CHAPTER III

EXPERIMENTAL

Equipments

1. Magnetic Stirrer (Model MR 3001, Heldoph, Germany)
2. Analytical Balance (Model PB3002, Mettler Toledo, Switzerland and Model A200S, Sartorius GmbH, Germany)
3. Water Bath (Model WB4P, Thermolek, USA)
4. Hygro-thermometer (Barico, Germany)
5. Hot Air Oven (Model UL80, Memmert, Germany)
6. Incubator (Model 4273, Laboratory Thermal Equipment, England)
7. Dissolution Apparatus (Model DT6R, Erweka, Germany)
8. UV-Visible Spectrophotometer (Model UV-160A, Shimadzu, Japan)
9. Flow-through Apparatus (DissotestCE70, collector-MS70, Sotax, Switzerland)
10. Universal Material Tester (Instron) (Model 5565H1624, System ID, England)
11. Scanning Electron Microscope (Model JSM-6400 LV, Joel Ltd., Japan)
12. pH Meter (Model 292, Pye Unicam Ltd., England)
13. Fluidized Bed Coater (Aeromatic, model STREA, Niro, Switzerland)
14. Perforated Pan Coater (Thai-coater 15"(L) ,PMS Pharmaceutical, Thailand)
15. Particle Size Analyzer (Malvern Instruments Ltd., UK)
16. Autopipet (Pipetman, Gilson Medical Electronic, France)
17. Viscometer (model Rotovisco RV20, Haake, Germany)
18. Disintegration Apparatus (Model ZT31, Erweka, Germany)
19. Micrometer (Teclock Corp., Japan)
20. Liquid Filling Machine (Model AR, Filamatic, USA)
21. Semiautomatic Capsule Filling Machine (Model PANVIV, The Union Chemical and Surgical, Thailand)
22. Paddle Stirrer (DT, Erweka GmbH, Germany)
23. Surface Roughness Tester (Taylor,USA)
24. Cenco.Dunouy Ring Tensiometer (Malvern Instruments Ltd., UK)

Materials

1. Mineral oil (Lot.No. 89-90/843, supplied by Srichand United Dispensary Co.,Ltd., Thailand)
2. Isopropyl merystate (Lot.No. 6483, supplied by Ektrong Co.,LTD., Thailand)
3. PEG400 (Lot.No. PID24/796, England) , distributed from Srichand
4. Soybean oil (Lot.No.0645 , Grape brand, Thailand)
5. Olive oil (Lot.No. OAR02/393, Spain)
6. Oleic acid (Lot.No. ACH 01/89, supplied by Srichand United Dispensary Co.,Ltd., Thailand)
7. MCT oil (Lot No. MJH91, Mead Johnson, USA)
8. Silicone oil(Lot.No.004 , supplied by Mansiang Co.,Ltd., Thailand)
9. Aerosil 200 (Lot.No. 2625, Degussa, Germany)
10. Aerosil R972 (Lot.No 1789, Degussa, Germany)
11. PEG 6000 (Lot.No. PIA03, supplied by Srichand United Dispensary Co.,Ltd., Thailand)
12. Pluronic F68 (Lot.No. 0871, BASF, Germany)
13. White bees wax (Lot.No. BC 30/657, supplied by Srichand United Dispensary Co.,Ltd., Thailand)
14. Cutina-HR (gift from Henkel, Germany)
15. White vaseline (Lot.No. CIB146, supplied by Srichand United Dispensary Co.,Ltd., Thailand)
16. Tween 80 (Lot.No. TGD15, supplied by Srichand United Dispensary Co.,Ltd., Thailand)
17. Span 80 (Lot.No. SGD 02, supplied by Srichand United Dispensary Co.,Ltd., Thailand)
18. Span 20 (Lot.No. SGA03, supplied by Srichand United Dispensary Co.,Ltd., Thailand)
19. Cremophor RH40 (Lot.No. Af0633, BSAF company, Germany)
20. Brij 72 (Gift from East Asiatic(Thailand) Public Company Limited)

