Development of mucoadhesive gelatin-based patches for aphthous ulcers

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Received: 18 April 2023; Revised: 28 June 2023; Accepted: 3 July 2023; Available online: 26 August 2023

Abstract

Mucoadhesive patches demonstrate considerable promise for the administration of therapeutics targeting oral mucosal diseases. This study employed the solvent casting technique to fabricate mucoadhesive patches and examine the influence of bloom strength variation, plasticizer concentration, gelatin concentration, and alpha-mangostin (α-MN) loading on patch properties. The mucoadhesive patches consisted of a 5% ethylcellulose backing layer, a mucoadhesive layer combining ethylcellulose and gelatin, and a gelatin layer loaded with α-MN. The investigation revealed that augmented gelatin bloom strength correlated with increased puncture strength and elongation at break, but diminished thickness. Owing to its superior characteristics, 300-bloom gelatin was chosen for further examination. The incorporation of glycerin as a plasticizer decreased puncture strength but enhanced elongation at break. An escalation in gelatin concentration from 1% to 7% resulted in amplified patch thickness and puncture strength, with 7% gelatin yielding the most pliable patches. Additionally, the *in vitro* residence time of the patches rose concomitantly with increasing gelatin concentrations, attributable to heightened interpenetration with mucin chains and the formation of mucoadhesive bonds. Successful α-MN loading into the patches was achieved, exhibiting an actual concentration range of 144.12 ± 27.10 μg to 441.05 ± 94.79 μg. In summary, this study successfully generated mucoadhesive patches exhibiting desirable properties for potential oral mucosal drug delivery applications. These findings serve as a foundation for subsequent optimization and development of mucoadhesive patches to address various oral mucosal diseases.

Keywords: mucoadhesive patches, gelatin, α-mangostin, plasticizer, *in vitro* residence time

Introduction

Aphthous ulcers, also known as canker sores, are a common oral mucosal disorder that affects approximately 20% of the population (Chiang et al., 2019). The ulcers can cause pain, discomfort, and difficulty in speaking, eating, and swallowing, which can have a significant impact on the patient's quality of life. While there are various topical treatments available for Aphthous ulcers, such as antimicrobial mouthwashes, corticosteroids, or anesthetics, they may have limitations in terms of efficacy, convenience, and patient compliance. Corticosteroids are commonly used to treat aphthous ulcers because they are effective anti-inflammatory agents. However, prolonged use of corticosteroids can lead to a range of negative side effects, including the development of candidiasis (a fungal infection) and other systemic effects (Belenguer-Guallar, Jiménez-Soriano, & Claramunt-Lozano, 2014). To address these limitations, there has been a growing interest in developing alternative dosage forms, such as mucoadhesive patches, for the treatment of aphthous ulcers. Mucoadhesive patches offer several advantages over traditional topical treatments, including targeted and sustained drug delivery, improved drug bioavailability, and patient convenience (Taokaew, Wattanaphraya, & Kriangkrai, 2020).

The objective of this research was to develop mucoadhesive patches based on gelatin as a potential new dosage form for the treatment of Aphthous ulcers. Gelatin is a biocompatible and biodegradable polymer that has been widely used in various drug delivery systems due to its excellent mucoadhesive properties and

biocompatibility. Alpha-mangostin (α-MN) was used as an active herbal ingredient because of its anti-inflammatory and antibacterial properties (Bafi-Yeboa, Arnason, Baker, & Smith, 2005; Chen, Yang, & Wang, 2008). Mohan, Syam, Abdelwahab, and Thangavel (2018) found that α-MN at doses of 8 and 14 μg/ml effectively inhibited cytokines nitric oxide, PGE2, TNF-α, IL-4, and COX-2. COX-2 activity was reduced by 31.5 ± 4.2% at 8 μg/ml and 74.04 ± 5.8% at 14 μg/ml. These results suggest the potential of α-MN as a therapeutic agent for cytokine regulation. To improve the patch formulation, we studied how various formulation variables, including the type of gelatin, quantity of gelatin, and plasticizer, impacted the mucoadhesive and mechanical characteristics of the patches.

Methods and Materials

Materials

The derived gelatin type A with a bloom strength of 90-110 and 300 (Sigma-Aldrich Company, Germany) were used as mucoadhesive layer, as well as gelatin with a bloom strength of 250 (Union Chemical 1986 Co., Ltd., Thailand). The backing layer used was ethylcellulose (EC) sourced from Dow Chemical Company, USA. Porcine stomach mucin type II (Sigma-Aldrich Company, Germany) was used in the study. Glycerin was used as the plasticizer for the gelatin, while castor oil (Namsiang Co., Ltd., Thailand) was used as the plasticizer for the ethylcellulose. Ethanol (95%) (RCI Labscan Co., Ltd., Thailand) was used as the solvent for ethylcellulose, and co-solvent of α-MN (ChromaDex Co., Ltd, Irvine, USA). We obtained α-MN from ChromaDex Co., Ltd, located in Irvine, USA. The mucoadhesive patches, Time patch (Jiangsu Yessen Biotech Co., Ltd., China), and Taisho patch (Taisho Pharmaceutical Co., Ltd., Japan), were purchased for comparison.

