CHAPTER IV

RESULTS AND DISCUSSION

A prime objective of this study is to prepare sustained release microcapsule from appropriate membranes by using coacervation, fluidization and spray drying techniques. To select the appropriate membranes, the study of diffusion of cephalexin through ethylcellulose and combination of Eudragit RL 100® and Eudragit RS 100® membrane were investigated. In diffusion study, one requirement for maximum flux is that the solute should be in saturated solution in the donor part in order that more drug contents would permeate and this also make it easier to analyze. But it is very difficult to control the experiments because the drug tends to precipitate despite the small change of temperature. So 75% w/v of the drug solubility in water had been determined and used in this study as the donor solution.

Membranes used in the diffusion study could be easily detached from the glass plate after drying with characteristics of flexibility and no brittleness. All membranes were transparency and clear color.

After diffusion study, the appropriate membranes which give a sustained release property were selected as the wall material of microcapsules. Three microencapsulation techniques were determined with the variation of wall material and the core: wall ratio. The particle sizes were evaluated by using microscope and surface topography were determined by using scanning electron microscope. Release characteristics of microcapsules were investigated by dissolution method.

1. Calibration Curve of Cephalexin.

The standard curve of cephalexin in water was shown in Fig. 12 and the correlation coefficient was calculated in Table. 11 in appendix II. It obeyed the Beer's law plot. The correlation coefficient of this straight line was 0.99995.

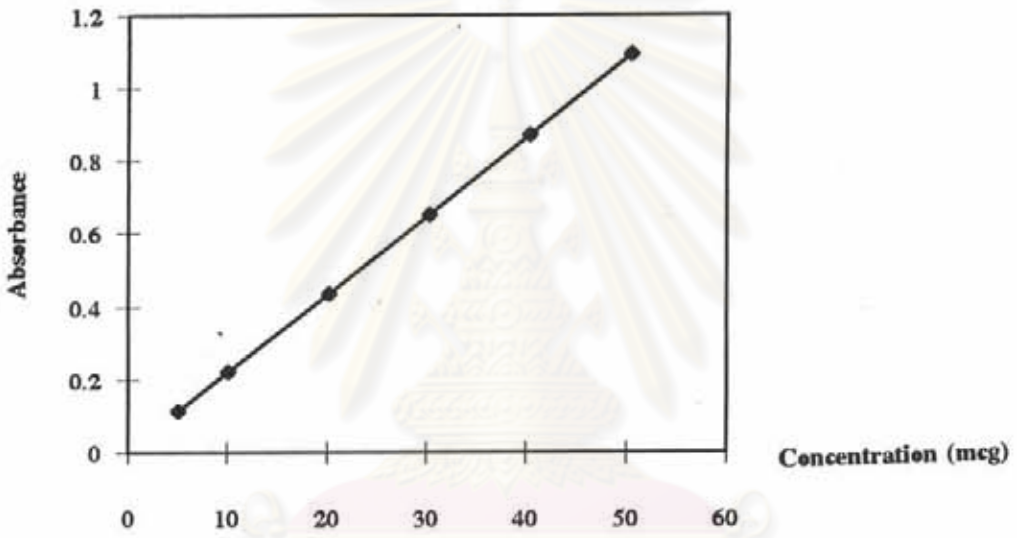


Fig.12 : Calibration curve of cephalexin in water at UV 262 nm.

2. Solubility of Cephalexin in Water at 33 ± 1°C.

The solution of cephalexin in water shows specific odor and off-yellow color. Table 2 showed equilibrium solubility at 48 hours, the solubility was dropped at 72 hours, the percent coefficient of variation was higher (1.27%). So the equilibrium solubility should be around 13.0232-13.7689. In order to prevent precipitation of cephalexin during the diffusion study, 75% solubility of cephalexin

in water was calculated. It was 9.7674 mg/ml: For convenience, 10 mg/ml of cephalexin solution was used as a donor solution in diffusion study.

Table 2 : Solubility of cephalexin studies in water at 33±1°C,

Time (hr)	Solubility (mg/ml)*	%CV
24	12.1375 ± 0.033	0.27
48	13.7689 ± 0.099	0.72
72	13.0232 ± 0.165	1.27

* n = 2, mean ± SD.

3. Preparation of membranes.

3.1 Ethylcellulose membrane.

3.1.1 Effect of plasticizers.

The physical characteristics of ethylcellulose membrane such as flexibility, brittleness, clarity, and easy to detachable were determined and results were shown in Table 3.

Ethylcellulose membrane when using PEG 6000 as a plasticizer showed the characteristic of cloudy and brittle, because of its own characteristics that is white, easy to break fragment, and immiscible with ethylcellulose when PEG 6000 is incorporated to the ethylcellulose resulted in brittleness, cloudy and also sticky. The chemical structure of PEG 6000 was shown in Fig. 13 (a), hydroxyl group of

its molecules show a hydrophilic property (Gennaro, 1990) but ethylcellulose is a hydrophobic polymer. Although PEG 6000 have a high molecular weight but its solubility power in ethylcellulose is very low thus PEG 6000 play no role in reducing the glass transition temperature. The same results occurred in PEG 1450, with the same reason of PEG 6000, PEG 1450 is more hydrophilic than PEG 6000 because PEG 1450 have lower molecular weight than PEG 6000 so PEG 1450 cannot miscible with ethylcellulose and cannot reduce glass transition temperature too.

Table 3 : Characteristics of ethylcellulose membrane when using various types and amounts of plasticizers (dried at 60°C).

Type of plasticizer	% of plasticizer														
	Flexibility*					Clarity#					Easy to detachable❁				
	0	10	20	30	40	0	10	20	30	40	0	10	20	30	40
PEG 6000	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PEG 1450	x	x	x	x	x	x	x	x	x	x	x	x	✓	✓	✓
Castor oil	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
triacetin	x	✓	✓	✓	✓	x	✓	✓	✓	✓	x	✓	✓	✓	✓
triethyl citrate	x	✓	✓	✓	✓	x	✓	✓	✓	✓	x	✓	✓	✓	✓

* Flexibility ✓ = good flexible, x = brittleness

\# Clarity ✓ = transparency, x = cloudy

❁ Easy to detachable ✓ = easy to detachable, x = sticky

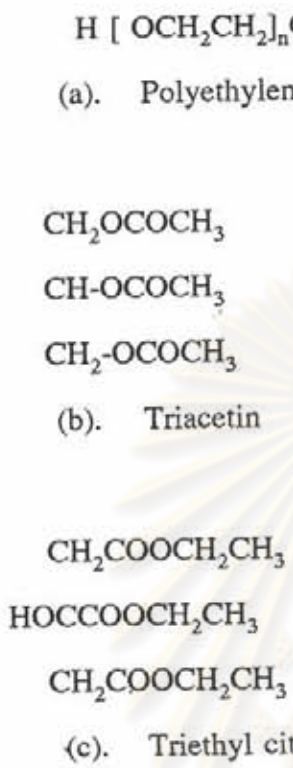


Figure 13 : Structure of some plasticizers

Castor oil is immiscible with ethylcellulose, so it cannot give an appropriate membrane. Because of castor oil is a fixed oil when ethanol is evaporated out in drying process, ethylcellulose will be gel and deposit on the glass plate with separation of castor oil. The membrane becomes sticky and cannot detach.

Triacetin and triethyl citrate are the most effective plasticizer for ethylcellulose in this study because they give a good flexibility, clear and easy to detach the membrane. Figure 13 (b), (c) show that their structures have both hydrophilic part and hydrophobic part with low molecular weight. They could distribute themselves between the polymer chains and interact with functional

groups, thereby reducing the interaction between the polymer chains and softening the matrix (Radebaugh, 1988) so there were the lesser pores on the membrane when the greater amount of plasticizer were used and the smoother membrane were obtained as shown in Fig. 14, 15, 16, 17, 18, 19, 20 and 21. These results are the same as the studies of Hutchings, Clarson and Sakr (1994). It was found that the lower molecular weight of plasticizer, the softer and smoother membranes were obtained from the higher amount of plasticizer (Radebaugh, 1992).

3.1.2 Effect of temperature on the drying process of ethylcellulose membranes.

In this study, the four different temperatures were used which are room temperature (33±1°C), 40°C, 50°C and 60°C. The ethylcellulose with 30% triacetin (based on weight of polymer) as the plasticizer which is dried at room temperature is not a homogeneous and detachable membrane. The reason is the glass transition temperature of ethylcellulose with 30% triacetin is between 35°-40°C (Hutchings, Clarson and Sakr, 1994) so at glassy state the intermolecular force of ethylcellulose is every strong, thus plasticizer cannot penetrate between their molecules and cannot help reducing glass transition temperature of ethylcellulose. In the event of using temperature of 40°, 50° and 60°C as the drying temperature, these three temperature reach to the glass transition temperature, thus the clear and soft membranes were obtained. Surface characteristics of the ethylcellulose membrane was shown in Fig. 22, 23 and 24. There are some pores on the surface of membrane when drying at 40°C but none on the membrane when drying at 50° and 60°C. The reason is at the temperature of 50° and 60°C that is higher than glass transition temperature of ethylcellulose, the coalescence of ethylcellulose molecules were occurred so the membranes were smoother and less porosity. Drying process at 40°C, even though there is low evaporation rate than at 50° and

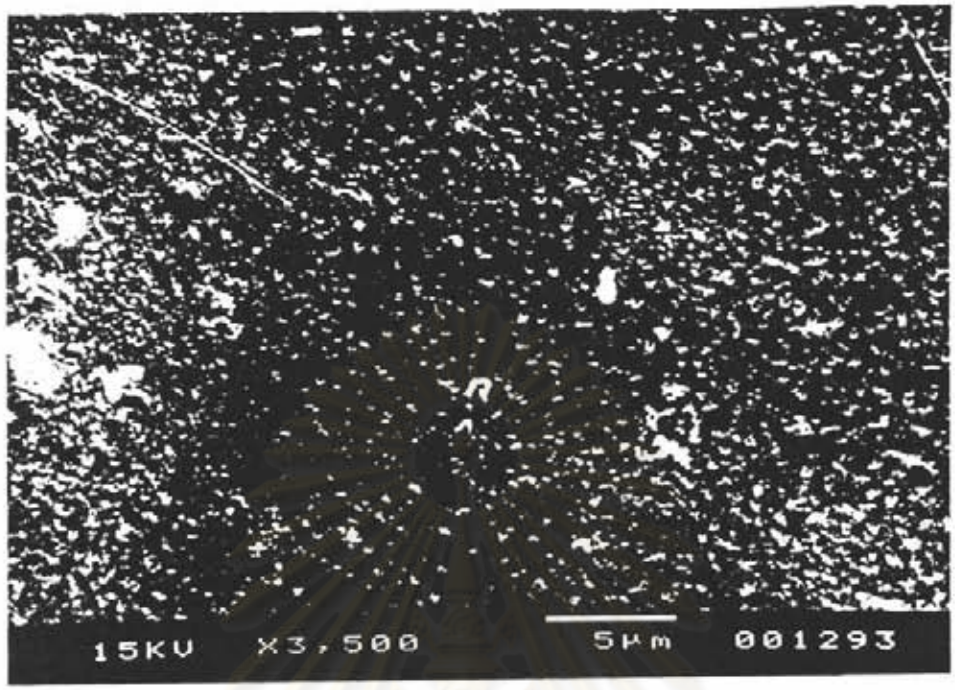


Fig. 14 : Surface characteristic of ethylcellulose membrane when using 10% triacetin as plasticizer (dried at 60°C).

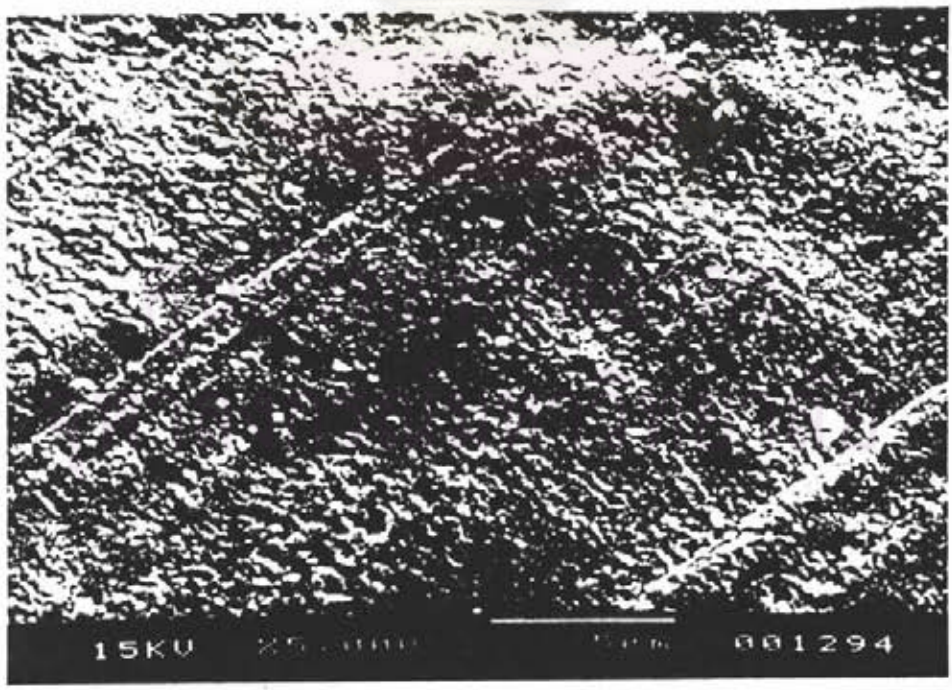


Fig. 15 : Surface characteristic of ethylcellulose membrane when using 20% triacetin as plasticizer (dried at 60°C).

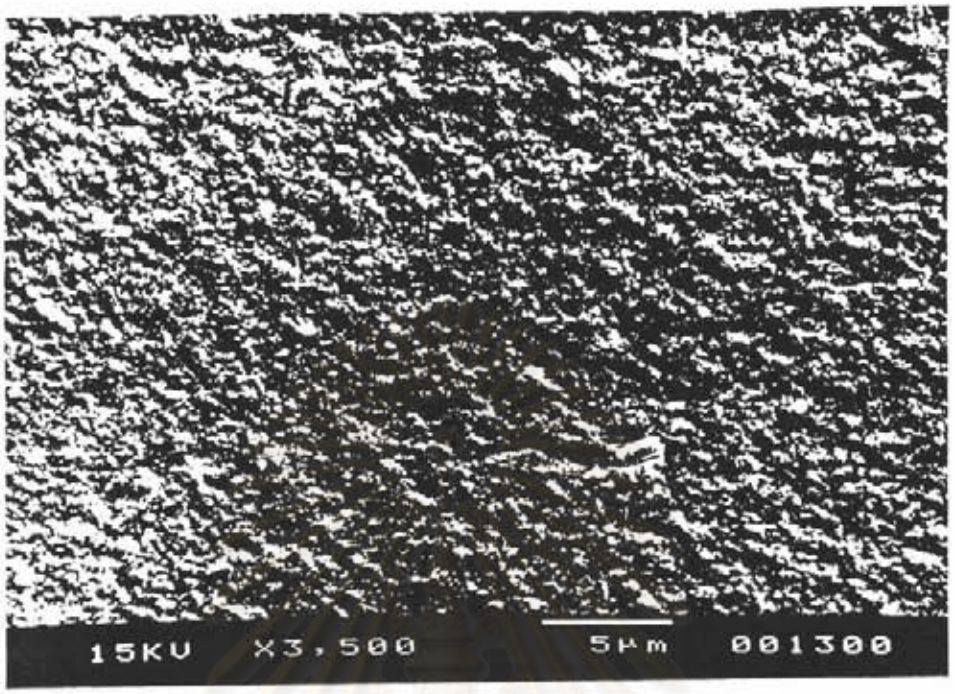


Fig. 16 : Surface characteristic of ethylcellulose membrane when using 30% triacetin as plasticizer (dried at 60°C).

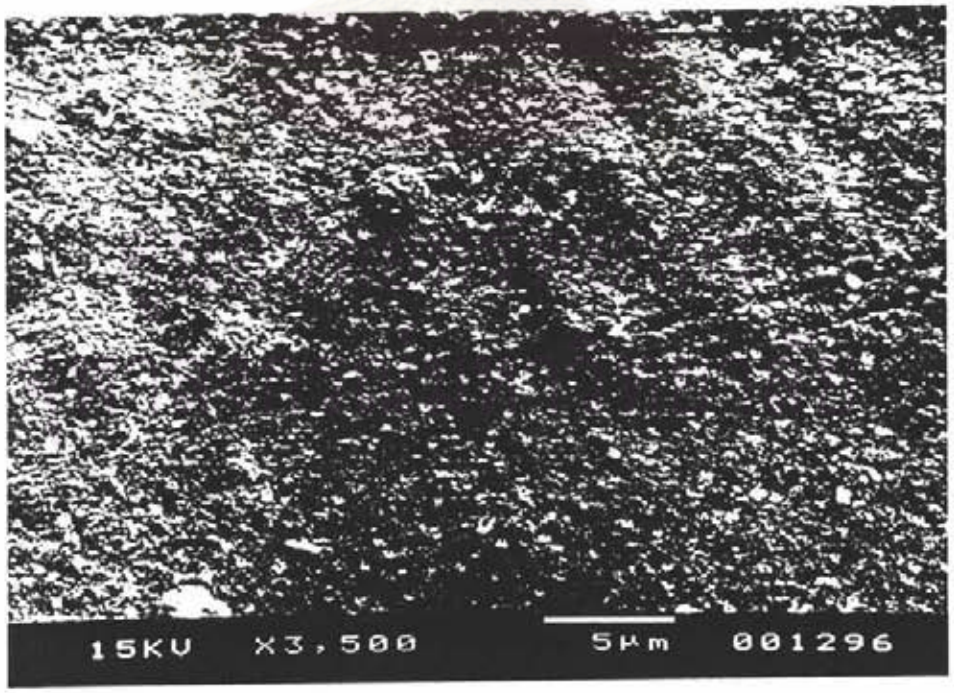


Fig. 17 : Surface characteristic of ethylcellulose membrane when using 40% triacetin as plasticizer (dried at 60°C).

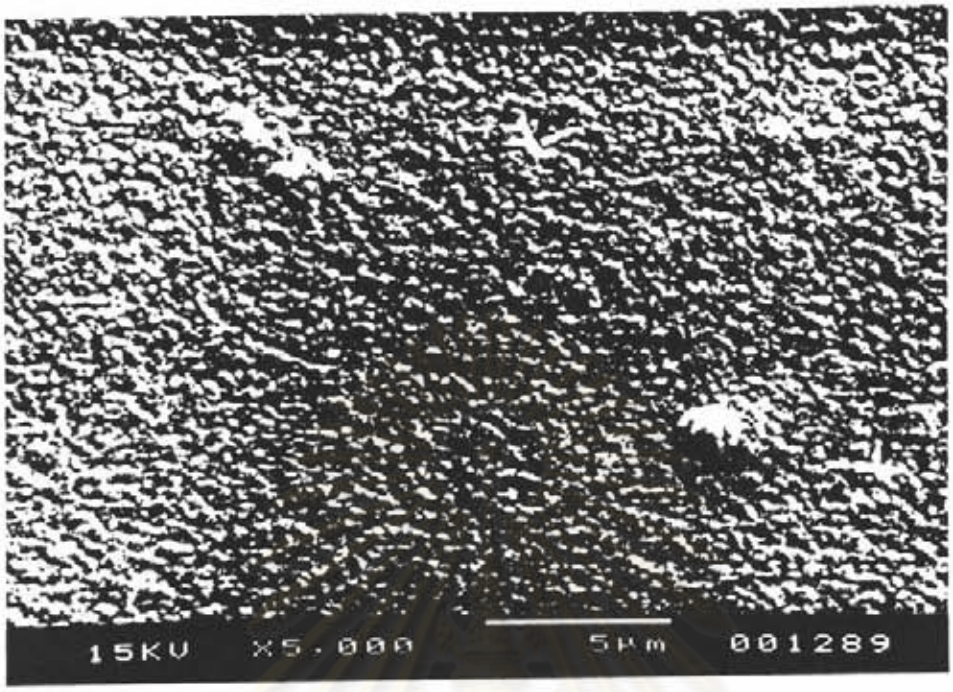


Fig. 18 : Surface characteristic of ethylcellulose membrane when using 10% triethyl citrate as plasticizer (dried at 60°C).

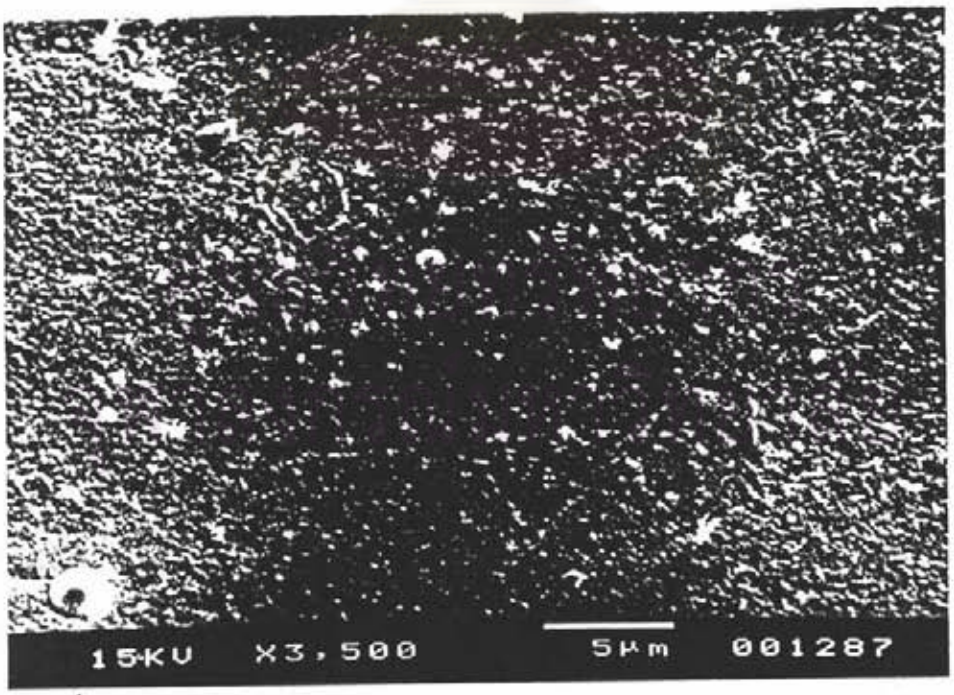


Fig. 19 : Surface characteristic of ethylcellulose membrane when using 20% triethyl citrate as plasticizer (dried at 60°C).

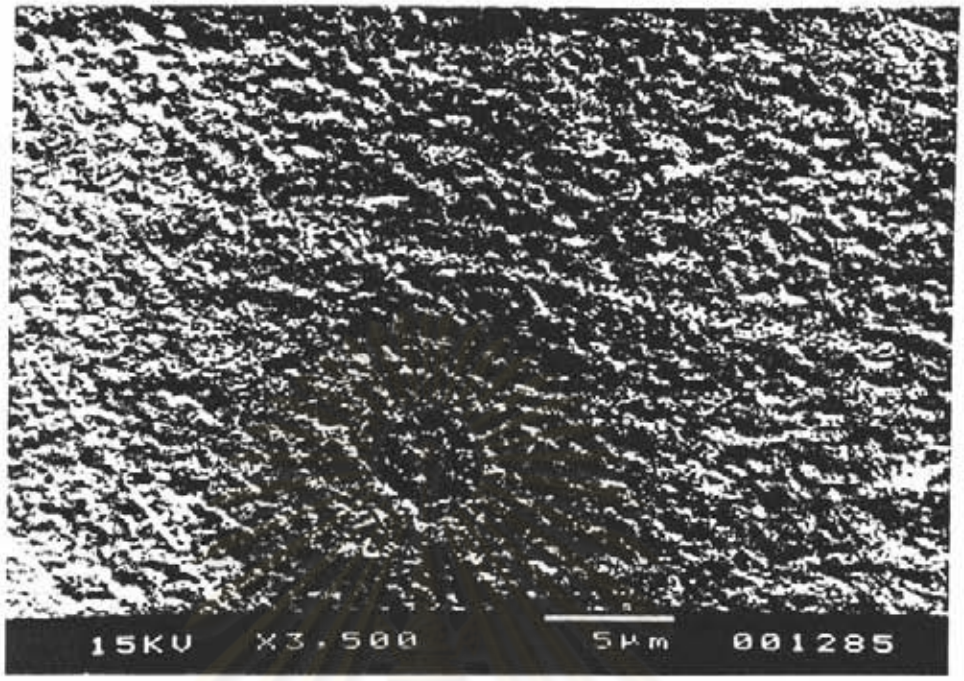


Fig. 20 : Surface characteristic of ethylcellulose membrane when using 30% triethyl citrate as plasticizer (dried at 60°C).

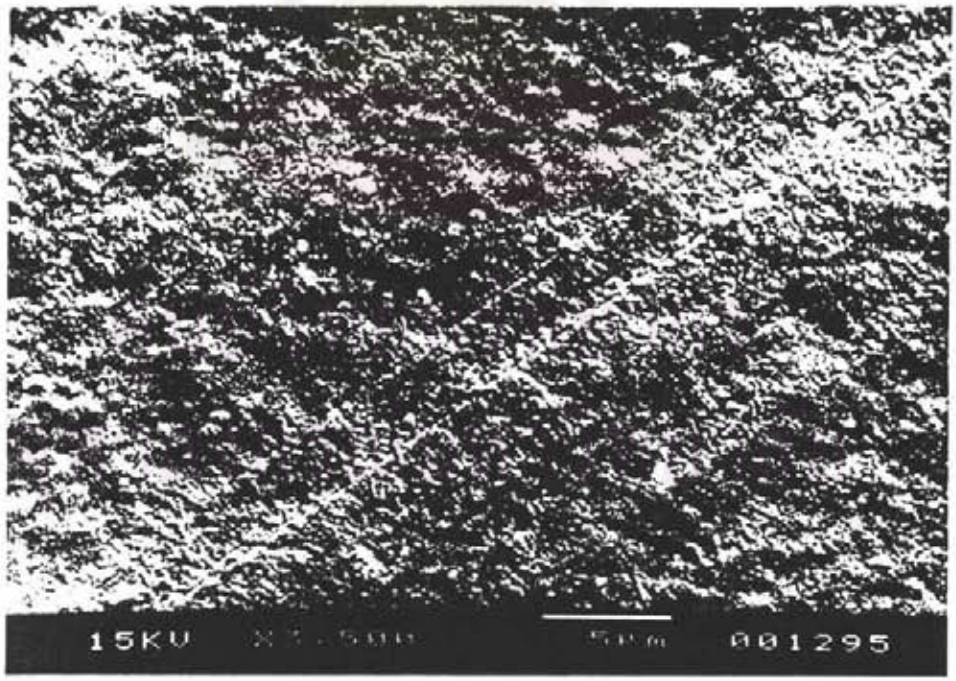


Fig 21 : Surface characteristic of ethylcellulose membrane when using 40% triethyl citrate as plasticizer (dried at 60°C).

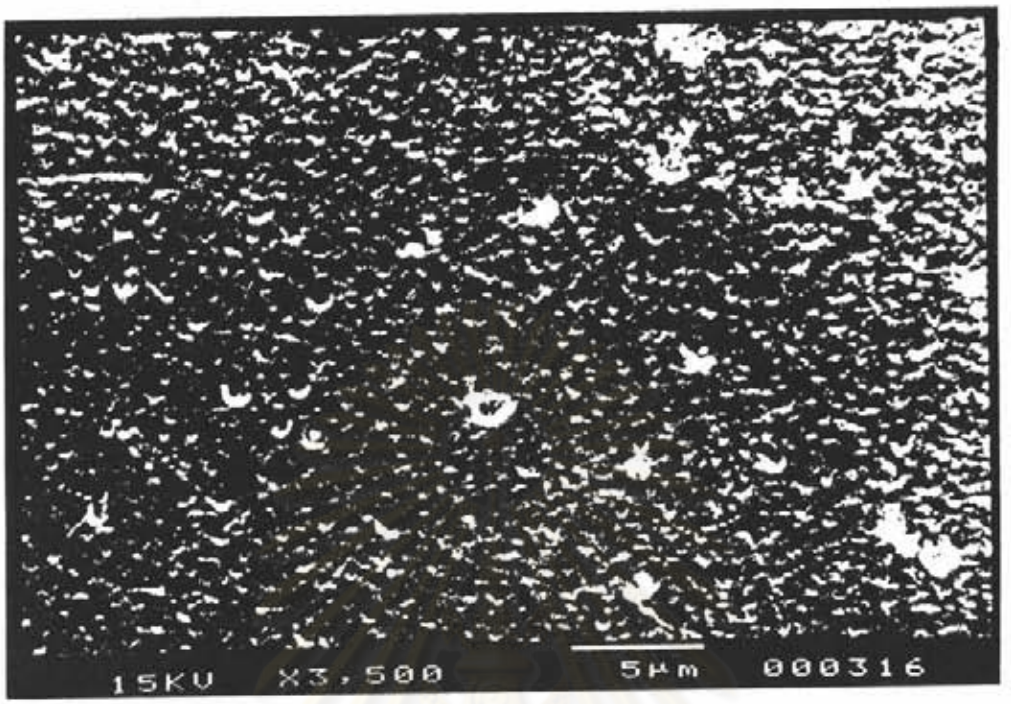


Fig. 22 : Surface characteristic of ethylcellulose membrane (30% TA) , dried at 40°C.

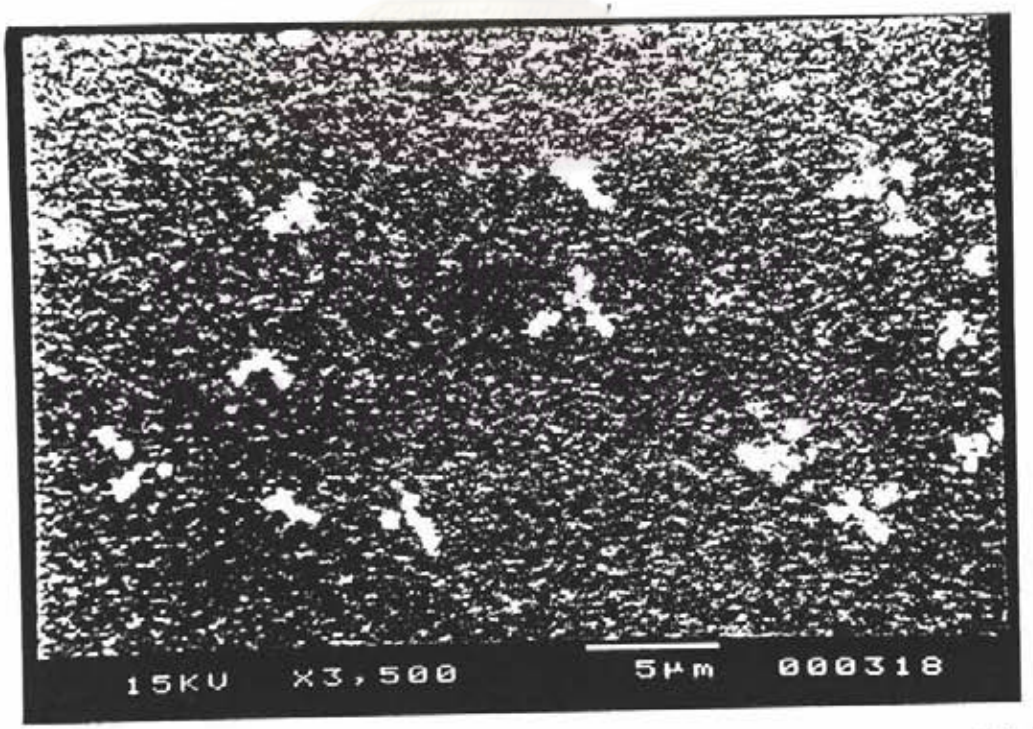


Fig. 23 : Surface characteristic of ethylcellulose membrane (30% TA) , dried at 50°C.

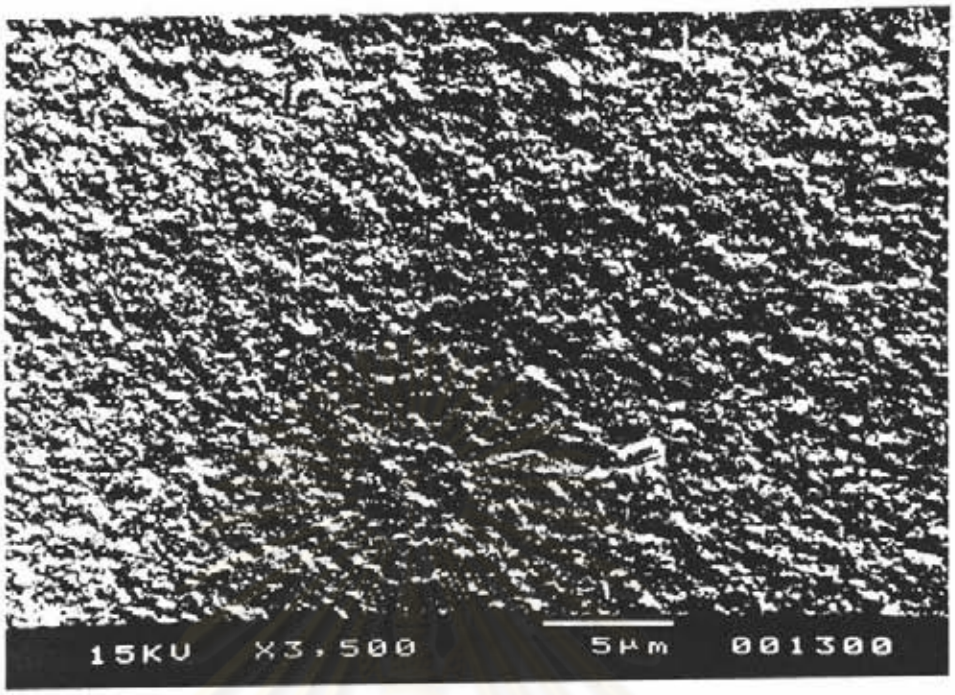


Fig. 24 : Surface characteristic of ethylcellulose membrane (30% TA) , dried at 60°C.

60°C that should has less pore than drying process at 50° and 60°C but at 40°C the temperature is just little higher than glass transition temperature thus curing process of ethylcellulose molecule is not complete yet.

From the results of the preparing of ethylcellulose membranes, 10-40% triacetin and 10-30% triethyl citrate were selected to be the plasticizers of ethylcellulose while a membrane which using 40% triethyl citrate gives a very soft and rubbery membrane. The drying temperature was selected at 60°C because at this temperature membranes was very smooth and had rarely pores. From this surface characteristic, these membranes should be a good barrier for drug that is the goal of the studies. All membranes were prepared again with the system selected as previously described and further used in diffusion study.

3,2 Eudragit RL 100®, Eudragit RS 100® and their combinations membranes.

3.2.1 Effect of plasticizers.

The same physical characteristics of Eudragit RL 100® and Eudragit RS 100® membranes were studied as in the case of ethylcellulose. The result is shown in Table 4 :

Table 4 : Effect of plasticizers on characteristics of Eudragit RL 100® and Eudragit RS 100® membranes (dried at 33± 1°C).

Type of plasticizer	% of plasticizer														
	Flexibility*					Clarity#					Easy to detachable❁				
	0	10	20	30	40	0	10	20	30	40	0	10	20	30	40
PEG 6000	x	x	x	x	x	✓	x	x	x	x	x	✓	✓	✓	✓
PEG 1450	x	✓	✓	x	x	✓	x	x	x	x	x	✓	✓	✓	✓
Castor oil	x	x	x	x	x	✓	x	x	x	x	x	x	x	x	x
triacetin	x	x	✓	✓	✓	✓	✓	✓	✓	✓	x	✓	✓	x	x
triethyl citrate	x	x	✓	✓	✓	✓	✓	✓	✓	✓	x	x	x	x	x

* Flexibility ✓ = good flexible, x = brittleness

\# Clarity ✓ = transparency, x = cloudy

❁ Easy to detachable ✓ = easy to detachable, x = sticky

The membranes which using PEG 1450 and PEG 6000 as the plasticizers were opaque and brittleness but PEG 1450 can improve membrane flexibility while PEG 6000 cannot. The membranes when using both PEG are crumbling thus it could not use in diffusion study. This could be explain that both PEG 1450 and PEG 6000 are white solid fragment at room temperature and easy to break. The lower molecular weight of PEG the greater flexible of membrane was occurred. Increment of plasticizer added give a good flexible membrane in a limited range. If percentage of plasticizer is over used, membranes will be brittle and break easily.

Castor oil is exactly immiscible with the Eudragit. Because of its high molecular weight and long chain fatty acid make it difficult to

interact between itself and Eudragit molecule. The separation of Eudragit and castor oil is obviously seen.

The good plasticizers for Eudragit are triacetin and triethyl citrate but the best is triacetin because it give a clear, good flexibility and very easy to detachable. Ten to twenty percent of plasticizer used are the optimum amount for plasticizing Eudragit. The same results were obtained as Lin, Lee and Lin (1991).

3.2.2 Effect of temperature on the drying process of Eudragit RL 100® and Eudragit RS 100® membranes.

Four temperatures of drying air were studied in drying process. The results are shown in Fig. 25-32. At room temperature (33±1°C), the drying process is occurred completely and give a good character of film in both Eudragit RL 100® and Eudragit RS 100®. There are some wrinkles on Eudragit RL 100® when drying at 40°C and 50°C because Eudragit RL 100® is more hydrophilic and hold more solvent during drying process. When hot air stream was applied, solvent was evaporated rapidly and molecular strands were shrink violently which make membranes wrinkle. This event did not occur in Eudragit RS 100® because they are less hydrophilic and hold less solvent during it swell, thus the membrane still smooth but brittle. The highest temperature of drying process studied is 60°C, the Eudragit RL 100® membrane transfigure to be smooth again. The reason is the curing process of polymer was occurred after shrinking of membrane as a previously occurring. Finally, the room temperature was selected to be a drying tempaerature because no shrinking effect on membrane resulted in the smooth and clear membranes were obtained.

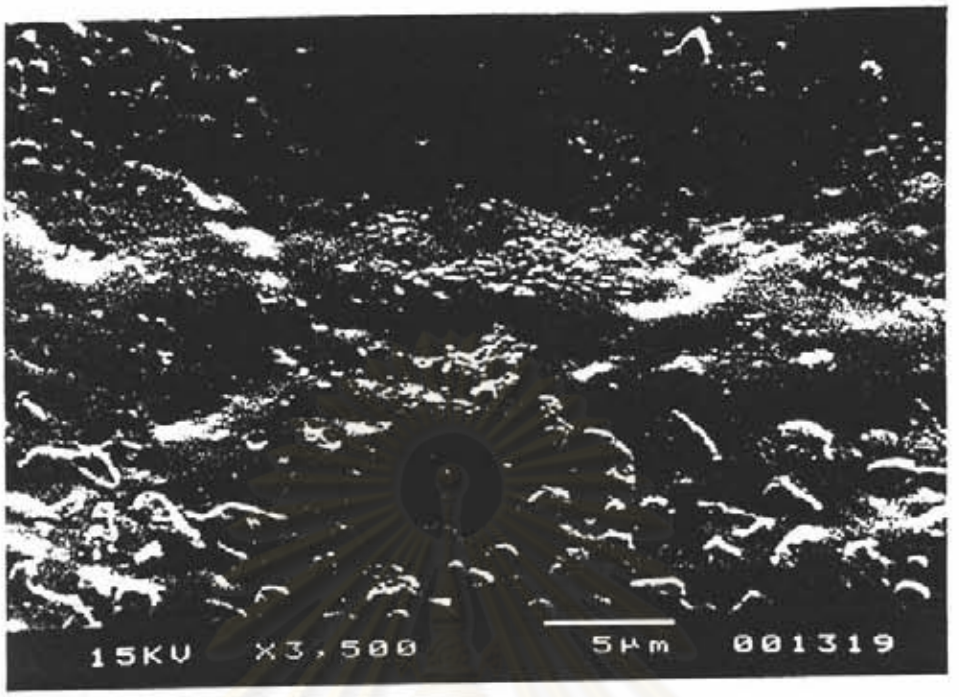


Fig. 25 : Surface characteristic of Eudragit RL 100® membrane (20% TA) , dried at room temperature (33±1° C).

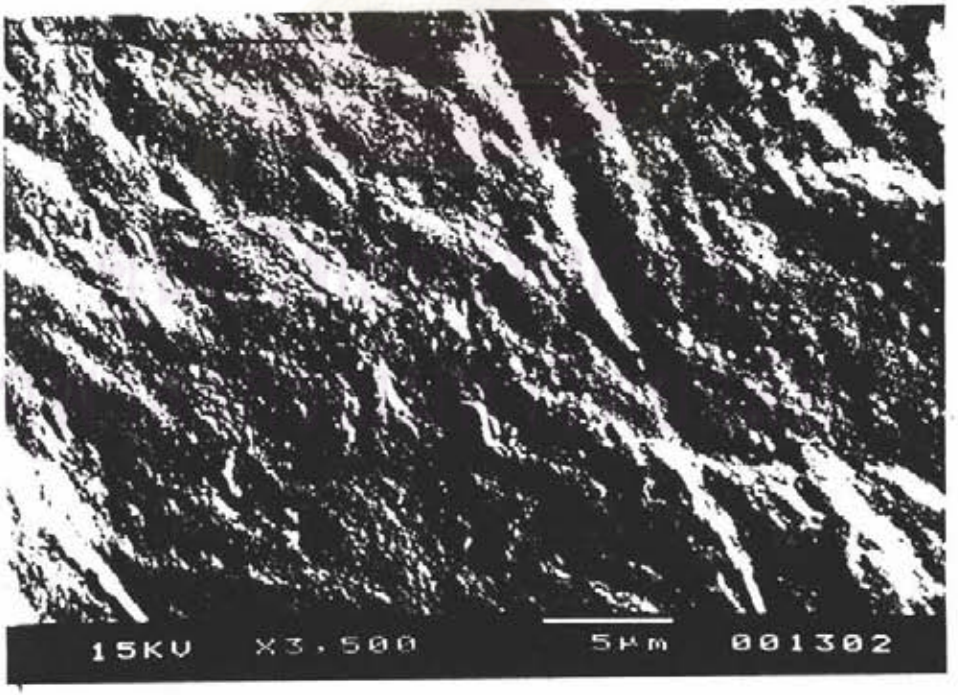


Fig. 26: Surface characteristic of Eudragit RS 100® membrane (20% TA) , dried at room temperature (33±1° C).