21. Cetostearyl alcohol (Lot.No. 56A0089, supplied by Ektrong Dispensary Co.,Ltd., Thailand)
22. Dextrose (Srichand United Dispensary Co.,Ltd., Thailand)
23. Lactose (Lot.No. 8111902, supplied by Srichand United Dispensary Co.,Ltd., Thailand)
24. Sodium chloride (Lot.No. SHE 04/33, E.Merck, Germany)
25. Icing sugar (Mitrapon, Thailand)
26. Sodium hydroxide (Lot.No. 7708 MVHT, Malinckrodt, USA)
27. Dimenhydrinate (Lot.No. 21005, supplied by Ektrong Dispensary Co.,Ltd., Thailand)
28. Dimenhydrinate Reference standard (Gift from GPO)
29. Methocel E5 (Lot.No. MM91042821E, Colorcon, England)
30. HPC type H (Lot.No. CE-211, supplied by Nippon Soda, Thailand)
31. HPC type M (Lot.No. BD-191, supplied by Nippon Soda, Thailand)
32. HPC type L (Lot.No. SD-645, supplied by Nippon Soda, Thailand)
33. Triethyl citrate (Lot.No. 371665/1 20598, Fluka, Switzerland)
34. Diethyl phtalate (Lot.No. 325384/1393, Fluka, Switzerland)
35. PEG 6000 (Lot.No. AN316, E.Merck, Germany)
36. Eudragit® L30D-55 (Lot.No. 1270814832, Rohm pharma, Germany)
37. Eudragit® E100 (Lot.No. 01-80018, Rohm Pharma, Germany)
38. 95 % EtOH (Sunpasamitr, Thailand)
39. Isopropyl alcohol (Lot.No.K43625, J.T.Baker, USA)
40. Potassium carbonate (Lot.No. 020A493528, E.Merck, Germany)
41. Sodium bromide (Lot.No. BI16/3, supplied by Srichand United Dispensary Co.,Ltd., Thailand)
42. Potassium nitrate (Lot.No. 00231, Vidthayasrom, Thailand)

Methods

1. Selection of Hard Gelatin Capsule

Hard gelatin capsules have many different features and leakage may occur when the interior content is in liquid form. In this part, different types of No.0, hard gelatin capsule in the market were selected to evaluate the appropriate type to be used liquid filling capsule. Capsule No.0, Coni-snap® from Capsugel Ltd., Licaps® from Capsugel Ltd. and Cap-lock® from Capsule Product Ltd. were investigated for liquid leakage.

Liquids of various properties, i.e., olive oil, soybean oil, medium chain triglyceride (MCT oil), mineral oil, isopropyl myristate, silicone oil, polyethylene glycol 400 and oleic acid, equivalent to 500 mg weight were transferred into each capsule body, then its individual cap was secured. The capsule was accurately weighed and kept in the container at 30 °C and 40-60% relative humidity for one month. Capsule leakage was detected by weighing the capsule every 2 days while observing an oil droplet on absorbance paper.

2. Selection of Liquid Vehicle

Liquid vehicle characteristics such as moisture sorption, viscosity and surface tension are one of the most important factors that affect both physical properties and leakage of preparation.

2.1 Characterization of Moisture Sorption of Liquid

The different conditions of relative humidity were maintained approximately at 45, 55, 75, 92 % by dissolving excess amount of analytical grade of potassium carbonate, sodium bromide, sodium chloride, potassium nitrate in distilled water, respectively. These saturated solutions were equilibrated in tightened, vacuum desiccator in a hot air oven at 60°C for 48 hours, then the desiccator with the sample glass vials was stored in an incubator at 30 °C (Nygvist, 1983).

Liquid vehicles were accurately filled into a glass vial of approximately one gram where the weights before and after filling were recorded. These vials were kept in the prepared desiccator at 30°C. Sample was weighed every two days for one month and observed physical appearance of liquid. Moisture absorption of each liquid was calculated from the weight recorded.

2.2 Characterization of Viscosity

Two milliliters of liquid vehicle was pipetted to a cup of viscometer and stirred constantly at a shear rate of $1000s^{-1}$ for one minute. The samples were then determined for the apparent viscosity value every 10 seconds. The results were reported as an average of five determinations.