Preparation of mucoadhesive patches

The mucoadhesive patches were prepared using the solvent casting method. The patches consisted of a backing layer and a mucoadhesive layer. To prepare the backing layer, EC was mixed with 95% ethanol and castor oil as a plasticizer to 25% of the EC until it was homogeneous. The mixed solution (6.54 g/cm^2 of EC) was then cast onto a Teflon sheet mold and dried in a hot air oven at 60°C for 4 h. For the mucoadhesive layer, α-MN was dissolved in ethanol and mixed with a gelatin solution to form a mixture containing 1-7% w/w of gelatin. The resulting mixture was cast onto the EC backing layer and dried in a hot air oven at a temperature of 60°C for 24 h.

Scanning electron microscopy (SEM)

To analyze the mucoadhesive patches, 1 cm x 1 cm-sized patches were placed on an aluminum stub that had been coated with gold using the sputtering method for 10 seconds. The cross-sections of the patches were then examined using a scanning electron microscope (model 1455VP, LEO Co., Ltd., England).

Thickness

The thickness of the mucoadhesive patches was measured using a coating thickness gauge (936 FN, Protronics Co., Ltd., Thailand).

Puncture test

The puncture strength and elongation at the break of the patch were investigated using a texture analyzer (TA.XT, Stable Micro Systems Co., Ltd., England) through puncture tests. The experimental conditions included a load cell of 30 kg, spherical probe P/5S, a contact force of 5 g, and a test speed of 0.30 mm/sec. Testing

was conducted on patches of size 2.25 cm^2. The puncture strength and elongation at break (%) were calculated using equations [1] and [2] respectively (Kriangkrai, Puttipipatkhachorn, Sriamornsak, Pongjanyakul, & Sungthongjeen, 2012; Taokaew, Phonsee, Woravut, Pitaksuteepong, & Kriangkrai, 2019). The experiment was performed five times, and the results were recorded.

$$\text{Puncture Strength} = \frac{\text{Max force (N)}}{2\pi \times \text{Support radius (mm)} \times \text{Film thickness (mm)}} \quad [1]$$

$$\%\text{Elongation at break} = \frac{\sqrt{\text{Support radius}^2 + \text{Max distance}^2} - \text{Support radius}}{\text{Support radius}} \times 100 \quad [2]$$

***In vitro* residence time test**

To simulate the residence time, which is the maximum length of time that the mucoadhesive patches remained on aphthous ulcers, mucin-coated cellophane was prepared to mimic oral mucosa. The cellophane was immersed in a 2% mucin solution (porcine stomach type II) and dried at 45°C for 4 h. Artificial saliva was prepared, containing NaCl (0.084%), KCl (0.12%), K_2HPO_4 (0.026%), and water (99.77%), and its pH was adjusted to 7.0 using lactic acid. Figure 1 demonstrates the simulation of the residence time test (Erweka ZT 221, Heusenstamm, Germany). The beaker containing the artificial saliva was maintained at 37±2°C, which mimics oral cavity temperature. The mucoadhesive patches were applied onto the mucin-coated cellophane with a controlled force of 20 N for 10 sec. The basket containing the mucoadhesive patches was shaken at 30 ± 1 strokes/min. The detachment time of the 5 patches was recorded as the *in vitro* residence time.

