

# Preparation of the Dermal Mucoadhesive Film Containing Mupirocin

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ISSN: 2578-0190



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Submission: 📅 November 30, 2019

Published: 📅 July 15, 2020

Volume 4 - Issue 1

**How to cite this article:** Mohammad Ali Darbandi, Mohadese Abbasi Mud, Majid Zand Karimi, Leily Mir. Bacteriological Examination of Cooked Meat and Chicken Meals. *Cohesive J Microbiol Infect Dis.* 4(1). CJMI. 000576. 2020.  
DOI: [10.31031/CJMI.2020.04.000576](https://doi.org/10.31031/CJMI.2020.04.000576)

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## Abstract

Direct drug delivery of the antibiotics to the site of infection has many advantages such as reducing the adverse effect and achieving the minimum inhibitory concentration in the infected tissue. The goal of the study is to formulate the skin patch containing mupirocin as the antibiotic for the local drug delivery to the skin lesions such as burning ulcers on the surface of the skin. The different skin patches with the different polymers as the film former were applied for formulating the patches containing 2% mupirocin as the antibiotics. The patches were fabricated by the different ratio of chitosan, hydroxyl propyl methyl cellulose (HPMC) and polyethylene glycol (PEG) as the film former. The important characteristics of each film such as antibacterial activity, mucoadhesive properties and the release rate of mupirocin from the patches were measured by the in vitro tests. The suitable formulations were selected for the animal test. The results of the in vitro tests showed that the type of the polymer which were applied for the fabrication of the films and the chitosan to HPMC ratio in the structure of the films are the important effective factor on the characteristics of the films such as antibacterial activity and mucoadhesive properties of the patches. Increasing the percentage of the HPMC and chitosan in the structure of the patches caused to increase the mucoadhesive properties of the films. The antibacterial activity for the patches which were fabricated by HPMC as the film former was more than the others. More than 50% of drug was released from the films during 2 hours in all the formulations. Application of chitosan in the structure of the films caused to decrease the release rate of mupirocin from the films. The results of the in vivo tests showed that the most suitable efficacy belonged to the slow release formulations [1-5].

**Keywords:** Dermal mucoadhesive; Drug delivery systems; Chitosan film; HPMC film-dermal; Ulcers; Mupirocin

## Introduction

Direct delivery of drugs to their site of effect is the considerable process in the recent. The local drug delivery of the antibiotics to the site of infection has many advantages such as decreasing the systemic side effects and increasing the probability of reaching the minimum inhibitory concentration (MIC) of the antibiotics. For local drug delivery of the drugs to the skin the drug should be dissolved or suspended in the semisolid bases such as Vaseline, eucerine and creams. There are several formulations from different antibiotics such as tetracycline, metronidazole, clindamycin and Mupirocin which apply locally for the treatment of the skin injuries. One of the extremely important disadvantages of the application of these semisolids' dosage forms is to decrease the contact time between the skin surface and the antibiotics. The different factors such as washing from the surface of the skin may lead to decrease the contact time between the skin surface and the antibiotics. An application of the patches on the surface of the skin with the purpose of drug delivery is one of the solving methods for this problem. The patches can stick to the surface of the skin and perform the drug delivery process for the longer period. It is prevalent to use from the bio adhesive polymers as the film former in the formulation of the patches. There are several and synthetic bio adhesive polymers that play the role of the film formers in the formulations of the skin patches. Some of the bio adhesive polymers that were applied in the formulation of the patches include cellulose derivatives, poly acrylic acid derivatives, chitosan, and gums. Among these different polymer's chitosan and HPMC have the suitable bio adhesive properties for fabrication of the skin patches. The advantages of chitosan such as safety, non-allergenic properties, biodegradation, biocompatibility and antibacterial characteristics make it a macromolecular polymer with

different application in the pharmaceutical formulations. The several different polymers have been applied in the formulation of the local drug delivery systems. These polymers classified in the biodegradable and non-biodegradable groups of polymers. Among this wide range of polymers, the biodegradable natural polymers have more application in the formulations because of their advantages such as low toxicity, abundant source and tissue compatibility and inability to affect periodontal tissue regeneration. Chitosan is one of these biodegradable natural polymers which are used in the pharmaceutical formulation as the excipient. The advantages of chitosan such as safety, non-allergenic properties, and biodegradation, biocompatibility and antibacterial characteristics make it a macromolecular polymer with different application in the pharmaceutical formulations. Another mucoadhesive material is hydroxyl propyl methyl cellulose (HPMC). It is derivative of cellulose. There are several studies that report the mucoadhesive properties of HPMC. In this study the different films containing Mupirocin were fabricated by HPMC, chitosan and polyethylene glycol (PEG) as the film former. The effect of the type of polymer, the ratio of the HPMC to PEG and the ratio of the chitosan to PEG in the structure of the films on the several characteristics of the patches such as mucoadhesive properties, antibacterial activity and the release pattern of Mupirocin from the films were evaluated [5-8].

## Materials and Methods

### Material

Chitosan medium molecular weight (MMW 490-310K Da), sodium di hydrogen phosphate and disodium hydrogen phosphate ( $\text{NaH}_2\text{PO}_4$ - $\text{Na}_2\text{HPO}_4$ ) and Hydroxy propyl methyl cellulose (HPMC) and Mupirocin and polyethylene glycol (PEG) from Sigma Aldrich Chemicals (Poole, UK). All solvents used throughout the study were supplied by Merck (Germany) and were at least analytical grade.

