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ORIGINAL PAPER

Effect of Eudragit® NE 40D on The Properties of Pectin Film-Based Polymer Blends

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Abstract

In this work, pectin was used as the primary polymer component while Eudragit® NE 40D was used as polymer blending for the preparation of the thin films. Glycerin was used as a plasticizer. The samples were prepared by a solvent casting method, and their thickness, physicomechanical properties, and moisture ability were characterized. The ratio of Eudragit® NE 40D to pectin was varied to obtain films with tunable mechanical properties and moisture ability. The appearance of the pectin-based blended films was yellowish and transparent by visual observation, and the thicknesses of the pectin-based blended films were in the range of 102–138 µm. The mechanical property of softness of the pectin-based blended films was measured after blending with Eudragit® NE 40D. Thermal stability of pectin-based blended film was also dependent on the amount of Eudragit® NE 40D added; a broadly endothermic and exothermic transition peak were observed. The amorphous state was found in the pectin-based blended films. The cross-sectional morphology of the pectin-based blended films showed a homogeneous film without pores, cracks, or cavities. The moisture content and moisture uptake of the pectin-based blended films were in the range of 18.89–27.52% and 3.38–6.00%, respectively. Overall, the pectin-based blended films showed good properties and these results indicate that pectin-based blended films can potentially be used to prepare thin films for medical and pharmaceutical applications, including drug delivery film dosage forms.

Keywords Eudragit® NE 40D · Pectin · Blended film

Introduction

A natural biopolymer of pectin is a structural heteropolysaccharide found of the primary cell walls and middle lamella in plant tissues. Its chemical structure consists of linear α-[1–4]-D-galacturonic acid molecules with have a high molecular weight [1]. Pectin can be used as a gelling agent, thickening agent, emulsifying agent, and stabilizer. The properties of pectin gel depend on the concentration, pH, molecular size, and characteristics of the pectin raw material. The appearance of pectin is a white or brown powder. The pectin powder can be isolated from the rinds and hulls of durian [2–7], the peels of papaya [8], the endocarps of *Citrus depressa* [9], the peels of mango [10], and the leaves of *Cissampelos pareira* [11–13]. Pectin is the most natural polymer used in a pharmaceutical dosage form. Pectin easily dissolves in water and can easily be prepared as a film formation. The pectin film based pharmaceutical dosage form can control the release of drugs such as nicotine [7, 13, 14], enrofloxacin [15], donepezil [16], indomethacin [17], and verapamil hydrochloride [18]. Therefore, it is interesting to prepare pectin as a film formation by blending it with different ratios of Eudragit® NE 40D using as a transdermal film preparation in the future.

Eudragit® is a versatile acrylic material that has a long history of use, depending on the individual types and grades. The Eudragit® L and S grades are the first reports in the year 1954 that is used for enteric-coated tablet dosage forms. The Eudragit® L and S grades-based products used for rapidly disintegrating and sustained release coatings, and expanding the widening potential applications considerably. With the development of various grades of Eudragit®, it becomes possible to handle many aspects of formulation development such as film coating, granulation, direct compression, melt

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extrusion, and mastery of technologies to engineer immediate or sustained release, as well as GI targeting, enteric coatings, pulsed release, and transdermal formulations [19]. Eudragit® NE 30D and 40D grades are a popular grade to use for the controlled release products. Eudragit® NE 30D and 40D are available in the form of 30% and 40% aqueous dispersions, respectively. The aqueous dispersions contains a neutral copolymer based on ethyl acrylate and methyl methacrylate. Eudragit® NE 30D and 40D appear to be milky white liquids of low viscosity with a faint characteristic odor. The minimum temperature of the film-forming preparation form of Eudragit® NE 30D or 40D grades is 5 °C. The glass transition temperature (T_g) of both Eudragit® 30D and 40D grades is ~8 °C. The usages of both Eudragit® NE 30D and 40D grades are as modified release formulations in various dosage forms i.e. (I) the multiparticulated floating drug delivery system of zolpidem tartrate designed to prolong the gastric residence time and to improve bioavailability [20], (II) the loratadine buccal films for allergic rhinitis developed to control the drug release and to enhance the mucoadhesion time [21], (III) the buccoadhesive film of prednisolone prepared by the solvent-casting method to enhance the bioavailability [22], and (IV) the nonocclusive dermal therapeutic system for miconazole nitrate prepared to control the drug release for at least 24 h [23]. As a literature review, the Eudragit® NE 40D is interesting to use for various pharmaceutical applications including modified release, enhancement of bioavailability, in the form of buccoadhesive films, and nonocclusive dermal therapeutic systems. Hence, Eudragit® NE 40D, a versatile polymer for drug delivery, was selected for this research.

