

The effect of polymeric films of hydroxypropyl methylcellulose (HPMC)/chitosan on ofloxacin release, diffusion, and biological activity

Saif Aldeen Jaber^{1,2} | Mohamed Saadh¹ | Mohammad A. Obeid^{3,4}

¹Faculty of Pharmacy, Middle East University, Amman, Jordan

²Applied Science Research Center, Applied Science Private University, Amman, Jordan

³Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Yarmouk University, Irbid, Jordan

⁴Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK

Correspondence

Saif Aldeen Jaber, Faculty of Pharmacy, Middle East University, Amman, Jordan.

Email: sjaber@meu.edu.jo

Mohammad A. Obeid, Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Yarmouk University, Irbid, Jordan. Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK.

Email: m.obeid@strath.ac.uk

Abstract

Infectious diseases caused by resistant bacteria have been investigated by several researchers recently. Ofloxacin is a quinolone antibiotic used against resistant microorganisms and in different routes of administration. Transdermal drug delivery is used to reduce drug toxicity, avoid first-pass metabolism, and reduce fluctuations in drug concentration in the body. Ofloxacin was formulated in a transdermal polymeric formula using hydroxypropyl methyl cellulose (HPMC) and chitosan at different ratios in the presence of palmitic acid as a permeation enhancer. Physical characterization, drug release and diffusion, drug matrix association, and antimicrobial assay have been investigated using different techniques including HPLC, fourier-transform infrared spectroscopy (FTIR), Franz cells diffusion, and UV spectroscopy. Ofloxacin release was successfully accomplished in many polymeric formulas containing a high ratio of HPMC with a maximum drug release of 53%. Formulas selected for antimicrobial assay indicate that sustained release patches have successfully inhibited microbial and biofilm growth with a percentage inhibition of more than 90%. In conclusion, antibiotics can be formulated in transdermal polymeric film to target skin infection and reduce drug toxicity and avoid drug first metabolism for drugs reaching systemic circulation which has a direct influence on drug activity.

KEYWORDS

antibiotic, biofilms, infection, microbial resistance, transdermal patch

Highlights

- Ofloxacin was formulated in a transdermal patch without decrease in the biological activity.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2023 The Authors. *Polymer Engineering & Science* published by Wiley Periodicals LLC on behalf of Society of Plastics Engineers.

1 | INTRODUCTION

Recently many efforts have been done by many pharmaceutical-related companies and labs in developing different dosage forms to overcome bacterial infections that have cost millions of lives over the past 10 years.¹ The biofilm layer formed by biofilm-forming bacteria has increased antibiotic resistance hundreds of times higher than regular floating bacteria.^{2,3} Thus, many researchers have tried to formulate antimicrobial agents in different dosage forms to increase the contact of antibiotics and to sustain its release for more activity.⁴ Unfortunately, not all formulated antibiotics were able to exert long and sustained acting behavior that prevents bacterial growth in addition to be suitable for all patients.^{5–8}

Polymeric film systems are a film containing a drug applied to the skin directly either to target a skin disease, to avoid first-pass metabolism and/or avoid possibly serious side effects by preventing fluctuation of drug levels.⁹ Two parameters are playing a vital role in drug administration from a transdermal film; the distribution of the drug in film matrix and the permeation enhancer used to enhance the drug diffusability through the skin.¹⁰ Ofloxacin is a quinolone antibiotic having broad spectrum activity acting via inhibiting DNA gyrase in bacteria and has the ability to be given in different dosage forms.¹¹ The severe side effects associated with the long use of ofloxacin like ototoxicity, nephrotoxicity, and neurotoxicity in addition to gastrointestinal disturbance put the pharmaceutical industry under pressure to formulate ofloxacin in a different formula.¹² Hydroxypropyl methylcellulose (HPMC), and chitosan, are naturally occurring polymers with interesting and important roles in matrix films for different transdermal patches.¹³ HPMC is a cellulose polymer and can carry hydrophilic drugs and is used in different controlled-release formulas.¹⁴ Chitosan is the second most important film polymer after cellulose polymers due to its magnificent functional and biological properties that suit pharmaceutical and biomedicine research and applications.¹⁵ The objective of this study is to find out which mixtures of HPMC and chitosan will provide the longer drug release with better drug diffusion through Franz cells without any effect on the microbial activity.

