = 46.07 g mol^{-1} (Neochim); Citric acid with Mw = 192.12 g mol^{-1}, (Sigma Aldrich, Darmstadt, Germany); sodium dihydrogen phosphate dihydrate with Mw = 156.01 g mol^{-1}, (Merck, Darmstadt, Germany); disodium hydrogen phosphate dodecahydrate with Mw = 358.14 g mol^{-1}, (Merck, Darmstadt, Germany).

0.01 M phosphate buffer, pH = 7.4 (500 mL), was prepared by mixing 0.0014 mol $NaH_2PO_4.2\,H_2O$, 0.0035 mol $Na_2HPO_4.12\,H_2O$, and 0.019 g NaCl. The solutions in this study were made with distilled water.

Preparation of composite materials

As a first step, cotton fabric was soaked in citric acid (1 % w/w chitosan) and left to dry at room temperature. A chitosan solution (2.7 % w/v) was prepared according to the procedure described earlier [23, 24], then diclofenac sodium, dissolved in ethanol, was added by stirring till a homogeneous solution was obtained. The fabric was impregnated with this solution in a 2:1 ratio to the weight of the fabric. After that, the fabric was divided into two samples. One of the samples was left to dry at room temperature, while the second material was subjected to heat treatment at 80°C for 180 min. The resulting materials are named as follows: CRTD (dry at room temperature) and CHTD (with thermal treatment).

Methods for the characterization of composite materials

The materials were examined using a B-290TB optical microscope (Optika ®, Ponternica, Italy). The magnification of the images was set to 40 × and 100 ×. The thermogravimetric analysis (TG) was performed using a STA PT1600 TG-DTG/DSCanalyser (LINSEIS Messgeräte GmbH, Selb, Germany) at a heating rate of 10°C min^{-1}, covering the temperature range from room temperature (20°C) to 600°C in an air atmosphere. Contact angles were measured on cotton fabric (CO) and composite materials (CRTD and CHTD) with distilled water at a constant temperature (24°C) using a THETA Flow Auto 1 optical tensiometer and a Basler acA-2500-60 µm digital camera (Biolin Scientific AB, Gothenburg, Sweden). The results shown are the average of three measurements. The pH of the prepared solution was measured by a Hanna instruments microprocessor pH meter.

The swelling behavior of composite materials

The swelling behavior of composite materials was investigated in order to monitor the controlled release of diclofenac on the surface of an infected wound with pH = 7.4 [25, 26]. The newly obtained modified textile materials, pre-dried and weighed, were immersed in 20 mL of phosphate buffer with pH = 7.4 at 37°C for 24 h. The samples were removed at specific intervals, excess water was absorbed from the surface of the materials with filter paper, and then they were weighed. Eq. (1) was used to determine the swelling behavior:

$$\text{Swelling (\%)} = \frac{w - w_d}{w_d} \cdot 100 \qquad (1)$$

where w_d and w are the weights of the dry and swollen material.

In vitro release of diclofenac sodium from the composite materials

In vitro release of diclofenac from composite materials was observed in phosphate-buffered saline (pH = 7.4, 0.01 M) at 37 ± 0.5°C by measuring the absorption intensity of the solution at λ = 277 nm using an ONDA UV-31SCAN spectrophotometer, 190 - 1100 nm. Each sample was immersed in 20.0 mL of buffer. At specific intervals, 5.0 mL of the solution was taken and replaced with 5.0 mL of fresh phosphate buffer at 37°C. The release of diclofenac sodium was performed three times for each sample to find the arithmetic mean value. A standard curve was used to determine the concentration of the analyzed solutions.

To clarify the mechanism for the release of diclofenac sodium from CRTD and CHTD composite materials, zero order, first order, Higuchi, and Korsmeyer - Peppas kinetic models Eq. (2) - (5) were used, as presented in Table 1. These models are used to describe the mechanism by which bioactive agents are released from polymer matrices [27, 28].

