CHAPTER II

MATERIALS AND METHODS

1. MATERIALS

The following substances were obtained from commercial sources.

diluents:

- α-lactose monohydrate (Tablettose, Meggle Milch Industrial GMBH & Co. Germany)

- dicalcium phosphate dihydrate (Emcompress , Edward Mendell Co. New York, USA)

disintegrants:

- sodium starch glycolate (Explotab, Edward Mendell Co. New York, USA)

- microcrystalline cellulose (Avicel PH101, FMC Corporation, Philadelphia, USA)

- cross-linked polyvinylpyrrolidone (Kollidon CL BASF , Germany)

- corn starch (Pharmaceutical Sciences, Bangkok, Thailand)

lubricants:

- magnesium stearate (Pharmaceutical Sciences, Bangkok, Thailand)

miscellaneous

- cyanoacrylate adhesive (Shinkoh,   Type CY-10,
  Japan)

- proofing wax (Kwoya, Type C-1A, Japan)

2. EQUIPMENTS

- single punch tablet machine (Modified   Stroke
  Model A-3, Thailand)
- strain   gauge   (Kwoya,   Type   KFC-5-C1-11L30,
  foil, lot no. Y419081, Japan)
- strain   indicator   amplifier   (Shikoh,   Model
  6003-F, Japan)
- oscilloscope (Tedtronic, series 3030367, USA)
- XY/XY-T recorder (Watanabe   Instrument   Corp.
  Model WX 4401 series, Japan)
- micrometer (Teclock Corp., 0.01 mm., Japan)
- hardness tester (Schleuniger-2E, Germany)
- disintegration   apparatus (Hanson   Reserch,
  USA)

3. METHODS

3.1 INSTRUMENTATION

3.1.1 The Instrumentation of a Tablet Machine.

The   instrumentation   of   tablet
machine has been described by Higuchi (60).   Strain gauges
were bounded to the frame of a single punch eccentric machine
to gave a measure of the applied force.   The disadvantage of

this was the non-linear relation between frame distortion and the applied force.

This investigation used a modified Stokes Model A-3 single punch tablet machine, driven at a constant speed through 1.5 horsepowers electric motor.

The type of strain gauge chosen can be used for dynamic measurements. It has an internal resistance of about 120.0 ± 0.3 Ohms, a gauge factor of about 2.1, a gauge factor change with temperature 0.015%/$^{\circ}$C . For mounting a cyanoacrylate adhesive which is stable at temperature range -50°C-70°C, was used. Then coated with moisture proofing wax. Two strain gauges - one an active gauge and the other a temperature and bending compensating gauge - for measuring the applied force from upper punch were mounted to the modified upper punch holder as shown in Figures 2 and 3. The gauge cables were taken through the space between the modified upper punch holder and steel-body. The compensating resistance consists of two similar guages on a piece of steel.

The active gauges (upper punch holder) and compensating resistances gauges formed two arms of a Wheatstone Bridge connected to one channel of a strain indicator amplifier as shown in Figure 4. These signals for the amplifier were recorded on a four channel oscilloscope and XY/XY-T recorder

Before modify   After modify

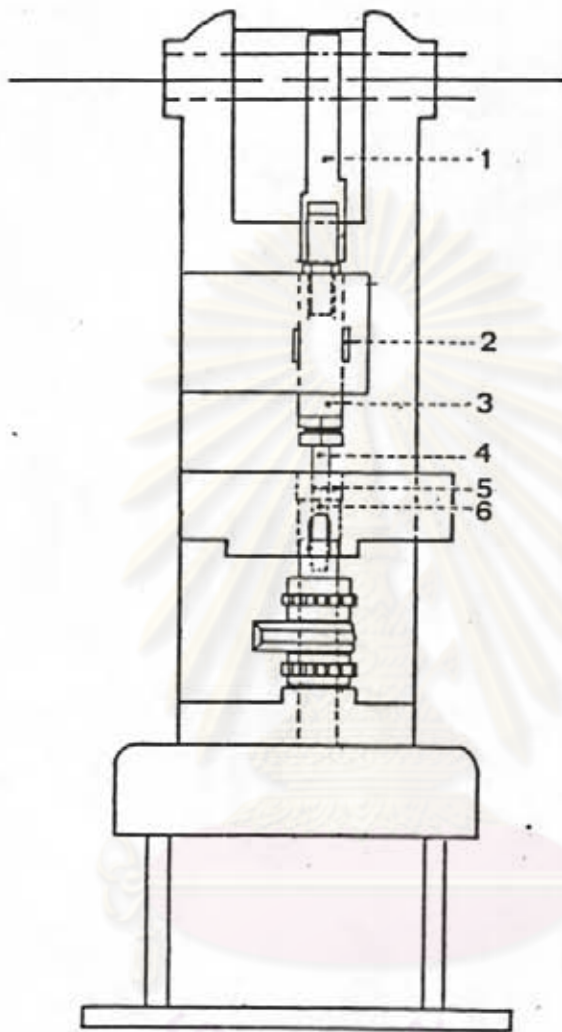Figure 2. A cross section of the upper plunger
          1. Strain gauge