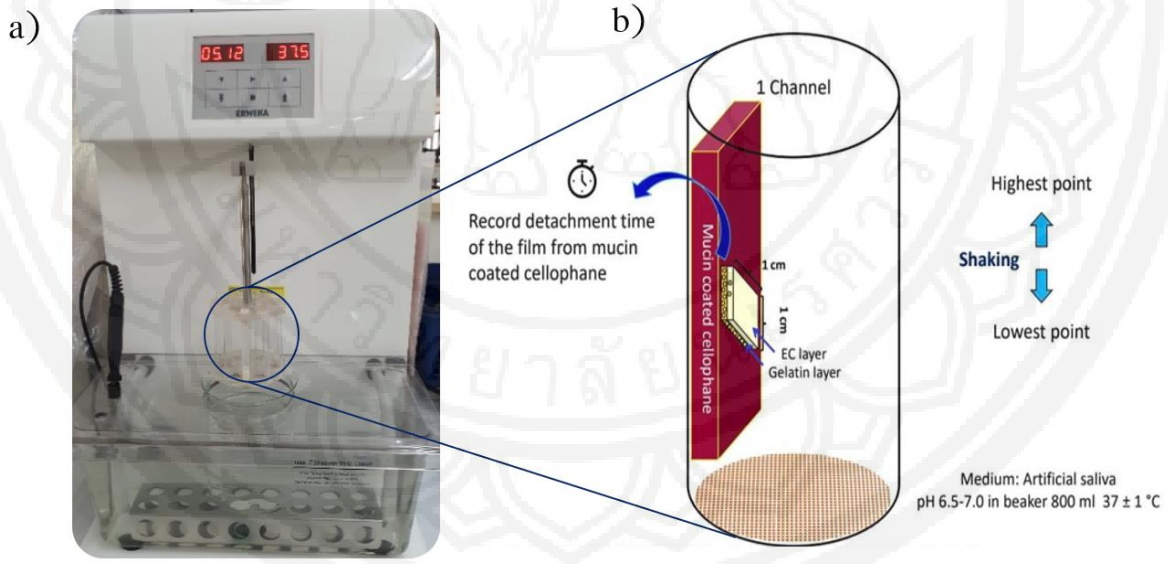

Figure 1 *In vitro* simulation of the residence time test. (a) Disintegration tester, (b) Mucin-coated cellophane cell used for assessing the residence time of a mucoadhesive patches

Wettability test

The wettability of the mucoadhesive patches was assessed using a drop shape analyzer (model DSA25E with tilting device, Scientific Promotion Co., Ltd., Hamburg, Germany). The contact angle between droplets of purified water and the mucoadhesive layer surface of the patches was measured using a sessile drop protocol with the following parameters: substance; water, temperature; 25°C, volume; 10 µL, rate; 10 µL/s, and needle

diameter; 0.5 mm (Wattanaphraya, Manchun, Taokaew, & Kriangkrai, 2021). The experiment was performed five times, and the results were recorded and averaged.

Quantification of α-mangostin in the mucoadhesive patches

To quantify the total amount of α-MN in the patches, the thickness and weight of each patch were initially measured. Subsequently, the patches were cut into small pieces. To dissolve the gelatin layer, 6 mL of water was added, followed by the addition of 10 mL of ethanol to dissolve EC and α-MN. The mixture was then vortexed and sonicated at 25°C for 30 minutes. The sample was then centrifuged at 31,514 × g for 5 minutes. The α-MN content in the supernatant was determined using a UV-vis spectrophotometer at its maximum absorbance wavelength of 320 nm. This method was modified from the previous study (Pham, Saelim, & Tiyaboonchai, 2019).

Statistical analysis

The data were reported as the mean ± standard deviation (S.D.), derived from a minimum of three experiments. To compare the different groups of data, a one-way analysis of variance (ANOVA) was conducted using SPSS software. A significance level of * $p < 0.05$ was employed to establish statistical significance.

Results and Discussion

Mucoadhesive patches were prepared using the solvent casting method. The blank patches, which contained 5% gelatin 300 blooms, glycerin 40%, and ethanol without α-MN, appeared clear. However, upon adding α-MN at concentrations of 0.054%, 0.108%, and 0.216%, the patches turned yellow with increasing color intensity observed at higher α-MN concentrations.

To examine the morphology of the patches using scanning electron microscopy (SEM), the mucoadhesive patches were divided into two layers: the EC layer (Figure 2a), acts as a barrier, covering the ulcer and reducing pain and discomfort and the Gelatin layer (Figure 2b), which functions as the mucoadhesive layer and enables targeted and sustained drug delivery. Figure 2 displays the SEM image of the double layer of mucoadhesive gelatin-based patches. The EC layer was observed to be thicker than the Gelatin layer, owing to the greater amount of ethylcellulose polymer solids present in comparison to the gelatin polymer.

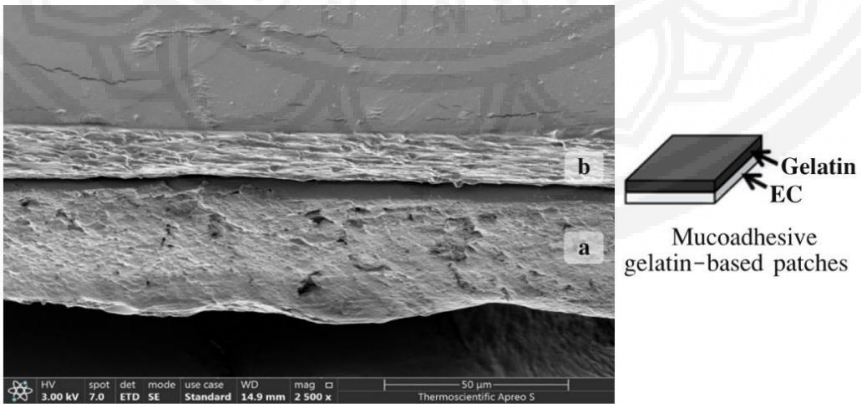

Figure 2 Cross-sectional scanning electron microscopy images of the double layer of mucoadhesive patches. (a) Ethylcellulose layer, (b) Gelatin layer