The experimental data were transformed into the

Table 1. Kinetic models for the release of bioactive agents.

Kinetic model name	Equation	No. Eq
Zero order	$Q_t = Q_0 - kt$	(2)
First Order	$\log Qt = \log Q_0 - \frac{kt}{2.303}$	(3)
Higuchi	$Q = kt^{1/2}$	(4)
Korsmeyer - Peppas	$\frac{Mt}{M\infty} = kt^n$	(5)

where Q_t is the cumulative amount of drug released at time t; Q_0 is the initial amount of drug in the solution; k is the release constant of the respective model. Mt/M∞ is the fraction of drug released at time t; n is the exponent. The value of n characterizes the drug release mechanism: 0.45 ≤ n corresponds to Fick's law and has a diffusion mechanism; in models that do not comply with Fick's law, depending on the value of n, there are differences: 0.45 < n < 0.89 - abnormal transport, n = 0.89 - case II; n > 0.89 - super case II transport.

linear form of Eq. (2) - (5) and analyzed by linear regression to determine the rate constant (k) and the coefficient of determination (R^2). In accordance with the methodology described by Siepmann & Peppas [29], the calculations were performed using OriginPro 2021 software (OriginLab Corp., USA).

Antibacterial activity of the composite materials

The antimicrobial activity of the studied composite materials CRTD and CHTD was tested against Gram-positive *Bacillus cereus* ATCC 11778 and Gram-negative *Pseudomonas aeruginosa* 1310. The microbial cultures were maintained at 4°C on slanted meat peptone agar (MPA) and transferred monthly. Test tubes containing sterile meat-peptone broth and cotton samples (10 mm × 10 mm) were inoculated with each bacterial suspension. Test tubes with untreated cotton samples (CO) and no samples were also prepared as controls. After incubation at 28°C for 18 h and shaking at 240 rpm, the samples were removed, and bacterial growth was determined by measuring the turbidity of the medium at 600 nm (OD_{600}). The antimicrobial activity of the treated cotton samples was evaluated by the reduction in cell density after incubation. All antimicrobial tests were performed in triplicate (standard deviations less than 5 %).

RESULTS AND DISCUSSION

Fig. 1 shows micrographs taken with an optical microscope of the original cotton fabric and the CHTD composite material at different magnifications of 40 × and 100 ×. In the pristine cotton fabric, individual twisted fibres can be observed in the yarn, which is structured with the plain weave, as well as gaps between the threads formed during weaving. The micrographs of the CHTD sample show that at 40 × magnification there is a layer of chitosan on the surface of the fibers, while at a higher magnification of 100 × a dense layer of chitosan is observed, which binds the individual fibers and fills the gaps between the threads.

Fig. 2 shows the TG analysis and differential thermogravimetric curve (DTG) for cotton fabric in Fig. 2a, for CRTD in Fig. 2b, and for CHTD in Fig. 2c. The results display a three-stage weight loss for all samples. At around 118°C, the first weight loss begins, which is due to moisture in the materials (4 % for the CO sample and 7 % for the CRTD and CHTD samples). The second stage is the most significant thermal degradation, which begins at around 271°C for the untreated cotton fabric (Fig. 2a). In comparison, for the CRTD and CHTD composite materials it starts at a lower temperature of 227°C (Fig. 2b and Fig. 2c) due to the presence of acids causing degradation of the polymers (chitosan and cellulose) [30]. Significant thermal degradation occurred earliest for the CRTD and CHTD samples at around 342°C and at a higher temperature of 351°C for the initial CO material. The mass loss at 370°C is 73.0 % for CO, 65.0 % for CRTD, and 67.0 % for CHTD. The first derivative also shows that the inflexion points for the CO starting material are at 335°C, for CRTD at 326°C,