Pectin film-based polymer blends were prepared for this research. The different ratios of Eudragit® NE 40D were blended in the pectin film and glycerin, which is widely used in pharmaceutical products, was used as a plasticizer. Glycerin is soluble in water, which is commonly used to prepare the film. Also, an advantage of glycerin is the compatibility with the skin without irritation after application. Thus, it is selected to use as a plasticizer in this research. The mechanical properties, differential scanning calorimetry (DSC), X-ray diffraction (XRD), scanning electron microscope (SEM), moisture content, and moisture uptake of pectin-based blended films were characterized and also reported.

Materials and Methods

Materials

Pectin powder was a commercial-grade that purchased from VR Bioscience Co., Ltd, Thailand. Eudragit® NE 40D was obtained from Jebsen & Jessen NutriLife (T) Ltd., Thailand. Glycerin was obtained from the P.C. Drug Center (Thailand).

Pectin Film-Based Polymer Blends Preparation

The pectin and Eudragit® NE 40D proportions employing in the study were 1:0, 1:0.5, and 1:1 (Table 1). Pectin powder was added to distilled water, allowed to swell, and glycerin was then slowly added to the pectin solution to act as a plasticizer. The amount of glycerin was added at 30% w/w, based on the amount of polymer. The pectin solution was sonicated to remove the air bubbles. The Eudragit® NE 40D solution was accurately weighed by analytical balance. The pectin solution was slowly poured into the Eudragit® NE 40D solution with continuous mixing until a clear solution was obtained. Twenty grams of the mixture was accurately weighed into a Petri dish and dried in a hot-air oven at 70 ± 2°C for 6 h. Subsequently, the dry pectin-based blended films were peeled off the Petri dish and kept in a desiccator before use in the next study.

Characterization of Pectin Film-Based Polymer Blends

Mechanical Properties

The mechanical properties of the pectin-based blended films were tested by the TA.XT Plus Texture Analyzer (Texture Technologies Corporation and Stable Micro Systems, Ltd., USA) with a 500-g loaded cell. The film sample was cut into a 10 mm × 60 mm rectangular shape. The gauge length of the tested area was 10 mm with a controlled cross-head speed at 10 mm/min. Six samples of each film sample were tested. The ultimate tensile strength (UTS) and elongation at break were reported. The UTS was defined as either a maximum distinct or a region of strong curvature approaching a zero slope in the stress–strain curve. The elongation at break was determined by measuring the distance between the gauge mark of the fractured specimen [24, 25]. The UTS value and percentage of elongation at break were calculated by Eqs. 1 and 2, respectively.

Table 1 Composition of pectin-based blended films

Formulas	Pectin (g)	Eudragit® NE 40D (g)	Glycerin[a] (g)	Water (g)
P1NE0	1.0	-	0.30	18.70
P1NE0.5	1.0	0.5	0.45	18.05
P1NE1	1.0	1.0	0.60	17.10

[a] The amount of glycerin was used at 30% w/w based on polymer

$$\mathrm{UTS\ (MPa)} = \frac{\mathrm{F}}{\mathrm{A}} \tag{1}$$

where F is the breaking load (N), A is the cross-sectional area of the specimen (width, mm × thickness, mm).

$$\text{Elongation at break (\%)} = \frac{\mathrm{L_s} - \mathrm{L_0}}{\mathrm{L_0}} \times 100 \tag{2}$$

where L_0 is the original length of the specimen (mm), and L_S is the length at the breaking point of the specimen (mm).