Influence of the bloom strength of the gelatin

Bloom strength is a parameter that measures the rigidity or firmness of gelatin. A higher bloom strength indicates firmer gelatin. In this study, the puncture strength and elongation at break were assessed to gain insights into the ability of mucoadhesive patches to withstand damage and maintain their structural integrity during use or application (as shown in Figure 3). The results demonstrated that the strength of the two-layer film was noticeably reduced compared to the backing layer film, which may suggest that the casting of the mucoadhesive layer interfered with the formation of the backing layer film. Furthermore, the puncture strength significantly increased with an increase in bloom strength (Figure 3a). The highest puncture strength value of 2.9 N/mm² was observed for gelatin with 300 blooms, which indicates the stiffness of the polymers due to their proline and hydroxyproline content (Khoirunnisa et al., 2018). The gelatin with 250 blooms also exhibited high puncture strength, but no significant difference was observed when compared to the gelatin with 300 blooms(Ahmady & Abu Samah, 2021). The elongation at break of the two-layer film was found to be slightly higher (Figure 3b). The flexibility of the two-layer patches was primarily determined by the backing layer (EC layer).

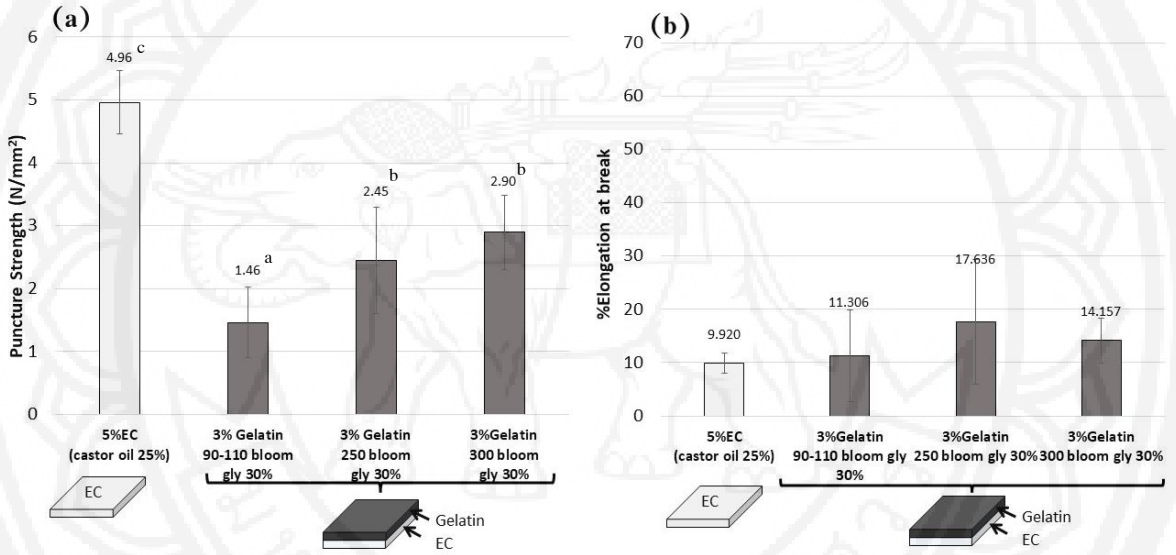

Figure 3 Effect of varying bloom strength on (a) puncture strength and (b) elongation at break of mucoadhesive patches

Figure 4 show the effect of varying bloom strength on the *in vitro* residence time of mucoadhesive patches. The *in vitro* residence time of the gelatin-based patches with 300 blooms was the longest, at 58 min, showing that the increase of bloom strength of gelatin increases the residence time due to the increase in the molecular weight of the gelatin and the entanglement of the polymer from the bonds with mucin. The residence times of the commercial patches were 24 and 50 min. The viscosity of hydrated gelatin varies depending on the bloom strength of the gelatin used, with higher bloom strengths exhibiting higher viscosity compared to those with lower bloom strengths, as reported in previous studies (Kadam, Pochat-Bohatier, Sanchez, & El Ghzaoui, 2015; Leuenberger, 1991).