### Methods

**Preparation of the film:** After preparing the 2%w/w polymeric solution containing the different ratio of the PEG and Chitosan and the different ratio of PEG and HPMC in the 2%V/V acetic acid as the solvent, the solvent was evaporated and the drug loaded films were fabricated. The formulation of each drug loaded film.

**Release of drugs from the film:** One  $\text{cm}^2$  of drug loaded films were dispersed in 5ml of the Phosphate buffer solution ( $\text{NaH}_2\text{PO}_4$ - $\text{Na}_2\text{HPO}_4$ ) at pH 5.8. The buffer solutions were replaced with fresh after each sampling time and the Mupirocin concentrations in the dispersing medium was measured spectrophotometric method.

**Method of analysis:** The spectrophotometric analysis method was applied for determination of mupirocin. the UV spectrophotometer ( $\lambda=219\text{nm}$ ) was used in analysis method. After measurement of the absorbance of each standard methanol solution the calibration curve was used for measuring the percentage of drug released from the films in each sampling time.

**Assessment of the mucoadhesive strength of the films:** To evaluate the mucoadhesive strength of the films. This apparatus was principally like those described in previous studies. The upper

stationary platform was linked to a balance, measuring the force needed to break contact between the film and mucosa. The test cell was filled with pH=6.8 isotonic phosphate buffer, maintained at 37 °C, and sections of rat intestine placed and fixed in place over the two cylindrical platforms and allowed to equilibrate in this solution for 2min. 0.5g of the gels prepared were then individually sandwiched between the two mucosa-covered platforms. Films were kept in place for 1min and then a constantly increasing force of 0.1g/sec was applied on the adhesive joint formed between rat intestine and the test film, by gradually lowering the lower platform. This trend was continued until the contact between the test films and mucosa was broken and the maximum detachment force measured was recorded.

**Evaluation of the antibacterial activity of the films:** The antibacterial activity of the films was evaluated by measuring the growth inhibition zone related to each formulation in the solid microbial culture medium contain Muller Hilton agar. For preparing the solid microbial culture medium 100 $\mu\text{l}$  of microbial suspension contain  $1 \times 10^8$  CFU/ml staphylococcus aureus were distributed in the surface of the sterile Muller Hilton agar solid culture medium [9-14].

## Results and Discussion

All the fabricated films were transparent and smooth. Increasing in the percentage of HPMC caused to increase the flexibility of the films. The antibacterial activity for each formulation. The summarized information that the maximum antibacterial activity belonged to F10 and F11. According to applications of HPMC as the film former caused to increase the growth inhibition zone and antibacterial activity of the patches. The antibacterial activity of chitosan films was less than the others. It may attribute to the water solubility of the chitosan in the culture medium and the release rate of drug from the films. The solubility of chitosan in water is the pH dependent phenomenon. The solubility of chitosan in water will be increased by decreasing the pH value to less than 2. Because in these acidic pH values the Amine groups on the molecular structure of chitosan will be protonated. In natural and basic pH values the Amine groups on the molecular structure of chitosan will be deprotonated and the water solubility of the chitosan will be reduced. Reducing the solubility of chitosan in these environmental conditions caused to decrease in the release rate of drug from the polymeric matrix. The release pattern of drug from the polymeric films. Application of chitosan in the structure of the patches as the film former caused to decrease in the release rate of drug from the polymeric films. Reducing the release rate of drug from the polymeric matrix caused to decrease in the diameter of the growth inhibition zone. All the films showed the initial burst release effect during the first 2 hours. The difference between the antibacterial activities for F1 and F11 was significant ( $p < 0.05$ ). The concentration of Mupirocin in F1 and F11 was similar but the antibacterial activity of F1 and F2 was different. These results showed that the characteristics of the films are more effective factor than the concentration of antibiotics on the antibacterial activity of the films. These results agreed with the results of the similar previous study performed by Ikinci

in 2002. İkinci showed that the antibacterial activity of the films could not be affected by increasing the concentration of Chlorhexidine digluconate in the films from 1% to 2%. Application of chitosan as the film former caused to decrease in the Mupirocin release rate from the films. In these conditions it will be supposed that the polymer act as the barrier. This barrier prevents from releasing of drug from the film. According to Fig3 mupirocin was released from chitosan formulations slowly. For this reason, these formulations can show the antibacterial effect for the longer period in the in vivo conditions. Increasing the percentage of PEG in the structure of the chitosan patches caused to increase the release rate of mupirocin from the films. The mean mucoadhesive force for each formulation was measured. According to the mucoadhesive properties of the films were increased by increasing the percentage of HPMC and chitosan as the mucoadhesive polymers. These observations were reported in several researches. The percentage of hydration of the films is the main effective factor on their mucoadhesive properties. The results of the previous researches were shown that the mucoadhesive property for anhydrate and super hydrated films is not suitable (Mortazavi S.A). These results are like the results of the mucoadhesive properties of the chitosan films in our study. According to the mucoadhesive property for F2, F7 and F8 was more than the others. Among these different formulations with the suitable mucoadhesive property F2 had the suitable sustained release pattern for mupirocin. Among the chitosan films the maximum mucoadhesive characteristic related to the Chitosan: PEG ratio of 65.3: 32.7. It is possible that the presence of 32.7% of PEG in the polymeric matrix of the film facilitated the hydration of the film.

## Conclusion

The results of the study showed that it is possible to fabricate the mucoadhesive skin patches containing Mupirocin by application of HPMC and chitosan as the film former. The type of the polymer as the film former has the significant effect on the physical characteristics of the films such as the mucoadhesive properties, antibacterial activity, and release rate of drug from the films.

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