DSC Study

The thermal analysis of each pectin-based blended film was determined by the DSC7 instrument (Perkin Elmer, USA). Ten milligrams of each blended film sample were weighed in the DSC pan and hermetically sealed. The heating scan was from 25ºC to 300ºC with a heating rate of 10ºC/min.

XRD Study

The atomic and molecular structure of a crystal of each pectin-based blended film were tested by the X-ray diffractometer (model: Empyrean, PANalytical, Netherlands). The conditions of the study were 40 kV, 45 mA, 5—40° (2θ), and 0.02° (2θ)/s for generator operating voltage, a current of the X-ray source, angular range, and stepped angle, respectively.

SEM Photography

Each pectin-based blended film was immersed in liquid nitrogen. It was deducted and then placed onto the stub and coated with the gold. The cross-sectional morphology was photographed by the SEM5800LV instrument (model: JSM-5800 LV, JEOL, Japan) using a high vacuum and a high voltage of 15.00 kV condition, and an Everhart–Thornley electron detector.

Moisture Content

The sample specimens were tested using 1 cm × 1 cm and placed on an aluminum pan, and heated to 120ºC. The percentage of moisture content was measured using a moisture analyzer (model: MAC 50/NH, Poland) and calculated according to Eq. 3.

$$\text{Moisture content (\%)} = \frac{\mathrm{W_{initial}} - \mathrm{W_{dry}}}{\mathrm{W_{initial}}} \times 100 \tag{3}$$

where $W_{initial}$ is the initial weight of the sample (g) and W_{dry} is the dry weight of the sample (g).

Moisture Uptake

The percentage of moisture uptake was tested using 1 cm × 1 cm sample specimens kept in a desiccator with silica gel beads for 24 h. The initial weight (W_0) was reported, and specimens were then moved to desiccators with a 75% relative humidity environment produced by a saturated sodium chloride solution. Every month for three months, the sample specimens were removed and weighed until constant values (W_u). The percentage of moisture uptake was calculated according to Eq. 4.

$$\text{Moisture uptake (\%)} = \frac{\mathrm{W_0} - \mathrm{W_u}}{\mathrm{W_0}} \times 100 \tag{4}$$

Statistical Analysis

The average value was calculated and reported as the mean ± standard deviation value. All results were statistically analyzed by one-way analysis of variance followed by post hoc analysis. A *p-value* of less than 0.05 was considered to be statistically significant.

Result and Discussion

The appearances of dry pectin-based blended films are shown in Fig. 1. The dry pectin-based blended films had a yellowish and transparent film. The dry pectin-based blended films could be easily removed from the Petri dish, where they were cast without observable damage. The thicknesses of the pectin-based blended films, determined from five different positions on the film, were 102 ± 32, 124 ± 39, and 138 ± 40 µm for P1NE0, P1NE0.5, and P1NE1 formulas, respectively. The lowest thickness of the pectin film (102 ± 32 µm) was observed in the film prepared without the addition of Eudragit® NE 40D, and the thickness of the films increased with increasing the ratio of Eudragit® NE 40D in film-forming ($p < 0.05$). Thicker films were produced due to the higher solid content introduced into the film matrix of pectin. The UTS and elongation at break of the pectin-based blended films are shown in Fig. 2. The pectin film showed a high UTS value and percentage of elongation at break compared to those blended films with the addition of the Eudragit® NE 40D. The Eudragit® NE 40D grade is the aqueous dispersion of a neutral copolymer based on ethyl acrylate and methyl methacrylate that is highly flexible and has a plasticizer in the solution [19]. Thus, when the Eudragit® NE 40D was added to the pectin film, the UTS value of the film significantly decreased ($p < 0.05$), representing the softness of the pectin-based blended film. However, the percentage of elongation at break of the

