CHAPTER IV
RESULTS AND DISCUSSION

The main goal of this work was to develop lidocaine mucoadhesive patch, consisting of a drug matrix layer, mucoadhesive layer and backing layer (figure 13). This structural design was expected to provided drug delivery in unidirectional to the mucosa and to avoid loss of drug due to wash-out by saliva. To avoid the toxicity of organic solvents, HPMC E15, HPC, chitosan and carbolpol 934P were chosen as polymers. Several researchers have used these polymers as vehicle for intraoral mucoadhesive films (Claus-Michael, et al., 1992, Hirokazu, et al., 2001 and Jian-Hwa, 1994). EC, being hydrophobic, has recently been reported to be an excellent backing material, given its low water permeability and moderate flexibility (Jian-Hwa and Cooklock, 1996).

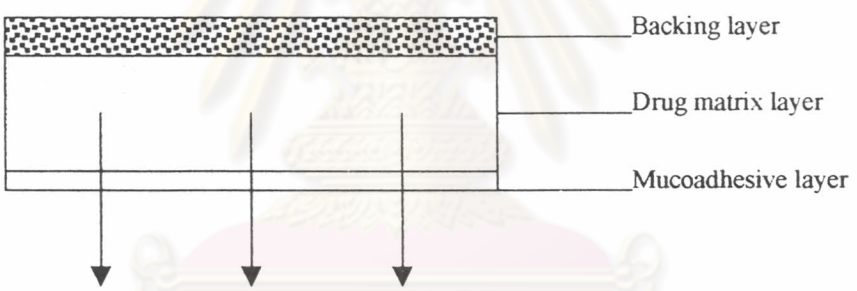


Figure 13 The structure of mucoadhesive patches

1. Physical characteristics of the lidocaine films.

The films were prepared by using casting method due to the ease of preparation with simple laboratory equipment. The components are listed in table 1 and 2. The duration to prepare the films was long of at least 12-20 hours. This result suggested that other accessible apparatus particularly a vacuum hot-air oven might be taken into consideration as an alternative for drying the films.

The physical appearances of the mucoadhesive films are shown in table 7 and 8 and figures 14, 15 and 16. Table 7 showed the physical characteristic of lidocaine base mucoadhesive film that all of them were translucent. It was likely that lidocaine base could not be completely dissolved in the water solution so that it was prepared as fine dispersion, after drying, the patches became tranlucent. HPMC films were glossy, and easy to peel off from glass plates but the lidocaine base film was less flexible than the salt film. HPC films was translucent, glossy, highly sticky and difficult to peel off whereas carbopol films was similar to the HPC film but more difficult to peel off than HPC film. Chitosan films were yellowish, translucent, not so glossy, brittle and difficult to peel off. Table 8 showed the physical characteristic of lidocaine HCl mucoadhesive film that all of them were transparent except chitosan film. Similar to lidocaine base films, the HPMC films of lidocaine HCl were glossy, flexible and easy to peel off from glass plates while HPC and carbopol 934P films were transparent, glossy, highly sticky and difficult to peel off. A previous investigation also reported that HPC could not form lidocaine HCl mucoadhesive film because of it's stickiness (Yu, et al., 1997). Chitosan films were yellowish, translucent, glossy, brittle and difficult to peel off.

The physical appearance of the obtained mucoadhesive film formulations depended mainly on the nature of the raw materials, particularly their color and water solubility. Chitosan is yellowish while the cellulose derivatives are almost white powder. In a previous study that screened for mucoadhesive properties by measuring the force of detachment revealed that chitosan was fairly mucoadhesive and carbopol had excellent mucoadhesive properties (Claus-Michael, et al., 1992). Another study used carbopol and HPC-H to develop a dosage form of local anesthetic for toothache containing lidocaine and the dosage form struck to the human gingival and afforded

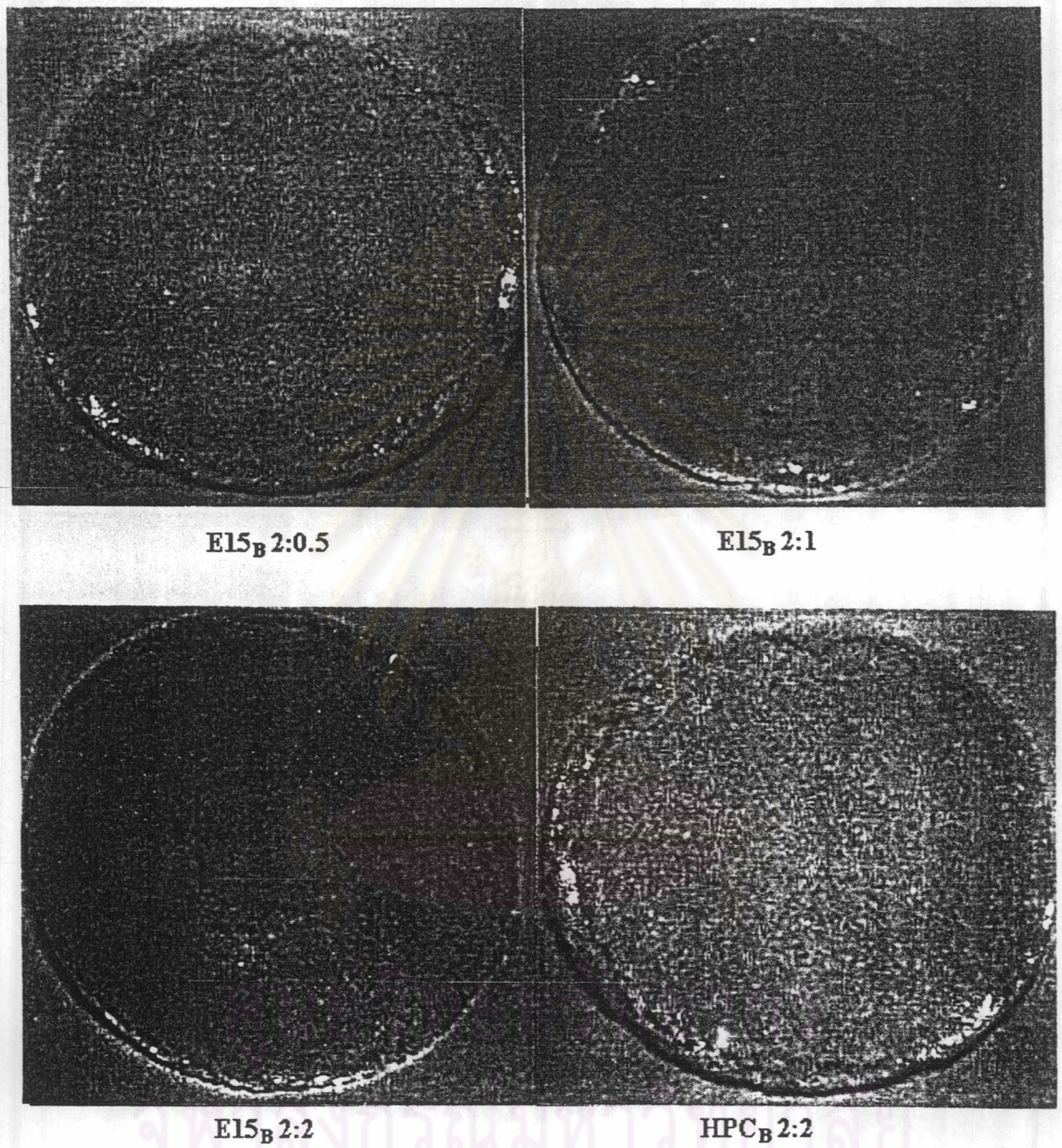


Figure 14 Physical appearance of lidocaine base by using HPMC and HPC

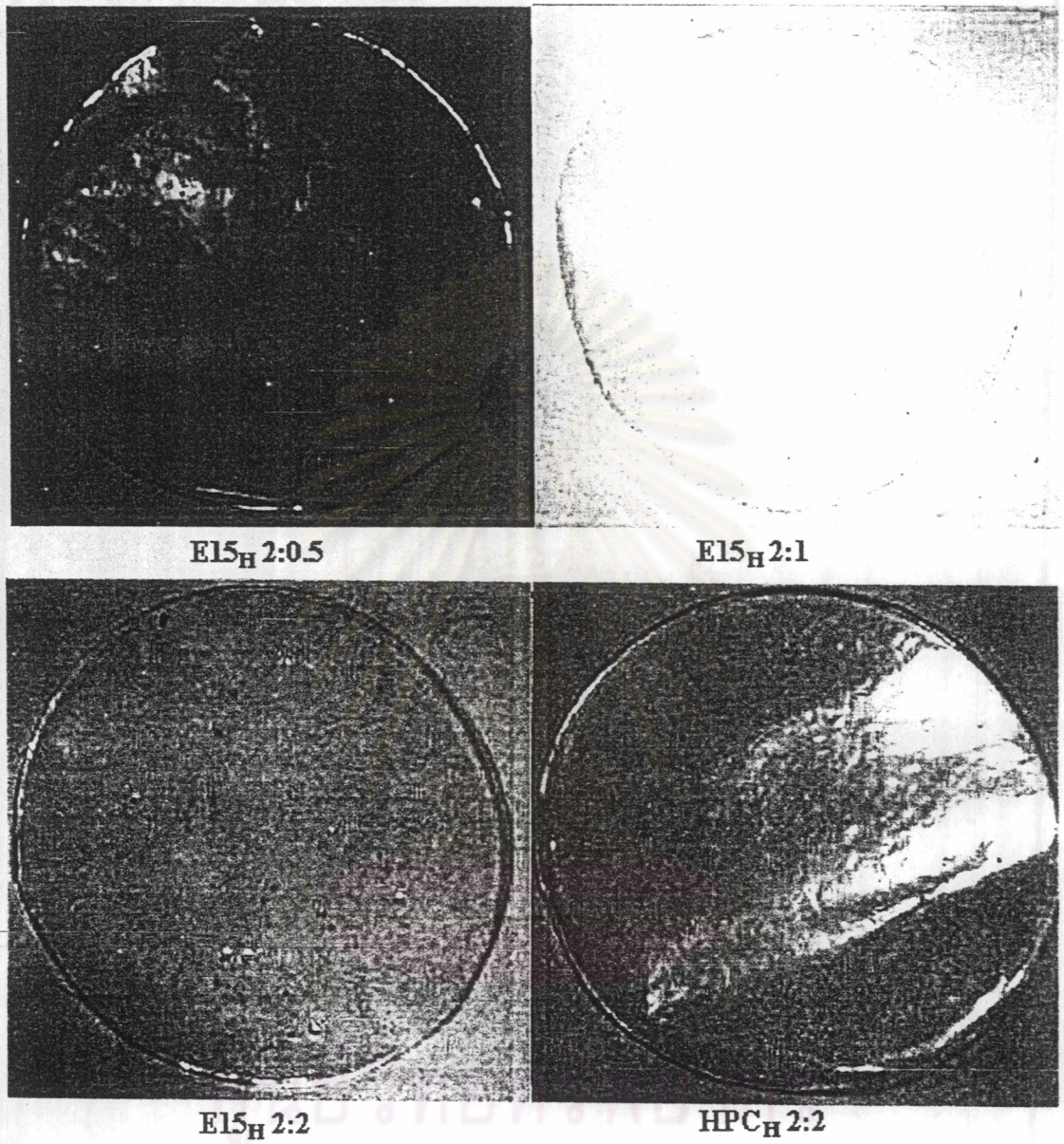


Figure 15 Physical appearance of lidocaine HCl films by using HPMC and HPC

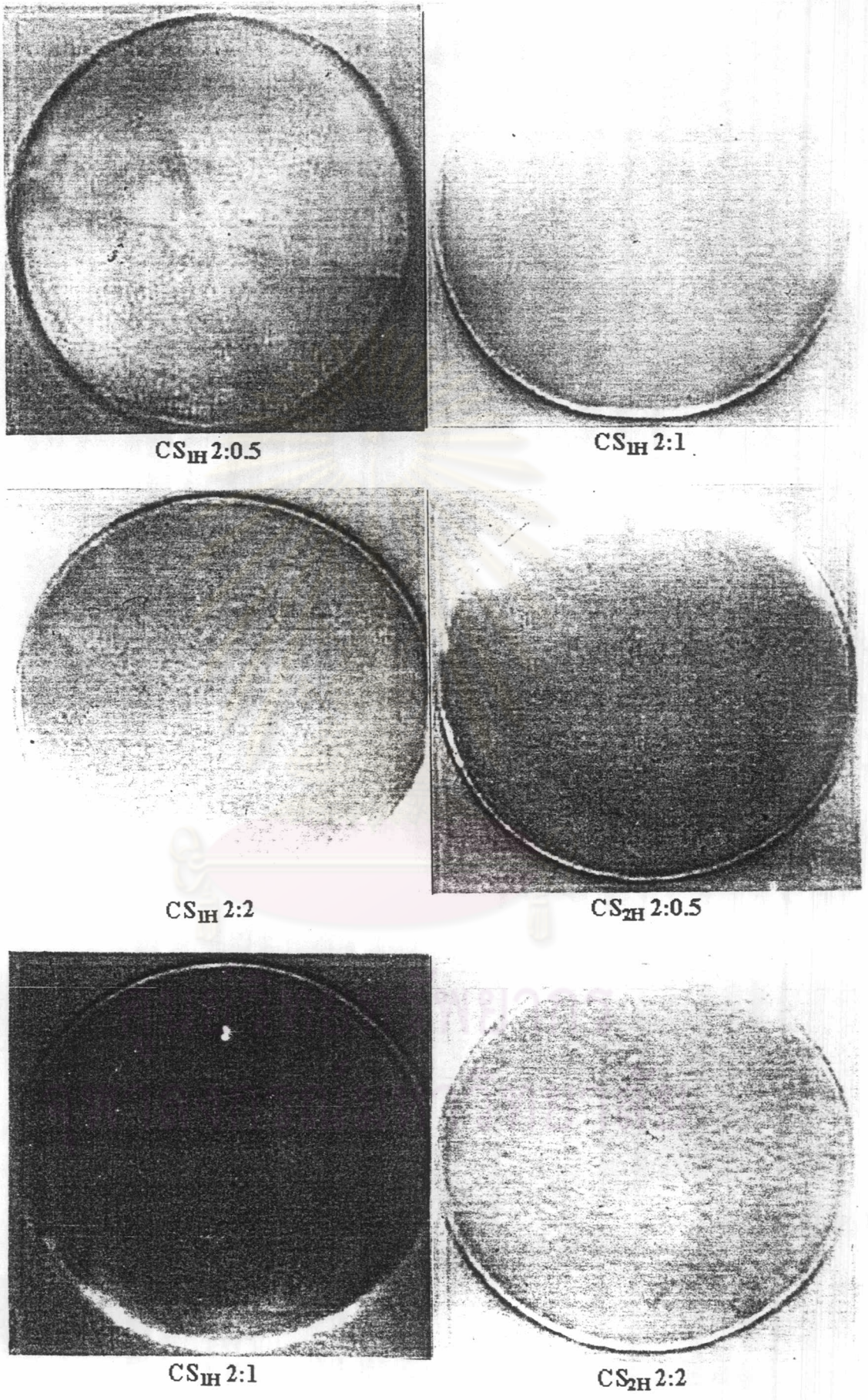


Figure 16 Physical appearance of lidocaine HCl films by using chitosan

prolonged action (Ishida, et al., 1981). HPMC film was easier to peel off from the glass plate than the others in both lidocaine HCl and base form. Moreover HPMC was nonionic polymers that would not interact with the drug and it had been reported that the drug permeation rate from HPMC was higher than from chitosan film (Kwabana, et al., 2001). Therefore HPMC E15 films were further investigated.

Table 7 Physical characteristics of lidocaine base mucoadhesive films

Formulas	Transparency	Glossiness	Flexibility	Stickiness	Ease of peeling
$E15_B$ 2:0.5	-	++	+	-	+++
$E15_B$ 2:1	-	++	++	-	++++
$E15_B$ 2:2	-	++	++	-	++++
HPC_B 2:0.5	-	++	++++	+++	-
HPC_B 2:1	-	++	++++	++++	-
HPC_B 2:2	-	++	++++	++++	+
CS_{1B} 2:0.5	-	-	-	+++	-
CS_{1B} 2:1	-	-	-	+++	-
CS_{1B} 2:2	-	-	-	+++	-
CS_{2B} 2:0.5	-	-	-	+++	-
CS_{2B} 2:1	-	-	-	+++	-
CS_{2B} 2:2	-	-	-	+++	-
CB_B 2:0.5	-	-	-	+++	-
CB_B 2:1	-	++	++++	++++	-
CB_B 2:2	-	++	++++	++++	-

The symbol of (+) and (-) showed the appearance and no appearance, respectively. The number of the symbol of (+) showed a degree of the appearance.

Table 8 Physical characteristics of lidocaine HCl mucoadhesive films

Formulas	Transparency	Glossiness	Flexibility	Stickiness	Ease of peeling
$E15_H$ 2:0.5	+++	++	++	+	+++
$E15_H$ 2:1	++++	+++	+++	-	++++
$E15_H$ 2:2	++++	+++	+++	-	++++
HPC_H 2:0.5	++++	+++	++++	++++	-
HPC_H 2:1	++++	++++	++++	++++	-
HPC_H 2:2	++++	++++	++++	+++	+
CS_{1H} 2:0.5	-	-	-	+++	++
CS_{1H} 2:1	-	-	-	+++	++
CS_{1H} 2:2	-	-	-	+++	++
CS_{2H} 2:0.5	-	-	-	+++	++
CS_{2H} 2:1	-	-	-	+++	++
CS_{2H} 2:2	-	-	-	+++	++
CB_H 2:0.5	+++	+++	++++	++++	-
CB_H 2:1	++++	+++	++++	++++	-
CB_H 2:2	++++	+++	++++	++++	-

The symbol of (+) and (-) showed the appearance and no appearance, respectively. The number of the symbol of (+) showed a degree of the appearance.