Figure 3. Schematic drawing of the instrumened tablet machine.
1. Eccentric sheave
2. Strain gauge
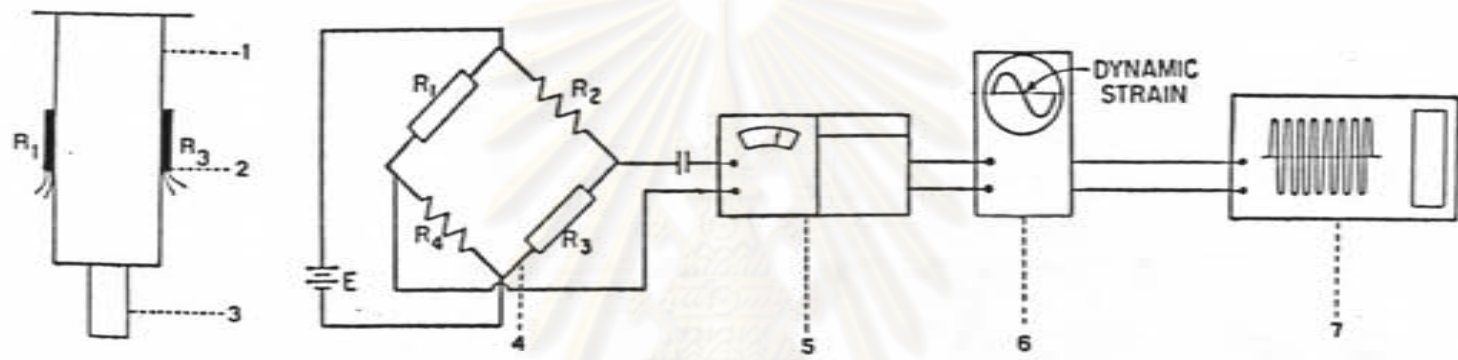3. Upper plunger
4. Upper punch
5. Die
6. Lower punch

Figure 4. Function block diagram of press and associated measuring system. 1. upper plunger 2. strain gauge 3.upper punch
4. wheatstone bridge 5. dynamic strain indicator 6. oscilloscope
7. recorder

Table 1   The Calibration Data obtained from the Upper Punch.

force (pound)	strain (cm)
0	0
300	0.19
600	0.38
900	0.61
1200	0.83
1500	1.06
1800	1.25
2100	1.47
2400	1.73
2700	1.92
3000	2.15

Table 2   The Regression Output Calculated from the Calibration Data.

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           Regression Output:
Constant                        -0.03090
Std Err of Y Est                 0.018866
R Squared                        0.999381
No. of Observations                   11
Degrees of Freedom                     9

