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ORIGINAL ARTICLE

Evaluation of the Mechanical Properties and Drug Permeability of Chitosan/Eudragit RL Composite Film

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Abstract
Objectives: The aim of this study was to design and evaluate a chitosan-based film that has properties required for successful wound dressing, and can control drug penetration and maintenance time in the location.
Methods: Several formulations of a film containing chitosan (3%) and different concentrations of Eudragit RL (0.5%, 1%, and 1.5%) were prepared using the casting/solvent evaporating technique. Mechanical properties, water vapor transmission rate (WVTR), oxygen permeability, water uptake, and nitrofurazone permeability through the films were investigated.
Results: The study results showed that by increasing the Eudragit RL content of composite films, their thickness and tensile strength were enhanced, while their elongation was decreased. No significant difference was observed between the oxygen permeability, WVTR, and water uptake results of pure chitosan films and different composite films containing Eudragit RL. Nitrofurazone permeability of chitosan films was increased by the inclusion of Eudragit RL in composite films, while by increasing the concentration of Eudragit RL, the permeation rate of drug was decreased.
Conclusion: In conclusion, addition of Eudragit RL can improve mechanical properties of chitosan films without any undesirable effect on their water uptake, oxygen permeability, and WVTR qualities. The permeation rate of drugs through the composite films can be modified by changing Eudragit RL/chitosan ratio.

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1. Introduction

Severe skin wounds such as burn injury recover through several disease stages, including infectious, necrosis (and agglutination), proliferation, and epidermis formation periods. In the infectious period, the healing process is delayed. Wound dressings are often used to protect wounds from infection and repair them. Rapid healing of wounds is desirable for patients, especially for people suffering from diabetes because they show an extremely slow rate of healing [1−3]. Several dressings are currently used in the treatment of burns, split graft donor sites, and chronic ulcers [4]. Unlike conventional wound dressing, which passively provides wound protection, nowadays new types of wound dressings are used that not only protect the wound from surrounding environments, but also effectively promote the healing process by providing an optimum microenvironment for healing, removing excess of wound exudates, and allowing continuous tissue reconstruction processes [2]. Application of an antibiotic can be effective for suppression of bacteria, but many drugs such as nitrofurazone have high skin permeability that decreases their efficacy and maintenance time in the location. A proper wound dressing can control drug penetration. Currently, natural polymers have become more popular due to their nontoxicity, degradability, biological compatibility, and low cost. Chitosan is one of the most abundant polysaccharides found in skeletal materials of crustacean cuticles of insects, crabs, shrimps, and cell walls of various fungi. It is a cationic biopolymer that is obtained by N-deacetylation of chitin [1,5,6]. Chitosan has received great attention for wound management due to its beneficial intrinsic properties such as hemostasis, wound healing, bacteriostatic properties, exudate absorption, and film-forming ability [7,8]. However, pure chitosan films are brittle and have poor mechanical strength. Hence, addition of other polymers is necessary to obtain films with improved strength and elasticity [2]. Polymers such as polyethylene oxide [9,10], Eudragit [11], and polylactic acid [12] are used for this purpose. Eudragit RL is a water-insoluble derivative of acrylate polymers with widespread use in pharmaceutical dosage forms [11]. Eudragit RS and Eudragit RL are neutral copolymers of poly(ethylacrylate, methyl methacrylate, and trimethylammonioethylmethacrylate chloride). These polymers are pH independent and capable of swelling. The RL type of polymer is more permeable to water than the RS type due to its higher quaternary ammonium concentration (RS: 1/40 ammonium/ester; RL: 1/20 ammonium/ester) [13].

The aim of the current study was to design a wound dressing containing chitosan and Eudragit RL for controlling the permeation of nitrofurazone cream (Ubichem, Hampshire, England) (as a highly permeable drug model) through it.

2. Materials and methods

Chitosan, with a deacetylation degree of 97% and viscosity grade of <25 cp, was purchased from Primex (Siglufjordur, Iceland), Iceland. Eudragit RL 30D and propylene glycol were obtained from Rohm Pharma (Darmstadt, Germany) and Merck (Haar, Germany), respectively. Nitrofurazone was kindly donated by Najo Co., Tehran, Iran. All other materials used in this study were of analytical reagent grade.

