CHAPTER IV

RESULTS AND DISCUSSION

1. Selection of Hard Gelatin Capsule

In this experiment, hard gelatin capsule size 0 was selected for investigation due to the comparable size to that of Gravol® suppositories and it was the largest size capsule for pharmaceuticals. Although the bigger size was available, it was mainly used in veterinary practice. Hard gelatin capsule that was used in this study is classified into two groups.

1. Plain capsules: this simply designed type that is closed by slipping the cap parts over the body section. While the security of the closure can be strengthened by pressing. Cap 0® is the example of this type.
2. Self-locking capsules: this type is specially designed to ensure that the contents do not leak during processing, packing and distribution. Capsule locking was easily done by tightening the cap and body. Coni-snap®, Cap-lock® and Licaps® are the examples of this type.

The various types of capsule were filled with mineral oil, soybean oil, silicone oil, olive oil, MCT oil, IPM, PEG 400 and oleic acid. Leakage time was recorded when liquid droplet was observed on a sheet of absorbance paper (Barnwell et al., 1996) according to Figure 14. Each capsule was also recorded for the decreased weight to confirm this test every two days and are shown in Appendix A. From the preliminary study, it was established that many factor especially the humidity and temperature must be controlled because they directly affected the breaking of capsule shell. In this study, the suitable condition was 50±10 % RH and 30±5 ^{o}C. Each type of capsule showed the different leakage time as displayed in Figure 15-18.

It was obvious that Licaps® could provide the best result for the prevention of liquid leakage. Mostly, the vehicles did not leak within 30 days except IPM and PEG400.

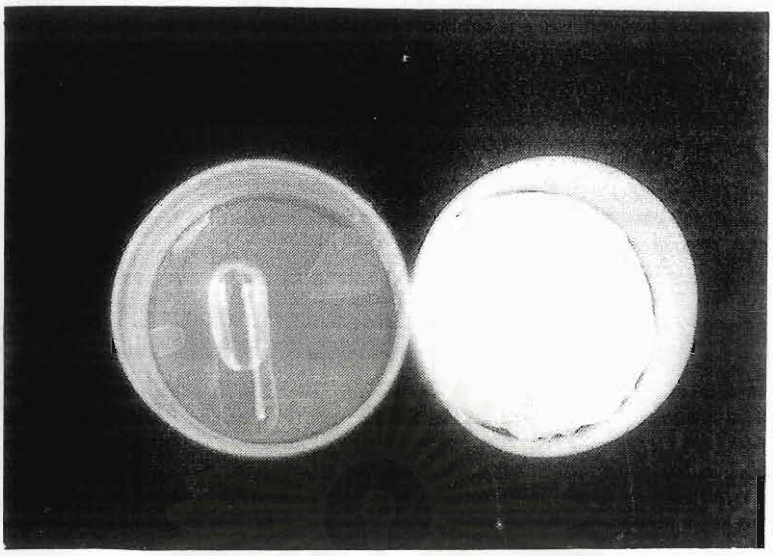
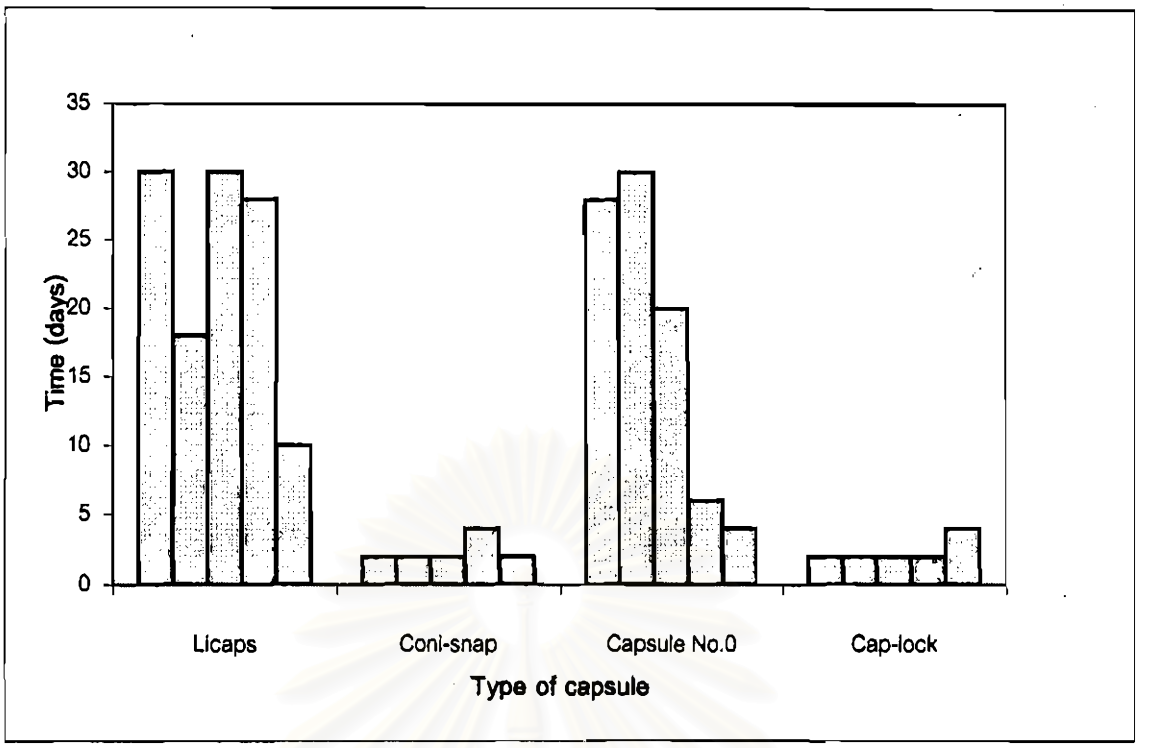


Figure 14 Picture of liquid leakage test; (left) leaked capsule,(right) unleaked capsule

This characteristic could explain due to special design of the capsule. Licaps® is intentionally designed for liquid-filling in hard gelatin capsule, as their features has longer body with no air-vent and include six dimples design maximized sealing zone. Licaps® is usually used in combination with the sealing equipment (Figure 5). Nevertheless, this type of capsule could give the best effect for reducing liquid leakage when compared to others. Cap 0® was found to resist leakage for 20 days whereas the self-locking type could not prolong the leakage time; mostly vehicle leaked after storage for 10 days. It was obvious that Cap 0® could prolong liquid leakage time better than Coni-snap® and Cap-lock®. Although it was simple design but the gap between cap and body part is closer than the self-locking type. In the case of Coni-snap® and Cap-lock®, they were designed to enhance locking between cap and body by consisting a pair of circumferential grooves that can reduce the reopen between cap and body but they are suitable only for solid product.

Although the results showed that Licaps® could reduce leakage time, it was not enough to prolong the prevention of all liquid vehicles for a long period time. Therefore, it was necessary to formulate the appropriate preparation to solve this problem.



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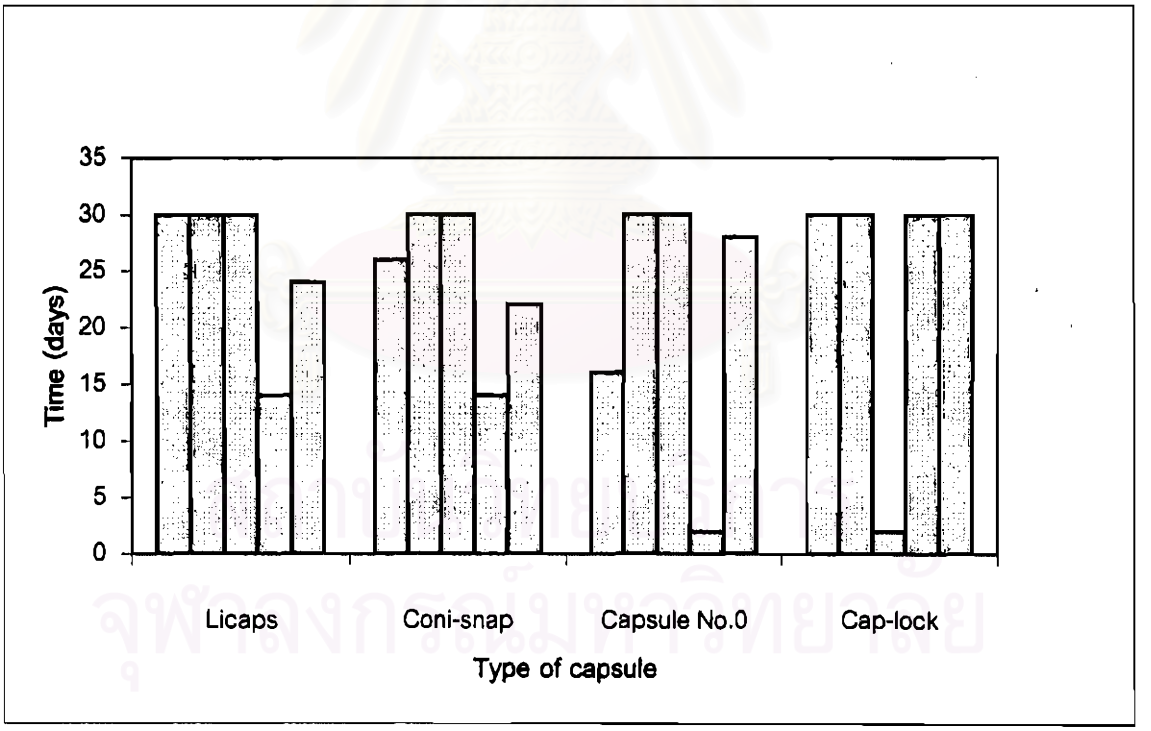
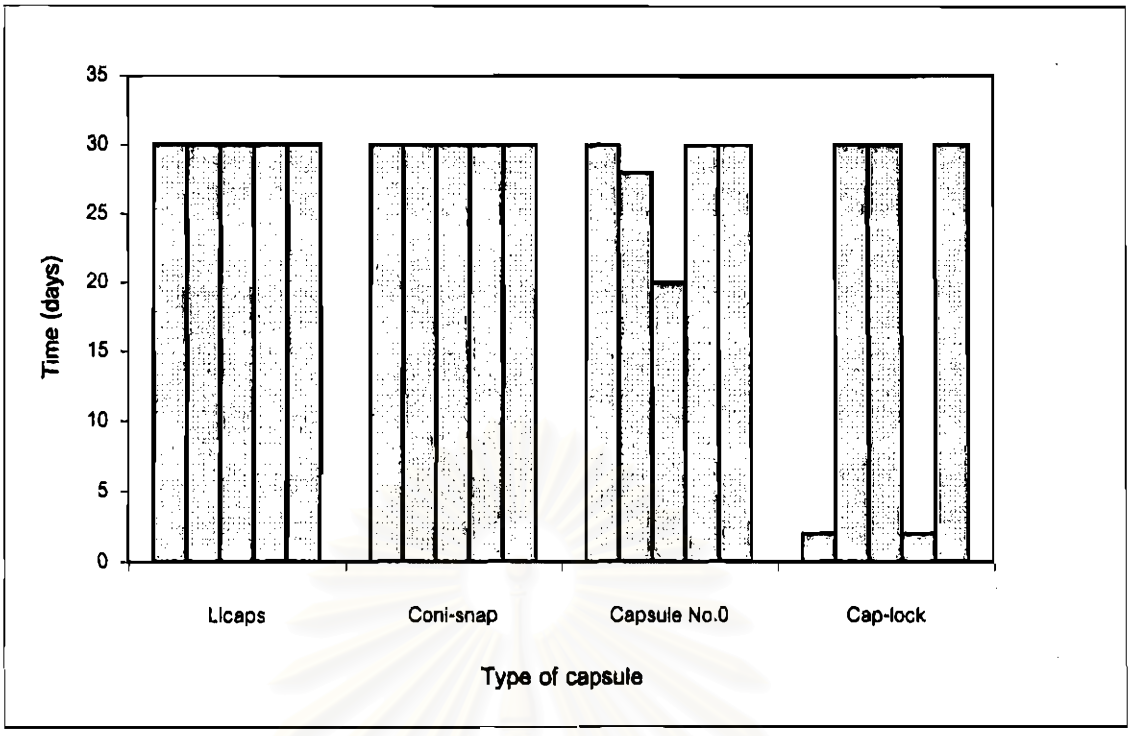


(b)

Figure 15 Leakage time of liquid vehicle from different types of hard gelatin capsules (Five capsules of each type were observed)

(a) Silicone oil (b) Olive oil



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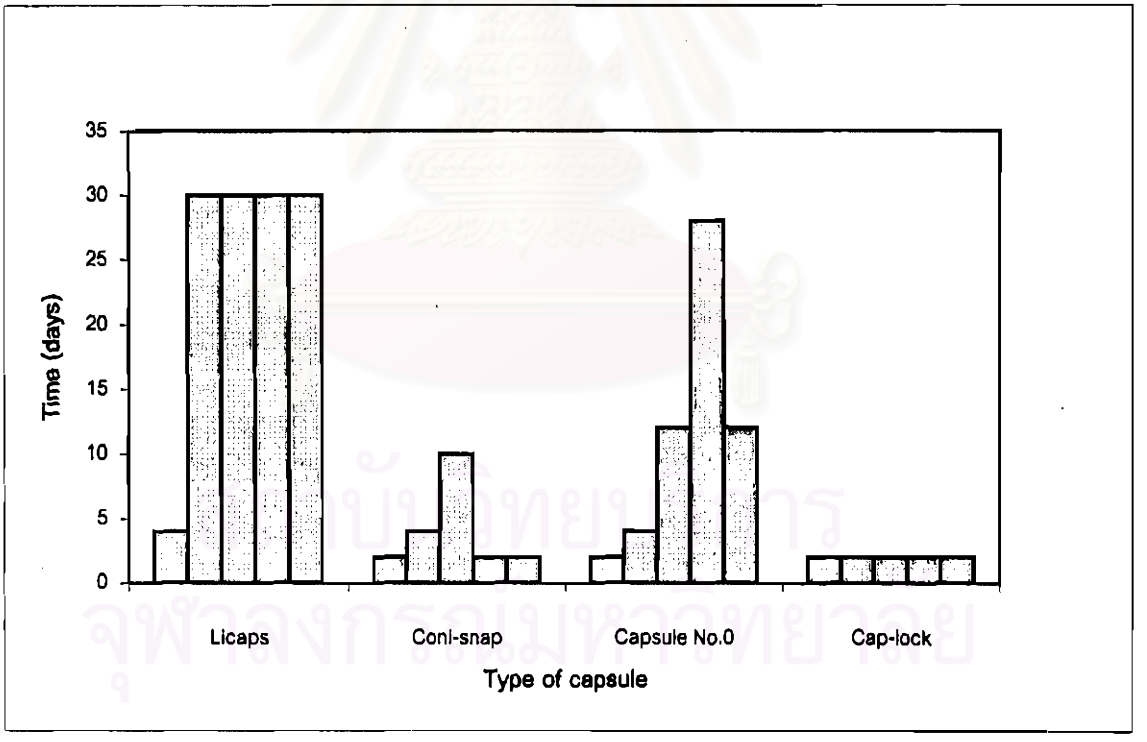
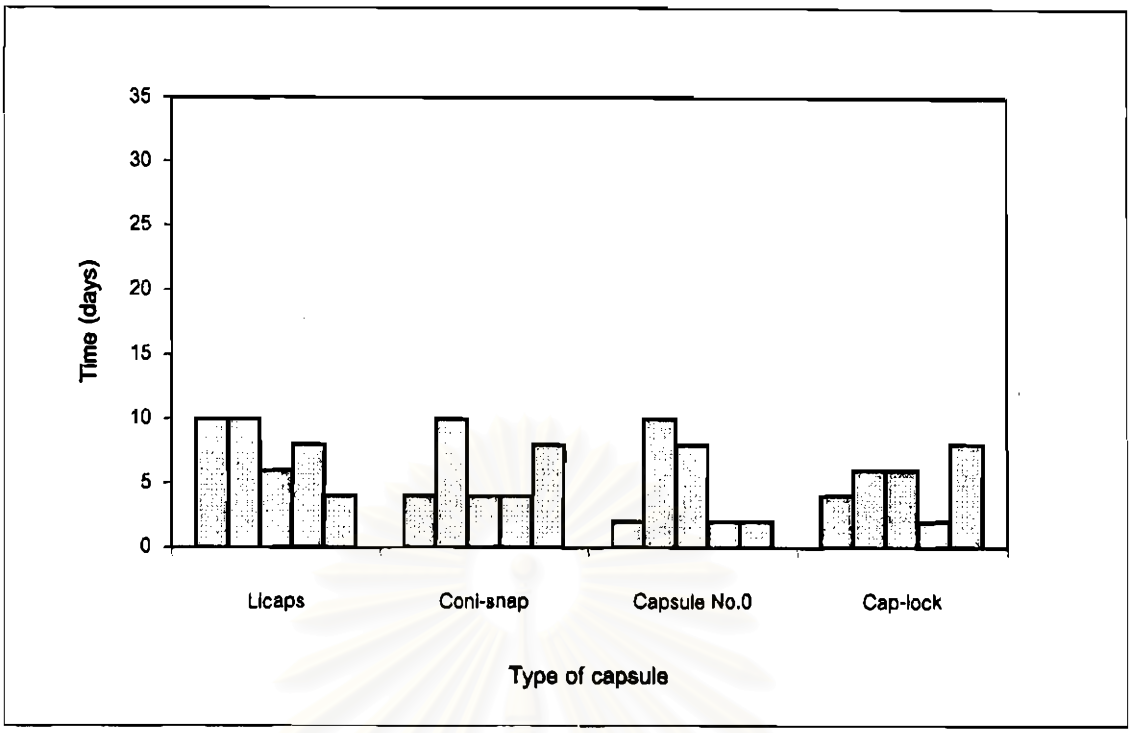


(b)

Figure 16 Leakage time of liquid vehicle from different types of hard gelatin capsules (Five capsules of each type were observed)

(a) Oleic acid (b) MCT oil



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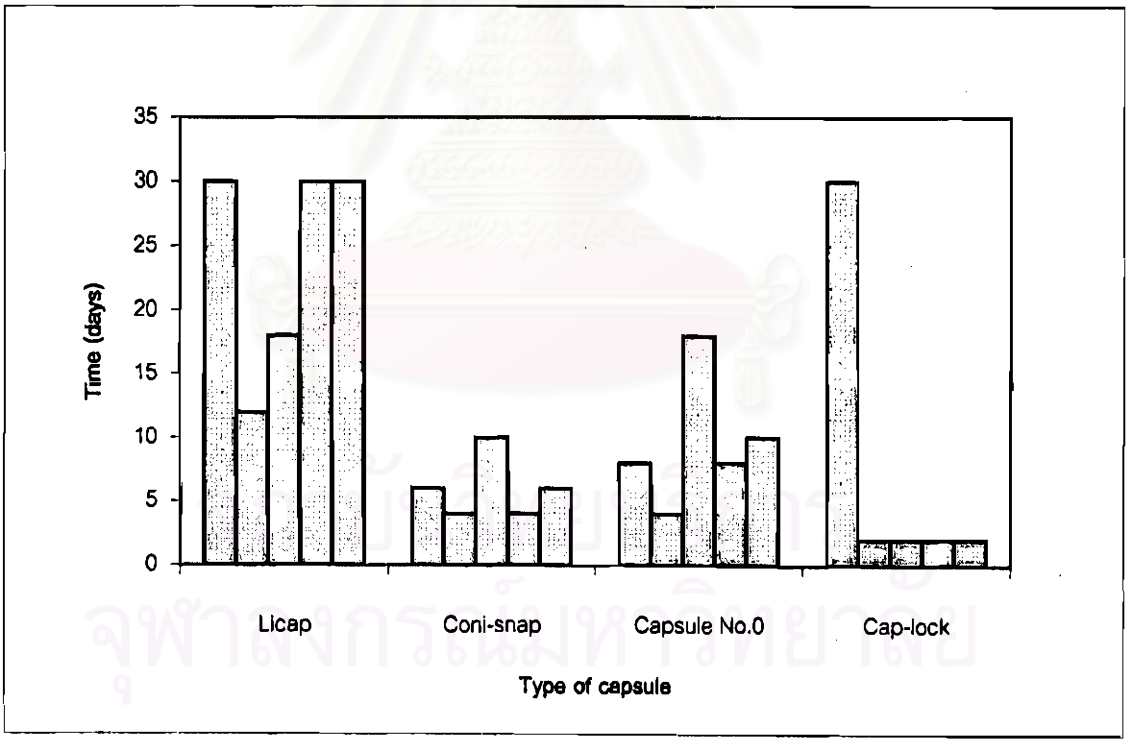
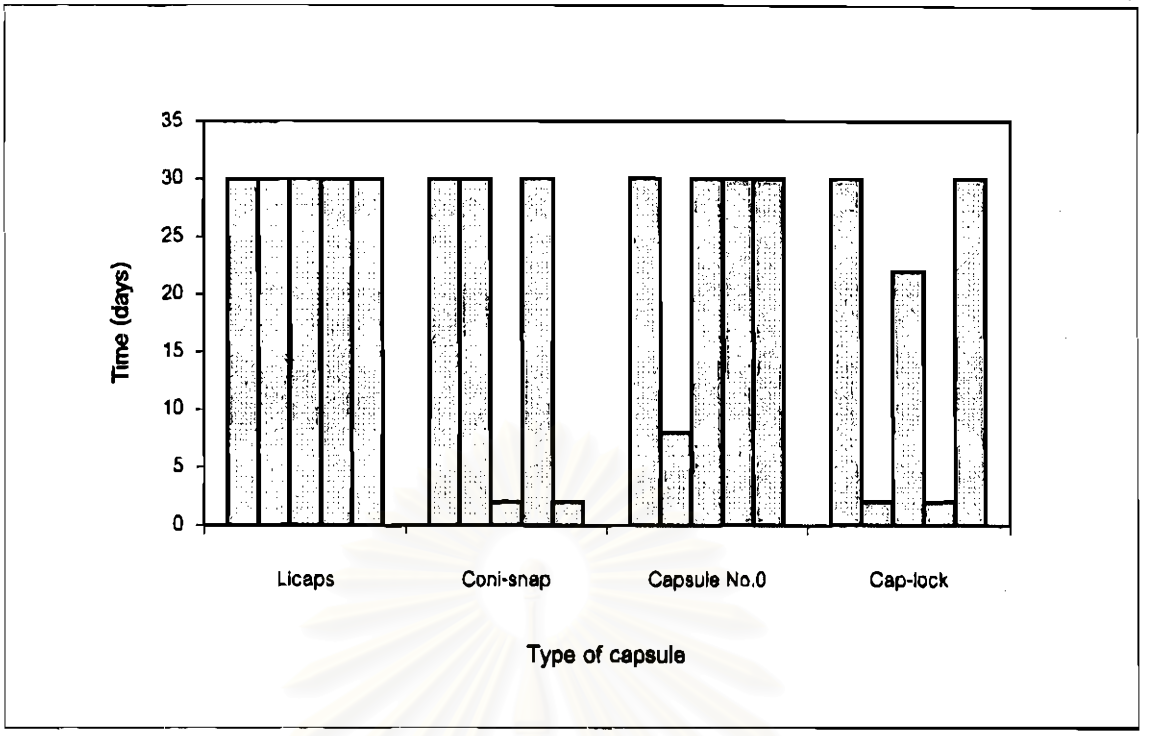


(b)

Figure 17 Leakage time of liquid vehicle from different types of hard gelatin capsules (Five capsules of each type were observed)

(a) PEG 400 (b) Mineral oil



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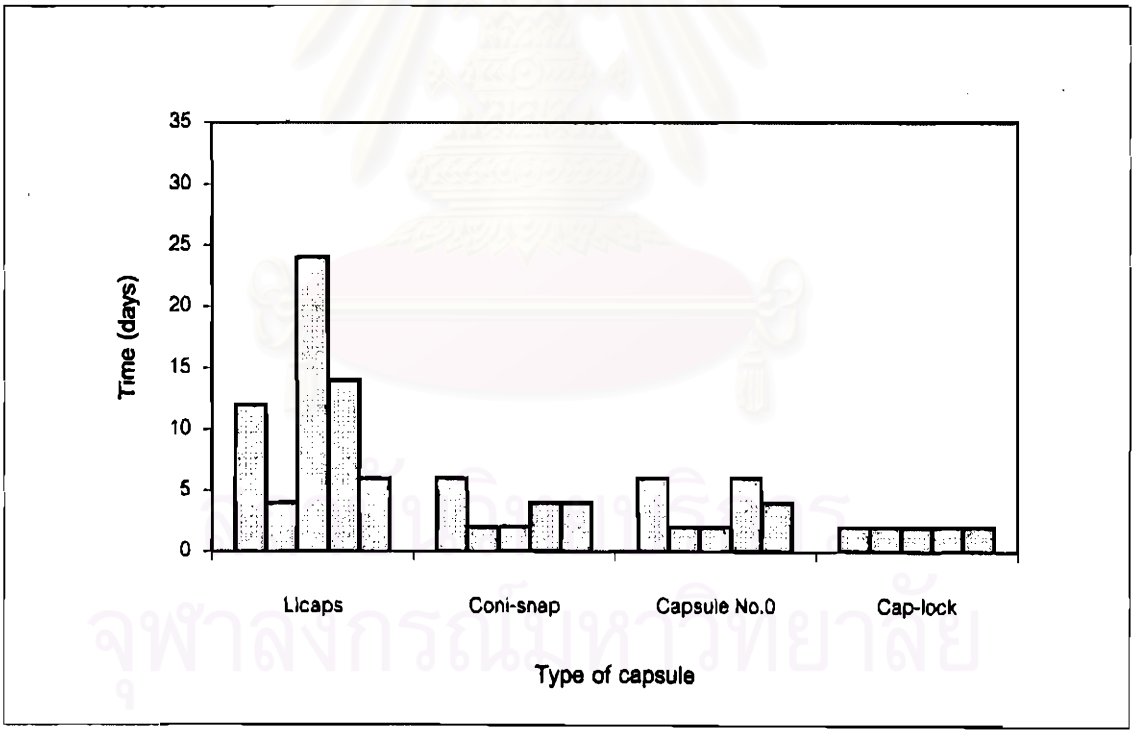

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Figure 18 Leakage time of liquid vehicle from different types of hard gelatin capsules (Five capsules of each type were observed)

(a) Soybean oil (b) IPM

2. Selection of Liquid Vehicle

2.1 Characterization of Moisture Sorption of liquid

Empty hard gelatin capsules have a tendency to gain or lose moisture as environmental conditions chang. Typically, hard gelatin capsule shells have optimum moisture content between 14-16% by weights. If moisture was reduced more than 2-3%, it might cause the shell to dehydrate and exhibit splitting characteristic when exposed to the external dryness and consequently lead to capsule leakage (Walker et al., 1992). On the other hand, if moisture in capsule shell increased more than 18% by weight, capsule might be softened, swollen and lose capacity to keep capsule rigidity or become stick together (Cade and Madit, 1996; Kontny and Mulski, 1989). Therefore, moisture uptake of liquid vehicle to be filled into capsule was one of the most important factors to be considered.

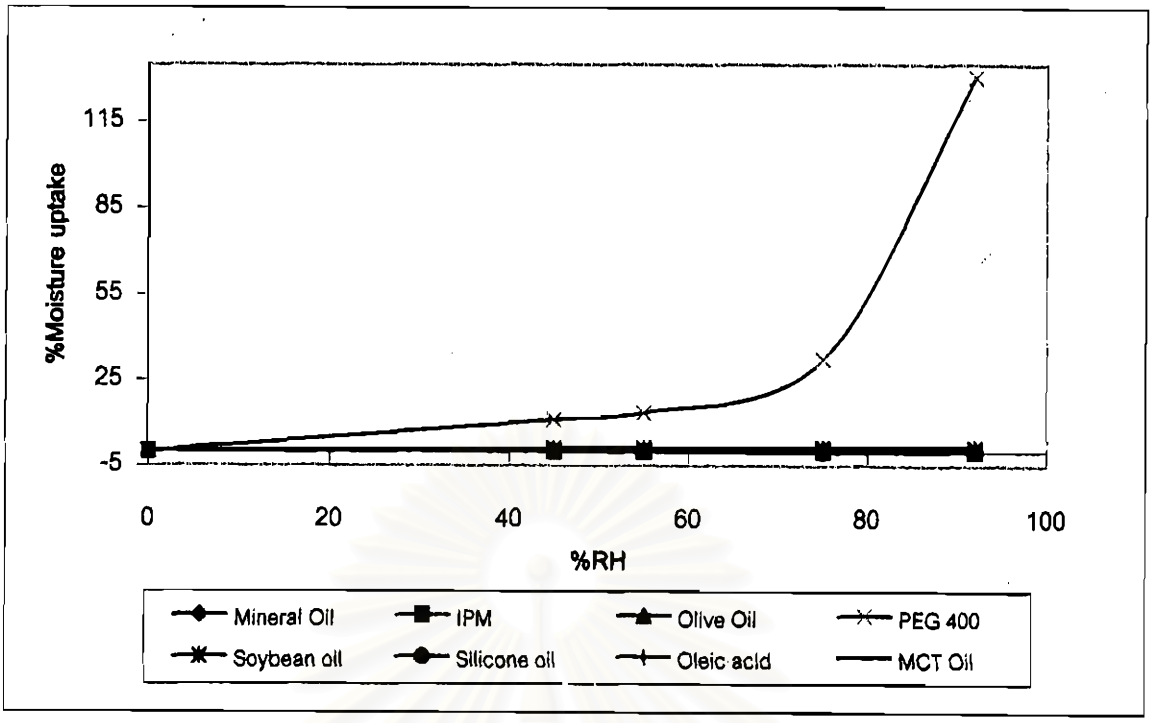
Gravimetric method has been defined to investigate the potential hygroscopicity of the filled excipients. Each liquid vehicle was filled into a glass vial that acts as non-absorption moisture container. The weights of liquid vehicle throughout the experiment were shown in Appendix A. The sorption isotherm of all liquid vehicle at the day thirtieth was compared and illustrated in Figure 19a. The result showed that PEG 400 was the only vehicle that had increased moisture content more than 10 % in all humidity within 30 days. The maximum water absorption was observed at 92 % RH, PEG 400 absorbed moisture more than 115 % (Figure 19a). The moisture uptake and tendency of leakage when storing at 75 % RH and 30^{o}C that used as common weather in tropical zone (Grimm, 1998) was shown in Table 8. It was indicated, that capsule filled with PEG 400, splitting would occur within two days. This effect was related to the fast leakage time of PEG 400 (see in Figure 26) and it was consisted with a previous study by Cole et al., 1989. It was concluded that glycerol, propylene glycol, sorbitol and low molecular weight of PEG that are commonly used in soft gelatin capsule, are too hygroscopic and unsuitable for being used as vehicle in liquid filled hard gelatin capsule production. All of oil vehicle expressed suitability as an excipient in the formulation for hard capsule because water exchange was limited to $\pm$2% under test condition and it did not alter

Table 8 Moisture uptake(%w/w) and prediction time to capsule leakage at 75% RH, 30 ^{o}C

Type of liquid	Moisture uptake (%w/w)	Time (days)
PEG 400	12.58	< 2
Mineral oil	0.05	> 30
IPM	0.05	> 30
Olive oil	0.30	> 30
Soybean oil	1.43	> 30
Silicone oil	-0.10	> 30
MCT oil	0.24	> 30
Oleic acid	0.59	> 30

capsule shell properties within 30 days. Figure 19b demonstrates the sorption isotherm of various oil vehicles which displayed the different pattern of sorption characteristics. Moisture uptake of some vehicle, i.e., soybean oil, olive oil, oleic acid and MCT oil showed tendency to increase in moisture absorption when storage time was longer, whereas silicone oil, mineral oil and IPM express less than 0.06 % of moisture uptake. This result was clearly observed as illustrated in Figure 20-23; the moisture absorption was higher especially at higher relative humidity. It might cause capsule shell splitting later particularly soybean oil that moisture increased more than one percent within 30 days (Figure 20-21). In the case of IPM, mineral oil and silicone oil, they almost unchanged moisture uptake all conditions (Figure 22-23).

The behaviors of natural oil in moisture sorption were anticipated that these vehicles contained more than single substance in the component and some of them might cause hygroscopic effect. MCT oil was lipid fraction of coconut oil, the major component were triglycerides of 8 and 10 carbon atoms of saturated fatty acid. Most of the compound were octanoic acid (C8, 67%), decanoic acid (C10, 23%) compounds, shorter than C8 was found to be less than 6% and longer than C10 less than 4%. The majority components of olive oil composed of mixed glycerides of oleic acid (83.5%),



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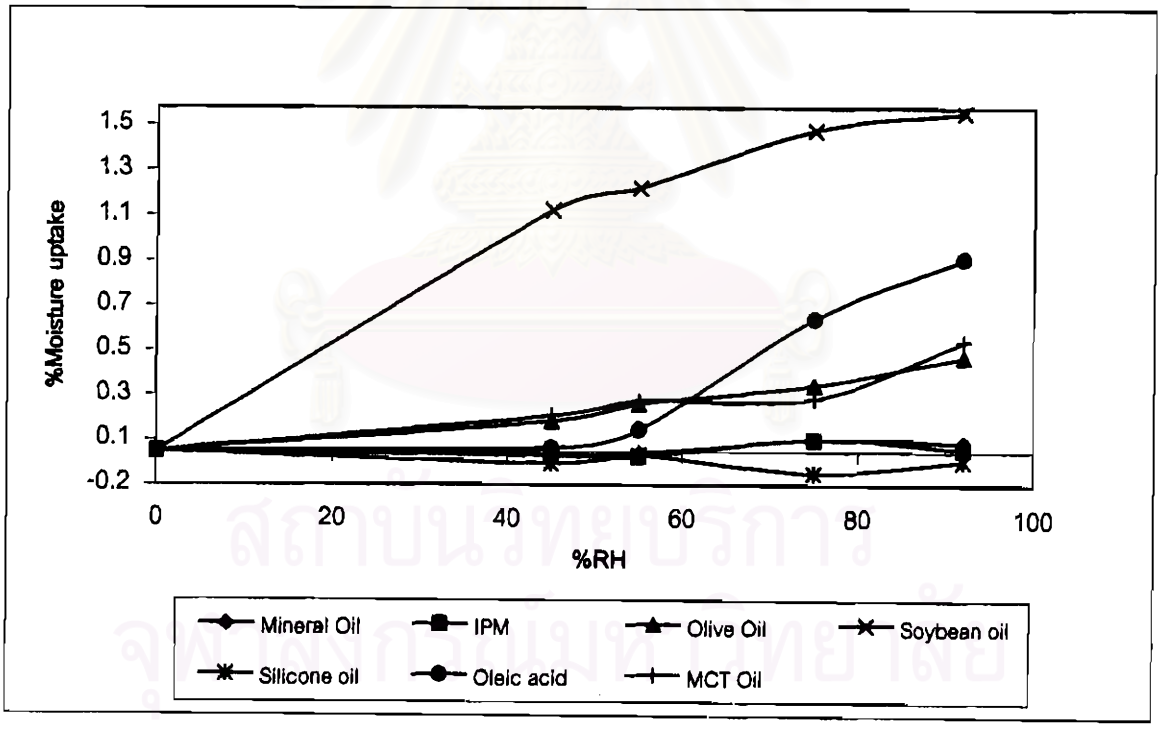
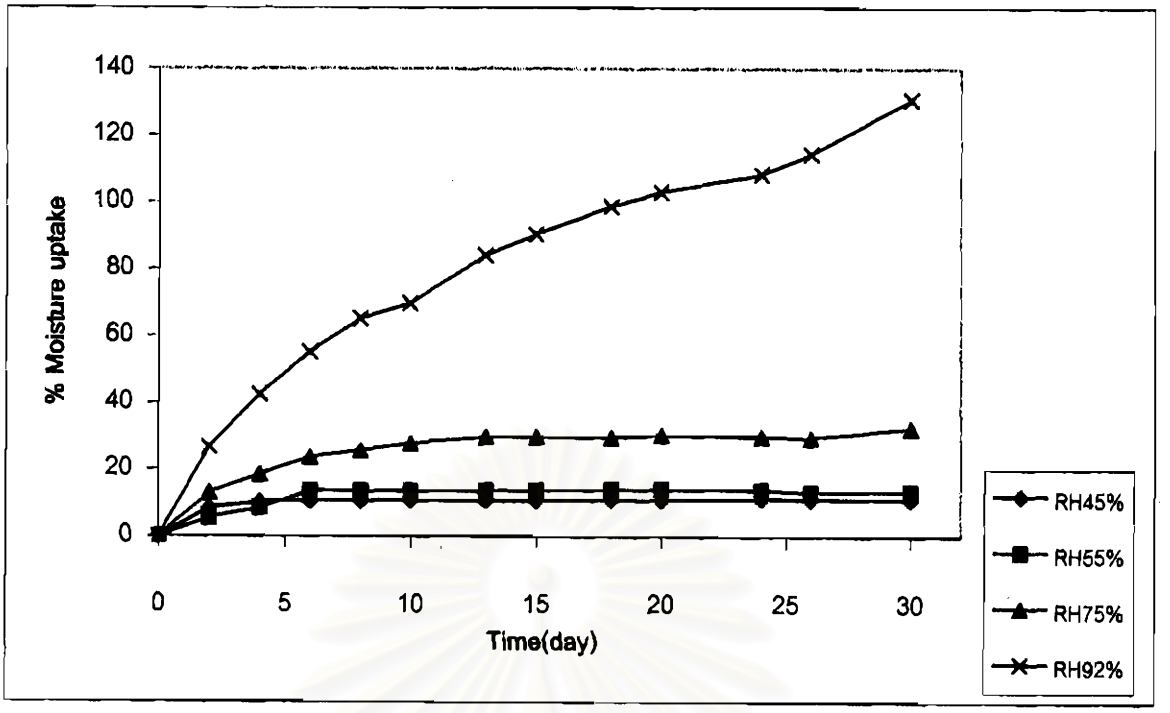


(b)

Figure 19 Sorption isotherm of liquid vehicle, storing in 45, 55, 75, 92% RH at 30^{o}C

(a) All liquid vehicle (b) Oily vehicle



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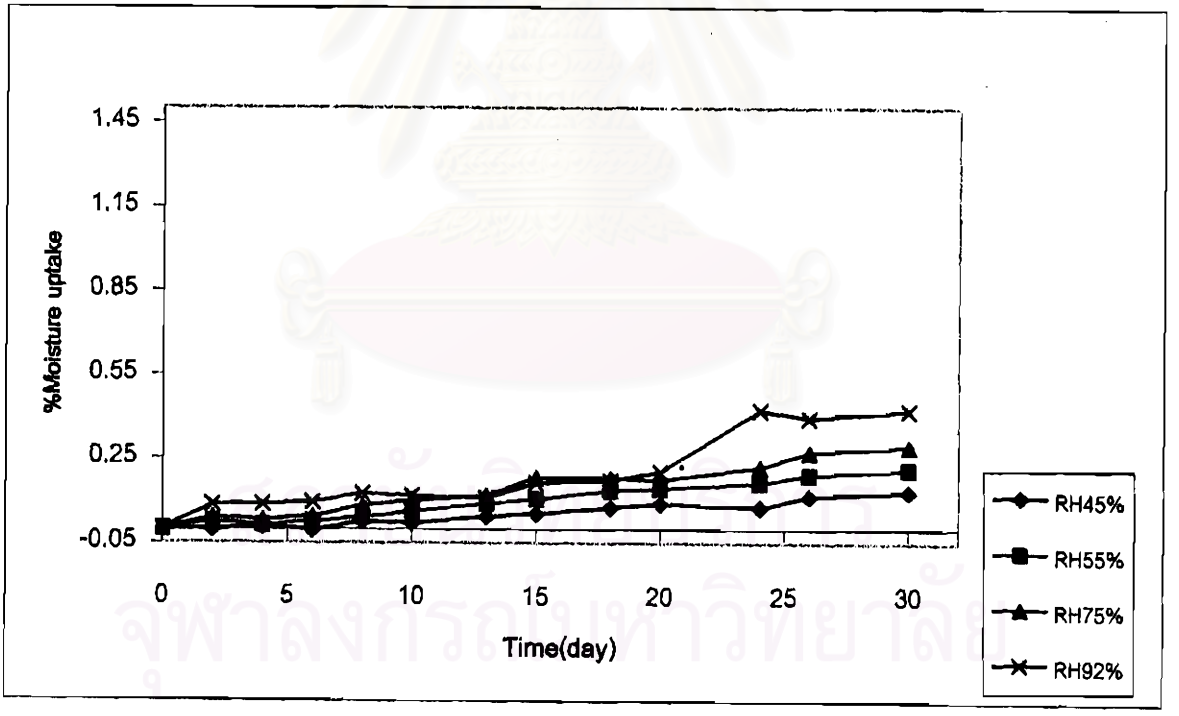
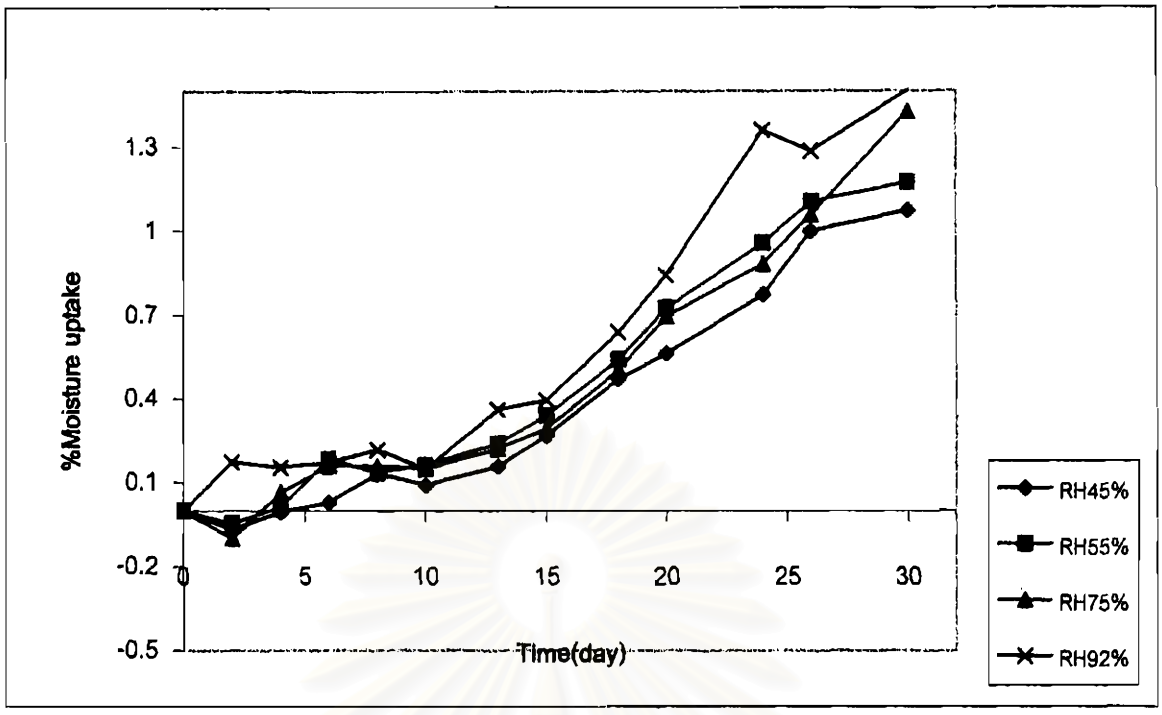


(b)

Figure 20 Moisture sorption of liquid vehicle, storage at 45, 55, 75, 92%RH at 30^{o}C

(a) PEG 400 (b) Olive oil



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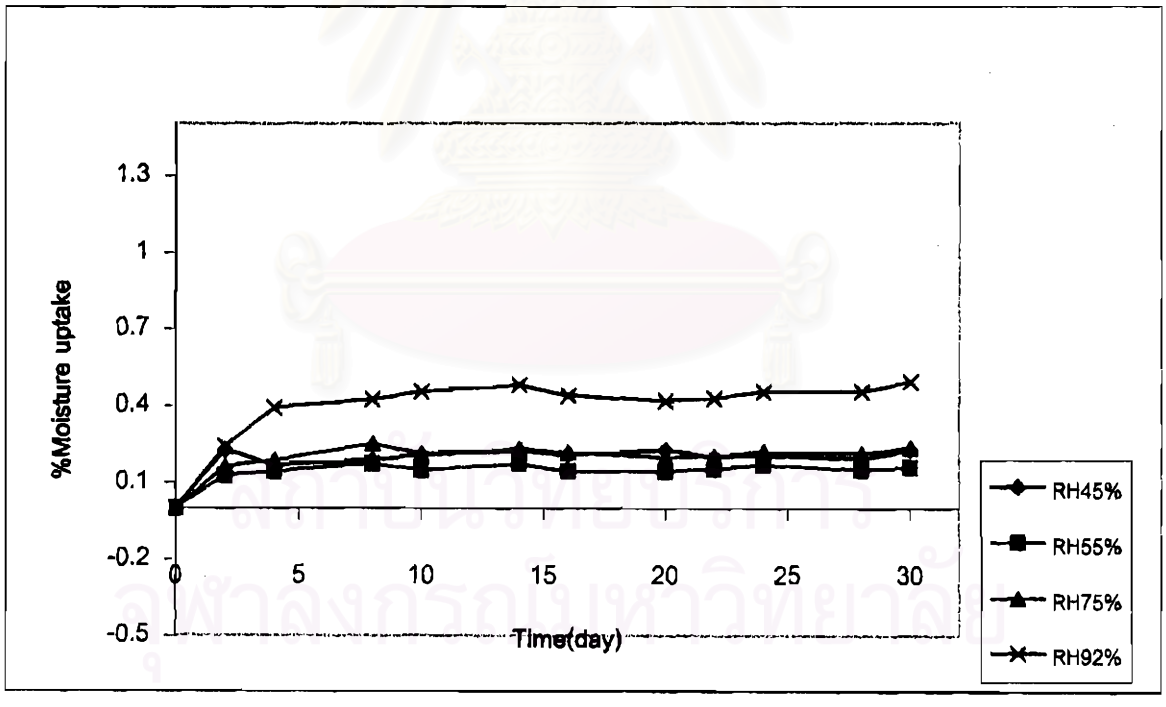
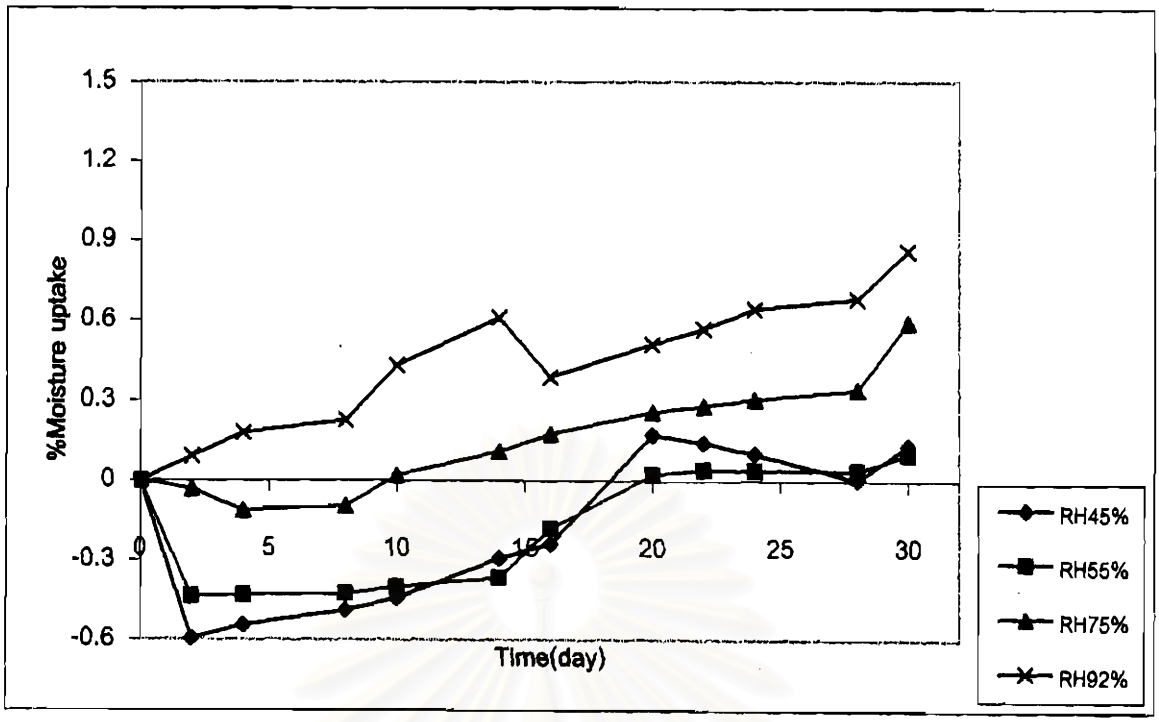