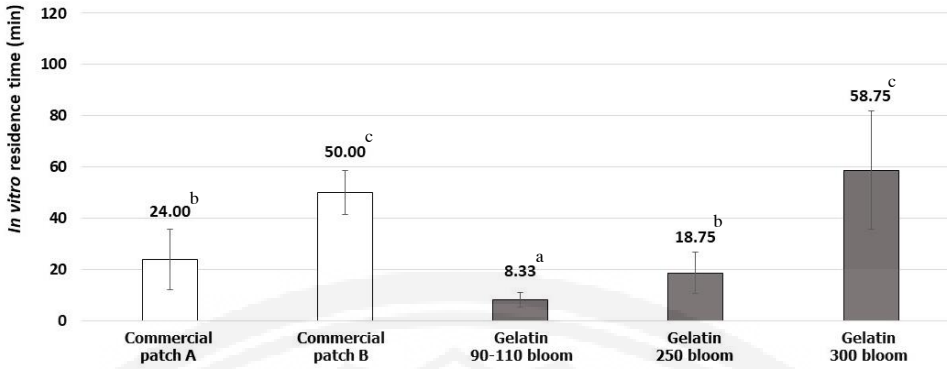

Figure 4 Effect of varying bloom strength on the *in vitro* residence time of mucoadhesive patches

The contact angle measurements were performed to evaluate the hydrophilicity of the mucoadhesive patches prepared using different bloom strengths of gelatin. The contact angle decreased with increasing bloom strength, with the gelatin with 300 blooms exhibiting the lowest contact angle, indicating higher hydrophilicity compared to the gelatin with 90–110 blooms and 250 blooms (Figure 5A). This result suggests that the gelatin with higher bloom strength has a higher affinity for the wetted mucosal surface, which could enhance the mucoadhesive property of the patches. Longer *in vitro* residence time was observed for the mucoadhesive patches prepared using gelatin with 300 blooms (Figure 4), which could be attributed to the lower contact angle value observed for this gelatin, indicating a stronger interaction with the mucosal surface and improved mucoadhesive properties. Higher bloom strength gelatins exhibit improved hydrophilicity and potentially smoother surfaces due to their denser structures and more extensive hydrogen bonding networks (Peppas, Hilt, Khademhosseini, & Langer, 2006). These properties can contribute to enhanced wettability by facilitating better water absorption and promoting liquid spreading and adhesion on the surface.

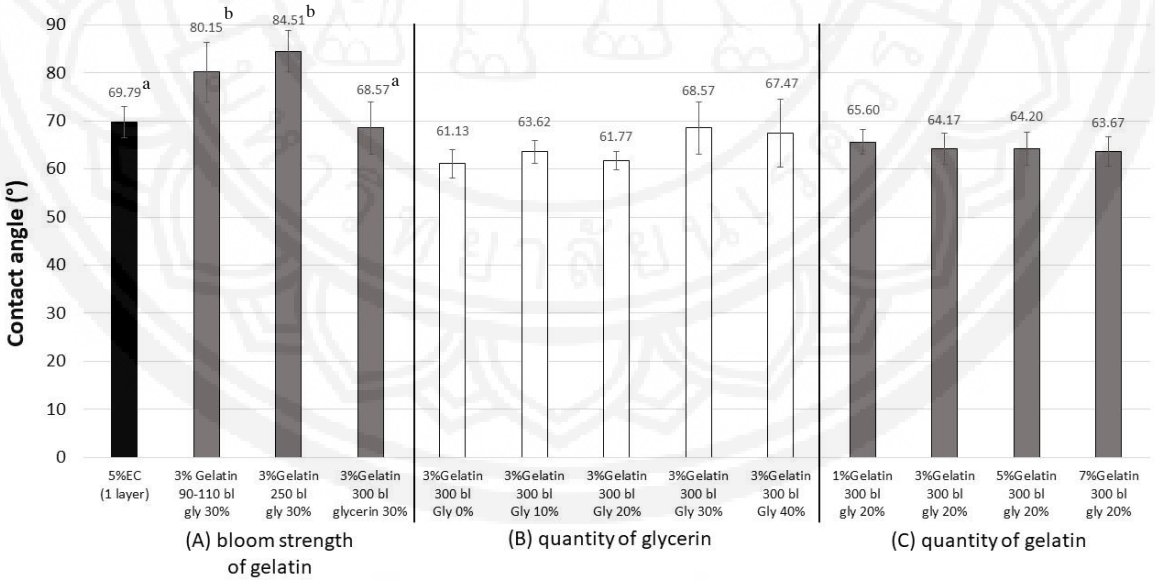

Figure 5 Effect of varying bloom strength on the water contact angle of mucoadhesive patches. (A) bloom strength of gelatin, (B) quantity of glycerin, (B) quantity of gelatin