2 | MATERIALS AND METHODS

2.1 | Materials

Ofloxacin powder 99.9% pure was obtained from MS pharma pharmaceutical company, Amman, Jordan. Acetonitrile HPLC grade was obtained from Sigma-Aldrich chemical company, Bengaluru, India. Palmitic acid, chitosan and HPMC were obtained from Sigma-

Aldrich, Poznan, Poland. Biofilm-forming bacteria *Staphylococcus aureus* ATCC 9144 and *Pseudomonas aeruginosa* ATCC 15442 were obtained from American Type Culture Collections (ATCC). Solvents used to prepare the different formulas and in diffusion and release apparatus like methanol, water and phosphate buffer were obtained from Sigma-Aldrich, St. Louis, USA.

2.2 | Methods

2.2.1 | Polymeric film formation and drug loading

The selected ratio of each polymer with a total amount of 900 mg was dissolved in 60 mL of 1:1 methanol and water. Mixing was done using a magnetic stirrer at 25°C followed by the addition of 100 mg (10 wt/wt%) of ofloxacin and 2 mL of palmitic acid as a permeation enhancer then 5 h of mixing was done. The code used for each sample is presented in Table 1. All prepared films were placed in 1 L beakers with inner diameter of 10.03 cm and left to dry under fume hood for 2 days.

2.2.2 | Polymeric film characterization

Film thickness

Film thickness was measured using a micrometer from three different places on the sample and the average and standard deviation were recorded.

Content uniformity

Content uniformity of each film was measured by cutting three different 1 cm² from each batch and dissolves the

TABLE 1 Code and composition of vancomycin hydrochloride and polymers in each patch.

| Formula code | Drug weight (mg) | Palmitic acid (mL) | HPMC% | Chitosan% |
|--------------|------------------|--------------------|-------|-----------|
| A1 | 100 | 2 | 100 | 0 |
| A2 | 100 | 2 | 90 | 10 |
| A3 | 100 | 2 | 80 | 20 |
| A4 | 100 | 2 | 70 | 30 |
| A5 | 100 | 2 | 60 | 40 |
| A6 | 100 | 2 | 50 | 50 |
| A7 | 100 | 2 | 40 | 60 |
| A8 | 100 | 2 | 30 | 70 |
| A9 | 100 | 2 | 20 | 80 |
| A10 | 100 | 2 | 0 | 100 |

Abbreviation: HPMC, hydroxypropyl methylcellulose.

sample in 1 mL of methanol. Each sample was injecting into an HPLC to calculate the concentration of ofloxacin. The average concentration and standard deviation for each formula have been calculated.

Moisture content

Three films from each formula containing drug were placed in desiccator in the presence of sodium chloride for 24 h. The weight of the films before and after dessication was measured and the moisture content was calculated as below. The average moisture content and standard deviation were calculated for each formula.

$$\% \text{moisture content} = \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} \times 100\%$$

2.2.3 | HPLC method

Content uniformity, drug diffusion, and drug release have been analyzed on Shimadzu Prominence-i LC 2030C HPLC instrument with an isocratic method. The mobile phase was composed of phosphate buffer with a pH of 7.4 and HPLC grade acetonitrile at a 50:50 ratio. The column used was ACS C18 (3 mm, 5 cm) with a flow rate of 600 $\mu\text{L}/\text{min}$ at a temperature of 27°C. All absorbance measurements were at 254 and 290 nm wavelengths. All calibration curves had a correlation coefficient >0.99.

2.2.4 | Drug release

A 1 cm^2 of each polymeric film was taken from three different patches and placed in a 25 mL beaker containing 20 mL phosphate buffer with pH of 7.4. Magnetic stirrer was very gentle to mimic human conditions. The beaker was sampled to calculate the cumulative concentration at the following intervals (5, 15, 30, 45, 60, 90, 120, 150, 180, 240, 900, and 1440 min). At each sampling interval, 1 mL sample was taken and 1 mL of fresh phosphate buffer was added to maintain solution volume. The temperature was maintained at 37°C.

