รายงานวิจัยฉบับสมบูรณ์

โครงการวิจัย

การพัฒนาตำรับยาน้ำกลั้วปากที่มีสารยึดเกาะเยื่อเมือกเพื่อนำส่งฟลูโอซิโนโลนอะซิโตไนด์ในการรักษาโรคไลเคนพลานัสในช่องปาก

Fabrication Development of Mucoadhesive Mouthrinse Delivered Fluocinolone Acetonide for Treating Oral Lichen Planus

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สนับสนุนโดย

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บทคัดย่อ

ตำรับฟลูโอซิโนโลนอะซิโตไนด์พอลิเมอร์ริกไมเซลล์ออกแบบการทดลองแบบ factorial design พบว่า คุณสมบัติทางกายภาพและเคมี สัมพันธ์โดยตรงกับปริมาณของสารพอลอคซาเมอร์407 ทั้งลักษณะของตำรับ ความคงตัว ความหนืด ขนาดของอนุภาคและค่าศักษ์ไฟฟ้าซีต้า เมื่อทดสอบด้วย Small angle X-ray scattering พบว่า ตำรับที่ FPM7 และ 8 มีการจัดเรียงอนุภาคแบบ hexagonal micelle ในทุกๆ อุณหภูมิ การปลดปล่อยฟลูโอซิโนโลนอะซิโตไนด์จากตำรับเป็นแบบ zero-order kinetic และการซึมผ่านเยื่อกั้นเป็นแบบ Higuchi model ตำรับ FPM7 และ 8 ถูกนำมาศึกษาต่อในด้านความคงตัวทางความร้อนและลักษณะของอนุภาค ด้วยวิธี DSC TGA XRD และ FTIR ซึ่งพบว่า อนุภาคของฟลูโอซิโนโลนอะซิโตไนด์ ถูกพบอยู่รอบๆ พอลิเมอร์ริกไมเซลล์ และมีอนุภาคระดับนาโนเมตร มีการยึดเกาะกับเยื่อเมือกที่ดี การซึมผ่านเยื่อกั้นของหลอดอาหารหมู ที่เวลา 5, 15 และ 30 นาที พบว่า FPM7 ซึมผ่านได้ไวและกักเก็บอยู่ในชั้น epithelium ตั้งแต่ 5 นาทีแรก และสะสมที่เนื้อเยื่อตลอด 30 นาที ในขณะที่ FPM8 ฟลูโอซิโนโลนอะซิโตไนด์ มีการซึมผ่านเยื่อกั้นได้ดี แต่ไม่ถูกกักเก็บที่ชั้นของเนื้อเยื่อ จากการศึกษานี้ได้ข้อสรุปว่า FPM7 มีการเกาะกับเนื้อเยื่อได้ทำให้เพิ่มระยะเวลาที่ยาสัมผัสกับเนื้อเยื่อและเพิ่มการซึมผ่านและการกักเก็บของยาที่ชั้นเนื้อเยื่อและควรนำไปศึกษาเพิ่มเติมในสัตว์ทดลองและในมนุษย์ต่อไป .

Title : Fabrication Development of Mucoadhesive Mouthrinse Delivered Fluocinolone Acetonide for Treating Oral Lichen Planus
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Abstract

Fluocinolone acetonide polymeric micelles (FPM) were fabricated using factorial design and their physicochemical properties were examined. Concentration of P407 affected FPMs appearance, stability, particle size and zeta potential. Small angle X-ray scattering (SAX) observed that only FPM7 and FPM8 provide hexagonal micelle structure for all temperature. The release of FA from FPMs were fitted into zero-order kinetic and the permeation of FPMs were fitted into Higuchi model. High storage temperature at 45°C for 30 days decreased the FA contents in FPMs excepted for FPM7 and 8, thus, they were selected for further investigation. Prominent characteristics of FPMs were revealed on DSC, TGA, XRD, and FTIR as crystalline state inside polymeric micelles. The morphology of both FPMs observed polymeric micelles surrounded the FA molecule and afforded nanosize particle size. The ex-vivo permeation results of FPM penetrated through porcine esophagus for 5, 15 and 30 min were investigated using ATR microscopic. FPM7 was fast penetrated though the epithelium, lamina propria, and submucosa and remained in all layers at 30 min whereas the FPM8 penetrated and pass through the layers. FA loaded in polymeric micelles was successfully developed with extending mucoadhesiveness, influencing drug-mucosal retention time, and increasing fluocinolone acetonide permeation which might be a promising innovative for increasing efficiency of mouthrinse and others topical pharmaceutical and dental applications.

สารบัญ

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หน้า

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Chapter 1

Introduction

Background and rationale

A common mucocutaneous disease such as oral lichen planus is typically found quite often and clinically appear as reticular, papular, plaque-like, atrophic, erosive, and bullous lesions which can occur separately or simultaneously (Lodi et al. 2020). Although the cause of oral lesions is still unclear, there is evidence to support its association with body immunity (Lodi et al. 2020). The standard treatment for oral lichen planus is corticosteroids such as fluocinolone (Voûte et al. 1993) in a dosage form of oral paste, gel and mouthrinse. The paste or gel is typically used according to the mucoadhesive (Voûte et al. 1993); however, some lesion of oral lichen planus is difficult to apply. Topical mouthrinse might provide less mucoadhesiveness but show advantage over others dosage form as the solution can disperse, flow, and cover some hidden areas of lesions. Moreover, topical mouthwash provided insignificantly different use in therapeutic efficacy than other commercial dosage forms for treating oral lichen planus (Ungphaiboon et al. 2005). The use of solution might face problems such as permeability through the pseudomembranous, drug-mucosal contact time, and rapid clearance of the formulation. Strategies to improve permeation and deposition of active into the mucosal tissues are thus the most desirable.

Polymeric micelles have been distinguished as one of the best promising systems to deliver poorly water-soluble drugs (Kwon et al. 2007) and enhanced hydrophobic drug deposition into the tissues (Uchegbu et al. 2021). Nano-polymeric micelles also demonstrated as kinetical stability carriers combined of amphiphilic block copolymers considered as the core-shell hold hydrophobic drugs within hydrophilic medium. Not only improving the solubilization of poor water-soluble active, but the micelle-forming copolymer also increasing stabilization of drugs in the polymeric micelles (Aliabadi and Lavasanifar 2006). Among polymers used to prepare the promising micelles, poloxamer is massively copolymer applied in drug delivery formulation (Aboud et al. 2019) and poloxamer mixed with polyethylene glycol (PEG) also help enhancing drug absorption (Sultan et al. 2017). To invent a desirable nanocarrier, the ratio of co-polymers should be optimized suitably.

Objectives

From the recent evidence, fluocinolone acetonide is the standard drug to treat oral lichen planus, but the uses of oral mount-rinse are quite less effectiveness due to the mucoadhesion related to drug-mucosal contact time and drug permeation to basal cells as steroid target receptor. Therefore, polymeric micelles solution was introduced to improve the mucoadhesiveness, drug-mucosal retention time, and increasing fluocinolone acetonide permeation. Fluocinolone acetonide polymeric micelles were fabricated using factorial design and their physicochemical properties including mucoadhesion, in vitro release, in vitro permeation, ex-vivo drug accumulation and drug stability were examined.

Scope of research

This study aims to prepare and evaluate whether the polymeric micelles solution containing fluocinolone acetonide could be formulated to be used as anti-inflammatory formulation which would lead to suggest further therapeutic options for treating oral lesion. Design and optimization would be used to carry out the suitable formulation along with physicochemical properties and stability of the formulations.

Duration of research

12 months

Conceptual framework

The research will be divided into 2 main parts

1. Design suitable formulation for polymeric micelles
2. Physicochemical properties of polymeric micelles

Beneficial of research

1. Suitable formulation for oral lesion caused from lichen planus in oral cavity
2. Improve mucoadhesiveness of the mouthrinse.
3. Improve drug-mucosal contact time which lead to increasing drug effectiveness.
4. The suitable formulation will apply for the patent.

