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Original Article

PREPARATION AND CHARACTERIZATION OF POLY (VINYL ALCOHOL)–POLY (VINYL PYRROLIDONE) MUCOADHESIVE BUCCAL PATCHES FOR DELIVERY OF LIDOCAINE HCL

NAPAPHAK JAIPAKDEE[a,b], THANED PONGJANYAKUL[a], EKAPOL LIMPONGSA[a,b*]

[a]Division of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Khon Kaen University, Khon Kaen, 40002, Thailand, [b]Center for Research and Development of Herbal Health Products, Khon Kaen University, Khon Kaen, 40002, Thailand
Email: ekapol@hotmail.com

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ABSTRACT

Objective: The objectives of this study were to prepare and characterize a buccal mucoadhesive patch using poly (vinyl alcohol) (PVA), poly (vinyl pyrrolidone) (PVP) as a mucoadhesive matrix, Eudragit S100 as a backing layer, and lidocaine HCl as a model drug.

Methods: Lidocaine HCl buccal patches were prepared using double casting technique. Molecular interactions in the polymer matrices were studied using attenuated total reflectance-fourier transform infrared spectroscopy (ATR-FTIR), differential scanning calorimetry (DSC) and X-ray diffractometry. Mechanical and mucoadhesive properties were measured using texture analyzer. *In vitro* permeation of lidocaine HCl from the patch was conducted using Franz diffusion cell.

Results: Both of the free and lidocaine HCl patches were smooth and transparent, with good flexibility and strength. ATR-FTIR, DSC and X-ray diffractometry studies confirmed the interaction of PVA and PVP. Mechanical properties of matrices containing 60% PVP were significantly lower than those containing 20% PVP (*P<0.05). Mucoadhesive properties had a tendency to decrease with the concentration of PVP in the patch. The patch containing 60% PVP had significantly lower muco-adhesiveness than those containing 20% PVP (*P<0.05). *In vitro* permeation revealed that the pattern of lidocaine HCl permeation started with an initial fast permeation, followed by a slower permeation rate. The initial permeation fluxes follow the zero-order model of which rate was not affected by the PVP concentrations in the PVA/PVP matrix.

Conclusion: Mucoadhesive buccal patches fabricated with PVA/PVP were successfully prepared. Incorporation of PVP in PVA/PVP matrix affected the strength of polymeric matrix and mucoadhesive property of patches.

Keywords: Poly (vinyl pyrrolidone), Poly (vinyl alcohol), Lidocaine HCl, Permeation, Buccal patch, Buccal drug delivery

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INTRODUCTION

Buccal drug delivery has gained considerable attention as an alternative dosage form [1]. Numerous retentive buccoadhesive devices [2-6], were developed in order to solve the conventional dosage form limitations. Buccal mucoadhesive patches are preferable over the buccal tablets for their flexibility, and the patches tend to be less obtrusive and are more likely to be accepted by patients. [7].

Mucoadhesive patches for buccal mucosa administration may have a number of different designs [7, 8]. These patches usually contain hydrophilic polymers that are able to form sticky hydrogels after getting in contact with water, and adhere to the buccal mucosa and the impermeable backing membrane [3]. The impermeable backing membrane is an important part to ensure the unidirectional drug release [9]. Materials with hydrophobicity, low water permeability and drug impermeability properties such as melted wax [10], ethyl cellulose [1, 4, 11], and Eudragit RL100 [12] have been used as a backing membrane. A wide range of polymers such as hydroxypropyl methylcellulose, carbopol, poly (vinyl alcohol) (PVA), and poly (vinyl pyrrolidone) (PVP) [13-17] have been employed as a matrix and mucoadhesive layer in buccal patches. In order to improve the film properties, including film-forming ability, mechanical and mucoadhesive properties, a combination of hydrophilic polymers is generally used.

This study will focus on the buccal mucoadhesive bilayered patches prepared with PVA and PVP as base matrix polymers. PVA is a well-known, water-soluble polymer with high transparency and flexibility [18]. However, it has a moderate swelling and mucoadhesive properties [14, 19]. PVP is a non-ionic, film-forming polymer. It has high swelling properties and has been used as coadjuvant to increase mucoadhesion [7, 16]. The combination of PVA and PVP leads to a more versatile property matrixes. The physical, mechanical and thermal properties of PVA and PVP matrixes can be modulated by varying the PVA/PVP ratio. These two polymers and their blends have been used in numerous applications, including biomedical films [20], transdermal [21, 22] and buccal patches [13, 14]. Nevertheless, to the best of our knowledge, the relationships between PVA/PVP ratios and the mucoadhesion property of buccal patches, as well as the permeation behaviour of the hydrophilic drug through the mucosa are not well established.

Lidocaine HCl was used as a hydrophilic model drug. It is very soluble in water [23]. It has been reported that lidocaine HCl diffused passively through porcine buccal membrane [24]. Lidocaine HCl has a primary indication as a local anaesthetic agent when applied topically [25, 26]. There are several pharmaceutical dosage forms of lidocaine HCl available on the market, i.e., solution for injection or infusion, nasal spray, oral gel and transdermal patch [24, 26]. Several authors have developed the buccal mucoadhesive systems of lidocaine and/or lidocaine HCl [25, 27-29]. However, in previous literature, no attempt has been taken to formulate lidocaine HCl buccal patches simply using PVA and PVP along with Eudragit S100.

Being different from the earlier investigations, the objective of this study was to prepare a buccal mucoadhesive patch using PVA and PVP as a mucoadhesive and drug reservoir layer. Eudragit S100 was used as a backing layer. Lidocaine HCl was used as a model drug. The effects of PVA/PVP ratios and lidocaine HCl addition on the appearance, thickness and mechanical properties of polymer matrices were investigated. Molecular interaction, thermal behaviour and solid-state characteristics of the drug within the polymer matrices were studied. The mucoadhesive properties of buccal patches containing lidocaine HCl and the in vitro permeation of lidocaine HCl were also evaluated.

