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Development and *ex vivo / in vitro* evaluation of sodium alginate/ hydroxypropyl methylcellulose films for dermal and/or transdermal delivery of *p*-hydroxycinnamic acid

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ABSTRACT

Objective: Skin diseases and chronic wounds are health problems that require solutions for health systems due to their high costs and difficulties in effective and rapid treatment. Hydroxycinnamic acid and its derivatives are powerful antioxidant molecules with widespread applications in medicine, cosmetics, and food industry. In this study, *p*-hydroxycinnamic acid was used as a potent agent for the management of skin diseases and other disorders.

Method: Herein, sodium alginate and hydroxypropylmethylcellulose-based films loaded with *p*-hydroxycinnamic acid at various concentrations were prepared by solvent-casting method and characterized in terms of mechanical, physicochemical, bioadhesive properties, and *in vitro* release kinetic modelling.

Results: The masses of the films were found to be between 16.933 ± 1.108 mg and 15.200 ± 0.432 mg and thicknesses between 135 ± 4 μm and 163 ± 6 μm. F1 formulation with higher sodium alginate concentration exhibited higher moisture absorption and moisture loss percentages (18.373% ± 2.610% and 8.281% ± 1.834%). In terms of water absorption, it was observed that F3 had up to 100% and F1 had the lowest absorption capacity. However, F1 degraded in a shorter time compared to other films. In terms of mechanical properties, F1 has shown that it has higher tensile strength, reaches 100% by providing continuous release with *in vitro* release studies, and has the highest bioadhesion. In addition, as a result of FTIR analysis and *ex vivo* permeation and penetration studies, the formulation F1 proved that it is suitable for dermal applications.

Conclusion: The developed formulations exhibited desired dermal film properties, making it a promising treatment option for dermal applications.

1. Introduction

Skin is the largest and among the most vital human organs, with a crucial role in many processes maintaining homeostasis.[1,2] Homeostasis can be impaired for various reasons, even from ultraviolet radiation, seasonal changes, and air pollution.[3] Skin-related diseases such as eczema, dermatitis, and psoriasis are quite common problems for both adults and children; such diseases can differentiate skin homeostasis and influence the function of skin barrier.[4] Disturbances of the skin integrity due to incidents such as burns and wounds can cause disruption of skin homeostasis, leading to unstable skin.[3,5] Both skin injuries and dermal disorders are accompanied by inflammation of the skin region, which

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alters or impairs the immune response and further skin healing procedures.

Acute and chronic wounds (disruptions or injuries of skin structure) have different features and time of healing; the main problem of chronic wounds is their easy contamination by microbes, leading to slow healing.[6] Therefore, the effective and rapid management of these skin injuries is significant for the patient and the health economic system.[1,7] Skin injuries can also occur due to skin disorders, dryness, acne, etc. Atopic dermatitis is a frequently seen, long-standing allergic skin disease presenting main clinical findings of dry and scaly skin and presence of inflammation. This skin disorder is characterized by higher skin permeability and increased susceptibility to skin infections as well as chronic eczema, pruritus, and high serum levels of IgE.[8,9] Psoriasis, another common, chronic papulosquamous skin disease, has been linked with many medical disorders such as psoriatic arthritis, depression, as well as cardiometabolic syndrome.[10] Despite many efforts of the scientific communities, the management of psoriasis and atopic dermatitis still has not been acquired, and patients suffer and have disrupted daily functions due to severe itchiness, pain, or generalized erythema.

Skin diseases and wounds involve numerous free radicals and/or abnormal inflammatory response,[3,11] with several differentiated molecular and metabolic pathways taking place. Consequently, finding a single molecular target for treating these disorders is quite difficult and expensive. Physicians recommend corticosteroid application for the management of such diseases, since pro-inflammatory mediators, i.e., chemokines and cytokines, have been identified.[12] However, incorporating molecules derived from nature into their clinical practice can be both cost-effective and biologically efficient which should be encouraged.

Last years, the concept of phytochemical compounds as part of treatment for various diseases such as cancer,[13] neurodegenerative disorders,[14] as well as wound management[1,15] has arisen; natural substances are biocompatible and present anti-oxidant, anti-inflammatory, and antimicrobial activities.[1,16,17] The phytochemicals are derived from various plant sources, such as fruits and herbs[18]; the major phytochemical classes, including alkaloids, phenolics, carotenoids, terpenoids, and tannins, have been studied for their potential against diabetes, obesity, cancer, and cardiovascular diseases.[19] A significant class of polyphenolic compounds are hydroxycinnamic acid derivatives, which are biosynthesized through Mavolanate-Shikimate pathways in plants. Examples of hydroxycinnamic acid derivatives are cinnamic acid, *p*-coumaric acid (PCA), ferulic acid, caffeic acid, rosmarinic acid, and chlorogenic acid.[20] The cinnamic acid derivatives can benefit health since they have been studied and found to prevent dyslipidemia, diabetes, and obesity.[20] PCA is one of the three isomeric forms of hydroxycinnamic acid with very low aqueous solubility, and is the dominant hydroxycinnamic acid found in citrus fruits and pineapple.[21] It has been used as an adjunctive compound for the management of kidney disease,[22] diabetic nephropathy,[23] acute lung injury in mice,[24] skeletal muscle atrophy,[25] acetic acid-induced ulcerative colitis,[26] inhibiting osteoclast formulation as well as bone erosion in rheumatoid arthritis,[27] promotion of wound healing,[28] skin cancer,[29] and others. PCA affects the inflammatory response in various cellular mechanisms as well as reactive oxygen species scavenging and antimicrobial activity.[30] In addition, being a potent tyrosinase inhibitor, PCA hinders human epidermal melanocytes, mouse melanoma cells, and human skin models that have been reconstituted.[31,32] PCA also provides protective action against UV-induced skin damage and can be used in cosmeceuticals and sunscreen products.[33] Nonetheless, the main drawback of PCA is that it cannot permeate the deeper skin tissues, halting its use for transdermal delivery. A recent study explored the application of the phospholipid complex of PCA for enhanced skin permeation into deeper skin layers, offering defense against photo-oxidative stress. The phospholipid complex was further incorporated into a gel formulation, and through this, it achieved its transdermal delivery.[33]