Influence of plasticizer concentration

Gelatin with 300 blooms was chosen as the foundation for a mucoadhesive layer in an ongoing investigation. One aspect of the objective study was to explore the impact of plasticizer concentration, specifically the quantity of glycerin, on the attributes of the mucoadhesive patches. An inverse relationship was observed between glycerin concentration and the puncture strength of the patches, as illustrated in Figure 6a. This phenomenon can be attributed to glycerin's interpenetration among gelatin polymer chains, consequently diminishing their entanglements. The integration of plasticizers into the polymer structure leads to a reduction in the glass transition temperature (Tg), subsequently increasing the amorphous nature and decreasing the rigidity of the material. Furthermore, plasticizers have been found to contribute to a decline in the entanglement density of polymer chains. This results in enhanced mobility of the polymer chains, which in turn diminishes the puncture strength of the material. Analogous findings were documented in a study by (Ballesteros-Mártinez, Pérez-Cervera, & Andrade-Pizarro, 2020), who reported that an increase in plasticizer concentration from 10% to 50% led to an 85.89% reduction in the puncture strength of glycerol-plasticized films. The enhanced flexibility of the gelatin layer film may be attributed to the elevated concentration of plasticizer. However, no significant increase in the elongation at break of the patches was observed (Figure 4b), which can be ascribed to the rigidity of the EC layer.

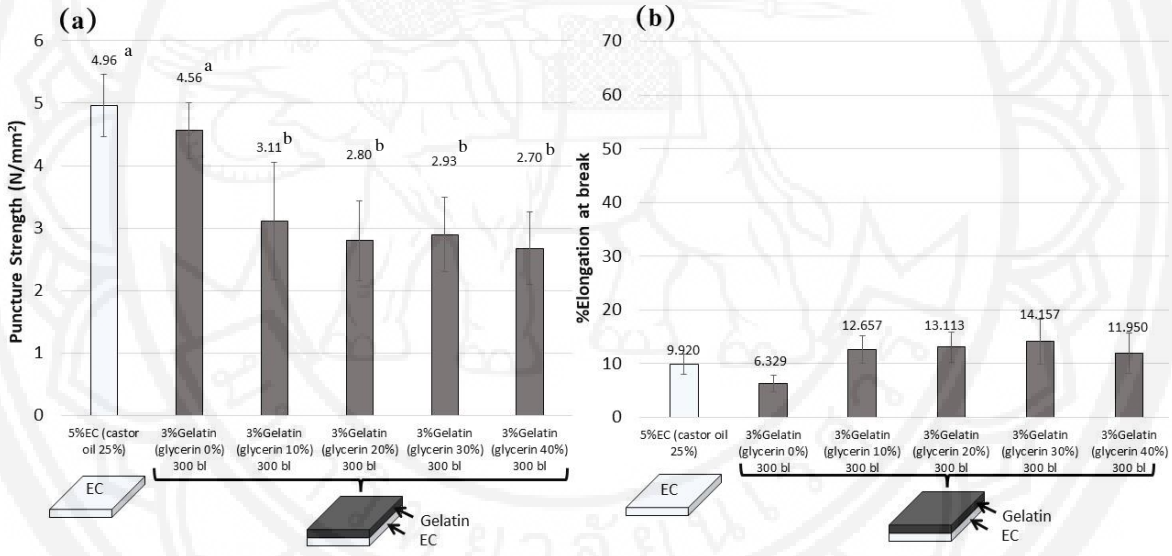

Figure 6 Effect of varying amounts of glycerin on (a) puncture strength and (b) elongation at break of mucoadhesive patches

Figure 7 illustrates the impact of plasticizer concentration on the *in vitro* residence time of mucoadhesive patches. Modification of glycerin concentrations to 20% w/w, 30% w/w, and 40% w/w revealed that the formulation comprising 3% gelatin (300-bloom value) and 40% w/w glycerin displayed the most extended *in vitro* residence time (108.00 ± 16.67 minutes). This outcome might be ascribed to glycerin's ability to absorb saliva within the mucoadhesive patch, consequently improving wettability (Figure 5b) and promoting polymer chain mobility. The progressive increase in glycerin concentration correlated with a slight elevation in the *in vitro* residence time, possibly due to the humectant characteristics of the absorbed saliva. Previous research has demonstrated that interpenetration between gelatin and mucin chains, facilitated by bond formation, contributes to an increased *in vitro* residence time (Hägerström, Paulsson, & Edsman, 2000).