2.2.5 | Drug diffusion

A 1 cm^2 of each film was placed in diffusion-apparatus over Franz cells membrane. The reservoir contains 20 mL of phosphate buffer with a pH of 7.4 and sampling intervals were similar to drug release profiling. Again, 1 mL of a fresh phosphate buffer was added to the reservoir after

each sampling interval and the temperature was again 37°C. Samples were analyzed using HPLC.

2.2.6 | FTIR characterization

Infrared spectra were collected using a Bruker TENSOR FTIR spectrometer with 32 scans within the wavenumber range of 4000–400 cm^{-1} were obtained and averaged for each sample. Three replicates were conducted for each sample.

2.2.7 | Antimicrobial assay

AlamarBlue[®] assay plates were prepared by placing 1 cm^2 of each transdermal batch over 1.5 mL of LB broth preinoculated with the bacteria to give a final bacterial concentration of 1×10^8 in each of the six-well plates. Gentamicin solution was used as a positive standard. The plates were incubated at 37°C in a shaking incubator at a speed of 150 rpm for 24 h. A 150 μL volume of Alamarblue[®] solution was added to each well. The plates were further incubated for 4 h in a shaking incubator at 37°C. Absorbance reading was taken at 560 nm excitation wavelength and 590 nm emission wavelength every 30 mins after 2 h of incubation. For the planktonic assay, assay plates were similarly prepared as in the AlamarBlue[®] assay. Six-well plates were emptied and washed twice with 1.5 mL of phosphate buffer saline after the incubation period. Absorbance readings for the plates were measured to determine the ability of the extracts to inhibit biofilm formation at a wavelength of 600 nm.

3 | RESULTS

3.1 | Polymeric characterization

3.1.1 | Polymeric film weight

Table 2 presents very small differences between overall weight for a given ratio as well as between different ratios. The range of average weights varied by only ~ 8 mg (<1%) and the highest SD for a given samples was 5.4 mg.

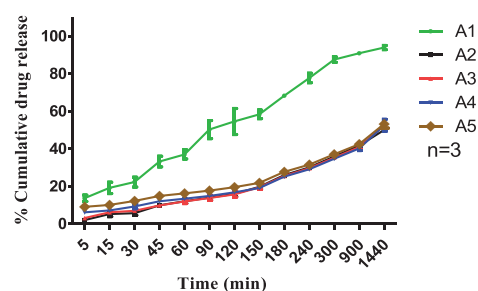
3.1.2 | Polymeric film thickness

Polymeric thickness differences were also very low and the difference between the thickest and thinnest sample averages was only 0.8 μm as given in Table 2.

TABLE 2 Weight and thickness of ofloxacin polymeric film, mean ± SD (n = 3).

| Formula code | Patch weight (mg) | Patch thickness (µm) | Content/cm ² (mg/cm ²) | % Moisture content |
|--------------|-------------------|----------------------|---|--------------------|
| A1 | 1096.7 ± 0.92 | 11.6 ± 01.0 | 1.23 ± 0.72 | 1.1 ± 0.92 |
| A2 | 1105.1 ± 2.7 | 11.1 ± 1.3 | 1.21 ± 0.19 | 0.53 ± 0.65 |
| A3 | 1097.2 ± 1.7 | 11.2 ± 0.53 | 1.16 ± 0.33 | 0.39 ± 0.72 |
| A4 | 1100.8 ± 1.1 | 11.1 ± 1.02 | 1.22 ± 0.41 | 0.93 ± 0.83 |
| A5 | 1097.5 ± 3.2 | 11.3 ± 1.07 | 1.23 ± 0.77 | 1.02 ± 0.41 |
| A6 | 1098.3 ± 1.1 | 11.8 ± 0.49 | 1.22 ± 0.23 | 0.42 ± 0.31 |
| A7 | 1096.3 ± 5.4 | 11.3 ± 0.45 | 1.21 ± 0.32 | 0.99 ± 1.01 |
| A8 | 1099.4 ± 1.2 | 11.3 ± 0.52 | 1.24 ± 0.22 | 0.61 ± 0.52 |
| A9 | 1101.6 ± 5.1 | 11.9 ± 1.1 | 1.27 ± 0.31 | 0.33 ± 0.95 |
| A10 | 1096.7 ± 4.1 | 11.3 ± 0.51 | 1.21 ± 0.79 | 0.79 ± 1.06 |