2.1. Film preparation

Films were prepared by casting and solvent evaporation. Chitosan solutions (3%) were prepared by dissolving chitosan in 1.8% acetic acid. Eudragit RL 30D was diluted using distilled water in order to prepare 0.5%, 1.0%, and 1.5% w/v dispersions, which were added to the chitosan solutions at a ratio of 1:4 (v/v). In addition, propylene glycol was added to the mixture as a plasticizer and agitated for 15 minutes at room temperature. The mixture was left to stand until air bubbles disappeared. The resultant mixture was poured onto a dry glass Petri dish and allowed to dry at 40°C for 24 hours. The prepared films were stored in airtight desiccators containing saturated magnesium nitrate solution (50% relative humidity) for further studies. Compositions of different formulations of films are shown in Table 1.

2.2. Mechanical properties

The thickness of the films was measured at five different places by using a micrometer. The mechanical properties of the films were evaluated using a texture analyzer (WDW-5; Berder, China) with a 5 kg load cell. Film specimens (2×5 cm^2) were positioned between two mounting clamps. The films were pulled by the top clamp at a rate of 10 mm/minute. The tensile strength and elongation at break were calculated using the following equations [14]:

$$\text{Tensile strength}\left(\text{N}/\text{mm}^2\right) = \text{break force}(\text{N})/\text{cross} - \text{sectional area of sample}\left(\text{mm}^2\right) \quad (1)$$

$$\text{Elongation at break}(\%) = [\text{increase in length at breaking point}(\text{mm})/\text{initial length})\text{mm})] \times 100 \quad (2)$$

Table 1. Compositions of different formulation of films (v/v ratio).

Formula	Chitosan (3%)	Eudragit RL	Propylene glycol
Cs	4	0	0.1
Cs Eu 0.5	4	1 (0.5%)	0.1
Cs Eu 1	4	1 (1%)	0.1
Cs Eu 1.5	4	1 (1.5%)	0.1

2.3. Oxygen permeability

The test of oxygen permeability through films was carried out by placing the films on top of open 250 mL flasks (test area: 1.075×10^{-3} m^2) containing deionized water. The test flasks were placed under constant agitation for 24 hours. The negative control was the closed flask with an airtight cap (preventing oxygen from entering the flask), while the positive control was the open flask (allowing oxygen to enter the flask). The dissolved oxygen was analyzed according to the Winkler's method. Oxygen permeability (g/m^2.day) was defined as the amount of oxygen penetration through the film during 24 hours [15].

2.4. Water uptake (swelling)

First, pieces of the films (2×2 cm^2) were dried in an oven at 60°C and weighed accurately. Then, they were immersed in 50 mL buffer phosphate (pH 7.4) at 37°C for 48 hours. The swollen samples were withdrawn from the medium and weighed after the removal of excess surface water by a filter paper. The swelling behavior of the films was assessed as follows:

$$\text{Water uptake}(\%) = [(W_s - W_i)/W_i] \times 100 \quad (3)$$

where W_s and W_i are the swollen film and the initial dry film weights, respectively.

2.5. Water vapor transmission rate

The films were cut and placed in sealed test tubes containing 5 g $CaCl_2$, and were placed in an oven at 60°C. The tubes were stored in a desiccator containing 500 mL saturated solution of NaCl (75% relative humidity). After 0 day, 1 day, 2 days, 3 days, 4 days, and 5 days, weights of tubes were determined. Then graphs of increase in weight with respect to time were plotted, and water vapor transmission rate (WVTR) (g/m^2.day) was calculated using the following equation:

$$\text{WVTR} = \text{slope}/\text{film area} \quad (4)$$

2.6. Nitrofurazone permeability

Permeability of the model drug across the films was determined using a diffusion cell. The film was mounted in a Franz-type diffusion cell. Nitrofurazone cream (0.2%; 1.2 g) was applied on the film. An aliquot of 3 mL of the sample was withdrawn from the receptor compartment (phosphate buffer, pH 7.4) at a predetermined time and replaced by the same volume of fresh phosphate buffer to keep the volume constant. The concentration of released drug was assayed using a UV spectrophotometer (Biowave II; Biochrom, Cambridge, England) at 377 nm. The rate of drug permeation via skin can be determined using the Fick's first law [equations (5)−(7)]. According to this law, the amount of drug (M) flowing through a unit cross-sectional area (S) of a barrier and appearing in the receptor solution in time t is known as the steady-state flux, J:

$$dM/Sdt = J = C_0KD/h \quad (5)$$

$$P = KD/h \quad (6)$$

$$J = C_0P \quad (7)$$

where D is the diffusion coefficient of the drug in the barrier, h denotes the diffusional path length or the film thickness, K is the partition coefficient of drug between the film and the receptor medium, C_0 stands for the applied drug concentration that was assumed to be constant during the experiment, and P is the permeability coefficient of the drug through the film.