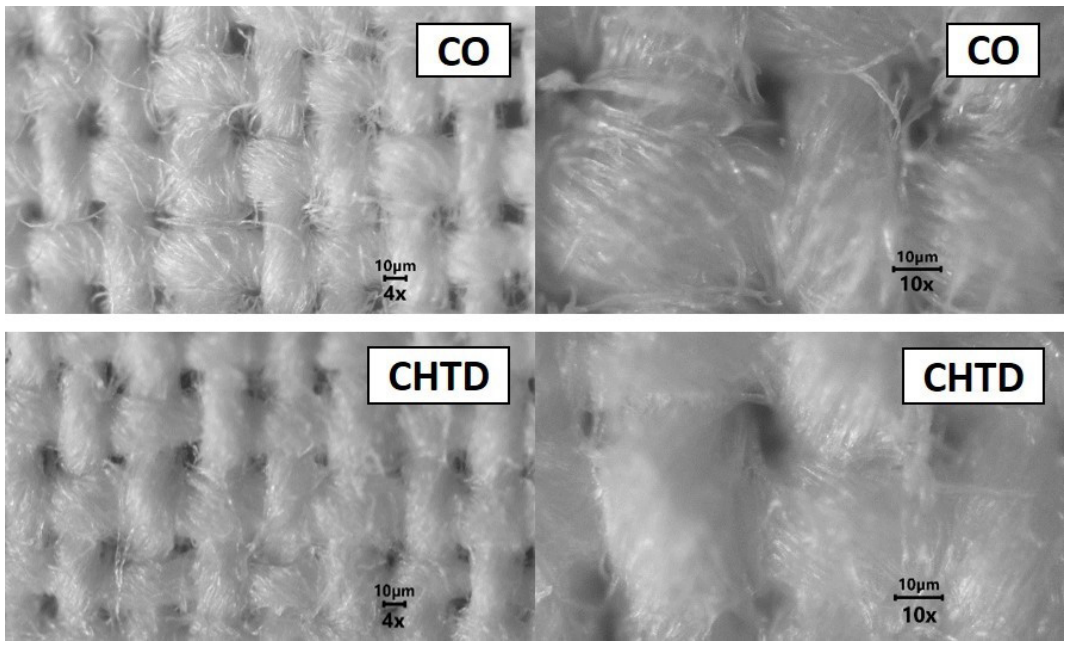

Fig. 1. Optical microscope photographs of cotton fabric (CO) and composite materials CHTD (magnification of the pictures is 40 × and 100 ×).

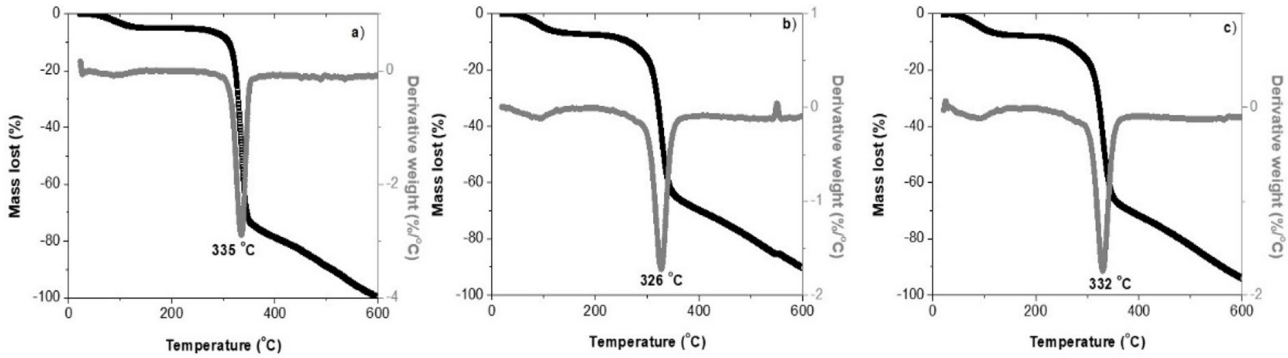

Fig. 2. TG - DTG curves of (a) raw cotton fabric and composite materials: (b) CRTD and (c) CHTD.

and for CHTD at 332°C. At 600°C, the cotton fabric burns completely, and no dry residues remain, while for the CRTD and CHTD samples, the dry residues are 10.0 % and 6.0 %, respectively. Therefore, coating the cotton fabric with crosslinked chitosan, containing citric acid and diclofenac, prevents the complete degradation of the materials.

