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Preparation, characterization, and antibacterial properties of biocompatible material for wound healing

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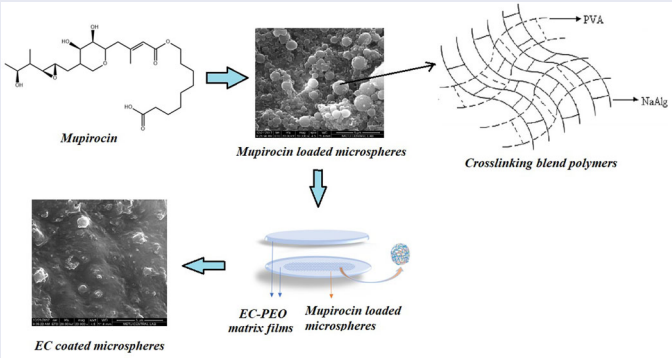
ABSTRACT

The development of wound dressing materials for effortless and easy treatment is crucial to accelerate the wound healing process. It is particularly preferred that the material used for this purpose is biocompatible. In this study, controlled release of the most commonly used antibiotic, mupirocin, against *Staphylococcus aureus* (ATCC 25923), gram-positive bacteria species and one of the leading causes of severe human infections in both health and community settings, has been studied. Polyvinyl alcohol (PVA) and sodium alginate (NaAlg) biopolymers were used to prepare microspheres. Microspheres were prepared by emulsion crosslinking method and crosslinked with calcium chloride ($CaCl_2$). The prepared microspheres were covered with ethyl cellulose (EC) to produce wound dressing materials. Antibacterial activities and swelling behaviors of prepared biomaterials were determined. The effects of PVA/NaAlg ratio, mupirocin amount and membrane thickness on mupirocin release were investigated. The release of mupirocin increased with the increasing PVA/NaAlg ratio from 1/2 to 2/1. At the end of 100 h, the highest release of mupirocin was found to be 86% for the PVA/NaAlg ratio 2/1, drug/polymer ratio 1/2 (C1 formulated) microspheres. The surface morphology and structure of the wound dressing material were investigated using Scanning Electron Microscopy and Fourier Transform Infrared Spectroscopy.

GRAPHICAL ABSTRACT



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KEYWORDS
Biopolymers; wound dressing material; mupirocin; microspheres; controlled drug release

1. Introduction

Development of wound dressing materials with good mechanical strength is of great importance for their excellent biocompatibility and biodegradability. So, these materials are made from biopolymers since a few years. Biopolymers are abundantly available in natural sources and are used in numerous biomedical applications as wound dressing materials. Biopolymer-based biomaterials have unique biological properties and have effectively control over the growth of microorganisms at the wound site. Over the last years the studies about microspheres for drug delivery have focused on natural biodegradable polymers. NaAlg and PVA have long been used in many applications such as drug delivery, separation techniques and food industries. Alginate is a linear and nontoxic polysaccharide composed of glucuronic and mannuronic acids which are located in the cell wall and in the matrix of the algae and bacteria. PVA is one of the most significant biocompatible polymers and has an excellent film forming property.[1–5]

Mupirocin (Pseudomonas acid A) is a new topical antibiotic agent that is produced by the fermentation of Pseudomonas fluorescents (Figure 1). Mupirocin has activity against Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* (ATCC 25923), some gram-negative bacteria and also affected the fungi as *Candida albinans*. It is reported in studies that

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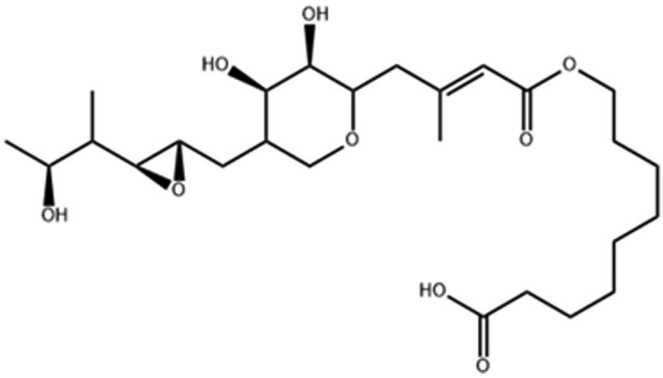

Figure 1. Structure of mupirocin.

