



Gelatin/Gelatinized Sago Starch Biomembranes as a Drug Delivery System Using Rubber Latex as Plasticizer

Suchipha Wannaphatchaiyong¹ · Jirapornchai Suksaeree² · Rungtiwa Waiprib¹ · Apassorn Kaewpuang¹ · Wiriya Saelee¹ · Wiwat Pichayakorn¹

Published online: 20 July 2019

© Springer Science+Business Media, LLC, part of Springer Nature 2019

Abstract

Preparation and properties of gelatin and gelatin/gelatinized sago starch biomembranes as a drug delivery system are presented. Deproteinized natural rubber latex (DNRL) was chosen to blend as a plasticizer in biomembranes due to its elasticity. The opaque biomembranes were formed, and the effect of DNRL amounts (10–50 part per hundred of gelatin; phg) on mechanical properties of biomembranes was investigated. It was discovered that increasing the amounts of DNRL could decrease the brittleness of biomembranes. However, these DNRL blended biomembranes still swelled, dissolved in water, and eroded within 2 h. The 50 phg DNRL was further chosen for biomembrane preparations. Then, the 5–30 phg gelatinized sago starch which was prepared in-house was added. These gelatin/gelatinized sago starch biomembranes were homogenous and opaque. They portrayed good water uptake properties, and the highest values occurred in 20–30 min, then these biomembranes eroded slowly. Increasing the amounts of sago starch in biomembranes raised the water uptake rates but reduced the erosion properties. Biomembranes with and without starch blends showed the same tensile strengths. Their elongations at break increased when the amounts of starch were raised but still were lower than that of gelatin/DNRL biomembranes. The morphology, scanning electron microscopy, atomic force electron microscopy, Fourier transform infrared spectroscopy, differential scanning calorimeter, and X-ray diffractometer confirmed the compatibility of ingredients in biomembranes. Lidocaine and its hydrochloride salt were successfully incorporated in these biomembranes with good properties. The drug release and permeation of biomembrane showed good drug controlled release and were able to permeate through the pig skin.

Keywords Gelatin · Sago starch · Natural rubber latex · Biomembranes · Drug delivery

Introduction

Nowadays, polymeric biomembranes are normally prepared from many natural biopolymers such as starch [1], gelatin [2], whey protein [3], chitosan [4], etc. These biopolymers can easily form films. Moreover, they are safe because of their biodegradability and biocompatibility [5]. Thus, they are of interest for film productions in several applications such as photography, foods, cosmetics and pharmaceuticals

[6]. Therefore, these systems are noteworthy for drug delivery in transdermal, buccal and oral systems.

Gelatin is a natural polymer derived from collagen of animal skin and bones. It is widely used in medicine and pharmaceuticals [7, 8]. Moreover, gelatin has good film forming property [9] which might provide a controlled release system for drug delivery [10]. However, gelatin films are quickly soluble and erodible; therefore, they are difficult to use in long-acting drug delivery systems. Gelatin has been prepared as transdermal films by the casting method and the effects of various proportions and concentrations of gelatin on their physical properties have been studied. It was found that all films of gelatin and glycerin blends were suitable as they had flexibility, clarity and elasticity. In that study, diclofenac sodium was used for studying in vitro drug release and in vitro permeation through cellophane membrane [10]. Moreover, gelatin has also been combined with other polymers such as chitosan [11], pectin [12] and starch

✉ Wiwat Pichayakorn
wiwat.p@psu.ac.th

¹ Department of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Songkhla 90112, Thailand

² Department of Pharmaceutical Chemistry, College of Pharmacy, Rangsit University, Pathum Thani 12000, Thailand

[13] for improving the films properties such as controlling drug release rate, physical property, etc.

Starch is also an interesting biodegradable material widely used in daily life as a food ingredient and pharmaceutical formulation as a binder, disintegrant, diluent, etc. [14]. Starch is a natural polymer which consists of amylose and amylopectin. Amylose is a linear molecule with a few branches which can give stronger films. Amylopectin is a highly branched molecule leading to different mechanical properties of films [15]. The starch can be suspended in water, and after being heated at or above gelatinization temperature, it is gelatinized, and starch granules swell to many times their original size and crystallize inside the granules [16]. Sago starch is the natural starch isolated from sago palms (*Metroxylon sagu* Rottb.) which are distributed in South Pacific islands and extend westward through Melanesia into Indonesia, Malaysia and Thailand [17]. Sago starch has been used for food preparation and in cosmetic formulations [18]. Due to the very high water uptake property of gelatinized sago starch, the combination of gelatin and gelatinized sago starch is interesting to study for drug delivery systems. However, in previous research, gelatin/gelatinized sago starch biomembranes were too brittle [19]. This mechanical problem could be improved with plasticizer addition. In film technology, there are many plasticizers such as glycerol, ethylene glycol, sorbitol, fatty acid, etc., which are used to increase the flexibility of the films [6, 20, 21].

The natural rubber latex (NRL) is natural polymer produced by *Hevea brasiliensis* or Para rubber trees. It is composed of cis-1,4-polyisoprene polymer. The properties of interest in NRL polymers are high elasticity and easy to prepare films [22]. NRL has been used in industrial products such as tires, gloves, balloons, tubes and condoms [23–25] and in developed pharmaceutical formulations such as film coated tablets [26] and transdermal patches [27]. Due to the high lipophilicity of NRL polymers, its property could be modified by blending NRL with several hydrophilic polymers [28]. Moreover, the protein allergens in NRL should also be removed due to their allergy causes [29]. There are several studies which use deproteinized NRL (DNRL) as a major polymer for transdermal drug delivery systems; for example, nicotine transdermal patches [30], lidocaine transdermal patches [31] and sulindac electrically controllable transdermal patches [32]. Thus, in this study, DNRL was chosen for use as a plasticizer to increase the flexibility of gelatin and gelatin/gelatinized sago starch blended biomembranes.

This study aimed to prepare gelatin/gelatinized sago starch biomembranes with DNRL as plasticizer. Lidocaine, the model drug in either base form (LB) or hydrochloride salt (LH), was loaded into the biomembranes, and the physicochemical properties of these biomembranes were evaluated.

Materials and Methods

Materials

The 160 bloom gelatin was purchased from PB Gelatins (Tessenderlo, Belgium). Sago starch was prepared in-house from sago trees in Nakorn-Srithammarat province, Thailand. DNRL was prepared in-house by our research group using the enzymatic method [33]. LB and LH were purchased from Sigma-Aldrich (Shanghai, China). Distilled water was used throughout the experiments. All other solvents and chemicals used were pharmaceutical or analytical grade and used without further modification. For drug permeation through pig skin, the pig skin was obtained from a newborn pig which had died naturally after birth. The weight of the newborn pig was between 1.4 and 1.8 kg. The dead newborn pigs were directly purchased from a local pig farm in Songkhla province which was regulated by the Department of Livestock Development, Thailand, and promptly prepared to surgically remove the skin. The hair, subcutaneous fat and other extraneous tissues were removed from the skin. The morphological integrity of this prepared skin was observed firstly. After that, the pig skin was stored at -20°C and used within 3 months [34–36].

Preparation of Biomembranes

Gelatin/DNRL biomembranes (GNR) were formed by a casting method in which 10, 20, 30, 40 or 50 phg of DNRL was used as the plasticizer. The gelatin was dissolved in distilled water, heated to 45°C , cooled to room temperature and adjusted to the final concentration of 15% w/w gelatin solution. DNRL was added into the gelatin solution. The mixed solution was poured into the Petri dish and heated at 50°C for 24 h until a dried film formed.

Gelatin/gelatinized sago starch biomembranes (GSR) were also prepared by the casting method. The 15% w/w gelatin was prepared in the same method as described above. The gelatinized sago starch was prepared by heating 5% w/w sago dispersion until it boiled and cooled down. The gelatin solution was mixed with various amounts of gelatinized sago starch at 5, 10, 15, 20, 25 and 30 phg. The 50 phg DNRL was chosen to add in the mixed gelatin/gelatinized sago starch and stirred until mixed well. For medicated biomembranes, LB was dissolved in 1:1 mixture of methanol:water to get 4% w/v of drug solution, while LH was dissolved in water in the same concentration. Either LB or LH solution was slowly added and stirred to get homogenous dispersion after mixing DNRL in gelatin solution. These mixtures were poured into the

Petri dish and dried at 50 °C for 48 h until a dried film formed. The amount of either LB or LH loading was calculated in advance until there was a final concentration of 5% drug in dry basis biomembranes.

Characterizations of the Biomembranes

The physical appearance of biomembranes was optically observed for film homogeneity. Five pieces of each biomembrane were prepared, and their thicknesses were measured by using vernier micrometer (Teclok Corporation, Japan) with an accuracy of 0.01 mm. The microstructure observation of biomembranes was studied by using an atomic force microscope (AFM; model nanosurf easyscan2, Switzerland) with a non-contact mode using static mode etched silicon probes (ACLA). The roughness of each biomembrane was calculated in three regions from AFM results using easyscan2 control software and Gwyddion. Scanning electron microscope (SEM; model FEI: SEM-Quanta 400, USA) was used for investigating the top surface, the bottom surface and a cross-section of biomembranes.

The five dried GNR and GSNR biomembranes and three dried medicated biomembranes were cut into 2 cm × 2 cm squares, weighed (W_0), and then immersed in distilled water at room temperature. The excess water of hydrated biomembranes was mopped by filtered paper and weighed at different intervals (W_w) for 2 h. They were then dried in a hot air oven at 50 °C overnight and weighed again (W_d). The water uptake and erosion studies of the biomembrane were evaluated. The percentages of water uptake and erosion were calculated by Eq. 1 and 2, respectively.

$$\% \text{ Water uptake} = ([W_w - W_0] / W_0) \times 100 \quad (1)$$

$$\% \text{ Erosion} = ([W_0 - W_d] / W_0) \times 100. \quad (2)$$

The five samples of dried biomembranes were cut into 1 cm × 4 cm. Their mechanical properties were determined by using TA.XT plus texture analyser (Stable Micro System, UK). The ultimate tensile strength (UTS) and elongation at break were evaluated.