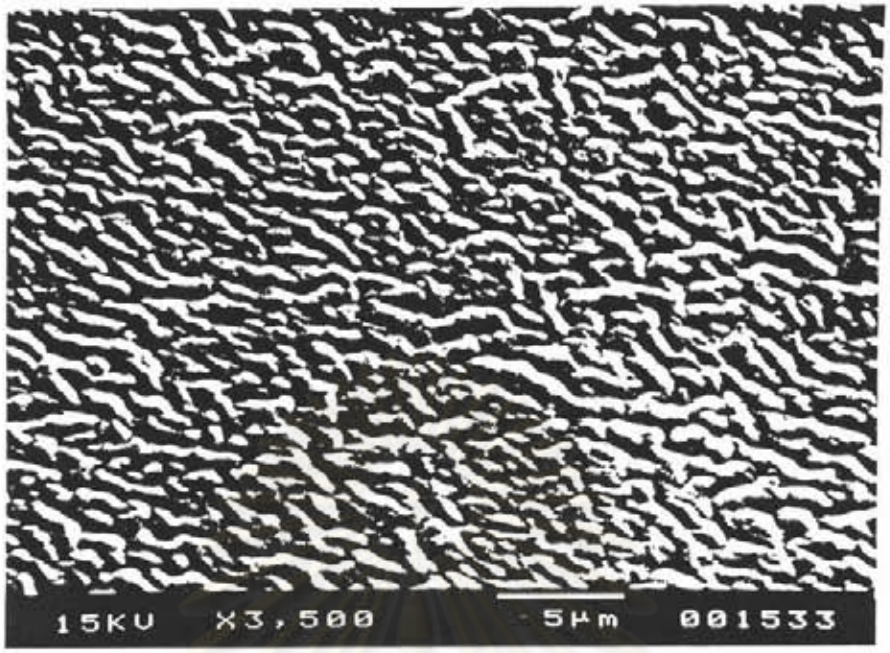


Fig. 27 : Surface characteristic of Eudragit RL 100® membrane (20% TA) , dried at 40° C.

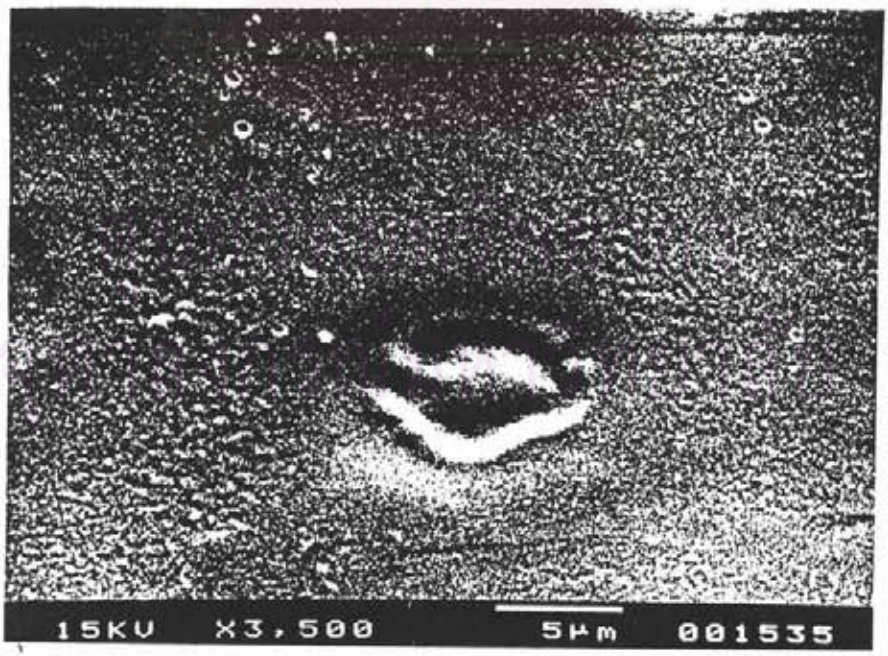


Fig. 28: Surface characteristic of Eudragit RS 100® membrane (20% TA) , dried at 40° C.

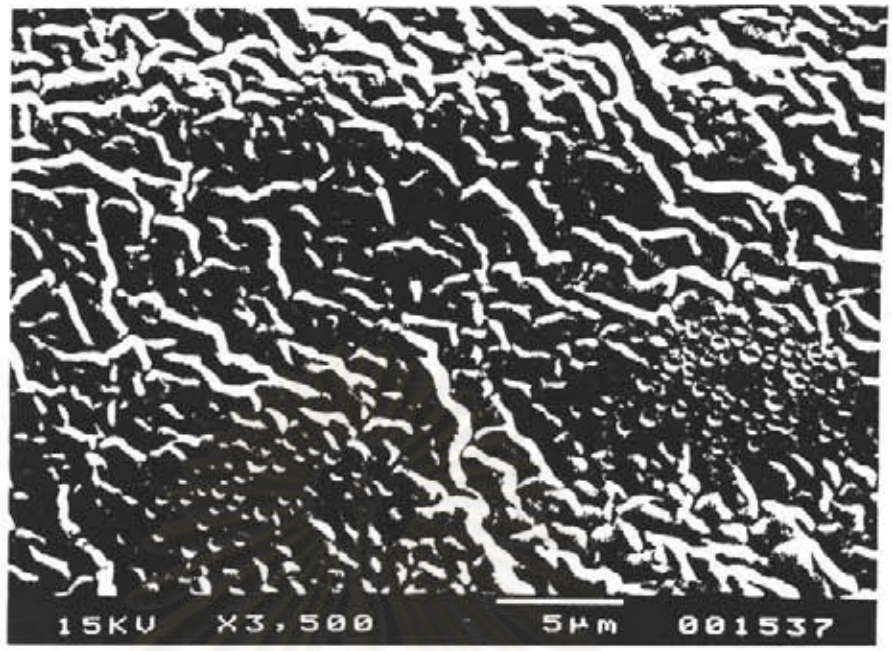


Fig. 29 : Surface characteristic of Eudragit RL 100® membrane (20% TA) , dried at 50° C.

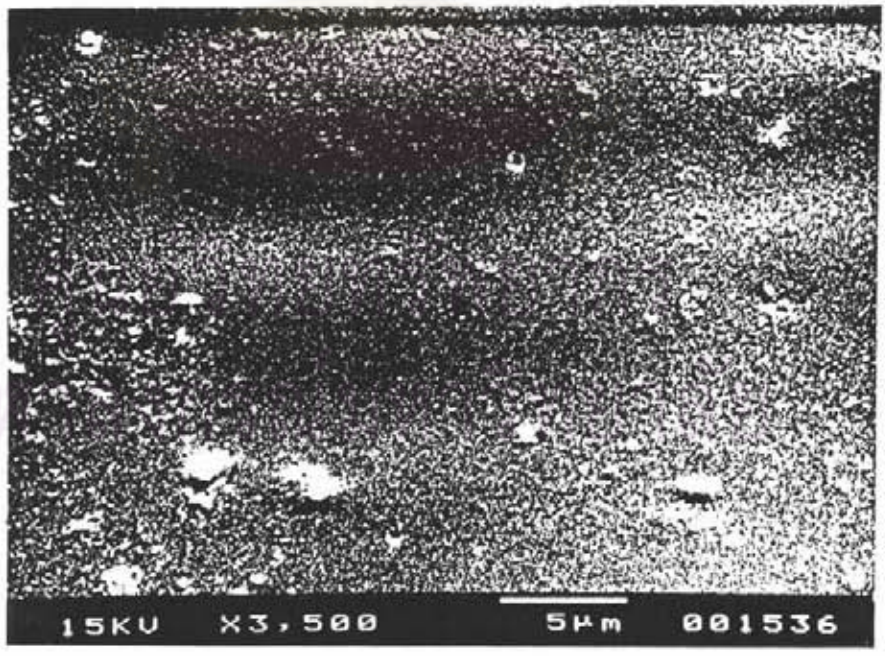


Fig. 30 : Surface characteristic of Eudragit RS 100® membrane (20% TA) , dried at 50° C.

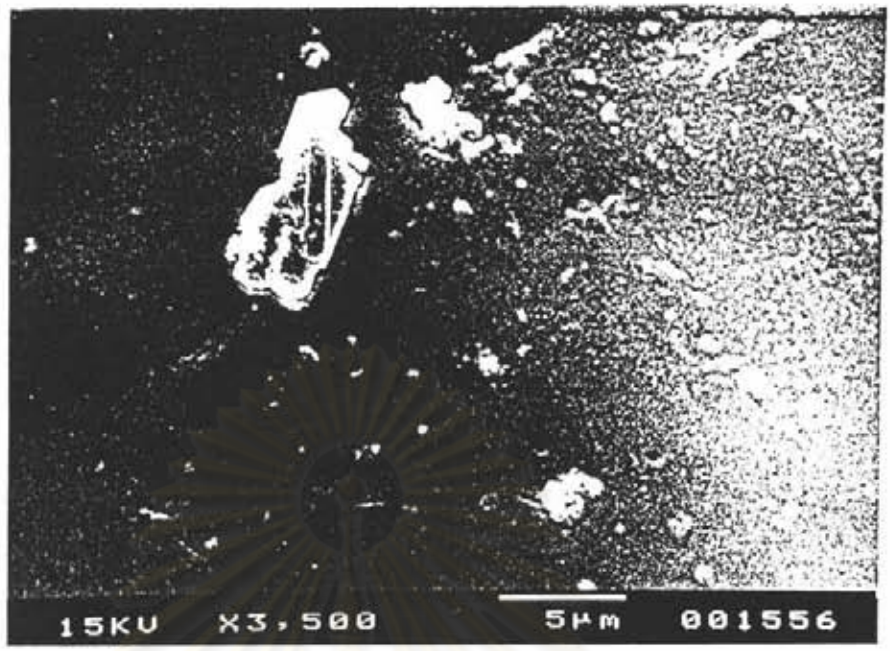


Fig. 31 : Surface characteristic of Eudragit RL 100® membrane (20% TA), dried at 60° C.

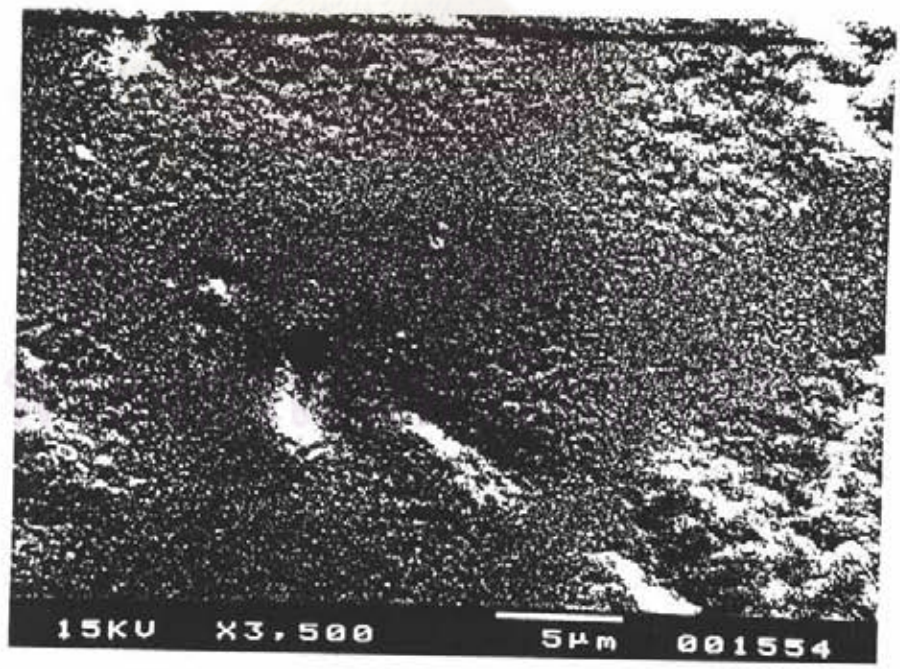


Fig. 32 : Surface characteristic of Eudragit RS 100® membrane (20% TA), dried at 60° C (× 3,500)

3.2.3 Combination of Eudragit RL 100® and Eudragit RS 100®

Six ratios of Eudragit RL 100® (RL) : Eudragit RS 100® (RS) were studied. All membranes were prepared in the same method as Eudragit RL 100® and RS 100® in previous experiment but using 20% triacetin as the plasticizer and room temperature as the drying temperature. The surface characteristics of membranes were studied by using scanning electron microscope (SEM) and their micrograph were shown in Fig. 33-38. There are no significant difference among various ratios of RL and RS because they contained the same amount of plasticizer and the same drying temperature, i.e., there was no factor to affect to membranes. Eudragit RL and RS differs only in ammonium group side chain that made them only differ in water permeability. Consequently, six ratios of combination of RL : RS are used in further diffusion study.

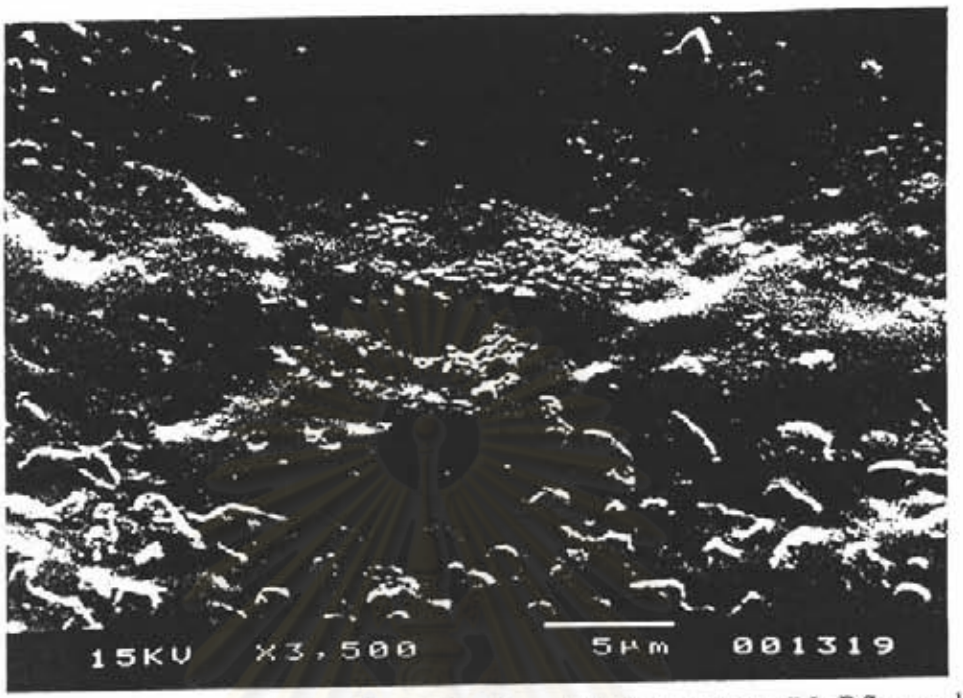


Fig. 33 : Surface characteristic of combination of 5:0 Eudragit RL:RS membrane when using 20% TA as plasticizer (dried at 33±1° C).

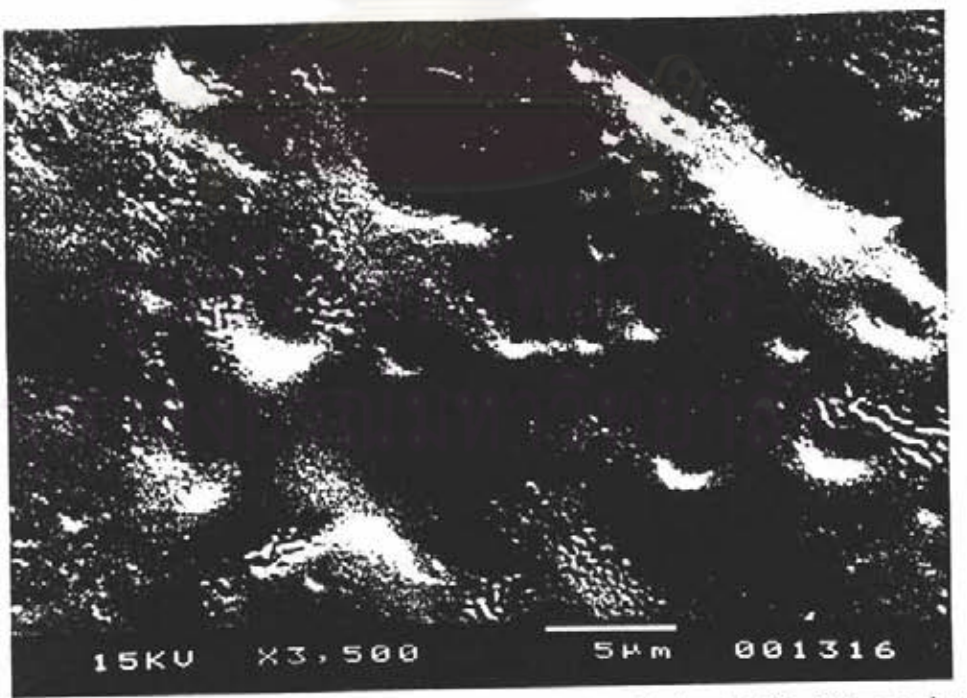


Fig. 34 : Surface characteristic of combination of 4:1 Eudragit RL:RS membrane when using 20% TA as plasticizer (dried at 33±1° C).

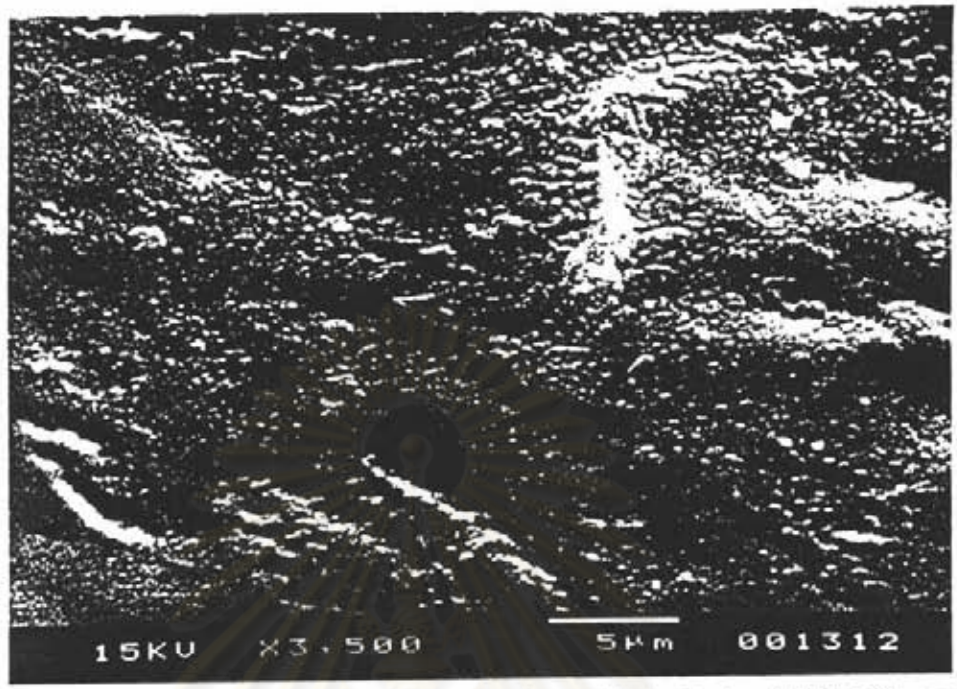


Fig. 35 : Surface characteristic of combination of 3:2 Eudragit RL:RS membrane when using 20% TA as plasticizer (dried at 33±1° C).

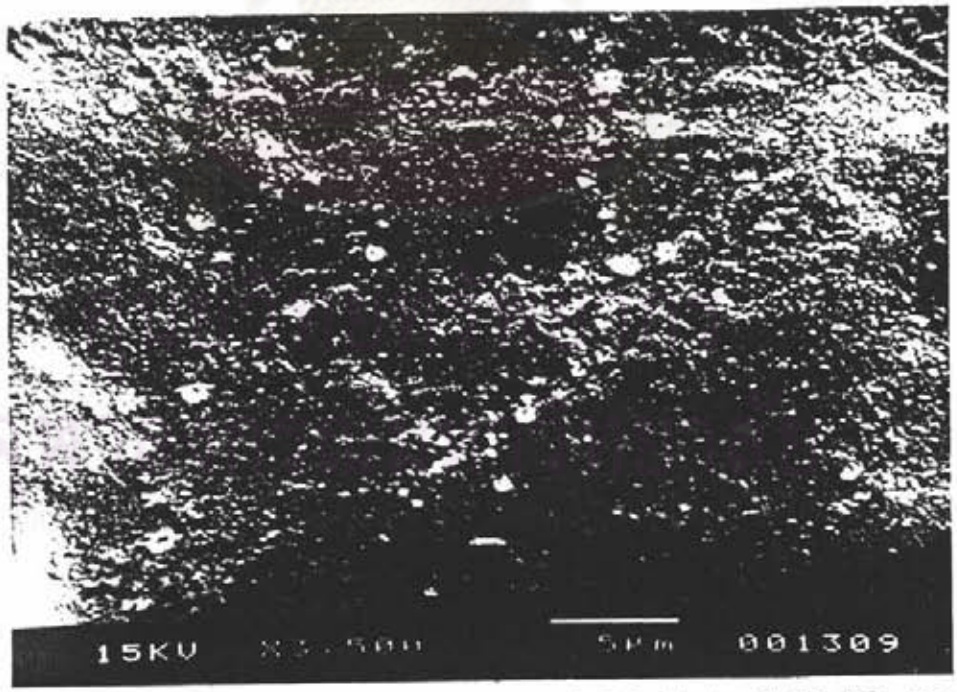


Fig. 36 : Surface characteristic of combination of 2:3 Eudragit RL:RS membrane when using 20% TA as plasticizer (dried at 33±1° C).

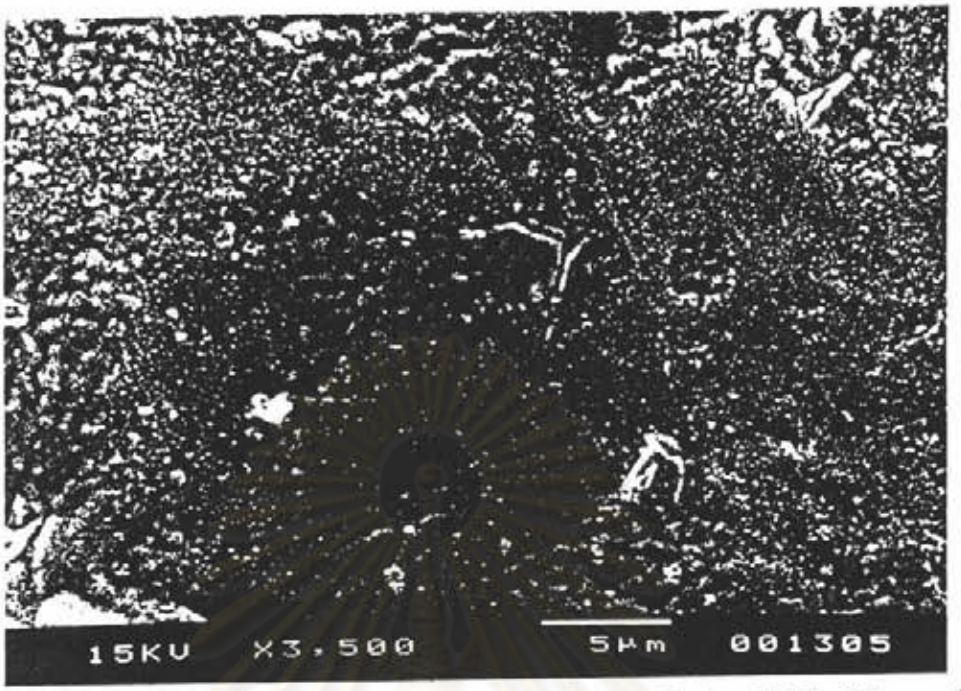


Fig. 37 : Surface characteristic of combination of 1:4 Eudragit RL:RS membrane when using 20% TA as plasticizer (dried at 33±1° C).

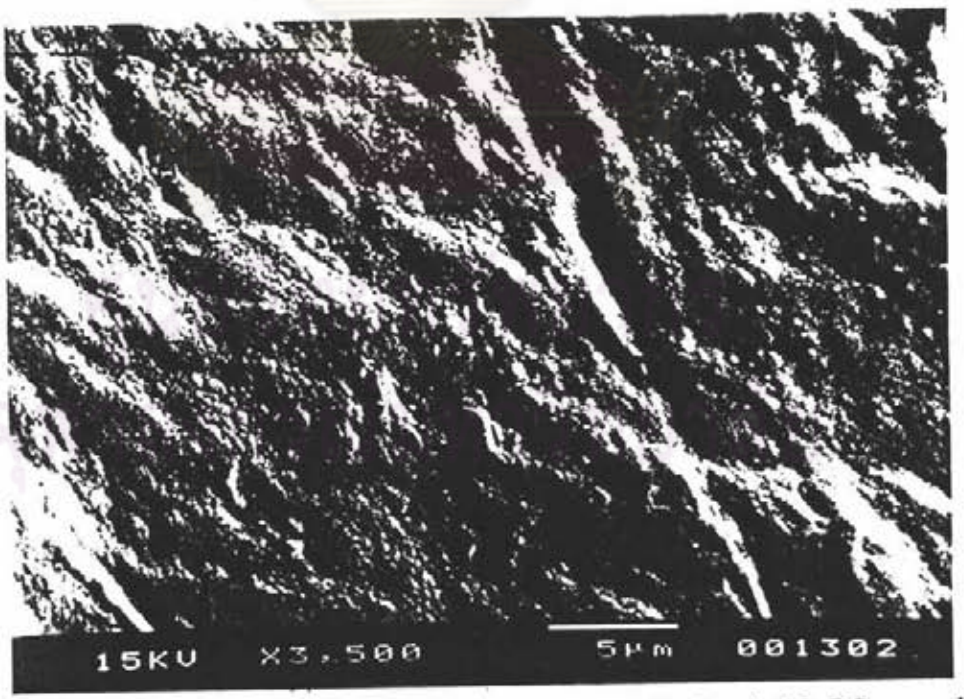


Fig. 38 : Surface characteristic of combination of 0:5 Eudragit RL:RS membrane when using 20% TA as plasticizer (dried at 33±1° C).

4. Diffusion study

Ethylcellulose membranes were prepared as previous experiment which containing 10, 20, 30 and 40% of triacetin and 10, 20 and 30% of triethyl citrate as the plasticizers. The Eudragit membranes was prepared by the same procedure using 20% triacetin as the plasticizer in every ratio of 5:0, 4:1, 3:2, 2:3, 1:4 and 0:5 RL:RS.

Rate of diffusion is calculated from slope of a cumulative amount-time curve in range of the steady state (2-10 hrs). From Fick's first law (Martin, 1993), equation (13), M is the amount of material flowing through a unit cross-section, S is a unit cross-section of a barrier, t is called a unit time and J is known as the flux.

$$J = \frac{dM}{S\,dt} \quad \text{.....(13)}$$

The flux in turn is proportional to the concentration gradient, dc/dx :

$$J = -D\frac{dC}{dx} \quad \text{.....(14)}$$

in which D is the diffusion coefficient of a penetrant (also called the diffusant) in cm^2/sec, C concentration in g/cm^3, and x the distance in cm of movement perpendicular to the surface of the barrier. The negative sign of equation (14) signifies that diffusion occurs in a direction opposited to that of increasing concentration. That is to say, diffusion occurs in the direction of decreasing concentration of diffusant ; thus, the flux is always a positive quantity. The diffusion constant, D, or diffusivity as it is often called, it may change in value at

higher concentrations. D is also affected by temperature, pressure, solvent properties, and the chemical nature of the diffusant.

An important condition in diffusion is that of the steady state. Fick's first law equation (14), gives the flux in the steady state of flow. The steady state may be described in terms of the second law, equation (15).

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} \qquad \text{.....(15)}$$

Consider the diffusant originally dissolved in a solvent in the donor compartment of the cell. Solvent alone is placed on the upper side of the barrier, and the solute diffuses through the central barrier from solution to solvents side (receptor side). In diffusion experiments, the solution in the receptor compartment is constantly removed and replaced with fresh solvent to keep the concentration at a low level. This is referred to as "sink conditions". Originally the diffusant concentration will fall in the donor compartment and rise in the receptor compartment until the system comes to an equilibrium, based on the rate of removal of diffusant from the sink and the nature of barrier. When the system has been existence in a sufficient time, the concentration of diffusant in the solutions at donor and receptor compartments become constant with respect to time, but obviously not the same in the two compartments. Then within each diffusional slice perpendicular to the direction of flow, the rate of change of concentration, dC/dt, will be zero, and by the second law,

$$\frac{dC}{dt} = D\frac{d^2C}{dx^2} = 0 \qquad \text{.....(16)}$$

where C is the concentration of the permeant in the barrier expressed in mass/cm^3. Equation (16) demonstrates that since D is not equal to zero, $d^2C/dx^2 = 0$. When a second derivative such as this equals zero, one concludes that there is no change in dC/dx. In other words, the concentration gradient across the membrane dC/dx is constant, signifying a linear relationship between concentration and distance, x. One can obtain diffusion rate, also called permeability (P), from the slope of M (amount) versus t (time).

Higuchi (Higuchi, 1967) developed an equation for the release of a drug dispersed in homogeneous and granular matrix dosage systems. From Fick's first law, Higuchi was developed the equation and it becomes :

$$Q = [D(2A-C_s)C_st]^{1/2} \quad \text{.....(17)}$$

in which Q is the drug released from surface of matrix ; D, the diffusion coefficient of the drug in matrix ; A, the total amount of drug in unit volume of matrix ; C_s, the solubility of drug in polymeric matrix ; and t, the time.

If the matrix of polymer have pores, the volume and length of the opening must be accounted for in the diffusional equation, leading to a second form of the Higuchi equation :

$$Q = \frac{D\varepsilon}{\tau}(2A-\varepsilon C_s) C_s t^{1/2} \quad \text{.....(2)}$$

in which ε is the porosity of the matrix and τ is the tortuosity of the capillary system.

From Higuchi's equation a release rate was obtained from the slope of the relationship between amount of drug released and the square root of time. The linear relationship was found in the steady-state as same as in the diffusion experiments. The diffusion rates and release rates of cephalexin from water through ethylcellulose membranes are shown in Table 5. The diffusion rates and release rates of cephalexin diffused through Eudragit membranes are shown in Table 6.

Table 5 : Diffusion and release rate of cephalexin through ethylcellulose membrane containing various amount of triacetin or triethyl citrate.

Type of membranes	Diffusion rate ⊛ (from 2-10 hrs)	r^2	Release rate ❖ (from 2-10 hrs)	r^2
10%TAEC	11.660	0.9863	53.996	0.9948
20%TAEC	31.827	0.9783	147.320	0.9857
30%TAEC	15.641	0.9733	72.116	0.9731
40%TAEC	32.654	0.9670	152.142	0.9873
10%TCEC	25.429	0.9349	113.550	0.8767
20%TCEC	68.069	0.9867	314.659	0.9917
30%TCEC	126.657	0.9741	589.927	0.9939

⊛ Diffusion rate is calculated from the slope of the plot between cumulative amount versus time.

❖ Released rate is calculated from the slope of the plot between cumulative amount versus square root of time.

Table 6 : Diffusion and release rate of cephalexin through Eudragit RL : RS membranes containing 20% triacetin as the plasticizer.

Ratio of Eudragit RL:RS	Diffusion rate ⊛ (from 2-10 hrs)	r^2	Release rate ❖ (from 2-10 hrs)	r^2
0 : 5	57.910	0.9543	259.705	0.8989
1 : 4	15.068	0.9975	68.771	0.9732
2 : 3	142.859	0.9897	663.491	0.9998
3 : 2	238.620	0.9995	1093.371	0.9852
4 : 1	334.462	0.9985	153.080	0.9800
5 : 0	585.892	0.9996	2692.071	0.9884

⊛ Diffusion rate is calculated from the slope of the plot between cumulative amount versus time.

❖ Released rate is calculated from the slope of the plot between cumulative amount versus square root of time.

The results of our study showed that the release of cephalexin through ethylcellulose, which had some pores and tortuous membranes, gave a good linear relationship between amount of drug released and square root of time. This result was supported by a study of Ruiz, Sakr and Sprockel (1990) whom studied the release of terbutaline sulfate from ethylcellulose microcapsules. They got the same results is the release of drug through ethylcellulose matrix more fit to Higuchi model than zero-order release model. The cumulative amount of cephalexin released through ethylcellulose containing triacetin as plasticizer were plotted against square root of time were shown in Fig. 39 and the membrane containing triethyl citrate were also shown in Fig. 40.

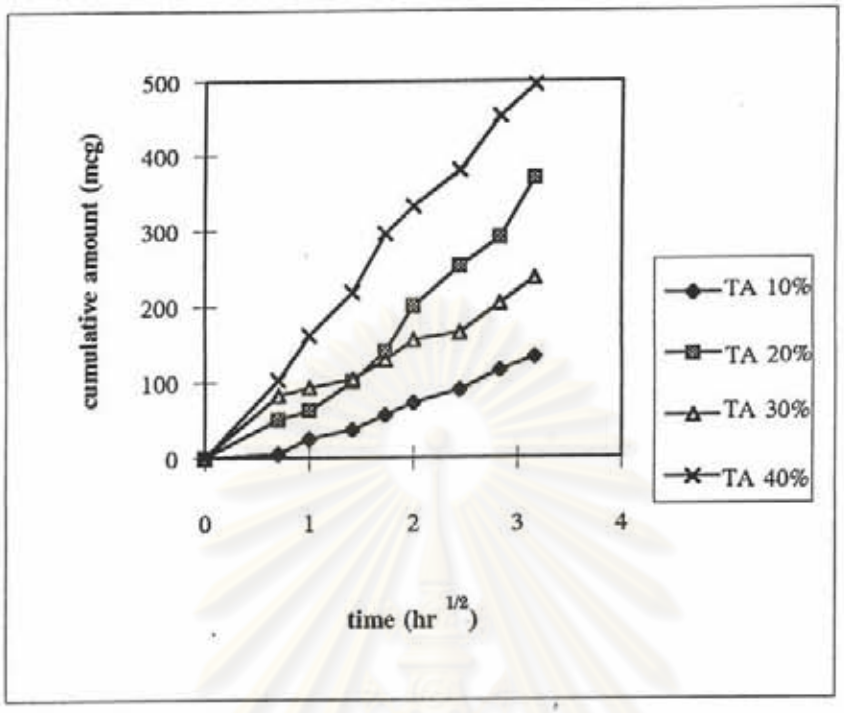


Fig. 39 : Cephalexin released from water through TAEC membranes.

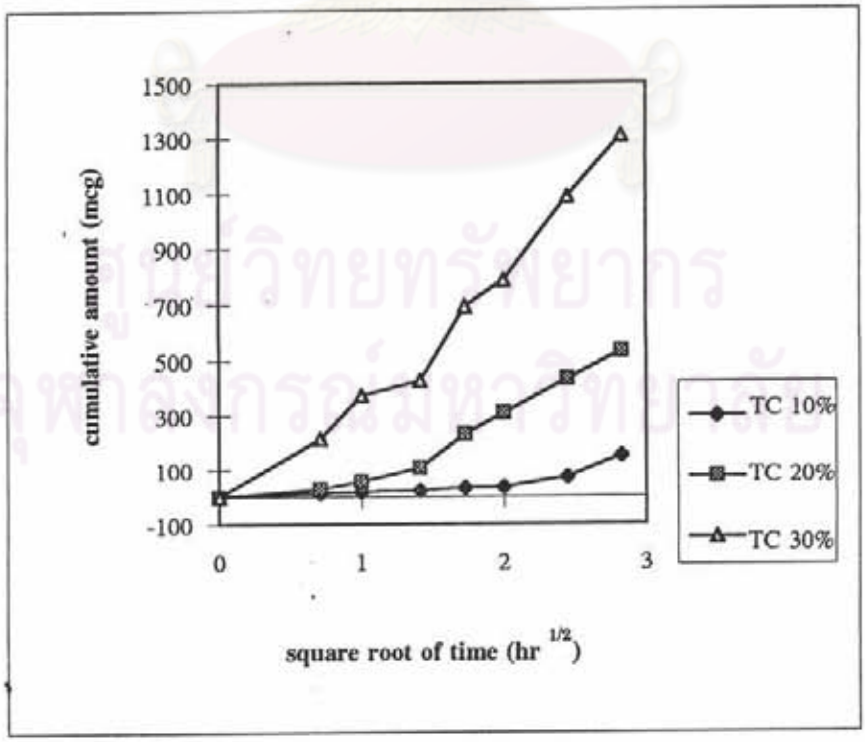


Fig. 40 : Cephalexin released from water through TCEC membranes.

The cephalexin released through Eudragit RL 100®, Eudragit RS 100® and their combinations in 5 ratios were shown in Fig. 41. They gave a good linear relationship between cumulative amount and time that followed the Fick's law. From SEM Eudragit membranes gave a very smooth membrane, they showed the few amount of very little pore sizes. The same results were also found in many researchers (Okor and Obi, 1990 ; Blanchon et. al., 1991 ; Thassu and Vyas, 1991). Eudragit RL : RS in the ratio of 5:0 showed more linearity in zero-order with percentage of correlation coefficient of 99.96 while 0:5 Eudragit RL : RS showed less linearity with the percentage of correlation coefficient of 95.43 because Eudragit RL was more hydrophilic and allowed more water to permeate through the polymer. From Fick's law of diffusion the more solvent penetrate through the membrane, the faster steady-state is reached and give a better linear relationship. Eudragit RS 100® have lesser ammonium side chain resulted in less hydrophilicity property. Thus the solvent could penetrate slowly in to the membrane and reach the steady state lately.

To compare between two types of wall materials, ethylcellulose and Eudragit, ethylcellulose gave a slower release rate than Eudragit because ethylcellulose exhibited very hydrophobic and it was very hard to wet. From all of the results of diffusion studies, ethylcellulose containing 30% triacetin as plasticizer, 2 : 3 and 3 : 2 Eudragit RL : RS were selected to be a wall of cephalexin microcapsules. The ethylcellulose film containing 30% triacetin as the plasticizer gave the best physical characteristics such as flexibility, clarity, uniformity of the polymer and showed lower released rate than the release from ethylcellulose containing a 20% triacetin. Although the addition 10% triacetin give the slowest release rate, the physical characteristics were not appreciated because of its more

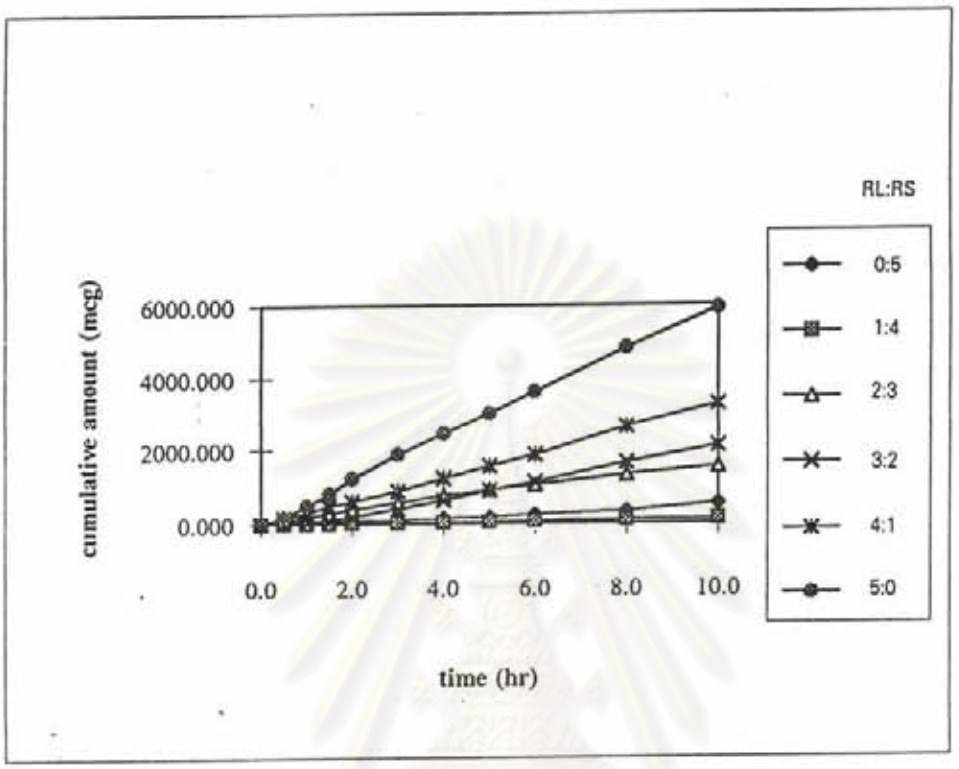


Fig. 41: Cephalexin released from water through combination of Eudragit membranes in various ratio of RL:RS.

brittleness and fragility. The same reasons are appeared in 2 : 3 and 3 : 2 Eudragit RL : RS , because of their good physical characteristics and both of them showed the released rate that are not significant difference, both of them should be selected to be the wall material.

5. Evaluation of Cephalexin Microcapsules.

5.1 Particle size analysis.

The size of microcapsules are readily expressed in terms of its diameter. Average or mean diameter was calculated by a general equation described by Edmunson (1967) whose derived an equation for the average as in eq. (18)

$$d_{mean} = \frac{\sum nd^{p+f}}{\sum nd^{f}}^{1/p} \quad \text{.....(18)}$$

In equation (18), n is the number of particles in a size range whose midpoint, d, is one of the equivalent diameters derived from mean of the size range. The term p is an index related to the size of an individual particle, since d raised to the power p=1, p=2 or p=3 is an expression to the particle length, surface, or volume, respectively. The value of the index p also decides whether the mean is arithmatic (p is positive), geometric (p is zero), or harmonic (p is negative). For a collection of particles, the frequency with which a particle in a certain size range occurs is expressed by nd^f. When the frequency index, f, has value of 0, 1, 2 or 3, then the size frequency distribution is expressed in terms of the total number, length, surface, or volume of the particles, respectively.

In this study, the arithmatic mean was used to compare the length of the diameter of microcapsules. Six hundred and twenty five particles were measured and calculated follow equation 18, when p=1 for measuring length of particle's diameter and p is a positive for arithmatic mean calculation, f=0 because we used the number of particles in each size range to calculate. So the equation used in this study is

$$d_{mean} = \frac{\sum nd}{\sum n} \quad \text{.....(19)}$$

The average diameters of microcapsules prepared by several wall types, core : wall ratio and microencapsulation techniques were shown in Table 7.

The mean of the particle size of microcapsules when preparing by spray drying technique gave an obviously smaller than the coacervated microcapsules and the fluidized microcapsules because from spray drying technique the spray nozzle can control the particle size when spraying process occurred while coacervation and fluidization technique can not controlled. The cumulative percentage frequency undersize was plotted against diameter as shown in appendix III.

Table 7 : Average mean diameter of particle size of microcapsules.