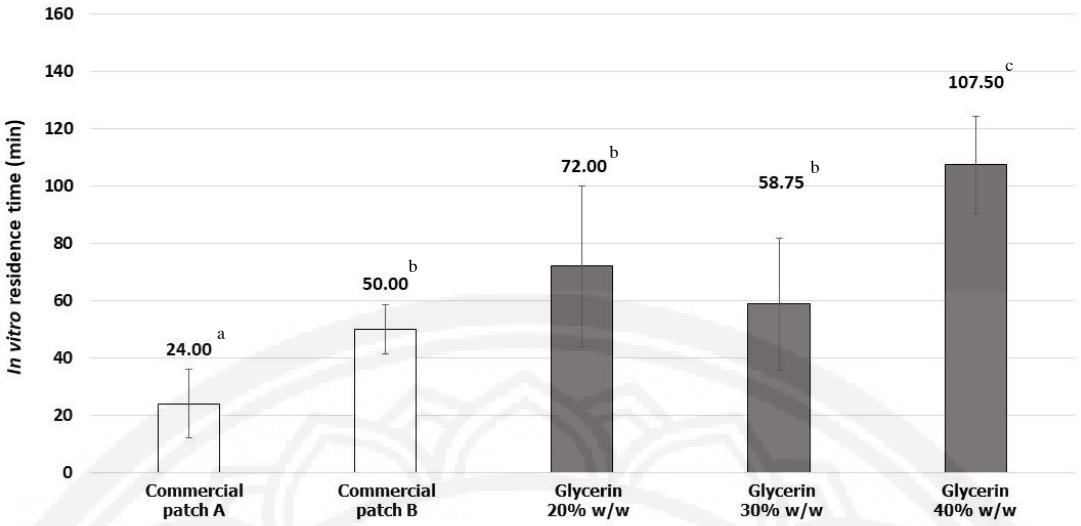

Figure 7 Effect of amount of glycerin on the *in vitro* residence time of mucoadhesive patches

Influence on the amount of gelatin

Increasing the concentration of gelatin from 1% to 7% resulted in a notable increase in patch thickness due to the thicker mucoadhesive layer (data not shown). This increase in gelatin concentration also led to an increase in puncture strength, as shown in Figure 8a. The increase in gelatin concentration also resulted in a change in the ratio of EC and gelatin layers. Figure 8b shows the increase in elongation at break for mucoadhesive patches with 7% gelatin concentration. It is noteworthy that the flexibility of the patch was not solely determined by the backing layer as mentioned earlier. The solid content of the polymer in each layer per cm^2 was uniform. A study by (Mali, Grossmann, Garcı´a, Martino, & Zaritzky, 2005) found that increasing the thickness of a film resulted in a corresponding increase in its puncture strength and elongation. In thicker films, the polymer matrix is denser and rich in inter and intramolecular interactions and, consequently, more resistant to rupture.

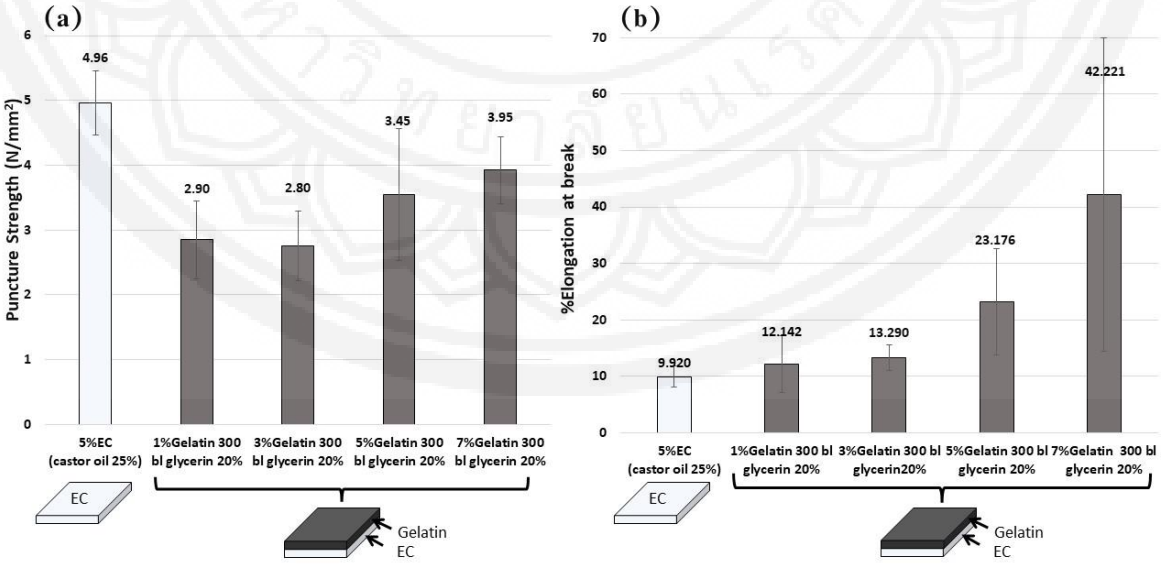

Figure 8 Effect of varying the amount of gelatin on (a) puncture strength and (b) elongation at break of mucoadhesive patches