(b)

Figure 21 Moisture sorption of liquid vehicle, storage at 45, 55, 75, 92%RH at 30^{o}C

(a) Soybean oil (b) MCT oil



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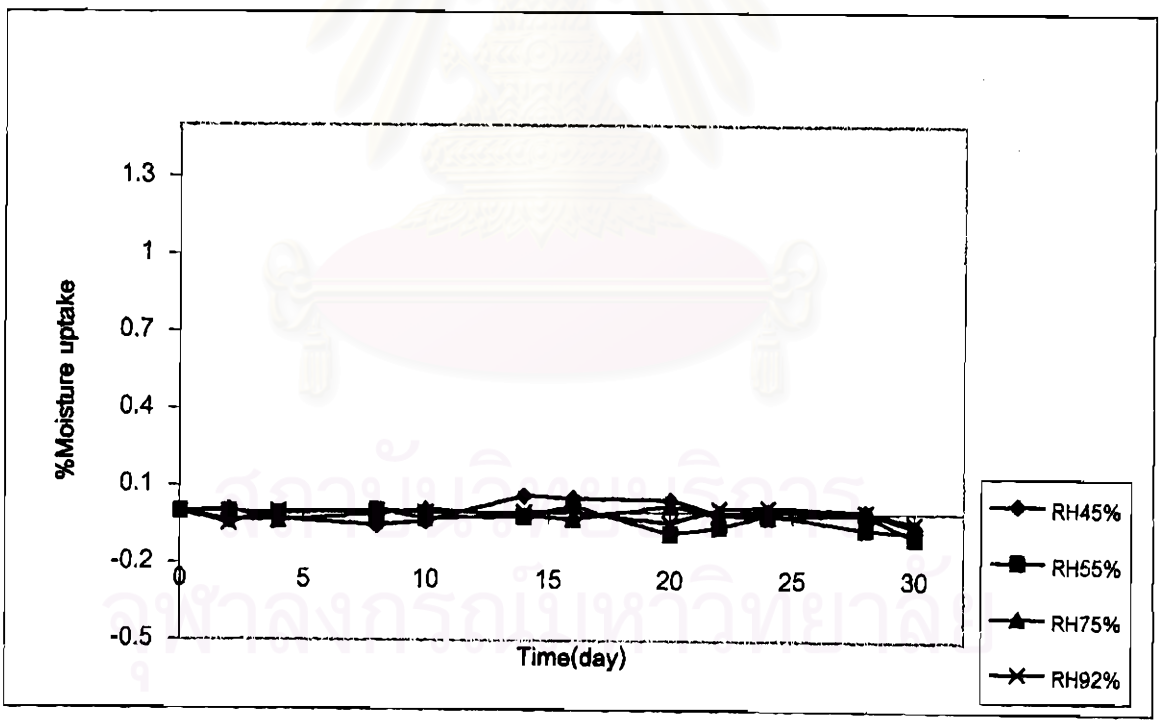
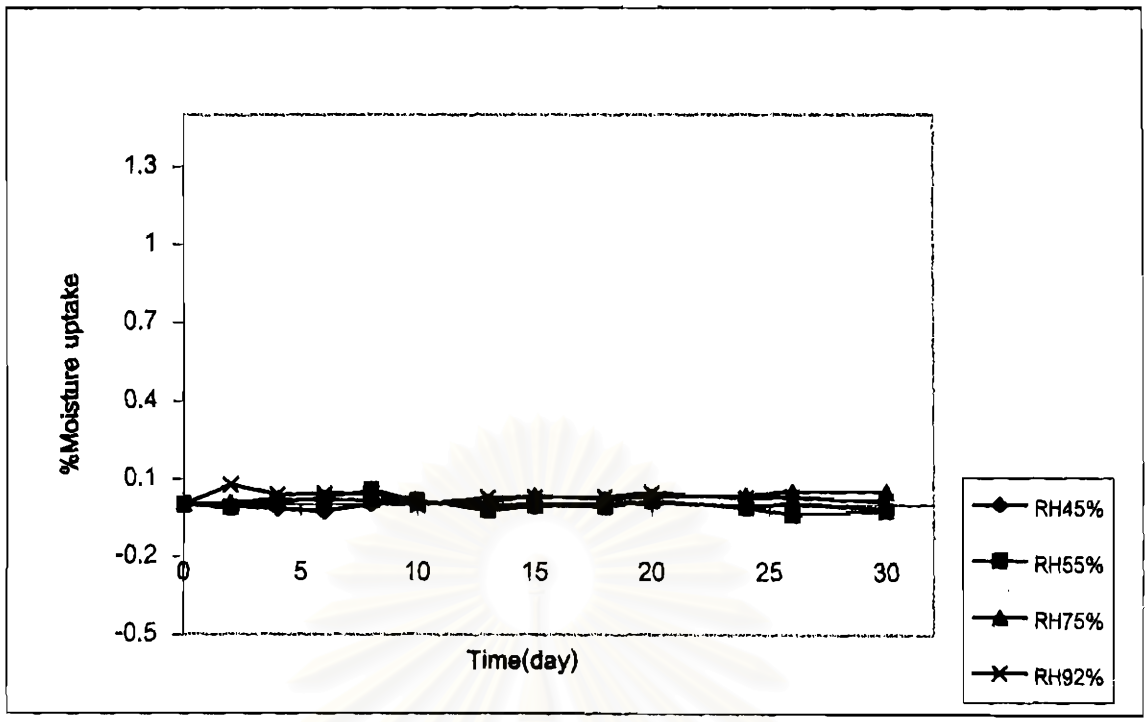


(b)

Figure 22 Moisture sorption of liquid vehicle, storage at 45, 55, 75, 92%RH at 30°C

(a) Oleic acid (b) Silicone oil



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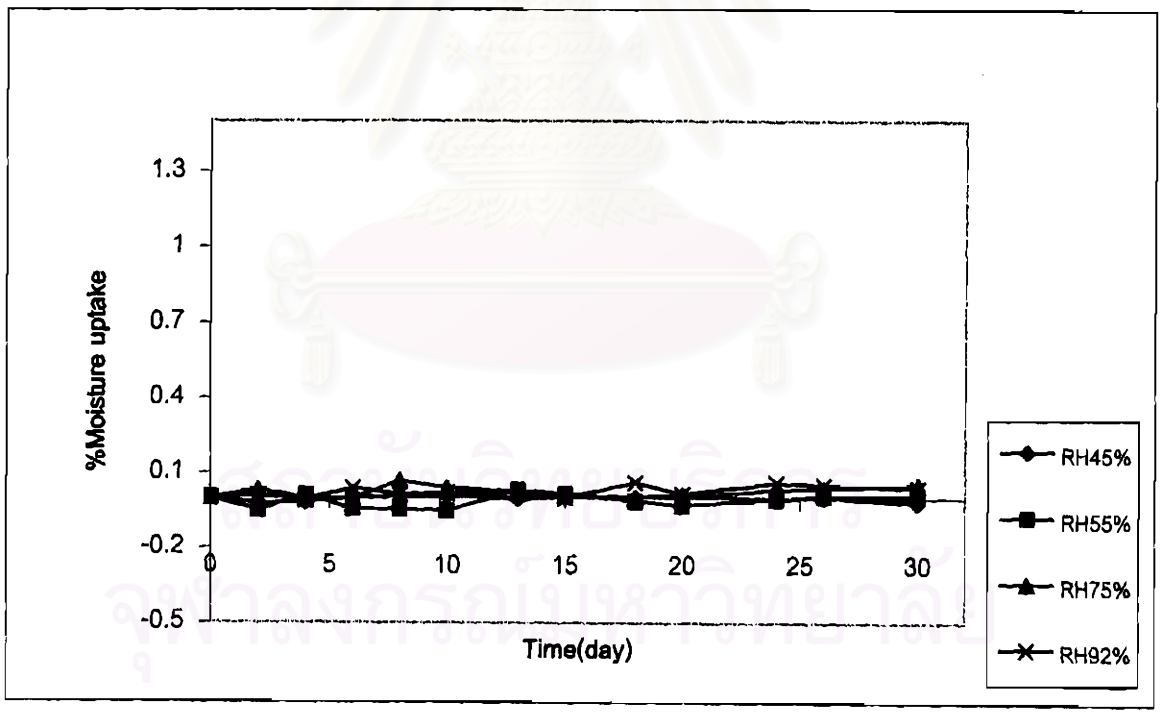


(b)

Figure 23 Moisture sorption of liquid vehicle, storage at 45, 55, 75, 92%RH at 30°C
(a) IPM (b) Mineral oil

palmitic acid (9.4%), lenolieic acid (4.0%), stearic acid (2%), arachidonic acid (0.9%). Minor constituents were squalene (up to 0.7%), phytosterol and tocopherol about 0.2%. Soybean oil composed of triglycerides of oleic acid (26%), linoleic acid (49%), lenolenic acid (11%), saturated fatty acid (14%), free fatty acid (less than 1%), phospholipid(1.5-4%). Other constituents were stimasterol, stiosterol and tocopherol (0.8%) (Merck Index, 1996).

Decomposition of natural oil may be another reason for the hygroscopicity. Since natural oil can be oxidized when exposed to oxygen and air, causes impurity substance to occur (Walker et al., 1992). It was observed that the color of natural oil becomes darken when storage for 30 days especially when kept at high humidity condition. The oily vehicles, i.e., IPM, mineral oil and silicone oil which contained only single component, were more stable than natural oil that usually composed of many constituents. They had lower hygroscopic property and did not cause capsule splitting. These groups were therefore considered for further investigation.

2.2 Viscosity

The viscosity of liquid vehicles are shown in Figure 24. Mineral oil had the highest viscosity and IPM had the lowest, however the viscosity of all vehicles was lower than 300-600 mPa.s which was the recommended value for filling suspension into hard gelatin capsule. This viscosity was almost constant and the newtonian rheological behavior was observed in shear flow within the normal ranges of testing temperature. Hence, all vehicles must be adjusted to achieve the desired viscosity and changed the rheologram to thixotropic behavior.

2.3 Surface Tension

The role of surface tension involved liquid happening between cap and body overlap. Although it was not fully understood in their mechanism about filling and leakage processes but the appropriate value of surface tension for liquid filled in capsule should be over 30 mNm^{-1} (Walker, 1992). The result of surface tensions in this

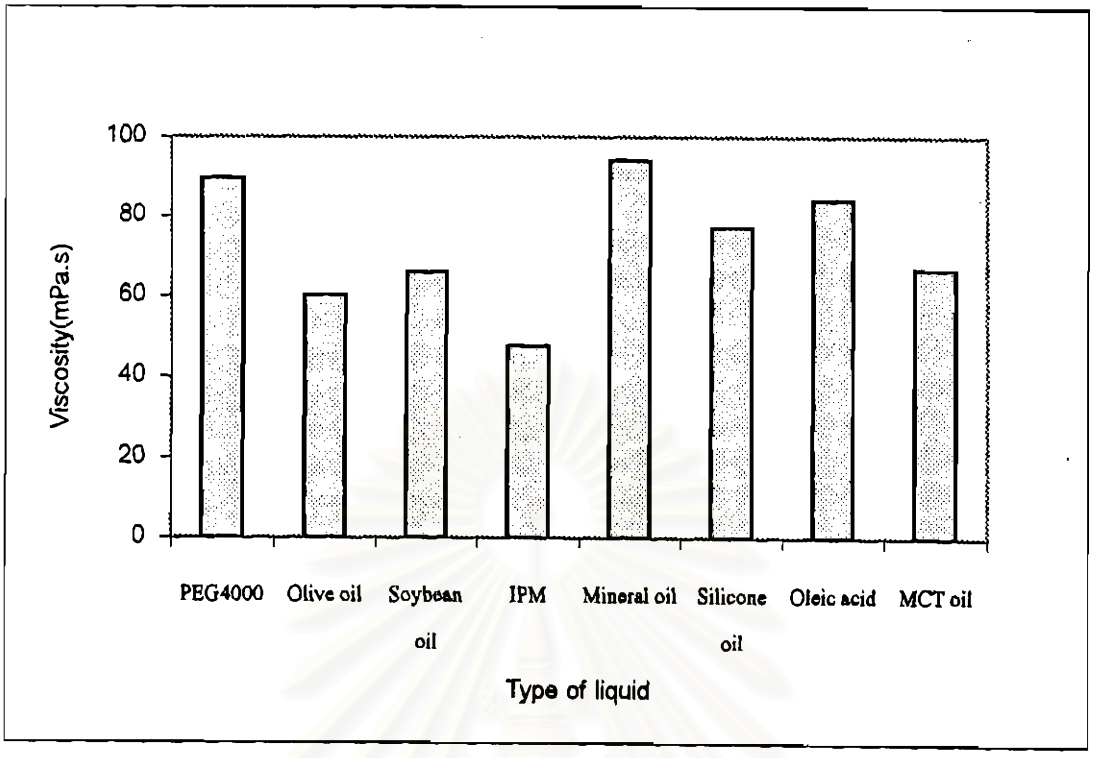


Figure 24 The viscosity of liquid vehicle recorded by viscometer

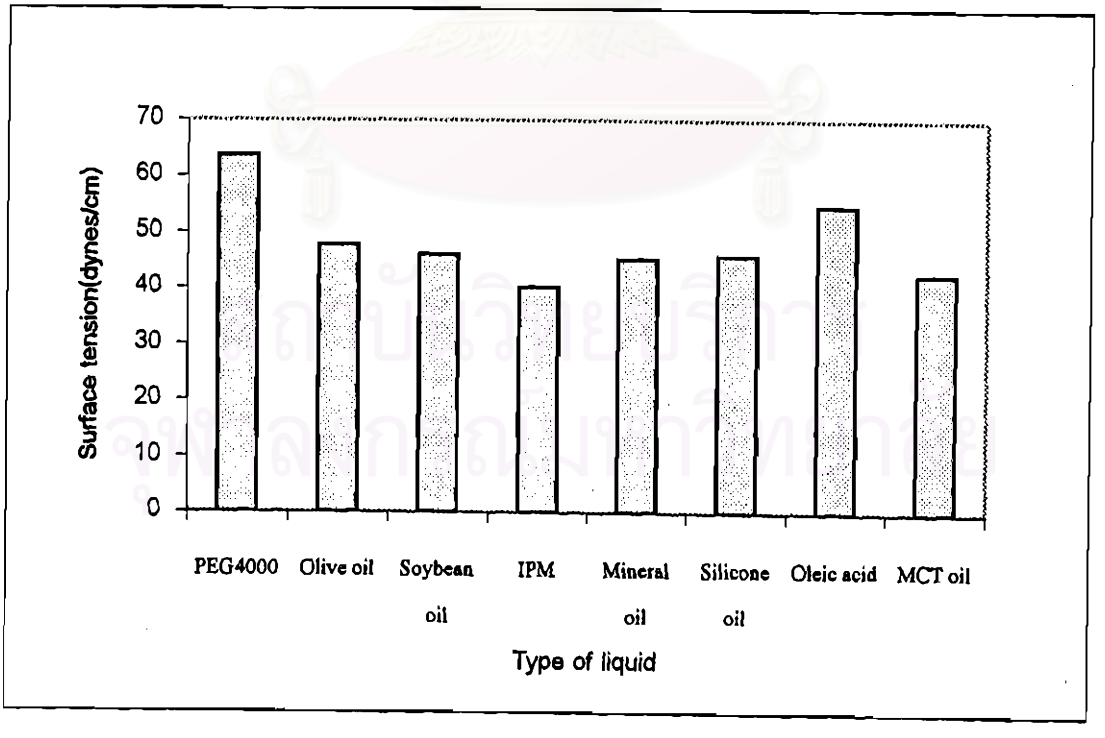


Figure 25 Surface tension of liquid vehicle recorded by DuNouy ring tensiometer

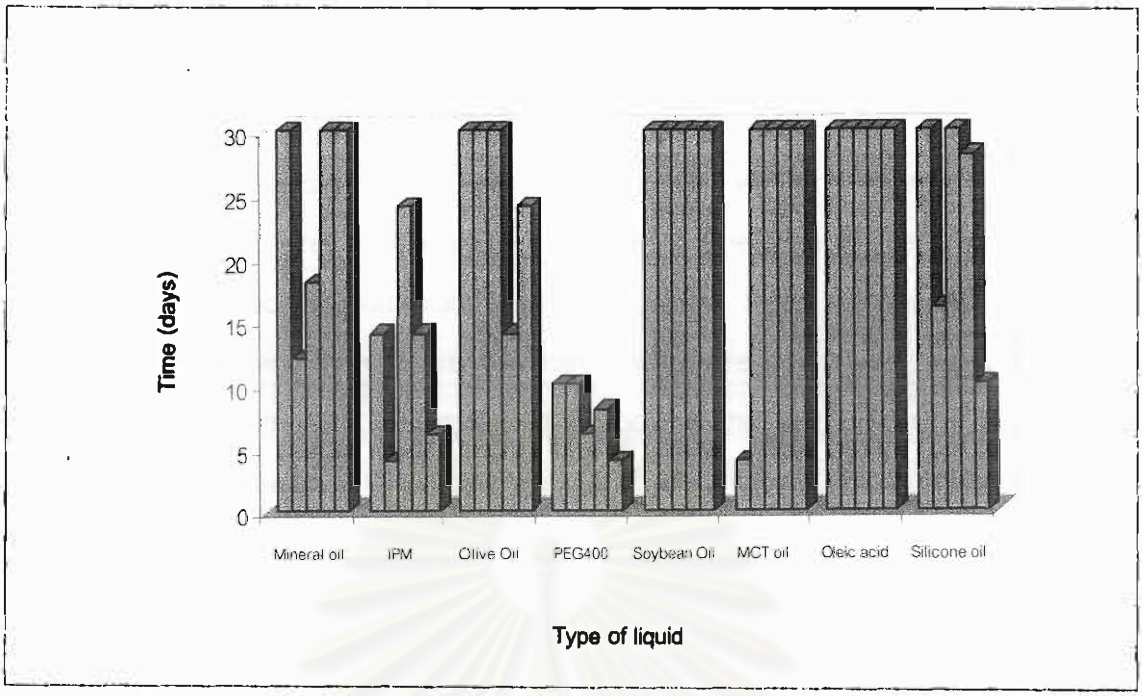


Figure 26 Leakage time of liquid vehicle, filled into Licaps® (Five capsules of each type were observed.)

study are displayed in Figure 25. Olive oil, soybean oil, mineral oil, IPM, silicone oil and MCT oil gave the lower value of surface tension than PEG 400 and oleic acid. However, all liquid vehicles had higher surface tension values than the suggested value.

2.4 Leakage Time

PEG 400 was the vehicle that leaked from capsule within 10 days, the leakage occurred rapidly when compared with the others(Figure 26). This might be the cause of splitting effect of PEG 400 as discussed in moisture sorption characteristic. In the case of oily vehicles, the average leakage time was longer than 20 days except IPM, which leak within 15 days and this could be explained by the low viscosity of IPM.

Mineral oil was chosen as the most appropriate vehicle for further study because they had many suitable characteristics including no moisture sorption, high viscosity, high surface tension and prolonging leakage time. In addition, mineral oil is the substance that has been commonly used in suppositories base.

3.Preparation of Dimenhydrinate Liquid-filled Hard Gelatin Capsule

3.1 Formulation of Liquid Base

Although the leakage time of mineral oil in Licaps® was longer than 20 days but it was not enough to prevent the leakage absolutely. The suitable preparation could reduce leakage problem from hard gelatin capsule. Since mineral oil exhibited Newtonian behavior and the viscosity was lower than the recommended value, hence it was necessary to improve rheological properties of the liquid bases. Thixotropic technique was introduced in this experiment due to the simplicity of the process without concerning with the filling temperature, cooling rate, shear rate for filling into hard capsule. Liquid filling formula was prepared by adding substance that increased viscosity and change in rheologram of preparation. These substances are called thickener and they can be divided into two groups.

1. The low melting point material including cetostearyl alcohol, white bees wax, white vaseline (white petrolatum), Cutina-HR®, poloxamer 188, magnesium stearate and stearic acid. These substances were melted and cooled down in room temperature in order to obtain high liquid viscosity.
2. The material that dissolved or swollen in oil and increased the liquid viscosity. Silicon dioxide (i.e. Aerosil®200 and Aerosil®R972) is the example of this substance.

The physical appearances of mixtures are shown in Table 10. For the first group, mineral oil was incompatible with PEG 6000, poloxamer188 (Pluronic®F 68), magnesium stearate and stearic acid because the separation of ingredients occurred when the preparation was cooled down and stored at room temperature. PEG 6000 and Pluronic®F 68 could not give homogeneous mixture; they formed solid mass and scattered in the mineral oil. For the stearic acid and magnesium stearate, it precipitated at the bottom of test tube when stored at the room temperature. Moreover these substance could not increase the viscosity of the mixture.

Table 9 Result of liquid base selection

Formula	Compatibility [1]	Viscosity [2]	Apparent rheologram [3]	Remark
1	-			
2	-			
3	-			
4	-			
5	-			
6	+	+++	0	
7	+	++	+	
8	+	+	+	
9	+	0	-	
10	+	+++	0	
11	+	++	-	
12	+	+	-	
13	+	0	-	
14	+	0	-	
15	+	+++	0	
16	+	++	+	
17	+	++	+	
18	-			
19	-			
20	-			
21	+	+++	0	
22	+	++	+	
23	+	+	+	

1. Compatibility (+) = Homogeneous
(-) = Separated

2. Viscosity (0) = water-like consistency
(+) = low viscosity
(++) = high viscosity
(+++) = wax or gel

3. Rheological characteristic by visual observation (+) = Thixotropic-like
(-) = Newtonian-like
(0) = wax or gel

Table 10 (Cont.) Result of liquid base selection

Formula	Compatibility [1]	Viscosity [2]	Apparent rheologram [3]	Remark
24	-			
25	-			
26	-			
27	-			
28	-			
29	-			
30	+	+++	0	Clear gel
31	+	++	+	
32	+	++	+	
33	+	+	+	
34	+	+++	0	Clear gel
35	+	++	+	
36	+	++	+	
37	+	+	+	

1. Compatibility (+) = Homogeneous
(-) = Separated

2. Viscosity (0) = water-like consistency
(+) = low viscosity
(++) = high viscosity
(+++) = wax or gel

3. Rheological characteristic by visual observation (+) = Thixotropic-like
(-) = Newtonian-like
(0) = wax or gel

Mineral oil was compatible with white bees wax, Cutina-HR® and cetostearyl alcohol. The mixture was turbid, white in color and homogenous mass. The viscosity was increased depending on the concentration of thickener and the suitable viscosity was observed when using less than 5 % w/w of concentration. If the thickener was incorporated to the preparation at 10 % concentration, the mixture became solid wax. Additionally, thixotropic behavior was observed at 5 % w/w concentration. The mixture

seemed to be wax-liked characteristic at rest but it returned to liquid when shaking. In the case of white petrolatum, although it was compatible with mineral oil but it must be used more than 30% w/w of formula in order to increase viscosity. Hence, it was not appropriate to be used because the amount of any additives should be used in lowest concentration in order to reduced the undesired effect.

For the second group, clear gels was obtained when adding of colloidal silicon dioxides to mineral oil but this preparation became less viscous when stirred. Aerosil was an example of pyrogenic silica, this is a very pure form of silicon dioxide obtained by high temperature oxidation and flame catalyzed hydrolysis of a volatile silane compound in an O_2/H_2 gas flame. The behavior of silicon dioxide in mineral oil suspension is dominated by particle-particle interaction through hydrogen bonding, resulting in a gel structure. Gel-like network in mineral oil was illustrated by static light scattering method (Khan and Zoeller, 1993).

From the experiment, the amount of less than 10% w/w of colloidal silicon dioxides both Aerosil®200 and Aerosil®R972 was suitable in preparing oleogel base since the formulation became thicken to viscous gel at higher concentration. However, after storage for few days, free mineral oil above the gel could be observed and they were constant even when stored for several months. This appearance resembled a previous study made by Wanchai et al., 1994. It was found that this phenomenon was observed in many vegetable oils. Although the same preparation of the oleogel bases was investigated in many published papers: there were no reports on these characteristics. It was possible that the appearance might be caused by high temperature of the environment in Thailand.

From this result, Aerosil®200, Aerosil®R972, white bees wax, Cutina-HR® and cetostearyl alcohol with less than 10% w/w of the formulation are compatible with mineral oil, increase the viscosity and change the rheology of the mineral oil. Silicon dioxide was the one substance that could give clear gel whereas the others gave white and turbid base. However, they would also be investigated in the next step.

3.2 Formulation of Dimenhydrinate in Liquid Base

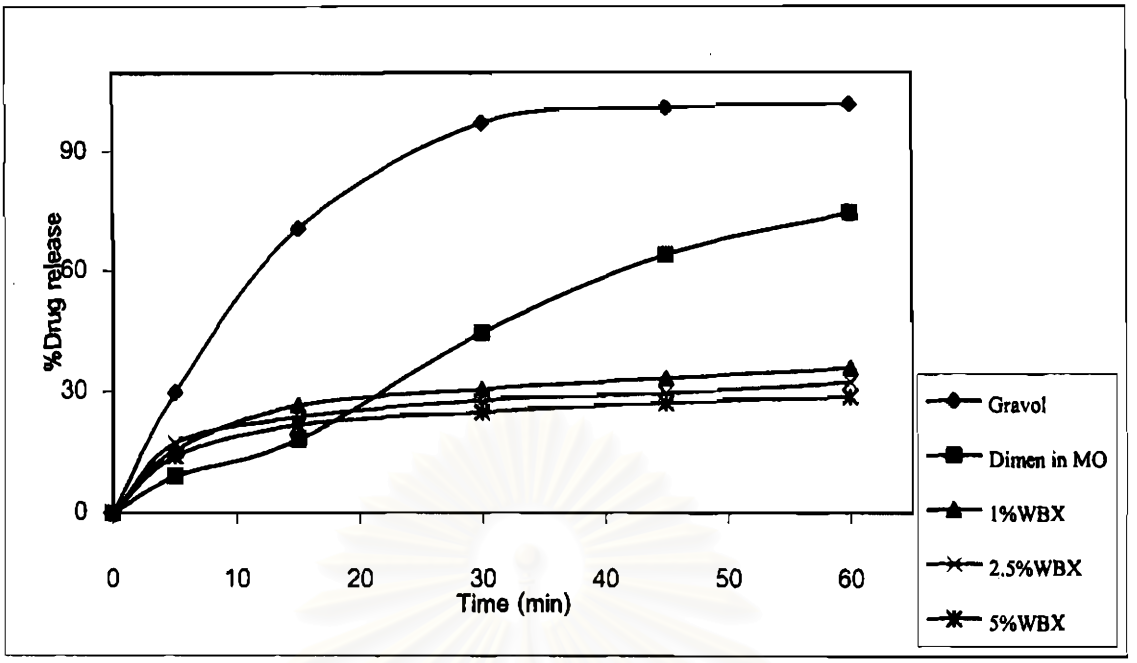
3.2.1 The Study of Release Profile

3.2.1.1 Basket Method

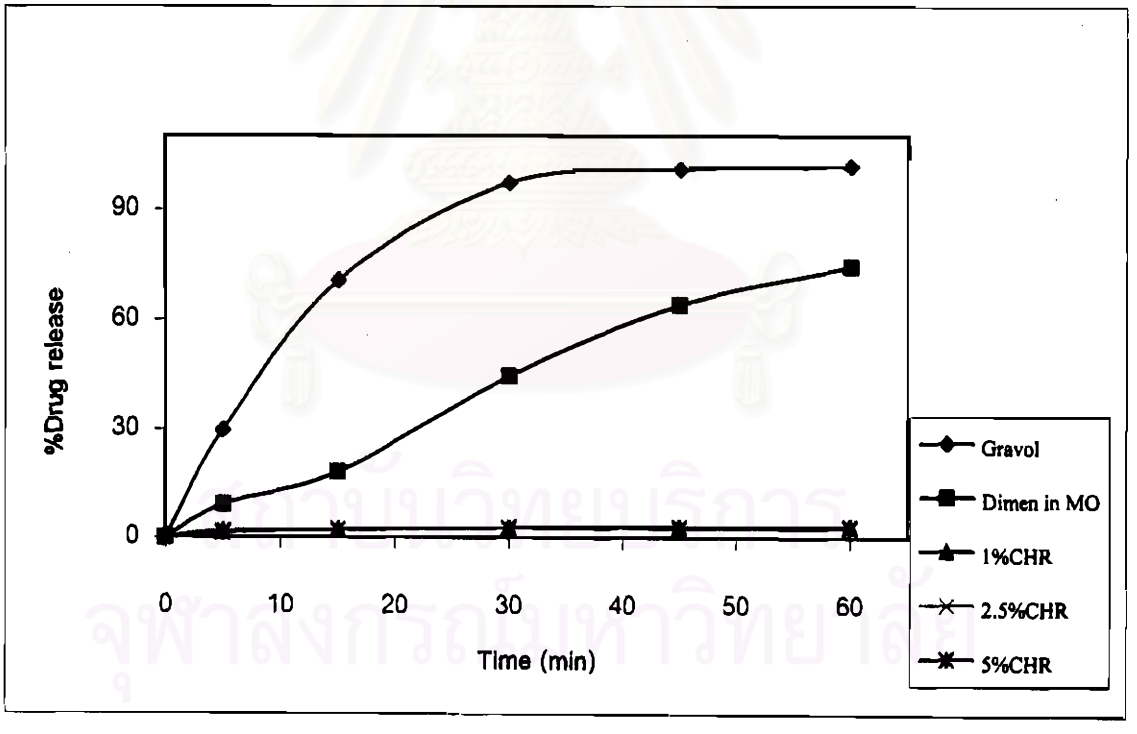
Dimenhydrinate was incorporated in the chosen formulation of liquid base. These preparations were evaluated for their release profile in phosphate buffer pH 7.2 that was similar to the pH of rectal fluid. Many techniques such as beaker, basket, paddle, membrane diffusion, dialysis and continuous-flow method, were employed in testing the suppository. However, there were no standard methods that could correlate the in vitro results with in vivo bioavailability (Banakar et al., 1986). In this experiment, basket method was selected to mainly study the release rate of dimenhydrinate from the liquid base hard gelatin capsule because the basket method can minimize floating of capsule on the media surface. However, the flow-through cell method was also studied to compare with basket method and discussed in 3.2.1.2. The condition contained 900 ml of phosphate buffer to maintain sink condition; the minimum rotating speed was used. The release rate of the drug was calculated from the calibration curve in Appendix B.

Effect of thickener on the release profile

The effect of thickeners that were selected from 3.1, on the release profile of dimenhydrinate was investigated. Illustrations of a typical drug release-time curve are given in Figure 27-29 and the data are presented in Appendix B. The addition of white bees wax to mineral oil would reduce drug release to less than 30% when compared with unthickened formula which showed drug release for 60% of drug loading at 60 minutes. The release of dimenhydrinate was greatly reduced when adding more percentage of these thickeners in the formulation (Figure 27a). It was possible that the higher viscosity and hydrophobic properties of thickener affected the systems. The same effect was found in formula containing with Cutina-HR®. Both of Cutina-HR® and white bees wax are lipophillic-thickening agents, which are generally accepted that they will give slow or sustained release effect. However, the release of drug in Cutina-HR® preparation was slower than the formula containing white bees wax (Figure 27b). It might be caused of higher viscosity of the preparation.



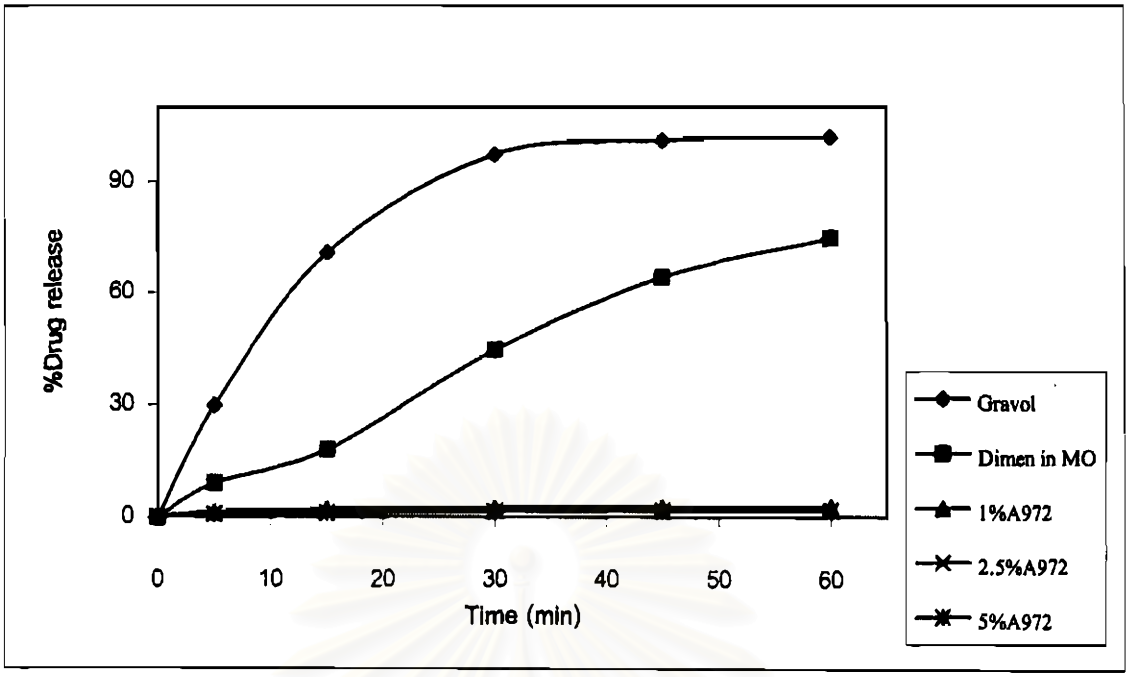
(a)



(b)

Figure 27 Effect of thickener on dissolution profiles of dimenhydrinate liquid-filled hard gelatin capsule in phosphate buffer pH7.2

(a) White bees wax (b) Cutina-HR



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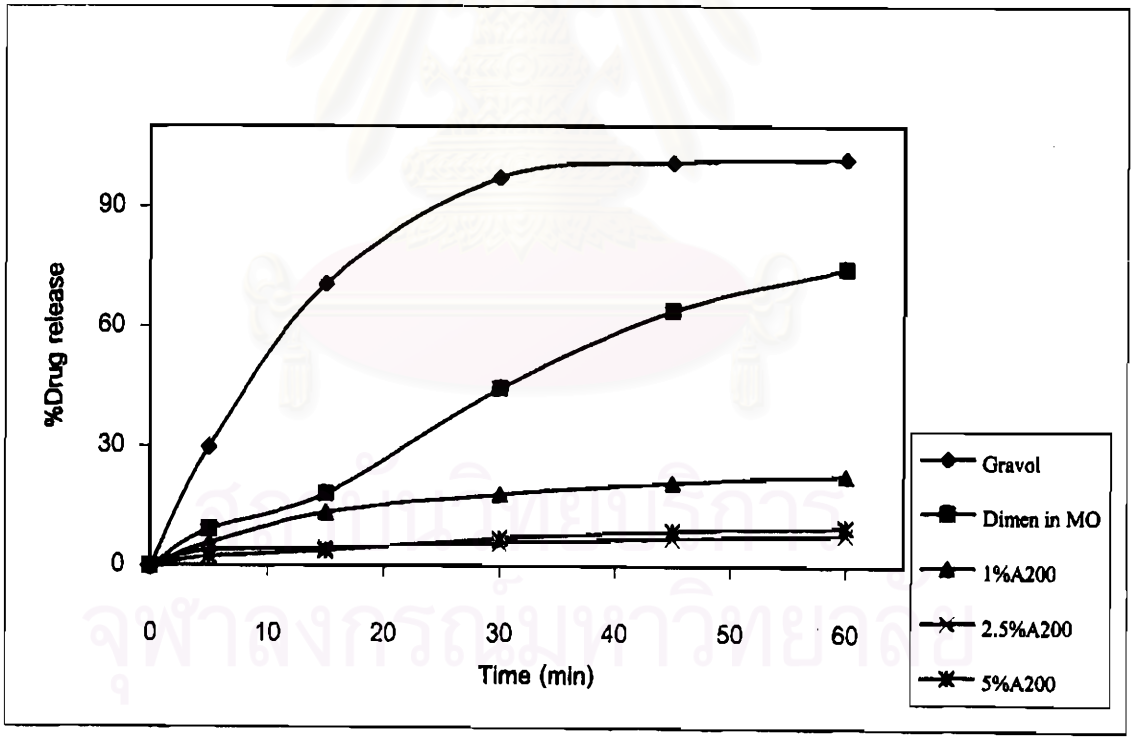


(b)

Figure 28 Effect of thickener on dissolution profiles of dimenhydrinate liquid-filled hard gelatin capsule in phosphate buffer pH7.2

(a) Aerosil R972 (b) Aerosil200

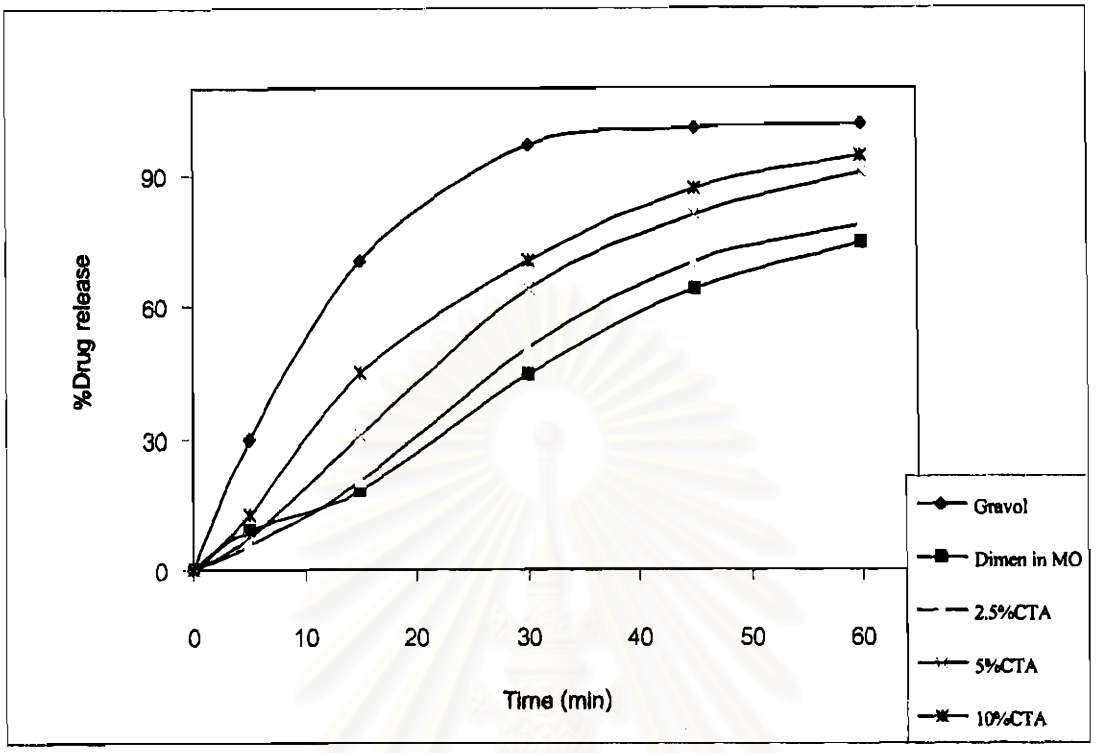


Figure 29 Effect of cetostearyl alcohol on dissolution profiles of dimenhydrinate liquid-filled hard gelatin capsule in phosphate buffer pH7.2

In case of colloidal silicon dioxide, it was apparent that drug release from this system decreased to less than 20% at 60 minutes when compared to unthickened formula (Figure 28b). The incorporation of higher percentage of Aerosil200 from 1% to 5% w/w, the release rate was reduced to the minimum. Although Aerosil200 has surface functional group that shows hydrophilic property but high viscosity of preparation could decrease drug release. Since the rod-shape of liquid formulation in the formula containing 5% w/w Aerosil® 200, remained intact at 60 minutes whereas this appearance could not find at the lower concentration of Aerosil® 200. The release characteristic was the same as previously reported by other researchers. Walker et al. (1992) found that increasing silica components up to 12 % w/w appeared to reduce rate of drug release. However, they found in contrast that the drug release from gel increased, closed to unthickened oil when adding more than 12 % w/w of Aerosil200. But in this experiment,

addition of Aerosil®200 more than 5 % w/w, too viscous and clear oleogel was obtained. Hence, it could not be filled into capsule as liquid preparation. Aerosil®R972 that had the hydrophobic behaviors to water gave less drug release than Aerosil®200 did (Figure 28a). Baykara and Yuksel (1992) found the same effect, it was found that the release of many drugs from Aerosil hydrophobic grade did not occurred, on the other hand, 5 % Aerosil®200 showed less than 10 % of drug release in IPM preparation within 60 minutes.

In contrast to cetostearyl alcohol, the release of drug was higher than unthickened formula as displayed in Figure 29. The faster release rate was observed when the higher amount of cetostearyl alcohol was incorporated into the preparation, in the opposite of the viscosity. This could be explained from the characteristic of cetostearyl alcohol that contained both of hydrophobic and hydrophilic components in molecule. The polar group in matrices induced wettability to water and then dispersed immediately. Nevertheless, the separation of these preparations occurred after storage for a long time; they separated into two phases, turbid and clear. So, it could not be use in the liquid-filled formulation.

From this study, the addition of thickener would retard drug release from liquid base. White bees wax, Aerosil®R972 and Cutina-HR® were not appropriate to improve due to hydrophobicity. Hence, Aerosil®200 was selected to develop the suitable preparation.

Effect of surfactant on the release profile

Surfactant is a common substance that used to enhance drug dissolution both in solid, liquid and semi-solid dosage form including suppositories (Corrigan and Anne, 1996). Surfactants are classified in many groups based on their structures. In this experiment, some of them were selected to incorporate in liquid base.

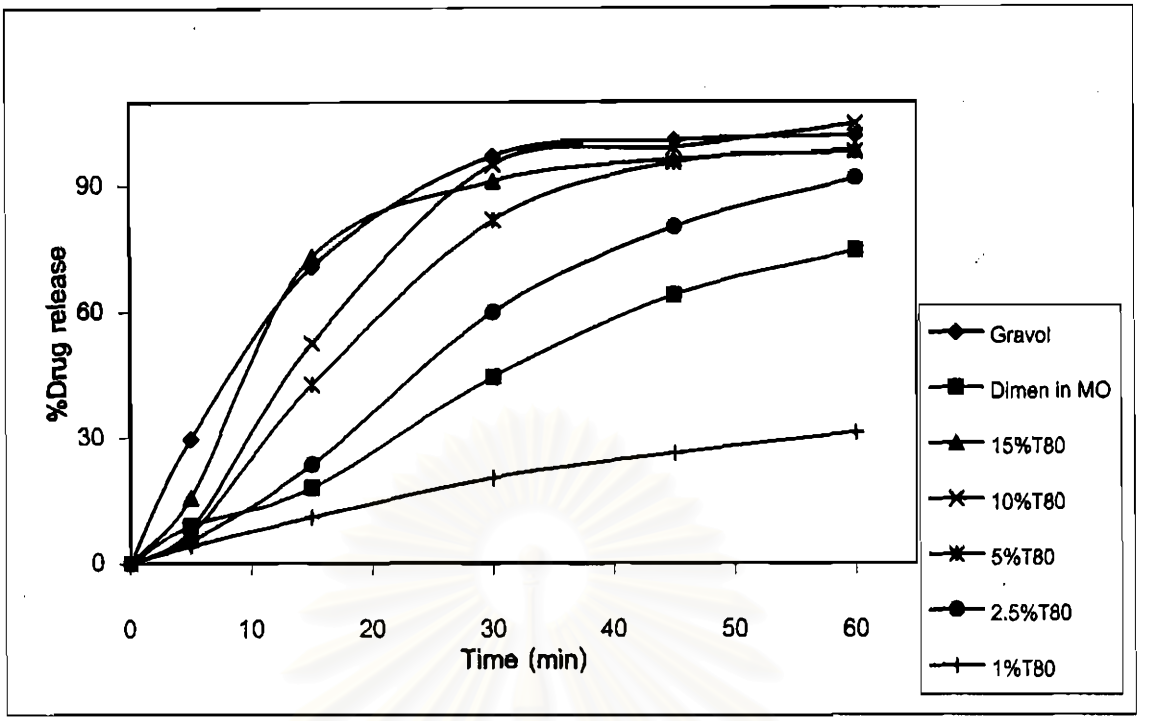
Group of polyoxyethyllene sorbitan fatty acid ester (Tween) and polyoxyethyllene stearate and the sorbitan fatty acid ester (Span) are the most widely used surfactants in liquid preparations and also used in suppository bases in order to enhance drug release from wax matrices of hard gelatin capsule (Dredan et al, 1998). Tween 80, Span 80 and Span 20 were represented of this group.

Polyoxyethylated hydroxygenated castor oil is the new semi synthetic group of surfactant that show good efficiency to facilitate drug release. Cremophor® RH40 was the representation of this group.

Brij® 72 are the solid surfactant of polyoxyethylene alkyl ethers group. The solid surfactant may not only enhance the dissolution but also increase the viscosity of preparation. Hence, it may reduce the amount of thickener in each preparation.

Gravol® suppository showed the fast release pattern, more than 90 percent of dimenhydrinate was released within 30 minutes and complete dissolution was obtained within 45 minutes. This pattern was comparable to the system containing dimenhydrinate, 2.5 % Aerosil®200 in mineral oil. In systems consisting of Tween 80, only the formula contained with 10 and 15 percent surfactant was able to provide more than 90% drug release within 30 minutes. At the low concentration of Tween 80, the release was found to less than 90% (Figure 30a). The enhancing effect of Tween 80 on drug release was presented by Fokkens et al., (1984). The result indicated that addition of 1% Tween 80 could increase release rate of zomopirac in liquid paraffin from less than 0.004 $mg.cm^{-2}.min^{-1}$ to 0.026 $mg.cm^{-2}.min^{-1}$. Whereas the formula containing with Cremophor® RH40 more than 5 % w/w could improve more than 90 percent of drug release within 30 minutes (Figure 31b). The dissolution pattern was similar to Gravol® suppository but it was slower in the first 15 minutes periods.