Traditional drug delivery systems for the management of dermal diseases include semi-solid dosage forms,[34] such as gels and creams, that present various advantages and disadvantages. Gels are water-based semi-solid dosage forms,[35] offering a clear and non-oily solution that has rapid absorption into the skin, providing a cooling effect. They can be easily applied and spread uniformly, thus becoming perfect for hydration without leaving an oily sensation. Due to their property of rapidly drying and evaporating, gels neither provide a prolonged duration of action nor provide a long-term release of the active ingredients.[36] Other issues associated with gels include skin dryness, especially when alcohol is used as an excipient, and reduced moisturizing properties as compared to creams or films. Creams,[37] as oil/water or water/oil emulsions, present desirable moisturizing properties due to their ability to create a protective barrier that retains moisture. Moreover, creams can release the active molecules over a prolonged duration, which is helpful for dry or sensitive skin. Creams consistency varies from light to thick and heavy; therefore, they are suitable for many skin conditions. However, many patients complain about a greasy sensation, and they do not prefer them. Moreover, creams could even aggravate oily or acne-prone skin types due to their slower absorption and possible clogging of pores. Compared to gels or films, creams are aesthetically less pleasing, due to their heavy feel. On the other hand, films provide the advantage of a thin, non-greasy layer, which can be attached to the skin, offering a controlled and sustained release of active ingredients over prolonged periods.[38] Polymer-based films are either transparent[39] or present a milky appearance,[40] leaving no visible changes when applied, while they do not erode; in further, films could be easily applied without leaving any residues as creams or gels. Films-based products are more preferable for a long-lasting effect without needing frequent application.[41] Although, films might not provide good hydration when synthetic polymers are used as their main components, their ability to prolong the release of the active molecules without frequent application is essential for dermal/transdermal delivery.[42]

In this investigation, the possibility of PCA loaded polymer-based films for transdermal/dermal delivery targeting various skin and probably systemic diseases is proposed. The application of polymer-based films or film-forming systems for dermal/transdermal delivery has been proposed many years ago.[43–47] Transdermal delivery offers various advantages compared to oral dosage forms, as it can bypass the hepatic first-pass metabolism to improve bioavailability; transdermal patches release a specified drug amount to the surface of intact skin at a controlled rate.[48] Solvent casting is an easy method to develop film-based drug delivery systems as possible dermal or transdermal carriers.[39,40,49] According to this technique, the chosen polymers and active ingredient are dissolved into a common solvent and then the solvent is evaporated developing a film. A past study analyzed the development of transparent films based on PCA and poly (vinyl pyrrolidone) (PVP) using ethanol as a solvent; the films demonstrated antiseptic and antioxidant properties and can be applied for various pharmaceutical applications.[50]

Herein, the chosen polymers are sodium alginate (SA), hydroxypropyl methylcellulose (HPMC) and PEG-400. SA is derived from brown seaweed and composed of mannuronic and guluronic acids of various combinations; its important mucoadhesion makes it an excellent candidate for dermal delivery.[51] HPMC is a derivative of cellulose, abundant in plants and a very common excipient in drug industry.[52] PEG-400 is a frequently used pharmaceutical excipient acting as stabilizer, which can also improve the absorption of drugs.[53] As far as we know, this is the first time that a film-based delivery system of PCA with the above polymers is proposed.

2. Materials and methods

2.1. Materials

SA and PEG-400 were sourced from Sigma-Aldrich, whereas HPMC E5 was generously provided by Colorcon, Turkey. $CaCl_2$ and NaCl as well as $NaHCO_3$ were supplied from Tekkim, Turkey and Yasin Teknik, Turkey, respectively.

2.2. Preparation of pure and drug loaded films

The development of the films was done using the known solvent casting method.[39,40,49] Firstly, SA was solubilized in purified water and stirred. The solution was then heated at 70 °C and stirred at 900 rpm. HPMC was subsequently added to the SA solution during stirring without additional heating, followed by the addition of PEG-400. The stirring speed was further lowered to 100 rpm for 3 h, eliminating air bubbles. Afterwards, the mixture was cast on a Petri dish, followed by its drying at 24.4 ± 0.5 °C. The obtained films were removed from the Petri dish surface and put into the sealed vessel (24.4 ± 1 °C, 60% ± 2% RH).[54] Table 1 demonstrates the composition of pure films.

