CHAPTER III

RESULTS & DISCUSSION

1. Preliminary study of film

About 100 uncoated capsules were the suitable amount for coating in the fluidized bed coater. 150 capsules was over loaded for coating resulting in non-uniformity of coating film. In the trial coating, the amount of the CA coating solution containing coloring agent (erythrosine) was sprayed on the core capsules. Color uniformity of coating film was used to determine the suitable amount of coating solution for capsule coating. It was found that 335 ml. of CA coating solution were proper amount to be coated on core capsule no.1.

Results which obtained from process 3.2 described in the experiment is shown in Table 11.

Table 11: The film properties of cellulose acetate in various solvent mixtures and temperatures. (cellulose acetate film obtained by pouring cellulose acetate solution on the plate.)

Solvent mixture	Ratio	Temperature (°C)	The character of cellulose acetate film
Methylene chloride	-	-	The cellulose acetate did not dissolve and formed lump in methylene chloride
Ethanol	-	-	The cellulose acetate did not dissolve ,but it was dispersed in ethanol.
Methylene chloride : Ethanol	95:5	70	Clear
Methylene chloride : Ethanol	95:5	55	Clear

Solvent mixture	Ratio	Temperature (°C)	The character of cellulose acetate film
Methylene chloride : Ethanol	90:10	70	Clear
Methylene chloride : Ethanol	90:10	55	Clear
Methylene chloride : Methanol	90:10	60	Clear
Methylene chloride : Methanol	90:10	30	Not clear
Methylene chloride : Isopropyl alcohol	90:10	60	Not clear
Methylene chloride : Isopropyl alcohol	90:10	30	Not clear

From this result, methylene chloride and ethanol mixture in the ratio of 95:5 and 90:10 gave clear films in temperature range of 55°C to 70 °C. Methylene chloride and methanol in the ratio of 90:10 formed clear film only at the temperature of 60°C and showed unclear film at the temperature of 30°C. Methylene chloride and isopropyl alcohol in the ratio of 90:10 did not form clear film at both temperature 30° C and 60°C.

Methanol was toxic so that ethanol was suitable to be mixed with methylene chloride as solvent mixture. Its ratios of 95:5 and 90:10 in the temperature of both 55°C and 70°C could provide clear film. However, in this study, one condition for coating film was selected. Thus its ratios of 95:5 and the temperature of 55°C were selected to form cellulose acetate film.

From the trial experiment with the coating conditions on fluidized bed coater, atomizing pressure of 1.4-1.6 bar, inlet air temperature of 55°C, feed rate of 5-10 rpm, resulted in smooth surface film covering on capsules, no agglomeration of coated capsules and no blockage of spray nozzle were observed.

2. Properties of core capsule.

2.1 Weight variation

The average weight of the content of capsules ranged from 243.00 to 297.00 mg. for formulation C21-C28 and 314.50 to 365.50 mg. for formulation C11 and C11a. The weight variations of all formulation conformed to BP 2002 specification. The weight variations were within acceptable limit.

Table 12 : Weight variation of various formulations. (n=20)

Formulation	Weight (g.) (mean±S.D.)
C11a	0.3426±0.0083
C11	0.3436±0.0086
C21	0.2716±0.0064
C22	0.2661±0.0062
C23	0.2660±0.0098
C24	0.2724±0.0078
C25	0.2739±0.0065
C26	0.2728±0.0072
C27	0.2722±0.0078
C28	0.2749±0.0071

Remark : C11a = The content formula was similar to C11. C11a was HPMC capsule no.1 , whereas, C11 was gelatin capsule no.1.

2.1 Content of propranolol HCl .

The percentage of drug content of all formulations conformed to USPXXVI specification. The values of percentage drug content ranged from 90.00 to 110.00%. The drug content was within acceptable limit . It indicated uniformity of content.

Table 13: Drug content of various formulations. (n=20).

Formulation	% Drug content (mean±S.D.)
C11a	103.6754±1.2559
C11	99.9385±1.1007
C21	93.1433±2.8340
C22	103.5096±0.7383
C23	103.8825±0.5814
C24	102.8716±1.7007
C25	101.5540±4.2417
C26	102.5236±0.8133
C27	101.8358±0.7866
C28	101.5458±1.2219

Remark : C11a = The content formula was similar to C11. C11a was HPMC capsule no.1 , whereas, C11 was gelatin capsule no.1.

3. Properties of coated capsule

3.1 Film thickness

SEM photomicrographs of the film thickness when coated with the 1% w/v cellulose acetate solution with 41.18 %w/w of PEG400 in polymer at 286, 572 and 858 millilitres are shown in Figure 6-11. The magnification of X150 was used to investigate the thickness of the cellulose acetate film. As displayed in Figure 6-11, the film thickness was measured from the six various positions of the capsules. Average thickness of cellulose acetate film which is presented in Table 14 obtained from two capsules.

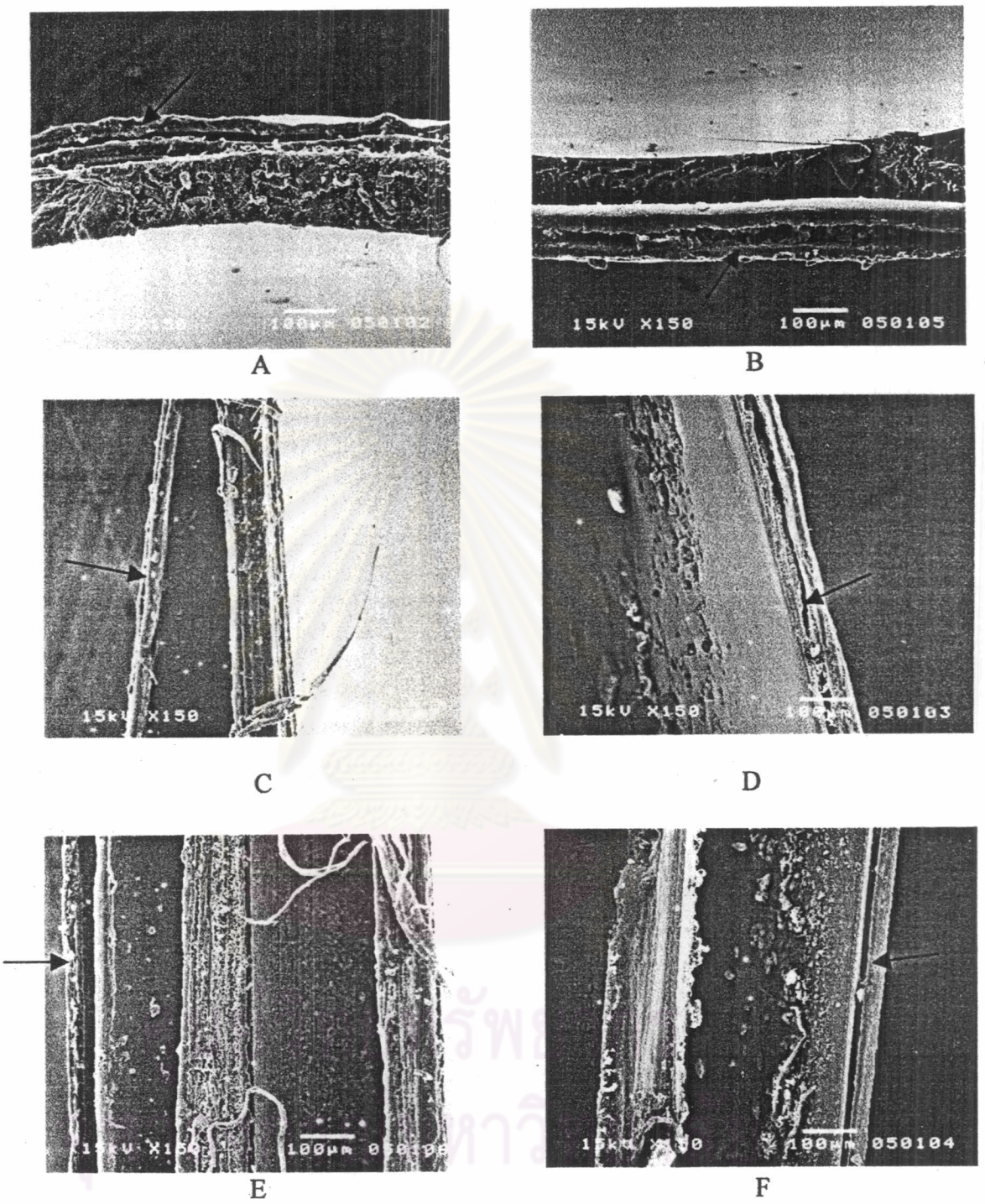


Figure 6: Scanning electron photomicrographs of the cross section of cellulose acetate film (indicated by arrow sign) to measure thickness of film (286 ml. of 1%w/v cellulose acetate solution, at various position of 1st capsules): the end of cap(A), the end of body (B) , both side of cap(C and D) , both side of body (E and F)

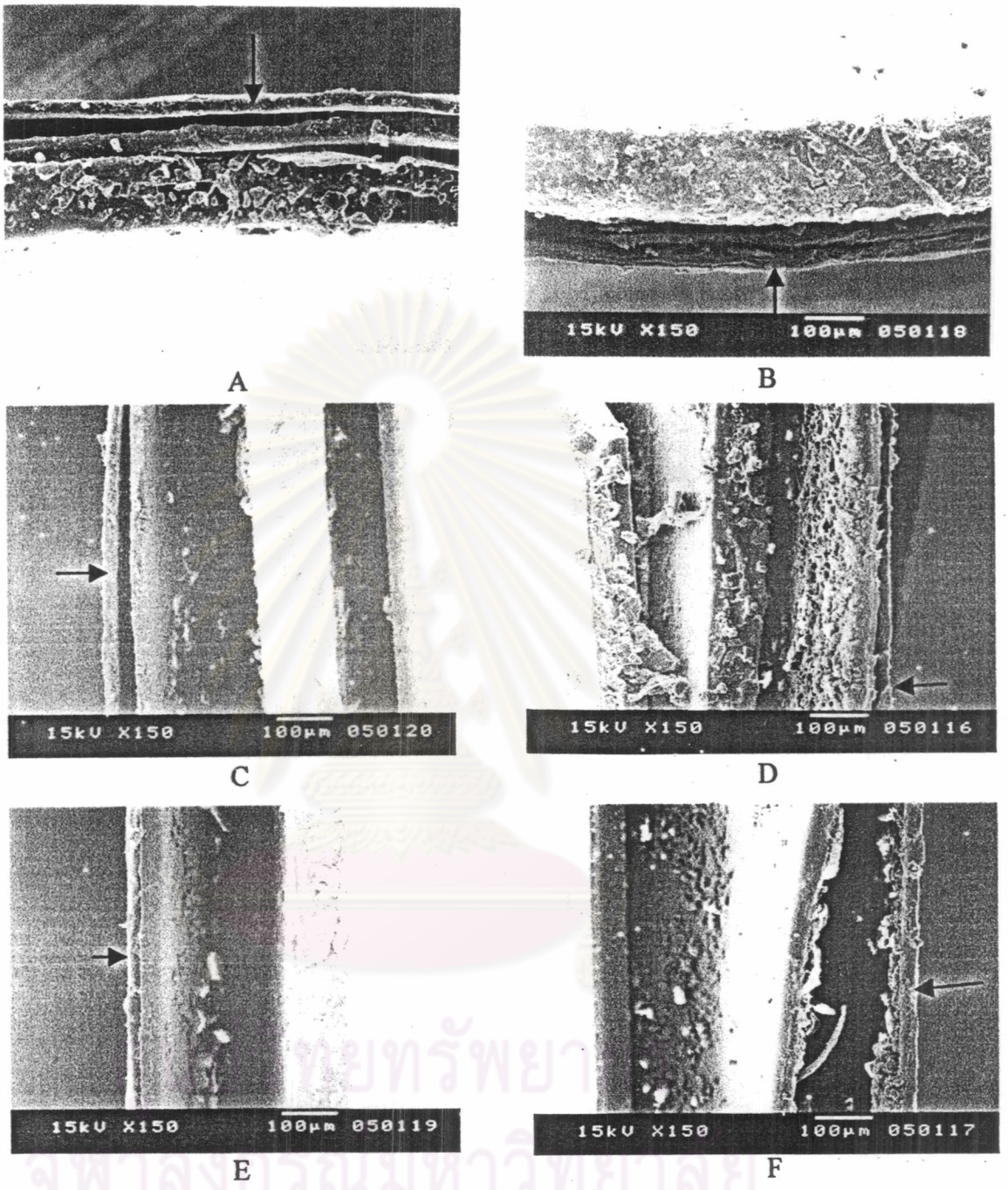


Figure 7: Scanning electron photomicrographs of the cross section of cellulose acetate film (indicated by arrow sign) to measure thickness of film (286 ml. of 1%w/v cellulose acetate solution , at various position of 2nd capsules) : the end of cap (A) , the end of body (B) , both side of cap (C and D) , both side of body (E and F).

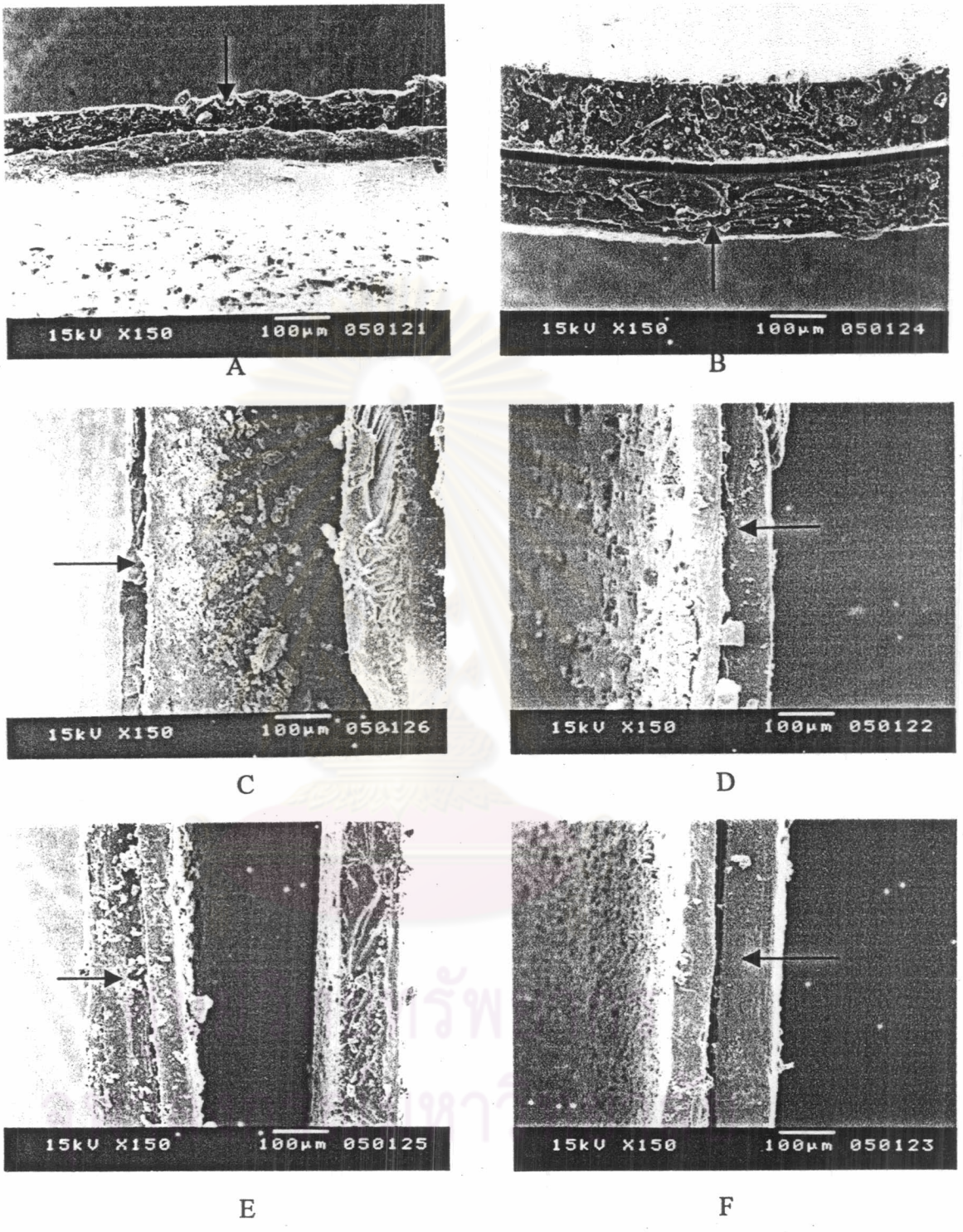


Figure 8: Scanning electron photomicrographs of the cross section of cellulose acetate film (indicated by arrow sign) to measure thickness of film (572 ml. of 1 %w/v cellulose acetate solution , at various position of 1st capsules) : the end of cap (A) , the end of body (B) , both side of cap(C and D) , both side of body (E and F).

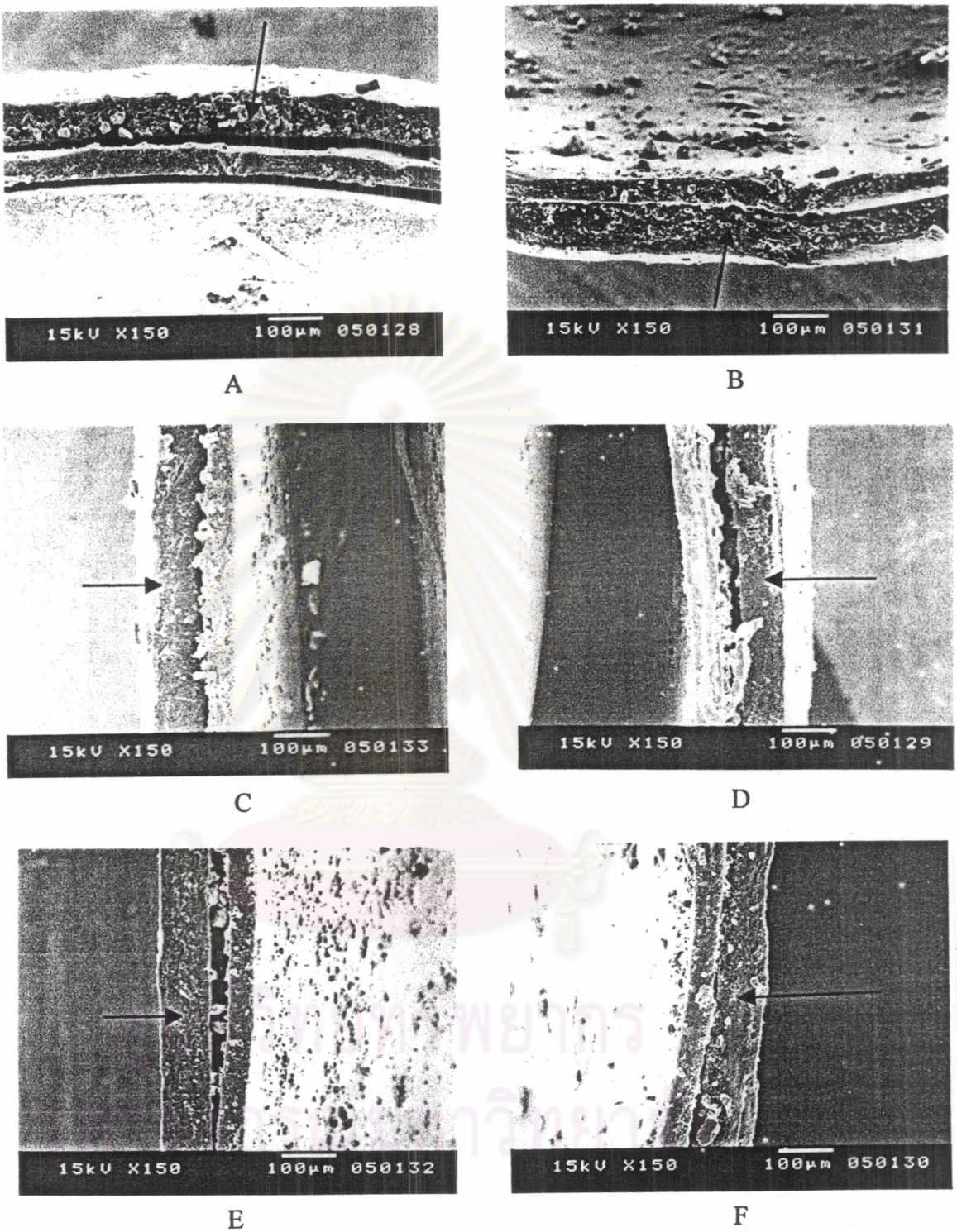


Figure 9 : Scanning electron photomicrographs of the cross section of cellulose acetate film (indicated by arrow sign) to measure thickness of film (572 ml. of 1%w/v cellulose acetate solution, at various position of 2nd capsules) : the end of cap (A) , the end of body (B) , both side of cap(C and D), both side of body (E and F).