Mupirocin has been successfully used in dermatitis, impetigo, and burn therapy on skin infections.[6–7]

In recent years, significant progress has been recorded in drug industry. These have included controlling drug dosage by developing smart release mechanism.[8–10] Drug release systems are designed to provide controlled release of drugs within a specified time. The main goal of these systems is to increase the healing effect of drugs on patients and to ensure that the drug reaches the target tissue or diseased area at the desired dose and time, without problems and exhibit the desired effect. For this purpose, for the last 20 years new drug release systems have been developed such as multi particle systems, biodegradable polymers, and non-degradable rate-controlled drug release systems. Thus, after a certain dose has been taken the plasma level of the active ingredient remains constant (10–12 h, one day or one week) and the patients are prevented from taking frequent drug. For the maximum therapeutic efficacy and minimum side effects, it is necessary to deliver the agent to the target tissue in the optimal amount in the right period of time. There are several approaches in delivering a therapeutic agent to the target site. One of these carrier systems is microspheres.[11–14] Microspheres are microcarriers that can be in different size from a few microns to mm, with or without porosity, degredation or not fragmented in the body and prepared in different surface and bulk structures.[15] Polymeric microspheres are biocompatible and biodegradable. For this reason, they are the most preferred encapsulation units in controlled release systems.[16]

In this study, we aimed to prepare a wound dressing material containing polymeric microspheres for the release of mupirocin. For this purpose, mupirocin was encapsulated with using Na-Alg and PVA, one of the most chosen biocompatible polymer, and then crosslinked with $CaCl_2$. After that polymeric microspheres were covered with EC to create wound dressing material. The effects of polymer and drug-polymer ratios, drug loading, and encapsulation efficiency and antibacterial activities were investigated. Characterization studies were carried out using SEM and FTIR analyses.

2. Materials and method

2.1. Materials

NaAlg (medium viscosity), Poly(ethylene oxide) (PEO) and Mupirocin were supplied from Sigma Chemical Co (Louis, USA). PVA, Tween-80, light liquid paraffin and $CaCl_2$ were supplied by Merck (Darmstadt, Germany). The molecular weight and degree of saponification of PVA were 72.000 and greater than 98%. Na_2HPO_4, and NaH_2PO_4 were all supplied from Carlo Erba. EC was provided from Fluka.

2.2. Characterization

The morphology and surface structure of the microspheres and wound dressing material were investigated using the Quanta 4000 F Field Emission SEM.

FTIR spectra of the mupirocin, mupirocin loaded microspheres, and polymer samples were obtained using a Mattson 1000 FTIR spectrometer (Welwyn Garden, England).

Swelling degree (SD) measurements of empty microspheres were carried out at pH 5.5 buffer solution at ambient temperature. The microspheres were permitted to swell for equilibrium in buffer solution and then taken from buffer solution and filtered. The swollen microspheres were weighed with electronic balance. The equilibrium swelling degree (%) was calculated as follows:

$$\text{Equilibriumswellingdegree}(\%) = \left(\frac{Ms - Md}{Md}\right) x100 \qquad (1)$$

*M*s and *M*d are the mass of the swollen microspheres and dry microspheres.

2.3. Antibacterial activity

The antibacterial study was carried out depending on the well diffusion method and prepared materials were tested against to *Staphylococcus aureus* (ATCC 25923). Gram-positive microorganism that act as the predominant pathogenic bacteria for severe skin wound infection.[17,18] The antibacterial activities of mupirocin antibiotic and polymer microsphere containing the best ratio of mupirocin, PVA/NaAlg ratio 2/1, drug/polymer ratio 1/2, were determined by well diffusion method using *Staphylococcus aureus* (ATCC 25923) standart strain thanks to Gazi University Life Sciences Research and Application Center. Both samples contain the same amount of active ingredient. After the microorganism to be cultivated in the medium was activated in Tryptic Soy Broth liquid medium for 2 h, the density of the active cultures was adjusted to McFarland 2.5 turbidity. The bacterial culture whose turbidity was adjusted was inoculated on Luria-Bertani (LB) solid media. With the help of sterile punches 7 mm diameter wells were opened on the agar. The 50 µl of the samples whose antimicrobial activity was to be investigated were added and left to incubate for 24 h at 37 °C. After the incubation, inhibition zones formed around the wells were measured with a caliper. The well diffusion study was performed in 4 parallel and mean and standard deviations were calculated.[19]

2.4. Preparation of microspheres

Empty microspheres of PVA/NaAlg were prepared by the emulsion-crosslinking method.[20–22] Briefly, PVA (8 wt%)