The functional groups of each ingredient and their composite biomembranes were investigated by Fourier transform infrared spectroscopy (FT-IR; model Spectrum One, Perkin-Elmer, USA). The range of wavelength scanning, resolution, scan interval and number of scans of FT-IR conditions were 450–4000 cm^{-1} , 4 cm^{-1} , 1 cm^{-1} and 8 scanning times, respectively. The thermal analysis was evaluated by differential scanning calorimeter (DSC; model DSC7, Perkin-Elmer, USA) heating from room temperature to 450 °C with the scanning rate of 10 °C/min in an atmosphere of nitrogen gas. The compatibility of each ingredient was evaluated. The X-ray diffractometer (XRD; model X'Pert MPD, Philips, the Netherlands) was used to detect the compounds in materials

and biomembranes. The running XRD parameter was 40 kV, 35 mA, scan range (2 θ) 5–90°, step size (2 θ) 0.05°, time/step 1 s and scan speed 3°/min. These evaluations were tested without any replication because these were only screening studies for the compatible evaluation, and each instrument was calibrated before determining each sample.

The drug extraction from biomembranes was evaluated by using methanol as a solvent because of its ability to dissolve both LB and LH. The 1 cm × 2 cm biomembrane was cut into small pieces and 10 mL of methanol was added. The biomembranes were extracted by sonicating for 15 min and resting for 24 h. After that, they were sonicated for 1 h, and diluted with phosphate buffer saline solution (PBS) to the suitable concentration for analysis by high performance liquid chromatography (HPLC, Agilent 1100 series, USA.) at 254 nm. The HPLC column was Thermo scientific BDS HYPERSIL C18 Diameter (150 × 4.6 mm, particle size of 5 μm) The mobile phase was 50 mM ammonium acetate with 1% v/v acetic acid:methanol (60:40% v/v) and 0.1% v/v triethylamine of the total volume, and the flow rate was 0.8 mL/min. The injection volume of sample was 50 μL . This extraction was done in triplicate. The drug content (% w/w) was calculated as the ratio of drug extraction (D_{analyze}) and the accurate weight of dried biomembranes (W_{accurate}) following Eq. 3. The percentage of drug entrapment efficiency (% Drug EE) was calculated from the drug extraction (D_{analyze}) compared with theoretical drug loading (D_{theory}) following Eq. 4.

$$\% \text{ Drug content} = (D_{\text{analyze}} / W_{\text{accurate}}) \times 100 \quad (3)$$

$$\% \text{ Drug EE} = (D_{\text{analyze}} / D_{\text{theory}}) \times 100 \quad (4)$$

Moreover, the methanol residues in the LB loaded biomembranes were determined in triplicate by a gas chromatography-flame ionization detector (GC-FID, Agilent HP 6850 GC, USA). The chromatographic column was HP 19091N-113E capillary column (30 m × 320 μm × 0.25 μm). GC oven temperature started at 50 °C and held for 6 min and then was raised to 200 °C. This experiment was done within a few days after the dried film was obtained.

The drug release and permeation of medicated biomembranes were evaluated by modified Franz diffusion cells. The biomembranes were placed on the donor compartment that was separated from the receptor compartment by a dialysis membrane (MW cut-off 12,000) for drug release study and on pig skin for permeation study, respectively. In this skin permeation study, the skin was obtained from the naturally dead newborn pig; therefore, the ethical approval was not needed [34–36]. The skin was thawed and soaked in PBS solution before use. In order to deliver the drug through the skin in transdermal drug delivery, the drug should release and permeate in the blood circulation. In this study, PBS pH 7.4, which is a similar pH to blood, was chosen to be added

in the receptor compartment, with a controlled temperature of 37 °C, and stirred with a magnetic stirrer at 200 rpm. A 1 mL aliquot of the solution was withdrawn from the receptor compartment at predetermined time intervals of 5, 10, 15, 30, 45 min and 1, 2, 3, 4, 6, 8, 12 and 24 h, with an equal volume of PBS added to replace the removed liquid in the receptor. The drug concentration in each sample was determined by HPLC at 254 nm. In vitro drug release and permeation profiles were further analyzed into three types of kinetics including zero order, first order and Higuchi's kinetics. Each sample analysis was performed in triplicate and quintuplicate in kinetics of drug release and drug permeation, respectively. All results were presented as mean $\pm$ standard deviation (S.D.). Statistical analysis was calculated using ANOVA with a statistical significance level set at $p < 0.05$, and the post hoc Tukey procedure was done with SPSS.

The stability of medicated biomembranes was studied by keeping them for 3 months at three various temperatures, i.e., 4 ± 1 °C, ambient temperature ($\approx 28 \pm 4$ °C), and 45 ± 1 °C. They were evaluated for changes in appearance, drug content, drug release and permeation profiles by the previously described methods. The replication of each evaluation was the same as above.

Results and Discussion

For film preparations, many parameters were used to decide on a good formula. Physical appearance and film thickness were simple parameters that could be observed immediately. These parameters represented the product's appeal when the user encountered it. Methanol residue was also measured to ensure that the prepared biomembranes were safe to use. Likewise, AFM and SEM also confirmed the microstructures of these films that related to their physical appearances. These also explained the compatibility of the film's ingredients. Moreover, some physical and mechanical properties of films could be important to the use of products. In this study, water uptake, erosion, UTS and elongation at break of developed biomembranes were evaluated to consider the DNRL property for acting as a plasticizer. The water uptake and erosion of films also affected the drug release and stability of biomembranes when used.

Our studies showed that DNRL could be used as a plasticizer. In our preliminary study (data were not shown), the 10, 20, 30, 40, 50, 75 and 100 phg of DNRL were mixed in gelatin/DNRL (GNR) biomembranes. It was found that increasing the amount of DNRL decreased the water uptake and erosion of GNR biomembranes. The 75 and 100 phg of DNRL in GNR provided less water uptake and less-erodable biomembranes. In this study, however, gelatin was chosen as the main polymer, and DNRL was intended for use as a plasticizer only. The developed biomembranes should have

the ability to absorb water and release the drugs; therefore, DNRL was further studied in the range of 10–50 phg for preparing gelatin/gelatinized sago starch/DNRL (GSRN) biomembranes. Both the GNR and GSRN biomembranes with or without drug (LB or LH) were prepared by the casting method in the Petri dish. In the drying process at 50 °C, the products in the Petri dish were weighted after 24 h. Then, they were further dried and weighed again every 12 h. The results showed that the weight of GNR biomembranes did not change after 24 h, but those of GSRN biomembranes changed until 48 h and then were constant. These findings indicated that GNR biomembranes could be dried within 24 h, but sago starch blended biomembranes could delay the drying time of films to 48 h. Therefore, these drying conditions were used in further study.

All GNR and GSRN with or without drug biomembranes were homogeneous and opaque in character. The average weight and thickness of all biomembranes were not different as shown in Table 1, because they could be controlled by forecasting the calculated dried weight of components in each Petri dish.

All blank GNR biomembranes showed the highest water uptake at 15–30 min; after that they eroded slowly as shown

Table 1 The weight and thickness of GNR, GSRN and medicated GSRN biomembranes (n = 5)

Sample	Weight $\pm$ S.D. (g/4 cm ²)	Thickness $\pm$ S.D. (mm)
GNR 10 phg	0.1152 $\pm$ 0.0120	0.277 $\pm$ 0.027
GNR 20 phg	0.1429 $\pm$ 0.0250	0.327 $\pm$ 0.037
GNR 30 phg	0.1230 $\pm$ 0.0098	0.289 $\pm$ 0.038
GNR 40 phg	0.1414 $\pm$ 0.0120	0.336 $\pm$ 0.017
GNR 50 phg	0.1306 $\pm$ 0.0230	0.329 $\pm$ 0.038
GS 5 phg NR	0.1296 $\pm$ 0.0069	0.368 $\pm$ 0.026
GS 10 phg NR	0.1334 $\pm$ 0.0093	0.348 $\pm$ 0.022
GS 15 phg NR	0.1460 $\pm$ 0.0050	0.396 $\pm$ 0.028
GS 20 phg NR	0.1444 $\pm$ 0.0105	0.374 $\pm$ 0.036
GS 25 phg NR	0.1350 $\pm$ 0.0085	0.396 $\pm$ 0.016
GS 30 phg NR	0.1465 $\pm$ 0.0058	0.367 $\pm$ 0.027
LB-GS 5 phg NR	0.1257 $\pm$ 0.0119	0.320 $\pm$ 0.033
LB-GS 10 phg NR	0.1184 $\pm$ 0.0163	0.319 $\pm$ 0.047
LB-GS 15 phg NR	0.1322 $\pm$ 0.0076	0.355 $\pm$ 0.023
LB-GS 20 phg NR	0.1447 $\pm$ 0.0085	0.358 $\pm$ 0.026
LB-GS 25 phg NR	0.1494 $\pm$ 0.0043	0.344 $\pm$ 0.005
LB-GS 30 phg NR	0.1623 $\pm$ 0.0120	0.355 $\pm$ 0.023
LH-GS 5 phg NR	0.1487 $\pm$ 0.0134	0.350 $\pm$ 0.021
LH-GS 10 phg NR	0.1433 $\pm$ 0.0112	0.348 $\pm$ 0.020
LH-GS 15 phg NR	0.1579 $\pm$ 0.0046	0.380 $\pm$ 0.007
LH-GS 20 phg NR	0.1397 $\pm$ 0.0056	0.349 $\pm$ 0.014
LH-GS 25 phg NR	0.1345 $\pm$ 0.0042	0.322 $\pm$ 0.011
LH-GS 30 phg NR	0.1466 $\pm$ 0.0037	0.347 $\pm$ 0.007