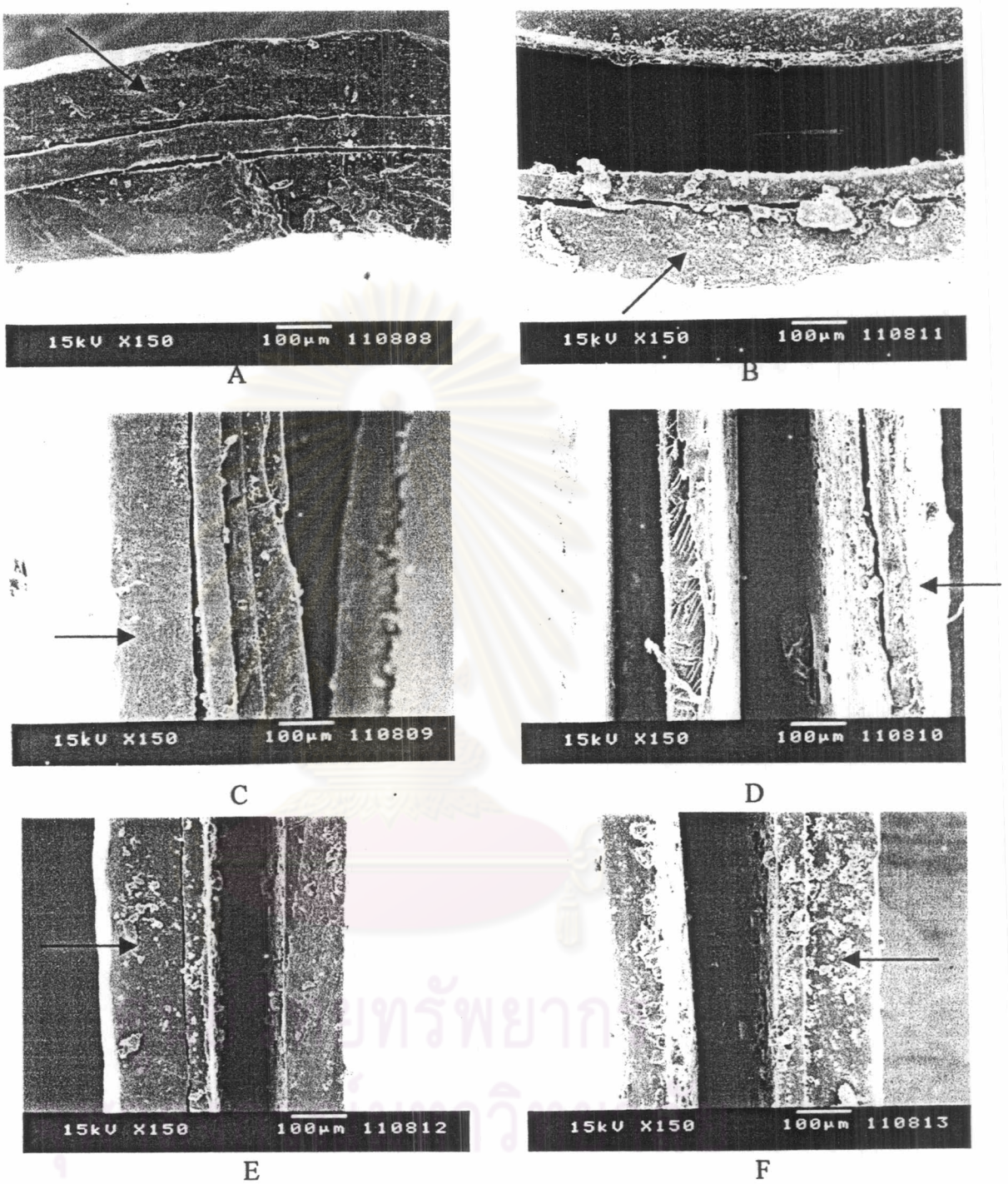


Figure 10: Scanning electron photomicrographs of the cross section of cellulose acetate film (indicated by arrow sign) to measure thickness of film (858 ml. of 1 %w/v cellulose acetate, at various position of 1st capsules) : the end of cap (A) , the end of body (B) , both side of cap(C and D), both side of body (E and F).

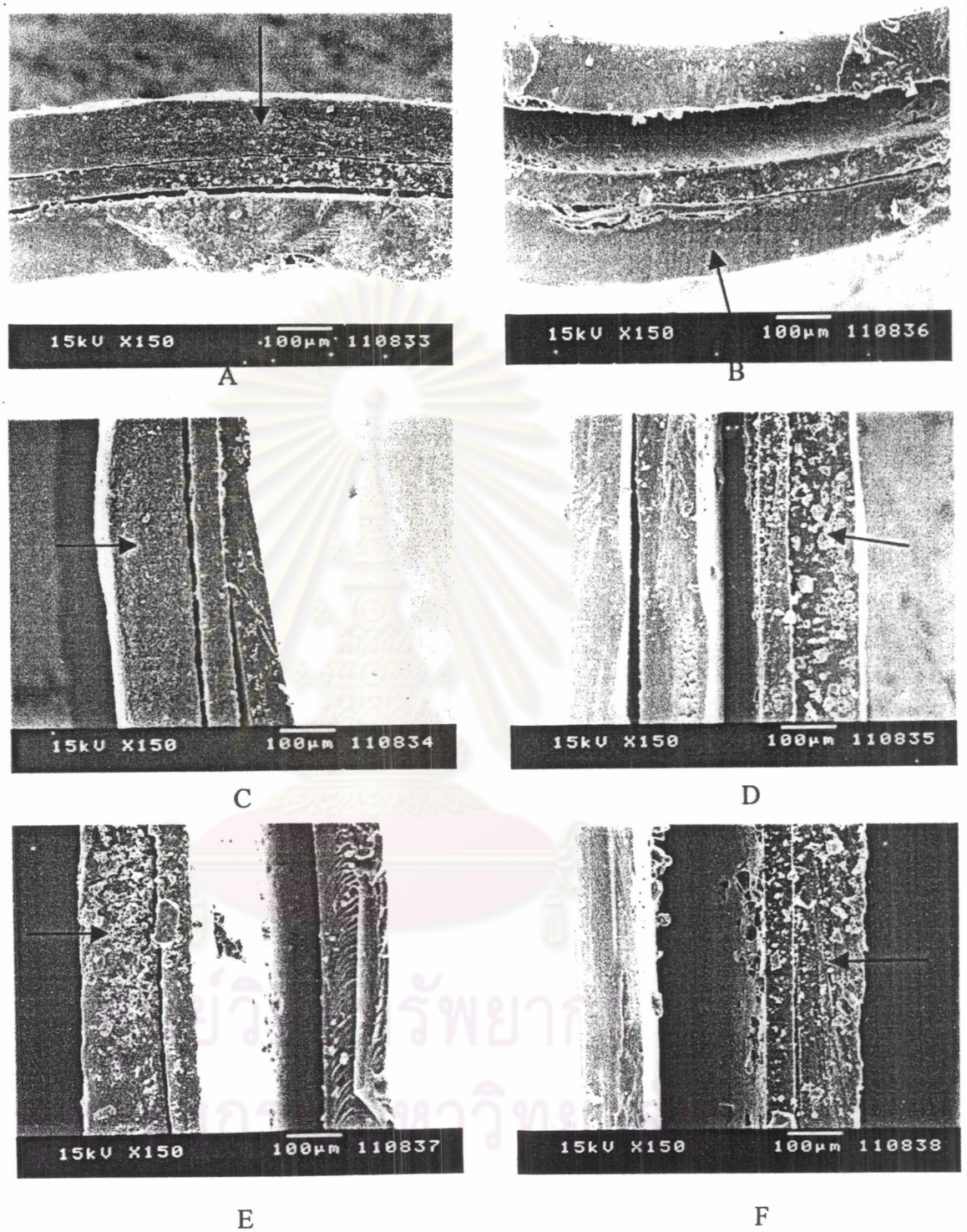


Figure 11: Scanning electron photomicrographs of the cross section of cellulose acetate film (indicated by arrow sign) to measure thickness of film (858 ml. of 1%w/v cellulose acetate solution, at various position of 2nd capsules) : the end of cap (A) , the end of bo dy (B) , both side of cap(C and D), both side of body (E and F).

Table14: Thickness of cellulose acetate film when spraying with various amounts of cellulose acetate solution on the core capsules.

Amount of 1 %w/v cellulose acetate solution (ml)	Average thickness of cellulose acetate film (μm) (mean±SD)*
286	31.5550± 3.4129
572	81.7217±15.6266
858	110.0008±11.9773

* Average of two capsules

3.2 Weight of coating

Table 15 showed average weight and standard deviation of the capsules (n=20) before and after coating with each layer.(HPMC was subcoating layer and CA was semipermeable membrane)

Table 15: Average capsule weights (mean±SD) of various batchs (n = 20) before and after coating.

Coated capsule code.	Average weight of core capsules before coating(g) (mean ± SD)	Average weight of core capsules after coating HPMC(g) (mean ±SD)	Average weight of core capsules after coating CA(g) (mean ± SD)	Average weight of CA(g)
C26 + CA1(*)	0.3276±0.0066	0.3473±0.0077	0.3628±0.0102	0.0155
C23 + CA1(*)	0.3262±0.0040	0.3446±0.0083	0.3625±0.0095	0.0179
C25 + CA1(*)	0.3290±0.0086	0.3451±0.0075	0.3598±0.0088	0.0147
C27 + CA1(*)	0.3289±0.0063	0.3444±0.0086	0.3597±0.0080	0.0153
C28 + CA1(*)	0.3339±0.0033	0.3516±0.0037	0.3646±0.0046	0.0130
C23 + CA2(*)	0.3331±0.0105	0.3473±0.0126	0.3598±0.0135	0.0125
C23 + CA3(*)	0.3321±0.0100	0.3424±0.0093	0.3529±0.0115	0.0105
C23 + CA3(**)	0.3271±0.0106	0.3440±0.0113	0.3825±0.0113	0.0385
C23 + CA3(***)	0.3297±0.0066	0.3492±0.0077	0.4104±0.0094	0.0612
C26 + CA3(***)	0.3274±0.0051	0.3483±0.0070	0.4106±0.0082	0.0623
C24 + CA3(***)	0.3290±0.0058	0.3451±0.0063	0.4046±0.0068	0.0595
C25 + CA3(***)	0.3301±0.0061	0.3455±0.0067	0.3963±0.0077	0.0508
C26 + CA4(*)	0.3295±0.0055	0.3500±0.0074	0.3735±0.0063	0.0235
C21 + CA4(*)	0.3270±0.0076	0.3470±0.0077	0.3706±0.0150	0.0236
C22 + CA4(*)	0.3294±0.0067	0.3494±0.0075	0.3700±0.0091	0.0206
C23 + CA4(*)	0.3299±0.0105	0.3342±0.0097	0.3497±0.0112	0.0155
C23 + CA4(**)	0.3304±0.0084	0.3484±0.0075	0.3949±0.0090	0.0465
C23 + CA4(***)	0.3302±0.0081	0.3443±0.0072	0.4182±0.0109	0.0739

* Cellulose acetate solution 286 ml. , ** Cellulose acetate solution 572 ml.

*** Cellulose acetate solution 858 ml.

Remark: C26+CA1(*) denotes the propranolol HCl capsule formulation C26(as shown in Table 4 of chapter II) coated with the cellulose acetate solution formula CA1(as shown in Table 7 of chapter II) 286 ml.(asterisk exhibits amount of volume of cellulose acetate solution.)

Table 16:Coefficient of weight variation of capsules of various batchs, before and after coating each layer.

	Coefficient of weight variation		
Batch	Before coating	After HPMC coating	After CA coating.
C26 + CA1(*)	2.01	2.21	2.81
C23 + CA1(*)	1.23	2.41	2.62
C25 + CA1(*)	2.61	2.17	2.45
C27 + CA1(*)	1.92	2.50	2.22
C28 + CA1(*)	0.99	1.05	1.26
C23 + CA2(*)	3.15	3.61	3.75
C23 + CA3(*)	3.01	2.72	3.26
C23 + CA3(**)	3.24	3.29	2.95
C23 + CA3(***)	2.00	2.21	2.29
C26 + CA3(***)	1.56	2.01	2.00
C24 + CA3(***)	1.76	1.83	1.68
C25 + CA3(***)	1.85	1.94	1.94
C26 + CA4(*)	1.67	2.11	1.69
C21 + CA4(*)	2.32	2.22	4.05
C22 + CA4(*)	2.03	2.15	2.46
C23 + CA4(*)	3.18	2.90	3.20
C23 + CA4(**)	2.54	2.15	2.28
C23 + CA4(***)	2.45	2.09	2.61

* Cellulose acetate 1 %w/v 286 ml.

** Cellulose acetate 1 %w/v 572 ml.

*** Cellulose acetate 1 %w/v 858 ml.

Figure 12 : Average weights of capsules before and after coating with HPMC and CA, using 286 ml. of CA solution, are presented as mean ± SD (n=20)

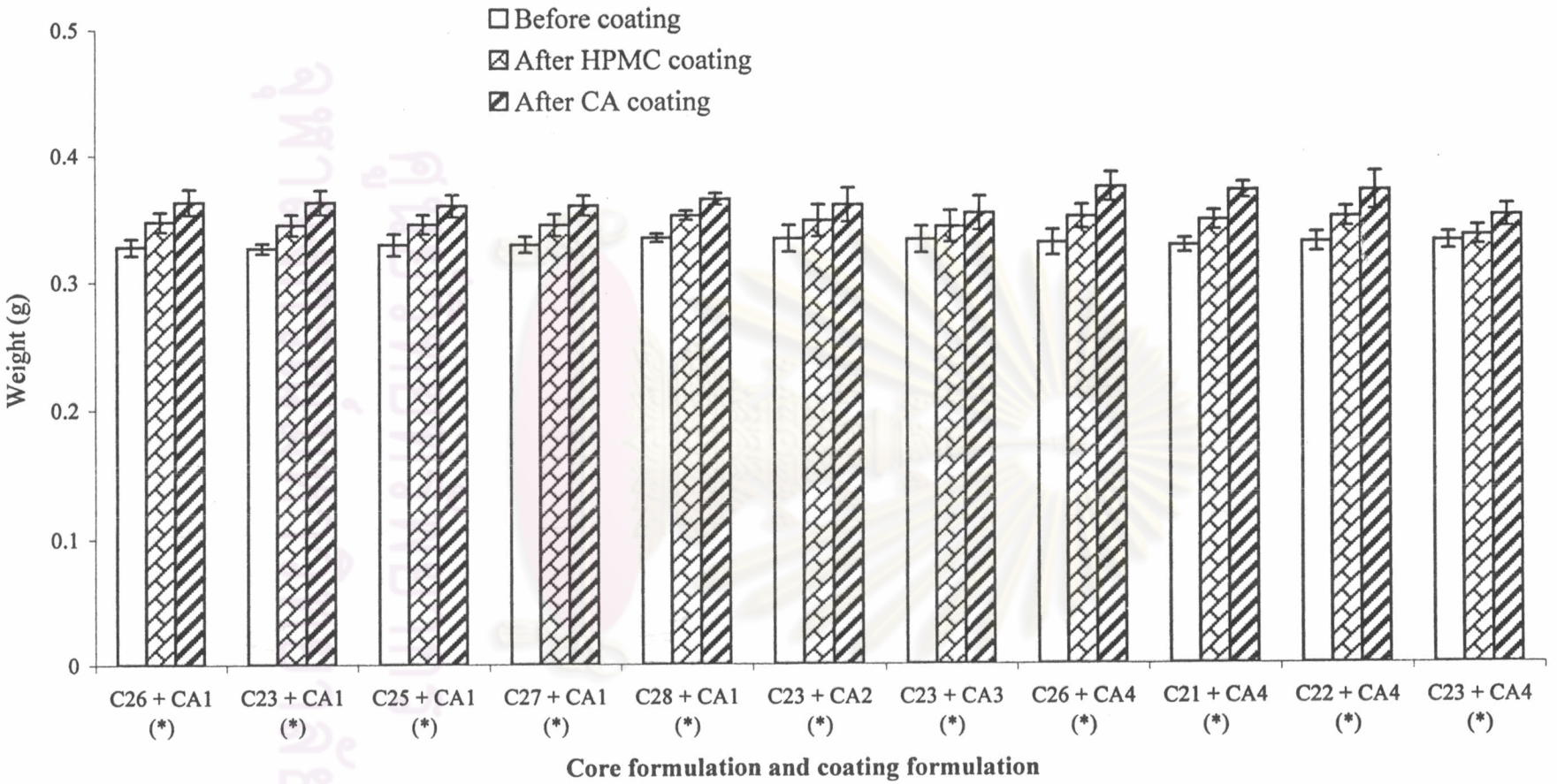


Figure 13 : Average weight of capsules before and after coating with HPMC and CA, using 572 ml. of CA solution, are presented as mean ± SD (n=20).

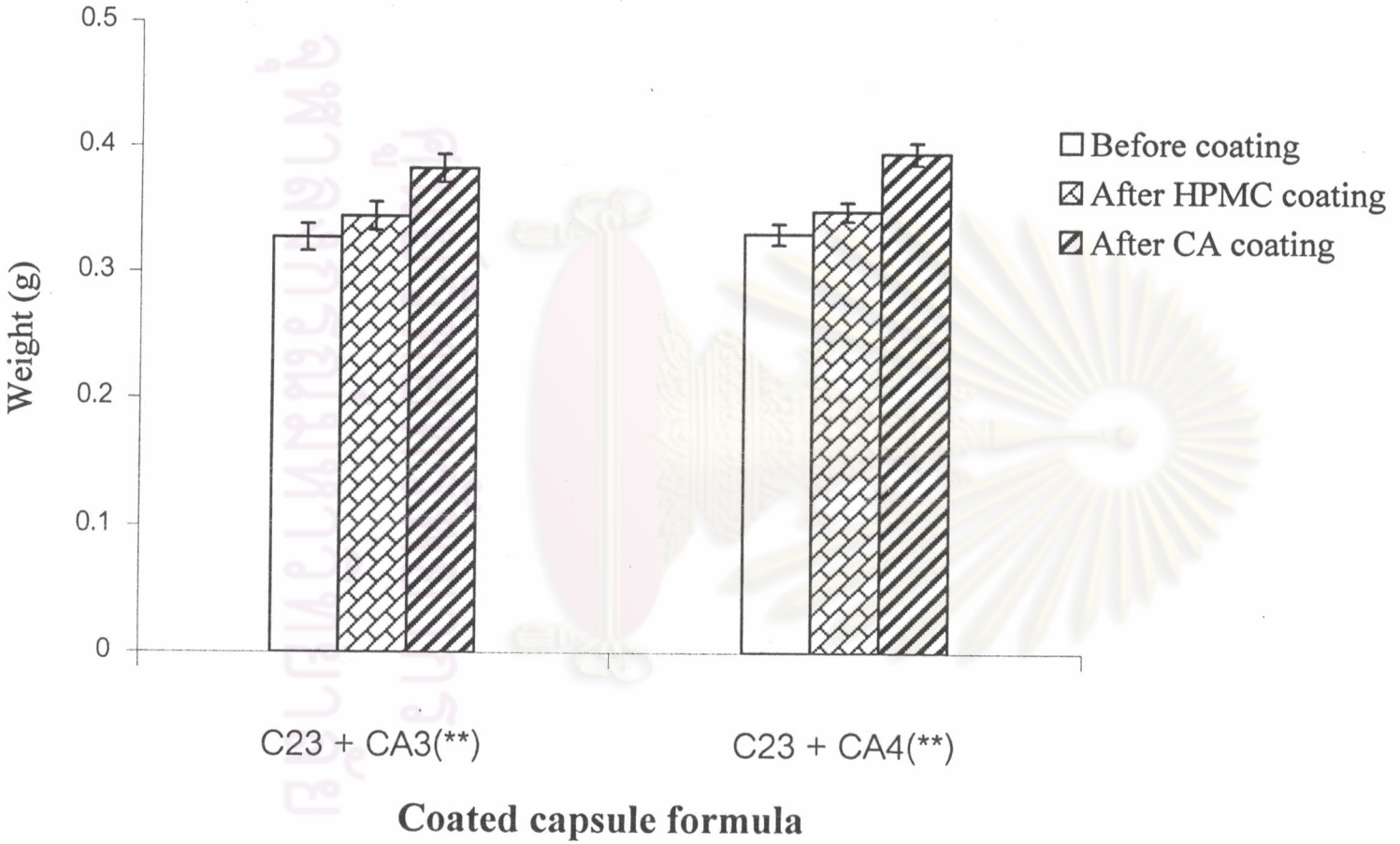
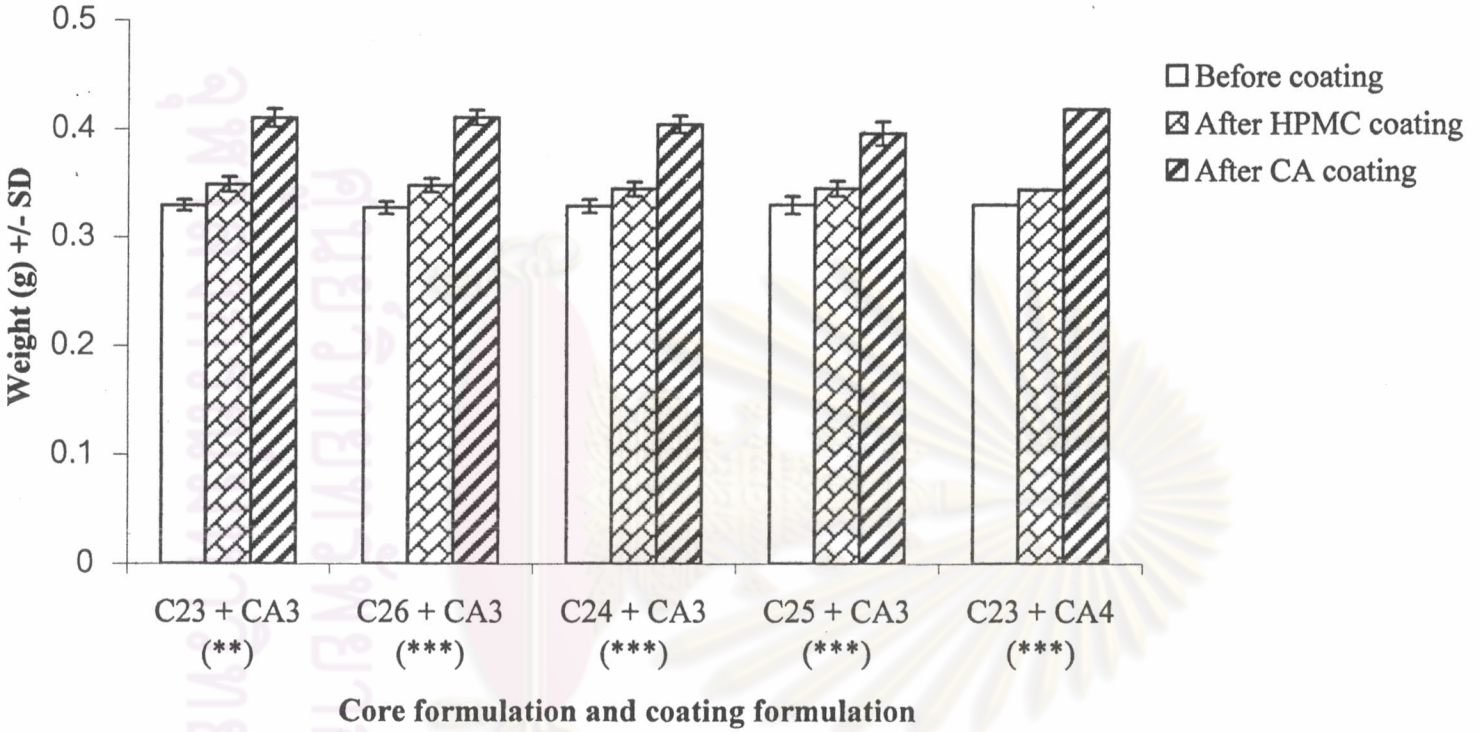


Figure 14 : Average weights of capsules before and after coating with HPMC and CA, using 858 ml.of CA solution, are presented as mean ± SD (n=20).