Table 9 The formulations of lidocaine base patches using HPMC as mucoadhesive polymers

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Lidocaine base (g)	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
HPMC E15 (g)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
PEG 400 (g)	-	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.50
PG (g)	-	-	0.25	0.50	0.75	1.00	1.25	1.50	1.75	2.00	-	0.25	0.50	0.75	1.00	1.25	1.50	1.75	2.00	-
Purified water qs. (g)	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00
	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
Lidocaine base (g)	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
HPMC E15 (g)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
PEG 400 (g)	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	3.00	3.00	3.00
PG (g)	0.25	0.50	0.75	1.00	1.25	1.50	1.75	2.00	-	0.25	0.50	0.75	1.00	1.25	1.50	1.17	2.00	-	0.25	0.50
Purified water qs. (g)	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00
	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55					
Lidocaine base (g)	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00					
HPMC E15 (g)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00					
PEG 400 (g)	3.00	3.00	3.00	3.00	3.00	3.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00					
PG (g)	0.75	1.00	1.25	1.50	1.75	2.00	-	0.25	0.50	0.75	1.00	1.25	1.50	1.75	2.00					
Purified water qs. (g)	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00					

Table 10 The formulations of lidocaine HCl patches using HPMC as mucoadhesive polymers

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Lidocaine HCl (g)	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
HPMC E15 (g)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
PEG 400 (g)	-	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.50
PG (g)	-	-	0.25	0.50	0.75	1.00	1.25	1.50	1.75	2.00	-	0.25	0.50	0.75	1.00	1.25	1.50	1.75	2.00	-
Purified water qs. (g)	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00
	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
Lidocaine HCl (g)	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
HPMC E15 (g)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
PEG 400 (g)	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	3.00	3.00	3.00
PG (g)	0.25	0.50	0.75	1.00	1.25	1.50	1.75	2.00	-	0.25	0.50	0.75	1.00	1.25	1.50	1.17	2.00	-	0.25	0.50
Purified water qs. (g)	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00
	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55					
Lidocaine HCl (g)	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00					
HPMC E15 (g)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00					
PEG 400 (g)	3.00	3.00	3.00	3.00	3.00	3.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00					
PG (g)	0.75	1.00	1.25	1.50	1.75	2.00	-	0.25	0.50	0.75	1.00	1.25	1.50	1.75	2.00					
Purified water qs. (g)	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00					

From tables 7 and 8, both lidocaine base and lidocaine HCl films by using HPMC as polymer in the ratio of drug to polymer 2:1 and 2:2 seemed to give better films than the others and could be removed easily from the glass plate but the formulation of lidocaine to polymer 2:1 were easier to prepare than that of ratio 2:2. The ratio 2:1 was the lowest ratio that polymer could be incorporated with the drug, remove air bubble faster and take less time to dry than the ratio 2:2. Therefor this formulation was chosen for further develop.

HPMC films at the ratio of drug to polymer 2:1 was chosen in both lidocaine base and HCl films. Both formulas could form film and easily be removed from glass plates. The lidocaine base film was translucent and brittle whereas the lidocaine HCl film was transparent and not flexible enough. After that the film was crystallized when kept in the desiccator about 24 hours. This was similar to a previous study that the lidocaine was crystallized on the surface of films (Yu, et al., 1997). Therefor these formulations were chosen to be further developed.

Tables 9 and 10 showed the lidocaine film at fixed ratio of drug and HPMC 2:1, PEG 400 and propylene glycol were added at proportions of 0 to 4 g and 0 to 2 g respectively. Table 11 and 12 showed the physical characteristics of lidocaine base films and lidocaine HCl mucoadhesive films after kept in desiccator for 12 hours. From the ratio of lidocaine: HPMC:PEG400 at 2:1:0 to 4, it was found that the crystallization of lidocaine film was decreased when increasing the amount of PEG400. Both lidocaine base film and lidocaine HCl film did not show crystallization on the surface at the ratio of lidocaine:HPMC:PEG400 at 2:1:4 and the film became more flexible than the others. In addition, lidocaine base could be more dissolved with PEG. This was consistent to the reveals that PEG exhibits useful properties such as low toxicity and immunogenicity. The hydrophillic parts could form a water-soluble shell and the inner core created by the aggregation of hydrophobic segments could accommodate hydrophobic drugs. Its functional group (-OH) on the surface proved useful for coupling molecules of the drug and holding drug molecules and increasing the water solubility of the drug. PEG and propylene glycol have also been used as a good plasticizer in the polymer industry (M. Zhang, et al., 2002). PEG400 had been reported that it could be used as an enhancer of drug release. Moreover it was not only

to improve wettability but also to the amorphism of lidocaine base film by using the ratio of lidocaine and PEG 400 at 2:2 to 4 (Kazumi, et al., 1995). Therefor drug:HPMC:PEG 400 at this ratio was chosen for further development.

Propylene glycol was used as platicizer to make the film more flexible. Table 13 and 14 showed the physical characteristic of lidocaine base mucoadhesive films at the ratio of lidocaine base:HPMC:PEG400:PG at 2:1:4:1 to 2. It found that increasing the propylene glycol the film became more flexible. Lidocaine base film and lidocaine HCl film which had the ratio of lidocaine:HPMC:PEG:PG at 2:1:4:1.5 and 2:1:4:1, respectively, gave the best film because it was easily to peel off from the glass plate, not sticky and flexible. This result was consistent with the reveal that propylene glycol has become widely used as a co-solvent, plasticizer and preservative in topical and semisolid by using 15-80 percent for co-solvent and 15-30 percent of the preparation for plasticizer and preservative. It is a better general solvent than glycerin and dissolves a wide variety of compounds such as corticoids, phenols, sulfa drugs and many local anesthetics. Propylene glycol is acceptable to the Food and Drug administration for use in foods and cosmetics. The Council on Pharmacy and Chemistry of the American Medical Association has also considered it as a harmless ingredient for pharmaceutical products. No ills effect from its industrial use have been reported (Kibbe, 2000).

From the result, this related to the 53rd formula of lidocaine base film and the 51st formula of lidocaine HCl film in table 9 and 10 that had lidocaine: HPMC:PEG400:PG at 2.:1:4:1.5 and 2:1:4:1 respectively. Therefor the 53rd formula of lidocaine base film and the 51st formula of lidocaine HCl film were chosen to be the drug matrix layer.

Table 11 Physical characteristic of lidocaine base mucoadhesive films in the ratio of lidocaine base:HPMC:PEG400 at 2:1:0 to 4 after kept in desiccator for 12 hours.

Lidocaine base: HPMC:PEG400	Transparency	Glossiness	Flexibility	Stickiness	Crystallization on the surface of film
2:1:0	-	++	++	-	++++
2:1:1	-	++	++	-	+++
2:1:1.5	-	++	++	-	+++
2:1:2	-	++	++	-	+++
2:1:3	-	+++	+++	-	++
2:1:4	-	++++	+++	-	-

The symbol of (+) and (-) showed the appearance and no appearance, respectively.
The number of the symbol of (+) showed a degree of the appearance.

Table 12 Physical characteristic of lidocaine HCl mucoadhesive films in the ratio of lidocaine base:HPMC:PEG400 at 2:1:0 to 4 after kept in desiccator for 12 hours.

Lidocaine HCl: HPMC:PEG400	Transparency	Glossiness	Flexibility	Stickiness	Crystallization on the surface of film
2:1:0	-	++	++	-	++++
2:1:1	+	++	++	-	++++
2:1:1.5	++	++	++	-	+++
2:1:2	+++	++	++	-	+++
2:1:3	+++	++	+++	-	++
2:1:4	++++	+++	+++	-	-

The symbol of (+) and (-) showed the appearance and no appearance, respectively.
The number of the symbol of (+) showed a degree of the appearance.

Table 13 Physical characteristic of lidocaine base mucoadhesive films in the ratio of lidocaine base:HPMC:PEG400:PG at 2:1:4:1 to 2 after kept in desiccator for 12 hours.

Lidocaine base: HPMC:PEG400:PG	Transparency	Glossiness	Flexibility	Stickiness	Ease of peeling
2:1:4:0	-	+++	+++	-	++++
2:1:4:0.25	-	+++	+++	-	++++
2:1:4:0.5	-	+++	+++	-	++++
2:1:4:0.75	-	+++	+++	-	++++
2:1:4:1	-	+++	+++	-	++++
2:1:4:1.25	-	+++	+++	-	++++
2:1:4:1.50	-	+++	++++	-	++++
2:1:4:1.75	-	+++	++++	+	++
2:1:4:1.2	-	+++	++++	+	++

The symbol of (+) and (-) showed the appearance and no appearance, respectively.
The number of the symbol of (+) showed a degree of the appearance.

Table 14 Physical characteristic of lidocaine HCl mucoadhesive films using ratio of lidocaine HCl:HPMC:PEG400:PG at 2:1:4:1 to 2.0 after kept in desiccator for 12 hours.

Lidocaine HCl: HPMC:PEG400:PG	Transparency	Glossiness	Flexibility	Stickiness	Ease of peeling
2:1:4:0	++++	+++	+++	-	++++
2:1:4:0.25	++++	+++	+++	-	++++
2:1:4:0.5	++++	+++	+++	-	++++
2:1:4:0.75	++++	+++	+++	-	++++
2:1:4:1	++++	+++	++++	-	++++
2:1:4:1.25	++++	+++	++++	+	+++
2:1:4:1.50	++++	+++	++++	+	+++
2:1:4:1.75	++++	+++	++++	+	+++
2:1:4:2	++++	+++	++++	++	++

The symbol of (+) and (-) showed the appearance and no appearance, respectively.
The number of the symbol of (+) showed a degree of the appearance.

2. Physical characteristic and adhesive of backing

Ethyl cellulose is one of the polymers that was well accepted for moisture protection and taste masking applications. It is hydrophobic and has been reported to be an excellent backing material, given low water permeability and moderate flexibility (Yi-Ming, et al., 1999). In this study, triacetin was used as plasticizer to improve its thermal behavior. Triacetin has an affinity for water. It induced slight water absorption for ethyl cellulose while other plasticizers such as dibutyl phthalate, caused little water uptake (Kiikka, et al., 1996). Therefore triacetin in ethyl cellulose film could uptake some water from the drug matrix solution. Thus after drying of the drug matrix, both layers would stick or interlock with each other. Table 15 showed the physical characteristic free film of ethyl cellulose and triacetin. All preparations were transparent and glossy. The flexibility increased when increasing the amount of plasticizer. By using plasticizer, it would decrease the glass transition temperature of ethyl cellulose, then the film could be more flexible. The formulations B1-4 and B5-8 which had ethyl cellulose 1% w/v and 2% w/v respectively were sticky and difficult to be removed from glass plates. Formulations B1-8 had the amount of polymer less than formulation B9-12 in the same volume, This might produce the films too thin to be peeled off whereas all films of formulation B9-12 which had ethyl cellulose 3%w/v can be removed easily.

Formulation B11 which had the ratio of ethyl cellulose to triacetin 3:2 was more flexible than formulations B9 and B10. Formulation B12 was the most flexible but difficult to peel off. The ratio of ethyl cellulose and triacetin 3:2 was the optimum ratio. The thickness of the film was about 0.043 mm. Therefore this ratio was chosen for further investigation.

Table 15 Physical characteristics of backing

Formulas	Transparency	Glossiness	Flexibility	Stickiness	Ease of peeling
B1	++++	+++	-	++++	-
B2	++++	+++	++	++++	-
B3	++++	+++	++++	++++	-
B4	++++	+++	++++	++++	-
B5	++++	+++	-	+++	-
B6	++++	+++	+++	+++	-
B7	++++	+++	+++	+++	-
B8	++++	+++	++++	+++	-
B9	++++	+++	-	+	++
B10	++++	+++	++	+	++
B11	++++	+++	+++	+	+++
B12	++++	+++	++++	++	+

B = formulations of backing

The symbol of (+) and (-) showed the appearance and no appearance, respectively. The number of the symbol of (+) showed a degree of the appearance.

After the preparation of the backing film, lidocaine solution was poured onto the dried backing film in the glass plate and dried. It was found that the film separated from each other. This might be that the prepared ethyl cellulose solution was completely soluble in ethanol and the air bubble was removed before drying so that the dried film had a smooth surface and there was no adhesion between the backing and the matrix layer. This result was consistent with the study of Jie, et al. that ethyl cellulose was non bioadhesive (Jie, et al., 2002). Therefore, inorganic substances were added in the backing solution in order to make the backing layer rough and be able to interlock to the drug matrix layer.

Inorganic substances such as aluminium hydroxide, dicalcium phosphate and calcium carbonate were selected to be added in the backing solution. These inorganic substances are insoluble in both ethanol and aqueous solvent that were the solvents of

backing layer and drug matrix layer respectively and they was normally used as abrasives in toothpaste (Eric, 1994).

The adhesiveness of backing and free film of HPMC was determined in term of detachment force by measuring the force required to pull the free film from the backing as shown in table 16. The formulation that had aluminium hydroxide which had particle size about 0.5 μm showed no adhesion between the backing and HPMC film. It might be due to the aluminium hydroxide particles were too fine and closed to each other so that it had less space to interlock with HPMC film. The formulation that had calcium carbonate 0.3%w/v showed more adhesiveness than the others. The statistic of one-way ANOVA showed that at 0.3%w/v of calcium carbonate gave significant difference of adhesive force from 0.3%w/v of dicalcium phosphate ($p < 0.05$). Figures 17, 18 and 19 showed the SEM photomicrographs of aluminium hydroxide, calcium carbonate and dicalcium phosphate respectively. Calcium carbonate had particle size less than 44 μm and cohesively flowable while dicalcium phosphate had less than 180 μm and 27.3 g/s of flowability (Kibbe, 2000). In addition the particle of calcium carbonate was needle shaped and had rough surface than dicalcium phosphate as compared in figure 17 and 18 which it could interlock better with the matrix layer. Increasing the amount of dicalcium phosphate and calcium carbonate up to 0.4%w/v showed decrease the adhesive force. This might be due to the particles were too close with each other and had less space to interlock with the matrix layer. Therefor calcium carbonate of 0.3%w/v was chosen.

Table 16 Adhesive of backing and free film of HPMC

Iorganic substance	% of inorganic substance per 100 ml of backing solution	Detachment force (N/cm^2) Mean ± SD
Aluminium hydroxide	0.1	-
	0.2	-
	0.3	-
	0.4	-
Dicalcium phosphate	0.1	5.193 ± 0.295
	0.2	6.297 ± 0.469
	0.3	6.607 ± 0.225
	0.4	3.027 ± 0.242
Calcium carbonate	0.1	5.629 ± 0.365
	0.2	6.434 ± 0.166
	0.3	7.759 ± 0.795
	0.4	3.551 ± 0.288

(-) the film cannot be removed from the plate

3. Physical characteristics and mucoadhesiveness of mucoadhesive layer

From table 7 and 8, although carbopol and HPC film had similar sticky and difficult to peel off from the glass plate more than the other films but carbopol had been reported to be used as bioadhesive of choice for the formulation. This result was consistent with the report that polycarbophil mucoadhesive properties reported in term of detachment (N/m^2) (Claus-Michael, et al., 1992) had detachment force more than chitosan, HPMC, CMC and xanthan gum so that carbopol was chosen to be further used as mucoadhesive layer.

The preparation of 1%w/v of carbopol was chosen to be evaluated because it could swell, completely easy to eliminate the bubble, easy to pour on the surface of free film better than the others. The 2%w/v and 3%w/v of carbopol obtained rough films because they had some of polymer that could not hydrate and swell completely in the solution and difficult to remove the air bubble.

Table 17 showed the results of mucoadhesive force. Carbopol 6 ml/plate was the minimum amount that produced sticky and mucoadhesive film. Addition of carbopol 4-5 ml into the formulation exerted mucoadhesive force of about 6 N/cm^2 and 6-10 ml, about 7 N/cm^2. It might be indicated that when pouring carbopol 4-5 ml the mucoadhesive solution which was aqueous solution might dissolve some polymer from interfacial of the HPMC film to mucoadhesive layer and might decreased their adhesive property. Increasing the amount of mucoadhesive solution, would make this layer thicker. The dissolved polymer from the interfacial of HPMC film layer could not sufficiently interfere the interfacial of mucoadhesive layer that contacted with the tested surface so more adhesion was obtained. Therefor the formulation containing carbopol 6 ml/plate was chosen. Similar study on bioadhesive strength of buccal patches revealed that the bioadhesive strength of buccal patches of buprenophine was increased with increasing the thickness up to a maximum value. The phenomenon could be explained by an alternative of the dissipation energy of patch polymers of increasing thickness under conditions of viscoelastics and plastic deformation and base on the diffusion theory of polymer adhesive was that the increased mucoadhesive was due to the inter-penetration of macromolecular chains at the polymr-polymer interface (Jian-Hwo, 1994).

Table 17 Mucoadhesiveness of mucoadhesive layer (n=3)

Amount of carbopol 1%w/v (ml/plate)	Mucoadhesive force (N/cm^2)
	Mean ± SD
4	4.591±0.578
5	6.075±0.379
6	7.184±0.655
7	7.182±1.157
8	7.220±1.056
9	6.927±0.677
10	7.781±0.410

Figure 17 SEM photomicrographs of aluminium hydroxide (x 5,000)

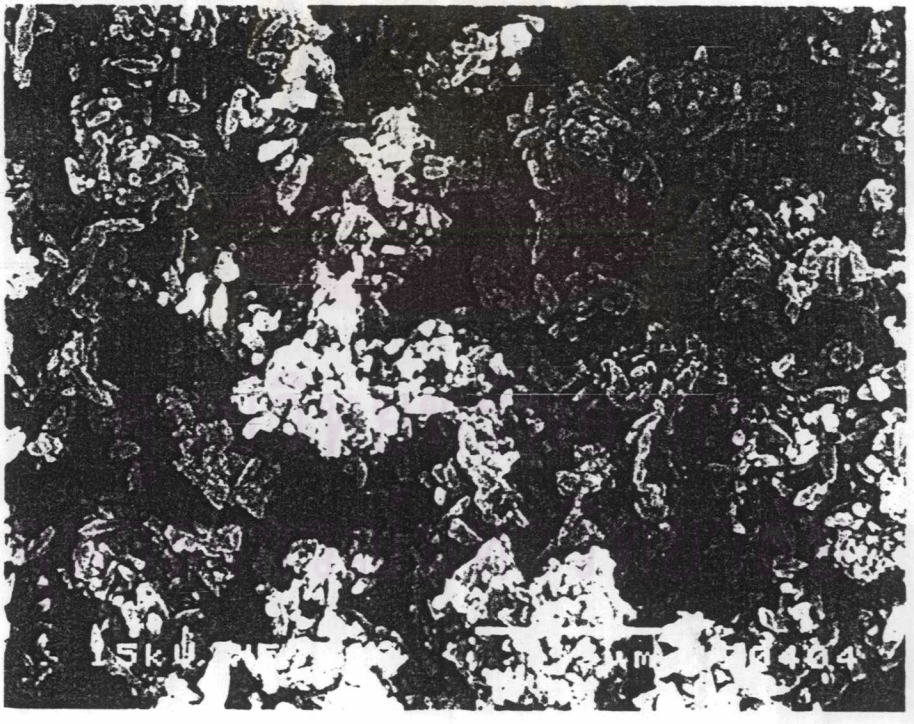


Figure 18 SEM photomicrographs of calcium carbonate (x 5,000)

Figure 19 SEM photomicrographs of dicalcium phosphate (x 1,000)

4. Thickness of mucoadhesive films

The results from the thickness measurement are presented in Appendix C. The average thickness of the prepared mucoadhesive patches is given in tables 18 and 19. At the same ratio of HPMC films, the lidocaine base film was thicker than lidocaine HCl films. This might be caused of that lidocaine base film had some undisolved fine particle of the drug and had some pore in the film while lidocaine HCl could be dissolved completely in the solution and gave smoother film than base patch. When increasing the quantity of polymer the thickness of both base and salt films was increased. The formulas HPC_B 2:2, $E15_H$ 2:0.5, $E15_H$ 2:1, $E15_H$ 2:2 and HPC_H 2:2 were about 0.4 mm. The thickness of films from formulas $E15_B$ 2:0.5 and $E15_B$ 2:1 were about 0.7 mm. The thickness of films from formulas $E15_B$ 2:2, CS_{1H} 2:0.5 and CS_{2H} 2:0.5 were about 0.9 mm. And the thickness of films from formulas CS_{1H} 2:1, CS_{1H} 2:2, CS_{2H} 2:1 and CS_{2H} 2:2 were about 1.0 mm.