In the case of drug-loaded films, PCA was dissolved in 0.5 mL ethanol and added slowly to the solution, PEG-400/SA/HPMC mixture. The drying and removal procedure was the same as that of pure films.

2.3. Characterization methods

2.3.1. Weight and thickness

For the determination of weight and thickness of the developed films, the samples were cut into circular pieces of 1.6 cm in diameter. The weight was calculated with a microbalance,[55] while thickness was measured with a manual micrometer with a sensitivity of 0.01 mm.[56]

2.3.2. Water absorption capacity

The films were suspended in glass beakers containing 50 mL of phosphate-buffered saline (PBS) (pH 7.4) maintained at room temperature. Films were removed at suitable time intervals and filtered using a paper to carefully wipe off any excess water and weighed. Eq. (1) shows the calculation of water absorption (%).

$$\text{Water Absorption } (\%) = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100 \qquad \text{(Eq.1)}$$

2.3.3. In vitro hydrolysis studies of films

Herein, the hydrolysis degree was associated with the loss of mass. Therefore, 2 cm diameter circular films were placed in Petri dishes loaded with PBS (pH 7.4) at 37 ± 1 °C for an incubation time of 30 min. The films were removed from the Petri plates every 24 h, rinsed with distilled water, dried at room temperature until they reached a constant weight, and weighed. [57]

2.3.4. Mechanical properties of developed films

The mechanical characteristics of the selected films were determined using a texture analyzer (TA.XTPlus, Stable Micro Systems, UK) equipped with a 5 kg load cell. Every sample was positioned 1 cm apart between the clamps. The clamps were then separated at a crosshead speed of 0.5 mm/s until the films broke. Tensile strength and elongation at break were computed according to Eq. (2) and Eq. (3).

$$\text{Tensile Strength } \left(\text{N}/\text{cm}^2\right) = \frac{\text{Breaking Force (N)}}{\text{Cross} - \text{sectional area of sample } (\text{cm}^2)} \qquad \text{(Eq. 2)}$$

$$\text{Elongation at Break } (\%) = \frac{\text{Increase in Length at Breaking Point (mm)}}{\text{Initial Length (mm)}} \times 100 \qquad \text{(Eq. 3)}$$

Table 1
The composition of the pure films and the content of loaded PCA.

	SA:HPMC	SA	HPMC	PEG-400 (1%)	PCA (1%)
F1	90:10	0.890 g	0.110 g	0.010 g	0.010 g
F2	70:30	0.690 g	0.310 g	0.010 g	0.010 g
F3	50:50	0.495 g	0.495 g	0.010 g	0.010 g

2.3.5. FT-IR spectroscopy measurement

The Fourier-Transform Infrared (FTIR) spectra of excipients and films were recorded using ATR-FTIR spectroscopy with a FTIR–spectrometer (FTIR–2000, PerkinElmer, USA). The spectra were acquired over a wavelength range of 400–4000 cm^{-1}, with 128 scans and a spectral resolution of 4 cm^{-1}.

2.3.6. Moisture loss and moisture absorption

Eq. (4) was utilized to determine the moisture loss; initially, the films were weighed (W_0), then placed in a desiccator containing anhydrous $CaCl_2$ for 72 h and weighed again (W_1) ($n = 3$).

$$\text{Percentage of moisture loss } (\%) = (W_0 - W_1)/W_0 \times 100 \qquad \text{(Eq. 4)}$$

Eq. (5) was applied to calculate the percentage of moisture absorption; initially, the films were weighed (W_0) and kept in a desiccator with a potassium chloride saturated solution for 72 h and weighed again (W_1) ($n = 3$).

$$\text{Percentage of moisture absorption } (\%) = (W_1 - W_0)/W_0 \times 100 \qquad \text{(Eq.5)}$$

2.3.7. Drug content uniformity

The drug content was measured via UV–VIS spectrometry employing a 1 × 1 cm^2 film-based sample, which was dissolved in 50 mL of ethanol prior to analysis.

2.3.8. In vitro drug release studies

In vitro drug release was investigated for a period of 24 h. The chosen temperature was 32 ± 0.5 °C and the speed of stirring was 50 rpm, mimicking skin surface conditions. Sink condition was ensured, using ethanol and PBS (pH: 7.4) mixed in a 50:50 ratio. Fifty mL of the mixture were added to 1 cm^2 films, and the mixture stirred at 50 rpm (32 ± 0.1 °C). Two mL of the solution were removed, and the drug concentration was determined by UV analysis.[58]

For maximum wavelength determination in the UV spectrophotometer, PCA was dissolved in ethanol, and the maximum wavelength was determined as 330 nm at a concentration of 50 μg/mL. To obtain the calibration curve, PCA concentrations were determined as 5, 10, 15, 20, 25, and 50 μg/mL. Calibration and validation studies were performed.