HPMC/Chitosan polymeric film release profiles



HPMC/Chitosan polymeric film release profiles B

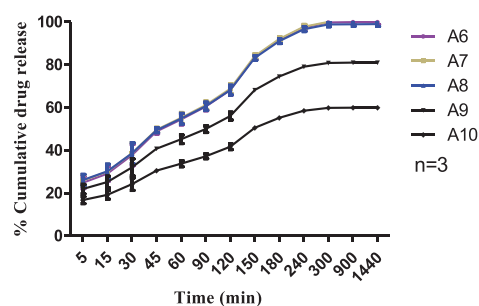


FIGURE 1 Drug release profiles for polymeric films with the loaded drug, HPMC, hydroxypropyl methylcellulose.

3.1.3 | Content uniformity

According to the content uniformity results presented in Table 2, all samples show similar drug contents with the highest difference between the averages of different ratios of 0.11 mg/cm. Thus, the highest deviation was from formula A3 with a difference of 0.099 mg/cm².

3.1.4 | Moisture content

The moisture content in each formula presented in Table 2 indicates a low difference in weight before and after desiccation. Thus, the drying process resulted in a dry film with very low water content.

3.2 | Drug release

According to the drug release profile presented in Figure 1, HPMC and chitosan-based films successfully released ofloxacin over many hours. Chitosan alone or high concentration chitosan film was found to have a burst release as 16.8% of the drug was released in the first

5 min only. HPMC alone film was better in drug release at the beginning but after 24 h more than 90% of the drug was released which indicates a failure in providing a sustained release profile.

3.3 | Drug diffusion

According to the drug diffusion shown in Figure 2, the drug diffusion process through Franz cells was controlled by drug release as both drug release and drug diffusion graphs are similar. Again, the formula with high content of HPMC except 100% of HPMC shows lowest drug diffusion rate, whereas the formulas with high chitosan ratio show highest drug diffusion.

3.4 | Drug matrix association

According to FTIR results presented in Figure 3, all major peaks produced by either biodegradable polymers or by ofloxacin are found in the drug polymer mixture. Thus, no interaction between drug and polymer has occurred, that is, the drug was successfully embedded without any chemical modifications.

FIGURE 2 Drug diffusion profiles for polymeric films with the loaded drug. HPMC, hydroxypropyl methylcellulose.