Fig. 3 shows the results of the contact angle of a water drop on the surface of CRTD and CHTD composite materials. The untreated cotton fabric exhibits high hydrophilicity, as the water droplet immediately spreads out on the surface and penetrates the material, due to the large number of hydroxyl groups in its structure. This result renders the measurement of the contact angle practically impossible, corresponding to a contact angle of 0° [31, 32].

Fig. 3 shows that after modifying the cotton fabric with chitosan containing a bioactive agent, the contact angles with water increase to 99.84° and 126.10° for the CRTD and CHTD samples, respectively. These results indicate that the composite materials are hydrophobic, as they exhibit a contact angle greater than 90° [33]. The CHTD sample has a larger contact angle, which may be due to high-temperature treatment, resulting in the

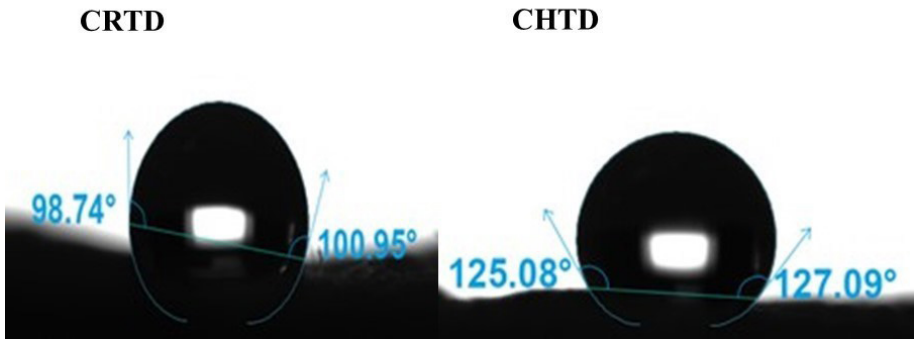

Fig. 3. Measurement of the contact angle of composite materials (CRTD and CHTD) with distilled water.

chitosan film being evenly distributed throughout the sample structure [34].

Fig. 4 shows the swelling of the composite materials CRTD and CHTD in pH = 7.4, at 37°C for 24 h. The obtained results can reveal the mechanism of release of the bioactive agent at neutral pH, specific for infected wounds [35]. The swelling is related to the degree of porosity, pore size, and hydrophilicity/hydrophobicity. Good absorption of wound secretions is essential for wound healing [36]. It was observed that at pH = 7.4, the CRTD swelled more, reaching 128.21 % in 6 h. In comparison, the CHTD sample swelled to 117.48 %, which may be due to the method of their preparation and the possibility for electrostatic repulsion of the same type of electric charge in the layer structure. At room temperature, chitosan with its protonated amino groups forms ionic bonds with the carboxylate ions of the crosslinking agent citric acid. However, when the temperature is increased to 80°C for 180 min, chitosan can bind to citric acid through covalent bonds [33]. Swelling was studied in a phosphate buffer with pH = 7.4. Under these conditions, there are no protonated amino groups in the chitosan structure and only free carboxylate ions from citric acid.