As shown in Figure 12-14 and Table 15, most average weights of coated capsule after HPMC and CA coating of each formulation in the same amount of CA solution were slightly different. The weight difference of capsule after HPMC and CA coating were weight of CA film. It was found that this value of each formula in the same thickness of cellulose acetate were not different. The CA film weight of capsule coated with 858 ml. and 572 ml. of coating solution was 3 and 2 folds greater than those coated with 286 ml of coating solution.

Standard deviation of average weight of capsules after CA coating was increased slightly. It is indicated that increasing of standard deviation was the result of both HPMC and CA coating.

As shown in Table 16, coefficient of weight variation of coated capsule changed slightly when coating with HPMC and CA solution. CV value of coated capsule weight after CA coating was low in a range of 1.2-4.1.

3.3 The weight of cellulose acetate film.

Table 17 shows actual weight of CA film after dissolution test 12 hours and complete washing(n=6). Average weight and standard deviation was calculated and shown in Table 17.

Table 17 : Average weight and standard deviation of dry shell after dissolution test and complete washing(n = 6)

Formulation	Dry shell weight (g) (mean ± SD) (n = 6)	Coefficient of weight variation
C23+CA1(*)+0mm.	0.0077±0.0002	2.60
C23+CA1(*)+0.4mm.	0.0078±0.0003	3.85
C23+CA1(*)+0.8mm.	0.0075±0.0003	4.00
C23+CA1(*)+1mm.	0.0077±0.0003	3.90
C25+CA1(*)+0mm.	0.0117±0.0002	1.71
C25+CA1(*)+0.8mm.	0.0118±0.0002	1.70
C28+CA1(*)+0mm.	0.0117±0.0006	5.13
C28+CA1(*)+0.8mm.	0.0114±0.0005	4.39
C26+CA1(*)+0mm.	0.0121±0.0002	1.65
C26+CA1(*)+0.8mm.	0.0119±0.0005	4.20
C27+CA1(*)+0mm.	0.0115±0.0003	2.61
C27+CA1(*)+0.8mm.	0.0119±0.0005	4.20
C23+CA2(*)+0mm.	0.0112±0.0005	4.46
C23+CA2(*)+0.4mm.	0.0112±0.0004	3.57
C23+CA3(*)+0mm.	0.0113±0.0003	2.65
C23+CA3(*)+0.4mm.	0.0114±0.0003	2.63
C21+CA4(*)+0mm.	0.0131±0.0003	2.29
C21+CA4(*)+0mm.(0.1588M KCl)	0.0140±0.0006	4.29
C21+CA4(*)+0mm.(0.5M KCl)	0.0138±0.0019	13.77
C21+CA4(*)+0mm.(1M KCl)	0.0134±0.0006	4.48
C21+CA4(*)+0mm.(2M KCl)	0.0135±0.0005	3.70
C21+CA4(*)+0mm.(isotonic phosphate buffer pH 1.2)	0.0120±0.0004	3.33
C21+CA4(*)+0mm.(isotonic phosphate buffer pH 6.8)	0.0128±0.0011	8.60

Formulation	Dry CA shell weight (g) (mean ± SD) (n = 6)	Coefficient of weight variation
C21+CA4(*)+0mm.(pH change)	0.0133±0.0006	4.51
C22+CA4(*)+0mm.	0.0113±0.0006	5.31
C23+CA4(*)+0mm.	0.0086±0.0005	5.81
C23+CA4(*)+0.4mm.	0.0087±0.0003	3.45
C26+CA4(*)+0mm.	0.0125±0.0006	4.80
C23+CA3(**)+0mm.	0.0281±0.0011	3.91
C23+CA3(**)+0.4mm.	0.0283±0.0006	2.12
C23+CA4(**)+0mm.	0.0283±0.0014	4.95
C23+CA3(***)+0mm.	0.0358±0.0005	1.40
C23+CA3(***)+0.4mm.	0.0356±0.0006	1.69
C23+CA3(***)+0.8mm.	0.0356±0.0005	1.40
C23+CA3(***)+1mm.	0.0357±0.0007	1.96
C23+CA3(***)+1mm.(1 orifice at the side of capsule)	0.0359±0.0005	1.39
C23+CA3(***)+1mm.(2 orifices at the end of capsule)	0.0344±0.0029	8.43
C24+CA3(***)+1mm.	0.0360±0.0011	3.06
C25+CA3(***)+1mm.(basket 50rpm.)	0.0343±0.0035	10.20
C25+CA3(***)+1mm.(basket100rpm.)	0.0372±0.0028	7.53
C25+CA3(***)+1mm.(paddle 50 rpm.)	0.0360±0.0010	2.78
C26+CA3(***)+1mm.	0.0358±0.0005	1.40
C23+CA4(***)+0mm.	0.0417±0.0004	0.96

* CA 1 %w/v 286 ml. ** CA 1 %w/v 572 ml. *** CA 1 % w/v 858 ml.

Remark : C26+CA1(*) denotes the propranolol HCl capsule formulation C26 (as shown in Table 4 of chapter II) coated with the 286 ml. of cellulose acetate solution formula CA1(as shown in Table 7 of chapter II, asterisk exhibits volume of cellulose acetate solution.)

As shown in Table 17, CA film weight of capsule that was coated with 572 and 858ml. of CA 1 %w/v was 2 and 3 folds greater than those coated with 286 ml. of coating solution. The weights of CA film from capsule coated with 286, 572 and 858 ml. of CA 1%w/v were in a range of 0.0075-0.0140 g., 0.0281-0.0283 g. and 0.0343-0.0417 g., respectively. Most formulas when coated with the same amount of coating solution had almost similar weight of coated film. The standard deviation of CA film weight was in a range of ±0.0002 to ±0.0035. Most batches, coefficient of variation of actual CA weight was low except a few batches which had CV value more than 6.

3.4 The size of orifice.

The actual sizes of orifice were measured by using optical microscope. Orifice size was the average length of the two lines perpendicular to each other which each line bisects the orifice. Table 18 presents the orifice size when made by using the driller with size of 0.4, 0.6, 0.8 and 1 mm. Figure 15 shows the orifice morphology that obtained from SEM photomicrograph.

Table 18 : Each size of orifice from optical microscope. (n=20)

The size of drill (mm.)	The size of orifice(mm.) (mean ± S.D)
0.4	0.4288+/-0.0198
0.6	0.6211+/-0.0086
0.8	0.8309+/-0.0087
1.0	1.0428+/-0.0120

Table 18 indicates the actual orifice size that was measured by optical microscope was almost similar with the size of driller. Disadvantage of using driller was the untrimmed rim around the orifice.

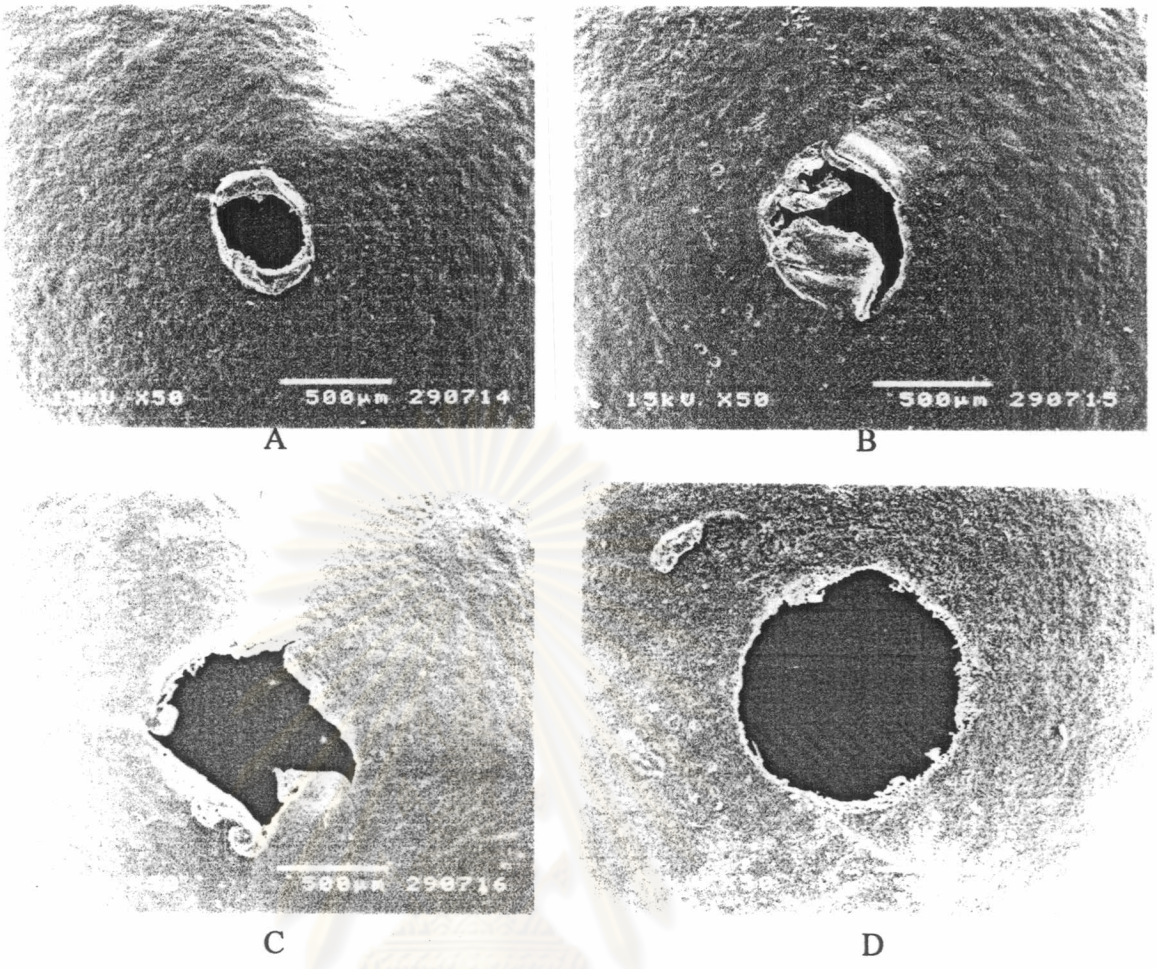


Figure 15 : SEM photomicrographs of cellulose acetate film with various orifice size when using driller with size of 0.4 mm.(A), 0.6 mm.(B), 0.8 mm. (C), 1 mm.(D)

3.5 Cellulose acetate film morphology

SEM photomicrographs of the surface and cross section of the cellulose acetate film from 286 ml. of CA solution with various PEG 400 concentrations (23.08%, 33.33 %, 41.18 %, 50 % w/w in polymer), before and after dissolution test for 12 hours , are shown in Figures 16-31. (Figures 16-19, 24-27 shows surface of the cellulose acetate film and Figures 20-23, 28-31 shows cross-section of the cellulose acetate film)

Before dissolution test, higher PEG 400 as plasticizer in the cellulose acetate film, a smoother film surface was observed. (Figures 16-19). Whereas, after dissolution, the membrane was rougher and more porous as plasticizer increased (Figures 24-27). The higher PEG 400 containing film when contacted with water will have more pores due to leaching out of PEG 400 from the membrane. So the membrane was rougher as higher PEG400 concentration.

As shown in Figures 20-23, the cross section topography of cellulose acetate film of coated capsule before contacting water exhibited fiber-like characteristic and became thicker fiber as more amount of PEG 400. SEM photomicrographs of cellulose acetate film after dissolution test (Figures 28-31) shows cavity-like characteristics due to leaching out of PEG400 from the membrane. The shape of cavity was continuous when concentration of PEG400 was increased to 50.00%. However; at low concentrations of PEG400(23.08 %-41.18 %), it was not continuous (Appel and Zentner, 1991).

When compared CA films before and after dissolution test, it was found that the CA film of coated capsule before dissolution test did not have any cavity or pore in the membrane, whereas, the CA film of coated capsule after the dissolution test had cavity or pore due to dissolved PEG400 by water. The SEM photomicrographs of surface and cross section proved that PEG400 was pore forming agent(Verma, Kaushal, and Garg ,2003; Ozdemir and Sahin, 1997).

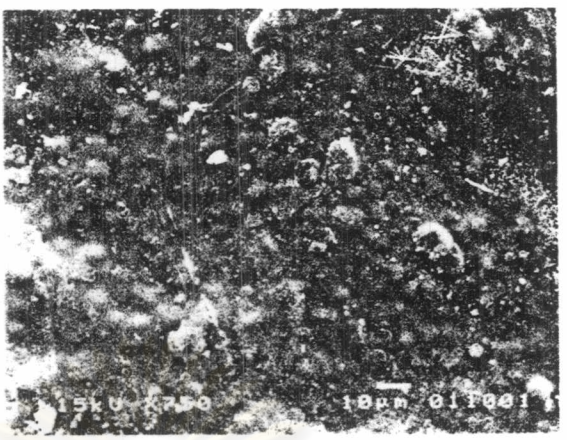


Figure 16: Scanning electron photomicrograph of the surface of cellulose acetate film plasticized with 23.08 % w/w of PEG 400 in polymer before dissolution test for 12 hours (X750).

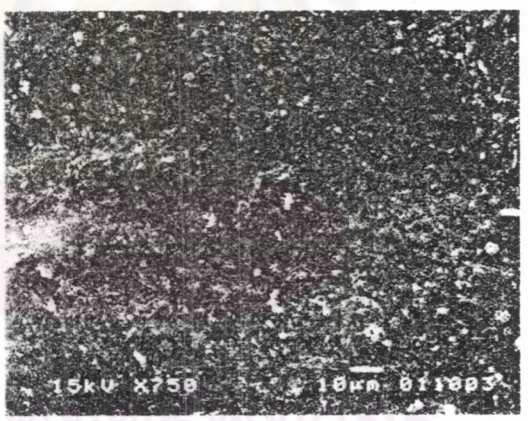


Figure 17: Scanning electron photomicrograph of the surface of cellulose acetate film plasticized with 33.33 % w/w of PEG 400 in polymer before dissolution test for 12 hours (X750).

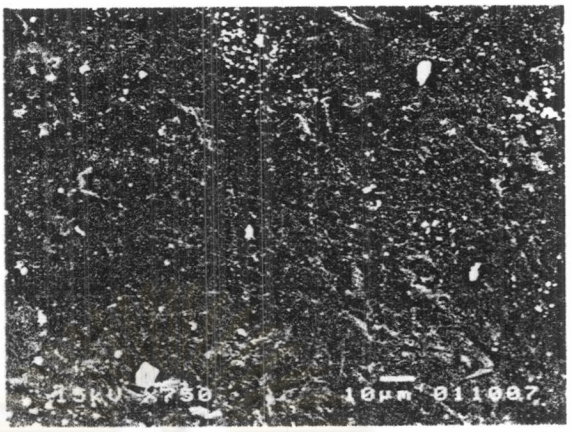


Figure 18: Scanning electron photomicrograph of the surface of cellulose acetate film plasticized with 41.18 % w/w of PEG 400 in polymer before dissolution test for 12 hours(X750).

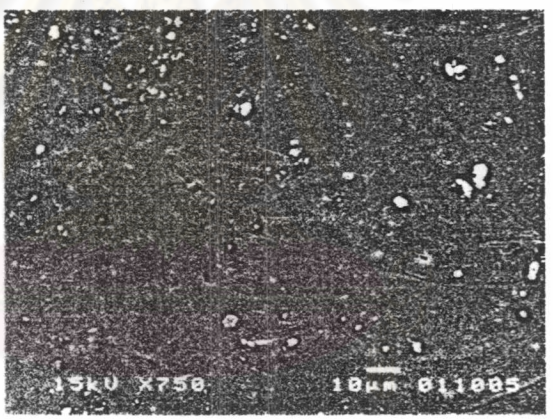


Figure 19: Scanning electron photomicrographs of the surface of cellulose acetate film plasticized with 50.00 % w/w of PEG 400 in polymer before dissolution test for 12 hours (X750).

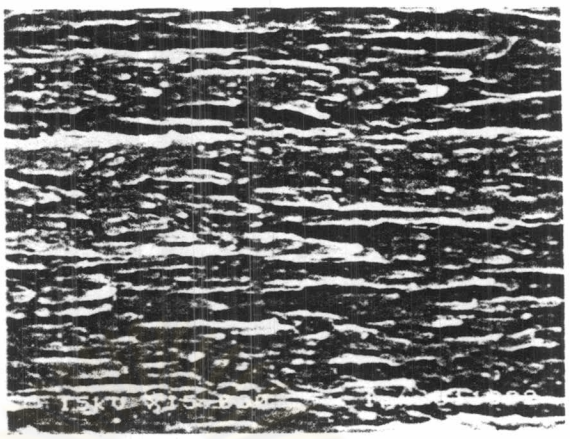


Figure 20: Scanning electron photomicrograph of the cross section of cellulose acetate film plasticized with 23.08 %w/w of PEG 400 in polymer before dissolution test for 12 hours(X15,000).

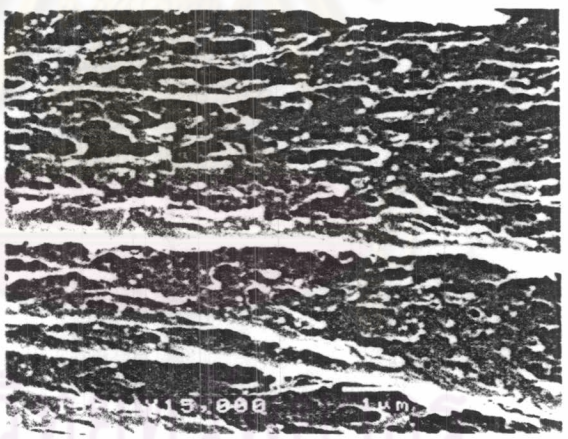


Figure 21: Scanning electron photomicrograph of the cross section of cellulose acetate film plasticized with 33.33 % w/w of PEG 400 in polymer before dissolution test for 12 hours(X15,000).

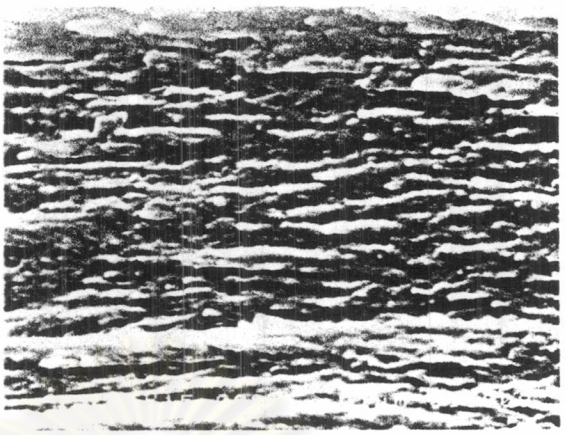


Figure 22: Scanning electron photomicrographs of the cross section of cellulose acetate film plasticized with 41.18 % w/w of PEG 400 in polymer before dissolution test for 12 hours (X15,000).

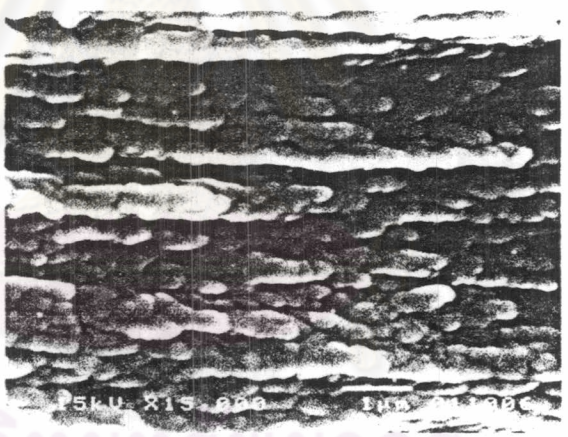


Figure 23: Scanning electron photomicrographs of the cross section of cellulose acetate film plasticized with 50.00%w/w of PEG 400 in polymer before dissolution test for 12 hours(X15,000).

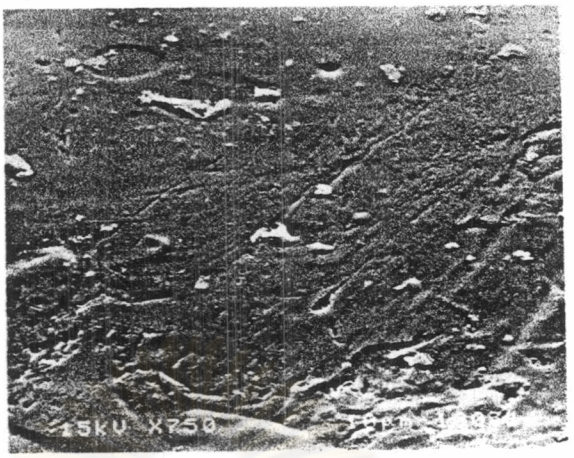


Figure 24: Scanning electron photomicrograph of the surface of cellulose acetate film plasticized with 23.08 %w/w of PEG 400 in polymer after dissolution test for12 hours (X750).