The flux, J, was determined from the slope of the steady-state portion of the amount of drug permeated divided by S versus time. Lag time values were determined from the x-intercept of the linear region at steady state.

2.7. Statistical analysis

All data were expressed as mean ± standard deviation. Statistical analysis of data was performed using one-way analysis of variance. Statistical significance was associated with a probability of $p < 0.05$. All experiments were carried out in triplicate.

3. Results

A suitable film for wound dressing should be strong and to some extent flexible [5]. The thickness, tensile strength, and elongation at break of the films are shown in Table 2. These results indicated that the tensile strength of the chitosan films decreased with inclusion of Eudragit RL ($p < 0.05$). However, by increasing the Eudragit RL content of composite films, the thickness and tensile strength of the films were enhanced, but their elongation was decreased. The films with Eudragit RL 1.5% showed the highest strength and the lowest elongation properties compared with the other films ($p < 0.05$). It is known that there is an inverse relationship between tensile strength and elongation of biopolymer films [5]. Our results are similar to the

Table 2. Mechanical properties of Cs films (mean ± SD, $n = 3$).

Formula	Thickness (μm)	Tensile strength (MPa)	Elongation (%)
Cs	94 ± 11.40	25 ± 4.25	20.873 ± 0.69
Cs Eu 0.5	104 ± 11.40	10.73 ± 1.54	12.18 ± 0.99
Cs Eu 1	130 ± 15.81	14.36 ± 0.80	9.634 ± 0.19
Cs Eu 1.5	156 ± 8.94	17.31 ± 2.56	7.93 ± 0.40

SD = standard deviation.

findings of Wittaya-areekul et al [15]. They evaluated chitosan−Eudragit RS 30D as wound dressings. According to their results, elongation was reduced by enhancing the concentration of Eudragit RS 30D (0.5%, 1%, and 1.5%).Our findings imply that increasing the density of the films by increasing the total solid content reduced their flexibility. High elasticity of chitosan films makes their handling and application as wound dressings difficult. However, elongation at break reduces with the addition of Eudragit RL. Mechanical properties of the composite films with lower elongation at break and reasonable tensile strength values suggest that they have high potential to be used in medical applications.

Oxygen penetration all of formulation was significantly different with positive and negative controls ($p < 0.05$) (Figure 1). It can be concluded that oxygen was able to penetrate through all the film formulations. It is believed that the presence of propylene glycol in these films helps in the movement of polymer chains, to allow the passage of oxygen molecules [16−18]. Oxygen penetration did not differ significantly among the composite films. These results are similar to the findings of Wittaya-areekul et al [15]. According to their results, oxygen penetration into the films with various Eudragit RS contents was somewhat similar.

Water uptake values and the WVTRs in different formulations are summarized in Table 3. The water uptake values indicated that all films had water retention capability, and no significant difference was observed between chitosan films and the films containing different concentrations of Eudragit RL. Our finding is contrary to the results of Wittaya-areekul et al [15], which showed the chitosan films had the highest water uptake values,

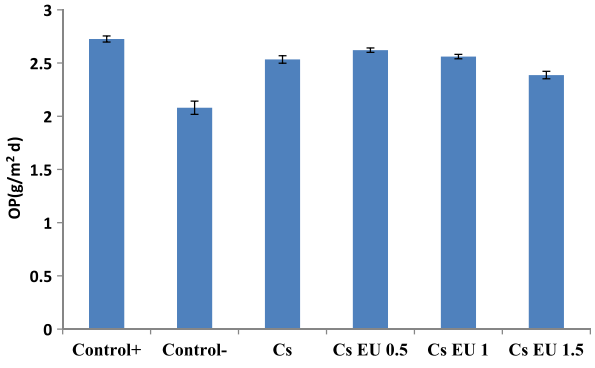

Figure 1. OP through different formulations (mean ± SD, $n = 3$). OP = oxygen permeability; SD = standard deviation.

Table 3. Value of water uptake and WVTR in different formulations.

Formula	Water uptake 48 h (%)	WVTR (g/m^2 d)
Cs	108.18 ± 1.61	205.63 ± 9.90
Cs Eu 0.5	112.74 ± 0.90	201.30 ± 0.00
Cs Eu 1	111.56 ± 2.77	205.63 ± 9.92
Cs Eu 1.5	116.70 ± 2.39	214.29 ± 6.5

WVTR = water vapor transmission rate.

while the presence of Eudragit RS reduced their swelling ability, although no significant difference was observed between the films containing various concentrations of Eudragit RS (0.5%, 1%, and 1.5%). Eudragit RL and Eudragit RS are acrylic and methacrylic acid esters with some hydrophilic properties due to the presence of quaternary ammonium groups. Eudragit RL contains a higher amount of such groups, and hence its water permeability is higher than that of Eudragit RS [19]. Owing to this property, the presence of Eudragit RL (in this concentration range) does not lead to lowering of water uptake by the composite films in comparison with the chitosan films. However, the ability of a film to preserve water is one of the most important aspects in skin tissue engineering, especially for wound healing [20]. Water-uptake capacity of a wound dressing should be considerably high for rapid absorption of exudates [21].