MATERIALS AND METHODS

Materials

Poly (vinyl alcohol) (PVA) was purchased from Ajax Finechem Pty Ltd, Seven Hills, Australia. Poly (vinyl pyrrolidone) (PVP) K30 was obtained

from K. Science Center and Medical, Khon Kaen, Thailand. Lidocaine HCl was purchased from S. Tong Chemicals, Bangkok, Thailand. Dibutyl phthalate (DBP) was obtained from Merck-Schuchardt, Hohenbrunn, Germany. Methacrylic acid copolymer type B (Eudragit S100) was gifted from Evonik Industries AG, Essen, Germany. Deionized water was used throughout the studies. All chemicals were of reagent or high-performance liquid chromatography (HPLC) grade.

Preparation of blank and lidocaine HCl matrices

Blank matrices were composed of different concentrations of PVA and PVP (table 1) which were prepared by a plate casting method [4, 15]. PVA was weighted and dissolved in boiled water, while PVP was weighted and dissolved in hot water to yield solutions at 12 % w/w. The required amount of each solvent was mixed to get the polymer solution. The resultant solution was poured into a polypropylene plate (12 cm x 12 cm), which was then oven-dried at 55 °C for 12 h. In the case of lidocaine HCl matrices, lidocaine HCl (20% of dry weight of polymers) was incorporated into the polymer solution. The clear drug-polymer solution was then cast onto the plate and subsequently oven-dried as mentioned above. The dry matrices were packed in aluminium foil and kept in a desiccator until used.

Evaluation of blank and lidocaine HCl matrices

Appearance and thickness

The appearance and thickness of matrix specimen (rectangular shape, 0.5 cm x 4 cm) were observed and measured at five different places using a dial thickness gauge (Peacock, Labtek, USA). The average of the five values was calculated.

Molecular interaction

Attenuated total reflectance-Fourier transform infrared (ATR-FTIR) spectroscopy

The spectra (4000 to 650 cm-1 at a resolution of 4 cm-1) of the samples were recorded using an ATR-FTIR spectrophotometer (Spectrum One, Perkin Elmer, Norwalk, CT). Each sample was cut and placed on a ZnSe prism of a sample holder.

Thermal study

Differential scanning calorimetry (DSC) curves of the samples were recorded using a differential scanning calorimeter (DSC822, Mettler Toledo, Switzerland). Each sample (3–5 mg) was accurately weighed into a 40-µl open aluminium pan. The measurements were performed over 30–300 °C at a heating rate of 10 °C/min.

X-ray diffractometry

X-ray diffraction (XRD) measurements of samples were performed on an X-ray diffractometer (D8 ADVANCE diffractometer, Bruker, Germany). The measurement conditions were Cu radiation generated at 40 kV and 40 mA as an X-ray source, angular 5–50 ° (2θ), and step angle 0.02 ° (2θ)/s.

Moisture absorption

A weighed matrix (1 cm x 1 cm) kept in a desiccator with silica gel for 24 h was taken out and transferred to a desiccator containing saturated sodium chloride solution (relative humidity 75%) at 25 °C. After equilibrium was attained, the matrix was taken out and weighed. Moisture absorption capacity was calculated based on the change in the weight with respect to the initial weight of the matrix.

Mechanical properties

Mechanical properties which are ultimate tensile strength (UTS), percent elongation at break (%E) and Young's modulus (YM) were determined following the method modified from Okhamafe and York [30] using a texture analyzer (TA. XT plus, Stable Micro Systems, UK) with a 50-N load cell equipped with a miniature tensile grip. The cross-head speed was controlled at 10 mm/min. The UTS and percent elongation at break were calculated from equations (1) and (2), respectively.

$$\text{UTS} = \frac{\text{breaking load}}{\text{cross - sectional area of specimen}} \quad \text{..... (1)}$$

$$\%\,\text{E} = \frac{\text{length at breaking point} - \text{original length of specimen}}{\text{original length of specimen}} \times 100 \quad \text{..... (2)}$$

Preparation of lidocaine HCl buccal patches

Lidocaine HCl buccal patches (lidocaine HCl matrices with backing) were prepared using double casting technique [3]. An ethanolic solution of the backing layer composed of Eudragit S100 and DBP (40%) as a plasticizer was poured into a glass plate (diameter = 10 cm) and subsequently oven-dried at 55 °C for 2 h. The second matrix solution composed of PVA, PVP and lidocaine HCl (table 1) was immediately cast on top of the pre-cast dried Eudragit S100 backing layer and then oven-dried at 55 °C for 12 h. The dried patches were packed in aluminium foil and kept in a desiccator until used. The patches were cut into a size of 20 mm diameter, stored in a desiccator until further use.

Evaluation of lidocaine HCl buccal patches

Determination of lidocaine HCl content in patches

A known weight of licocaine HCl matrices was dissolved and diluted in water. The licocaine HCl content was determined by an HPLC system as described below.

Determination of mucoadhesive properties of patches

The mucoadhesive properties of the patches were measured using a texture analyzer (TA. XT plus, Stable Micro Systems, UK) with a 50-N load cell equipped with a bioadhesive test rig. The patch was attached to a 10-mm diameter cylindrical probe using a two-sided adhesive tape. The esophageal mucosa of the pig was also obtained from a local slaughterhouse (Non-Muang Village, Khon Kaen, Thailand). The mucosal membrane from the porcine esophagus (about 2 cm × 2 cm) without heat treatment and elimination of the connective tissue that had been hydrated with pH 6.8 isotonic phosphate buffer (IPB) for 20 min was placed on the stage of bioadhesive holder and gently blotted with tissue paper to remove excess water on the surface of the mucosal membrane. Next, 100 µl of pH 6.8 IPB was pipetted onto the membrane surface before testing. The probe and attached patches were moved down at a constant speed of 1 mm/s with 0.5-N contact force and 2-min contact time. Immediately afterwards, the probe was moved upwards with a constant speed of 0.5 mm/s. The relationship between the force and patch displacement was plotted. The maximum detachment force (F_{max}) and work of adhesion (W_{ad}, the area under the force versus distance curve) were calculated using the Texture Exponent 32 program version 4.0.9.0 (Stable Micro Systems).