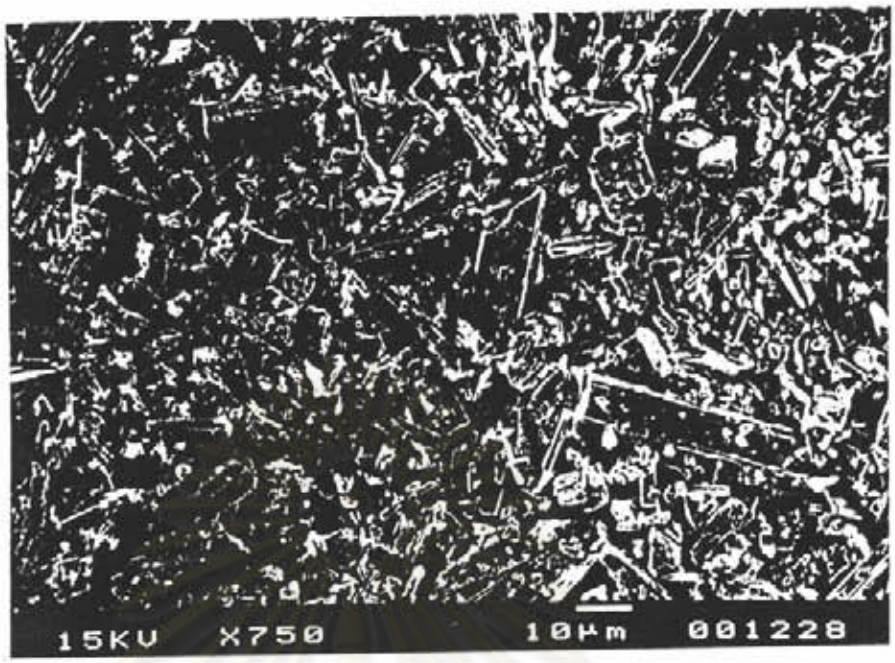
wall type	core : wall ratio	microencapsulation technique	mean (μ)	%CV
Ethylcellulose	2:1	Coacervation	174.66	50.20
Ethylcellulose	1:1	Coacervation	367.13	41.75
Ethylcellulose	1:2	Coacervation	270.50	35.97
3:2 ERL:RS	2:1	Coacervation	74.17	33.74
3:2 ERL:RS	1:1	Coacervation	95.28	38.08
3:2 ERL:RS	1:2	Coacervation	79.59	36.89
2:3 ERL:RS	2:1	Coacervation	135.60	56.56
2:3 ERL:RS	1:1	Coacervation	214.66	32.33
2:3 ERL:RS	1:2	Coacervation	398.67	19.64
Ethylcellulose	2:1	Fluidization	125.09	15.32
Ethylcellulose	1:1	Fluidization	212.67	30.11
Ethylcellulose	1:2	Fluidization	554.13	16.96
3:2 ERL:RS	2:1	Fluidization	38.36	24.40
3:2 ERL:RS	1:1	Fluidization	72.38	30.28
3:2 ERL:RS	1:2	Fluidization	72.61	31.92
2:3 ERL:RS	2:1	Fluidization	52.61	34.02
2:3 ERL:RS	1:1	Fluidization	63.06	33.05
2:3 ERL:RS	1:2	Fluidization	73.84	40.70
Ethylcellulose	2:1	Spray drying	42.82	48.53
Ethylcellulose	1:1	Spray drying	63.19	40.45
Ethylcellulose	1:2	Spray drying	46.85	50.76
3:2 ERL:RS	2:1	Spray drying	26.93	47.16
3:2 ERL:RS	1:1	Spray drying	47.84	41.76
3:2 ERL:RS	1:2	Spray drying	38.53	46.72
2:3 ERL:RS	2:1	Spray drying	39.84	44.18
2:3 ERL:RS	1:1	Spray drying	40.51	45.79
2:3 ERL:RS	1:2	Spray drying	41.98	46.88

5.2 Surface characteristics of microcapsules.

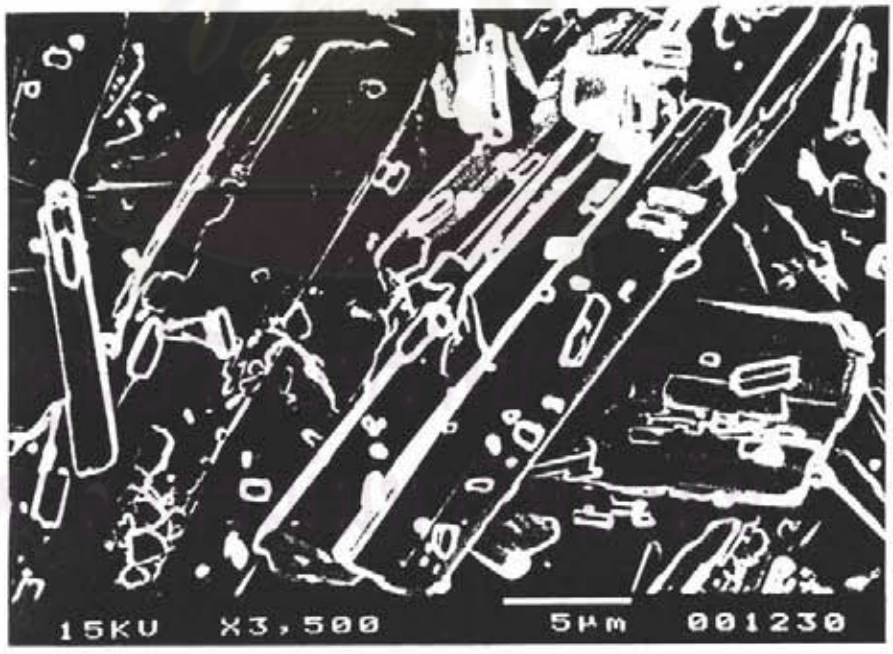
The surface characteristics of cephalexin microcapsules were examined by using scanning electron microscope (SEM) in 35, 100, 750, 1000, 1500, and 3500 magnifications. The results from SEM showed that relatively thicker of film layer was obtained by increasing amount of the film coated. Cephalexin monohydrate is a crystal which is rod shape as shown in Fig. 42.

Microcapsules of cephalexin prepared by coacervation technique showed aggregation of microcapsules because of drying process of preparing microcapsules which let them dry in a room temperature. During the cooling process, it might have the traces of polymer separated from the solution. In drying process these microcapsules fused together to produce larger particle size. This effect was observed both in ethylcellulose and Eudragit microcapsules. Their surface characteristic were shown in Fig. 43-51. The increment of coating polymer gave larger particle size and more tacky among particles.

The fluidization technique showed a better physical characteristics which gave a smaller particle size, less tackier particles and better complete coated of polymer than microcapsules which prepared from coacervation technique. The electron micrographs of microcapsules prepared by fluidization technique were shown in Fig. 52-60. The surface of 2:3 Eudragit RL:RS give the smoothest surface, 3:2 Eudragit RL:RS are worse and ethylcellulose microcapsules are the worst. The higher amount of polymer, the smoother and more complete microcapsules were obtained. This techniques gave almost complete coated of microcapsules among 3 technique studied.



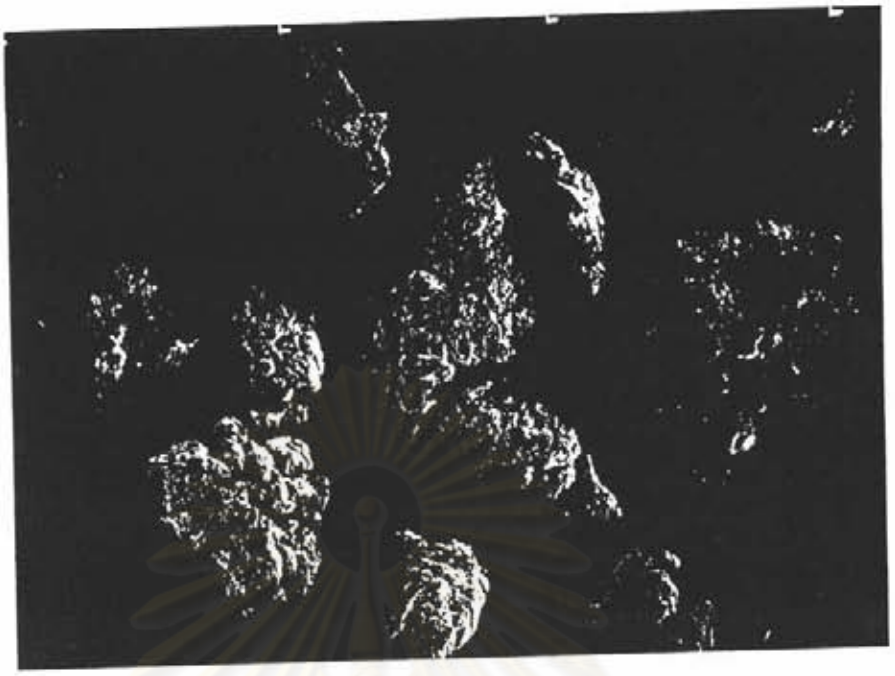
(a)



(b)

Fig. 42 : Illustrate cephalexin monohydrate crystal.

(a) x750, (b) x3500



(a)

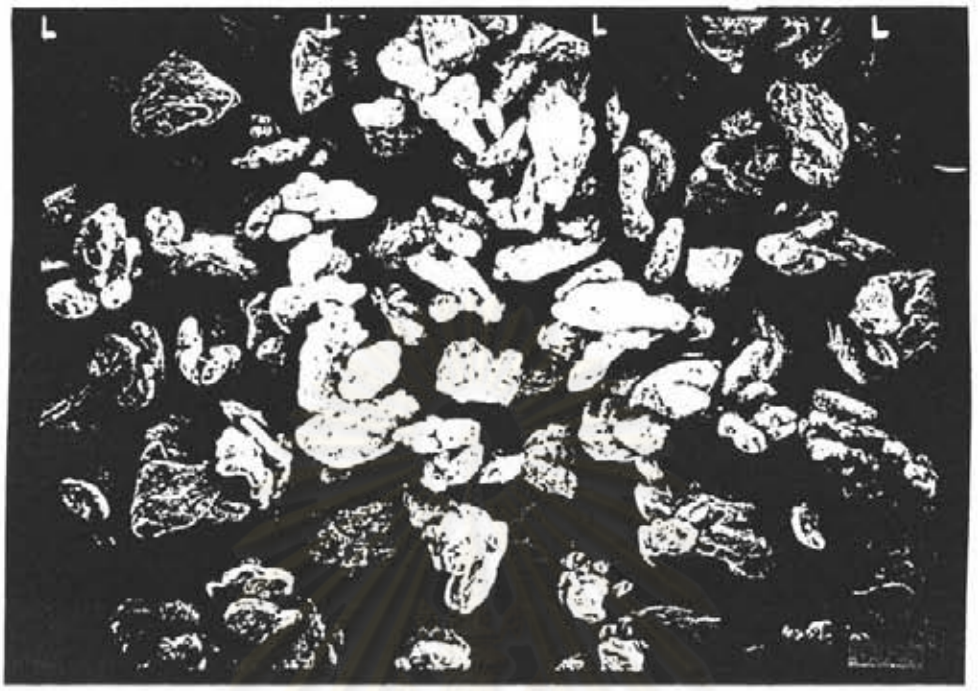
(b)

Fig. 43 : Surface characteristic of cephalexin microcapsules prepared by coacervation technique , using ethylcellulose as wall material, the core : wall ratio is 2:1 , (a) × 35 , (b) × 1500.

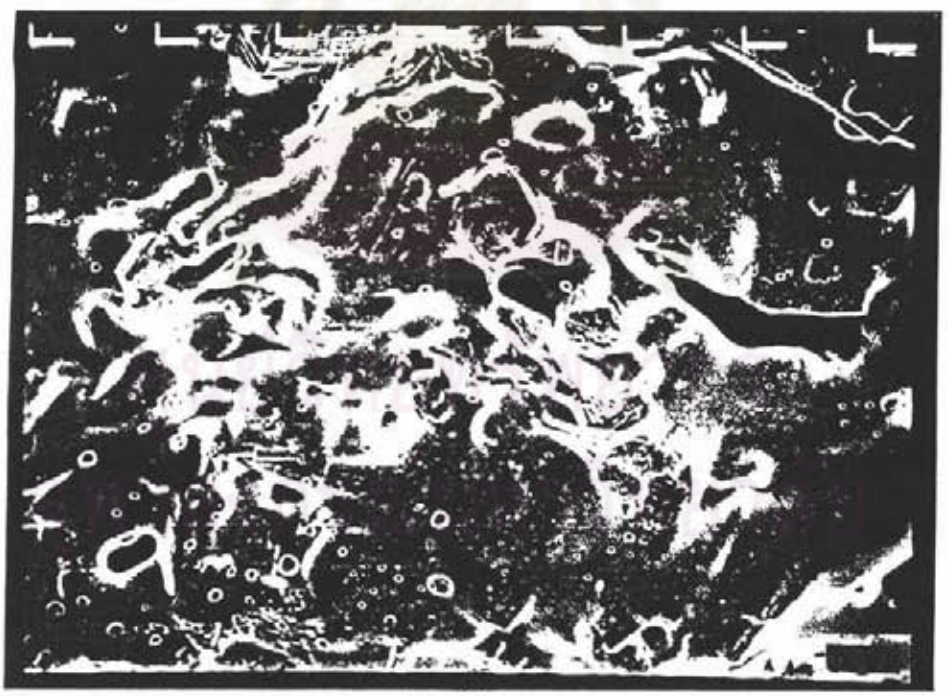
(a)

(b)

Fig. 44 : Surface characteristic of cephalexin microcapsules prepared by coacervation technique , using ethylcellulose as wall material, the core : wall ratio is 1:1 , (a) × 35 , (b) × 1000.

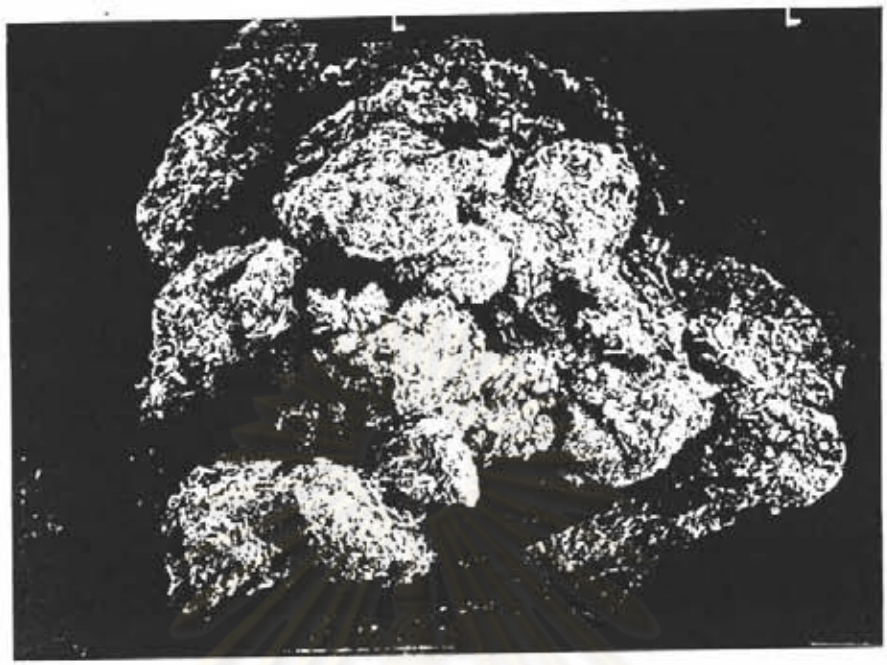


(a)

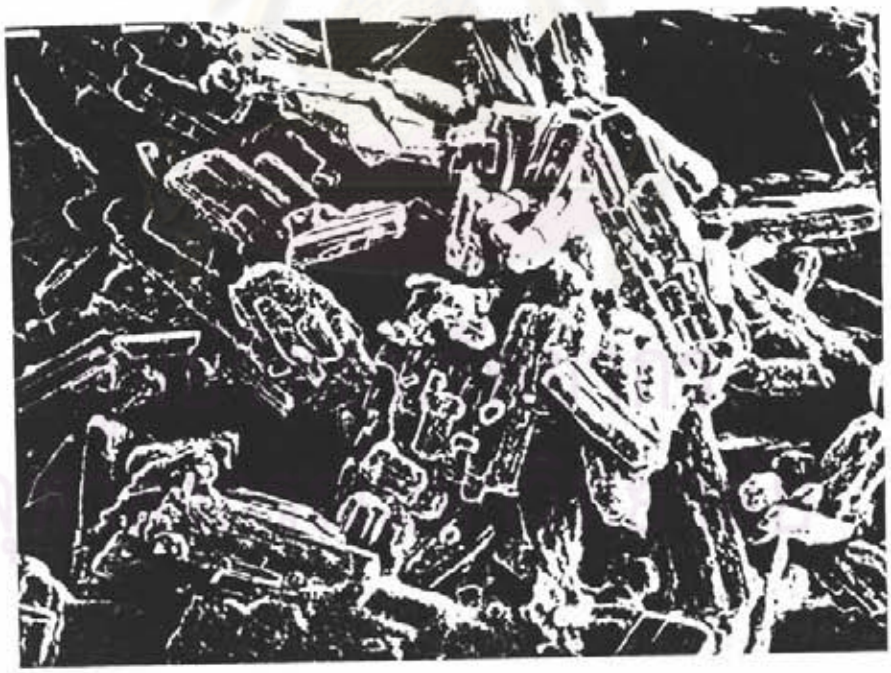


(b)

Fig.›45 : Surface characteristic of cephalexin microcapsules prepared by coacervation technique , using ethylcellulose as wall material, the core : wall ratio is 1:2 , (a) ×35 , (b) × 1500.

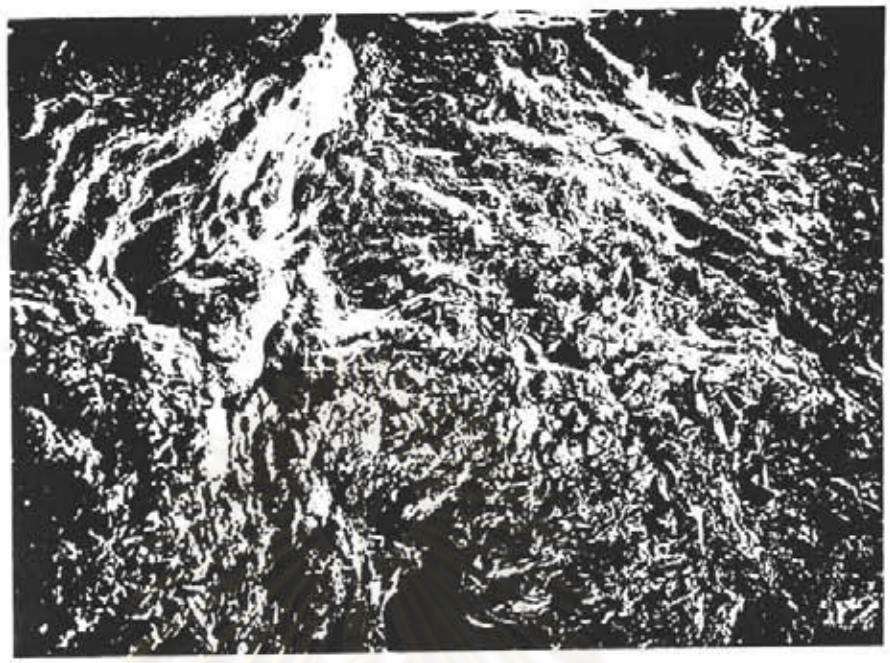


(a)

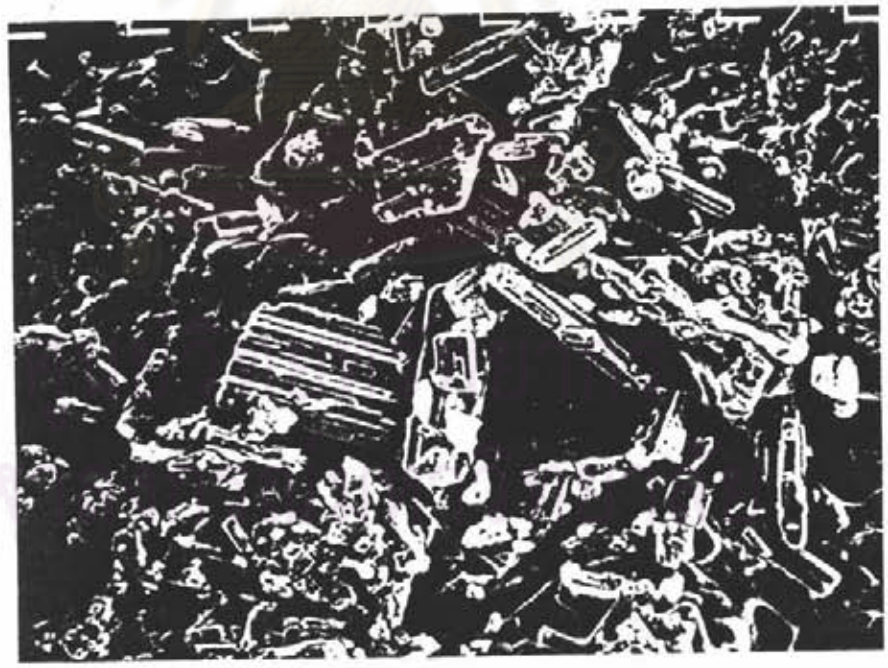


(b)

Fig. 46 : Surface characteristic of cephalexin microcapsules prepared by coacervation technique , using 3:2 ERL:RS as wall material, the core : wall ratio is 2:1 , (a) × 50 , (b) × 1000.

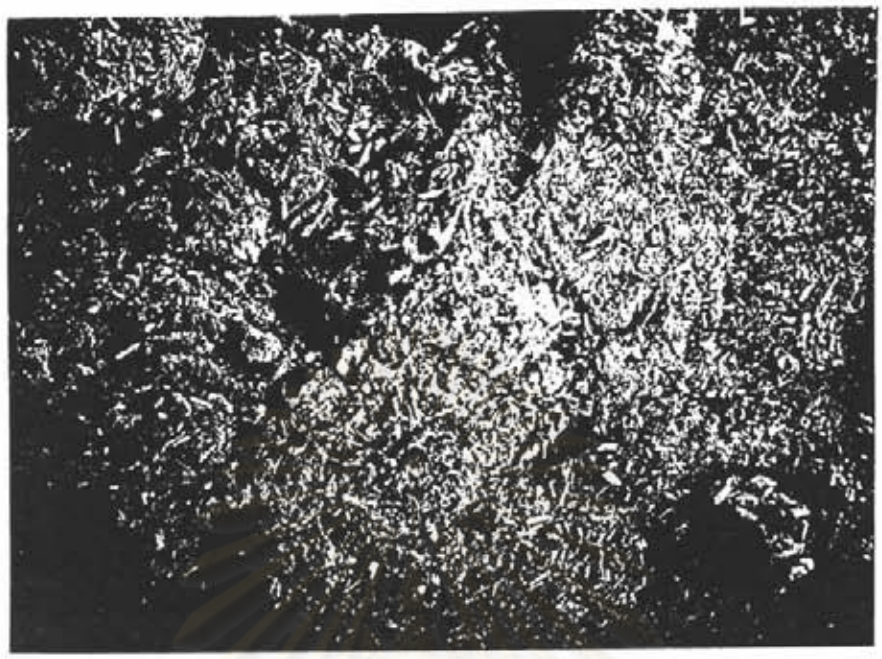


(a)



(b)

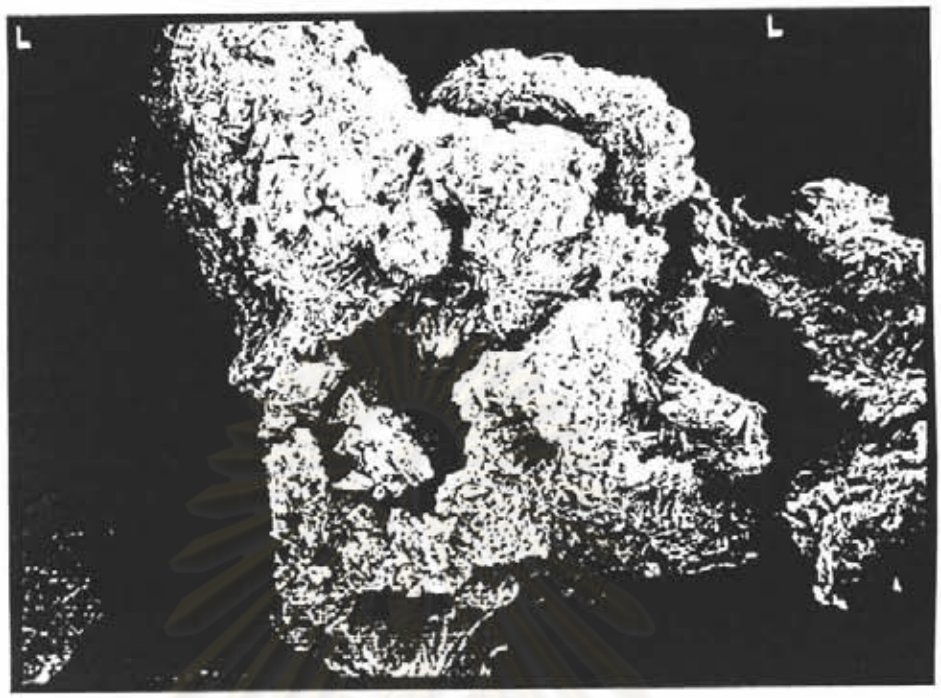
Fig. 47 : Surface characteristic of cephalexin microcapsules prepared by coacervation technique , using 3:2 ERL:RS as wall material, the core : wall ratio is 1:1 , (a) × 100 , (b) × 1500.



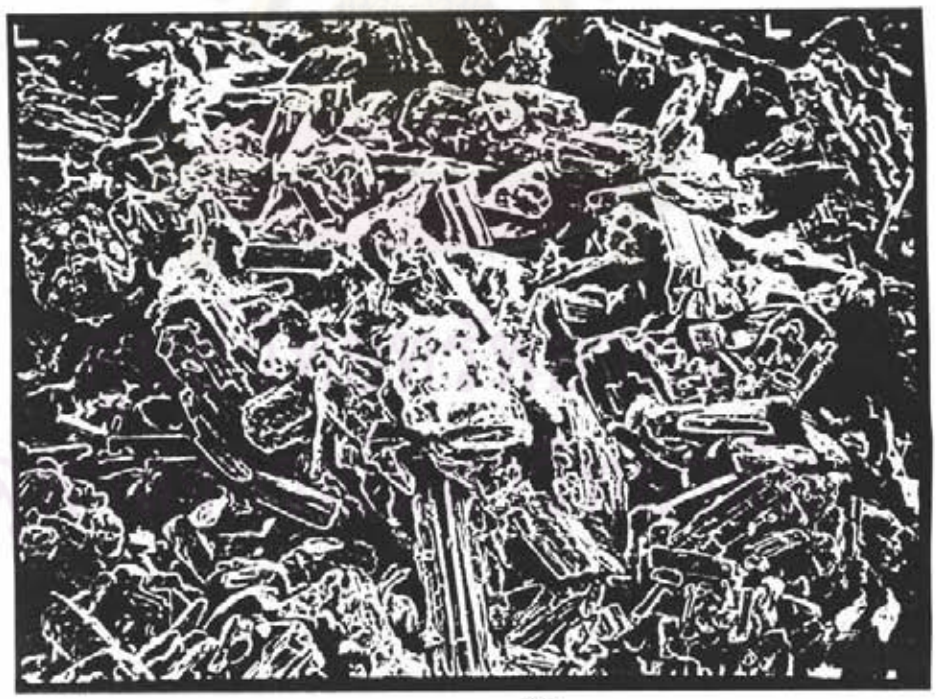
(a)

(b)

Fig. 48 : Surface characteristic of cephalexin microcapsules prepared by coacervation technique , using 3:2 ERL:RS as wall material, the core : wall ratio is 1:2 , (a) × 100 , (b) × 1000.

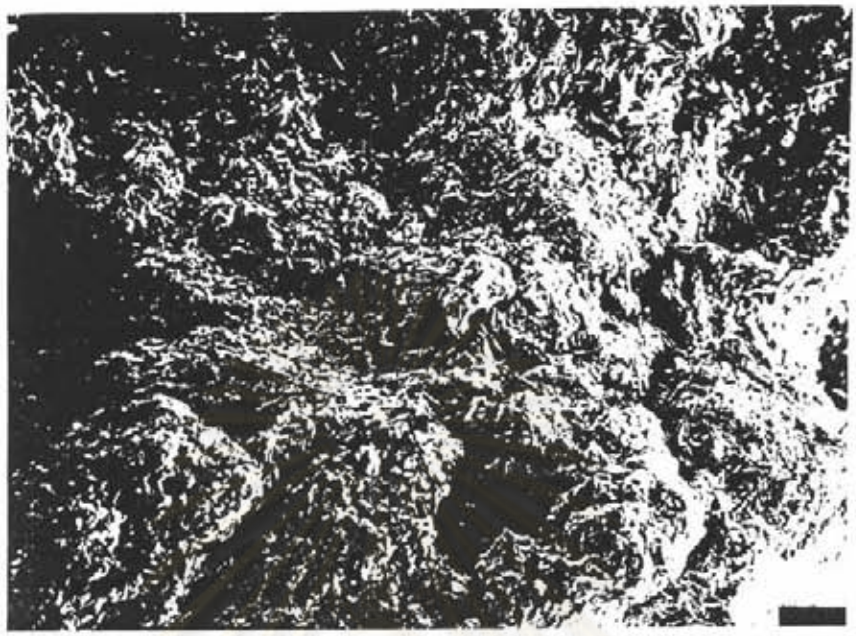


(a)



(b)

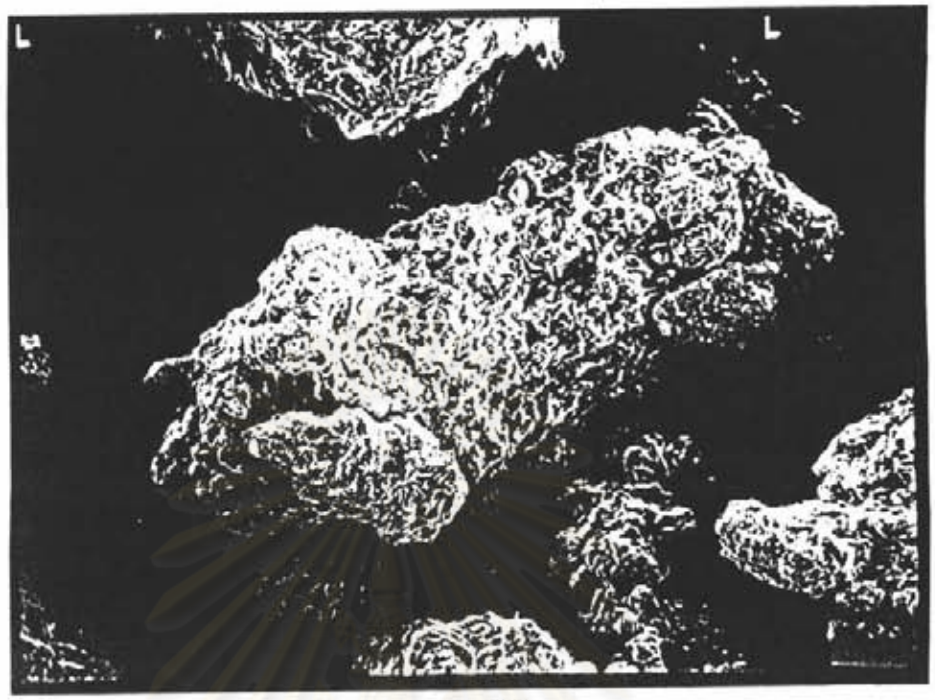
Fig. 49: Surface characteristic of cephalexin microcapsules prepared by coacervation technique , using 2:3 ERL:RS as wall material, the core : wall ratio is 2:1 , (a) × 100 , (b) × 1000.



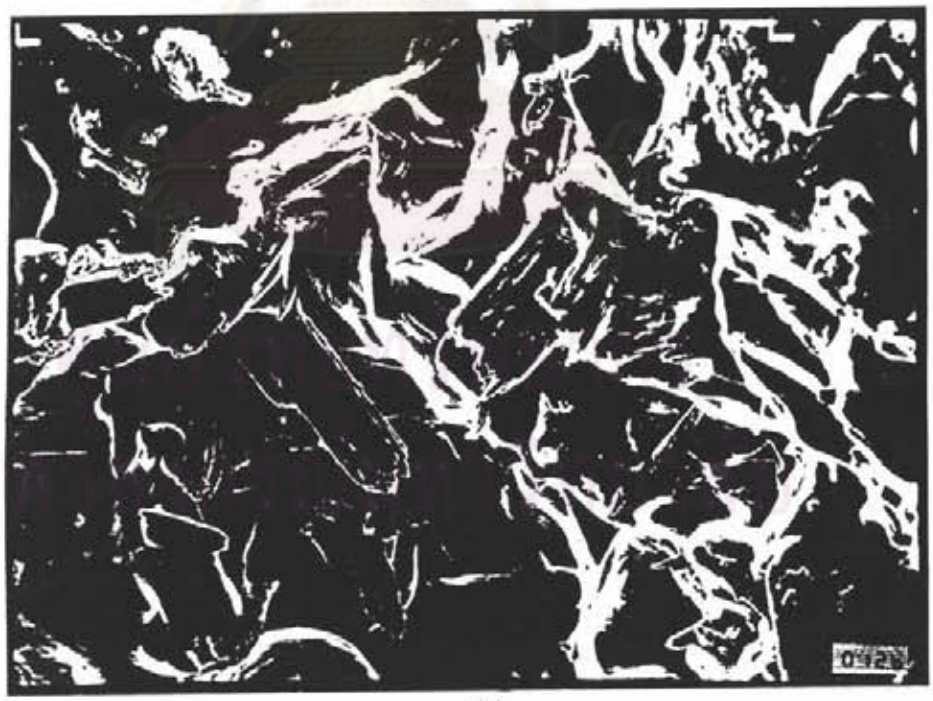
(a)

(b)

Fig. 50: Surface characteristic of cephalexin microcapsules prepared by coacervation technique , using 2:3 ERL:RS as wall material, the core : wall ratio is 1:1 , (a) × 100 , (b) × 1000.

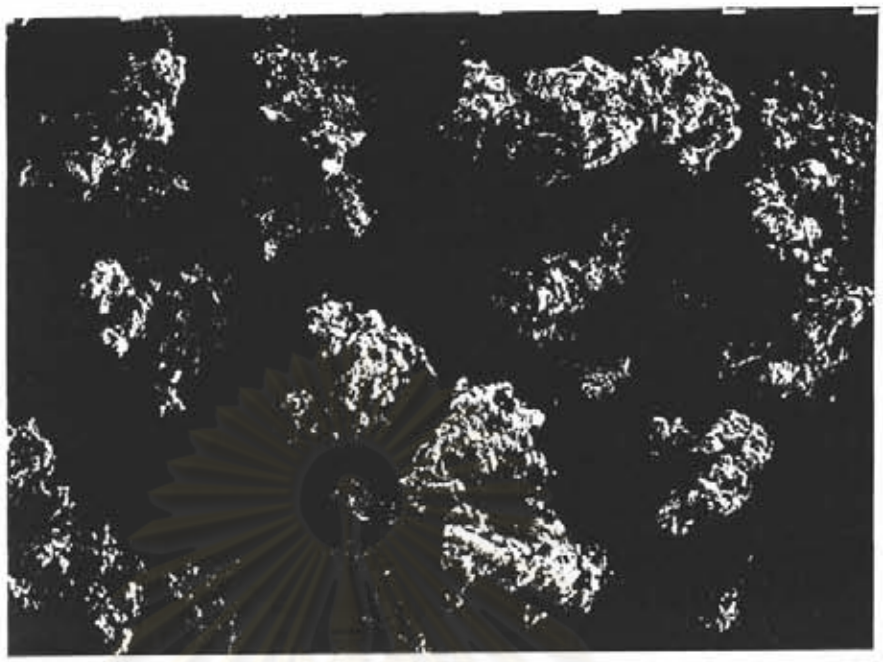


(a)

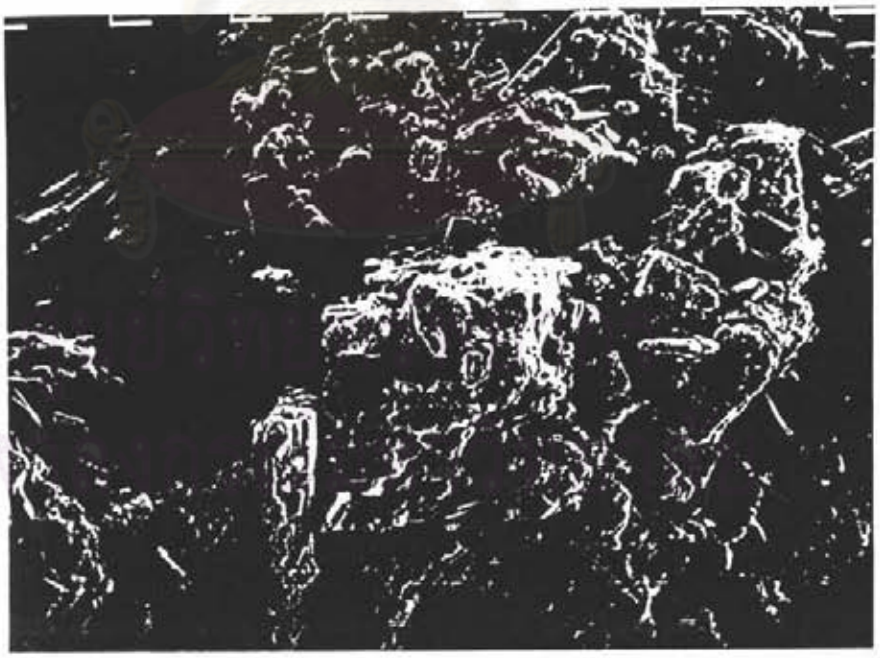


(b)

Fig. 51 : Surface characteristic of cephalexin microcapsules prepared by coacervation technique , using 2:3 ERL:RS as wall material, the core : wall ratio is 1:2 , (a) × 100 , (b) × 1000.

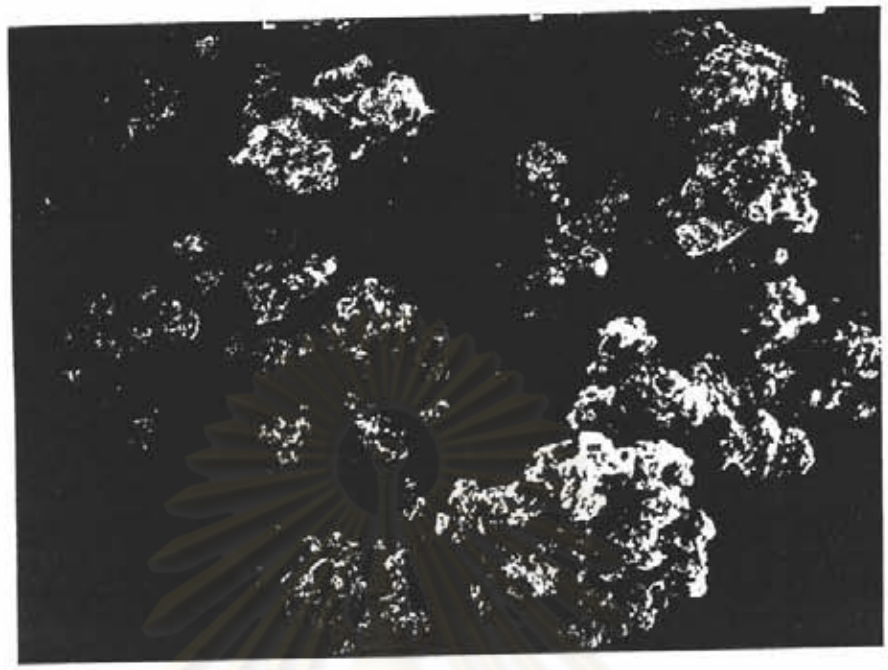


(a)



(b)

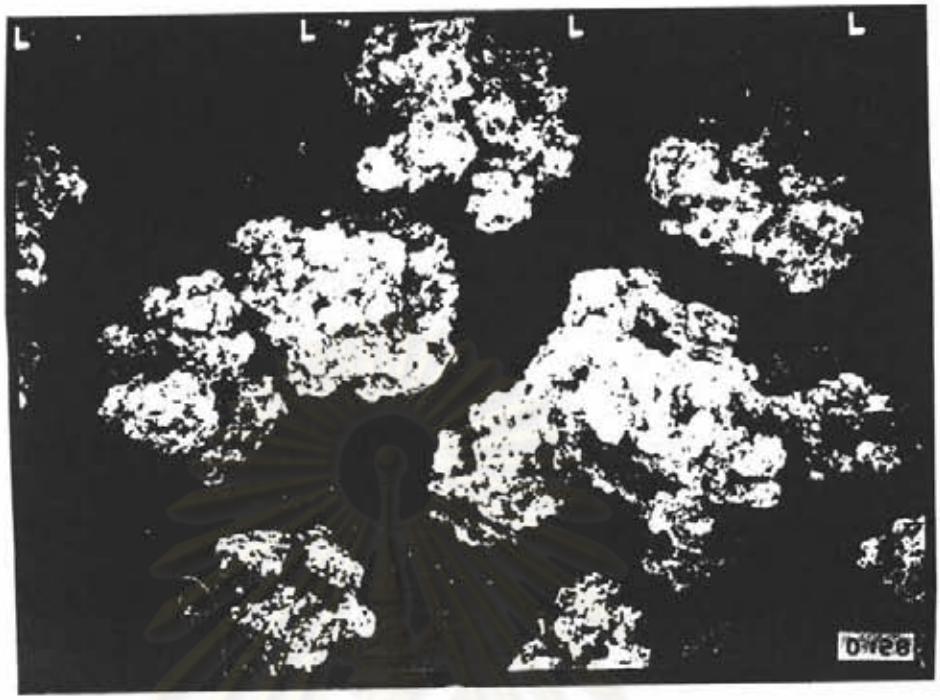
Fig. 52: Surface characteristic of cephalexin microcapsules prepared by fluidization technique , using ethylcellulose as wall material, the core : wall ratio is 2:1 , (a) × 150 , (b) × 1500.



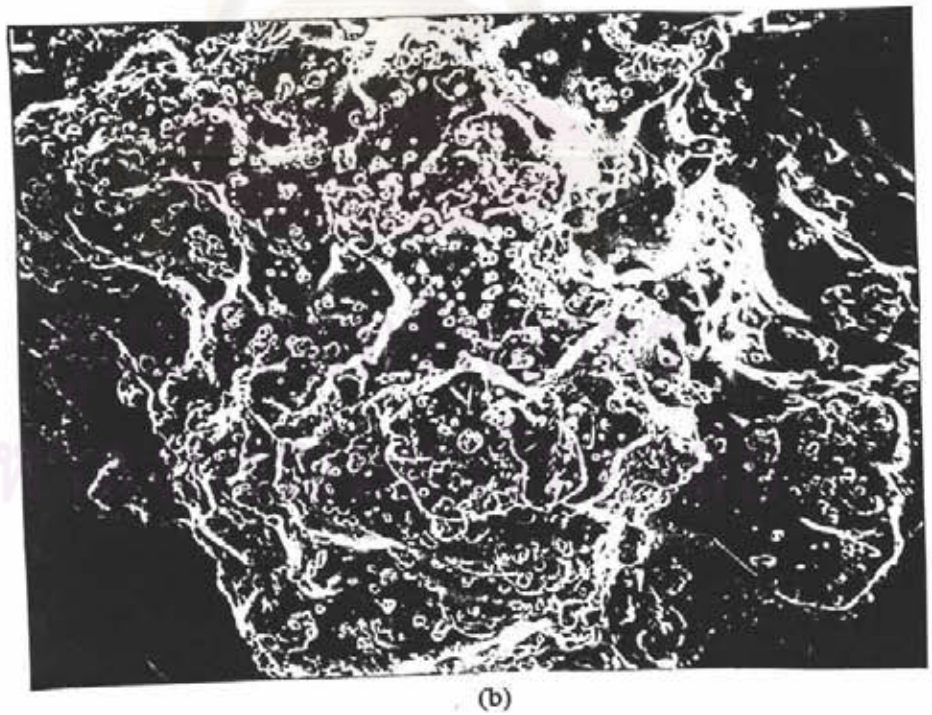
(a)

(b)

Fig. 53: Surface characteristic of cephalexin microcapsules prepared by fluidization technique , using ethylcellulose as wall material, the core : wall ratio is 1:1 , (a) $\times 35$, (b) $\times$ 1000.