X Coefficient(s)    0.000723
Std Err of Coef.    0.000005
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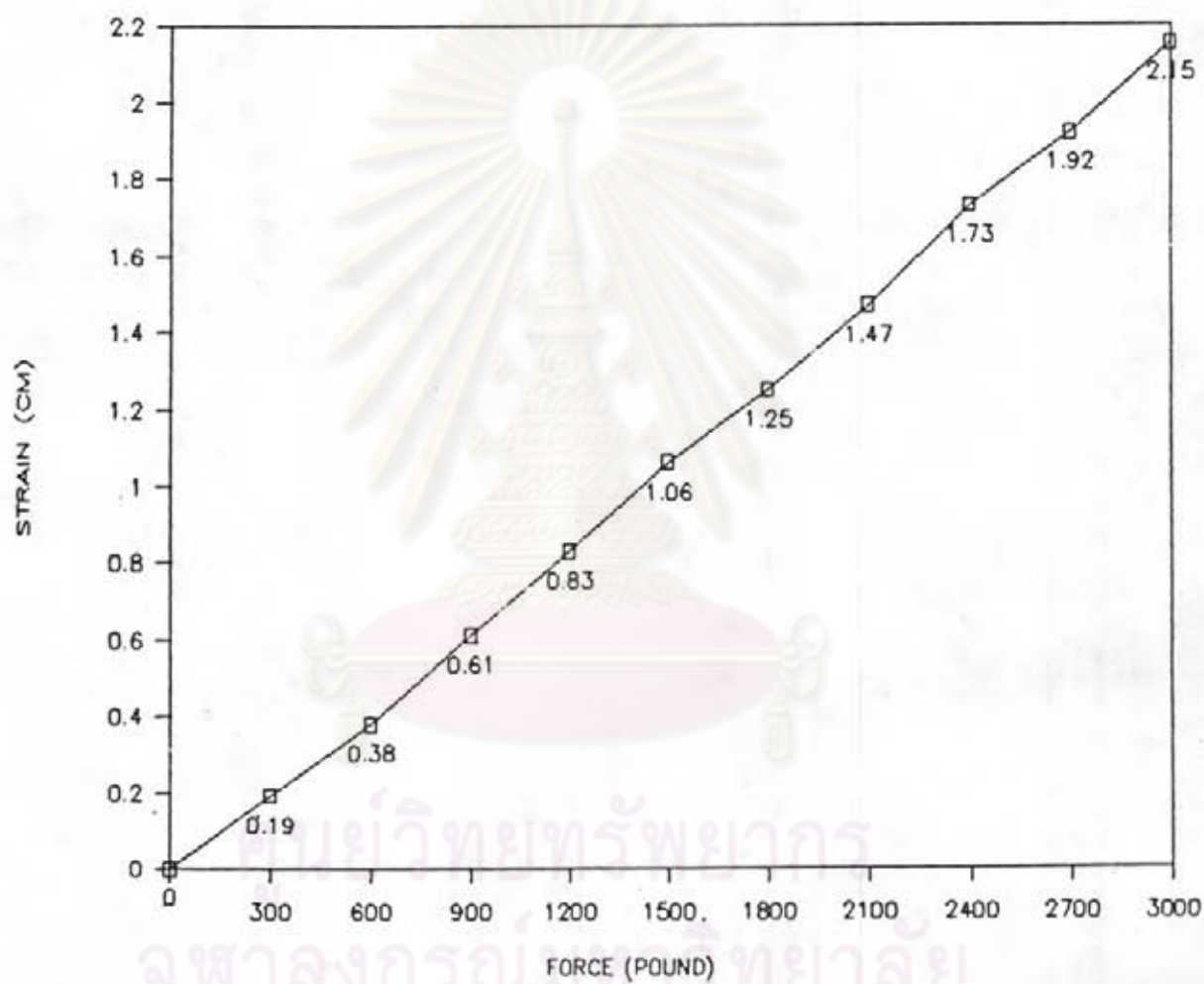
Figure 5. The calibration curve of the upper punch

Table 3 Tablet Composition

	% w/w per tablet			

Series 1	A	B	C	D
Emcompress	96.5	93.5	90.5	87.5
corn starch	3.0	6.0	9.0	12.0
magnesium stearate	0.5	0.5	0.5	0.5

Series 2				
Emcompress	79.5	69.5	59.5	49.5
Avicel PH101	20.0	30.0	40.0	50.0
magnesium stearate	0.5	0.5	0.5	0.5

Series 3				
Emcompress	96.5	93.5	90.5	87.5
Explotab	3.0	6.0	9.0	12.0
magnesium stearate	0.5	0.5	0.5	0.5

Series 4				
Emcompress	98.5	96.5	94.5	92.5
Kollidin CL	1.0	3.0	5.0	7.0
magnesium stearate	0.5	0.5	0.5	0.5

Series 5				
Tablettose	96.5	93.5	90.5	87.5
corn starch	3.0	6.0	9.0	12.0
magnesium stearate	0.5	0.5	0.5	0.5