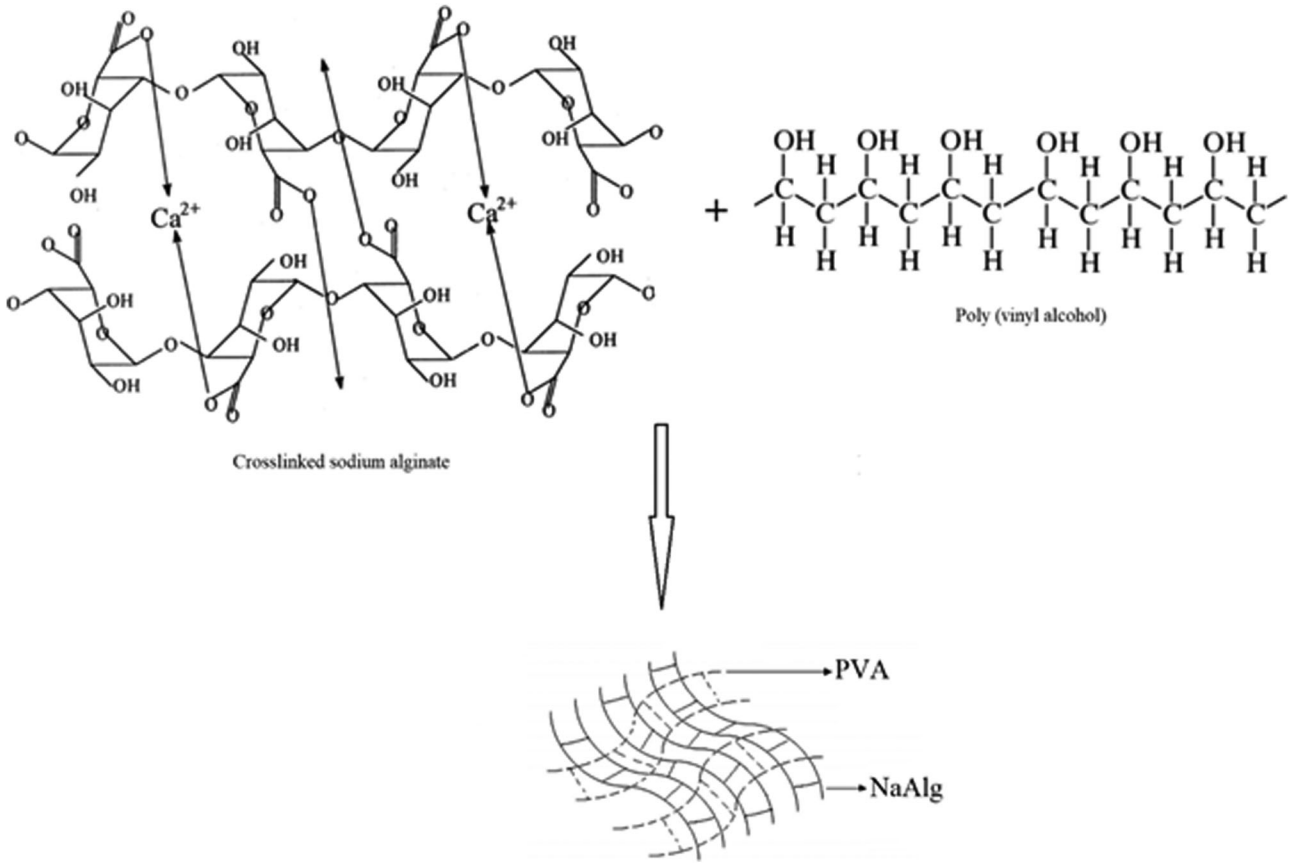

Figure 2. Expected crosslinking reaction mechanism.

Table 1. Formulation codes of the prepared microspheres (exposure time to crosslinking: 15 min, crosslinking concentration: 5 %wt).

Formulation code	Polymer ratio PVA/Na-Alg (w/w)	Drug/Polymer ratio (w/w)	Drug loading (% DL)	Encapsulation efficiency (% EE)
A	1/1	–	–	–
A1	1/1	1/2	33.33	38.75
A2	1/1	1/4	20.05	36.63
A3	1/1	1/8	11.13	26.69
B	1/2	–	–	–
B1	1/2	1/2	53.34	61.95
B2	1/2	1/4	30.11	40.91
B3	1/2	1/8	21.05	29.32
C	2/1	–	–	–
C1	2/1	1/2	68.19	75.50
C2	2/1	1/4	50.23	66.40
C3	2/1	1/8	41.08	53.40

and NaAlg (2 wt%) were dissolved distilled water by stirring. Blend polymer solutions were prepared by mixing these solutions in different ratios (w/w). Possible reaction mechanisms with $CaCl_2$ for the crosslinking of PVA and NaAlg are presented in figure 2. The polymer solution was emulsified using a high-speed stirrer in light liquid paraffin (50 ml) containing Tween® 80 (0.5 ml) to form a water in oil (W/O) emulsion. Then, $CaCl_2$ (5 wt%) was added slowly, and the emulsion was further stirred for 30 min. Later, the microspheres were collected using an ultracentrifuge (MPV-251), washed repeatedly with *n*-hexane and 2-propanol, and then dried in an oven at 40 °C and stored for further analysis. For prepare of the mupirocin loaded microspheres the required amount of mupirocin was dispersed into the polymer mixture for 12 h. Then the process was continued analogously to the preparation of empty microspheres. The preparation conditions of microspheres containing Mupirocin have been presented in Table 1.

