รายงานวิจัยฉบับสมบูรณ์

โครงการ การพัฒนาระบบนำส่งนิโคตินทางผิวหนังจากน้ำยางธรรมชาติในรูปพอลิเมอร์เกิดฟิล์ม

โดย วิวัฒน์ พิชญากร และคณะ

พฤศจิกายน 2553

สัญญาเลขที่ MRG5180243

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บทคัดย่อ

รหัสโครงการ: MRG5180243

ชื่อโครงการ: การพัฒนาระบบนำส่งนิโคตินทางผิวหนังจากน้ำยางธรรมชาติ ในรูปพอลิเมอร์เกิดฟิล์ม

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บทคัดย่อ:

พอลิเมอร์เกิดฟิล์มรูปของเหลว เป็นผลิตภัณฑ์ของพอลิเมอร์ในรูปของเหลวซึ่งใช้ทาบนผิวหนังแล้วจะเกิดฟิล์มใสขึ้นเมื่อตัวกลางระเหยออก ในขณะที่แผ่นแปะเป็นพอลิเมอร์ในรูปฟิล์มที่ใช้แปะบนผิวหนังโดยตรง การศึกษานี้เป็นการเตรียมพอลิเมอร์เกิดฟิล์มรูปของเหลว และแผ่นแปะ ซึ่งใช้น้ำยางธรรมชาติโปรตีนต่ำ (DNRL) เป็นพอลิเมอร์หลัก ใช้ไฮดรอกซีโพรพิลเมทิลเซลลูโลส (HPMC), เมทิลเซลลูโลส (MC), โซเดียมคาร์บอซีเมทิลเซลลูโลส (SCMC), พอลิไวนิลแอลกอฮอล์ (PVA), พอลอกซาเมอร์ 407 (P407), หรือ โซเดียมอัลจิเนต (SAG) เป็นพอลิเมอร์ผสม ใช้ไดบิวทิวพทาเลต (DBP), ไดเอทิลพทาเลต (DEP), ไดบิวทิวซีบาเคต (DBS), ไตรเอทิลซิเทรต (TEC), หรือกลีเซอรีน (GLY) เป็นพลาสติไซเซอร์ พบว่า DNRL สามารถเกิดฟิล์มที่ยืดหยุ่น แต่ติดผิวหนังน้อย การผสม DNRL กับพอลิเมอร์และพลาสติไซเซอร์ชนิดต่างๆ สามารถเกิดฟิล์มที่น่าพอใจ ซึ่งมีสมบัติด้านความยืดหยุ่นและการยึดติดที่แตกต่างกัน DNRL ผสมกับ HPMC หรือ PVA และ DBP หรือ GLY ทำให้เกิดฟิล์มที่ดีที่สุดสำหรับนำส่งยาทางผิวหนัง ทำการผสมนิโคตินลงในตำรับของพอลิเมอร์เกิดฟิล์มรูปของเหลวที่เลือก ก่อนทำการศึกษาการปลดปล่อยยาในฟรานซ์ดิฟฟิวชันเซลล์ พบการปลดปล่อยนิโคตินเป็นสองช่วงจากพอลิเมอร์เกิดฟิล์มรูปของเหลว คือ ปลดปล่อยเร็วเหมือนการปลดปล่อยยาในรูปของเหลวในช่วงแรก และตามด้วยการปลดปล่อยยาอย่างช้าๆ เมื่อเกิดฟิล์มแล้ว สำหรับแผ่นแปะนิโคตินพบการปลดปล่อยยาช่วงเดียวแบบช้าๆ การผสมพอลิเมอร์และพลาสติไซเซอร์ทำให้เกิดการปลดปล่อยยาเร็วขึ้นเนื่องจากความชอบน้ำของสารเหล่านี้ จลนศาสตร์ของการปลดปล่อยนิโคตินจากทั้งพอลิเมอร์เกิดฟิล์มรูปของเหลวและแผ่นแปะ เป็นแบบการแพร่ ซึ่งยืนยันโดยโมเดลของฮิกูชิ การซึมผ่านผิวหนังของนิโคตินมีจลนศาสตร์แบบอันดับศูนย์ โดยสรุป การนำส่งนิโคตินทางผิวหนังสามารถทำได้โดยทั้งรูปแบบพอลิเมอร์เกิดฟิล์มรูปของเหลวและแผ่นแปะ ซึ่งให้รูปแบบการปลดปล่อยยาที่แตกต่างกัน และสามารถใช้กับผิวหนังได้อย่างปลอดภัยโดยไม่เกิดการระคายเคือง

คำหลัก: น้ำยางธรรมชาติ, ระบบนำส่งยาทางผิวหนัง, พอลิเมอร์เกิดฟิล์มรูปของเหลว. แผ่นแปะ, นิโคติน

Abstract

Project Code: MRG5180243

Project Title: Development of Nicotine Transdermal Delivery Systems from Natural Rubber as Film-Forming Polymers

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Abstract:

Film-forming polymeric solution is a product of polymer in liquid dosage form which upon applying to the skin can subsequently form an almost invisible film *in situ* by solvent evaporation, while patch is a polymer film directly applied to the skin. In this study, both film-forming polymeric solutions and patches for transdermal nicotine delivery were prepared using deproteinized natural rubber latex (DNRL) as major polymer. Hydroxypropyl methylcellulose (HPMC), methylcellulose (MC), sodium carboxymethylcellulose (SCMC), polyvinyl alcohol (PVA), poloxamer 407 (P407), or sodium alginate (SAG) was added as a blended polymer. Dibutylphthalate (DBP), diethylphthalate (DEP), dibutylsebacate (DBS), triethylcitrate (TEC), or glycerin (GLY) was also used as a plasticizer. It was found that DNRL could form good elastic film but could provide low skin adhesive property. Blending DNRL with different polymers and plasticizers formed satisfactory films with different elastic and adhesive properties. DNRL blended with HPMC or PVA and DBP or GLY provided the best film for transdermal drug delivery. Nicotine was mixed into the selected preparations of film-forming polymeric solution prior to the release in Franz diffusion cells. The biphasic nicotine release from film-forming polymeric solution was found as the initial fast release which similar to the release of nicotine solution and followed by the slow release upon film formation. For nicotine patch, the monophasic slow release pattern was found. Addition of blended polymer and plasticizer showed faster release rate due to their more hydrophilicity. Kinetics of nicotine release from both DNRL polymeric solution and patch dosage forms was diffusion type which confirmed by Higuchi model. The skin permeation of nicotine was zero order kinetics. In conclusion, transdermal nicotine delivery could be obtained as both film-forming polymeric solution and patch dosage forms of which provided different drug release patterns and safety to apply on the skin without irritation.

Keywords: natural rubber latex, transdermal drug delivery systems, film-forming polymeric solution, patch, nicotine

Executive summary

Film-forming polymeric solution is a product of polymer in liquid dosage form which upon applying to the skin can subsequently form an almost invisible film *in situ* by solvent evaporation, while patch is a polymer film directly applied to the skin. In this study, both film-forming polymeric solutions and patches for transdermal nicotine delivery were prepared using deproteinized natural rubber latex (DNRL) as major polymer. Hydroxypropyl methylcellulose (HPMC), methylcellulose (MC), sodium carboxymethylcellulose (SCMC), polyvinyl alcohol (PVA), poloxamer 407 (P407), or sodium alginate (SAG) was added as a blended polymer. Dibutylphthalate (DBP), diethylphthalate (DEP), dibutylsebacate (DBS), triethylcitrate (TEC), or glycerin (GLY) was also used as a plasticizer. It was found that DNRL could form good elastic film but could provide low skin adhesive property. Blending DNRL with different polymers and plasticizers formed satisfactory films with different elastic and adhesive properties. DNRL blended with HPMC or PVA and DBP or GLY provided the best film for transdermal drug delivery. Nicotine was mixed into the selected preparations of film-forming polymeric solution prior to the release in Franz diffusion cells. The biphasic nicotine release from film-forming polymeric solution was found as the initial fast release which similar to the release of nicotine solution and followed by the slow release upon film formation. For nicotine patch, the monophasic slow release pattern was found. Addition of blended polymer and plasticizer showed faster release rate due to their more hydrophilicity. Kinetics of nicotine release from both DNRL polymeric solution and patch dosage forms was diffusion type which confirmed by Higuchi model. The skin permeation of nicotine was zero order kinetics. In conclusion, transdermal nicotine delivery could be obtained as both film-forming polymeric solution and patch dosage forms of which provided different drug release patterns and safety to apply on the skin without irritation.

Development of Nicotine Transdermal Delivery Systems from Natural Rubber as Film-Forming Polymers

Introduction

Transdermal drug delivery systems (TDDSs) are an effectively alternative route to deliver the small molecules into systemic blood circulation [1, 2]. They provide several advantages over the conventional drug therapy including avoid first-pass biotransformation and metabolism, minimize absorption and metabolism variations, possibly to attain sustained and constant drug levels, increase drug bioavailability and efficacy, provide good patient compliance, and enable fast drug delivery termination by removing the systems [2-4].

Generally, TDDSs are in patch dosage form which is a polymer film directly applied to the skin. They can be categorized as i) drug in matrix and ii) drug in reservoir systems. The matrix system is formed by dispersing or dissolving the drug in polymer matrix and lays on an adhesive layer which contacts to the skin. In some case, polymer matrix can act as adhesive layer by itself. Polymer matrix layer or the added adhesive layer is act as rate controller. For reservoir system, the drug and excipients in the form of solutions, suspensions, or gels are embedded between an impervious backing layer and a rate controlling layer which contact to the skin [5].

Film-forming polymeric solution is a novel approach of TDDSs that might present an alternative to the conventional dosage forms used on the skin, such as ointments, creams, gels or patches. The polymeric solution is a product of polymer in liquid dosage form which upon applying to the skin can subsequently form an almost invisible film *in situ* by solvent evaporation [6].

Nicotine (NCT) is a pyridine alkaloid derived from the tobacco plant. It is volatile, highly lipid that is miscible with water and also in hydrophobic solvents. It is colorless in nature, but becomes yellow or brown when exposed to air or light by auto-oxidation. It is easily to absorb and permeate through the skin when applied topically and can across the blood-brain barrier [7-9]. Nicotine patch is widely used to treat smoking cessation. Nowadays, a number of nicotine transdermal patch has been designed and marketed to deliver nicotine of 7, 14 and 21 mg over a period of 24 h. These patches are approved by the US-FDA which gave the therapeutic effect by releasing a controlled amount of nicotine through the skin into the blood stream [10].

For the development of TDDSs, polymer selection and product design are important because they must be good physicochemical properties, adhesion-cohesion balance, compatible and stable with other ingredients as well as with the skin [11]. Many classes of polymers such as cellulose derivatives, polyvinyl alcohol, chitosan, polyacrylate could apply on the skin as gelling agents, thickening agents and film formers [2]. However, the use of polymer from natural rubber latex (NRL) for TDDSs is rare.

NRL obtained from *Hevea brasiliensis* consists of naturally occurring cis-1,4-polyisoprene (Fig. 1). NRL is a white-milky fluid or slight yellow liquid which undergoes acid-coagulation to solid elastic rubber in 4-6 hours at room temperature [12]. In freshly tapped latex, it contains about 30% rubber fraction, 5% non-rubber, and other components which dispersed in water. The rubber particles are enrobed in a continuous monolayer of negatively charged phospholipid-protein complex that provides colloidal stability (Fig. 2). The most abundant of non-rubber solids are lutoids and Frey-Wyssling particles [13]. Polymer from NRL presents interesting physical properties such as high tensile strength, high elongation at break, outstanding resilience, impermeability of gases and liquids, and easily film-forming [12-15]. In fresh NRL, however, the 14 NRL proteins (Hev b1-14) are recognized by the International Union of Immunological Societies (IUIS) as causative agents of NRL-allergy [16, 17]. Hev b1 and Hev b3 are the two major proteins located on the surface of the rubber particles. Hev b1 is found mainly on large rubber particle whereas Hev b3 is more abundant in smaller rubber particles [18]. Deproteinized NRL (DNRL) prepared by enzymatic deproteinization to remove the protein from fresh NRL could reduce the problem of latex allergy [14, 18-21].

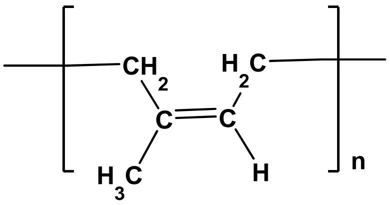


Fig. 1 Chemical structure of cis-1,4-polyisoprene

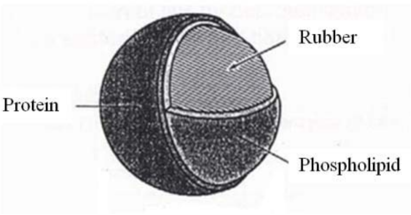


Fig. 2 Rubber particles.

This research focused on the formulation and evaluation nicotine TDDSs using DNRL as major polymer. However, DNRL film is quite low adhesiveness. Blending with the other bioadhesive polymers is one choice to improve this property. Hydroxypropylmethyl cellulose (HPMC), sodium carboxymethyl cellulose (SCMC), methyl cellulose (MC), poloxamer 407 (P407), polyvinylalcohol (PVA) or sodium alginate (SAG) were chosen as blended polymer.

HPMC is a cellulose derivative polymer which contains a basic repeat in structure of anhydroglucose units. It is slightly off-white powder, and hygroscopic. It is widely used as tablet binder, film-coating and matrix in extended release formulations. It is also used as a suspending and thickening agents in topical formulations [22, 23], and matrix former in patches [24]. It has been shown to yield clear films because of the adapted solubility of the drug in the polymer.

SCMC is also a cellulose derivative polymer which is white to almost white, odorless, tasteless, granular powder, and hygroscopic. It is widely used in oral and topical pharmaceutical formulations, primarily for its viscosity-increasing properties. Viscous aqueous solutions are used to suspend powders intended for topical applications. It is also used in self-adhesive ostomy, wound care and dermatological patches as a mucoadhesive and to absorb wound exudate or transepidermal water and sweat [22, 23].

MC is also a cellulose derivative polymer which is white, fibrous powder or granules. It is widely used in oral and topical pharmaceutical formulations. Low-viscosity grades of MC are used as emulsifying, suspending or thickening agents for orally administered liquids. High-viscosity grades of MC are used to thicken topically applied products such as creams and gels [22, 23].

Poloxamer is the polyoxyethylene-polyoxypropylene copolymers used primarily in pharmaceutical formulations. It occurs as white, free-flowing prilled granules, or as cast solids. It composes both hydrophobic (polyoxypropylene) and hydrophilic (polyoxyethylene) segments [23]. P407 is a series of poloxamer that is used mainly as a gel former, thickening agent, viscosity enhancer in creams, and solubilizer in oral and topical preparations. It could be prepared the buccal drug delivery system by blending with chitosan salt [25].

PVA is a water-soluble synthetic polymer represented by the formula $(C_2H_4O)_n$, where the value of n for commercially available materials is between 500 and 5000. It is a white to cream-colored granular powder. It is used in ophthalmic formulations such as artificial tears and contact lens solutions for lubrication purposes and in sustained-release formulations for oral and transdermal administrations. It is also used as a viscosity-increasing agent for viscous formulations [23]. Novel skin-bioadhesive patches produced from PVA was as film-forming agent which gave the good adhesive properties [26].

Alginates are extracted from brown seaweed and are available in sodium, ammonium and potassium derivatives. SAG is white to yellowish-white, fibrous powder. It can use in various pharmaceutical preparations such as oral and topical pharmaceutical formulations. It is widely used as a thickening or suspending agent in a variety of pastes, creams, and gels; and as a stabilizing agent for oil-in-water emulsions [23]. SAG mixed with chitosan was studied as a vehicle in buccal tablets [27].

Objectives

The aim of this study was to prepare the nicotine transdermal delivery systems in film-forming polymeric solution and patch dosage forms using DNRL as major component. The properties of blended films were characterized including their physical appearances, mechanical properties, moisture uptakes, and compatibilities. Consequently, *in vitro* nicotine release and skin permeation were studied in the best film formulations compared with the commercial nicotine patches.

Materials and Methods

Materials

DNRL was prepared in-house as described in the next section. (-)-Nicotine (≥99%) was purchased from Merck (Germany). HPMC, SCMC, MC, P407, PVA or SAG was used as blended polymer for improving the adhesive property. HPMC E5 was purchased from Onimax (Thailand). SCMC 1500 and MC 4000 were supplied from Srichand united dispensary (Thailand). P407 was obtained from BASF (Germany). PVA was purchased from Aldrich (Germany). SAG was purchased from Sigma (USA.). Dibutylphthalate (DBP), diethylphthalate (DEP), dibutylsebacate (DBS), triethylcitrate (TEC), or glycerin (GLY) was also added in order to reduce the brittleness and a good appearance of the finished blended films. DBP and DBS were purchased from Fluka (USA.). DEP and TEC were purchased from Aldrich (USA.). GLY, sodium dodecyl sulphate (SDS), Uniphen P-23, and sodium hydroxide were purchased from P.C. drug center (Thailand). Alcalase enzyme was purchased from Calbiochem (Germany). Polyacrylic ester (Voncoat AN868-S) was gifted from Siam chemical industry (Thailand). Three types of backing layer; 3M Scotchpack 1109 backing, 3M CoTran 9720 backing, and 3M Scotchpack 9733 backing were gifted by 3M (Singapore). The other chemicals were of analytical grade.

Preparation of DNRL

The fresh NRL was collected from *Hevea brasiliensis* (RRIM 600 clone). It was filtered through sieve, stabilized with SDS solution (1%v/v) and preserved with Uniphen P-23 (2%v/v). It was deproteinized with 0.2 phr alcalase enzyme and adjusted with 2M sodium hydroxide solution to pH 7-8, and then incubated at 37°C for 48 h. Then, the mixture was centrifuged with a Hermle Z232K Centrifuge (Hermle Labortechnik GmbH, Germany) at 10,000 rpm for 45 min. The lower aqueous layer was replaced by an equal volume of distilled water. The mixture was then centrifuged again at 10,000rpm for 30 min. The obtained DNRL was redispersed in distilled water and kept at 4ºC for further use.