Fig. 5 shows the cumulative release of diclofenac sodium from CRTD and CHTD samples in phosphate buffer with pH = 7.4 at 37°C for 26 h. The results show that during the first 6 h, diclofenac is released more rapidly from composite materials, with 100.59 μg cm^{-2} for the CRTD sample and 85.66 μg cm^{-2} for CHTD, which is due to the desorption of molecules from the surface of the materials, as observed in the analysis

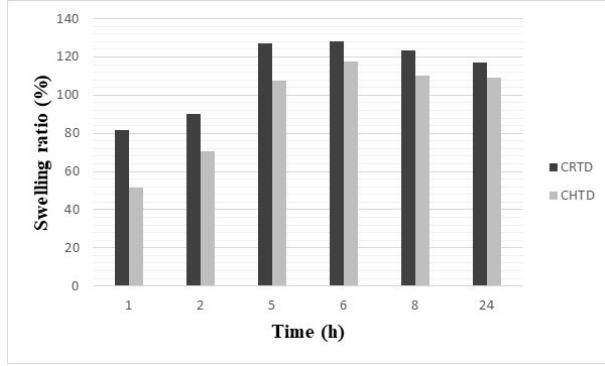

Fig. 4. Swelling of the composite materials CRTD and CHTD in phosphate buffer pH = 7.4, at 37°C for 24 h.

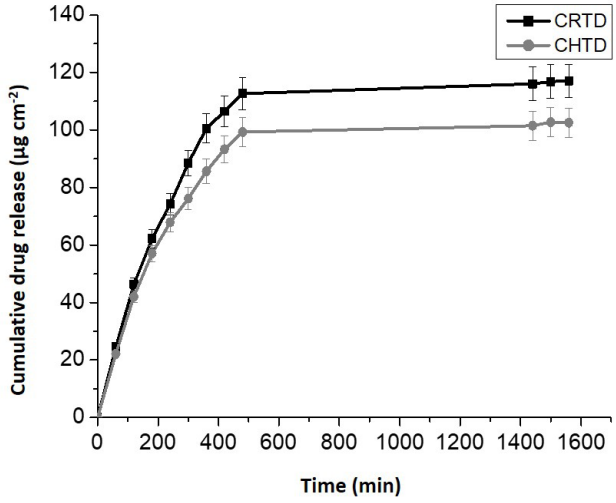

Fig. 5. Release of diclofenac in phosphate buffer pH = 7.4 at 37°C from composite materials CRTD and CHTD, at λ = 277 nm.

Table 2. Values, obtained by several kinetic models for drug release.

	Zero order		First order		Higuchi		Korsmeyer - Peppas		
Samples	R^2	K_0	R^2	K	R^2	K_H	R^2	K	n
CRTD	0.967	12.465	0.897	0.139	0.996	49.31	0.993	0.654	0.442
CHTD	0.964	10.604	0.822	0.106	0.997	42.03	0.995	0.614	0.423

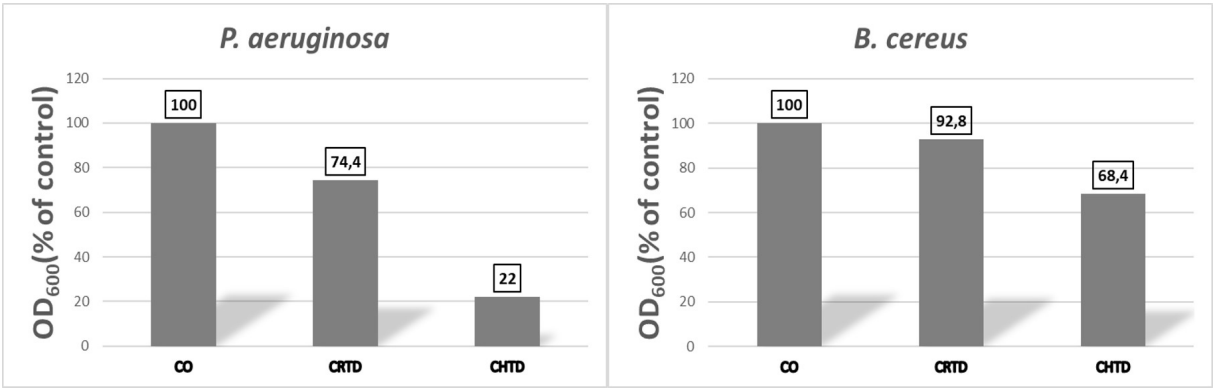

Fig. 6. Antimicrobial activity of original cotton fabric (CO) and composite materials (CRTD and CHTD) on the growth of model strains *P. Aeruginosa* and *B. Cereus*.

of chitosan swelling [37]. Subsequently, the release continued uniformly, with 117.08 μg cm^{-2} of CRTD and 102.55 μg cm^{-2} of CHTD bioactive agents being released from the samples over 26 h. The reason may be the difference in the structure of the hydrogel and the distribution of the drug in the matrix, as well as the processing of the obtained materials.