2.5. Drug loading % (DL) and encapsulation efficiency % (EE) measurements

Mupirocin loading was determined as percent ratio mupirocin in the microspheres. To determine mupirocin loading in the PVA/NaAlg microspheres known amount of sample was weighed, placed in a flask with phosphate buffer solution (50 ml) (pH 5.5) and incubated in a shaking water bath at 37 °C. At the end of 2 h period the precipitated microspheres were filtered and Mupirocin was analyzed with UV–VIS Spectrophotometer at a wavelength of 225 nm, with buffer solution as a blank.

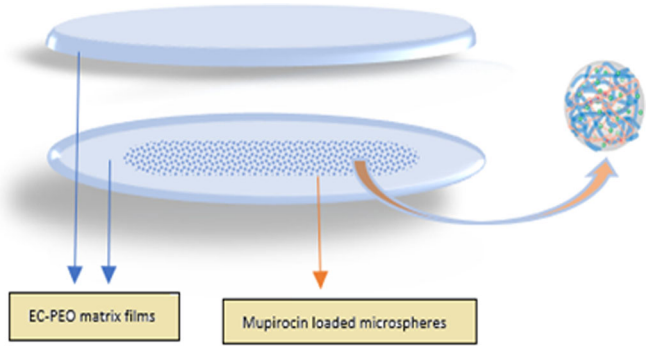

Figure 3. Schematic representation of the synthesis of EC coated wound dressing material.

$$\%DL = \frac{Amount\,of\,mupirocin\,in\,the\,microspheres}{weight\,of\,microspheres} x100 \quad (2)$$

$$\%EE = \frac{Amount\,of\,mupirocin\,in\,the\,microspheres}{total\,mass\,of\,mupirocin\,added\,in\,the\,microspheres} x100 \quad (3)$$

2.6. Preparation of wound dressing material

EC was dissolved in acetone to give a 5 wt% solution. PEO was added as a plasticizer in a proportion of 20 wt% by mass of EC. Predetermined volumes were taken from the prepared casting solution and the casted membranes (support membrane) were set at 40 °C for jellify. The previously prepared mupirocin added PVA/NaAlg microspheres were placed on the gelling EC film (Figure 3). The same volume EC solution was casted onto EC membrane containing mupirocin loaded microspheres and then the film was dried at 40 °C. After the drying process the matrix films which were coated at different thicknesses were used for the release studies.

2.7. In vitro release study

In vitro drug release from the microspheres was studied in a phosphate buffer solution (PBS) (50 ml) with pH 5.5 and incubated in a shaking water bath at 37 °C. At specific time intervals (1 h), samples precipitated and supernatants were withdrawn and replaced by fresh PBS to maintain a constant volume. The study continued 100 h until the completion of the dissolution study. The amount of the Mupirocin released at each time interval was analyzed spectrophotometrically at 225 nm. With the use of the absorbance values, the cumulative percentage of the amount of release was determined using calibration curve of Mupirocin.

3. Results and discussion

3.1. Characterization of microspheres

Figure 4 showed the FTIR spectra of pristine PVA, pristine NaAlg, pristine Mupirocin and C1 formulated microspheres. As shown in Figure 4, the broad band between 3000 and 3500 cm^{-1} attributed to the O–H stretching vibrations of