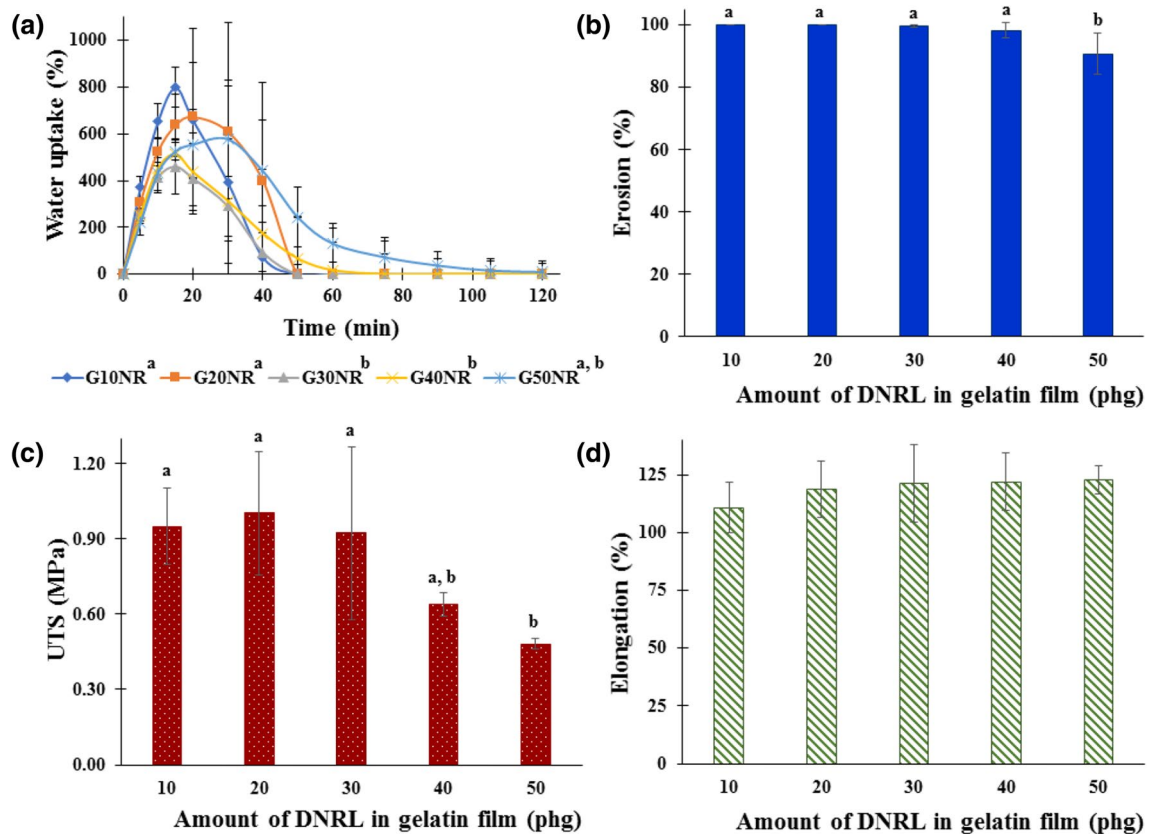


Fig. 1 The **a** water uptake, **b** erosion, **c** UTS and **d** elongation at break of GNR biomembranes ($n = 5$). (a) and (b) meant the symbol of significant statistics. The different symbols meant the significant difference ($p < 0.05$)

in Fig. 1a. Surprisingly, the GNR biomembranes with 10–20 phg DNRL revealed a significantly higher maximum water uptake than those of 30–40 phg DNRL ($p < 0.05$), while the 50 phg DNRL in GNR biomembrane showed a water uptake with no significant difference between these 2 groups ($p \geq 0.05$). This might be due to the erosion effect that interfered with the water uptake results because both phenomena occurred at the same time. However, the higher DNRL amounts affected the lower erosion. The 40–50 phg of DNRL in GNR biomembranes resulted in retarding the time of erosion and dissolving the blended biomembranes to 2 h as shown in Fig. 1b. The erosion of G50NR was the lowest and was statistically different from the other amounts of DNRL in GNR biomembranes ($p < 0.05$) (Fig. 1b). This indicated that DNRL increased the lipophilicity of gelatin films and might sustain the gelatin film structure in an aqueous medium.

The 50 phg DNRL in GNR biomembranes presented the lowest UTS which was significantly different from those of 10–30 phg DNRL in GNR biomembranes ($p < 0.05$) as shown in Fig. 1c. This indicated that DNRL could improve the elasticity of gelatin films. Increasing the amount of DNRL decreased UTS because of the elastic characteristic

of DNRL [37]. However, the values of elongation at break of GNR biomembranes were not different as shown in Fig. 1d. Therefore, the 50 phg DNRL was chosen for use as a plasticizer in gelatin biomembranes. Next, the 5–30 phg gelatinized sago starch was further studied to blend in the GNR biomembranes.

All amounts of gelatinized sago starch in the studied range could be blended in a gelatin film which used 50 phg DNRL as a plasticizer. The characteristics of GSNR biomembranes were also opaque. Increasing the sago starch in biomembranes, the drying time of the biomembrane was longer than that of GNR biomembranes and the appearance was somewhat rough because the gelatinized sago starch could trap the water in its film structure. Similar to GNR, there were no differences in the average weight and thickness of GSNR which had different amounts of sago starch as shown in Table 1. However, GSNR biomembranes showed a slightly higher thickness value than GNR biomembranes. This might be due to the higher water uptake of gelatinized sago starch in the biomembranes, which then provided a lower density of GSNR biomembranes. The increased amounts of gelatinized sago starch could increase the water uptake and decrease the erosion of GSNR biomembranes

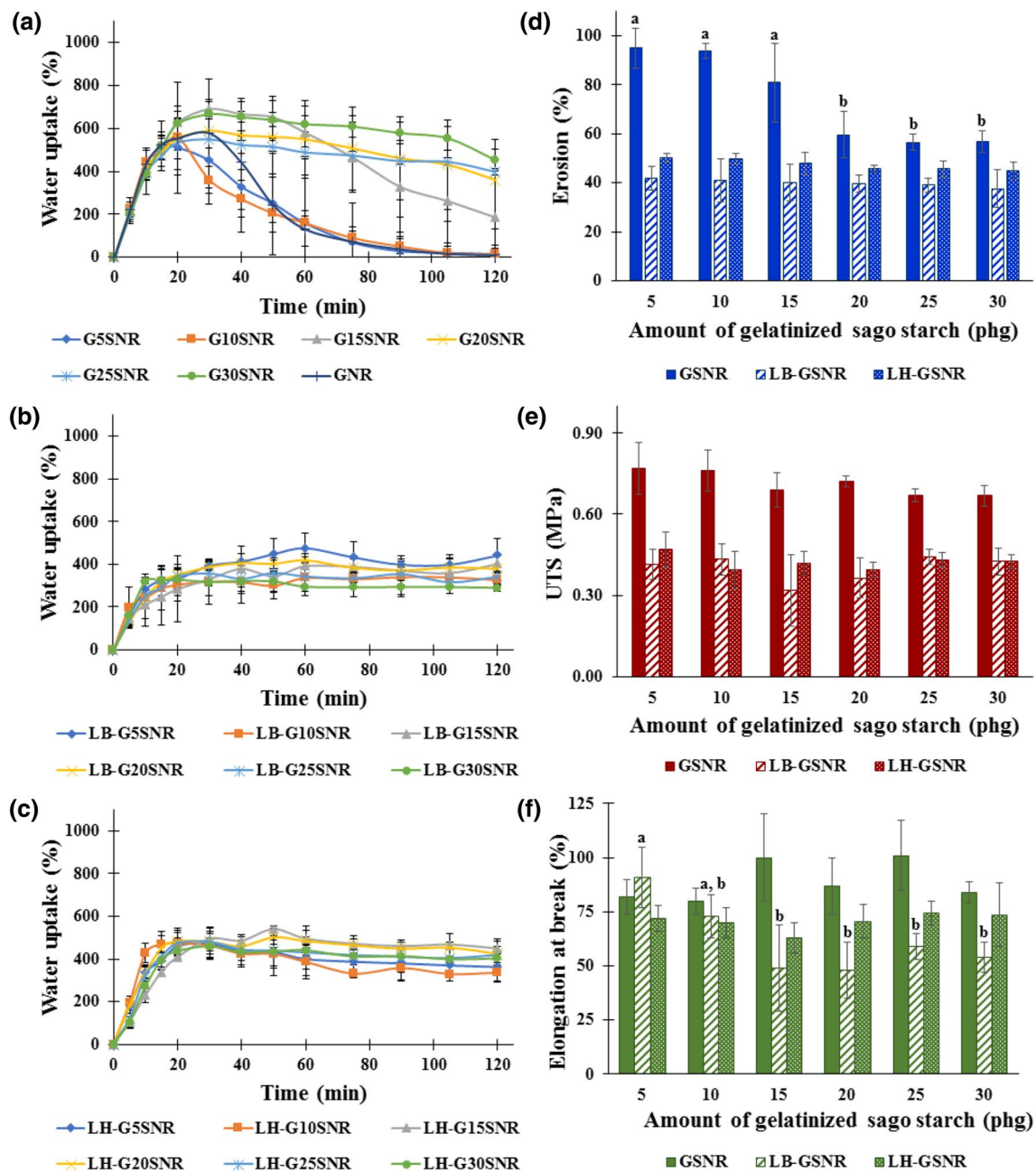


Fig. 2 The water uptake of **a** blank GSNR ($n=5$), **b** and **c** LB and LH loaded GSNR biomembranes ($n=3$), and **d** erosion, **e** UTS and **f** elongation at break of GSNR, LB-GSNR and LH-GSNR biomem-

branes ($n=5$). (a) and (b) meant the symbol of significant statistics. The different symbols meant the significant difference ($p < 0.05$)