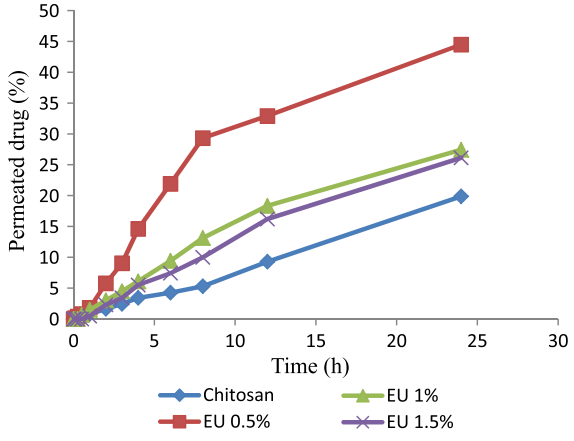

Figure 2. Profile of nitrofurazone permeability of different formulations.

Table 4. Values of flux (J), permeability coefficient (P), and drug release for each formulation after 24 hours (R_{24}).

Formula	J (mg/cm^2 h)	P (cm/h)	R_{24} (%)
Cs	0.004 ± 0.0004	0.0019 ± 0.0002	19.874 ± 3.125
Cs Eu 0.5	0.022 ± 0.0001	0.0112 ± 0.000	44.478 ± 0.333
Cs Eu 1	0.009 ± 0.0001	0.0044 ± 0.000	27.435 ± 0.331
Cs Eu 1.5	0.008 ± 0.0001	0.0038 ± 0.000	26.125 ± 0.159

4. Discussion

It was reported that permeability of moisture through the film is important for wound dressing, to keep the wound moist and comfortable, to help in the healing process [5]. An ideal dressing must be permeable to the extent that moist exudates under the dressing are maintained, to inhibit excess fluid absorption and evaporation leading to desiccation of the wound bed [14]. The rate of water vapor transmission through all films was partly high. Chitosan has good hydrophilic characteristics. It is well known that the hydrophilic nature of a polymer membrane induces water vapor tendency and increases the WVTR [22]. The results demonstrated that the WVTR was not affected by different concentrations of Eudragit RL or by different thicknesses of films ($p > 0.05$). As mentioned in the section on mechanical strength, the presence of Eudragit RL in the chitosan films led to decreases of integrity and strength of intermolecular forces in the primary structure of chitosan. This phenomenon can facilitate permeation of water. Besides, it is expected that an increase in the film thickness decreases the WVTR due to an increase in the total solid content. It seems that simultaneous occurrence of these two phenomena led to the same WVTR values in the presence of different concentrations of Eudragit RL 100.

The profile of nitrofurazone permeability of different formulations is shown in Figure 2, and the values of flux (J) and KP are presented in Table 4.

According to the results, permeability of chitosan films increased with the inclusion of Eudragit RL in composite films ($p < 0.05$). Eudragit RL causes the network of cross-linked chitosan to discontinue and reduces the integrity of the films, facilitating the diffusion of nitrofurazone through the films. Of course by an increase in the concentration of Eudragit RL, the permeation rate of drug through the films is decreased ($p < 0.05$). This decrease might be a result of the enhancement of the total solid content and thickness of composite films with the higher ratios of Eu:Cs. In this study, chitosan films with the lowest content of Eudragit RL (0.5%) exhibited the highest and most acceptable level of drug release (44.478%) after 24 hours.

This study revealed that Eudragit RL can be incorporated into a chitosan film to improve its mechanical properties, while substantially maintaining vapor penetration, water uptake, and oxygen penetration requirements to provide a good wound-healing environment. The films comprising 3% chitosan and 0.5% Eudragit RL showed the highest amount of drug release after 24 hours, exhibiting potential to be used as wound dressings.

Conflicts of interest

The authors declare no conflicts of interest.