Series 6				
Tablettose	79.5	69.5	59.5	49.5
Avicel PH101	20.0	30.0	40.0	50.0
magnesium stearate	0.5	0.5	0.5	0.5

Series 7				
Tablettose	96.5	93.5	90.5	87.5
Explotab	3.0	6.0	9.0	12.0
magnesium stearate	0.5	0.5	0.5	0.5

Series 8				
Tablettose	98.5	96.5	94.5	92.5
Kollidon CL	1.0	3.0	5.0	7.0
magnesium stearate	0.5	0.5	0.5	0.5

3.1.2 Calibration of the Instrumentation.

The strain gauges mounted of the upper punch holder were calibrated under static condition by using hydraulic press over a range of force 1200 pounds up to 3000 pounds.

A linear relationship between oscilloscope deflection and applied force was found as shown in Table 1. The calibrtion data in Table 2 and regression output of the upper punch calibration were shown in Figure 5.

3.2 Preparation of Tablets.

3.2.1 Granule Preparation

Batch of the various formulations from Table 3 (500 gm) were prepared by mixing two types of direct compression diluents, α-lactose monohydrate and dicalcium phosphate dihydrate with four disintegrants, using a laboratory scale Twin Shell V-blender rotation speed of 60 rpm as mixer. After mixing for 10 minutes magnesium stearate was added, as lubricant, mixing procedure continue for 5 minutes. Granule was dried in hot air oven at $70°C$ for 30 minutes.

Before mixing, all excipients passed through No.60 handle screen to break aggromulates except magnesium stearate which passed through No.80 handle screen.
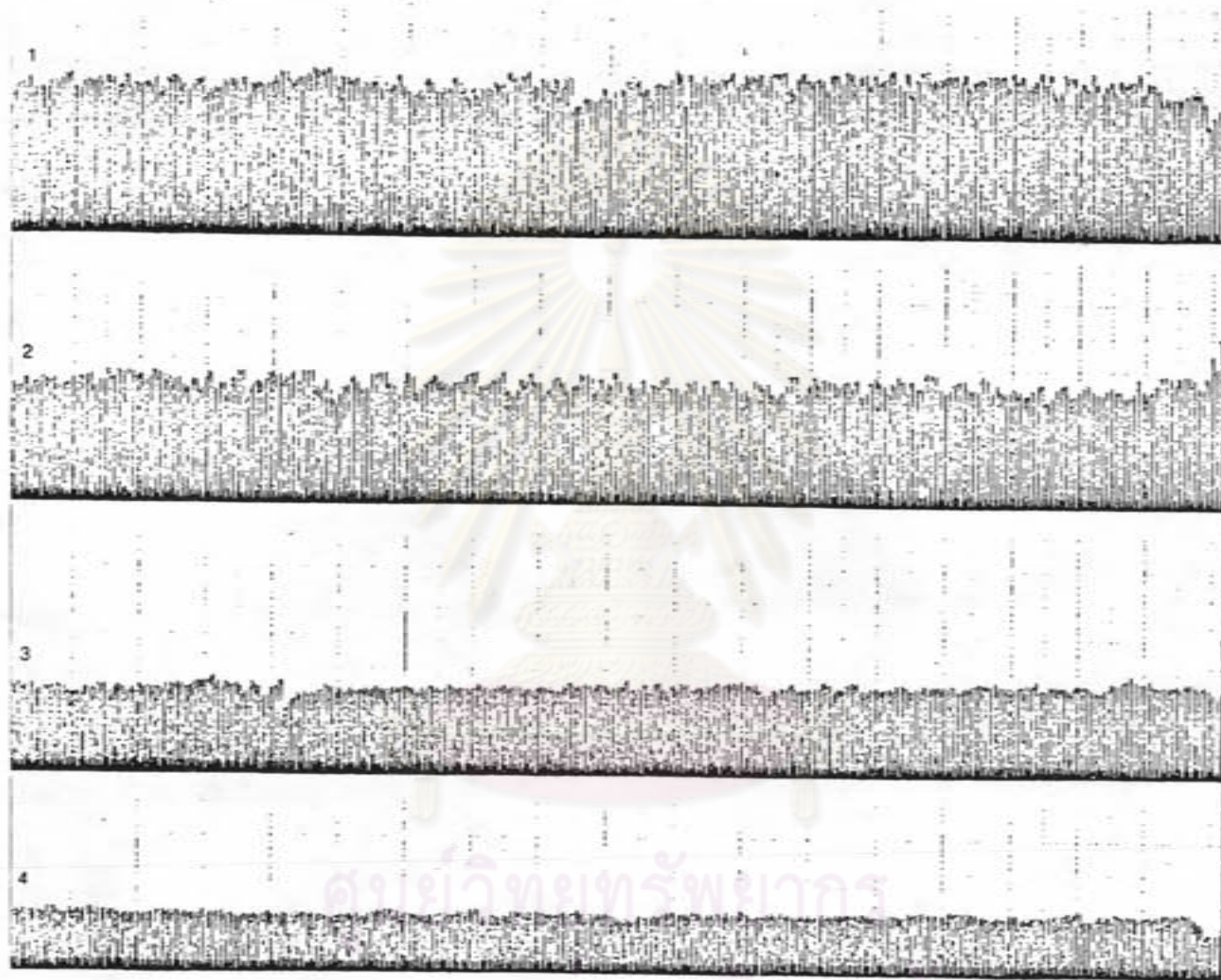
Figure 6. Tracing of compressional forces of Emcompress + 3% Kollidon
CL   a. 1200 pounds   b. 1800 pounds   c. 2400 pounds   d. 3000 pounds