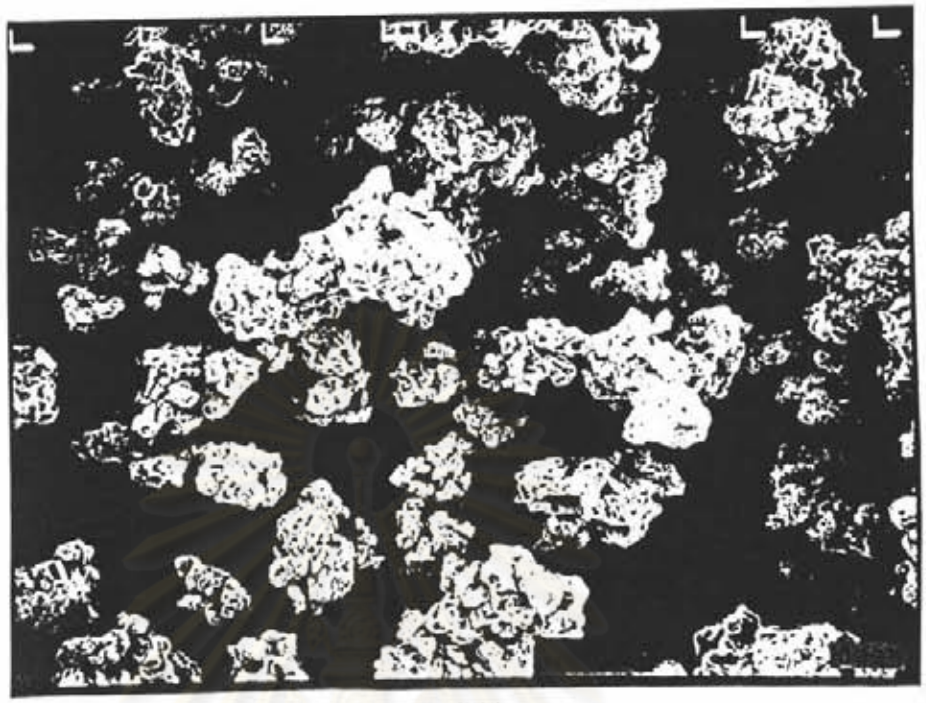


(a)



(b)

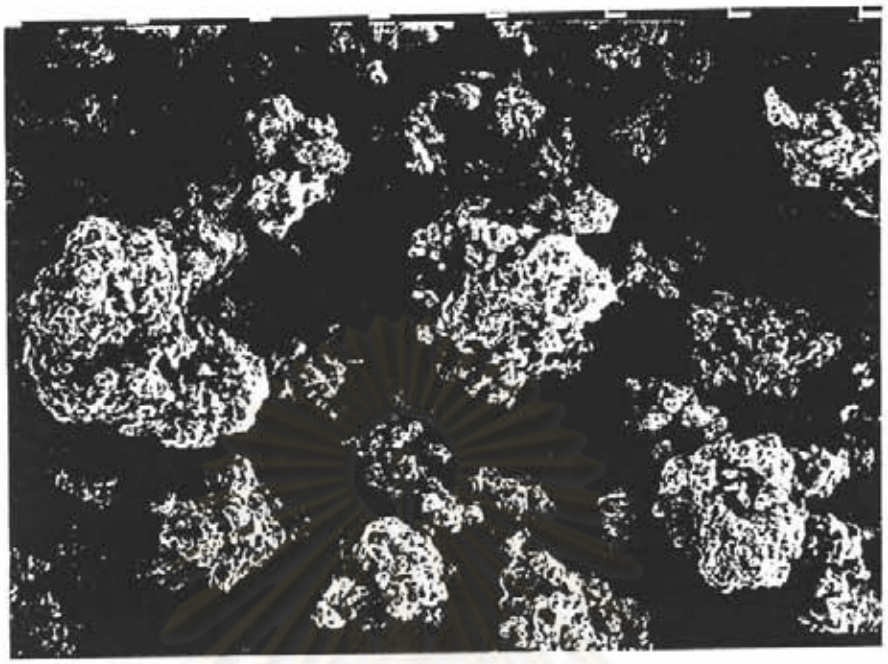
Fig. 54: Surface characteristic of cephalexin microcapsules prepared by fluidization technique , using ethylcellulose as wall material, the core : wall ratio is 1:2 , (a) $\times 35$, (b) $\times$ 1000.



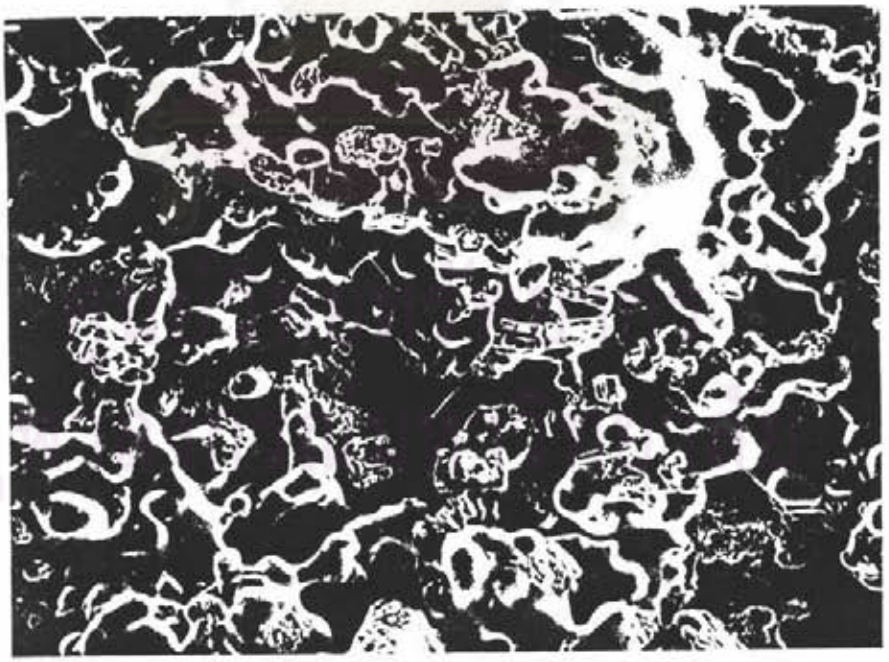
(a)

(b)

Fig. 55: Surface characteristic of cephalexin microcapsules prepared by fluidization technique , using 3:2 ERL:RS as wall material, the core : wall ratio is 2:1 , (a) × 200 , (b) × 1500.

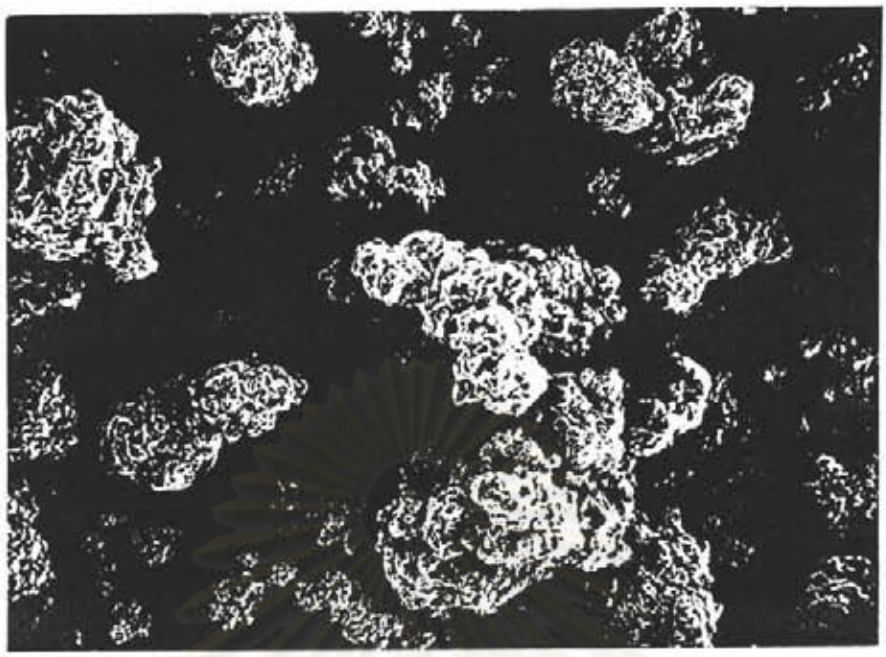


(a)

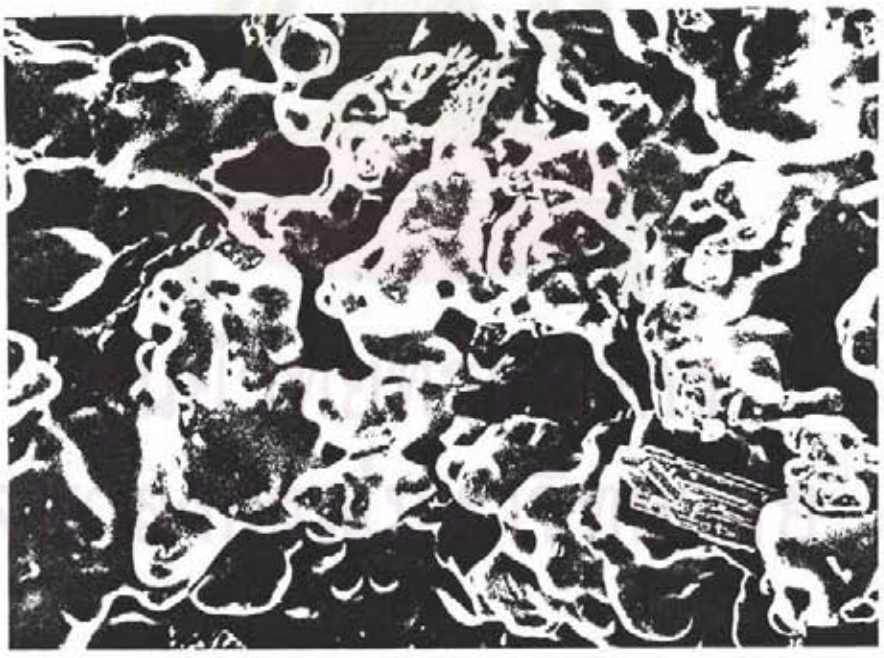


(b)

Fig. 56: Surface characteristic of cephalexin microcapsules prepared by fluidization technique , using 3:2 ERL:RS as wall material, the core : wall ratio is 1:1 , (a) × 200 , (b) × 1000.

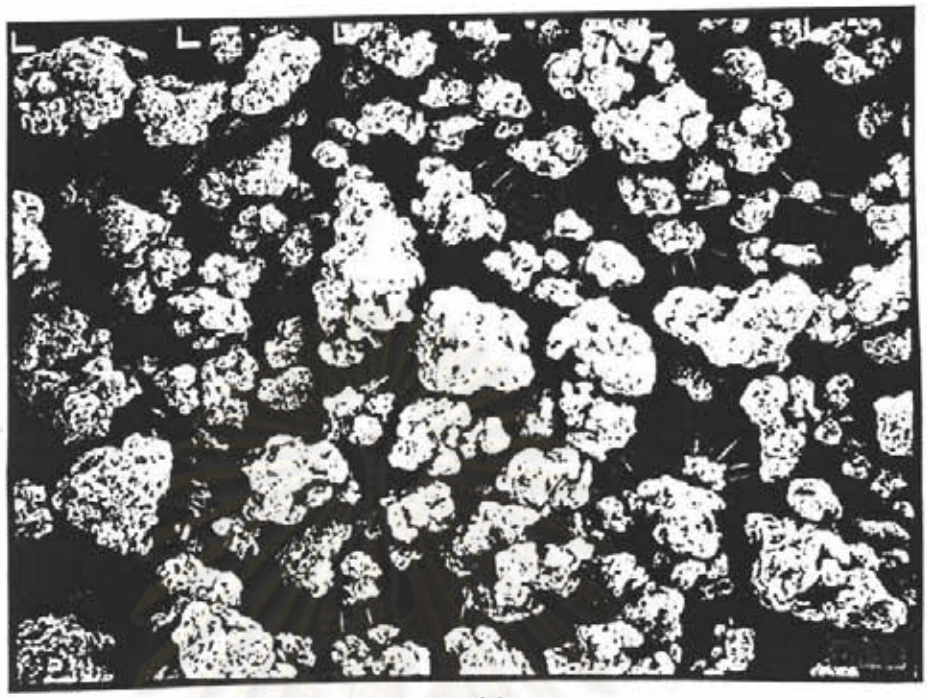


(a)

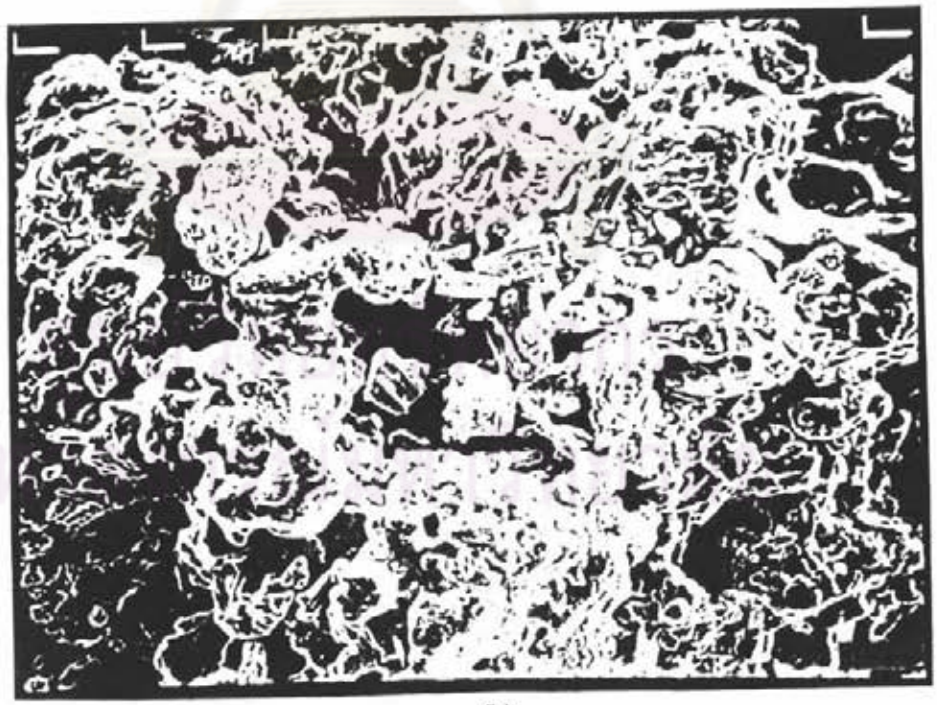


(b)

Fig. 57: Surface characteristic of cephalexin microcapsules prepared by fluidization technique , using 3:2 ERL:RS as wall material, the core : wall ratio is 1:2 , (a) × 200 , (b) × 1500.

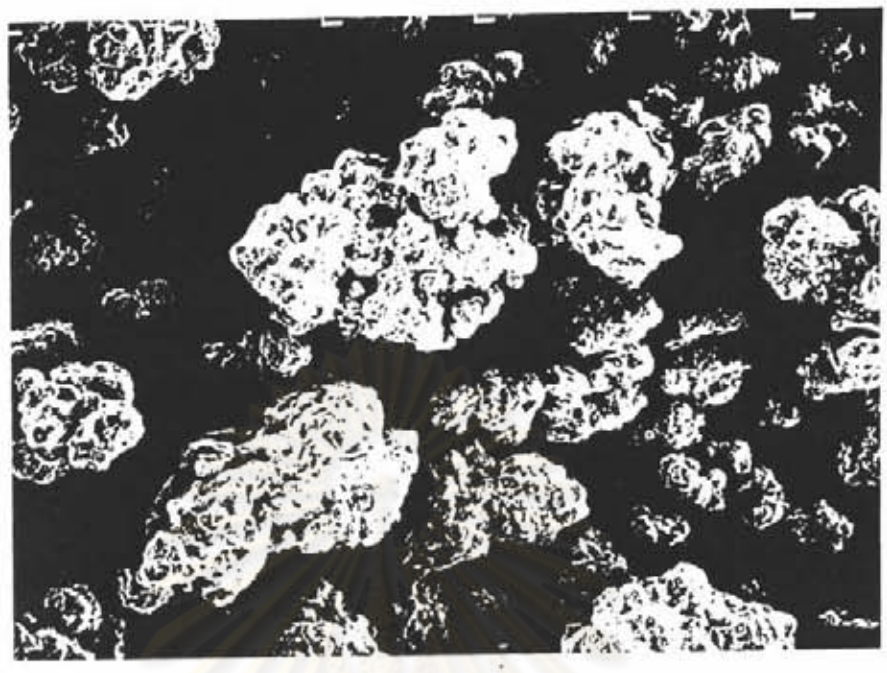


(a)



(b)

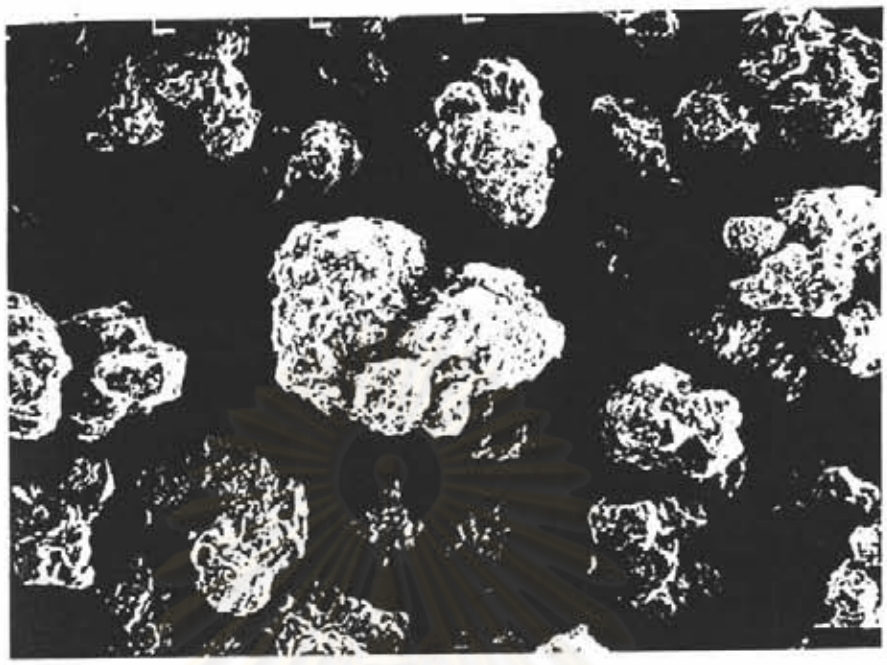
Fig. 58 : Surface characteristic of cephalexin microcapsules prepared by fluidization technique , using 2:3 ERL:RS as wall material, the core : wall ratio is 2:1 , (a) × 200 , (b) × 1500.



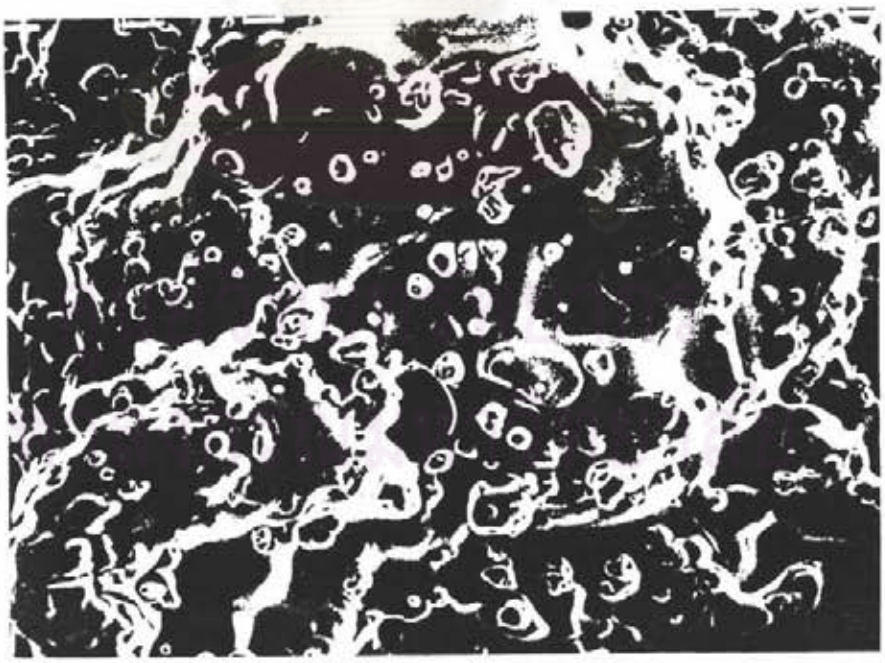
(a)

(b)

Fig. 59: Surface characteristic of cephalexin microcapsules prepared by fluidization technique , using 2:3 ERL:RS as wall material, the core : wall ratio is 1:1 , (a) × 200 , (b) × 1000.



(a)



(b)

Fig. 60: Surface characteristic of cephalexin microcapsules prepared by fluidization technique , using 2:3 ERL:RS as wall material, the core : wall ratio is 1:2 , (a) × 200 , (b) × 1500.

The Fig. 61-69 showed surface characteristic of cephalexin microcapsules prepared by spray-drying technique. The incomplete coating process were found in all types of wall materials. Because of nozzle size fixed the volume of the sprayed droplets and the size of particle after spraying was controlled by a nozzle size resulted in the crystal which were too large to encapsulated could not be coated with wall material. A lot of uncoated and incomplete coated particles were usually found in spray-drying technique however the complete one showed a good surface characteristic with smooth spherical microcapsules. A smoother surface were obtained from both 3:2 and 2:3 Eudragit which was softer and tougher than ethylcellulose membrane, thus coating power of Eudragit is also better than ethylcellulose.

5.3 Drug content of microcapsules.

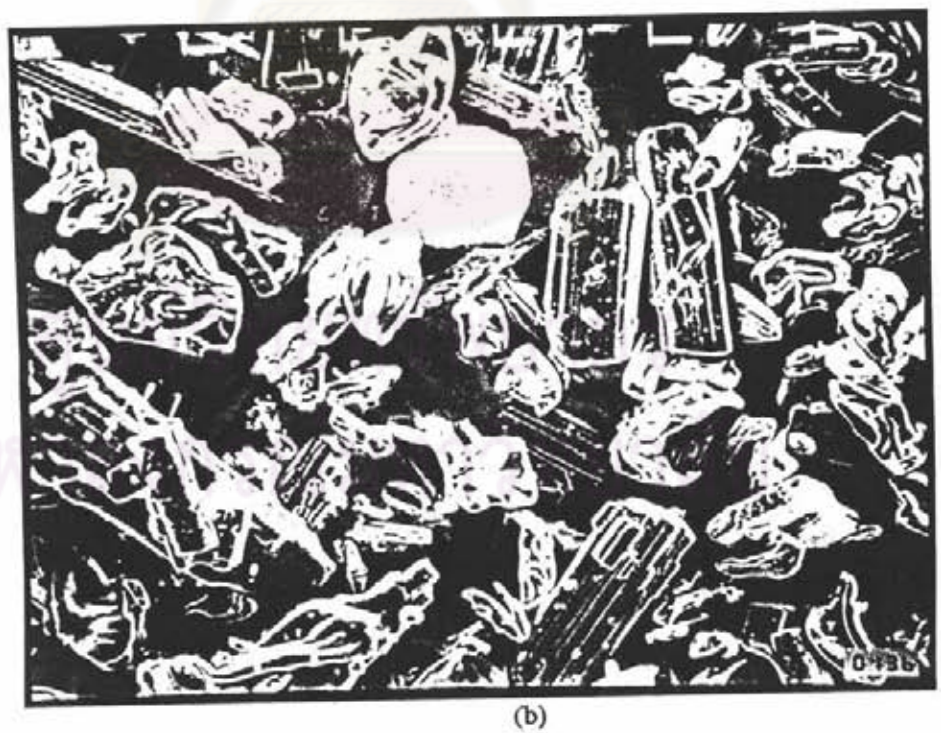
The determination of the percentage recovery was done by extraction of cephalexin from chloroform/water solution. Five successive portion of extraction could get the efficient extraction results of 99.70% of cephalexin recovered in water phase that make sure that in determining the amount of cephalexin from microcapsules by using this process could extract cephalexin from polymer solution completely. The cephalexin content in several wall types, drug : polymer ratios and microencapsulation techniques were shown in Table 8.

(a)

(b)

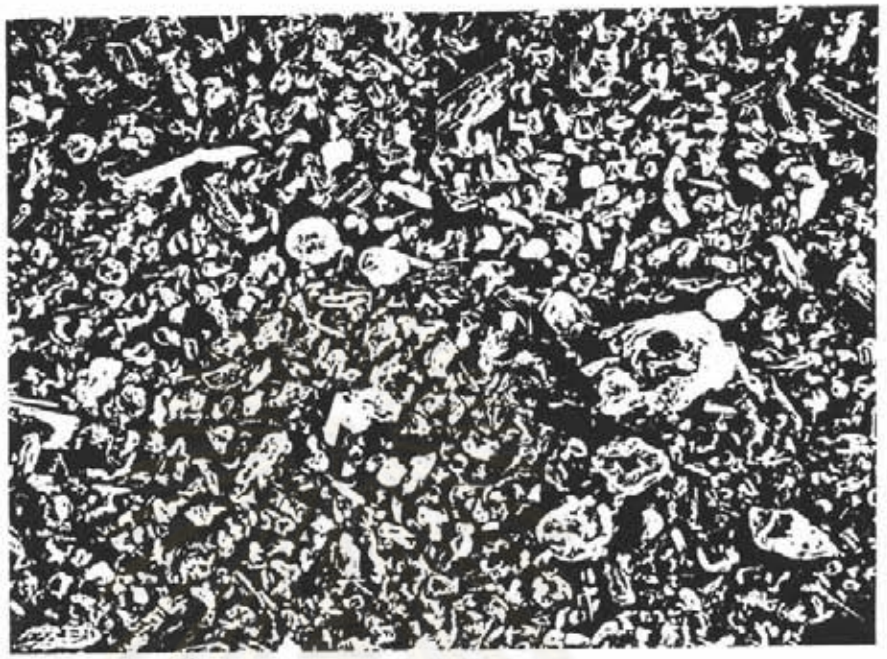
Fig. 61 : Surface characteristic of cephalexin microcapsules prepared by spray drying technique , using ethylcellulose as wall material, the core : wall ratio is 2:1 , (a) × 350 , (b) × 2000.

(a)

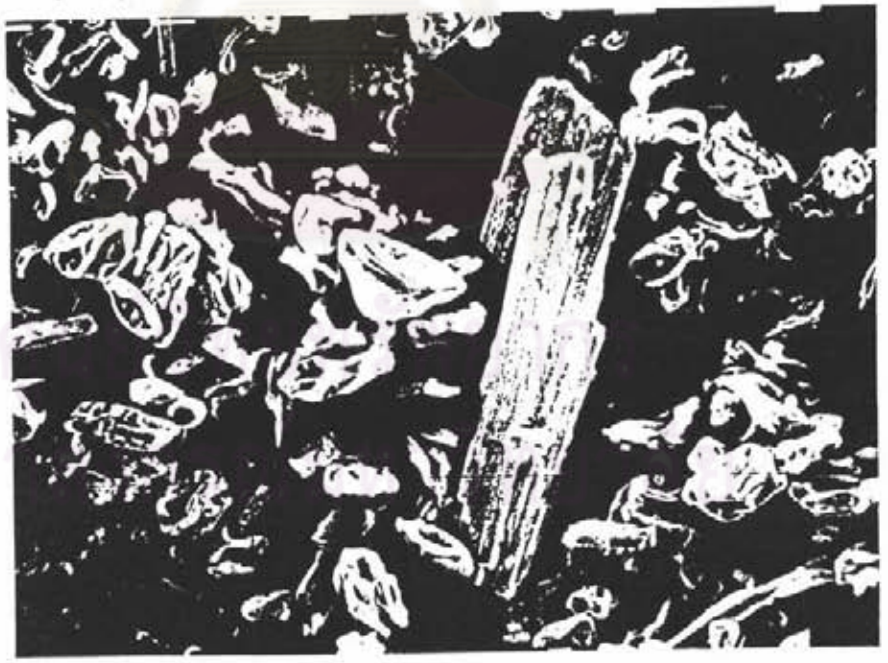


(b)

Fig. 62 : Surface characteristic of cephalexin microcapsules prepared by spray drying technique , using ethylcellulose as wall material, the core : wall ratio is 1:1 , (a) × 350 , (b) × 2000.



(a)



(b)

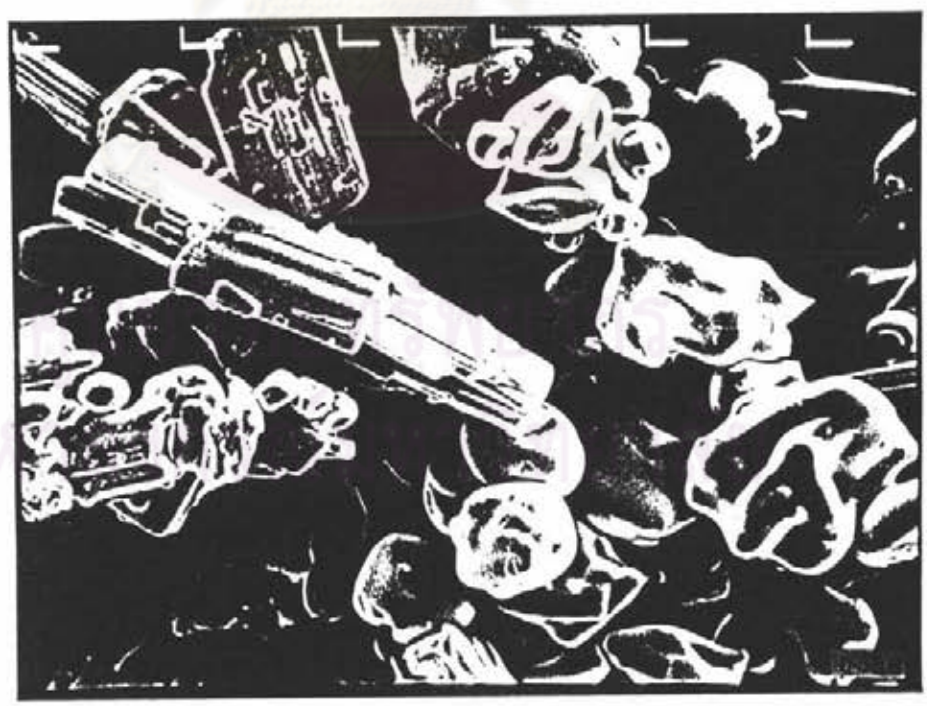
Fig. 63 : Surface characteristic of cephalexin microcapsules prepared by spray drying technique , using ethylcellulose as wall material, the core : wall ratio is 1:2 , (a) × 500 , (b) × 2000.

(a)

(b)

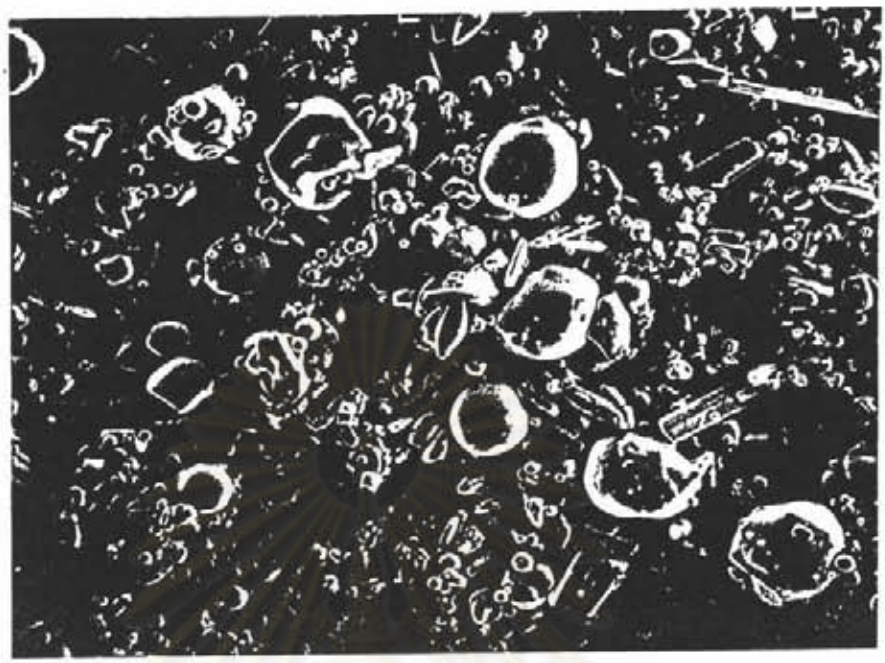
Fig. 64 : Surface characteristic of cephalexin microcapsules prepared by spray drying technique , using 3:2 ERL:RS as wall material, the core : wall ratio is 2:1 , (a) × 500 , (b) × 2000.

(a)

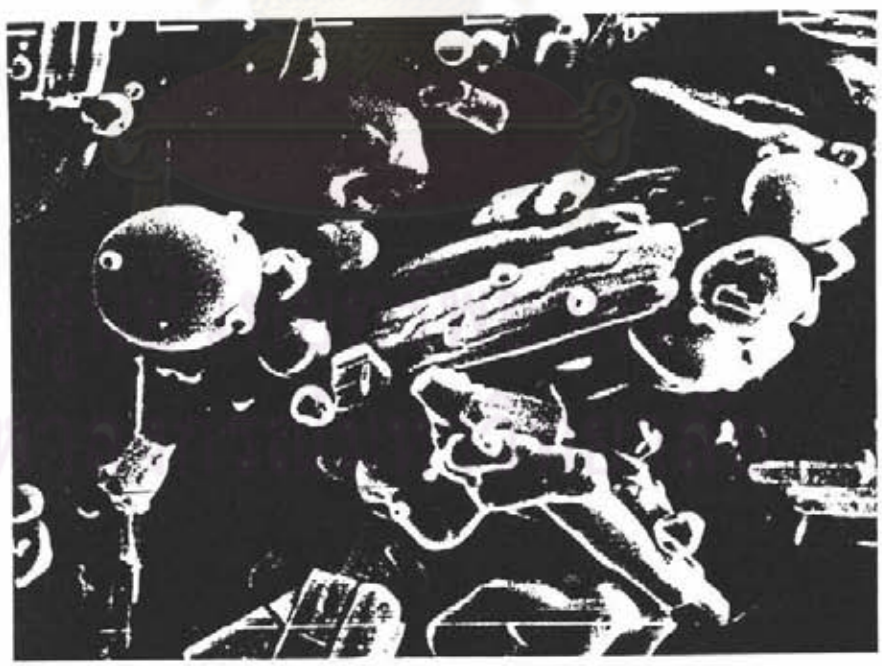


(b)

Fig. 65 : Surface characteristic of cephalexin microcapsules prepared by spray drying technique , using 3:2 ERL:RS as wall material, the core : wall ratio is 1:1 , (a) × 500 , (b) × 2000.



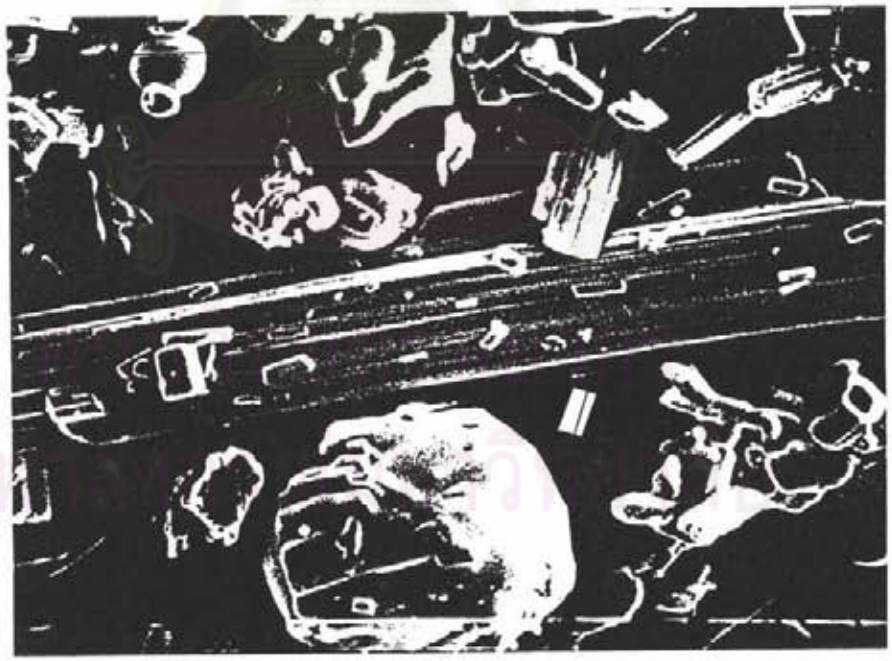
(a)



(b)

Fig. 66 : Surface characteristic of cephalexin microcapsules prepared by spray drying technique , using 3:2 ERL:RS as wall material, the core : wall ratio is 1:2 , (a) × 500 , (b) × 2000.

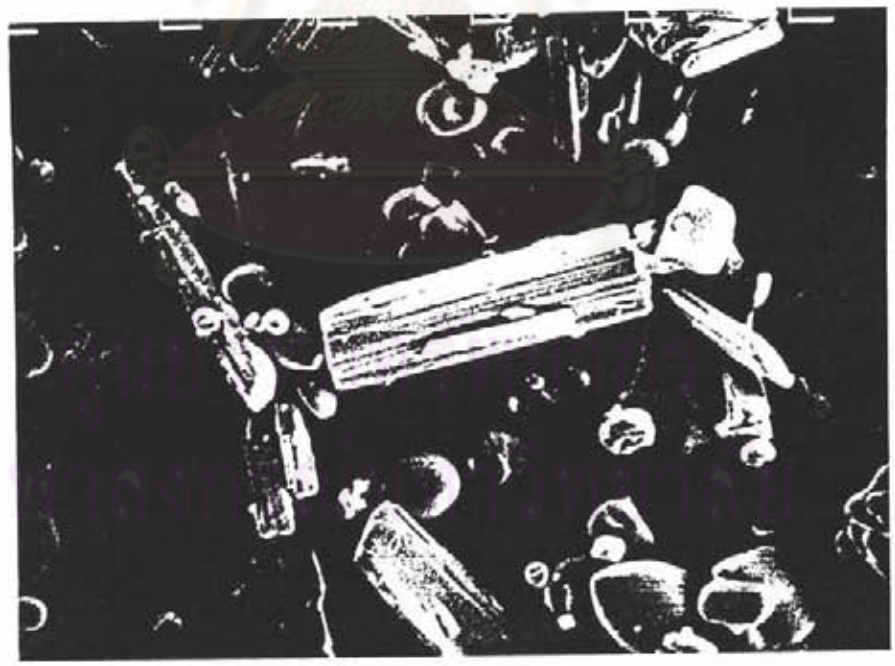
(a)



(b)

Pig. 67 : Surface characteristic of cephalexin microcapsules prepared by spray drying technique , using 2:3 ERL:RS as wall material, the core : wall ratio is 2:1 , (a) × 500 , (b) × 2000.

(a)



(b)

Fig. 68 : Surface characteristic of cephalexin microcapsules prepared by spray drying technique , using 2:3 ERL:RS as wall material, the core : wall ratio is 1:1 , (a) × 500 , (b) × 2000.

(a)

(b)

Fig. 69 : Surface characteristic of cephalexin microcapsules prepared by spray drying technique , using 2:3 ERL:RS as wall material, the core : wall ratio is 1:2 , (a) × 500 , (b) × 2000.

Table 8 : Percentage of cephalexin contents in microcapsules prepared by various wall types and technique.

wall type	core : wall ratio	microencapsulation technique	% drug content
Ethylcellulose	2:1	Coacervation	94.53
Ethylcellulose	1:1	Coacervation	97.98
Ethylcellulose	1:2	Coacervation	94.18
3:2 ERL:RS	2:1	Coacervation	92.08
3:2 ERL:RS	1:1	Coacervation	82.50
3:2 ERL:RS	1:2	Coacervation	78.57
2:3 ERL:RS	2:1	Coacervation	93.06
2:3 ERL:RS	1:1	Coacervation	77.38
2:3 ERL:RS	1:2	Coacervation	70.92
Ethylcellulose	2:1	Fluidization	85.59
Ethylcellulose	1:1	Fluidization	82.86
Ethylcellulose	1:2	Fluidization	80.92
3:2 ERL:RS	2:1	Fluidization	77.96
3:2 ERL:RS	1:1	Fluidization	94.54
3:2 ERL:RS	1:2	Fluidization	97.78
2:3 ERL:RS	2:1	Fluidization	96.97
2:3 ERL:RS	1:1	Fluidization	80.96
2:3 ERL:RS	1:2	Fluidization	83.74
Ethylcellulose	2:1	Spray drying	97.25
Ethylcellulose	1:1	Spray drying	113.36
Ethylcellulose	1:2	Spray drying	96.73
3:2 ERL:RS	2:1	Spray drying	89.13
3:2 ERL:RS	1:1	Spray drying	95.80
3:2 ERL:RS	1:2	Spray drying	90.21
2:3 ERL:RS	2:1	Spray drying	87.98
2:3 ERL:RS	1:1	Spray drying	94.13
2:3 ERL:RS	1:2	Spray drying	90.81

All of microencapsulation techniques gave a high percent entrapment it means that only a little of cephalexin losses in a preparation process. Percentage of cephalexin content in ethylcellulose-walled microcapsules prepared by spray-drying technique were very high because there had some of unencapsulated cephalexin particle occurred in this process and some of ethylcellulose were separated out as shown in Fig. 103-105.

5.4 Percent yield of microcapsules.

Microcapsules received form each preparation were accurately weighed and divided by expected weight of each batch to obtain percentage of yield. The percent yield from every wall types, core : wall ratios and microencapsulation techniques are shown in Table 9.

In coacervation technique, cephalexin microcapsules prepared from ethylcellulose gave a very high yield of over 90% the high yield was probably that ethylcellulose and cephalexin were insoluble in solvent (hexane) and no water for dissolving cephalexin. Therefore there would not be any problem of them going into solution resulting in a lower yield. The losses that occurred were the deposition on the side of the vessel and stirrer. Whilst cephalexin prepared from Eudragit RL:RS gave the lower yields because Eudragit had the glass transition temperature lower than ethylcellulose resulted in less deposition of Eudragit around cephalexin. It indicated in electron micrograph that microcapsules showed incomplete of microencapsulation and the particle size were very small resulted in some of them were loss during filtration step thus made the percent yield of microcapsules prepared from Eudragit RL:RS lower than prepared from ethylcellulose.