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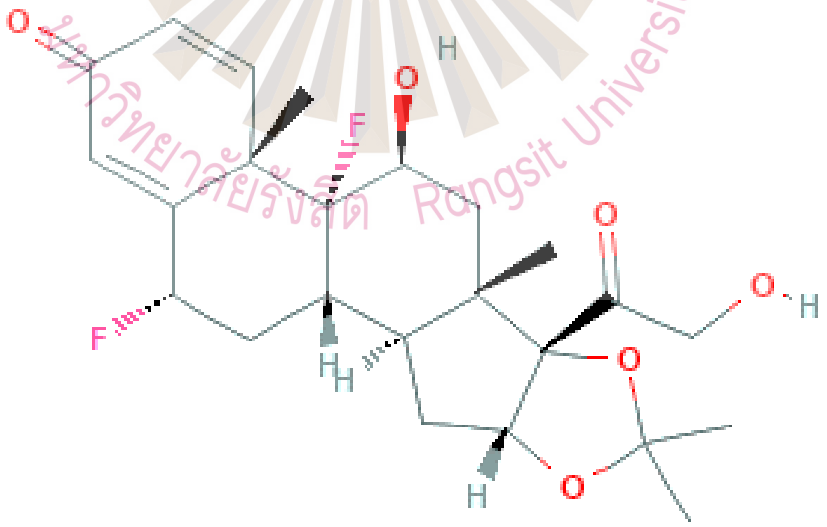
Chapter 2

Review literature

Oral lichen planus

Oral lesions such as oral lichen planus (OLP) is a common mucocutaneous disease. OLP found quite often and clinically appear as reticular, papular, plaque-like, atrophic, erosive, and bullous lesions which can occur separately or simultaneously (Lodi et al. 2020). Although the cause of OLP is still unclear, there is evidence to support its association with body immunity (Lodi et al. 2020). The standard treatment for OLP is corticosteroids such as fluocinolone in a dosage form of oral paste, gel and mouthrinse (Voûte et al. 1993). The paste or gel is typically used according to the mucoadhesive, however, some lesion of OLP is difficult to apply. Topical mouthrinse might provide less mucoadhesiveness but show advantage over others dosage form as the solution can disperse, flow, and cover some hidden areas of lesions (Ungphaiboon et al. 2005). The use of solution might face problems such as permeability through the pseudomembranous, drug-mucosal contact time, and rapid clearance of the formulation. Strategies to improve permeation and deposition of active into the mucosal tissues are thus the most desirable.



Fluocinolone Acetonide structure

Fluocinolone acetonide (FA) is used as standard drug for treating oral lichen planus. FA is in Biopharmaceutics Classification System (BCS) class II which is a system to differentiate the drugs on the basis of their solubility and permeability. FA shows low solubility and high permeation, which is practically insoluble in water, soluble in acetone and in ethanol.

Polymeric micelles

Polymeric micelles have been distinguished as one of the best promising systems to deliver poorly water-soluble drugs (Kwon et al. 2007) and enhanced hydrophobic drug deposition into the tissues (Uchegbu et al. 2021). Nano-polymeric micelles also demonstrated as kinetical stability carriers combined of amphiphilic block copolymers considered as the core-shell hold hydrophobic drugs within hydrophilic medium. Not only improving the solubilization of poor water-soluble active, but the micelle-forming copolymer also increasing stabilization of drugs in the polymeric micelles (Aliabadi and Lavasanifar 2006). Among polymers used to prepare the promising micelles, poloxamer is massively copolymer applied in drug delivery formulation (Aboud et al. 2019) and poloxamer mixed with polyethylene glycol (PEG) also help enhancing drug absorption (Sultan et al. 2017). To invent a desirable nanocarrier, the ratio of co-polymers should be optimized suitably.

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Chapter 3
Methodology

Materials

Fluocinolone acetonide (FA) received as a gift from Siam Chemi-Pharm (1997) Co., Ltd (Thailand). Poloxamer 407 (P407), sodium polyacrylate (SPA), type II mucin from the porcine stomach (lot no. SLCC7713) were purchased from Sigma-Aldrich®, USA. Polyethylene glycol (PEG) was purchased from Aketong Chemipun, Thailand.

Fluocinolone acetonide loaded in co-polymeric micelles (FPM) preparation

1. Formulation development

Fluocinolone acetonide loaded in co-polymeric micelles (FPMs) were created by incorporated 0.1% of FA into polymeric micelles which were composed of P407, PEG and with or without SPA. The 18 formulations (FPMs), varying in P407, PEG and SPA concentration, are shown in Table 1. P407 was dissolved in phosphate buffer pH 7.4 solution and allowed to completely swell at 4°C overnight before mixing with FA (0.1%) in PEG under magnetic stirring at controlled temperature at 28-32°C. SPA in phosphate buffer pH 7.4 solution was added in the odd number of the formulation. Phosphate buffer pH 7.4 solution was added for final volume adjustment.

2. Blank co-polymeric micelles (BPMs)

The blank co-polymeric micelles solution was prepared by the same method of FPMs preparation without adding FA and labeled as BPs.

3. Dried power of FPMs and BPMs

The FPMs and BPMs solution were lyophilized under -80°C and 1 bar for 2 days to obtain the dried powder using freeze dryer (Modulyo benchtop freeze dryer, Thermo Electron Corporation, USA).

Physicochemical characteristics

1. Particle size, poly dispersion index (PDI), and zeta potential

Particle size, PDI, and zeta potential were measured using dynamic light scattering (DLS) in a nanoparticle size and zeta potential analyzer (NanoPlus®, DLS Model NanoPlus-3 Serial no. 409314, USA). Each FPM formula was dispersed in distilled water which the dilution factor equal 6 before measurement.

2. Small angle X-ray scattering (SAXS) study of polymeric micelles solution

Reflection SAXS was carried out on Synchrotron Light Research Institute, Thailand using Multipole wiggler X-rays with voltage of 9 keV, Rayonix SX165 detector, beam divergence equals 0.4 mrad and photon flux ~2e9 phs/sec. The incident slit and length limiting slit using in the analysis were 0.4 and 4.5 mm, respectively, under the vacuum of 112 mV. The FPM samples were fixed at 4, 25, and 37 °C in order to observe polymeric micelles structure of these 3 different temperatures.

3. Viscosity and mucoadhesiveness

Viscosity (η, cps) of the formulations were measured (n = 6) using a viscometer (Brookfield Model DV-II+ viscometer; USA) at 100 rpm and room temperature (25±5°C).

Mucoadhesiveness was performed by observed the interaction of the FPMs and mucin type II by measuring of the bond strength between the formulation and glycoproteins in mucus via the changed of viscosity (Graça et al. 2018; da Silva et al. 2018) followed by our previous study (Supachawaroj et al. 2021). Each FPM was mixed with mucin type II in the test tube and inverted the tube five times without shaking. The viscosity of the mixtures was measured at 100 rpm at 0, 15, 30, and 60 min without re-shaking the sample. The percentage mucoadhesiveness was calculated by the following equation (eq. 1):

$$\%\ \text{Mucoadhesiveness} = \frac{\text{average } \eta \text{ of the mixture} - \text{average } \eta \text{ of formulation}}{\text{average } \eta \text{ of formulation}} \times 100\% \qquad \text{(eq. 1)}$$

4. Functional group interaction by fourier transforms infrared spectroscopy (FTIR)

FTIR was used to determine the fingerprint and molecular structure of dried FPMs samples. Each Either FPMs or FPMs mixed with mucin sample was mixed with potassium bromide (KBr) using the KBr technique with a ratio of 1:150 mg (sample: KBr) with 10 ton of hydraulic pressure. IR spectra were recorded on FTIR spectrometer (PerkinElmer Inc., Spectrum One program, Massachusetts, USA) in the region from 4000–400 cm–1.

5. Thermal characteristic analysis by differential scanning calorimetry (DSC), thermal gravimetric analysis (TGA) and Powder X-ray diffraction analysis (PXRD)

Thermal analysis by DSC8000 (PerkinElmer, USA) for determining of melting points, transition temperatures (exothermic or endothermic), etc. after each sample powder was placed in a pierced aluminium pan and heated at a scanning rate of 10°C/min from 25-300 °C with Nitrogen rate of 20 mL/min. under air atmosphere using blank aluminum pan as a reference. Simultaneous thermal analyzer (STA) 6000 (PerkinElmer, USA) is used to determine physical changes in materials by monitoring the weight loss on heating.

The TGA with cooling machine in a nitrogen bath (20 mL/min) was employed to analyze samples (5 mg) in a pre-weighted aluminum pan with cover lid and heated at a scanning rate of 20°C/min from 25-400 °C under air atmosphere.

PXRD scan patterns were performed at 30 kV and 15 mA in the 2θ range of 5°C to 45°C with the speed of 5°C/min using Cu Kα radiation (λ = 0.154 nm) by MiniFlex II, Rikaku, Japan.

6. Microscopic morphology

Transmission electron microscope (TEM, FEI Company, USA) were used microscopically observed the samples pretreated by dropped onto a copper grid with carbon-film-coating (200 mesh copper) and then air-dried.

7. Stability

All FPM formulas were stored at 3 different temperatures as 4, 25, and 45°C to determine their stability. At 7 and 30 days of storage, the samples were determined their pH and percentage of FA containing compared with their freshly prepared.

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***In vitro* release and permeation**

In vitro release experiments were conducted using Franz diffusion cells (Crown Glass, U.S.A.) and a dialysis membrane (dialysis membrane standard RC Tubing MWCO 3.5K Da, Spectra/Por®, USA) was used as the barrier membrane. Approximately 5 g of FPMs were placed on the membrane, avoiding the gas bubble and the receptor chamber, containing artificial saliva (11 mL, composed of 0.17% sodium bicarbonate, 0.05% sodium dihydrogen orthophosphate and 0.02% calcium chloride in water at pH 7), with stirring (600 rpm) at 37±2 °C (n=6).

In vitro permeation experiments were performed using Franz diffusion cells (Crown Glass, U.S.A.) and the epithelial layer of porcine esophagus as the barrier membrane, which was obtained after soaking fresh esophagus in water (60 °C) for 45 s and removing the underlying layers of supportive tissue. FPMs (approximately 5 g) was placed into the donor chamber, while the receptor chamber was filled with 1% of bovine serum albumin (Sigma=Aldrich, U.S.A.) in phosphate buffer at pH 7.4, with stirring (600 rpm) at 37±2 °C (n=6).