***In vitro* permeation study of lidocaine HCl from patches**

Mucosa preparation

The porcine oesophagal mucosa was employed in this study because it has a lipid composition similar to that of the porcine buccal mucosa, but requires a simpler preparation method [31]. The esophageal mucosa was obtained from crossbred pigs (hybrid kinds of Duroc Jersey–Landrace-Large White) that weighed between 80-100 kg and was purchased from a local slaughterhouse (Non-Muang Village, Khon Kaen, Thailand). The porcine esophageal tube was opened longitudinally and immersed in 0.9% sodium chloride at 60 °C for 1 min [31, 32]. The epithelium was then peeled away from the connective tissue.

The in vitro permeation of lidocaine HCl from the patch through the porcine esophageal mucosa was conducted using a Franz diffusion cell with a diffusion area of 0.636 cm2 (Crown Glass Company, Q1 Branchburg, NJ). The system was connected to a water bath maintained at a temperature of 37.0±0.5 °C. The thickness of a mucosa was measured using a dial thickness gauge (Peacock, Labtek, Scotts Valley, CA). The mucosa was then mounted on the diffusion cell, which contained pH 6.8 IPB as a receptor medium. The lidocaine HCl patch was placed over the mucosa and the cell was then fixed and tightly fastened with a clamp. At predetermined times, 0.5-ml samples were taken from the receptor compartment and equal volumes IPB were immediately added after each sampling. The concentration of lidocaine HCl was

analyzed by HPLC. The cumulative amount of drug that permeated the mucosa was plotted against time.

Data analysis

The lidocaine HCl permeation rates from the patches were analyzed using both zero-order and Higuchi models [33], which can be expressed as equations 3 and 4, respectively, as follows:

$$Q = K_0 t \text{ ..... (3)}$$

and

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

Where Q is the amount of lidocaine HCl permeated, t is time, and K_0 and K_H are the zero-order and Higuchi permeation rates, respectively.

HPLC analysis

Lidocaine HCl content was determined using an HPLC system (Perkin-Elmer, MA) consisting of a UV/VIS detector (model 785A) and a pump (series 200 LC). The chromatographic separation was achieved on a Hypersil Gold C-18 column (250 mm × 4.6 mm, 5 µm; Thermo Electron Corporation, USA) with a flow rate of 1 ml/min and UV detection at 254 nm. The mobile phase consisted of methanol, acetic acid, triethylamine and water at a volume ratio of 55: 1.5: 0.5: 43. The retention time of lidocaine was approximately 4.3 min. The standard curve was linear over a concentration range of 5 to 120 µg/ml with an *R2* value>0.99. The day-to-day relative standard deviations (RSD) for this assay were less than 5%.

Statistical analysis

Each experiment was repeated at least three times. The results are expressed as the mean±SD One-way analysis of variance was used to test the statistical significance of differences among groups. Statistical significance of the differences of the means was determined by Student's t-test. All statistical tests were run using the SPSS program for MS Windows, release 19 (SPSS (Thailand) Co. Ltd., Bangkok, Thailand). The significance was determined with 95% confident limits (α = 0.5) and was considered significant at a level of P less than 0.05.

RESULTS AND DISCUSSION

Blank and lidocaine HCl matrices

Both of the blank and lidocaine HCl matrices were prepared by a solvent casting method using an aqueous solution of 12% polymer. The result shows that the blank matrix made from PVA alone was very hard, while the matrix made from PVP alone was very brittle. On the contrary, the matrices prepared from PVA and PVP, at all concentrations investigated, were flexible, clear with a smooth surface and ready to be peeled off from the mould. According to Preis *et al.* [3], the polymer solid content of 10-15% was desirable to yield the matrix films with a suitable thickness that could easily be peeled off from the release liner. As shown in table 1, the thicknesses of formulations F1, F2 and F3 were comparable (P>0.05) and were in the average range of 125 to 130 µm. The matrix thickness is an important factor affecting the strength, flexibility, swelling, drug loading capacity and physicochemical stability of the buccal patches [1]. All of the lidocaine HCl matrices, formulations LDC-F1, LDC-F2 and LDC-F3, were also clear, smooth and uniform, similar to the blank matrices. The clearness and transparency of lidocaine HCl matrices suggest that lidocaine HCl was solubilized in the polymer matrix. The thicknesses of lidocaine HCl matrices were in the average range of 136 to 142 µm (table 1) which were not different from those of the matrix formulations (P>0.05). Therefore, the addition of lidocaine HCl, 20% of polymers dry weight, had no effect on the physical appearance of the lidocaine HCl matrices.

Table 1: Thickness and mechanical properties of blank and lidocaine HCl matrices as a function of PVA and PVP concentrations

Formulation	Concentration (%)		LDC	Thickness (µm)[a]	UTS (MPa)[a]	%E (%)[a]	YM (MPa)[a]
	PVA	PVP					
F1	80	20	-	125±18	59.2±7.0	121.7±54.0	4.6±0.4
F2	60	40	-	128±27	54.4±6.4	130.2±61.5	4.0±0.5
F3	40	60	-	130±31	40.4±2.7	40.1±6.0	2.6±0.3
LDC-F1	80	20	20%	136±14	29.8±2.9	268.8±60.9	2.9±0.3
LDC-F2	60	40	20%	137±13	19.2±1.4	258.1±48.8	2.1±0.2
LDC-F3	40	60	20%	142±13	9.0±0.7	261.2±61.1	1.1±0.3

UTS: ultimate tensile strength, %E: percent elongation at break, YM: Young's modulus, [a]mean±SD, n = 5.

Molecular interactions

Molecular interactions between PVA and PVP in the blank and lidocaine HCl matrices were investigated using ATR-FTIR spectroscopy and XRD analysis.