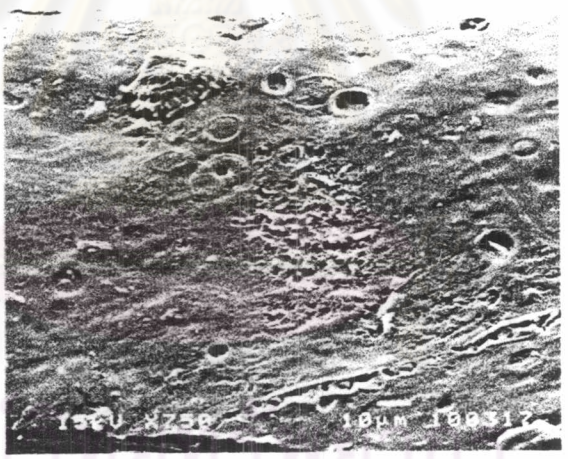


Figure 25: Scanning electron photomicrograph of the surface of cellulose acetate film plasticized with 33.33 %w/w of PEG 400 in polymer after dissolution test for 12 hour(X750).

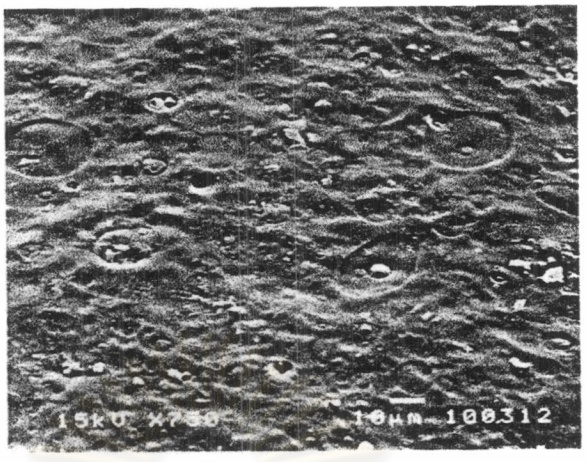


Figure 26: Scanning electron photomicrograph of the surface of cellulose acetate film plasticized with 41.18 %w/w of PEG 400 in polymer after dissolution test for 12 hours.

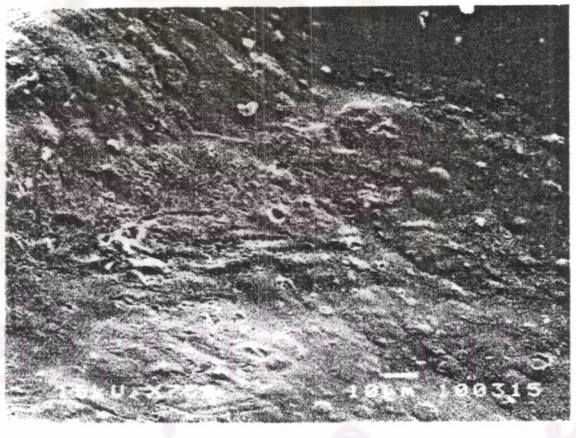


Figure 27 : Scanning electron photomicrograph of the surface of cellulose acetate film plasticized with 50.00%w/w of PEG 400 in polymer after dissolution test for 12 hours.

Figure 28: Scanning electron photomicrograph of the cross section of cellulose acetate film plasticized with 23.08 %w/w of PEG 400 in polymer after dissolution test for 12 hours (X15,000).

Figure 29: Scanning electron photomicrograph of the cross section of cellulose acetate film plasticized with 33.33 %w/w of PEG 400 in polymer after dissolution test for 12 hours (X15,000).

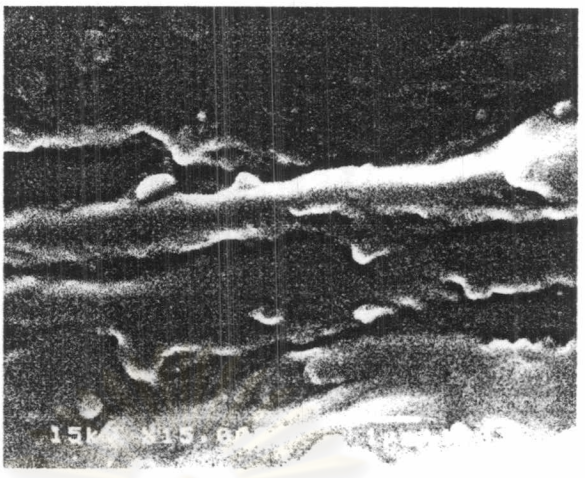


Figure 30: Scanning electron photomicrograph of the cross section of cellulose acetate film plasticized with 41.18 %w/w of PEG 400 in polymer after dissolution test. for 12 hours(X15,000).

Figure 31:Scanning electron photomicrograph of the cross section of cellulose acetate film plasticized with 50.00 %w/w of PEG 400 in polymer after dissolution test for 12 hours(X15,000).

3.6 Dissolution study

The amount of propranolol HCl released from coated capsules in various dissolution media, i.e., deionized water, isotonic buffer solution pH 1.2, isotonic buffer solution pH 6.8 and potassium chloride solution were studied. The percentage of accumulated amount of drug release was plotted against time. In this study, drug release was observed for 12 hours. It should be noted that at absorbance value was lower than 0.2, propranolol HCl amount could not be detected accurately.

3.6.1 Drug release from hydroxypropylmethylcellulose capsule no.1

The drug release profiles from HPMC capsules containing drug and NaCl (1:1) coated with 335 ml. of CA solution plasticized with DEP (coating solution formula DP1) and punctured with various orifice sizes, i.e., 0.25, 0.4, 0.6, 0.8 and 1 mm and various number of orifice (1-6) are shown in Figures 33 and 34. Deionized water was used as dissolution medium. Position of orifice was shown in Figure 32.

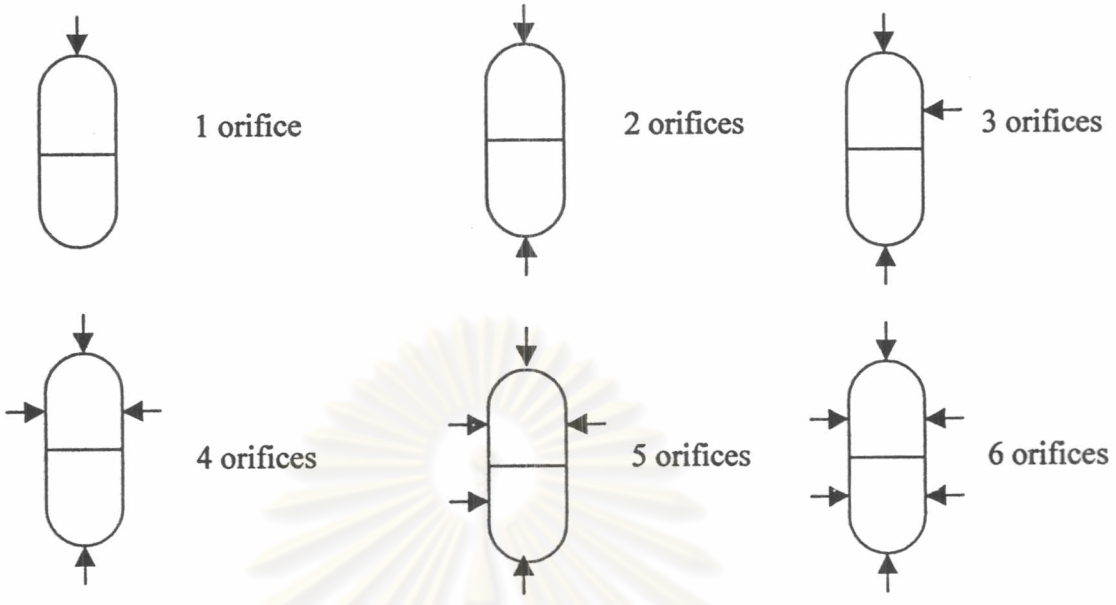


Figure 32 :Diagramatic illustration of the orifice position of capsules

Figure 33 shows that the drug release from HPMC capsule no.1 was not increased with increasing orifice size , the numbers of orifices size of 0.6 mm. were then increased in the later trial. As shown in Figure 34, drug release was very slow even through six orifices was made on the capsule. The time of gelatin and HPMC capsule shells to be completely dissolved in 900 ml of deionized water were tested using USP Dissolution Apparatus Type I (basket at 50 rpm). It was observed that the dissolution time of gelatin and HPMC capsules were 28.33 and 48.67 minutes(n = 3), respectively. Since Gelatin capsule No.1 dissolved faster than HPMC capsule No.1. and the drug release rate of coated gelatin capsule was higher than coated HPMC capsule (plasticized with DEP and punctured to have orifice size of 0.8 mm. as shown in Figure 36), whereas, no difference of drug release rate in both type of capsule when coated capsule punctured to have orifice size of 0.4.(Figure 35). Gelatin capsule was therefore selected for further study under topic 3.6.2.

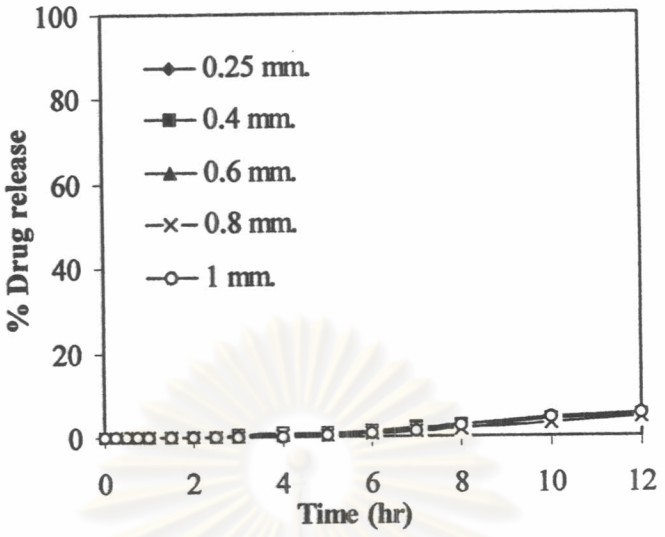


Figure33 : The release profiles of various orifice size of propranolol HCl coated capsules(HPMC capsule No.1)containing drug:NaCl(1:1) were coated with 335 ml. of CA solution plasticized with 23.08 %w/w of DEP in polymer.

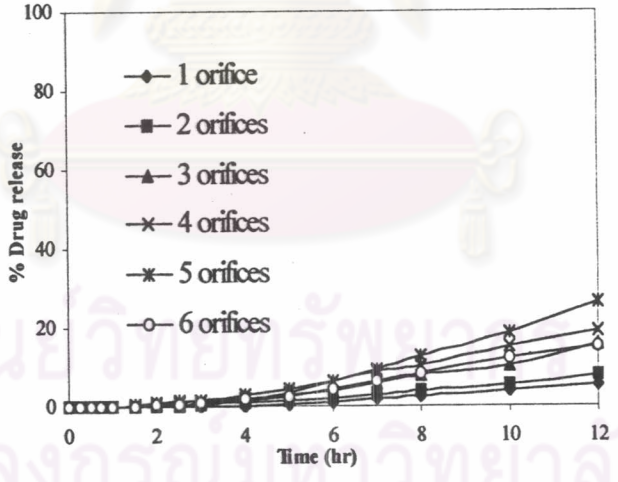


Figure 34 : The release profiles of various number of orifice size of 0.6 mm from propranolol HCl capsules (HPMC capsule No.1) containing drug:NaCl (1:1) were coated with 335 ml. of CA solution plasticized with 23.08% w/w of DEP in polymer.

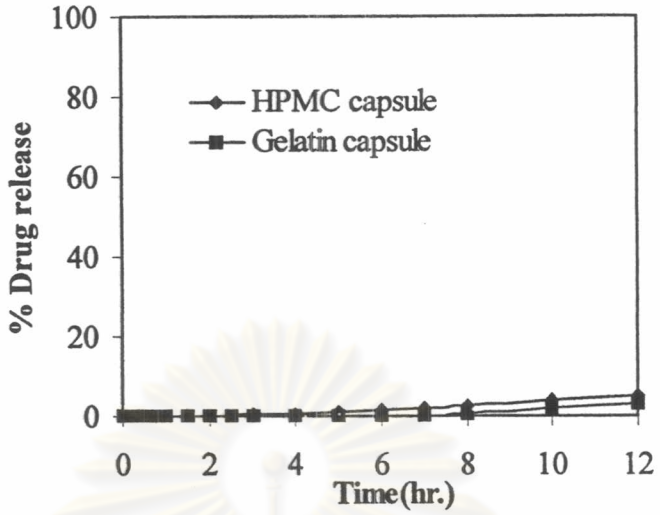


Figure 35: Comparative release profiles between propranolol HCl coated HPMC capsules and gelatin capsule(capsule no.1) from capsules containing drug:NaCl(1:1) were coated with 335 ml of CA solution plasticized with 23.08 %w/w of DEP in polymer when punctured to have orifice size of 0.4 mm.

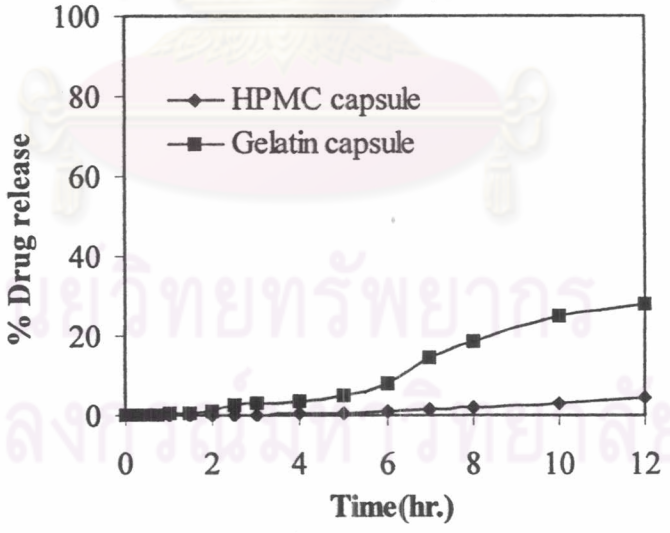


Figure 36: Comparative release profiles between propranolol HCl coated HPMC capsules and gelatin capsules(capsule no.1) from capsules containing drug:NaCl(1:1) were coated with 335 ml of CA solution plasticized with 23.08 %w/w of DEP in polymer when punctured to have orifice size of 0.8 mm.

3.6.2 Drug release from coated gelatin capsule no.1.(preliminary)

Effects of plasticizer type, PEG400 and DEP, on the drug release from coated gelatin capsule No.1 were studied. Deionized water was used as dissolution medium. The drug release profiles from gelatin capsule no.1 coated with 335 ml. of CA solution plasticized with 23.08 %w/w of PEG 400 in polymer and DEP when punctured with orifice size of 0.4 mm are shown in Figures 37 and 38.

As shown in Figures 37, 38, the drug release of coated capsule plasticized with PEG400 was higher than those plasticized with DEP, owing to water-soluble property of PEG400. As shown in Figure 37, at duration of 2 to 12 hours, the drug release of capsule coated with PEG400-plasticized film was higher than those with DEP-plasticized films. Figure 38 illustrated that at duration of 2 to 7 hours, drug release rate of capsule coated with CA film plasticized with PEG400 was higher than those plasticized with DEP , whereas, duration of 7 to 12 hours, they were similar. Since PEG400 was water-soluble plasticizer, so CA formed porous film after contacted with water and water influx through CA membrane to dissolve the gelatin shell which was higher than coated capsule with DEP-CA film, as DEP was water-insoluble plasticizer. When gelatin dissolved partially, increase of water influx through membrane to dissolve drug and osmotic agent. Therefore , the drug was released through both orifice and pores. On the contrary, coated capsule with DEP as plasticizer, the drug was released only through the orifice because the film did not form porous film due to water-insoluble property of DEP.

As shown in Figures 37 and 38, capsule that was coated with DEP-plasticized film with orifice size of 0.4 mm. released less drug than those with orifice size of 0.8 mm. Small size of orifice caused less water influx through orifice, the capsule shell was dissolved difficultly resulting in obstructing water influx through CA film. Thus, the drug and osmotic agent was less dissolved due to less water influx through orifice and membrane resulting in less drug release. Moreover, the drug did not release through pore of cellulose acetate film due to water-insoluble property of DEP.

Since drug release of coated capsule with PEG400-CA film was higher than those with DEP-CA film. Thus, PEG400 was used as plasticizer for further study.

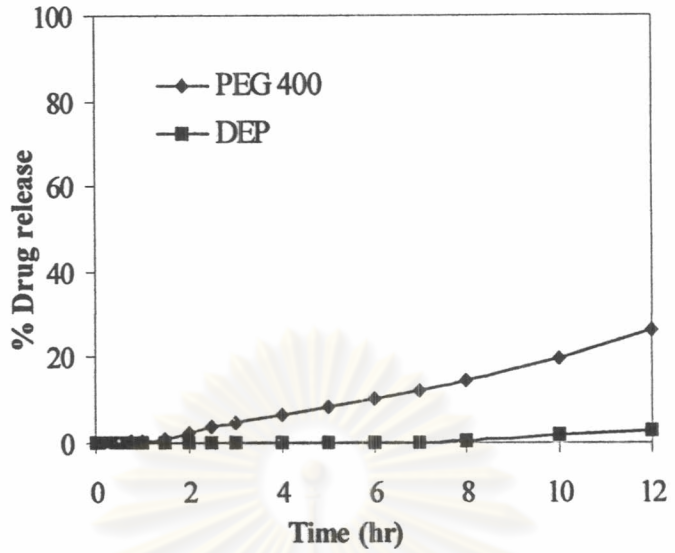


Figure 37: Comparative release profiles of propranolol HCl capsule(gelatin capsule no.1) containing drug:NaCl(1:1) were coated with 335 ml. of CA solution plasticized with 23.08 %w/w of PEG 400 in polymer and with 23.08 %w/w of DEP in polymer when punctured to have orifice size of 0.4 mm.

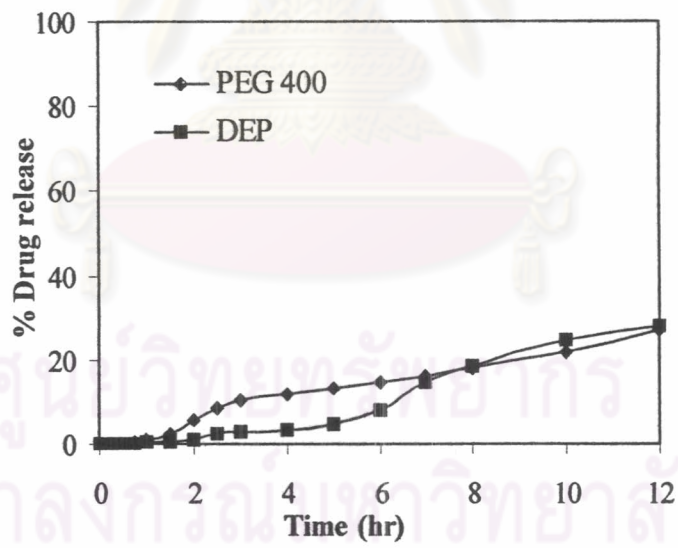


Figure 38: Comparative release profiles of propranolol HCl coated capsule(gelatin capsule No.1) containing drug:NaCl(1:1) were coated with 335 ml. of CA solution plasticized with 23.08 %w/w of PEG 400 in polymer and with 23.08 %w/w of DEP in polymer when punctured to have orifice size of 0.8 mm.

3.6.3 Drug release study of coated gelatin capsule no. 2

As mention under topic 3.4.12, since gelatin capsule no.1 was not suitable to load 80 mg. of propranolol HCl , so the smaller size of gelatin capsule no.2 was used as shell instead of capsule no.1. The other reason to change the capsule size was that the drug release from coated gelatin capsule size no. 2 was higher than coated gelatin capsule size 1 at orifice size of 0.8 mm.(Figure 39 and 40). Following factors ie, the size and number of orifice, amount of plasticizer, thickness of membrane, position of orifice, amount of osmotic agent, the type and speed of rotating apparatus, various tonicity of dissolution medium, different pH of dissolution medium, and interaction between osmotic agent and gelatin on drug release was studied to observe theirs influence on drug release. Deionized water was used as dissolution medium except study in influence of different tonicity and pH of dissolution medium.

Typical calibration curve data for propranolol HCl in various dissolution media type ie, deionized water, buffer solution pH 1.2, buffer solution pH 6.8, isotonic buffer solution pH 1.2, isotonic buffer solution pH 6.8, isotonic potassium chloride solution (0.1588 M) , 0.5 M potassium chloride solution , 1 M potassium chloride solution , 2 M potassium chloride solution were shown in Table 1A and 3A-10A (Appendix A)

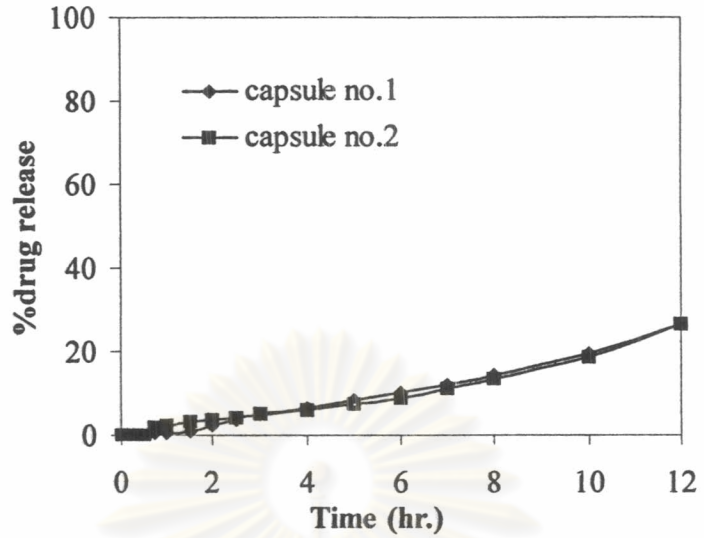


Figure 39 : Comparative release profile of propranolol HCl coated gelatin capsule no.1 and no.2 from capsule containing drug:NaCl(1:1) were coated with 335 ml.(no.1) and 286 ml.(no.2) of CA solution plasticized with 23.08 % w/w of PEG400 in polymer when punctured to have orifice size of 0.4 mm.