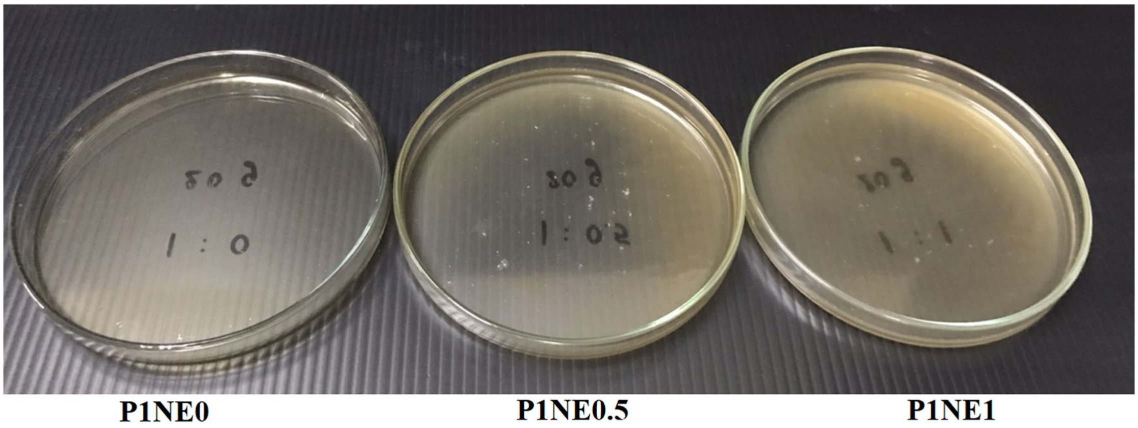
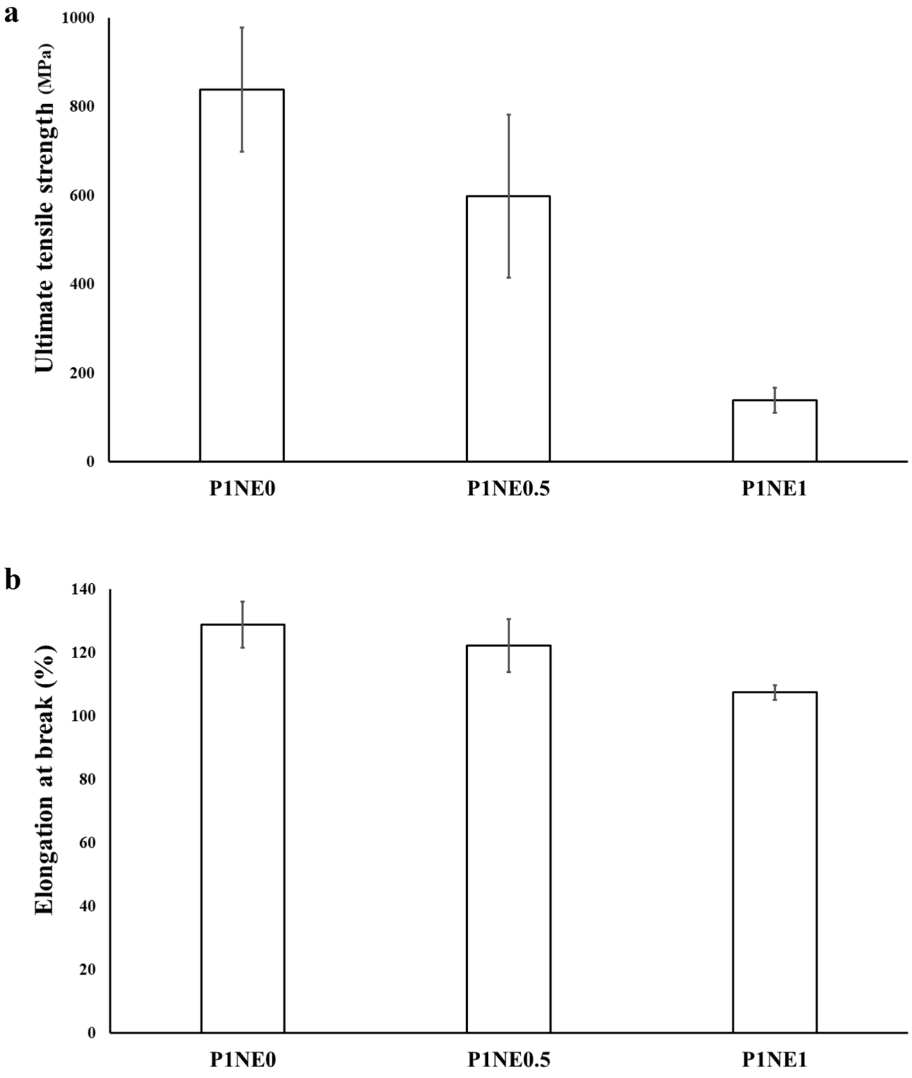