Table 18 The average thickness of the prepared lidocaine base mucoadhesive patches (n=3, each sample was measured at 5 locations)

Formulas	Thickness ± SD (mm)			
	No.1	No.2	No.3	Mean ± SD
$E15_B$ 2:0.5	0.72 ± 0.05	0.70 ± 0.03	0.73 ± 0.04	0.72 ± 0.04
$E15_B$ 2:1	0.77 ± 0.03	0.80 ± 0.04	0.77 ± 0.07	0.78 ± 0.05
$E15_B$ 2:2	0.96 ± 0.08	1.01 ± 0.12	0.96 ± 0.08	0.98 ± 0.09
HPC_B 2:0.5	-	-	-	-
HPC_B 2:1	-	-	-	-
HPC_B 2:2	0.48 ± 0.05	0.48 ± 0.05	0.48 ± 0.02	0.48 ± 0.04
CS_{1B} 2:0.5	-	-	-	-
CS_{1B} 2:1	-	-	-	-
CS_{1B} 2:2	-	-	-	-
CS_{2B} 2:0.5	-	-	-	-
CS_{2B} 2:1	-	-	-	-
CS_{2B} 2:2	-	-	-	-

Table 18 The average thickness of the prepared lidocaine base mucoadhesive patches (n=3, each sample was measured at 5 locations) (cont.)

Formulas	Thickness ± SD (mm)			
	No.1	No.2	No.3	Mean ± SD
CB_B 2:0.5	-	-	-	-
CB_B 2:1	-	-	-	-
CB_B 2:2	-	-	-	-

(-) The film cannot be removed from the plate

Table 19 The average thickness of the prepared lidocaine HCl mucoadhesive films (n=3, each sample was measured at 5 locations)

Formulas	Thickness±SD (mm)			
	No.1	No.2	No.3	Mean ± SD
$E15_H$ 2:0.5	0.42 ± 0.02	0.41 ± 0.03	0.36 ± 0.02	0.39 ± 0.02
$E15_H$ 2:1	0.48 ± 0.08	0.47 ± 0.06	0.47 ± 0.06	0.48 ± 0.07
$E15_H$ 2:2	0.49 ± 0.07	0.52 ± 0.06	0.47 ± 0.04	0.49 ± 0.06
HPC_H 2:0.5	-	-	-	-
HPC_H 2:1	-	-	-	-
HPC_H 2:2	0.42 ± 0.02	0.41 ± 0.03	0.36 ± 0.02	0.39 ± 0.02
CS_{1H} 2:0.5	0.92 ± 0.05	0.91 ± 0.04	0.93 ± 0.02	0.92 ± 0.04
CS_{1H} 2:1	0.96 ± 0.04	1.03 ± 0.08	1.09 ± 0.10	1.03 ± 0.07
CS_{1H} 2:2	1.06 ± 0.04	1.07 ± 0.03	1.06 ± 0.04	1.06 ± 0.04
CS_{2H} 2:0.5	0.97 ± 0.03	0.92 ± 0.02	0.95 ± 0.04	0.95 ± 0.03
CS_{2H} 2:1	0.96 ± 0.04	1.02 ± 0.04	0.98 ± 0.04	0.99 ± 0.04
CS_{2H} 2:2	1.05 ± 0.17	0.99 ± 0.04	0.97 ± 0.04	1.00 ± 0.09
CB_H 2:0.5	-	-	-	-
CB_H 2:1	-	-	-	-
CB_H 2:2	-	-	-	-

(-) The film cannot be removed from the plate

5. *In-vitro* evaluation of mucoadhesive patches

5.1. Tensile properties

In this investigation, the tensile properties of lidocaine films were studied. The tensile testing provided an indication of strength and elasticity of the film, which could be reflected by tensile strength, Young's modulus and strain. It was suggested that films suitable for intraoral administration had to be preferably strong but flexible.

Tensile properties including, percent strain at point of break, Young's modulus and ultimate tensile strength are presented in tables 20 and 21. The ultimate tensile strength is the ability of a material to resist breaking under tensile stress. At the same ratio of drug to HPMC, lidocaine base film had less ultimate tensile strength than the lidocaine HCl film. It might be that lidocaine base was partially dissolved as fine dispersion in the preparation before drying while lidocaine HCl could be completely dissolved so that lidocaine HCl film would had more density and less porous than the base film. The highest ultimate tensile strength was from HPC film. It was consistent with the physical property of HPC which was soft and tough film had provided. It was likely that the hydroxypropyl constituent groups of HPC contained almost entirely secondary hydroxyls. The secondary hydroxyl present in the side chain was available for further reaction with the oxide, and chaining-out may take place. The formation of side chains with more than one mole of combined propylene oxide resulted in the longer side chains of HPC than other polymer (Rodu, et al., 1998), thus HPC were flexible than the others.

The Young's modulus is the ratio of stress to elastic strain in tension. A high Young's modulus means that the material is rigid. HPMC base films showed the highest value of Young's modulus. The Young's modulus of lidocaine base film at ratio of drug to HPMC 2:1 and 2:2 were significantly different ($p<0.05$) when tested with one-way ANOVA. It might be indicated that increasing the amount of polymer the rigidity of the film would be decreased because the drug could be more dissolved in the polymer and made the film softer. The lidocaine HCl film at ratio of drug to HPMC 2:1 and 2:2 showed less Young's modulas than lidocaine base films. This

indicated similarly as the ultimate tensile strength that lidocaine base had some particles of lidocaine that were undissloved in the films and would made the film more rigid than in lidocaine HCl films. Among lidocaine HCl patches, chitosan MW 50,000, chitosan MW 200,000 and HPMC 2:2 exhibited no significant difference in Young's modulas from each other ($p>0.05$).

Focused on percent strain at point of break, at the same ratio of drug:HPMC, lidocaine salt film exhibited more percent strain at point of break than base film. It might be indicated that lidocaine HCl had more toughness film than lidocaine base film. This result was consistent with the ultimate tensile strength and Young's modulas that the lidocaine base that had fine dispersion might be made the brittle films. In addition, increasing the proportion of all polymers increased the percent strain, it might be caused of increasing polymer, the drug could be more dissolved in the polymer that made the film more dense and tough.

From the result, although HPC and carbopol gave the more flexibles film but they were difficult to be removed from the glass plate while HPMC could form film of both lidocaine base and lidocaine HCl. In lidocaine HCl film, HPMC film had more %strain than chitosan. It was indicated that HPMC had gain more flexible film than chitosan. Moreover it could be removed from the glass plate easily.

Table 20 Tensile properties of lidocaine base mucoadhesive films (n = 6)

Formula	% strain at point of break ± SD	Young's modulus ± SD (MPa)	Ultimate tensile strength ± SD (MPa)
$E15_B$ 2:0.5	-	-	-
$E15_B$ 2:1	4.89 ± 0.67	6.05 ± 0.69	4.43 ± 0.33
$E15_B$ 2:2	7.50 ± 0.81	7.60 ± 0.95	7.42 ± 0.96
HPC_B 2:0.5	-	-	-
HPC_B 2:1	-	-	-
HPC_B 2:2	>10 N	>10 N	>10 N
CS_{1B} 2:0.5	-	-	-
CS_{1B} 2:1	-	-	-
CS_{1B} 2:2	-	-	-

Table 20 Tensile properties of lidocaine base mucoadhesive films (n = 6) (cont.)

CS_{2B} 2:0.5	-	-	-
CS_{2B} 2:1	-	-	-
CS_{2B} 2:2	-	-	-
CB_B 2:0.5	-	-	-
CB_B 2:1	-	-	-
CB_B 2:2	-	-	-

(-) the films cannot be removed from the glass plate

Table 21 Tensile properties of lidocaine HCl mucoadhesive films (n = 6)

Formula	% strain at point of break ± SD	Young's modulus ± SD (MPa)	Ultimate tensile strength ± SD (MPa)
$E15_H$ 2:0.5	4.41 ± 0.61	7.85 ± 1.59	0.10 ± 0.00
$E15_H$ 2:1	168.34 ± 9.12	2.13 ± 0.31	75.54 ± 4.39
$E15_H$ 2:2	249.87 ± 6.20	0.30 ± 0.04	51.65 ± 9.97
HPC_H 2:0.5	-	-	-
HPC_H 2:1	-	-	-
HPC_H 2:2	>10 N	>10 N	>10 N
CS_{1H} 2:0.5	54.22 ± 4.18	0.26 ± 0.04	0.77 ± 0.12
CS_{1H} 2:1	70.03 ± 5.61	0.04 ± 0.01	7.48 ± 7.67
CS_{1H} 2:2	75.18 ± 8.50	0.06 ± 0.01	0.85 ± 0.05
CS_{2H} 2:0.5	66.05 ± 7.00	0.05 ± 0.01	19.92 ± 2.45
CS_{2H} 2:1	74.83 ± 6.97	0.07 ± 0.01	21.73 ± 3.37
CS_{2H} 2:2	84.75± 3.69	0.08 ± 0.01	18.81 ± 0.73
CB_H 2:0.5	-	-	-
CB_H 2:1	-	-	-
CB_H 2:2	-	-	-

(-) the films cannot be removed from the glass plate

5.2. Content uniformity

The results for content uniformity of the patches are presented in Appendix C. The selected formulas were the 53rd formula of lidocaine base film which ratio of

lidocaine base:HPMC:PEG:PG was 2:1:4:1.5 and 51st formula of lidocaine HCl film which ratio of lidocaine HCl:HPMC:PEG:PG was 2:1:4:1. It was seen in table 22 that the concentration of all tested films was within the limit of 95-105% label amount with low %CV.

Table 22 The mean of percent content of lidocaine in the prepared mucoadhesive films (n =10)

Formulas	%Content±SD	%CV
Lidocaine base patch	99.88±1.43	1.43
Lidocaine HCl patch	100.56±1.87	1.86
Dentipatch®	99.08±1.20	1.21

5.3. Surface topography

Figures 20 and 21 showed topography the surface by cross section of lidocaine base and HCl patches. The SEM photomicrographs of lidocaine patches showed that both lidocaine base and lidocaine HCl patches had three layers and Dentipatch® which was a commercial product had two layers. The drug matrix layer of lidocaine base patch and Dentipatch® showed not smooth matrix and had precipitation or aggregation of the particle in their matrix whereas lidocaine HCl patch had smooth matrix. This indicated that in lidocaine HCl patch, the drug was homogeneously dispersed as amorphous or molecular dispersion state. For lidocaine base patch and Dentipatch®, it might be the powder that did not dissolve in the prepared solution, due to the fact that during the preparation of drug matrix solution, some of lidocaine base could not be dissolved and was dispersed in solid form within the solution.

The backing layer of lidocaine base and HCl films had an organic substance to interlock the drug matrix layer whereas Dentipatch® as shown in figure 22 had 2 layers, backing and drug matrix, where the backing layer had some fiber to interlock the drug matrix. The drug matrix layer was not so smooth. It contained some undissolved powder of lidocaine base.