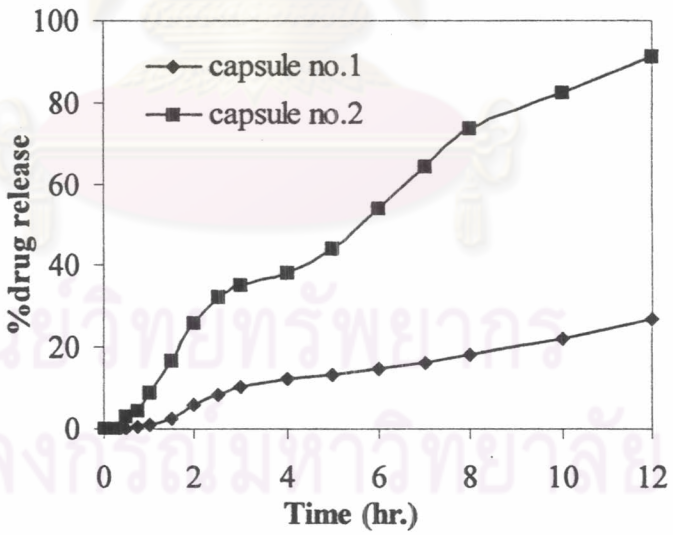


Figure 40 : Comparative release profile of propranolol HCl coated gelatin capsule no.1 and no.2 from capsule containing drug:NaCl(1:1) were coated with 335 ml.(no.1) and 286 ml.(no.2) of CA solution plasticized with 23.08 % w/w of PEG400 in polymer when punctured to have orifice size of 0.8 mm.

a) The effect of orifice size on drug release.

The effect of orifice sizes on drug release was investigated. The release profiles of various orifice size, i.e., 0, 0.4, 0.8 and 1mm. of capsules containing drug and NaCl(1:1)(formula C23) coated with 286 ml. of CA solution plasticized with 23.08 %w/w PEG400 (coating solution CA1) are shown in Figure 41. The drug release profiles of various orifice size(0,0.4,0.8 and 1mm.) of capsule containing drug and NaCl(1:1)(capsule formula C23) coated with 858 ml.of CA solution plasticized with 41.18 %w/w of PEG400 in polymer were shown in Figure 42.

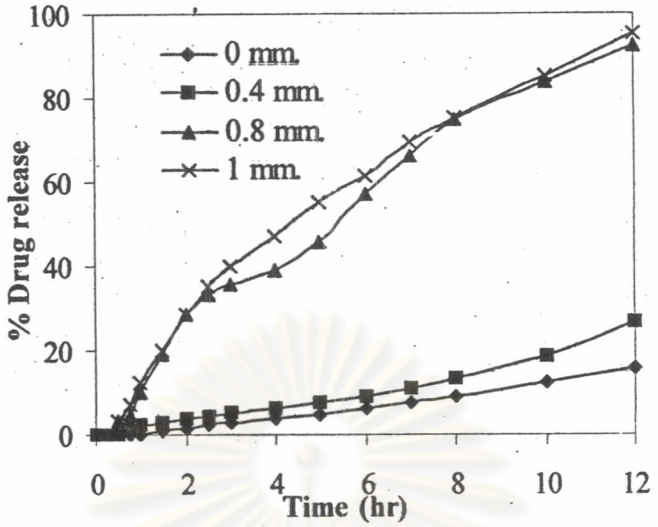


Figure 41: The release profiles of various orifice size of propranolol HCl coated capsules containing drug:NaCl(1:1) were coated with 286 ml. of CA coating solution plasticized with 23.08%w/w of PEG400 in polymer.

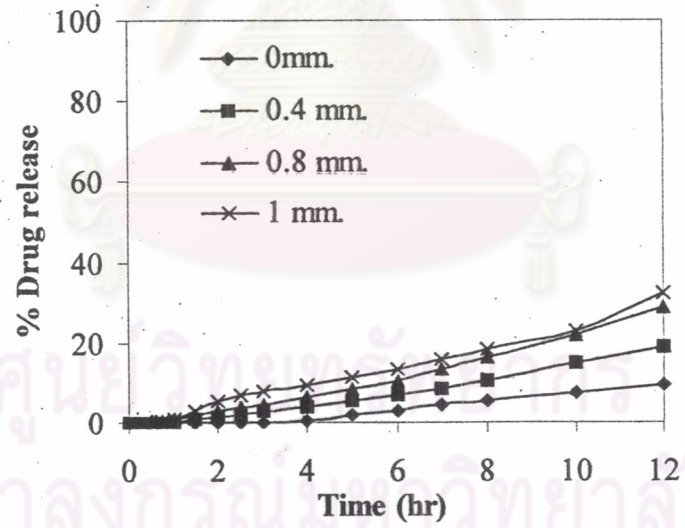


Figure 42: The release profiles of various orifice size of propranolol HCl coated capsules containing drug:NaCl(1:1) were coated with 858 ml. of CA coating solution plasticized with 41.18 %w/w of PEG400 in polymer.

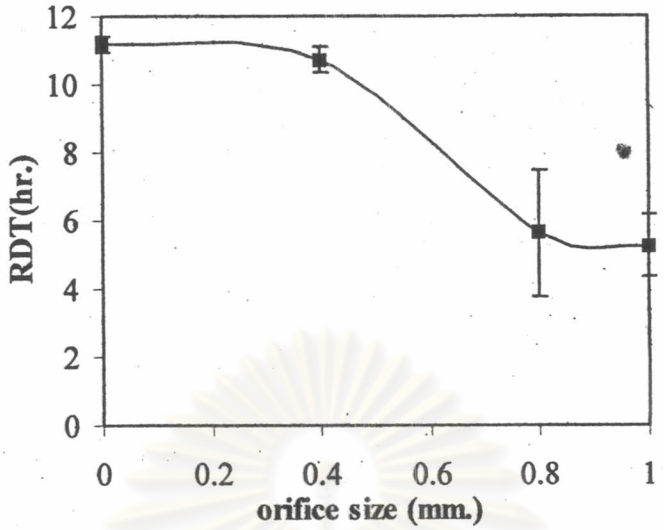


Figure 43: RDT of drug release from propranolol HCl capsules containing drug:NaCl (1:1) were coated with 286 ml. of CA solution plasticized with 23.08 %w/w of PEG 400 in polymer when punctured to have various orifice size.

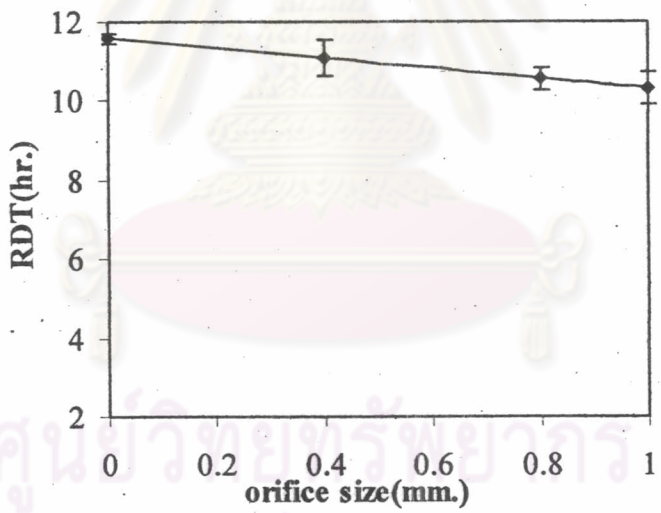


Figure 44: RDT of drug release from propranolol HCl capsules containing drug:NaCl (1:1) were coated with 858 ml. of CA solution plasticized with 41.18 %w/w of PEG 400 in polymer when punctured to have various orifice size.

Previous paper reported the effect of orifice size on drug release (Ozdemir and Sahin, 1997; Mahammadi-Samani, 2000; Lui et al.,2000; Lu et al.,2003)

Lui et al.,2000; Lu et al.,2003 reported that there was an appropriated range of orifice sizes for elementary osmotic pump; these must be smaller than the maximum limit to minimize the contribution to the delivery rate made by diffusion through the orifice. Also, they must be larger than a minimum limit, to minimize hydrostatic pressure inside the system. They found no difference of drug release rate in an appropriate range of orifice size.

On the contrary, Ozdemir and Sahin, 1997; Mahammadi-Samani, 2000 found difference of drug release in various orifice size. Increasing orifice size resulted in an increase in release rate.

Figure 41 shows that the drug release rate of coated capsules with orifice size of 0.4 and without orifice were almost similar, the same as those between the orifice of 0.8 and 1 mm. Average RDT of drug release from coated capsules without orifice and with orifice size of 0.4, 0.8 and 1 mm. were 11.1907, 10.7203, 5.6372 and 5.2645 hours, respectively. As shown in Figure 43, the order of average RDT of drug release of coated capsule was without orifice >orifice size of 0.4 > 0.8 > 1 mm. RDT indicated that the drug release rate increased with increasing the orifice size. The one way ANOVA test showed statistically non-significant difference ($P > 0.05$) of RDT of drug release from coated capsule punctured with 0.8 and 1 mm.,the same as those of without orifice and 0.4 mm. When the orifice size increased, the gelatin shell might be dissolved easier owing to more water influx through orifice. Consequently, water influx through pore of cellulose acetate film was not obstructed by gelatin lump, thus, the drug release increased. The result shows that orifice size effected on drug release.

As shown in Figure 42, using 858 ml. of coating solution, the statistically significant difference($P < 0.05$) of RDT of drug release among various orifice size of coated capsules (no orifice, 0.4, and 0.8 mm.) was found. The result was in contrast with those the coated capsule with orifice size of 0.8 and 1 mm. ($P > 0.05$). The average RDT of drug release of coated capsule without orifice and with orifice size of 0.4, 0.8 and 1 mm. was 11.5815 , 11.0752 , 10.5554 and 10.3262, respectively. The

order of average RDT of drug release of coated capsule was without orifice>orifice size of 0.4>0.8>1mm.(Figure 44). The RDT showed that the drug release increased with increasing orifice size. The result showed that orifice size effected on drug release. The cause was mentioned in the previous paragraph. The orifice sizes of 0.8 and 1 mm. was found to give the minimum lag time and could be explained as same as the previous reason.

b) The effect of plasticizer level on drug release

The effect of the plasticizer on drug release was investigated. The data and the drug release profiles of coated capsule with various levels of PEG 400 as plasticizer from capsule containing drug:NaCl(1:1) (formula C23) coated with 286 ml. of coating solution and punctured with orifice size of 0 and 0.4 mm. were shown in Figure 45 and 46 respectively.

As shown in Figure 45 and 46, the drug release rate increased with increasing PEG400 concentrations as plasticizer from concentration of 33.33 to 50.00% w/w in polymer. Whereas, the drug release rate was not apparently different when increasing PEG400 concentration from 23.08 to 33.33% w/w of polymer ($P > 0.05$). When amount of PEG 400 increased, permeability of water increased as more leaching out of PEG400 which formed more void space in the membrane, consequently, the gelatin shell could be dissolved rapidly , and more drug release from the capsule. It may be explained that PEG 400 was plasticizer for controlling membrane porosity (Lu et al., 2003). According to the result of surface topographys of cellulose acetate film, after dissolution test (Figure 24-27), more pores of cellulose acetate film was observed when coated capsule contacted with water. Coated capsule that plasticized with 50.00%w/w of PEG 400 in polymer had minimum lag time. It was explained that the highest amount of PEG400 gave more porous film, so much water could diffuse through cellulose acetate film causing the minimum lag time of drug release.

Deepak and Kilambi (2003) reported that the drug release rate increased linearly as PEG400 increased. Whereas, Figure 47 shows that RDT decreased non-

linearly as amount of PEG400 increased. The drug release rate was dependent on dissolvable behavior of gelatin shell. So, osmotic system in tablet form behaved differently from those making using gelatin capsule whose drug release was dependent on the dissolution of gelatin shell.

As shown in Figure 49-52 and 47-48, the statistically significant difference of RDT of drug release($P<0.05$) between coated capsule without orifice and with orifice size of 0.4 mm. of capsule formula C23 (drug:NaCl = 1:1) coated with 286 ml of CA solution with certain concentration of PEG400 as plasticizer (23.08%, 33.33%, 41.18% and 50.00%) was found. The result indicated that the orifice influenced on drug release rate. At low concentration of PEG400 in polymer (23.08% and 33.33 % w/w), the orifice influenced slightly on the drug release, whereas at high concentration of PEG400 in polymer (41.18% and 50.00%w/w), the orifice substantially effected on the drug release as PEG400 at high concentration providing more porous film and fastly dissolving gelatin.

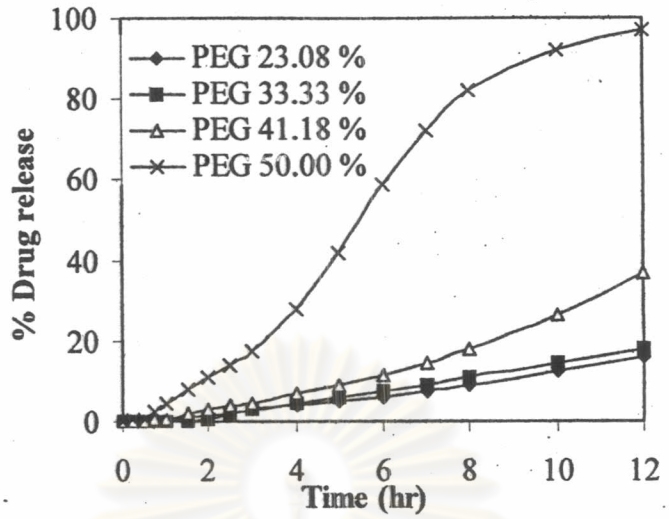


Figure 45 : The release profiles of propranolol HCl coated capsules containing drug:NaCl(1:1) were coated with 286 ml. of CA solution plasticized with various level of PEG400 without orifice.

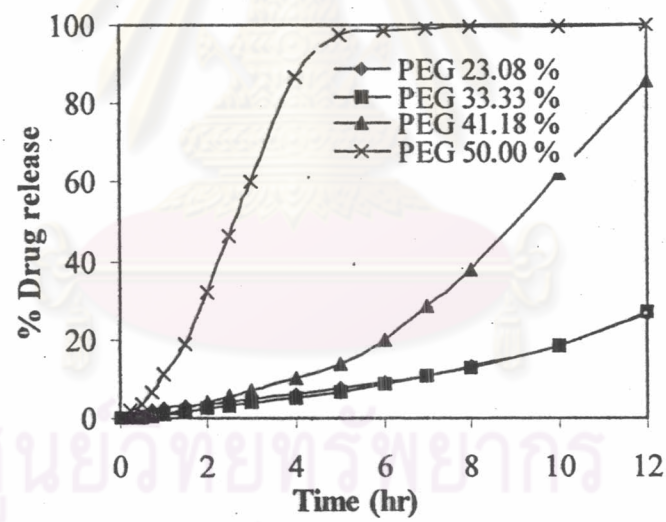


Figure 46 : The release profiles of propranolol HCl coated capsules containing drug:NaCl(1:1) were coated with 286 ml. of CA solution plasticized with various level of PEG400 when punctured to have orifice size of 0.4 mm

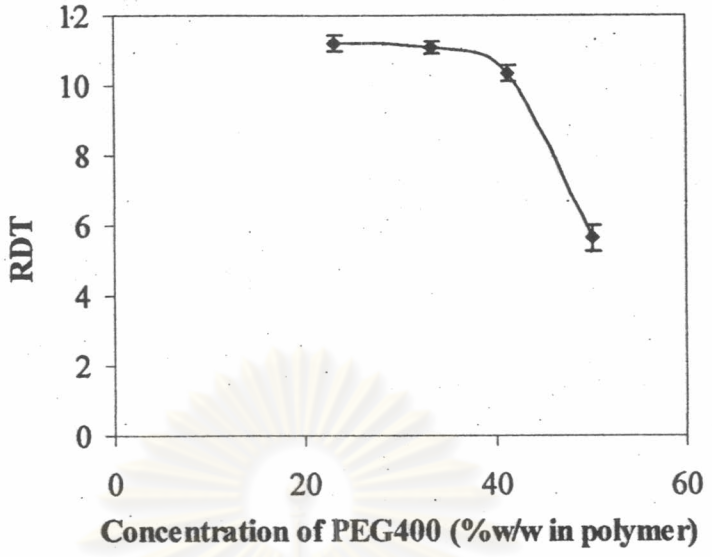


Figure 47: The influence of concentration of PEG400 (w/w of polymer) in the cellulose acetate film on the RDT (relative dissolution time) of propranolol HCl capsule containing drug:NaCl(1:1) coated with 286 ml. of CA solution plasticized with various levels of PEG400 and without orifice.

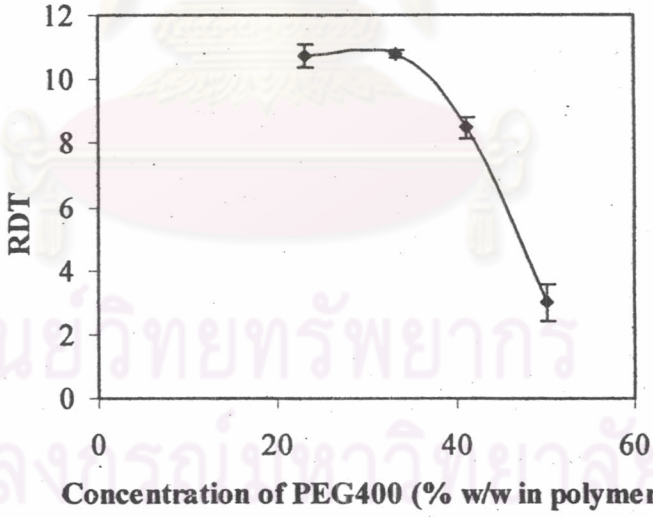


Figure 48 : The influence of concentration of PEG400 (w/w of polymer) in the cellulose acetate film on the RDT (relative dissolution time) of propranolol HCl capsule containing drug:NaCl(1:1) coated with 286 ml. of CA solution plasticized with various levels of PEG400 when punctured to have orifice size of 0.4 mm.

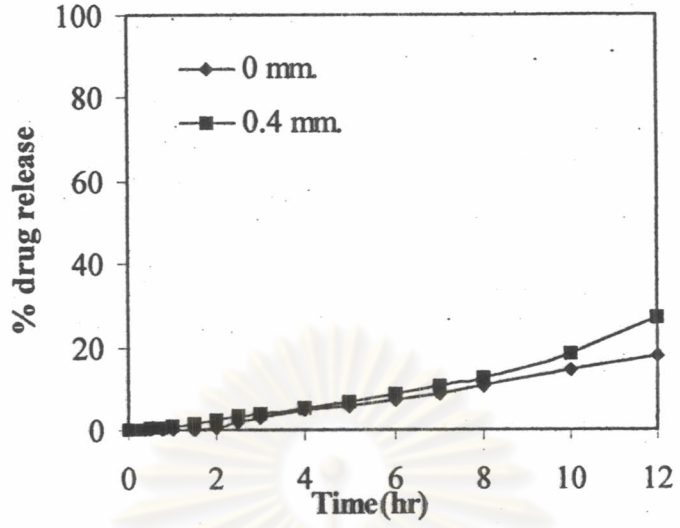


Figure 49: The release profiles of propranolol HCl capsules containing drug:NaCl (1:1) were coated with 286 ml. of CA solution plasticized with 23.08%w/w of PEG400 in polymer without orifice and orifice size of 0.4 mm.

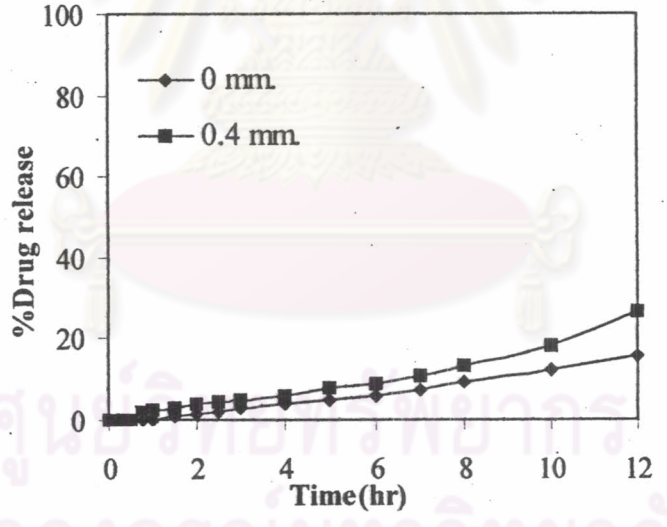


Figure 50:The release profiles of propranolol HCl capsules containing drug:NaCl (1:1) were coated with 286 ml. of CA solution plasticized with 33.33%w/w of PEG400 in polymer without orifice and orifice size of 0.4 mm.