Other surfactants including Span80 could also improve the release rate but it was less than Tween 80 and Cremophor® RH40 even though 10% of surfactant



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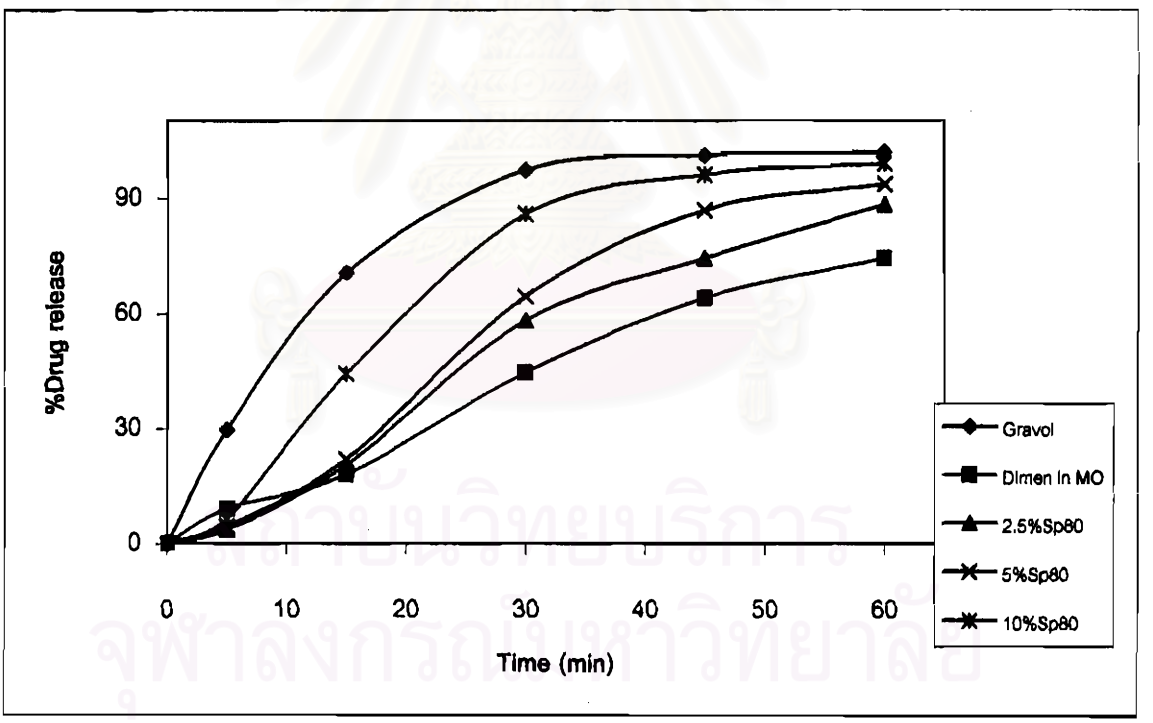
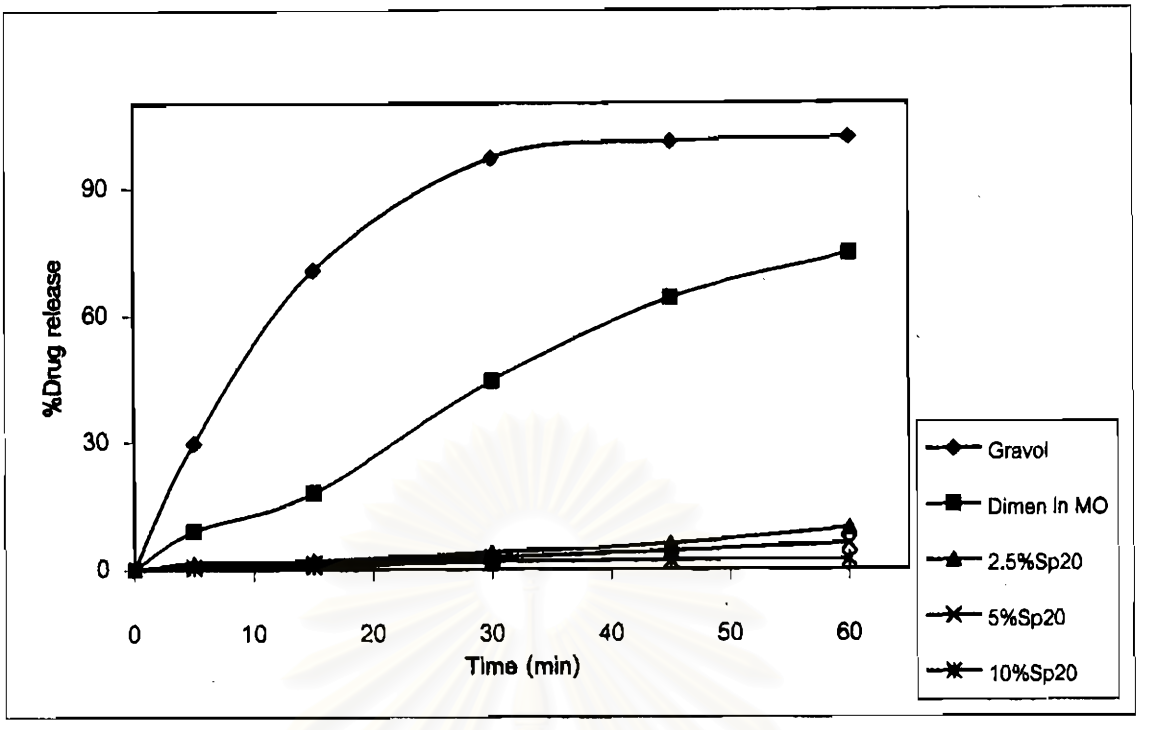


(b)

Figure 30 Effect of surfactant on dissolution profiles of dimenhydrinate liquid-filled hard gelatin capsule in phosphate buffer pH7.2

(a) Tween 80 (b) Span 80



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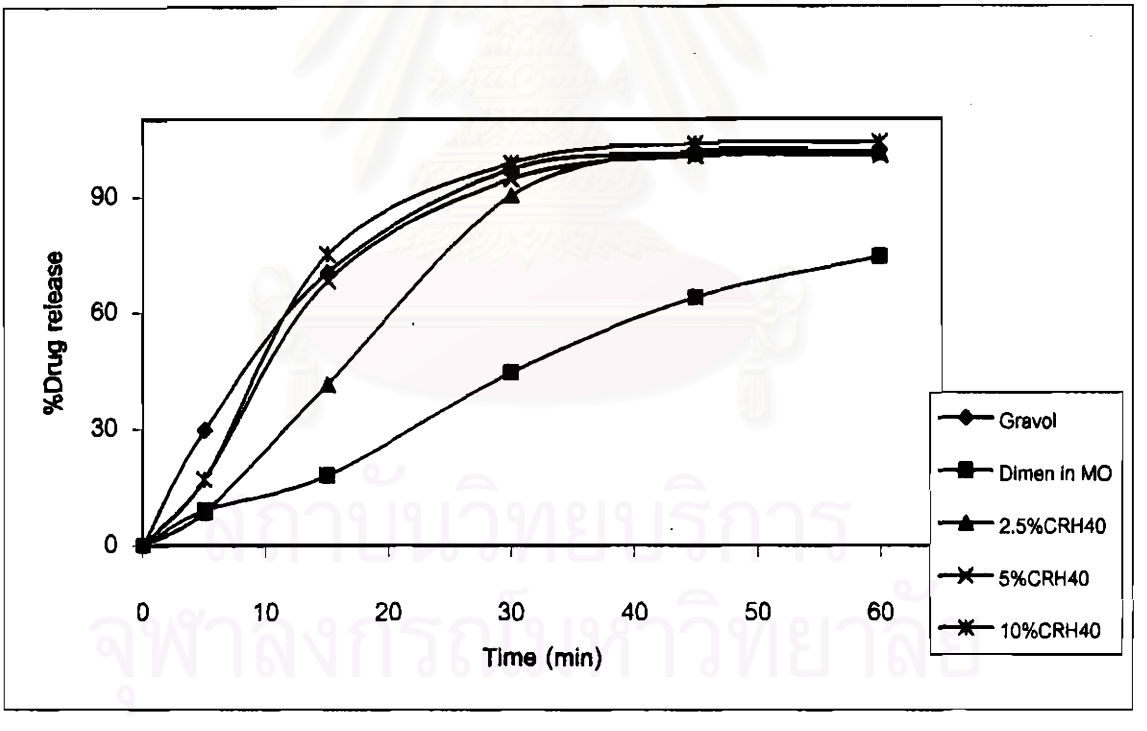
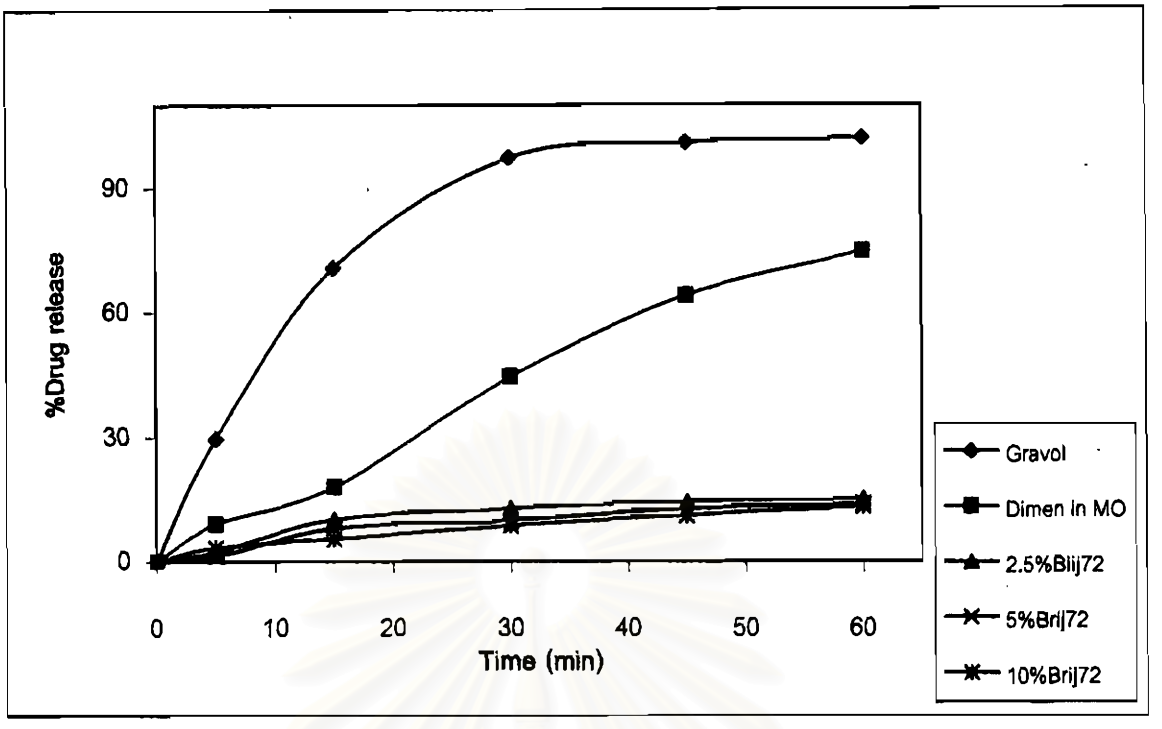


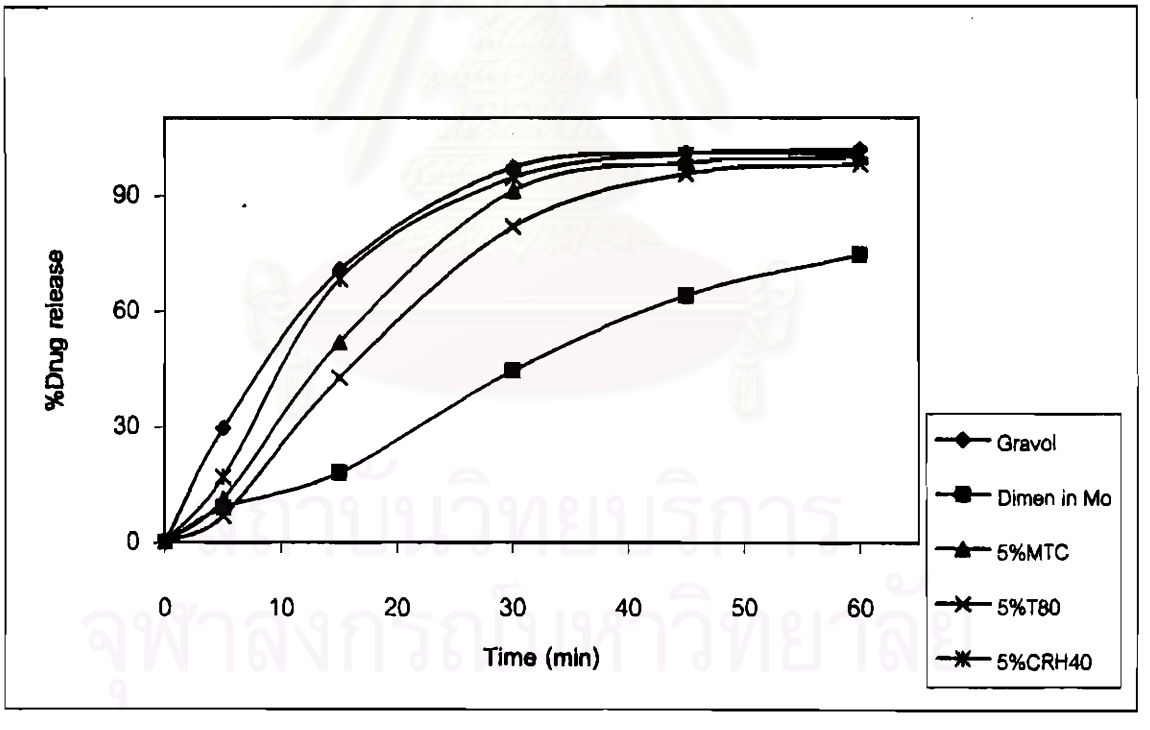
(b)

Figure 31 Effect of surfactant on dissolution profiles of dimenhydrinate liquid-filled hard gelatin capsule in phosphate buffer pH7.2

(a) Span 20 (b) Cremophor RH40



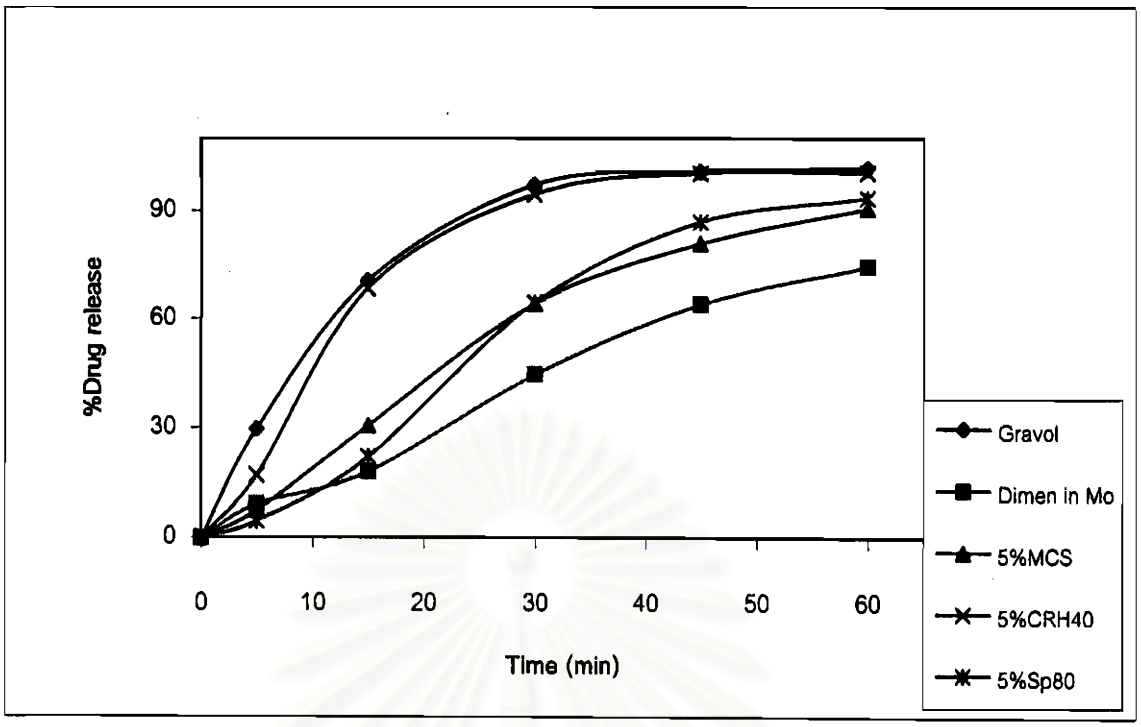
(a)



(b)

Figure 32 Effect of surfactant on dissolution profiles of dimenhydrinate liquid-filled hard gelatin capsule in phosphate buffer pH7.2

(a) Brij72 (b) Mixture of T80 and CRH40



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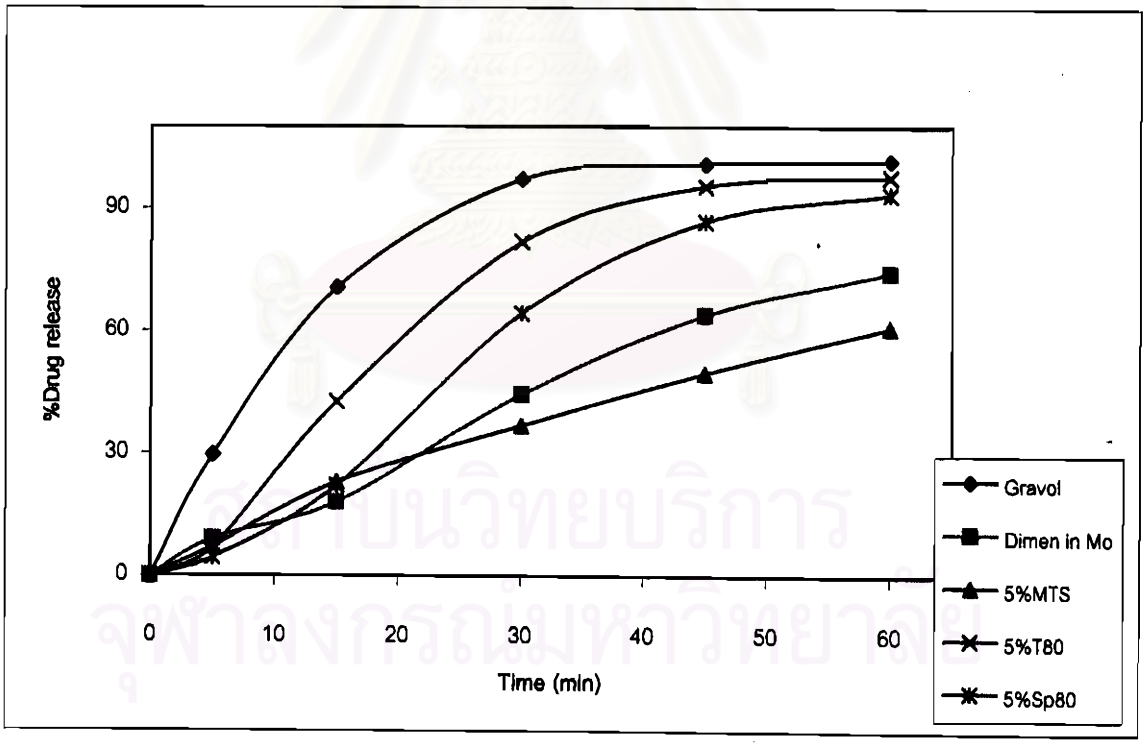


(b)

Figure 33 Effect of surfactant on dissolution profiles of dimenhydrinate liquid-filled hard gelatin capsule in phosphate buffer pH7.2

(a) Mixture of CRH40 and Span80 (MCS) (b) Mixture of Tween80 and Span80 (MTS)

was added in formula, there was only 85 percent of drug release at 30 minutes (Figure 30b). In the system containing of Brij®72, and Span20 hardly had any effects on the release profiles. There were less than 20 and 10% drug release and the release was considerably decreased when adding these surfactants in the formulation (Figure 31a and 32a).

Generally, surfactants could improve the drug release rate by increasing wettability and reducing interfacial tension of the system. The presence of surfactant causes the forming of emulsion when in contact with water. The oleaginous system was induced to small droplet size. It was obvious that the dissolution medium became turbid and rod shape of formula disappeared within 60 minutes when compared to the system without surfactant. The ability of each formula to facilitate drug solubility might be caused by HLB of each surfactant. The HLB of Tween 80, Span 80 and Cremophor® RH40 was 15, 14.8 and 14-16, whereas HLB of Span20 and Brij72 was 3.7 and 4.9, respectively. Higher HLB was accepted that it could facilitate water permeability and increased in the hydrophilicity of preparation (Shah et al., 1994). The factor of HLB was considered to modify the release of wax matrix in order to prepare fast or sustained release dosage form (Bowtle, 1999; Malick et al, 1997).

Figure 32b and 33 shows the effect of mixed surfactant, the mixing ratio 1:1 of Cremophor®RH40: Tween 80, Cremophor®RH40: Span80 and Span80: Tween 80 in 5% w/w concentration was investigated. The addition of two surfactants could not enhance drug release, on the contrary, decreasing drug release was observed when compared to adding single surfactant. Only the preparation composed of mixture of Cremophor®RH40: Tween 80 showed more than 90% drug release within 30 minutes (Figure 32b). It might because of complexation of the combination with various surfactants but the mechanism underlying this effect was not clear.

However, liquid-filled hard gelatin capsule containing high concentration of surfactant might cause the embrittlement of capsule shell and subsequent leakage of the contents. It is probably caused by the removal of water from the protein structure of

capsule with resulting loss of mechanical strength (Storey, 1991; Cole et al., 1992). Hence, the amount of surfactant employed to improved release of drug in each preparation should be used at lowest concentration.

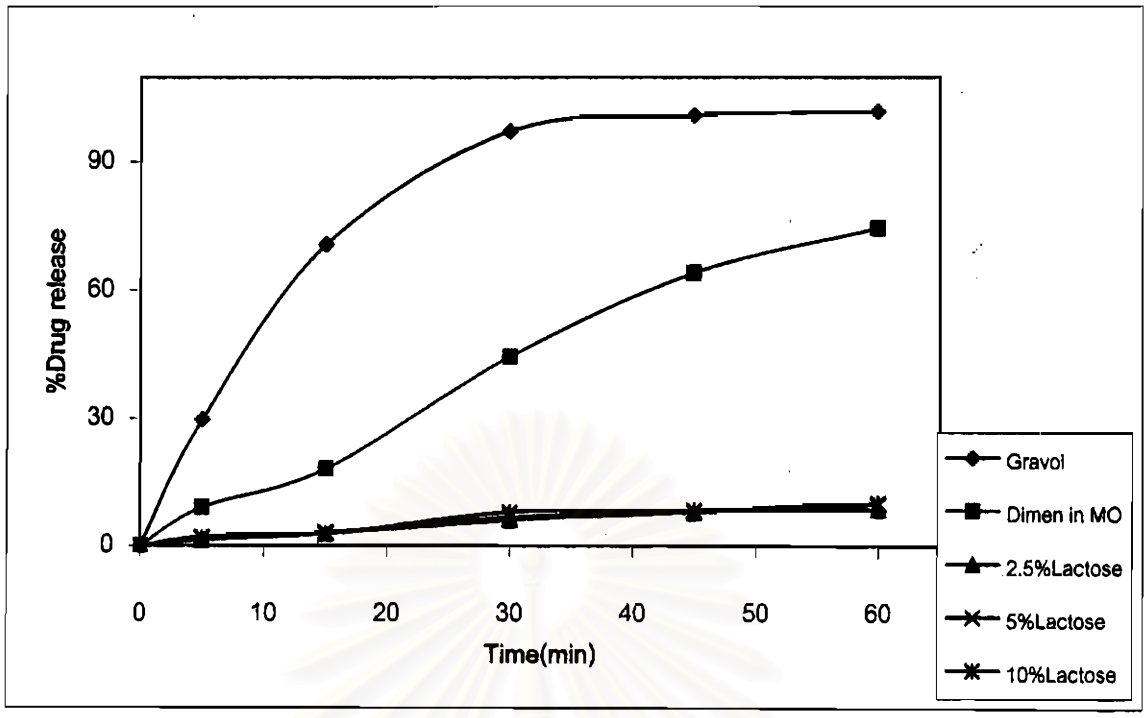
It was noted that some of the liquid systems could dissolve in phosphate buffer, induced the cloudy appearance of medium and slightly contributed to the background absorbance of medium. Therefore, the control of these systems was deducted from the absorbance of the sample of each and every time point. The absorbance spectra were also monitored periodically throughout the experiment.

Effect of drug dragger on the release profile

Drug dragger is the term used to define water soluble substances that can carry the drug out of the lipophillic capsule filling masses. It was found that addition of drug dragger into liquid base formulation could increase average drug release about four folds of system without them (Bauer, 1984). The definition of this word is similar to channeling agent. Dextrose, lactose, sodium chloride and icing sugar were investigated for their effect on release patterns. These substances were grinded to reduce particle size and screened through sieve No. 80 before incorporated into selected liquid formula.

Figure 34 and 35 shows that all drug dragger in liquid formulation could slightly improve only 10 percent of drug release in 60 minutes. As can be seen from this curve, the release was not changed although the amount of drug dragger was increased to 10%w/w concentration. This was probably explained by high viscosity of preparation kept oil-base rigidity and the water around them was not permitted to pass through liquid preparation. So these water soluble substances could not act to full capacity and the little increasing release might happen because drug dragger on surface came out.

An attempt to increase the rate of dimenhydrinate release from hard gelatin capsule by adding drug dragger alone could not alter the release rate but combination of surfactant and drug dragger was later investigated. Tween 80 was fixed



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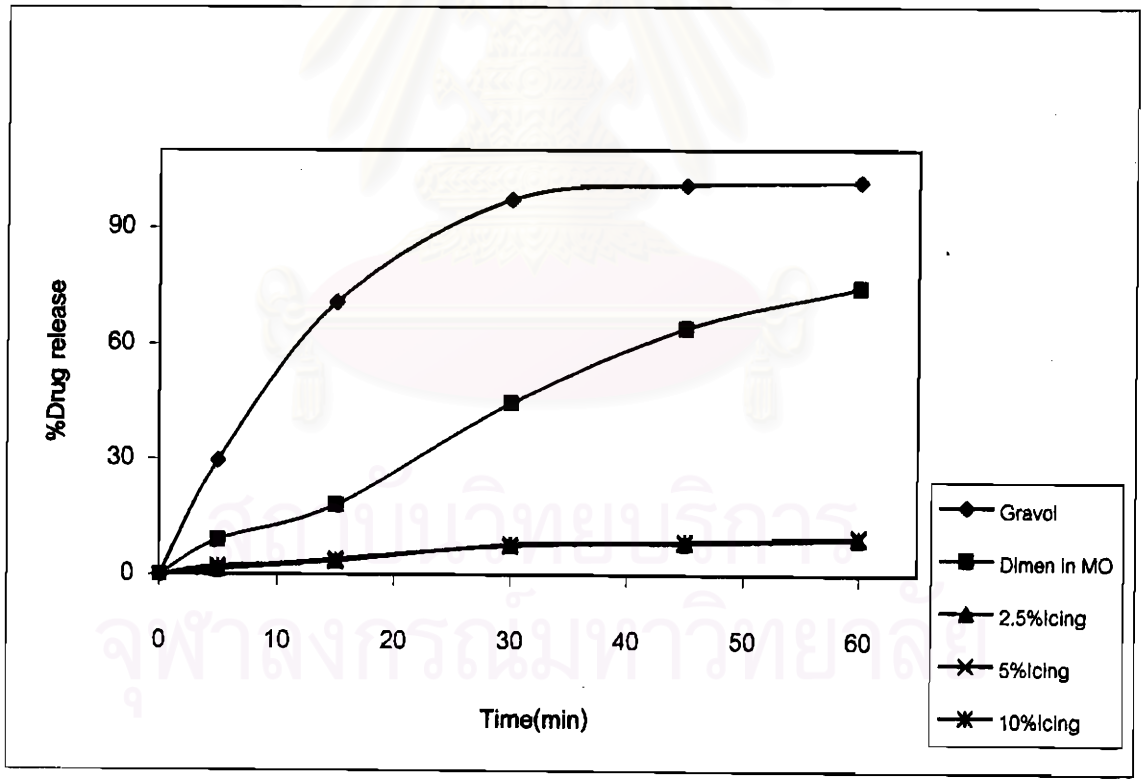
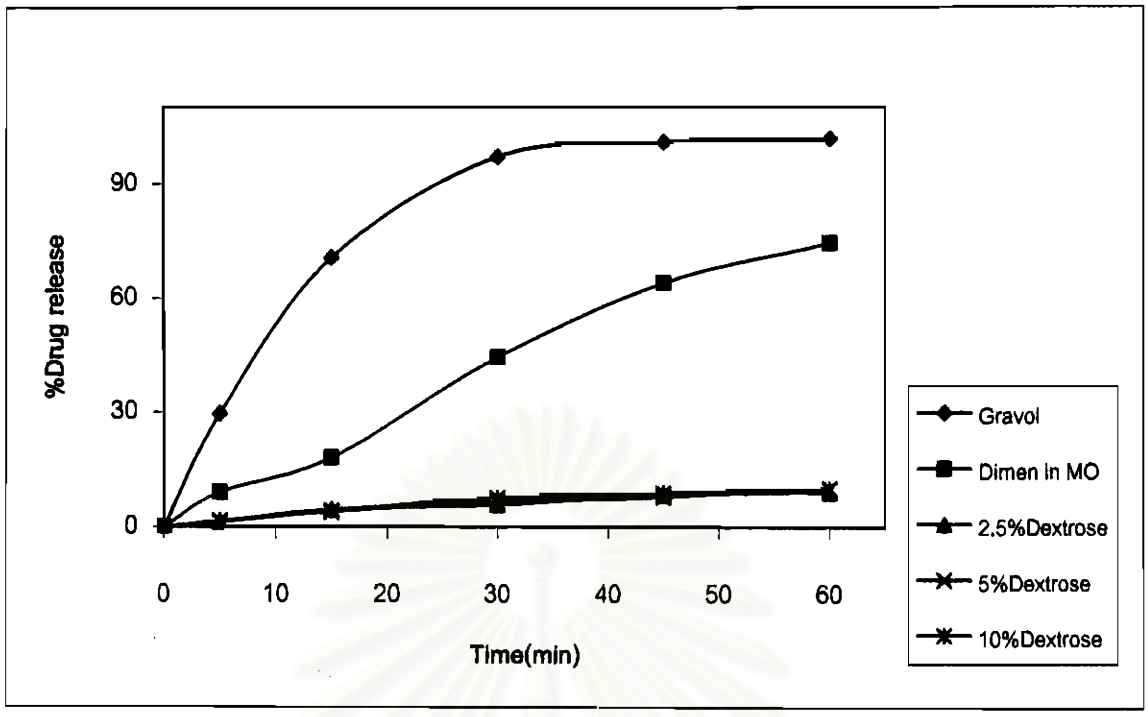


(b)

Figure 34 Effect of drug dragger on dissolution profiles of dimenhydrinate liquid-filled hard gelatin capsule in phosphate buffer pH7.2

(a) Lactose (b) Icing sugar



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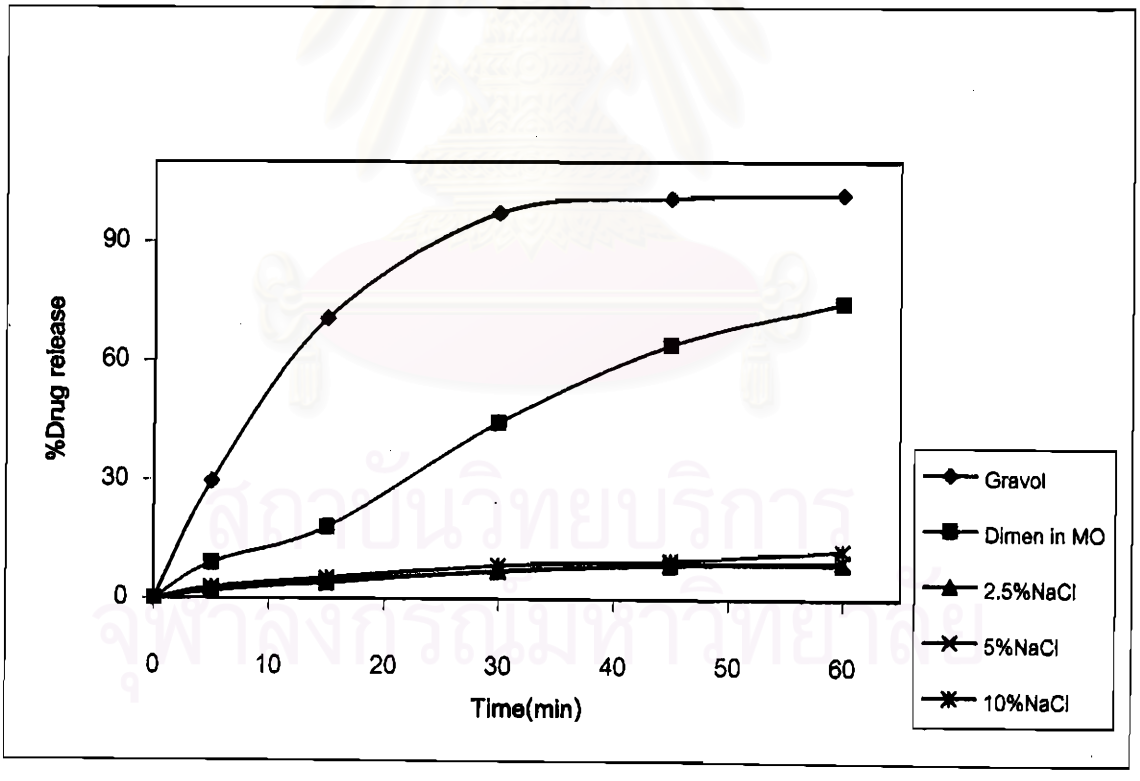
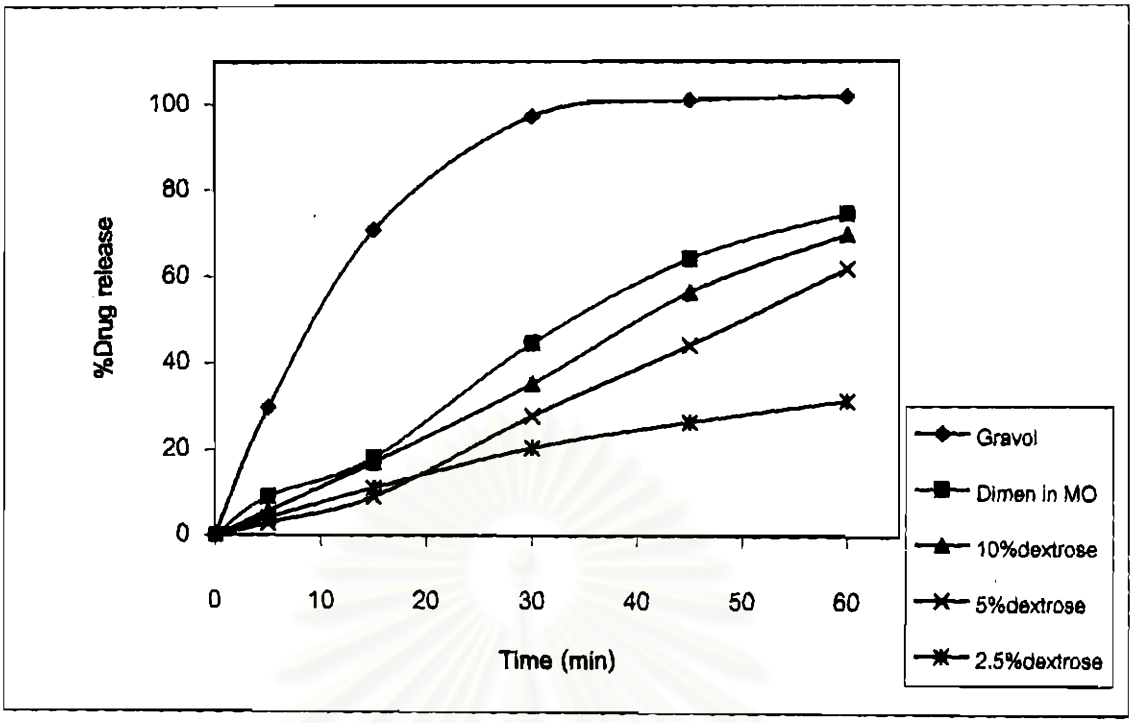


(b)

Figure 35 Effect of drug dragger on dissolution profiles of dimenhydrinate liquid-filled hard gelatin capsule in phosphate buffer pH7.2

(a) Dextrose (b) Sodium chloride



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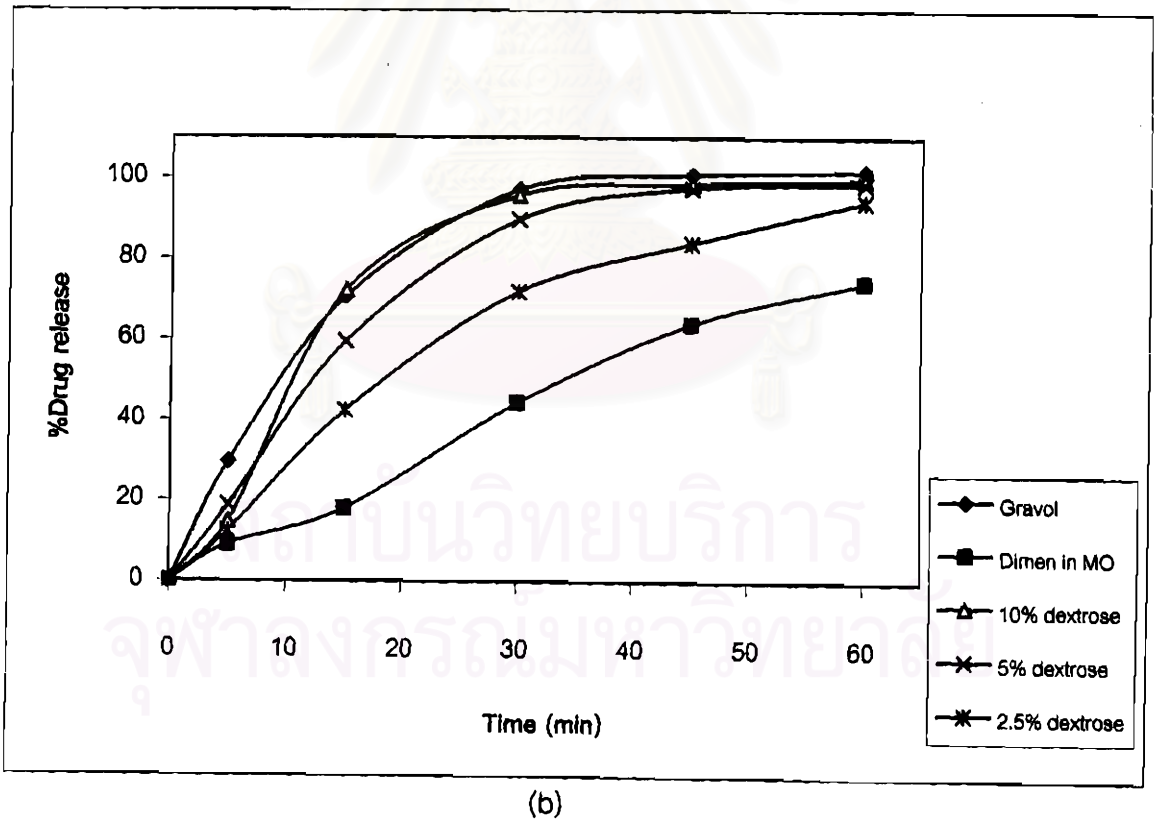


(b)

Figure 36 Effect of dextrose on dissolution profiles of dimenhydrinate liquid-filled hard gelatin capsule in phosphate buffer pH7.2, which contained (a) 1% Tween 80 (b) 5% Tween 80

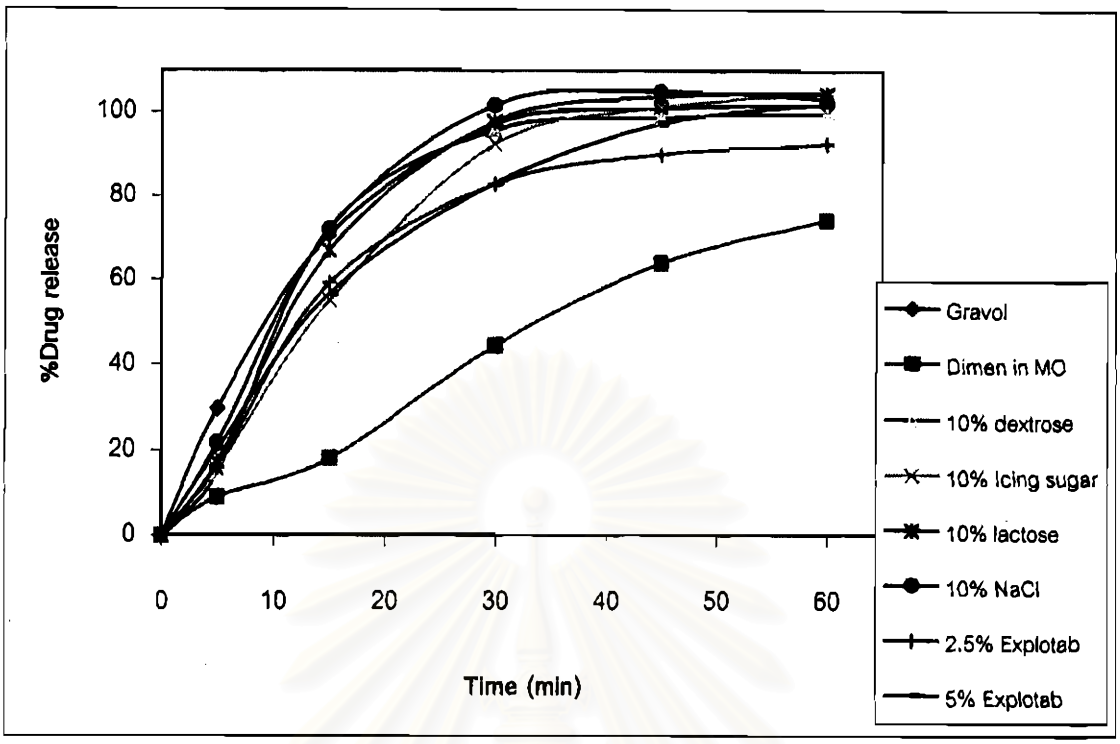


Figure 37 Effect of drug dragger on dissolution profiles of dimenhydrinate liquid-filled hard gelatin capsule which containing 5% Tween 80, in phosphate buffer pH 7.2

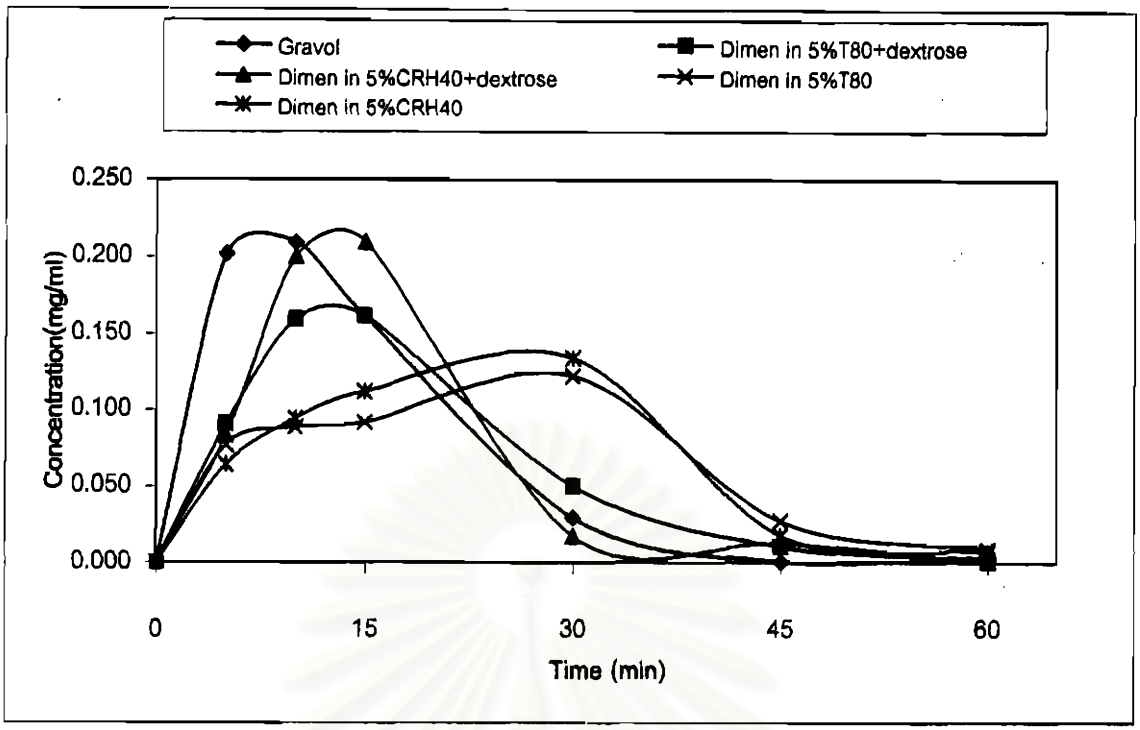
at 1 % and 5 % w/w concentration and the amount of dextrose was varied from 2.5 % to 10 % w/w. The release profiles are shown in Figure 36, drug releases were increased in all formulation that containing the mixture of Tween 80 depending on the amount of dextrose. At 10% concentration of dextrose in 5% Tween 80, the releasing pattern was improved comparable to Gravol®. Other drug dragger, including icing sugar, lactose and sodium chloride, could also increase the releasing of dimenhydrinate (Figure 37). Sodium chloride, dextrose, icing sugar and lactose improved drug dissolving from 81.82% to 101.8, 95.75, 93.84 and 92.38 % at 30 mins, respectively. This effect might be explained that surfactant brought water into oil-base and induce emulsion droplet, then drug dragger was contacted to water and later dissolved. This effect might carry drug out of the liquid base and this efficiency might depend on water solubility or osmotic pressure of the substance.

Although the effect of sodium chloride was greater than that of other drug draggers, it was coarse particle size and felt grittiness. Dextrose showed good release as the second and it is appropriate to be use in the preparation. The same result was observed when changing from Tween 80 to Cremophor® RH40 in the preparation, as displayed in Figure 38.

3.2.1.2 Flow Through Cell Method

The flow through method is one of the commonly used to determine the release profile of suppositories due to familiarity to the actual condition. It is the only few technique that can produce continuous release of the drug in vertical direction. The correlation between time and concentration exhibited the sigmoid curve as illustrated in Figure 38a, Gravol® suppositories showed the fastest dissolving, the maximum peak occurred within 10 minutes while the release of dimenhydrinate from liquid filled capsule was slower than marketed product. The maximum drug release occurred within 10-15 minutes and the curve showed that the release almost completed after 30 minutes. The cumulative release data from flow-through method was plotted in comparison with the basket method. As seen in Figure 37 and Figure 38b, the basket method at 50 rpm produced the faster dissolution rate than testing in the flow-through method. The basket procedure showed a complete dissolution within 30 minutes, while the flow-through within 45 min. Nevertheless, the release profile of two methods produced similar shape of the dissolution profile.