Table 4   Relative Humidities of Saturated
Salt Solutions at Room Temperature

Salt	% R.H.
NaOH	25
$MgCl_2$	44
NaBr	67
K_2SO_4	98

Table 5   Equlibrium Rates of Relative Humidities over Saturated
Salts Solutions after open Desiccator for 15 seconds

Time (min.)	Salts			
	NaOH	$MgCl_2$	NaBr	K_2SO_4
1	25.0	46.0	65.0	96.0
5	26.5	45.0	66.0	97.0
10	26.0	45.0	66.5	97.5
15	26.0	44.5	66.5	98.0
20	25.5	44.0	66.5	98.0
30	25.0	44.0	67.0	98.0

3.2.2 Tablet Compression.

Tablets were compressed using an instrumented single punch machine tooled with 3/8 inches round flat faced punch. The tablet weight of each formulation was 350 mg. Each batch from each formulation was compressed at four different compressional forces of 1200, 1800, 2400 and 3000 pounds. The tracing of compressional forces were shown as Figure 6.

3.3 TABLET EVALUATION.

3.3.1 Moisture sorption

Ten tablets from each batch were stored on a dish in disiccators contain saturated salt solution at room temperature for maintaining at 24%, 44%, 65% and 98% relative humidity (70,71). Relative investigated are given in Tables 4,5. If any care was taken to mininal opening the desiccators the humidity remain quite constant. For each sampling for evaluation points are 6, 24, 48 and 72 hours.

3.3.1.1 Moisture Uptake

The moisture uptake of the tablet was determined by gravimetrically. Sets of ten tablets were weighed initially and after storage at the four humidity levels for 6, 24, 48 and 72 hours; moisture

pickup was expressed as percent weight gain.

3.3.1.2 Volume Change

Volume change was calculated from thickness and diameter of ten tablets which were measured in millimeter by using of micrometer spring gauge after storage at various humidities and time intervals. The ratio of volume change was expressed by the ratio of apparent tablet density and initial tablet density which were calculated from thickness and diameter.

3.3.1.3 Hardness

Hardness of the tablets was determined by using a Schleuniger-2E Hardness Tester and expressed in Strong-Cobb-Arner units. The hardness was an average of ten determinations.

3.3.2 RELATIVE DENSITY

Relative density was used in the study to evaluate the porosity of the compressed tablets. Relative density was calculated from the effective particle density and apparent tablet density.

The procedure utilized to determine effective particle density refered to as the cylinder - drop technique. An accurately weight sample of 50.0 grams was introduced into a 100 ml. graduated cylinder. The cylinder

was dropped on to a hard wood surface 50 times for height of 1 inches at 1 second interval. The density was then calculated by dividing the weight of sample (grams) by the final average tapped volume (milliliters) of at least five determinations of sample containing in the cylinder.