Figure 9 shows that as the concentration of gelatin increased from 1%, 3%, and 5%, up to 7% w/w, the thickness of the gelatin increased, leading to an increase in the *in vitro* residence time of the mucoadhesive patches. This suggests that patches with higher concentrations of gelatin may adhere to the oral mucosa for longer. The increased concentration of gelatin led to an increase in the number of gelatin polymer chains that interpenetrated with mucin chains, building mucoadhesive bonds and ultimately increasing the *in vitro* residence time (Tiwari, Sause, Madan, & Goldman, 1999). However, it should be noted that film thickness has a greater impact on the overall mouthfeel and comfort of the patient compared to film mass (Tzanova, Hagesaether, & Tho, 2021). Therefore, it is essential to strike a balance between increasing the gelatin concentration for improved *in vitro* residence time and maintaining a comfortable mouthfeel for the patient. Increasing the concentration of gelatin did not result in any significant change in the water contact angle, as shown in Figure 5c. This is likely because the surface of the material remained the same, despite the increase in gelatin concentration.

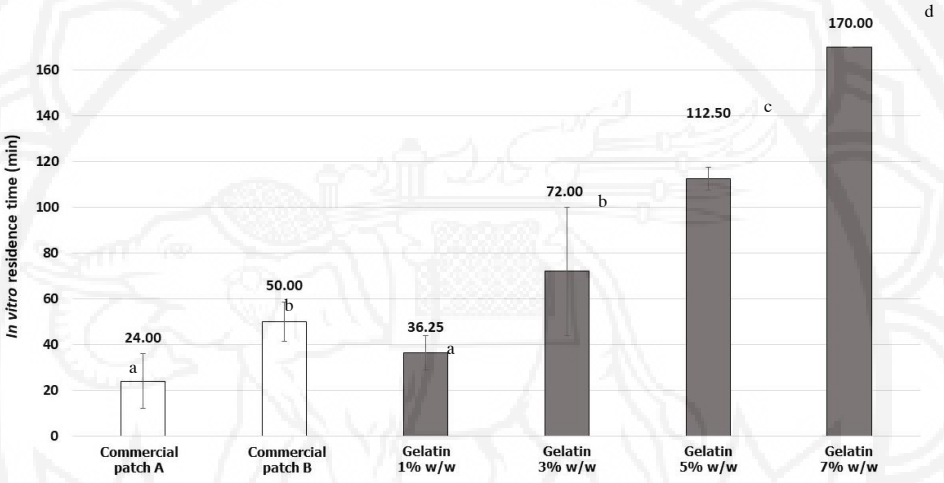

Figure 9 Effect of amount of glycerin on the *in vitro* residence time of mucoadhesive patches

Loading of α-MN in mucoadhesive gelatin-based patches

The loading of α-MN in mucoadhesive gelatin-based patches was investigated for potential topical applications due to its potent anti-inflammatory and antibacterial properties. α-MN was incorporated into the gelatin layer at concentrations ranging from 0.054% to 0.216% w/w to achieve a theoretical concentration range of 142.12 to 568.48 μg/cm². The actual concentrations of α-MN in the patches were determined to be 144.12 ± 27.10 μg for the patches containing 0.054%, 273.35 ± 17.20 μg for the patches containing 0.108%, and 441.05 ± 94.79 μg for the patches containing 0.216% α-MN. However, a decrease in the actual concentrations compared to the theoretical concentrations was observed at higher concentrations, which may be attributed to the solubility limitations of α-MN.

Table 2 Amount of α-MN loading in the mucoadhesive gelatin-based patches (5% Gelatin, 300 bl, and glycerin 40%)

Formulation	theoretical concentrations (μg /cm²)	actual concentrations (μg/cm²)
α-MN 0.054%	142.12	144.12 ± 27.10
α-MN 0.108%	284.24	273.35 ± 17.20
α-MN 0.216%	568.48	441.05 ± 94.79

Conclusion and Suggestions

In conclusion, the present study elucidates the significant influence of gelatin bloom strength on the characteristics of mucoadhesive patches. A higher bloom strength corresponds to increased puncture strength and *in vitro* residence time. Additionally, the glycerin concentration, employed as a plasticizer, impacts the properties of the patches: elevated concentrations result in diminished puncture strength but augmented elongation at break. By increasing the gelatin concentration within the mucoadhesive layer, patch thickness, puncture strength, and *in vitro* residence time are enhanced, with the 7% gelatin formulation yielding the most pliable patches. Successful incorporation of α-MN in the mucoadhesive layer was achieved, with actual concentrations ranging from 144.12 to 441.05 μg, contingent upon the theoretical concentration and solubility constraints.

Acknowledgements

The authors express their gratitude to the Faculty of Pharmaceutical Sciences at Naresuan University for their technical support and partial financial assistance. We also acknowledge the support received from the Global and Frontier Research University Fund (grant no. R2566C053) provided by Naresuan University.

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