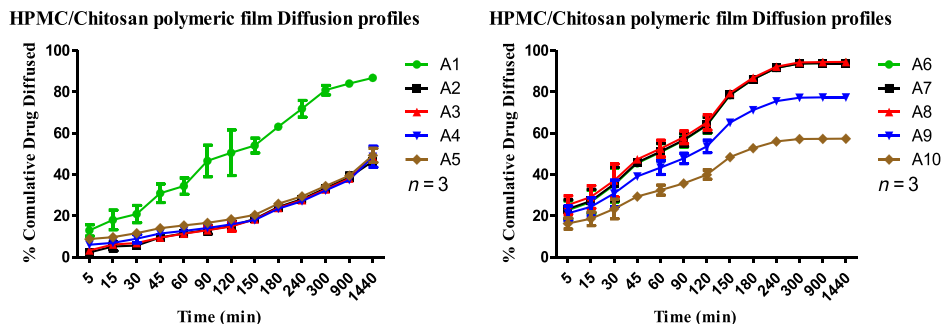
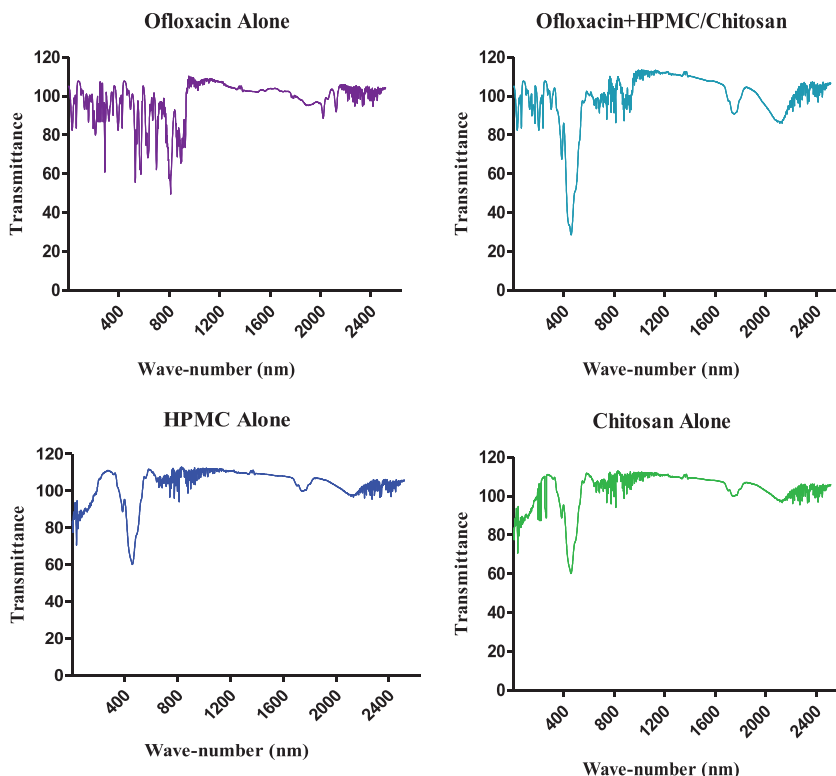


FIGURE 3 FTIR results of ofloxacin alone, hydroxypropyl methylcellulose (HPMC) alone, Chitosan alone, and HPMC/Chitosan loaded polymeric films.



3.5 | Antibiofilm-forming assay

All formulas with sustained release property were subjected to AlamarBlue® and Planktonic biological assay against both biofilm-forming *S. aureus* and *P. aeruginosa* to monitor the effect of drug release rate on drug activity. A2–A5 formulas were selected and show high biological activity even with the slow drug release with a bacterial viability of <15%. All polymeric films subjected to antibiofilm assay show strong biological activity by allowing < 10% of biofilm formation (Figure 4).

4 | DISCUSSION

Ofloxacin is a quinolone broad spectrum antibiotic that inhibits DNA gyrase in bacteria and can be given in different routes of administration like oral, IV, and topical

preparations.¹¹ The loading of ofloxacin in a polymeric film transdermal patches can decrease the major gastrointestinal problems of oral dosage form.¹⁶ In addition, HPMC and chitosan have been used before in different types of formulas through different routes of administrations with an ability to control drug release without any side effect.¹³ According to different characterization techniques, moisture content in all patches was <1.1% due to using methanol: water system for polymeric film preparation. This dryness could be related to the eutectic mixture of water/methanol system that can be more completely dried with a fume hood. Moreover, the films, especially those with high HPMC ratio, show high transparency. This transparency of the polymeric film has a great positive influence on patient compliance for a treatment.^{7,8} Finally, all transdermal polymeric films prepared from HPMC and chitosan mixtures have film thickness of <11.9 mm with a high similarity drug content uniformity