Fig. 1 Appearance of dry pectin-based blended films (Color figure online)

Fig. 2 Mechanical properties of pectin-based blended films: **a** UTS and **b** Elongation at break



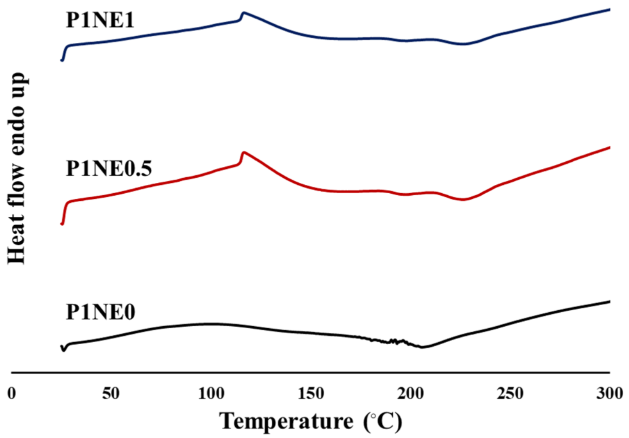


Fig. 3 DSC thermograms of pectin-based blended films (Color figure online)

pectin-based blended film showed no significant difference after the Eudragit® NE 40D ratio increased (*p > 0.05*). However, the higher concentration of the Eudragit® NE 40D could not be prepare because the precipitation of the Eudragit® NE 40D occurred in the mixture solution. The optimum ratio of the Eudragit® NE 40D successfully blended in the pectin was a 1:1. Thus, the mechanical properties of the pectin-based blended film depended on the addition of Eudragit® NE 40D.

Figure 3 shows the DSC thermograms of pectin-based blended films. According to a previous study, the thermal behavior of pectin depends primarily on the chemical composition and state transitions that occurred during processing [26, 27]. In the present study, the pectin film presented two intense peaks in the DSC thermograms, including a broad endothermic transition peak at a temperature around 93.33 °C attributed to the loss of adsorbed and structural water, and an exothermic transition peak at a temperature around 220 °C related to the decomposition of pectin [28]. After the Eudragit® NE 40D was added to the pectin film, the DSC thermograms presented endothermic transition peaks at a temperature of around 108.43 °C and 116.50 °C for P1NE0.5 and P1NE1, respectively, which were associated with the evaporation of water. The hydrogen bonding between the water and the copolymer of ethyl acrylate and methyl methacrylate in Eudragit® NE 40D increased the endothermic temperature of the pectin-based blended film [26] when the Eudragit® NE 40D ratio increased. The endothermic peaks of the pectin-based blended films (P1NE0.5 and P1NE1 formulas) were also found to be broader than the control films (pectin film, P1NE0 formula). The decomposition of the pectin-based blended films produced an exothermic transition peak at a temperature of around 213.48 °C and 210.50 °C for P1NE0.5 and P1NE1, respectively. The thermal stability of the blended film was increased when the Eudragit® NE 40D ratio increased. Thus, the enthalpy of melting (ΔH_m) in the exothermic peak increased, indicating increased thermal stability of the pectin-based blended films and heat generated by the decomposition of pectin. The thermal behavior of the pectin molecule is largely defined by its internal and external bonding and its configuration [26, 29]. The increase in degradation temperature for pectin-based blended films might be linked to the hydrogen bonds formed between the ethyl acrylate and the methyl methacrylate copolymer in Eudragit® NE 40D and the structure of the pectin. Therefore, an increased amount of hydrogen bonding in the pectin-based blended film required more heat to break down the film. Similar results have also been observed for biodegradable citrus pectin films incorporated with young apple polyphenols [26], chitosan films incorporated with tocopherol [30], and edible pectin films incorporated with açaí (*Euterpe oleracea*) [31].