Preparation of free film formulations

As shown in Table 1, DNRL and the aqueous solution of blended polymer (10%HPMC, 2.5%SCMC, 2.5%MC, 20%P407, 10%PVA or 10%SAG) with or without plasticizer were mixed homogeneously, stored at 5ºC to decrease the air bubbles and form a clear viscous solution. Then, the films could be prepared by pouring the mixtures into petri-dish and dried by hot air oven at 70ºC for 4 h. Subsequently, dry free films were peeled from petri-dish and kept in desiccators. The preparations which gave the good films were selected to further formulate as both film-forming polymeric solution and patch dosage forms for nicotine delivery.

Table 1 DNRL/polymer blending as free film formulations.

Formula (phr)	H1	H2	H3	H4	H5	H6	H7	H8	H9	H10	H11	H12	H13	H14	H15	M1	M2	M3	M4	M5	M6
DNRL	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
HPMC	5	10	15	5	10	15	10	15	10	15	10	10	10	10	15	-	-	-	-	-	-
MC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	10	15	10	15	10	15
SCMC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PVA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
P407	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SAG	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
DBP	-	-	-	10	10	10	20	20	30	30	-	-	-	-	-	-	-	10	10	-	-
DEP	-	-	-	-	-	-	-	-	-	-	10	-	-	-	-	-	-	-	-	-	-
DBS	-	-	-	-	-	-	-	-	-	-	-	10	-	-	-	-	-	-	-	-	-
TEC	-	-	-	-	-	-	-	-	-	-	-	-	10	-	-	-	-	-	-	-	-
GLY	-	-	-	-	-	-	-	-	-	-	-	-	-	10	10	-	-	-	-	10	10

Formula (phr)	C1	C2	C3	C4	C5	C6	V1	V2	V3	V4	V5	V6	P1	P2	P3	P4	A1	A2	A3	A4	R
DNRL	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
HPMC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
MC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SCMC	10	15	10	15	10	15	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PVA	-	-	-	-	-	-	10	15	10	15	10	15	-	-	-	-	-	-	-	-	-
P407	-	-	-	-	-	-	-	-	-	-	-	-	10	15	10	15	-	-	-	-	-
SAG	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	10	15	10	15	-
DBP	-	-	10	10	-	-	-	-	10	10	-	-	-	-	10	10	-	-	10	10	-
DEP	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
DBS	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
TEC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
GLY	-	-	-	-	10	10	-	-	-	-	10	10	-	-	-	-	-	-	-	-	-

Preparation of nicotine formulations

(-)-Nicotine was mixed into the selected preparations to be film-forming polymeric solutions. The preparations were storage in well-close container, and kept in the refrigerator. For patch dosage form, these mixtures were poured into petri-dish and dried by hot air oven at 70ºC for 3 hours to form dry film. Subsequently, the dry nicotine films were peeled from petri-dish and kept in desiccators. The nicotine content in the formulations was modulated to be alike in each preparation in order to get the final concentration of 30 mg/ml for film-forming, and 2.5 mg/cm^2 for patches. The compositions of these formulations are shown in Table 2.

Table 2 Nicotine loaded DNRL/polymer blending formulations.

Formula (phr)	RN	H2N	H5N	H6N	H14N	H15N	C1N	C3N	M1N	M3N	V1N	V3N	V5N
DNRL	100	100	100	100	100	100	100	100	100	100	100	100	100
HPMC	-	10	10	15	10	15	-	-	-	-	-	-	-
SCMC	-	-	-	-	-	-	10	10	-	-	-	-	-
MC	-	-	-	-	-	-	-	-	10	10	-	-	-
PVA	-	-	-	-	-	-	-	-	-	-	10	10	10
DBP	-	-	10	10	-	-	-	10	-	10	-	10	-
GLY	-	-	-	-	10	10	-	-	-	-	-	-	10
Nicotine	The nicotine amount was justified to the final concentration of 30 mg/ml for film-forming, and 2.5 mg/cm^2 for patches												

Evaluation of NRL, DNRL, and film-forming polymeric solution

The pH was measured by SevenEasy S-20 pH meter (Mettler Toledo, Switzerland) at room temperature. The viscosity was measured by Brookfield DV-II ULTRA Programmable-Rheometer (Brookfield engineering laboratories, USA.) at 25ºC. These parameters were measured in triplicate.

The particle size, size distribution, and surface charge on the particles were measured by ZetaPALS (Brookhaven, Germany) at 25ºC, and presented as effective diameter, polydispersity index (PI), and zeta potential (ζ), respectively. The sample was diluted with distilled water in an appropriate concentration prior to determine. Ten sub-runs were recorded, and shown in terms of mean and deviation.

For NRL and DNRL, the dry rubber contents (DRC) and total solid contents (TSC) were measured as described in ASTM D1076-9702 [28]. In case of DRC, 10 g latex was accurately weighted (W_0) into a petri-dish and diluted with 20 ml distilled water, then glacial acetic acid was added, stirred, and placed on a steam bath for 30 min to coagulate rubber mass into coagulum completely. The coagulum was washed with distilled water and passed the roll to make thin rubber sheet (0.2 cm) and dried at 60 ± 2ºC in hot air oven for overnight. Finally, the dry coagulum was cooled in desiccators to room temperature and weighed (W_{DRC}). Percentage of DRC was calculated by eq. (1). Several replications were determined, and mean ± SD was reported.

$$\%DRC = \frac{W_{DRC}}{W_0} \times 100 \qquad (1)$$

For TSC, 10 g latex was accurately weighted (W_0) into a petri-dish and dry at 60 ± 2ºC in hot air oven for overnight. Then, the dry mass was cooled in desiccators to room temperature and weighed (W_{TSC}). Percentage of TSC was calculated by eq. (2). Several replications were determined, and mean ± SD was reported.

$$\%TSC = \frac{W_{TSC}}{W_0} \times 100 \qquad (2)$$

Moreover, the amount of protein content was also determined as nitrogen content (%N) by using Kjeldahl method as described in ASTM D3533-90 [29]. Protein content can be calculated by multiplying the percentage of nitrogen by a Kjeldahl factor as follows by eq. (1).

$$\text{Protein } (\%) = 6.25 \times \%N \qquad (1)$$

where 6.25 = Kjeldahl factor

Evaluation of film formulations

Thickness

The thickness of the free films was measured at five different points in each patch using a micrometer and mean values were calculated.

Mechanical properties

The film specimens were cut into rectangular shape of 10 x 60 mm. The mechanical studies of films were identified by the tensile strength in term of Young's modulus, ultimate tensile strength (UTS), elongation at break, and the adhesion properties in term of peel strength and tack adhesion.

Tensile strength was determined following the method modified from the ASTM D412-98 [30] using a model 5569 Instron testing machine (Instron Corporation, USA.). The cross-head speed was controlled at 10 mm/min and the machine was equipped with a 500 N loaded cell. The Young's modulus, which is the manifestation of stiffness of a material, is calculated from the initial slope of the stress–strain plot within the range of elastic limit of stretching. The UTS is defined as either a distinct maximum or a region of strong curvature approaching zero-slope in the stress–strain curve. The elongation at break is determined by removing the fractured specimen from the grips, fitting the broken ends together and measuring the distance between gage marks [31]. These tensile values were calculated by eq. (2-4).

$$\text{Young's modulus} = \frac{\text{Stress}}{\text{Strain}} \qquad (2)$$

$$\text{UTS} = {}^{F}\!/_{A} \tag{3}$$

$$\%\text{Elongation at break} = \frac{(L_s\text{-}L_0)\times 100}{L_0} \tag{4}$$

where F = breaking load, A = cross section area of the specimen (width x thickness), L_0 = original length of the specimen, and L_S = length at breaking point of the specimen.

Peel strength measures the force required to peel away an adhesive from a surface of substrate. Most test methods for TDDSs have been developed in the adhesive industrial tapes, generally using stainless steel as the substrate [32]. This measurement is greatly influenced by the experimental parameters such as dwell time, substrate (e.g. stainless steel, skin, HDPE), peel angle, peel speed, etc. [33]. In this study, peel measurement by means of a T-peel method was modified from the ASTM D1876 [34]. The film specimens were determined by a model 5569 Instron testing machine using transparence sheet as substrate which was previously cleaned with distilled water and dried. The cross-head speed was controlled at 300 mm/min dwell time and the machine was equipped with a 500 N loaded cell.

Tack adhesion is the force to separate the adhesive from the surface of another material at interface shortly after they have been brought into contact under a load equal only to the weight of the pressure-sensitive article on contact area by means of a loop tack method. In other words, it is a definition of the 'stickiness' of the adhesive [32]. Too great a tack may cause nearly as many problems in removing and refitting, while too low a tack give the leading to bond failure during bonding assembly. Thus, measurement of tack is important for adhesive and process selection as well as in quality control. Tack adhesion measurement was modified from the ASTM D6195-97 [33]. The loop tack of the adhesive was determined by a model 5569 Instron testing machine using stainless steel surface as substrate. A tensile tester and vertical jaw with separation rate of 300 mm/min dwell time and the machine was equipped with a 500 N loaded cell.

Moisture uptake and swelling ratio studies

The moisture uptake study was modified from the ASTM E104-02 [35] using the 1 x 1 cm film specimens. The test specimens were kept in desiccators for 24 h. Then, the films were weighed (W_0) and moved to keep in saturated sodium chloride environment which be 75% relative humidity (RH). The film specimens were taken out and weighed every week until the weight is constant (W_u). Percentage of moisture uptake was calculated by eq. 5.

$$\%\text{Moisture uptake} = \frac{(W_u\text{-}W_0)\times 100}{W_0} \tag{5}$$

For the swelling ratio study, the 1 x 1 cm film specimens were immersed in 5 ml distilled water at room temperature for 48 h. After removal of excess water, the hydrated films were weighed (W_s) and then dried at 60ºC for overnight, and weighed again (W_d). The swelling ratio was calculated by eq. 6.

$$\%\text{Swelling ratio} = \frac{(W_s - W_d)\times 100}{W_d} \qquad (6)$$

Compatibility study

A differential scanning calorimetry (DSC) was used to investigate the endothermic transition of the substances. The 5-10 mg of film was transferred to the DSC pan which hermetically sealed, and then run in DSC instrument (Model DSC7, Perkin Elmer, USA) from -80ºC to 200ºC at the heating rate of 10ºC/min under nitrogen atmosphere. DSC thermogram was reported, and the endothermic transition was investigated.

The compatibility also confirmed by fourier transform infrared (FT-IR) spectroscopy. The sample was mixed with dry potassium bromide (KBr) and ground into a fine powder using an agate mortar before compressing into a KBr disc sample. In some cases, the transparent thin films were prepared, and used to investigate instead of KBr disc sample. They were scanned at a resolution of 4 cm^{-1} with 16 scans over a wavenumber region of 400-4000 cm^{-1} using FT-IR spectrophotometer (Perkin Elmer, USA.). The characteristic peaks of IR transmission spectra were recorded.

Microscopic morphology

Film surfaces were preliminary observed by CK2 inverted microscope (Olympus, Japan) at 100X magnifications. Moreover, surface and cross section morphologies of the film formulations were examined by scanning electron microscopy (SEM). Film samples were coated with gold in a sputter coater and their surface and cross section morphology were photographed with JSM-5800 LV SEM (JEOL, Japan) in an appropriate magnification.

Chemical evaluation of nicotine formulations

Determination of nicotine content

The nicotine content in each formulation was determined by extraction with water and the UV absorbance was analyzed by spectrophotometrically measurement at 260 nm (Spectronic® Genests™5 Spectrophotometer, Milton Roy, USA.). In film-forming formulations, an accurate volume of samples was diluted to 10 ml distilled water in centrifuge tube (Corning Incorporated, Mexico). The mixture was then centrifuged with a Hermle Z232K Centrifuge (Hermle Labortechnik FmbH, Germany) at 10,000 rpm for 30 min. Then, the 1 ml of lower solution was collected and diluted with distilled water to 100 ml [36]. In patch formulations, a known weight of nicotine samples was extracted in 5 ml of distilled water by sonication at 30 min, filtered and then diluted with 20 ml of distilled water[37, 38]. The nicotine amount in each sample was determined comparing with the calibration curved. Triplicate observations of each sample were measured.

In vitro nicotine release study

In vitro release of nicotine from the preparations and the commercial nicotine patch (Nicotinell TTS-20; 1.75 mg/cm^2) was investigated using a modified Franz-type diffusion cell comparing to a commercial nicotine patch. The film-forming polymeric preparations were added to the donor phase which separated to the receptor compartment by dialysis membrane (MW cut-off 12,000). While the patch preparations were cut in a circular shape and directly placed between the donor and receptor cells without the dialysis membrane. The effective diffusion area of Franz diffusion cells was 1.77 cm^2. The receptor medium was 12 ml isotonic phosphate buffer solution (PBS) pH 7.4. The diffusion cell was thermoregulated with a water jacket at 37ºC and the receptor compartment was stirred constantly at 100 rpm with magnetic stirrer. The 1 ml solution was withdrawn from the receptor compartment at predetermined time interval of 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 hours, and an equal volume of freshly PBS was then replaced. The nicotine concentrations in these samples were determined by HPLC method. Triplicate observations of each sample were measured. The kinetic of nicotine release was determined.

In vitro skin permeation study

In vitro skin permeation of nicotine from the preparations was performed using a modified Franz-type diffusion cell which diffusion area was 1.77 cm^2, and hairless pig skin as partitioning membrane. Full thickness flank skin was obtained from newborn pigs, weighed 1.4 to 1.8 kg and died natural causes shortly after birth. The dead newborn pigs were freshly purchased from a local pig farm in Songkhla Province, where is regulated by Department of Livestock Development, Thailand. This pig skin was excised, surgically removed hair off, and the subcutaneous fat and other extraneous tissues were trimmed with a scalpel, cleaned with PBS, blotted dry, wrapped with aluminium foil and stored frozen. Before permeation experiments were performed, the full-thickness skin prepared in aforementioned way was soaked overnight in PBS. The isolated skin was mounted on the Franz diffusion cells which the stratum corneum (SC) surface faced upward on the donor compartment. The film-forming polymeric preparations were added to the donor phase, while the patches were laid onto the isolated skin as same as the release study. The receptor compartment was 12 ml of pH 7.4 PBS whose temperature was maintained as 37 ºC. The receptor compartment was stirred constantly at 600 rpm with magnetic stirrer

[39-41]. A 1 ml solution was withdrawn from the receptor compartment at predetermined time interval of 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 hours, and an equal volume of freshly PBS was then replaced. The nicotine concentrations in these samples were determined by HPLC method. Triplicate observations of each sample were measured.

HPLC condition for nicotine analysis

The solution collected from the receptor of Franz diffusion cell was filtered through a cellulose acetate membrane (0.22μm pore size). Then, the nicotine analysis was carried out using an HPLC system (Agilent 1100 series, Thermo electron corporation, USA.) with a column (BDS HYPERSIL C18, 150x4.6 mm diameter, 5 μm particle size, Thermo scientific, USA.). The mobile phase consisted of 0.05 M sodium acetate:methanol = 9:1 v/v containing 1.3% triethanolamine, and the pH was adjusted to 4.2 with acetic acid. The flow rate was 0.7 ml/min, and the injection volume was 10 μl. The absorbance was detected by the UV detector at the wavelength of 260 nm. The nicotine amount was calculated comparing with the calibration curved.

Stability study

The selected DNRL blending film-forming polymeric solutions and patches were storage in well close container, and kept in different 3 conditions: 4 ºC, ambient temperature, and 45 ºC. In each appropriate time intervals, the preparations were withdrawn and nicotine was analyzed by the validated UV method.

Skin irritation test

The selected DNRL blending film-forming polymeric solutions and patches were further studied in acute dermal irritation test in rabbit. This test was determined by Thailand Institute of Scientific and Technology Research (TISTR). The test of acute dermal irritation/corrosion was conducted according to the OECD guidelines for testing of chemicals (TG 404). Briefly, three healthy adult albino rabbits of New Zealand white hybrid strain were purchased from Department of Animal Science, Faculty of Agriculture, Kasetsart University. Their body weight range was 2-3 kg. One day before experimentation, an area of skin approximately 10x10 cm on the dorso-lumbar region of each rabbit was clipped free of hairs. Two areas of the shaven skin approximately 2.5x2.5 cm were selected. The volume 0.5 ml of solutions or the weight 0.5 g of DNRL patched was introduces onto a 2.5x2.5 cm gauze patch, which was served as a treated patch while 0.5 ml of distilled water on another patch was served as a control patch. Both patches were applied to the selected skin sites on each rabbits. The patches were then secured to the skin by transpore adhesive tape. The entire trunk of the rabbit was wrapped with elastic cloth to avoid dislocation of the patches for 4 hours. At the end of the exposure period, all patches were removed and gently wiped the treated skin with moistened cotton wool to remove any residual test materials. The animals were assessed for the degree of erythema and oedema evidence on each site at 1, 24, 48, and 72 hours after removal of the patches. Further observation would be needed, as necessary, to establish the reversibility if the irritation sign(s) still existed, but would not exceed 14 days after application. In addition to the observation of irritation, any lesions and other toxic effects were recorded. The skin reactions were independently scored by two inspectors using the numerical scoring system as follows in Table 3.

Table 3 The scoring criteria for acute dermal irritation test

Sign	Scaling
Erythema and eschar formation:	
No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4
Oedema formation:	
No oedema	0
Very slight oedema (barely perceptible)	1
Slight oedema (edges of area well-defined by definite raising)	2
Moderate oedema (raised approximately 1 mm)	3
Severe oedema (raised more than 1 mm and extending beyond the area of exposure)	4

Results and Discussion

NRL and DNRL characterizations

DNRL could be prepared by enzyme treatment method. Its physical appearance was not much different from fresh NRL. The pH of NRL was 6.68 ± 0.19, while that of DNRL was 7.47 ± 0.01. The viscosities of both NRL and DNRL were quite low with the Newtonian behavior (7.45 and 7.35 centipoises, respectively) which easy to apply directly on the skin or to formulate in any preparations. The DRCs of NRL and DNRL were 38.43 ± 3.01%, and 39.55 ± 2.42%, respectively. The TSC of DNRL was 40.72 ± 2.22%. The protein contents of NRL and DNRL determined as percentage of nitrogen were 0.258

± 0.018% and 0.028 ± 0.024% which further calculated to the value of protein content as 1.61 ± 0.11% and 0.17 ± 0.15%, respectively. These values indicated the efficacy of protein reduction by enzyme treatment in DNRL which was more than 89.21 ± 9.45%. The protein in NRL might be hydrolyzed by alcalase enzyme and solubilized with SDS which could be separated by centrifugation from rubber latex.