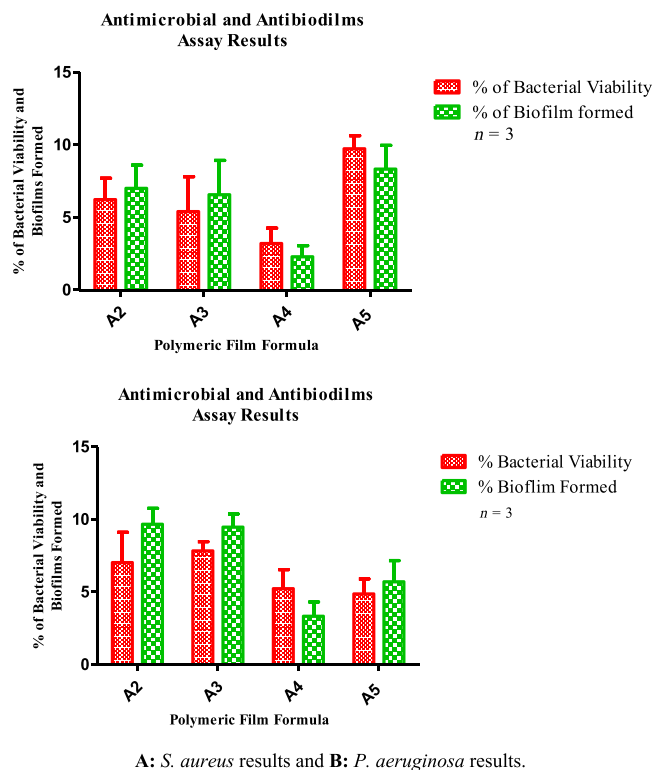


FIGURE 4 Antimicrobial and antibiofilm results. (A) *Staphylococcus aureus* results and (B) *Pseudomonas aeruginosa* results.

(1.16–1.27 mg/cm²) with low variability in thickness or uniformity. Thus, drug loading errors and patient compliance should not cause issues when scaling to a larger transdermal patch.¹⁷ Films with high HPMC ratio exerted more sustainable release property when compared with films with high chitosan ratio. Films with HPMC composition of more than 60% show <53% drug release in 24 h, while 50% and less show either more than 95% cumulative drug release or burst release. Previously, a similar chemical compound diclofenac sodium with similar physicochemical property was formulated in a transdermal patch composed of HPMC and was found to have a sustained release property.¹⁸ On the other hand, drug diffusion through Franz cells shows a high dependence on the rate of drug release from the polymeric matrix. This result shows that amount of the drug reaching systemic circulation will depend on the patch, not the patient's skin.¹⁹ One possible reason for diffusion enhancement is the use of palmitic acid in film formulation. Previously, palmitic acid was used in transdermal formula of vancomycin to improve large-molecule permeation through the skin.^{20,21} All films with sustainable release property were subjected to AlmarBlue[®] and planktonic assay solution to monitor the antimicrobial activity of release ofloxacin. All

prepared films show a strong antimicrobial and anti-biofilm activity against biofilm-forming *S. aureus* and *P. aeruginosa* after incubation at 37°C for 24 h. Both bacterial viability and biofilm formed were <10% when compared with the control. Thus, like many drugs, ofloxacin activity was not affected with the slow release of the film and drug fluctuation in the systemic circulation will be reduced.⁹

5 | CONCLUSION

Ofloxacin can be prepared in a transdermal patch with natural biodegradable polymers of HPMC and chitosan to slow drug release. The formulated ofloxacin show a good release and diffusion property that helps for extended release behavior of it. In addition, ofloxacin in vitro biological activity has not been affected after formulating the drug in a polymeric film. Further investigation is needed to see in vivo behavior of the drug on animal model to see the feasibility of this formula and check the effect of palmitic acid on a real skin.

ACKNOWLEDGMENTS

The author is grateful to MS pharmaceutical company for its generous corporations in providing instruments and materials for this project.

CONFLICT OF INTEREST STATEMENT

This research has no conflict of interest.

DATA AVAILABILITY STATEMENT

Data are available upon request.