when compared with GNR biomembrane as shown in Fig. 2a, d, respectively. However, GSNR biomembranes showed no significant difference in the maximum water uptake of all amounts of sago starch blends in biomembranes ($p > 0.05$) in both blank GSNR and drug loaded GSNR biomembranes as shown in Fig. 2a–c. The erosion of both medicated LB and LH loaded GSNR biomembranes showed no significant difference ($p > 0.05$) between various amounts of gelatinized sago starch as shown in Fig. 2d. However, the

erosion of different amounts of sago starch in blank biomembranes was significantly different in two groups ($p < 0.05$) in which sago starch at 20–30 phg in GSNR biomembranes was significantly lower than sago starch at 5–15 phg in GSNR biomembranes. The gelatinized sago starch might reduce the hygroscopic effect of gelatin in blended biomembranes and then might decrease the erodible rate of film. Normally, the composition of sago starch is reported as 27% amylose and 73% amylopectin [38], and the water uptake property might

be affected by amylose and amylopectin compositions of each starch. Although the amylopectin shows higher hydrophobicity than amylose, it has been reported that amylopectin has better water uptake property of starch because of its network structure [39]. Therefore, in this study, increasing the hydrophobicity by the addition of sago starch could decrease the erosion in biomembranes, but it increased the water uptake because of a higher amylopectin ratio. This result was consistent with the study of Biaopiotrowicz in gel properties of starch [40] which showed that increasing starch concentration decrease the hydrophilicity. This was due to the surface attempt to maintain the hydrophobic character with D-glucose units. In addition, blank GSNR biomembranes had higher water uptake and erosion values than medicated GSNR biomembranes because drug molecules might insert in the polymer networks which could increase the compactness of medicated biomembranes. Therefore, the water molecules were difficult to diffuse into the polymer networks. Moreover, LB-GSNR biomembranes had lower water uptake and erosion properties than LH-GSNR biomembranes. This was due to LB having more hydrophobicity than water soluble LH drugs.

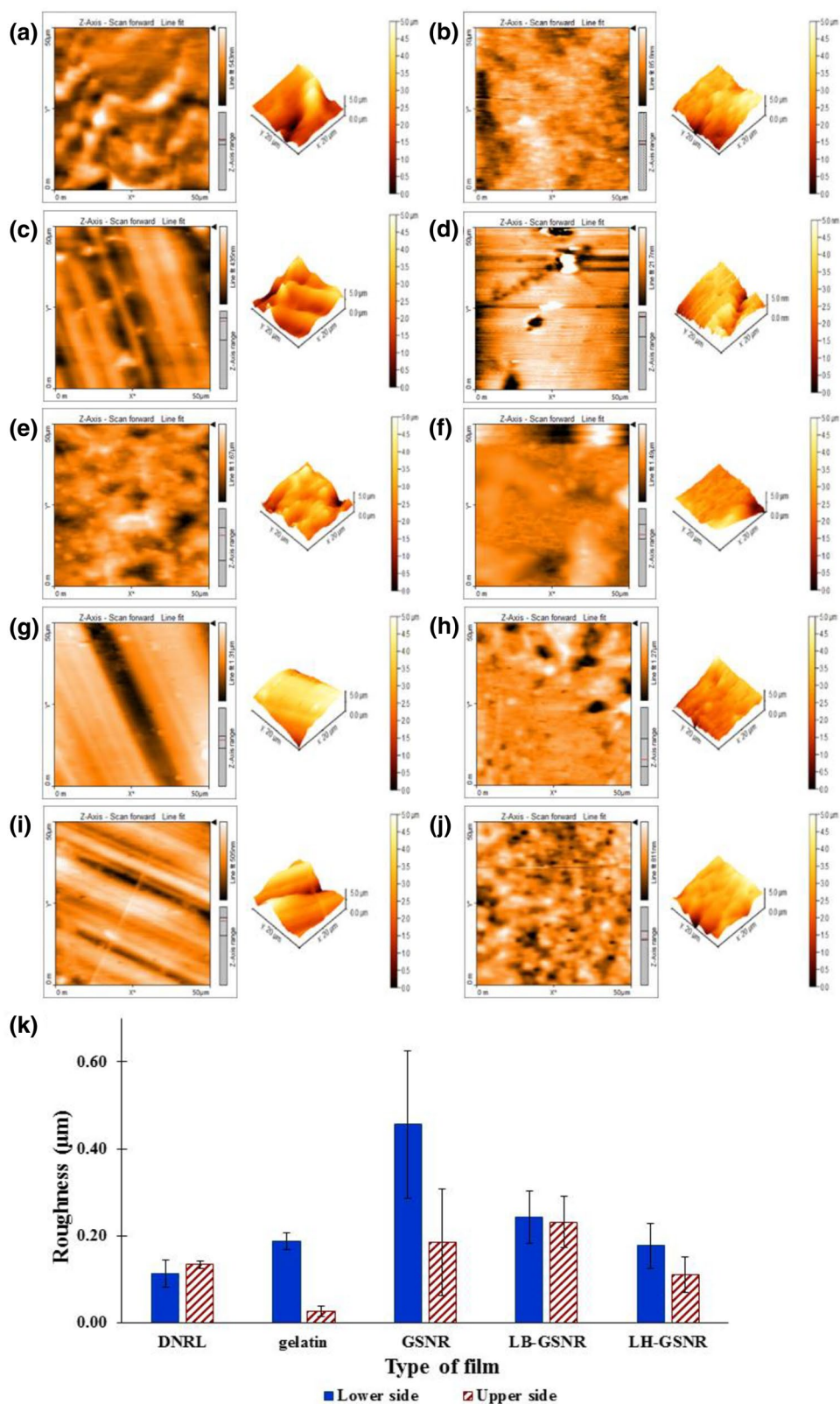
There was no significant difference in elongation at break of blank GSNR biomembranes or medicated LH loaded GSNR biomembranes ($p > 0.05$). However, there was a significant difference between groups in elongation at break of LB-GSNR in which the elongation at break of biomembranes with 15–30 phg sago starch were lower than that of biomembranes with 5 phg sago starch ($p < 0.05$) as shown in Fig. 2f. The UTS of blank GSNR biomembranes was higher than those of medicated LB and LH loaded GSNR biomembranes in all amounts of gelatinized sago starch as shown in Fig. 2e. This might be due to the insertion of drug molecules as the composite biomembranes which decreased the mechanical properties. However, the different amounts of gelatinized sago starch did not significantly affect the physical properties of their biomembranes, but higher amounts of gelatinized sago starch gave a lower erosion rate due to the hydrophobicity of starch. In the next step, therefore, the 5 phg of gelatinized sago starch was further used to prepare the medicated biomembranes and evaluate the other properties. This amount was chosen because of ease of drying, smooth surface, increased water uptake, decreased erosion and good elongation property as described above.

The AFM images of GSNR biomembranes were compared to pure gelatin and DNRL films as shown in Fig. 3a–j. These images indicated the continuous films with a slight roughness on the surface in both upper and lower sides. The roughness results calculated from AFM data are shown in Fig. 3k. Gelatin film and DNRL film had less roughness on both upper and lower side surfaces compared with GSNR biomembranes. This might occur from the smoothness and rigidity of the film of pure material during the drying

process. Although the GSNR biomembranes showed slight roughness, blank GSNR and medicated GSNR biomembranes were similar in roughness on the upper surface. The SEM images in Table 2 showed no small particles on the surface of the biomembranes. Nonetheless, the cross section of LH loaded GSNR biomembranes contained small particles. This might be due to the acid properties of LH which could induce the aggregation of DNRL before drying [41]. However, this indicated the non-segregation of ingredients in biomembranes.

Besides SEM as mentioned above, FT-IR, DSC and XRD were also used to confirm the compatibility of the ingredients in the biomembranes. In the FT-IR spectra, the broad band at $3275\text{--}3300\text{ cm}^{-1}$ was OH and/or NH stretching. The band at 2930 cm^{-1} was C–H stretching. The bands from 1635 to 1660 and $1525\text{--}1550\text{ cm}^{-1}$ were C=O stretching (amide I) and NH bending (amide II), respectively. These spectra could be found in general substances including DNRL, gelatin, starch, and LB and LH drugs. The FT-IR spectra of gelatin showed peaks at 1650 (amide I) and 1541 (amide II) cm^{-1} [8, 42, 43]. The LB and LH showed a similar peak at 1650 cm^{-1} . The LH had two sharp bands at the range $1450\text{--}1550\text{ cm}^{-1}$ because of C–N stretching and the higher energy peak was O–C–N bond. On the other hand, LB appeared to only have one peak at the same range due to the two C–N bonds [44]. In the combination biomembranes, all DNRL blended biomembranes showed the peak at 780 and 990 cm^{-1} as shown in Fig. 4. The FT-IR spectra at 1250 , 1320 and in the range $450\text{--}770$ of DNRL and gelatin were also different. The amide I peak of DNRL blended gelatin slightly shifted. Moreover, the intensity of amide I, amide II and OH/NH stretching peaks in DNRL blended biomembranes also changed. These results might indicate that there were interactions between gelatin and DNRL in the biomembrane. DNRL molecules might insert intermolecularly with --NH_2 groups, --OH groups or --COOH groups of gelatin [45]. Moreover, the hydroxyl group in gelatin could form hydrogen bonds with water after film preparation as shown in OH stretching bands in FT-IR of blended biomembranes [46]. These were consistent with the mechanical results above that DNRL could improve the elasticity of gelatin films. FT-IR spectra of gelatin and sago starch were quite similar showing a difference in the range $800\text{--}1000\text{ cm}^{-1}$. There was also a slight difference of peak in the range $570\text{--}660\text{ cm}^{-1}$ between GNR and GSNR biomembranes. However, sago starch was mixed in a few amounts in biomembrane; therefore, this change was quite small. The results showed that OH stretching of sago starch was also broader than those of gelatin and DNRL alone as shown in Fig. 4. This might indicate that amylopectin in sago starch was disrupted and water molecules could form a hydrogen bond which resulted in higher water uptake of starch blended biomembranes [43, 47].