ATR-FTIR

The ATR-FTIR spectra of PVA and PVP powders, PVA/PVP matrix (F3), lidocaine HCl matrix containing 60% PVP (LDC-F3) and lidocaine HCl powder are shown in fig. 1. In ATR-FTIR spectrum of PVA powder (fig. 1a), the wide peak located at 3271 cm-1 is for the O-H stretch vibration. Absorption for asymmetrical stretching vibration and symmetrical stretching vibration of CH_2 occurred at 2932 and 2908 cm-1, respectively. The two peaks of 1414 and 1326 cm-1 are attributed to the coupling of the secondary O-H in-plane bending and the C-H wagging vibrations. Absorption at 1085 cm-1 was produced by C-O stretching vibration [34]. The main absorption bands of PVP powder were observed at 1661, 1420, 1371 and 1283 cm-1 (fig. 1b). These bands were assigned as C=O symmetric stretching, CH_2 bending, O-H bending (in-plane) and C-H deformation, respectively [18].

The PVA/PVP matrix spectra (fig. 1c, d and e) were similar to those of PVA and PVP powders. Nevertheless, the differences between the relative ATR-FTIR absorbance of PVA and PVP powders can be seen at 3271 cm-1 and in the region of 1800-1500 and 1260-1000 cm-1. Blending of PVP with PVA caused the O-H stretching peak of PVA to move to higher wavenumbers: 3298-3280 cm-1 and the C-O stretching of PVA shifted from 1085 cm-1 to 1091-1089 cm-1. Moreover, the C=O stretching of PVP shifted from 1660 cm-1 to 1655-1651 cm-1. These results indicate the intermolecular hydrogen bonding between hydroxyl groups of PVA and carbonyl groups of PVP. This result was in agreement with the previous report [35]. PVP contains a proton-accepting carbonyl moiety in its pyrrolidone ring, whereas hydroxyl groups as side groups are presented in the PVA. In PVP/PVA matrices, the hydrogen bonding interaction is able to occur between these two moieties [36].

As shown in fig. 1g, lidocaine HCl powder showed a N-H stretching at 3383 cm-1, a C-H stretching at 3011 cm-1, an amide I (C=O) at 1654 cm-1 and an amide II (C-N) at 1472 cm-1. These values are in good agreement with the results obtained in other studies [29, 37, 38]. Regardless of the PVP content, the ATR-FTIR spectrum of lidocaine HCl matrices showed no absence of any functional peak in the spectra, revealing that there is no significant chemical interaction between the drug and polymers. The example of the spectrum of lidocaine HCl matrix prepared with 60% PVP is shown in fig. 1f. Additionally, there were no new bands observed in drug-polymer matrices, which confirms that no new chemical bonds were formed between lidocaine HCl and polymers.

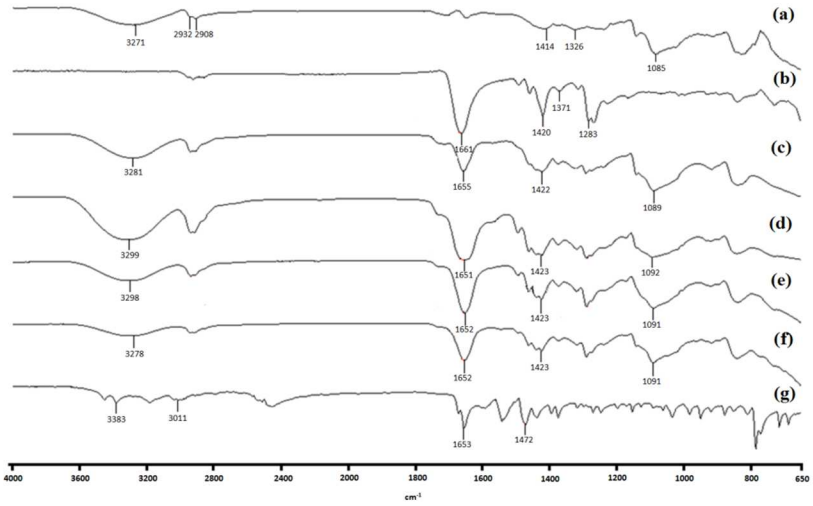

Fig. 1: ATR-FTIR spectra of PVA powder (a), PVP powder (b), PVA/PVP matrices containing 20% PVP (c), 40% PVP (d), 60% PVP (e), lidocaine HCl matrix containing 60% PVP (f) and lidocaine HCl powder (g)

Thermal study

The DSC thermograms of the PVA and PVP powders and PVA/PVP matrices are presented in fig. 2. The PVA powder showed an endothermic peak at about 213.8 °C (fig. 2a). This was due to the melting of the crystalline phase present in this polymer [36]. Incorporation of 20 %w/w PVP into the PVA had no effect on the DSC pattern as the PVA endothermic peak was at 213.8 °C (fig. 2b). A shift of this PVA endothermic peak to lower temperature (205.3 °C) was observed for 40% PVP/PVA matrix, and a disappearance of this peak occurred at 60% PVP/PVA matrix (fig. 2c-d). However, the endothermic peak of their physical mixtures was present at almost the same temperature (213.7, 211.0, 213.9 °C for 20, 40 and 60 % w/w PVP to PVA, respectively; data not shown). This was presumably due to the decreases in the degree of crystallinity and crystallization rate of PVA by the PVP [36]. In addition, Seabra and De Oliveira [20] reported that the depression in melting temperature peak of the crystalline phase of PVA by PVP indicated the specific multiple hydrogen bonding interactions between the two polymers.

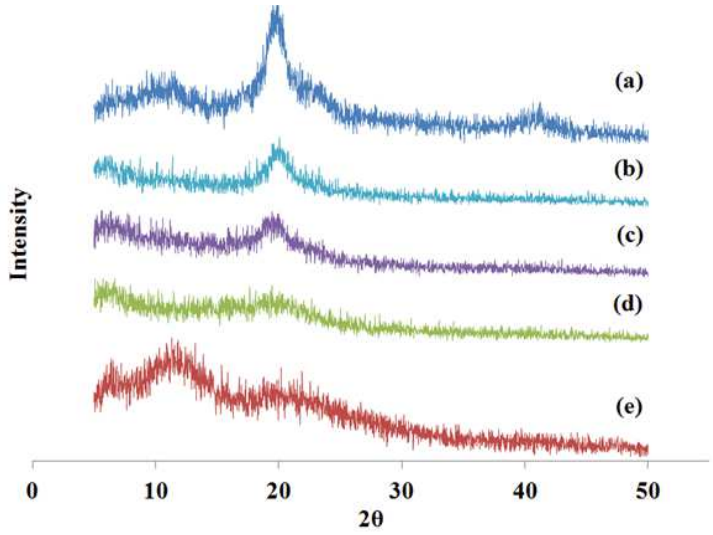

Fig. 2: XRD patterns of PVA powder (a), PVA/PVP matrices containing 20% PVP (b), 40% PVP (c), 60% PVP (d) and PVP powder (e)