The X-ray diffraction patterns of pectin and pectin-based blended films are shown in Fig. 4. The pectin film showed a very broad curve with the intensity of diffraction peak at 21.32°, indicating its largely amorphous nature. P1NE0.5 and P1NE1 formulas of the pectin-based blended films showed the intensity of diffraction peaks at 21.08° and 21.24°, respectively which showed a very broad curve. The nature of Eudragit® is known to have an amorphous state [32]. These results suggested that the pectin-based blended films were in an amorphous state, meaning the crystals were not observed in the films. This phenomenon could describe the presence of the largely amorphous nature of the pectin was not affected by the addition of Eudragit® NE 40D.

Each pectin-based blended film was cut into a 10 mm × 60 mm rectangular shape and then immersed in liquid nitrogen. After that, the sample was deducted and then placed onto the stub and coated with gold. The cross-sectional morphology of the sample was photographed by the SEM technique are shown in Fig. 5. The cross-section of the

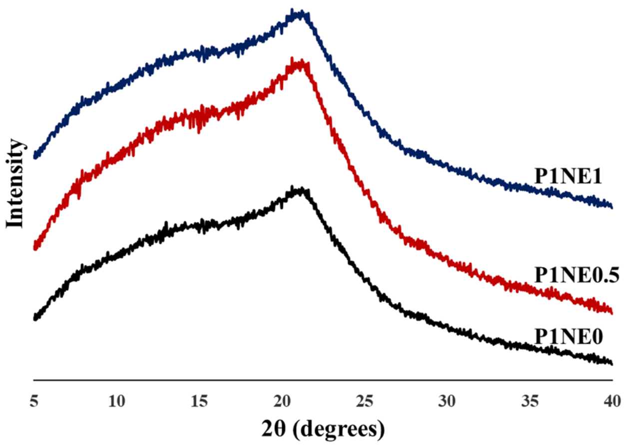


Fig. 4 XRD patterns of pectin-based blended films (Color figure online)