The mean effective sizes of NRL and DNRL were 294.7 nm and 485.9 nm. Their PIs were 0.22 and 0.24, and their zeta potentials were -37.02 ± 6.53 mV and -40.34 ± 4.51 mV, respectively. These results showed narrow size distribution of latex dispersion with moderate stability. DNRL dispersion was stable when storage in the refrigerator for more than 4 months. However, the particle size of DNRL was larger than raw NRL. This was due to the aggregation of some latex particles after centrifugation process.

Thus, the deproteinization process in this research was successful to produce DNRL with low protein content and good properties. This process was good reproducibility. The obtained DNRL dispersion was used to formulate both film-form polymeric solution and patch dosage forms.

Evaluation of free film formulations

Film formation from DNRL was preliminarily studied. It was found that the amount of DNRL in the formulations directly affected the film-forming time, film appearances, and the peeling from the petri-dish. Thus, the appropriate amount of each formulation (as in Table 1) was optimized to pour into the petri-dish, and dried to form the complete films. In the formulation V2, V4, and V6, however, they could not peel out from the petri-dish to get the complete films, due to their much sticky.

Thickness

The thickness of dried films varied between 0.208 and 0.379 mm (raw data were not showed). These values depended on the amount of mixtures poured into the petri-dish, and the solid content in each formulation. However, the thickness uniformity of each film was good which be indicated by the low deviation in each position of film in the same petri-dish.

Mechanical properties

In general, mechanical properties of films can define in 5 groups, 1) hard and tough film which showed the high modulus, high UTS and high elongation, 2) hard and strong film which showed the high modulus, high UTS and moderate elongation, 3) hard and brittle film which showed the high modulus, high UTS and low elongation, 4) soft and weak film which showed the low modulus, low UTS and moderate elongation, and 5) soft and tough film which showed the low modulus, low UTS and high elongation [42].

The mechanical properties of each film formulations are shown in Fig. 3-6. It was found that DNRL could form good elastic film (high %elongation at break) with low adhesive property (as peel strength and tack adhesion). Blending DNRL with different type and amount of polymers and plasticizers formed satisfactory films with different mechanical properties, as following results.

Effect of HPMC amount

Blending DNRL with HPMC (5-15 phr) could construct the blended film with improving the mechanical properties of DNRL film (Fig. 3). The results showed the same trends in both with and without DBP as plasticizer. The modulus, UTS, elasticity, and adhesive properties increased when increasing HPMC amount. However, the elasticity of HPMC blended film was lower than that of pure DNRL film. This was due to the bulkiness of anhydroglucose in HPMC structure. However, it increased with increasing HPMC amount because it is directly related to the concentration of the methoxyl groups in HPMC molecule, the more flexible and viscous film was occurred. This indicated the mechanical improvement, and the hard and strong film was obtained by HPMC blending in DNRL polymer.

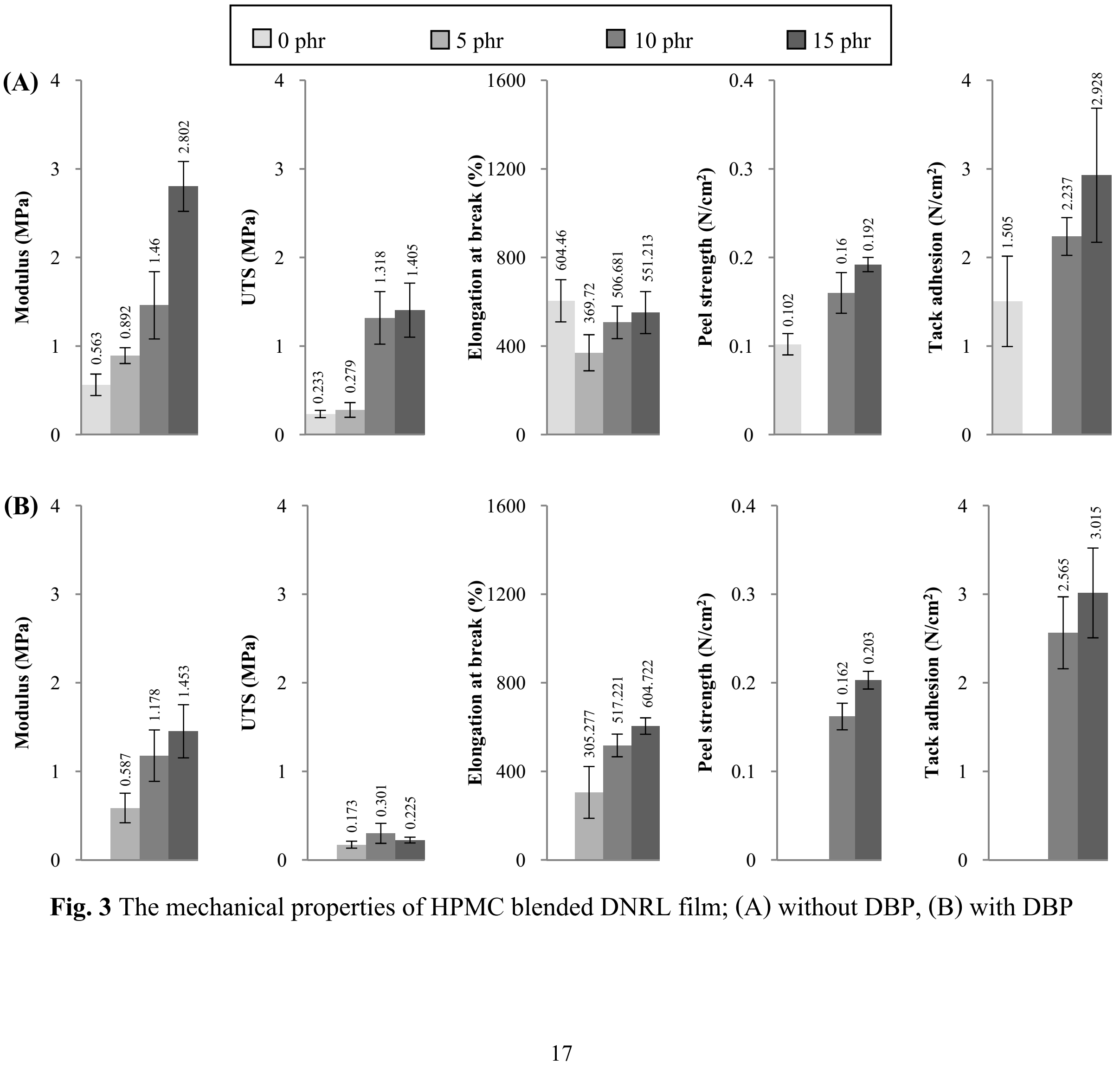


Fig. 3 The mechanical properties of HPMC blended DNRL film; (A) without DBP, (B) with DBP

Effect of DBP amounts

Plasticizers are mixed in order to enhance the flexibility or reduce the brittleness. Contrast to the effect of HPMC amount, the results showed the decreasing of the modulus, UTS, and adhesive properties, and increasing of elastic property when increasing DBP amount in both 10 phr and 15 phr HPMC blending ratios (Fig. 4). The significant differences of modulus and UTS properties, and the slightly differences of elongation and adhesive properties were observed between without and with DBP. Increasing differences of these properties were observed when increasing DBP amount. The plasticizer would interpose in the inter-molecular forces between polymer chains by extending and softening of films, basically causing to a decrease in the tensile strength and glass transition temperature of films [43]. DBP acted as plasticizer which affected the blended polymers to be the softener and more elastic film. However, the slippery and soft surface film was observed when using the DBP more than 20 phr, which was difficult to prepare the completely dry film and showed the poor adhesive film. Thus, the 10 phr plasticizer was chosen for the further studies.

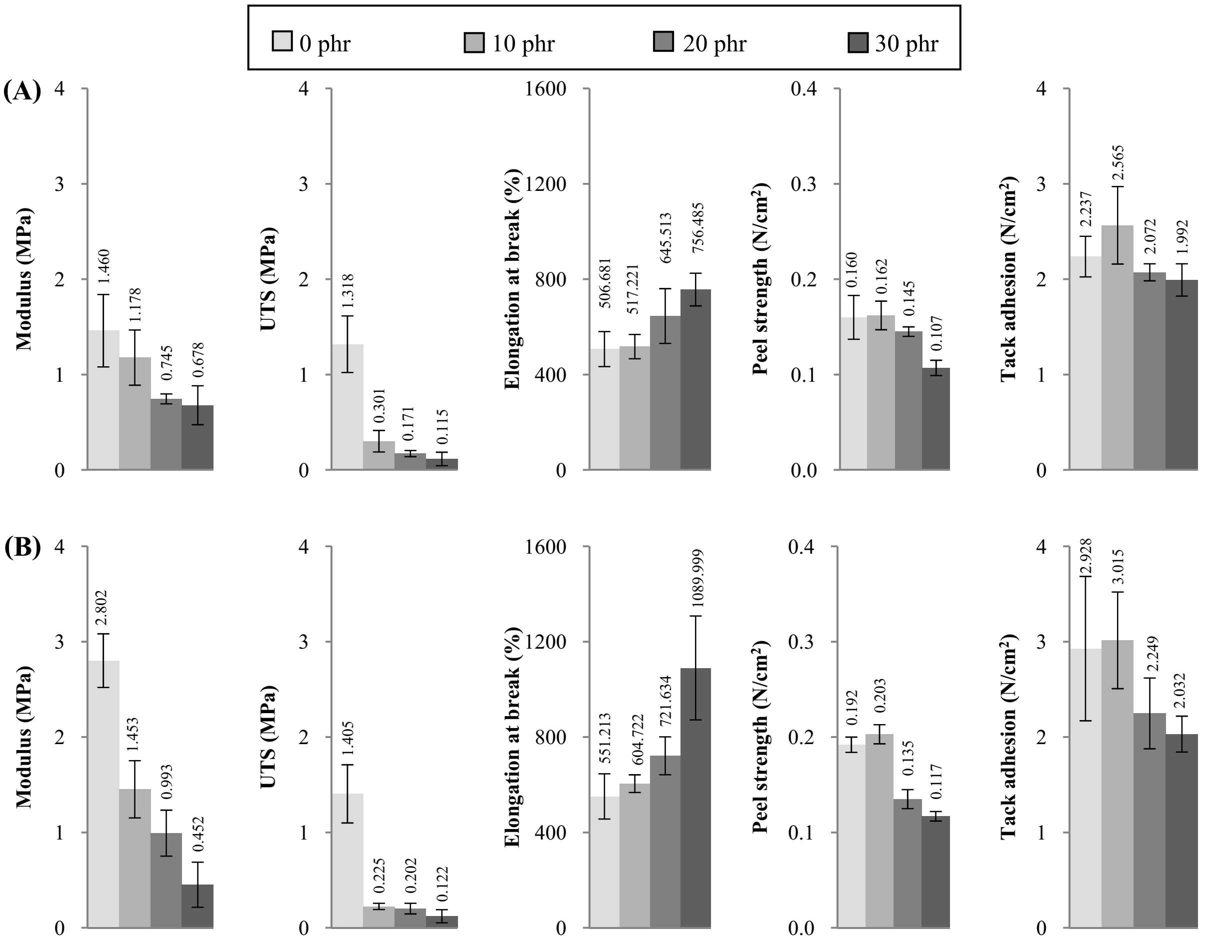


Fig. 4 The mechanical properties of HPMC blended DNRL film with various amounts of DBP; (A) HPMC 10 phr, (B) HPMC 15 phr

Effect of plasticizer types

The free films with various plasticizer types were flexible than the unplasticized films and easily to remove from petri-dish. Their mechanical properties are shown in Fig. 5. The addition of plasticizers resulted in decreasing of Young's modulus and UTS which indicated the softener film, but the elasticity properties was not significantly different in each plasticizer type. The blended film using DBS gave the lowest modulus and UTS indicating the most softness film, while the using of TEC gave the lowest %elongation at break indicating the most brittle film. Unlikely, TEC and GLY made the slightly hazy film. However, the most important of transdermal films was the adhesive property. From the result of this study, the blended films composed of DBP or GLY were higher adhesive property than the unplasticized films, while DEP, DBS, and TEC showed the opposite results. Thus, DBP and GLY were the most suitable plasticizer for blended film formation with the good mechanical properties.

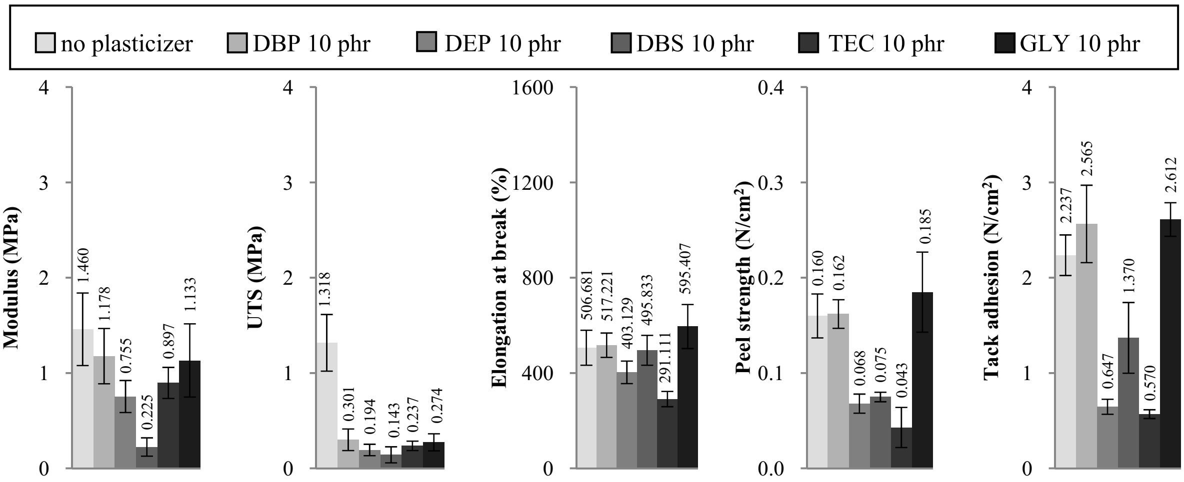


Fig. 5 The mechanical properties of 10 phr HPMC blended DNRL film with various types of plasticizer

Effect of polymer types and amounts

Similar to the DNRL/HPMC blended films, the blended film of DNRL with MC, SCMC, PVA, P407, or SAG with/without DBP or GLY as plasticizer showed the increasing of the modulus, UTS, elasticity, and adhesive properties when increasing the polymer amount. DNRL/MC blending exhibited the highest tensile property film, and DNRL/P407 blending showed the lowest tensile property film. In addition, all polymer blended DNRL films increased the adhesion properties. DNRL/PVA, HPMC, or MC blended film exhibited highest adhesion properties but DNRL/P407 blended film shown lowest adhesion properties (Fig. 6). In these results, HPMC, MC, SCMC and PVA were the suitable polymers for using as polymer blending with DNRL for nicotine transdermal formulations. P407 and SAG gave the untoward properties which were not chosen when mixing with GLY. High viscosity of MC and SCMC caused

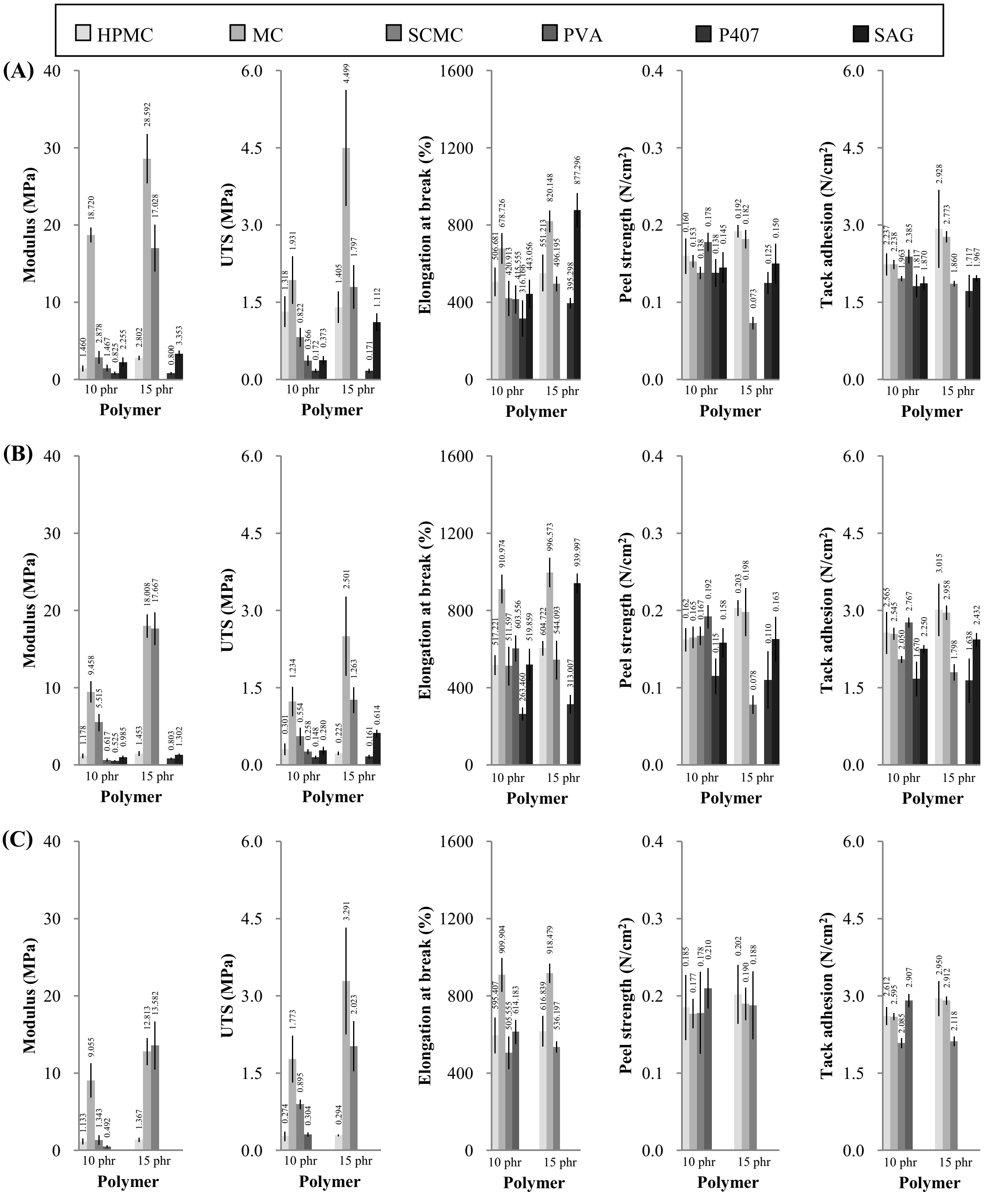


Fig. 6 The mechanical properties of polymer blended DNRL film with various types and amounts of polymer and plasticizer; (A) without plasticizer, (B) with DBP 10 phr, (C) with GLY 10 phr

much air bubbles which could be eliminate. Moreover, polymer blending of 15 phr PVA produced the sticky films which were difficult to peel-off from petri-dish in film preparations, and the reforming film had gained. Thus, some properties were abstained in these preparations. Only HPMC and PVA were chosen for further study because they were easy to prepare in solution form and mix with DNRL dispersion without air bubbles.