According to the report by Gjellan and Graffner (1989), it was found that the paddle, the basket and the flow-through method are considered to be equivalent method for the suppository dissolution test. The composition of rectal system has a greatest influence on the behavior in each of the three *in vitro* dissolution techniques. However, The flow rate of flow-through method has to control not to exceed 16 ml/min since non-sink condition and the blocking of the filter device might happen. The flow rated of 8 ml/min was recommended because it could solve the problem of filter clogging. The coefficient of variation of the rectal capsules, which determined by the flow through method, usually higher than suppositories due to the differences in capsule



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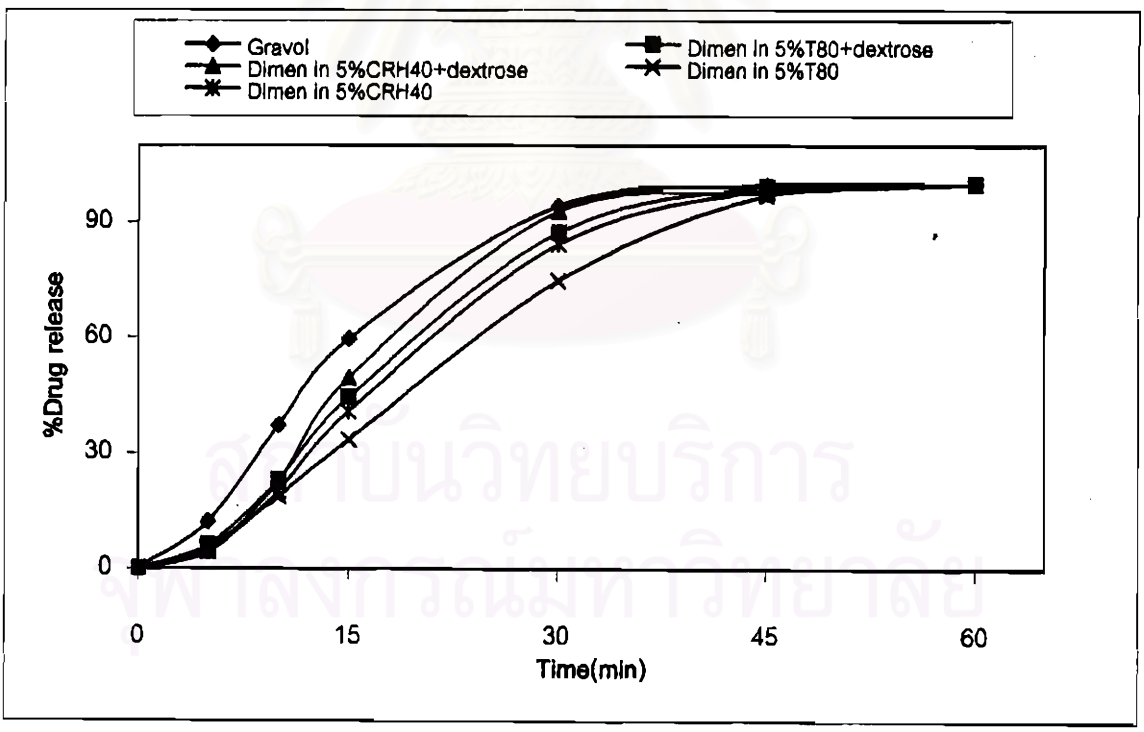


(b)

Figure 38 Dissolution profiles of Dimenhydrinate liquid filled capsule determined by Flow-through apparatus

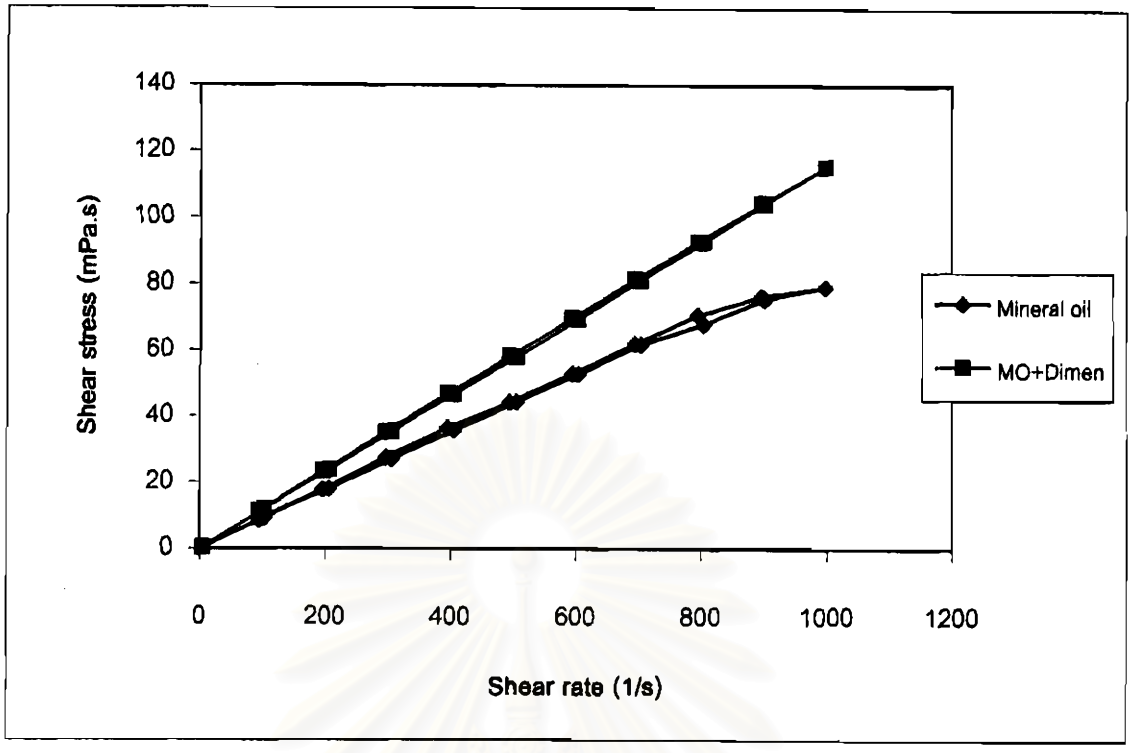
(a) Time & release curve (b) Cumulative curve

shell disintegration. As a result, the dissolution process will start at different times for each capsule content. This could explain the great variation of coefficients in the results especially from the first sample interval. Hence, the basket method may be taken in consideration for simply *in vitro* dissolution techniques.

3.2.2 Rheological Determination

The viscosity of liquid formula is one of the most important parameters governing the release of a drug from preparation. A liquid base with low viscosity should spread further up the rectum giving an increased surface area for diffusion and absorption. The drug suspend in liquid formulation of low viscosity would give rise to a higher rate of sedimentation of the drug, on the contrary high viscosity would retard drug release. The appropriate formulation for filling into hard gelatin capsule should be pseudoplastic thixotropic characteristic and the liquid viscosity should be in the range of 300-600 mPa.s (Shah et al.,1996). These parameters were proved to show good uniformity of filling weight because there is no bridging effect and it can prevent fast sedimentation of suspended drug in the preparation. However, the particle sizes and shape of drug was also affect to the sedimentation of liquid preparation.

The viscosity of mineral oil was about 100 mPa.s at 25^{o}C and Newtonian behavior was observed. Dimenhydrinate that incorporated into mineral oil showed slightly different in rheogam and viscosity (Figure 39). As displayed in the Table10 when adding 2.5, 3.5 and 5 % w/w of Aerosil$^{®}$200, the viscosity of mineral oil increased from 105.73 mPa.s to 313.58, 479.91 and 977.97 mPa.s, respectively, and the pattern of rheologram changed. It was illustrated that the mixture behaved like Newtonian fluids at low concentrations, whereas concentration of 2.5 % produced higher viscosity, and thixotropic behavior was observed when the concentration of Aerosil$^{®}$200 up to 5 % (Figure 40a). Adding more concentration of Aerosil$^{®}$200 can increase both viscosity and thixotropic hysteresis loop.



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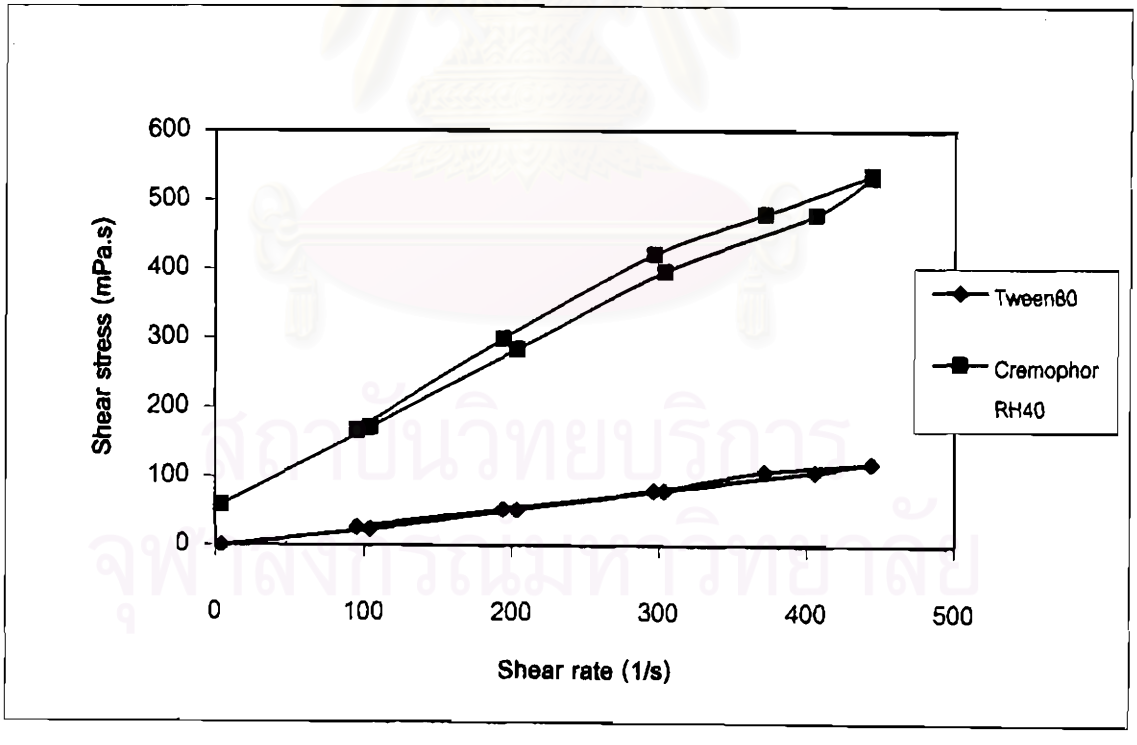
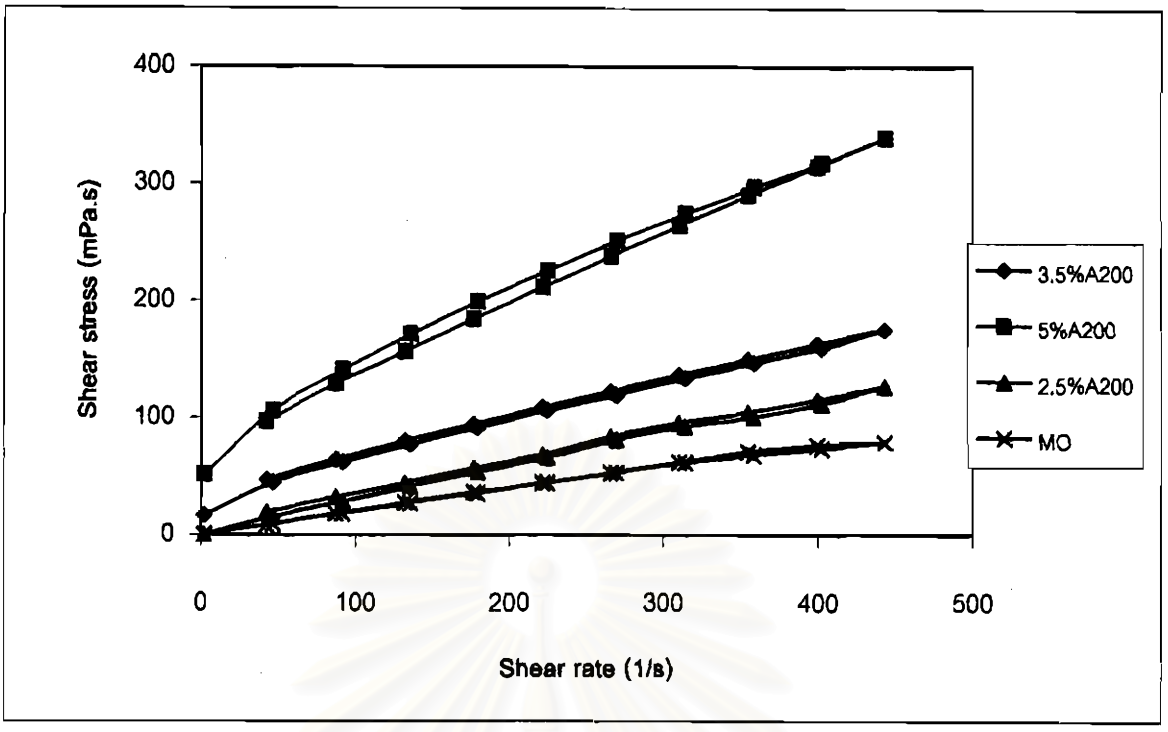


(b)

Figure 39 Rheologram of liquid substance determined by Rotoviscometer

(a) Mineral oil (b) Surfactant



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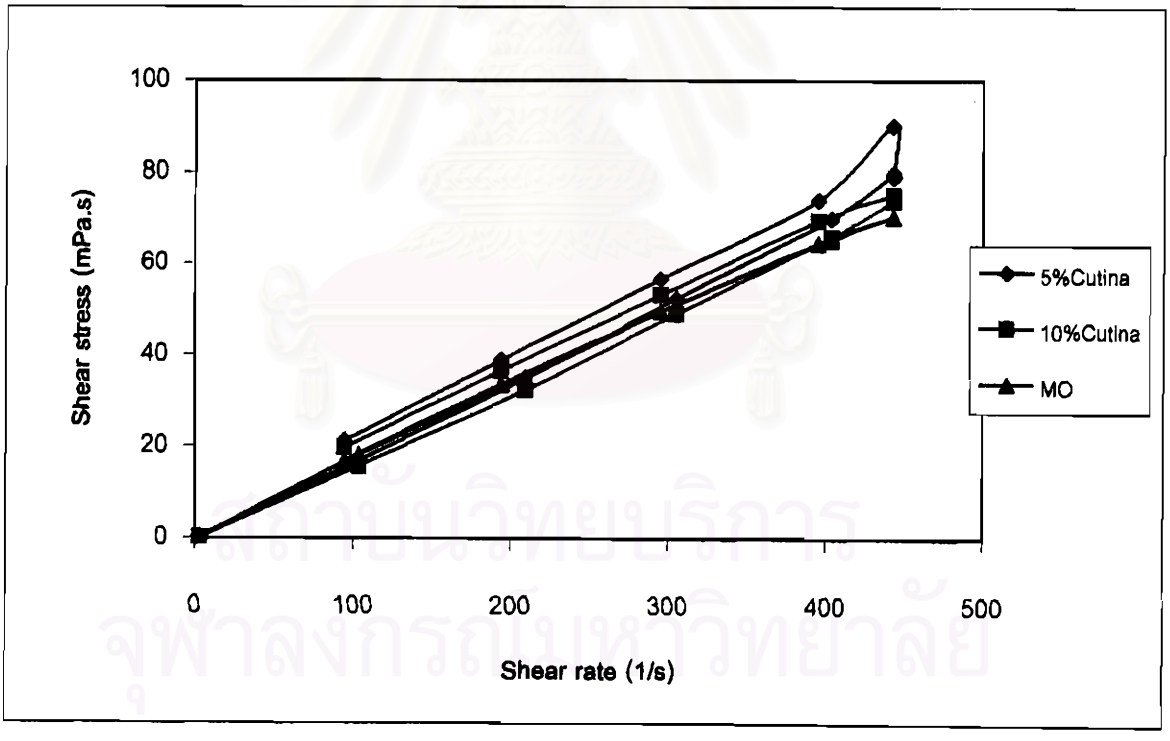
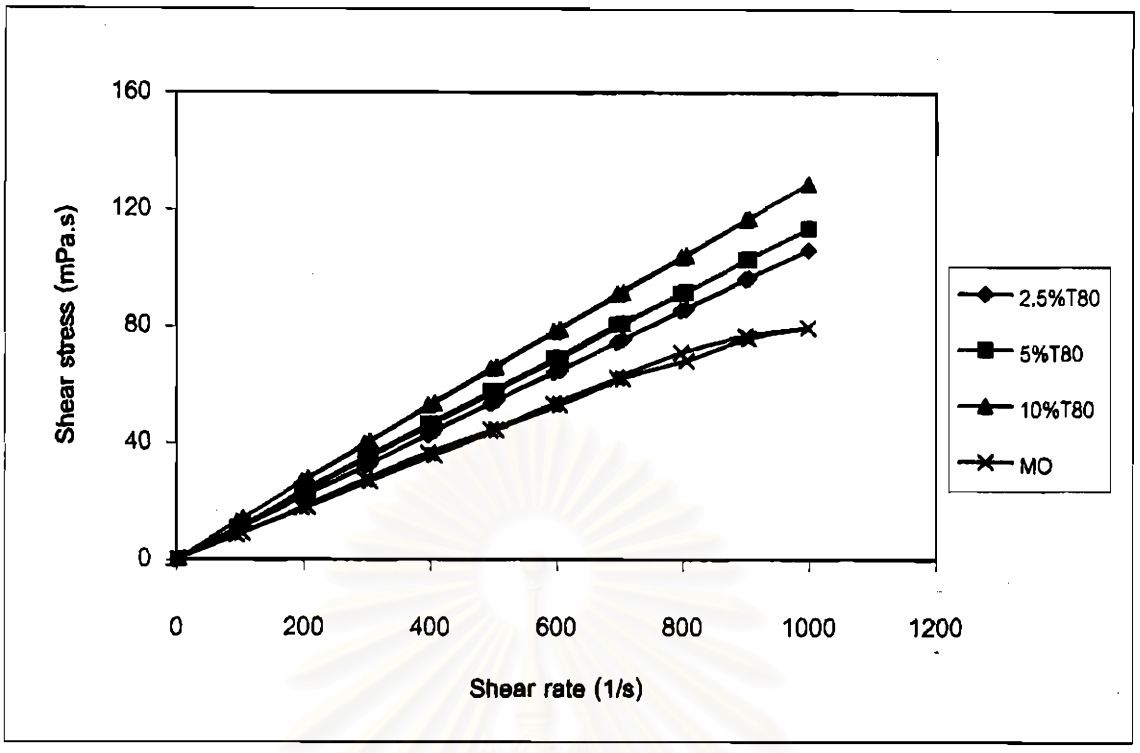


(b)

Figure 40 Effect of thickener on the rheologram of mineral oil, determined by Rotoviscometer

(a) Aerosil 200 (b) CutinaHR



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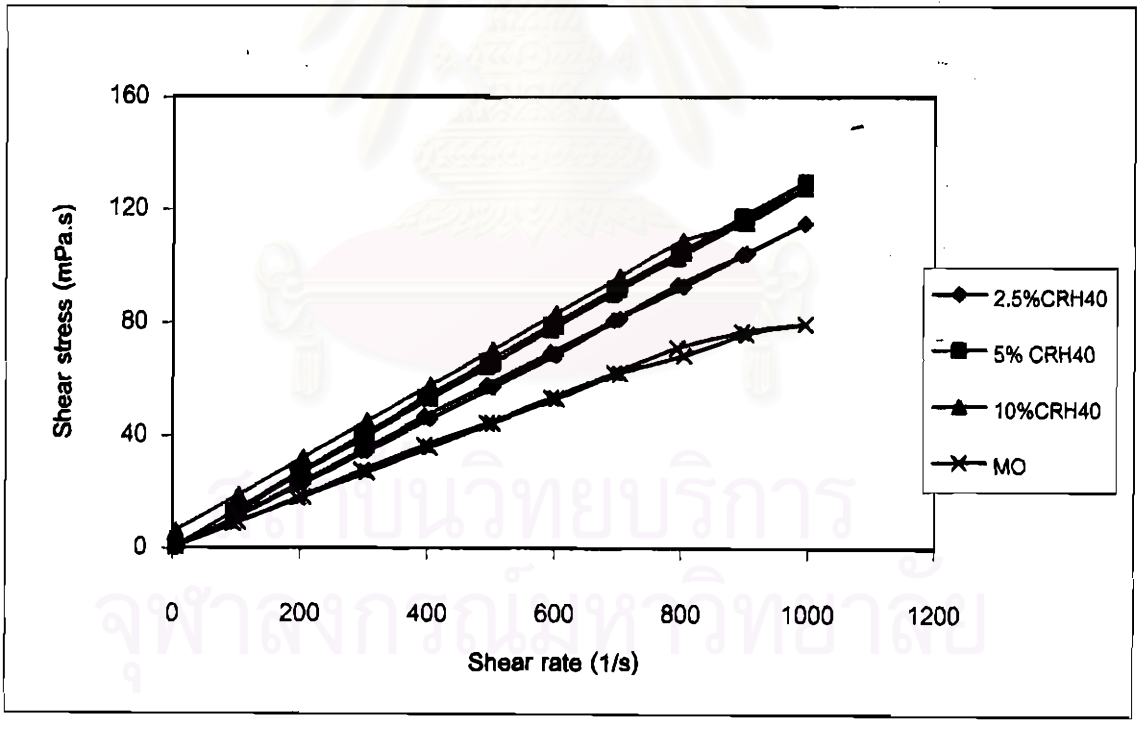


(b)

Figure 41 Effect of surfactant on the rheologram of mineral oil,determined by Rotoviscometer

(a) Tween 80 (b) Cremophor RH40

Table 10 Viscosity of liquid formula recorded by viscometer

Type of formula	Viscosity(mPa.s)			Average	SD	CV
	1	2	3	(mPa.s)		
Mineral oil	106.423	109.401	101.374	105.73	4.06	3.84
MO+2.5%Aerosil200	312.42	308.681	319.644	313.58	5.57	1.78
MO+3.5%Aerosil200	483.581	473.3	482.85	479.91	5.74	1.20
MO+5%Aerosil 200	1008.3	1027.413	898.206	977.97	69.74	7.13
Tween80	118.31	124.35	122.325	121.66	3.07	2.53
MO+2.5% Tween 80	107.344	106.68	110.694	108.24	2.15	1.99
MO+5% Tween80	114.889	115.774	116.945	115.87	1.03	0.89
MO+10% Tween80	129.1	135.616	132.549	132.42	3.26	2.46
CremophorRH40	1287.94	1109.76	1200.627	1199.44	89.10	7.43
MO+2.5%CRH40	119.067	125.122	122.04	122.08	3.03	2.48
MO+5%CRH40	131.94	128.624	127.633	129.40	2.26	1.74
MO+10%CRH40	129.067	125.122	130.269	128.15	2.69	2.10
MO+2.5%Cutina-HR	179.328	164.29	168.234	170.62	7.80	4.57
MO+5%Cutina-HR	184.428	167.575	170.428	174.14	9.02	5.18
MF+2.5%T80	342.216	342.163	358.566	347.65	9.46	2.72
MF+5%T80	290.063	286.147	296.485	290.90	5.22	1.79
MF+10%T80	270.216	290.842	287.203	282.75	11.01	3.89
MF	492.64	423.718	460.097	458.82	34.48	7.51
MO+Dimenhydrinate	155.247	159.447	143.327	152.67	8.36	5.48

MF = Dimenhydrinate+10% dextrose+2.5% Aerosil 200 in mineral oil

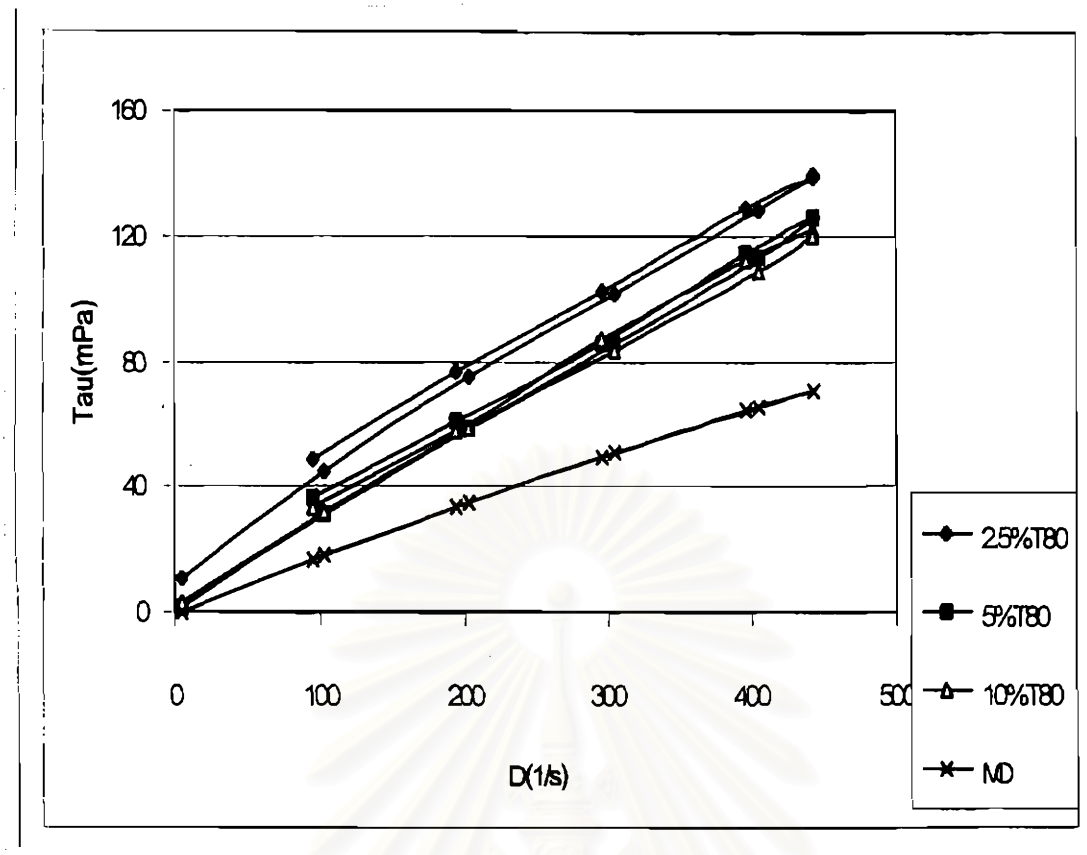


Figure 42 Effect of concentration of Tween 80 on rheologram of liquid mixture, containing dimenhydrinate

The thixotropic loop can be explained by three-dimensional linkage of silanol groups of Aerosil® 200 to oil, it is readily broken down by high shearing and became reestablished when the system is at rest. The higher viscosity has an advantage to prevent leakage but it may reduce drug diffusion rate and also release of the drug from gel matrix, so the optimum amount of silicon dioxide must be investigated for appropriate preparation. Additionally, the degree of viscosity modification or gelation of adding colloidal silica depend upon the method of manufacturer, impurities, pore characterization, particle size, aggregate size, strength and the nature of silica surface (Wallter, 1992). The same characteristic was found when using Cutina-HR® as displayed in Figure 40b, that was according to the study of liquid base selection and it was probably be the reason of prevention of liquid leakage.

In the presence of Tween 80, liquid formula had exhibited Newtonian flow and slightly increased in viscosity (Figure 41a). On the contrary, increasing the

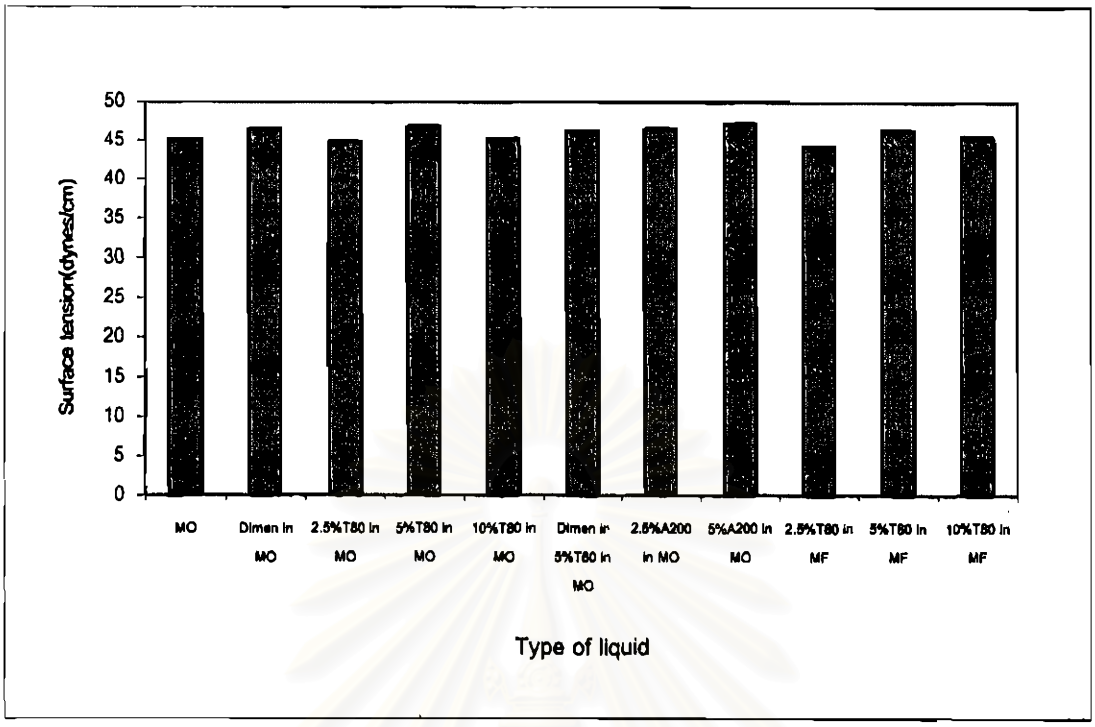


Figure 43 Surface tension of liquid formula, determined by Du-nouy ring tensiometer

concentration of Cremophor® RH40 from 2.5 to 10% w/w resulted in slightly increase in viscosity and showed thixotropic loop in the preparation containing 10% w/w of Cremophor® RH40 (Figure 41b). That was because of the viscosity of Tween 80 and Cremophor® RH40 were 129.1 and 1000 mPa.s respectively, moreover, the Cremophor® RH40 exhibited the thixotropic rheogram (Figure 39b). In the case of preparation containing Aerosil® 200, the increasing concentration of Tween 80 gradually decreased its viscosity but the thixotropic rheogram remained unchanged (Figure 42). This phenomenon meant that surfactant disturbed structural network of Aerosil® 200 in mineral oil so it reduced viscosity of mixture. Nevertheless, the final viscosity was in the range of recommended value.

3.2.3 Surface tension

From the Figure 43, surface tension of all preparations were between 44-47 dyne/cm^2. There was no difference in value when increasing level of thickener or surfactant although these were added up to 10 % w/w of concentration. It was probably due to the equipment did not have enough sensitivity to determine the difference of

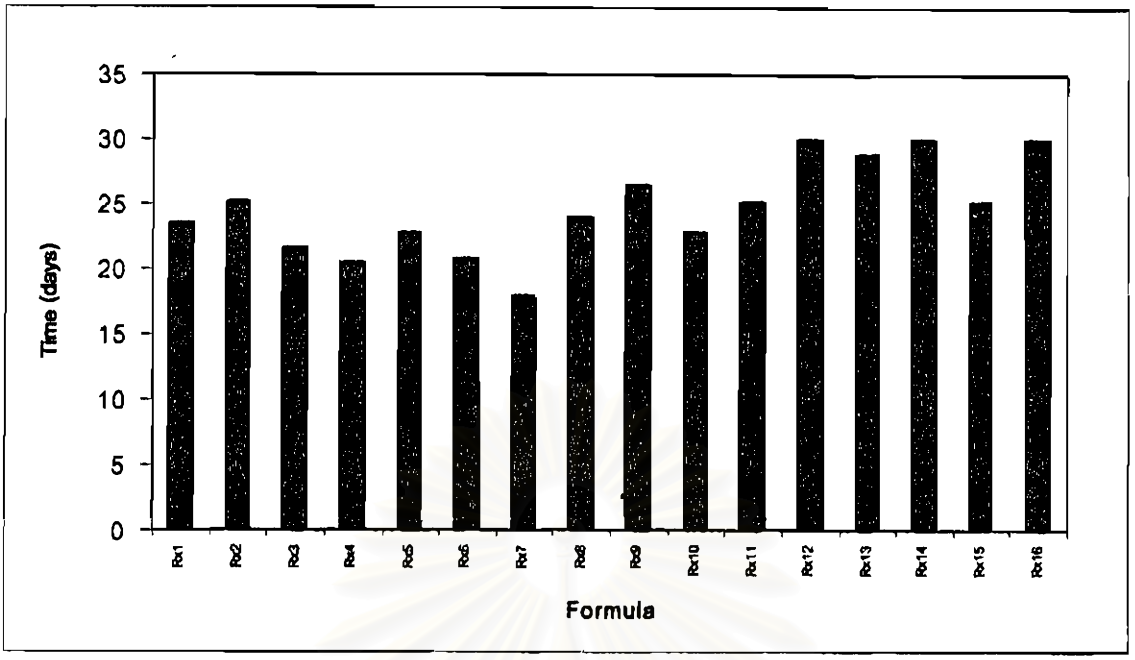


Figure 44 Leakage time of liquid formula, filled into Licaps®

surface tension in the formulation or it might be due to very slight effect of surfactant to surface tension in dosage form. However, it was higher than the recommended value that is preferably more than 30 dyne/cm^2.(Walter, 1992)

3.2.4 Leakage

As illustrated in Figure 44, the addition of thickener i.e. Aerosil®200 and Cutina-HR® (formula 8-13) could prolong leakage time of mineral oil filling in hard gelatin capsule but the incorporation of surfactant i.e. Tween 80 and Cremophor®RH40 (formula 2-7) induced faster leakage time. In the case of mixed formula, although the addition of Tween 80 could reduce the viscosity but the leakage time was longer than that in mineral oil. It probably caused of thixotropic behavior of the preparation.

3.2.5 Particle size analysis

The results of the particle size analysis are shown in Table 11. The bimodal peak in all formula was observed , this pattern indicated that it was not completely formed into emulsion states(Figure 45-46). The system containing surfactant gave smaller and narrow size distribution. When the concentration of Tween 80 in oil

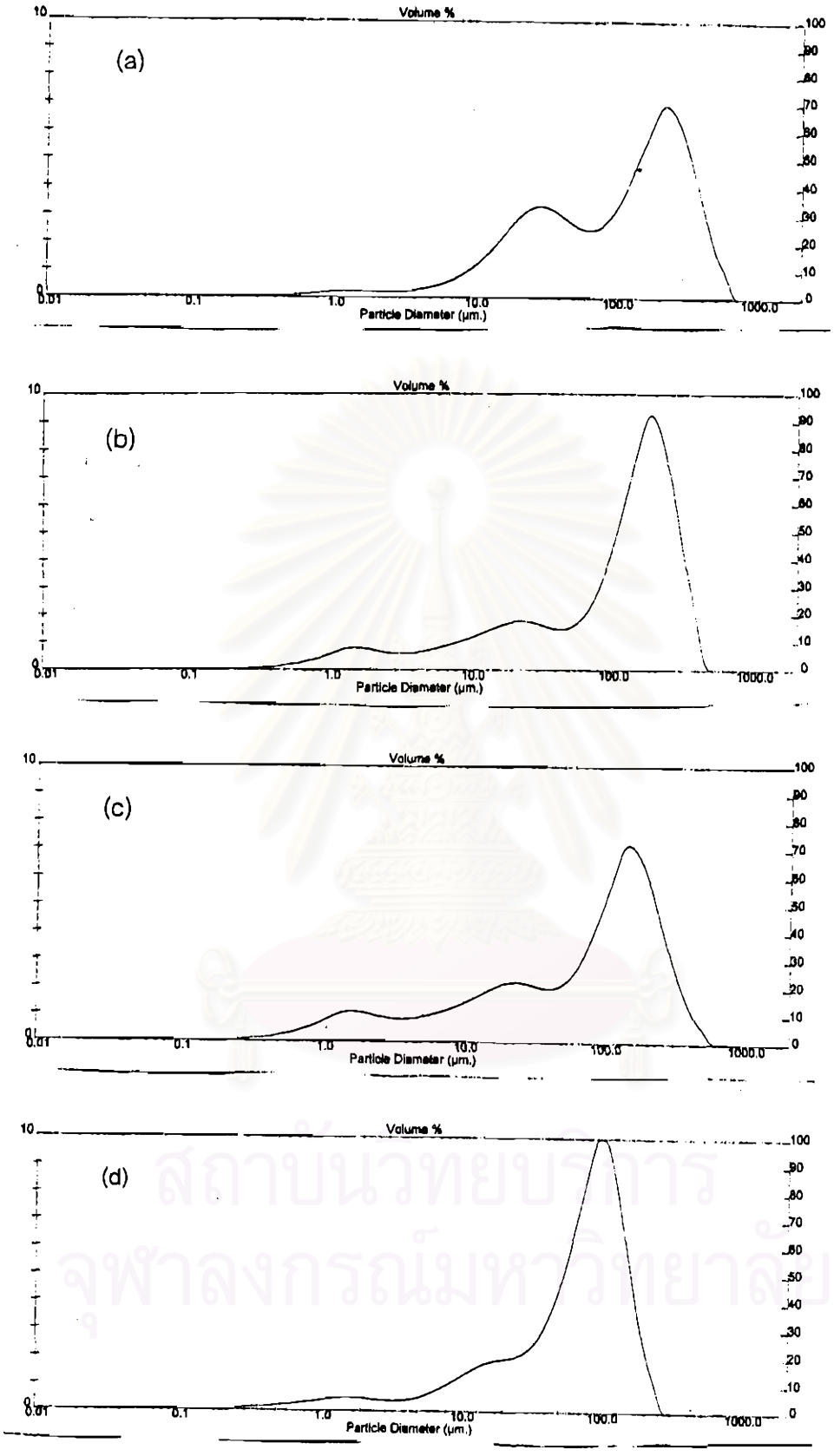


Figure 45 Droplet size distribution of liquid mixture containing

(a) without surfactant (b) with 2.5% Tween80

(c) with 5% Tween80 (d) with 10% Tween80

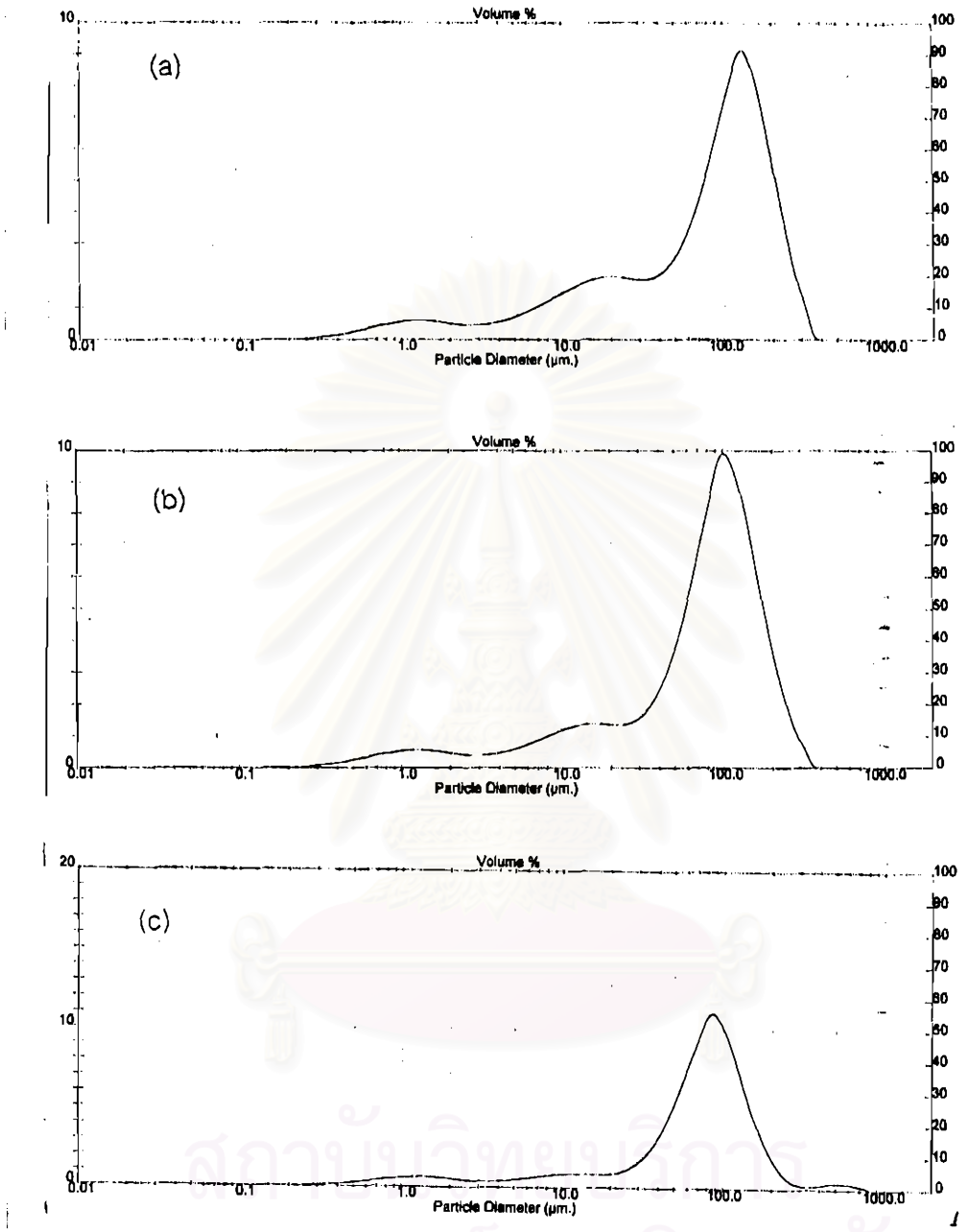


Figure 46 Droplet size distribution of liquid mixture containing

(a) with 2.5% Cemophor RH40

(b) with 5% Crempphor RH40

(c) with 5% Tween80+10% Dextrose

Table 11 Droplet size of liquid formula

Formula	Average diameter of maximum droplet size distribution(micron)	Average Mean diameter (micron)
No surfactant	190.8±5.67	146.13±8.76
2.5% Tween80	163.77±4.38	124.86±6.63
5% Tween80	140.58±3.67	103.50±3.16
10% Tween80	88.91±6.43	78.61±2.41
5%Tween80+ 10% Dextrose	76.32±7.01	86.06±1.73
2.5%CRH40	103.58±3.62	89.45±6.54
5%CRH40	93.58±8.87	92.00±2.64

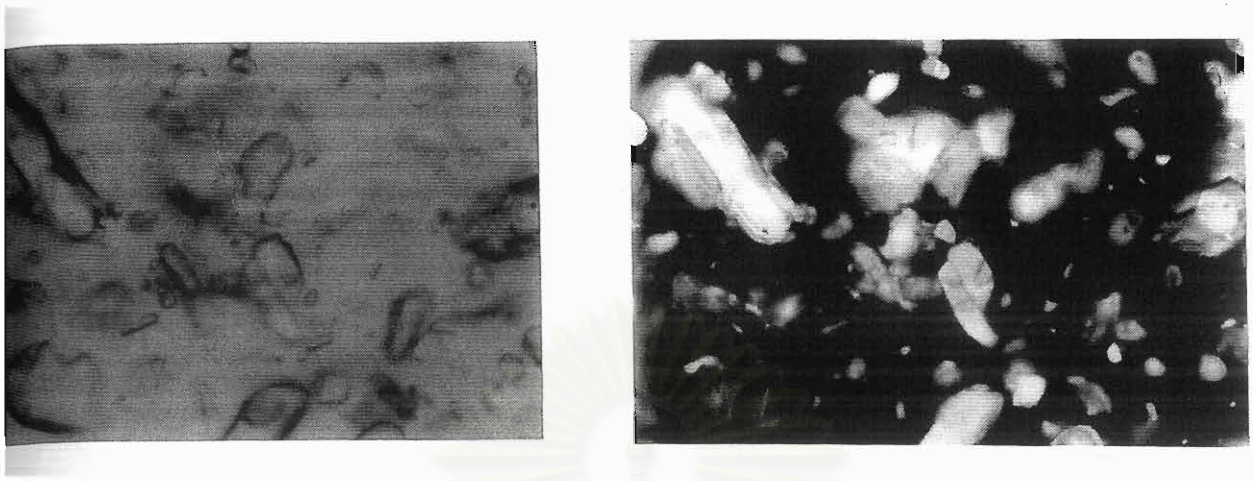
mixture was increased from 2.5 to 10%w/w, the mean diameter became smaller from 146 to 78 μm. Systems without surfactant produce extremely coarse dispersion.

In the case of Cremophor® RH40, particle size of emulsion droplet was similar in all formulation, mean diameters was between 84-89 microns. The particle size of formula containing 5%Tween 80 and dextrose was about 87 microns that was also similar to that of Cremophor® RH40. That may be the reason why the release pattern of system containing Cremophor® RH40 was almost not different when compared to system containing Tween 80.

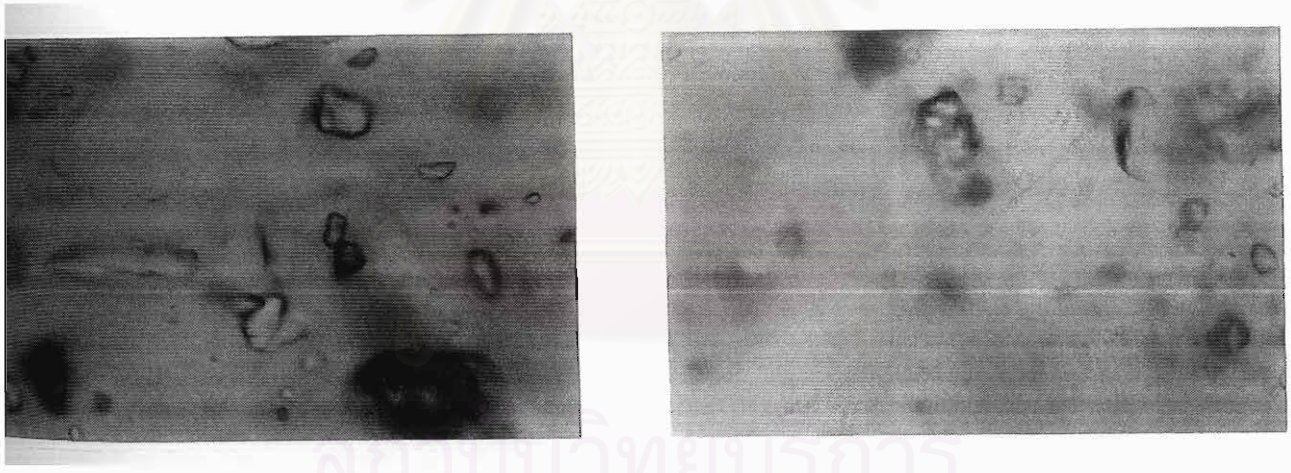
However, the oil layer was found on the surface of the medium. The oil that remained from emulsification process would aggregate to oil layer even an increase of surfactant to 10% w/w concentration.