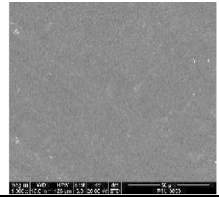
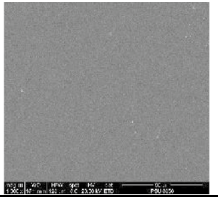
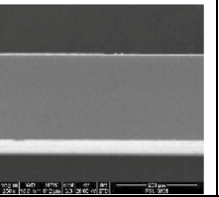
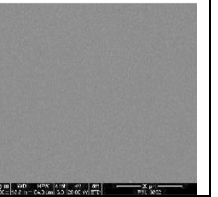
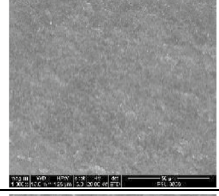
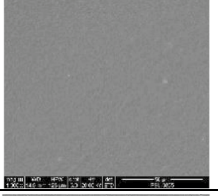
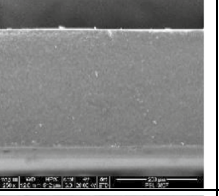
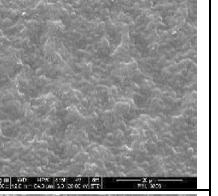
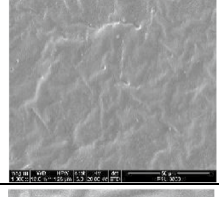
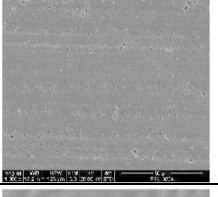
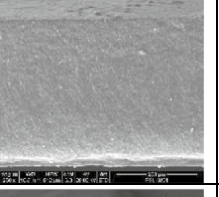
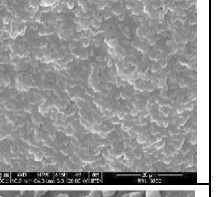
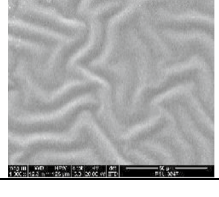
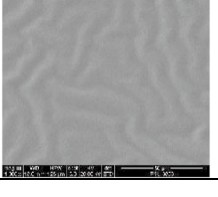
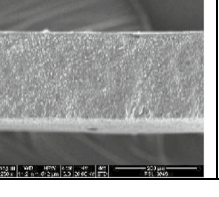
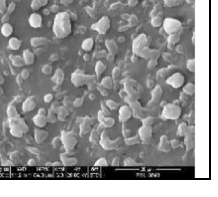
Fig. 3 The lower (**a, c, e, g, i**) and upper (**b, d, f, h, j**) AFM images of **a, b** DNRL films, **c, d** gelatin films, **e, f** GSNR biomembranes, **g, h** LB-GSNR biomembranes, **i, j** LH-GSNR biomembranes and **k** the roughness value of the biomembranes calculated from AFM ($n=5$)



The DSC thermograms (Fig. 5) showed peaks at 69 and 80 °C which were the intrinsic peaks of LB and LH, respectively. These DSC thermograms showed the results only

from room temperature (25 °C) to 250 °C for all samples and 25–95 °C for DNRL sample because there was no significant transition of endothermic peak after these over range

Table 2 SEM images of upper and lower biomembranes at 1000X and cross section at 250X and 2000X

Biomembrane samples	Upper (1000X)	Lower (1000X)	Cross section	
			(250X)	(2000X)
GNR				
GSNR				
LB-GSNR				
LH-GSNR				

temperatures to 450 °C. In this study, the DSC thermogram of DNRL was done only until 95 °C because the previous study concluded that it could not observe the peak over the range 25 to 170 °C [48]. However, peaks of either LB or LH disappeared from the blended GSNR biomembranes. It might be that the amorphous form of drug occurred after being solubilized during film preparation. On the other hand, the amount of drug in the biomembranes was less than 10% which might be difficult to observe as clear results in DSC thermograms. From both FT-IR and DSC results, these might preliminarily confirm the compatibility of gelatin/gelatinized sago starch biomembranes.

The XRD diffractograms are shown in Fig. 6. The XRD patterns of LB and LH revealed many peaks of crystalline characteristic. The highest sharp peak at 16.53° and 24.98° were found for LB, and 16.58° and 25.98° for LH. The raw materials of gelatin and DNRL showed the amorphous patterns of XRD diffractogram, while sago starch presented the crystalline peaks at 15°, 17°, and 23° from both amylose and amylopectin components [49]. The diffractogram of GSNR showed the disappearance of the crystalline peak of sago starch; however, the pattern of the diffractogram was mixed between gelatin, sago starch, and DNRL. This amorphous character was due to the amorphous property of most gelatin

and DNRL composition of GSNR biomembrane, and only 5 phg of crystalline sago starch was blended. These indicated the amorphous character of GSNR biomembrane that easily uptakes water and is good for drug release. LH-GSNR exhibited the same broad spectrum as GSNR. No crystallinity of drug was exhibited in LH-GSNR. Even if LB-GSNR appeared as very small crystalline peaks, the intensity of peaks was much lower than the pure LB because of the low amount of LB in biomembranes. The slight crystalline in LB-GSNR biomembranes might occur from the low solubility of LB that could precipitate during the drying process. The crystalline of drug in STR-5L was also found in 10–15% w/w lidocaine-loaded transdermal patch as reported previously [50]. However, this phenomenon did not influence the drug release [51].

From preliminary study, it was found that methanol was a good solvent to extract both LB and LH from biomembranes. For content determination, therefore, methanol was chosen to use as solvent extraction. With the theoretical drug loading in each biomembrane at 5% w/w, the drug extraction results of LB-GSNR and LH-GSNR were 95.38 ± 6.41 and $99.12 \pm 10.59\%$, respectively. These indicated that the biomembranes prepared by casting method could keep all drug content in the biomembrane without any loss. Since

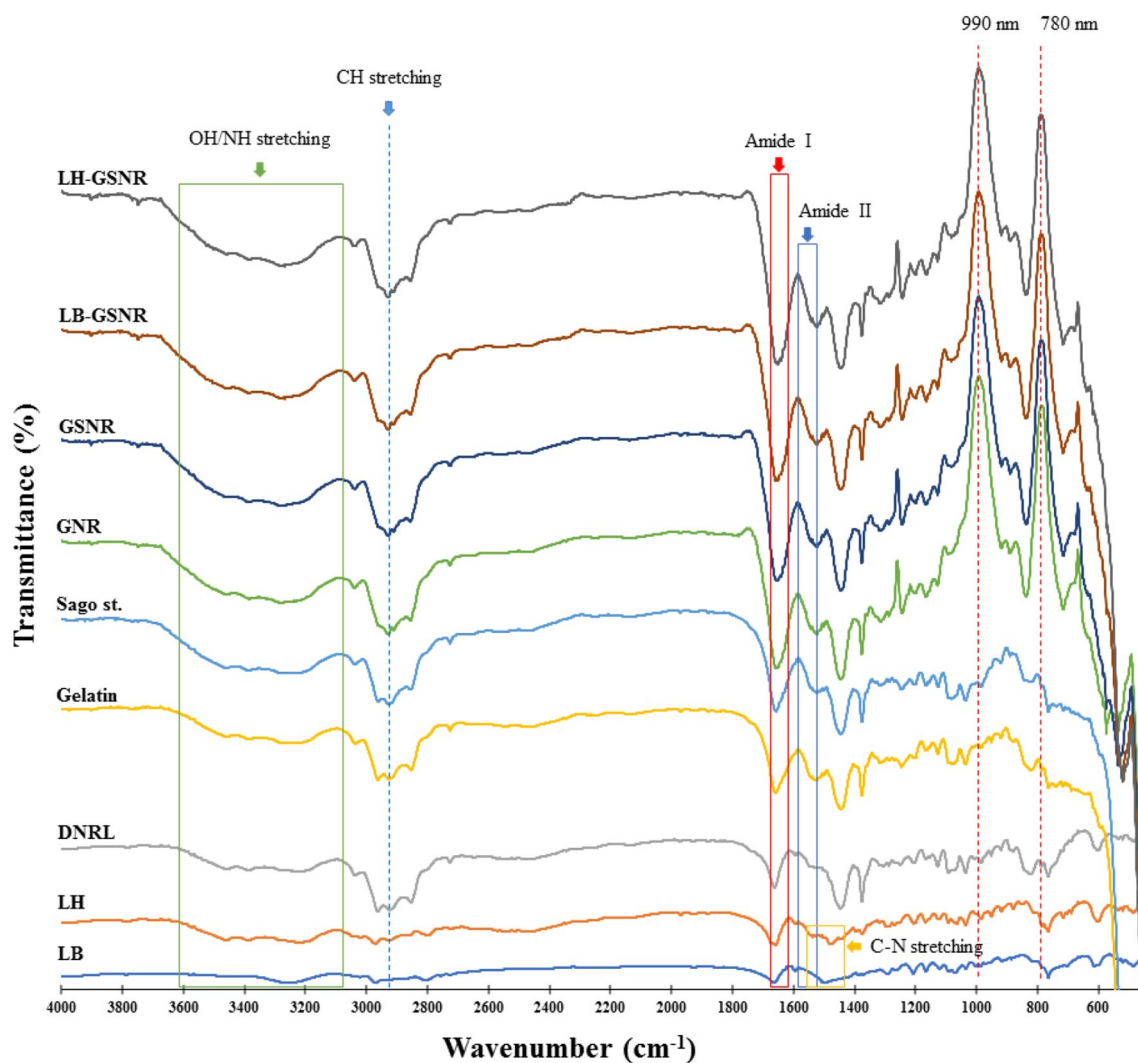


Fig. 4 FT-IR spectra of materials and biomembranes

LB is not soluble in water, in the preparation process, a 1:1 mixture of methanol:water was used in LB-GSNR biomembranes to solubilize the drug before mixing it into the other ingredients and drying. Methanol is a toxic residual solvent which the ICH guideline has limited. The concentration limit of methanol in pharmaceutical products is 3000 ppm [52]. From methanol determination, the result showed that the methanol residue in LB-GSNR biomembrane was less than 125 ppm, and, therefore, the methanol peak could not be detected ($LOQ = 125$ ppm). This indicated that it was safe to use this biomembrane in pharmaceuticals. During film preparations and other processes of methanol use, our university does not require ethics clearance for methanol pollution in air.