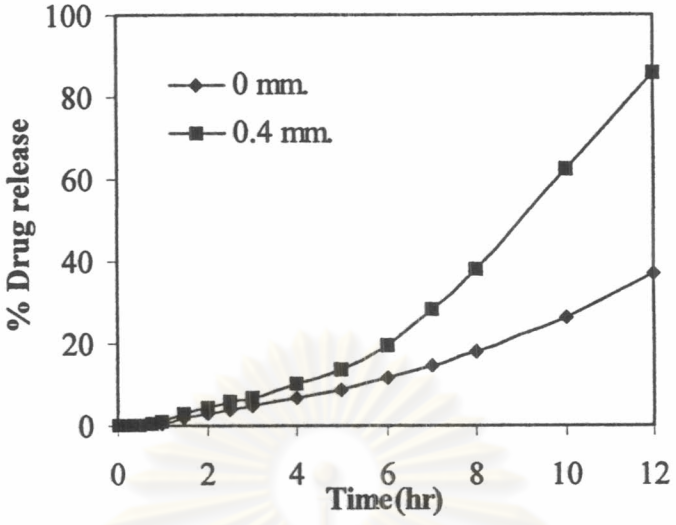


Figure 51: The release profiles of propranolol HCl capsules containing drug:NaCl (1:1) were coated with 286 ml. of CA solution plasticized with 41.18% w/w of PEG400 in polymer without orifice and orifice size of 0.4 mm.

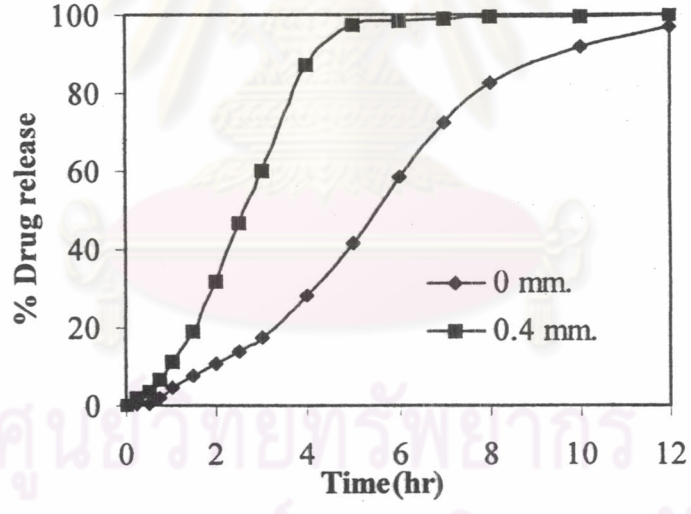


Figure 52 : The release profiles of of propranolol HCl coated capsules containing drug:NaCl(1:1) coated with 286ml. of CA solution plasticized with 50.00% w/w of PEG400 in polymer without orifice and orifice size of 0.4 mm.

C) Effect of membrane thickness on drug release.

The effect of thickness of cellulose acetate film on drug release was investigated. The drug release profiles of various CA thickness levels of capsule containing drug:NaCl(1:1)(formula C23) coated with CA solution plasticized with 41.18 %w/w of PEG400(formula CA3) without orifice and punctured with orifice size of 0.4 mm. were shown in Figure 53 and 54. Those of capsules containing drug:NaCl(1:1) (formula C23) coated with CA solution plasticized with 50.00 %w/v PEG400 in polymer(coating formula CA4) and without orifice are shown in Figure 55.

Table 19 : RDT(relative dissolution time) of formula A,B and C with various thicknesses of cellulose acetate film.

Amount of 1 % w/v CA (ml.)	Thickness of CA film.(μm.) *	RDT of formula A	RDT of formula B	RDT of formula C
286	31.56	10.3403	8.4735	5.6340
572	81.72	11.3606	10.6225	11.0197
858	110.00	11.5815	11.0752	11.3087

A = Capsule containing drug and NaCl (1:1) (capsule formula C23) was coated with CA solution plasticized with 41.18% w/w of PEG 400 in polymer (coating solution formula CA3) without orifice.

B = Capsule containing drug and NaCl (1:1) (capsule formula C23) was coated with CA solution plasticized with 41.18%w/w of PEG 400 in polymer (coating solution formula CA3) when punctured to have orifice size of 0.4 mm.

C = Capsule containing drug and NaCl (1:1) (capsule formula C23) was coated with CA solution plasticized with 50.00%w/w of PEG 400 in polymer (coating solution formula CA4) without orifice.

* Thickness of cellulose acetate film obtained from topic 3.1.

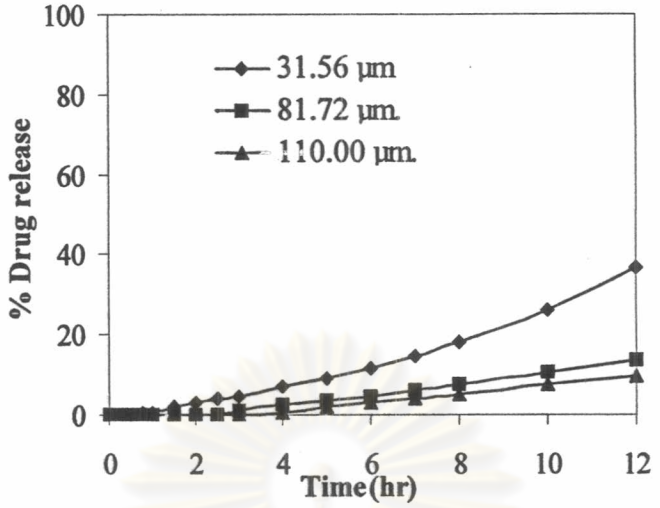


Figure 53:The release profiles of propranolol HCl capsules containing drug:NaCl (1:1) were coated with various amount of CA solution plasticized with 41.18 %w/w ofPEG400 in polymer without orifice.

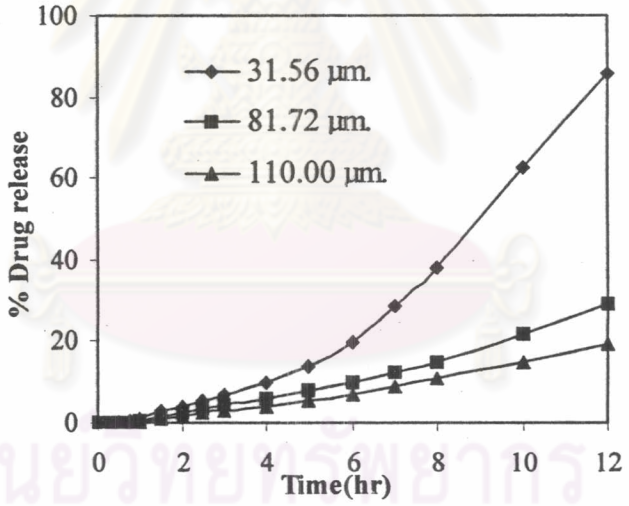


Figure 54: The release profiles of propranolol HCl capsules containing drug:NaCl (1:1) were coated with various amount of CA solution plasticized with 41.18 %w/w of PEG400 in polymer when punctured to have orifice size of 0.4 mm.

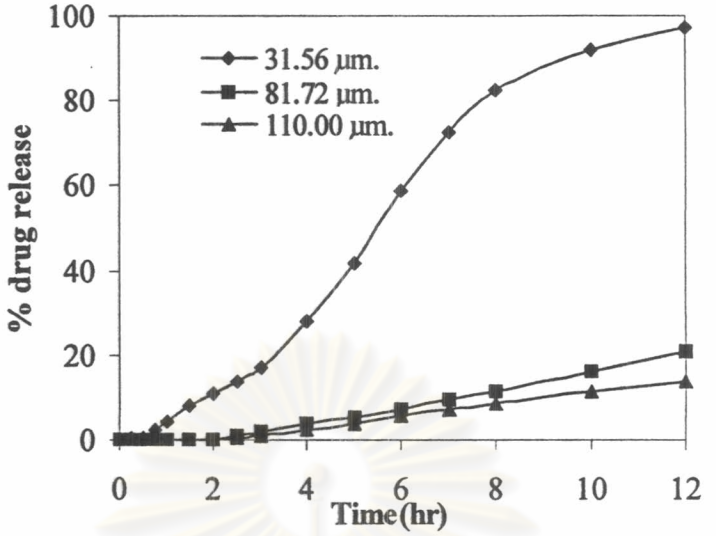


Figure 55 : The release profiles of propranolol HCl capsules containing drug:NaCl (1:1) were coated with various amount of CA solution plasticized with 50.00%w/w of PEG400 in polymer without orifice.

As shown in Figures 53-55, the thickness of cellulose acetate film influenced on drug release rate. The drug release rate decreased as the thickness was increased. The drug release decreased dramatically when the thickness was increased from 31.56 to 81.72 μm., whereas it decreased slightly as increasing thickness from 81.72 to 110.00 μm. According to ANOVA test, it was not different significantly between the film thickness of 81.72 and 110.00 μm.

The relationship between RDT and thickness of cellulose acetate film is shown in Figures 56 and 57. RDT increased as the thickness of cellulose acetate membrane increased. Since increased thickness of cellulose acetate membrane caused decreasing membrane permeability of water through CA film (Deepak and Kilambi, 2003) resulting in decrease of drug release rate. A cause that membrane thickness had a profound effect on drug release rate could be explained according to the report of Theeuwes(1983). Increased membrane resistance to water diffusion caused decreasing drug release rate. The relationship between RDT and membrane thickness was not linear. This relationship differed from reports of Theeuwes et al.,1983; Appel and Zentner,1991; Okimoto et al.,1998; Okimoto, Rajewski, and Stella,1998; Okimoto et al.,1999; Liu et al.,2000; Deepak and Kilambi,2003. They reported that the relationship between release rate and membrane thickness was linear. Gelatin shell might cause the difference between this study and reports of previous mentioned papers. The drug release might be dependent on dissolving gelatin as previously described.

Figure 58-60 show that PEG400 concentration affected on drug release when the film thicknesses were different. PEG400 had more influence on drug release at less film thickness. The drug release rate increased when amount PEG400 was increased from 41.18% to 50.00% w/w at each film thickness level. ANOVA indicated significant difference of RDT between 41.18% and 50.00% w/w of PEG400 in polymers.

The coated capsule with high thickness film showed maximum lag time, in contrast with the coated capsule with low film thickness.

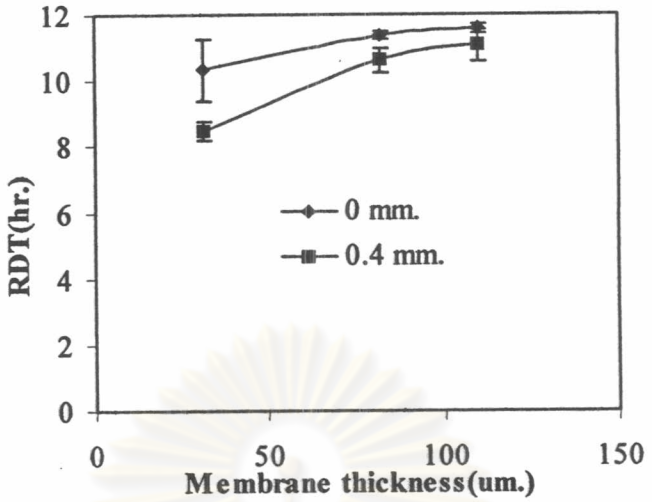


Figure 56:The relationship of thickness of CA film and RDT of capsules containing drug:NaCl(1:1) were coated with various amount of CA solution plasticized with 41.18%w/w of PEG400 in polymer without orifice size and orifice size of 0.4 mm.

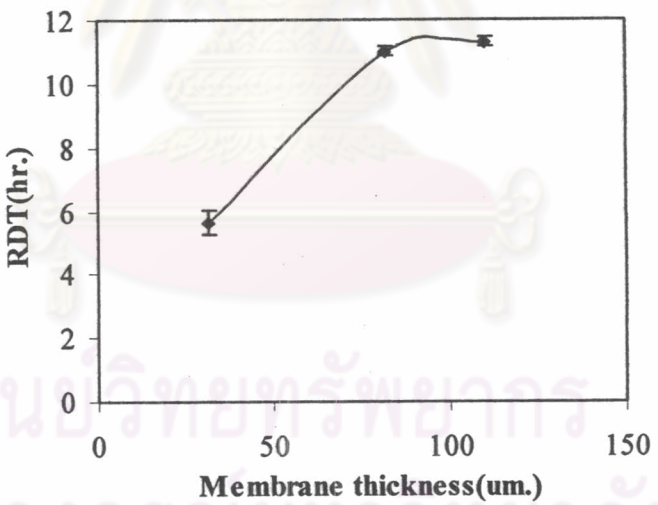


Figure 57: The relationship of thickness of CA film and RDT of capsules containing drug:NaCl(1:1) were coated with various amount of CA solution plasticized with 50.00%w/w of PEG400 in polymer without orifice.

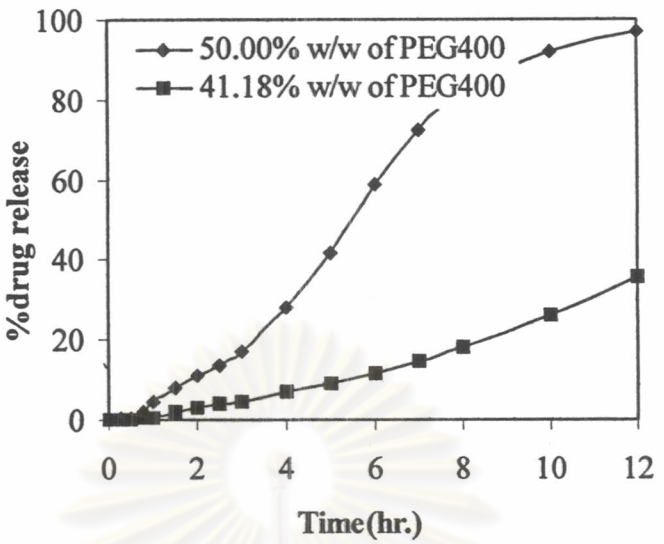


Figure 58: The release profiles of propranolol HCl coated capsules with 41.18% and 50.00% w/w of PEG400 as plasticizer from capsules containing drug and NaCl(1:1) were coated with 286 ml.of CA solution without orifice.

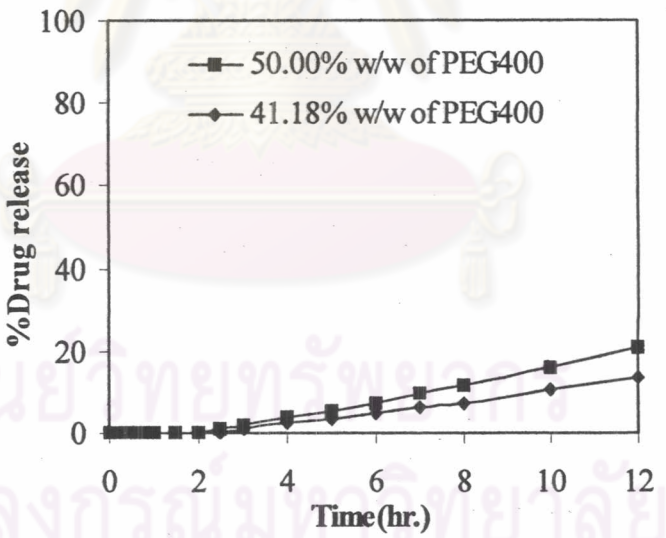


Figure 59: The release profiles of propranolol HCl coated capsules with 41.18% and 50.00% w/w of PEG400 as plasticizer from capsules containing drug and NaCl (1:1) were coated with 572 ml of CA solution without orifice.

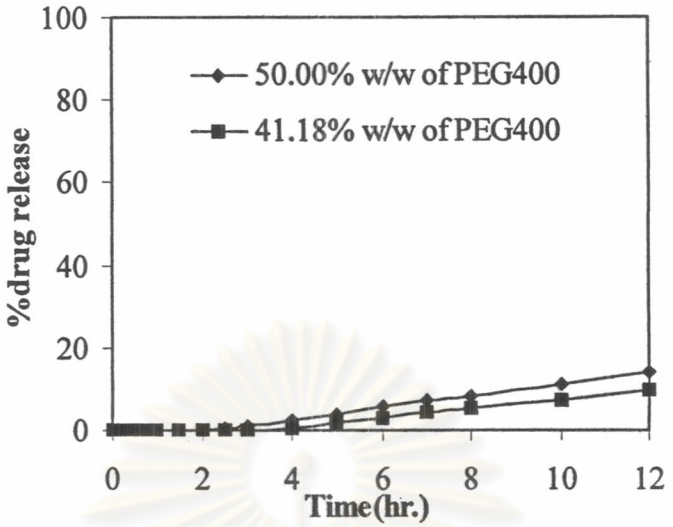


Figure 60: The release profiles of propranolol HCl coated capsules with 41.18% and 50.00% w/w of PEG400 as plasticizer from capsules containing drug and NaCl (1:1) (capsule formula C23) were coated with 858 ml. of CA solution without orifice.

D) Effect of osmotic agent on drug release

The effect of osmotic agent on drug release was observed. The release profiles of capsule containing various amount of NaCl coated with 858 ml. of CA solution plasticized with 41.18 %w/w of PEG400 in polymer(coating formula CA3)and punctured with orifice size of 1 mm. are shown in Figure 61. Those of capsules containing various amount of NaCl coated with 286 ml. of CA solution plasticized with 50.00 %w/w of PEG400 in polymer(coating formula CA4) without orifice are shown in Figure 62.

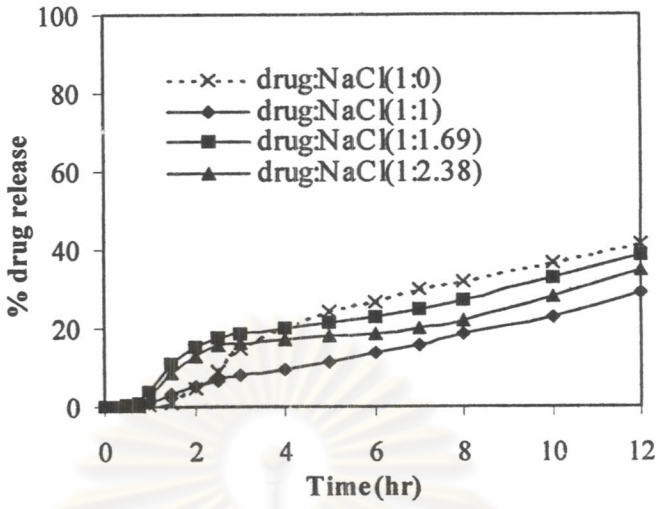


Figure 61 : The release profiles of propranolol HCl coated capsules containing various amount of NaCl were coated with 858 ml. of CA solution plasticized with 41.18%w/w PEG400 in polymer when punctured to have orifice size of 1 mm.

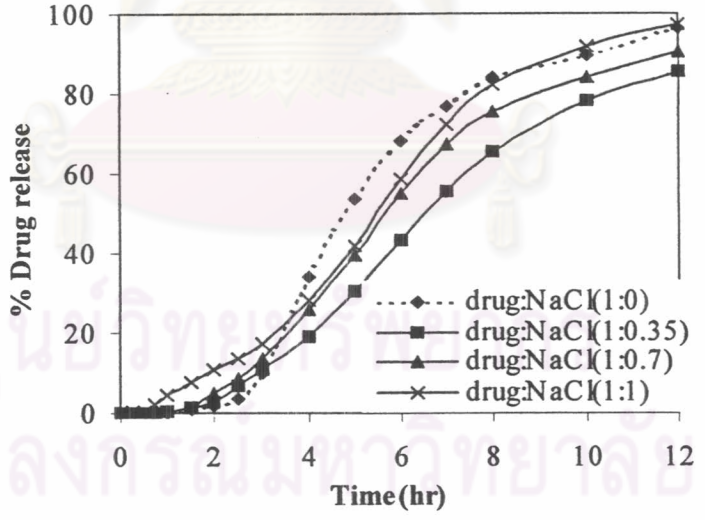


Figure 62: The release profiles of propranolol HCl coated capsules containing various amount of NaCl were coated with 286 ml. of CA solution plasticized with 50.00%w/w PEG400 in polymer without orifice.

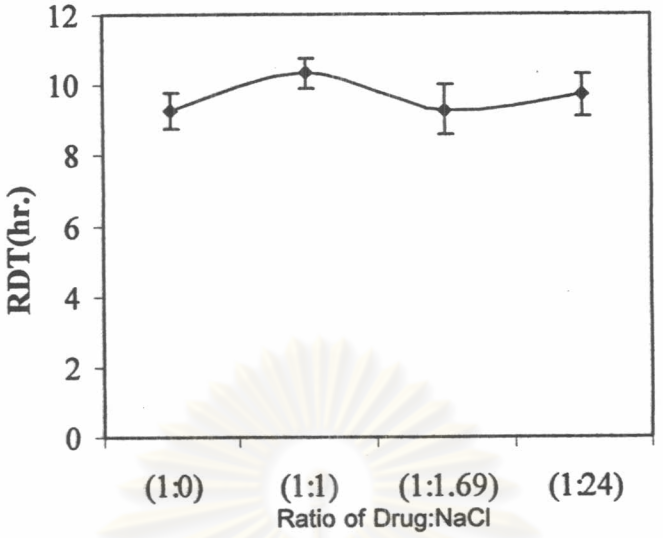


Figure 63 : The relationship of amount of NaCl and RDT of drug release from capsules coated with 858 ml. of CA solution plasticized with 41.18%w/w of PEG400 in polymer when punctured to have orifice size of 1 mm.