Kinetic release analysis: The *in vitro* release data were analyzed through mathematical models such as Zero-order, First-order, Higuchi, Hixson Crowell, and Korsmeyer-Peppas. To decide the best fit model, the highest regression values (r^2) for correlation coefficients of the formulations were selected.[59]

2.3.9. Ex vivo bioadhesion studies

The *ex vivo* bioadhesive investigation was conducted using a TA-XT Plus Texture analyzer. The skin samples used in the *ex vivo* experiments are obtained from the killed animals of other experiments. According to EU Directive 2010/63/EU for animal experiments, ethics approval waived.

The force required to separate the film from the skin following the application of 0.5 N force for 200 s (0.5 mm/s rate), which was determined as the bioadhesion strength. One g of each formulation was placed in the beaker. After applying the formulation to the animal tissue (which was tightly attached to the probe using rubber) for a predetermined length of time and strength, the *ex vivo* bioadhesion data were calculated.[60]

2.3.10. Ex vivo permeation and penetration study

To examine the PCA penetration and permeation through the skin, a vertical Franz diffusion cell (Permeation FDC-6T Series) was employed. Films with a size of 0.636 cm^2 and a 9 mm diameter were placed into the donor compartment. The moistening of the films was done by adding 100 μL of distilled water while the receptor compartment was filled with a 50:50 ethanol:phosphate buffer (pH = 7.4) solvent mixture. The water bath of the jackets of the receptor compartments was set at 32 °C. The

Balb-C mouse skin was fixed with its epidermal surface facing upwards, between the donor and receptor compartments. To maintain the receptor volume of the medium and the sink condition, 2 mL of each sample was taken from the receptor sampling point at the following time intervals: 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 24 h. Then, 2 mL of the solvent mixture was supplied to the receptor and the UV spectrophotometer was used to analyze the samples. After one day, the skin pieces were washed with ethanol, chopped into tiny pieces and dispersed in 10 mL of ethanol. Finally, after the samples had undergone vortexing for 5 min and were centrifuged for 10 min at 10,000 rpm, the supernatants were examined via UV spectrophotometer.

3. Results

3.1. Characterization results for the formulations

As shown in Fig. 1, all formulations present similar weight and thickness. F1 exhibits the lowest thickness (135 ± 4 μm) and the highest weight (16.933 ± 1.108 mg) compared to F2 (163 ± 5 μm with 15.867 ± 1.372 mg weight) and F3 (151 ± 4 μm with 15.200 ± 0.432 mg weight), which can be attributed to the lower percentage of HPMC.

The experimental data of moisture absorption and moisture loss (Fig. 1) indicated that F1 has greater moisture absorption and loss (18.373% ± 2.610% and 8.281% ± 1.834%, respectively), compared to F2 and F3. In fact, F3 presents the lowest moisture loss (5.177% ± 1.338%) of all formulations.

3.1.1. Water absorption study and hydrolysis degree

According to Fig. 2a, which depicts the water absorption of the developed films, F3 revealed the greater water absorption, followed by F2 and F1. It can be noted that F1 depicts a steady and consistent water absorption (almost 50% at 10 min) while F3 illustrates a very rapid initial aqueous absorption reaching 99%–100% maximum water absorption capacity. Moreover, F2 although has a rapid initial water absorption, continues with a slower rate and the maximum rate which achieves was near 90%.

In hydrolysis study, the developed films were immersed in PBS at 37 °C and pH 7.4 to simulate body fluids. Fig. 2b depicts that F1 film exhibited the quickest mass loss within 5 min, while F2 and F3 demonstrated a slower mass loss rate which was very similar. F1 is composed of a higher percentage of SA, which is very soluble in water, demonstrating 100% mass loss compared to F2 and F3 (both around 90%).

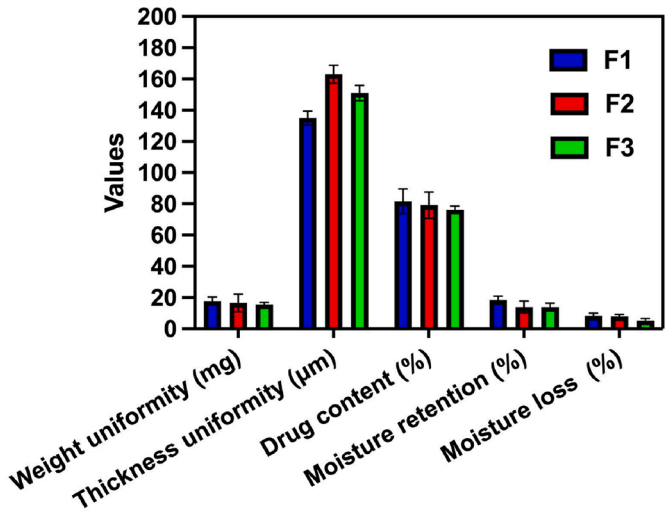

Fig. 1. Summary of characteristics of the PCA-loaded films.

3.1.2. Mechanical properties of the films

The mechanical properties were analyzed to estimate the endurance of the films on a skin surface. Accordingly, among the films developed, F1 showed the highest tensile strength and elongation at break percentage. Table 2 summarizes the obtained results.