At 5, 10, 15, 30, 60, 120, 240, 480, 720, and 1440 min, 0.5 ml of the receptor medium was collected and replaced with fresh receptor medium. Each sample was then collected from the receptor media and analyzed for FA percentage at a wavelength of 254 nm. Cumulative total FA permeated from each sample was calculated as a percentage of its donor's total FA content.

***Ex vivo* drug accumulation**

The barrier membranes of porcine esophagus used in the in vitro permeation studies, were sampled for cross-sectioned observations by attenuated total reflectance FTIR (ATR-FTIR) microspectroscopy (Hyperion 3000 FTIR microscope, Bruker Optics, MA, USA) with FPA detector using transmission mode with 36x Lens detected 64 scans, spectral resolution 4 cm-1 and binning 4x4, after being vacuum dried, fixed (-80°C for 5 days) with a OCT reagent (OCT Tissue-Tek, CA, USA) and then microtome cross-sectioned for tissue samples, about 8-10 mm thick and 1 mm wide. The cross-sectioned tissue samples were placed on a Barium Fluoride (BaF2) crystal slide (Crystran Ltd., UK), vacuum dried and scanned for IR spectra which were integrated within the wavenumber range of 4000–800 cm-1 for 2D and 3D images using colors to represent intensities of the IR spectra at each point.

Statistical analysis

Categorical variable data were estimated into percentages or ratios (n = 6). Continuous variable data were reported as averages and standard deviations (SD) and the normality was tested. Student t-test and analysis of variance (ANOVA) were performed to test differences between or among experimental groups using SPSS 13 software (SPSS Inc, Chicago, IL, USA). For statistical significance ($p < 0.05$), either a Student's t-test or ANOVA were used to compare the average values.

Chapter 4

Results and discussion

1. Effects of independent variables on polymeric micelles characterization

The FPMs formulation contained FA concentration 0.1% w/w and varied three factors as P407, PEG and with or without SPA were designed. The P407 varied as 5, 7.5 and 10% w/w, PEG as 5, 10 and 15 %w/w and/or without 0.1%w/w of SPA created 18 different formulation as shown in Table 1.

Table 1: The composition of fluocinolone acetonide (0.1%) in polymeric micelles (FPMs) by varying in P407, PEG and SPA concentration generated 18 different formulations and characterizations.

Rx	P407 (%)	PEG (%)	SPA (%)	Appearance (after prepared)	Particle size (nm)	PDI	Zeta potential (mV)	Appearance (at 7 days)
FPM1	10	15	0.01	suspension	3827.47±300.36	0.52±0.03	-6.41±1.27	suspension
FPM2	10	15	0	suspension	2080.8±945.62	0.44±0.04	4.83±9.18	suspension
FPM3	10	10	0.01	suspension	2341.93±635.85	0.54±0.02	-13.28±1.59	precipitated
FPM4	10	10	0	suspension	1212.70±886.53	0.42±0.04	6.50±1.15	precipitated
FPM5	10	5	0.01	suspension	316.63±158.44	0.20±0.01	ND	precipitated
FPM6	10	5	0	suspension	188.80±92.59	0.21±0.08	ND	precipitated
FPM7	7.5	15	0.01	clear solution	96.20±11.17	0.07±0.004	-21.23±1.70	clear solution
FPM8	7.5	15	0	clear solution	93.50±12.98	0.08±0.002	19.70±1.80	clear solution
FPM9	7.5	10	0.01	clear solution	103.22±36.87	>0.6	ND	precipitated
FPM10	7.5	10	0	clear solution	98.62±46.72	>0.6	ND	precipitated
FPM11	7.5	5	0.01	clear solution	54.03±32.11	>0.6	ND	precipitated
FPM12	7.5	5	0	clear solution	48.14±24.87	>0.6	ND	precipitated
FPM13	5	15	0.01	clear solution	24.12±0.48	0.22±0.08	-3.23±0.47	clear solution
FPM14	5	15	0	clear solution	12.34±0.12	0.24±0.11	0.11±0.70	clear solution
FPM15	5	10	0.01	precipitated	ND	ND	ND	precipitated
FPM16	5	10	0	precipitated	ND	ND	ND	precipitated
FPM17	5	5	0.01	precipitated	ND	ND	ND	precipitated
FPM18	5	5	0	precipitated	ND	ND	ND	precipitated

*ND represented not determined.

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FPM1-6 appeared white turbid solution while FPM7-14 earned clear solution and FPM15-18 observed precipitation. The particle size of the formulation depended on P407 concentration (shown in Table1). After storage for 7 day, only FPM1, 2, 7, 8, 13, and 14 remained homogeneous mixture. The characteristic of FPMs solution also associated to the particle size and PDI which also related to P407 ratio and SPA concentration. High concentration of P407 composed large particle size, as obtained in micrometer range, and expresses as white suspension (turbid) not clear solution. Low concentration of P407 created small molecule of polymeric micelles. However, SPA addition to FPMs formulas exhibited higher particle size than not added formulas. The ratio of P407 and PEG affected to the stability of the micelle solution. These concentration of P407 might facilitate as solubilization of poor water soluble and forms self-micelles aggregation with other co-solvent or co-polymer to increase the FA solubility (Dumortier et al. 2006).

Zeta potential of the formulations comprised of SPA showed to be negatively charged while the absent of SPA formulas provided positively charged. The proportion of P407 and PEG affected to the zeta potential which the ratio of P407:PEG equals 7.5:15 provided the highest zeta potential on both negative and positive charge.

Thermo-reversible sol–gel transition of FPMs occurred in high concentration of P407 (FPM1-6) when exposed to high temperature (more than 45°C) and at 25°C phase separation of FPM3-6 and FPM15-18 were found.

Micelle structure of FPM1, 2, 7, 8, 13, and 14 were observed by SAX profile (Fig.1). FPM1 and FPM2 observed poorly ordered hexagonal structure for all temperatures (25, 30 and 37 °C). FPM7 obtained similar hexagonal micelle structure for all temperatures (25, 30 and 37 °C). FPM8 also found hexagonal micelle structure for all temperatures (25, 30 and 37 °C), however, from the higher amplitude of the first peak of 25 °C, it is most likely that the 25 °C have higher order hexagonal structure in comparison with the 30 and 37 °C. FPM13 and FPM14 found that the 1st peak at q = 0.3 cannot be observed which it is difficult to confirm that this system has hexagonal structure in all temperatures (25, 30 and 37 °C). The hexagonal structure of micelles depended on P407 concentration related on the ratio of PEO-PPO-PEO interaction (Artzner et al. 2007) and complex conformation of the P407 and PEG in the mixtures (Ivanova et al., 2002).

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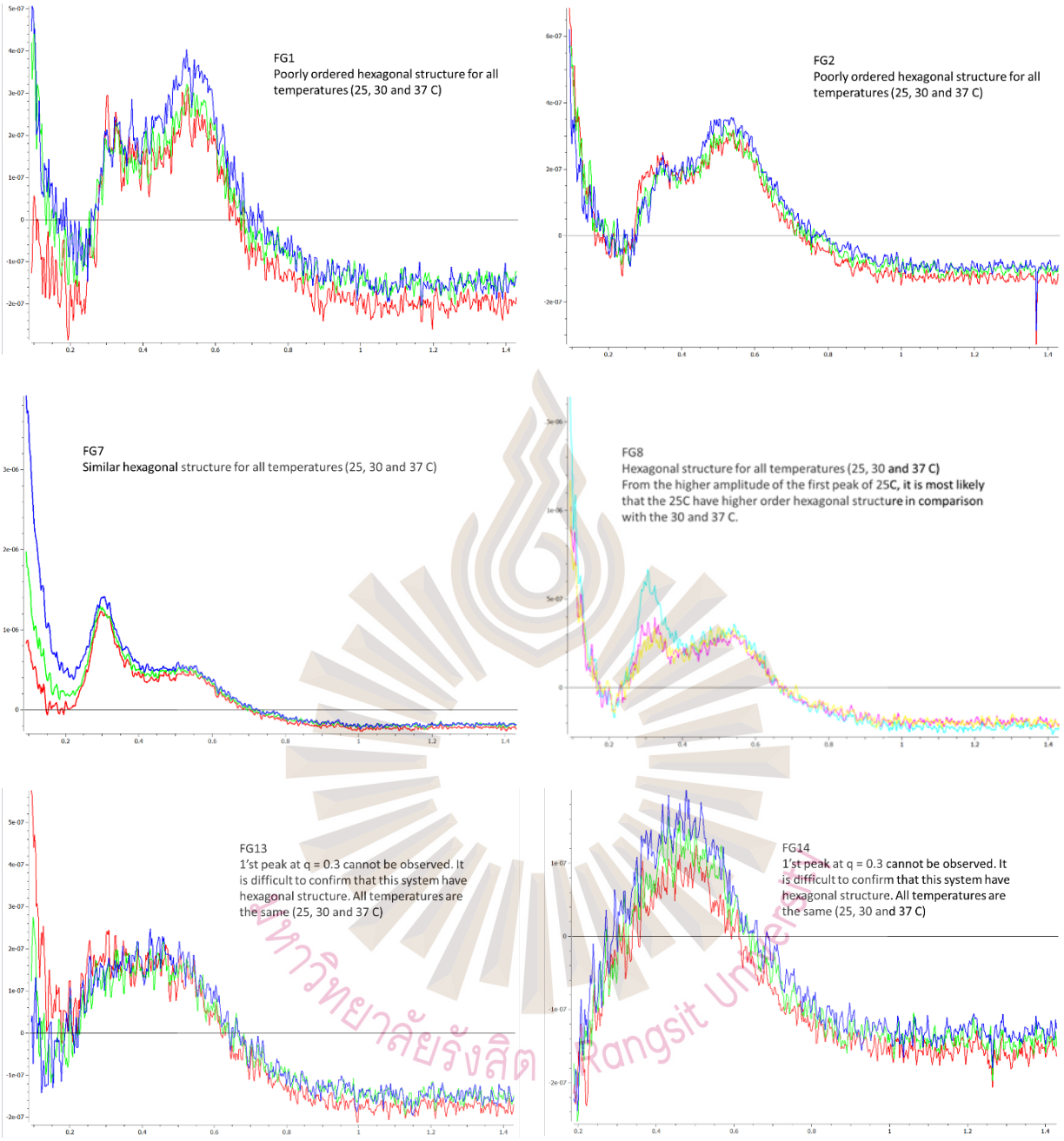