In fluidization technique almost all of these preparation gave a very high yield around 85% except on the ratio of 3:2 Eudragit RL:RS with 1:1 and 1:2 core:wall ratio. This process provided a continuous coating and drying that made the uniformity of the product. The losses was occurred from taching on the chamber side and collecting house. If the batch size was increased the percent yield could be increased. This technique was suitable for manufacturing in the large scale and their final product were good free flowing.

In spray drying technique, all of these preparations gave a very low yield. It was lower than 50% this technique was suitable for the dispersion of drug in aqueous phase, but in this experiment cephalexin was dispersed in alcoholic polymer solution which resulted in difficulty in controlling a constant evaporation rate of solvent at high temperature. The aspirator should be adjusted to maintain a difference between inlet and outlet air temperature for a constant evaporation rate of solvent. Even though the aspirator was adjusted in a low level but the high exhausted air occurred resulted in the fine microcapsules were blown away from the process, especially when prepared in a small batch, the calculated percent yield will be low.

Table 9 : Percentage of microcapsules yield from various wall types and techniques.

wall type	core : wall ratio	microencapsulation technique	% yielded
Ethylcellulose	2:1	Coacervation	90.67
Ethylcellulose	1:1	Coacervation	90.90
Ethylcellulose	1:2	Coacervation	84.67
3:2 ERL:RS	2:1	Coacervation	60.78
3:2 ERL:RS	1:1	Coacervation	56.95
3:2 ERL:RS	1:2	Coacervation	55.31
2:3 ERL:RS	2:1	Coacervation	54.67
2:3 ERL:RS	1:1	Coacervation	53.60
2:3 ERL:RS	1:2	Coacervation	52.98
Ethylcellulose	2:1	Fluidization	87.03
Ethylcellulose	1:1	Fluidization	86.63
Ethylcellulose	1:2	Fluidization	85.84
3:2 ERL:RS	2:1	Fluidization	87.33
3:2 ERL:RS	1:1	Fluidization	73.75
3:2 ERL:RS	1:2	Fluidization	65.53
2:3 ERL:RS	2:1	Fluidization	91.84
2:3 ERL:RS	1:1	Fluidization	78.75
2:3 ERL:RS	1:2	Fluidization	89.67
Ethylcellulose	2:1	Spray drying	32.93
Ethylcellulose	1:1	Spray drying	32.50
Ethylcellulose	1:2	Spray drying	48.80
3:2 ERL:RS	2:1	Spray drying	30.69
3:2 ERL:RS	1:1	Spray drying	41.35
3:2 ERL:RS	1:2	Spray drying	25.50
2:3 ERL:RS	2:1	Spray drying	35.40
2:3 ERL:RS	1:1	Spray drying	49.95
2:3 ERL:RS	1:2	Spray drying	32.11

Spray drying technique give a very low in percentage microcapsules yield because the dispersion is sprayed from the nozzle and drying in one process then give a very fine powders that can be easily exhausted out by the exhausted air which limitedly adjustment because one must adjust aspirator control to maintain a difference between inlet/outlet air temperature for a constant solvent evaporation rate. Adjustment of aspirator cause a difficulty to collect fine powder because high level of aspirator control refer to high exhausted air happened that means fine powders are blown away from the process.

5.5 Dissolution studies

The release patterns of cephalexin from microcapsules were investigated. The experiment performed at 37±1°C cephalexin was detected by spectrophotometrically at 262 nm at each interval for 10 hours. The percentage of drug released (%Q) is calculated the amount of cephalexin at each interval divided by the total amount of cephalexin which placed in a dissolution cell at the beginning of the experiment.

Many workers (Ruiz, Sakr and Sprockel, 1990 ; Hasan Najib, Suleiman, El-sayed and Abdel-Hamid, 1992 ; Tirkonen and Paronen, 1993) found that the release pattern of drugs from microcapsules mostly characterize to fit Higuchi's model. The overall release mechanism of drugs encapsulated in the polymer is thought to involve by the permeation of the solvent into the microcapsules, dissolution of the drug, and diffusion through the wall of microcapsules to the surrounding fluid. The time which used for the permeation of the solvent into the microcapsule is called the lag time. The lag time was different in each wall type and core to wall ratio of microcapsule because the different in polymer gave the different in porosity and tortuosity. The different in core to wall

ratio will give the different in pathlength from surface to the core of microcapsules. Usually the lag time was too short to be observed. In this studied the lag time could not determined because in some preparations of microcapsules they showed the incomplete microcapsules with deposition of crystal of cephalexin. There were another two rates of cephalexin from microcapsules were studied, rate 1 was refer to the rate of solvent penetrated into the wall and dissolved core material, cephalexin solution, the time depending on the dissolution of cephalexin and the different wall material, core to wall ratio and particle size. Rate 2 was refer to the rate of diffusion of the cephalexin solution through the wall of microcapsules. This referred to the sustained release portion. The dissolution profile of cephalexin and the Higuchi's plot of cephalexin released from microcapsules and their dissolution profiles are shown in Fig. 70-132.

The dissolution data are also shown in appendix V, percent of coefficient variance (% C.V.) was very low. It can confirm that there were some little errors in our study which could be occurred in different dissolution cell and dilution process before determining the cephalexin concentration.

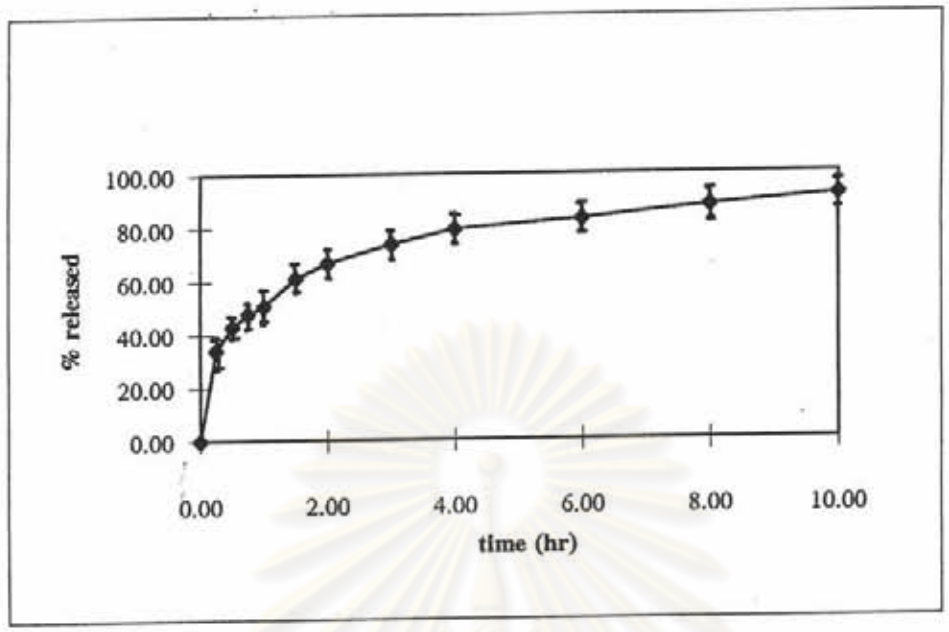


Fig. 70: Dissolution profile of cephalexin released from EC microcapsules prepared by coacervation technique, core: wall ratio is 2:1.

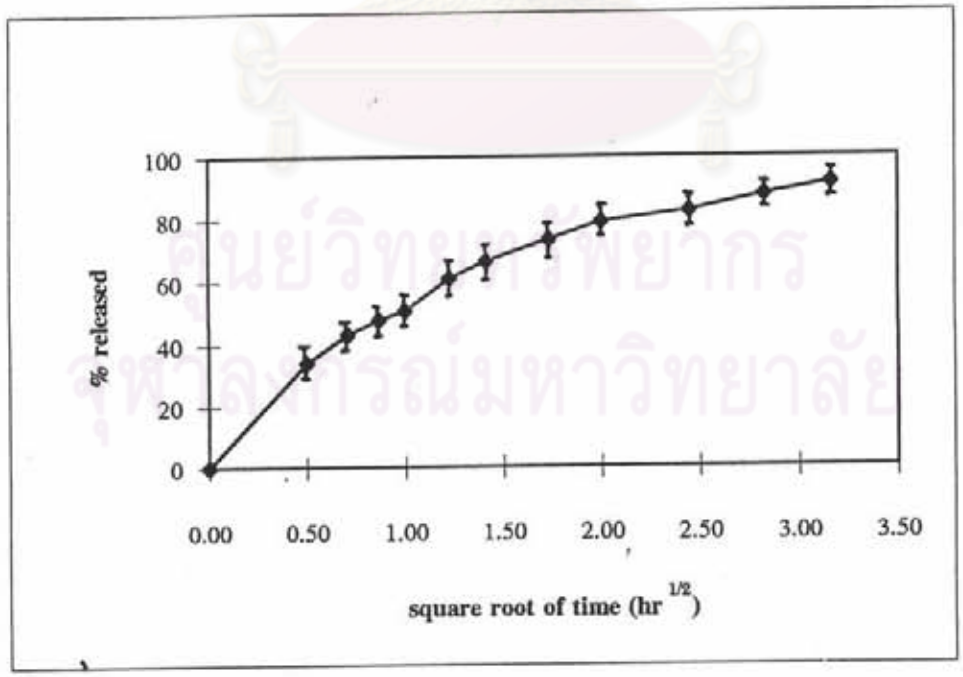


Fig. 71 : Higuchi's plot of cephalexin released from EC microcapsules prepared by coacervation technique, core: wall ratio is 2:1.

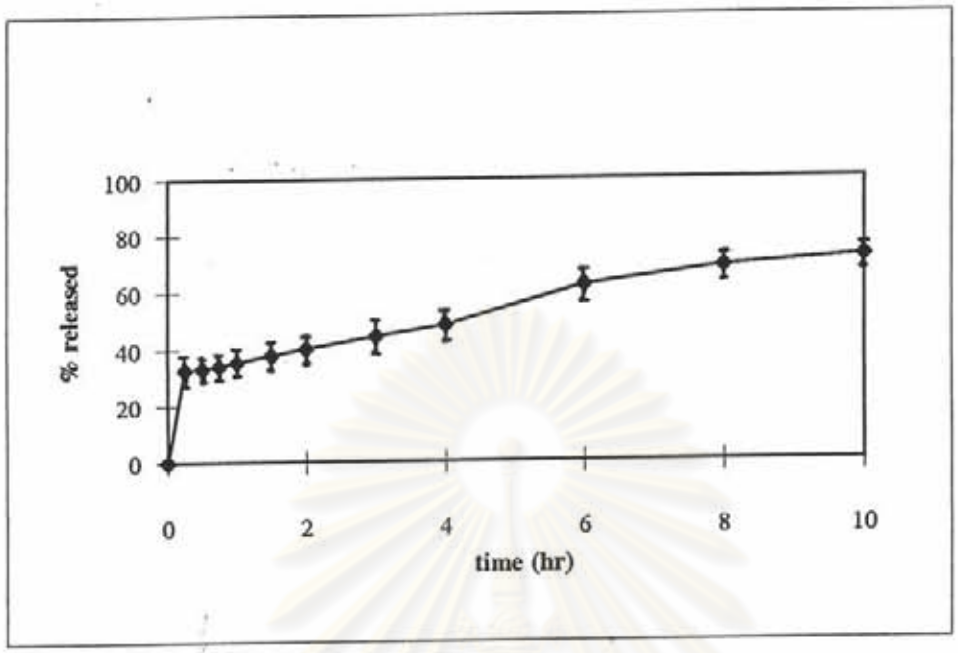


Fig. 72 : Dissolution profile of cephalexin released from EC microcapsules prepared by coacervation technique, core: wall ratio is 1:1.

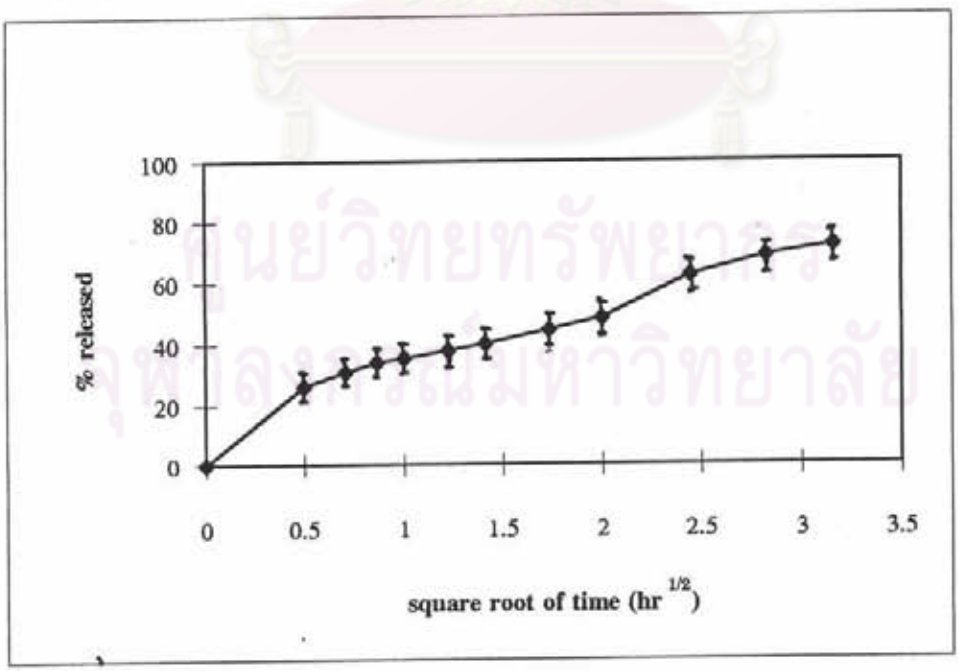


Fig. 73 : Higuchi's plot of cephalexin released from EC microcapsules prepared by coacervation technique, core: wall ratio is 1:1.

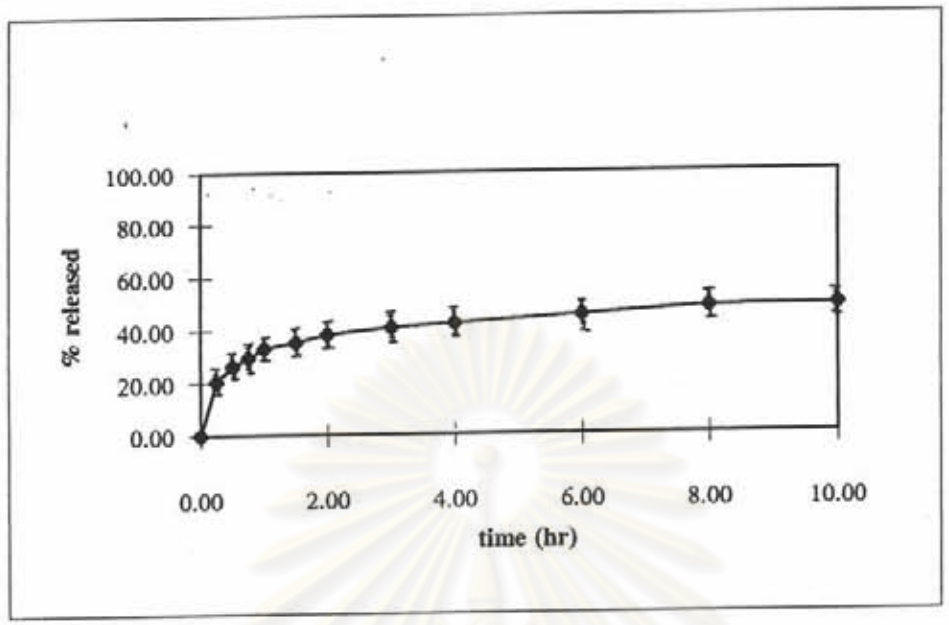


Fig. 74 : Dissolution profile of cephalexin released from EC microcapsules prepared by coacervation technique, core: wall ratio is 1:2.

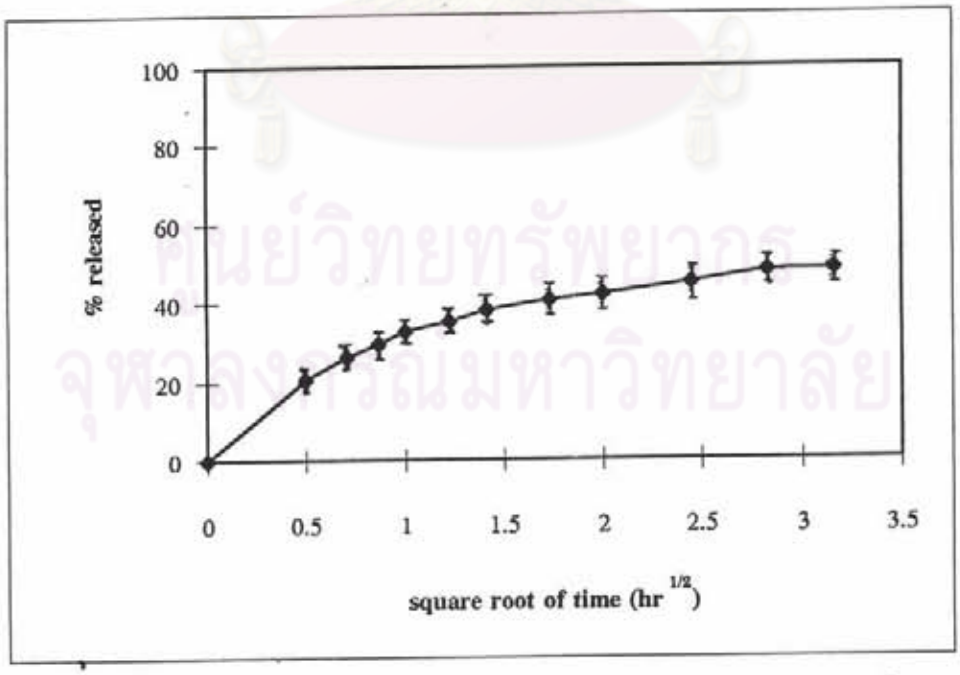


Fig. 75 : Higuchi's plot of cephalexin released from EC microcapsules prepared by coacervation technique, core: wall ratio is 1:2.

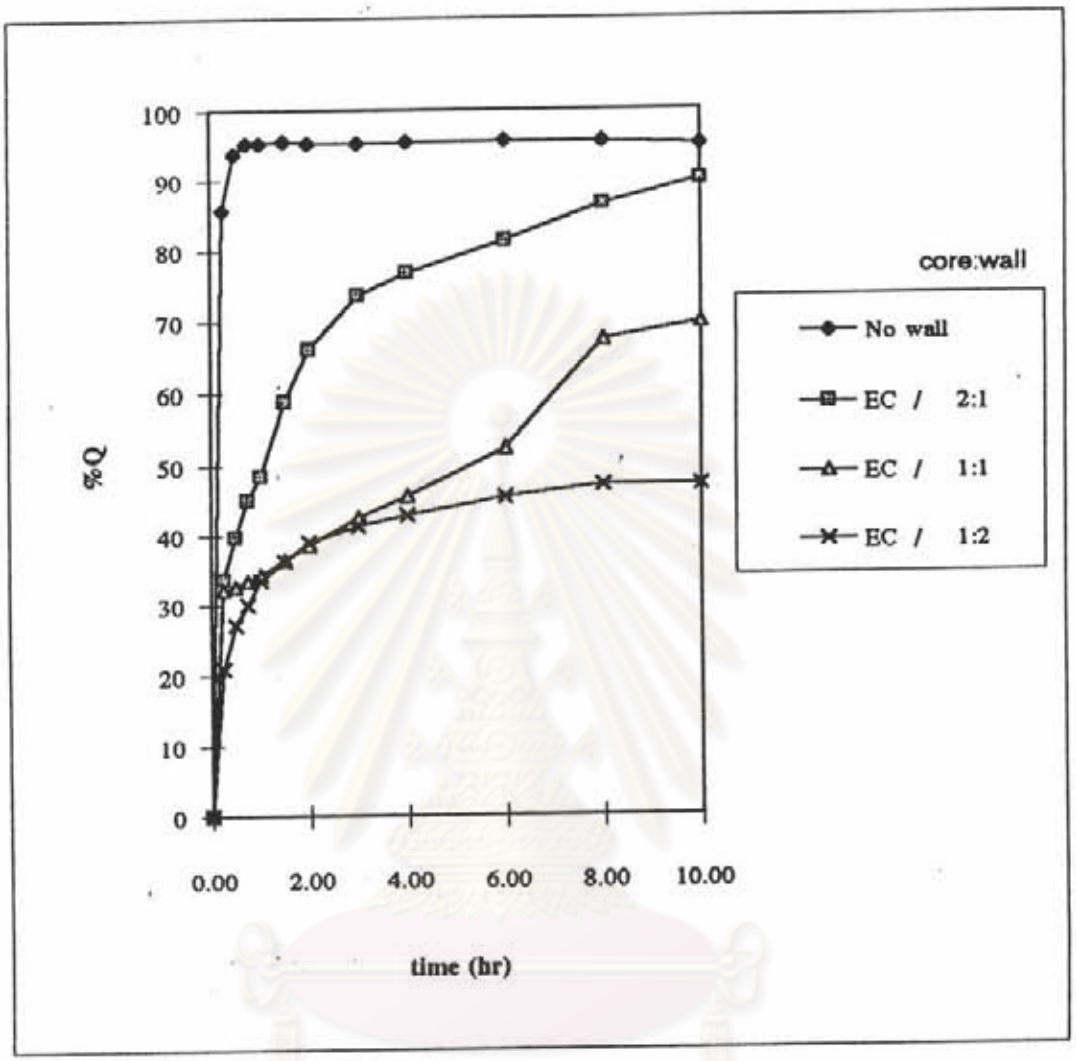


Fig. 76 : Dissolution profiles of cephalexin released from EC microcapsules in various core: wall ratio prepared by coacervation technique.

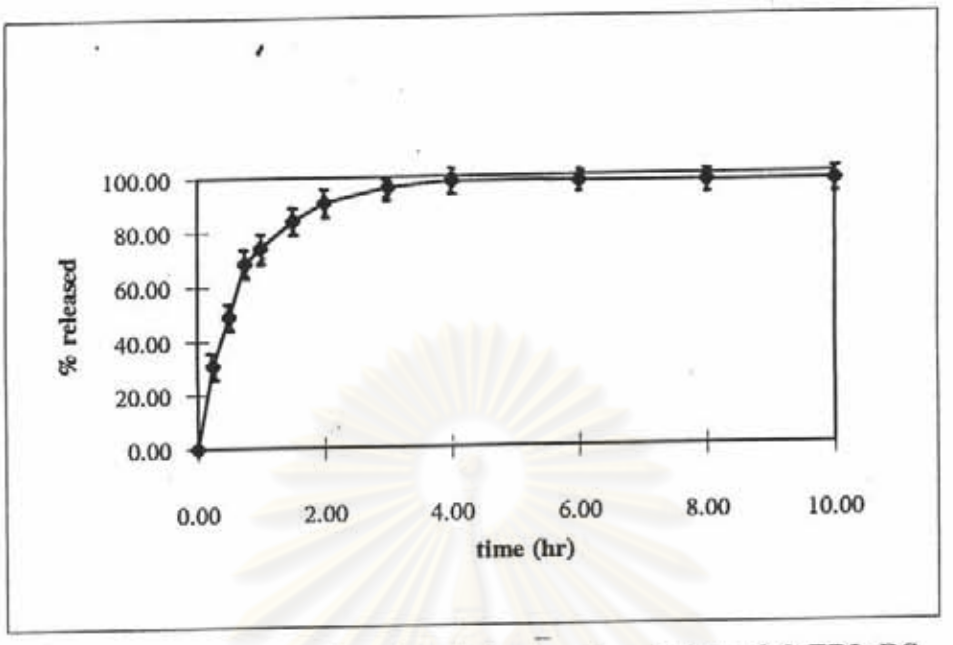


Fig. 77 : Dissolution profile of cephalexin released from 3:2 ERL:RS microcapsules prepared by coacervation technique, core: wall ratio is 2:1.

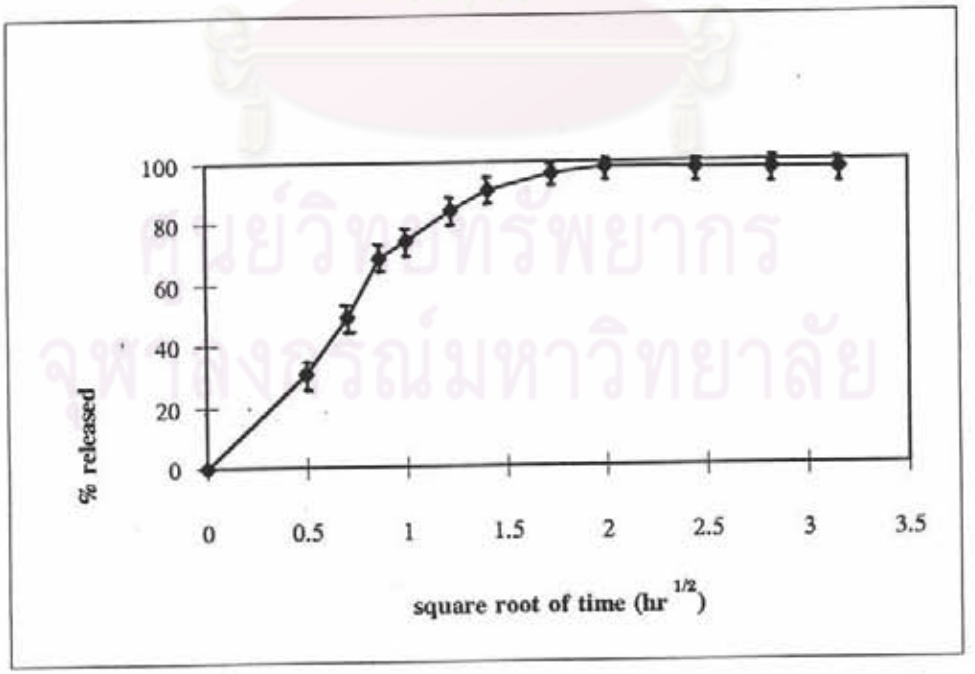


Fig. 78 : Higuchi's plot of cephalexin released from 3:2 ERL:RS microcapsules prepared by coacervation technique, core: wall ratio is 2:1.

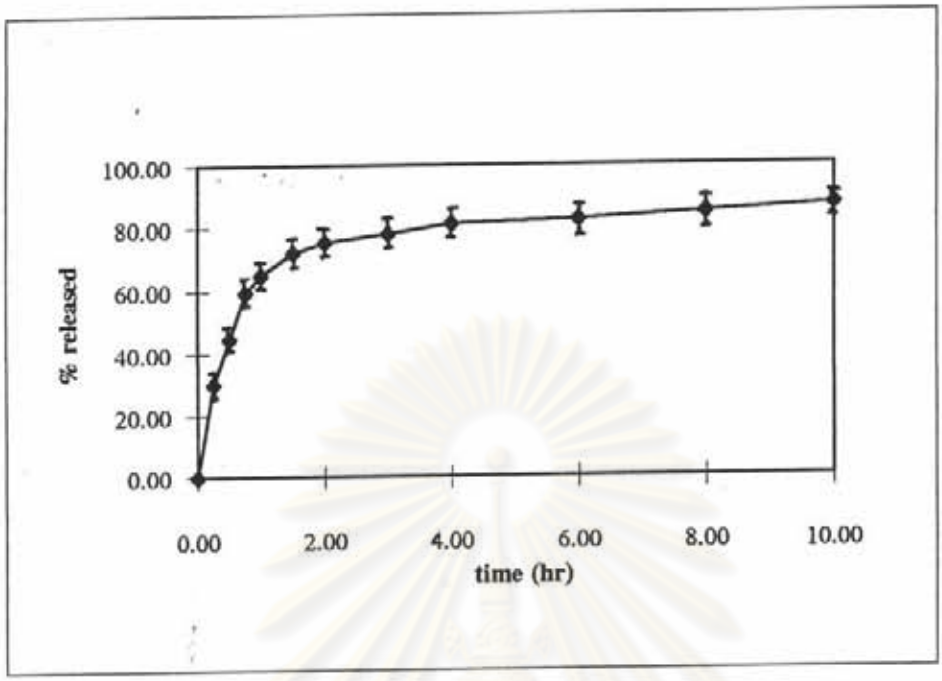


Fig. 79 : Dissolution profile of cephalexin released from 3:2 ERL:RS microcapsules prepared by coacervation technique, core: wall ratio is 1:1.

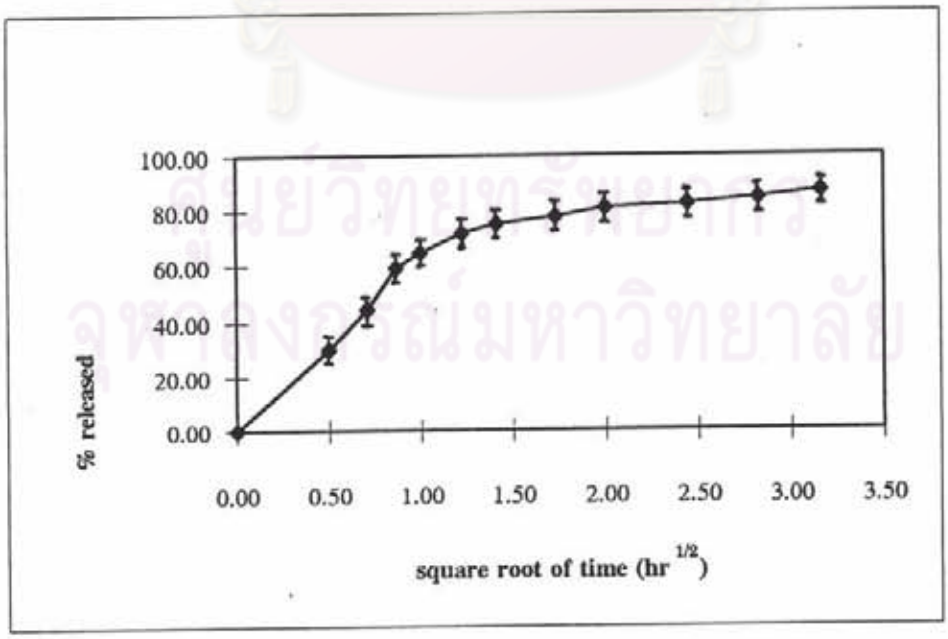


Fig. 80 : Higuchi's plot of cephalexin released from 3:2 ERL:RS microcapsules prepared by coacervation technique, core: wall ratio is 1:1.

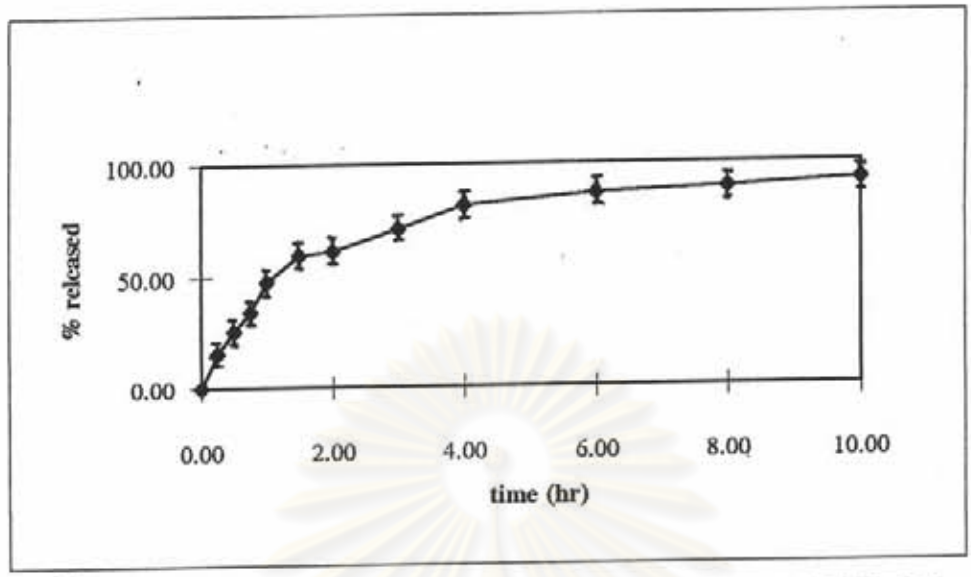


Fig. 81 : Dissolution profile of cephalexin released from 3:2 ERL:RS microcapsules prepared by coacervation technique, core: wall ratio is 1:2.

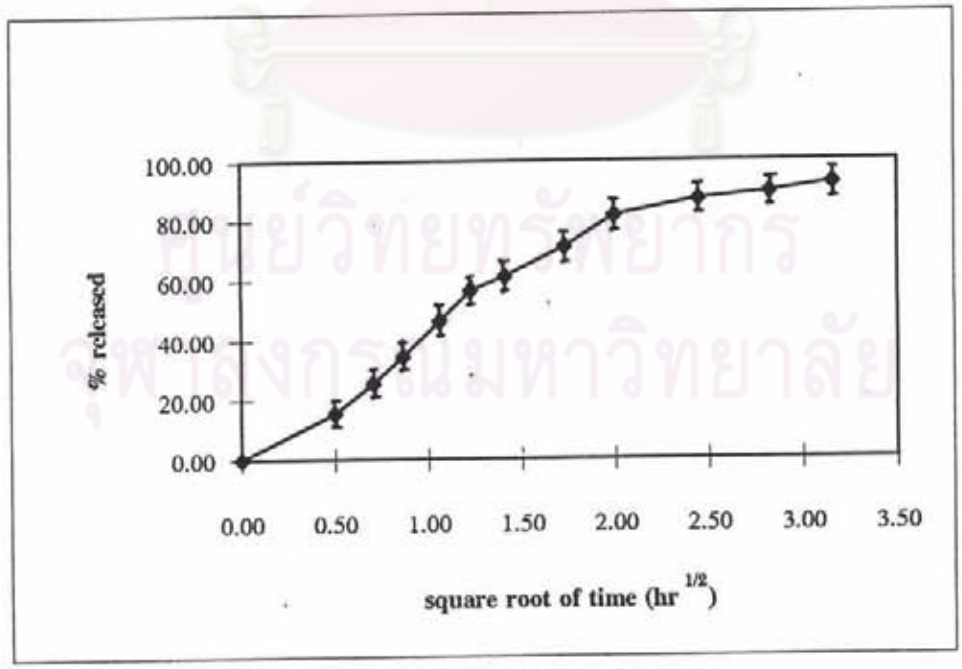


Fig. 82 : Higuchi's plot of cephalexin released from 3:2 ERL:RS microcapsules prepared by coacervation technique, core: wall ratio is 1:2.

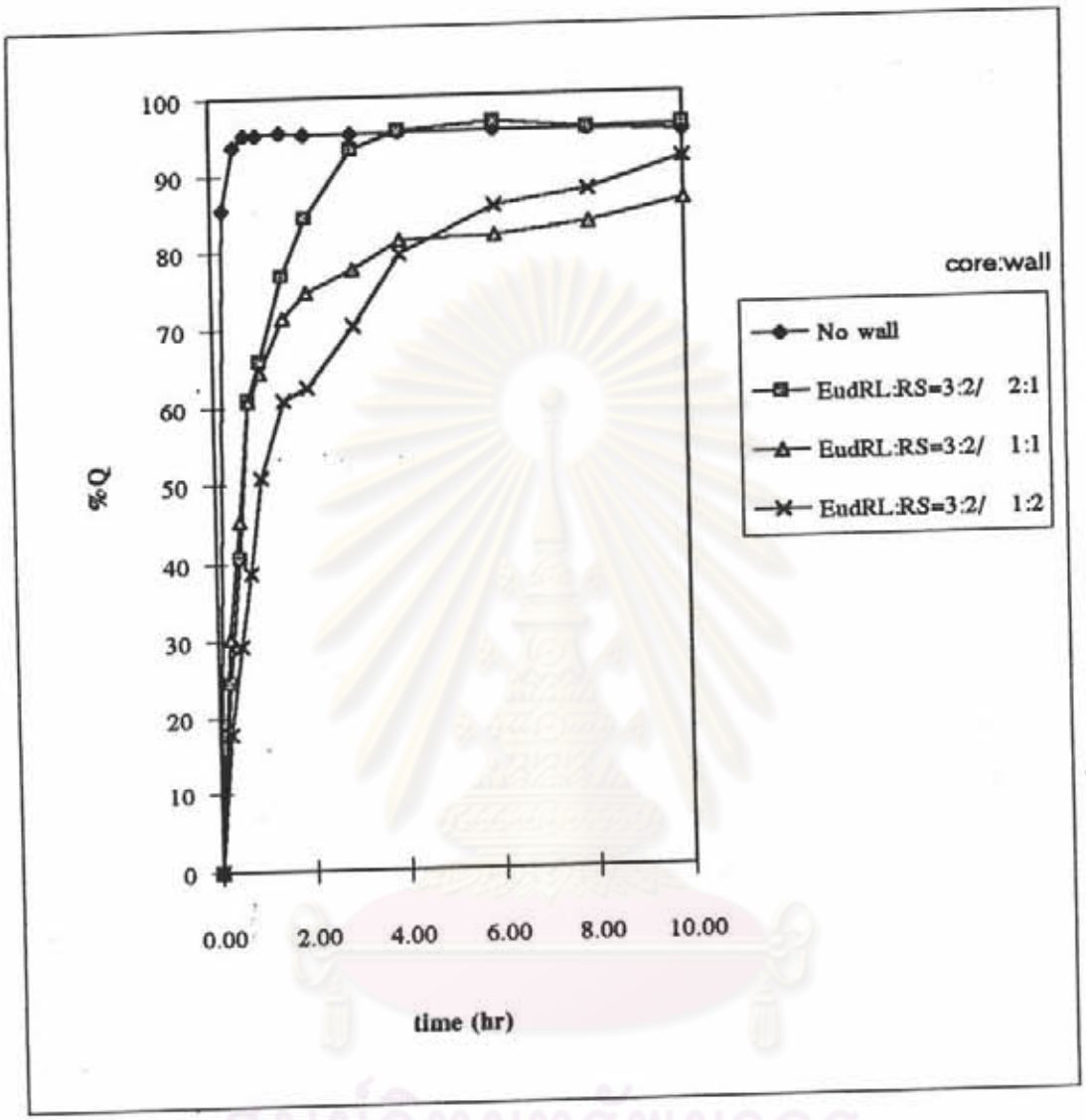


Fig. 83 : Dissolution profiles of cephalexin released from 3:2 ERL:RS microcapsules in various core: wall ratio prepared by coacervation technique.

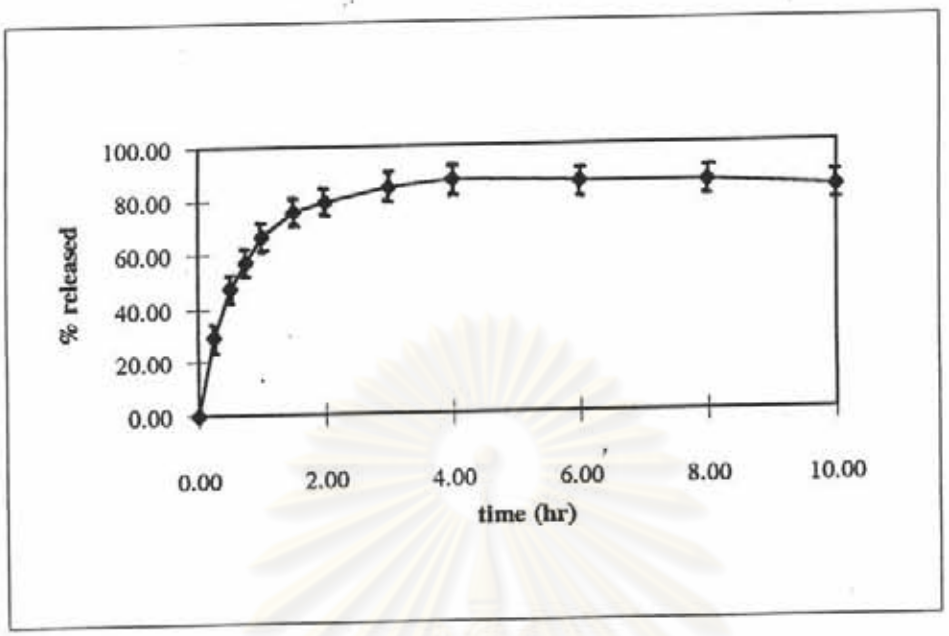


Fig. 84 : Dissolution profile of cephalexin released from 2:3 ERL:RS microcapsules prepared by coacervation technique, core: wall ratio is 2:1.

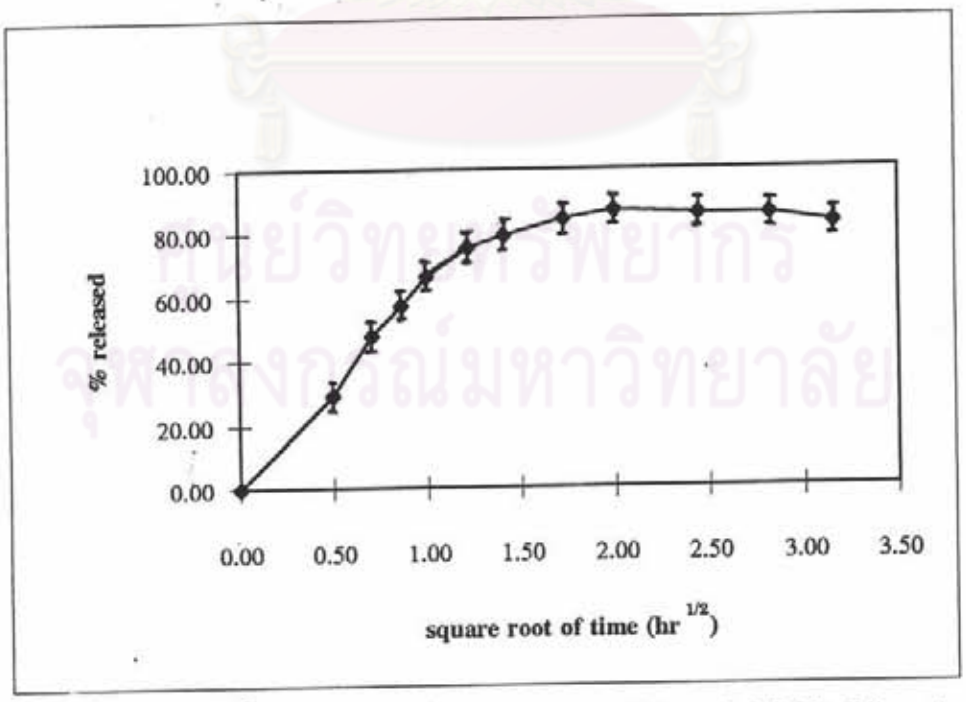


Fig. 85 : Higuchi's plot of cephalexin released from 2:3 ERL:RS microcapsules prepared by coacervation technique, core: wall ratio is 2:1.