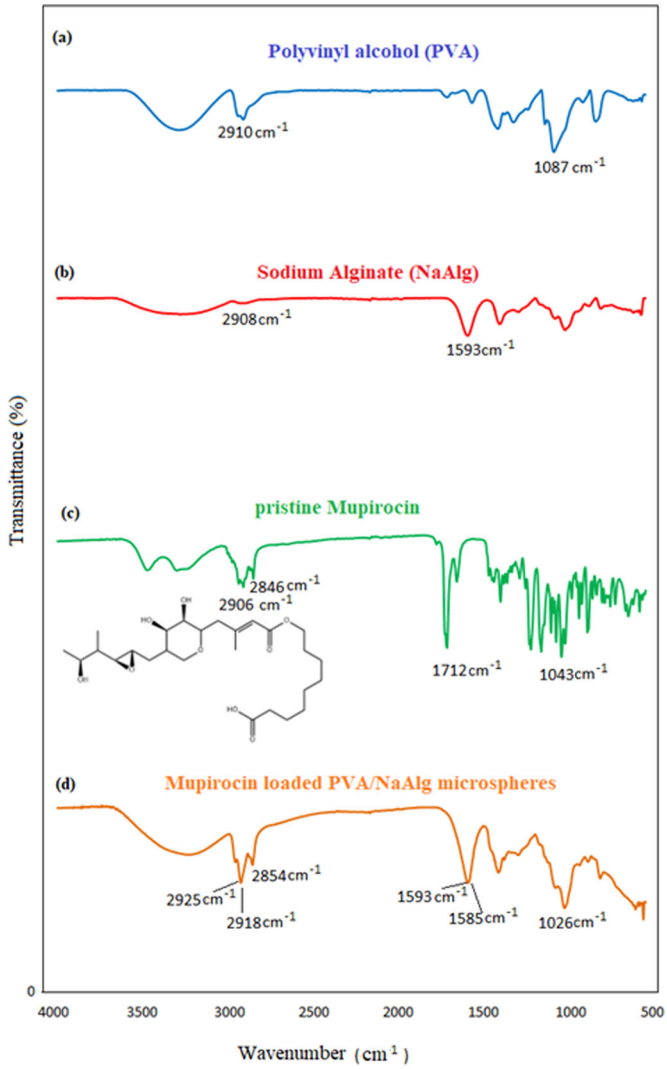

Figure 4. FTIR spectrum of (a) pristine PVA, (b) pristine NaAlg, (c) pristine Mupirocin, and (d) C1 formulated microspheres.

PVA and NaAlg. The C–H stretching bands appearing at 2910 and 2908 cm^{-1} were assigned to C–H groups of PVA and NaAlg, respectively. This peak was observed in the spectra of C1 formulated microspheres at 2925 cm^{-1}. In the spectrum of NaAlg the characteristic bands of C = O appeared at 1593 cm^{-1}. This characteristic peak was also observed in the spectra of C1 formulated microspheres, indicating the absence of chemical interactions between PVA and NaAlg during the process. A sharp band at 1087 cm^{-1} corresponds to the C–O–C symmetrical stretching (in acetyl group) present on the PVA backbone due to the non-hydrolyzed acetate groups of poly(vinyl acetate). This band is also seen in the spectra of C1 formulated microspheres at 1026 cm^{-1}.

The FTIR spectrum of mupirocin (Figure 4(c)) showed characteristic bands at 1712 cm^{-1} corresponding to C = O stretching, at 2906 and 2846 cm^{-1} corresponding to C-H deformation and at 1043 cm^{-1} corresponding to the C-O-C stretching vibration.[21] C1 formulated microspheres showed a strong characteristic band at 1585 cm^{-1} corresponding to C = O stretching and two bands at 2918 and 2854 cm^{-1} due to C-H group stretching. In the FTIR spectra of Figure 4(d),

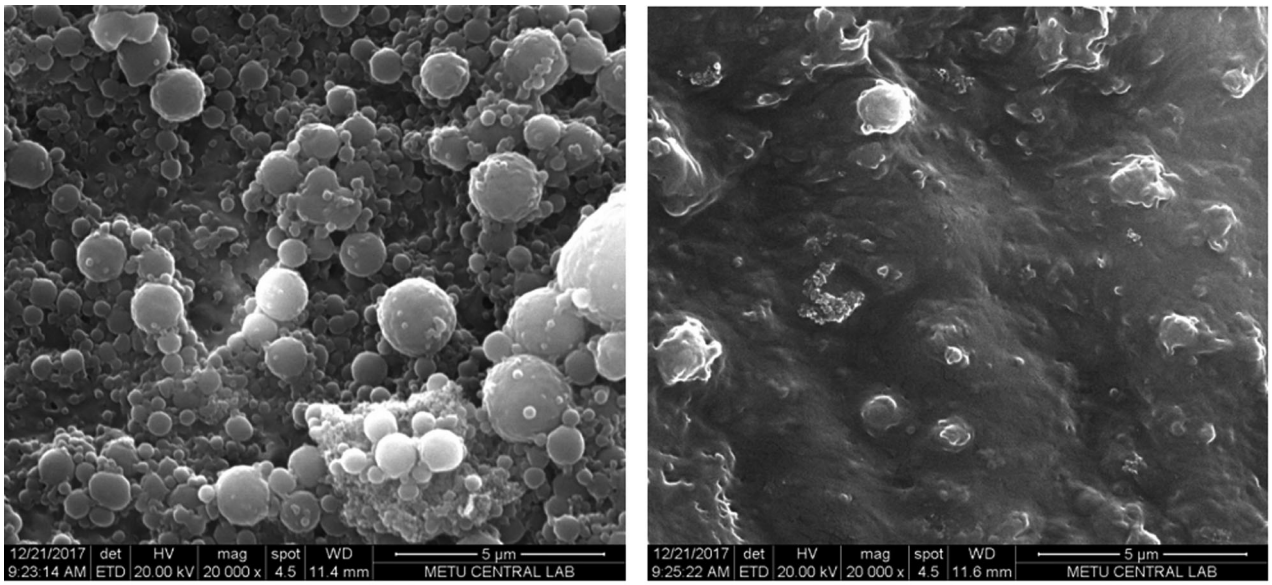

Figure 5. Microscopic pictures of (a) C1 formulated microspheres and (b) ethyl cellulose coated C1 formulated microspheres.

the absorbance band obtained at 1026 cm^{-1} was attributed to the characteristic group C-O-C. These confirmed the presence of mupirocin in the C1 formulated microspheres.