After stability studies at 1 and 3 months, the appearance and color of medicated GSNR biomembranes were quite similar to the initial preparation. The percentage of drug

content of both the LB-GSNR and LH-GSNR biomembranes after stability studies in various temperatures including 4 °C, ambient temperature, and 45 °C for 3 months are presented in Fig. 7. It was found that the percentage of drug content of LB in GSNR biomembranes was above 90% until 3 months after storage in 4 °C and room temperature, and 2 months for 45 °C. LB-GSNR biomembranes at 4 °C were the most stable; the drug content had a lower decrease than those of ambient temperature and 45 °C in 1, 2 and 3 months. However, the percentages of drug content of LH in GSNR biomembranes were above 90% only 2 months after storage at 4 °C, but chemical instability of LH in biomembranes was found when stored at room temperature and 45 °C for 1, 2, and 3 months. This might be due to greater hydrophilicity of LH representing higher moisture absorption of LH biomembranes than LB biomembranes and enhanced oxidation of drug. In addition, oxidative reaction could occur at

Fig. 5 DSC thermograms of materials and biomembranes

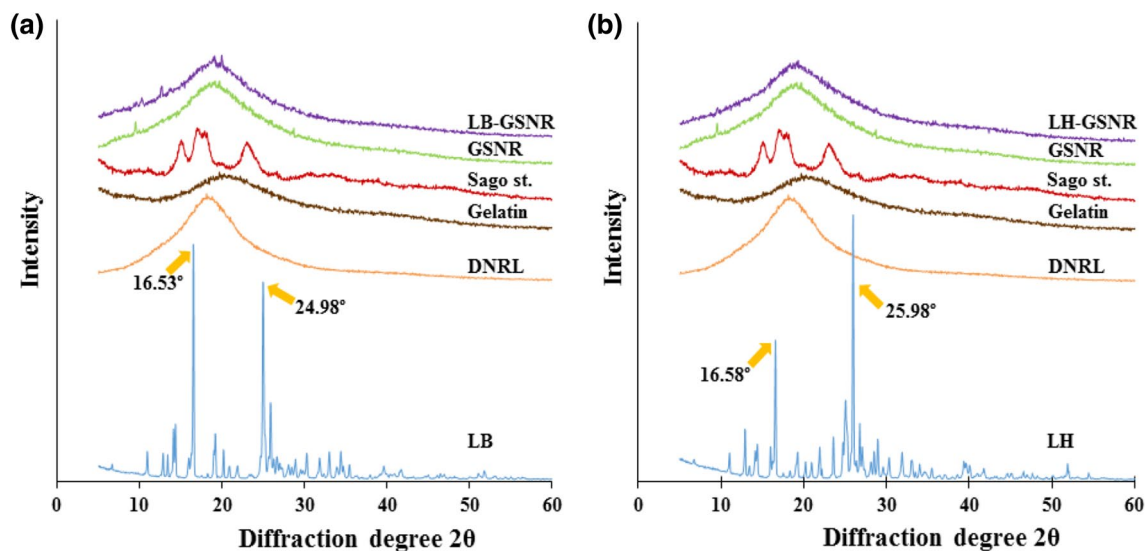
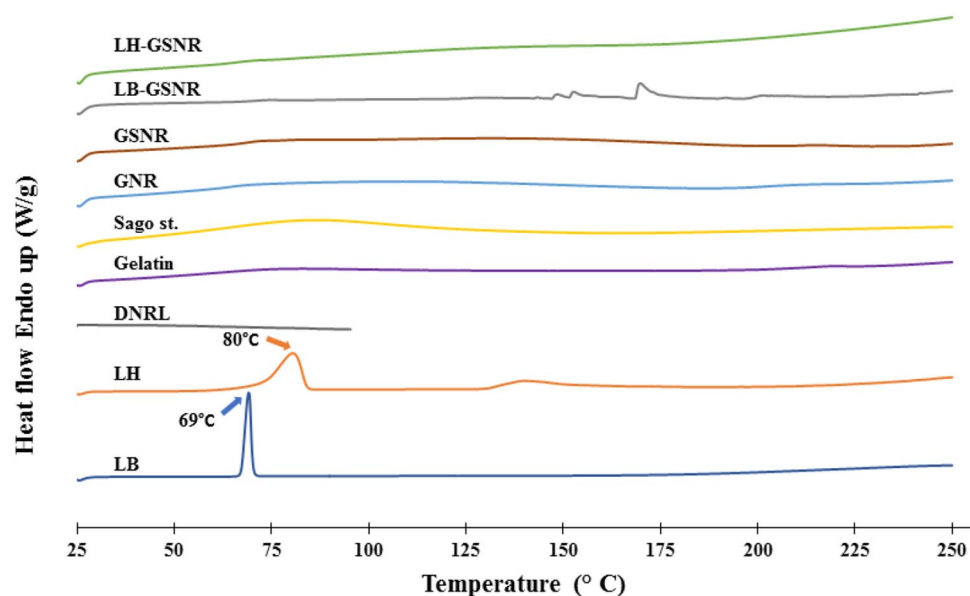


Fig. 6 XRD diffractograms of materials and **a** LB-GSNR and **b** LH-GSNR biomembranes

the nitrogen groups of LH which was suggested in the degradation study by hydrogen peroxide (H_2O_2) for oxidation at room temperature [53]. This indicated that LB was more stable in GSNR biomembranes than LH.

The drug release and permeation studies were important parameters to confirm the utility of this biomembrane as transdermal drug delivery systems. These parameters might depend on many physical, chemical, and mechanical parameters. Some on them are described above. For example, the higher water uptake and erosion films should release the drug from polymer matrix easier than lower water uptake and erosion films. In this study, the drug release and permeation profiles of LB and LH loaded GSNR biomembranes

are shown in Fig. 8. For initial preparations, the LH release (Fig. 8c) was higher than LB release (Fig. 8a). This might be due to the aqueous soluble property of LH, which made dissolving and releasing from the membrane easier than LB [54]. However, drug releases in 24 h showed minimal difference. This also confirmed that the slight crystalline form observed in XRD diffractograms did not affect the drug release as described above, and as found in a previous study [51]. On the other hand, the permeation of LB (Fig. 8e) was slightly higher than that of LH (Fig. 8g) because the skin barrier should be more permeable for the lipophilic LB than the hydrophilic LH [55]. The stability of biomembranes after being kept at various temperatures showed that the

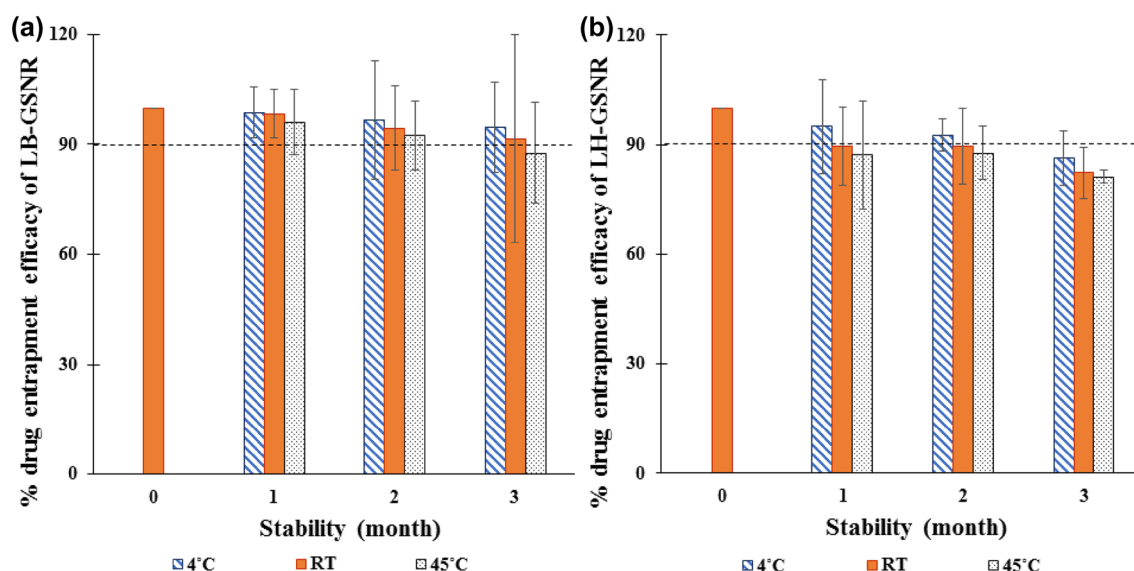


Fig. 7 The percentage of drug EE of **a** LB-GSNR and **b** LH-GSNR biomembranes ($n=3$)

release of LB decreased in all GSNR biomembranes especially LB-GSNR biomembranes kept at 45 °C for 3 months (Fig. 8b). However, there was no difference in the release of LH-GSNR biomembranes (Fig. 8d). The permeation of LB and LH loaded GSNR after storage for 1 and 3 months were not significantly different from those of the initial preparations. All permeation results (Fig. 8e–h) showed lower values than the release amounts of drugs from the GSNR biomembranes. This indicated that the skin property was the significant determining step that could limit the permeation amount of the drug through the skin. Nevertheless, drug loaded GSNR biomembranes at 4 °C seemed to be the slowest and least changed drug release and permeation pattern compared to others. Lidocaine is resistant to the temperature in the range of –20 to 70 °C [56]. In the solution, it is also stable in all regions of pH and resistant to hydrolysis at room temperature. However, lidocaine degrades slowly at higher temperature [57, 58]. Thus, a decrease of drug content might be influenced by high temperatures during the drying and keeping of GSNR biomembranes.