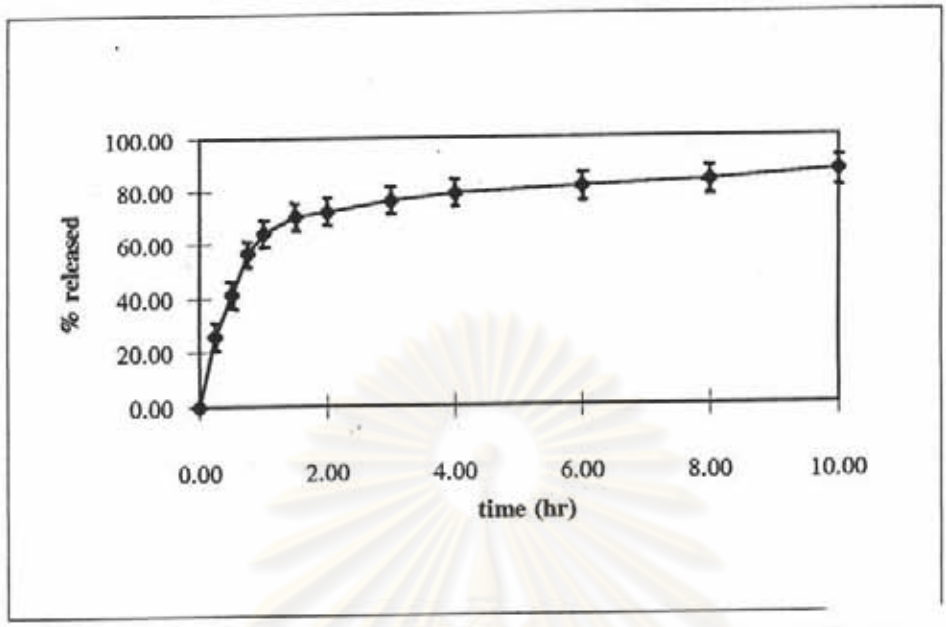


Fig. 86 : Dissolution profile of cephalexin released from 2:3 ERL:RS microcapsules prepared by coacervation technique, core: wall ratio is 1:1.

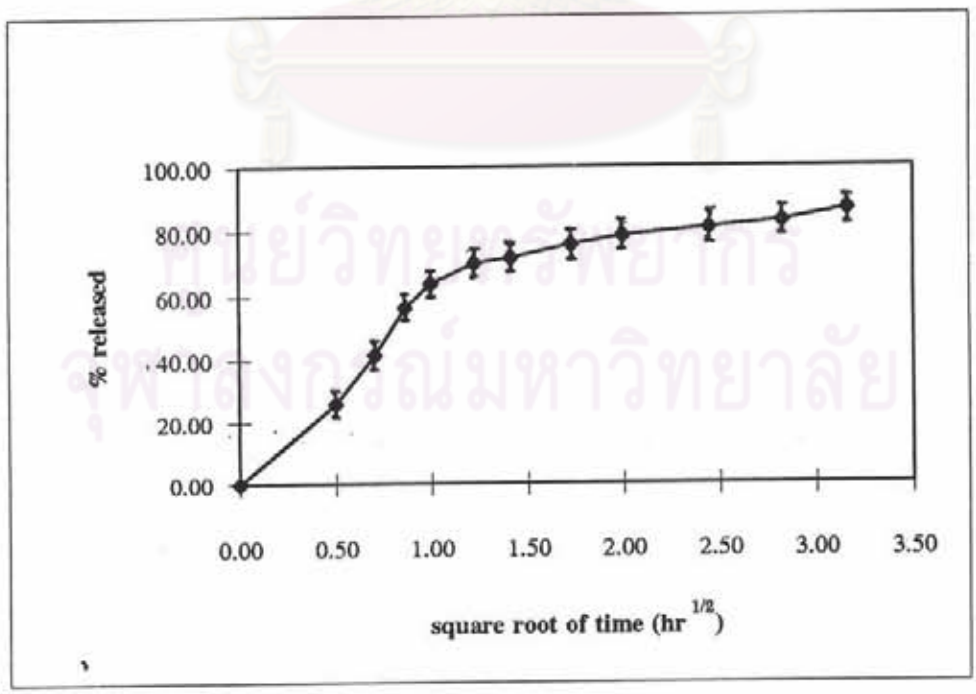


Fig. 87 : Higuchi's plot of cephalexin released from 2:3 ERL:RS microcapsules prepared by coacervation technique, core: wall ratio is 1:1.

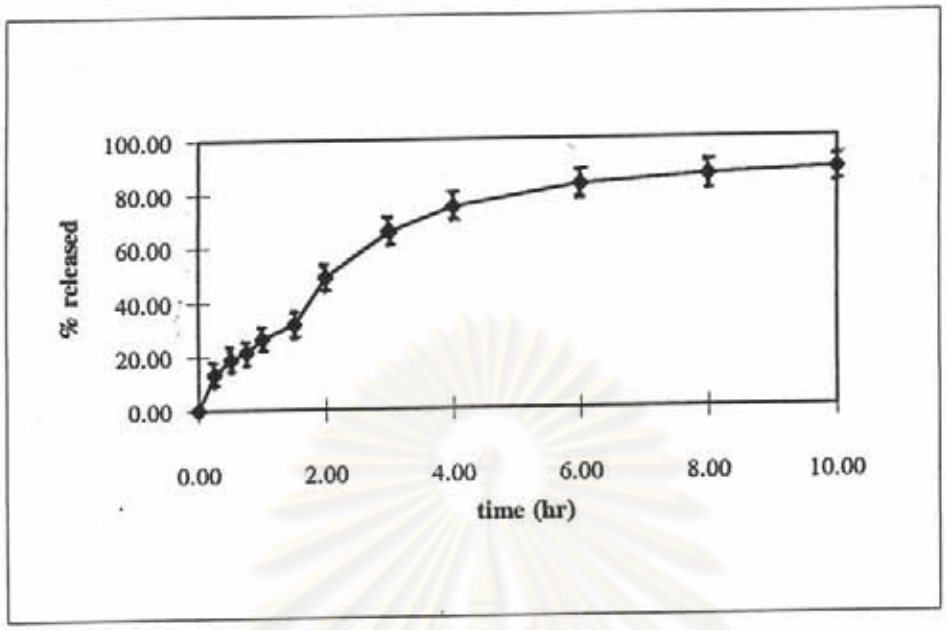


Fig. 88 : Dissolution profile of cephalexin released from 2:3 ERL:RS microcapsules prepared by coacervation technique, core: wall ratio is 1:2.

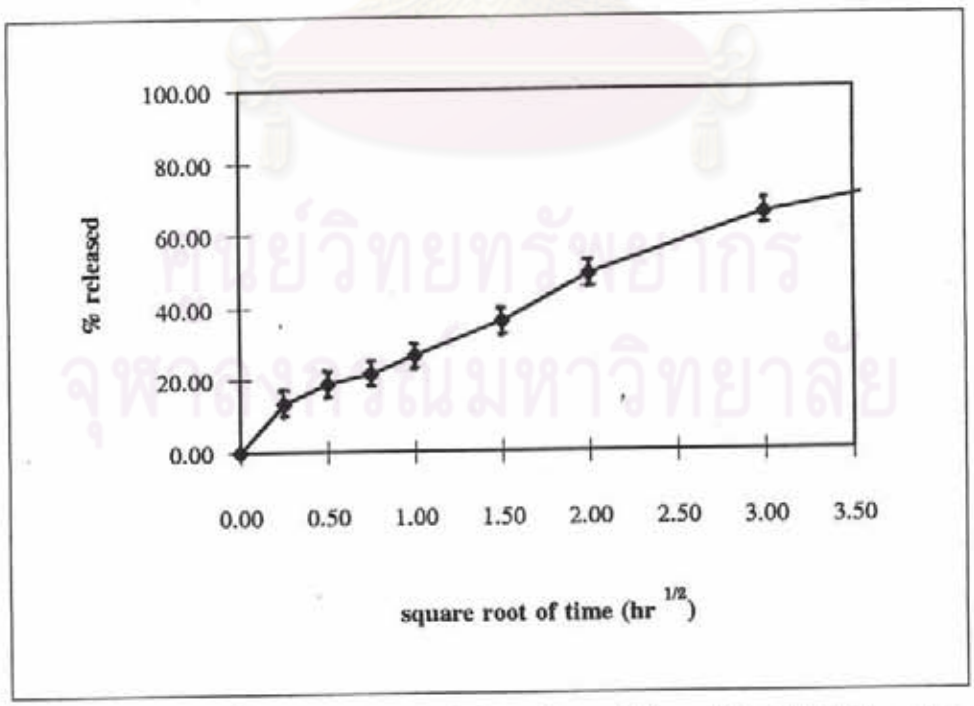


Fig. 89 : Higuchi's plot of cephalexin released from 2:3 ERL:RS microcapsules prepared by coacervation technique, core: wall ratio is 1:2.

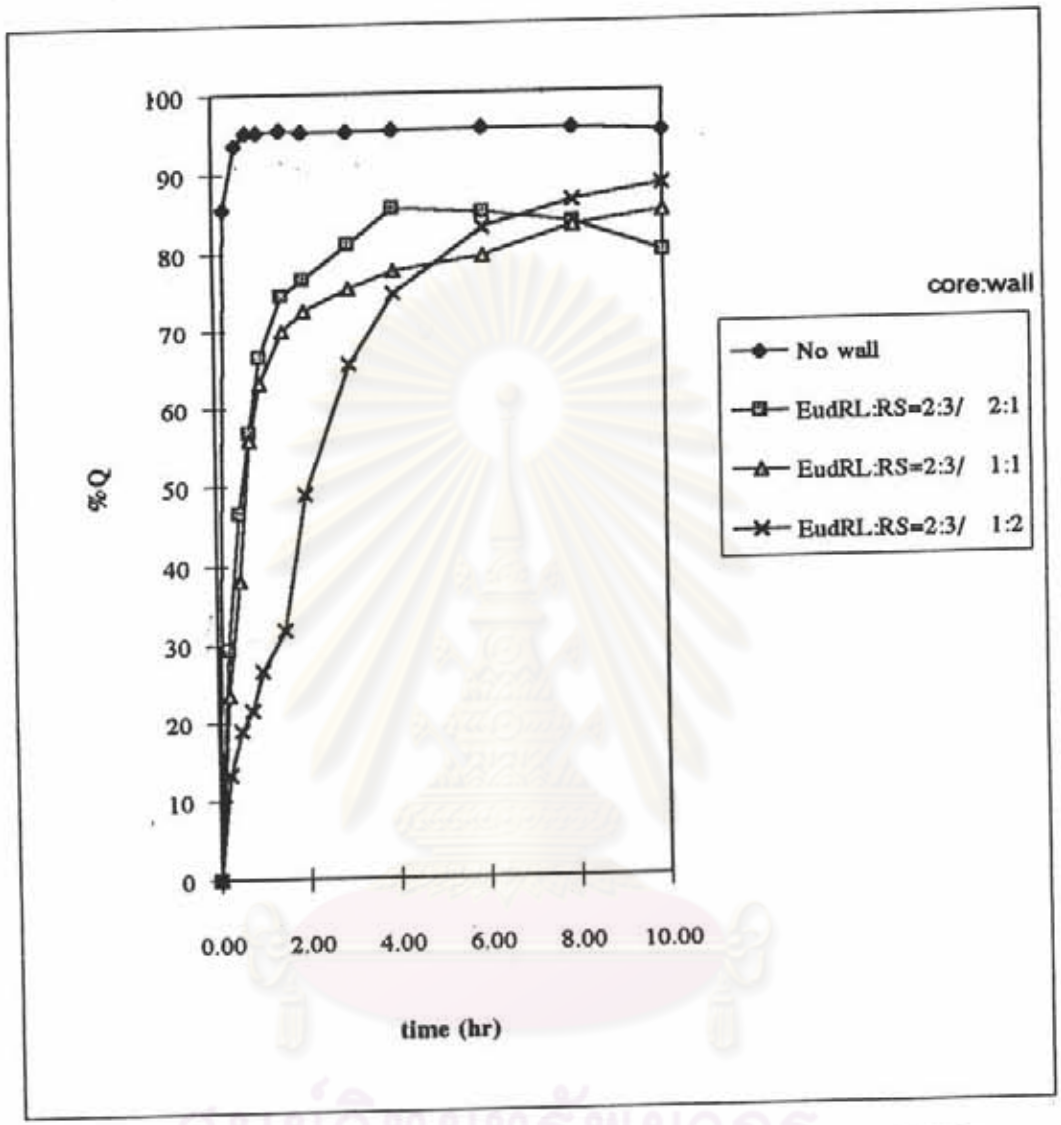


Fig. 90 : Dissolution profiles of cephalexin released from 2:3 ERL:RS microcapsules in various core: wall ratio prepared by coacervation technique.

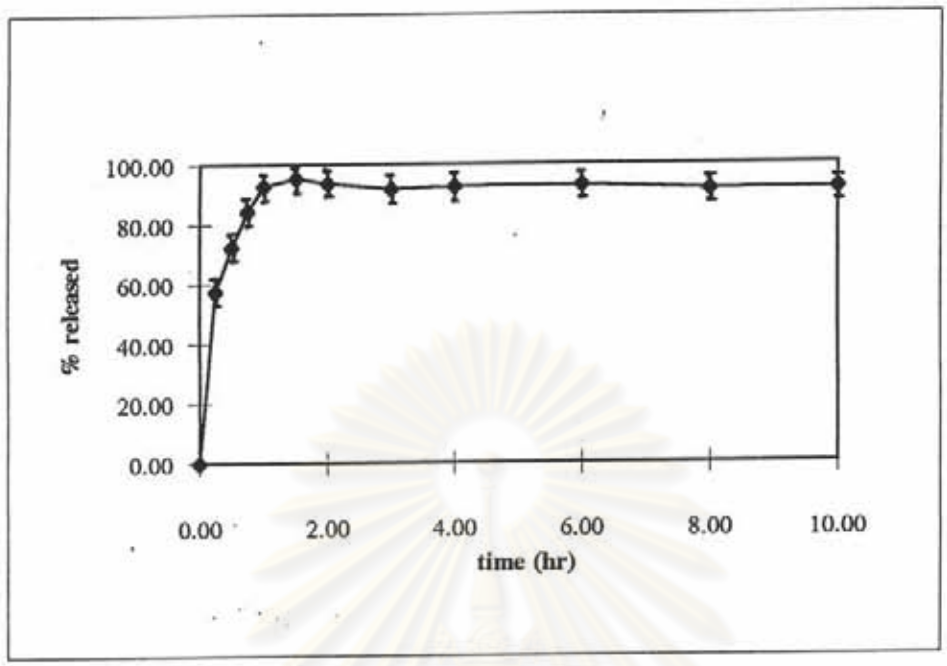


Fig. 91 : Dissolution profile of cephalexin released from ethylcellulose microcapsules prepared by fluidization technique, core: wall ratio is 2:1.

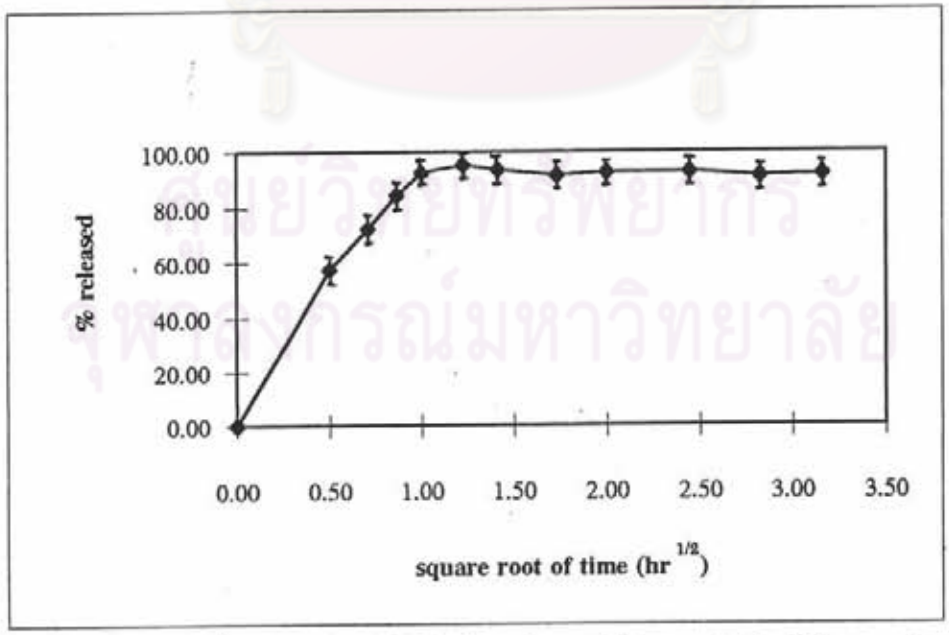


Fig. 92 : Higuchi's plot of cephalexin released from ethylcellulose microcapsules prepared by fluidization technique, core: wall ratio is 2:1.

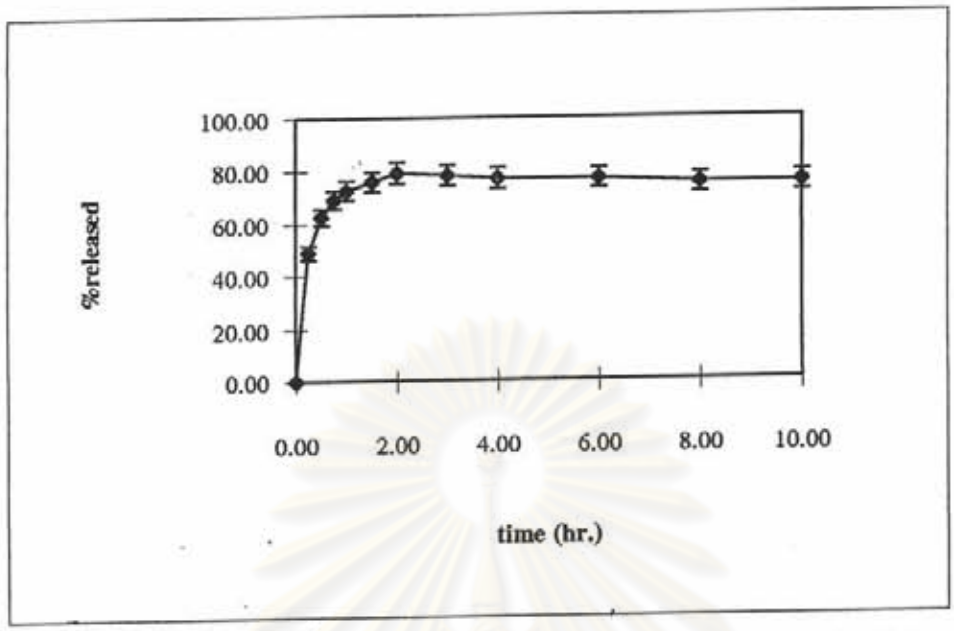


Fig. 93 : Dissolution profile of cephalexin released from ethylcellulose microcapsules prepared by fluidization technique, core: wall ratio is 1:1.

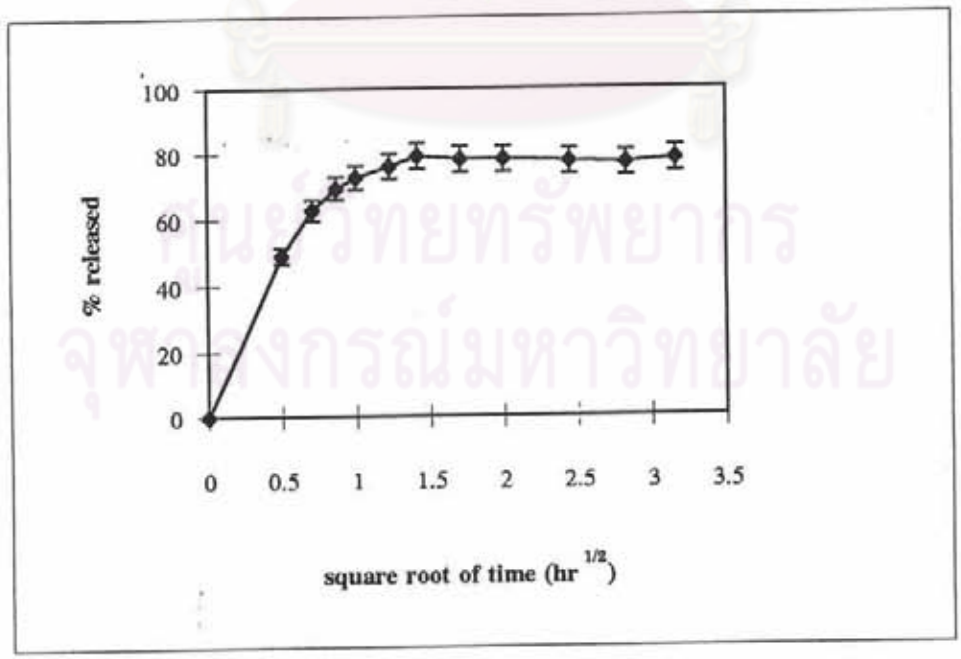


Fig. 94 : Higuchi's plot of cephalexin released from ethylcellulose microcapsules prepared by fluidization technique, core: wall ratio is 1:1.

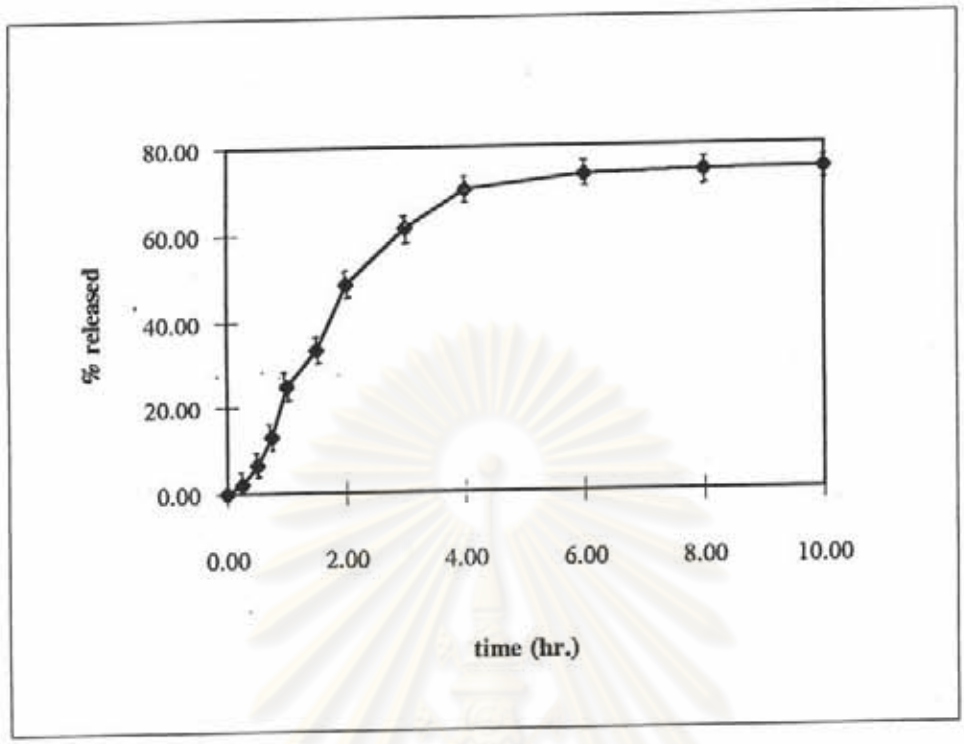


Fig. 95 : Dissolution profile of cephalexin released from ethylcellulose microcapsules prepared by fluidization technique, core: wall ratio is 1:2.

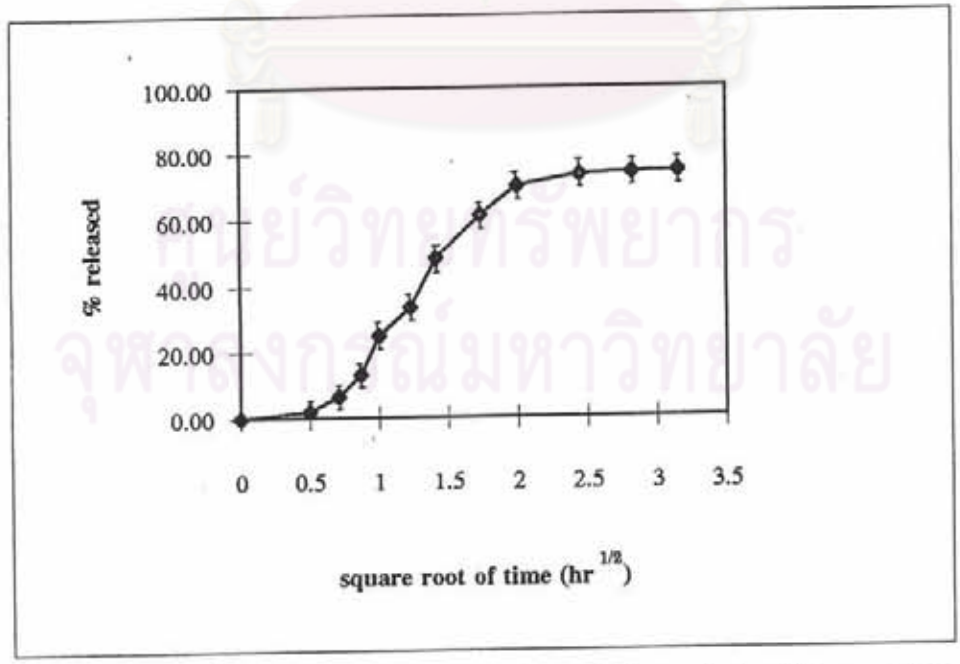


Fig. 96 : Higuchi's plot of cephalexin released from ethylcellulose microcapsules prepared by fluidization technique, core: wall ratio is 1:2.

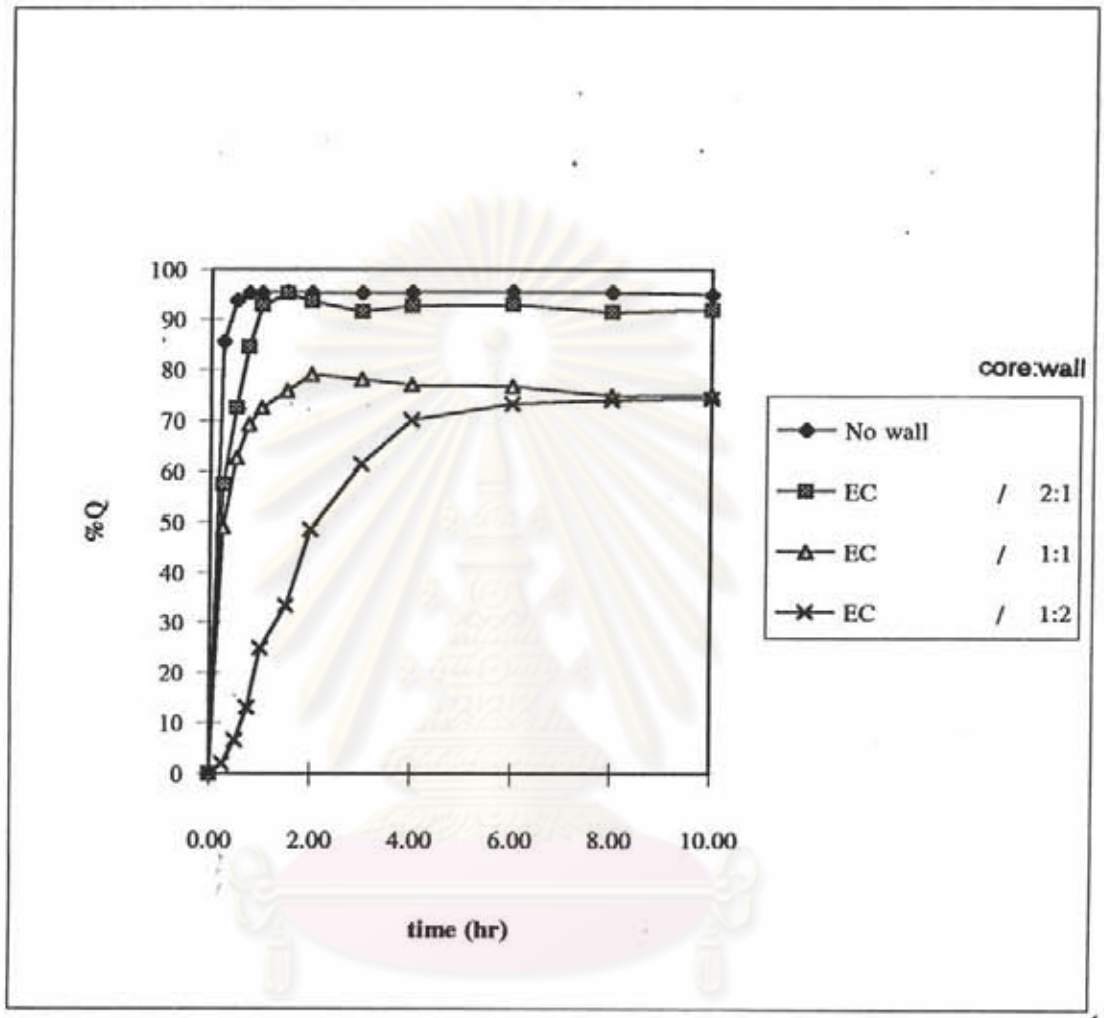


Fig. 97 : Dissolution profiles of cephalexin released from ethylcellulose microcapsules in various core: wall ratio prepared by fluidization technique.

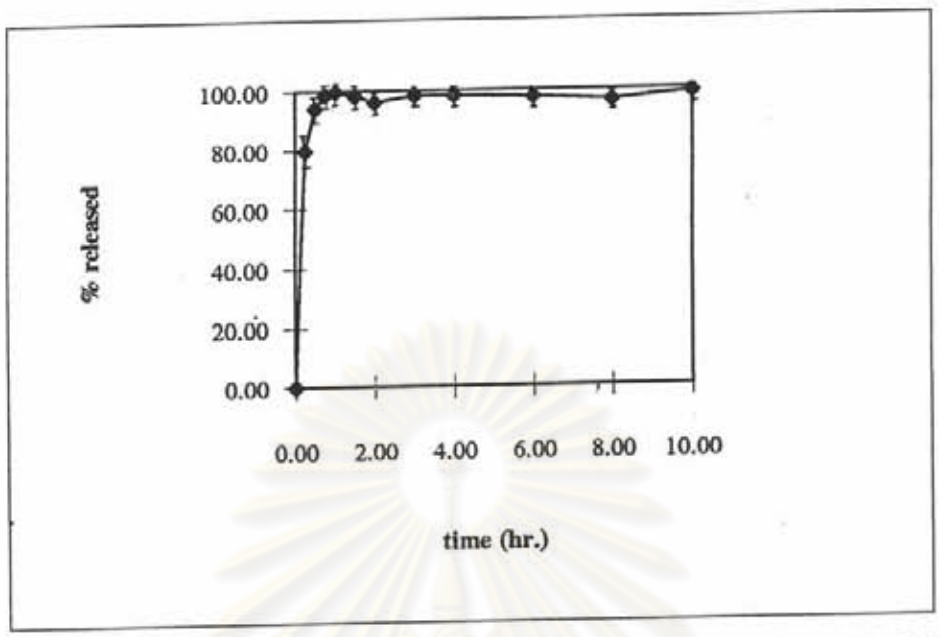


Fig. 98 : Dissolution profile of cephalexin released from 3:2 ERL:RS microcapsules prepared by fluidization technique, core: wall ratio is 2:1.

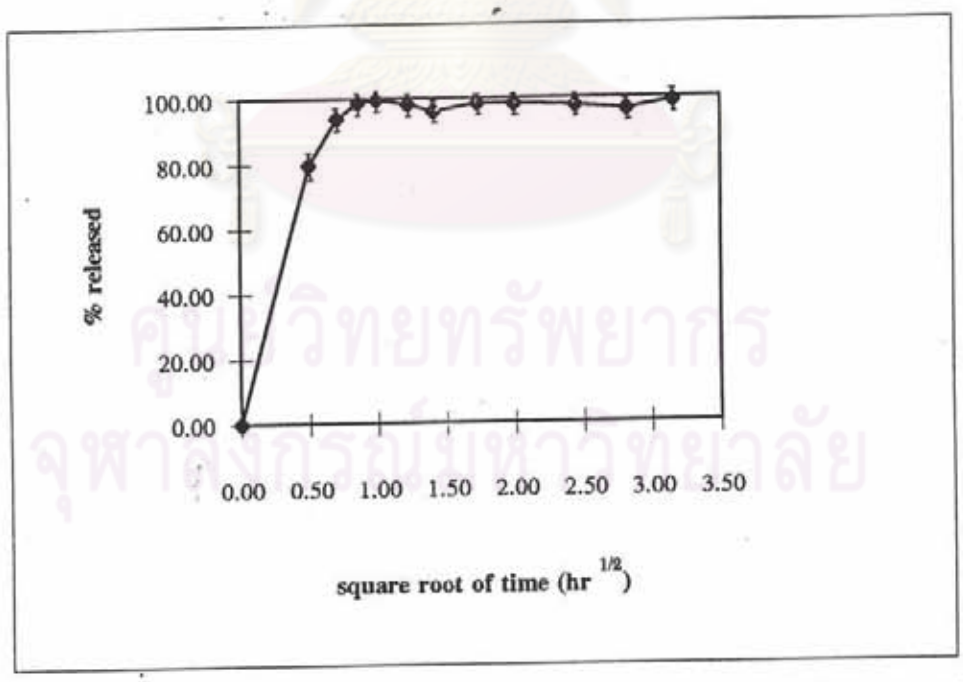


Fig. 99 : Higuchi's plot of cephalexin released from 3:2 ERL:RS microcapsules prepared by fluidization technique, core: wall ratio is 2:1.

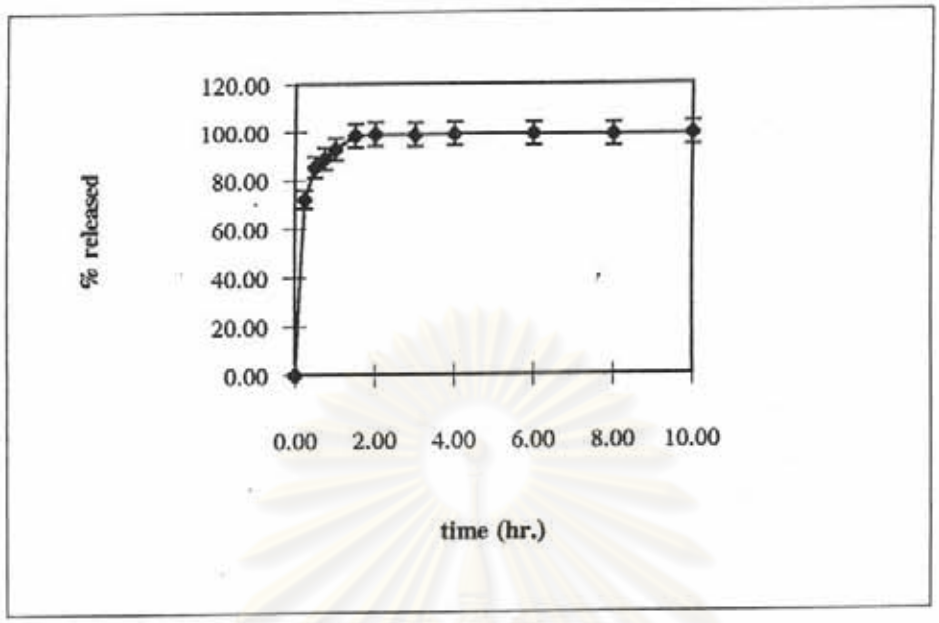


Fig. 100 : Dissolution profile of cephalexin released from 3:2 ERL:RS microcapsules prepared by fluidization technique, core: wall ratio is 1:1.

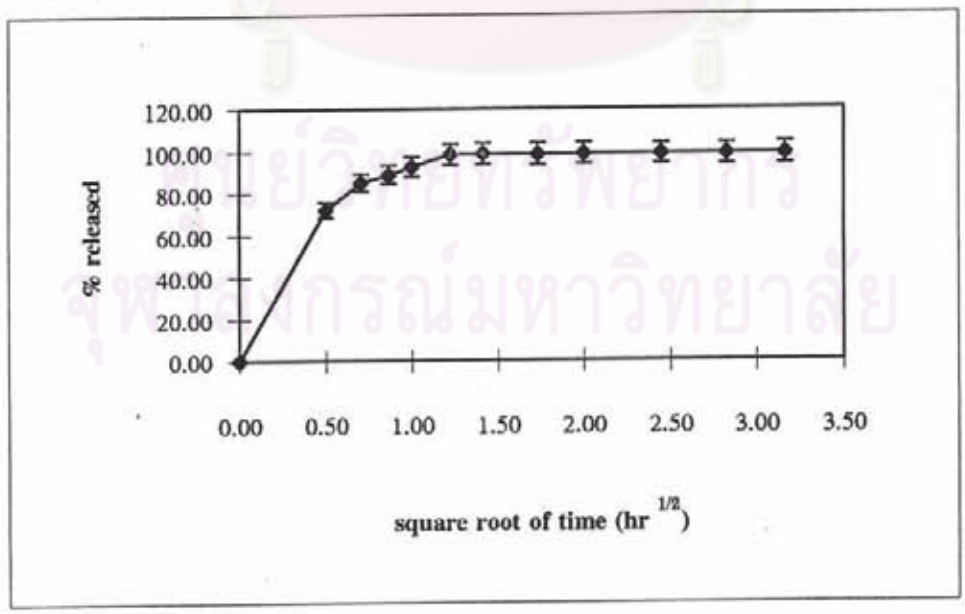


Fig. 101 : Higuchi's plot of cephalexin released from 3:2 ERL:RS microcapsules prepared by fluidization technique, core: wall ratio is 1:1.

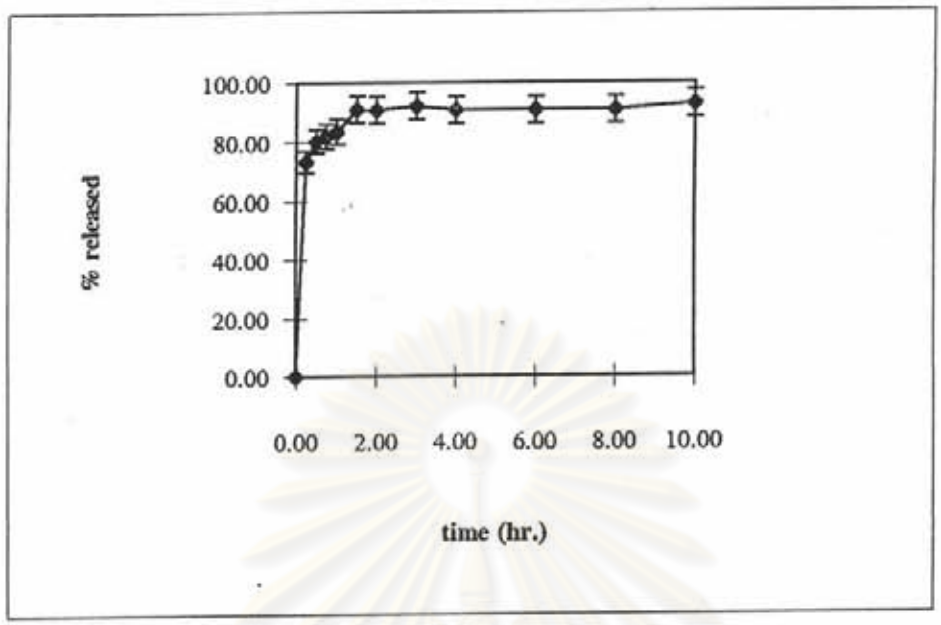


Fig. 102 : Dissolution profile of cephalexin released from 3:2 ERL:RS microcapsules prepared by fluidization technique, core: wall ratio is 1:2.

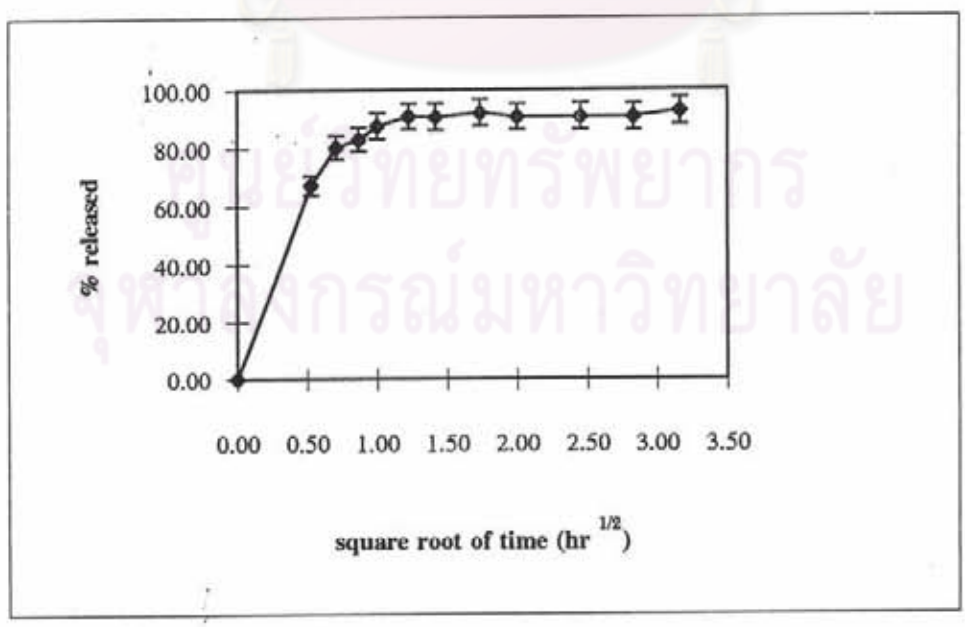


Fig. 103 : Higuchi's plot of cephalexin released from 3:2 ERL:RS microcapsules prepared by fluidization technique, core: wall ratio is 1:2.