The surface morphologies of microspheres and biopolymer materials were investigated by SEM. The SEM micrographs of the surface of both mupirocin loaded C1 formulated microspheres (Figure 5(a)) and wound dressing material (Figure 5(b)) were shown in Figure 5. Figure 5 indicated that the microspheres have maintained a spherical form. The SEM micrographs were taken at magnifications of 20,000.

Many factors, such as EC film thickness, drug and polymer ratios were affected the EE and DL percentage. The results of % EE and % DL were shown in Table 1. As could be seen from the table, the % EE was slightly affected with the increase in drug/polymer ratio. However, by increase in the amount of PVA, increase in both % EE and % DL were observed.

3.2. In vitro drug release

The in vitro release of mupirocin from the PVA/NaAlg microspheres was studied in skin pH conditions (pH: 5.5) at 37 °C. Figures 6–8 shows the cumulative release of microspheres with different PVA/NaAlg ratios. The percentage of the highest and the lowest cumulative mupirocin releases were obtained as 86 and 55 in formulation of C1 and B3 microspheres at the end of 100 h, respectively. As the blend ratio (PVA/NaAlg) increased from 1/2 to 2/1, the release of mupirocin increased. Alginate is a natural and water-soluble polymer, contains hydroxyl and carboxyl groups, which impart hydrophilicity to the molecule. On the other hand, PVA is virtually a linear polymer and has small hydrated volume, thus PVA produces a compact network of macromolecular chains in the microspheres. In Table 1, it was seen that the drug loading capacity and swelling measurements supported the mupirocin release results. As the PVA ratio increased, the drug loading capacity increased.

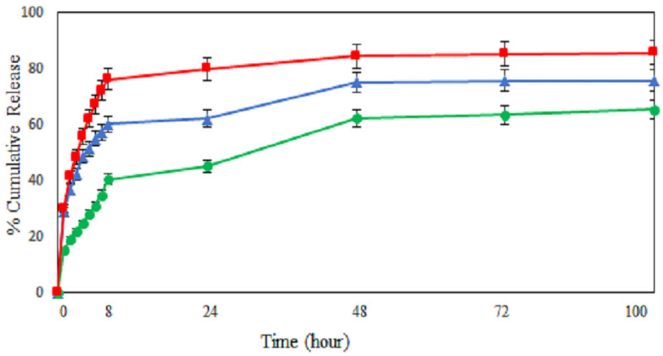

Figure 6. Effect of the PVA/NaAlg ratio on Mupirocin release: (■):2/1 (▲):1/1, (●):1/2 (Drug/Polymer ratio: 1/2, concentration of $CaCl_2$: %5(w/v), exposure time to $CaCl_2$:15 min).

Equilibrium swelling experiments were performed in distilled water for A, B, and C formulated empty microspheres and were presented in Table 2. As shown in Table 2, increases in the amount of the PVA increased the swelling percentage. Thus, the diffusion of mupirocin from the C1 formulated microspheres to an external medium was easier than the A1 and B1 formulated microspheres.

Another parameter that affects the release of mupirocin from the microspheres is the drug/polymer ratio. The effect of the mupirocin/polymer ratio on the release of mupirocin is shown in Figures 9–11. The figures show that the cumulative release of mupirocin from the microspheres increases with the increasing amount of drug in the microspheres.

One of the most effective ways to change the release pattern of microspheres is to change the thickness of EC film. The effect of the EC film thickness on the release rate of mupirocin was investigated for 5 and 7 ml. C1 formulated microspheres were coated at different amount of EC film thicknesses as 5 and 7 ml. The results were given in Figure 12, which clearly indicated that with increasing amount of the EC film thickness from 5 to 7 ml, the cumulative release of the mupirocin decreased. The maximum mupirocin release was found to be 70% at the EC film thickness as 7 ml.

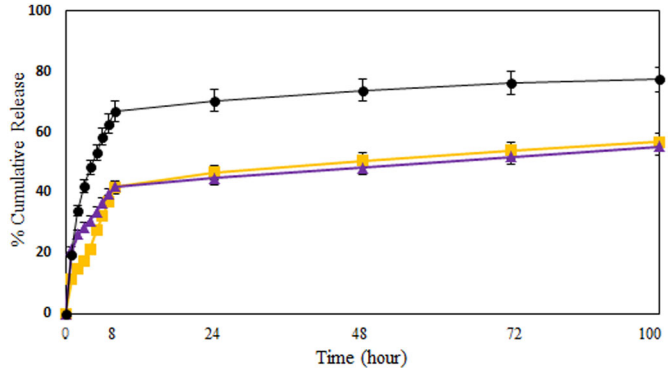

Figure 7. Effect of the PVA/NaAlg ratio on Mupirocin release: (■):1/1, (▲):1/2, (●):2/1 (Drug/Polymer ratio: 1/4, concentration of $CaCl_2$: %5(w/v), exposure time to $CaCl_2$: 15 min).