The DSC curves of the lidocaine HCl and lidocaine HCl matrices are presented in fig. 3. Lidocaine HCl showed an endothermic peak at 77.9 °C followed by a boiling and volatilization peak starting from 188 °C (fig. 3a). The endothermic peak of lidocaine HCl was not present in the DSC patterns of lidocaine HCl matrices, irrespective of PVP concentration in the matrix (fig. 3b-d). This is presumably explained by the fact that lidocaine HCl is being solubilized in the PVA/PVP matrices. This hypothesis was supported by the DSC thermograms of the physical mixture of lidocaine HCl, PVP and PVA (data not shown) and other characterization technique shown later.

DSC curves of the lidocaine HCl matrices revealed that incorporation of lidocaine HCl (at 20 %w/w of polymer) into the PVA/PVP matrices caused a shift of PVA endothermic peak to lower temperature at 20% and 40% PVP and disappearance of the endothermic peak at 60% PVP (fig. 3b-d). These presumably suggested that lidocaine HCl may act as the plasticizer. It is known that plasticizers generally affect the thermal and mechanical properties of a polymer matrix. Similar findings were observed by Aitken-Nichol *et al.* [39] who found that the glass transition temperature of the melting endothermic peak of Eudragit E100 films was lower with the addition lidocaine HCl.

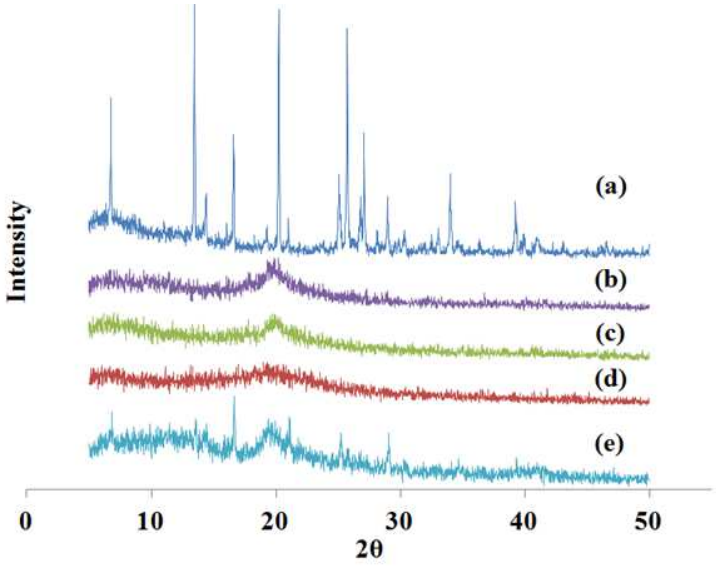

Fig. 3: XRD patterns of lidocaine HCl powder (a), lidocaine HCl matrices containing 20% PVP (b), 40% PVP (c), 60% PVP (d) physical mixture of lidocaine HCl, 40% PVP-PVA (e)

X-ray diffractrometry

The XRD patterns of the same materials support the ATR-FTIR and DSC results. XRD measurement is a versatile, non-destructive technique that reveals the crystallographic structure of materials and can be used to investigate the complex formation between the polymers. The XRD patterns of PVA and PVP powders and PVA/PVP matrices are shown in fig. 4. The XRD pattern of PVA powder exhibits diffraction peak angle at 2θ = 10.5 °, 19.8 ° and 41.0 ° (fig. 4a). The strong and broad peak at 19.8 ° corresponds to the (1 0 1) reflection, a plane which contains the extended planar zig-zag chain direction of the crystallities [40, 41]. The XRD pattern of PVP powder in fig. 4e exhibits amorphous features characterized by two halos centered at 2θ = 11.7 ° and 20.2 °.

For the PVA/PVP matrices, the sharp peak was clearly observed in the XRD patterns of the matrices with high PVA content (fig. 4b and 4c). The intensity of PVA pattern decreased with the addition of PVP. This was due to the amorphous nature of the matrix that increased with the addition of PVP [35]. The PVA/PVP matrices containing 60% PVP exhibited the highest amorphous nature as the peak at 2θ = 20.0 ° was small and broad (fig. 4d). Based on these findings, it could be implied that the degree of crystallization of PVA decreased with the increase of PVP content [42].

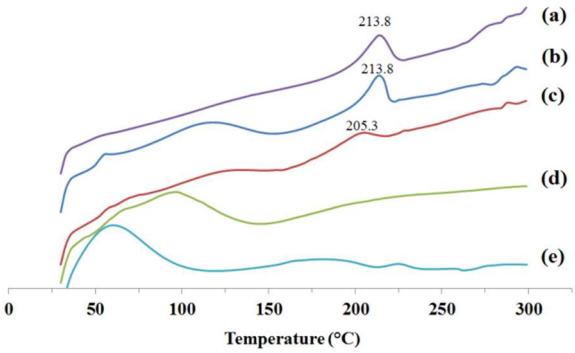

Fig. 4: DSC thermograms of PVA powder (a), PVA/PVP matrices containing 20% PVP (b), 40% PVP (c), 60% PVP (d), and PVP powder (e)

Fig. 5 reveals the XRD patterns of lidocaine HCl, lidocaine HCl matrices and physical mixture of lidocaine HCl and 40% PVP. Lidocaine HCl was highly crystalline in nature as shown by numerous characteristic sharp peaks in its XRD pattern. However, the XRD patterns of lidocaine HCl matrices (fig. 5b-d) showed one broader peak which were similar to those of PVA/PVP matrices (fig. 4b-d). There was no crystalline pattern corresponding to that of lidocaine HCl observed. The crystallinity nature of lidocaine HCl in lidocaine HCl matrices was absent, whereas their physical mixture exhibited a sharp crystalline peak (fig. 5e). This suggested that lidocaine HCl embedded in the matrix as a solution. In addition, the absence of drug indicated peaks in the DSC patterns and matrix physical clarity characteristic. These results assured that lidocaine HCl was dispersed with the polymer network as a molecular dispersion level. Previous studies showed that lidocaine HCl was present in the amorphous condition in a hydroxypropyl cellulose film [27] and carbopol film [29].