3.2.5 Microscopic Determination

The liquid systems containing dimenhydrinate, Aerosil 200, Tween 80 in mineral oil were examined by microscopy at room temperature. Dimenhydrinate crystals was found scattering in oil preparation (Figure 47a) and this picture was clearly observed under the polarized light (Figure 47b). When adding water in the liquid



(a) (b)



(c) (d)

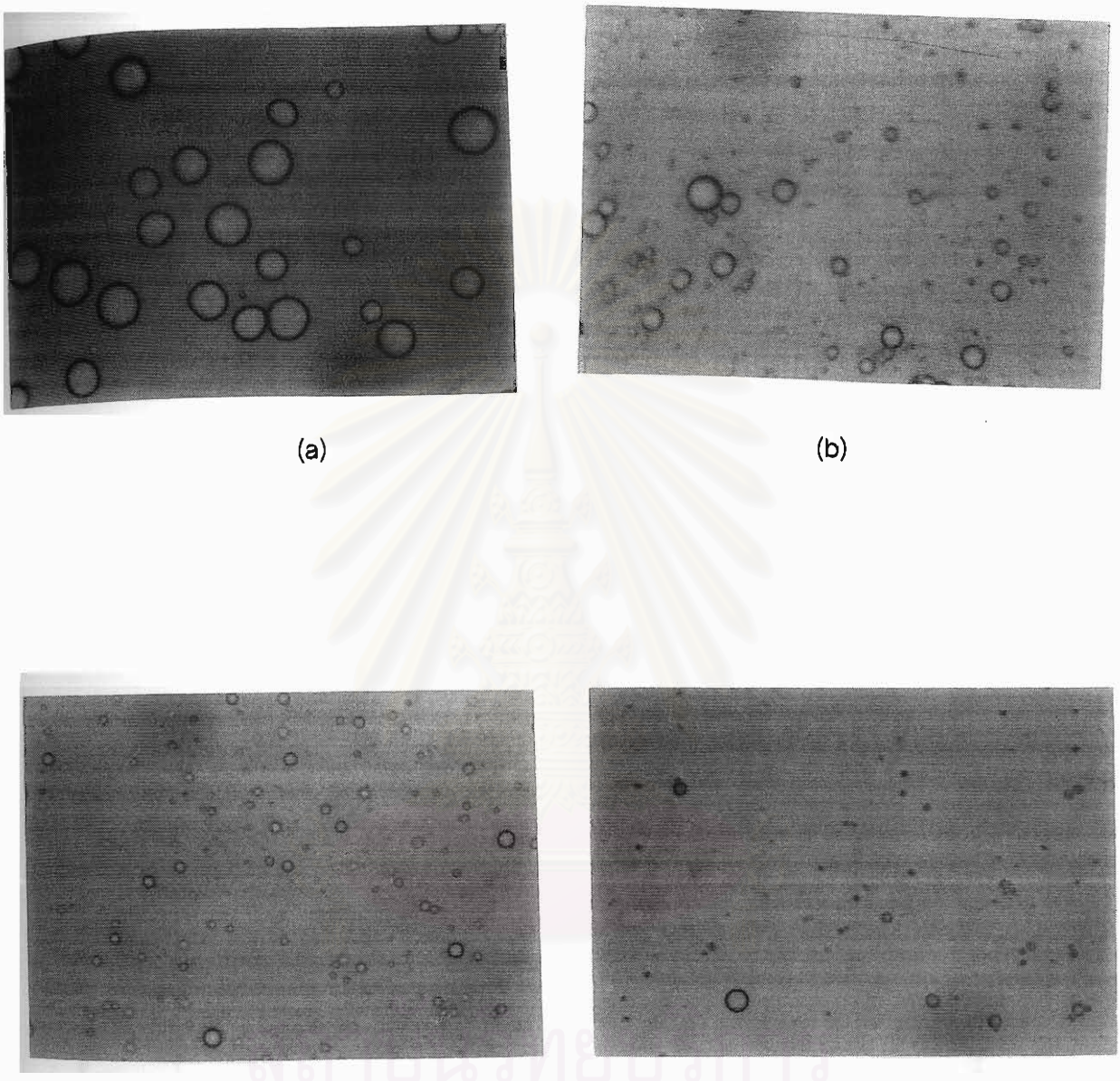
Figure 47 Photomicrograph of liquid mixture containing

(a) Dimenhydrinate in mineral oil

(b) Dimenhydrinate in mineral oil (under polarized light)

(c) Dimenhydrinate in mineral oil, Tween 80 and Aerosil 200 when mixed with water

(d) Dimenhydrinate in mineral oil, Tween 80 and Aerosil 200 when mix with water after 15 min.



(a) (b)

(c) (d)

Figure 48 Photomicrograph of the dispersion of liquid mixture containing surfactant after mixing with water

(a) No surfactant (b) 2.5% Tween 80

(c) 5% Tween 80 (d) 10% Tween 80

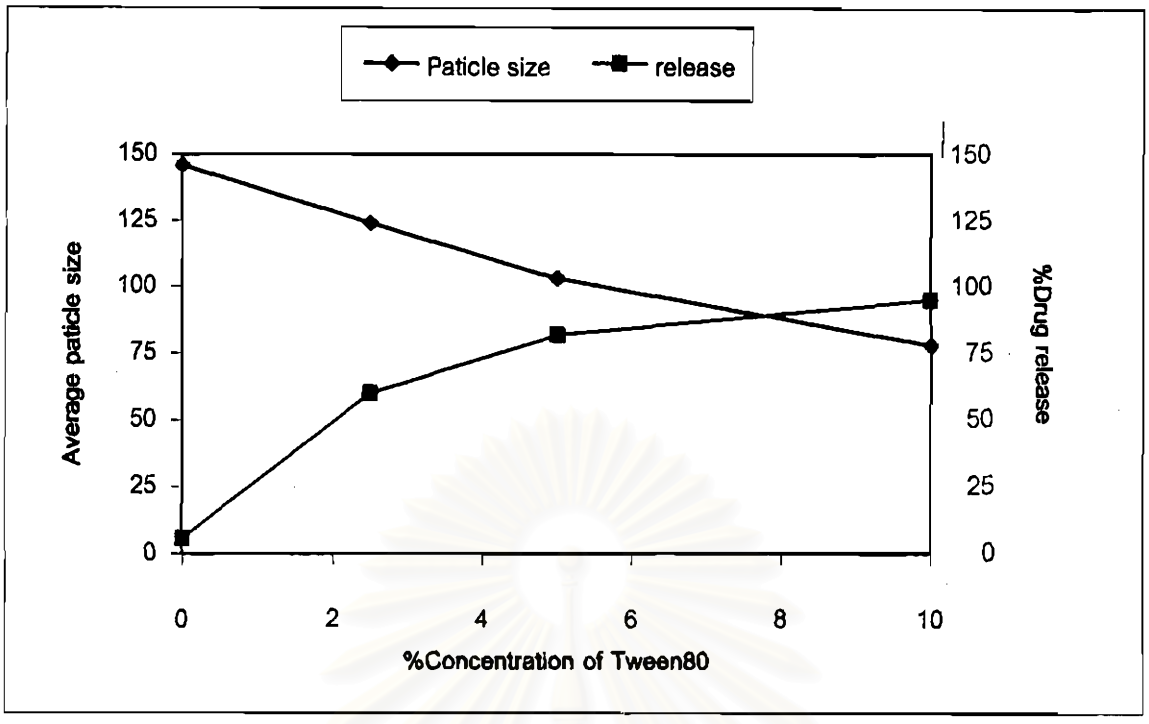


Figure 49 Effect of Tween 80 on particle size and %drug release at 30 mins of liquid filled preparation

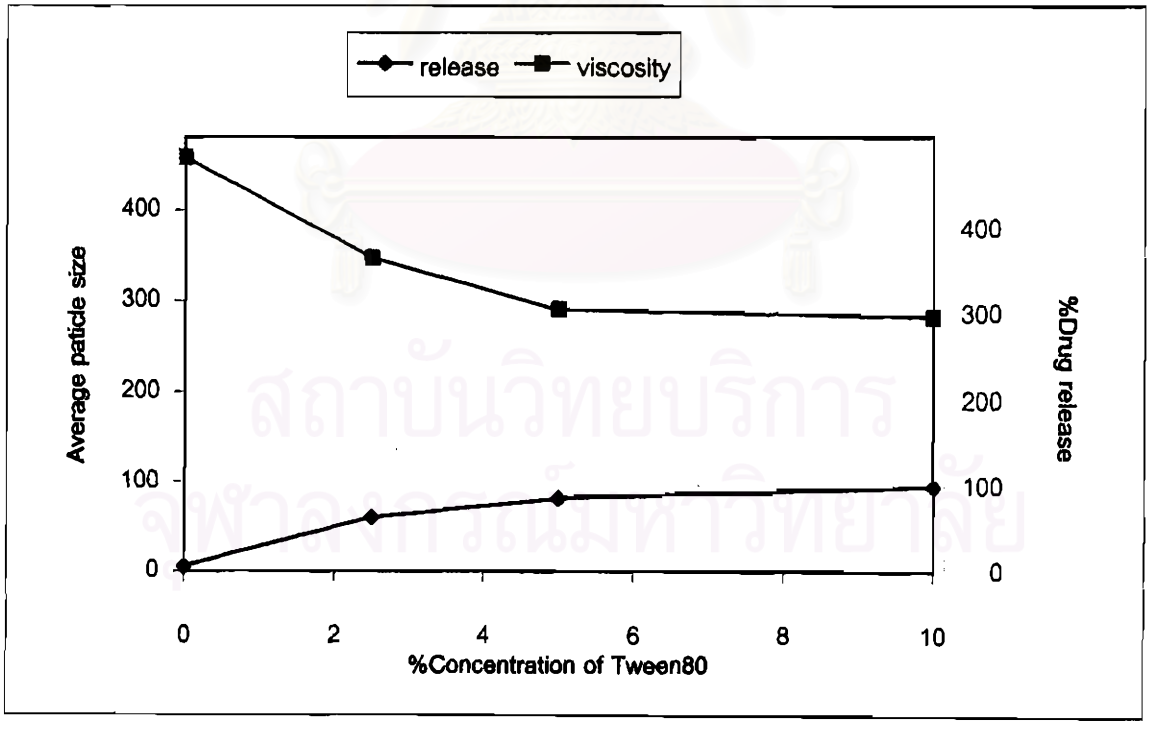


Figure 50 Effect of Tween 80 on viscosity and %drug release at 30 mins of liquid filled

preparation, oil droplets were observed (Figure 47c and 47d). In each system, various sizes of oil droplet were observed but mostly found that oil droplet size would changed depending on increasing proportion of surfactant from 5 to 10% w/w. As shown in Figure 48, comparison of the micropicture of particle size obtained at 37 ^{o}C, smaller droplet size was seen at high concentration of surfactant as visual observed. This result was in the same direction as for particle size analysis.

However, this system showed the solid aggregate that separated and sank to the bottom of preparation. Figure 47d showed photomicrograph of this result, the turbid pieces were the solid aggregate. The same phenomena was presented by Albaut and et al.,(1996). It was concluded that the solid formation have been identified as surfactant aggregates, mainly formed by polyoxyethylene group. This characteristic indicated that the proportion of surfactant and oil was not appropriate to form complete ideal spontaneous emulsion. The microscopic examination of the mixture before and after the water addition consisted that the system became emulsion. In summary, addition of surfactant to the preparation could improve the dissolution rate in relation to the reduction of particle size of oil droplet and viscosity of systems (Figure 49-50).

4. Filling Dimenhydrinate Liquid Base in Hard Gelatin Capsule

From the studied in previous section, the most appropriate formulation in term of drug release, viscosity, surface tension and leakage time, containing dimenhydrinate, Tween 80, dextrose and Aerosil 200 in mineral oil was further evaluated. The selected formula was subjected to scale up(batch size one Kg). Liquid filling equipment was used to fill the preparation into hard gelatin capsule and the products were evaluated for their properties as follows.

4.1 Weight Variation

Ten capsules were weighed every 10 minutes, weight variations are shown in Figure 51. It was found that their weights were between $\pm$5% in normal range. The average net fill weights of 20 capsules containing target doses of 50 mg of drug

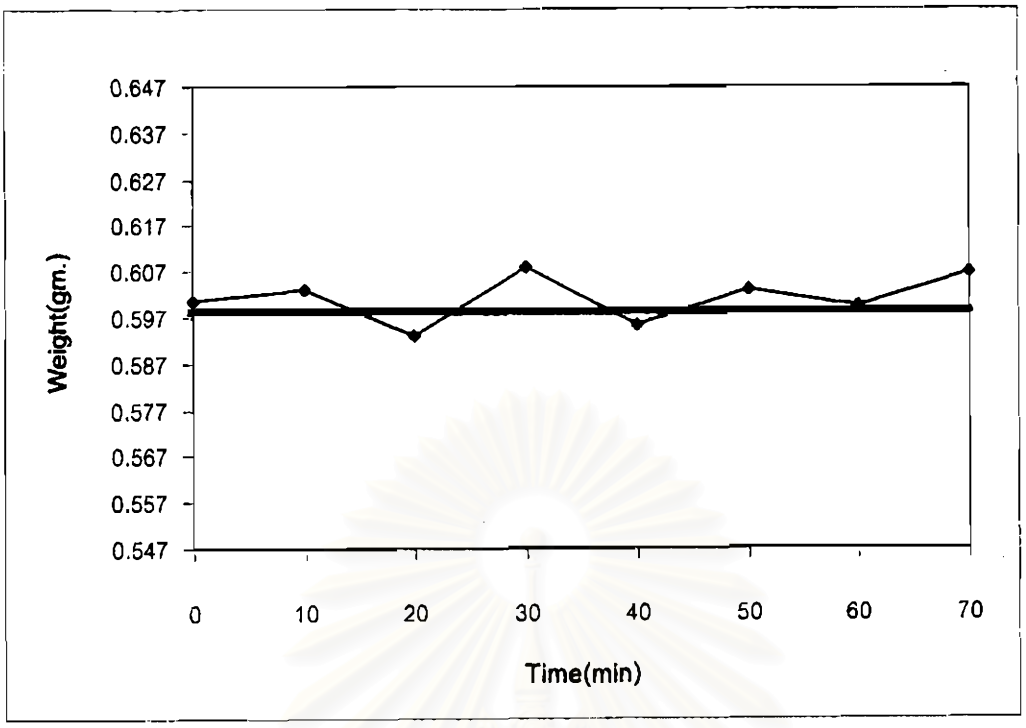


Figure 51 Weight variation of liquid-filled hard gelatin capsule

in 500 mg of liquid base were 498 mg (SD ± 9 mg). Maximum and minimum capsule weight was 520 mg and 486 mg, respectively. Each capsule weight was displayed in Appendix C.

4.2 Disintegration Time

From the preliminary study, the capsule disintegration was determined according to the BP suppositories test. It was found that the capsule began breaking at 3 minutes, the content leaked out of capsule shell and all of content diffused and disappeared within 30 minutes. However, this equipment had some limitations due to capsule floating and only single capsule could be tested one at a time. Disintegration equipment was applied instead of suppository disintegration apparatus because it could determined six capsules at the same time and the observation of capsule breaking could be taken easily.

For this method, each capsule was placed in a basket tube without operating and the disk was put over to prevent capsule floating. The result of disintegration time

Table 12 Disintegration time of uncoated capsule in phosphate buffer pH7.2 using different disintegration testing method

Sample No.	BP test	Applied DT apparatus
1	2.50	2.30
2	3.25	2.25
3	2.75	2.75
4	3.00	3.10
5	3.00	2.25
6	2.15	2.50
Ave.DT	2.78	2.53

Table 13 Content uniformity of liquid filled hard gelatin capsule

Sample no.	%Drug content
1	101.43
2	99.34
3	103.92
4	100.27
5	101.46
6	100.5
7	98.29
8	99.11
9	100.82
10	99.01
Averg	100.415
SD.	1.631
CV.	1.624

from two apparatus was similar; it started by the rupture of gelatin shell, allowing the release of liquid content within 3 minutes (Table 12). Hence, the disintegration apparatus was applied for disintegration determination. The comparative disintegration time of rectal capsules prepared and Gravol® suppositories are slightly different. Gravol® would dissolve immediately when in contact with water whereas rectal capsule would break within 3 minutes, however, both of them completely distributed within 30 minutes.

In addition, Suppotest was one of the equipment used to compare the disintegration time of suppositories. Sample was placed in a glass of vessel containing 8 ml of water at 37±2 °C and subjected to a load of 0.3 N with ram. As soon as the ram has reached a distance of less than 1 mm from the bottom of vessel, the suppository was considered melt. Rectal capsule was tested in this equipment; disintegration time was 4 minutes and it was similar to BP method. The data of rectal capsules tested by Suppotest are shown in Appendix C. However, disintegration time of capsule in this method was different from the case of Gravol® suppositories, it rapidly dissolved when in contact with the medium and completely dissolve within 25-30 minutes in both BP test and suppotest.

4.3 Content uniformity

The percentage drug content in each capsule is shown in Table 13. The average drug content was 100.415% with standard deviation 0.6 and the content lies within the limit as specified in the monograph of dimenhydrinate suppositories USP, 1985 which must be in the range of 90 percent to 110 percent of the label claimed.

5. Coating of Hard Gelatin Capsule

For the objective of rectal gliding and addition of protective coat, polymer which dissolves in pH range 7.0-7.5 was selected. The liquid-filled capsules were coated with two polymeric groups; cellulose and polyacrylate groups are the most popular polymers used at present. Low viscosity grade of hydroxypropylmethylcellulose (HPMC)

represents the cellulose group due to many advantages such as excellent film formation, rapid dissolving in water, good stability and compatibility and minimum toxicity. Additionally, HPMC was usually mentioned in the case as precoated action of hard capsule coating (Cherrette et al., 1992, Thoma et al., 1989). For polyacrylate groups, Eudragit® L (methacylic acid and methylmethacylate copolymer) was employed due to good stability under tropical condition, high resistance to water vapor permeability, dissolving in neutral pH (6-7). It was reported that capsule coated with Eudragit® L 30D showed excellent physical stability and there were no change in dissolution characteristics after storage at 37 °C and 80% RH for three months and after storage for nine months at room temperature (Murthy et al., 1986).

From the preliminary study, the amount of HPMC (Methocel® E5) used in coating solution should not exceed 5 % w/w since higher concentration gave too viscous liquid to be sprayed and the obstruction of spraying nozzle was encountered in both coating with perforated pan coater and fluidized bed coater. Hence, this concentration of coating solution was also used for Eudragit® L 30D-55 in order to compare effect of different polymers in the same coating conditions.

Plasticizers is one of the most important substance that used to alter the physicomechanical properties of polymer such as tensile strength, glass transition temperature, elasticity and flexibility including Young's modulus. It is a necessary component to reduce brittleness, improve flow, impart flexibility and increase toughness, strength and tear resistance of the film coat (Banaka, 1966). The plasticizers are generally classified as being water-soluble and water insoluble group. As part of Eudragit® L, various plasticizers were found to change minimum film forming temperature (MFT). Water soluble plasticizer such as triethyl citrate, triacetin, PEG could reduce MFT from 27 °C (without plasticizer) to lower than 10 °C, whereas water insoluble plasticizer such as dibutyl phthalate showed the opposite effect. MFT was increase to 35-40 °C because it was not homogeneously mixed with aqueous polymeric dispersion. However, the controversial effect was found in diethyl phthalate, water

insoluble plasticizer, that it could also reduce MFT to the same level as water soluble plasticizer (Porter and Ridway, 1983). Hence, both water soluble and water insoluble could be incorporated to two polymeric groups in order to modify the film properties.

From the preliminary study, The thin film of HPMC (70-90 μm) was prepared from plate casting method. The pure polymeric film was transparent, as were the films that were obtained when TEC, TRI, PEG 6000 were used as plasticizer up to 20% by weight of the polymer. In contrast to the film incorporated with PEG 20000 and DBP, the films are changed from clear to opaque and orange-peeled characteristic especially in the high concentration of these plasticizers while incorporation of DEP showed slightly cloudy and smooth films. The immisicibility was attributed to the differences in polarity and refractive index, as well as the inability of these plasticizers to disrupt the intermolecular bonding in molecular chain. From the preliminary study, HPMC film with TEC displayed better effect than TRI in term of water vapor permeability. Hence, TEC, PEG 6000 (water soluble plasticizer) and DEP (water insoluble plasticizer) was selected to incorporate to coating solution.

Coating conditions

5.1 Coating Capsule with Fluidized Bed Coater

Aqueous film coating technique is of current trend in the pharmaceutical industry. The aqueous colloidal latex dispersion of Eudragit® L 30D-55 was used and the condition performed based on describing by Hagenlocher et al. (1986). There were slightly changed in some parameters since agglomeration of capsule occurred, then they stuck together and clogging in inner column of the fluidized bed coater (Wurster column). Feed rate was set at 8-12 rpm while inlet temperature was set at 45 °C; it was above the minimum film forming temperature that was between 27-30 °C. Lechmann et al. (1989) studied condition of coating with aqueous latex film and concluded that the application temperature should exceed the minimum film forming temperature by 10 to 20 °C. It was the appropriate temperature at which a polymer emulsion formed a continuous film and reduced cracking on free film. The optimizing air pressure should be

adjusted in corresponding with the feed rate, otherwise it might cause overwetting and formation of capsule agglomeration and later blockage including breaking of capsule.

Nevertheless, coating solution of Methocel® E5 could not be used in aqueous system because high temperature must be employed to complete drying of capsule. The separation (sliping between cap and body part of Licaps®) of hard gelatin capsules were found during the coating process above 45 °C, so it caused the liquid leakage. But if temperature was reduced to lower than 45 °C, capsule clogging in coating column occurred. Hence, it was necessary to use combination of organic solvent and water in order to reduce these effects. Ethanol was selected as combined solvent in coating solution due to low toxicity, miscible to water. With this purpose the different 95% ethanol: water ratios were investigated. From the preliminary study, as a consequence of the ratio 1:9 to 9:1 ethanol: water. The results, in terms of sprayability (feasible spraying: neither clogging of the nozzle nor powdering during spraying) showed that at the 1:1 ratio of ethanol: water was the lowest amount of ethanol that could reduce drying temperature to 40-45 °C without slipping of hard gelatin capsule.

The bottom spraying method was found to be appropriate in providing excellent capsule suspending in air steam, no blockage of capsule and good flowability around the product container while the top spray could not make suitable capsule floating during spraying because atomized pressure was not enough to blow capsule up. Hence, the bottom spray was selected to coat hard gelatin capsule and the suitable coating condition presented in method no. 5.2 were found to be optimal and completion of coating by visual observation.

5.2 Coating Capsule with Perforated pan coater

The same polymers, outlet temperature and feed rate that used for coating with fluidized bed coater, was used to compare the effect of equipment. Nevertheless, the tackiness of capsule coated with Eudragit® L 30D-55 was usually observed in higher degree than using fluidized bed coater. The suitable coating conditions presented in Table 7 were found to be optimal and completion of coating by visual observation.

Figure 52 Feature of hard gelatin capsule
(left) uncoated (middle) coated with HPMC (right) coated with Eudragit

The film properties and drug release characteristics of coated capsule based on two type of polymers, amount and type of plasticizer and coating equipment were compared.

6. Evaluation of Film Coated Capsules

6.1 Film thickness

The feature of coated film using HPMC, Eudragit® L30D-55 and uncoated capsule are shown in Figure 52. HPMC polymer showed the continuous film and could wrap around the junction between body and cap of hard gelatin capsule whereas Eudragit® polymer could not show the continuous film. The film thickness of coated capsule was determined using micrometer. HPMC film was easily peeled from the capsule shell. The average film thickness of 10 capsules in each batch is shown in Table 14. The amount of coated films was quantities of total film solid (mg/cm^2) and it was calculated from the average thickness of coated capsule, divided by capsule surface areas. The capsule surface of Lcaps® no.0 is 5.14 cm^2 that was calculated from their feature and it is similar to the capsule surface of ordinary capsule as shown in Table 4.

Table 14 Thickness of peeled cellulosic film

Formula	Fluid bed coater		Perforate pan coater	
	Averg. Thickness (micron)	S.D.	Averg. Thickness (micron)	S.D.
1	77.1	4.07	75.1	3.75
2	78.6	3.57	72.5	1.90
3	79.0	2.49	78.6	2.27
4	76.5	2.80	76.2	2.78
5	71.0	2.49	71.4	2.72
6	80.8	4.05	78.9	2.51
7	82.8	4.13	77.6	3.31
8	80.0	4.81	80.1	3.03
9	75.5	5.50	73.6	3.05
10	82.9	2.33	77.2	2.53

In the case of HPMC, the average amount of polymer coated with fluidized bed coater was 10.07 mg/cm^2 whereas the amount was 9.86 mg/cm^2 for perforated pan coater. The lower amounts indicated that capsule coating with perforated pan coater had greater chance to loss of polymer during coating process. In the case of Eudragit® L 30D-55, the equivalent amount of polymer was used but Eudragit® L 30D-55 film could not be determined by micrometer. Because this film became homogeneously deposited on capsule shell and it was broken to small pieces during the peeling process from the surface of capsule shell.

6.2 Water Vapor Permeation

Water-gas vapor permeation is an important factor in protective coating that enhance stability by preventing the substrate from gases such as oxygen or carbon dioxide or from water vapor. The permeation involved transportation of permeant in the polymer film and the movement of the unbound fraction of the permeant through the polymer. Film permeability is usually related to the hydrophilic or hydrophobic nature of

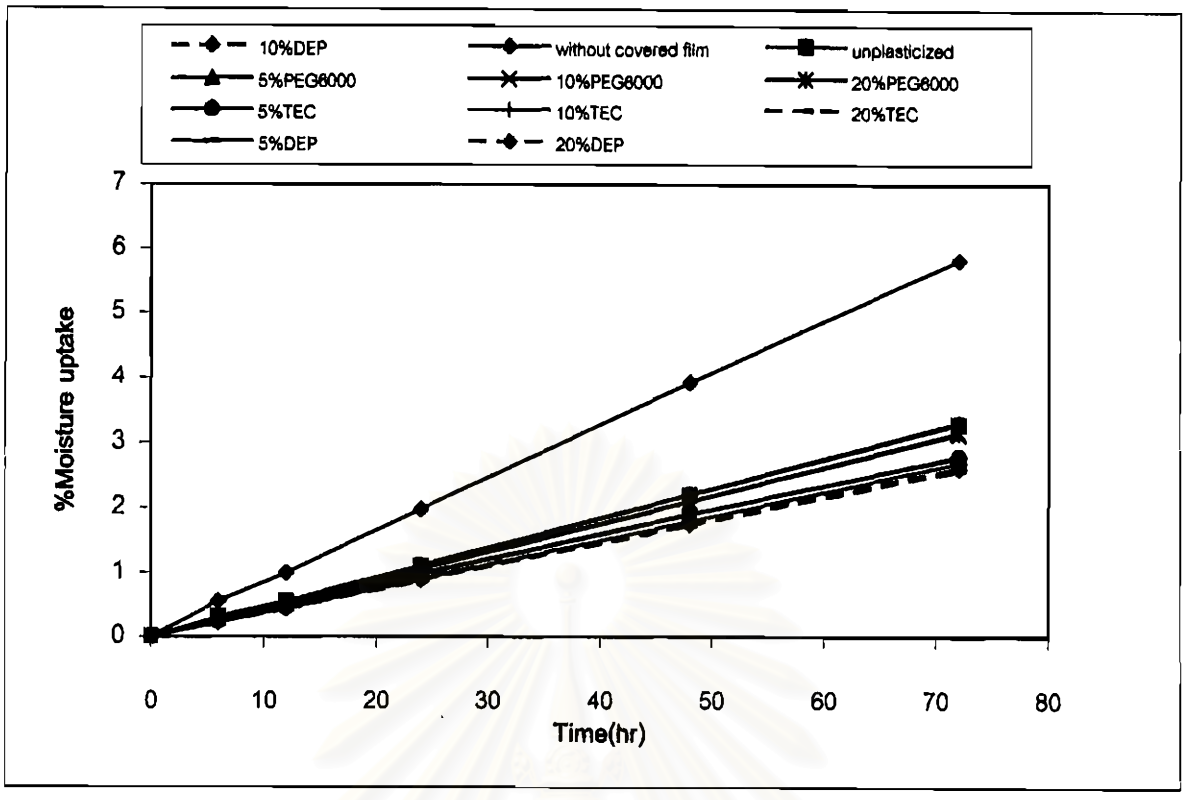


Figure 53 Water vapor permeation of HPMC film incorporated with various types of plasticizer

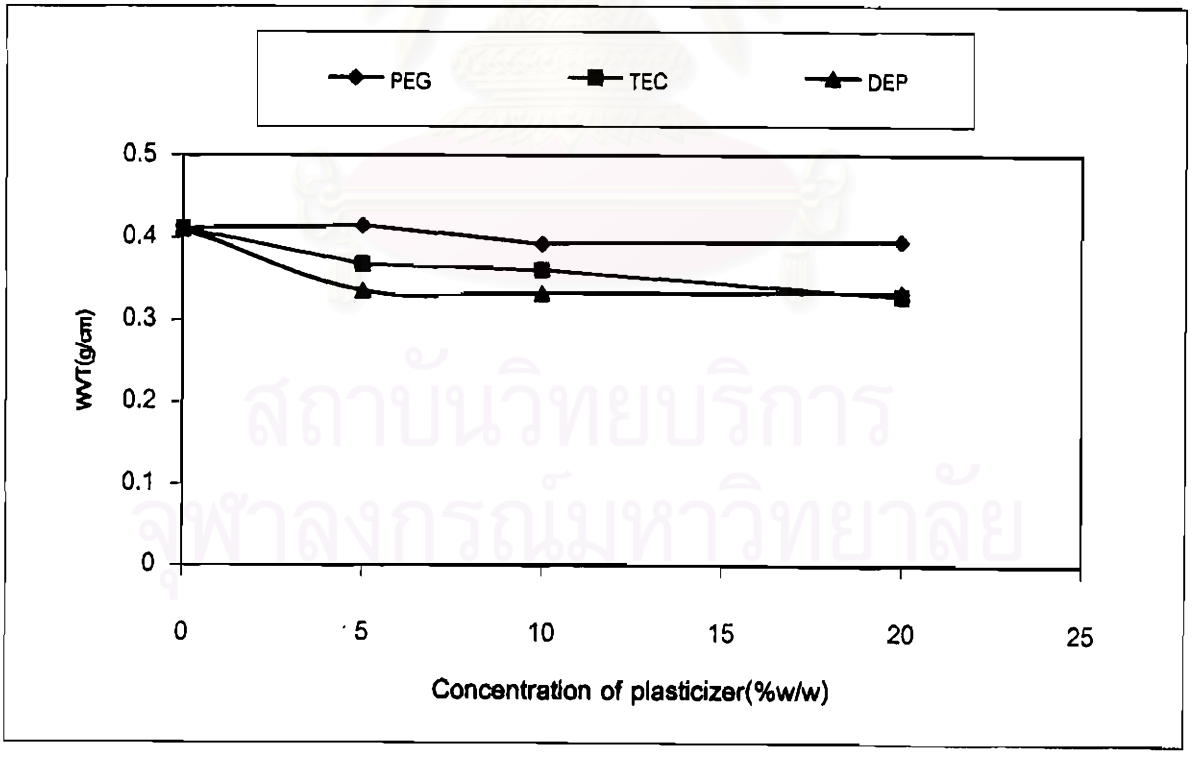


Figure 54 Effect of plasticizer on water vapor transmission rate of HPMC film

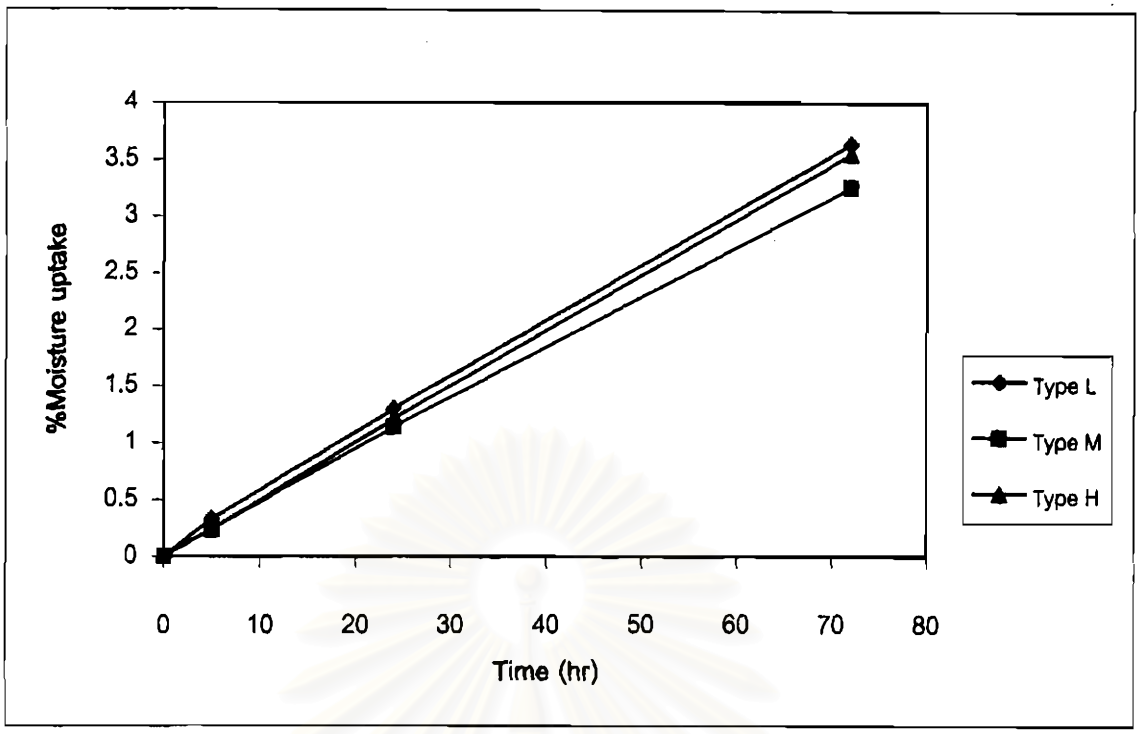


Figure 55 Water vapor permeation of HPC film

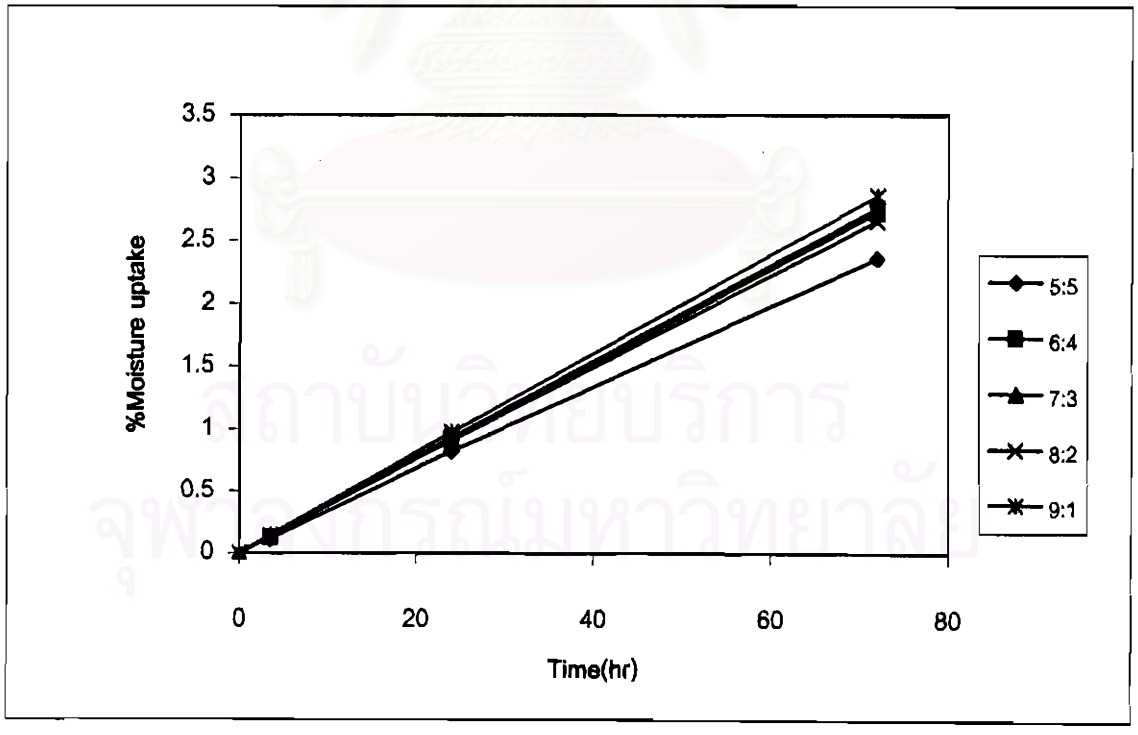


Figure 56 Water vapor permeation of different ratio of HPMC:HPC film

the polymer and it depended on the film compositions, film thickness, and isolation technique, thermal treatment and also relative humidity (Sprockel et al., 1990; Baert and Remon, 1993). Hence, testing condition during the experiment was strictly controlled.

As seen in Figure 53, the pattern of water permeability of these films was shown in linear pattern. The highest curve was the absorption of calcium chloride without passing through free films. The water vapor transmission rate of unplasticized film was higher than all plasticized film and over the range of plasticized level, the tendency of permeation of these films decreased as amount of plasticizer increased. To explore the effect of higher plasticizer levels on film permeability, the results of these are shown in Figure 54, where the range of plasticizer levels was varied from 0 to 20%w/w of polymer. As the TEC level was increased, the water vapor permeability was slightly decreased, whereas films platicized by PEG 6000 showed an initial increase of permeability at the 5% plasticizer level, followed by decreased in permeability at the higher plasticizer level to 20%. As water vapor permeability of film plasticized with DEP was decreased at 5% plasticizer and remained unchanged although increasing to 20% of DEP. The lowest permeability was found in films containing DEP and 20% TEC. The water vapor transmission rate was decreased in the following order DEP<TEC<PEG 6000< unplasticized film. It was indicated that plasticized film could resist to water vapor as reported by Rao and Diwan (1997) and Johnson et al. (1991). They found that PEG 400 could enhance water vapor permeability of the free film due to densification of the smaller plasticizer molecules. For the films plasticized with DEP showed the lowest water vapor transmission rate due to water insoluble property of DEP that protect water vapor passing through the molecule of HPMC.

From the preliminary study, hydroxypropylcellulose (HPC) that was commonly used in moisture protective coating formula was selected to combine with HPMC. They are three types; L, M and H depended on their viscosity. As seen in Figure 55, HPC type M showed the most suitable polymer due to its appropriate viscosity for preparing and lower water vapor transmission rate compared to other films. The water vapor transmission rate of the different ratio of HPMC: HPC type M is displayed in Figure 56.

The result showed that the lowest value was obtained at the ratio of 6:4 of HPMC: HPC type M and it is slightly lower than HPMC plasticized with DEP.

In the case of Eudragit® L30D-55, the film was broken when pressing between covering the hole of glass vial due to high brittleness of these films. Hence, the water vapor permeation rate could not be determined. The Eudragit® L film characteristic was discussed in 6.3.

6.3 Mechanical Film Characteristic

Film coating system which produced tough film with high mechanical strength and elongation are the best suited for tablet and also capsule coating (Hutchings et al., 1994) The mechanical properties of polymeric films are usually evaluated on spraying or casting film. In this experiment, casting dry film with the same thickness and drying temperature of coating machine was performed in order to investigate the effect of different types and levels of plasticizers on physico-mechanical properties of HPMC films. An equilibration period for 30 days at 30°C and 45% relative humidity was employed to facilitate the removal of ethanol from HPMC cast film.

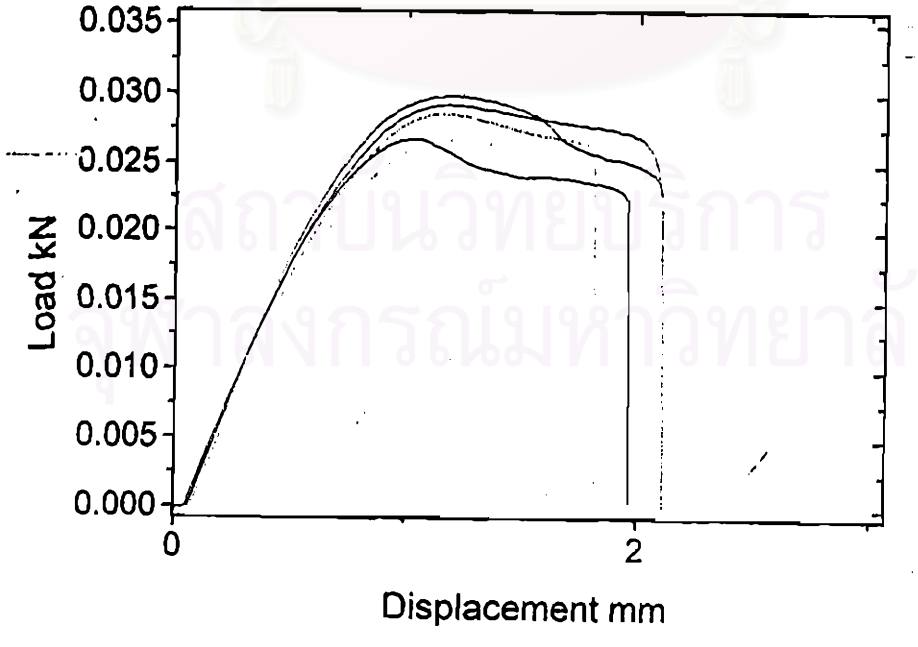


Figure 57 Stress-strain curve of HPMC film characteristic

Table 15 Mechanical properties of free film

Platicizer added	Load at max (KN)	Max.Stress (mPa)	% Elongation	Modulus	Energy at break (KN)
Unplasticized film	0.029	31.27	5.045	1684	0.062
5%DEP	0.026	28.996	5.834	1510	0.041
10%DEP	0.029	30.489	6.339	1405	0.038
20%DEP	0.024	25.98	7.82	1218	0.03
5%PEG 6000	0.029	36.14	6.542	1662	0.044
10%PEG 6000	0.024	29.19	6.261	1461	0.031
20%PEG 6000	0.025	25.45	8.26	1297	0.034
5%TEC	0.028	31.46	5.76	1577	0.034
10%TEC	0.027	27.82	6.26	1299	0.035
20%TEC	0.023	23.44	7.334	1108	0.032
HPC type M	0.03	32.55	5.24	1571	.058

The film of HPMC without plasticizer resulted in hard and tough with high value of maximum stress, %strain and modulus of elasticity (Figure 57). The results of the influence of three levels, different plasticizer on the tensile strength, %elongation (maximum percent strain) and modulus of elasticity (Young's modulus) are shown in Table 15. Tensile strength is defined as the maximum tensile stress, which a material is sustainable. A comparison of the tensile strength value for the free films containing 5 to 20% plasticizer level is displayed in Figure 58. In all cases, the addition of the plasticizers included DEP, TEC and PEG 6000 resulted in a reduction of the tensile strength of the films. TEC containing film showed the highest effect when compared to the other types. However, the plasticized film in which the incorporation of 5% w/w concentration was not significantly different from unplasticized film. This result was resembled to a previous study by Mcginity et al. (1994). It was found that a plasticizer concentration of 10% by weight of the polymer might be a critical concentration, since below this concentration no significant plasticizing effect could be obtained.

Percent strain or elongation which is defined as the distance at break related to original distance of free film. The percent elongation was found to increase with

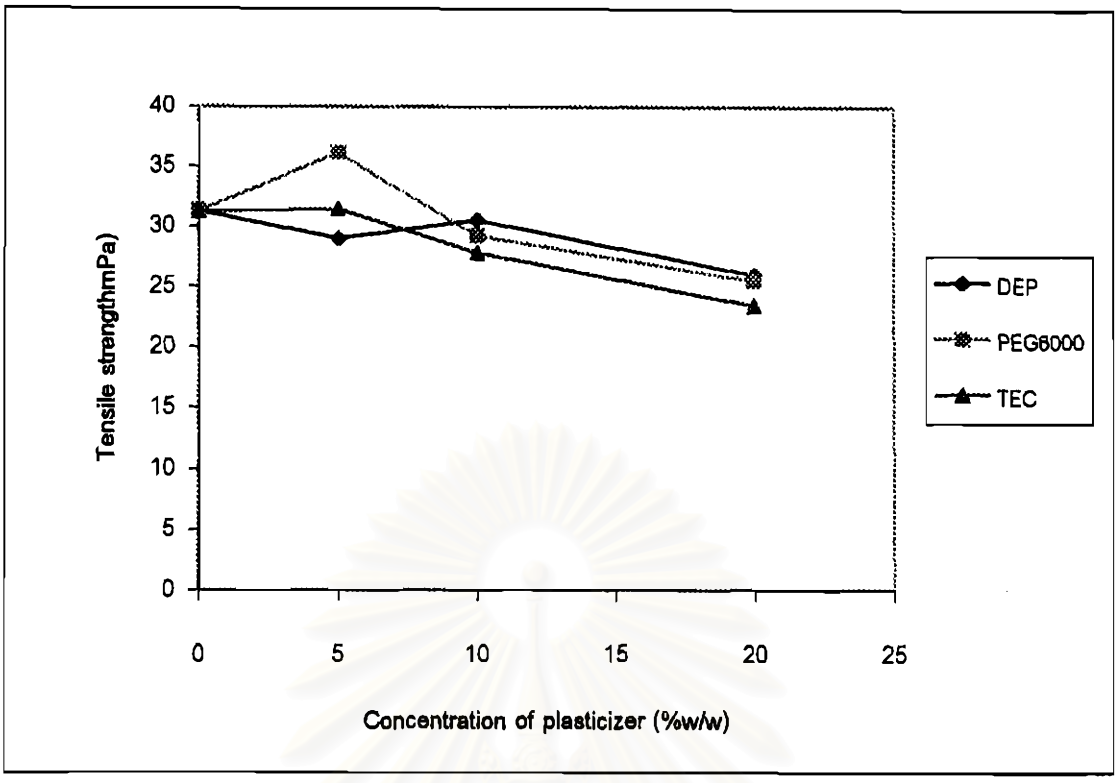


Figure 58 Effect of plasticizers on tensile strength

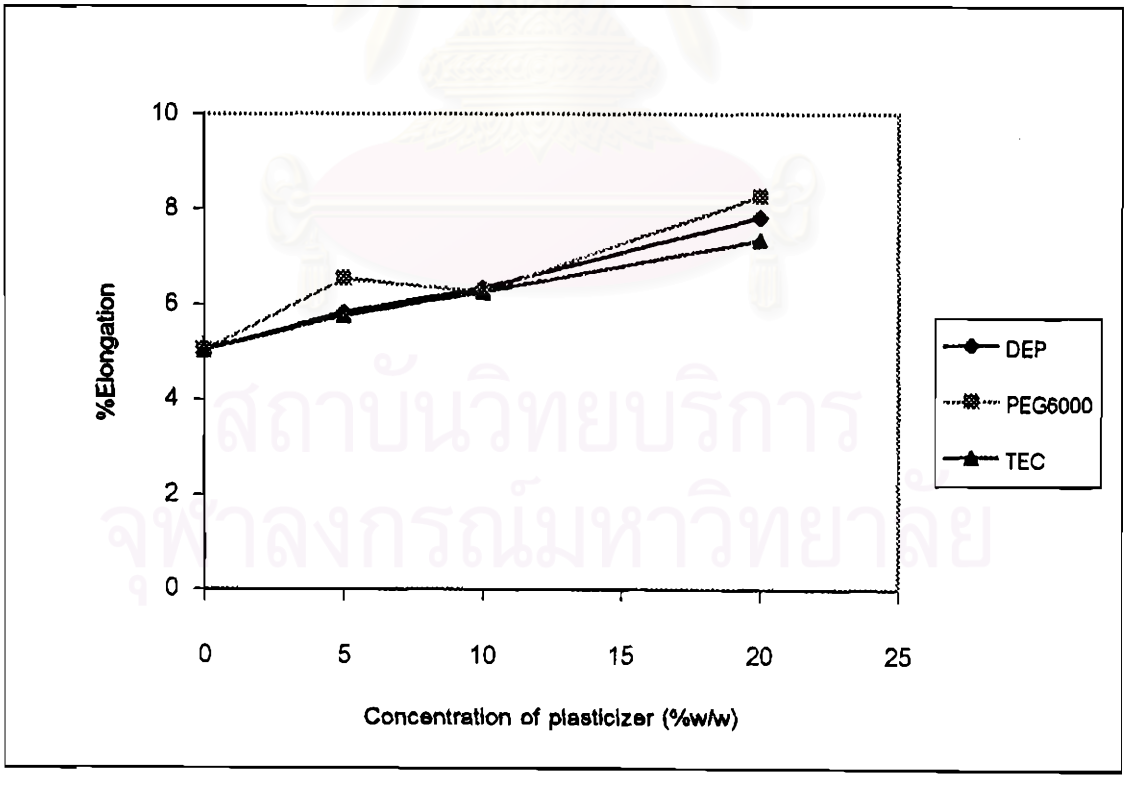


Figure 59 Effect of plasticizers on %elongation

a corresponding presence of all type of plasticizer. As expected, the increasing amount of plasticizer led to greater elongation of HPMC film. The elongation of HPMC film was higher depending on the concentration of plasticizer and this effect was resemble among the equal amount of each plasticizer (Figure 59).