3.1.3. FT-IR characterization of the films

Fig. 3 summarizes the FTIR spectroscopy results. First of all, Fig. 3a demonstrated the spectra of the neat materials utilized for the development of the films. The FTIR spectrum of HPMC depicts an absorption band at 3395 cm^{-1} corresponding to the stretching frequency of the hydroxyl group. Moreover, at 1373 cm^{-1} the bending vibration of -OH is observed while the band at 2851 cm^{-1} is indexed to C-H stretching.

The FTIR spectrum of SA depicts the stretching vibrations of O–H bonds at 3270 cm^{-1}. Moreover, the bands at 883 cm^{-1} and 1012 cm^{-1} correspond to the mannuronic and uronic acid functional groups. [39,61] Pure PEG-400 exhibited strong absorption bands at 3303 cm^{-1} due to O–H stretching while at 2862 cm^{-1} is recorded the C–H stretching vibrations of the $–CH_2$ group. At 1446 cm^{-1}, the C–H bending vibrations of the $–CH_2$ group can be seen while the band at 1240 cm^{-1} is attributed to C–O stretching vibration.[62] Fig. 3b displays the spectra of the developed films obtained after the solvent casting of HPMC and SA, and PEG-400 as plasticizer. It can be said that the films present the corresponding bands of the polymer used and mostly SA.

Moreover, PCA spectrum exhibits a strong band at 3317 cm^{-1} assigned to OH stretching, and another band at 1664 cm^{-1} because of the existence of the −CO group. The recorded bands at 1507 and 1442 cm^{-1} correspond to the phenolic ring of the PCA.[63] Moreover, the spectra of PCA loaded films (Fig. 3c) follow the pattern of the spectra of neat formulations (Fig. 3b), but also here the bands moved to lower wavenumbers.

3.2. In vitro drug release study

Fig. 4a depicts the *in vitro* release data. The films were added into a mixture of ethanol and PBS(at 32 ± 0.5 °C) to mimic the release on the skin surface. It can be concluded that films provided a sustained release, but only one formulation (F1) reached 100% release within 24 h.

According to the release kinetic analysis data (Fig. 4b), it can be revealed that F1 fits better to the first order, followed by Hixson-Crowell. In the case of F2 and F3, since the release was around 40% and never reached 100%, no mathematical model was fitted.

3.3. Ex vivo bioadhesion experiments

The bioadhesion of the formulations was done by examining the bioadhesion strength (Fig. 5); F1 displayed the greatest adhesion, followed by F3 and F2. Herein, both SA and HPMC are bioadhesive polymers, but SA exhibits higher mucoadhesion strength.

3.4. Ex vivo permeation and penetration study

Fig. 6 summarizes the obtained data of % permeation and penetration. In general, all the formulations show permeation close to 45% within 3 h, while penetration ranges from 22% to 26%. The obtained results advocate for the efficient transdermal delivery of PCA as it has already been reported. [32]

4. Discussion

Herein, SA and HPMC were chosen as the main components of the film due to their ability to form homogeneous films. SA, a known natural polymer, has been widely utilized for dermal applications and especially for skin diseases. Xia et al. developed [64] tetramethyl pyrazine loaded liposomes which entrapped in a hydrogel from SA and chitosan for atopic dermatitis management. Similarly, You et al. [65] formulated SA

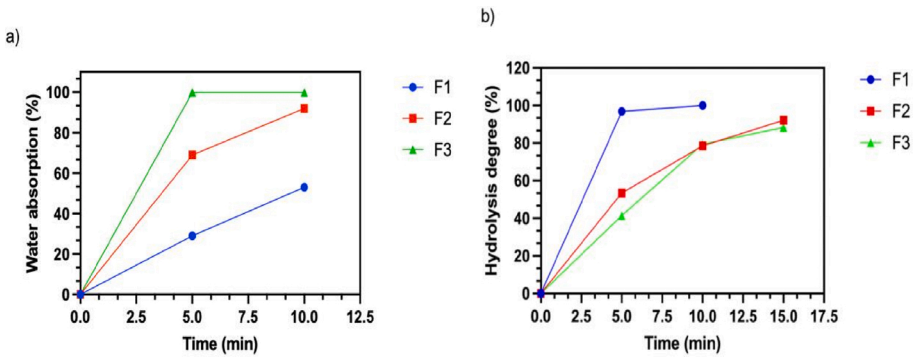

Fig. 2. Water absorption (a) and hydrolysis degree (b) studies of F1, F2 and F3 compared to time.

Table 2
Texture profile analysis results of PCA-loaded films.

	F1	F2	F3
Tensile Strength (N/cm^2)	3.115 ± 1.718	1.401 ± 1.263	0.710 ± 0.192
Elongation at Break (%)	14.793 ± 3.909	6.103 ± 4.192	8.037 ± 2.532

and poly (vinyl alcohol) hydrogels incorporated with nano zinc oxide as dressings.