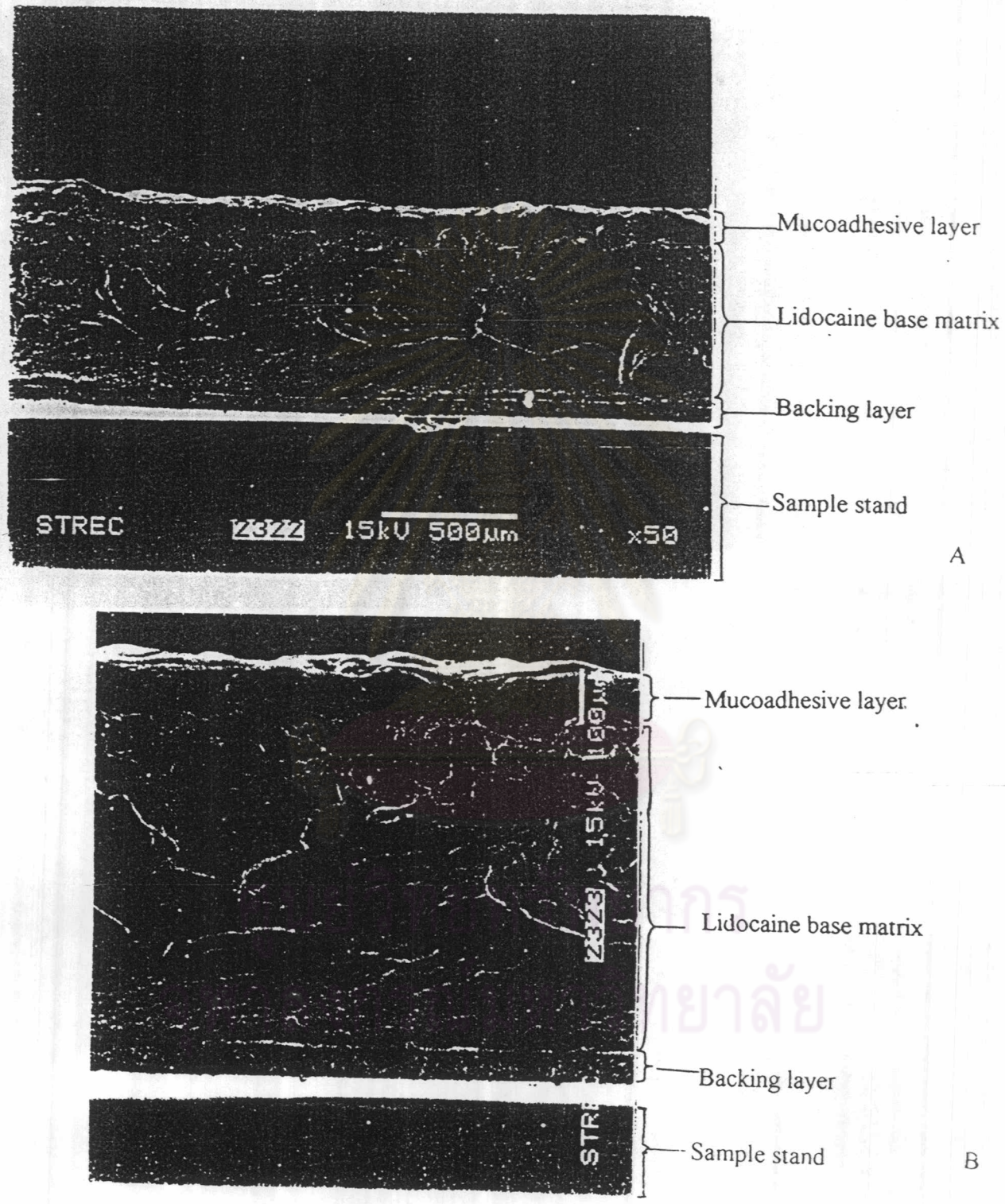


Figure 20 Cross-section of lidocaine base patch (A) x 50 ; (B) x 100

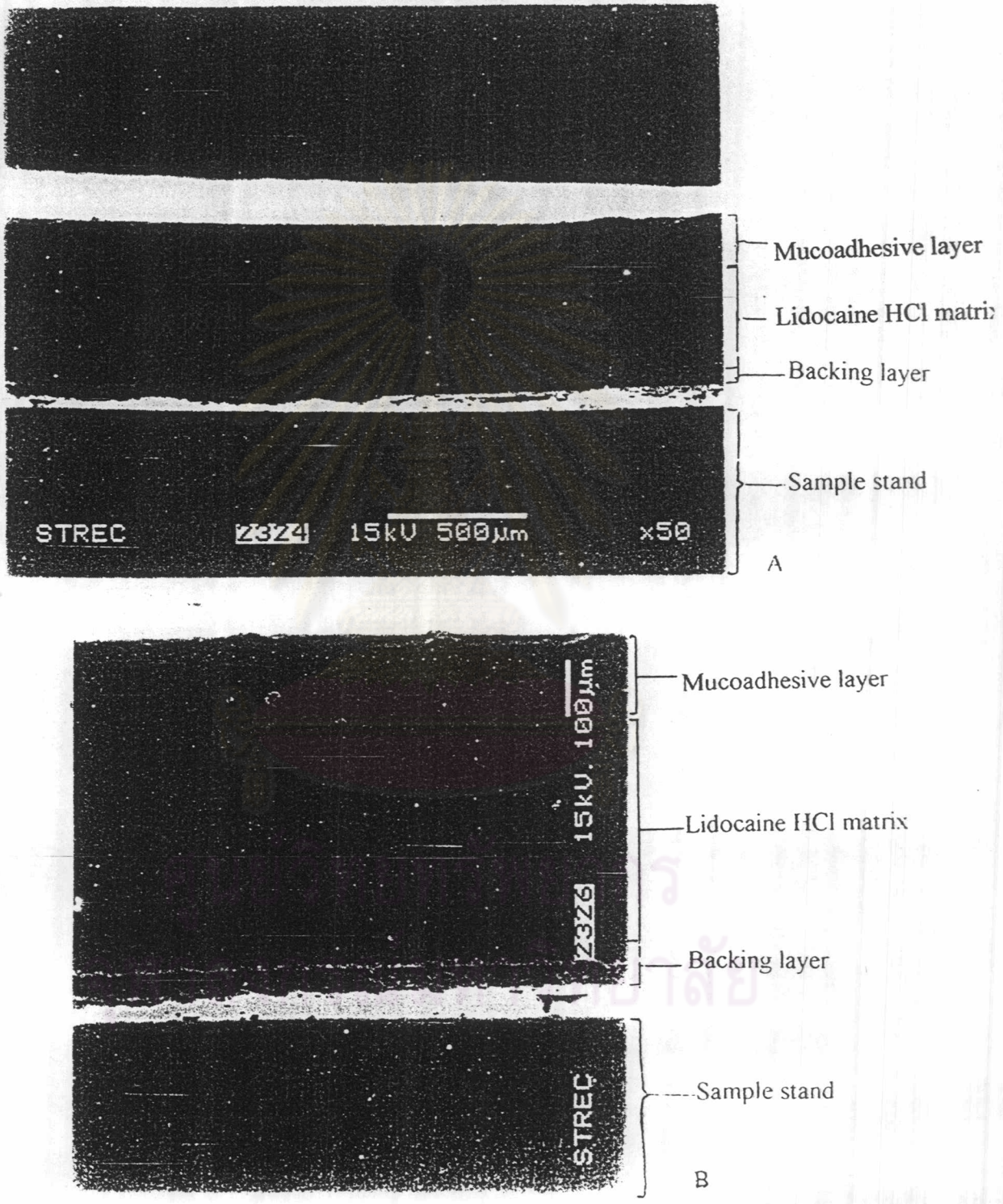


Figure 21 Cross-section of lidocaine HCl patch (A) x 50 ; (B) x 100

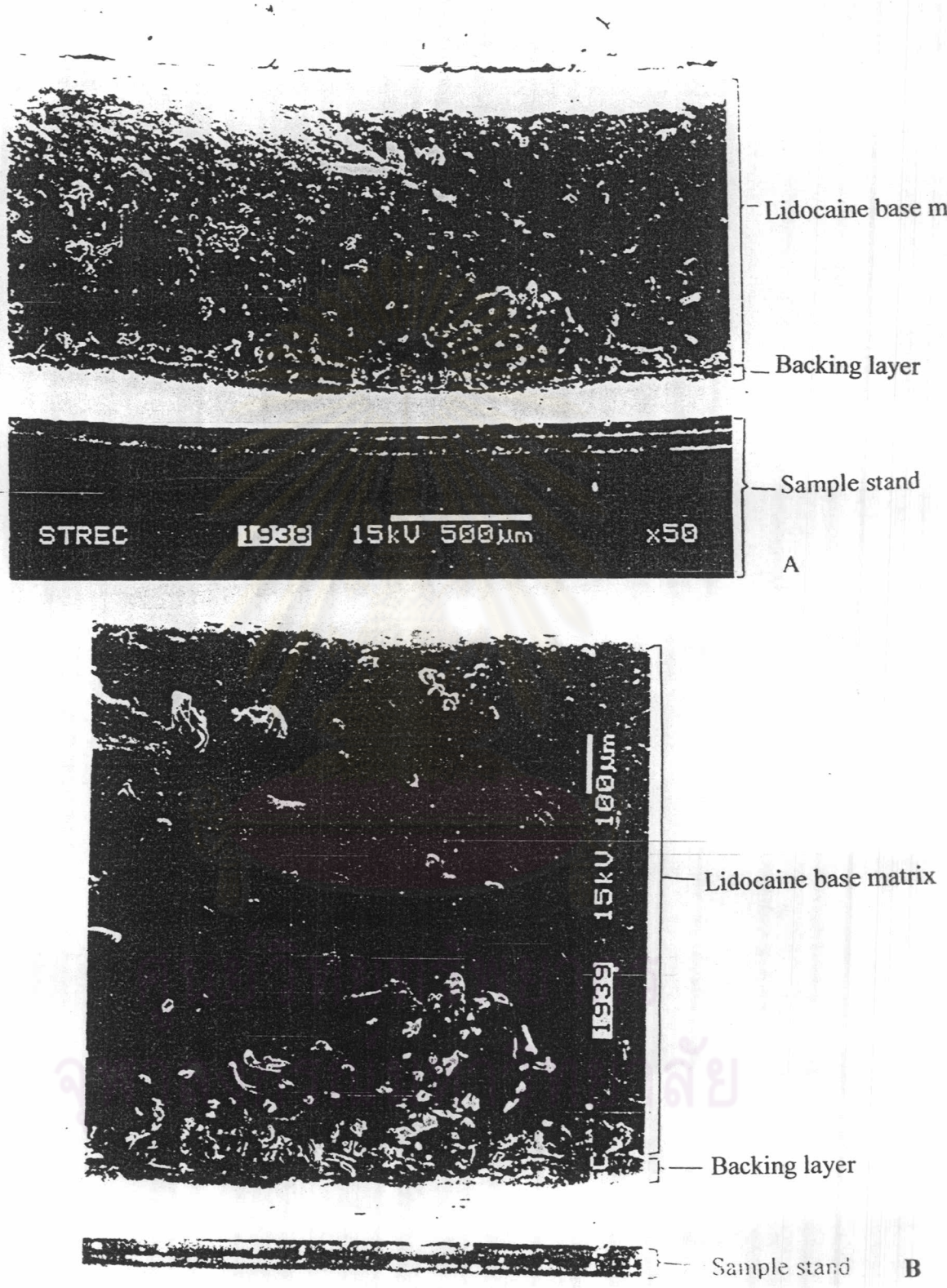


Figure 22 Cross-section of Dentipatch® (A) x 50 ; (B) x 100

5.4. The physicochemical characterization

The lidocaine patches using the 53rd formula of lidocaine base and 51tst formula of lidocaine HCl film as drug matrix layer were investigated for the physicochemical characteristic compared with Dentipatch®.

5.4.1 Infrared spectrometry

FT-IR spectra of lidocaine base powder and lidocaine HCl powder in figures 23 and 24 compared with those of lidocaine base patch and lidocaine HCl patch respectively. The other FT-IR spectra of HPMC powder, carbopol powder and ethyl cellulose powder were also compared. The FT-IR assignments are given in table 23.

Table 23 Infrared spectral assignment for lidocaine base and lidocaine HCl powder

Lidocaine base		Lidocaine HCl	
Band cm^{-1}	Assignment	Band cm^{-1}	Assignment
3253	amide N-H	3495, 3388, 3188	amide N-H
2970	C-H	2994	C-H
1665	amide I	2485	NH^{+}
1594	C=C	1655	amide I
1497	amide II	1544	amide II
765	aromatic C-H	787	aromatic C-H

The FT-IR spectra of lidocaine base patches, pure drug and HPMC powder are illustrated in figure 23. The spectrum of film containing drug was different from that of pure drug. The peak intensity of amide I band was slightly shifted from 1665 cm^{-1} to 1664 cm^{-1} and amide II band was slightly shifted from 1497 cm^{-1} to 1501 cm^{-1}. No new peak was observed from these spectra. The FT-IR spectra of lidocaine HCl patches, pure drug and HPMC powder are illustrated in figure 24. The spectrum of film containing drug was different from that of pure drug. The peak intensity of amide I band was slightly shifted from 1655 cm^{-1} to 1651 cm^{-1} and amide II band was from 1540 cm^{-1} to 1544 cm^{-1}.

The spectra of lidocaine loaded with HPMC and other combination showed compatibility of all ingredients. There was no new peak in the FT-IR spectra of prepared patches. These results could be explained similarly to the oxprenolol HCl in

previous report (Ozeki, et al., 1995) that lidocaine and other ingredient were dissolved in the solvent during the preparation of the films and when the solvent was evaporated, the solid dispersion was formed while lidocaine and polymer was interacting with each other by hydrogen bonding.

5.4.2. Powder X-ray diffraction

The powder X-ray diffraction pattern of lidocaine base, lidocaine HCl, HPMC are illustrated in figures 25, 26 and 27 respectively. Lidocaine base was crystalline which had major peaks at 8.460°2θ, 10.600°2θ, 12.920°2θ, 15.360°2θ and 25.420°2θ while lidocaine HCl was crystalline and showed peaks at 16.500°2θ, 24.960°2θ, 25.880°2θ and 30.280°2θ.

By comparison, the diffractogram of lidocaine base patch was different from HPMC powder and lidocaine base powder as presented in figure 25. Lidocaine base had many dominant peaks. The intensity of the dominant peak of crystalline was reduced after casting, indicating that the drug had changed to amorphous state or molecular dispersion. However obtained patch showed small peak at 9.700°2θ. Figure 26 showed that lidocaine HCl patch diffractogram was also different from HPMC powder and lidocaine HCl powder. The intensity of the dominant peak of crystalline was reduced after casting, indicating that the drug had changed to amorphous state or molecular dispersion. However obtained patch showed peak at 9.30°2θ. The small peak of the patches were very low intensity indicating that the drug was rarely in crystalline form in polymeric film. By comparison, lidocaine base powder, HPMC, lidocaine base patch and Dentipatch® in figure 27 showed that lidocaine base patch and Dentipatch® had similar diffractogram but different from lidocaine base powder. From the result, it might be caused of during the preparation of the patches, the lidocaine had to be pulverized, dissolved with HPMC solution, dried in hot air oven which the solvent was slowly evaporated therefore those might be made the drug in amorphous form. These result was similar to the experiment of lidocaine in the solid dispersion films by using HPC as a polymer. The peaks of X-ray diffractogram were

not also observed. They suggested that lidocaine exists as an amorphous form in the solid dispersion film (Yukinao, et al., 1997).

5.4.3. Differential thermal analysis

Figures 28 and 29 showed the differential scanning calorimetry (DSC) thermal curves for lidocaine base and lidocaine HCl respectively. The lidocaine base had melting point at 70°C and lidocaine HCl was 81.7°C

Figures 28 and 29 present the DSC thermograms of lidocaine base patches and lidocaine HCl patch consisting of drug, HPMC, EC, and carbopol. The thermogram of both patches had no peak. Similarly, figure 30 presented the DSC thermograms of lidocaine base patches and Dentipatch®.

This indicated that the drug existed as molecular dispersion or amorphous state in the film. Confirmation with powder X-ray diffraction, all of the patches showed that there was very small peak in X-ray diffractograms. The intensity of the peaks of the drug were very low indicating that the drug was rarely in crystalline form in polymeric films. The result was consistent with a previous study that lidocaine and lidocaine HCl were present as an amorphous form in the solid dispersion films of HPC (Danjo, et al., 1995, Kohda, et al., 1997 and Okamoto, et al.,2001).

5.5. Moisture sorption and swelling properties

The moisture sorption and swelling of mucoadhesive patches was investigated by exposing the films to moisture at various percentages relative humidity.

5.5.1. Moisture sorption study

As shown in figure 31, the moisture sorption of mucoadhesive patches showed an increase in moisture sorption with an increase of relative humidity. Lidocaine HCl patch could absorb more moisture than patch of lidocaine base and Dentipatch®. It might be indicated that when the lidocaine patches uptake the moisture from various

%RH, the lidocaine HCl could be more dissolved in aqueous than lidocaine base so that lidocaine HCl patches showed the highest moisture sorption than the others.

Normally, the solution process of the drug can be considered to occur in two separate steps. The first step, separation of ion from the crystal state to the gaseous state which the energy required to completely separate one mole of a solid ionic compound in to gaseous ions is called lattice energy. The second step, hydration of the gaseous ions which the separated ions and stabilized in solution by their interaction with water molecules that these ions are said to be hydrated (Chang, 2002). It might be that lidocaine base needed more energy to separate in ion form than its salt form. Therefore the salt form could be separated as ion form and hydrated more readily than base form. This result was in consistent with the general characteristic properties of lidocaine that the solubility salt form was more than that base form. The solubility are about 0.68 g/ml and 0.004 g/ml in lidocaine HCl and lidocaine base respectively (K.Groningsson, et al., 1985).

In addition, at 53%RH and 75%RH, all the patches were at equilibrium within 24 hours after exposing to moisture while at 84%RH and 94%RH the patches could absorb more moisture. It was found that increasing %RH, all of the patches would be increased the moisture sorption. At the same time and the same relative humidity, when testing with one-way ANOVA, lidocaine HCl had the percent of moisture sorption more than lidocaine base patch and Dentipatch® with significant difference ($p<0.05$), while lidocaine base patch and Dentipatch® were not significantly different from each other ($p>0.05$).

5.5.2. Swelling property of mucoadhesive patches

Normally, swelling of the polymer film caused of liquid molecules separated in the interstices of the polymer caused the polymer to hydrate, the polymer started to swell and increased in size. The polymer chains began to unfold and gradually become solvated. The coiled nature of the polymer was still retained but with a very much expanded coil volume (Wan, et al., 1991).

From figure 32, the swelling of mucoadhesive patches increased with the increasing relative humidity. Lidocaine base and Dentipatch® exhibited slower swelling rate than lidocaine HCl patch but after the 7th day, they had similar swelling ability. This result was consistent with the result of moisture sorption that lidocaine HCl could be more dissolved and uptook more moisture than base form. Therefore the salt form film would be more swollen than the base form film. At the same time and the same relative humidity, when testing with one-way ANOVA, lidocaine HCl had the percent of moisture sorption more than lidocaine base patch and Dentipatch® with significant difference ($p<0.05$), while lidocaine base patch and Dentipatch® were not significant different from each other ($p>0.05$).

At the same time and the same relative humidity, the 1st day and 3rd day, when testing with one-way ANOVA, lidocaine HCl had the percent of swelling more than lidocaine base patch and Dentipatch® with significant difference ($p<0.05$), while lidocaine base patch and Dentipatch® were not significant different from each other ($p>0.05$). At 5th day and 7th day, at 84%RH and 94%RH all of the lidocaine HCl patch patches were not significant different to lidocaine base ($p>0.05$) but significant different to the Dentipatch® ($p<0.05$). This indicated that HPMC film might be swelled more than the polymer in the commercial product but took time to swell.

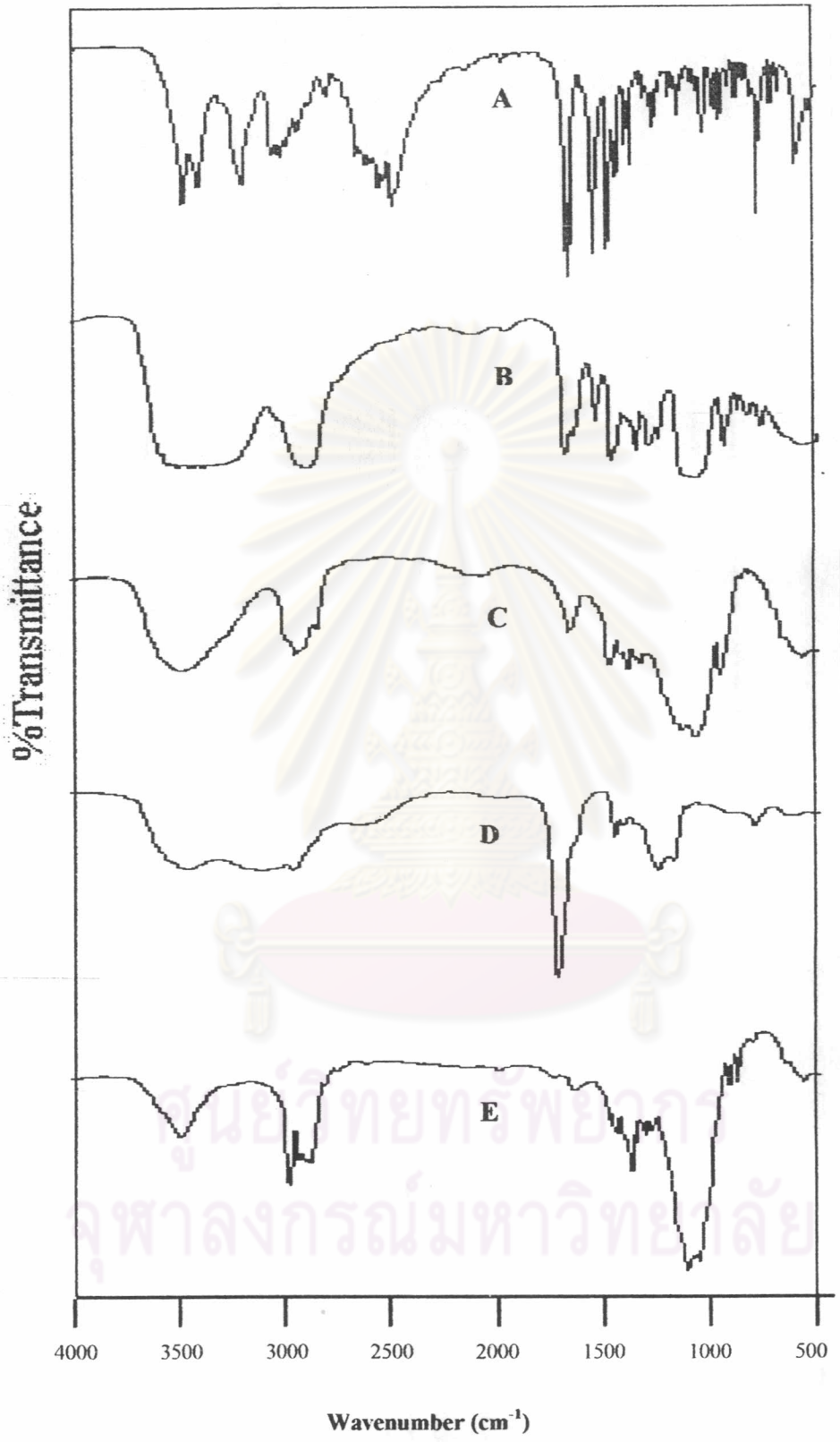


Figure 23 FT-IR spectra of (A) lidocaine base powder; (B) lidocaine base patch; (C) HPMC powder; (D) carbopol powder; (E) ethyl cellulose powder