An important parameter determined from physical-mechanical testing is the Young's modulus, which is a measure of the hardness, flexibility or stiffness of a polymer (Mcginity et al., 1994). The modulus of elasticity of film was decreased when incorporating of plasticizer to HPMC film and it also depended on the concentration of plasticizer. The incorporation of different levels of plasticizer resulted in soften and more flexible films because it reduced the number of active centers available for binding sites and polymer-polymer contacts, decreasing the rigidity of the polymer structure.

In the case of mixed cellulose film between HPMC and HPC, there were not different in any parameters of mechanical testing when compared to unplasticized HPMC film. In contrast to Eudragit® L30D-55, dry films were weak and very brittle so it could not be evaluated for mechanical test due to breaking. Bodmeier and Peanratakul (1994) reported that the elongation of dry film was less than 1% and the possible explanation could be strong interchain hydrogen bonding caused by the presence of the carboxyl groups. The Mcginity et al. (1993) reported the similar effect, the percentage elongation of unplasticized of Eudragit® L30D-55 film was less than 1% however it was improved by incorporation of more than 20% TEC.

6.4 Surface Texture

The surface morphology of coated capsules was examined using scanning electron microscopes (SEM) at X1000 magnification that showed appropriate size of surface topography of coated film. Scanning electron micrograph of cellulose coated capsule both HPMC and mixed cellulose film of two different coating equipment's revealed that the polymer films were homogenous and continuous surface in all case. There was no porous, tearing and cracking, even at the higher magnification than X1000 but many spots of polymer were found (Figure 60-64). For the casting method, HPMC

incorporated with DEP produced rough and the little cloudy in free film. However, the peeled film was smooth, transparent and the picture of SEM illustrated that although the plasticizer content increased to 20% level of DEP, it had no effect on the surface morphology. It was homogenous and continuous film, and also in the case of changing plasticizer to TEC and PEG 6000.

In the case of scanning electron micrograph of coated capsule produced by Eudragit® L 30D-55, it apparently exhibited a roughness appearance in some picture, as compared to the surface of HPMC film (Figure 65-68). The Eudragit film without plasticizer showed non-continuos feature and cracked creature was scattered on the film. These characteristics were disappeared when incorporating plasticizers including PEG 6000 and TEC into coating solution. The compact, smooth and uniform appearance was observed, however at 10%w/w of DEP sponge-like characteristic was observed (Figure 66 and 68). The opposite consequence was revealed from those of Murthy et al. (1986) that the scanning electron micrograph of a capsule surface coated of Eudragit® L 30D with DEP was continuous, homogenous and there were no pores evident at magnification of 1000X. Nevertheless, the similar feature was both found in the coated capsule prepared by perforated pan coater and fluid bed coater.

Nevertheless, when considering the surface roughness of HPMC film determined by roughness tester. There are some parameters to estimate of the roughness texture (Radebaugh, 1988). The arithematic mean roughness (Ra) is defined as the average value of the departure of a profile above and below the reference line. It can be shown by a graphical representation, but Ra itself is usually inadequate to fully describe the surface, and additional parameters are necessary. Rq is defined as the average distance between measured from a line parallel to the reference line but not crossing the profile. Since Rz can only be determined graphically, another parameter, the Rtm value, which is defined as the average of five peaks to valley distance, is often used. Rt value, defined as the distance between the highest peak and the deepest valley, Rp is defined as the maximum height and Rv is the maximum depth of the graphical representation and Rsm is defined as mean spacing between profile peak at the mean lines.

Table 16 Roughness of coated capsule

Sample no.	Parameter (micron)						
	Ra	Rp	Rt	Rtm	Rq	Rv	Rsm
R1	0.6249	4.3137	8.0842	1.49	0.8629	3.7711	128.1896
R2	0.589	3.131	6.1113	1.3535	0.7471	2.9809	99.8287
R3	0.6495	2.8176	5.6719	1.8615	0.8701	2.8543	50.7697
R4	0.5806	2.6635	5.7083	1.5075	0.7302	3.0448	31.542
R5	0.6784	3.0535	5.9105	1.4677	0.8555	2.8569	118.28
R6	0.6149	2.828	5.052	1.421	0.7746	2.201	107.6043
R7	0.4531	2.7426	4.5436	1.2422	0.5835	1.801	48.9754
R8	0.5071	3.0368	5.2374	1.2255	0.6715	2.2006	126.5518
R9	1.3202	4.8719	10.2605	2.8939	1.6958	5.3886	110.5109
R10	0.9672	3.9779	7.9245	2.2637	1.2178	3.9466	99.0733

From these parameters: Ra, Rp, Rt, Rtm, Rv indicating of the different of peak size in micron, whereas the frequency of peak is demonstrated in Rsm. The comparative between type of polymer, coating equipment and the effect of plasticizer is shown in Table 16 and the roughness graphical representation was illustrated in Figure 69-73. It was concluded that the interval of roughness of Eudragit® film was more than HPMC while the depth of roughness was similar to HPMC film. The most roughness was found in the case of mixed film of cellulose. The result was according to film feature that preparing from casting method. This film exhibited the rough and little turbid that may cause by the compatibility of intermolecular bonding between HPMC and HPC. Plasticizer displayed no effect to roughness in the case of HPMC film: Ra, Rtm is similar value but Rsm of was higher that mean the number of roughness of plasticized film was little than unplasticized HPMC film. On the contrary of Eugragit® film, plasticizer induced film smoothness by reducing both the height and the frequency of peak. When considering to effect of coating equipment, the result obtained from Roughness tester showed that coated capsule from fluid-bed coater expressed smoother surface texture due to lower Ra, Rtm and Rsm both cellulose and Eudragit® groups.

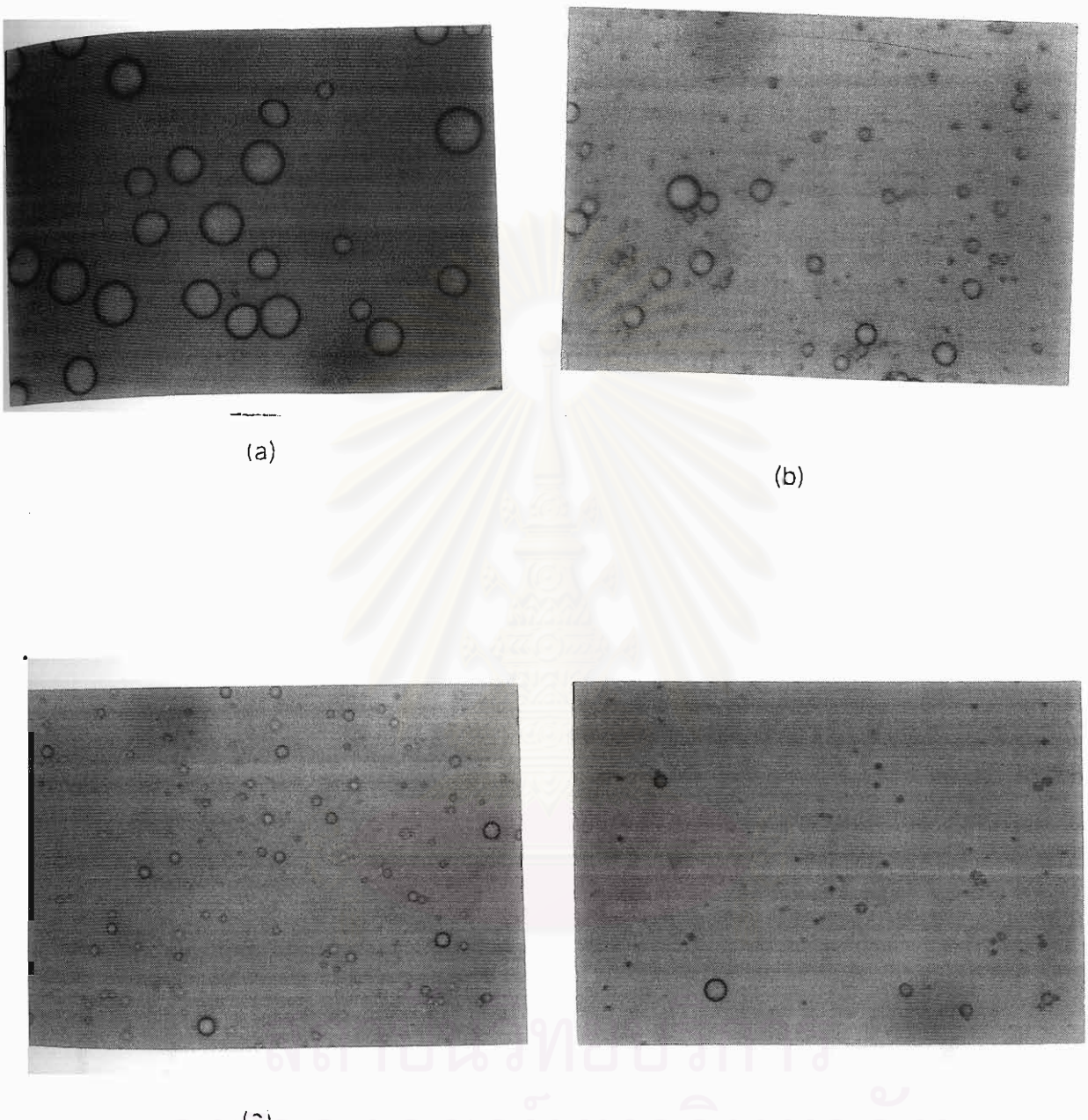
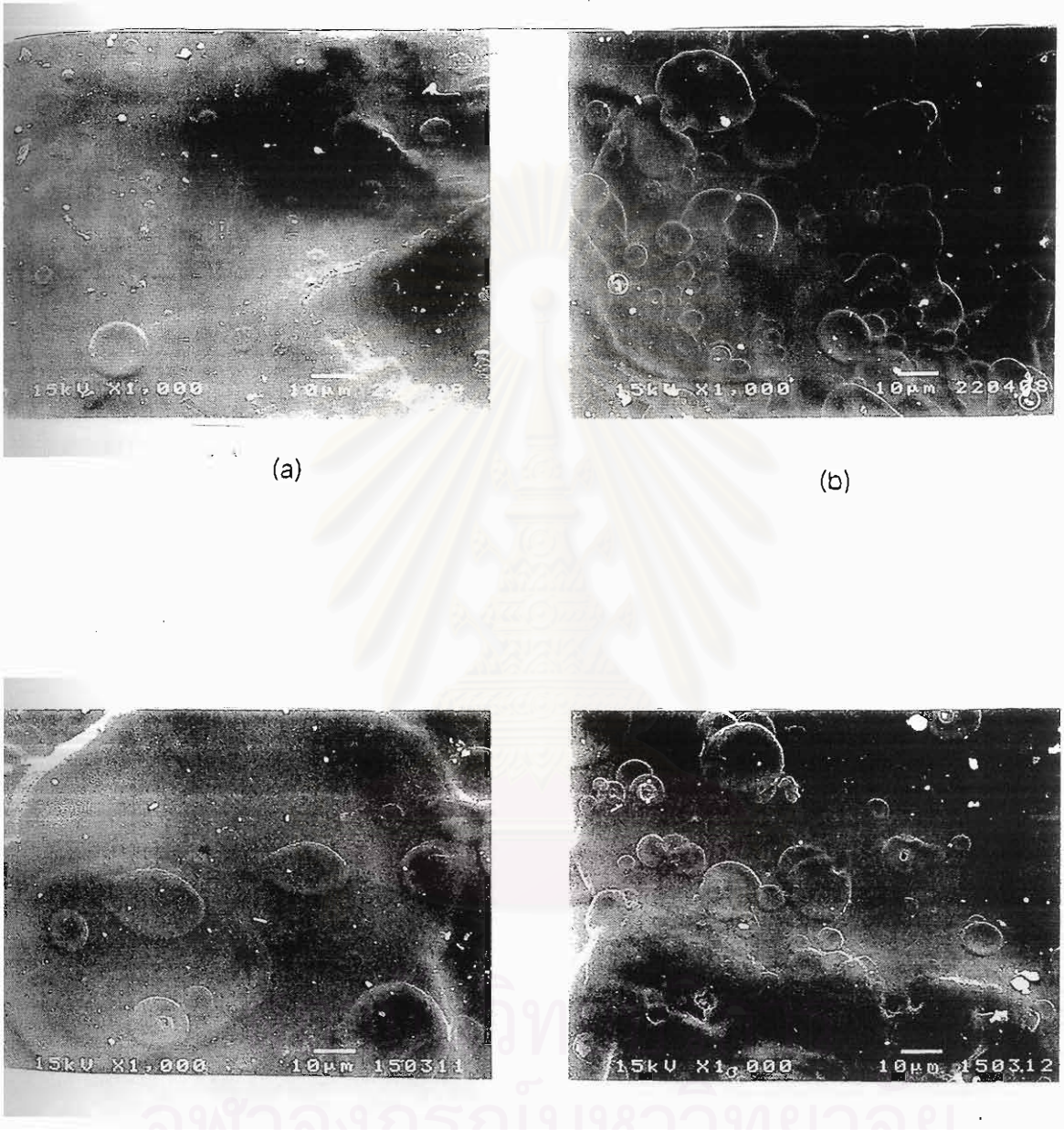


Figure 60 Scanning electron micrograph of capsule coating surface using Methocel ®E5 , coated with perforated pan coater :effect of amount of TEC

(a) No plasticizer (b) 5%TEC

(c) 10%TEC (d) 20%TEC



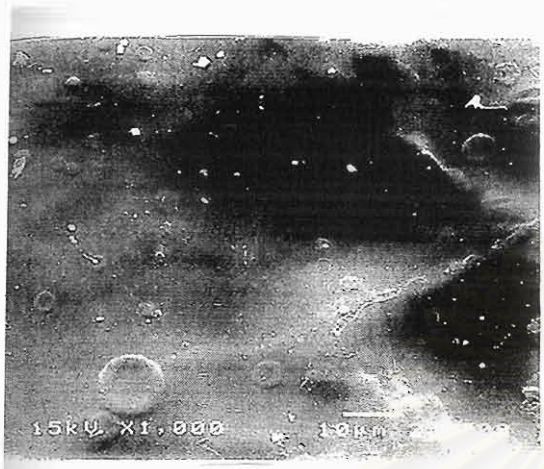
(a) (b)

(c) (d)

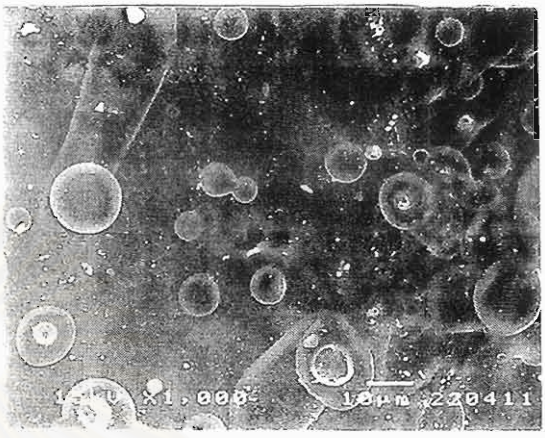
Figure 61 Scanning electron micrograph of capsule coating surface using Methocel ®E5 , coated with perforated pan coater :effect of type of plasticizer

(a) No plasticizer (b) 10%TEC

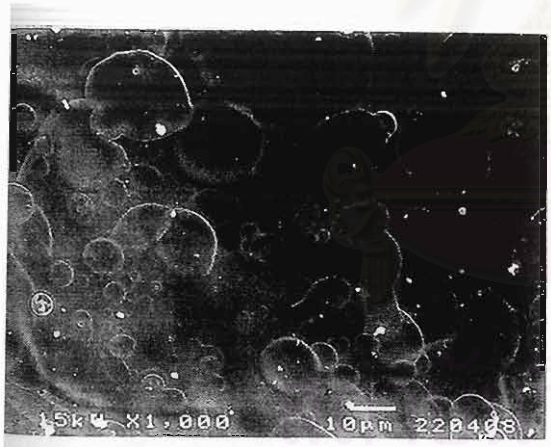
(c) 10%DEP (d) 20%PEG6000



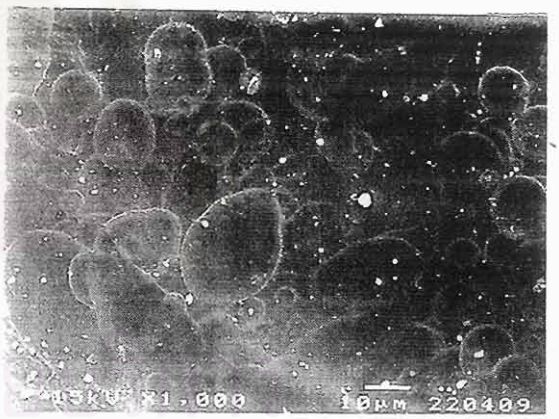
(a)



(b)



(c)

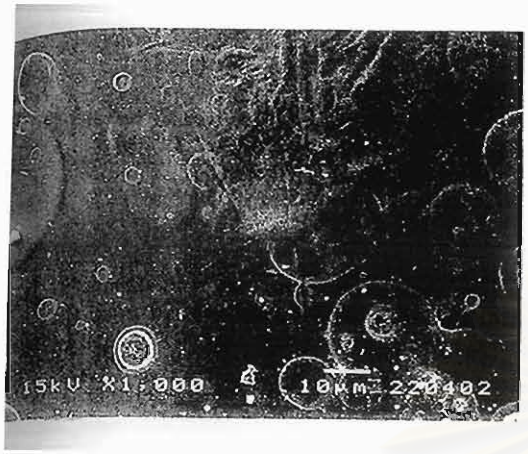


(d)

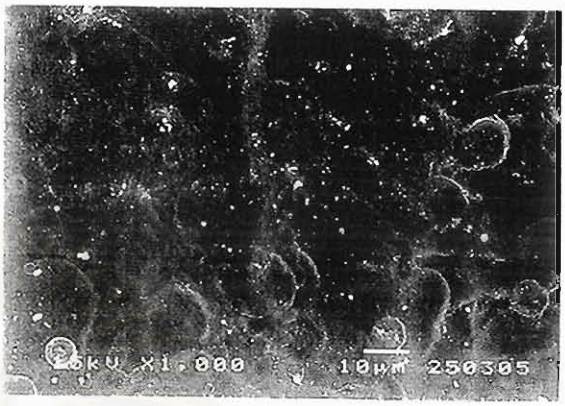
Figure 62 Scanning electron micrograph of capsule coating surface using Methocel ®E5 , coated with fluid bed coater :effect of amount of TEC

(a) No plasticizer (b) 5%TEC

(c) 10%TEC (d) 20%TEC



(a)



(b)

(c)

(d)

Figure 63 Scanning electron micrograph of capsule coating surface using Methocel ®E5 , coated with fluid bed coater :effect of type of plasticizer

(a) No plasticizer (b) 10%TEC

(c) 10%DEP (d) 20%PEG6000

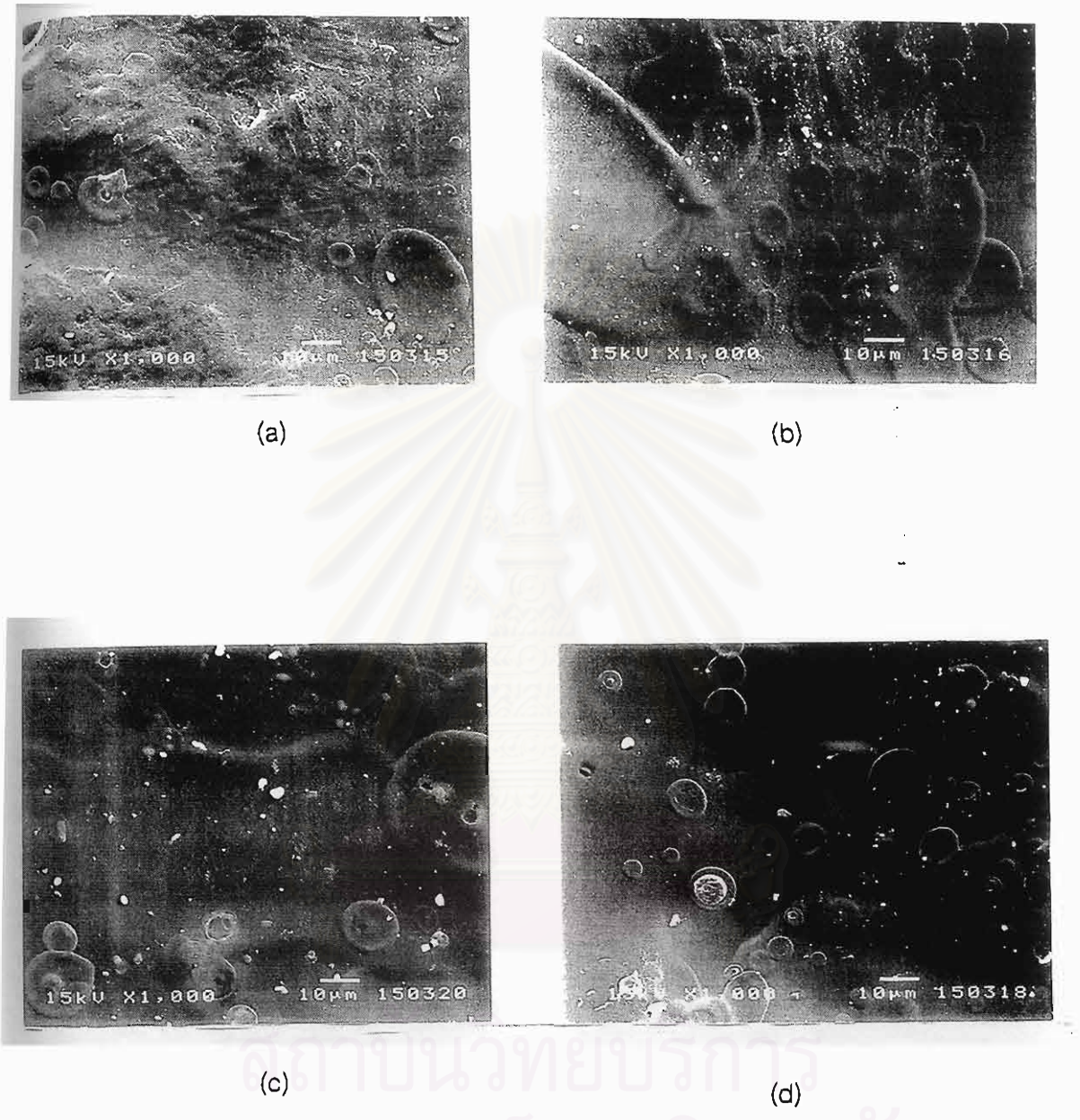
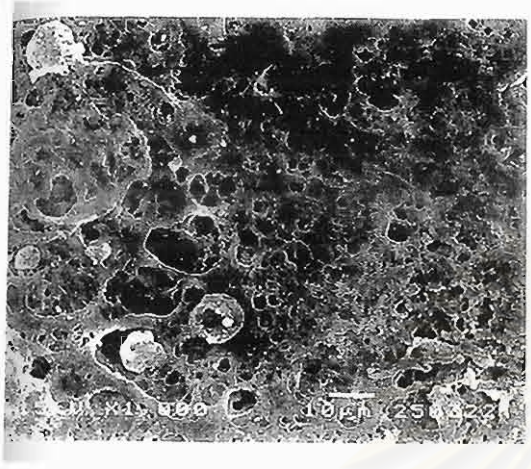


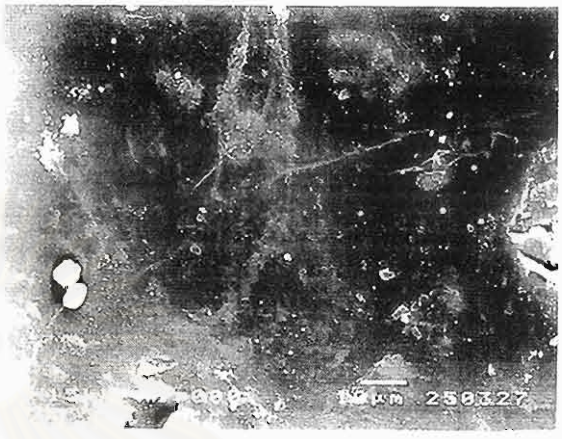
Figure 64 Scanning electron micrograph of capsule coating surface using Methocel ®E5 and HPC film, coated with fluid bed coater :effect of coating machine and plasticizer

(a) No plasticizer, Perforated pan coater (b) 10%TEC, Perforated pan coater

(c) No plasticizer , Fluid bed coater (d) 10%TEC, Fluid bed coater



(a)



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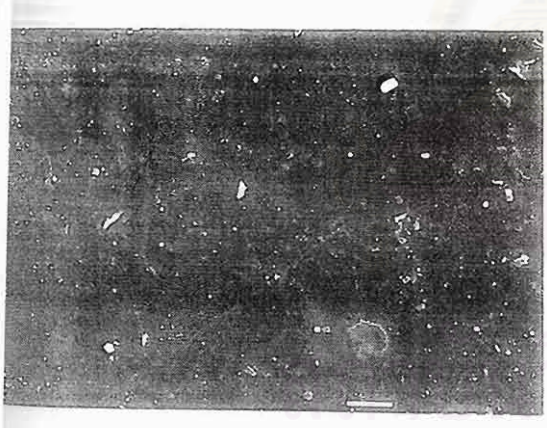

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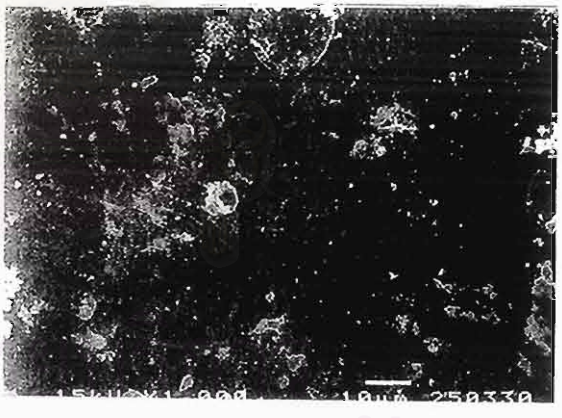
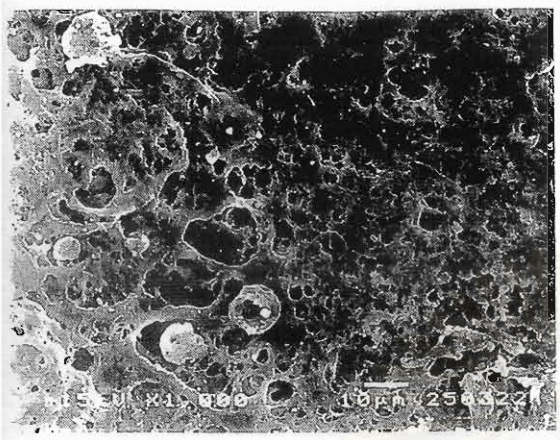


(d)

Figure 65 Scanning electron micrograph of capsule coating surface using Eudragit® L30D-55 film, coated with perforated pan coater :effect of amount of TEC

(a) No plasticizer (b) 5%TEC

(c) 10%TEC (d) 20%TEC



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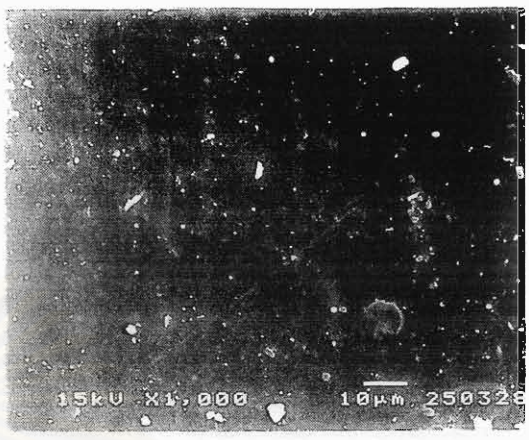
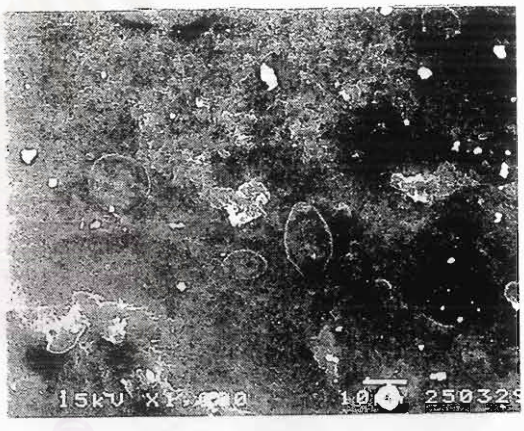


(b)

(c)

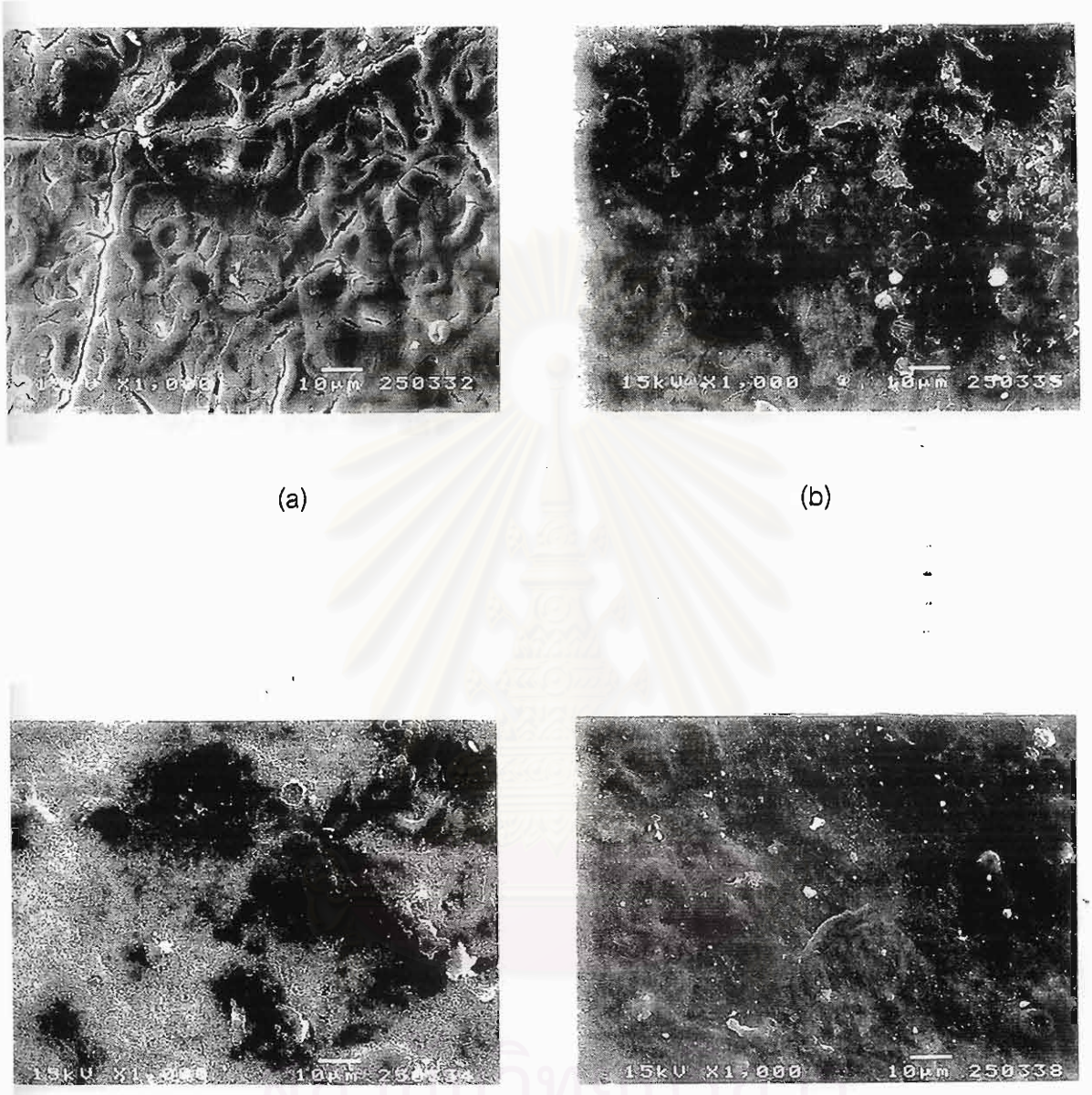


(d)

Figure 66 Scanning electron micrograph of capsule coating surface using Eudragit® L30D-55 film, coated with perforated pan coater :effect of type of plasticizer

(a) No plasticizer (b) 10%TEC

(c) 10%DEP (d) 20%PEG6000



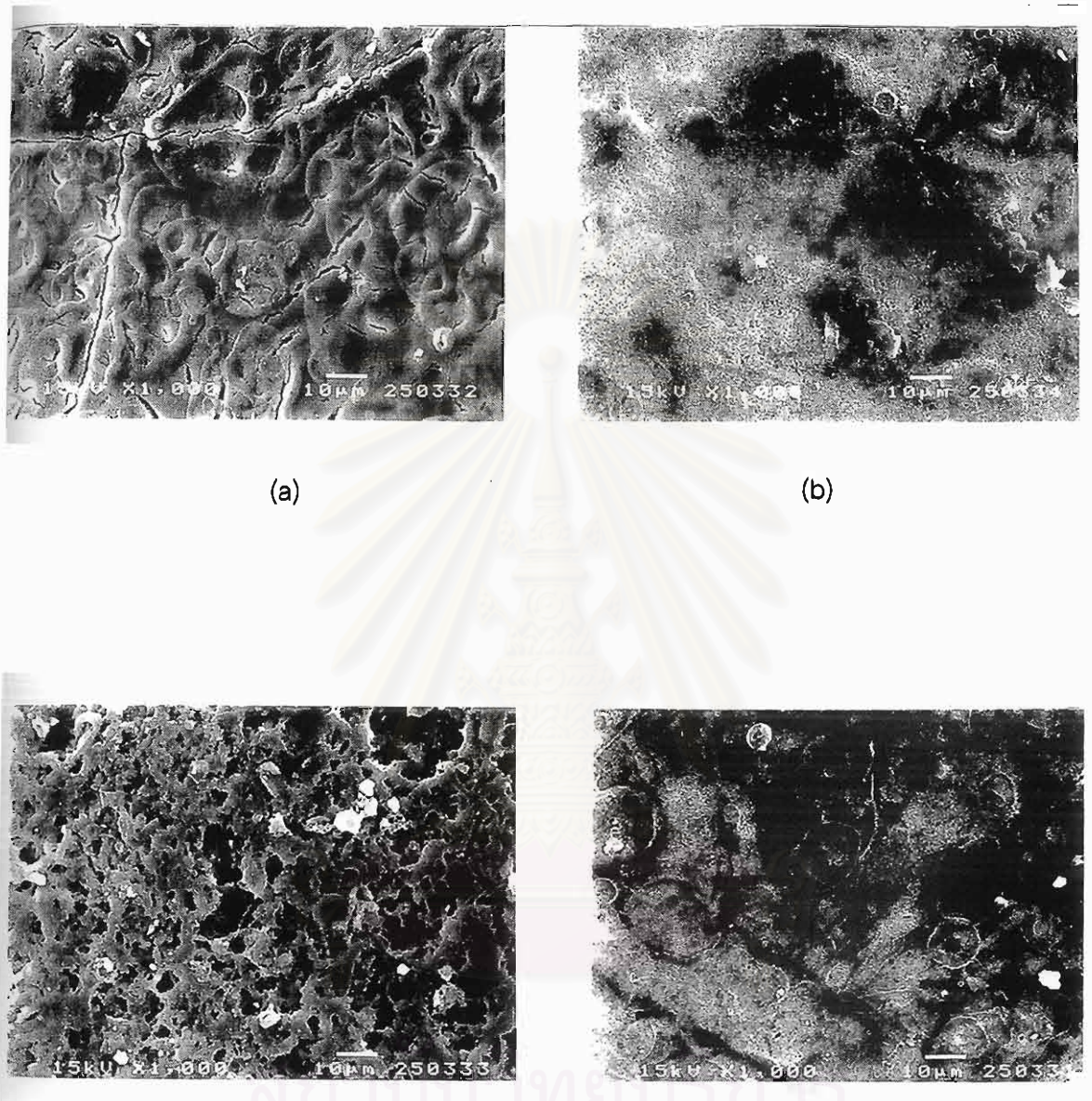
(a) (b)

(c) (d)

Figure 67 Scanning electron micrograph of capsule coating surface using Eudragit® L30D-55 film, coated with fluid bed coater :effect of amount of TEC

(a) No plasticizer (b) 5%TEC

(c) 10%TEC (d) 20%TEC



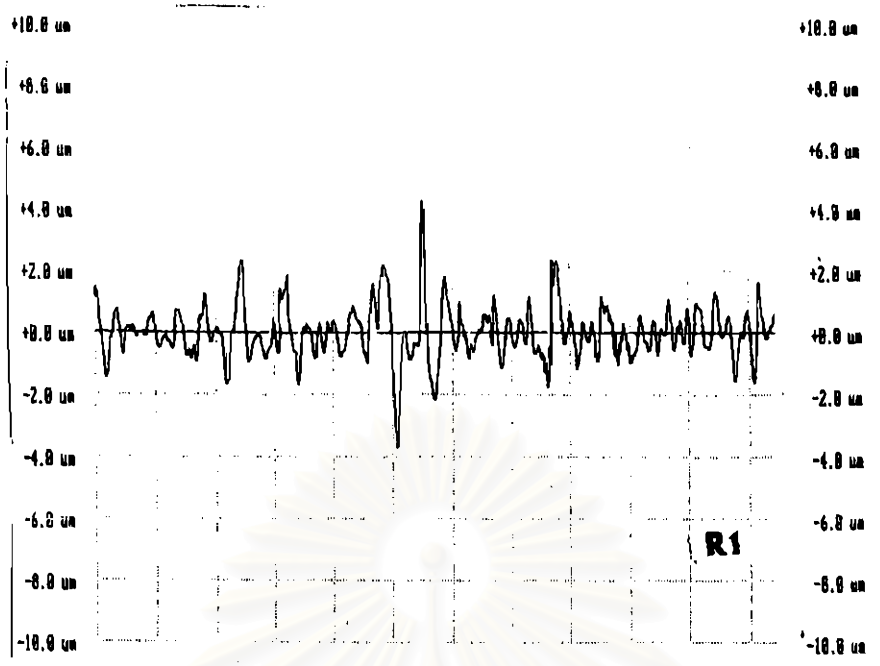
(a) (b)

(c) (d)

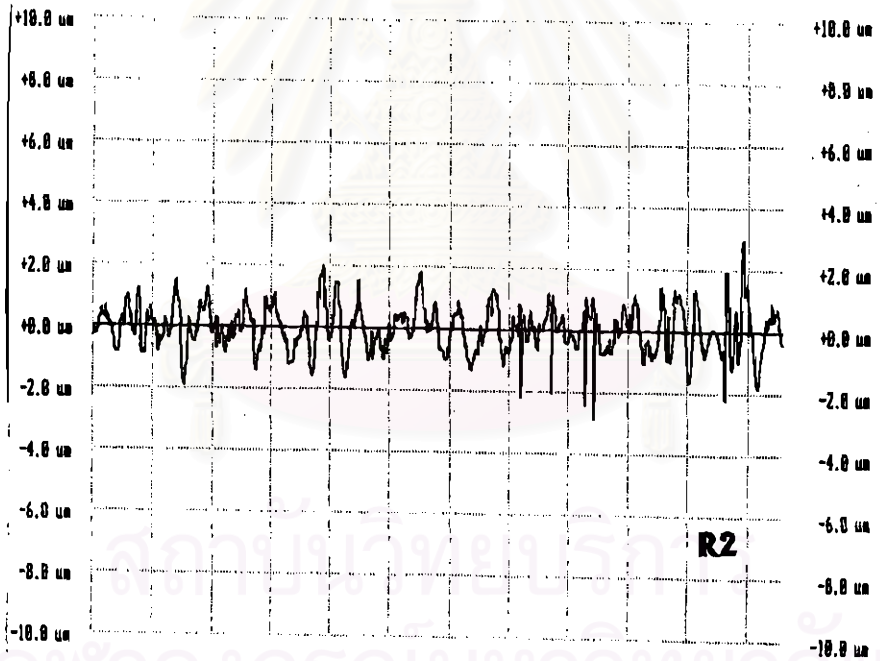
Figure 68 Scanning electron micrograph of capsule coating surface using Eudragit® L30D-55 film, coated with fluid bed coater :effect of type of plasticizer

(a) No plasticizer (b) 10%TEC

(c) 10%DEP (d) 20%PEG6000



(a)

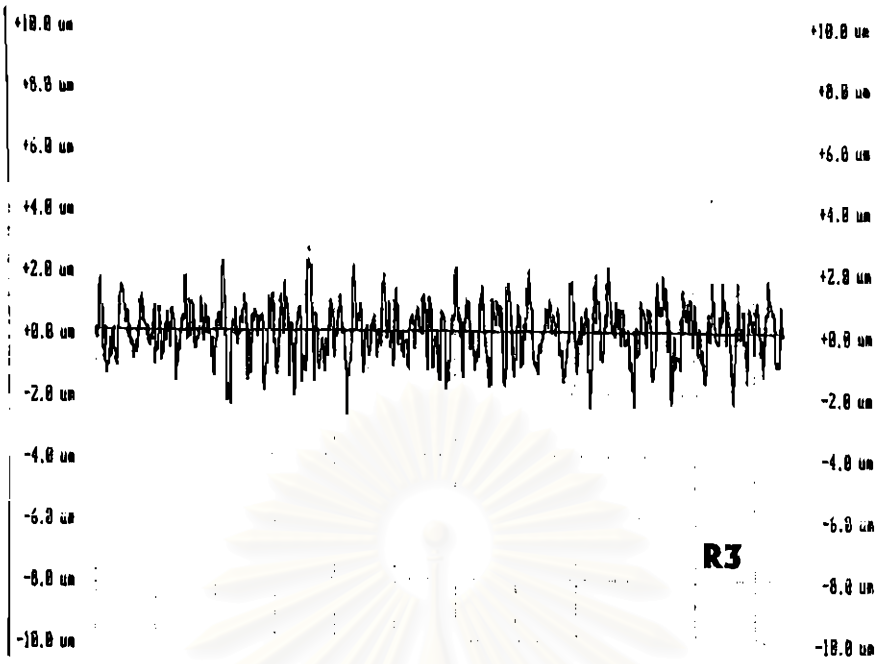


(b)

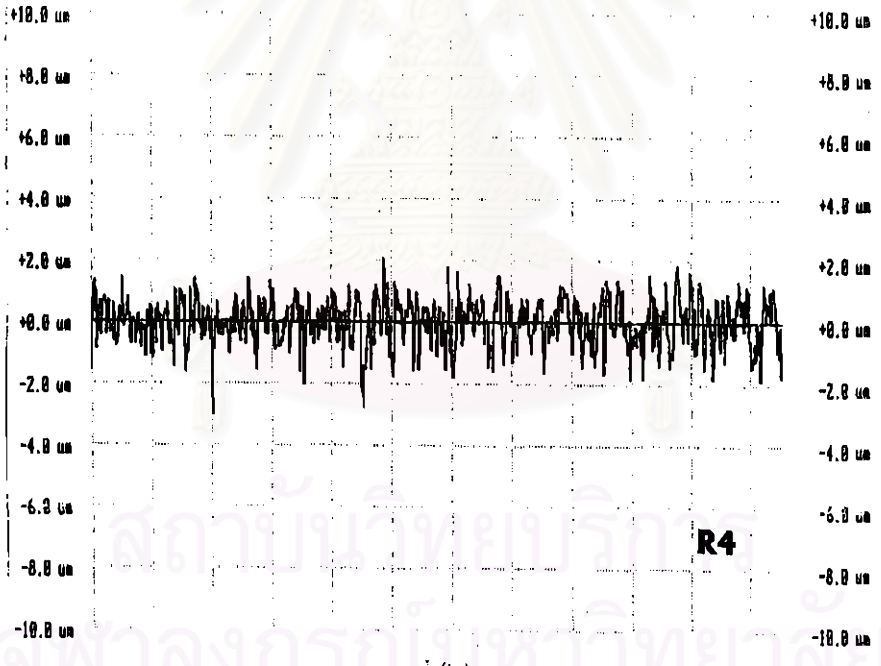
Figure 69 Surface roughness of coated capsule

(a) Methocel ® E5 coated with fluid bed coater

(b) Methocel ® E5 coated with perforated pan coater



(a)



(b)