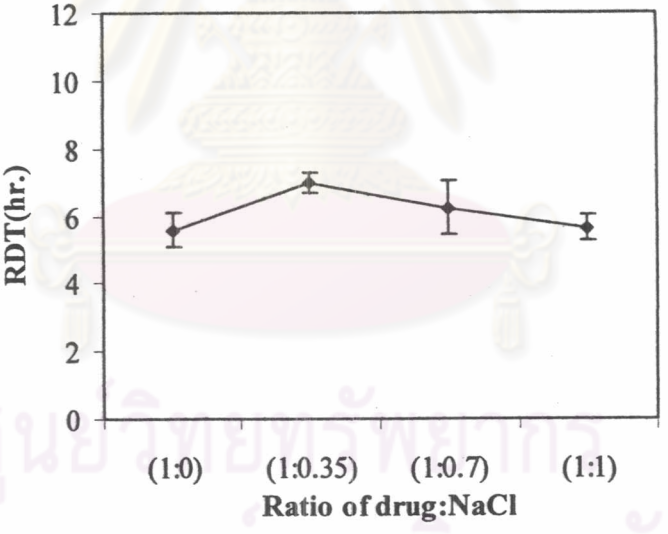


Figure 64 : The relationship of amount of NaCl and RDT of drug release from capsules coated with 286 ml. of CA solution plasticized with 50.00%w/w of PEG400 in polymer without orifice.

The previous published paper reported that the release of drug was enhanced as the concentration of osmotic agent was increased(Ozdemir and Sahin, 1997 ; Thombre et al., 1999; Liu et al., 2000) As shown in Figure 61, the slight difference of drug release rate was observed while amount of sodium chloride was changed. After 4 hours, the drug release rate that obtained from capsule formula without sodium chloride was higher than those containing sodium chloride. This finding might be aggregation of gelatin from interaction with sodium chloride. (Hwang et al.,1998). The lump of gelatin from aggregation obstructed water influx through the pore of cellulose acetate film resulting in only a slight drug dissolve inside the system and lower released drug was observed. In consideration of RDT values, capsule formula C26(drug:NaCl = 1:0) provides the least RDT value(9.273)(Figure 63) and the highest drug release rate. Whereas, capsule formula C23(drug:NaCl = 1:1) provides the highest RDT value (10.3262)(Figure 63) and the lowest drug release rate. RDT of dissolution profiles that obtained from capsule formula C24 (drug:NaCl = 1:1.69) were non-significantly different(P >0.05) from those of capsule formula C26 (drug:NaCl = 1:0). Similarly, no difference of capsule formula C24 (drug:NaCl = 1:1.69) from capsule formula C25 (drug:NaCl = 1:2.38). As shown in Figure 63, RDT of capsule formula C23, C25, C24, and C26 were 10.3262, 9.6988, 9.2835, and 9.2743 respectively. Based on RDT values, the drug release rate of capsule formula were ranked in order of C26>C24>C25>C23. The lag times of four formulas were almost similar which were in a range of 0.5-0.7 hours.

As shown in Figure 62, the result of effect of osmotic agent on drug release was similar to those shown in Figure 61. The slight difference of drug release in each formula was observed. Drug release rate increased while amount of sodium chloride was increased. Since the more amount of sodium chloride that accelerated diffusion of water into capsule resulted in higher drug release rate. However, formula without sodium chloride had the highest release rate during 4-8 hr. This behavior was mentioned in previous paragraph. The drug release rate of coated capsule without sodium chloride(capsule formula C26) was almost similar to capsule formula C23 (drug:NaCl = 1:1) duration 8-12 hr. As shown in Figure 64, The RDT of drug release of capsule formula of C21, C22, C23, C26 were 6.9743, 6.2180, 5.6340, 5.5769.

Based on RDT values, the drug release rate of capsule formula were ranked in order of C26>C23>C22>C21. ANOVA showed no significant difference between capsule formula C23(drug:NaCl = 1:1) and C26(drug:NaCl = 1:0), the same as between capsule formula C23(drug:NaCl = 1:1) and C22(drug:NaCl = 1:0.7). The lag times of four formulas that were almost similar approximately in a range of 0.25-0.75 hours.

E) The effect of an osmotically active dissolution medium on the drug release.

Influence of various tonicity of dissolution medium on the drug release was studied. KCl solution in various concentrations were used as dissolution medium for the study. Osmotic pressure of isotonic solution was 300 mosm. that KCl solution with concentration of 0.1588 M. was isotonic solution. So KCl solution that possesses more solute than 0.1588 M was hypertonic solution. (0.5 M, 1 M , 2 M.). The drug release profiles in deionized water and concentration of various KCl solution ie, 0.1588 M, 0.5 M, 1 M. and 2 M are shown in Figure 65.

Figure 65 shows that the drug release rate decreased with increasing KCl concentration in the release media. When the KCl concentration was increased, the osmotic pressure difference across the membrane decreased resulting in decreasing the drug release rate. The other cause, while ionic strength of KCl was increased, higher KCl diffused through CA film resulting in higher aggregation of dissolved gelatin shell, higher obstructing water influx through pore of cellulose acetate film, and lower drug release. Using deionized water as dissolution medium, less aggregation of dissolved gelatin shell to obstruct water influx. Thus, the drug release rate was highest(85.64% at 12 hours). In this case, there was very small amount of NaCl inside the capsule(only 35%w/w of drug) as cause of those aggregation. When concentration of KCl solution was increased up to 2 M, very small amount of drug release was observed and no significant difference between 2 M and 1 M of KCl solution (P>0.05). The result was similar to the observation of several reported papers, i.e., Ozturk and Palsson,1990; Okimoto et al ,1998; Deepak and Kilambi, 2003 ; Zhang and Wu, 2003.

As shown in Figure 66, RDT increased as the concentration of KCl was increased. RDT of the drug release in the deionized water had the least value that exhibited the highest drug release. On the contrary, RDT of drug release in 2 M of KCl solution was the highest value that exhibited the highest drug release.

The lag time increased while the concentration of KCl was increased, the lag time was as long as 3 hours in 2 M of KCl solution.

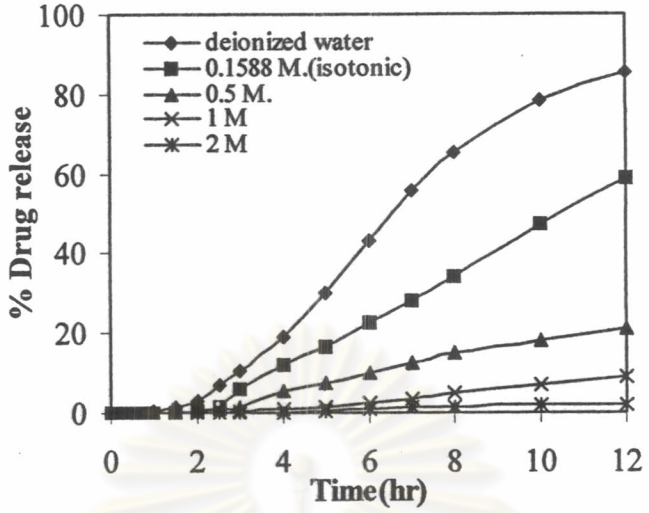


Figure 65 : The release profiles of propranolol HCl coated capsules in various KCl concentration from capsules containing drug:NaCl(1:0.35) were coated with 286 ml. of CA solution plasticized with 50.00 %w/w of PEG400 in polymers without orifice.

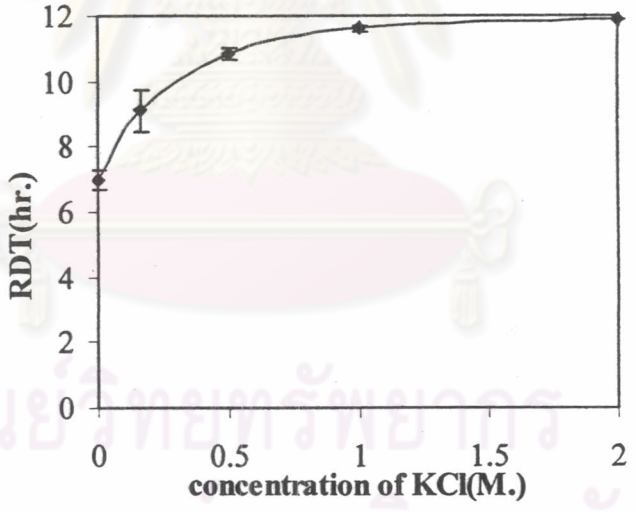


Figure 66: The relationship of concentration of KCl and RDT of drug release from capsules containing drug:NaCl(1:0.35) were coated with 286 ml. of CA solution plasticized with 50.00 %w/w of PEG400 in polymers without orifice in various KCl concentration.

F) Effect of pH on drug release.

Influence of pH of dissolution medium on drug release was studied. Dissolution media, i.e., buffer solution pH 1.2 and buffer solution pH 6.8 that followed USP XXVI were adjusted to isotonic with KCl or deionized water. The solution was adjusted to isotonic that was measured by Osmomat®. This instrument expresses unit as osmolarity(osm/l). The drug release profiles of coated capsule containing drug:NaCl(1:0.35) and coated with 286 ml. of 1%w/v CA solution plasticized with 50.00 %w/w of PEG400 in polymer without orifice in isotonic buffer solution pH 1.2 and pH 6.8 are shown in Figure 67, those in pH change and deionized water shown in Figure 68.

Theeuwes et al.(1983) reported that no difference of drug release in gastric fluid and in intestinal fluid from elementary osmotic pump of indomethacin. Lui et al. (2000) reported about monolithic osmotic tablet system for nifedipine delivery, it was same as paper of Theeuwes et al(1983), no significant difference of release profile in simulated gastric fluid and simulated intestinal fluid was found.

Figure 67 shows no difference of drug release rate in duration of 0 to 6 hours because gelatin shell might be dissolved incompletely in this interval time. Whereas, it was different in duration of 6 to 12 hours . At duration of 6-12 hours, the drug release rate was higher in buffer pH 1.2 than buffer pH 6.8 because solubility of propranolol HCl was higher in buffer pH1.2 than in buffer pH6.8. Solubility of propranolol HCl is reported by Takka, Rajbhandari and Sakr(2001). They reported that propranolol hydrochloride has the characteristics of a weakly basic drug; therefore, it shows a pH-dependent solubility in the pH range of the gastrointestinal tract. The solubility is found to be 225 mg/ml at pH1.2, 130 mg/ml. at pH 6.8, and 360 mg/ml in water. At 12 hours, amount of drug released in buffer pH 1.2 and buffer pH 6.8 was 71.7819 % and 57.5220 %, respectively. ANOVA showed significant difference($P<0.05$) between RDT of drug release in buffer pH 1.2 and in buffer pH 6.8. The lag time of propranolol HCl release was longer in buffer pH1.2 than in buffer pH6.8. The result in dicated that pH of dissolution medium affected on drug

release. Since this system had pore in cellulose acetate film for water influx and diffusion of substance into the system due to smaller size of substance than pore of the film. Thus, dissolvable of drug was dependent on pH of dissolution medium.

As shown in Figure 68, pH change of phosphate buffer followed USPXXVI. (The first hour, pH 1.2 phosphate buffer was used as dissolution medium, after that pH 1.2 phosphate buffer was replaced by pH6.8 phosphate buffer for the last eleven hours). At the first hour, the drug was not released because the gelatin shell might be dissolved in this interval time. Whereas, the drug began release after the first hour that was the time of change dissolution medium from phosphate buffer pH 1.2 to pH 6.8. The drug release rate was higher in deionized water than in phosphate buffer because osmotic pressure difference across the membrane of coated capsule was larger in deionized water than in phosphate buffer and solubility of propranolol HCl was higher in deionized water than in phosphate buffers. Using phosphate buffer as dissolution medium, amount of drug release was 53.27% in 12 hours providing RDT of drug release as 8.7976. Whereas, in deionized water, amount of drug release was 85.64% in 12 hours providing RDT of drug release as 6.9743 (Figure 69). The result exhibited that phosphate buffer affected on drug release when compare to deionized water.

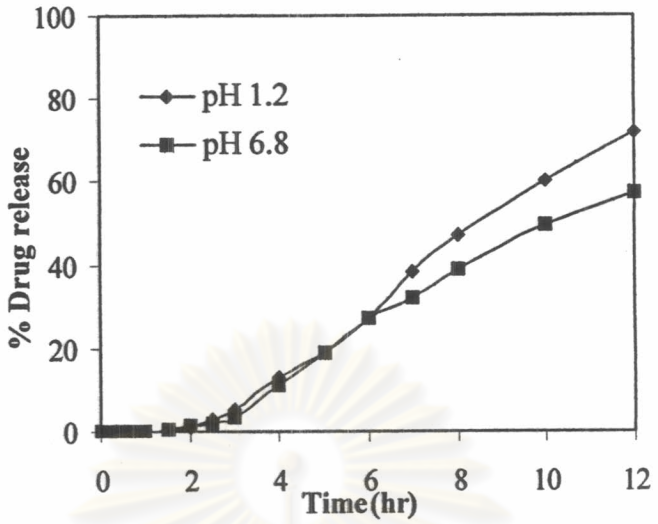


Figure 67: The release profiles of propranolol HCl coated capsules in pH 1.2 and 6.8 phosphate buffer that were adjusted as isotonic solution from capsules containing drug:NaCl(1:0.35) were coated with 286 ml. of CA solution plasticized with 50.00 % w/w of PEG 400 in polymer(coating formula CA4) without orifice.

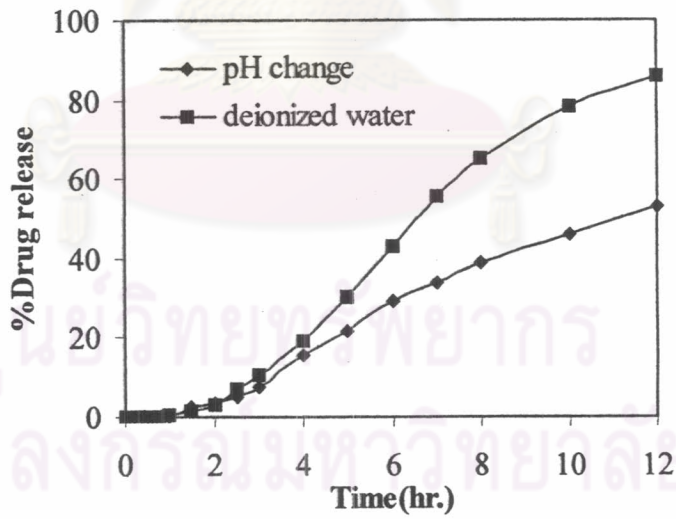


Figure68: The release profiles of propranolol HCl coated capsule in pH change (no adjustment to be isotonic solution) and in deionized water, from capsule containing drug:NaCl(1:0.35) were coated with 286 ml. of CA solution plasticized with 50.00 % w/w of PEG 400 in polymer (formula CA4) without orifice.(0-1 hr.in pH 1.2 , 1-12 hr.in pH 6.8).

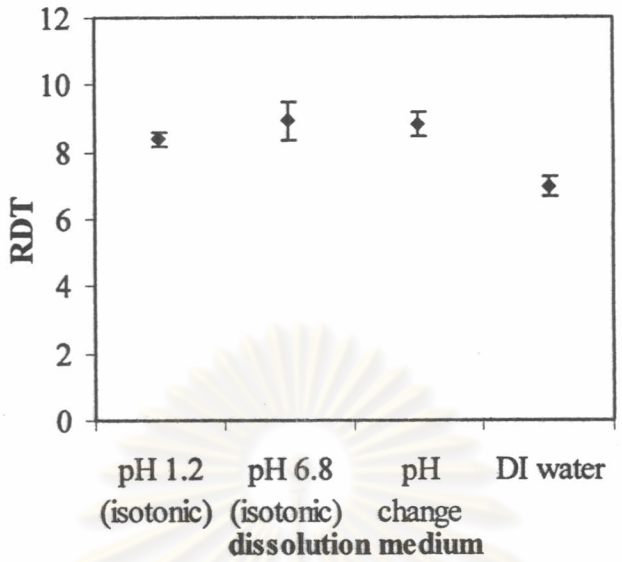


Figure 69: The relationship between RDT and various dissolution medium of capsule containing drug:NaCl(1:0.35) were coated with 286 ml. of CA solution plasticized with 50.00 % w/w of PEG400 in polymer.

G) The effect of interaction between osmotic agent and gelatin on drug release.

Since gelatin had charge and may interact with ionic charge of osmotic agent such as NaCl. Thus, effect of ionic species of osmotic agent on aggregation of dissolved gelatin shell was studied. In this experiment, osmotic agent ie, NaCl, KCl, lactose and sucrose were used. Pure osmotic agent was blended with propranolol HCl to observe ionic effect of each osmotic agent on gelatin shell. Figure 69 and 70 shows the drug release from capsules containing various osmotic agents without orifice and orifice size of 0.8 mm.,respectively.

As shown in Figure 70 and 71, the drug release rate of propranolol HCl coated capsule containing sucrose exhibited the highest drug release. The drug release rate of coated capsule containing sucrose was higher than those containing lactose because osmotic pressure of saturated sucrose solution was higher than saturated lactose solution. Drug release rate of coated capsule containing NaCl and KCl were almost similar. As shown in Figure 72 and 73, RDT value of coated capsule containing sucrose and lactose was less than those containing KCl and NaCl. Drug release rate of coated capsule containing sucrose and lactose was more than those containing KCl and NaCl. ANOVA shows no significant difference of RDT between coated capsule containing KCl and NaCl. Whereas, it shows significant difference of RDT between coated capsule containing sucrose and lactose.

Generally, coated capsule containing NaCl or KCl that had the osmotic pressure at saturated solution condition is higher than those containing lactose and sucrose. It should provide drug release coated capsule containing NaCl and KCl in higher rate than coated capsule containing lactose and sucrose, whereas, this result is not in accordance with previous mention. The drug release rate of coated capsule containing NaCl and KCl was lower than coated capsule containing lactose and sucrose. It might be explained based on the report by Hwang et al.(1998). They reported that at low ionic strength solvent, the chance for charged particles of gelatin to collide and form hydrogen bonded aggregates is reduced by the repulsive Coulombic forces between charges on the macromolecules of gelatin. As solvent

ionic strength is increased, however, the Coulombic interactions are screened out more and more completely by the charges on the solvent ions, allowing the marcromolecules to aggregate more readily. Thus, this explanation supported that the high ionic strength of saturated solution of NaCl and KCl caused aggregation of dissolved gelatin shell resulting in obstructing water influx through CA film. Consequently, the drug release rate was low. On the contrary, lactose and sucrose had low ionic strength resulting in no aggregation of dissolved gelatin shell and obstructing water influx. Thus, the drug release rate was high.

Figure 74-77 shows that influence of orifice on drug release from coated capsule containing KCl or NaCl was in higher degree than those containing lactose or sucrose. Aggregation of dissolved gelatin shell might decreased due to water influx through orifice to dissolve gelatin shell, thus the release was less inhibited by lump of gelatin, Moreover, saturated KCl and NaCl solution had more osmotic pressure than saturated lactose and sucrose solution causing more influence of orifice on drug release.

The lag times of coated capsule without orifice was in a range of 1-2.5 hours. Whereas, the lag time of coated capsule with orifice size of 0.8 mm. was decreased to about of 0.25-0.5 hours.

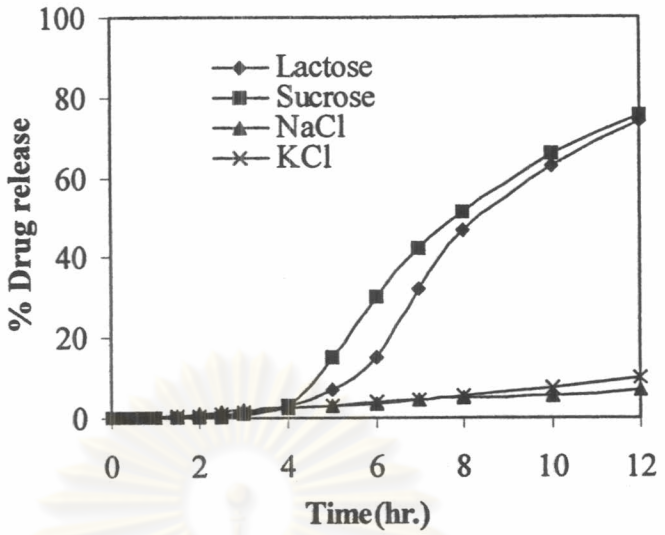


Figure 70: The release profiles of propranolol HCl coated capsules from capsules containing amount of various pure osmotic agent were coated with 286 ml. of CA solution plasticized with 23.08 %w/w of PEG400 in polymer without orifice.

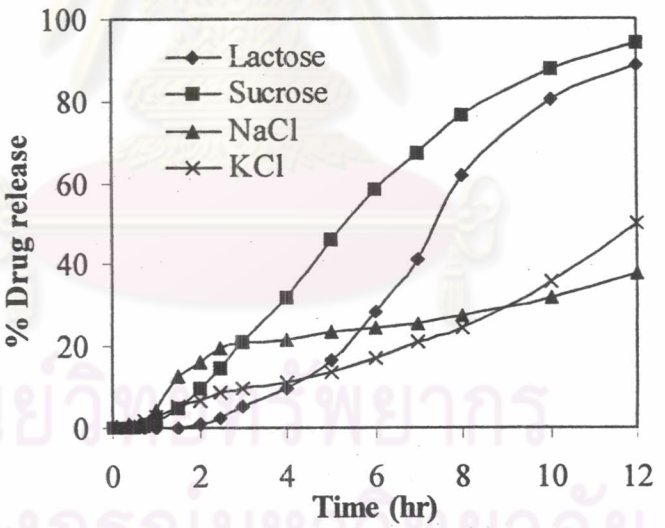


Figure 71: The release profiles of propranolol HCl coated capsules from capsules containing amount of various pure osmotic agent were coated with 286 ml. of CA solution plasticized with 23.08 %w/w of PEG400 in polymers when punctured to have orifice size of 0.8 mm.