Fig. 1. SAX structure of fluocinolone acetonide polymeric micelles (FPM) 1, 2, 7, 8, 13, and 14 for all temperatures (25, 30 and 37 °C).

2. Effects of independent variables on responses in design formulation

The maximum concentration of P407 and PEG provided the greatest viscosity of the FPM1 and FPM2 (Table 2 and Fig. 2A) whereas the present of SPA did not significantly affect the viscosity and %mucoadhesiveness. The influences the FPMs viscosity caused by P407 concentration might explain by the nature of self-molecule micelle which acts as a reservoir in a polymeric matrix (Chen et al. 2003). However, the increasing of P407 ratio did not rise the percentage of mucoadhesiveness (Fig. 2A) because of FPM7 and FPM8 showed the greatest formula-mucin bond as the duration of formula-mucin interaction was highest observed at 0 min and 15 min (Table 2). The highest mucoadhesion (%) of all FPMs illustrated at 15 mins and decreased after 30 and 60 min of bonding. As for the use of mouthrinse, low mucoadhesivity might not promise the required retention time to treat or relief symptoms. Thus,15 min formula-mucin contact time of the binding provided a suitable *in vitro* method to evaluate this factor. Varying temperature did not significant the FPM7 and FPM8 viscosity (Fig. 2B), thus, sol-gel phase transition did not occur.

Table 2: Effects of independent variables as poloxamer407 (P407) and PEG400 (PEG) with and without sodium polyacrylate (SPA) containing 0.1% fluocinolone acetonide (FA) on the viscosity (cps), mucoadhesive (%) of FA interacted with mucin at 0 min, mucoadhesive (%) of FA interacted with mucin at 15 min, percentage of drug release and percentage of drug permeation over 8 hours

Rx	Viscosity (cps)	%mucoadhesive at 0 min	%mucoadhesive at 15 min	%Drug release	%Drug permeation
FPM1	41.8±0.35	6.2±0.88	15.8±2.63	2.47±0.001	14.58±0.03
FPM2	41.2±0.35	4.9±2.27	15.5±1.62	1.64±0.004	9.15±0.001
FPM7	20.4±0.02	38.2±5.88	82.4±0.04	1.70±0.001	17.76±0.001
FPM8	19.8±0.60	41.4±7.16	89.0±5.93	0.76±0.003	12.37±0.03
FPM13	10.6±0.69	17.8±4.90	57.1±11.84	0.07±0.000	17.54±0.03
FPM14	10.8±0.60	8.6±1.69	51.4±11.49	0.01±0.000	15.74±0.04

*ND represented not determined.

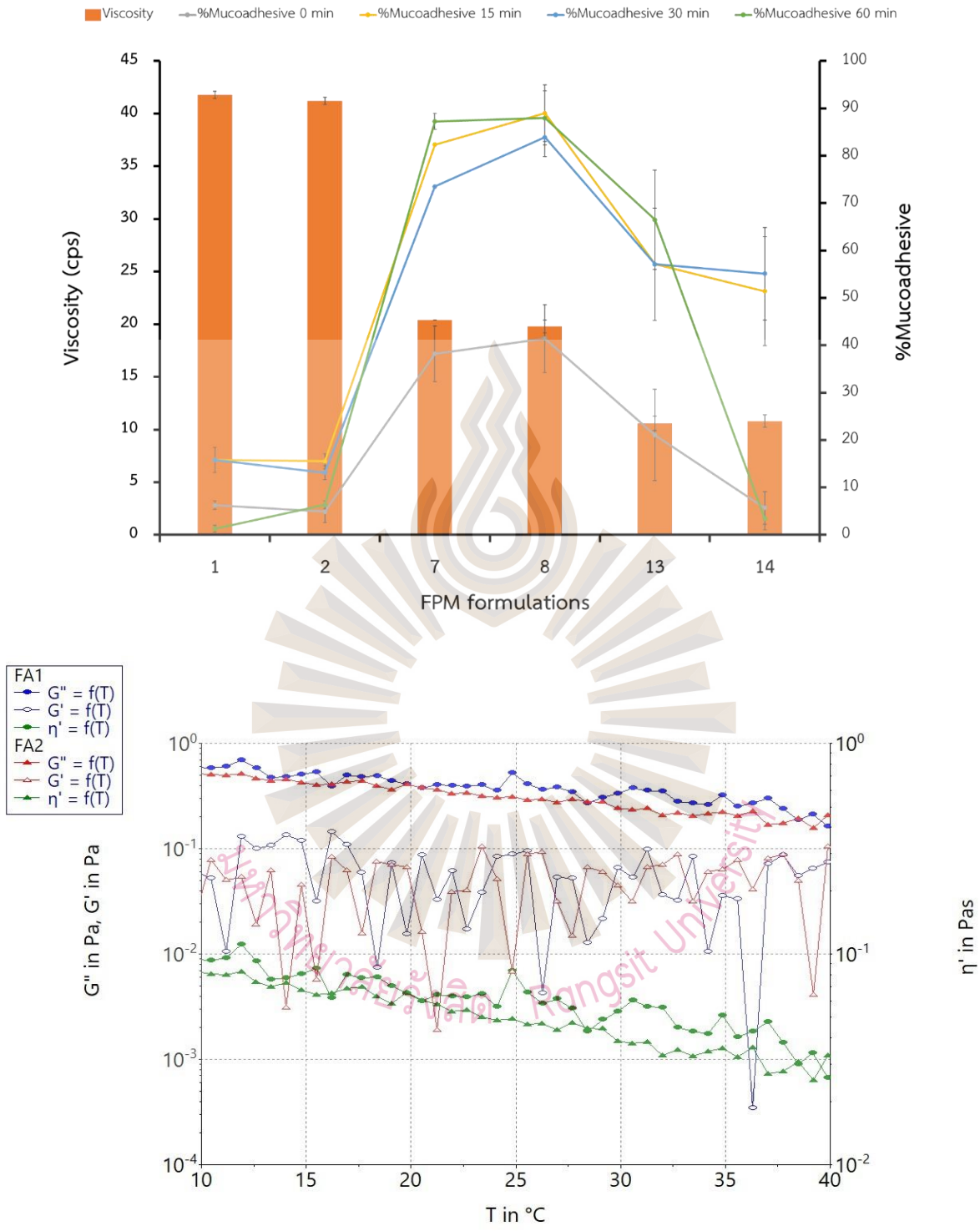

Fig. 2. Comparison (A) of the formulation viscosity (orange columns) and % mucoadhesiveness at 0 (grey line), 15 (yellow line), 30 (blue line) and 60 min (green line) and (B) rheology of FPM7 and FPM8 between 10°C to 40°C

3. Percentage of fluocinolone acetonide (FA) release and permeation in *in vitro* studies.

The cumulative release of FA from FPMs were considered *in vitro* over 8 h as shown in Fig. 3A. This time point was used to assess the phase action of oral mouth-rinse formulations for oral lichen planus treatment, which requires to use 3 times daily (Lodi et al. 2020). Therefore, an FA burst effect is essential, along with mucoadhesive and drug penetration. However, FA released profile shown slow released in saliva medium.

Table 3: Drug release for 8 hr which the coefficient of correlation (r^2), slope (k) and intercept demonstrated in zero- order, first-order, and Higuchi release model.