Figure 70 Surface roughness of coated capsule

(a) Methocel ® E5+10%TEC coated with fluid bed coater

(b) Methocel ® E5+10%TEC coated with perforated pan coater

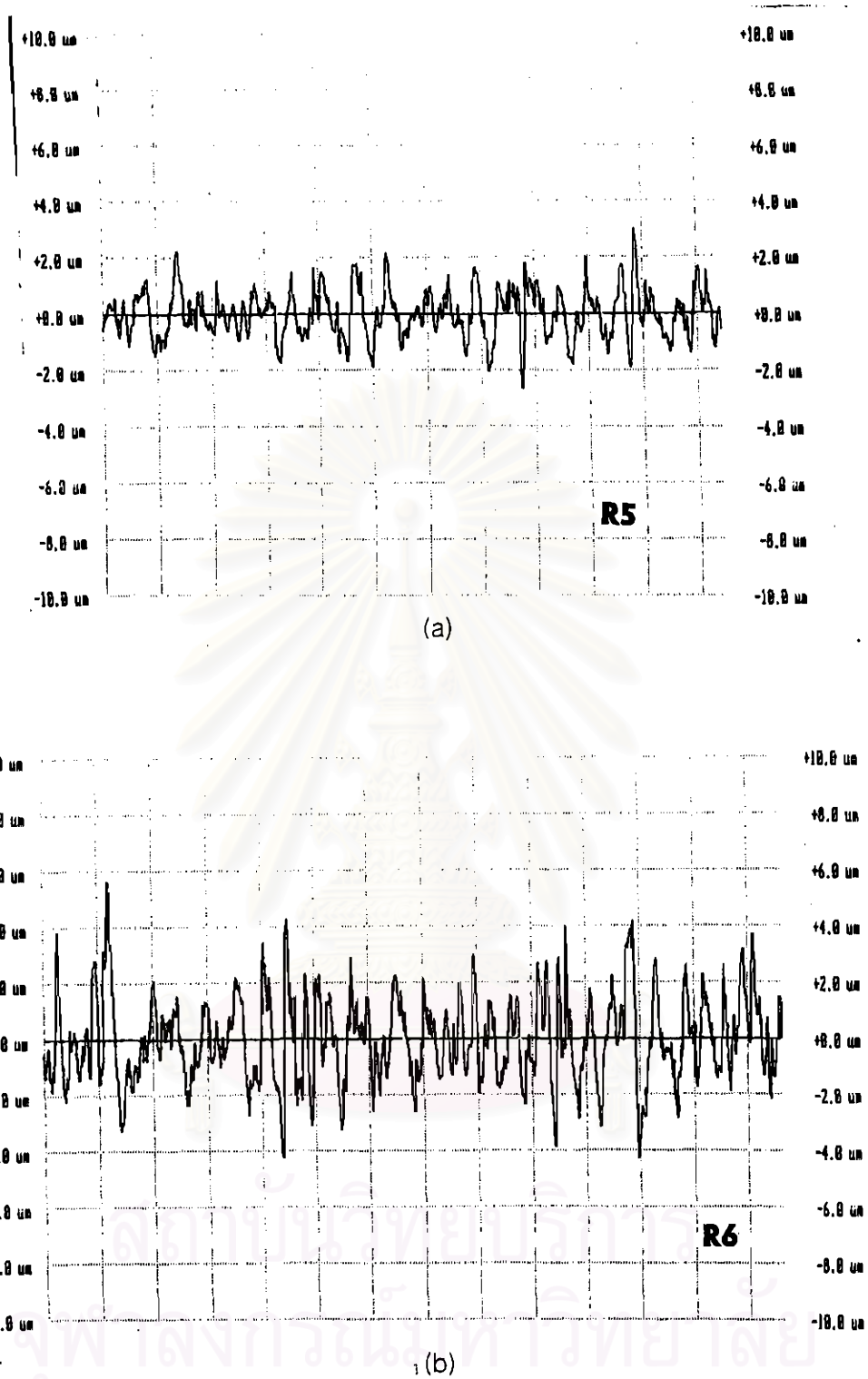
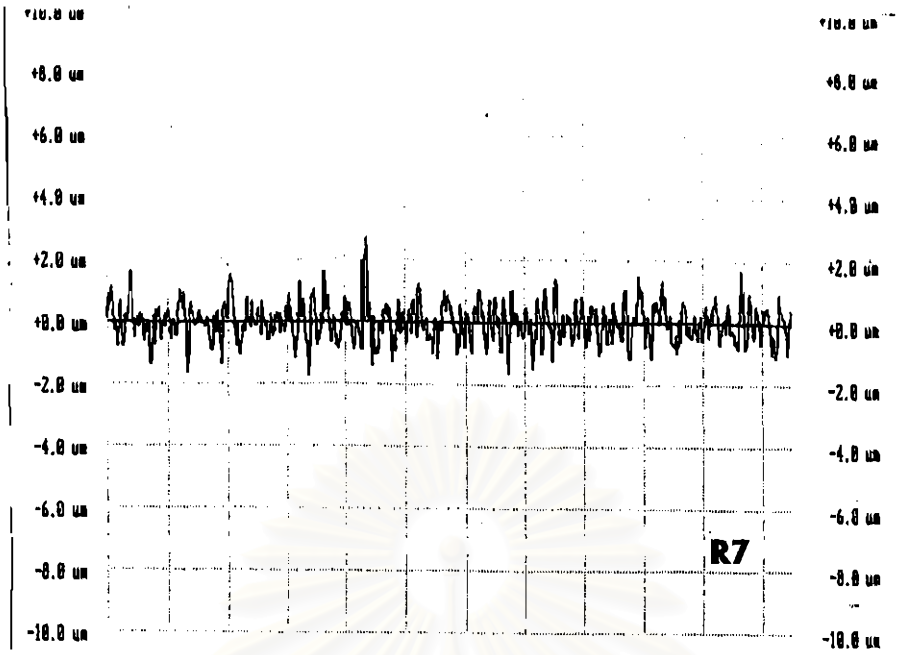


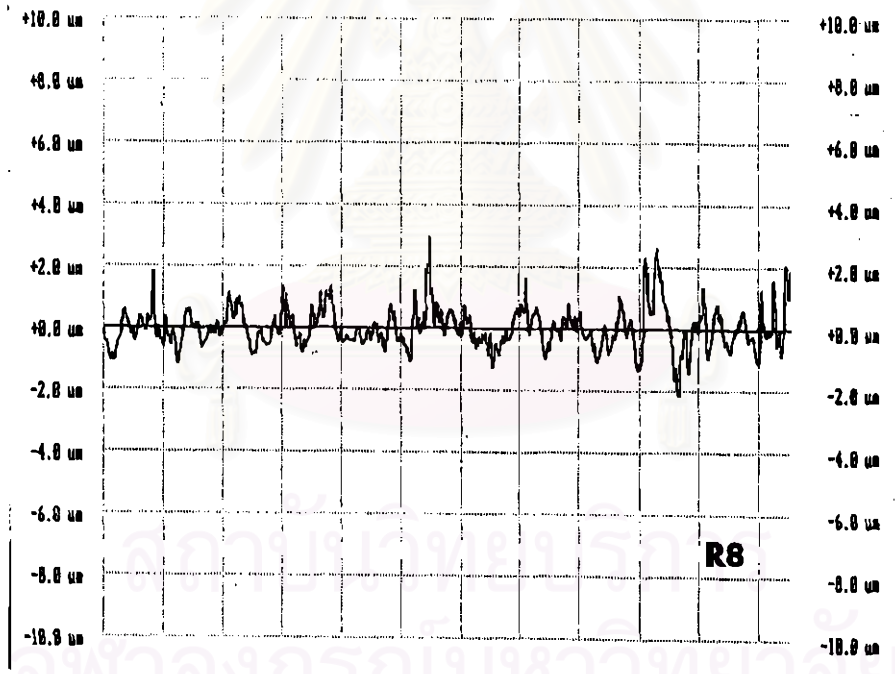
Figure 71 Surface roughness of coated capsule

(a) Eudragit® L30D-55 coated with fluid bed coater

(b) Eudragit® L30D-55 coated with perforated pan coater



(a)

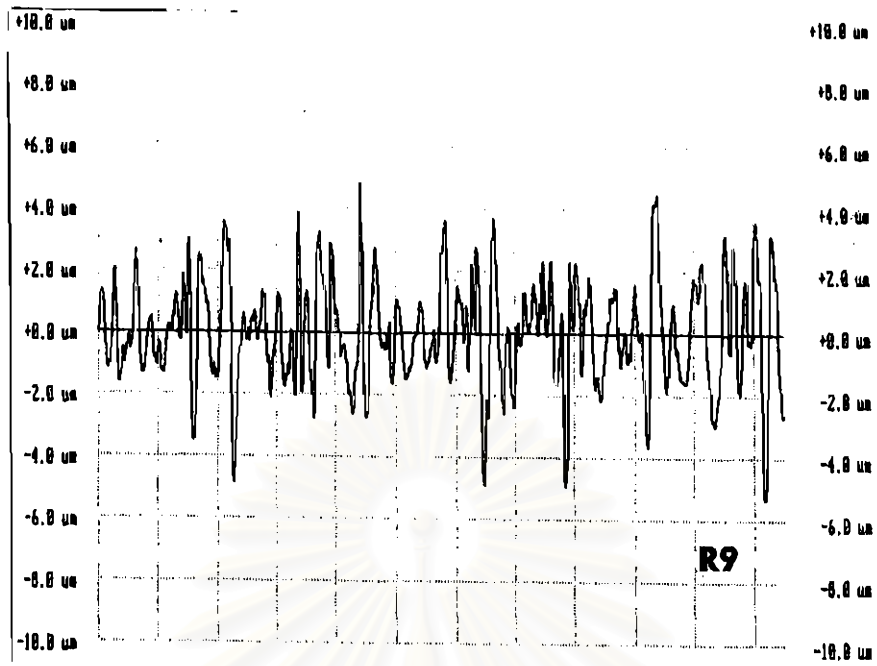


(b)

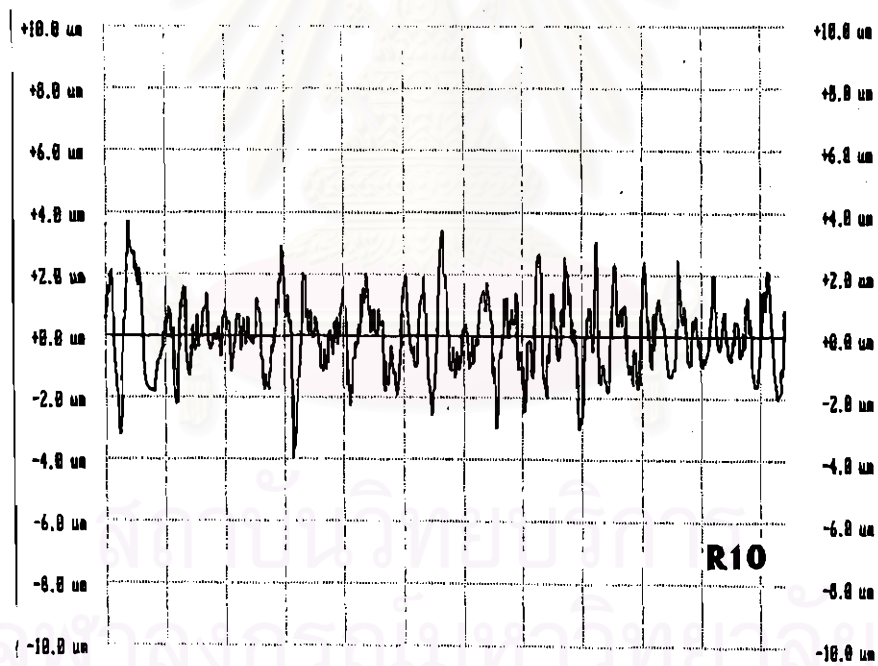
Figure 72 Surface roughness of coated capsule

(a) Eudragit® L30D-55 +10%TEC, coated with fluid bed coater

(b) Eudragit® L30D-55 +10%TEC, coated with perforated pan coater



(a)



(b)

Figure 73 Surface roughness of coated capsule

(a) Methocel ®E5+HPC type M+10%TEC, coated with fluid bed coater

(b) Methocel ®E5+HPC type M+10%TEC, coated with perforated pan coater

6.5 Gliding effect

There are no special methods to measure the gliding effect of coated capsule for rectal application. The determination was followed by Hannula et al. (1986), the organoleptic (finger test) was suggested to use. However, this test could give only good or bad gliding. The coated capsule using HPMC showed the good gliding, the capsule had an excellent slip when contacted to water whereas the uncoated capsule showed that it was hard to slip on the surface. It could be explained that cellulose polymer would swell and form clear hydrogel in water, then produced gliding effect. However, it was found that the swelling polymer caused sticky layer when storing for along time. In the case of Eudragit®, this polymer did not have swelling property in water; hence they showed the little effect of gliding property.

Exceptionally of organoleptic test, determination of surface friction of coated capsule was applied to judge the difference of coated capsule. The apparatus was designed based on principle of friction. Friction between two contacted surface area of material when there were in the rest called static friction. The maximum static friction was equal to the minimum force for moving the material. After motion of material, the friction between two of that would reduced and the friction that occurred after the moving of the material called dynamic friction. From the definition, dynamic friction was represented of gliding property. As seen in Figure 74, the force was raise up to maximum peak and then down to constant value. The dynamic friction was then recorded and the result exhibited that gliding effect was increased in the following order: HPMC coats > uncoated capsule > Eudragit coats. Although HPMC film could enhance the gliding property of capsule, it must used immediately after dipping in water due to sticky effect. The gliding coat of high molecular weight of PEG was suggested to solve these problems, however the poor adherence between capsule shell and PEG was the limitation. Hannular et al. (1986; 1988) found that the degree of adherence and the quality of the coats varied between different PEG. Smooth and rather well adhering coats were obtained when PEG 50000 was used, powdery and non-gliding surfaces with

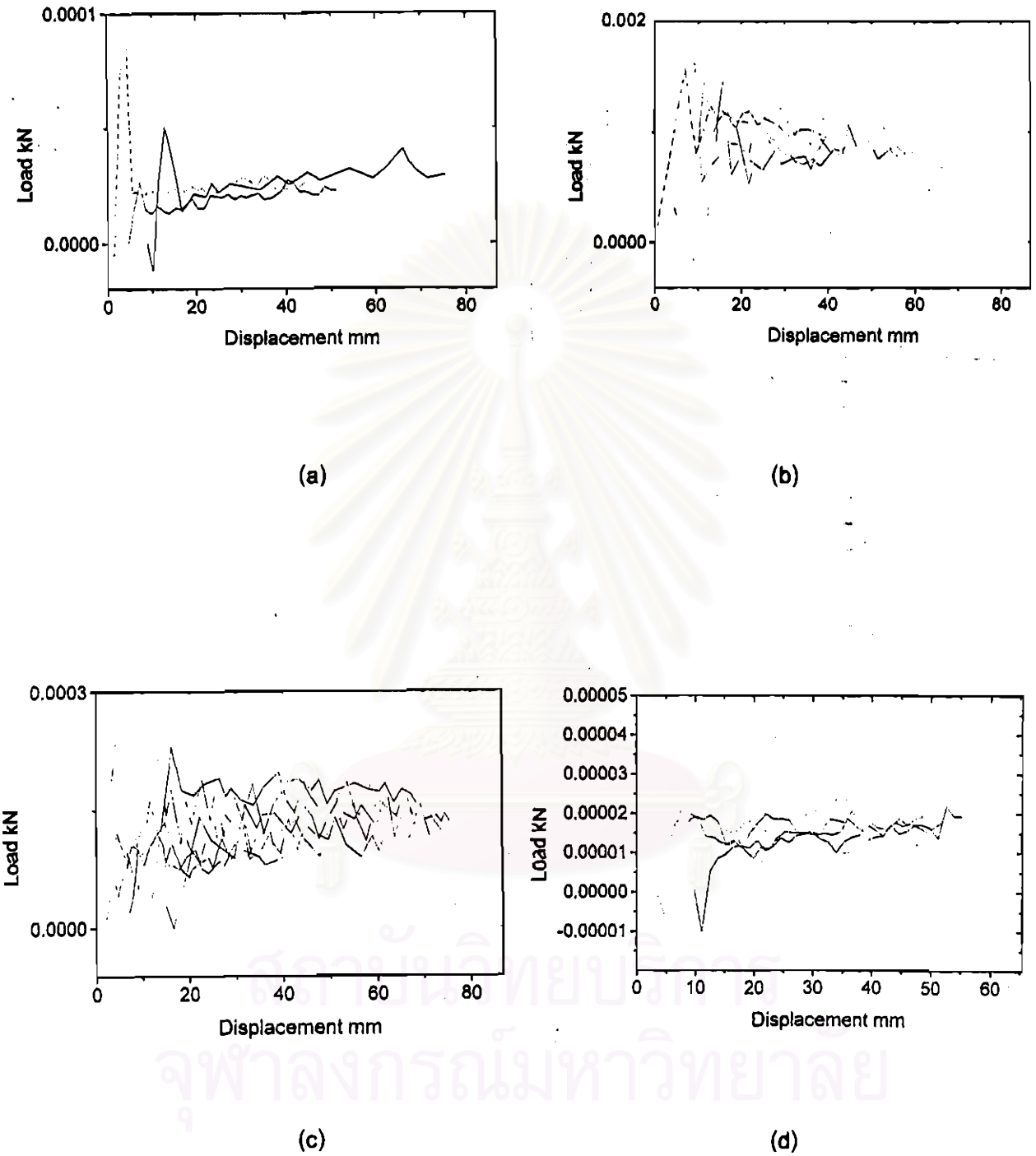


Figure 74 Comparison of friction on surface of coated capsule, determined by Instron Universal material testing : film of

(a) HPMC (b) Eudragit

(c) plained capsule (d) Coated PEG

PEG 35000. Additionally, PEG layer was not prolonging disintegration time when compared to uncoated capsule and in this experiment, PEG coat showed the lowest friction (Figure 74)

6.6 Brittleness

It was obvious that coated capsule with Eudragit® L would be break easier by pressing the capsule manually than plained capsule. The result was agreed with the finding of Hannula et al. (1986), the anionic polyacrylate group such as Eugragit® L showed good as a subcoat regarding gliding, smoothness and adherence of most the coats, but all the capsules had entirely lost their elasticity. It was explained that strong acid dispersion particle penetrate into the capsule shell producing brittleness. But this result was not mentioned in many reports although the capsules were coated with Eugragit®L (Burn et al., 1994; Murthy, 1986). Hence, compression test of coated hard gelatin capsule containing different polymer was studied using an Instron universal testing apparatus. When the capsule was compressed, it was loss of shape rigidity and finally breaking depended on their elasticity. Many similarities exist between tension tests and compression tests, including the manner of conducting test, collecting data and the interpretation of the results. The similar parameters such as maximum stress, %elongation, Young's modulus and tensile toughness were determined. Tensile toughness is a measured of the ability of the polymer to absorb energy without fracture. The good characteristic of the coated capsule was higher tensile strength, tensile toughness and a lower Young's modulus (Felton et al., 1996).

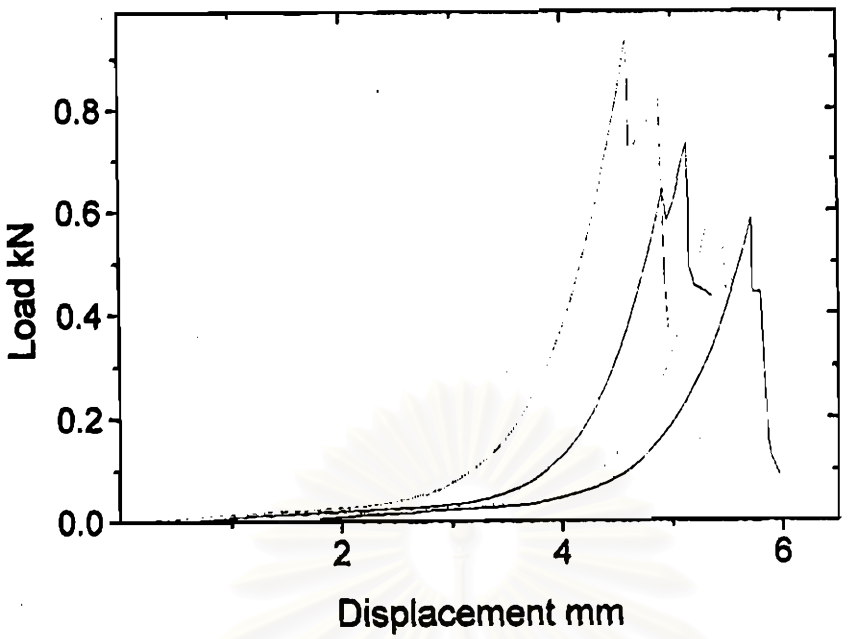
The result from Table 18-19 demonstrated that maximum stress at first breaking tensile toughness and energy at break of Eudragit® L coated capsule was lower than HPMC coated capsule and also plained capsule. These parameters indicating high brittleness property of coated capsule, consisting to the visual observation that capsule was broken quickly after applying the stress. Incorporating the plasticizers could not improved the flexibility of coated capsule except in the case of 20% TEC. It was found that higher tensile strength and toughness including %elongation was measured.

Table 18 Brittleness testing of HPMC coated capsule, prepared by fluid bed coater

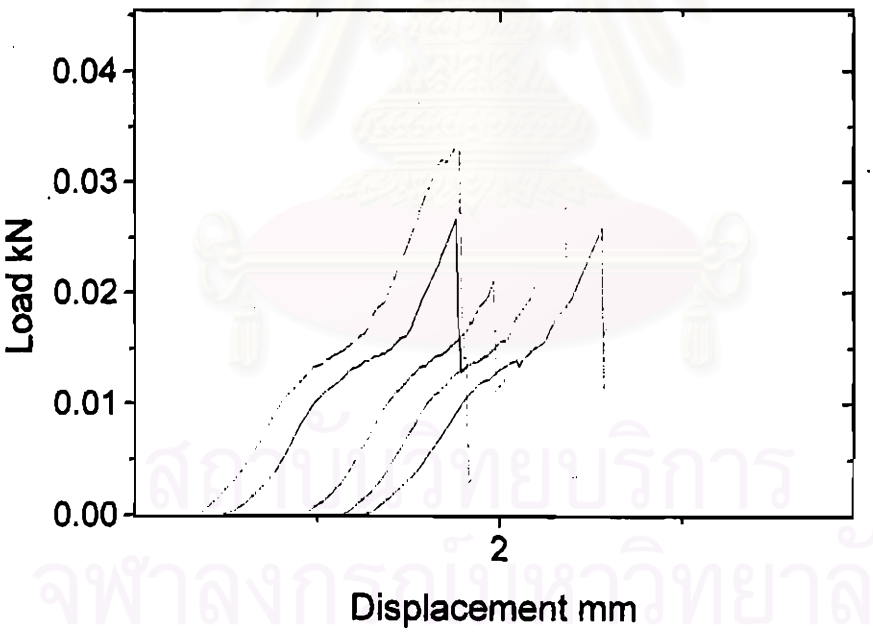
Formula	Max%Strain	Max Stress (mPa)	Modulus (mPa)	Toughness (mPa)	Energy at break (J)
5%PEG 6000	4.55	16.64	367	0.722	57.6
10% PEG 6000	4.65	15.3	388	0.636	50.74
20% PEG 6000	4.73	14.18	295	0.693	65.04
5%DEP	4.59	14.12	488	0.96	77.32
10%DEP	5.3	18.07	383	0.862	68.8
20%DEP	4.38	15.49	310	0.594	57.42
5%TEC	4.34	19.52	449	0.874	69.71
10%TEC	4.45	18.64	305	0.617	59.21
20%TEC	4.55	21.37	476	0.965	76.98
Unplasticized	5.01	14.37	306	0.582	58.43
HPMC+HPC type M	4.19	16.25	409	0.761	64.29
Plained capsule	4.36	9.86	225	0.46	36.67

Table 19 Brittleness testing compression of Eudragit® L30D-55 coated capsule, prepared by fluid bed coater

Formula	Max%Strain	Max Stress (mPa)	Modulus (mPa)	Toughness (mPa)	Energy at break (J)
5%PEG 6000	3.19	0.452	16.99	0.012	0.012
10% PEG 6000	4.21	0.414	13.93	0.011	0.011
20% PEG 6000	3.52	0.499	16.01	0.014	0.013
5%DEP	4.32	0.509	13.76	0.16	0.015
10%DEP	4.54	0.552	14.61	0.017	0.016
20%DEP	4.15	0.468	14.64	0.017	0.016
5%TEC	4.46	0.505	15.91	0.015	0.014
10%TEC	3.97	0.413	13.12	0.011	0.011
20%TEC	6.49	2.201	35.74	0.251	0.204
Unplasticized	4.57	0.581	15.12	0.013	0.013
Plained capsule	4.36	9.86	225	0.46	36.67



(a)



(b)

Figure 75 Stress-strain curve of coated capsule determined by Universal material testing

(a) HPMC coated capsule (b) Eudragit coated capsule

The pressing of capsule manually agreed with this result. As a report by Feldon et al. (1996) concluded that TEC was the better plasticized the acrylic polymeric coating, as evidenced by a higher percent fracture strain, tensile strength and toughness when compared to unplasticized and tributyl citrate.

Additionally, Hannula et al. (1986) suggested that the use of cationic polyacrylate as a sublayer did not cause any brittleness of the capsule shell, neither was the disintegration time of bilayer coated capsules significantly prolonged, when compared to the uncoated capsule. The capsule subcoated with Eudragit® E was determined and the result indicated that it could increase the toughness from 0.013 mPa to 0.124 mPa, however, the coated capsule was more brittle than HPMC coats.

The high maximum stress, tensile toughness of HPMC coated capsules were measured and these parameters were similar to uncoated capsule. It was indicated that celluosic film did not affected capsule shell and the tendency of higher level of all plasticizer causing the brittleness of capsule was according to tensile strength of free film. That means adding plasticizer caused lower strength of the film. The different of coating equipment did not showed any effects on these parameters.

In addition, the stress-strain curve using universal material testing equipment can illustrate the ability of adhesion of the polymeric coat to the capsule shell. For the Eudragit group, the single peak of fracture was demonstrated while two peak of fracture was found in HPMC group (Figure 75a). The result indicated that HPMC coated capsule showed the poor adhesion characteristic between polymer and capsule shell as evidenced by a fracture of the film, followed by fracture of the gelatin shell, probably due to higher internal stress within the film coating. As displayed in Figure 75b, the capsule shell and Eudragit® film fracture exhibited simultaneously, usually at the seam of the capsule, indicating good adhesion between polymer and gelatin capsule shell. This characteristic agreed with the observation that HPMC film could easily peeled off the capsule shell whereas Eudragit® could not, but it did not mean that HPMC film usually produced fracture and easy to rupture.

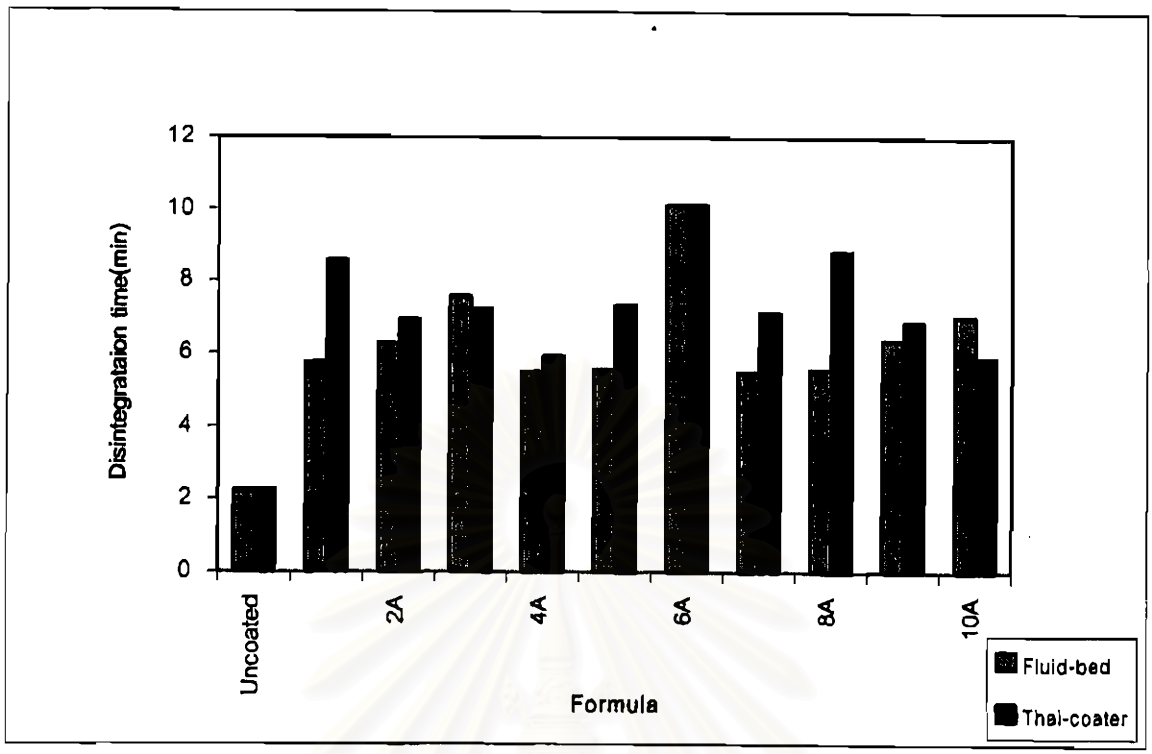


Figure 76 Disintegration time of uncoated and coated liquid filled capsule, coated of perforated pan coater and fluid bed coater

6.7 Disintegration of coated capsule

Disintegration time of hard gelatin capsule coated with HPMC groups was between 4-7 minutes (Figure 76). It was longer than uncoated capsule that was first ruptured and allowed releasing the liquid content within 3 minutes. The various types, amount of plasticizer and also two different coating equipments did not affect the capsule disintegration time. Additionally, the same disintegration time was recorded when using method of Suppotest. Disintegration time of each coated capsule is displayed in Appendix C.

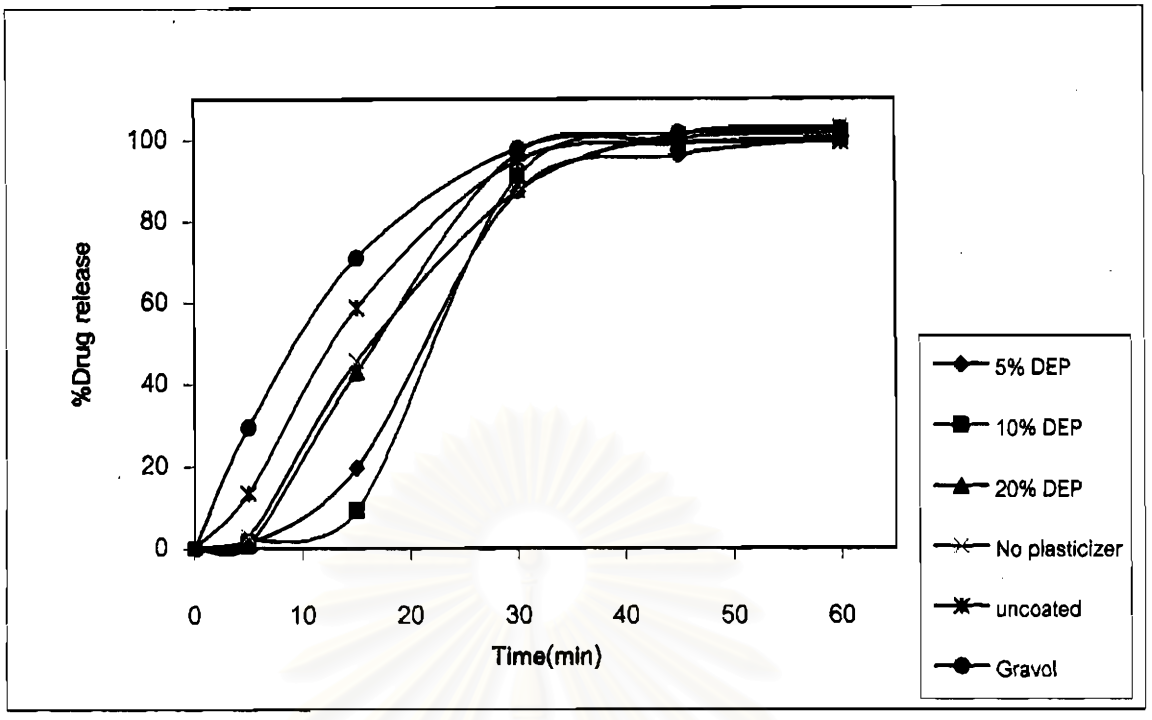
In the case of Eudragit® L coated capsule, all capsule did not break within 30 minutes that is the maximum limited of disintegration time of suppositories, they still be the same feature before and after testing both coated with perforated pan coater and fluidized bed coater. Hannular et al. (1986) found that disintegration time of hard gelatin capsule coated with anionic polymer (Eudragit® L) would occurred within 17

minutes that was longer than the other polymer, however, the method of disintegration time was not described. The result indicated that anionic film played some effect on to capsule shell due to the longer disintegration time when compared between uncoated and cationic polyacrylate coated capsule that was 2.0 and 8.4 minutes, respectively. This effect might relate to the brittle of Eudragit® L coated capsule. Anionic polyacrylate could change the elasticity of capsule shell and might be also solubility propertiy.

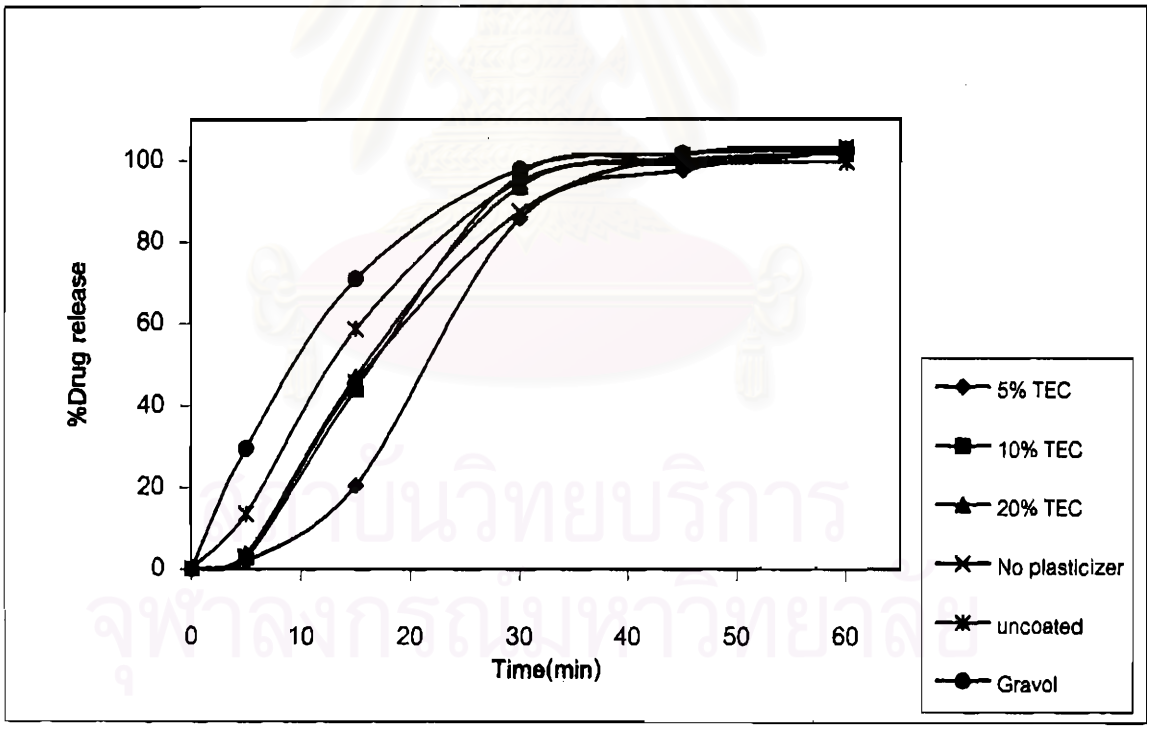
6.8 Dissolution Profile of Coated Capsule

The comparative release characteristics of dimenhydrinate in coated capsule using two types of polymer, Eudragit® and Methocel®, at the same coating level are shown in Figure 77-82. The release profile of all coated capsules exhibited a characteristic lag time. For the capsule coated with HPMC, when the capsule contacted with the dissolution medium, the polymeric coating layer swell and spent about 5 minutes before allowing drug release (Figure 77-79). Drug release reached to 90 % within 30 minutes and completed within 60 minutes, which was similar to uncoated capsule. This result was according to disintegration time that started between 7-10 minutes before complete capsule rupture.

It was reported that the lag time increased as a function of the amount and type of the coating layer, the high viscosity grade of Methocel® retarded drug release without changing in the pattern of dissolution profile(Maffione et al., 1992). As well as the increasing level of coating polymer, the approach can be exploited for the design of delay release dosage form. On the other hand, Methocel® E5 was the low viscosity grade of HPMC that showed little effect on the release profile. The longer lag time of Eudragit® coated capsules are shown in Figure 80-82. Drug release began after 15 minutes and the complete release spent more than 60 minutes. Furthermore, the amount of dimenhydrinate released at 30 minutes of coated capsules were less than that of HPMC. The same releasing pattern of Eudragit® L was illustrated in a previous study by Murthy et al. (1986). It was found that the lag time of capsules coated with Eudragit® L 30D using DEP as plasticizer were prolong to 30 minutes when the amount of polymer



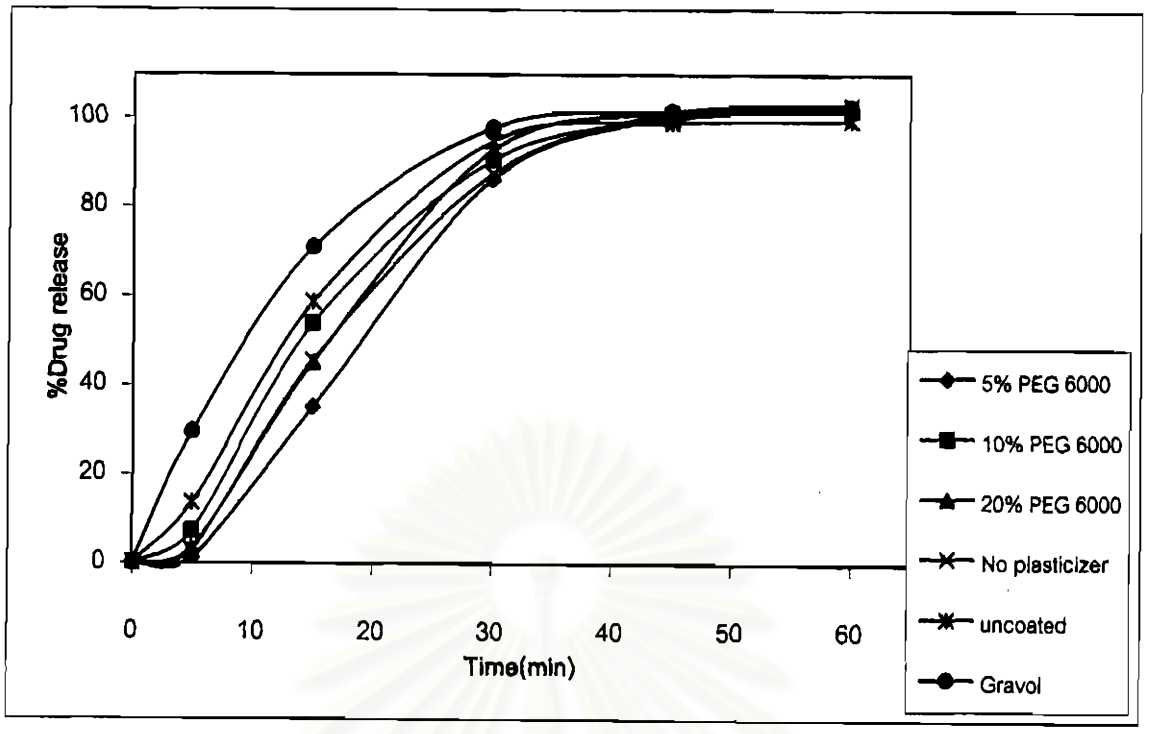
(a)



(b)

Figure 77 Effect of plasticizer on dissolution profiles of Dimenhydrnate from hard gelatin capsule coated with Methocel E5, prepared by fluid bed coater

(a) DEP (b) TEC



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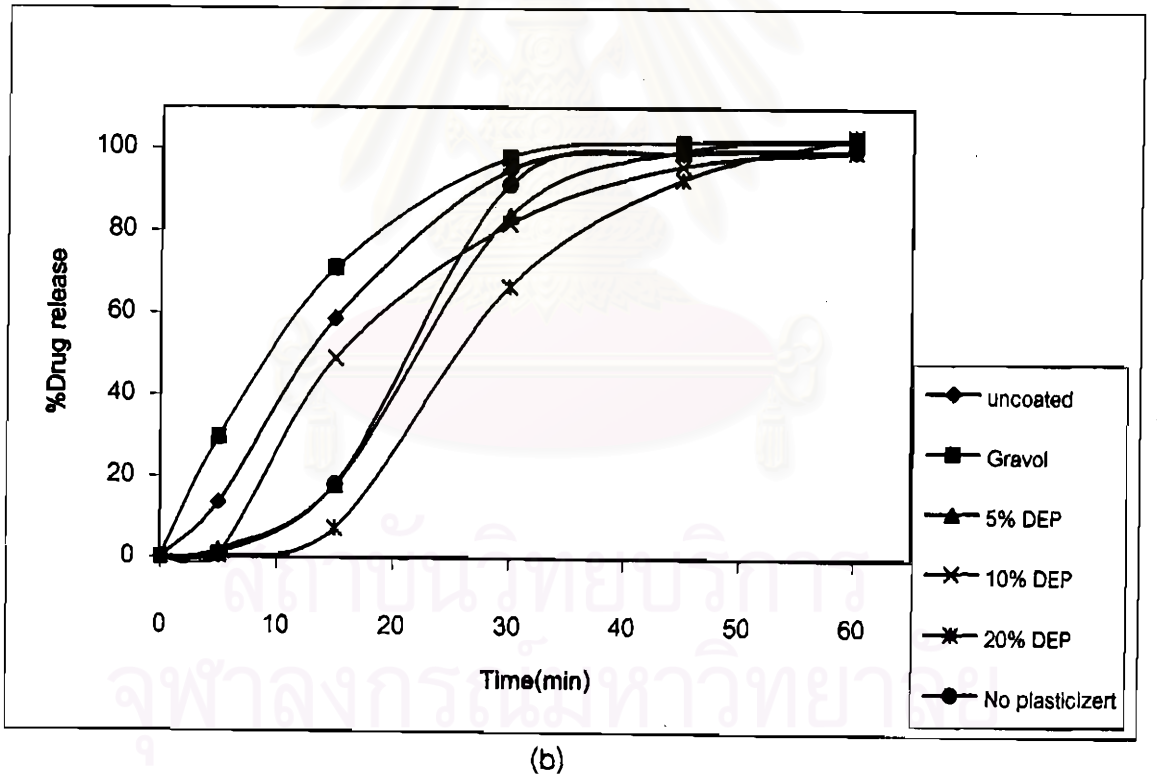
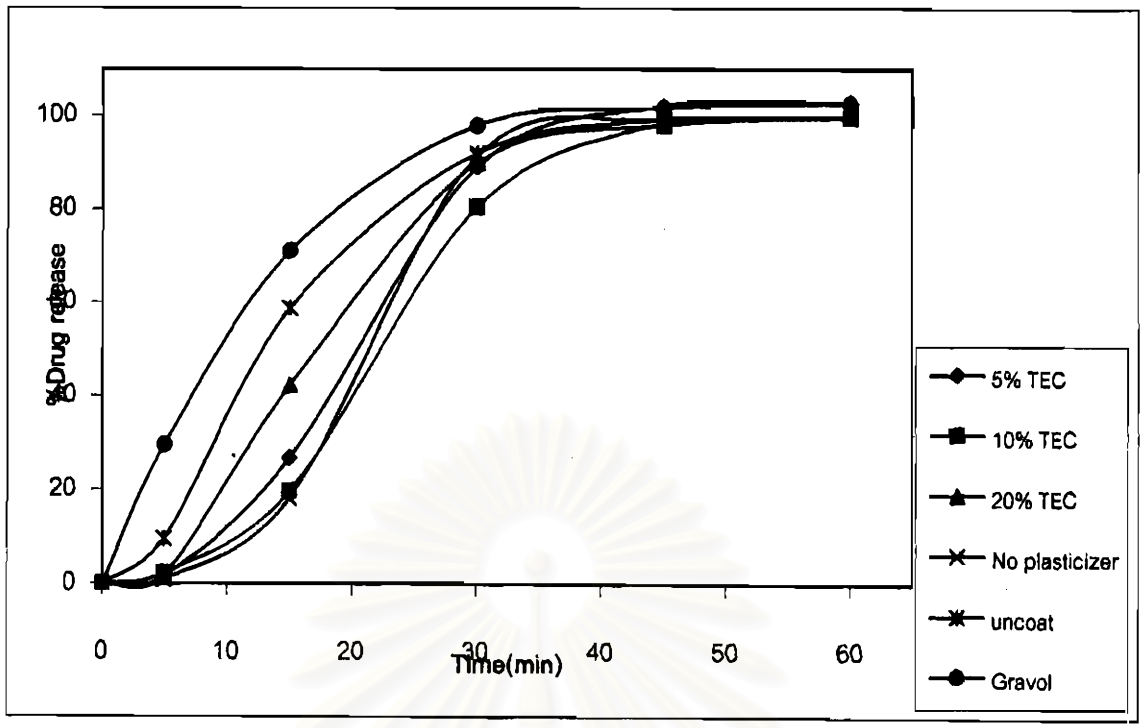


(b)

Figure 78 Effect of plasticizer on dissolution profiles of Dimenhydrnate from hard gelatin capsule coated with Methocel E5,