2.3 Characterization of Surface Tension

An accurate volume of 40 ml of each liquid vehicle was measured into a 50 ml beaker. A platinum ring of a Du-nouy tensiometer was later immersed in the liquid vehicle and was slowly raised up until the ring came into contact with the surface of the liquid. Surface tension was recorded by adjusting the screw until the ring just separated from the liquid surface. The surface tension was the average of five determinations and standard deviations were recorded.

2.4 Leakage Test

Five hundred milligrams of liquid vehicles were accurately weighed and transferred into Licaps®. These capsules were stored at 30 °C and 40-60% relative humidity. The presence of leakage was observed by the method as described in 1.

3. Preparation of Dimenhydrinate Liquid-filled Hard Gelatin Capsule

3.1 Formulation of Liquid Base

All liquid formulas were prepared, on a weight by weight (w/w) basis, by varying the ratio of thickener to mineral oil. The amount of ingredients used in each formula is

presented in Table 4 and the procedures of preparation differed depending on the property of each component.

Method A (Formula No.1-29)

Mineral oil and other ingredients were weighed and transferred into 15 ml test tube. The mixture was immersed in water bath at 80°C until solid substance was completely molten. Mixture was subsequently stirred at the room temperature until homogenous mixture was attained.

Method B (Formula No.29-37)

Mineral oil and colloidal silicone dioxide was individually weighed. Colloidal silicone dioxide was added portion by portion into the mineral oil. The mixture was blended together in 15-ml test tube by vortex until clear gel was obtained.

Characteristics of each formula are recorded as follows.

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

Systems, which exhibited good homoginity, high viscosity and expressed thixotropic property, were selected for further investigation.

3.2 Formulation of Dimenhydrinate in Liquid Base.

Dimenhydrinate was screened through sieve No.80 mesh and incorporated into liquid base of each formula. The effect of ingredients such as thickener, surfactant and

Table 4 Liquid base formula

Formula	The ratio of substance										
	MO	PEG6000	WBX	WV	C-HR	MgSt	CA	PF68	SA	A200	AR972
1	20	80	-	-	-	-	-	-	-	-	-
2	40	60	-	-	-	-	-	-	-	-	-
3	60	40	-	-	-	-	-	-	-	-	-
4	80	20	-	-	-	-	-	-	-	-	-
5	90	10	-	-	-	-	-	-	-	-	-
6	90	-	10	-	-	-	-	-	-	-	-
7	95	-	5	-	-	-	-	-	-	-	-
8	97.5	-	2.5	-	-	-	-	-	-	-	-
9	99	-	1	-	-	-	-	-	-	-	-
10	60	-	-	40	-	-	-	-	-	-	-
11	70	-	-	30	-	-	-	-	-	-	-
12	80	-	-	20	-	-	-	-	-	-	-
13	90	-	-	10	-	-	-	-	-	-	-
14	95	-	-	5	-	-	-	-	-	-	-
15	90	-	-	-	10	-	-	-	-	-	-
16	95	-	-	-	5	-	-	-	-	-	-
17	97.5	-	-	-	2.5	-	-	-	-	-	-
18	90	-	-	-	-	10	-	-	-	-	-
19	95	-	-	-	-	5	-	-	-	-	-
20	97.5	-	-	-	-	2.5	-	-	-	-	-
21	90	-	-	-	-	-	10	-	-	-	-
22	95	-	-	-	-	-	5	-	-	-	-
23	97.5	-	-	-	-	-	2.5	-	-	-	-
24	90	-	-	-	-	-	-	10	-	-	-
25	95	-	-	-	-	-	-	5	-	-	-
26	97.5	-	-	-	-	-	-	2.5	-	-	-
27	90	-	-	-	-	-	-	-	10	-	-
28	95	-	-	-	-	-	-	-	5	-	-
29	97.5	-	-	-	-	-	-	-	2.5	-	-
30	90	-	-	-	-	-	-	-	-	10	-
31	95	-	-	-	-	-	-	-	-	5	-
32	97.5	-	-	-	-	-	-	-	-	2.5	-
33	99	-	-	-	-	-	-	-	-	1	-
34	90	-	-	-	-	-	-	-	-	-	10
35	95	-	-	-	-	-	-	-	-	-	5
36	97.5	-	-	-	-	-	-	-	-	-	2.5
37	99	-	-	-	-	-	-	-	-	-	1

drug dragger was evaluated by varying the level of each additives. The amount of thickener incorporated into each formula was 1, 2.5, 5 and 10% w/w. The level of surfactants and drug dragger was 2.5, 5 and 10% w/w of each formulation. The preparations were investigated for their properties as follows:

3.2.1 The Release Profile

The formulation containing 50 mg of dimenhydrinate was filled into No. 0 Licaps® and the release pattern of each formula were studied according to the following methods.