Rx	Zero-order			First-order			Higuchi		
	r^2	Slope (k)	Intercept	r^2	Slope (k)	Intercept	r^2	Slope (k)	Intercept
FPM1	0.9933	0.0610	0.7943	0.9464	0.0025	0.4113	0.9191	1.4362	4.7711
FPM2	0.9949	0.0633	0.2394	0.9364	0.0028	0.3218	0.9243	1.4923	5.5646
FPM7	0.9710	0.1095	2.3308	0.9130	0.0035	0.2368	0.8694	2.5346	11.861
FPM8	0.9944	0.0732	0.7784	0.8979	0.0027	0.4297	0.9323	1.7334	6.0177
FPM13	0.9979	0.0721	1.2527	0.8261	0.0038	0.0344	0.9368	1.7084	7.9589
FPM14	0.9963	0.0922	1.8429	0.7507	0.0049	0.2962	0.9300	2.1798	10.357

Table 4: Drug permeation for 60 minutes which the coefficient of correlation (r^2), slope (k) and intercept demonstrated in zero- order, first-order, and Higuchi release model.

Rx	Zero-order			First-order			Higuchi		
	r^2	Slope (k)	Intercept	r^2	Slope (k)	Intercept	r^2	Slope (k)	Intercept
FPM1	0.9688	1.1750	12.246	0.8683	0.0125	1.2234	0.9913	12.129	14.061
FPM2	0.9604	1.1113	7.1788	0.8073	0.0142	1.0818	0.9480	11.266	16.712
FPM7	0.9132	1.0338	16.997	0.7463	0.0115	1.2659	0.9824	10.942	7.4553
FPM8	0.9389	0.9142	14.174	0.7751	0.0115	1.2064	0.9921	9.5896	7.0318
FPM13	0.8755	0.7322	17.321	0.7894	0.0094	1.2661	0.9515	7.7891	0.1893
FPM14	0.9024	0.8113	20.027	0.7828	0.0092	1.3269	0.9764	8.6120	0.7161

From Table 3 and Table 4, FA release and permeation were examined using multiple kinetic models, zero-order is a model that plotted as cumulative amount of drug released and

time as equation (eq. 2), first-order is a model that plotted as log cumulative amount of drug released and time (eq. 3), and Higuchi is a model that plotted as cumulative amount of drug released and square root of time. (eq. 4):

$$Q = k_0 t \quad \text{(eq. 2)}$$

$$\ln Q = \ln Q_0 - k_1 t \quad \text{(eq. 3)}$$

$$Q = k_H t^{1/2} \quad \text{(eq. 4)}$$

Where Q is the amount of drug release at time, Q_0 is the initial drug concentration, k_0 is the rate constant corresponding to zero order model, k_1 is the rate constant corresponding to first order model, k_h is the rate constant corresponding to Higuchi order model, t is time in hour, and $t^{1/2}$ is the square root of time.

The profile of drug release within 8 h was analyzed by linear regression (Table 3) and each formula was fitted into zero-order, first-order, and Higuchi models (Mhlanga and Ray, 2015). FA release was best fitted to zero-order kinetics, as the r^2 approached 1, indicating that the FPMs provided steady release rate delivery (Swain et al. 2019). Optimal duration of drug release for oral lichen planus management depends on the size of the exposed area which about 8-12 hours. All of FPM formulation showed the zero-order release pattern which FPM7 showed the highest release rate (Fig. 3 and Table 3).

The *in vitro* permeation for 8 hours was showed in Fig.3B. Even though FPM1 provided the highest percentage of FA release, FPM7 gave the utmost percentage of FA permeation. Moreover, mucoadhesiveness between mucin and formulation of FPM7 directly related to the FA permeation due to the drug-mucin interaction, as the use of mouthrinse which contact time between formula and mucosal are diminutive, the mucoadhesive of FPM7 promoted FA penetration to the mucosal (Said et al. 2021). Within 60 minutes, linear regression of drug permeation profile was analyzed (Table 4) and each formula was fitted into zero-order, first-order, and Higuchi models (Mhlanga and Ray, 2015). FA permeation was best fitted to Higuchi model, as the r^2 approached 1, indicating that the FPMs provided steady release rate (controlled) delivery (Swain et al. 2019) and exhibited drug permeation by diffusion mechanism.

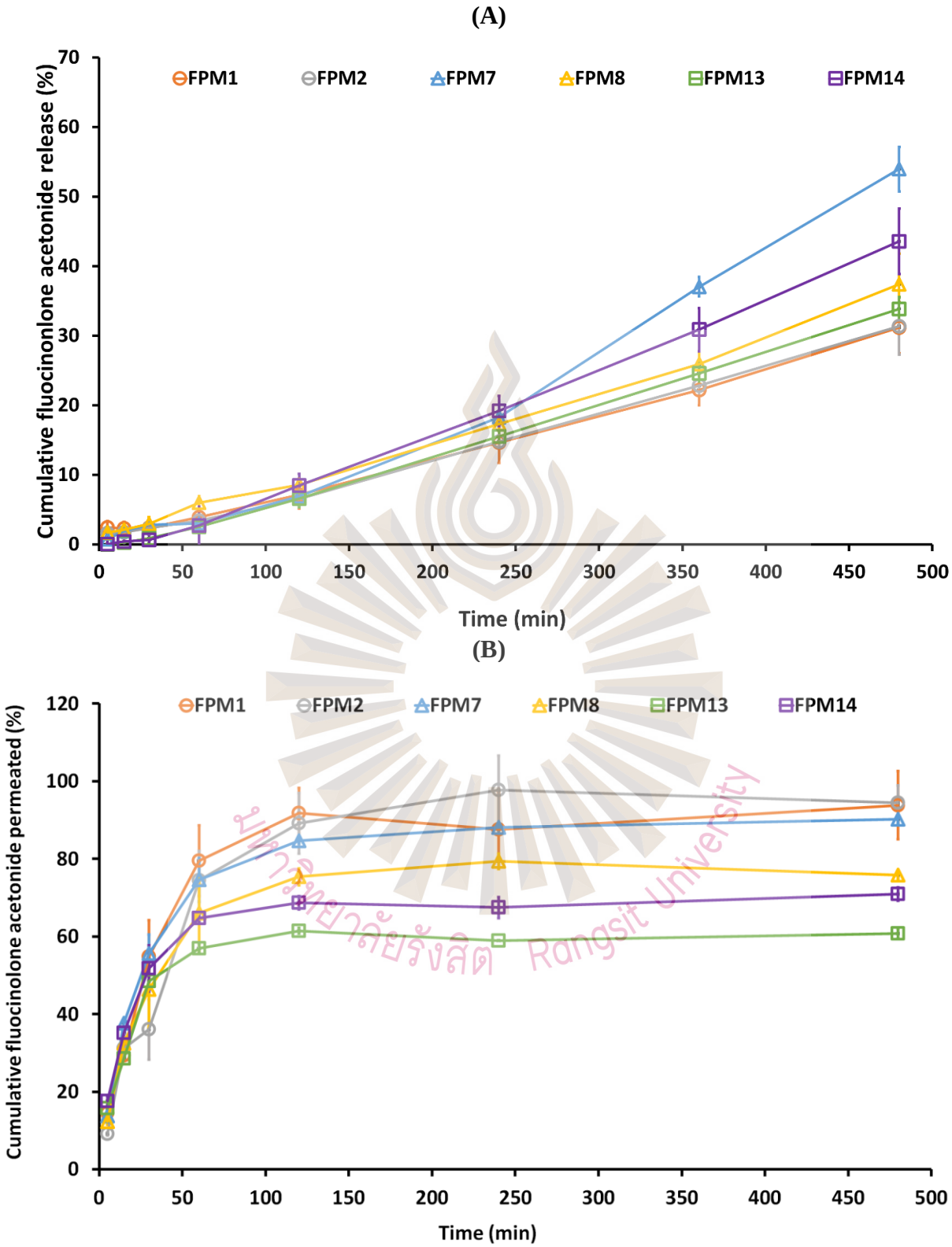

Fig. 3. Percentage of fluocinolone acetonide (FA) release (A) and percentage of fluocinolone acetonide (FA) permeation (B) of all FPMs formulation

The release profile in saliva of all formulation shown slow released but high permeation thru epithelium layer in the first hour. The high mucoadhesive promoted contact time on epithelium layer that increased amount of FA thru epithelium layer. FPM1 FPM2 and FM7 have shown similar permeation rate. Nevertheless, FPM7 exhibited high mucoadhesive high permeation and low release in saliva in the first hours according to the hexagonal micelle structure formation from the polymeric surfactant. The interaction between sidechain of polymeric surfactant and glycoprotein in mucus layer exhibited high mucoadhesiveness and involved diffusion mechanism from hexagonal micelle structure. FA follows BCS class II which acts as low solubility and high permeation, thus, contact time of mucoadhesive between FPM7 and mucin allows FA to enter epithelium.

4. Stability

All FPM formulas were stored in a desiccator at 3 different temperature as 4, 25, and 45°C to determine the percentage of FA stability. After 30 days of storage, the pH of all formula did not change. The percentage of FA contents was shown in Table 5 which reveal that storage at 45°C affected the remaining of FA while storage at 4 and 25°C the percentage of FA remain intact. The percentage of drug content of FPM7 and FPM8 found to be the most stable for 30 days in all temperatures. Therefore, the hexagonal micelle structure (FPM7, 8) might serve as barrier to prevent FA from contraction with water in the external medium.