Apparent tablet density was calculated from quotient of the weight and the geometric volume of the tablet.

3.3.3 WATER UPTAKE

The apparatus consists of a sintered glass filter connected to a horizontal graduated pipette by a rubber bung as showed in Figure 7. The entire assembly was immersed in a water bath, thermostatically controlled at 37 $\pm$ 1 $^{\circ}$C . A continuous water column was maintained from the sintered glass filter through the glass bottle to the end of the pipette. A pieced of filter paper was placed on top of the sintered glass base. The top of rubber bung was covered with slide to prevent evaporating of penetration liquid. The uptake rate was read from the graduated pipette. The mean of at least five tablets was taken to represent the uptake volume.

3.3.4 DISINTEGRATION TIMES

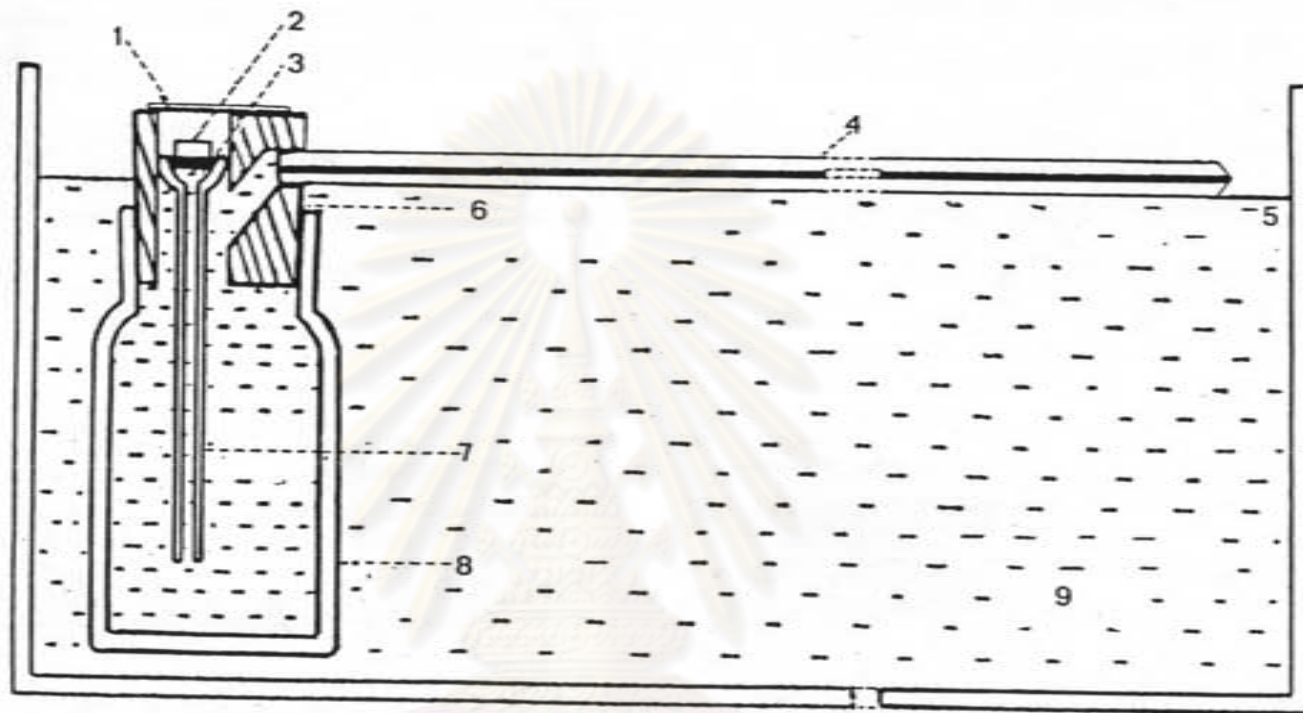Disintegration times of the tablets was determined in distilled water using

Figure 7. Apparatus for determination of water penetration into tablets. 1. cover slide 2. tablet 3. filter paper 4. pipette 4. pipette 5. water level 6. rubber bung 7. filter stick 8. glass bottle 9. thermostated at 37 °C

Disintegration Apparatus according to the USP XX method. This value was measured in seconds. The means of at least six determinations of each batch was used.