3.2.1.1 The USP Dissolution Test Type II

The drug release was determined according to USP dissolution test using the basket method. Five hundred milliliters of phosphate buffer pH 7.2 were placed in a glass vessel and the medium was equilibrated at 37±0.5 °C. One capsule was placed in a dry basket and immersed in the medium. The apparatus was operated at a speed of 50 rpm. Three capsules of each formulation were investigated for the dissolution characteristics.

Ten milliliters of each sample was withdrawn at the time interval of 5, 15, 30, 45 and 60 minutes. The same quantity of medium was replaced immediately after each sampling to keep a constant volume of the medium during the experiment. Each sample was filtered through filter paper No.1. The absorbance of this solution was measured by UV-Visible spectrophotometer at 279 nm. The absorbance of dimenhydrinate released at various time intervals was calculated from the standard absorbance-concentration curve. A cumulative correction was made for the previously removed sample to determine the total amount of drug released.

<u>Calibration curve of dimenhydrinate</u>

One hundred milligrams of dimenhydrinate were accurately weighed and dissolved in few milliliter of absolute ethanol. The solution was adjusted to 100 ml with phosphate buffer pH 7.2, then 4 ml of the solution was pipetted and adjusted to

100 ml. The final dilution was used as stock solution.

The standard stock solution which contained the known concentrations of 4, 8, 12, 16, 20, 24 μg/ml was then prepared in a triplicate by dilution of the stock solution with phosphate buffer pH 7.2 and analyzed using UV-Visible spectrophotometer in a 1-cm cell at 279 nm. Phosphate buffer pH 7.2 was used as a blank solution.

3.2.1.2 The USP Dissolution Test type IV

The release of drug was determined according to USP dissolution using the flow-through cell apparatus, composed of a diameter 12 mm of flow through cell with flow rate of 10 ml/min. Sample was placed in chamber with upward continuous stream of phosphate buffer pH 7.2, equilibrated at 37±0.5 °C and was filtered through a filter head (Figure 12). The dissolution medium was collected at chosen time intervals of 5, 10, 15, 30, 45 and 60 minutes. The absorbance of dimenhydrinate released at any time interval was calculated from the standard absorbance-concentration curve.

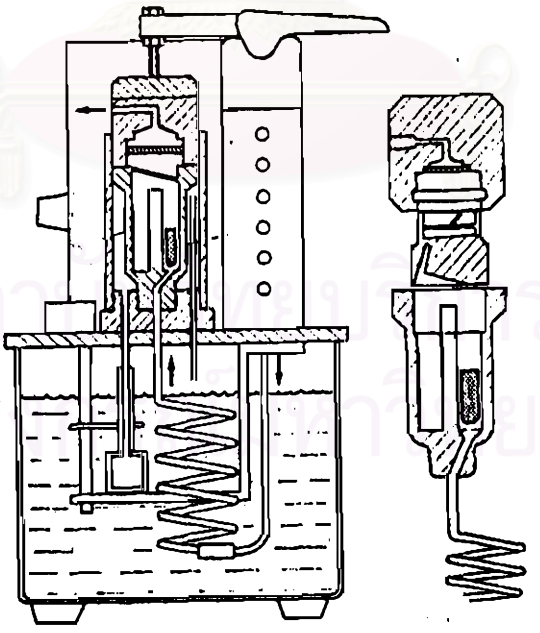

Figure 12 Flow-through cell for testing drug release of rectal capsule (reproduced from Gjellan and Graffner, 1989)

3.2.2 Rheological Determination

The rheological behaviors of these liquid bases were subsequently evaluated by Hakke viscometer at 27 ^{o}C. The measuring system was different between the highly viscous compound; a SV1 sensor was used while the NV1 was selected for low viscosity compound and the shear rate used was 1000 s^{-1}. One cycle consisted of two minutes to allow the shear rate to reach 1000 s^{-1}, and then the shear rate was decreased in two minutes back to 0 s^{-1}. The viscosity of liquid preparation was calculated and shear stress values from 20 different points of triplicate observations were collected to plot a rheogram.