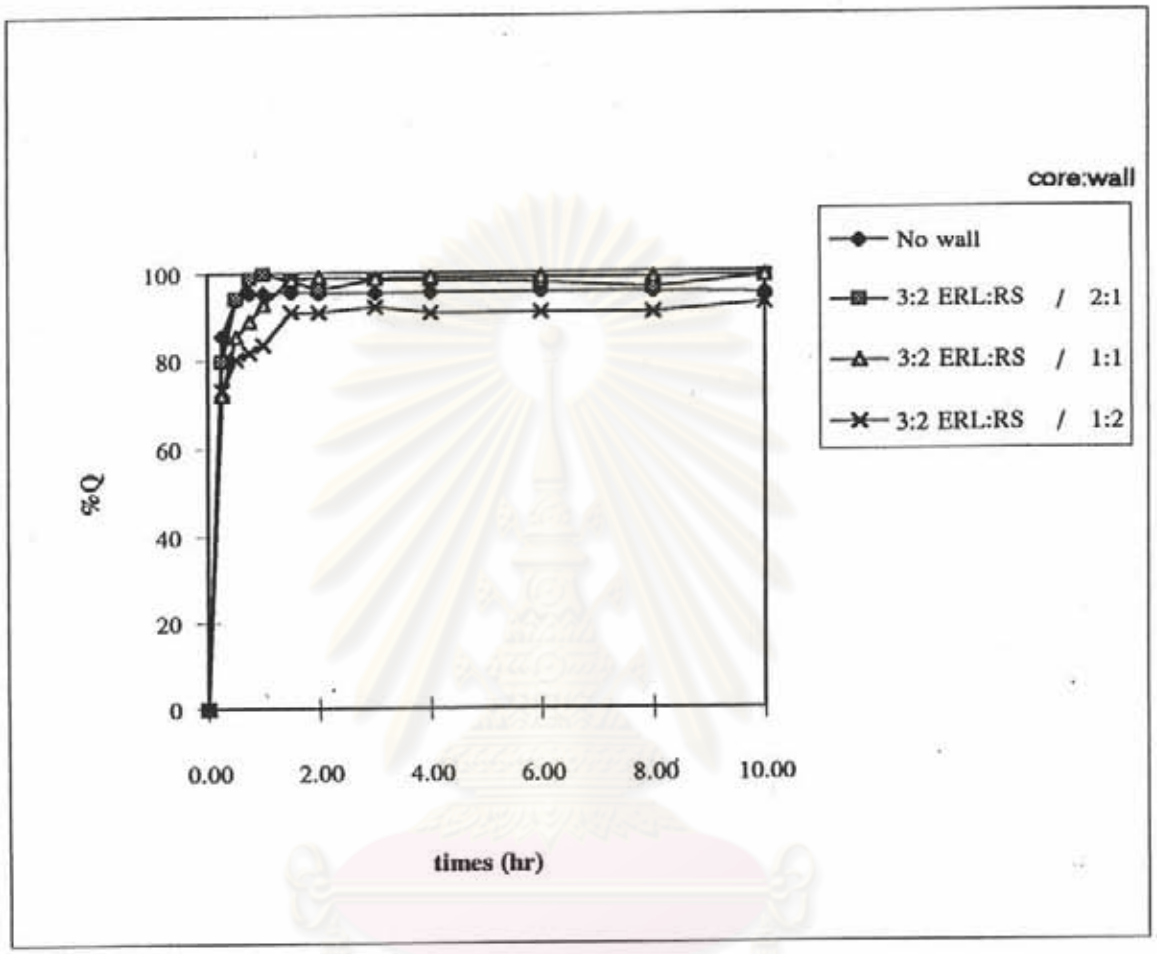


Fig. 104: Dissolution profiles of cephalexin released from 3:2 ERL:RS microcapsules in various core: wall ratio prepared by fluidization technique.

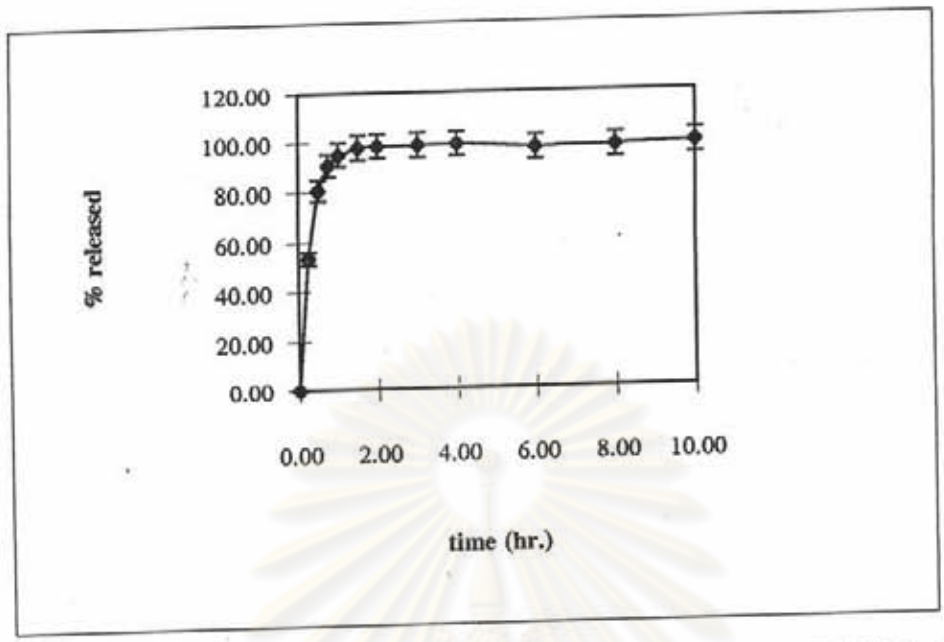


Fig. 105: Dissolution profile of cephalexin released from 2:3 ERL:RS microcapsules prepared by fluidization technique, core: wall ratio is 2:1.

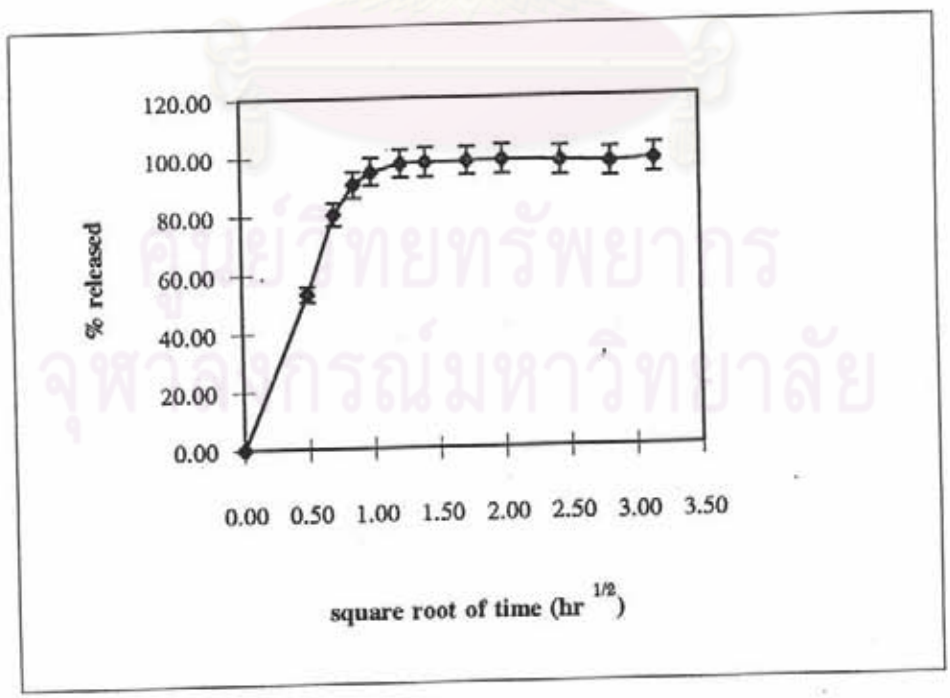


Fig. 106: Higuchi's plot of cephalexin released from 2:3 ERL:RS microcapsules prepared by fluidization technique, core: wall ratio is 2:1.

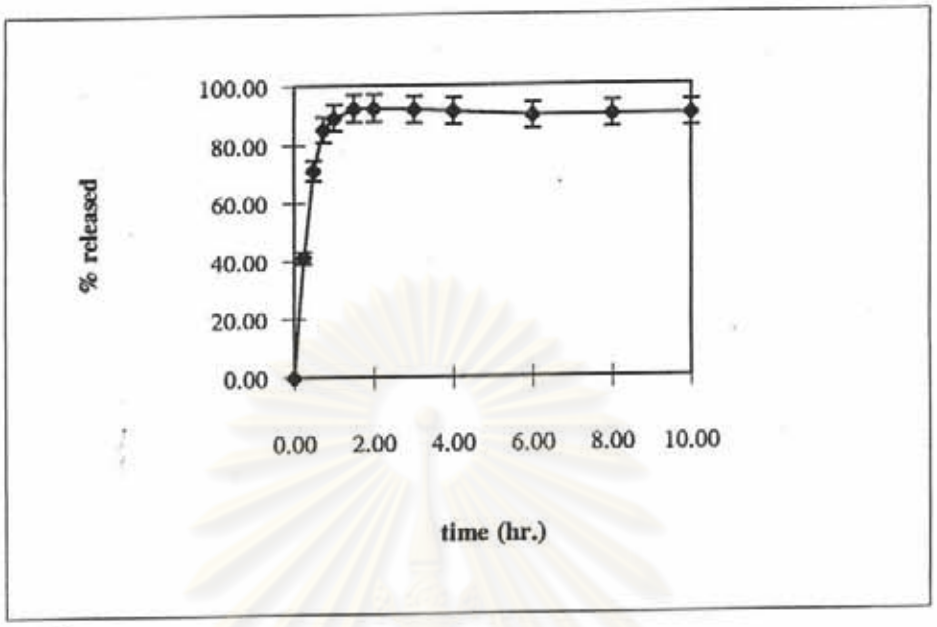


Fig. 107: Dissolution profile of cephalexin released from 2:3 ERL:RS microcapsules prepared by fluidization technique, core: wall ratio is 1:1.

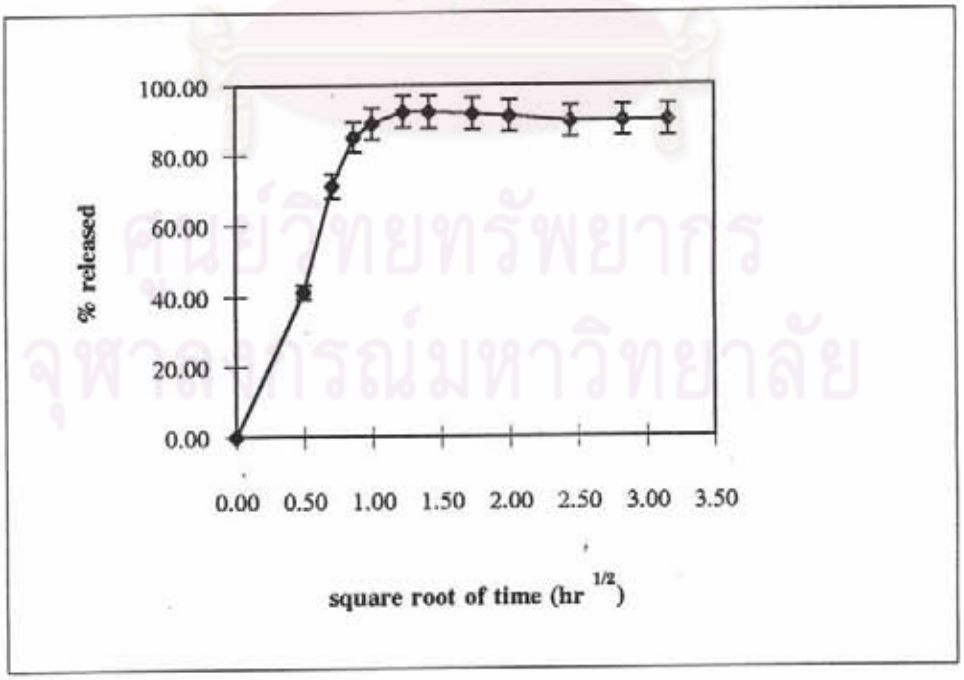


Fig. 108: Higuchi's plot of cephalexin released from 2:3 ERL:RS microcapsules prepared by fluidization technique, core: wall ratio is 1:1.

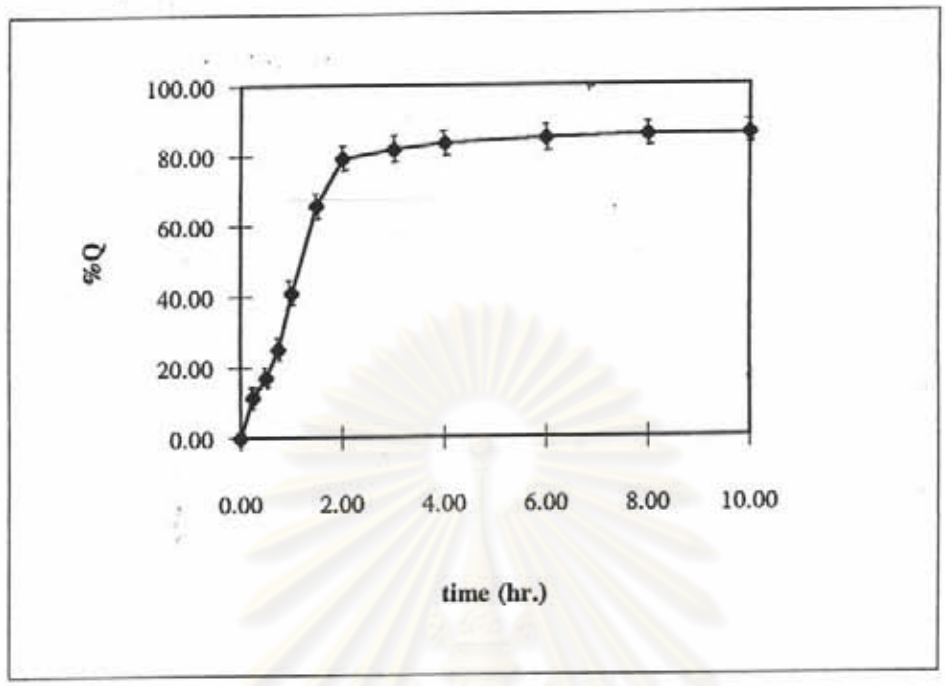


Fig. 109 : Dissolution profile of cephalexin released from 2:3 ERL:RS microcapsules prepared by fluidization technique, core: wall ratio is 1:2.

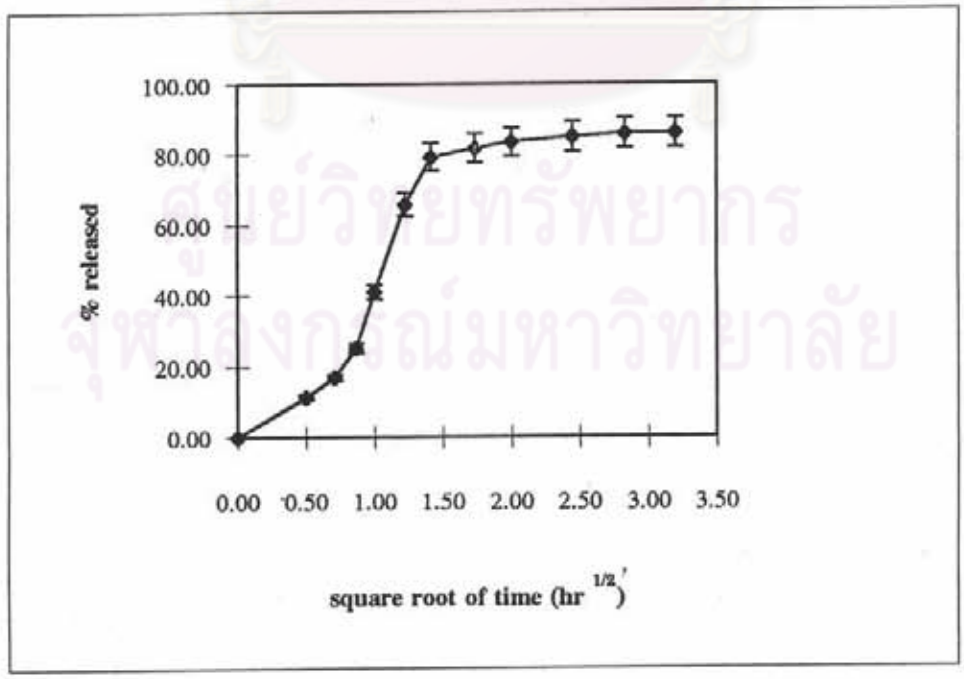


Fig. 110 : Higuchi's plot of cephalexin released from 2:3 ERL:RS microcapsules prepared by fluidization technique, core: wall ratio is 1:2.

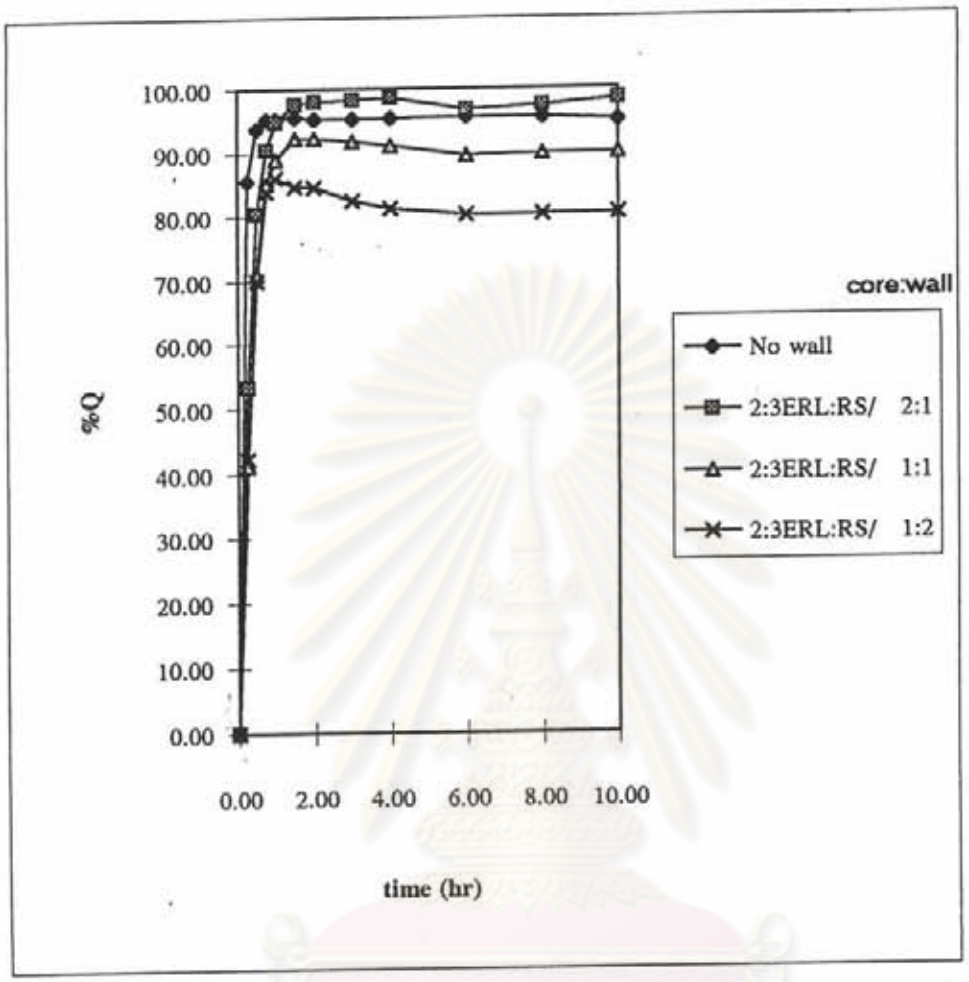


Fig. 111 : Dissolution profiles of cephalexin released from 2:3 ERL:RS microcapsules in various core: wall ratio prepared by fluidization technique.

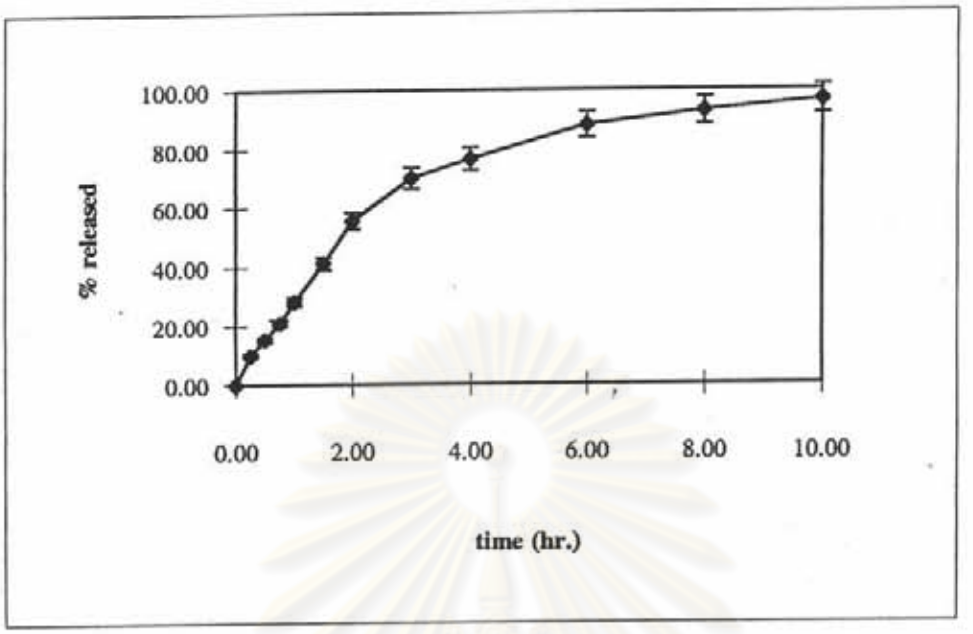


Fig. 112 : Dissolution profile of cephalexin released from ethylcellulose microcapsules prepared by spray drying technique, core: wall ratio is 2:1.

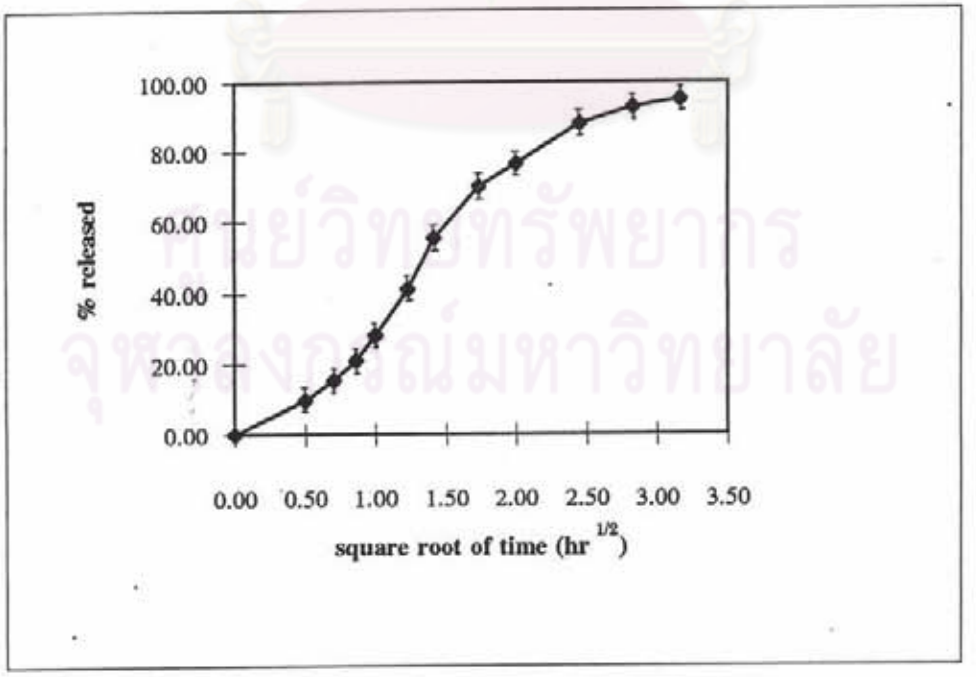


Fig. 113 : Higuchi's plot of cephalexin released from ethylcellulose microcapsules prepared by spray drying technique, core: wall ratio is 2:1.

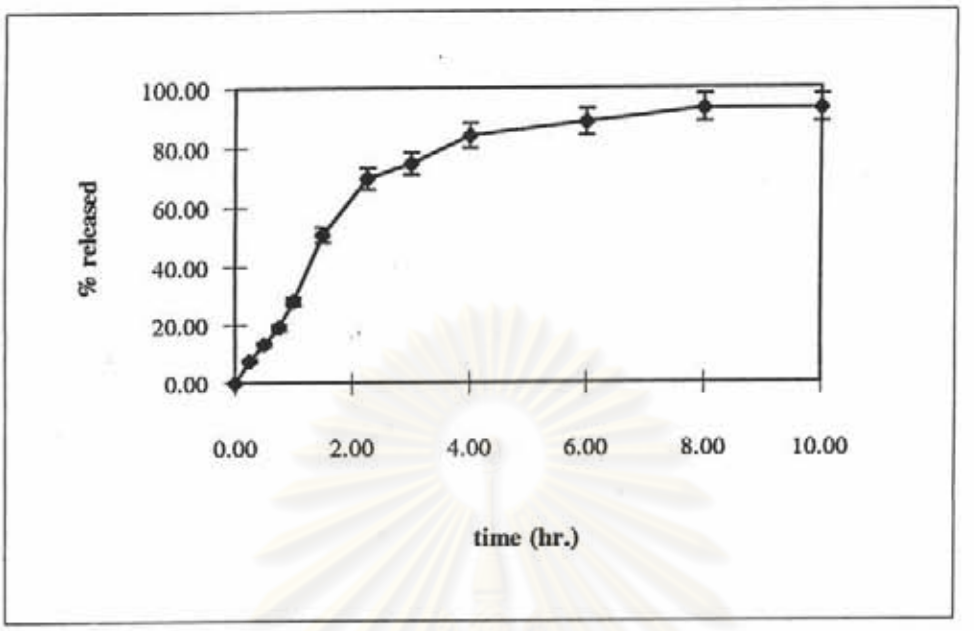


Fig. 114 : Dissolution profile of cephalexin released from ethylcellulose microcapsules prepared by spray drying technique, core: wall ratio is 1:1.

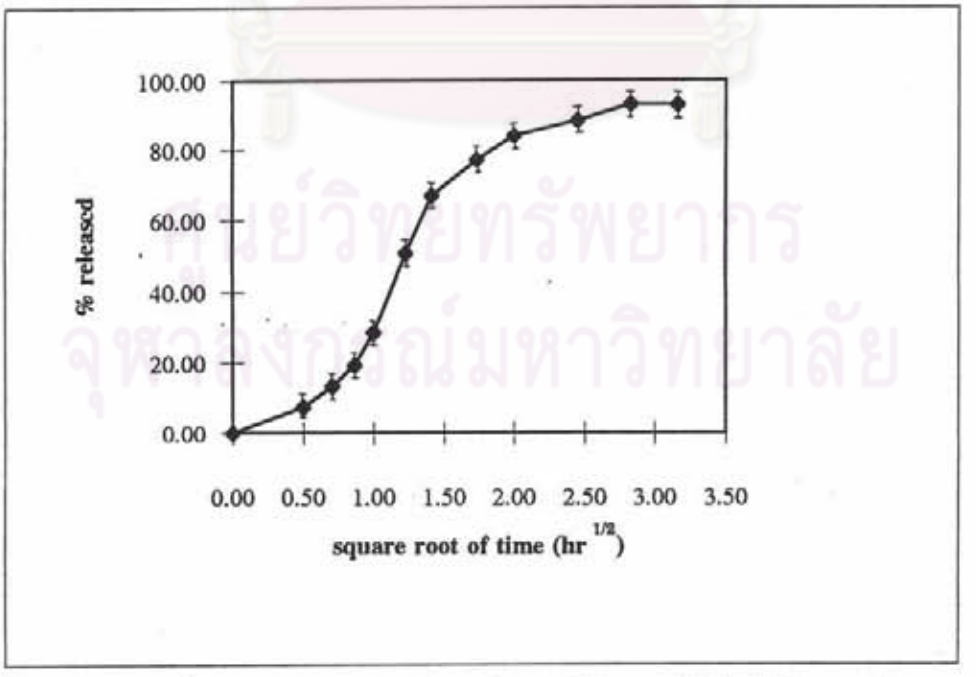


Fig. 115 : Higuchi's plot of cephalexin released from ethylcellulose microcapsules prepared by spray drying technique, core: wall ratio is 1:1.

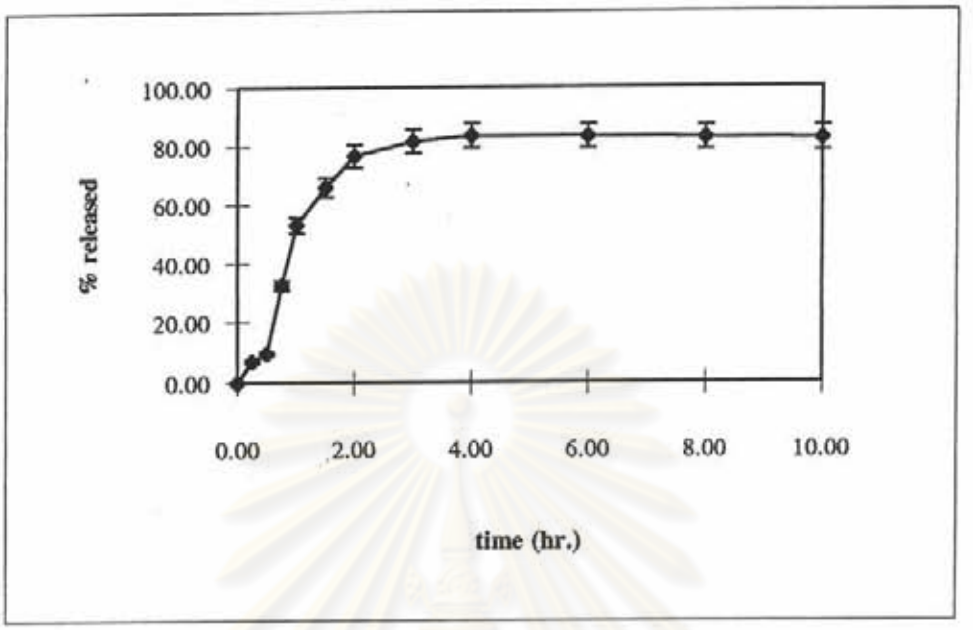


Fig. 116 : Dissolution profile of cephalexin released from ethylcellulose microcapsules prepared by spray drying technique, core: wall ratio is 1:2.

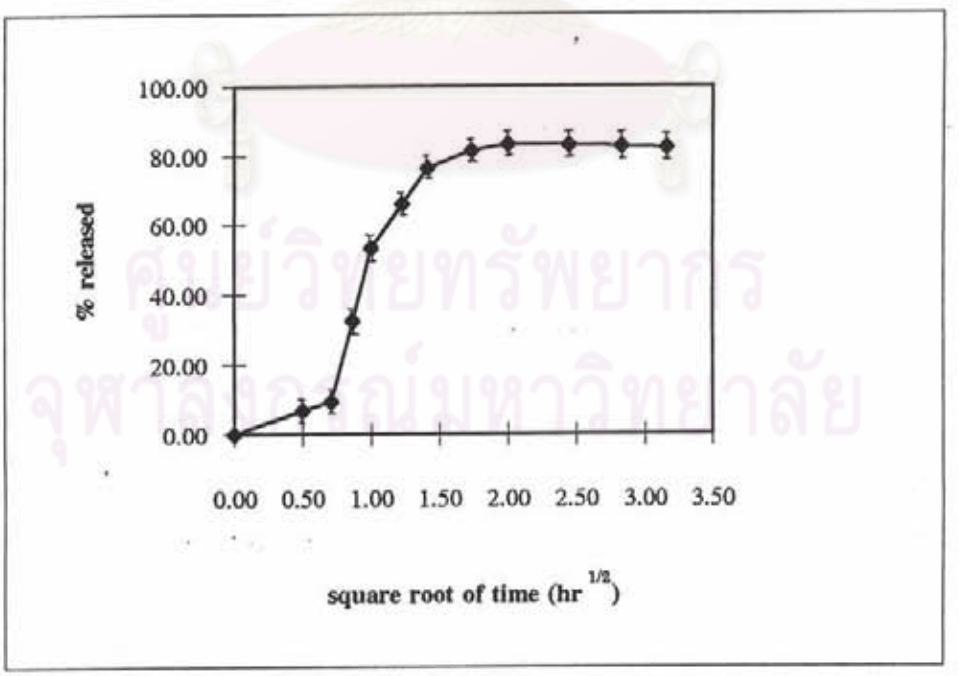


Fig. 117 : Higuchi's plot of cephalexin released from ethylcellulose microcapsules prepared by spray drying technique, core: wall ratio is 1:2.

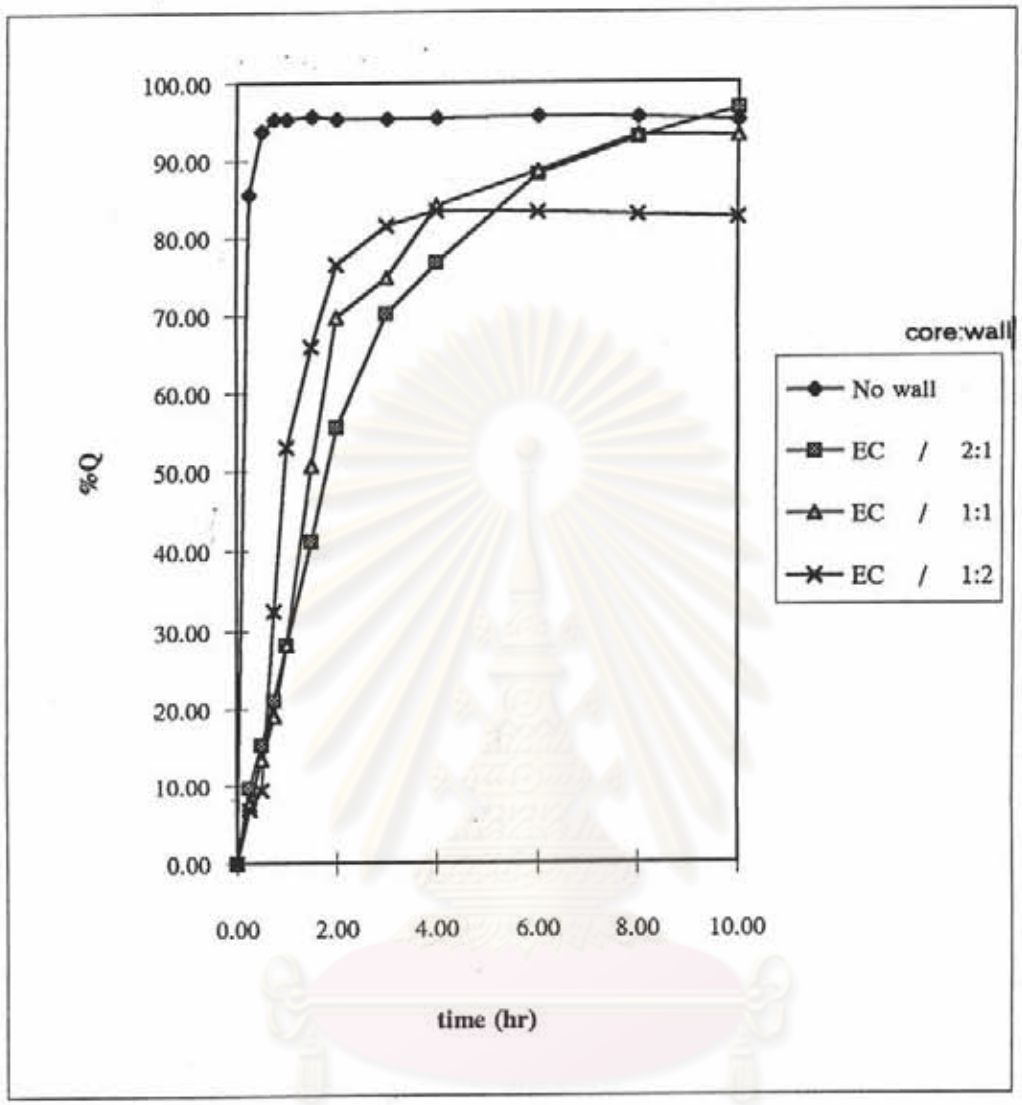


Fig. 118 : Dissolution profiles of cephalexin released from ethylcellulose microcapsules in various core: wall ratio prepared by spray drying technique.

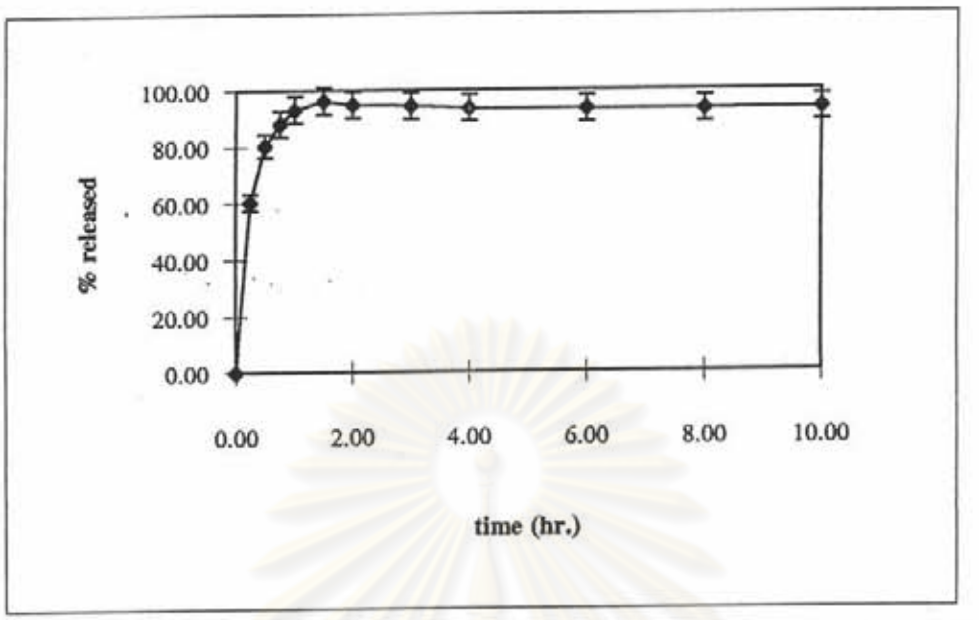


Fig. 119 : Dissolution profile of cephalexin released from 3:2 ERL:RS microcapsules prepared by spray drying technique, core: wall ratio is 2:1.

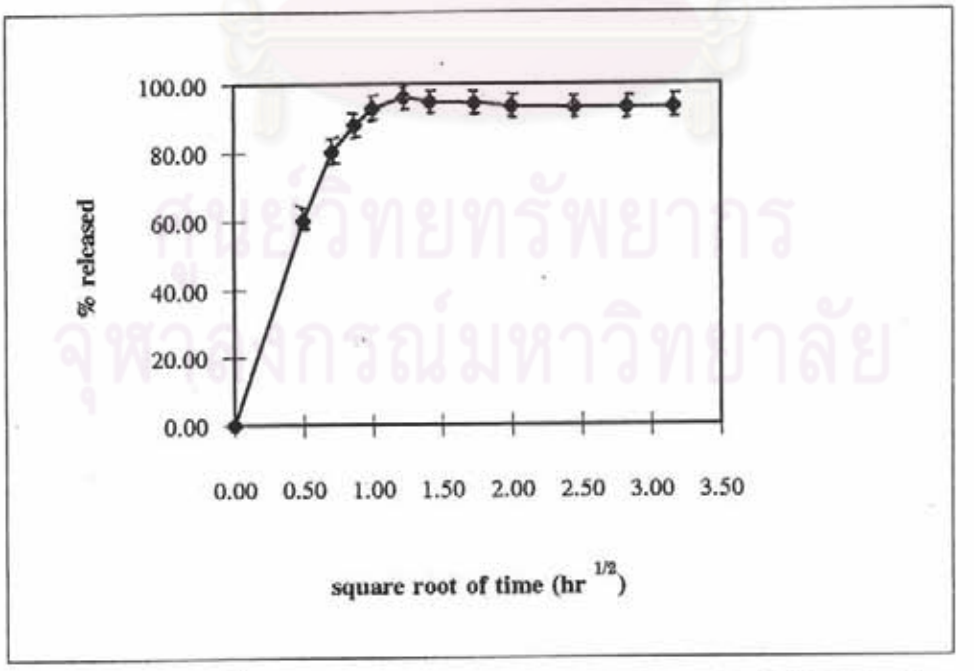


Fig. 120 : Higuchi's plot of cephalexin released from 3:2 ERL:RS microcapsules prepared by spray drying technique, core: wall ratio is 2:1.

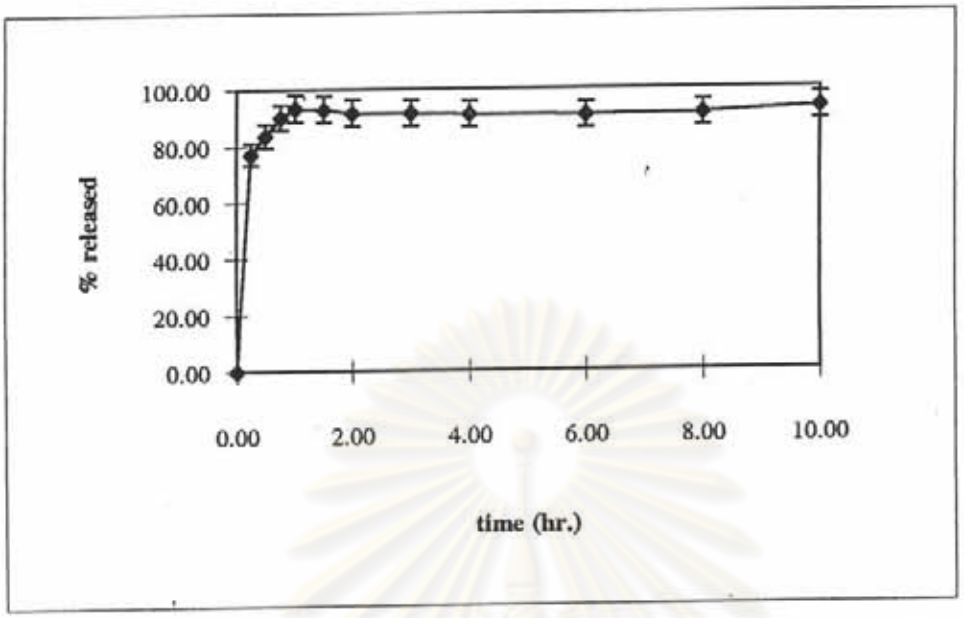


Fig. 121 : Dissolution profile of cephalexin released from 3:2 ERL:RS microcapsules prepared by spray drying technique, core: wall ratio is 1:1.

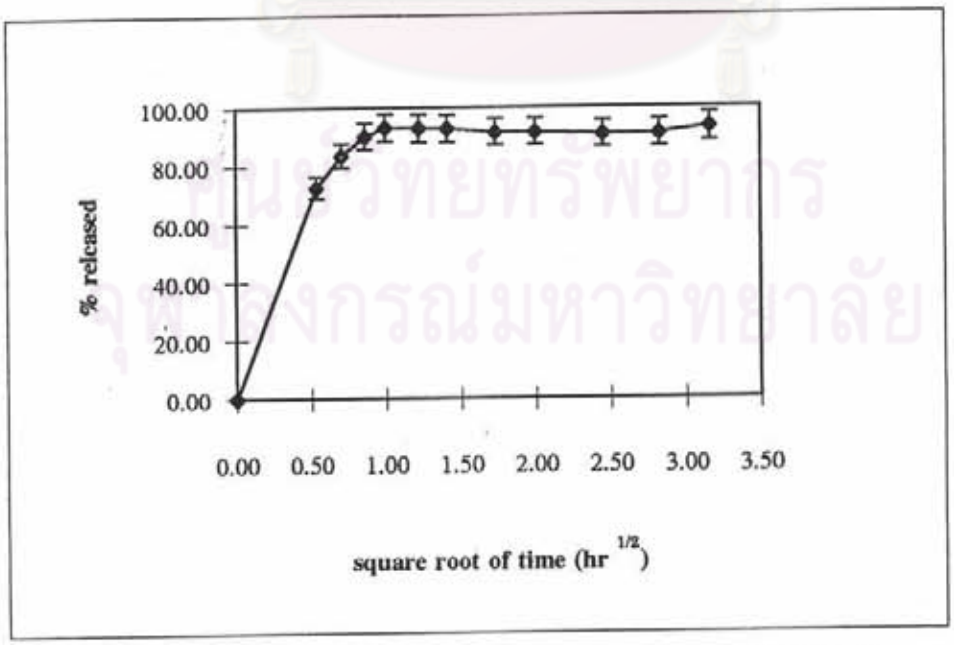


Fig. 122 : Higuchi's plot of cephalexin released from 3:2 ERL:RS microcapsules prepared by spray drying technique, core: wall ratio is 1:1.