Moisture uptake and swelling ratio studies

The moisture uptake and swelling ratio of free films contains various types and mounts of polymer and plasticizer are presented in the Fig. 7-8. Both moisture uptake and swelling ratio were increased when DNRL blended with HPMC and more increased when the various plasticizers were added. In Fig. 7, it could be found that these values directly depended on the amounts of HPMC and DBP, the increasing HPMC and DBP amount increased the moisture uptake and swelling ratio. These could be due to more hydrophilicity of the free film when increasing the HPMC and DBP amount. Moreover, these values were affected by plasticizer types. They could be ranged of GLY > TEC > DBP > DBS > DEP. The water uptake and swelling behaviors of the polymeric film plays an important role at the beginning stage of drug release from patch. Thus, the film with higher moisture uptake and swelling ratio supposed to give higher drug release rate [4, 44].

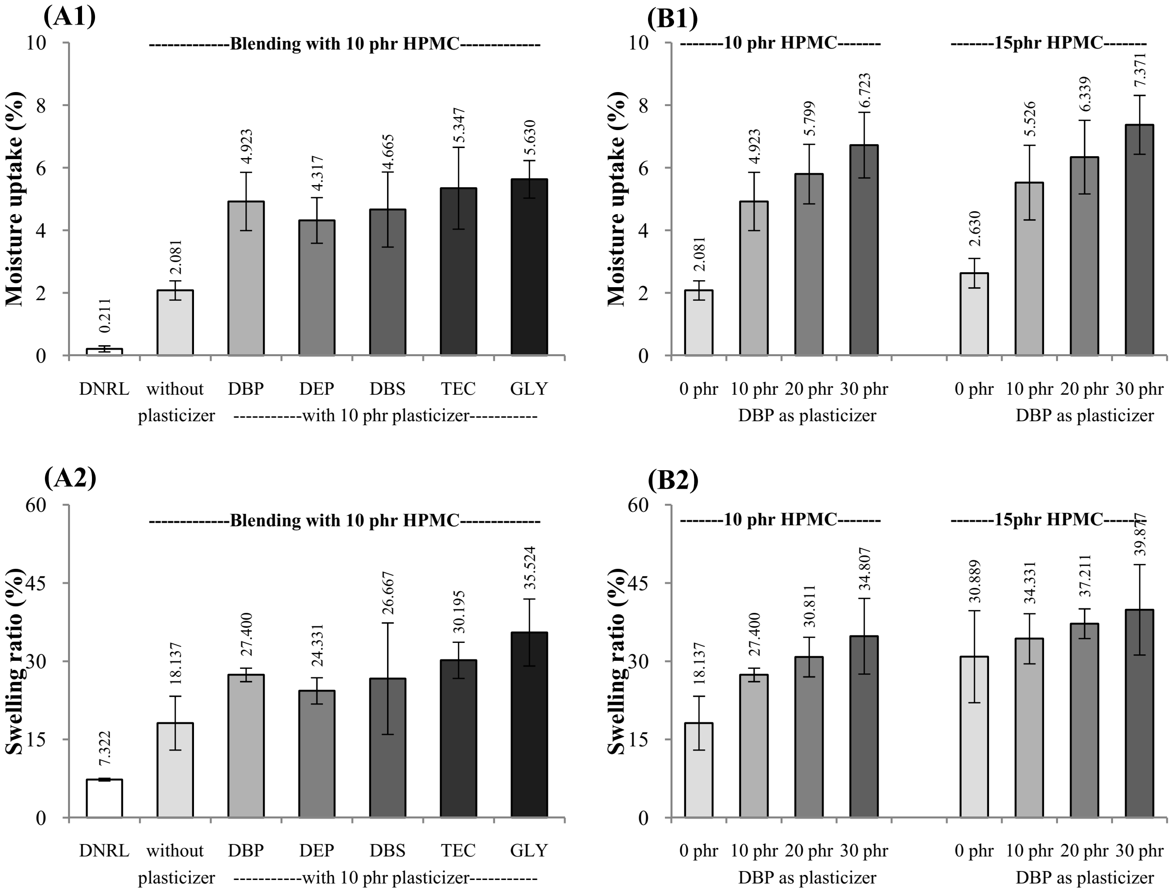


Fig. 7 Effects of different (A) types and (B) amounts of plasticizer on (1) moisture uptake and (2) swelling ratio of DNRL/HPMC blended films (n=6).

Fig. 8 showed that the moisture uptake and swelling ratio increased when various polymers was blended into DNRL films. These values were very slightly affected by polymer types. They could be ranged of MC > SCMC > P407 > PVA >HPMC > SAG in both 10 phr and 15 phr polymer blending. In addition, these values increased significantly when DBP was used as plasticizer, and the same pattern was observed in each polymer blending. These could be due to the hydrophobic of the DNRL films was changed to be higher hydrophilic property when various polymers and plasticizers were added. The plasticizer was major component to increase the moisture uptake and swelling ratio of DNRL films.

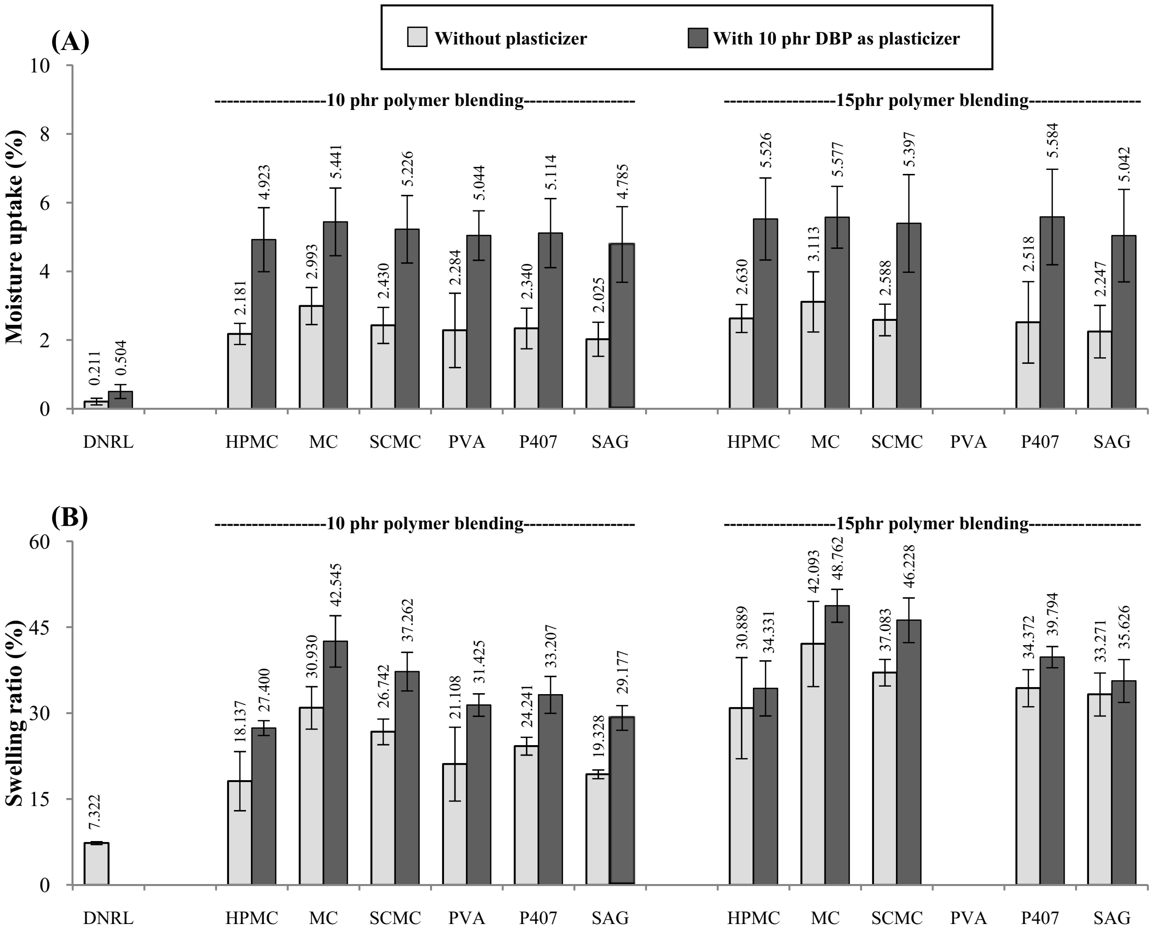
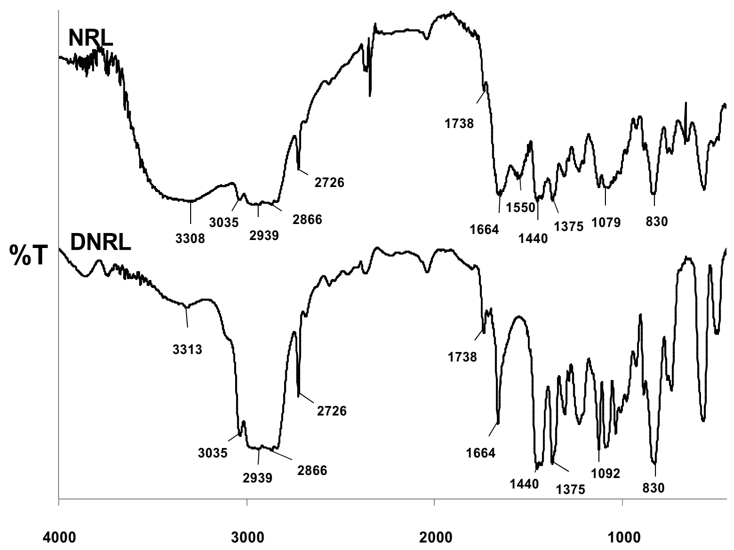


Fig. 8 Effect of different types and amounts of polymer blending on (A) moisture uptake and (B) swelling ratio of DNRL/polymer blended films (n=6).

Compatibility study

Fourier transform infrared spectroscopy study

The FT-IR spectra of NRL and DNRL films are presented in Fig. 9. The principle absorption peaks of NRL spectrum was observed corresponding with isoprene functional groups of NRL and protein/phospholipids in NRL [15]. After removing the proteins from NRL, the principal peak of isoprene functional groups showed more clearly, and the protein/phospholipids spectra decreased or disappeared in DNRL film. These confirmed that the deproteinized process by enzyme treatment could completely reduce the protein amount in NRL.



Wavenumber (cm^{-1})	Isoprene
3035	=CH stretching
2939	C–H stretching of CH_3
2866	C–H stretching of CH_2
2726	C–H stretching of CH_2 and CH_3
1664	C=C stretching
1440	C–H bending of CH_2
1375	C–H bending of CH_3
830	C=CH wagging
Wavenumber (cm^{-1})	**Protein/phospholipid**
3308	–OH stretching, N–H stretching
1738	C=O stretching
1550	N–H bending
1079	C–O
1014	–O–O–

Fig. 9 FT-IR spectra of NRL and DNRL films.

In the major peaks of DNRL and various polymers (HPMC, MC, SCMC, PVA, P407 or SAG) are also found in the DNRL/polymer blended films and it was found a slightly broader peak occurs at 1738 cm^{-1} (C=O stretching of DBP) in the DNRL/polymer blended films with DBP as plasticizer (Fig. 10). No new peak which shifted from those of raw materials was found in these polymer blended. These results indicated the compatibility of each ingredient in the blended films.

Differential scanning calorimeter study

The DSC thermograms (Fig. 11) did not show the glass transition temperature (T_g) of DNRL in the range of -80ºC to 200ºC, but the major temperature transition appeared as the melting endotherm at 39.3ºC. However, Naskar and De reported the T_g of cis-polyisoprene or natural rubber at -75ºC to -70ºC [45]. This might be due to some purity change in deproteinized process. The melting endotherm of HPMC and DNRL/HPMC blended films also presented at 37.5 ºC and 41.2ºC, while that of PVA and DNRL/PVA blended films was 38.3 ºC and 37.3ºC, respectively. This indicated the slightly change in the structure of blended film. Moreover, the DBP blended as plasticizer slightly reduced the melting endotherm of DNRL/HPMC/DBP and DNRL/PVA/DBP blended films to 40.0 and 24.7ºC, respectively. However, no disguised signal was observed in DSC thermograms which indicated the compatibility of each ingredient in blended film.

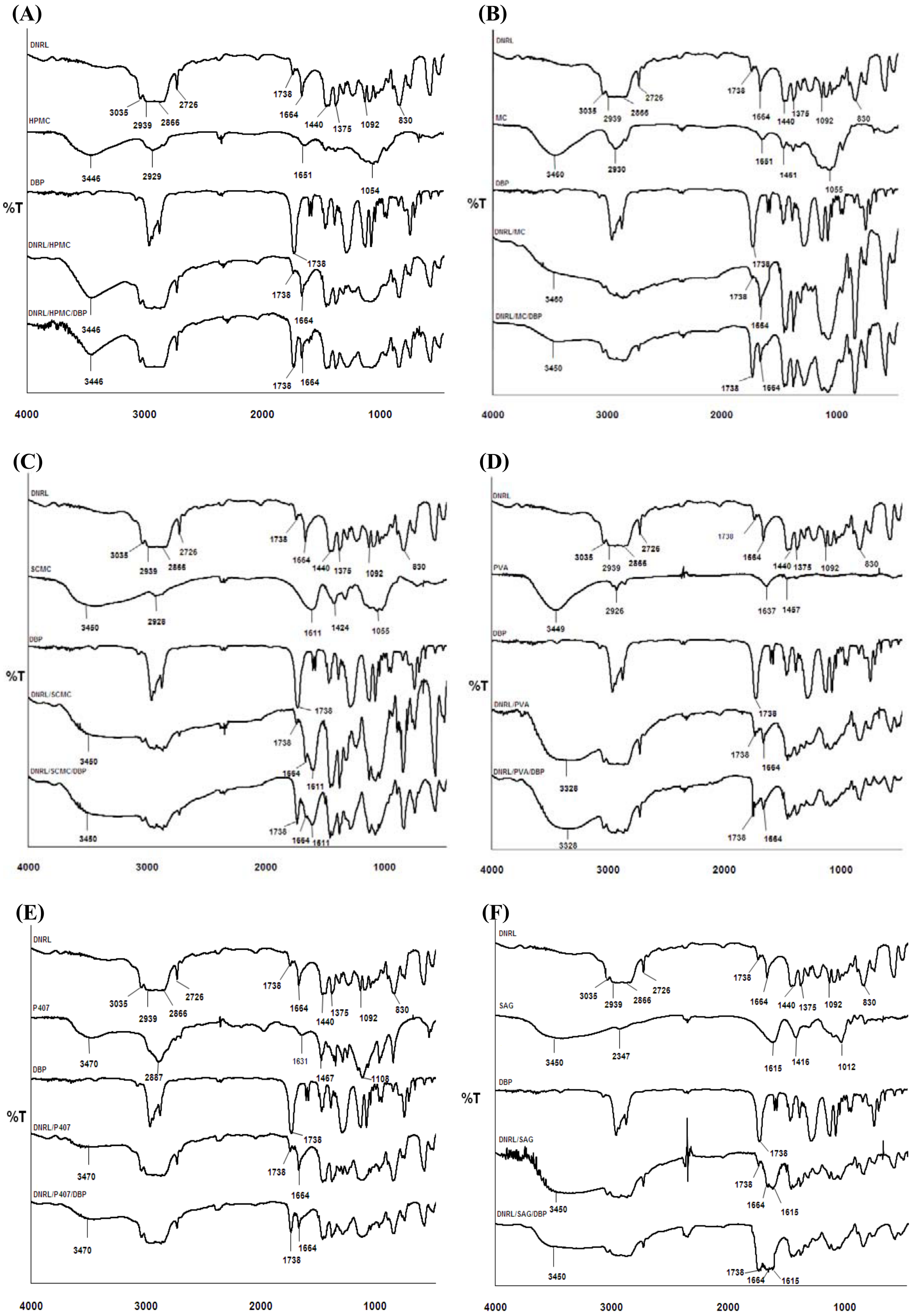


Fig. 10 FT-IR spectra of DNRL film, the blended polymers (A) HPMC, (B) MC, (C) SCMC, (D) PVA, (E) P407, and (F) SAG, DBP as plasticizer, and their blended films.