Furthermore, HPMC has been employed as a main component of formulations for controlled release since it presents thickening, gelling, and swelling activities; cyclodextrin/HPMC films crosslinked with citric acid were studied for ketoconazole delivery.[66] Therefore, SA and HPMC were chosen as the main ingredients of the dermal films. PEG-400 was applied as a plasticizer; plasticizers such as PEG, glycerol, and propylene glycol were used to enhance the flexibility and extensibility of the films. Plasticizers can induce the stretching of the polymer chains, leading to the formulation of the continuous films. Moreover, PEG-400 might act as a penetration enhancer or skin retention vehicle, which is beneficial for dermal diseases and topical delivery. [67,68]

Li et al. successfully developed PCA grafted 2-hydroxypropyltrimethyl ammonium chloride chitosan-based nanoparticles in pursuit of reducing cytotoxicity, increasing antioxidant effect of the formulation and contributing to the antibacterial activity. According to the findings, PCA provided higher radical scavenging activity and diminished cytotoxicity of the developed formulation.[69] Another study focused on penetration of polyphenols including PCA loaded squalene-based emulsions through the pig skin to investigate their efficiency in dermal diseases. Permeation and penetration studies revealed that PCA permeated from the water-in-oil emulsion and formulation was found to be a promising candidate for topical applications.[70]

4.1. Characterization results of the formulations

It is critical to characterize the films for their weight and thickness uniformity, given that for industrial processes all the films should possess similar weight and thickness. All formulations presented similar weight and thickness while F1 exhibited lower thickness and the highest weight compared to other films, which can be attributed to the lower percentage of HPMC. This is a rational result due to the chosen preparation method; using the solvent casting method, the obtained polymer based films demonstrate similar weight and thickness.[39,54] Moreover, from drug content analysis, F1 displays slightly higher drug content and weight compared to F2 and F3. However, the results are statistically similar.

It has been reported that the moisture amount can impact the mechanical properties and bioadhesion of films.[71,72] The moisture retention and loss of F1 was greater compared to F2 and F3. It was documented that reducing SA led to a decrement in water content in films of SA and Gelatin composition.[73] Consequently, herein the greater moisture retention of F1 is linked to the higher percentage of SA.

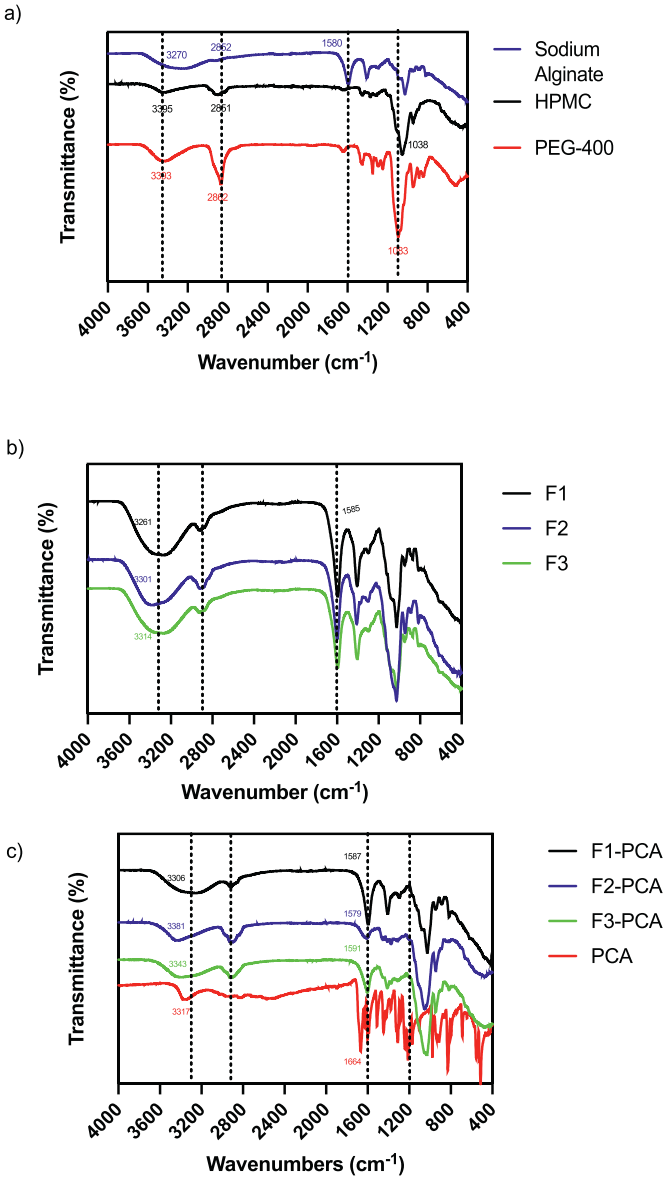

Fig. 3. FTIR spectroscopy studies of pure components SA, HPMC, PEG-400 (a), pure formulations F1, F2, F3 (b) and formulations loaded with PCA (c).