3.2.3 Surface Tension

They were determined in the same manner as 2.3.

3.2.4 Leakage Test

They were determined as described in 2.4

3.2.5 Microscopically Determination

The selected liquid preparation was mounted on a slide with small amount of purified water. Each sample was determined under the microscope at X400 magnification. The comparative study of liquid formula was then evaluated by physical appearance and then photographed under the camera connected to the microscope.

3.2.6 Particle Size Analysis

The selected formulation was diluted with phosphate buffer pH 7.2 in an exactly the same proportion of liquid formula. Particle size analyzer with light scattering technique was used to determine the mean emulsion droplet diameter of the dilution and the particle size distributions. The average diameter was calculated after three determinations in each formula.

Dimenhydrinate liquid filled formulation which exhibited the release profiles comparable to Gravol suppository, having viscosity and surface tension in the recommendation value and prolonging the leakage time was selected to further study.

4. Filling Dimenhydrinate Liquid Base into Hard Gelatin Capsule

One kilogram of selected formula was prepared and filled into Licaps® using liquid filling machine which one compartment connected to container, continuously stirred preparation, and the other connected to semi-automatic capsule filling machine. The volume-adjusting knob of liquid filling machine was set to obtain the appropriate speed and good liquid flowability that controlled weight of 500 mg. (±10% range). The product was tested as follows.

4.1 Weight Variation

During filling process, the weight variation was determined by sampling and

weighing 10 capsules every 10 minutes and the final product of 20 capsules were weighed individually. The average weight of liquid-filling capsules and standard deviation were calculated.

4.2 Disintegration Time

The determination was based on BP disintegration test for rectal capsule but the disintegration testing apparatus was applied. Six capsules were tested by placing a capsule in each tube of the baskets, then immersed in phosphate buffer pH 7.2 maintained at 37±2°C without operating apparatus and adding a disk to each tube to prevent floating of capsules. Disintegration was considered achieved when the gelatin shell ruptured, allowing release of the content and base. The average disintegration time and standard deviation of 6 capsules were calculated.

4.3 Content Uniformity

The amount of dimenhydrinate was determined by sampling one capsule and dissolving it in 40 ml of absolute ethanol. The extraction was filtered through filter paper No.1. The residual of oil that dissolving in ethanol, was separated by freezing in refrigerator overnight. The filtrate was collected and adjusted to 100 ml in volumetric flask; 2 ml was pipetted and diluted to 50 ml in a volumetric flask. The dimenhydrinate RS solution was prepared in the same operation. The content of dimenhydrinate was

determined using UV-Visible spectrophotometer at 277 nm using absolute ethanol as the blank. The quantity, in mg, of dimenhydrinate in the capsule was calculated by the formula:

$$(T/25)C(Au/As)$$

in which T is the quantity, in mg, dimenhydrinate in each capsule, C is the concentration, in μg per ml, of dimenhydrinate in the standard solution, and Au and As are the absorbances of the solution from the capsule and the standard solution, respectively.

5. Coating of Hard Gelatin Capsule

5.1 Preparation of Film Coating Solutions

The cellulosic coating formulations are shown in Table 5. Their coating solutions were prepared by dissolving polymer in the mixture of ratio 1:1 of ethanol: purified water. Plasticizer was incorporated and stirred at least one hour after the polymer was stored over night in order to complete swelling.

Table 5 Cellulosic-coating formulations used for hard gelatin capsule coating

Formula No. / Ingredient	Amount (%w/w)									
	1	2	3	4	5	6	7	8	9	10
HPMC 5 cps	5	5	5	5	5	5	5	5	5	5
TEC	-	0.25	0.5	1.0	-	-	-	-	-	-
DEP	-	-	-	-	0.25	0.5	1.0	-	-	-
PEG6000	-	-	-	-	-	-	-	0.25	0.5	1.0
95%Ethanol:Distilled water q.s.	100	100	100	100	100	100	100	100	100	100

The Eudragit® L 30D-55 coating formulation is displayed in Table 6. The coating solution containing Eudragit® were prepared by pouring the amount of purified water into beaker filled with Eudragit® L 30D-55, stirred in portion by portion and plasticizer was then incorporated as follow in Table 6.