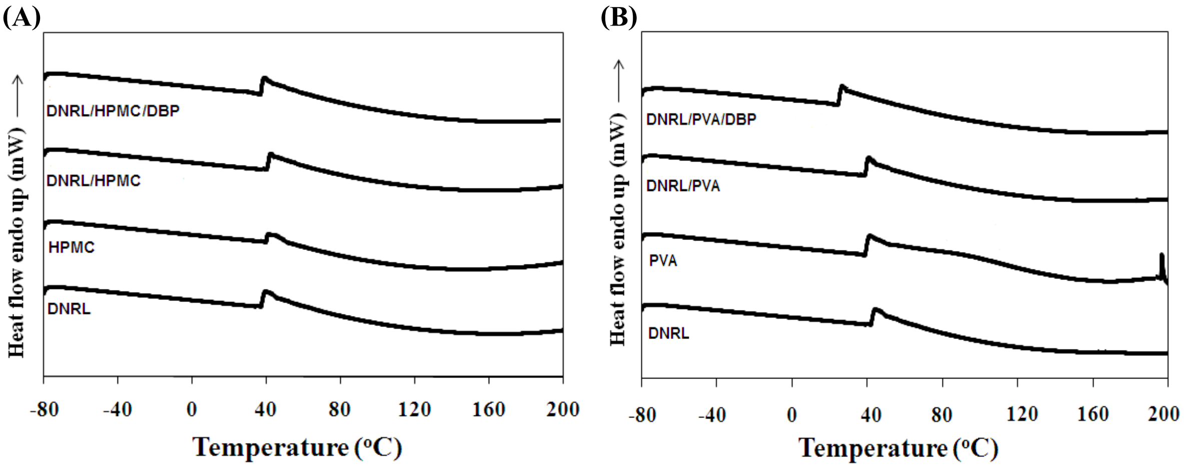


Fig. 11 DSC thermograms of DNRL, the blended polymers (A) HPMC, (B) PVA, and their blended films.

Microscopic morphology

The optical microscope photographs of various NRL, DNRL, and DNRL/polymer blending preparations are shown in Fig. 12. The smooth films with slight roughness were obtained in many formulations. There were some air bubbles in P407 blended DNRL films. However, the overall image was good in each film formulation.

The SEM was used to confirm the high resolution microscopic morphology in each film. It was found that the DNRL film had smooth surface as show in Fig. 12-13. After HPMC and DBP were mixed in DNRL, no obvious change was observed in the patches. In contrast, DNRL blended with HPMC and GLY was presents minimal cracking on the surface. The cracking were believed to be cause by the water lost through surface evaporation rapidly [46]. In addition, DNRL blended with PVA and DBP or GLY were presented the smooth on the surface. From these results, it could be concluded that the patch made from PVA had smoother surface than that from HPMC, as well as the patch made from DBP was smoother surface than that from GLY as plasticizer.

Evaluation of nicotine formulations

Nicotine film-forming polymeric solutions were prepared using the selected blending formulations which gave the good physical and mechanical properties as discussed in the previous section. The nicotine transdermal patches were also prepared in the same compositions as solution dosage forms, but the drying process was stepped up for film formation.

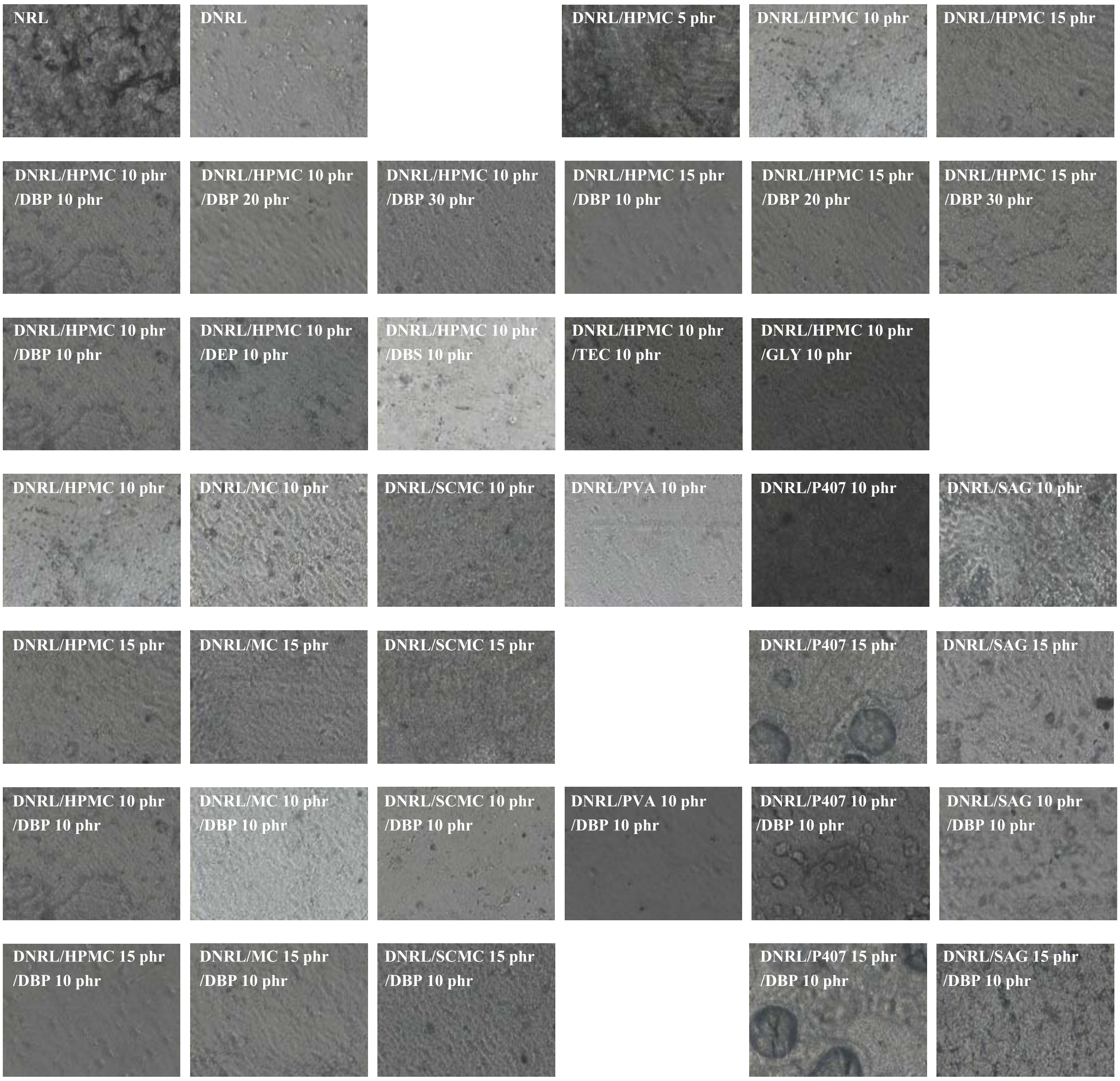


Fig. 12 Photomicrographs of films in various formulations (100X magnifications).

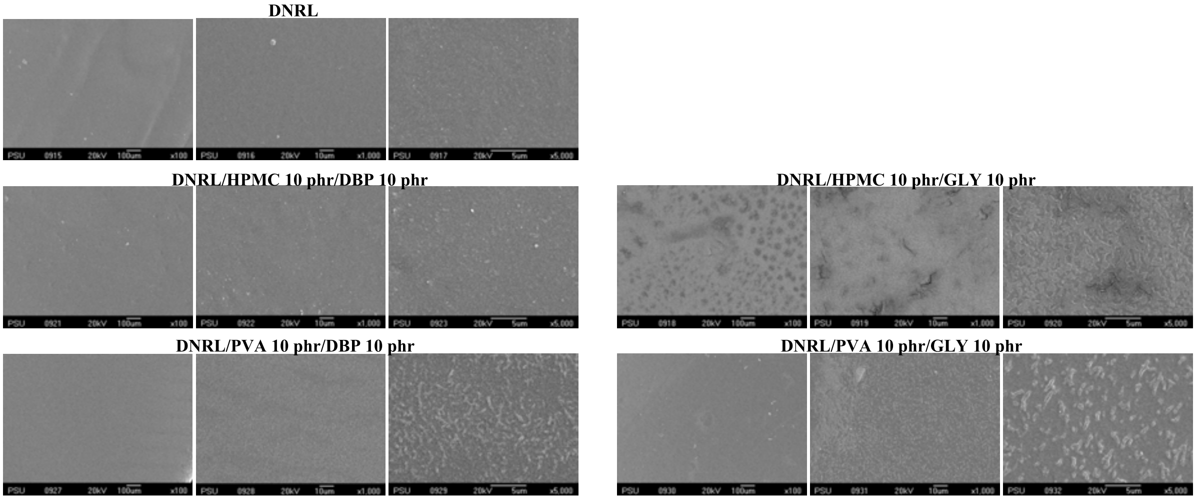


Fig. 13 SEM micrographs of films in various formulations.

pH, viscosity, particle size and zeta potential of film-forming polymeric solutions

The pH and viscosity of nicotine film-forming polymeric solutions containing DNRL as major polymer are shown in Fig. 14. Nicotine resulted in increasing pH due to its basic property. However, these pH values were safe to use for skin application. The viscosity was slightly decreased by nicotine. But the type of polymer blending was the important factor affecting this property. Polymer blending resulted in the increasing viscosity compared with DNRL preparation. PVA blending was higher viscous than that of HPMC blending. The 10-60% ethanol was mixed in the solution dosage forms in order to decrease the film-forming time on the skin. This was no effect to pH values. The viscosity slightly decreased when ethanol was mixed due to the dilution effect, but it slightly increased when increasing the ethanol amount. This was due to the slight aggregation of polymer solution by ethanol which could be observed when storage.

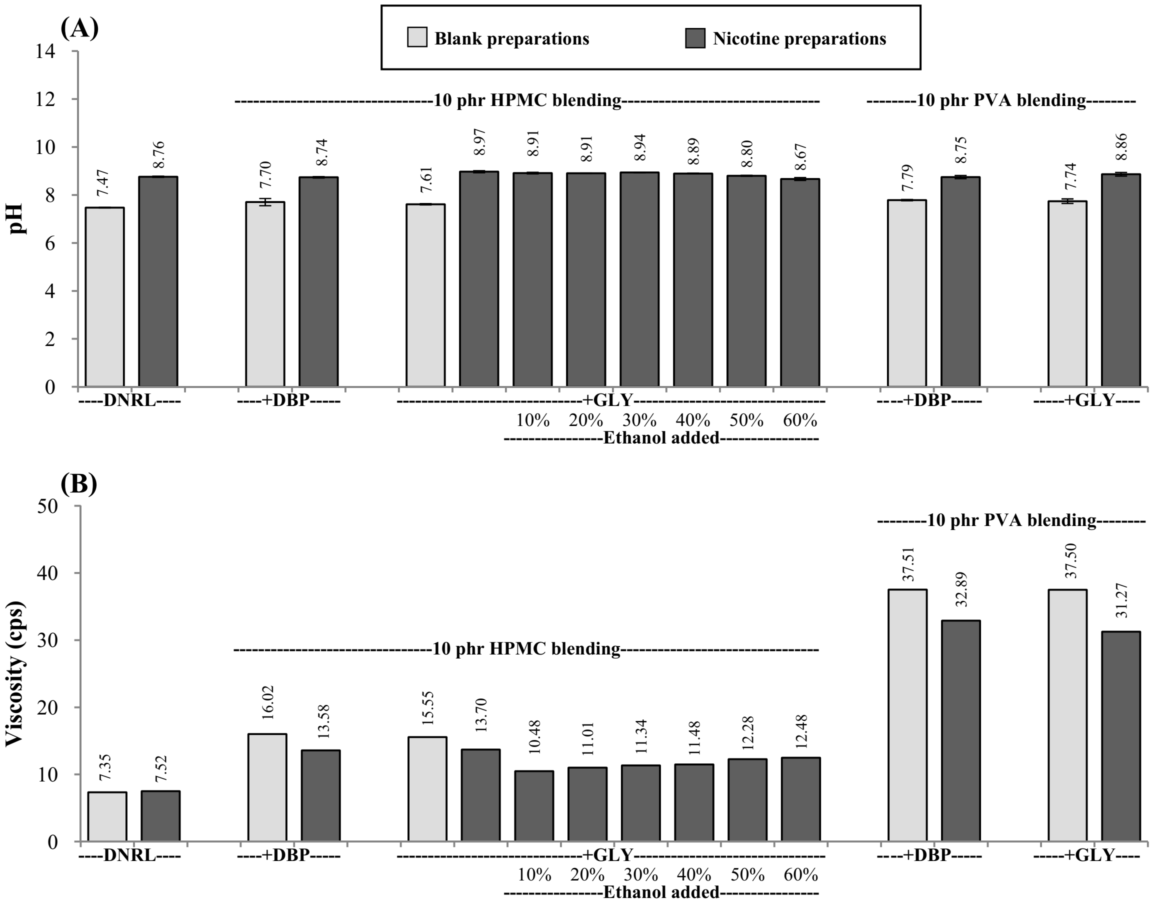


Fig. 14 (A) pH and (B) viscosity of nicotine film-forming polymeric solutions using 10 phr HPMC or PVA as polymer blending, and 10 phr DBP or GLY as plasticizer

The particle size and zeta potential of polymer particles in nicotine film-forming polymeric solutions were also determined. These values of formulation H14N (DNRL/HPMC(10)/GLY(10)/NCT) were 474.0 ± 5.2 nm (PI 0.23 ± 0.01) and -43.22 ± 0.53 mV, respectively. While those of V5N (DNRL/PVA(10)/GLY(10)/NCT) were 482.9 ± 3.9 nm (PI 0.24 ± 0.01) and -31.88 ± 0.57 mV, respectively. These values were not different from those of raw DNRL, except the zeta potential of PVA blending formulation which had the lower value than raw DNRL which mentioned to be lower stable. This might bring to get some aggregation when storage. However, this value was too high to be sufficient in a moderate stable in colloidal systems.

Nicotine content

The UV method for nicotine content determination in each formulation was validated which showed the correlation coefficients of calibration curve in the range of 2-40 μg/ml for more than 0.9996. The nicotine content in film-forming polymeric solutions and patches is presented in Table 4. The entrapment efficiencies of film-forming polymeric solutions were close to the initial concentration, while those of patches decreased to the range of 55.35-65.68%. This was due to the volatility of nicotine in drying process to form film. These nicotine contents could be modulated to get the required concentration.

Table 4 Nicotine content in various DNRL formulations.

Code	Composition	Film-forming polymeric solutions		patches	
		Nicotine loading (mg/ml)	Entrapment efficiency (%)	Nicotine loading (mg/cm^2)	Entrapment efficiency (%)
RN	DNRL	29.21±4.05	97.52±13.53	2.59±0.15	65.68±5.96
H2N	DNRL/HPMC(10)	-	-	2.52±0.04	56.10±0.80
H5N	DNRL/HPMC(10)/DBP(10)	30.01±7.50	100.21±25.05	2.52±0.03	55.93±0.60
H6N	DNRL/HPMC(15)/DBP(10)	-	-	2.57±0.11	57.03±2.40
H14N	DNRL/HPMC(10)GLY(10)	28.72±11.76	95.91±39.27	2.55±0.18	56.63±4.02
H15N	DNRL/HPMC(15)/GLY(10)	-	-	2.58±0.07	57.25±1.63
C1N	DNRL/SCMC(10)	-	-	2.50±0.12	55.64±2.69
C3N	DNRL/SCMC(10)/DBP(10)	-	-	2.52±0.08	55.94±1.72
M1N	DNRL/MC(10)	-	-	2.49±0.20	55.35±4.45
M3N	DNRL/MC(10)/DBP(10)	-	-	2.54±0.21	56.33±4.76
V1N	DNRL/PVA(10)	-	-	2.56±0.12	56.82±2.66
V3N	DNRL/PVA(10)/DBP(10)	29.37±6.21	98.06±20.75	2.60±0.12	57.69±2.72
V5N	DNRL/PVA(10)/GLY(10)	29.53±3.02	98.60±10.08	2.62±0.10	58.17±2.33

In vitro nicotine release

The HPLC method of nicotine was validated on the purpose of aqueous stability indicating for nicotine determination in *in* vitro release and permeation studies. The validation parameters were addressed in terms of limit of detection (LOD), limit of quantitation (LOQ), specificity, accuracy, linearity, and precision.

The results showed the validated LOD and LOQ as 0.91 and 1.92 µg/ml, respectively. No peak interfere in the same retention time of nicotine peak was observed. Correlation coefficient for the calibration curve in the range 2-60 µg/ml for nicotine standard solutions was 0.9992 showing linearity. In addition, the coefficient of variation (CV) was less than 2% in both intra-day and inter-day. The %CV values for both intra-day was found to be 0.11-0.71 (n=6) and inter-day on seven different days was found to be 0.12-0.80 (n=3) over the range 2-60 µg/ml. At the same concentrations, this method was found to afford the accuracy of 97.35-124.68% for intra-day and 97.06-123.59% for inter-day.

The biphasic nicotine release from film-forming polymeric solutions was found as the burst release in 3-4 hours which similar to the release of nicotine solution, and followed by the slow release upon film formation as shown in Fig. 15-16. The type of blended polymer and plasticizer affected the release profiles. PVA blending showed faster release profiles than those of HPMC blending formulations. Using GLY as plasticizer also showed faster release profiles than those of DBP formulations (Fig. 15). PVA and GLY were higher hydrophilic than HPMC and DBP. Hence, they increased the hydrophilicity of preparations and films after formation after 3 hour (in the release study condition), resulting in faster release profiles. The kinetic of nicotine release in the second period was diffusion type which confirmed by the Higuchi model, due to the complete film formation on the donor compartment after 3 hours. Thus, nicotine had to diffuse through DNRL blending film before passing through release membrane. These biphasic nicotine release patterns might be gainful for nicotine delivery which desired the initial fast release and followed by the sustained action.

Moreover, the effect of ethanol dilution on film-forming polymeric solutions on their release patterns was studied (Fig. 16). The nicotine release of ethanol diluted preparations was lower than that of no diluted film-forming polymeric solutions at initial. This correlated with the viscosity of these colloidal dispersions which explained some aggregations after ethanol dilution. However, the higher release rate after 4-6 hours was observed by the series of ethanol amount. The higher ethanol amount gave the higher dilution. Thus, the nicotine was easy to diffuse through the release membrane. However, ethanol dilution preparations were not predominant that the origin film-forming polymeric solutions, and some unstable signs were observed.