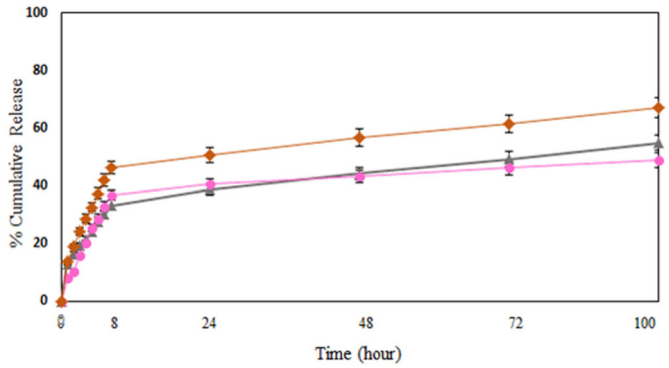

Figure 8. Effect of the PVA/NaAlg ratio on Mupirocin release: (▲):1/1, (●):1/2, (◆):2/1 (Drug/Polymer ratio: 1/8, concentration of $CaCl_2$: %5(w/v), exposure time to $CaCl_2$:15 min).

Table 2. Results of equilibrium swelling degree of empty microspheres.

Formulation code	Distilled Water
A	82.6
B	60.5
C	97.5

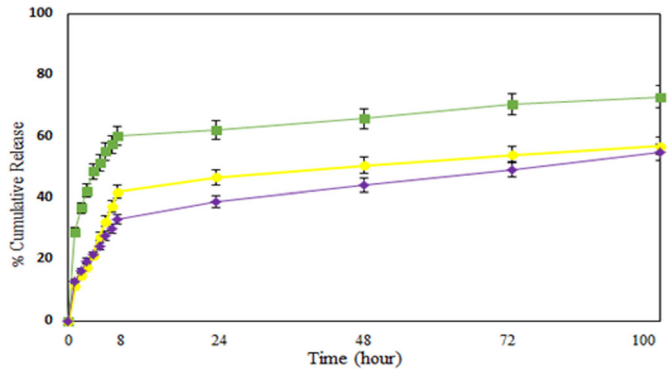

Figure 9. Effect of the drug/polymer ratio on Mupirocin release (■):1/2, (◆):1/4, (●):1/8 (PVA/Na-Alg ratio: 1/1, concentration of $CaCl_2$: %5(w/v), exposure time to $CaCl_2$:15 min).

3.3. Antibacterial activity

Antibacterial properties would benefit to characterize the wound dressing material.[23–27] Thus, we performed a test for antibacterial assessment using Gram *positive Staphylococcus aureus* (ATCC 25923) microorganism by the well diffusion method in this study. The results of

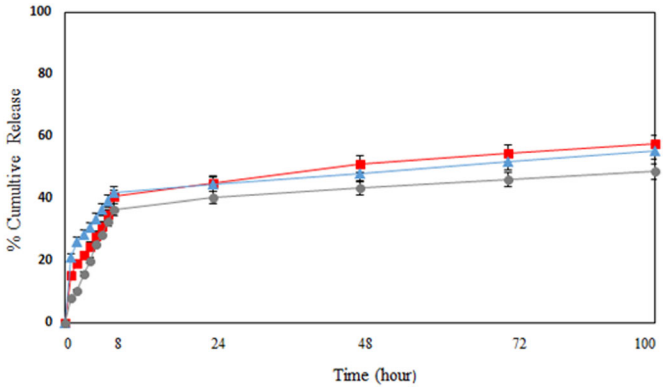

Figure 10. Effect of the drug/polymer ratio on Mupirocin release (■):1/2, (▲):1/4, (●):1/8 (PVA/Na-Alg ratio: 1/2, concentration of $CaCl_2$: %5(w/v), exposure time to $CaCl_2$:15 min).

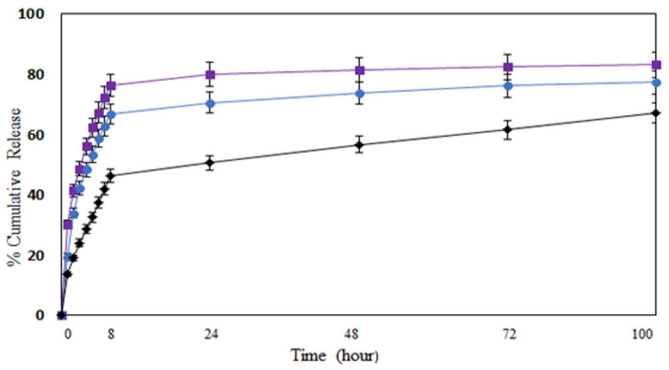

Figure 11. Effect of the drug/polymer ratio on Mupirocin release (■):C1, (●):C2, (◆):C3 (PVA/Na-Alg ratio: 2/1, concentration of $CaCl_2$: %5(w/v), exposure time to $CaCl_2$:15 min).