Table 2 presents the values of the coefficient of determination (R^2) and the release rate constant K obtained by linear regression of the experimental data, with the corresponding Eq. (2) - (5) used in their linear form for the two composite materials. The Higuchi diffusion model best describes the release kinetics for both CRTD and CHTD samples, as it was developed for hydrogel swollen systems releasing biologically active substances [38].

In this case, the Korsmeier - Peppas model is also suitable for describing the drug release mechanism as the coefficient of determination (R^2) is close to one, and the diffusion exponent (n) can be used to characterize drug release kinetics from matrices. The diffusion exponent of diclofenac for both samples is lower than 0.5. For sample CRTD - n is 0.442, and for sample CHTD - n is 0.423. Therefore, diffusion of the bioactive agent is the dominant mechanism for drug release and is described by Fick's law rather than by the polymer chain relaxation process or the erosion of the polymer matrix [39]. The value of n is much lower than 0.45 for the sample CHTD, which means that diffusion is hindered by a denser matrix after thermal treatment during its preparation [40].

At pH = 7.4, chitosan began to lose its positively charged amino groups, which influenced its interaction with diclofenac sodium, as this compound is ionized and soluble at this pH [41]. The crosslinking agent of the chitosan layer is citric acid ($pKa_1 = 3.13$, $pKa_2 = 4.76$ and $pKa_3 = 6.39$) and its free carboxyl groups are negatively charged at pH = 7.4, so they can promote the diffusion of diclofenac sodium into the layer through increased electrostatic repulsion, without, however, erosion of the polymer network being observed under these conditions.

Fig. 6 presents the antimicrobial activity studies of the original cotton fabric (CO) and the new composite materials CRTD and CHTD against model bacterial strains Gram-negative *P. Aeruginosa* and Gram-positive *B. Cereus* in MPB. From the obtained results, it is observed that both materials exhibit antimicrobial activity, unlike the untreated cotton fabric (CO). The

composite material CHTD prepared at high temperature has a more pronounced hydrophobic character, having a higher activity of 78.0 % for *P. Aeruginosa* and 31.6 % for *B. Cereus*. In contrast, the sample CRTD, treated at room temperature, has activity of 25.6 % and 7.2 %, respectively. The CHTD composite material can be used as wound dressings, since it has greater antimicrobial properties, and also controls better the release of the active substance, which makes it a potential candidate for wound treatment.

CONCLUSIONS

Two new cotton materials modified with crosslinked chitosan containing diclofenac sodium were obtained. Both materials release the active substance. The material CHTD, processed at a high temperature, releases the biologically active substance more slowly, unlike the CRTD sample, which was gained at room temperature. Drug delivery analysis showed that diclofenac was discharged for more than 24 h in phosphate buffer with pH = 7.4 at 37°C. The Higuchi and Korsmeier - Peppas equation describe the diffusion process of the drug, coupled with the swelling of chitosan. Due to their hydrophobicity and thermal stability, materials CHTD and CRTD possess antimicrobial activity against Gram-positive bacteria *B. cereus* and Gram-negative bacteria *P. aeruginosa*, with CHTD showing better results. These materials may find application as wound dressings, as they possess antimicrobial properties in combination with controlled release of an analgesic agent.

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Authors' contributions: *D.A.: Research execution, data analysis, draft manuscript preparation; D.S.: Conceptualization, discussions, proofreading, supervision.*

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