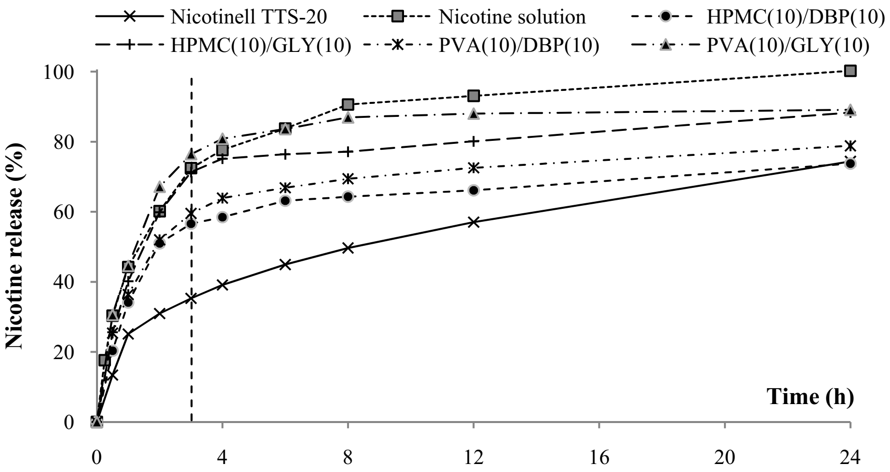


Fig. 15 Nicotine release from DNRL/HPMC or PVA film-forming polymeric solution with DBP or GLY comparing with nicotine solution and Nicotinell TTS-20 (n=3).

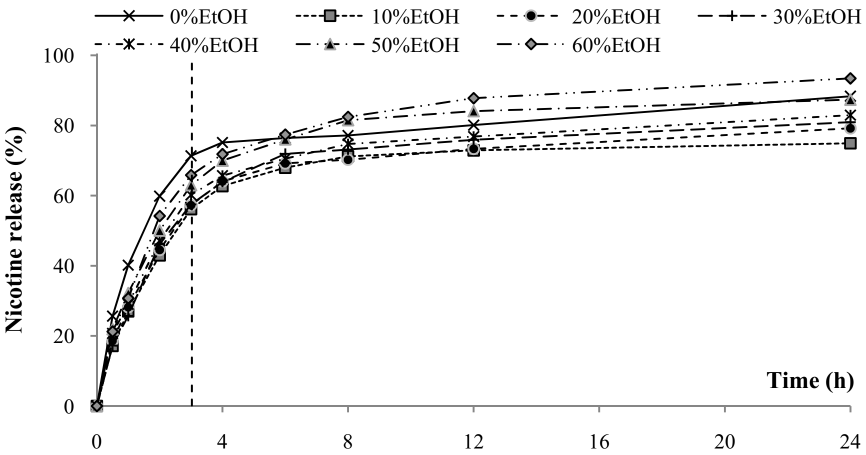


Fig. 16 Nicotine release from DNRL/HPMC(10)/GLY(10) film-forming polymeric solution in different ethanol amounts comparing with nicotine solution and Nicotinell TTS-20 (n=3).

For nicotine patch, the monophasic slow release pattern was found. Addition of blended polymer and plasticizer showed faster release rate due to their more hydrophilicity. The MC blending showed the highest release profile, while HPMC, SCMC, and PVA were similar (Fig. 17). The DNRL/MC blending films had some air bubbles in preparing process, thus the film was loose which easy to water uptake in the film. These results correlated to their water uptake and swelling ratio data (Fig.8). However, these release profiles were much higher than that of commercial nicotine patch (Nicotinell TTS-20).

Fig. 18-21 present the effect of plasticizer type on nicotine release from DNRL patches using HPMC, MC, SCMC, and PVA as polymer blending, respectively. The release patterns were similar in all blended polymers. The nicotine release rate of blended patches was ranged: no plasticizer < DBP < GLY.

In addition, the higher amount of polymer blending also showed the higher release amount. The DNRL films without plasticizer and polymer blending obtained the lowest release amount. These could be explained by their hydrophilic properties. The blending of plasticizer and hydrophilic polymer resulted in the higher hydrophilicity of blending patches. Thus, more water uptake and swelling were obtained, which resulted in the fast release amount. The kinetics of nicotine release from these DNRL/polymer blending patch dosage forms was diffusion type which confirmed by Higuchi model.

As these results, however, it was found that all formulations were greater release than Nicotinell TTS-20.

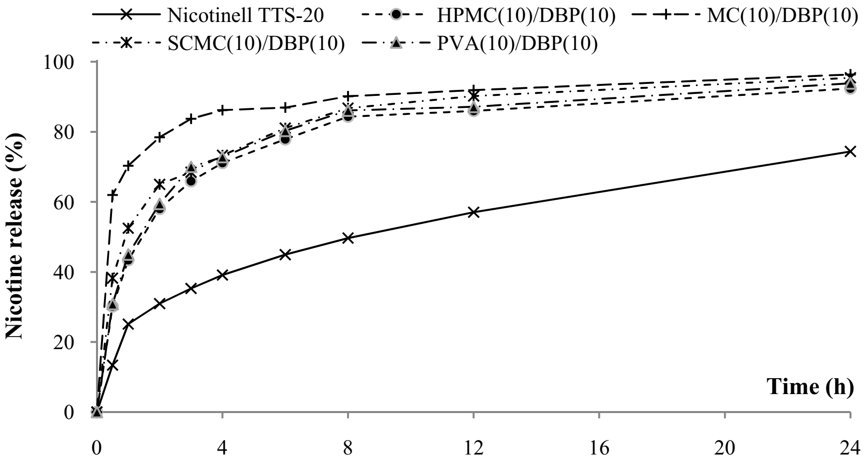


Fig. 17 Nicotine release from DNRL/DBP(10) films in different types of polymer blending comparing with Nicotinell TTS-20 (n=3).

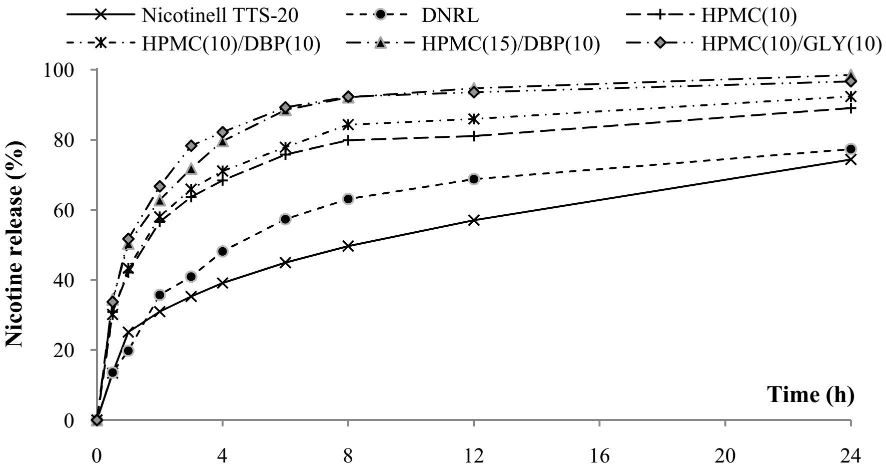


Fig. 18 Nicotine release from DNRL alone and DNRL/HPMC films with DBP or GLY comparing with Nicotinell TTS-20 (n=6).

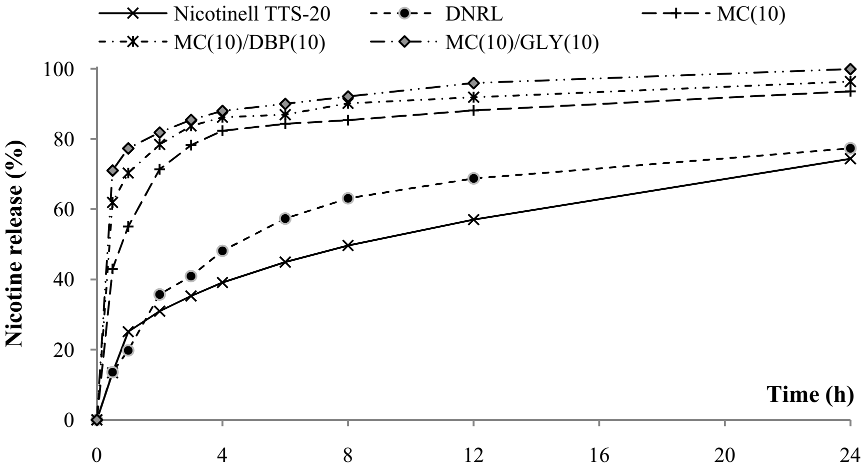


Fig. 19 Nicotine release from DNRL alone and DNRL/MC films with DBP or GLY comparing with Nicotinell TTS-20 (n=3).

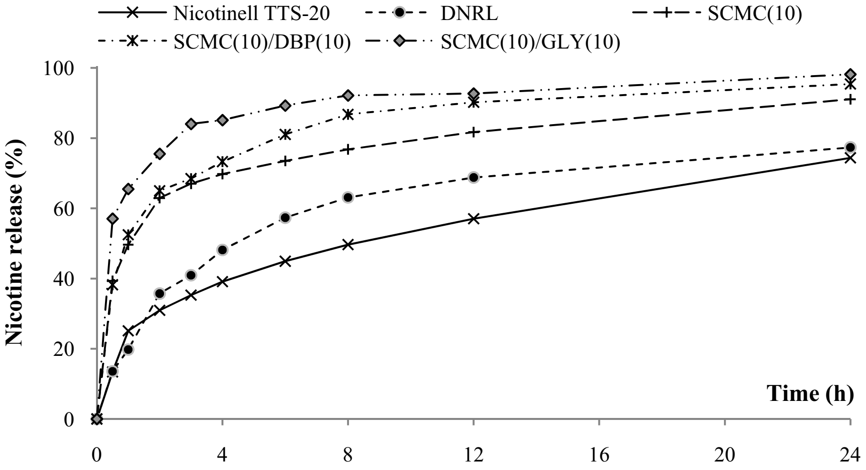


Fig. 20 Nicotine release from DNRL alone and DNRL/SCMC films with DBP or GLY comparing with Nicotinell TTS-20 (n=3).

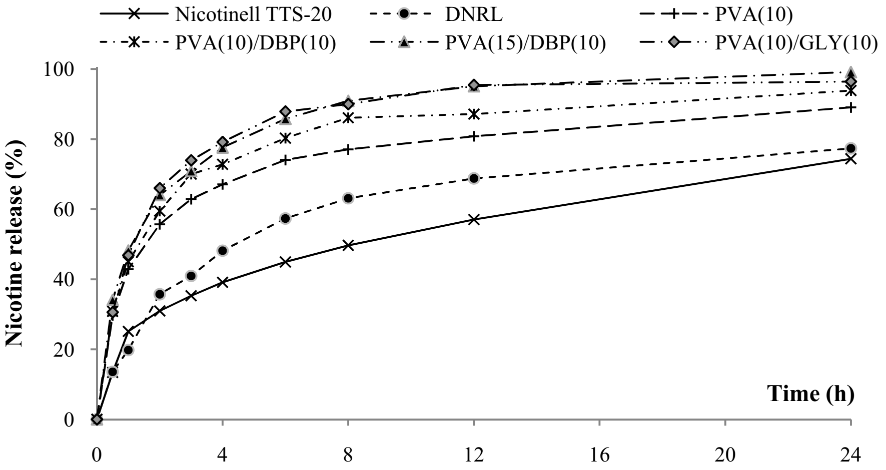


Fig. 21 Nicotine release from DNRL alone and DNRL/PVA films with DBP or GLY comparing with Nicotinell TTS-20 (n=3).

Moreover, Fig. 22 showed some effects of drug loading on the nicotine release of DNRL blending films. Higher drug loading in patches gave the higher percentage of nicotine release. This was due to the higher drug amount which had higher concentration gradient in film matrix. Thus, the diffusion was faster. However, the 2.5 mg/cm^2 and 3.5 mg/cm^2 nicotine patches obtained the similar release pattern.

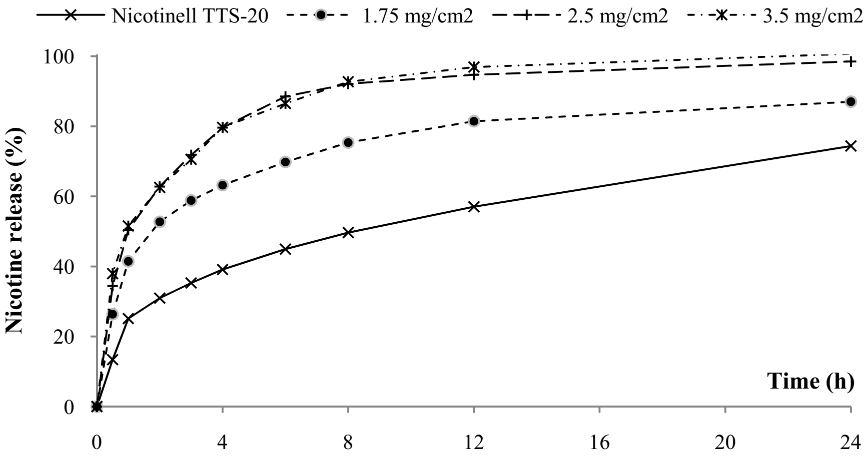


Fig. 22 Nicotine release from DNRL/HPMC(15)/DBP(10) films in different nicotine amounts comparing with Nicotinell TTS-20 (n=3).

As in Fig. 23, when coating DNRL films with the adhesive layer of Voncoat AN868-S (special self crosslink type acrylic ester copolymer emulsion), the nicotine release decreased significantly comparing to that of non adhesive layer. This profile was close to that of the commercial Nicotinell TTS-20. However, the addition of backing layer slightly increased the nicotine release. Three types of backing layer; 3M Scotchpack 1109 backing (polyester film laminate with low oxygen transmission and low moisture vapor transmission rate; backing(1)), 3M CoTran 9720 (polyethylene monolayer film with high oxygen transmission and medium moisture vapor transmission rate; backing(2)), and 3M Scotchpack 9733 backing (polyester film laminate with medium oxygen transmission and high moisture vapor transmission rate; backing(3)) showed the similar release pattern. This indicated some effects of backing layer on drug release.

The SEM micrographs of nicotine loading DNRL/polymer blending patches are presented in Fig. 24. The uneven surface of nicotine patches was observed. The cross section morphology of these patches showed the dense films without poring, cracking, or cavity. However, these films after release study presented the various numbers of poring and cavity, and the patches became rough. The pores and roughness might be attributed to the diffusion of nicotine molecules and some erosion of hydrophilic

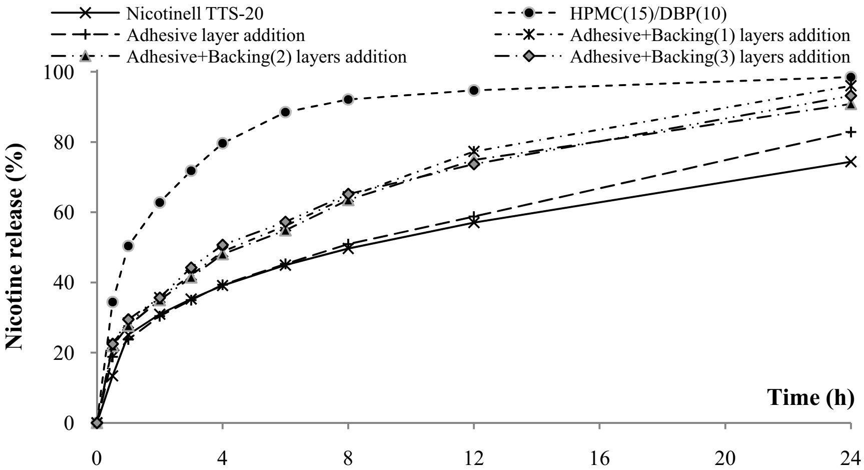


Fig. 23 Nicotine release from DNRL/HPMC(15)/DBP(10) films in the addition of adhesive and backing layers comparing with Nicotinell TTS-20 (n=3).

polymer in patches. The patches containing GLY generated more pores and cavities compared with DBP. The nicotine patches made from HPMC showed fewer numbers of pore and cavity than those from PVA, but PVA blending films had discrete and small pores, and deep cavities than HPMC blending films. These related to their release patterns which described above.

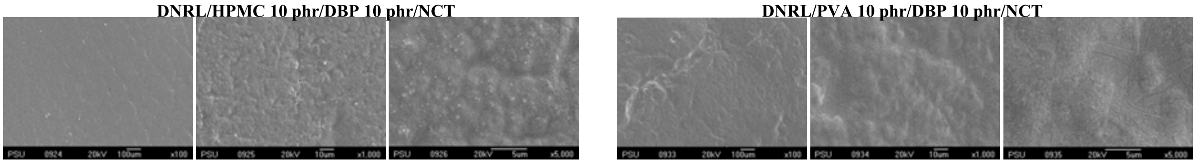
Although the release pattern of DNRL/polymer blending film-forming polymeric solution and patch dosage forms were much higher than that of commercial Nicotinell TTS-20, the permeation of these preparations was further studied. These DNRL preparations did not have some enhancers and other components addition which enhanced drug permeation. Thus, the effect of DNRL/polymer blending component of these formulations on nicotine permeation was further investigated.