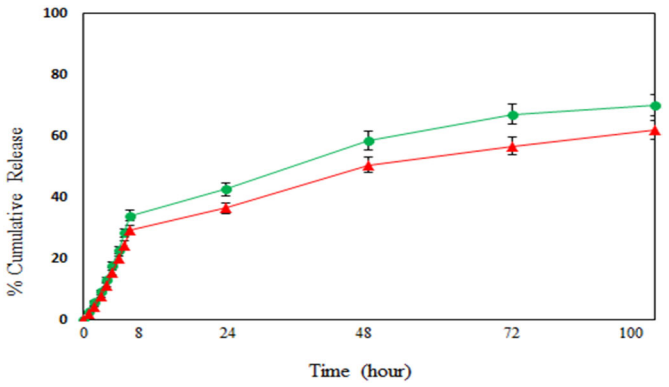

Figure 12. Effect of the EC film thickness on Mupirocin release: (●): 5 ml, (▲): 7ml (PVA/Na-Alg ratio:2/1, Drug/Polymer ratio: 1/2, concentration of $CaCl_2$: %5(w/v), exposure time to $CaCl_2$:15 min).

antibacterial studies on mupirocin and C1 formulated mupirocin-containing microspheres were shown in Figure 13 and Table 3. When the results of the well diffusion test are examined, the formation of a zone is clearly seen on the plate that is cultivated on polymer microspheres containing Mupirocin antibiotic and Mupirocin. It has been determined that polymer microspheres containing Mupirocin are significantly less effective than pure Mupirocin antibiotic against *Staphylococcus aureus* (ATCC 25923). Apart from this, it has been noted that the two samples have a similar tendency. In addition, we are of the opinion that the amount of active substance released into the medium from the microsphere is

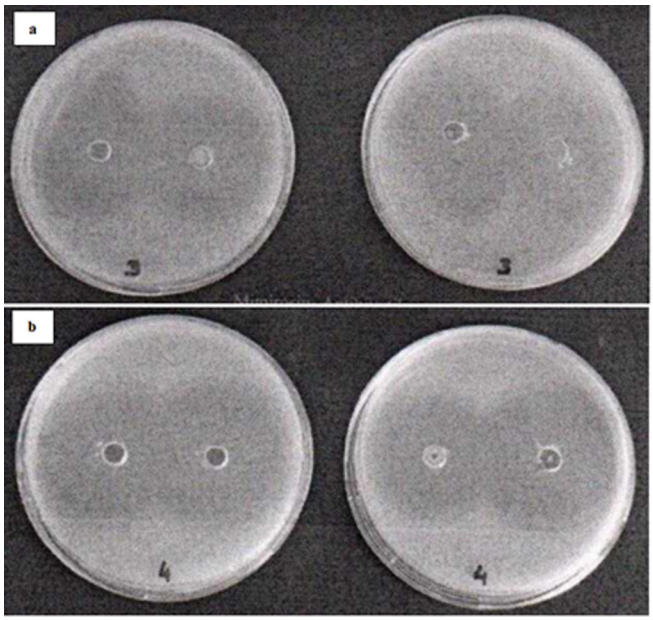

Figure 13. Antibacterial performance of (a) Mupirocin and (b) Mupirocin loaded microspheres.

Table 3. Measured zone diameters for *Staphylococcus aureus* (ATCC 25923) in well diffusion method.

	Well diffusion* (mm)	
Samples	Mean	SD
Control	No	
PBS (Phosphate buffered saline)	No	
Pristine mupirocin	37,25	1,26
Mupirocin loaded C1 formulated microspheres	36,75	0,96

*The well diffusion study was performed in 4 parallel and the mean and standard deviation were calculated.

both released in a controlled manner and has the same effect on microorganisms. Therefore, the developed biomaterial could be effective in treating infections.

4. Conclusion

In this study, Mupirocin-loaded microspheres were embedded in the EC films to design new wound dressing materials. The prepared biomaterials were characterized and their antibacterial activities were examined. Antibacterial tests were performed against the *Staphylococcus aureus* (ATCC 25923) gram-positive bacteria species. C1 formulated microspheres showed antibacterial activity similar to mupirocin, so we thought the developed biomaterial could be effective in treating infections.

Conflict of interest

The authors declare that they have no conflicts of interest.

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