REFERENCES

- Hu J, Quan Y, Lai Y, et al. A smart aminoglycoside hydrogel with tunable gel degradation, on-demand drug release, and high antibacterial activity. *J Control Release*. 2017;247:145-152.
- Hoffman LR, D'Argenio DA, MacCoss MJ, Zhang Z, Jones RA, Miller SI. Aminoglycoside antibiotics induce bacterial biofilm formation. *Nature*. 2005;436(7054):1171-1175.
- Traba C, Liang JF. Bacteria responsive antibacterial surfaces for indwelling device infections. *J Control Release*. 2015;198:18-25.
- Ko S-J, Jung JS, Gwak GH, Kim HJ, Salles F, Oh JM. Sustained antibacterial effect of levofloxacin drug IN a polymer matrix by hybridization with a layered double hydroxide. *Clays Clay Miner*. 2021;69(4):443-452.
- Ragel CV, Vallet-Regí M. In vitro bioactivity and gentamicin release from glass-polymer-antibiotic composites. *J Biomed Mater Res*. 2000;51(3):424-429.
- Hong Y, Xi Y, Zhang J, et al. Polymersome-hydrogel composites with combined quick and long-term antibacterial activities. *J Mater Chem B*. 2018;6(39):6311-6321.

7. Kathe K, Kathpalia H. Film forming systems for topical and transdermal drug delivery. *Asian J Pharm Sci.* 2017;12(6):487-497.
8. Agarwal N, Sarthi P. The necessity of psychological interventions to improve compliance with tuberculosis treatment and reduce psychological distress. *J Family Med Prim Care.* 2020;9(8):4174-4180.
9. Saleem MN, Idris M. Formulation design and development of a Unani transdermal patch for antiemetic therapy and its pharmaceutical evaluation. *Scientifica.* 2016;2016:7602347.
10. Vickers NJ. Animal communication: when I'm calling you, will you answer too? *Curr Biol.* 2017;27(14):R713-R715.
11. Deng Y, Debognies A, Zhang Q, et al. Effects of ofloxacin on the structure and function of freshwater microbial communities. *Aquat Toxicol.* 2022;244:106084.
12. Sharma K. Skin permeation of candesartan Cilexetil from transdermal patch containing aloe Vera gel as penetration enhancer. *Asian J Pharm.* 2016;10(2).
13. Sabbagh F, Kim BS. Recent advances in polymeric transdermal drug delivery systems. *J Control Release.* 2022;341:132-146.
14. Siepmann J, Peppas NA. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). *Adv Drug Deliv Rev.* 2012;64:163-174.
15. Rashki S, Asgarpour K, Tarrahimofrad H, et al. Chitosan-based nanoparticles against bacterial infections. *Carbohydr Polym.* 2021;251:117108.
16. Bloomfield D, Kost JT, Ghosh K, et al. The effect of Moxifloxacin on QTc and implications for the Design of Thorough QT studies. *Clini Pharmacol Ther.* 2008;84(4):475-480.
17. Jain G, Patel R. A comprehensive review on transdermal drug delivery. *Int J Pharm Life Sci.* 2019;10(11/12):6421-6428.
18. Abdullah HM, Farooq M, Adnan S, et al. Development and evaluation of reservoir transdermal polymeric patches for controlled delivery of diclofenac sodium. *Polym Bull.* 2022;80:6793-6818.
19. Li Y, Yang J, Zheng Y, et al. Iontophoresis-driven porous microneedle array patch for active transdermal drug delivery. *Acta Biomater.* 2021;121:349-358.
20. Datta D, Panchal DS, Venuganti VVK. Transdermal delivery of vancomycin hydrochloride: influence of chemical and physical permeation enhancers. *Int J Pharm.* 2021;602:120663.
21. Sangboonruang S, Semakul N, Obeid MA, et al. Potentiality of melittin-loaded niosomal vesicles against vancomycin-intermediate staphylococcus aureus and staphylococcal skin infection. *Int J nanomedicine.* 2021;7639-7661.

How to cite this article: Jaber SA, Saadh M, Obeid MA. The effect of polymeric films of hydroxypropyl methylcellulose (HPMC)/chitosan on ofloxacin release, diffusion, and biological activity. *Polym Eng Sci.* 2023;1-7. doi:[10.1002/pen.26411](https://doi.org/10.1002/pen.26411)