The types of both LB and LH release kinetics from GSNR biomembranes were not different as shown in Table 3. Most of both medicated LB and LH release kinetics from GSNR biomembranes were fitted to first order or Higuchi's kinetics, which they are not different statistically ($p \geq 0.05$); however, these kinetics were significantly different from zero order kinetics ($p \geq 0.05$). The release of first order kinetics depends on drug concentration and can be found in the swellable system with the dissolution of polymer matrix [59]. The Higuchi's model can be exhibited in a transdermal system with hydrophilic drugs that can diffuse through the matrix system [60]. In this study, both gelatin and gelatinized sago

starch are hydrophilic polymers that can swell and dissolve in aqueous solution; therefore, both diffusion and dissolution mechanisms of drug release from GSNR could occur. For the kinetics of permeation profiles, LB-GSNR biomembranes kinetics were zero order or first order in different biomembranes which meant the independent or dependent permeations by drug concentration, respectively. These kinetics of LB permeation were significantly different from the Higuchi's model ($p < 0.05$). On the other hand, most LH-GSNR permeation profiles presented no difference in the statistics of 3 types of kinetics ($p \geq 0.05$). The variability of kinetics could have occurred because of either the drug properties or the variability of the skin [61]. This also confirmed that the lidocaine permeation was determined by the skin property as concluded above.

Conclusions

DNRL could successfully act as plasticizer for gelatin films. Gelatin or gelatin/gelatinized sago starch mixed with DNRL produced good films without any problem of brittleness. Increasing the amount of DNRL resulted in decreasing the UTS and erosion of biomembranes. The gelatinized sago starch could increase the water uptake and decrease the erosion of gelatin/gelatinized sago starch biomembranes. LB or LH could be added in the gelatin/gelatinized sago starch biomembranes. However, the water uptake and UTS of medicated LB and LH loaded GSNR biomembranes were lower than those of blank GSNR biomembrane. FT-IR spectra and DSC thermograms showed good compatibility of all ingredients. However, the SEM cross-section image of LH-GSNR

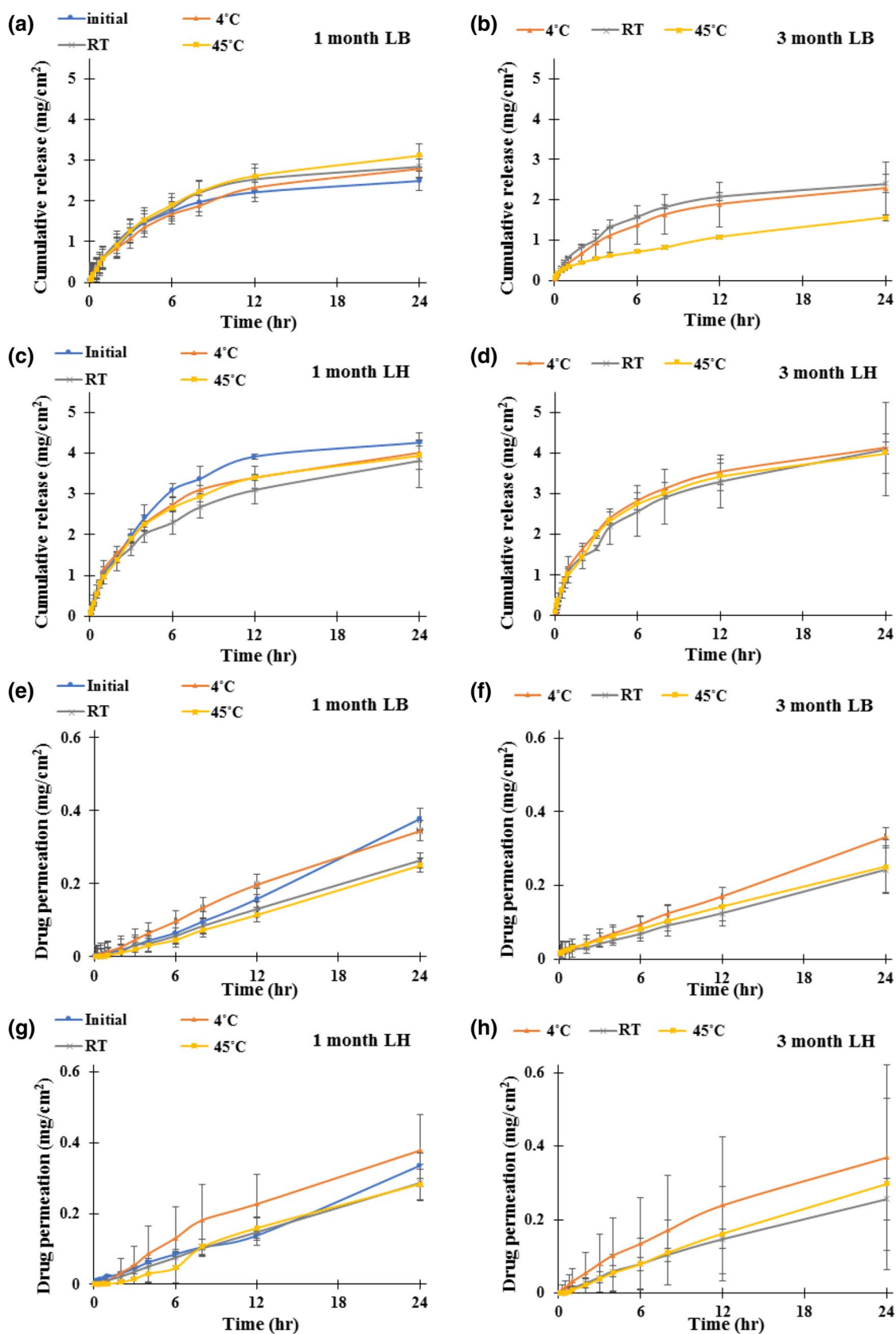


Fig. 8 The drug release profiles (a–d) ($n=3$) and the permeation profiles (e–h) ($n=5$) of (a, e) LB-GSNR 1 month, (b, f) LB-GSNR 3 month, (c, g) LH-GSNR 1 month, (d, h) LH-GSNR 3 month

Table 3 The kinetics of drug release (n = 3) and permeation (n = 5) in LB-GSNR and LH-GSNR biomembranes

Sample	month	Temp. (°C)	kinetics of drug release (R^2) (mean $\pm$ S.D.)			kinetics of drug permeation (R^2) (mean $\pm$ S.D.)		
			Zero order	Higuchi's	First order	Zero order	Higuchi's	First order
LB-GSNR	0	RT	0.8810 $\pm$ 0.0610 ^a	0.9789 $\pm$ 0.0171 ^b	0.9939 $\pm$ 0.0066 ^b	0.9763 $\pm$ 0.0207 ^b	0.8859 $\pm$ 0.0663 ^a	0.9572 $\pm$ 0.0328 ^b
	1	4	0.9267 $\pm$ 0.0249 ^a	0.9940 $\pm$ 0.0022 ^b	0.9897 $\pm$ 0.0079 ^b	0.9884 $\pm$ 0.0099 ^b	0.8858 $\pm$ 0.0440 ^a	0.9705 $\pm$ 0.0208 ^b
		RT	0.9072 $\pm$ 0.0410 ^a	0.9870 $\pm$ 0.0042 ^b	0.9892 $\pm$ 0.0093 ^b	0.9686 $\pm$ 0.0256 ^b	0.8771 $\pm$ 0.0789 ^a	0.9632 $\pm$ 0.0338 ^b
		45	0.9259 $\pm$ 0.0196 ^a	0.9904 $\pm$ 0.0022 ^b	0.9962 $\pm$ 0.0039 ^b	0.9860 $\pm$ 0.0087 ^b	0.8612 $\pm$ 0.0249 ^a	0.9679 $\pm$ 0.0082 ^b
	3	4	0.9279 $\pm$ 0.0345 ^a	0.9871 $\pm$ 0.0041 ^b	0.9951 $\pm$ 0.0003 ^b	0.9856 $\pm$ 0.0029 ^b	0.9466 $\pm$ 0.0259 ^a	0.9903 $\pm$ 0.0116 ^b
		RT	0.9023 $\pm$ 0.0192 ^a	0.9898 $\pm$ 0.0008 ^b	0.9947 $\pm$ 0.0030 ^b	0.9546 $\pm$ 0.0359	0.9336 $\pm$ 0.0202	0.9668 $\pm$ 0.0231
LH-GSNR		45	0.9100 $\pm$ 0.0219 ^a	0.9915 $\pm$ 0.0038 ^b	0.9696 $\pm$ 0.0080 ^b	0.9701 $\pm$ 0.0268	0.9496 $\pm$ 0.0270	0.9782 $\pm$ 0.0144
	0	RT	0.9006 $\pm$ 0.0190 ^a	0.9871 $\pm$ 0.0064 ^b	0.9914 $\pm$ 0.0081 ^b	0.9765 $\pm$ 0.0115 ^a	0.9683 $\pm$ 0.0055 ^a	0.9911 $\pm$ 0.0071 ^b
	1	4	0.8645 $\pm$ 0.0104 ^a	0.9822 $\pm$ 0.0036 ^b	0.9777 $\pm$ 0.0100 ^b	0.8888 $\pm$ 0.0918	0.7744 $\pm$ 0.1684	0.8795 $\pm$ 0.0889
		RT	0.8758 $\pm$ 0.0135 ^a	0.9874 $\pm$ 0.0043 ^b	0.9789 $\pm$ 0.0130 ^b	0.9823 $\pm$ 0.0192 ^b	0.8930 $\pm$ 0.0716 ^a	0.9743 $\pm$ 0.0313 ^b
		45	0.8787 $\pm$ 0.0297 ^a	0.9852 $\pm$ 0.0072 ^b	0.9848 $\pm$ 0.0137 ^b	0.9289 $\pm$ 0.0952	0.7807 $\pm$ 0.1368	0.9164 $\pm$ 0.0914
	3	4	0.8607 $\pm$ 0.0237 ^a	0.9826 $\pm$ 0.0093 ^b	0.9502 $\pm$ 0.0161 ^b	0.8999 $\pm$ 0.1135	0.8091 $\pm$ 0.2262	0.9005 $\pm$ 0.1344
		RT	0.8792 $\pm$ 0.0072 ^a	0.9855 $\pm$ 0.0068 ^b	0.9783 $\pm$ 0.0164 ^b	0.8884 $\pm$ 0.1945	0.7923 $\pm$ 0.2560	0.8917 $\pm$ 0.1963
		45	0.8700 $\pm$ 0.0346 ^a	0.9827 $\pm$ 0.0090 ^b	0.9791 $\pm$ 0.0202 ^b	0.9452 $\pm$ 0.1011	0.8623 $\pm$ 0.1758	0.9436 $\pm$ 0.1040

Each datum represents the mean $\pm$ S.D.