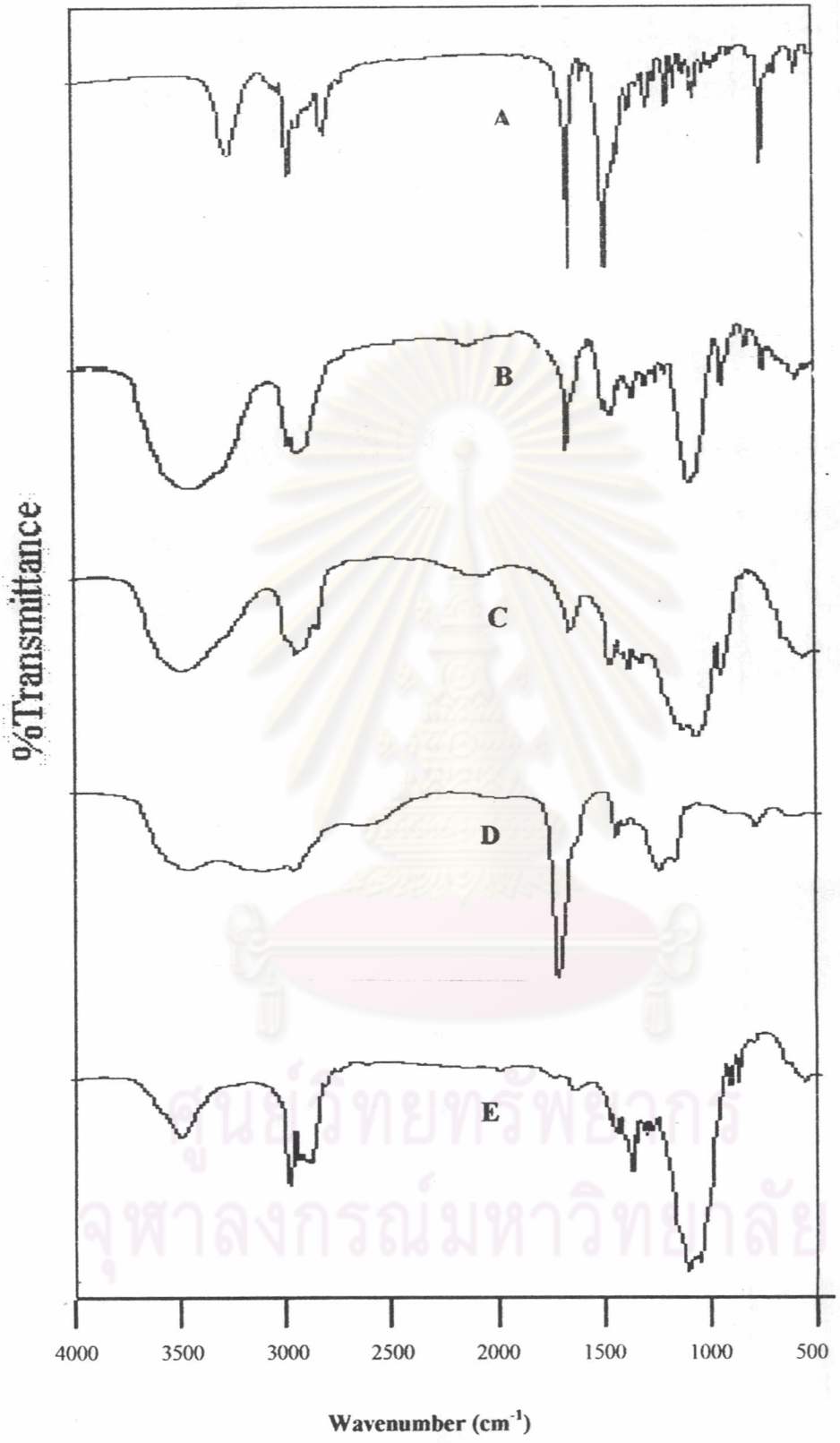


Figure 24 FT-IR spectra of (A) lidocaine HCl powder; (B) lidocaine HCl patch; (C) HPMC powder; (D) carbopol powder; (E) ethyl cellulose powder

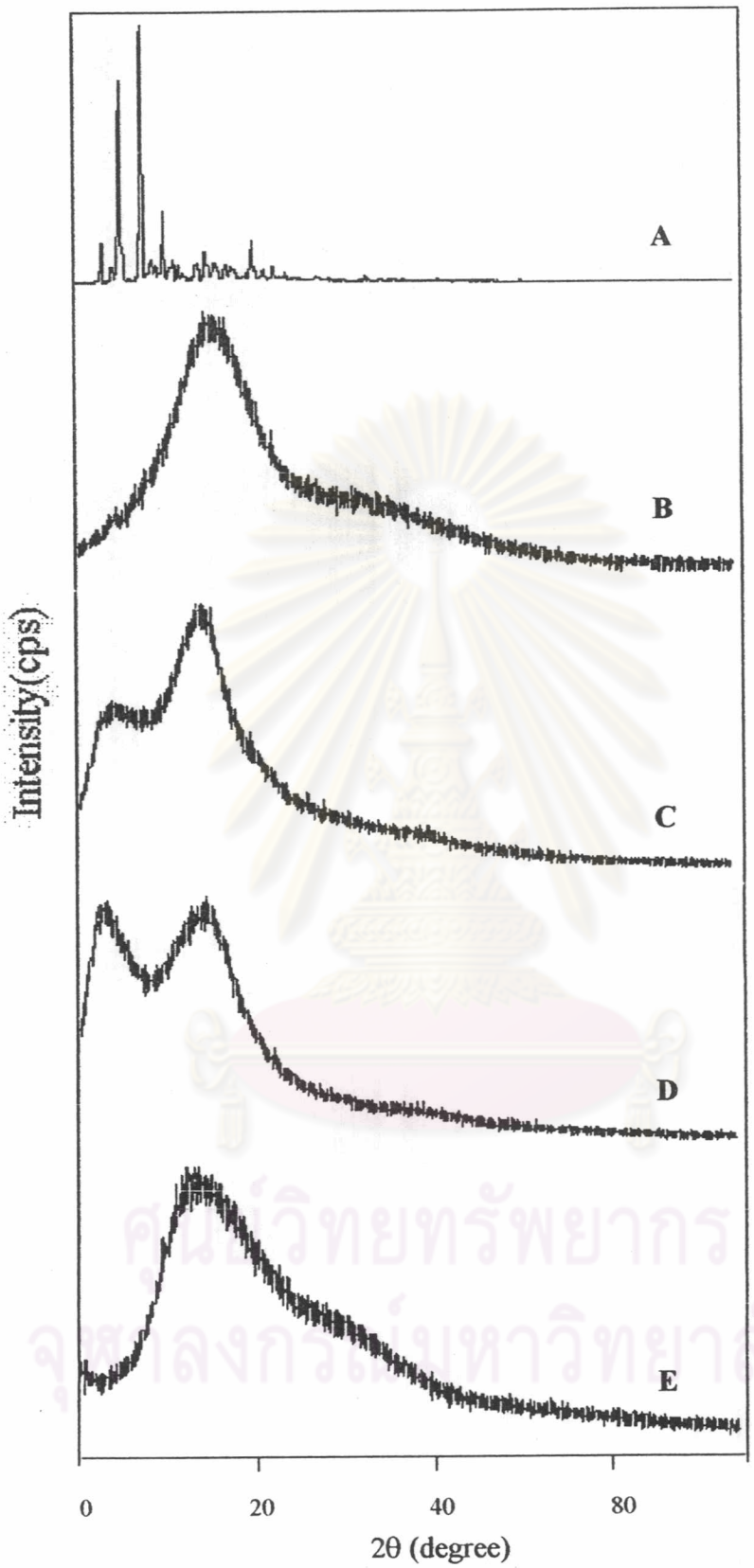


Figure 25 X-ray diffractograms of (A) lidocaine base powder; (B) lidocaine base patch; (C) HPMC powder; (D) carbopol powder; (E) ethyl cellulose powder

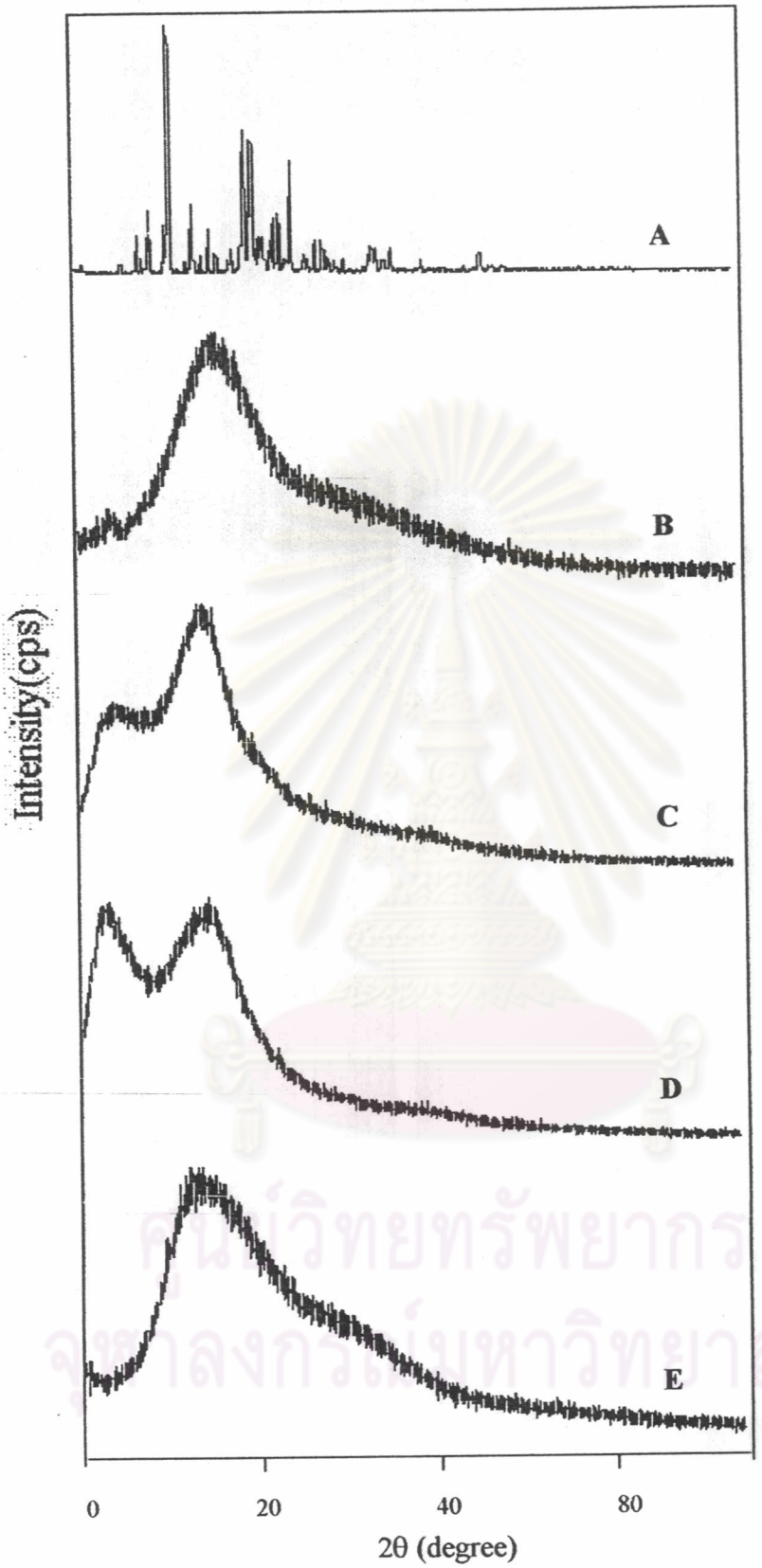


Figure 26 X-ray diffractograms of (A) lidocaine HCl powder; (B) lidocaine HCl patch; (C) HPMC powder; (D) carbopol powder; (E) ethyl cellulose powder

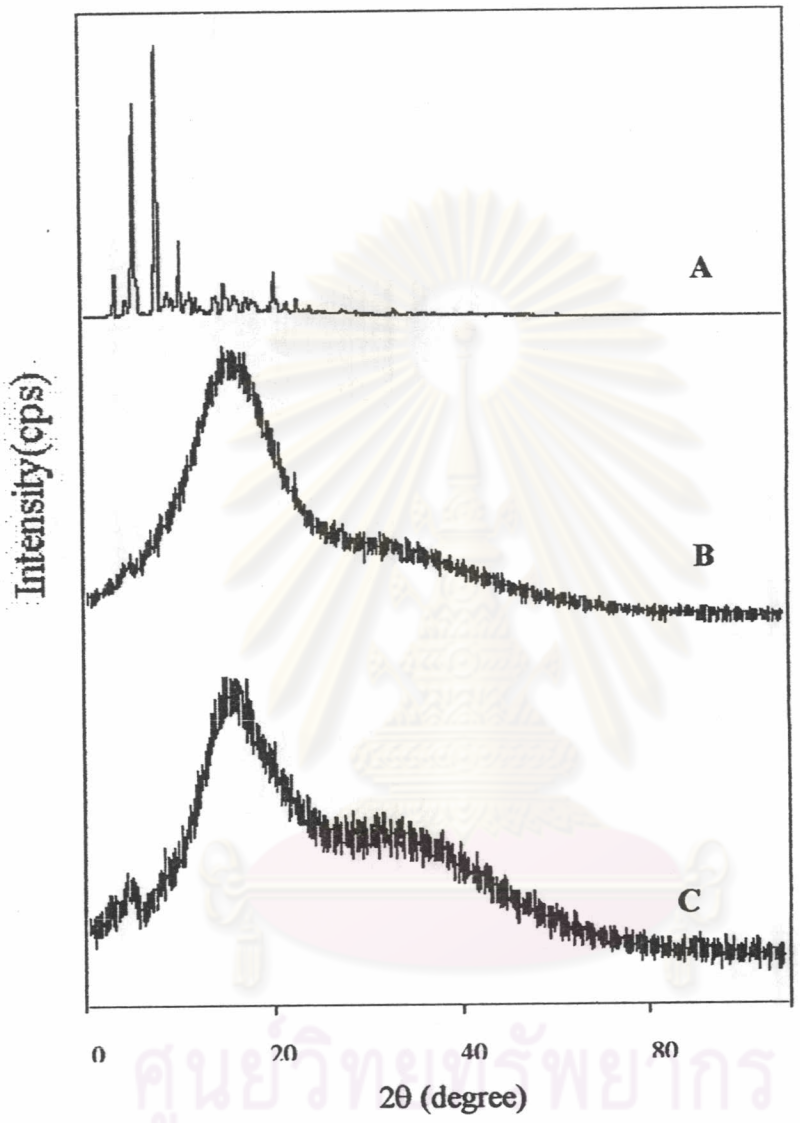


Figure 27 X-ray diffractograms of (A) lidocaine base powder; (B) lidocaine base patch; (C) Dentipatch®

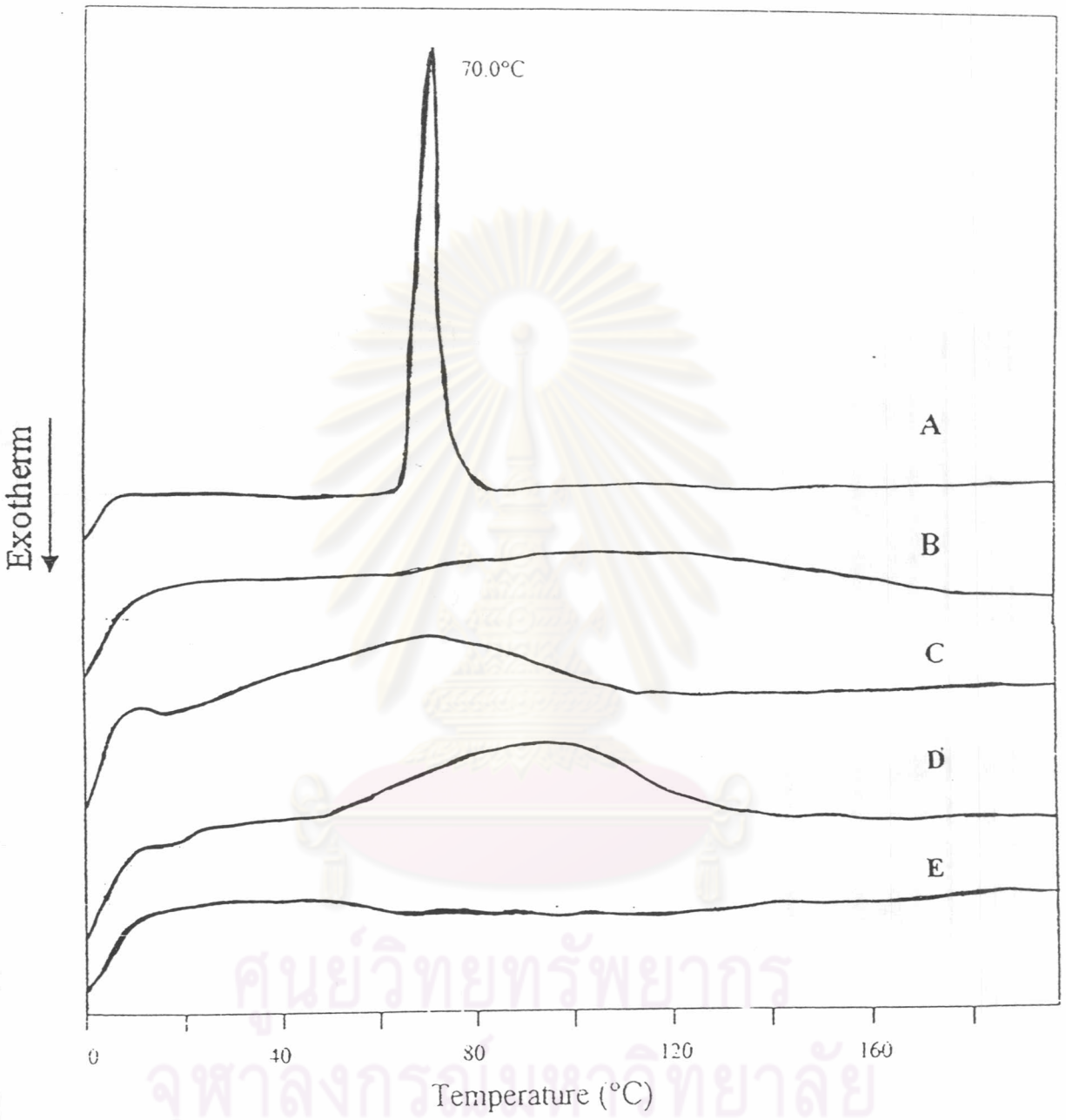


Figure 28 DSC thermograms of (A) lidocaine base powder; (B) lidocaine base patch; (C) HPMC powder; (D) carbopol powder; (E) ethyl cellulose powder