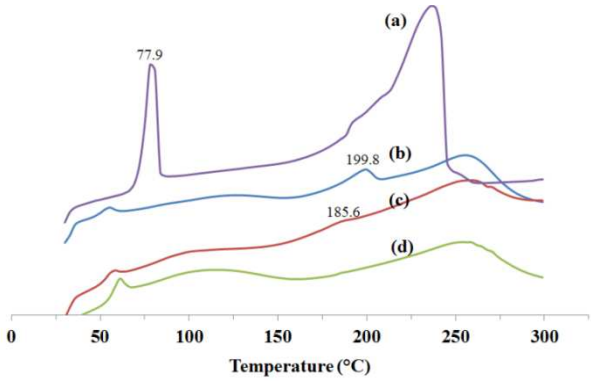

Fig. 5: DSC thermograms of lidocaine HCl powder (a) and lidocaine HCl matrices containing 20% PVP (b), 40% PVP (c) and 60% PVP (d)

Moisture absorption

Moisture absorption study provides information regarding the stability of the formulation. Low level of moisture absorption can protect the materials from microbial contaminations and bulkiness of the polymer matrices [4, 43]. The effects of PVA and PVP concentration on moisture absorption of blank matrices were shown in fig. 6. The moisture absorption of blank matrices containing PVP at 20% and 40% were comparable. However, the moisture absorption of a matrix containing 60% PVP was significantly higher than that of the

one containing 20% PVP (*P<0.05). The relationship between the PVP concentration and moisture absorption blank matrices with a high coefficient of determination (*R2* of 0.9965) was shown. It is obvious that the increase of PVP concentration resulted in the increased moisture absorption of blank matrices. It is well known that PVA is soluble in water while PVP is hygroscopic and freely soluble in water, indicating that PVP has more hydrophilicity [44]. The increase of PVP content could lead to the higher hydrophilic matrix, leading to the high affinity for water and inducing the higher moisture uptake [30].

The effects of lidocaine HCl on moisture absorption of lidocaine HCl matrices were shown in fig. 6. The moisture absorption of matrices increased with lidocaine HCl addition. Significant effects of lidocaine HCl addition on the matrix moisture absorption were shown, irrespective of the PVP concentration in the matrices (*P<0.05). Lidocaine HCl is freely soluble in water [37]. Incorporation of lidocaine HCl into the matrix led to an increase in the hydrophilic property, which affected the moisture absorption of the matrix.

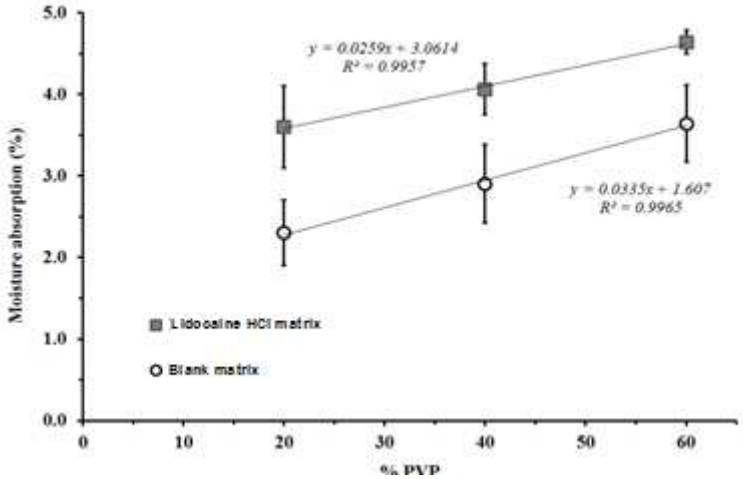

Fig. 6: Effect of PVP concentration on moisture absorption of blank and lidocaine HCl matrices (mean±SD, *n* = 5)

Mechanical properties

Selection of polymeric matrix as potential buccal mucoadhesive system required knowledge of mechanical properties of the matrix. Therefore, the mechanical properties of blank matrices prepared from various ratios of PVA and PVP were characterized and presented in table 1. The ultimate tensile strength (UTS), percent elongation at break (%E) and Young's modulus (YM) of blank matrices containing PVP at 20% and 40% were not different. However, the UTS, %E and YM of a blank matrix containing 60% PVP were significantly lower than those of blank matrices containing PVP at 20% and 40% (*P<0.05).

The relationships between the PVP concentration and UTS and YM of blank matrices with a high coefficient of determinations (*R2* of 0.9243 and 0.9478, respectively) are shown in fig. 7. It is obvious that the increase of PVP concentration resulted in the decreased UTS and YM of blank matrices. Based on the results of ATR-FTIR spectroscopy, the hydroxyl groups of PVA and the pyrrolidone rings of PVP [36] may have a hydrogen-bonding interaction, resulting in the decrease in the inter-molecular forces between polymer chains of PVA, leading to the decreases of the UTS and YM.

The effects of lidocaine HCl on mechanical properties of lidocaine HCl matrices were investigated and shown in table 1. The addition of lidocaine HCl had effects on the mechanical properties of the lidocaine HCl matrix. The UTS and YM of PVA/PVP matrices decreased significantly when lidocaine HCl was added to all concentrations of lidocaine HCl matrices (*P<0.05). However, the percent elongation at break of lidocaine HCl matrices at all ratios increased significantly (*P<0.05). From XRD and DSC studies, it was confirmed that lidocaine HCl was dissolved as a solution in the matrices. Therefore, lidocaine HCl as molecular dispersion, may act as a plasticizer which resulted in the increase of %E of the matrix.