(a) prepared by fluid bed coater, incorporated with PEG 6000

(b) prepared by perforated pan coater, incorporated with DEP



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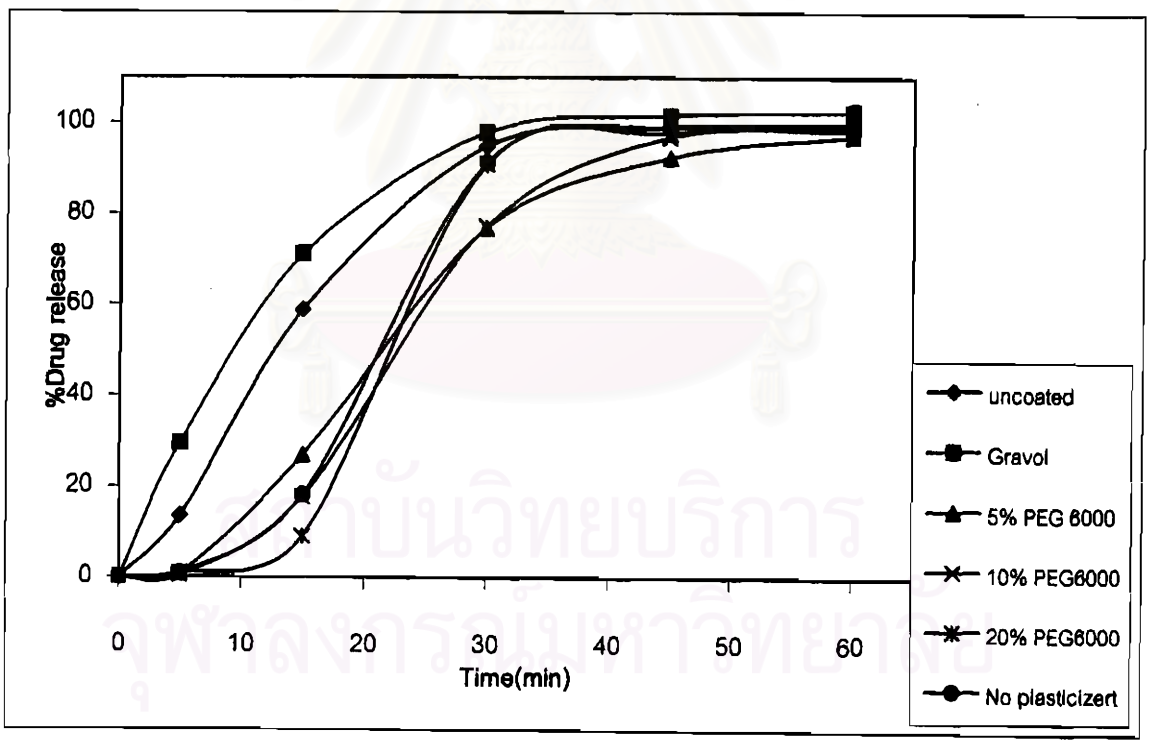
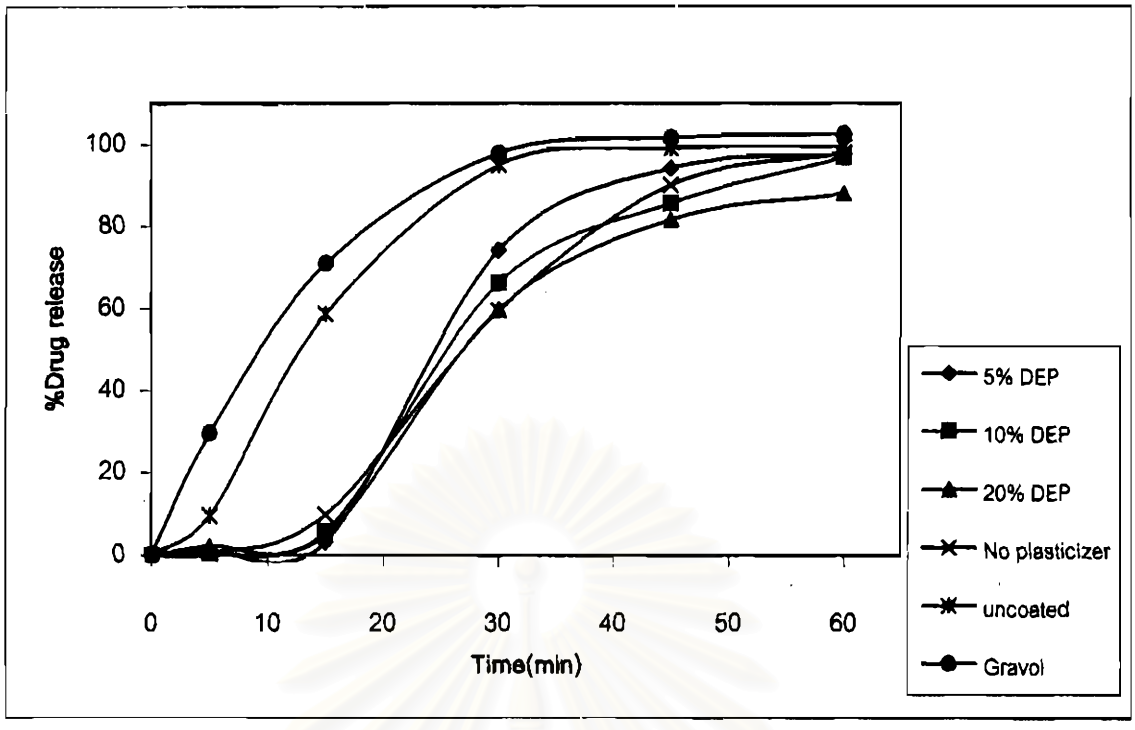


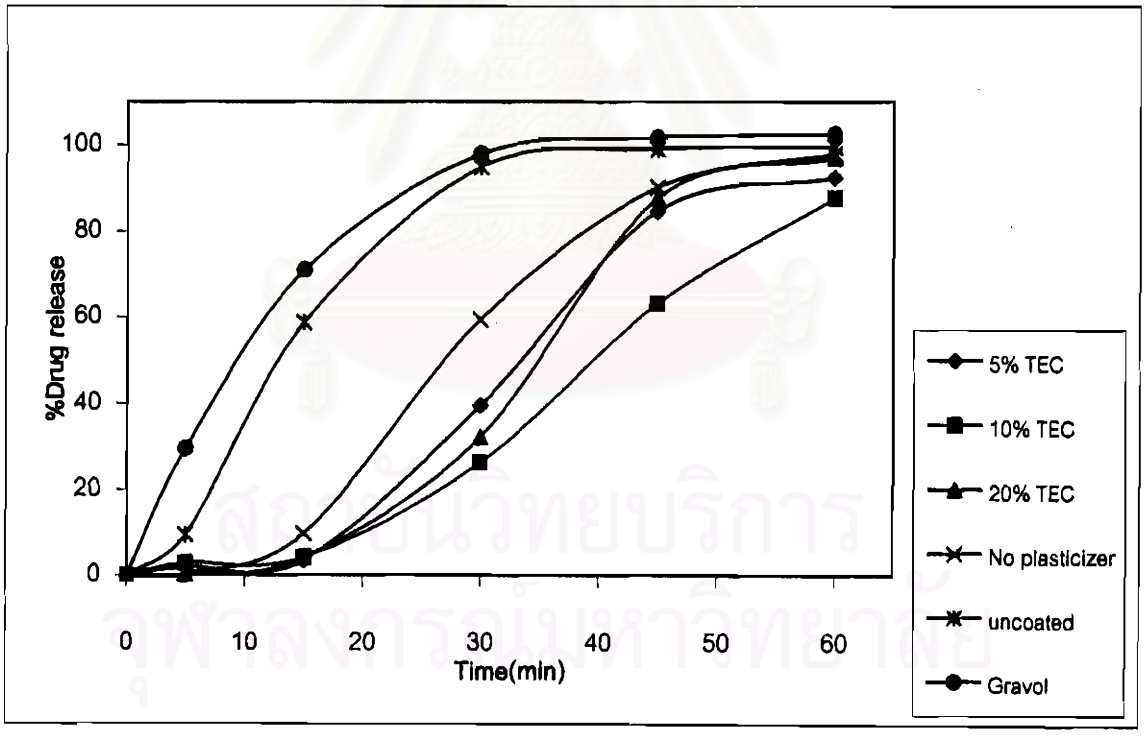
(b)

Figure 79 Effect of plasticizer on dissolution profiles of Dimenhydrnate from hard gelatin capsule coated with Methocel E5, prepared by perforated pan coater

(a) TEC (b) PEG 6000



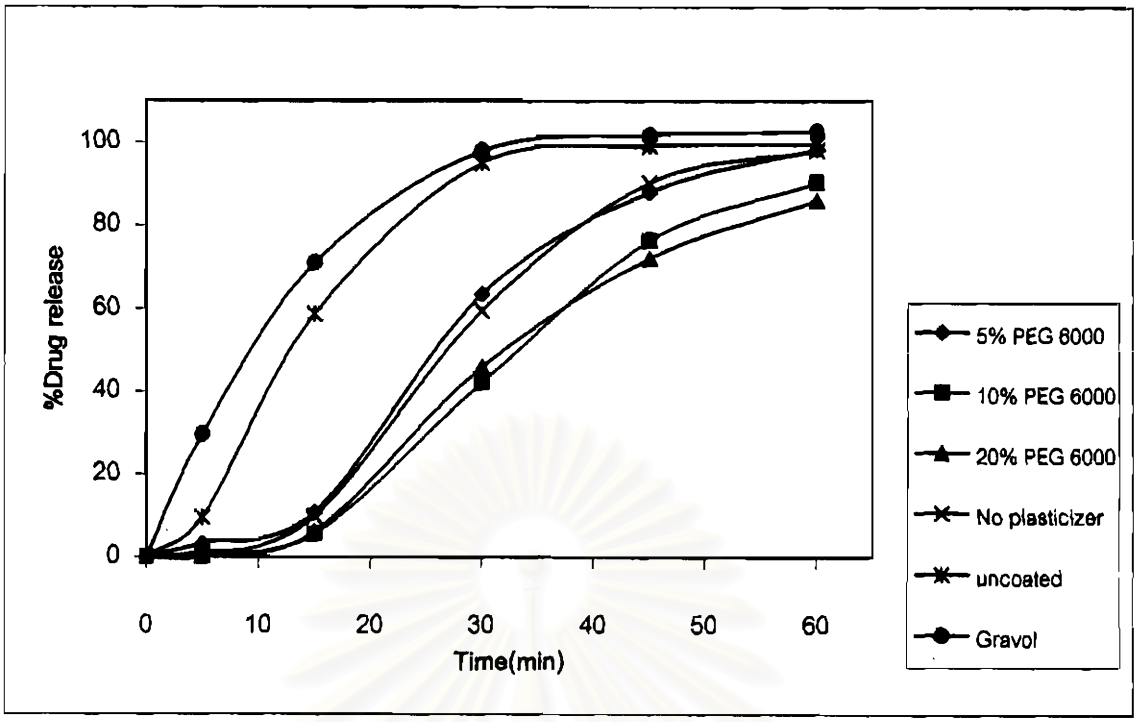
(a)



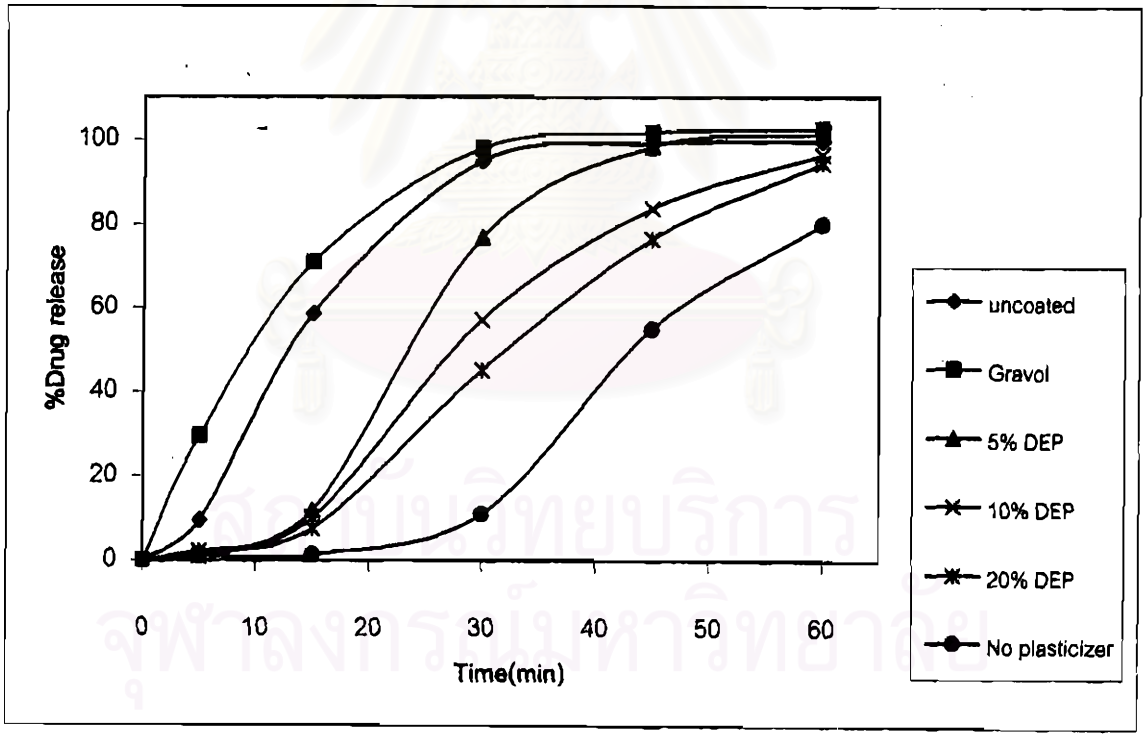
(b)

Figure 80 Effect of plasticizer on dissolution profiles of Dimenhydrnate from hard gelatin capsule coated with Eudragit L30D-55, prepared by fluid bed coater

(a) DEP (b) TEC



(a)

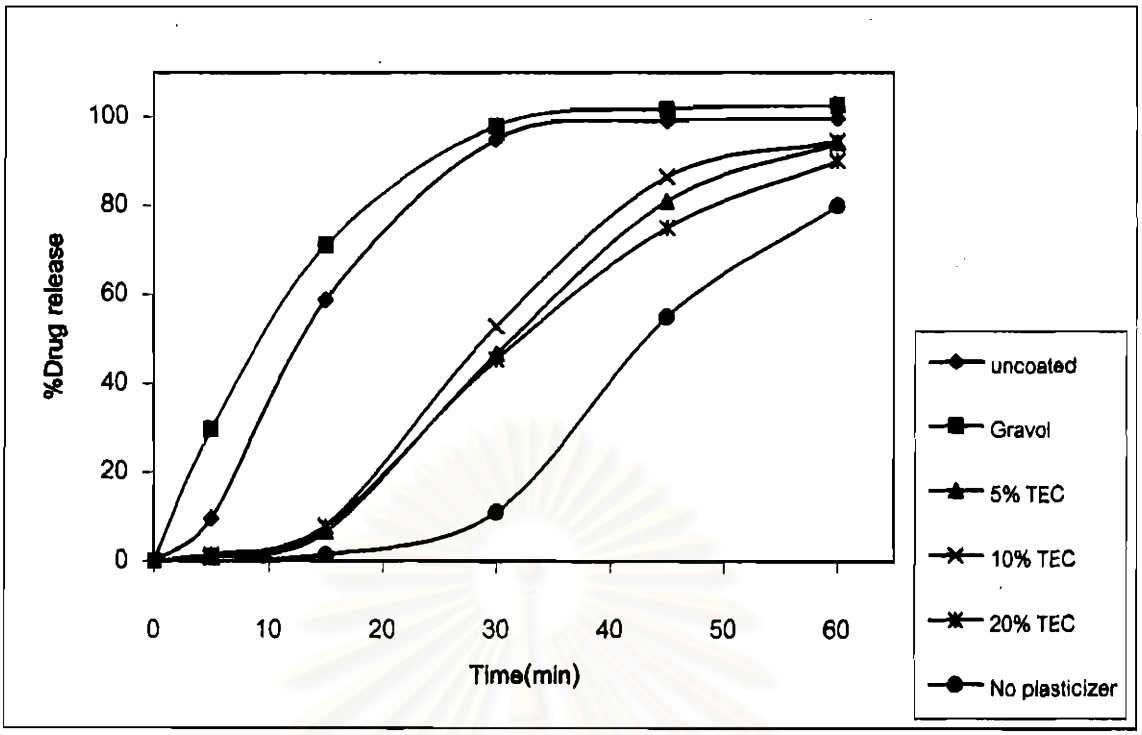


(b)

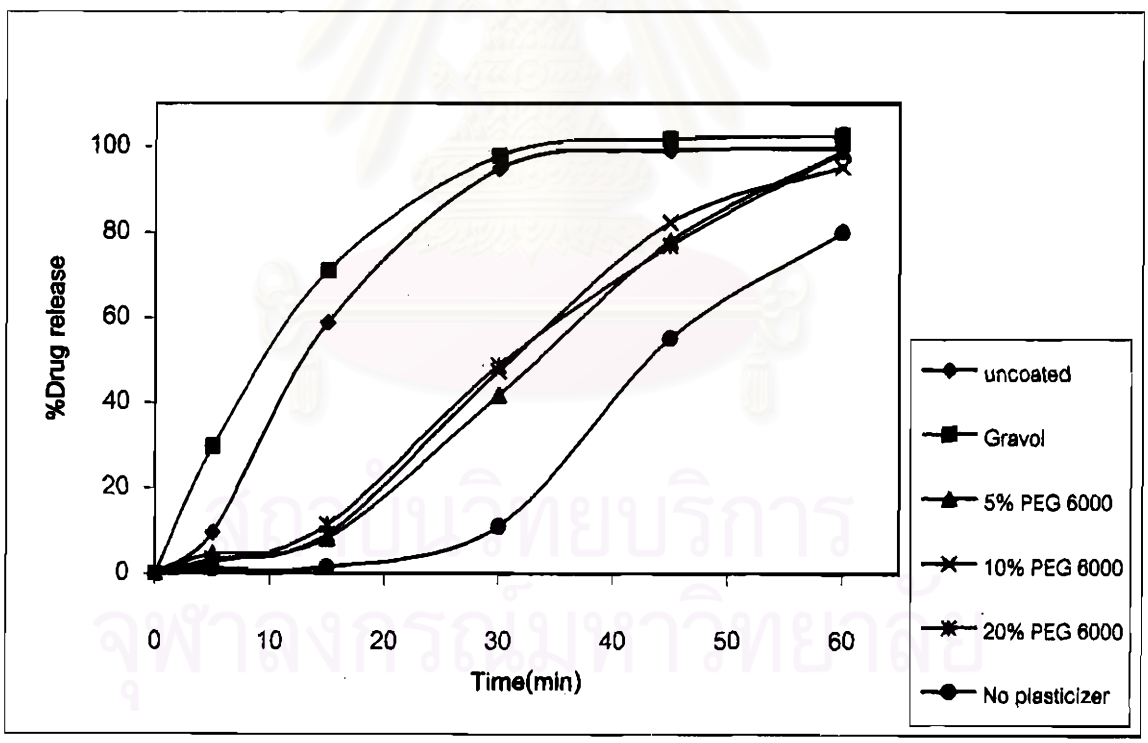
Figure 81 Effect of plasticizer on dissolution profiles of Dimenhydrnate from hard gelatin capsule coated with Eudragit L30D-55,

(a) prepared by fluid bed coater, incorporated with PEG 6000

(b) prepared by perforated pan coater, incorporated with DEP



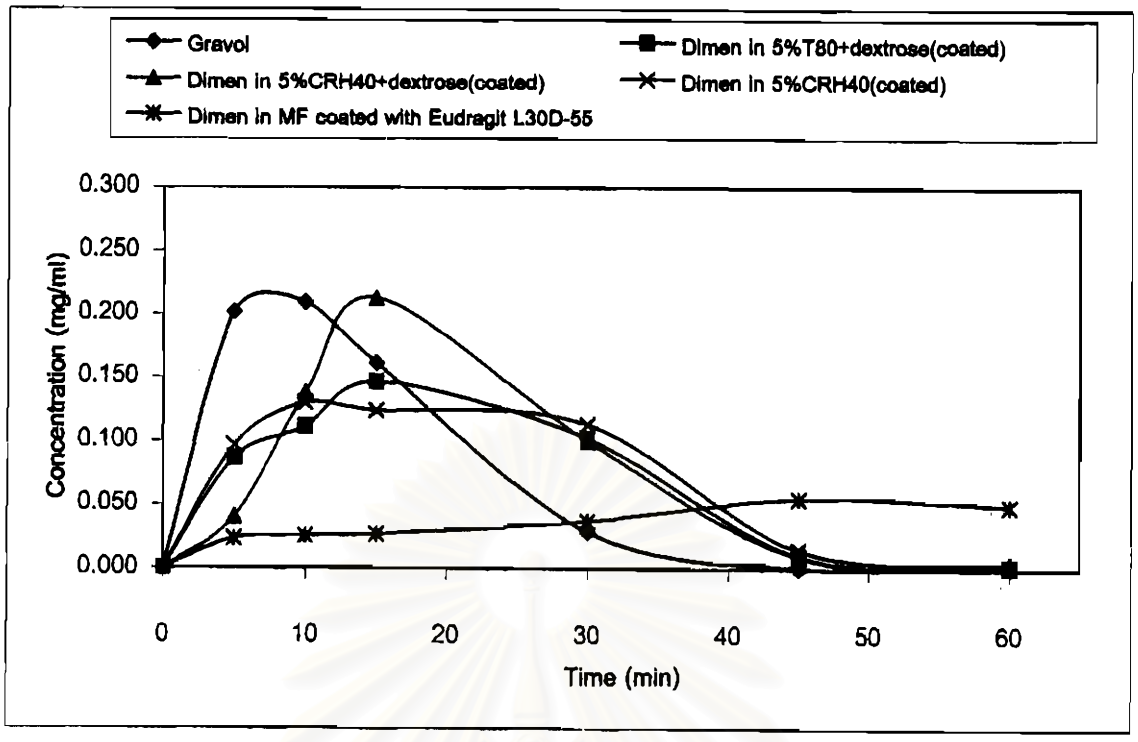
(a)



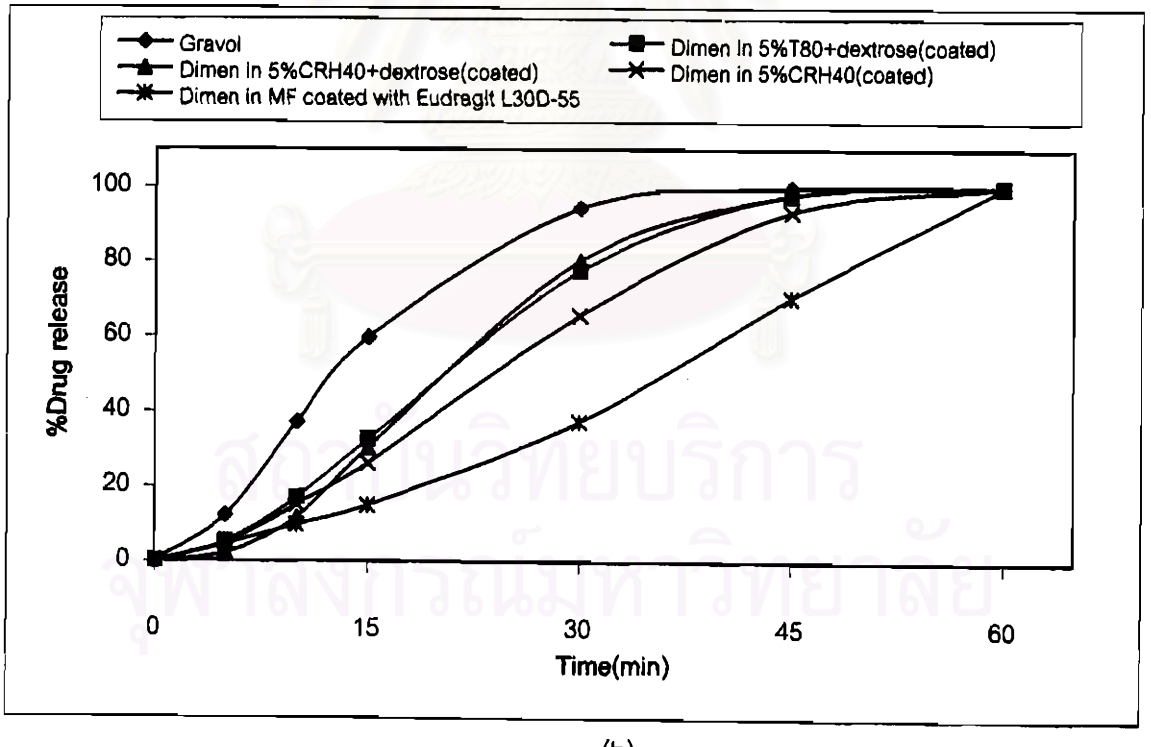
(b)

Figure 82 Effect of plasticizer on dissolution profiles of Dimenhydrnate from hard gelatin capsule coated with Eudragit L30D-55, prepared by perforated pan coater

(a) TEC (b) PEG 6000



(a)



(b)

Figure 83 Dissolution profiles of Dimenhydrinate liquid filled, coated capsule determined by Flow-through apparatus

(a) Time & release curve (b) Cumuative curve

increase from 5.6 to 20.6 mg/cm^2 at pH 6.8. The result was in the same direction of disintegration time of Eudragit® coated capsule that was not disintegrated within 30 minutes.

The dissolution profile of capsules coated with the different type and various level of plasticizer were evaluated. As shown in Figure 77-82, the chemical nature of the plasticizer has an influence on the release curves: diethyl phthalate, a water insoluble plasticizer, gave slightly retard of the drug release greater than PEG 6000 and TEC. For Eudragit® coated capsule, it was corresponding with the results reported by Schmidt and Niemann (1992). Eudragit® film plasticized with dibutylphthalate were less permeable than films containing the same amount of TEC. It could be explained that DBP did not leach from the film due to its hydrophobic property, whereas the more hydrophilic TEC was eluted from the coating. The obtained result indicated that the higher level of PEG 6000, TEC and DEP from 5% to 20% led to lower permeability of films in buffer system. TEC had more pronounced effect on drug release than PEG 6000, whereas DEP showed the least effect. From the previous study, the latex particles were insufficiently plasticized resulted in faster release at the low concentration. The 10-30% concentration of water soluble plasticizer showed good film formation. But the leaching out of water soluble plasticizer occured evidently at higher plasticizer levels more than 30% (Bodmeier and Paeratakul, 1990).

The comparison of dimenhydrinate release from coated capsules using perforated pan coater and fluid bed coater are displayed in Figure 77--82. There was no different in the dissolution profile both coating with HPMC and Eudragit®.

Figure 83 show the release characteristic of coated capsule when using flow through apparatus It also gave a lower release rate when compared to uncoated capsule. In addition, the result showed that all coating slightly retarded drug release due to the film to be dissolved and cellulosic film could be dissolved faster than Eudragit® L 30 D-55 film.

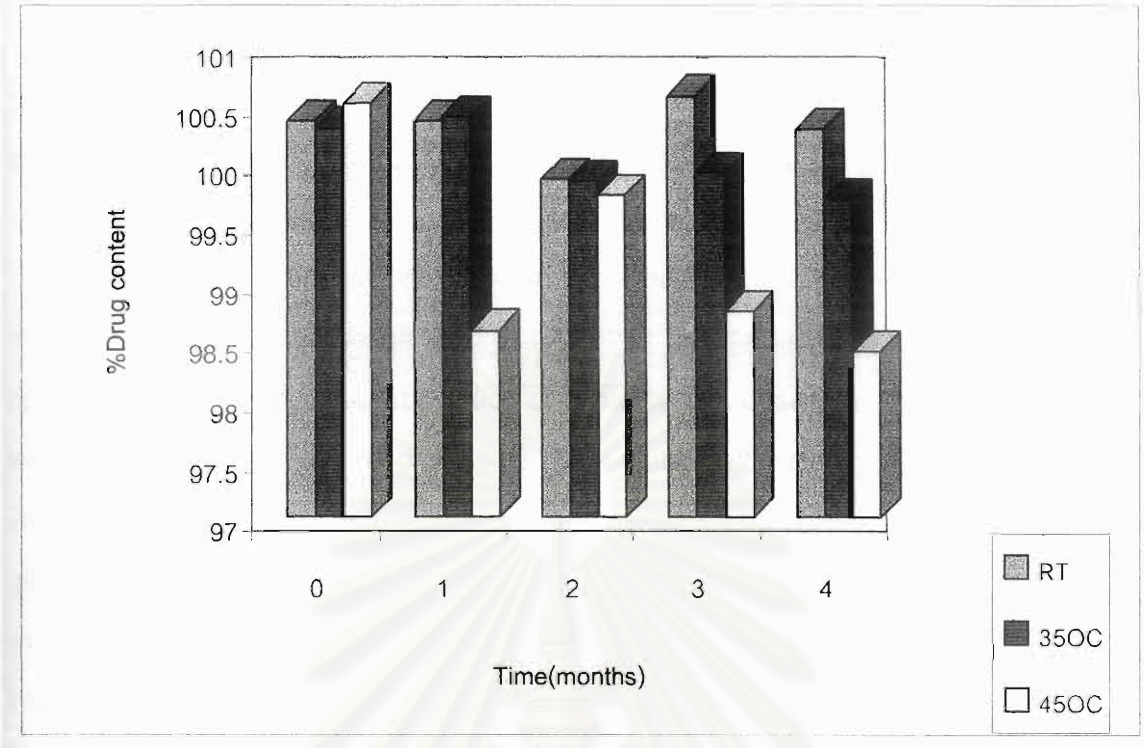


Figure 84 Effect of storage time on drug content at different temperature

7. Stability of Dimenhydrinate Rectal Coated Capsule

The coated capsules were stored at room temperature, 35 °C and 45 °C with 75% RH for four months. All coated capsules displayed good physical appearance. Cracking, wrinkling or tearing of the film was not visually observed. These capsules were investigated as follows.

1) Effect of aging on drug contents

The results of assay of dimenhydrinate content in liquid-filled and coated capsule prior to and after storage in the condition specified above are shown in Appendix D. It was found that percent drug amount of capsule kept at 35 °C and room temperature remained in the range of 97-101%, which is the normal range. There was no interaction between liquid content and the gelatin capsules. Nevertheless, the tendency of slight decrease of drug content was observed after storage at 45 °C for 4 months. The average contents at the fourth month are shown in Figure 84.

2) Effect of aging on moisture sorption and leakage time.

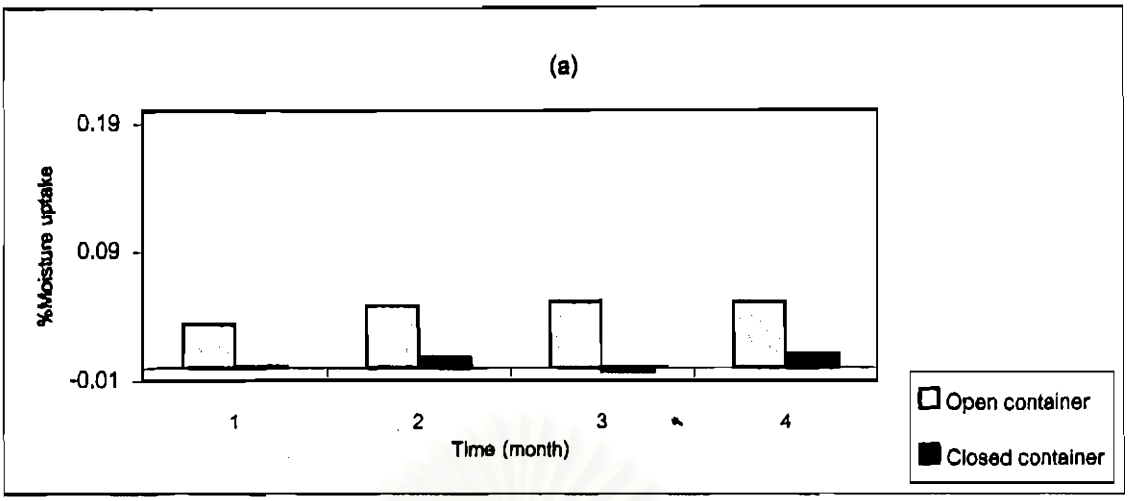
In order to evaluate of coated film on moisture absorption, the capsules would be kept in two conditions. First condition, the coated capsules were kept in glass-closed container and the second, the coated capsule were kept in opened glass container.

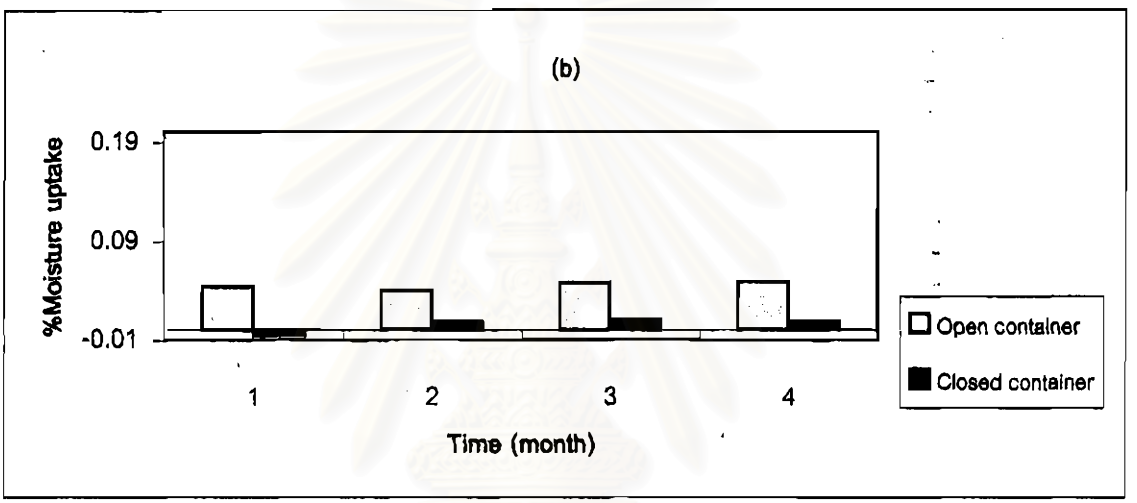
There was no visually liquid leakage from coated capsule after storage for four months. The results of change in capsule weight are displayed in Figure 85. In the open container, the moisture absorption of contents was observed. Moisture uptake of less than 0.06 % w/w was recorded in all temperature after storage for 4 months. For investigation the effect of coated film, liquid preparation was filled directly to an opened glass vial. As illustrated in Figure 86, the percentage of moisture uptake all temperature was in the range of 0.1-0.2 %. It could be concluded that thickness of cellulosic film improved moisture protective property of liquid-filled capsule but the result showed that the film could not enough to prevent the moisture permeation. Hence, the coated capsule should be kept in a close container that the capsule weights were almost unchanged (Figure 85-86).

The result indicated that some of ingredient exhibited moisture absorption. The further study proved that Tween 80 increased 0.03% moisture uptake whereas Aerosil® 200 increased only 0.007%. However, the tested relative humidity was higher than recommended RH for capsule storage that is between 40-60% and the moisture absorption of selected formula was less than 2% that is the value affecting to capsule splitting.

3) Effect on disintegration time and dissolution profile

Disintegration time of coated capsule in phosphate buffer pH7.2 is illustrated in Figure 87. It was found that disintegration time occurred within 4-7 minutes and was not different in all condition. For the dissolution profile, after the defined period (0,2,4 months) drug release from capsule was found slightly decreased at longer time storage (Figure 88). In the fourth month, the drug release was decrease to 86.92% in 30 minutes





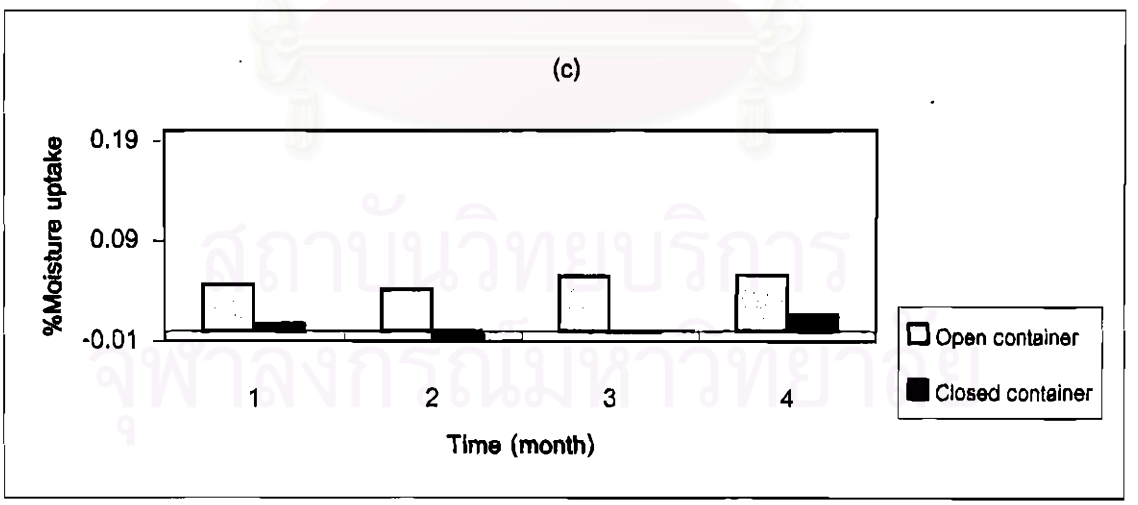
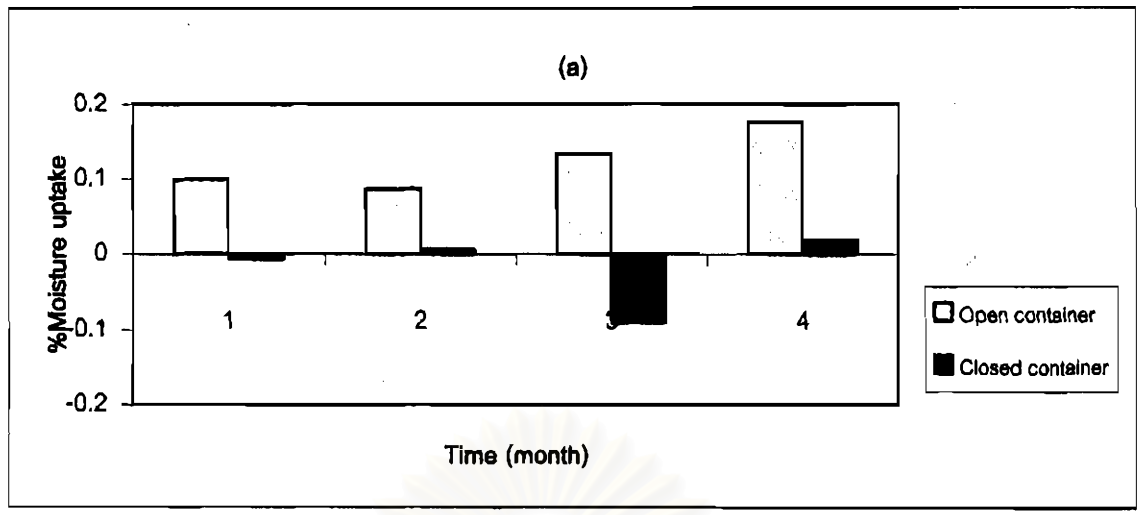
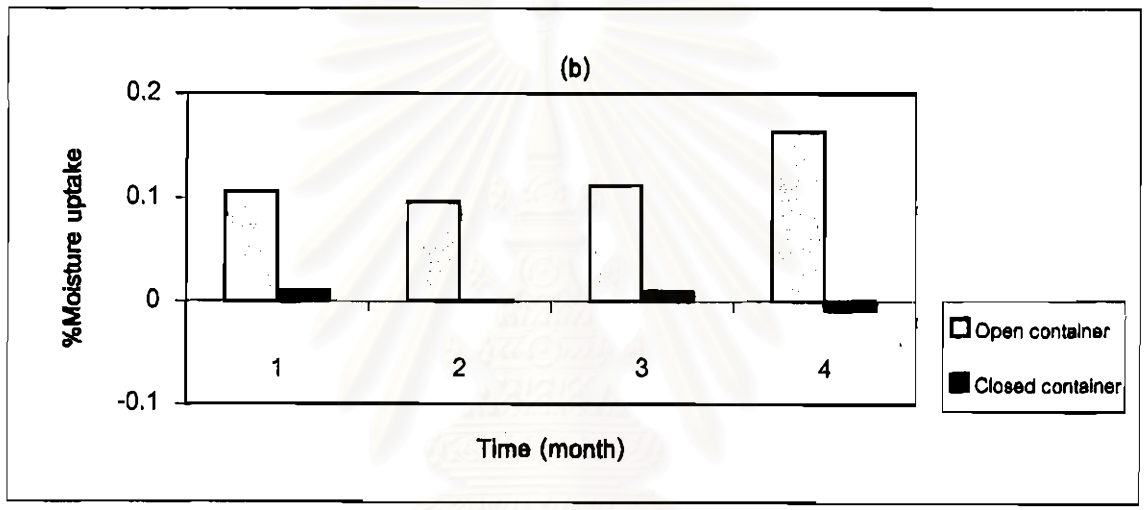


Figure 85 Moisture sorption of liquid filled coated capsule, storage in open and closed container at,

(a) room temperature (b) 35°C (c) 45°C





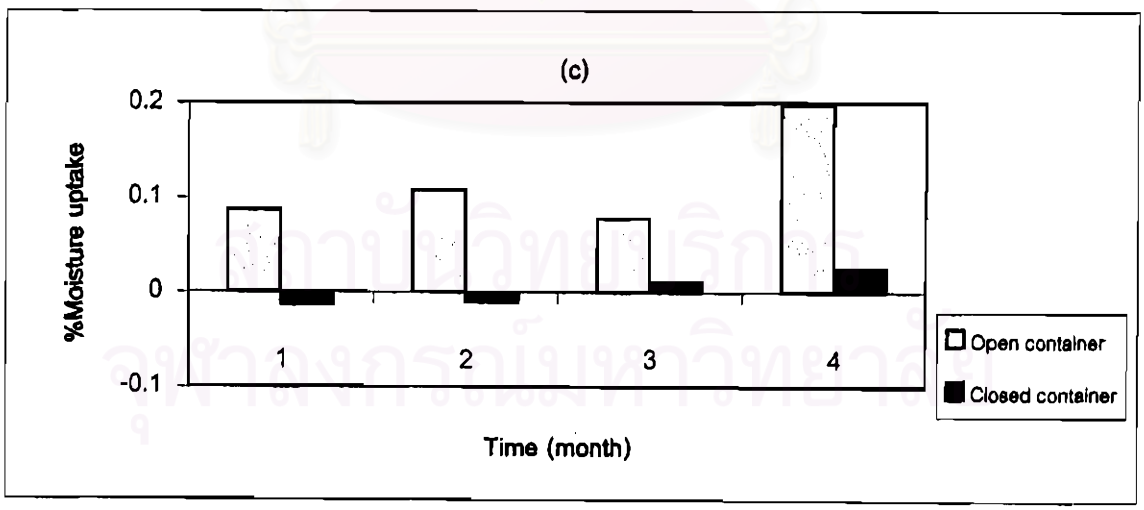


Figure 86 Moisture sorption of liquid mixture filled into a glass vial, storage in open and closed container at,

(a) room temperature (b) 35°C (c) 45°C

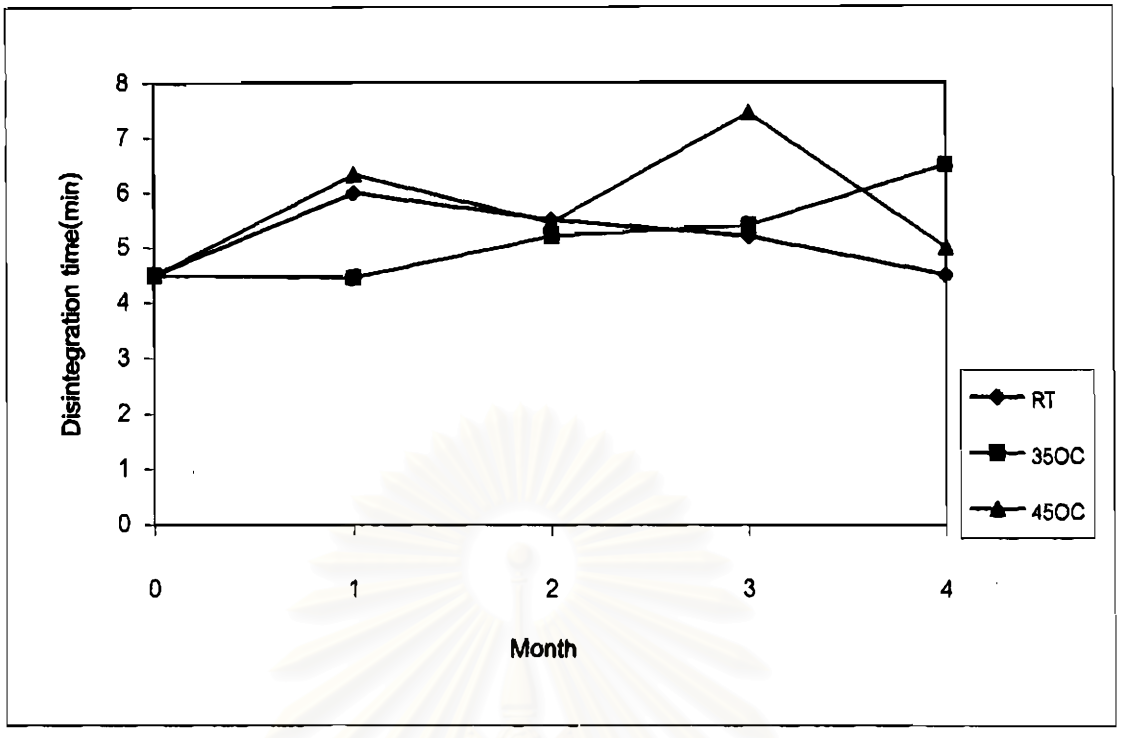


Figure 87 Effect of storage time on disintegration time of rectal capsule

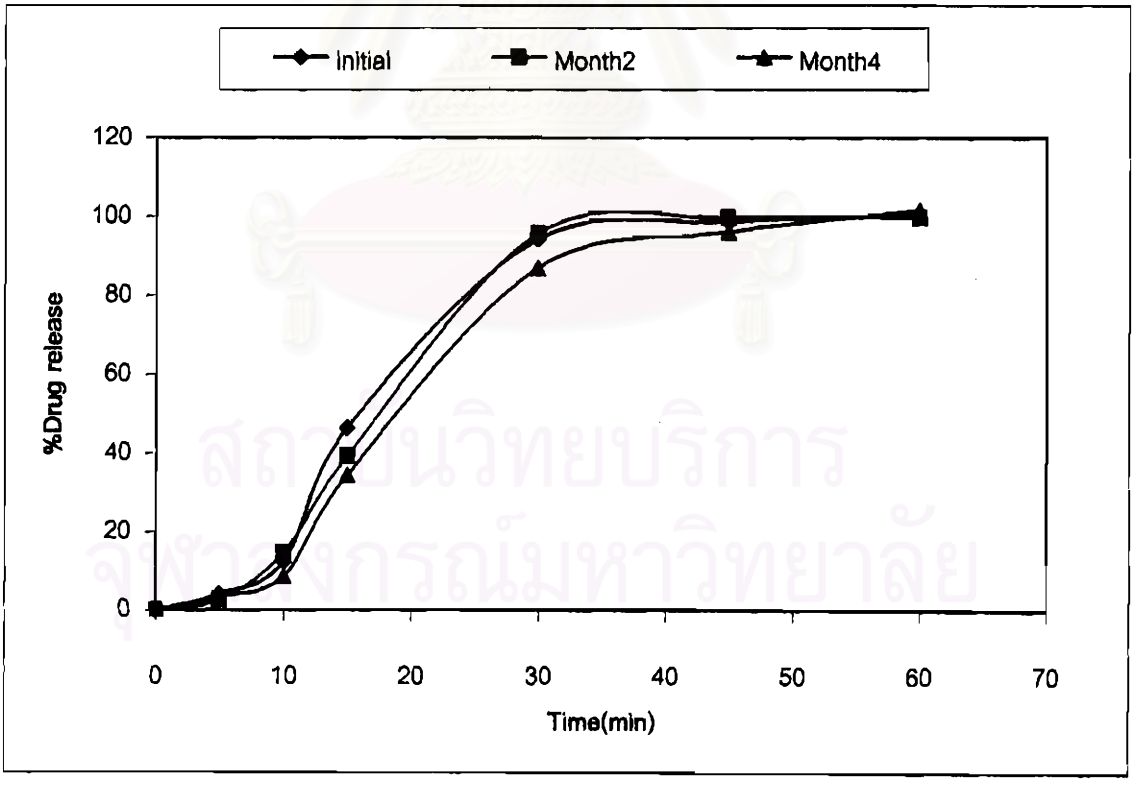


Figure 88 Effect of storage time on dissolution profiles of rectal capsule

when comparing to 94.13 % from beginning and 95.67 % in the second month. However, drug release was completely occurred within 60 minutes in all formulation.