Moisture loss is defined as the loss of water during storage due to water evaporation into ambient air.[74] Inhibition of moisture loss is important, since it can improve the quality of the films for dermal delivery. Since alginate films are hydrophilic, they act as inadequate moisture barriers

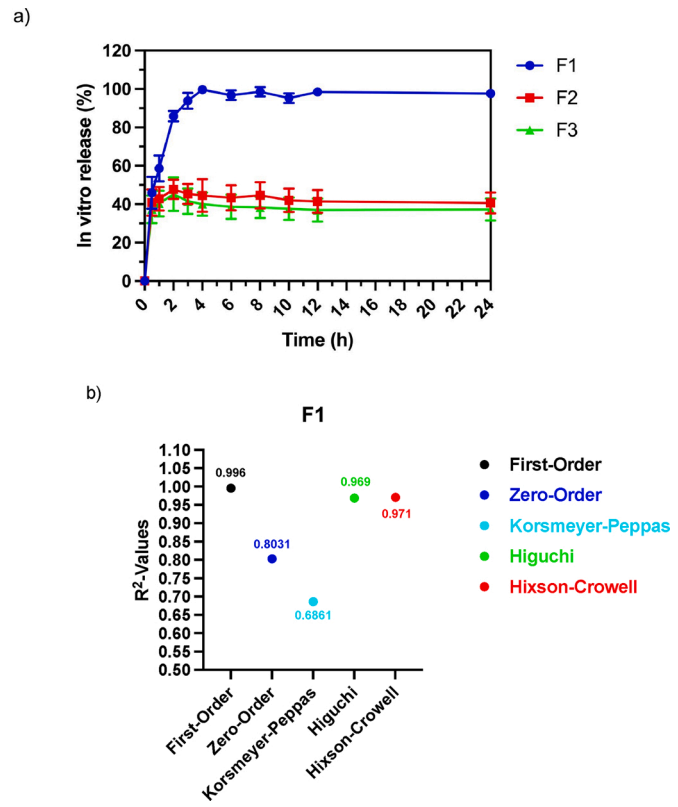

Fig. 4. *In vitro* release studies of PCA from the developed films (a); Kinetic release data according to R^2 (b).

and therefore, it is expected to present high moisture retention.[75] Herein, for all formulations moisture loss is very low, which can be attributed to the addition of HPMC which can act as a moisture barrier.[76]

4.1.1. *Water absorption study and hydrolysis degree*

The water absorption ability is a significant parameter when dermal/transdermal films are developed, given that moisture impacts the control of drug release and is required for bioadhesion.[72] It is well known that both HPMC and SA, absorb water quickly and swell rapidly, producing hydrogels. According to the results, F3 revealed greater water absorption, followed by F2 and F1, in order of increasing HPMC concentration. In a similar study, Okeke et al.[84] fabricated films for buccal delivery containing nicotine with various ratios of HPMC and SA and the swelling index was investigated based on weight alteration. The researchers found that increasing the amount of SA engenders the swelling index to decline in the same concentrations of HPMC which is a highly hydrophilic polymer.

Another crucial parameter to consider during the preparation of films is the hydrolysis rate, since hydrolytic degradation can affect the drug release and various other general properties.[40] The improved hydrolysis can be ascribed to the water solubility of the materials, the higher SA concentration the faster mass loss of the formulations.

4.1.2. *Mechanical properties of the films*

The tensile strength is a feature that exhibits the maximum force per the analyzing area applied to a point that the film breaks and means fragility or hardness of the material.[77] The reason for the highest tensile strength and elongation at break of F1 is attributed to the highest SA concentration which contributes to the resilience of the films. It was observed that when SA/gelatin emulsion based films were developed, the presence of SA led to improved mechanical strength.[73] Similar mechanical properties were recorded when SA films loaded with thyme essential oil were analyzed.[78]

4.1.3. *FT-IR characterization of the films*

FTIR is an important technique when pharmaceutical formulations such as films are being studied, since it can provide significant observations for their nature and possible incompatibility between the components.[40] The bending vibration of −OH and C−H stretching was found to be similar to that obtained by Zupanc et al.[79]

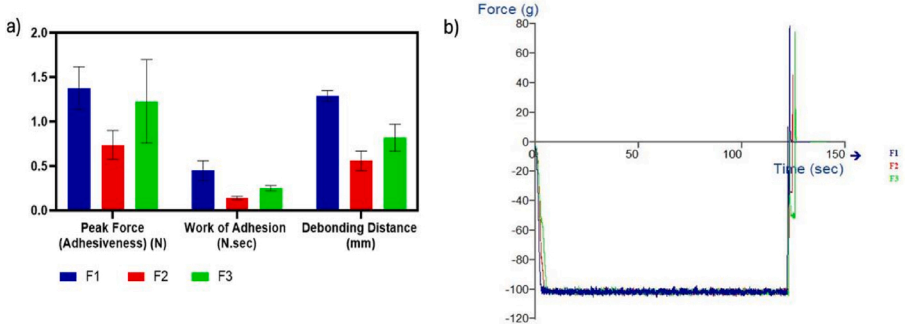

Fig. 5. Bioadhesion results (a) and force-time plot (b) of the PCA-loaded films.