In vitro nicotine permeation thought pig skin

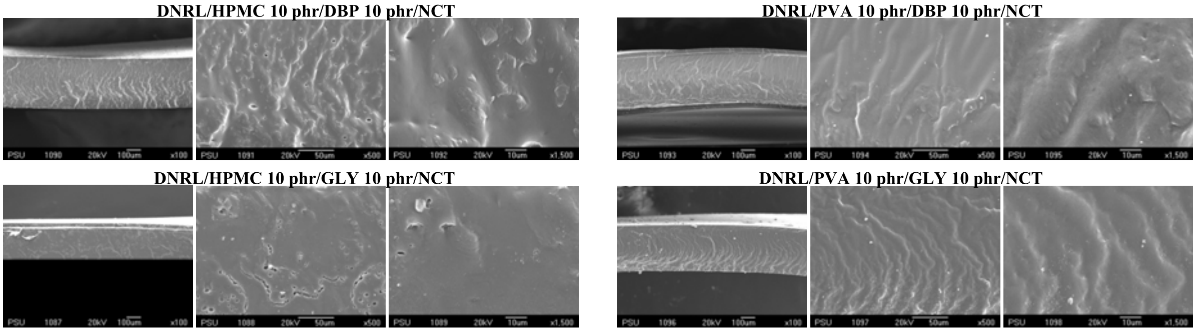
For HPLC validation, no peak interfere in the same retention time of nicotine peak was observed in permeation study condition. Correlation coefficient for the calibration curve in the range 2-60 μg/ml for nicotine standard solutions was 0.9989. In addition, the linearity and CV was less than 3% in both intra-day and inter-day. The %CV values for both intra-day was found to be 1.41-2.47 (n=6) and inter-day on seven different days was found to be 1.12-1.94 (n=3) over the range 2-60 μg/ml. At the same concentrations, this method was found to afford the accuracy of 95.22-100.85% for intra-day and 93.06-98.46% for inter-day.

As shown in Fig. 25, the nicotine solution presented the high skin permeation due to its high permeability properties. The skin permeation of nicotine from commercial Nicotinell TTS-20 was quite good. Its permeation rate was regular with zero order kinetics. The DNRL film-forming polymeric

Film surface before nicotine release study



Cross section before nicotine release study



Cross section after nicotine release study

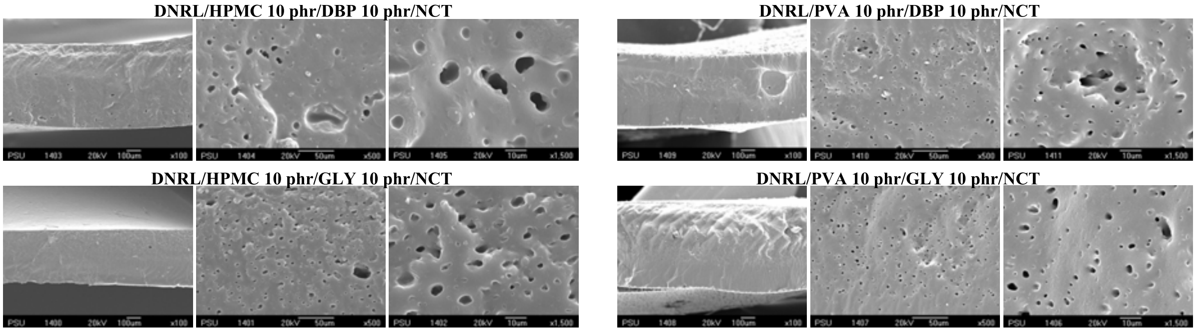


Fig. 24 Surface and cross section SEM micrographs of nicotine films before and after release study.

solutions showed the higher permeation amount than Nicotinell TTS-20. The permeation pattern was not zero order. The high permeation rate of nicotine at initial followed by the slower rate which same as their release pattern was produced. DNRL/polymer blending formulations using GLY as plasticizer showed slight high permeation than those using DBP. This was also similar pattern as the release results. However, the PVA blending polymer which gave higher nicotine release amount did not superior permeate than HPMC blended. This indicated some effects of polymer blending on permeation property. It might be due to the bioadhesive effect, mechanism of drug absorption through the skin, etc.

The ethanol dilution effect was also investigated on the permeation property. Higher ethanol amount provided the slight increasing nicotine permeation in both DNRL/HPMC and DNRL/PVA blending polymers as shown in Fig. 26-27. Ethanol could act as skin enhancer which was reported elsewhere. However, some physical changes were observed on DNRL film-forming polymeric solutions which be diluted with ethanol, thus they would not be chosen for development for the good product.

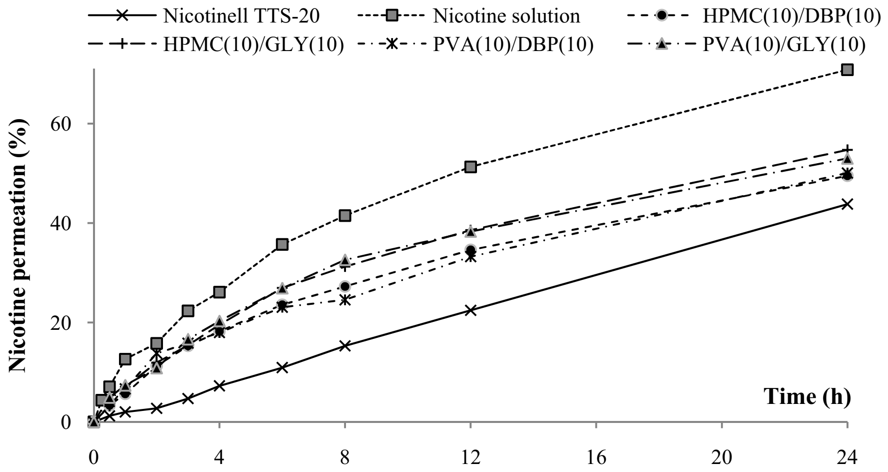


Fig. 25 Nicotine permeation from DNRL/HPMC or PVA film-forming polymeric solution with DBP or GLY comparing with nicotine solution and Nicotinell TTS-20 (n=3).

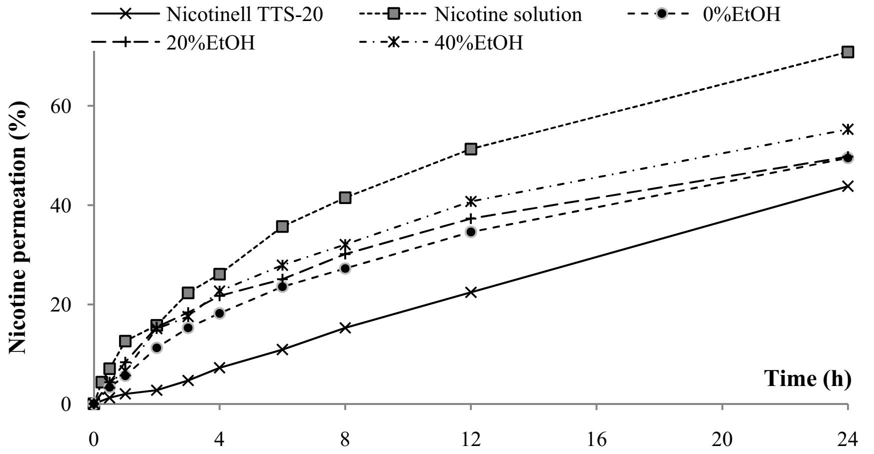


Fig. 26 Nicotine permeation from DNRL/HPMC(10)/DBP(10) film-forming polymeric solution in different ethanol amounts comparing with nicotine solution and Nicotinell TTS-20 (n=3).

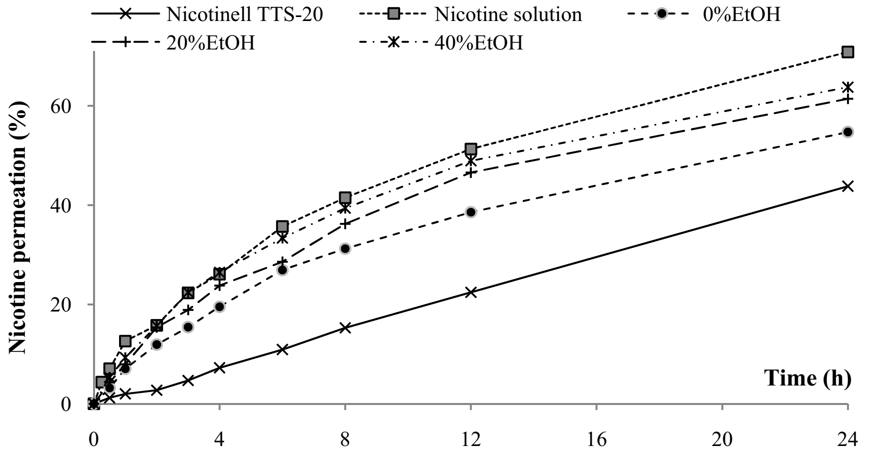


Fig. 27 Nicotine permeation from DNRL/HPMC(10)/GLY(10) film-forming polymeric solution in different ethanol amounts comparing with nicotine solution and Nicotinell TTS-20 (n=3).

The skin permeations of nicotine from all DNRL/polymer blending patches were zero order kinetics which was similar to that of commercial Nicotinell TTS-20 (Fig. 28). DNRL film showed the lowest nicotine permeation. This was due to the hydrophobicity of DNRL which be difficult to release the nicotine from its film. Surprisingly, DNRL/HPMC blending which released the larger nicotine amount, but showed the lower nicotine permeation comparing with Nicotinell TTS-20. This might be due to no enhancer effect from DNRL/polymer blending preparation, but there were some enhancers or some factors which enhanced nicotine absorption from Nicotinell TTS-20. Patches which had GLY as plasticizer still increased nicotine permeation when comparing with DBP, and the higher HPMC amount also gave higher skin permeation of nicotine. PVA blending polymer also gave the higher nicotine permeation which be shown in Fig. 29. These results were similar to the other results which indicated the majority effect of hydrophilic property on drug release and permeation.

The effect of drug loading on skin permeation of nicotine is shown in Fig. 30. The higher nicotine loading gave the higher nicotine permeation. In this study, the skin permeation of 2.5 mg/cm^2 nicotine loading DNRL/HPMC(15)/DBP(10) was similar to that of commercial Nicotinell TTS-20. As in Fig. 31, when coating DNRL films with the adhesive layer of Voncoat AN868-S, the skin permeation of nicotine slightly decreased due to the addition layer which drug had to diffusion through it. Surprisingly, the addition of backing layer also significantly affected their permeation pattern. The 3M Scotchpack 1109 backing (backing(1)) showed the very high skin permeation of nicotine due to its occlusive effect. The 3M Scotchpack 9733 backing (backing(3)) showed the quite high skin permeation of nicotine due to its moderate occlusive effect. The 3M CoTran 9720 backing (backing(2)) showed the low skin permeation of nicotine which close to that of commercial Nicotinell TTS-20. This indicated that the oxygen transmission was the important factor giving the occlusive effect and affecting the skin permeation of nicotine. The lowest oxygen transmission backing affected the highest occlusive phenomena, and the highest skin permeation occurred. Thus, the skin permeation of nicotine could also be adjusted by backing type.

Stability study

The nicotine content in DNRL/polymer blending film-forming polymeric solution and patch dosage forms decreased quickly when storage. The shelf-life of nicotine in both dosage forms was 4 weeks when kept in 4 °C and ambient temperature, and it decreased to 2 weeks in 45 °C. The nicotine was unstable substance which easy to volatile caused to decrease nicotine remaining in the preparations. Thus these preparations should be suggested to keep in very tight container.

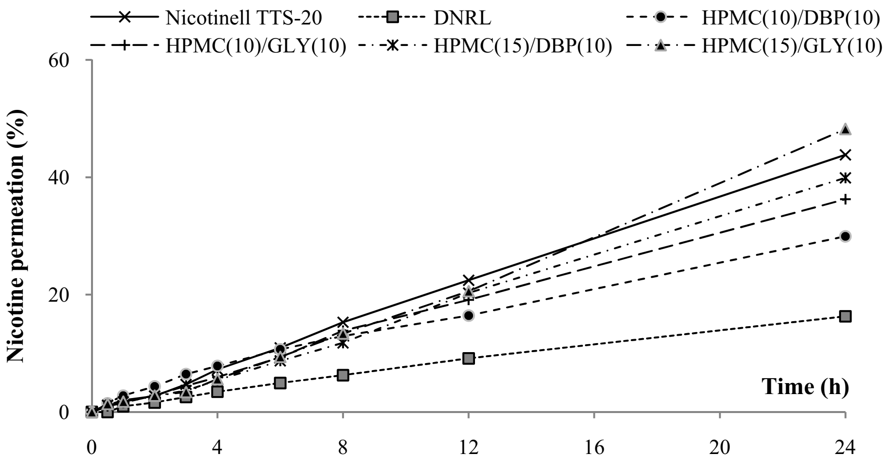


Fig. 28 Nicotine permeation from DNRL alone and DNRL/HPMC films with DBP or GLY comparing with Nicotinell TTS-20 (n=3).

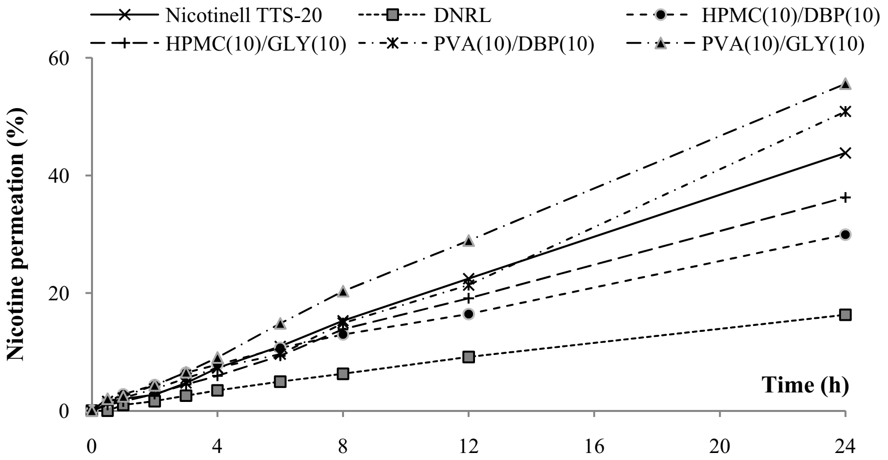


Fig. 29 Nicotine permeation from DNRL alone and DNRL/HPMC or PVA films with DBP or GLY comparing with Nicotinell TTS-20 (n=3).

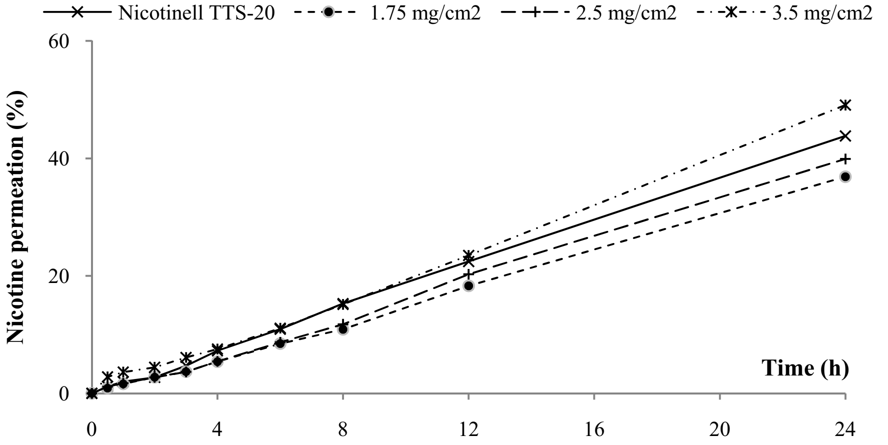


Fig. 30 Nicotine permeation from DNRL/HPMC(15)/DBP(10) films in different nicotine amounts comparing with Nicotinell TTS-20 (n=3).

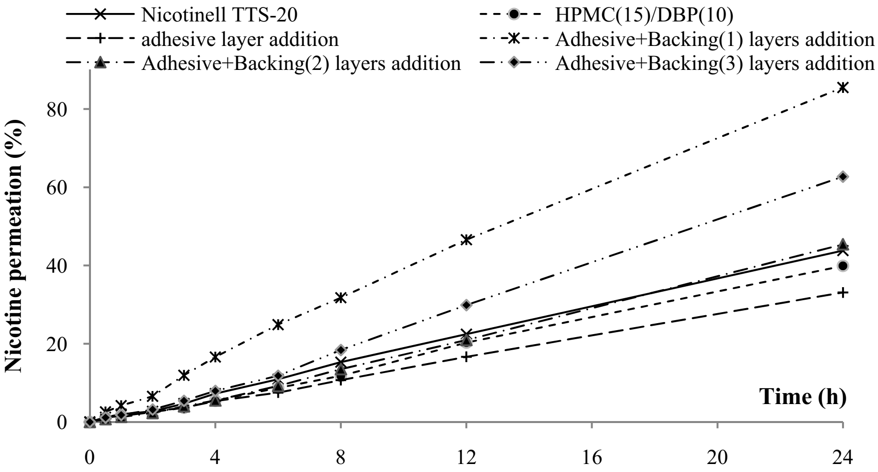


Fig. 31 Nicotine permeation from DNRL/HPMC(15)/DBP(10) films and the addition of adhesive and backing layers comparing with Nicotinell TTS-20 (n=3).