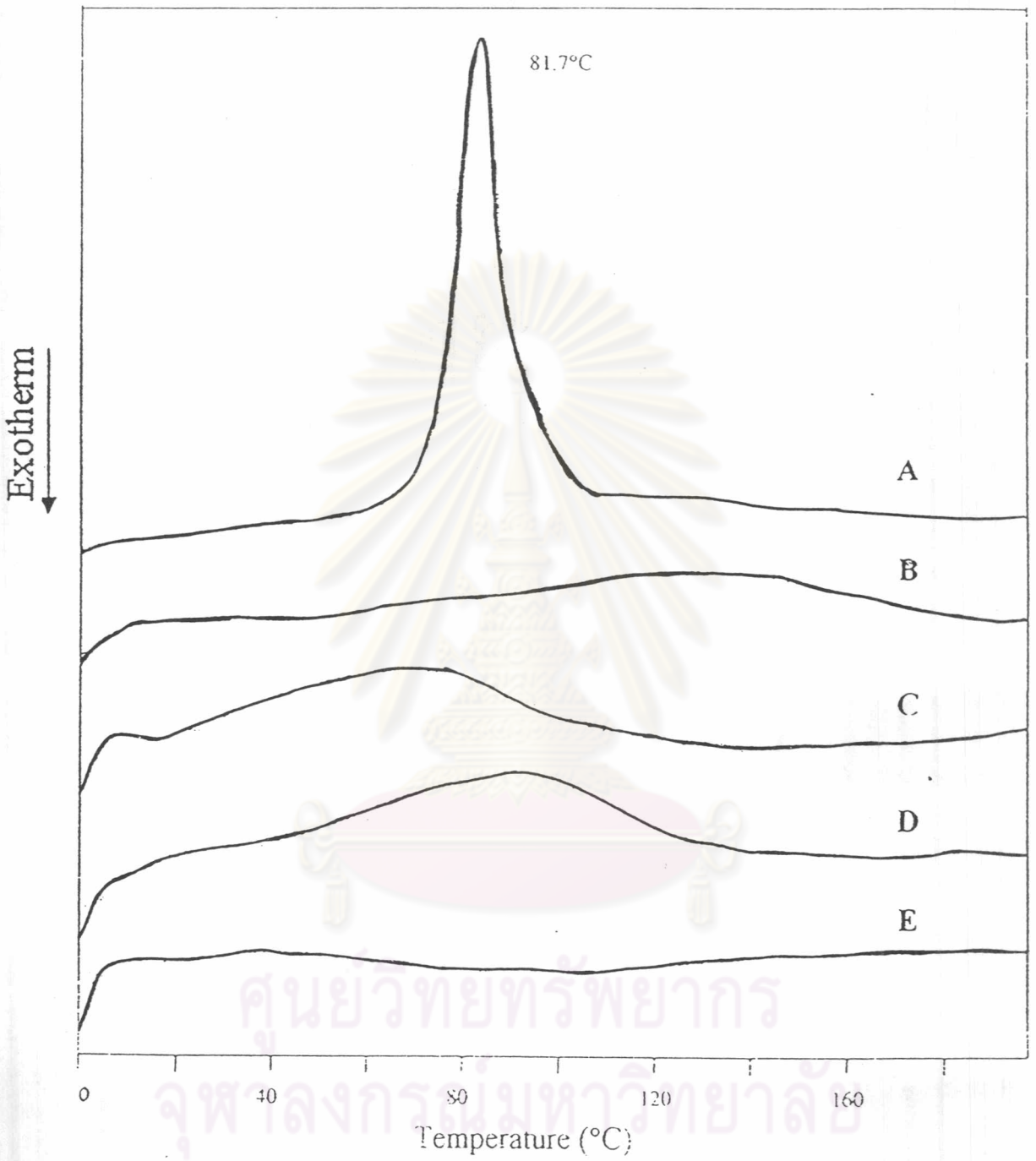


Figure 29 DSC thermograms of (A) lidocaine HCl powder; (B) lidocaine HCl patch; (C) HPMC powder; (D) carbopol powder; (E) ethyl cellulose powder

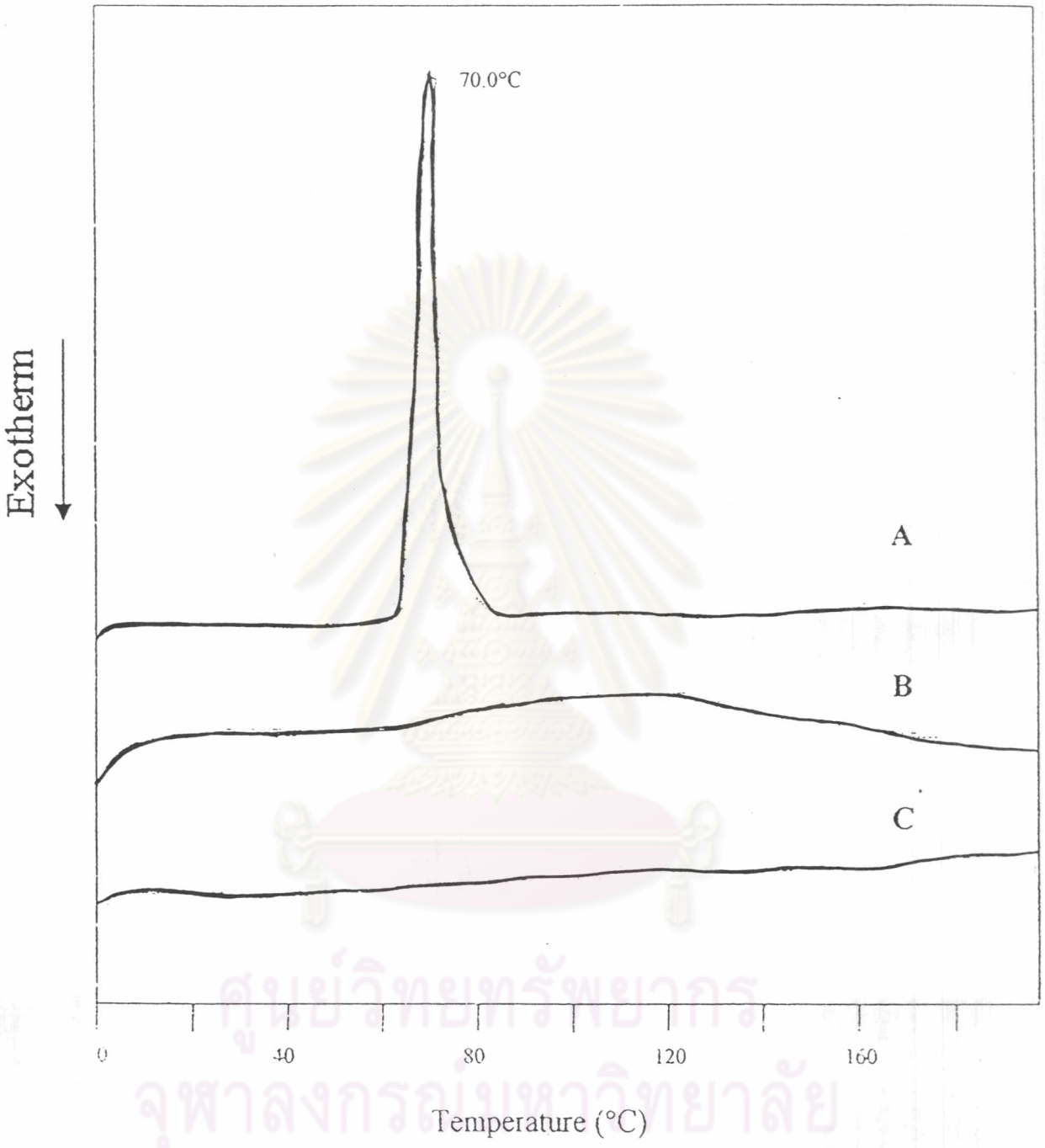


Figure 30 DSC thermograms of (A) lidocaine base powder; (B) lidocaine base patch; (C) Dentipatch®

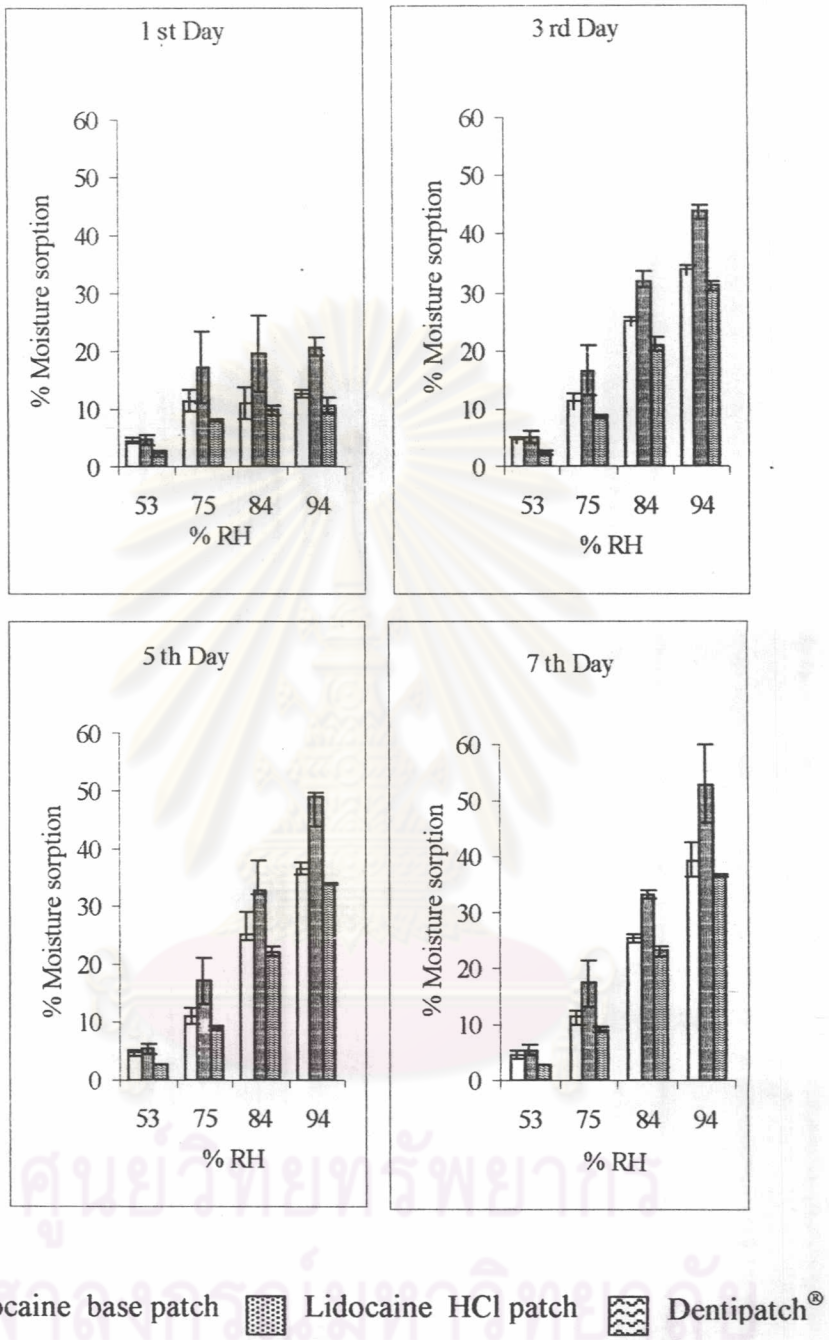


Figure 31 Percentage of moisture sorption of mucoadhesive patches

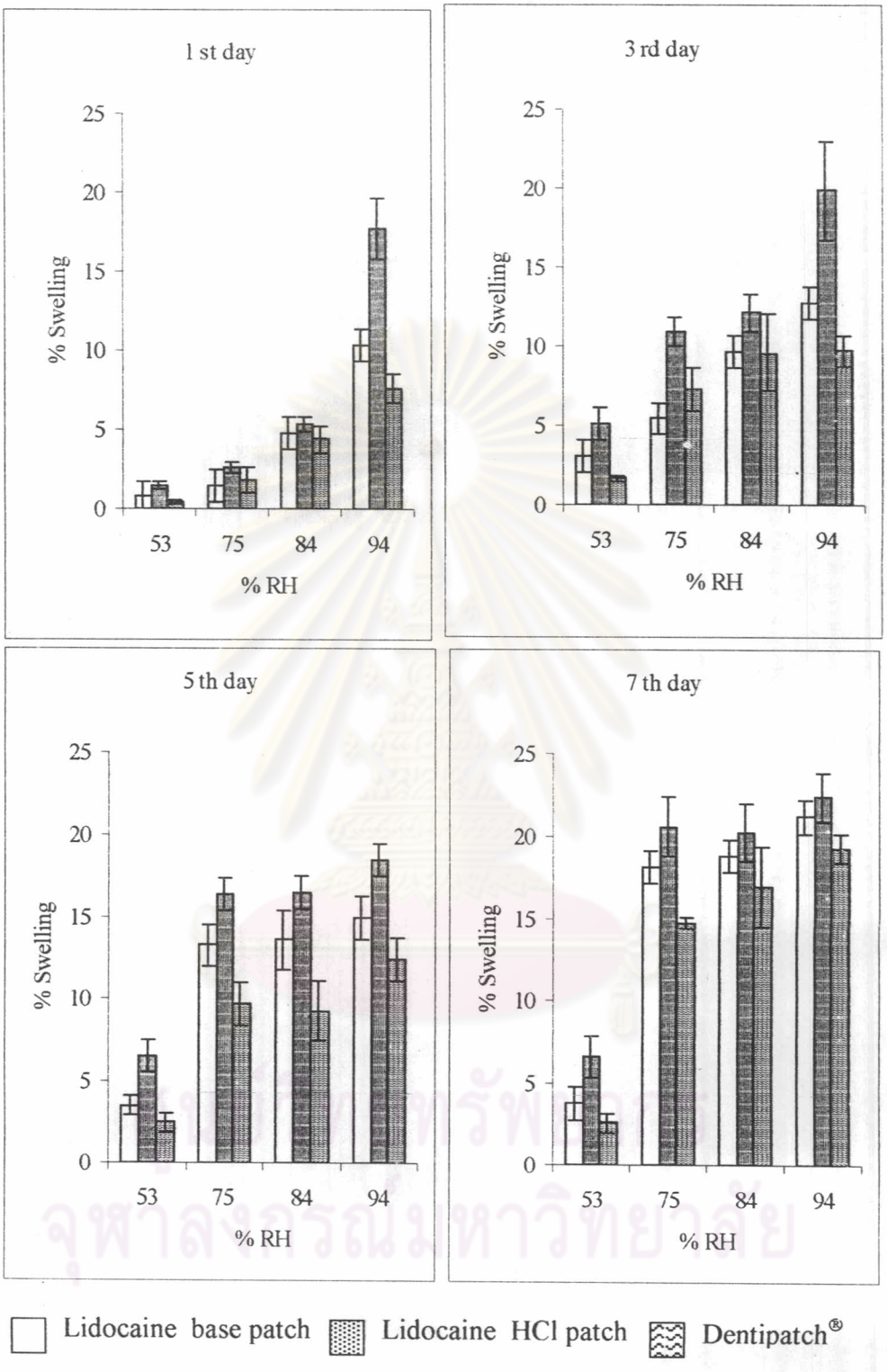


Figure 32 Percentage swelling of mucoadhesive patches

5.6. Mucoadhesive property

Table 24 showed the mucoadhesiveness determined in term of detachment force by measuring the force required to pull the test film, prehydrated with artificial saliva pH 7.0 and attached on the surface of pig intestine mucous membrane (n=10). The mucoadhesive force results are presented in Appendix C. The mucoadhesive force of lidocaine HCl patch was the least. That lidocaine base had no significant different ($p>0.05$) mucoadhesive force from Dentipatch® when tested with one-way ANOVA. From the result, it was likely indicated that while pouring carbopol solution on the drug matrix film and then contacted the lidocaine base, the lidocaine base could be dissolved at the interface and might increase the pH of carbopol solution so that carbopol could form gel. This was consistent with the property of carbopol that could be neutralized by base as a gelling agent (Kibbe, 2000). Due to the coiled conformation of carbopol, many of the adhesively active groups were shielded inside the coils and were not active to participate in the adhesion process due to the intramolecular hydrogen bonds that rendered them ineffective. Thus, neutralizing the carbopol would to form an expanded gel network would form and made the film more adhesiveness (C. Eouni, et, al., 2001).

Table 24 Mucoadhesive force of lidocaine mucoadhesive patches (n =10)

Sample	Mucoadhesive force (N/cm^2)±SD
Lidocaine base	8.620±0.605
Lidocaine HCl	5.725±0.622
Dentipatch®	8.278±0.207

5.7. *In vitro* drug release and penetration through and without dialysis membrane from the mucoadhesive patches

In this study, three model of penetration kinetics: zero order, first order, and Higuchi model were used to assess the drug penetration model. The equations for the drug penetration model are shown in table 25.

Table 25 The release kinetic models

Model	Equation
Zero order	$Q_t = Q_0 + kt$
First order	$LnQ_t = InQ_0 + kt$
Higuchi	$Q_t = kt^{1/2}$

Q_t was the amount of drug released at time t, Q_0 was the initial amount of drug in the solution (most time, $Q_t = 0$)

The plots of these kinetic models of each preparation was constructed. The higher coefficient of determination (R^2) was accepted as the model for drug release.

The concentration of lidocaine base and lidocaine HCl saturated solution used in drug release study were 4 mg/ml and 691.04 mg/ml respectively. The drug was released through dialysis membrane into pH 6.8 phosphate buffer. Accurately 0.5 ml of lidocaine base saturated solution and 0.065 ml of lidocaine HCl saturated solution were released within 180 minutes.

The release-time profile of lidocaine saturated solution is shown in figure 33. It was found that the drug release rate from saturated solution of lidocaine HCl was faster than lidocaine base because of lidocaine in salt form could dissolved more than base form and. Their release kinetic was fitted to zero order (R^2 of saturated lidocaine base was 0.9994 and saturated lidocaine HCl was 0.9961 which calculated from 0 to 60 percent cumulative amount).

The drug release data in this study are presented in Appendix C. The release-time profile of lidocaine mucoadhesive patches and Dentipatch® are shown in figure

34 and 35. Fifty four percent of lidocaine HCl patches of drug loaded was released through dialysis membrane within 180 minutes whereas lidocaine base patch and Dentipatch® release fifty one and fifty three percent respectively. For release without dialysis membrane throughout 180 minutes, it was found that ninety four percent of lidocaine HCl patch was released whereas seventy four and seventy six percent were from lidocaine base patch and Dentipatch®. Comparison the released rate by using kinetic constants with one-way ANOVA found that the release rate through dialysis membrane, all of the patches had no significant different ($p>0.05$). It might be indicated that the dialysis membrane was barrier to the patch to freely contacted the phosphate buffer at the receptor compartment, then the patches could not swell or dissolve completely so that it made the amount of drug release less than the released without dialysis membrane. The release rate without dialysis membrane, Dentipatch® and lidocaine base patch had significantly different release rate from lidocaine HCl ($p <0.05$) while there was no significant difference between Dentipatch® and lidocaine base patch ($p>0.05$). The drug released without dialysis membrane showed that the percent cumulative drug release and drug release rate were higher than the drug released through dialysis membrane. These results were in consistent with the moisture sorption and swelling properties study that lidocaine HCl can dissolved and hydrated when exposed to the moisture more than lidocaine base resulting the polymer to swell and the void spaces to increase. The drug then substantially diffused through these voids.

Coefficient of determinations and kinetic constants of release kinetic models of lidocaine patches through and without dialysis membrane are summarized in tables 26 and 27. The release kinetic constants through dialysis membrane calculated at 0 to 50 percent cumulative amount because when finish the release at 180 minutes, all the patches could be released at about 50 percent while the kinetic constant without dialysis membrane were calculated at 0 to 60 percent cumulative amount. When treated with first order kinetic to all formulas, the highest coefficients of determination were observed. The results indicated that released rate of the drug depended on the log of drug concentration that remained in the patches.

Table 26 The coefficients of determination and kinetic constants of lidocaine released through dialysis membrane.