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Table 5 The percentage fluocinolone acetonide (FA) remaining and pH value after storage stored at 4, 25 or 45 °C (expressed as mean±standard deviation, n = 6)

Rx	Day	pH	Percentage of drug content (%)		
			4±2°C	25±2°C	45±2°C
1	0	7.42±0.01	100.5±0.01	100.5±0.01	100.5±0.01
	7		101.2±0.01	100.2±0.01	101.2±0.01
	30		103.0±0.04	97.6±0.06[a]	91.8±0.01[a]
2	0	7.42±0.01	100.9±0.01	100.9±0.02	100.9±0.02
	7		103.2±0.09	101.1±0.04	99.12±0.01
	30		97.8±0.07[b]	91.7±0.03[b]	91.0±0.04[b]
7	0	7.42±0.01	104.1±0.01	101.4±0.01	104.1±0.01
	7		100.6±0.04	100.3±0.02	102.3±0.02
	30		100.4±0.03	100.0±0.01	100.4±0.01
8	0	7.42±0.01	100.3±0.03	100.3±0.03	100.3±0.03
	7		100.2±0.01	100.2±0.01	100.6±0.03
	30		100.0±0.04	100.1±0.01	100.0±0.01
13	0	7.42±0.01	100.4±0.01	100.4±0.01	100.4±0.01
	7		100.2±0.02	99.4±0.05	95.2±0.07[c]
	30		100.1±0.01	98.5±0.08[c]	87.4±0.09[c]
14	0	7.42±0.01	100.3±0.01	100.3±0.01	100.3±0.01
	7		102.2±0.04	100.2±0.01	87.9±0.07[d]
	30		95.3±0.06[d]	97.4±0.08[d]	59.0±0.08[d]

[a] represented p > 0.005 compared to formulation FPM1 at day 0, [b] represented p > 0.005 compared to formulation FPM2 at day 0, [c] represented p > 0.005 compared to formulation FPM13 at day 0 and [d] represented p > 0.005 compared to formulation FPM14 at day 0

5. Polymeric micelles characteristic and physicochemical properties

To determine the FA–polymeric micelle interactions, FTIR, XRD, DSC and TGA were performed. FTIR spectra (Fig. 4) revealed the interaction between drug-excipients functional groups changes caused from the interaction. FTIR of SPA observed the main peak on 1600 cm^{-1} which represented C=O group and PEG observed OH at 3500 cm^{-1}, C-CH_3 at 2800 cm^{-1} and C-O-C at 1200 cm^{-1}. P407 also found the peaks at 3500 cm^{-1}, C-CH_3 at 2800 cm^{-1} and expressed C–H stretch aliphatic at

1280 cm^{-1}, plane O–H bend at 1340 cm^{-1} and C-O stretch at 1100 cm^{-1}. After composed polymeric micelles, the functional groups of BPs still represented the key peaks at 3500 cm^{-1} of O-H group and at 1200 cm^{-1} of C-O-C group. FA showed the sharp peaks at 3500 cm^{-1} of OH group, 2700-2900 cm^{-1} of CH and C-CH_3 cm^{-1}, aromatic ring at 1600 cm^{-1}, and C-O-C at 1200 cm^{-1}. FTIR results observed no different peaks between FPM 7 and 8 which the strong bands such as the carbonyl peak and aromatic ring were visible in formulation, and it indicated no chemical interaction during synthesis of FPMs.

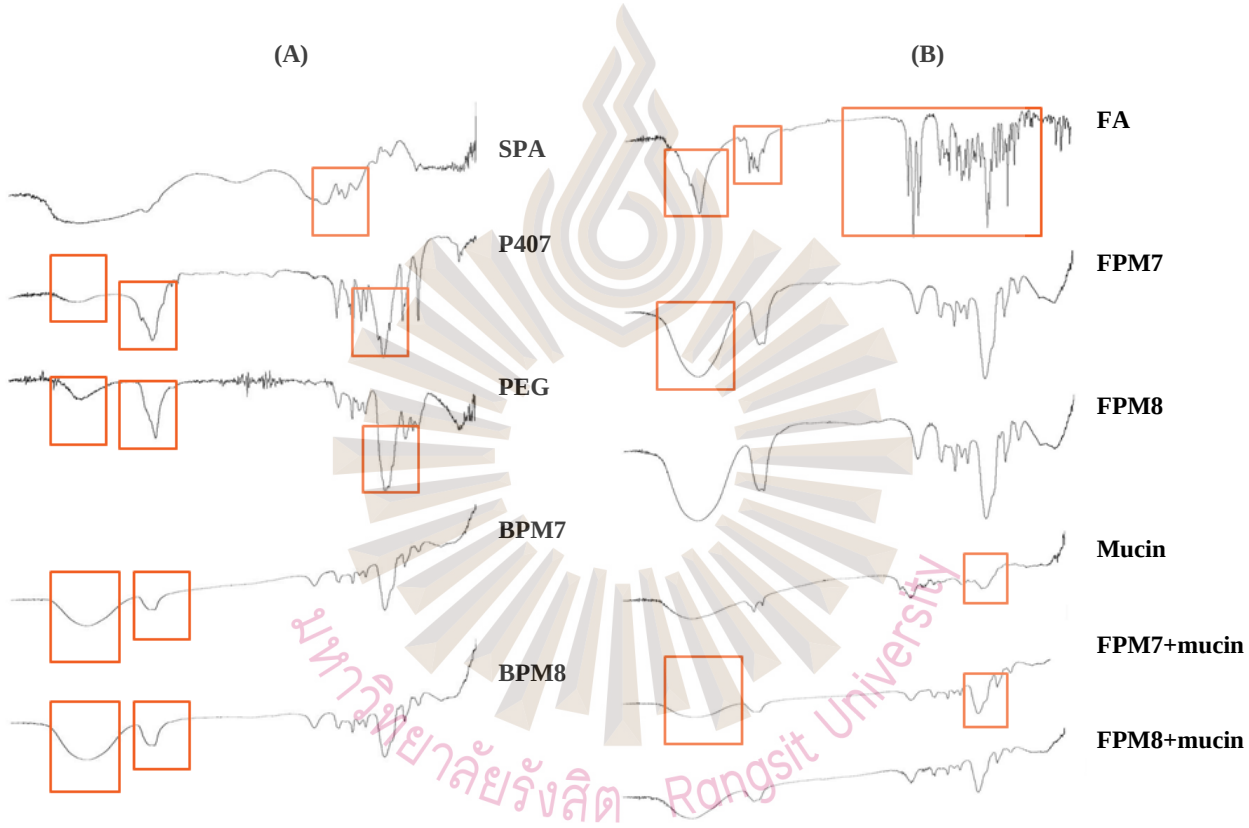

Fig. 4. Representative FTIR spectra of (A) sodium polyacrylate (SPA), poloxamer 407 (P407), polyethylene glycol 400 (PEG) compared to the blank polymeric micelles (BPMs) and (B) fluocinolone acetonide (FA) compared to FPM7 and FPM8, mucin type II and formulation with mucin.

Lyophilized of formula-mucin was performed FTIR analysis to observe the change of functional group interaction. Mucin showed dominate peaks of 2700-2900 cm^{-1} of CH and C-CH_3

cm^{-1} and and C-O-C at 1200 cm^{-1}. IR peak at 1200 cm^{-1} (Fig. 4). The mixture of formula-mucin was found OH group at 3500 cm^{-1} C-O-C at 1200 cm^{-1} were reduced which might represent the covalent bond interaction between FPMs and mucin. The bonding of formula–mucin of FPMs was not very strong possibly due to the hydrogen bonding between the hydroxyl and carboxyl groups (Graça et al. 2018). The non-ionic bond of the formula–mucin complex can be active, but the formula and mucin's negative charges allow for a weak bond that could decrease over time (Supachawaroj et al. 2021). Moreover, we observed external forces (or stimuli), such as vibration, made the formula–mucin interaction stronger. This result is likely important in formula application.