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References

1. Queiroz AAA, Ferraz HG, Abraham GA, et al. Development of new hydroactive dressings based on chitosan membranes: characterization and *in vivo* behavior. Hoboken: Wiley Periodicals, Inc; 2003 Jan;64(1):147–54.
2. Wittaya-areekul S, Prahsarn C. Development and *in vitro* evaluation of chitosan–polysaccharides composite wound dressings. Int J Pharm 2006 Apr;313(1-2):123–8.
3. Rodrigues LB, Leite HF, Yoshida MI, et al. *In vitro* release and characterization of chitosan film as dexamethasone carrier. Int J Pharm 2009 Feb;368(1-2):1–6.
4. Kim JO, Park JK, Kim JH, et al. Development of polyvinyl alcohol–sodium alginate gel-matrix-based wound dressing system containing nitrofurazone. Int J Pharm 2008 Jul;359(1-2):79–86.
5. Sasikala L, Durai B, Rathinamoorthy R. Manuka honey loaded chitosan hydrogel films for wound dressing applications. Int J Pharm Tech Res 2013;5(4):1774–85.
6. Krkic N, Lazic V, Petrovic L, et al. Properties of chitosan-laminated collagen film. Food Technol Biotechnol 2012 Nov; 50(4):483–9.
7. Alsarra IA. Chitosan topical gel formulation in the management of burn wounds. Int J Biol Macromol 2009 Jul;45(1):16–21.
8. Wang Q, Dong Z, Du Y, et al. Controlled release of ciprofloxacin hydrochloride from chitosan/polyethylene glycol blend films. Carbohydr Polym 2007 Jun;69(2):336–43.
9. Zivanovic S, Li J, Davidson PM, et al. Physical, mechanical and antibacterial properties of chitosan PEO blend films. Biomacromolecules 2007 May;8(5):1505–10.
10. Djokic JD, Kojovic A, Stojanovic D, et al. Processing and nanomechanical properties of chitosan/poly(ethylene oxide) blend films. J Serb Chem Soc 2012;77(12):1723–33.

11. Sadeghi F, Shahabi M, Afrasiabi Garekani H. Comparison of physicomechanical properties of films prepared from organic solution and aqueous dispersion of Eudragit RL. Daru 2011;19(2):100−6.
12. Suyatma NE, Copinet A, Tighzert L, et al. Mechanical and barrier properties of biodegradable films made from chitosan and poly (lactic acid) blends. J Polym Environ 2004 Jan;12(1):1−2.
13. Filippis PD, Zingone G, Gibellini M, et al. Dissolution rates of different drugs from solid dispersions with Eudragit RS. Eur J Pharm Sci 1995 Oct;3(5):265−71.
14. Khan TA, Peh KK, Ch'ng HS. Mechanical, bioadhesive strength and biological evaluations of chitosan films for wound dressing. J Pharm Pharm Sci 2000 Sep−Dec;3(3):303−11.
15. Wittaya-areekul S, Prahsarn C, Sungthongjeen S. Development and *in vitro* evaluation of chitosan−Eudragit RS 30D composite wound dressings. AAPS PharmSci Tech 2006 Mar;7(1):E30.
16. Vásconez MB, Flores SK, Campos CA, et al. Antimicrobial activity and physical properties of chitosan−tapioca starch based edible films and coatings. Food Res Int 2009 Aug;42(7):762−9.
17. Gutiérrez-Rocca J, McGinity JW. Influence of water soluble and insoluble plasticizers on the physical and mechanical properties of acrylic resin copolymers. Int J Pharm 1994 Mar;103(3):293−301.
18. Lecomte F, Siepmann J, Walther M, et al. Polymer blends used for the aqueous coating of solid dosage forms: importance of the type of plasticizer. J Control Release 2004 Sep;99(1):1−13.
19. Omari DM, Sallam A, Abd-Elbary A, et al. Lactic acid induced modifications in films of Eudragit RL and RS aqueous dispersions. Int J Pharm 2004 Apr;274(1-2):85−96.
20. Li X, Kong X, Shi S, et al. Biodegradable MPEG-g-chitosan and methoxy poly(ethylene glycol)-b-poly(ε-caprolactone) composite films: Part 1. Preparation and characterization. Carbohydr Polym 2010 Jan;79(2):429−36.
21. Pandima Devi M, Sekar M, Chamundeswari M, et al. A novel wound dressing material—fibrin−chitosan−sodium alginate composite sheet. Bull Mater Sci 2012 Dec;35(7):1157−63.
22. Wei H, Li-Fang F, Bai X, et al. An investigation into the characteristic of kitosan/kollicoat SR30D film for colonic drug delivery. Eur J Pharm Biopharm 2009 May;72(1):266−74.