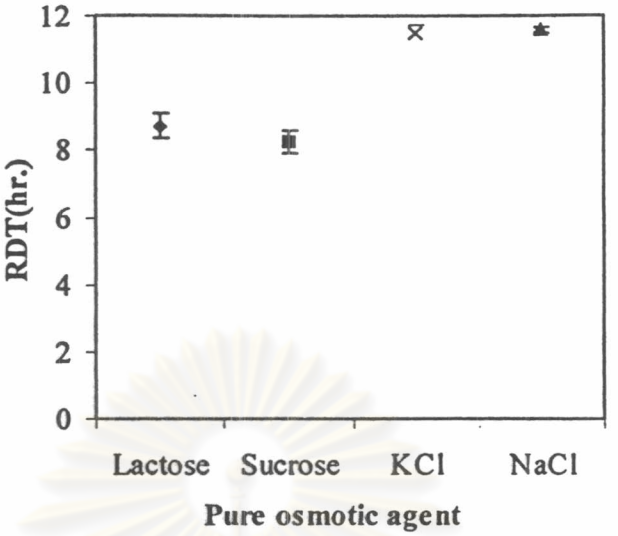


Figure 72: The relationship of capsules containing various pure osmotic agent and RDT of drug release from capsules were coated with 286 ml. of CA solution plasticized with 23.08 %w/w of PEG400 in polymers without orifice.

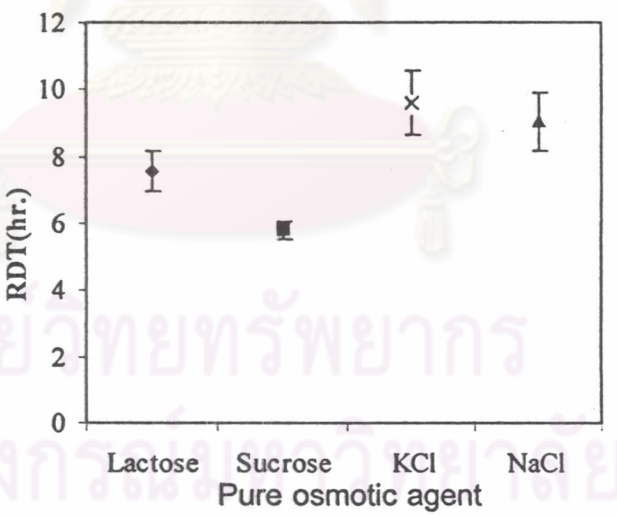


Figure 73: The relationship of capsules containing various pure osmotic agent and RDT of drug release from capsules were coated with 286 ml. of CA solution plasticized with 23.08 %w/w of PEG400 in polymers when punctured to have orifice size of 0.8 mm.

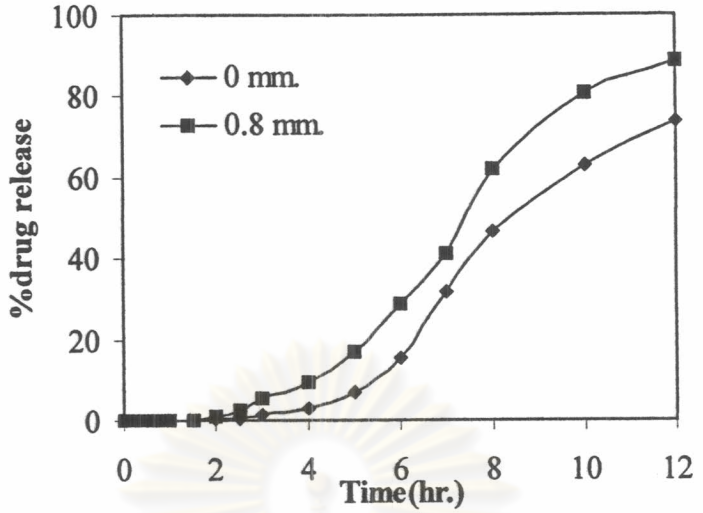


Figure 74: The release profiles of without orifice and orifice size of 0.8 mm. of propranolol HCl coated capsules from capsules containing pure lactose (formula C26) were coated with 286 ml. of CA solution plasticized with 23.08 %w/w of PEG400 in polymers.

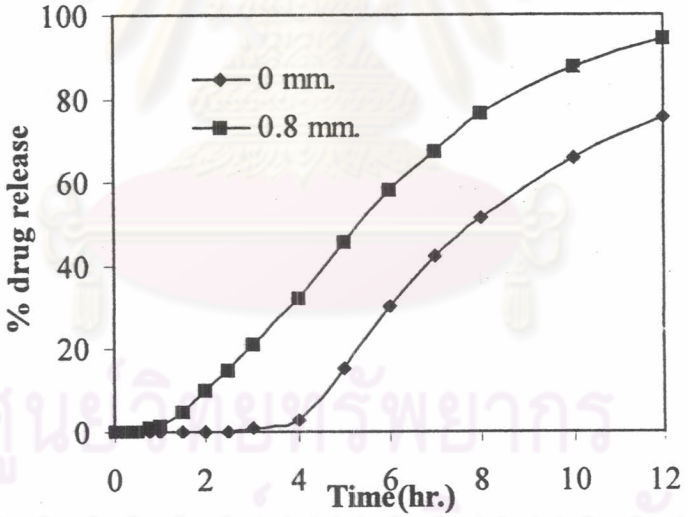


Figure 75: The release profiles of without orifice and orifice size of 0.8 mm. of propranolol HCl coated capsules from capsules containing pure sucrose (formula C27) were coated with 286 ml. of CA solution plasticized with 23.08 %w/w of PEG400 in polymers.

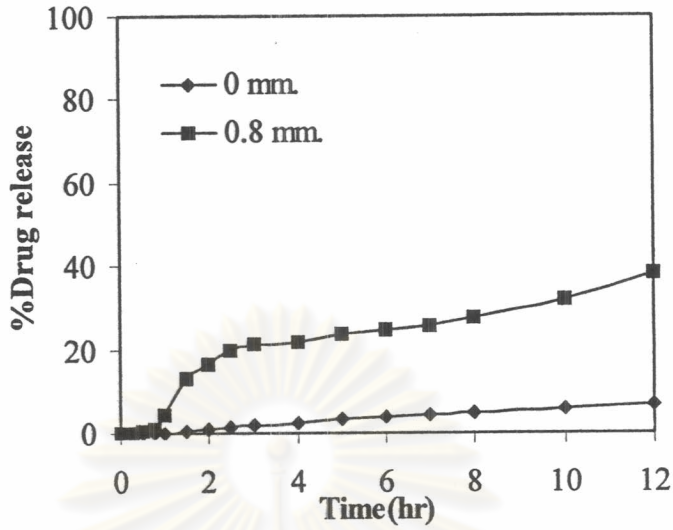


Figure 76 :The release profiles of without orifice and orifice size of 0.8 mm. of propranolol HCl coated capsules from capsules containing pure NaCl (formula C25) were coated with 286 ml. of CA plasticized with 23.08 %w/w of PEG400 in polymers.

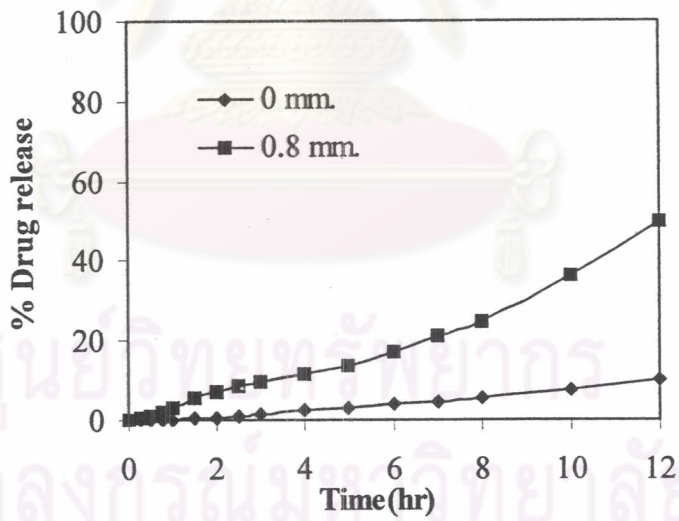


Figure 77: The release profiles of without orifice and orifice size of 0.8 mm. of propranolol HCl coated capsules from capsules containing pure KCl (formula C28) were coated with 286 ml. of CA solution plasticized with 23.08 % w/w of PEG400 in polymers.

H) Effect of agitational intensity on drug release.

Effect of rotating apparatus type and speed on drug release was studied. The drug release profiles of capsule containing drug:NaCl (1:2.38)(formula C25) was coated with 858 ml. of CA solution plasticized with 41.18 %w/w of PEG 400 in polymer(coating solution CA3) and orifice size of 1 mm. were shown in Figure 78, respectively. Figure 79 shows the relationships between RDT with various rotating apparatus types and speeds.

As shown in Figure 78 and 79, RDT values indicated that the increasing order of drug release rate was paddle at 50 rpm > basket at 100 rpm > basket at 50 rpm . The difference of hydrodynamic of each rotating apparatus might cause the difference of drug release. The movement of paddle was more intensive than of basket resulting in more influx of water through both pore of the membrane and orifice accelerating the transport of propranolol HCl and providing higher release rates. However, ANOVA test showed no significant difference ($P > 0.05$) of RDT between basket 50 and 100 rpm. and paddle 50 rpm. The result indicated that 50-100 rpm of basket and 50 rpm of paddle did not affect on drug release. The result was similar to reports of several reported papers, i.e., Theeuwes et al., 1983; Okimoto, Rajewski and Stella, 1999 ; Liu et al., 2000 ; Lu et al.,2003; Verma, Kaushal, and Garg, 2003; Zhang and Wu, 2003; Verma and Garg, 2004. Thus, the mobility of the gastrointestinal tract might only slightly affect the drug release of the coated capsule. Lag time of drug release using various rotating apparatus type and speed which were in a range of 0.5-0.75 hours were almost similar.

Figure 79 shows that variation of RDT was higher when increasing the speed of basket. It indicated that the difference of drug release was greater as increasing speed of rotating apparatus. Comparison between basket and paddle at 50 rpm, variation of RDT of drug release when using paddle was more than using basket at 50 rpm. It might be explained by the different fluid movement in rotating apparatus type caused different variation of RDT.

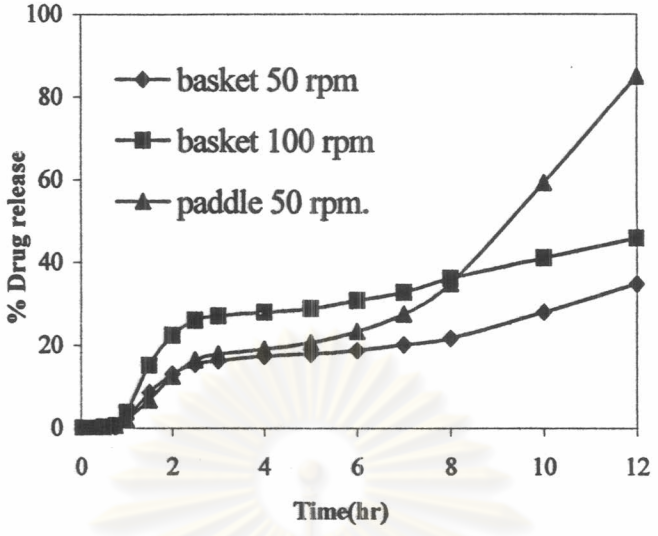


Figure 78: The release profiles of propranolol HCl coated capsules, using various rotating apparatus type and speed from capsules containing drug:NaCl (1:2.38) were coated with 858 ml. of CA solution plasticized with 41.18% w/w ofPEG400 in polymer and when punctured to have orifice size of 1 mm.

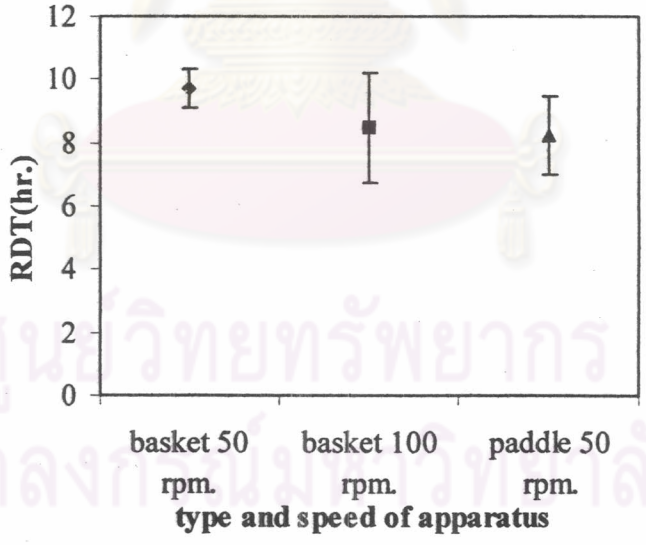


Figure 79 : The relationship between the relative dissolution time (RDT value) of propranolol HCl coated capsules and rotating apparatus type and speed from capsules containing drug:NaCl(1:2.38) were coated with 858 ml. of CA solution plasticized with 41.18 %w/w of PEG 400 in polymers when punctured to have orifice size of 1 mm.

I) Effect of the orifice position on coated capsule on drug release.

Influence of orifice positions on coated capsules on dug release were studied. The drug release profiles from capsules containing drug:NaCl(1:1)(capsule formula C23) coated with 858 ml. of CA solution plasticized with 41.18 %w/w of PEG400 in polymer(coating solution CA3) and punctured with orifice size of 1 mm at various orifice positions were shown in Figure 80.

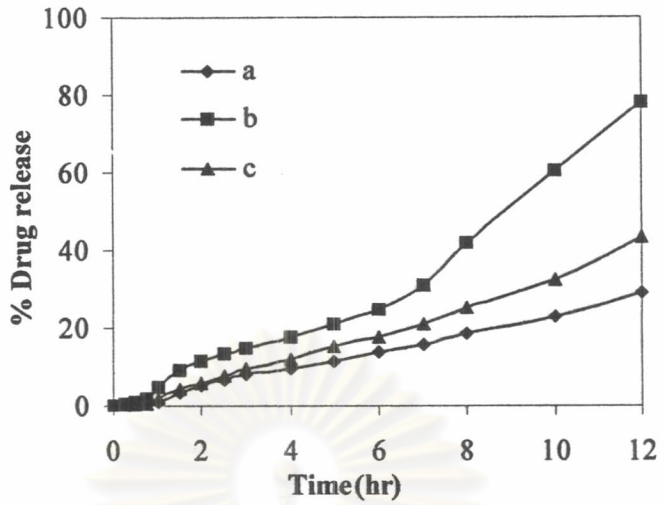


Figure 80 : The release profile of propranolol HCl coated capsules containing drug:NaCl (1:1) were coated with 858 ml. of CA solution plasticized with 41.18 %w/w of PEG400 in polymer when punctured to have orifice size of 1 mm.: a) 1 orifice at the end of the capsule, b) 2 orifices at the both end of the capsule , c) 1 orifice at the side of the capsule.

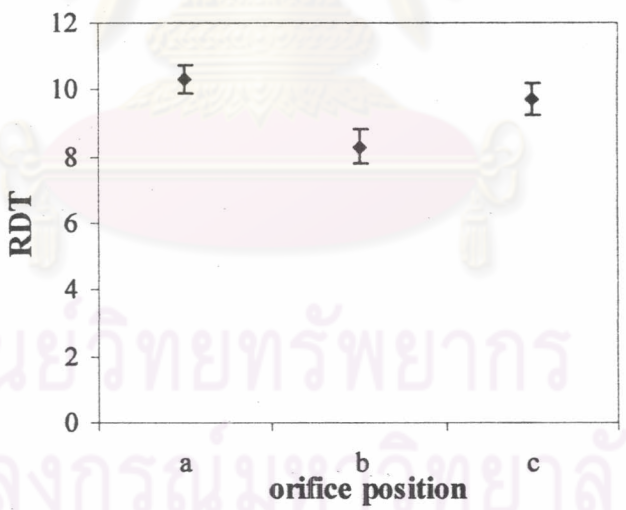


Figure 81: The relationship of orifice position and RDT of drug release from capsules were coated with 858 ml. of CA solution plasticized with 41.18 %w/w of PEG400 in polymer orifice when punctured to have orifice size of 1 mm.: a) 1 orifice at the end of the capsule, b) 2 orifices at the both end of the capsule , c) 1 orifice at the side of the capsule.

As shown in Figure 80 and 81, the drug releases that have the least RDT value(8.3006) was from coated capsules with two orifices at the both end of capsules and was faster than coated capsule with one orifice at the side position of capsule and with one orifice at the end of capsule(RDT=9.7105 and 10.3262, respectively). ANOVA shows statistically significant difference of RDT of drug release in three formula. RDT showed drug release rate of coated capsule with one orifice at the side position of capsule greater than with one orifice at the end of capsule. It might be explained by gravity effect. When the direction of drug release was in the direction of gravity, the saturated drug solution was released rapidly due to contribution of gravity force. While during dissolution test, the coated capsules with one orifice at the side position of capsule, occasionally moved downward, consequently, the direction of drug release was in the direction of gravity. Thus, the drug from coated capsule with one orifice at the side position of capsule released was faster than those with one orifice at the end of capsule whose direction of drug release was not similar to the direction of gravity. However, variation of RDT of coated capsule with one orifice at the side position of capsule (SD=0.4730) was greater than those with one orifice on the end of capsule (SD=0.4038) due to previous cause. This might be due to some coated capsule with orifice at the side position in the dissolution vessel during dissolution test did not have position orientation provides the drug release from the orifice in the same direction of gravity force. Therefore, the more difference of drug release resulted higher SD value of RDT. On the contrary, the more uniformity of drug release of coated capsule with one orifice at the end of capsule provided less SD value. Moreover, coated capsule with two orifice at the both end of capsule whose the highest value of SD of RDT and drug release rate indicated that the number of orifice effected on uniformity and amount of drug release. Lag times of three formulas that were almost similar approximately in the range of 0.25-0.5 hours.

j) Photographs of propranolol HCl capsules at various dissolution time.

Figure 82 shows the coated capsule between dissolution test at various time, 0, 4, 8 and 12 hours. At the time of 4 hour, a partial gelatin and ingredients inside the capsule were dissolved. The total volume of the capsule appears to remain essentially unchanged so that the decrease in the volume of the core occupied by the drug solution must correspond to the release of the drug solution through the delivery port and porosity in the film. At the time of 8-hr, the medium amount of white drug-ingredient material is still visible inside the tablet. The total volume of the capsule was still unchanged. At the time of 12 hours, no appearance of white drug-ingredient material inside the capsule, the photograph shows only a shell of the cellulose acetate membrane and clear solution inside the capsule. It indicates that the cellulose acetate membrane was not dissolved by the water. The total volume of the capsule was increased slightly due to force of osmotic pressure and swelling of gelatin.

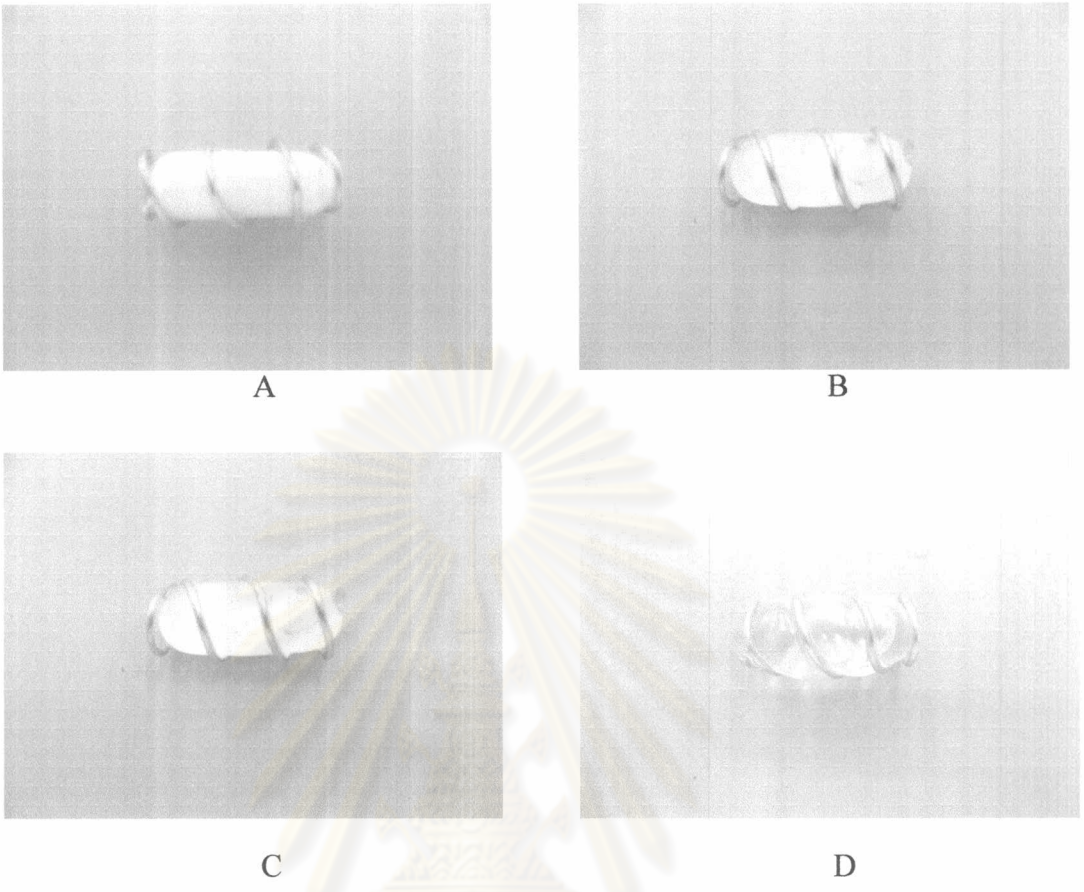


Figure 82: Photographs of propranolol HCl capsules at various dissolution time, A) 0 hr., B) 4 hr., C) 8 hr., and D) 12 hr. from capsule containing drug:NaCl (1:1) was coated with 286 ml. of CA solution plasticized with 23.08 %w/w of PEG 400 in polymer when punctured to have orifice size of 1 mm.