Table 6 Eudragit® L 30D-55 coating formulation used for hard gelatin capsule

Formula No. / Ingredient	Amount (%w/w)									
	1	2	3	4	5	6	7	8	9	10
Eudragit® L30D-55	16.67	16.67	16.67	16.67	16.67	16.67	16.67	16.67	16.67	16.67
TEC	-	0.25	0.5	1.0	-	-	-	-	-	-
DEP	-	-	-	-	0.25	0.5	1.0	-	-	-
PEG6000	-	-	-	-	-	-	-	0.25	0.5	1.0
Distilled water q.s.	100	100	100	100	100	100	100	100	100	100

5.2 Coating Capsule with Fluidized Bed Coater

Liquid-filled hard gelatin capsules of 250 gm. were coated in each batch using bottom spraying with the coating solution present in Table 5 and 6. The capsules were warmed for 5 minutes in stainless steel container, with inlet temperature set up at 45 °C, when outlet temperature reached to 40 °C and spraying was then operated. The Coating solution was continuously fed into a spraying nozzle by a peristaltic pump at flow rate 6-8 ml/min, Atomized pressure was approximately 1.1 bar at fluid bed pressure setting no. 9-10. These conditions were found to be optimal because there were no blockage of the spray nozzle, no aggregate of capsule, no sliding between body and cap and completely dried, total coating time was about 80 min for one batch. After finishing, capsules were dried in the chamber for 5 minutes.

Table 7 Process parameters of coating hard gelatin capsule with perforated pan coater

Inlet air temperature (°C)	65-70
Outlet air temperature (°C)	40-45
Atomized pressure	2.5 bar
Pan speed	30 rpm
Spraying rate	5-7 ml/min
Warming time	10 min
Drying time	10 min

5.3 Coating Capsule with Perforated Pan Coater

Capsule batches of 1 Kg were coated with the coating solution as described. The operative coating conditions are presented in Table 7. These conditions were found to be optimum, total coating time was about 180 min for one batch. Coated capsule were finally dried in perforated pan for 10 minutes.

6. Evaluation of Film Coated Capsule

6.1 Film Thickness

Film thickness was measured by micrometer at 5 different points on the peeled-capsule film. The average thickness was calculated from ten determinations and this thickness was used as criteria for further investigation of free film.

6.2 Water Vapor Permeation

The method of Rama et al. (1997) was adopted to determine of water vapor transmission (WVT) through free film. The glass vials of equal diameter were used as transmission cells. The polymeric film under investigation was cut and its thickness was measured before testing. The transmission cell was filled about one gram of calcium chloride and then the equal film was fixed over the brim of a glass vial with an aluminium hole-cap. The effective area of transmission was 1.13 cm^2. The cells were accurately weighed and placed in a closed dessicator containing saturated solution of sodium chloride to provide the 75% relative humidity and temperature of 35 ^{o}C. These vials were taken out and weighed after 6, 24, 48 and 72 hours of storage. A linear relationship between time and the amount of water permeated was observed and the water vapor transmission was calculated. The WVT rate was calculated using the equation :

$$Rate = WL/S$$

Where W is gram of water absorbed by calcium chloride through the film/24 hr, L is thickness of the film in cm and S is exposed surface area of the film.

6.3 Mechanical Film Characteristic

The free film was prepared by casting polymeric solution on surface of 270 cm^2 glass-petridish to give 70-100 μm thickness. The different film thickness was prepared by changing volume of solution. The polymeric solution was carefully poured onto the glass petridish and placed on the leveled surface, then the solution was dried overnight at 45 ^{o}C in hot air oven until the dried film was obtained. This film was peeled off from petridish and stored in 45% RH dessicator before testing.

The free film was evaluated for tensile strength, percentage elongation, modulus of elasticity and water vapor permeation. The film was cut to 5x1 cm^2 rectangular dimension. The puncture test was performed on a tensiometer which was interfaced to a computer (Instron model 5565, 10 KN load detecting transducer), environmental conditions were 25±1 ^{o}C, 50±10% RH. Film was measured using 10 KN load cell, gauge length 4 cm and crosshead speed of 5 mm/min. Parameters were recorded and calculated from stress-strain curve and each sample was tested 10 times.