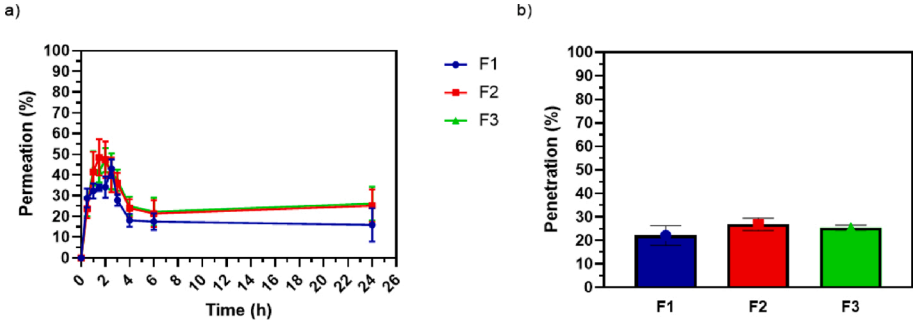

Fig. 6. *Ex vivo* permeation (a) and penetration (b) results.

It can be said the spectra of the neat films demonstrate similar absorption bands to those of the neat materials, i.e., SA and HPMC; this is a rational result considering that also the pure materials present very similar functional bonds, i.e., −OH, CH, CH_2, CO. Therefore, the bands of their absorption are in a similar region.[40] However, some of the bands are at lower or higher wavenumbers compared to the neat materials. This fact can be attributed to interactions between the hydroxyl groups of HPMC and the carboxyl group of SA,[80] providing stability to the formulations. Moreover, when PCA loaded into the films, new peaks have not been identified. However, the addition of PCA altered slightly the spectra of the loaded films compared to the pure films.

PCA structure comprises both hydroxyl and carboxyl groups which can interact with SA and HPMC components. Therefore, the results indicate possible hydrogen bonding between the drug and the components. However, no new bands have been identified demonstrating the stability of the system.[39]

4.2. *In vitro drug release study*

In vitro release studies should always be conducted since they help predict the *in vivo* behavior of the drug. Considering that PCA has only limited solubility in water but is freely soluble in ethanol and other solvents, the release mechanism is mostly up to the polymeric interaction and its positioning within the entanglement. With a sustained manner, F1 reached 100% release in 24 h which can be attributed to many reasons. In addition, according to hydrolysis studies, F1 showed a 100% hydrolysis degree within 10 min, while F2 and F3 needed more time. From a different viewpoint, PCA is likely to adhere to the film surface, transition occurred from the surface of them, hence rapid release was observed at the beginning. Latif et al. came up with the increase of HPMC caused a decrease in release rate since water uptake was reduced and hereby less substance was release. [81]

Release kinetic analysis revealed that F1 fits better to the first order. As reported by the literature, when the release of polymeric films fits the first-order model, it can be indicated that the drug release mechanism depends on concentration, meaning that over time the drug amount released, the drug diminishes as its concentration lower.[82]

4.3. *Ex vivo bioadhesion*

The data show that the bioadhesive strength is desirable for transdermal patches and dermal dressings. In general, bioadhesion can be established through hydrogen bonding between the skin and functional groups of the bioadhesive macromolecules, i.e., free carboxyl and hydroxyl groups; nonetheless, there is not one theory under bioadhesion.[60,83] For example, Okeke and Boateng developed a composite HPMC and SA based buccal formulations; according to their bioadhesion data, as the amount of SA gets greater, the higher the bioadhesion strength.[84] Given that F1 presents a higher amount of SA, it is quite rational that herein, it possesses higher bioadhesive strength.

4.4. *Ex vivo permeation and penetration study*

Preliminary studies of patches/dressings are always performed to predict the *in vivo* behavior of the drug delivery system; therefore, an *ex vivo* permeation and penetration study was done to check whether the PCA loaded film can deliver the drug to deeper tissues than epidermis. The results demonstrated the efficient transdermal delivery of PCA similar to the literature.[32] According to Song et al., cream formulations containing PCA showed increased *in vitro* skin permeation of PCA. [85] In further, Biswas et al. developed an optimized phospholipid complex of PCA for UVA (the long wave of solar ultraviolet radiation ranging from 320 to 400 nm) mediated oxidative stress. *Ex vivo* skin permeation data demonstrated that due to the enhanced permeation, the delivery system is suitable for transdermal delivery of PCA.[33]

5. Conclusions

In this preliminary study for the development of dermal/transdermal films, PCA was employed as a potent pharmaceutical agent, owing to biological effects for dermal/transdermal applications. PCA-loaded films were successfully formulated by solvent-casting method, presenting weight and thickness uniformity. Among them, F1 displayed the highest moisture retention as well as continuous and linear water absorption behavior, which is favorable for wound treatment to maintain moisture and to promote the healing process. Moreover, the release of PCA exhibited 100% in 4 h, suggesting effective drug release to the target site. This finding was also supported by the *ex vivo* bioadhesion study of the films, where F1 displayed the highest bioadhesion. In addition, PCA can also permeate and penetrate skin. Herewith, PCA-containing HPMC and SA-based films are a promising candidate for dermatological diseases as well as transdermal delivery.

CRediT authorship contribution statement

Ayşe Pınar Yağcılar: Writing – original draft, Methodology, Investigation. **Gökçe Karaotmarlı Güven:** Writing – original draft, Methodology, Investigation. **Emre Şefik Çağlar:** Writing – original draft, Methodology, Investigation. **Neslihan Üstündağ Okur:** Writing – original draft, Supervision, Methodology, Investigation. **Panoraia I. Siafaka:** Writing – original draft, Supervision, Methodology, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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