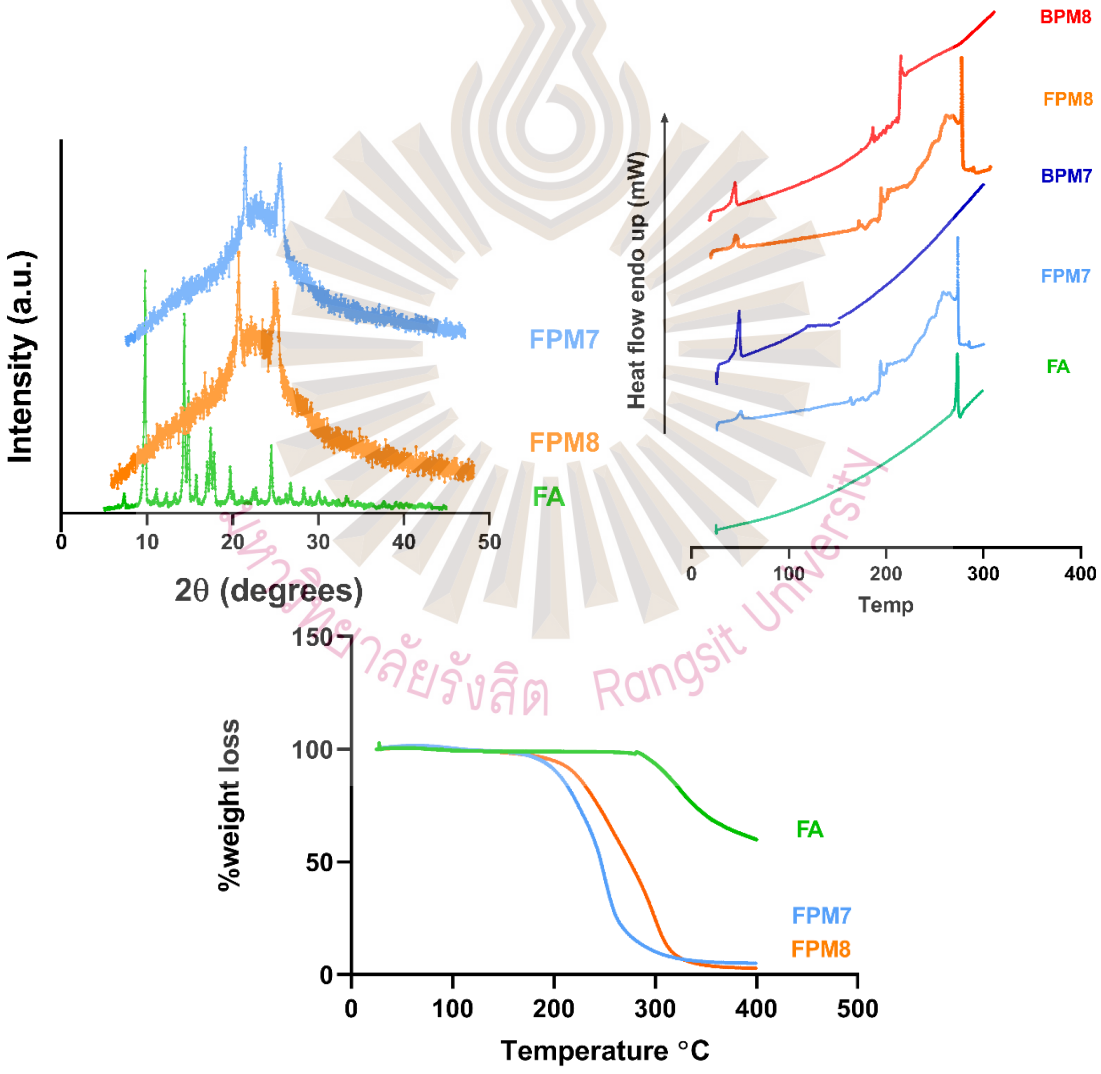

Fig. 5. Physical characteristics of FA polymeric micelles: XRD (A), DSC (B), and TGA (C) thermograms

FPM7 and FPM8 were selected for further investigation on DSC, TGA, XRD. In comparison of FA, FPM7 and FPM8 were subjected to PXRD analysis to study the crystalline state of FA inside polymeric micelles. Prominent characteristic peaks of drug crystallinity at 20 and 25 (2θ) was observed after incorporated FA in the micelle solution, indicating the presence of FA in crystalline form (Fig. 5A). FA, FPM7, FPM8, and their BPMs were subjected for DSC studies. A large endothermic peak at 273.37°C was observed for FA (Fig. 5B) that is consistent with the literature and represents FA crystallinity. The peak at 273.32°C and 274.02°C were hold in FPM7 and FPM8, respectively, suggesting the existence of FA in crystalline form inside polymeric micelles, supporting the observations from PXRD.

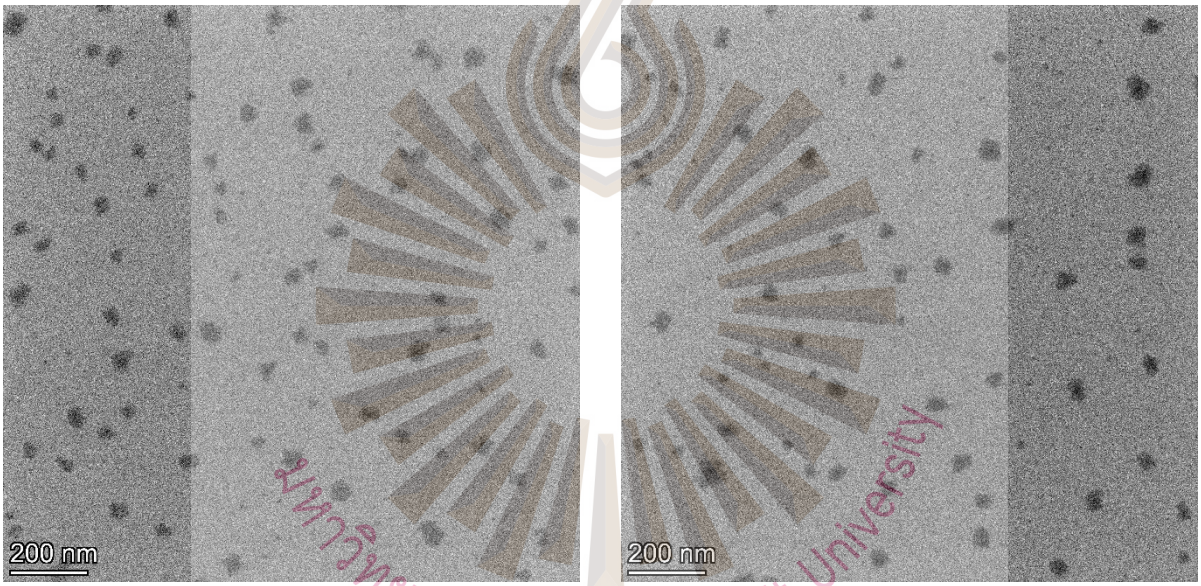

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Fig. 6. Microscopic morphology photograph of FG7 and FG8 by transmission electron microscope (TEM)

TEM microscopic pictures appear as irregular shape vesicles with nanometer-sized particles. The photographs of FPM7 and FPM8 provided the same morphology. The TEM-based size estimates were consistent with the results of DLS particle size analyses, which showed that these polymeric micelles surrounded the FA molecule.

6. *Ex vivo* drug accumulation

Ex vivo permeation results obtained from the ATR-FTIR microspectroscopic images of the epithelial, laminar propria and submucosa layer of the microtome cross-sectioned barrier membrane as shown in Fig. 7. The 2D image blank porcine esophagus was used as at initial mucosal sample before treated (Fig. 7A). 2D image by ATR-FTIR at 5 min, 15 min and 30 min of cross section of porcine esophagus exposed to FPM7 compared to FPM8 were shown in Fig. 7B and C, respectively. At 5 min, the intensity of epithelium exposed to both FPM7 and FPM8 increase whereas at 15 min of exposure, all layers of porcine esophagus express the growth of absorbances. At 30 min, FPM7 still observed the increase of intensity while exposed to FPM8 indicating low intensities detected throughout the cross-sectional tissue sample. Each layer of porcine esophagus represented not only the membrane barrier but also the drug target of action. Corticosteroid as FA reduced inflammatory by interacted with the receptor on basal cells with in between epithelium and lamina propria (Thongprasom et al. 2017; Said et al. 2021). FPM7 was shown the increase of intensity from initial to 30 min which represented the formulation deposition while FPM8 allowed the FA pass through the mucosal epithelium but did not struct in the layer.

ATR-FTIR microspectroscopic of tissue sample exposed to FPM7 (Fig. 8A) and FPM8 (Fig. 8B) represented the epithelial, lamina propria, and submucosa layer of the microtome cross-sectioned barrier membrane as blank esophagus (red line), fluocinolone acetonide powder (grey line) and exposed to FPMs for 5 min (blue line), 15 min (pink line) and 30 min (green line). Cross section of epithelium was found that the greatest peak was observed at 30 min from both FPM7 and FPM8. However, at 5 min of permeation, FPM7 was also found in the epithelium layer. Cross section of lamina propria detected the different of FPM7 and FPM8 permeation. The greatest peak of 30 min permeation of FPM7 was found whereas the peak of 5 min provided the highest absorbance of FPM8. Submucosal layer, on the other hand, blank mucosal IR spectrum showed the greatest absorption which represented that submucosal did not hold the drug on the membrane but let them pass through to other layers. However, FPM7 still observed the peak of 5, 15 and 30 min of permeation and FPM8 still observed the peak of 30 min of permeation.