6.4 Surface Texture

Film morphology of coated capsules was studied by using surface roughness tester and scanning electron microscopes (SEMs). Roughness of film was examined by sliding probe of the equipment on surface of coated capsule for 6-mm distance. The result was shown by the many roughness parameters and displayed by graphical representation. SEMs at X1000 magnification was used to display the surface feature of the film that was peeled off from the surface of the coated capsule.

6.5 Gliding Effect

Organoleptic investigation (finger test) was basically recommended tested for coated capsules, this method was estimated to give qualitative results to judge between good or bad gilding effect (Hannular et al., 1986).

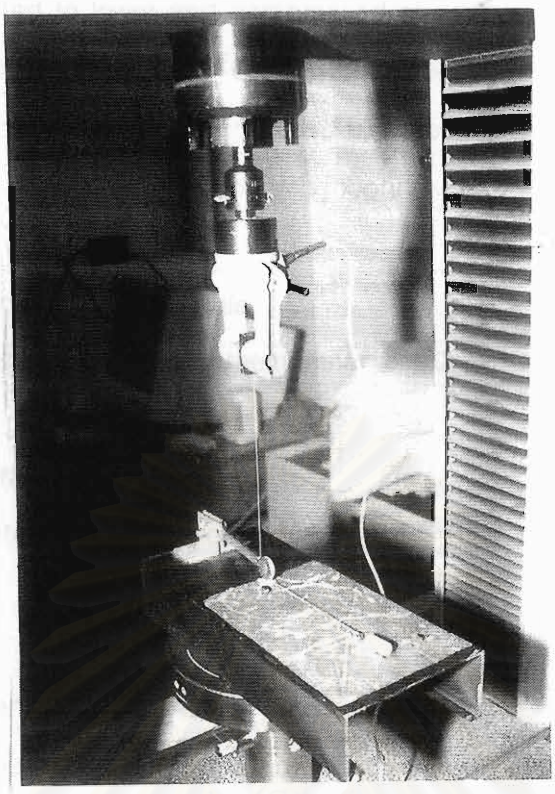

Figure 13 The determination of friction on surface of coated capsule.

Another method for evaluation of gliding effect was the comparative study of the average friction of coated capsule by sliding capsule on tissue paper. The friction on surface of capsule was determined by the application of the apparatus. The sample was tightened by nylon and passed through a pulley, which was fixed on the stand, without any movement. The another end of nylon was gripped by the part of Instron universal material testing as illustrated in Figure 13. The coated capsule was dipped in the water before testing. The determination was started when the crosshead moved up, the nylon was pulled and coated capsule was then dragged along the wetted tissue paper. The friction was recorded and displayed by computer of universal material testing instrument.

6.6 Brittleness

The brittleness of coated capsules was measured using universal material testing (Instron). The coated capsule was placed on the lower stationary platform and the upper plate was adjusted until it was just in contact with the capsule shell. The upper

part was then activated to lower and compressed at crosshead speed of 8 mm/min, environmental conditions were 25±2 °C, 50±10% RH. The procedure was stopped when first broken capsule occurred. Ten capsules were tested and were calculated the average of maximum stress, % elongation and toughness of coated capsule.

6.7 Disintegration of Coated Capsule

They were determined in the same manner as 4.2.

6.8 Dissolution Profile of Coated Capsule

They were determined as described in 3.2.1.1 and as 3.2.1.2

7. Stability of Dimenhydrinate Rectal Coated Capsule

500 mg of liquid-filled formula with drug content 50 mg of dimenhydrinate was kept in glass vial. This preparation was stored over saturated sodium chloride solution in the desiccator, which would give the 75%RH. Then the desiccators were stored in the incubator whose temperature was set at 35, 45°C and at room temperature (approximated to 30°C) for 4 months.

The rectal capsule was evaluated in physical appearances, the content of dimenhydrinate by UV-Visible spectrophotometer. The comparison was based upon the dissolution profile, leakage time, and moisture absorption.