Superscript letters (a) and (b) in the same row meant the symbol of significant statistics. The different symbols meant the significant difference ($p < 0.05$)

biomembranes had small particles which might occur when LH as an acid induced the aggregation of DNRL. LB and LH could be controlled by the release from the GSNR biomembranes and permeated by a constant rate through pig skin. However, the obtained LB-GSNR biomembranes should be kept at a low temperature for good stability.

Acknowledgements The authors would like to thank the Natural Rubber Innovation Research Institute (NR-IRI), Prince of Songkla University, for research financial support (Grant No. PHA590307S) and Prince of Songkla University for facilities support. The first author gratefully acknowledges the grant support provided by the Ph.D. scholarship of Prince of Songkla University and the Scholarship Awards for Thai Ph.D. Students under Thailand's Education Hub for Southern Region of ASEAN Countries. In addition, sincere thanks are sent to Miss Maria Suzanne Mullet for her diligent proof-reading of this paper.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest.

References

- Riyajan S, Patisat S (2018) *J Polym Environ* 26:2845–2854
- Sukhlaaied W, Riyajan S (2018) *J Polym Environ* 26:2708–2719
- Díaz O, Candia D, Cobos A (2017) *Int Dairy J* 73:84–91
- Chen H, Hu X, Chen E, Wu S, McClements DJ, Liu S et al (2016) *Food Hydrocoll* 61:662–671
- Yadav P, Yadav H, Shah VG, Shah G, Dhaka G (2015) *J Clin Diagn Res* 9(9):ZE21–ZE25
- Vieira MGA, da Silva MA, dos Santos LO, Beppu MM (2011) *Eur Polym J* 47:254–263
- Jongjareonrak A, Benjakul S, Visessanguan W, Prodpran T, Tanaka M (2006) *Food Hydrocoll* 20(4):492–501
- Promsopha T, Baimark Y (2014) *Int J Biomater*. <https://doi.org/10.1155/2014/829490>
- Achet D, He XW (1995) *Polymer* 36(4):787–791
- Jadhav RT, Kasture PV, Gattani SG, Surana SJ (2009) *Int J ChemTech Res* 1(4):1507–1511
- Subramanian K, Indumathi S, Vijayakumar V (2014) *Int J Pharm Sci Res* 5(2):438–447
- Mazzitelli S, Pagano C, Giusepponi D, Nastruzzi C, Perioli L (2013) *Int J Pharm* 454(1):447–457
- Ling MH, Chen MC (2013) *Acta Biomater* 9(11):8952–8961
- Satyam G, Shivani S, Shivam G, Shobhit J, Sanjeev V, Arvind K (2010) *IJBPR* 1:56–60
- Alves VD, Mali S, Belêia A, Grossmann MVE (2007) *J Food Eng* 78:941–946
- Noel TR, Ring SG, Wittam MA (1993) In: Dickinson E, Walstra P (eds) *Food colloids and polymers: stability and mechanical properties*. Woodhead Publishing Limited, Cambridge, p 126
- Karim AA, Tie APL, Manan DMA, Zaidul ISM (2008) *CRFSFS* 7(3):215–228
- Boonme P, Pichayakorn W, Prapruit P, Boromthanarat S (2012) 2nd ASEAN Sago Symposium 2012, advances in Sago research and development, p 24
- Al-Hassan AA, Norziah MH (2012) *Food Hydrocoll* 26:108–117
- Zhong QP, Xia WS (2008) *Food Technol Biotech* 46:262–269
- Rodríguez M, Osés J, Ziani K, Maté JI (2006) *Food Res Int* 39:840–846
- Simchareon W, Amnuait T, Boonme P, Taweeprada W, Pichayakorn W (2012) *Procedia Chem* 4:308–312
- Industrial Rubber Goods. <http://www.industrialrubbergoods.com/natural-rubber.html>
- Hirata Y, Kondo H, Ozawa Y (2014) In: Kohjiya S, Ikeda Y (eds) *Chemistry, manufacture and applications of natural rubber*. Woodhead Publishing Limited, Cambridge, pp 325–352
- Hasma H, Alias O, Fauzi MS (2003) *J Rubber Res* 6(4):231–240

26. Panrat K, Boonme P, Taweepreda W, Pichayakorn W (2012) *Procedia Chem* 4:322–327
27. Floriano JF, de Barros NR, Cinman JLF, da Silva RG, Loffredo AV, Borges FA et al (2018) *J Polym Environ* 26:2281–2289
28. Pichayakorn W, Suksaeree J, Boonme P, Amnuait T, Taweepreda W, Ritthidej GC (2012) *J Membr Sci* 411–412:81–90
29. Deval R, Ramesh V, Prasad G, Jain AK (2008) *Indian J Dermatol Venereol Leprol* 74:304–310
30. Pichayakorn W, Suksaeree J, Boonme P, Amnuait T, Taweepreda W, Ritthidej CG (2013) *Pharmaceut Dev Technol* 18:1111–1121
31. Waiprib R, Boonme P, Taweepreda W, Kalkornsurapranee E, Suksaeree J, Pichayakorn W (2017) *Monatsh Chem* 148:1223–1228
32. Banpean A, Paradee N, Sirivat A, Niamlang S (2018) *J Polym Environ* 9:3745–3753
33. Suksaeree J, Boonme P, Taweepreda W, Ritthidej GC, Pichayakorn W (2012) *Chem Eng Res Des* 90:906–914
34. Kaewbanjong J, Amnuait T, Souto EB, Boonme P (2018) *Skin Pharmacol Physiol* 31:292–297
35. Boonme P, Boonthongchuay C, Wongpoowarak W, Amnuait T (2016) *Pharmaceut Dev Technol* 21(1):116–120
36. Songkro S, Purwo Y, Becket G, Rades T (2003) *STP Pharma Sci* 13:133–139
37. Ibrahim A, Dahlan M (1988) *Prog Polym Sci* 23(4):665–706
38. Wattanachant S, Muhammad SKS, Mat Hashim D, Rahman RA (2002) *Songklanakarin J Sci Technol* 24(3):431–438
39. Sjöqvist M, Boldizar A, Rigdahl M (2010) *J Cell Plast* 46(6):497–517
40. Białopiotrowicz T (2003) *Food Hydrocoll* 17(2):141–147
41. de Oliveira Reis G, Menut P, Bonfils F, Vaysse L, Hemar Y, Sanchez C (2015) *Colloids Surf A* 482:9–17
42. Asma C, Meriem E, Mahmoud B, Djafer B (2014) *J Chil Chem Soc* 59:2279–2283
43. Zhang N, Liu X, Yu L, Shanks R, Retinaks E, Liu H (2013) *Carbohydr Polym* 95:649–653
44. Abu-Huwajj R, Assaf S, Salem M, Sallam A (2007) *Drug Dev Ind Pharm* 33:855–864
45. da Cruz AGB, Góes JC, Figueiró SD, Feitosa JPA, Ricardo NMPS, Sombra ASB (2003) *Eur Polym J* 39:1267–1272
46. Tainter CJ, Ni Y, Shi L, Skinner JL (2013) *J Phys Chem Lett* 4(1):12–17
47. Singh N, Singh J, Kaur L, Sodhi NS, Gill BS (2003) *Food Chem* 81:219–231
48. Sansuk C (2016) Master's thesis. Thammasat University
49. Okazaki M (2018) In: Ehara H, Toyoda Y, Johnson D (eds) *Sago palm*. Springer, Singapore, pp 247–259
50. Pichayakorn W, Boontawee H, Taweepreda W, Suksaeree J, Boonme P (2014) *Ind Eng Chem Res* 53(4):1672–1677
51. Preis M, Woertz C, Schneider K, Kukawka J, Broscheit J, Roewer N, Breitreutz J (2014) *Eur J Pharm Biopharm* 86(3):552–561
52. Hu C, Liu Y (2011) In: Isin A (ed) *Wide spectra of quality control*. IntechOpen, London, p 185
53. Kadioglu Y, Atila A, Gultekin MS, Alp NA (2013) *Iran J Pharm Res* 12(4):659–669
54. Liu X, Ma X, Kun E, Guo X, Yu Z, Zhang F (2018) *Int J Pharm* 547:291–302
55. Banks SL, Pinninti RR, Gill HS, Crooks PA, Prausnitz MR, Stinchcomb AL (2008) *Pharm Res* 25(7):1677–1685
56. Küpper TE, Schraut B, Rieke B, Hemmerling AV, Schöffl V, Steffen J (2006) *J Travel Med* 13:35–47
57. Goto S, Itano T (1978) *Yakugaku Zasshi* 99:146–154
58. Powell MF (1987) *Pharm Res* 4:42–45
59. Singh J, Gupta S, Kaur H (2011) *Trends Appl Sci Res* 6(4):400–409
60. Dash S, Murthy PN, Nath L, Chowdhury P (2010) *Acta Pol Pharm* 67(3):217–223
61. Boix-Montañes A (2004) *J Drug Deliv Sci Technol* 14(6):485–488

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.