Formula	Zero order		First order		Higuchi model	
	R^2	*k*	R^2	*k*	R^2	*k*
[a]Lidocaine base saturated solution	0.9994	0.6725	0.9925	0.0037	0.8963	5.3019
[a]Lidocaine HCl saturated solution	0.9961	1.1798	0.9821	0.0072	0.8860	7.8546
[b]Lidocaine base patch	0.9672	0.2771	0.9896	0.0017	0.982	4.0262
[b]Lidocaine HCl patch	0.9431	0.3628	0.9861	0.0019	0.9798	4.4641
[b]Dentipatch®	0.9817	0.2978	0.9985	0.0018	0.9741	4.2777

[a] Calculated from range of 0-60 percent cumulative amount

[b] Calculated from range of 0-50 percent cumulative amount

R^2 was coefficient of determination and *k* was correlation constant

Table 27 The coefficients of determination and kinetic constants of lidocaine released without dialysis membrane.

Formula	Zero order		First order		Higuchi model	
	R^2	*k*	R^2	*k*	R^2	*k*
Lidocaine base patch	0.9674	0.4201	0.9980	0.0031	0.9821	5.3697
Lidocaine HCl patch	0.9624	0.6019	0.9939	0.0051	0.9900	8.9389
Dentipatch®	0.9531	0.5149	0.9896	0.0033	0.9879	5.5710

Calculated from range of 0-60 percent cumulative amount

R^2 was coefficient of determination and *k* was correlation constant

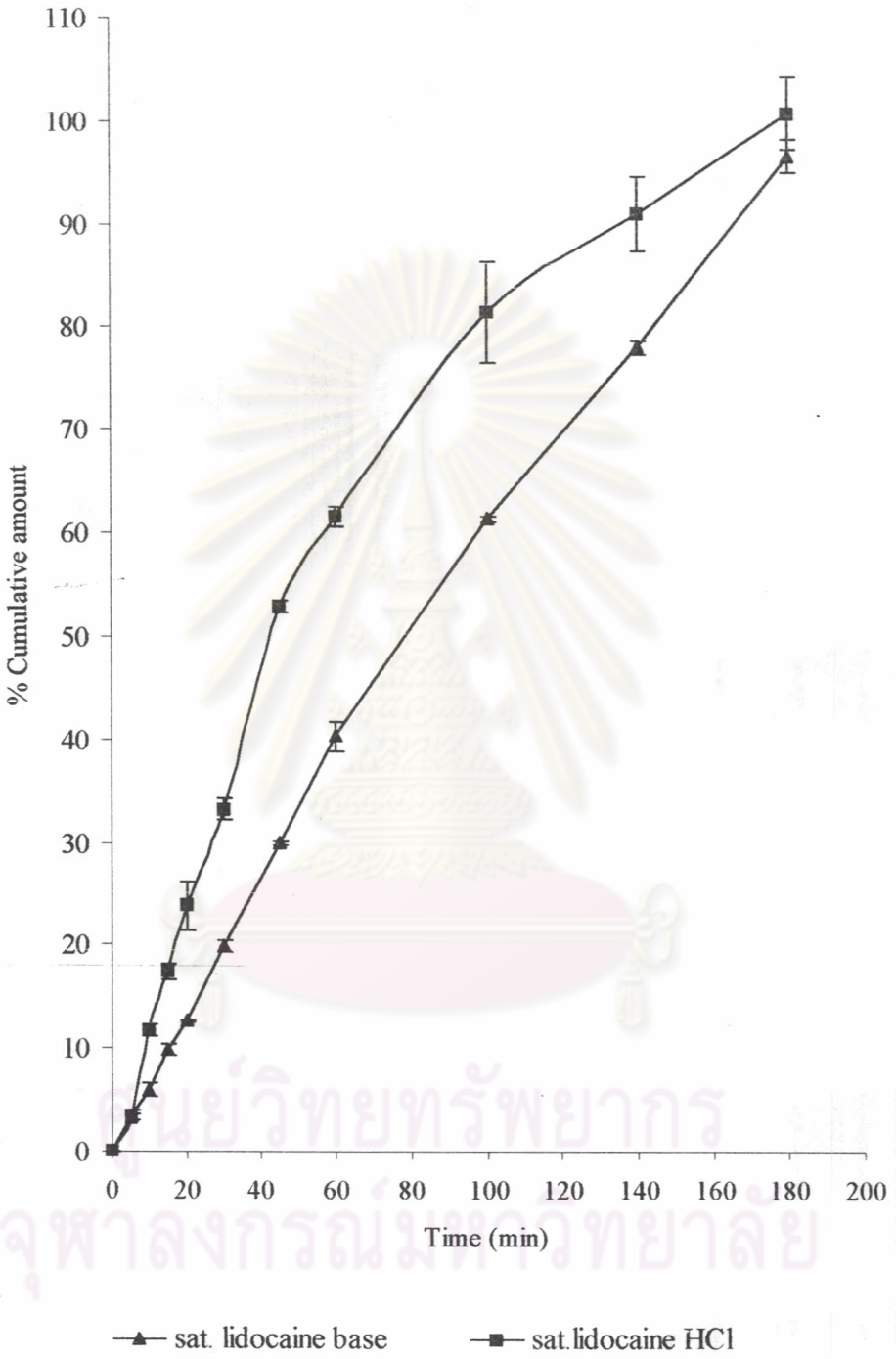


Figure 33 The release-time profile of lidocaine saturated solution through dialysis membrane

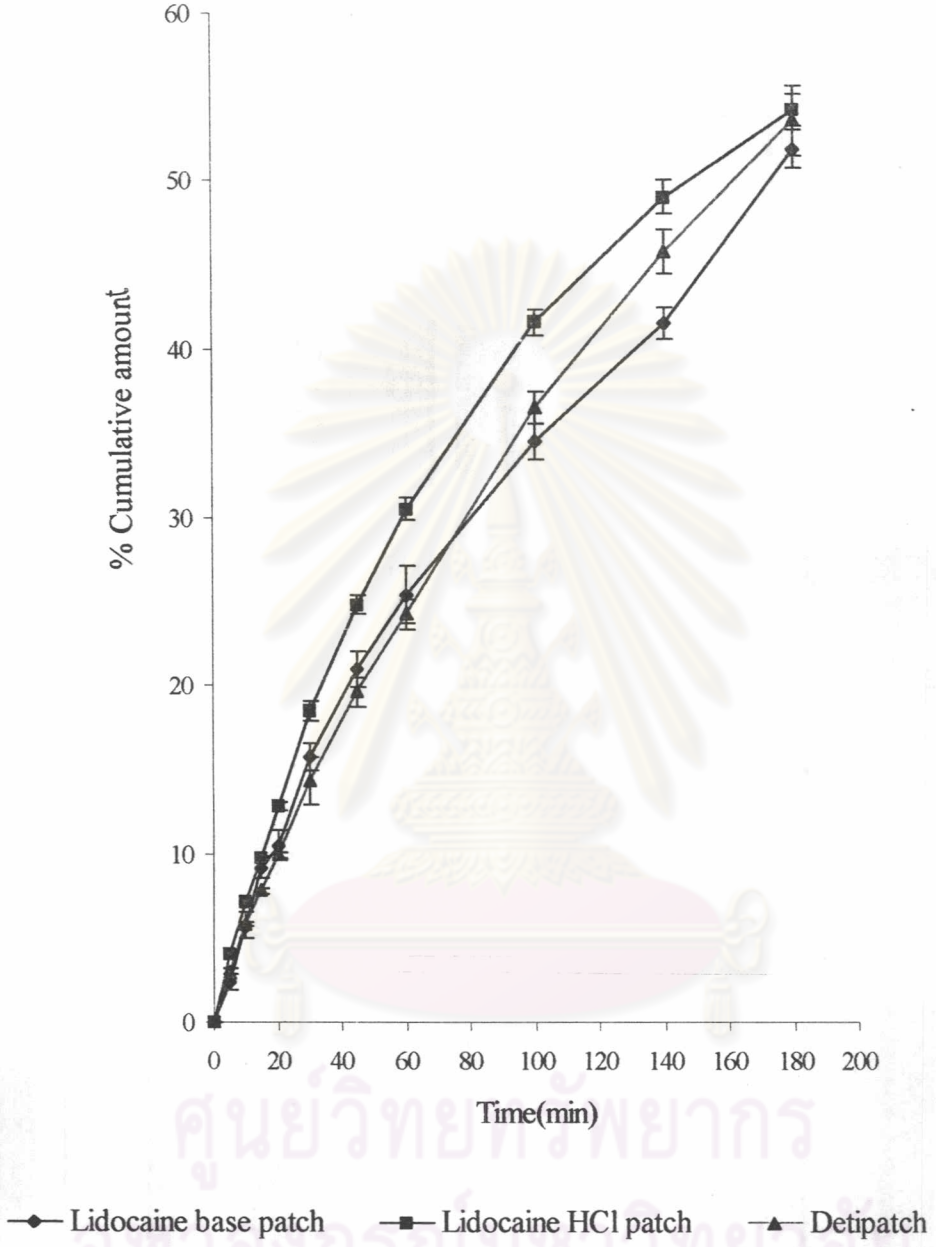


Figure 34 The release-time profile of lidocaine patches and Dentipatch® through dialysis membrane

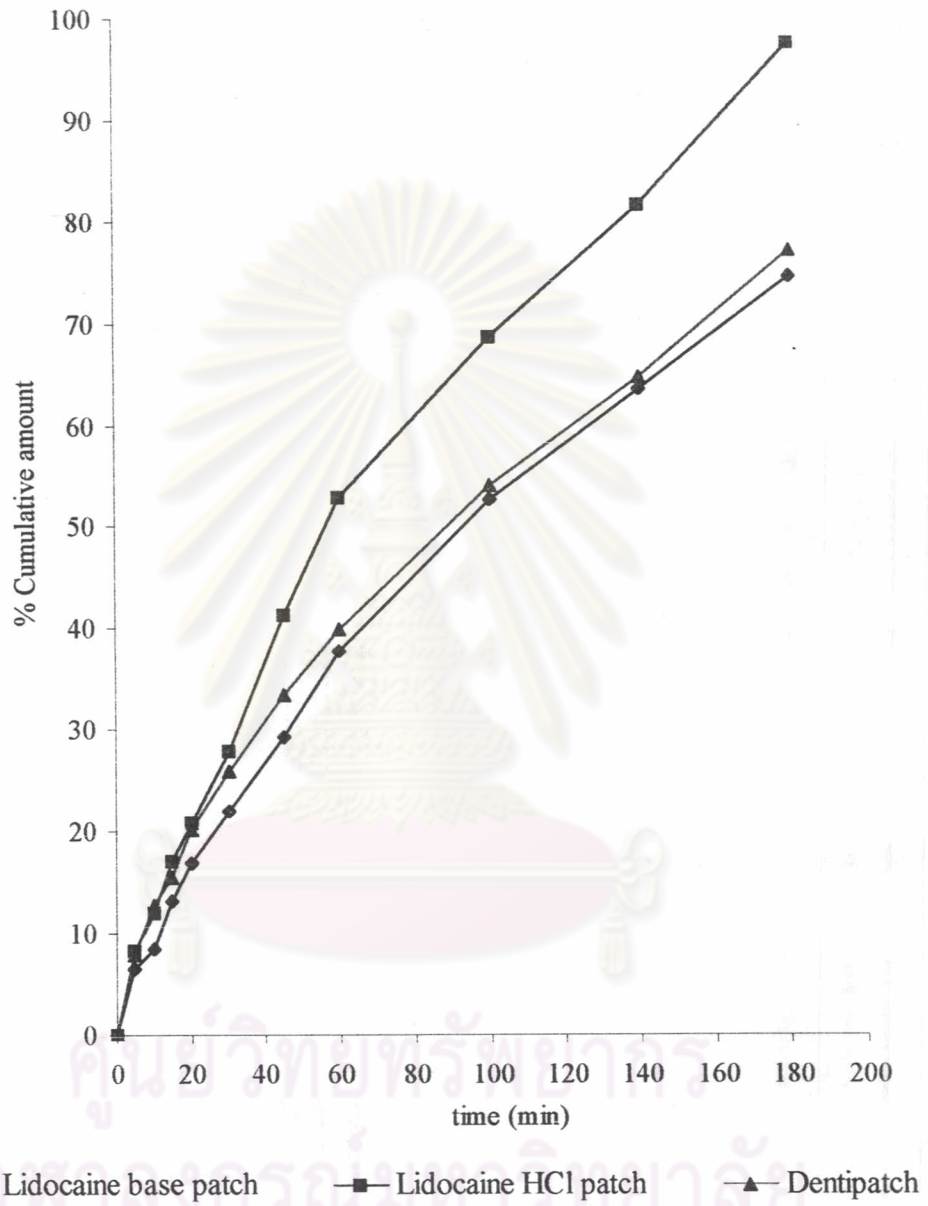


Figure 35 The release-time profile of lidocaine patches and Dentipatch® without dialysis membrane

5.8. Stability of mucoadhesive patches

From figure 36 showed the content of lidocaine mucoadhesive patches determined by HPLC method after packaging at 25°C, 0%RH; 25°C, 75%RH and 45°C, 75%RH for 30, 60, 90 at 120 days.

Figure 36A showed that at 25°C, 0%RH, the content of lidocaine base patch, lidocaine HCl patch and Dentipatch® after 120 days were 99.60, 100.01 and 99.81 percent label amount respectively which they were not less than 90 percent label amount.

Figure 36B showed that at 25°C, 75%RH the patches were degraded to 90.93, 90.50 and 90.72 label amount for lidocaine base patch, lidocaine HCl patch and Dentipatch® respectively after 120 days. After 120 days at this condition lidocaine HCl had drug content more than of after 90 days but they had no significant different by compared with one-way ANOVA ($p>0.05$). This indicated that moisture affected the degradation of lidocaine, however all patches were still had content not less than 90 percent label amount.

After 120 days, figure 36C showed that at 45°C 75%RH, the content of lidocaine base patch, lidocaine HCl patch and Dentipatch® were decreased to 89.59, 88.12 and 90.48 percent label amount respectively. After 60 days at this condition, lidocaine HCl patch had the content more than of after 30 days. After 120 days, lidocaine base patch and lidocaine HCl patch had content more than after 90 days. These might cause of using too little sample during the study ($n=3$) but when compared by using one-way ANOVA, the content between them were not significantly different ($p>0.05$).

After 120 days, at 45°C 75%RH, the drug content of lidocaine base patch and lodocaine HCl patch were less than 90 percent label amount. Although the drug content of them were less than 90 percent label amount.

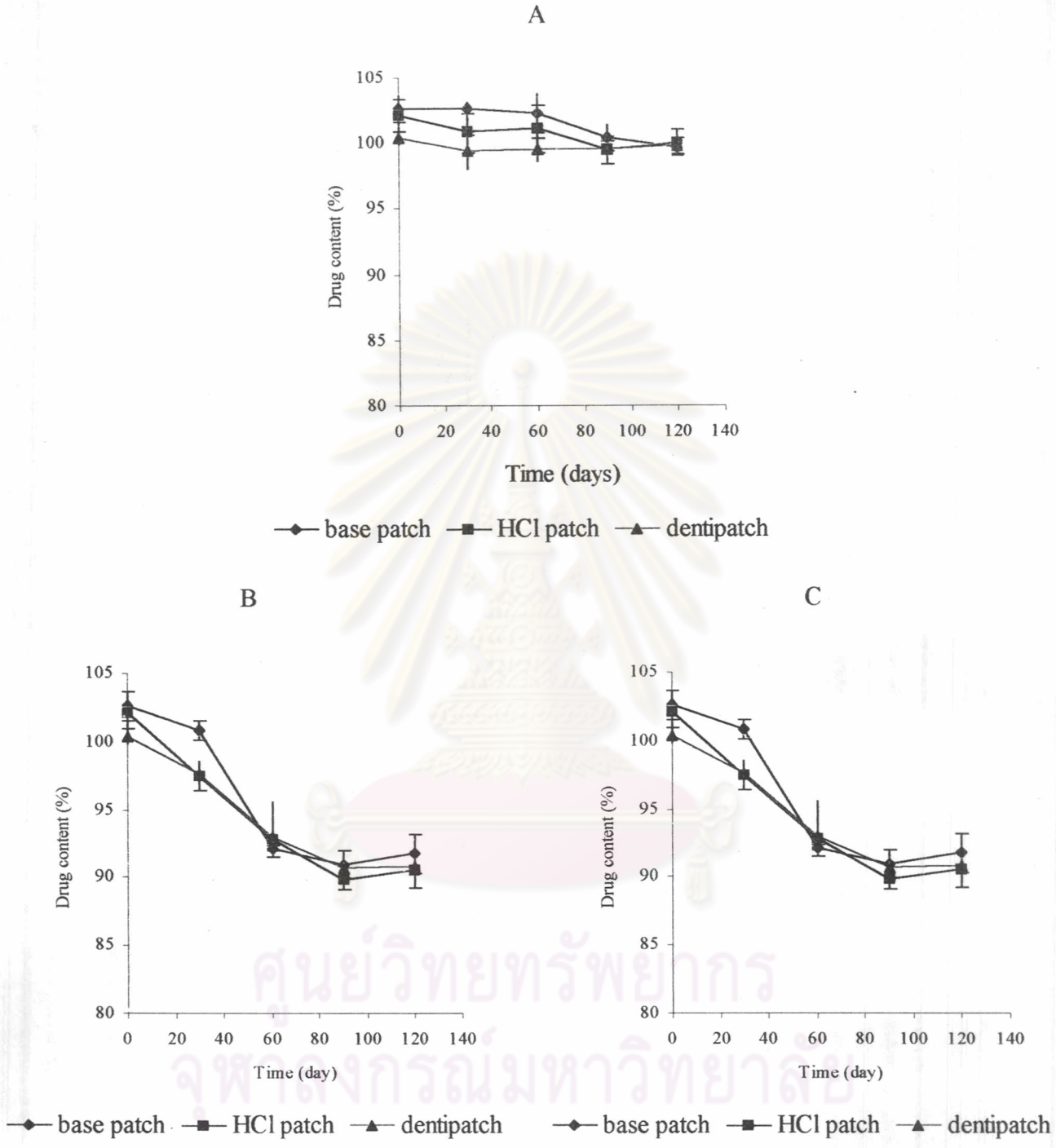


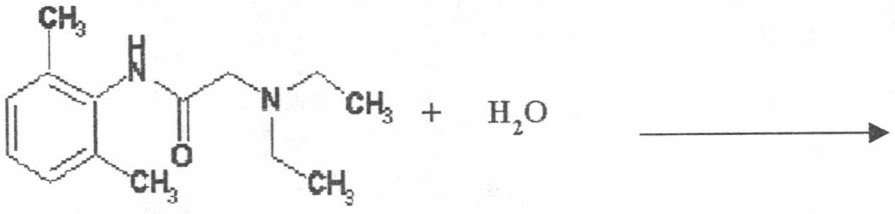
Figure 36 The degradation profile of lidocaine patches at 0, 30, 60, 90 and 120 days: (A) 25°C, 0%RH; (B) 25°C, 75%RH and (C) 45°C, 75%RH

Table 28 showed the percent degradation of the patches, The results showed that after 120 days at every conditions, all the patches had significant different with each other ($p<0.05$). Lidocaine HCl patch had the most percent degradation while Dentipatch® had the least. It was consist of the result of moisture sorption and swelling that lidocaine HCl patch had the most percent moisture and percent swelling while lidocaine base patch had no significant different percent swelling when increasing the percent relative humidity. These result might be indicated that the HPMC patches could uptake and swell more than the commercial patch, then it might made lidocine base patch and lidocaine HCl patch degraded more than Dentipatch®.