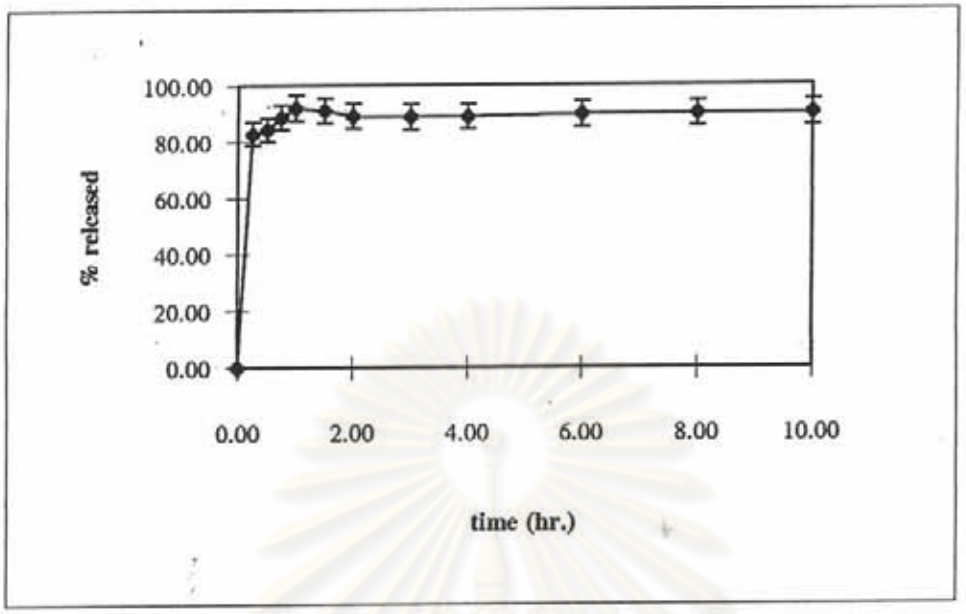


Fig. 123 : Dissolution profile of cephalexin released from 3:2 ERL:RS microcapsules prepared by spray drying technique, core: wall ratio is 1:2.

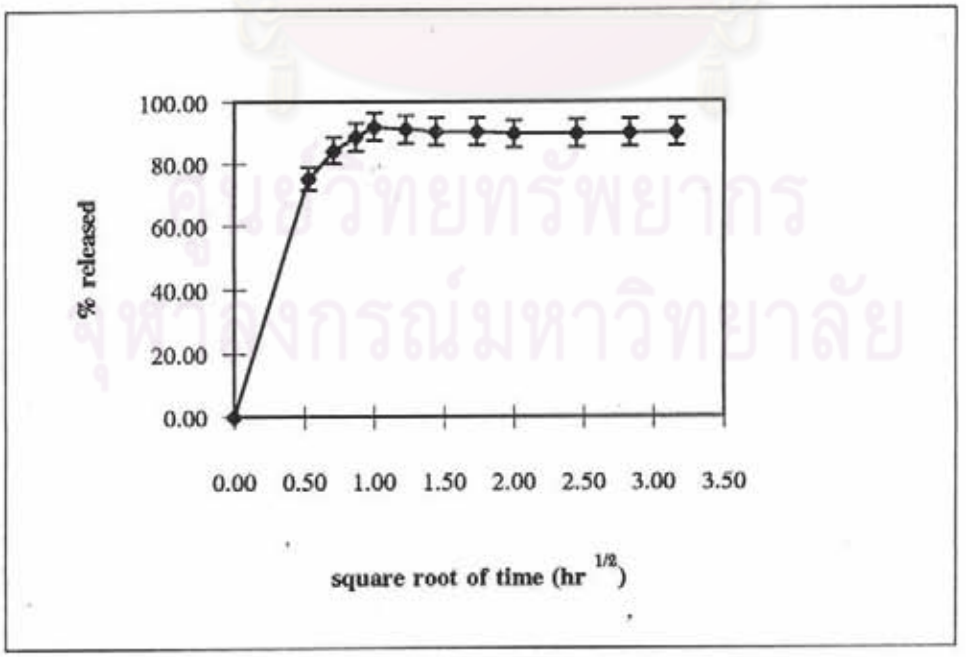


Fig. 124 : Higuchi's plot of cephalexin released from 3:2 ERL:RS microcapsules prepared by spray drying technique, core: wall ratio is 1:2.

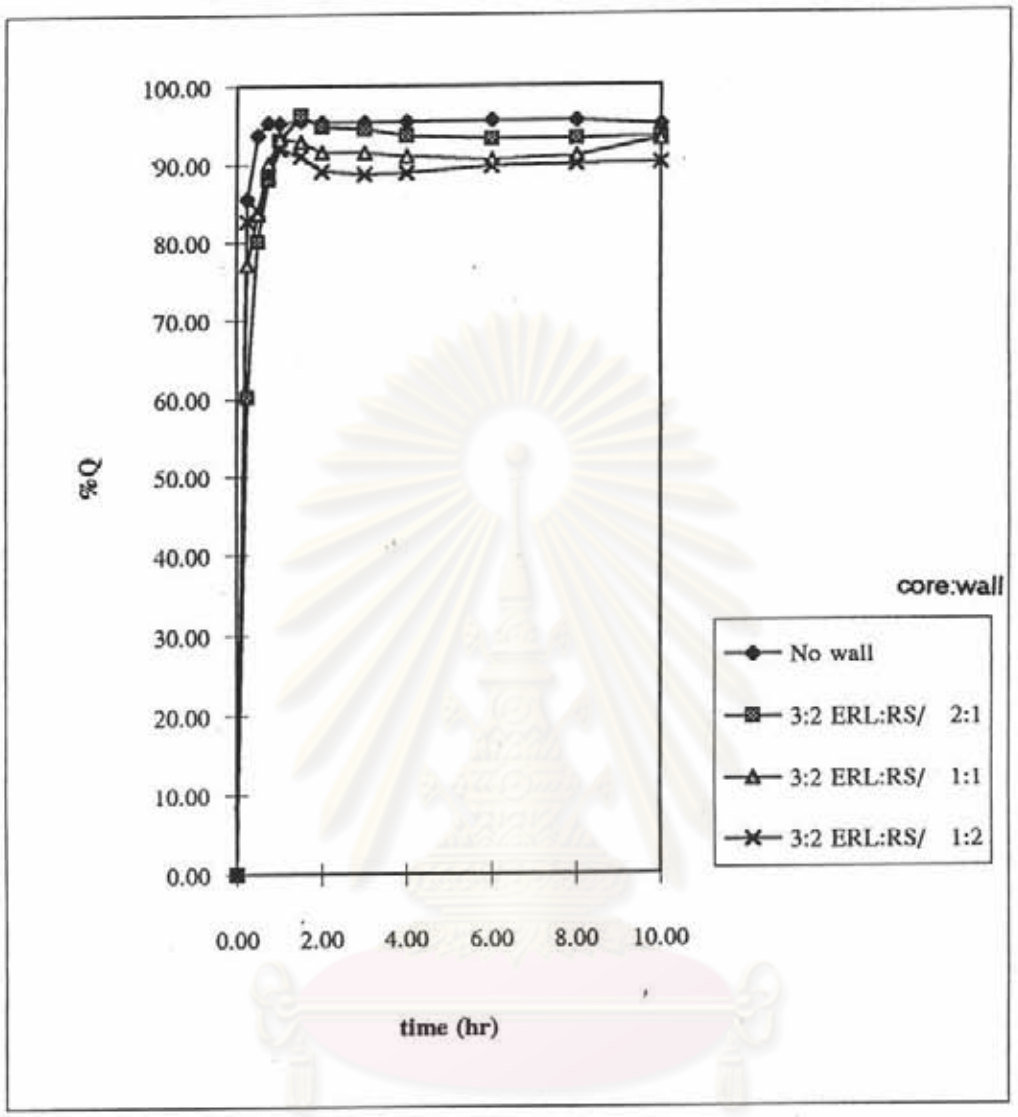


Fig. 125 : Dissolution profiles of cephalexin released from 3:2 ERL:RS microcapsules in various core: wall ratio prepared by spray drying technique.

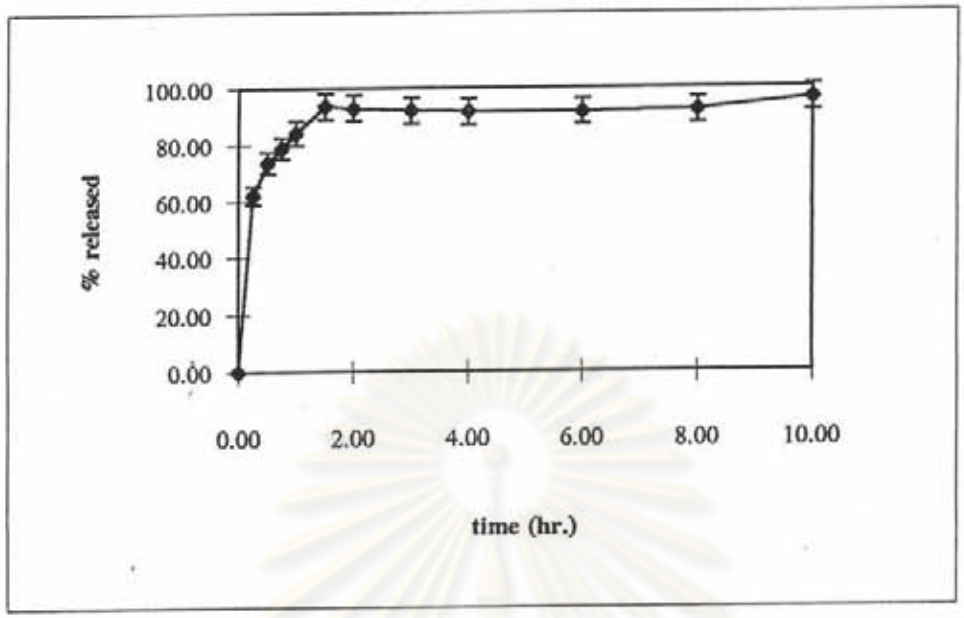


Fig. 126 : Dissolution profile of cephalexin released from 2:3 ERL:RS microcapsules prepared by spray drying technique, core: wall ratio is 2:1.

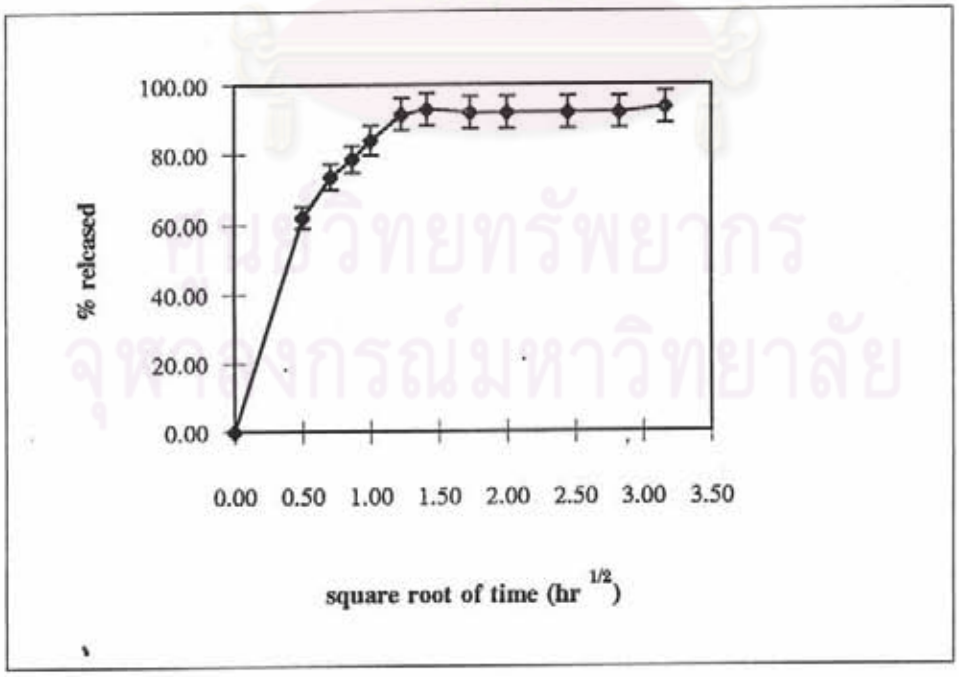


Fig. 127 : Higuchi's plot of cephalexin released from 2:3 ERL:RS microcapsules prepared by spray drying technique, core: wall ratio is 2:1.

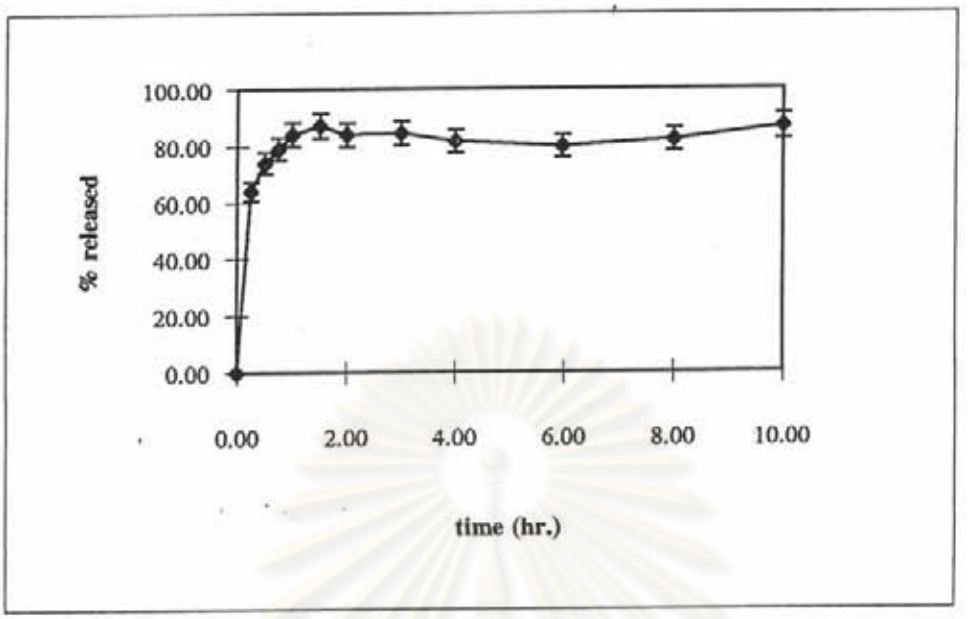


Fig. 128 : Dissolution profile of cephalexin released from 2:3 ERL:RS microcapsules prepared by spray drying technique, core: wall ratio is 1:1.

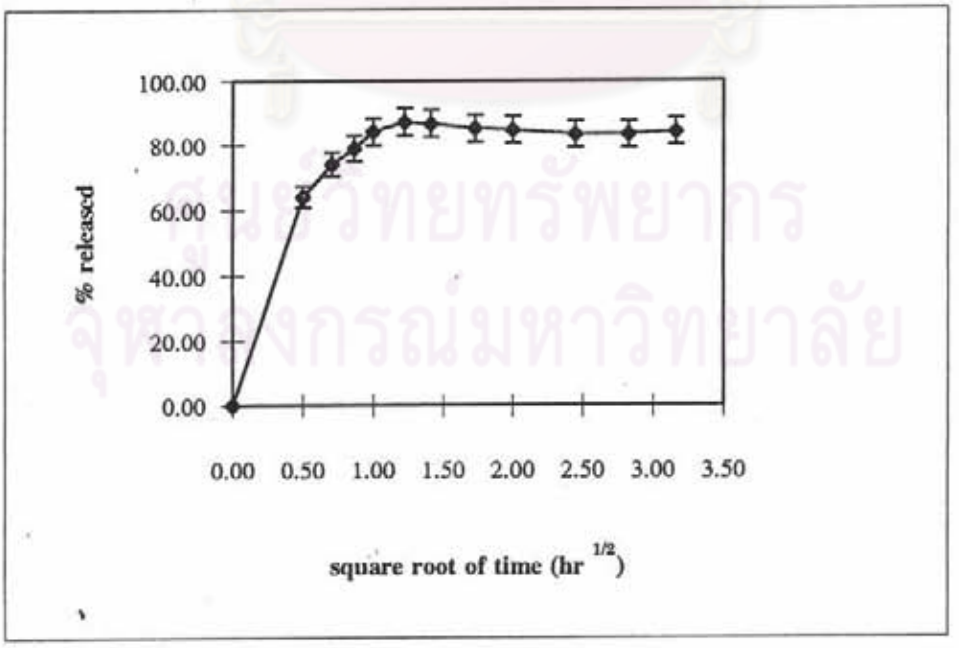


Fig. 129 : Higuchi's plot of cephalexin released from 2:3 ERL:RS microcapsules prepared by spray drying technique, core: wall ratio is 1:1.

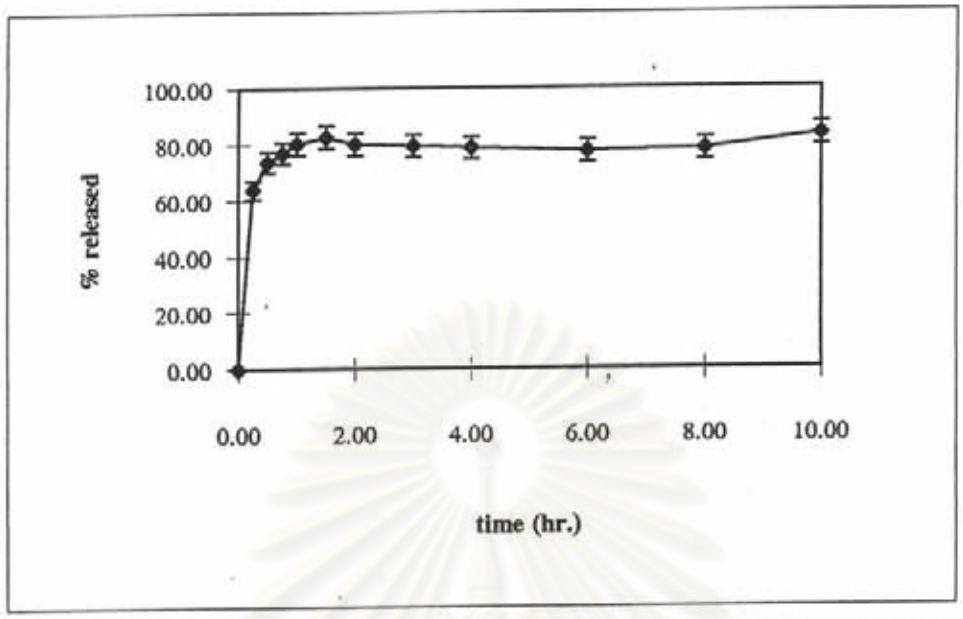


Fig. 130 : Dissolution profile of cephalexin released from 2:3 ERL:RS microcapsules prepared by spray drying technique, core: wall ratio is 1:2.

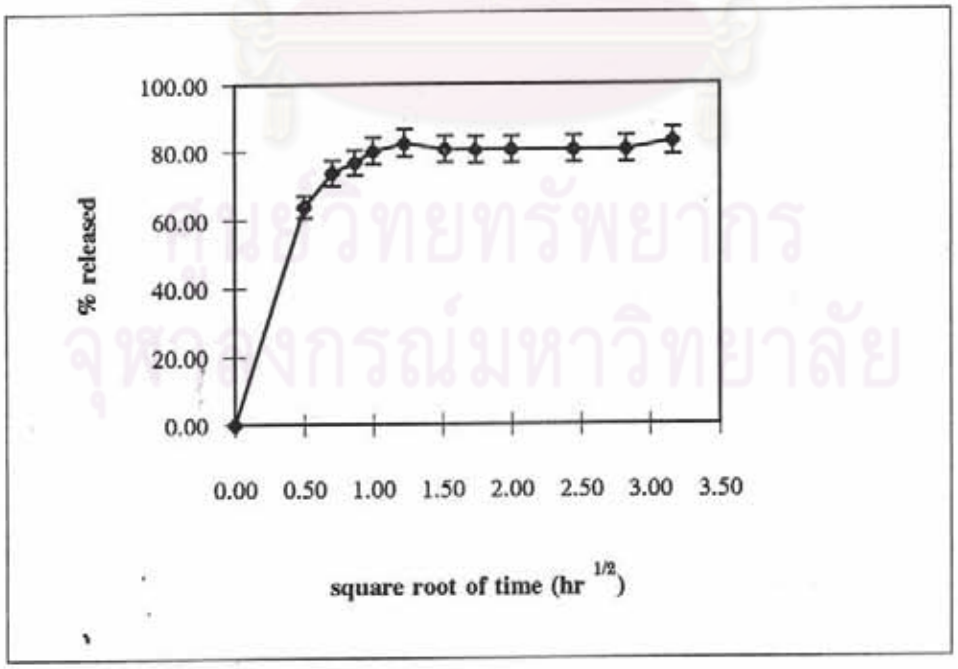


Fig. 131 : Higuchi's plot of cephalexin released from 2:3 ERL:RS microcapsules prepared by spray drying technique, core: wall ratio is 1:2.

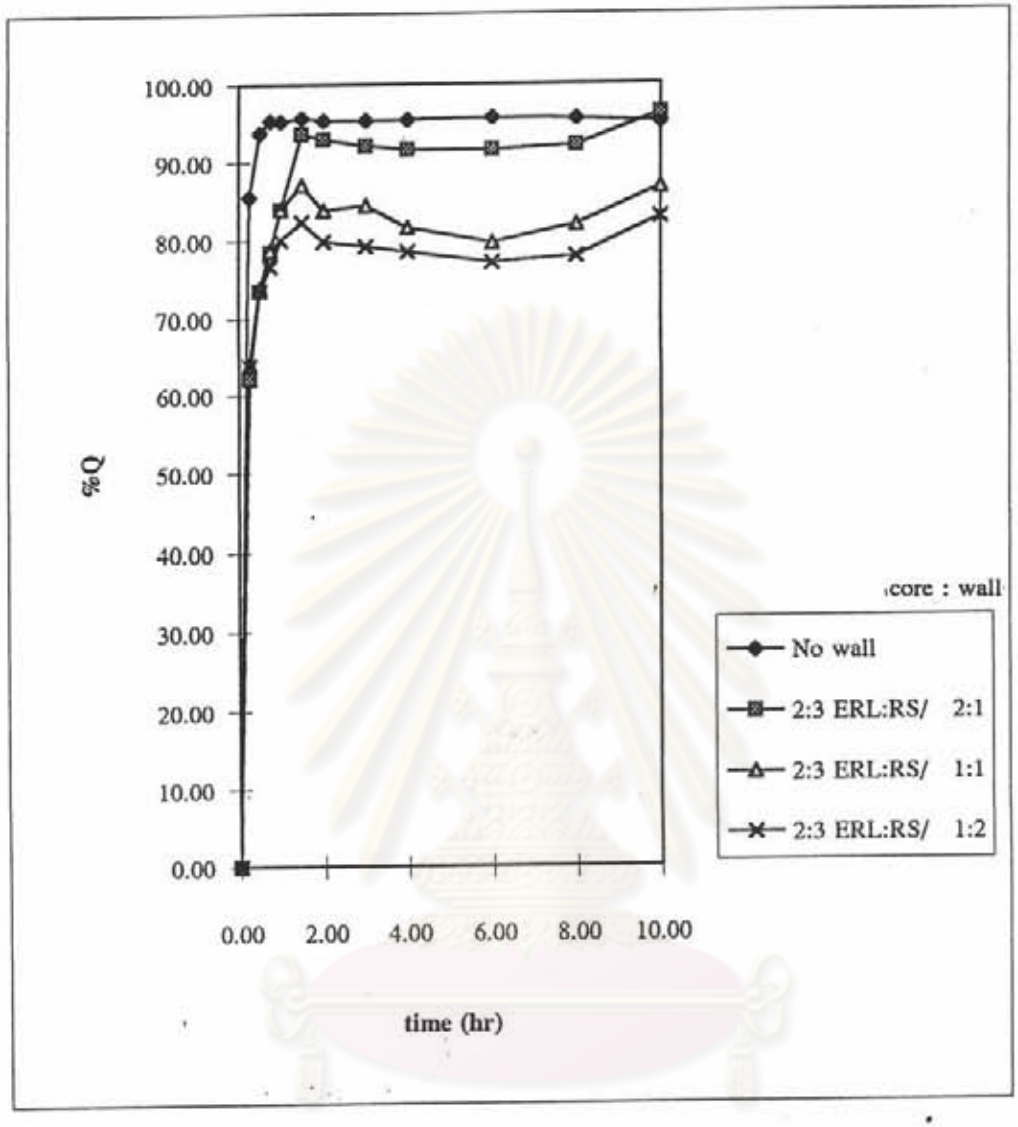


Fig. 132 : Dissolution profiles of cephalexin released from 2:3 ERL:RS microcapsules in various core: wall ratio prepared by spray drying technique.

Table 10 : Release rate of cephalexin from microcapsules, * Rate 1 : derived from slope of the ascending Higuchi's plot., $^{\Delta}$ Rate 2 : derived from the steady state of Higuchi's plot.

wall type	core : wall ratio	microencapsulation technique	rate 1*	rate 2$^{\Delta}$
Ethylcellulose	2:1	Coacervation	35.358	13.488
Ethylcellulose	1:1	Coacervation	10.884	20.434
Ethylcellulose	1:2	Coacervation	18.861	6.128
3:2 ERL:RS	2:1	Coacervation	64.849	2.841
3:2 ERL:RS	1:1	Coacervation	59.561	7.042
3:2 ERL:RS	1:2	Coacervation	46.919	13.308
2:3 ERL:RS	2:1	Coacervation	63.803	3.490
2:3 ERL:RS	1:1	Coacervation	51.375	7.761
2:3 ERL:RS	1:2	Coacervation	42.379	15.308
Ethylcellulose	2:1	Fluidization	71.183	-0.972
Ethylcellulose	1:1	Fluidization	47.482	-2.366
Ethylcellulose	1:2	Fluidization	41.756	1.469
3:2 ERL:RS	2:1	Fluidization	119.035	0.182
3:2 ERL:RS	1:1	Fluidization	94.417	0.157
3:2 ERL:RS	1:2	Fluidization	71.138	0.422
2:3 ERL:RS	2:1	Fluidization	99.231	0.588
2:3 ERL:RS	1:1	Fluidization	69.032	-1.512
2:3 ERL:RS	1:2	Fluidization	57.788	-2.443
Ethylcellulose	2:1	Spray drying	43.673	11.882
Ethylcellulose	1:1	Spray drying	47.151	6.546
Ethylcellulose	1:2	Spray drying	53.422	-0.850
3:2 ERL:RS	2:1	Spray drying	95.726	-0.752
3:2 ERL:RS	1:1	Spray drying	94.061	-0.421
3:2 ERL:RS	1:2	Spray drying	91.614	-0.465
2:3 ERL:RS	2:1	Spray drying	75.015	0.709
2:3 ERL:RS	1:1	Spray drying	71.009	-0.871
2:3 ERL:RS	1:2	Spray drying	66.881	-0.352

From table 10, rate 1 and rate 2 were shown when microcapsules were prepared by several wall types, core to wall ratio and microencapsulation techniques. The cephalexin released from ethylcellulose microcapsules gave a lower released rate than Eudragit microcapsules. Although ethylcellulose microcapsules have more porous than the Eudragit but the effect of the hydrophobicity of ethylcellulose which is very hydrophobic and very hard to wet, resulted in a slower penetration rate of dissolution medium into microcapsules and rate of cephalexin diffused through ethylcellulose membranes to the outside of microcapsules. In the case of Eudragit microcapsules, Eudragit is a polymer which was insoluble in water but accept water to permeate through it thus the faster of the water penetration through the polymer, the higher released rates were obtained. There were no significant differences of the release rate in the same wall type when using different microencapsulation technique ($p > 0.05$) and no significantly difference between using ethylcellulose and Eudragit microcapsules (both 3:2 and 2:3 RL:RS).

The same reason could be discussed in Eudragit RL 100® and Eudragit RS 100®. Eudragit RL 100® was owed higher water to penetrate through its membrane than Eudragit RS 100®. Which in turn Eudragit 3:2 RL:RS microcapsules will give a higher released rate than ERL:RS 2:3 microcapsules. The comparison of dissolution profiles are shown in Fig.133 when microcapsules were prepared by coacervation technique, Fig. 134 when microcapsules were prepared by fluidization technique and Fig. 135 when microcapsules were prepared by spray-drying technique.

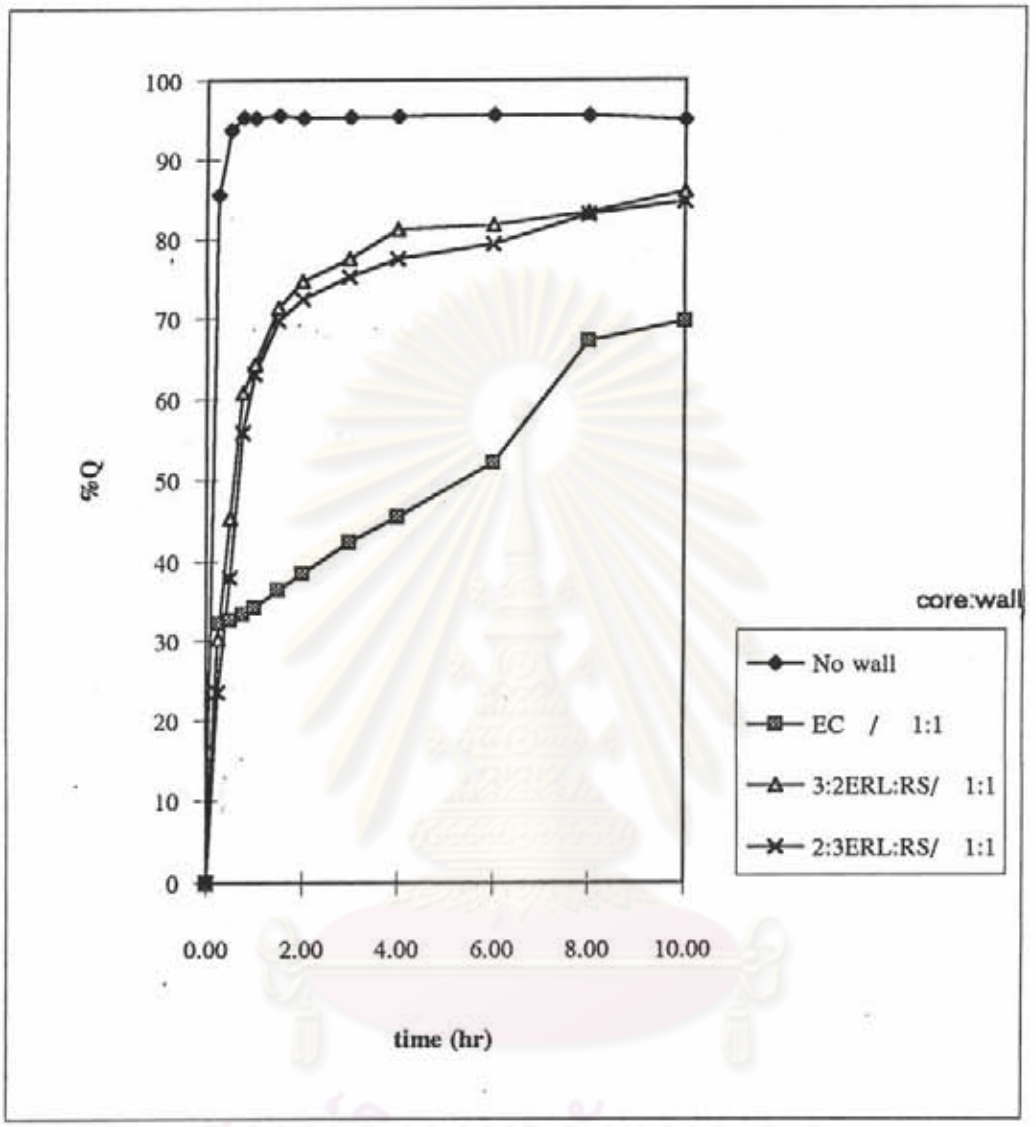


Fig. 133 : Dissolution profile of cephalexin microcapsules , core: wall ratio is 1:1, prepared by coacervation technique.

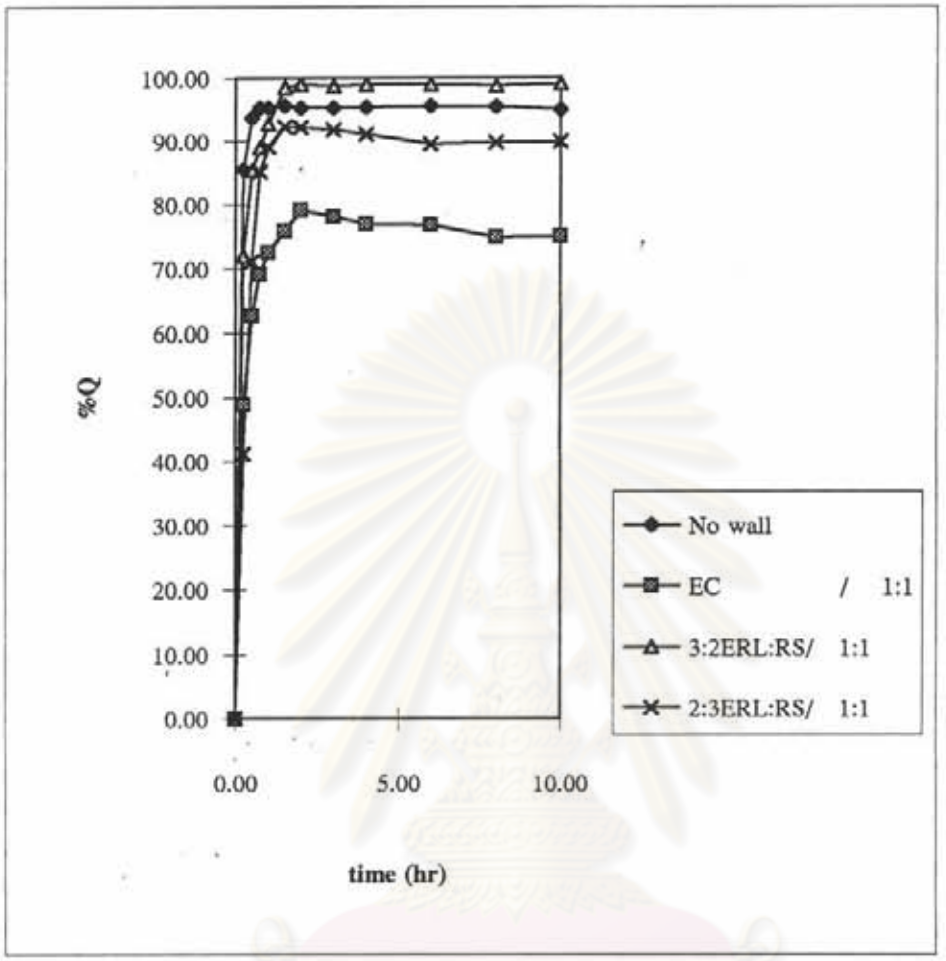


Fig. 134: Dissolution profiles of cephalexin microcapsules, core:wall ratio is 1:1, prepared by fluidization technique.

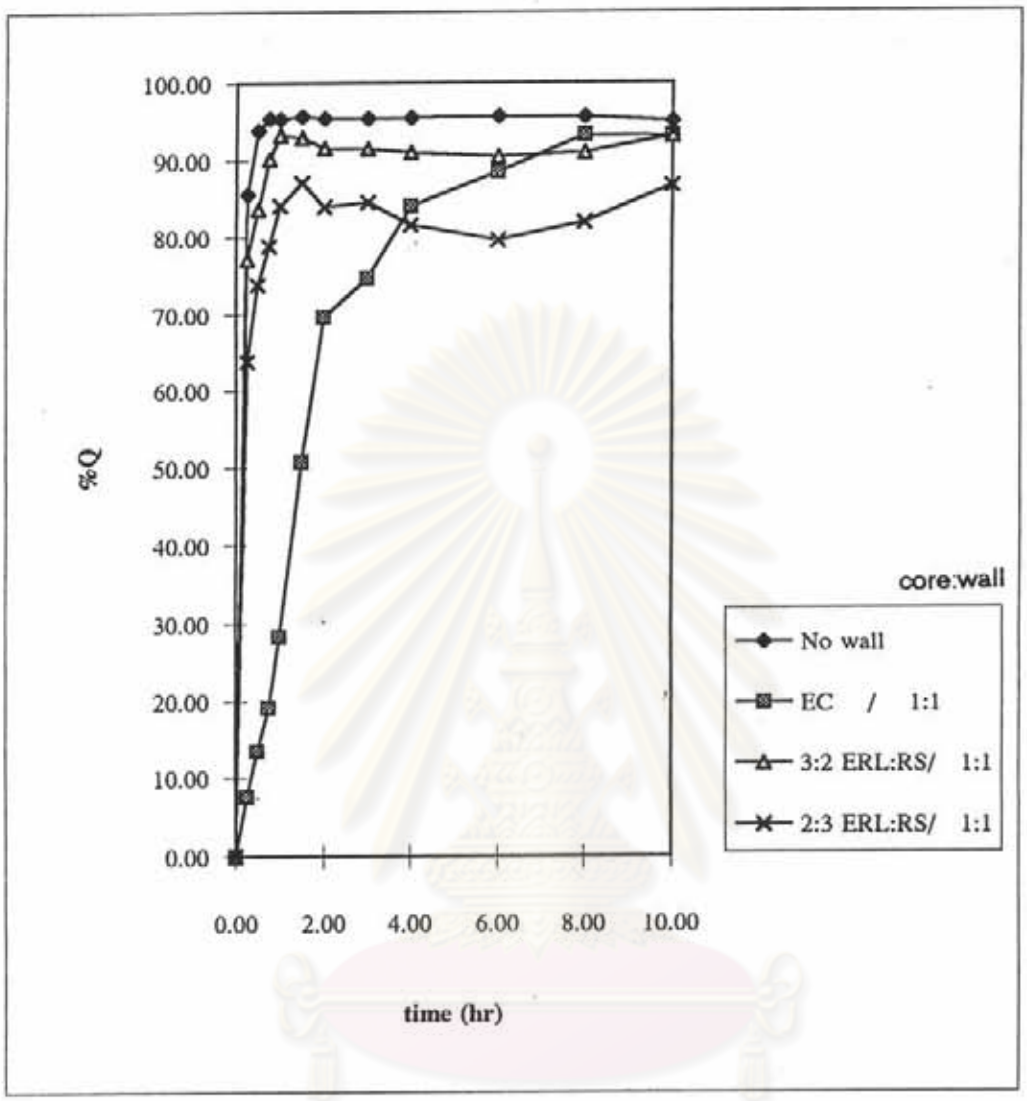


Fig. 135 : Dissolution profile of cephalexin microcapsules , core: wall ratio is 1:1, prepared by spray drying technique.

Most of Higuchi's plot of our study show no lag time. The reason of absence of lag time is the dissolved of unencapsulated cephalexin which cannot discharge from the microencapsulation process exhibits a present dissolution of cephalexin in the lag time period. The present of lag time can find in Fig. 96 which represent to the released profile of ethylcellulose microcapsules prepared by fluidization technique and core : wall ratio is 1:2. Because of the completely coated of this microcapsule, thus the release profile follow to the ideal Higuchi's plotted.

Rate 2 was very small because this rate is calculated from maintenance period of the core which has a little change in rate of diffusion of drug released from microcapsules.

While the ratio of core to wall decrease, the increment of deposition of wall materials will increase resulted in the released rate of cephalexin from microcapsules decreased. There were 2 reasons. The first is the pathlength from the surface of the microcapsule to the core of cephalexin will be increase when the amount of wall material increases. So that it takes more time for water to penetrate into core materials that make the release rate decreases. The second is the hydrophobicity of the polymer will cause more difficult for dissolution medium to penetrate when increase the amount of wall material. This effect was obviously seen in ethylcellulose microcapsules because ethylcellulose is very hydrophobic but scarcely change in Eudragit microcapsule because of its water permeability, thus the increment of wall material will prominently change the released rate if using hydrophobic polymer as wall material. Fig. 97, 104, 111 showed the dissolution profile of cephalexin microcapsules with respect to the difference in core : wall ratio but the same microencapsulation technique. It was fluidization which was

selected to represent because there are no significant difference between microencapsulation technique.

The released rate form ethylcellulose microcapsules which prepared by coacervation technique, 1:1 core : wall ratio is not follow the rule. It can be discussed that the particle size played a role for decreasing the release rate. Because of their larger in particle size than 2:1 and 1:2 core to wall ratio microcapsules, thus there are much more the length of the path not only the time when they take dissolution medium diffuse into microcapsules core but also the pathway of the cephalexin dissolved pass through the barrier to the surrounding of microcapsules.

Among 3 different microencapsulation techniques, coacervation technique gives the lowest released rate because the final products of this technique are coalesced together occurring in drying process. It take more time for water to penetrate into aggregation of microcapsules. They have to separate as a single microcapsule before dissolution medium penetrated into microcapsules so it took more time to make cephalexin released from the core.

Fluidization technique and spray-drying technique gave a non-distinguishable released rate. From SEM fluidization technique gave the porous microcapsules which dissolution medium can penetrate through easily even though most of cephalexin crystals are coated. The spray drying technique gave a smooth and complete coated microcapsules but there are some particles have not been coated and some of polymer separated out. Thus, the dissolution of microcapsules prepared from both techniques gave an insignificant difference in dissolution rate in the same wall material and core : wall ratio.

The released rate of microcapsules which prepared by spray-drying technique were not related to the core : wall ratios. Because of the incomplete coated of cephalexin. It exhibited nearly the same as the release of cephalexin instead of microcapsules. Thus released rates were not corresponded to the fact that the increment of wall materials would decrease the released rate of cephalexin from microcapsules.

From this study it found that microcapsules which prepared by fluidization technique give the good physical characteristics of microcapsules such as free flowing, task masking and complete coated. Above all this technique is easy to operate because it is a one step process. The released rate of microcapsules, prepared from this technique gave a good sustained release characteristics. Ethylcellulose gave the lowest released rate when using 1:2 core : wall ratio.

To improve the physical characteristics of microcapsules which prepared by coacervation technique, the rate of cooling and drying process should be concerned. It should be better to dry under air stream in order to prevent coalescence aggregation like spray-drying method. The problem about coalescence of microcapsule particles during drying process can be solved. Adding of lubricant or glidant should be avoid because they can interfere the released process.

Spray drying technique give a smooth surface of microcapsules but most of cephalexin is not coated. The resolution of this problem is using the larger nozzle size and use the higher concentration of coating polymer because at the time which the droplet is sprayed, the coating polymer should have much enough quantity to coat the cephalexin crystal. The alternative to solve this problem is to select the solvent or solvent mixture which provide lower evaporated

rate to let the polymer deposit on the surface of drug. This method can develop for the drug which stable to heat and moisture. If the drug is sensitive, all factor should be concerned.