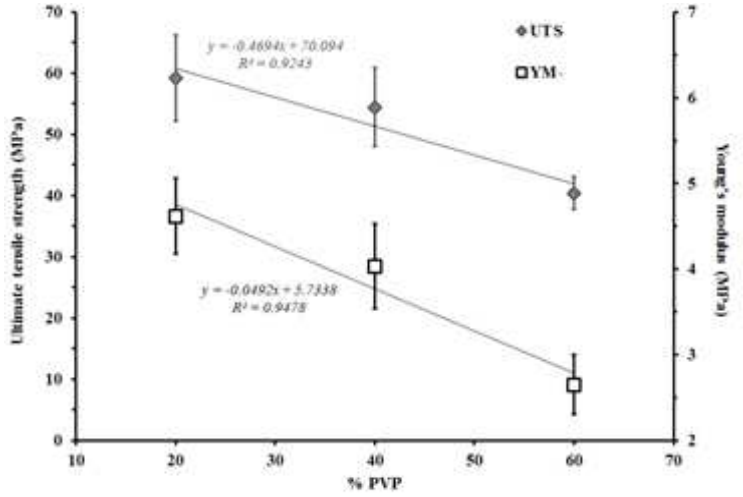

Fig. 7: Effects of PVP concentration on ultimate tensile strength (UTS) and Young's modulus (YM) matrices of PVA/PVP (mean±SD, *n* = 5)

Lidocaine HCl patches

Lidocaine HCl patches (LDC-P1, LDC-P2 and LDC-P3) were prepared by laminating one side of formulation LDC-F1, LDC-F2 and LDC-F3 with a water impermeable backing layer for unidirectional drug release. An impermeable backing membrane of Eudragit S100 was therefore incorporated into the matrices. Eudragit S100 was used as a backing membrane because of its hydrophobicity property. Eudragit S100 is an anionic pH-sensitive copolymer that can be dissolved at pH 7 [10]. In preliminary studies, it was found that the Eudragit S100 films were brittle and could not be processed into elastic films. Therefore, DBP was used as a plasticizer to reduce the brittleness, impart flexibility, and increase toughness, strength, tear resistance, and impact resistance of the films. The studies revealed that the addition of DBP 40 %w/w of polymer produces smooth, uniform, and flexible films. The thicknesses of Eudragit S100 backing layer was approximately 28±3 µm. The double-casting protocol employed in this study was able to produce the tightly bound, homogeneous and smooth surface bilayered patches. The patches of all formulation have good flexibility, strength, transparency, and smooth surface. The thickness of lidocaine HCl patches ranged between 164±15 and 170±15 µm, and mass varied between 19.4±1.6 and 19.6±1.5 mg/cm2 (data not shown). The thickness range was found to be satisfactory which should not cause any discomfort to patients when applied [45]. The lidocaine HCl content of all formulations was in the average range of 2.53 to 2.57 mg/cm2 (the percentage labeled amount of 97.4 to 100.0) with a low standard deviation (<3%). These results confirmed content uniformity of lidocaine HCl in the patches.

Mucoadhesive properties

Selection of polymeric matrix as potential buccal system required knowledge of mucoadhesive properties of patches. Therefore, the mucoadhesive properties in terms of maximum detachment force (F_{max}) and work of adhesion (W_{ad}) of blank and lidocaine HCl patches were characterized using a texture analyzer and presented in **f**ig. 8. All blank patches (polymer matrices with backing) showed appreciable work of adhesion and maximum detachment force, which ranged between 2.7-3.6 N·mm and 2.8-3.6 N, respectively. The addition of lidocaine HCl had no effect on the mucoadhesive properties of the patches compared to those of blank patches. The F_{max} and W_{ad} of the patches had a tendency to decrease with the concentration of PVP in the patch. However, the F_{max} and W_{ad} of free patches containing PVP at 20% and 40% were comparable. The patch containing 60% PVP had significantly lower F_{max} and W_{ad} than those of patch containing 20% PVP (*P<0.05). In contrast to the moisture absorption, the inverted relationship between the PVP concentration and the F_{max} and W_{ad} of blank patches with a high coefficient of determination (*R2* of 0.9882 and 0.9981, respectively) is shown. However, there is no standard formula available for the mucoadhesive buccal drug delivery. This PVA/PVP patch containing 20 % PVP seems to be appropriate, with a high degree of mucoadhesion.

Mucoadhesion can be defined as the adhesion between a polymer and mucus. For the mucoadhesion to occur, an intimate contact between polymer and mucus has to take place as a result of a good wetting of the matrix surface with saliva [1]. Therefore, the intensity of adhesion is closely affected by the moisture absorption of the matrices. PVA is a non-ionic polymer that possess mucoadhesive properties [46-48] because of numerous hydrogen bond forming groups, i.e., hydroxyl groups, contained in its structure. It has been proposed that the interaction between the mucus and hydrophilic polymers occurs by physical entanglement and chemical interactions, such as hydrogen bonding [46]. The interaction of PVA with PVP may possibly lower the mobility and flexibility of PVA molecules, resulting in a decrease in the physical entanglement of PVA and mucus, and bring about a reduction in the number of hydroxyl groups of PVA available to interact with the mucus. For these reasons, the PVA/PVP patch with a higher concentration of PVP displayed a lower mucoadhesive property than that with a lower concentration of PVP. These results agree with the study of Nafee *et al.* [13] which reported the decrease in *in vitro* residence time with rabbit intestinal mucosal membrane of PVA patch containing miconazole nitrate with PVP concentrations. On the other hand, Nappinnai *et al.* [14] reported that films fabricated with PVA and PVP K30 were able to retain the mucosa for a longer period, compared to the one prepared with PVA.