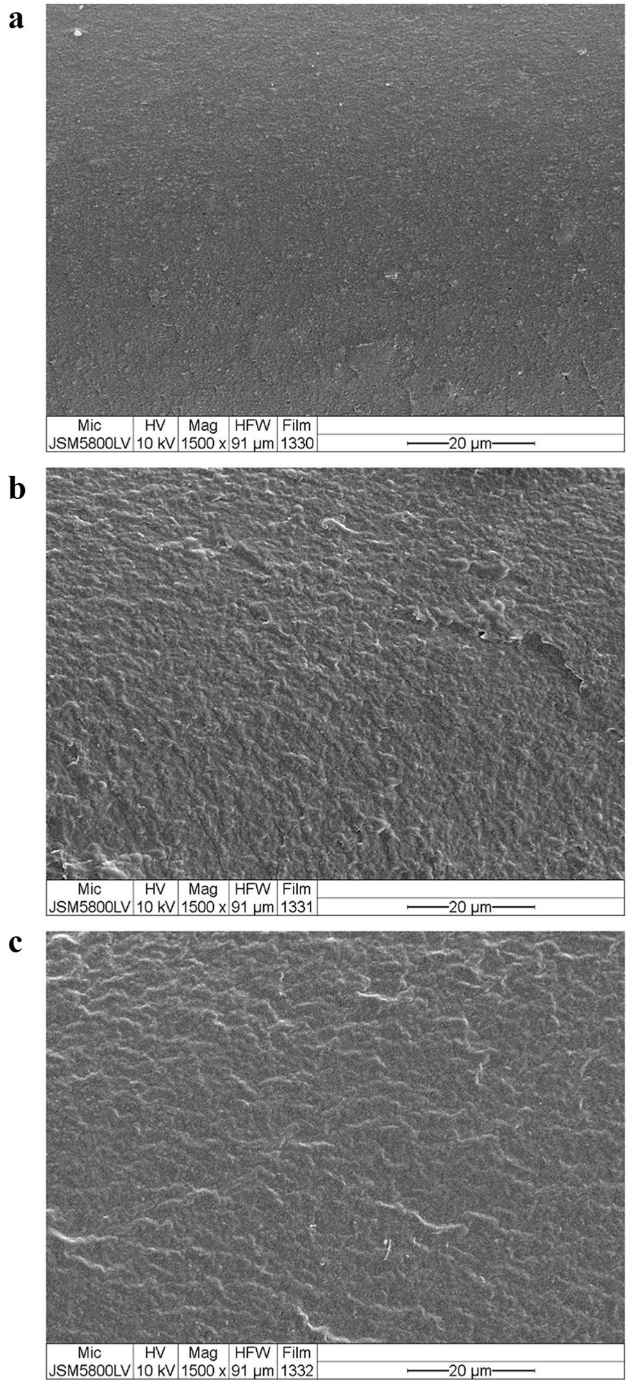


Fig. 5 Cross-sectional morphology of pectin-based blended films at × 1500: **a** P1NE0, **b** P1NE0.5, and **c** P1NE1

P1NE0 sample showed a smooth and dense film (Fig. 5a), while the cross-sections of the P1NE0.5 and P1NE1 samples showed rough and uneven films (Fig. 5b and c, respectively). However, all pectin-based blended films had a compact film without pores, cracks, or cavities. The homogeneous pectin-based blended films were confirmed by visual observation of the cross-sectional images.

The moisture contents of the pectin-based blended films were 27.52 ± 2.18%, 23.84 ± 5.33%, and 18.89 ± 1.92% for P1NE0, P1NE0.5, and P1NE1, respectively. The moisture uptakes of the pectin-based blended films were 6.00 ± 0.88%, 4.41 ± 1.18%, and 3.38 ± 0.37% for P1NE0, P1NE0.5, and P1NE1, respectively. The pectin film had a high moisture content and moisture uptake, while the moisture content and moisture uptake decreased after Eudragit® NE 40D was blended into the pectin film. The Eudragit® NE 40D is a copolymer of ethyl acrylate and methyl methacrylate [19]. Thus, these changes might be due to decreasing the hydrophilicity of the Eudragit® NE 40D in the pectin film. In the future, the possibility of hydrophilicity of the pectin film by blending with Eudragit® NE 40D will be used to predict the release behavior of the drug. The moisture uptake and moisture content of the polymeric film would play an important role during the early stages of the drug release from the films [24].

Conclusion

The present study prepared the pectin-based blended films by adding different ratios of Eudragit® NE 40D. All the films had a yellowish and transparent film in appearances, and the thicknesses were in the range of 102–138 µm, depending on the solid content added to the film matrix of pectin. A natural biopolymer of pectin film resulted after blending with the different ratios of Eudragit® NE 40D. The thermal behaviors of the pectin-based blended films were also found to be broadly endothermic and exothermic transition peak after the Eudragit® NE 40D was added to the matrix film of pectin, represents an increase in the thermal stability of the pectin-based blended films. All pectin-based blended films were in an amorphous state. The cross-sectional morphology of the pectin film was smooth and dense film. After Eudragit® NE 40D was added, the cross-sectional morphology was rough and uneven. However, all pectin-based blended films showed a homogeneous film without pores, cracks, or cavities. The moisture contents and moisture uptakes of pectin-based blended films ranged from 18.89–27.52% and 3.38–6.00%, respectively. These results provide clear evidence for the feasibility of using pectin-based blended films as materials for medical and pharmaceutical skin applications including drug delivery film formulations. Future research will involve the preparation and evaluation of some drug delivery systems derived from these blended films.

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Compliance with Ethical Standards

Conflict of interest The authors report no conflicts of interest.

Informed Consent The authors alone are responsible for the content and writing of the paper.

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