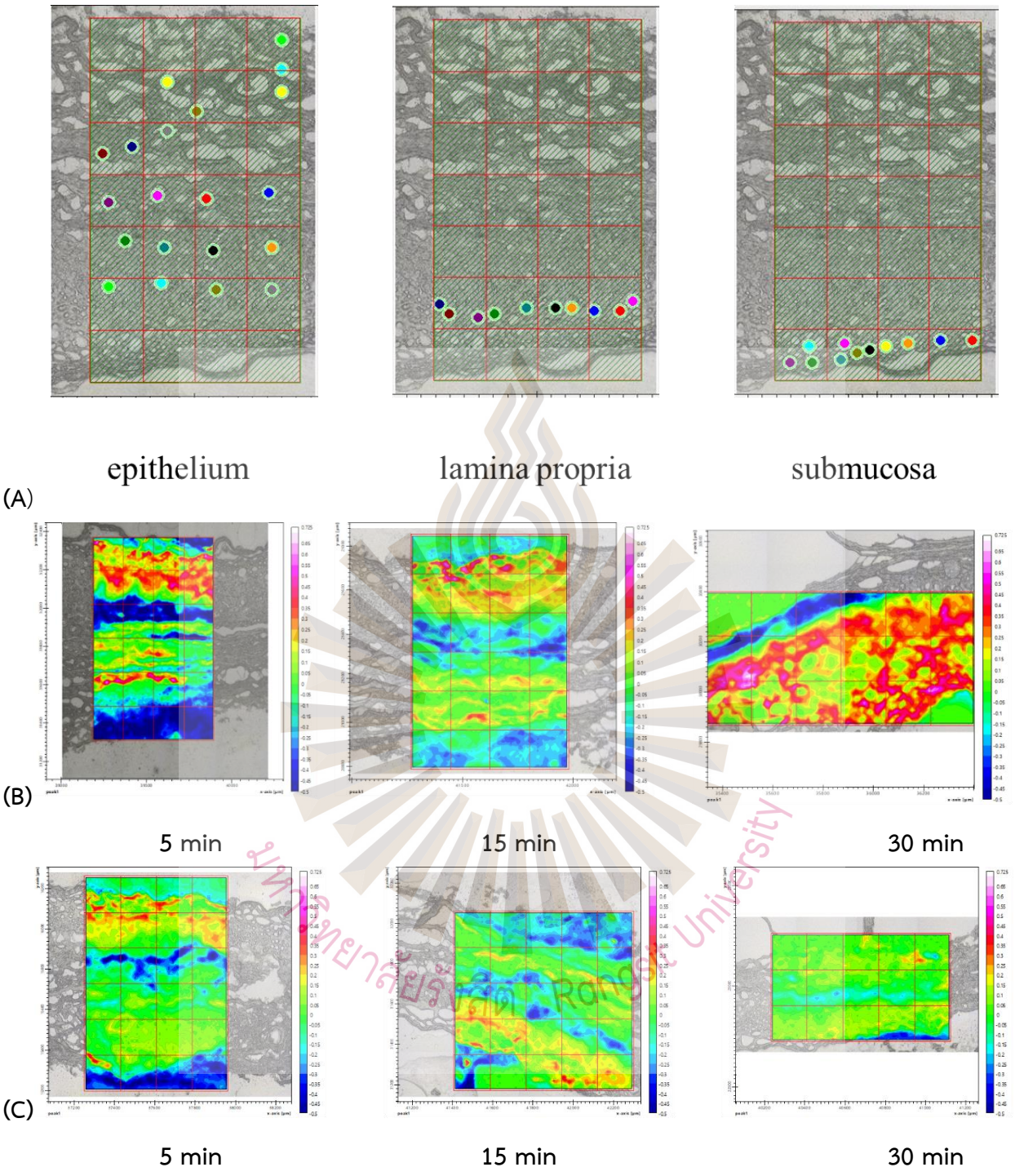

Fig. 7. *Ex vivo* permeation results obtained from the ATR-FTIR microspectroscopic images of the epithelial, laminar propria and submucosa layer of the microtome cross-sectioned barrier membrane, as follows: (A) 2D image at initial (blank porcine esophagus), (B) 2D image by ATR-FTIR at 5 min, 15 min and 30 min of cross section of porcine esophagus exposed to FPM7 (C) compared to FPM8.

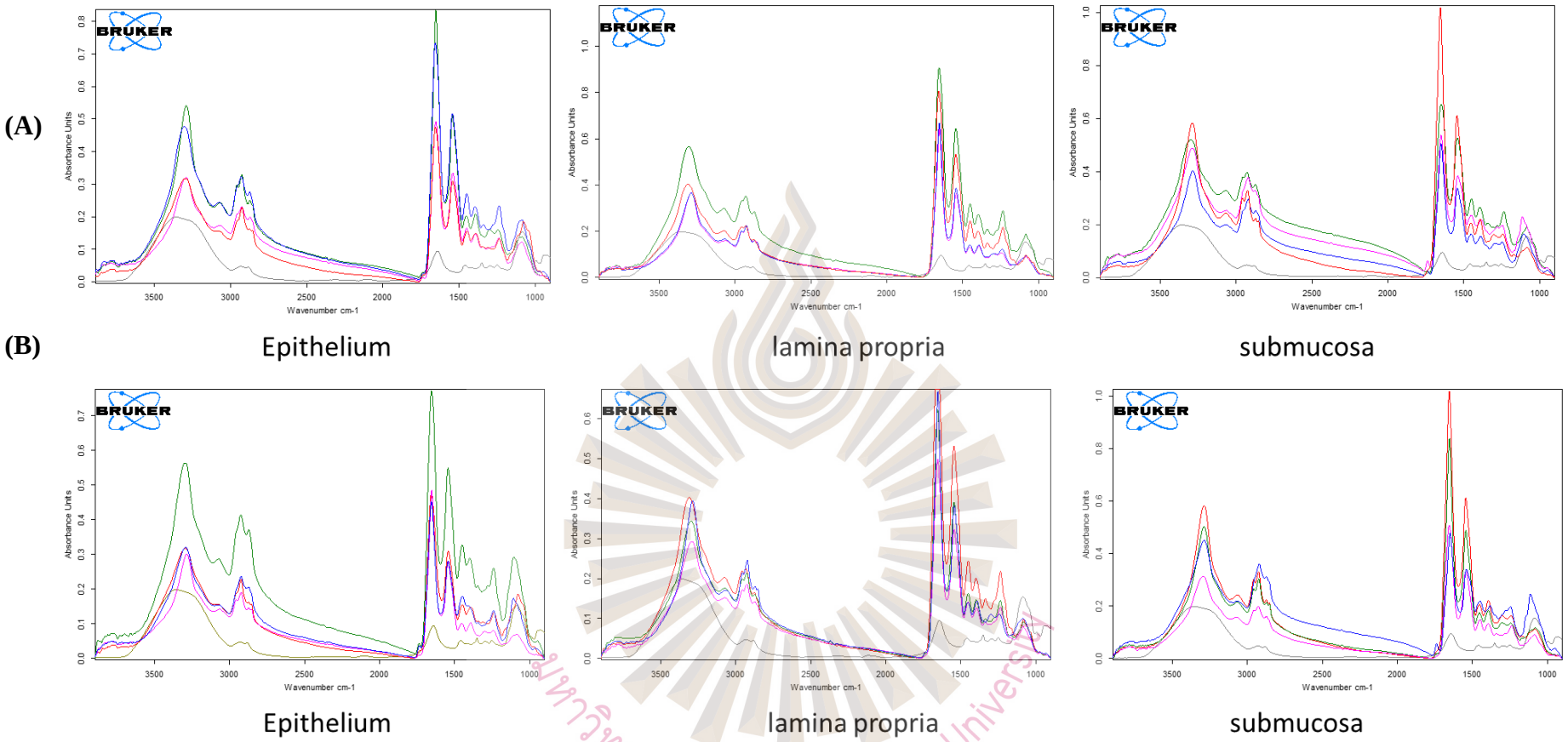

Fig. 8. ATR-FTIR microspectroscopic of the epithelial, lamina propria, and submucosa layer of the microtome cross-sectioned barrier membrane as fluocinolone acetonide powder (grey line), non-exposure esophagus (red line), and the esophagus exposed to FPM7 (A) and FPM8 (B) for 5 min (blue line), 15 min (pink line) and 30 min (green line)

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Chapter 5
Conclusion

FA loaded polymeric micelles composed of co-polymers as P407 and SPA was effectively invented. The FPM formular help increasing of mucoadhesion which related to drug-mucosal retaining time and allowed FA penetrated and remained in mucoasal layers. Therefore, the FPM could be a superior applicant for a polymeric micelles mounthrinse form to be used as dental material. However, clinical investigations including quality of life study are still needed for its applied development.

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ภ.บ.	เภสัชศาสตร์	เภสัชศาสตร์	มหาวิทยาลัยรังสิต	2547
ภ.ม.	เภสัชภัณฑ์	เภสัชศาสตร์	มหาวิทยาลัยขอนแก่น	2555
Diploma course certificate	Research and development of products to meet public health needs	เภสัชศาสตร์	Nagasaki University	2558
ปรด	วิจัยและพัฒนาเภสัชภัณฑ์	เภสัชศาสตร์	มหาวิทยาลัยขอนแก่น	2559
Postdoctoral training	วิจัยและพัฒนาเภสัชภัณฑ์	เภสัชศาสตร์	มหาวิทยาลัยขอนแก่น	2560

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สาขาวิชาที่นักวิจัยเชี่ยวชาญ

1. Research and development in pharmaceutical sciences
2. Dental materials
3. Intranasal delivery
4. Nano Sciences

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