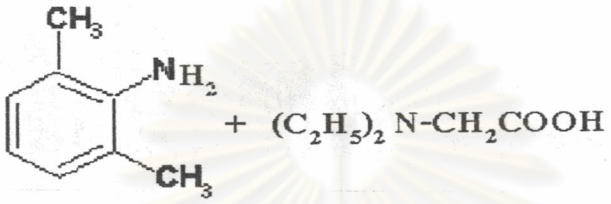
Table 28 The percent degradation of the lidocaine patches

Condition	days	% degradation of lidocaine patches		
		Lidocaine base patch	Lidocaine HCl patch	Dentipatch®
25°C, 0%RH	30	0.00	1.20	0.01
	60	0.40	0.97	0.87
	90	2.14	2.64	0.89
	120	2.11	2.93	0.56
25°C, 75%RH	30	1.72	4.63	2.73
	60	10.20	9.18	7.43
	90	11.38	12.10	9.66
	120	10.58	11.42	9.61
45°C, 75%RH	30	9.81	10.63	7.02
	60	10.12	10.06	7.67
	90	13.54	14.80	9.69
	120	12.75	13.75	9.85

From the result of condition at 25°C, 75%RH and 45°C, 75%RH, these indicated that moisture and high temperature might cause lidocaine degraded. It was consistent with the reveal of the degradation of lidocaine, which would be expected to be decomposed by hydrolysis as follows: (K.Groningsson, et. al.,1985).



Lidocaine



2,6- Xylidine Diethylaminoacetic acid

Figure 37-39 showed the X-ray diffractogram of lidocaine patches in various conditions at 0 day and after 120 days. They had very small peak at 0 day and no peak was found in all of the patches after 120 days in every condition. It was indicated that all of the patches were still in solid dispersion or amorphous form.

From figure 40, all patches were exposed to air without packaging, and the linear of the patches was removed. The patches were placed on a glass dish by exposing the mucoadhesive site to the air for 12 hours. It was found that lidocaine base patch and Dentipatch® had crystals on the surface while lidocaine HCl patch were swelled. This might be indicated that lidocaine base patch and Dentipatch® were in solid dispersion and lidocaine HCl patch was in amorphous form. Moisture had effect on both lidocaine base patch and Dentipatch® thus interfere their stability of the patches. Confirmation with the patch that kept at 75%RH also showed the content of these patches were decreased. From the result, packaging was interesting to be further developed to protect the product from other contamination, moisture, light and high temperature. In addition, the patch should be used immediately after removed from the packaging.

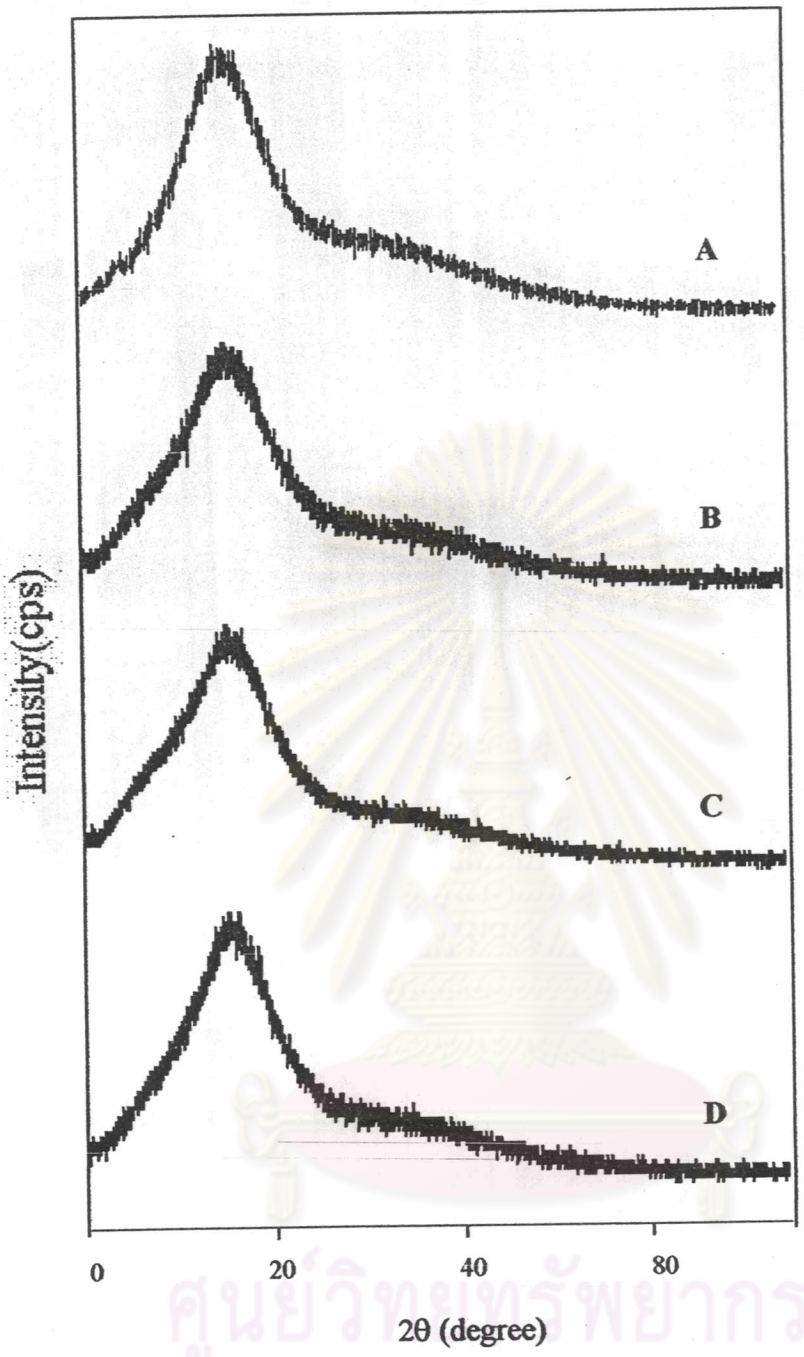


Figure 37 X-ray diffractograms of lidocaine base patches kept in packaging (A) 25°C, 0%RH at 0 day; (B) 25°C, 0%RH after 120 day; (C) 25°C, 75%RH after 120 day; (D) 45°C, 75%RH after 120 day

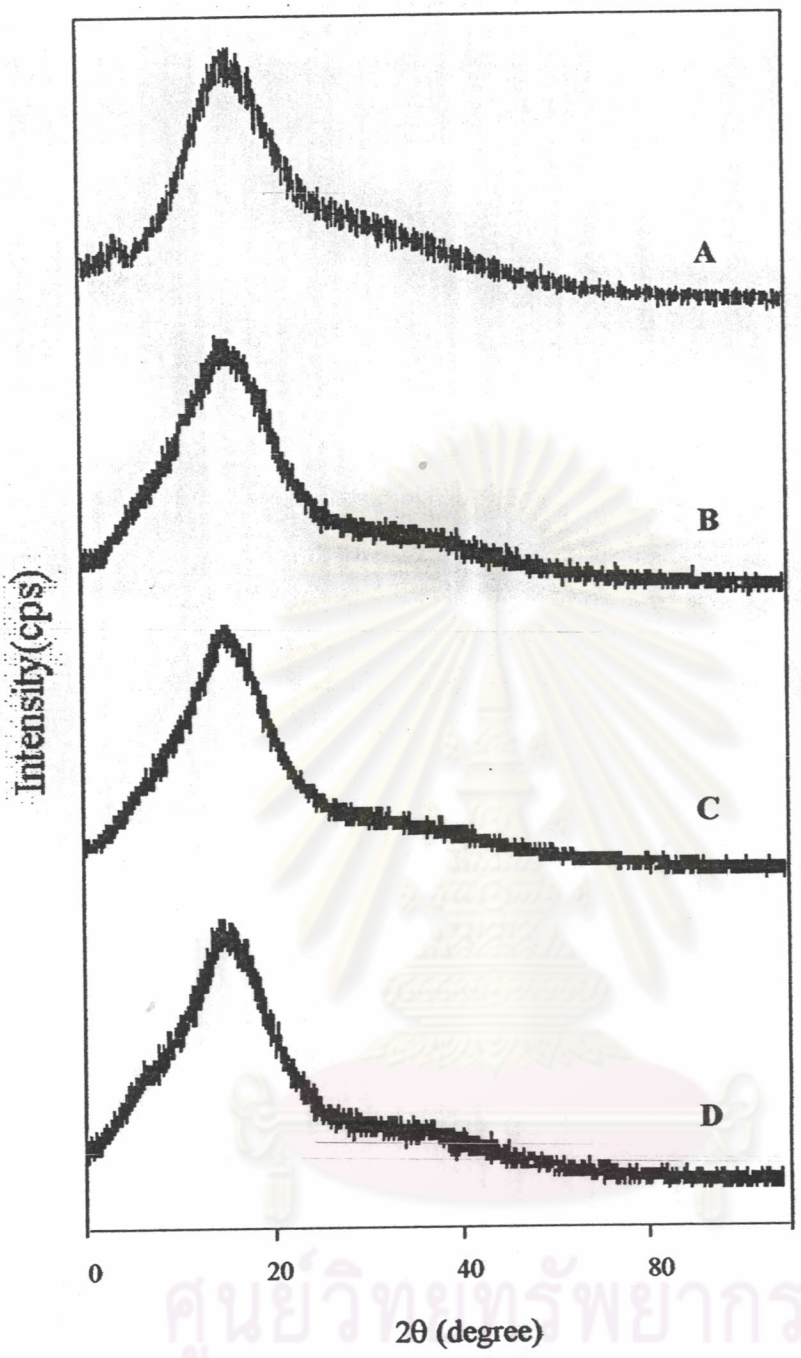


Figure 38 X-ray diffractograms of lidocaine HCl patches kept in packaging (A) 25°C, 0%RH at 0 day; (B) 25°C, 0%RH after 120 day; (C) 25°C, 75%RH after 120 day; (D) 45°C, 75%RH after 120 day

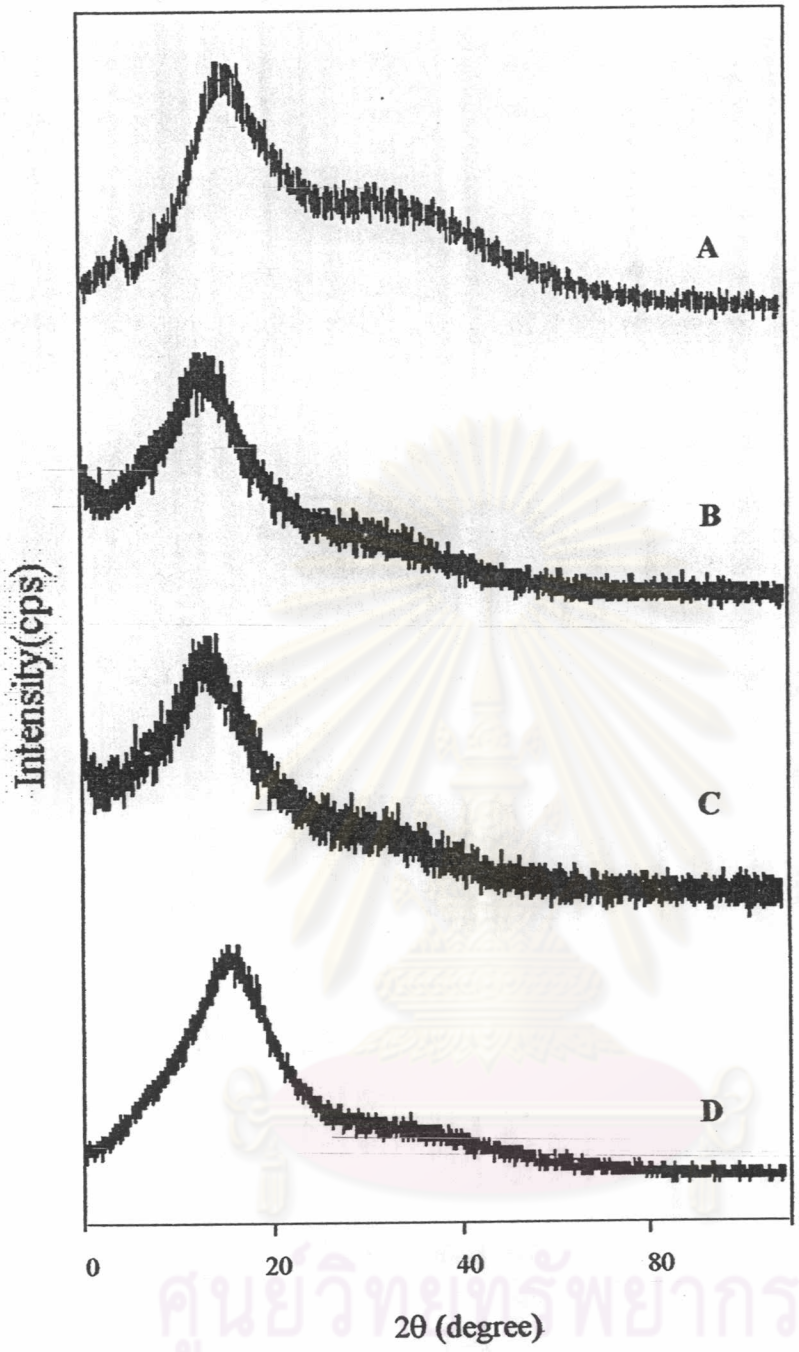


Figure 39 X-ray diffractograms of Dentipatch® kept in packaging
(A) 25°C, 0%RH at 0 day; (B) 25°C, 0%RH after 120 day;
(C) 25°C, 75%RH after 120 day; (D) 45°C, 75%RH after 120 day

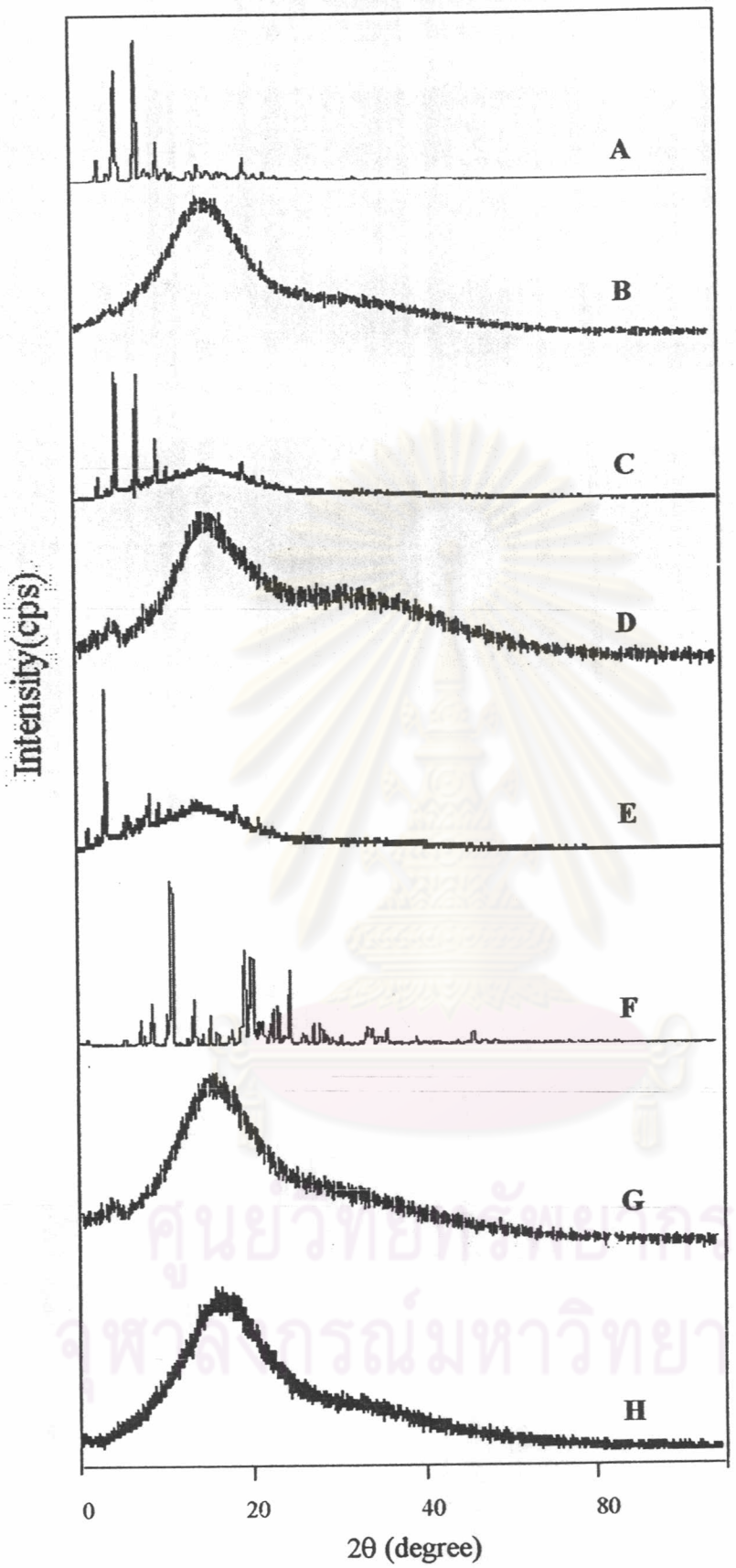


Figure 40 X-ray diffractograms of the patches when exposed about 12 hours to the air without packaging (A) lidocaine base powder; (B) lidocaine base patch before exposed to the air; (C) lidocaine base patch after exposed to the air; (D) Dentipatch® before exposed to the air; (E) Dentipatch® after exposed to the air; (F) lidocaine HCl powder; (G) lidocaine HCl patch before exposed to the air; (H) lidocaine HCl patch after exposed to the air