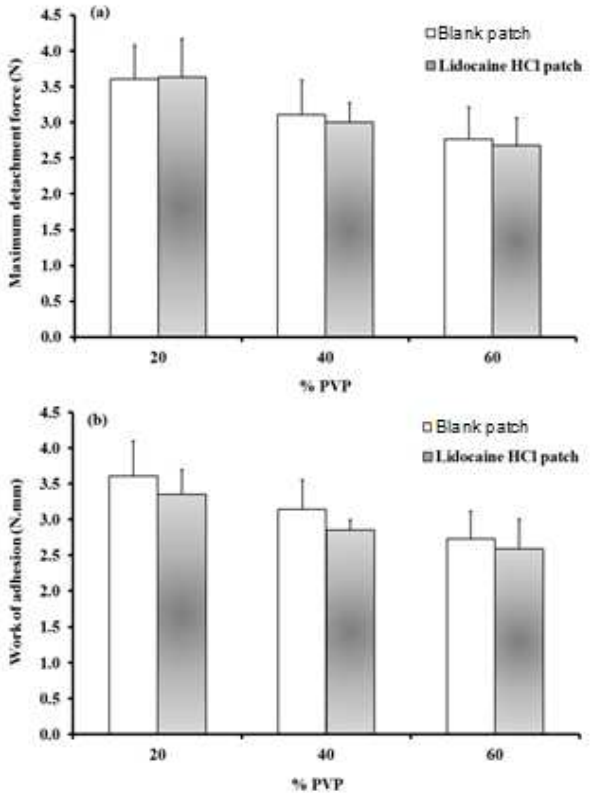

Fig. 8: Effects of PVP concentration on maximum detachment force (a) and work of adhesion (b) of blank patches and lidocaine HCl patches (mean±SD, *n* = 5)

***In vitro* permeation**

In vitro permeation study is one of the important tools to predict how the drug is going to behave *in vivo*. In the present study, *in vitro* permeation study was performed using porcine esophageal mucosa as permeation barrier because it has lipid composition which was comparable to that of the porcine buccal mucosa, but required a simpler preparation method [31]. The cumulative amount of drug permeated per centimetre squared was plotted against time as shown in fig. 9. As observed that the pattern of lidocaine HCl permeation started with an initial fast permeation followed by a slower permeation rate. The steady-state permeation fluxes were calculated from the slope of a linear portion of the curve using the zero-order and Higuchi models as shown in table 2. It was found that the initial permeation rates fit well with the zero-order model (equation 1), with *R2*>0.98. Based on the zero-order model, lidocaine HCl permeation rates ranged from 8.8±1.3 to 10.2±1.8 µg/cm2/min. Insignificant difference between the initial permeation fluxes from lidocaine HCl patches prepared with different PVP concentrations was observed (P>0.05). It was noted that, irrespective of the PVP concentrations in the polymer matrix, the cumulative permeation rates in the first 120 min of these lidocaine HCl patches were comparable; after that, the permeation rates gradually differed. At 240 min, the cumulative permeation from LDC-P3 which was prepared with 60% PVP was significantly lower than that from LDC-P1 which was prepared with 20% PVP. These might be attributed to the higher hydrophilicity and swelling capacity of the patch prepared

with 60% PVP. When the PVA-PVP layer is placed in contact with the mucosa, the drug compound migrates through the polymer and partitions across the interface of polymer/mucosa, which consequently migrates into the mucosa. The initial fast permeation may be attributed to the rapid diffusion of the drug to the surface of the film [16]. With time, swelling of polymer matrix occurred and varied the entanglement of polymeric pathways to control the drug diffusion from the matrix. Extensive swelling of the PVP contained in LDC-P3 might create a thick gel barrier, leading to increasing in mean diffusional path length. In addition, similar to transdermal delivery, the transmucosal delivery is a phenomenon governing the permeation properties and partitioning into the skin of drug and the drug release from the polymer matrix. Lidocaine HCl is a hydrophilic drug with Log $P \leq 0$ [23]. The fact that the latter showed slower permeation of drug from LDC-P3 compared to that of LDC-P1 patches could also be explained by the higher affinity of lidocaine HCl to the hydrated PVP, which lowered the tendency of lidocaine HCl to migrate and part into the mucosa.

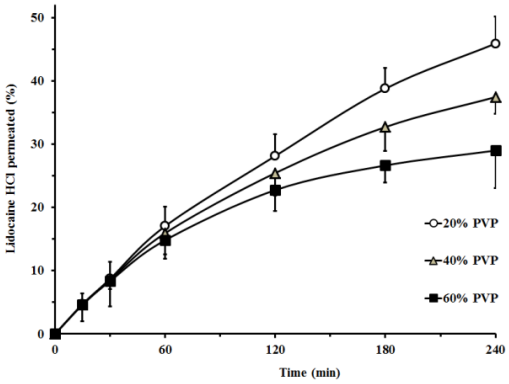

Fig. 9: Effect of PVP concentration on lidocaine HCl permeation from patches across the esophageal mucosal membrane (mean±SD, *n* = 3)

Table 2: Permeation characteristics of lidocaine HCl patches containing difference concentration of PVP

Formulation	Lidocaine HCl permeation rate*		Lidocaine HCl permeated at 240 min (µg/cm2) [a]
	K_0 (µg/cm2/min)[a]	K_H (µg/cm2/min1/2)[a]	
LDC-P1	10.2±1.8 (*R2* = 0.999)	76.5±15.1 (*R2* = 0.945)	1653.9±155.0
LDC-P2	9.5±2.2 (*R2* = 0.981)	71.9±20.0 (*R2* = 0.905)	1349.2±96.3
LDC-P3	8.8±1.3 (*R2* = 0.993)	67.3±10.1 (*R2* = 0.947)	1044.5±213.8

*calculated from 0 to 60 min [a]mean±SD, *n* = 5.

CONCLUSION

In the present study, mucoadhesive patches fabricated with PVA/PVP for buccal delivery of a hydrophilic compound were prepared and evaluated. Effects of PVP content in the PVA/PVP matrix on the mechanical, mucoadhesive and permeation properties were demonstrated. Incorporation of PVP in PVA/PVP matrix caused the decrease of crystallization degree of PVA, resulting in the decreased strength of polymeric matrix and mucoadhesive property of patches. Using lidocaine HCl as a model drug, lidocaine HCl was present as a molecular dispersion state in PVA/PVP matrices. The dissolved hydrophilic drug affected the mechanical property of patch. *In vitro* permeation results showed the insignificant effect of PVA/PVP ratio on the initial permeation fluxes across the mucosa of lidocaine HCl from the patches.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors report no conflicts of interest

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