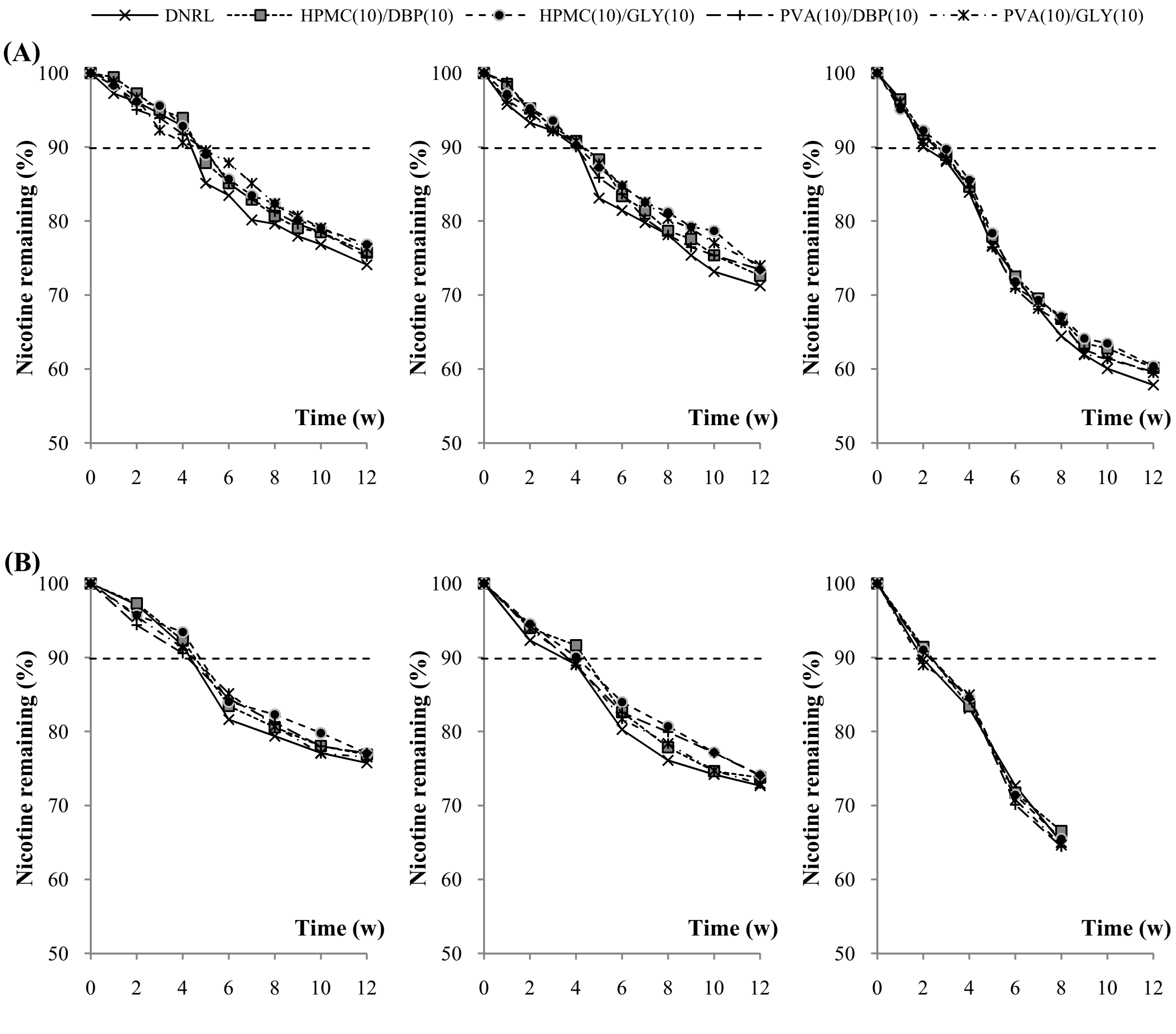


Fig. 32 The percentage of nicotine remaining of (A) film-forming polymeric solutions and (B) patches after storage in different conditions.

Skin irritation test

The 16.6 mg/ml nicotine loaded DNRL/HPMC/GLY blending film-forming polymeric solutions were tested in acute irritation test. It was found that two out of three treated rabbits exhibited slight erythema of skin (scaling 1) observed at 1 hour, and still be at 24, and 48 hours, while the another one was not exhibit any erythema (scale 0) in all time investigations. The recovery of this skin reaction was found within 72 hours following treatment in both irritation exhibited rabbits. In addition, no oedema reaction (scale 0) was observed in all time investigations.

The 2.5 mg/cm^2 nicotine loaded DNRL/HPMC/DBP blending films were also tested in acute dermal irritation test. The results showed that all three treated rabbits did not exhibit the dermal irritation. All scores of dermal reactions of the treated and control groups were 0 scaling in all time investigations.

These results indicated the slight irritation in DNRL/HPMC blending nicotine film-forming polymeric solutions. This data were similar to those of DNRL raw materials (data were not shown). While the DNRL/HPMC blending nicotine patched was no skin irritation. It might be due to the polymer in solution forms which could adjoin onto the skin completely, thus could considerably affect the skin higher than in the patch dosage form.

Conclusions

DNRL could form good elastic film with low skin adhesive property. Blending DNRL with different type and amount of polymers and plasticizers formed satisfactory films with different mechanical properties and moisture uptake. DNRL blended with HPMC or PVA and DBP or GLY provided the best film for skin delivery. The compatibility of each ingredient in the blended films was observed by FT-IR spectra and DSC thermograms. These results had been used in the selection of the appropriate film formulations for nicotine patches. The transdermal nicotine delivery could be obtained as both film-forming polymeric solution and patch dosage forms of which provided different release patterns. In addition, *in vitro* release and skin permeation studies of nicotine release were affected by the amount and types of polymer, as well as the types of plasticizers. Moreover, the adhesive layer and type of backing layer also influenced the skin permeation due to their occlusion effects. The skin irritation test confirmed the safety to use of DNRL patches with no irritation and oedema. However, DNRL film-forming polymeric solutions showed very slightly irritation which could recover. The results indicated that the polymeric film composed of HPMC or PVA blended with DNRL was suitable for developing nicotine transdermal patches.

Suggestions for the future researches

The stability of nicotine loaded DNRL formulations should be confirmed by kept the products in very tight container to protect nicotine volatility, and storage in the experimental conditions.

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Appendix

1. Jirapornchai Suksaeree, Prapaporn Boonme, Wirach Taweepreda, and Wiwat Pichayakorn. Mechanical and physicochemical properties of the deproteinized natural rubber latex /hydroxypropyl methylcellulose blended films. ***The Sixth Thailand Materials Science and Technology Conference (6th MSAT)***. 26-27 Aug 2010. Miracle Grand Convention Hotel, Bangkok. ***Proceedings***. p. 218-220. (Oral #HO-03 by J. Suksaeree)

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Mechanical and physicochemical properties of the deproteinized natural rubber latex / hydroxypropyl methylcellulose blended films

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Abstract

This work involved a study of polymer blended films made from deproteinized natural rubber latex (DNRL) having 35% dry rubber content (DRC), and hydroxypropyl methylcellulose (HPMC). Glycerin, dibutylphthalate (DBP), diethylphthalate (DEP), dibutylsebacate (DBS) or triethylcitrate (TEC) was used as a plasticizer. The mixtures of blended polymers were homogeneous, and the films could be prepared. The properties of blended films were characterized including mechanical properties, FT-IR and DSC characteristics. The mechanical properties of the free films depended on the amount of HPMC, the amount and type of plasticizers. Their elasticity and adhesion properties were in the useful range for transdermal patch preparations in pharmaceutical applications.

***Keywords**: Deproteinized natural rubber latex, Hydroxypropyl methylcellulose, Blended film, Plasticizer*

1. Introduction

Natural rubber latex (NRL) obtained from *Hevea brasiliensis* consists of naturally occurring poly-cis-1,4-isoprene. It presents interesting physical properties such as high tensile strength, high elongation at break, outstanding resilience, and easily film-forming [1-3]. DNRL was prepared by enzymatic deproteinization to remove the protein from fresh NRL resulting in reducing the problem of latex allergy [3-4]. HPMC is the most hydrophilic swellable polymer used as film former for the preparation of transdermal drug delivery systems [5]. It has been used as a matrix former in the design of patches of nortriptyline hydrochloride which provided the clear films [6]. In this study, the film formulas of modification DNRL by blending with HPMC and several plasticizers were prepared for improving some properties such as adhesion properties and more flexibility.

2. Methods

The films were prepared by mixing DNRL and HPMC aqueous solution with and without various plasticizers (Table1). The mixture was then poured into glass plates and transferred to hot air oven at 37ºC for water evaporation. The mechanical properties of blended films were characterized using universal tensile testing. FT-IR and DSC characteristics were also investigated.

3. Results and discussion

Effect of HPMC amount on mechanical properties

DNRL could form a good film with high elasticity (as %elongation at break) but low adhesive properties (as peel strength and tack adhesion). The blending DNRL with HPMC also constructed the blended film with better properties. The modulus, ultimate tensile strength (UTS), and adhesive properties increased when increasing HPMC amount. The elasticity of blended film was lower than that of DNRL film, but it could increase with increasing HPMC amount.

Table 1 Mechanical and adhesion properties of DNRL/HPMC blended films with and without plasticizer

Code	DNRL (phr)	HPMC (phr)	Glycerin (phr)	DBP (phr)	DEP (phr)	TEC (phr)	DBS (phr)	Thickness (mm)	Modulus (MPa)	UTS (MPa)	Elongation at break (%)	Peel strength (N/cm)	Tack adhesion (N/cm)
DNRL	100	-	-	-	-	-	-	0.22±0.06	0.56±0.12	0.23±0.04	604.46±5.38	0.10±0.01	1.51±0.51
H1	100	5	-	-	-	-	-	0.26±0.04	0.89±0.09	0.28±0.08	369.72±1.40	*	*
H2	100	10	-	-	-	-	-	0.25±0.01	1.46±0.38	1.31±0.30	506.68±73.47	0.16±0.02	2.24±0.21
H3	100	15	-	-	-	-	-	0.25±0.03	2.80±0.28	1.41±0.30	551.21±94.92	0.19±0.01	2.93±0.76
H4	100	10	10	-	-	-	-	0.32±0.06	1.13±0.38	0.27±0.09	595.41±92.32	*	*
H5	100	5	-	10	-	-	-	0.33±0.04	0.59±0.17	0.17±0.04	305.28±116.88	*	*
H6	100	10	-	10	-	-	-	0.27±0.04	1.18±0.29	0.30±0.11	517.22±51.05	0.16±0.02	2.57±0.41
H7	100	15	-	10	-	-	-	0.26±0.03	1.45±0.30	0.23±0.03	604.72±37.17	0.20±0.01	3.02±0.51
H8	100	10	-	-	10	-	-	0.48±0.05	0.76±0.17	0.19±0.06	403.13± 47.25	0.07±0.01	0.65±0.08
H9	100	10	-	-	-	10	-	0.21±0.01	0.90±0.16	0.24±0.05	291.11±32.02	*	*
H10	100	10	-	-	-	-	10	0.46±0.03	0.23±0.10	0.14±0.08	495.83±62.52	0.08±0.01	1.37±0.37
H11	100	10	-	20	-	-	-	0.22±0.04	0.75±0.05	0.17±0.03	645.51±114.81	0.15±0.01	2.07±0.09
H12	100	15	-	20	-	-	-	0.20±0.02	0.99±0.24	0.20±0.06	721.63±79.28	0.14±0.01	2.25±0.37
H13	100	10	-	30	-	-	-	0.18±0.03	0.68±0.20	0.12±0.07	756.49±68.59	0.11±0.01	1.99±0.17
H14	100	15	-	30	-	-	-	0.26±0.03	0.45±0.24	0.12±0.07	1089.99±217.84	0.12±0.01	2.03±0.19

* = Not available

Effect of plasticizer types on mechanical properties

Formulas H2, H4, H6, H8, H9, and H10 were the DNRL films blended with 10 phr HPMC without and with five different plasticizers, respectively. The addition of plasticizers resulted in decreasing of the Young's modulus, UTS, and elongation at break of film, except the film containing glycerin and DBP which increasing elasticity. The blended film using DBS gave the lowest UTS indicating the most softness film, while the using of TEC gave the lowest %elongation at break indicating the most brittle film. Unlikely, TEC and glycerin made the slightly turbidity film which inappropriate to use as plasticizer for clear film formation. From the result of this study, DBP was the most suitable plasticizer for blended film formation with the good mechanical properties.

Effect of HPMC and DBP amounts on mechanical properties

Similar to the blended film without plasticizer, the blended film with DBP as plasticizer showed the increasing of the modulus, UTS, elasticity, and adhesive properties when increasing HPMC amount. The increasing of DBP amount decreased the films modulus, UTS, and adhesive properties, but significantly increased the elasticity properties. However, the slippery and soft surface films were observed when using the DBP more than 20 phr resulting the difficulty to prepare and gave the poor adhesive film.

Fourier transform infrared spectroscopy study

The FT-IR spectra of the pure ingredients and blended films are presented in Figure 1. The DNRL spectrum was district the principal peak at 3035 cm^{-1} (=CH str.), 2939-2726 cm^{-1} (C-H str.), 1664 cm^{-1} (C=C str.), 1440-1375 cm^{-1} (C-H bending) and 830 cm^{-1} (C=CH wagging). The HPMC showed the broad band spectrum at 3446 cm^{-1} due to a stretching vibration in the hydroxyl group. The major peaks of DNRL and HPMC are also found in the DNRL/HPMC blended film and it was found a slightly broader peak occurs at 1738 cm^{-1} (C=O str. of DBP) in the DNRL/HPMC film with DBP as plasticizer. No markedly changeable spectrum was observed indicating no incompatibility of each ingredient in blended film.

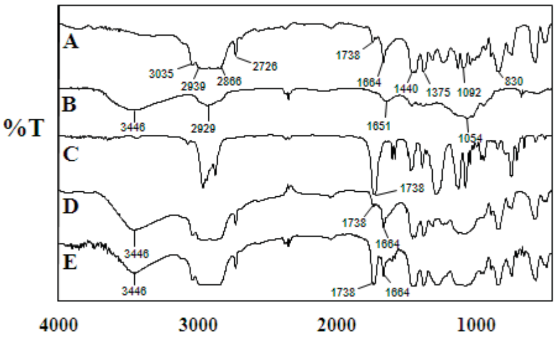

Figure 1 FT-IR spectra of (A) DNRL, (B) HPMC, (C) DBP, (D) DNRL/HPMC blended film, and (E) DNRL/HPMC/DBP blended film

Differential scanning calorimeter study

The DSC thermograms from -80ºC to 200ºC at an increasing rate of 10ºC/min were determined in each ingredient and blended films (Figure 2). The thermograms showed the endothermic transition at the glass transition temperature (T_g) point of DNRL, HPMC and DNRL/HPMC blended films in around 39.3, 37.5, and 41.2ºC, respective. This indicated the slightly change in the structure of blended film. Moreover, the DBP blended as plasticizer slightly reduced the T_g value to 40.0ºC. However, no incompatibility signal was observed in DSC thermograms. This result also indicated the compatibility of each ingredient in blended film.

4. Conclusion

The miscible blends between DNRL and HPMC with and without plasticizer could form the good films. The mechanical and physicochemical properties of the blended films depended on the amount of HPMC, as well as the amount and type of plasticizers. DBP was the most appropriate plasticizer for DNRL/HPMC blended film.

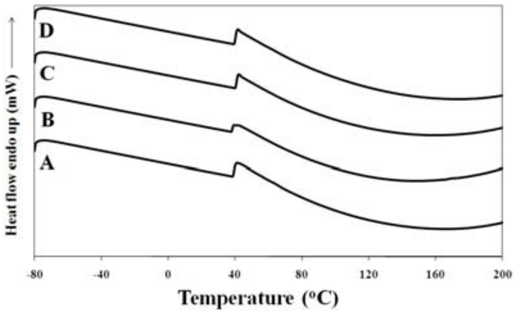

Figure 2 DSC thermograms of (A) DNRL, (B) HPMC, (C) DNRL/HPMC blended film, and (D) DNRL/HPMC/DBP blended film

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Outputs จากโครงการวิจัยที่ได้รับทุนจาก สกว.

1. ผลงานตีพิมพ์ในวารสารวิชาการนานาชาติ (ระบุชื่อผู้แต่ง ชื่อเรื่อง ชื่อวารสาร ปี เล่มที่ เลขที่ และหน้า) หรือผลงานตามที่คาดไว้ในสัญญาโครงการ

กำลังเตรียมต้นฉบับสำหรับตีพิมพ์ในวารสารวิชาการนานาชาติ (ยังไม่ระบุชื่อวารสาร) จำนวน 2 เรื่อง คือ

1. Biphasic nicotine release from transdermal natural rubber film-forming systems for smoking cessation
2. Nicotine transdermal patches using natural rubber as matrix controlling systems

2. การนำผลงานวิจัยไปใช้ประโยชน์

- เชิงพาณิชย์ (มีการนำไปผลิต/ขาย/ก่อให้เกิดรายได้ หรือมีการนำไปประยุกต์ใช้โดยภาคธุรกิจ/บุคคลทั่วไป)
- เชิงนโยบาย (มีการกำหนดนโยบายอิงงานวิจัย/เกิดมาตรการใหม่/เปลี่ยนแปลงระเบียบข้อบังคับหรือวิธีทำงาน)
- เชิงสาธารณะ (มีเครือข่ายความร่วมมือ/สร้างกระแสความสนใจในวงกว้าง)
- เชิงวิชาการ (มีการพัฒนาการเรียนการสอน/สร้างนักวิจัยใหม่)

สามารถนำมาประยุกต์ใช้ในการเรียนการสอนในหัวข้อระบบนำส่งยา รวมถึงได้สร้างนักวิจัยภายในโครงการ โดยกำหนดเนื้อหาบางส่วนเป็นส่วนหนึ่งของหัวข้อวิทยานิพนธ์นักศึกษาระดับปริญญาเอก 1 คน และสามารถต่อยอดเพื่อขยายขอบเขตการวิจัยเพิ่มเติมสำหรับนักศึกษาระดับปริญญาโทอีก 1 คน

3. อื่นๆ (เช่น ผลงานตีพิมพ์ในวารสารวิชาการในประเทศ การเสนอผลงานในที่ประชุมวิชาการ หนังสือ การจดสิทธิบัตร)

เนื้อหาส่วนต้นของโครงการวิจัย ได้นำเสนอในที่ประชุมวิชาการ 1 เรื่อง คือ

1. Jirapornchai Suksaeree, Prapaporn Boonme, Wirach Taweepreda, and Wiwat Pichayakorn. Mechanical and physicochemical properties of the deproteinized natural rubber latex /hydroxypropyl methylcellulose blended films. ***The Sixth Thailand Materials Science and Technology Conference (6th MSAT)***. 26-27 Aug 2010. Miracle Grand Convention Hotel, Bangkok. ***Proceedings***. p. 218-220. (Oral #HO-03 by J. Suksaeree)

และกำลังเตรียมเนื้อหาสำหรับจดสิทธิบัตร จำนวน 1 เรื่อง คือ

1. แผ่นแปะผิวหนังนิโคตินสำหรับอดบุหรี่รูปแบบเมทริกซ์ที่เตรียมจากน้ำยางธรรมชาติโปรตีนต่ำและการประเมินผล