CHAPTER VI

COMPRESSION EVALUATION OF COMPOSITE PARTICLES OF RICE STARCH AND MICROCRYSTALLINE CELLULOSE AS DIRECTLY COMPRESSIBLE DILUENT

Introduction

From chapter V, the quantity of RS/MCC from different lots of preparation were combined into a bulk powder of 7 kg for evaluation and utilization of composite particles of rice starch and microcrystalline cellulose as directly compressible diluent. This material was examined for the physical properties and tabletting characteristics compared with other DC diluents (Vivapur®, Eratab®, Tablettose®, Cellactose®) by using instrumented single punch tabletting machine. Topics of evaluation were the effect of lubricant (magnesium stearate) quantity, dilution potential ability (using paracetamol as a model drug) on the physical properties of prepared tablets e.g. hardness, % friability, and disintegration time. The application of this developed excipient in manufacture of pharmaceutical products was demonstrated. Two model drugs e.g. isoniazid (INH) and hydrochlorothiazide (HCTZ) which are freely soluble drug (Brewer, 1977) and very slightly soluble drug (Deppeler, 1981), respectively, were used in this experiment. Tablet physical properties and dissolution of the obtained drug products were also evaluated. Moreover, compression behavior (deformation under compaction or volume reduction mechanisms) of composite particles was also investigated and compared to other DC diluents by using Heckel analysis. The objectives of the study described in this chapter are:

1. To compare the physical properties and tabletting characteristics of composite particles of RS and MCC with commercially available DC diluents
2. To study the effect of lubricant concentration on tabletting properties of coprocessed excipient compared with other DC diluents
3. To study the dilution potential of composite particles of RS and MCC with low compressible drug (paracetamol) in comparison with other DC diluents

4. To use composite particles as direct compression diluent in production of two drug products e. g. freely soluble drug (INH) and very slightly soluble drug (HCTZ) in comparison with other DC diluents
5. To investigate the volume reduction mechanisms of coprocessed excipient and other DC diluents by using Heckel analysis

THEORY

To study pharmaceutical materials, the mathematical functions according to Heckel, 1961a, 1961b (cited from Duberg and Nystrom, 1986) has been used for the characterization of the behavior of the particle deformation, particle fragmentation and the degree of plastic deformation, during the compression. This is based on the relationship between the porosity changes during compaction against the compression load as follows.

Heckel considered the compression of metal powders as analogous to first order kinetics. The pores in the powder act as the reactant and the densification obtained is the product. The relation was described by the following equation.

$$\frac{dD}{dP} = K\varepsilon = K(1-D) \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

When equation (1) is integrated, equation (2) is obtained.

$$\ln\left(\frac{1}{1-D}\right) = KP + A \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (2)$$

where D is relative density at the applied pressure and equal to the ratio of the density of the compact at the applied pressure to the density of the compact at zero void or true density of the powder. ε is the porosity and P is the applied pressure. K and A are a measure of the ability of the compact to deform plastically and a constant describing densification by particle movement and rearrangement, respectively. The constant A can be defined by the equation (3).

$$A = \ln\left(\frac{1}{1-D_o}\right) + B \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3)$$

where A and B represent densification by particle deformation after interparticulate bonding has become appreciable and densification by individual particle

movement and rearrangement, respectively. ln $(1/(1-D_o))$ is densification by filling the die. The relationship of these relative densities can be deduced from equation (3) as following equation (4).

$$D_A = D_o + D_B \quad \text{.....(4)}$$

D_o is experimentally determined and equal to the ratio of bulk density of the powder before compression to true density. D_A is given by the equation (5).

$$A = \ln \left(\frac{1}{1 - D_A} \right) \quad \text{.....(5)}$$

From D_o and D_A, D_B can then be calculated. The values of D_o, D_A and D_B are only affected by particle shape and size. Moreover, the bulk properties of the particles have no significant effect on these parameters then they are of limited interest and not use to discuss consolidation mechanisms. K is considered as material constant and used to determine the deformation mechanisms of the material. K may be presented in the reciprocal form and defined as the yield pressure (P_y). The less P_y value obtained, the more ductile material, more plastic and easily compressible even at low compression force.

There are two methods to measure the compact density. Firstly by compression a number of tablets at different pressures and determining the dimension of the tablets after ejection, is called ejected tablets method. In the second method, tablets in die method, the compression load and the tablet thickness are continuously recorded during one compression cycle. The latter method has the advantage of fast speed and requires less powder. The disadvantage is the consolidation time is different at each pressure used and could then result in a concave plot for the materials having pronounced time dependent consolidation.

From porosity pressure curve, the volume reduction mechanisms would then be characterized and evaluated. Moreover, this curve could also use to predict the behavior of the powder when subjected to compression. The volume reduction mechanisms of the pharmaceutical materials are different from the metal materials as shown in Table 6-1 (Duberg and Nystrom, 1986). For metals and other materials having a high crystalline

Table 6-1 Sequences of volume reduction mechanisms[a] (Duberg and Nystrom, 1986).

Expected mechanisms for metals[b]	Expected mechanisms For organic compounds[c]	Experimentally observed Mechanisms for organic compounds[d]
	E_1 : Elastic deformation of initial, weak particles	
	P_1 : Plastic deformation of initial, weak particles	
	F_1 : Fragmentation of initial particles into a number of smaller discrete particles of higher strength	F_1
E : Elastic deformation	E_2 : Elastic deformation of smaller particles formed	E_2
P : Plastic deformation	P_2 : Plastic deformation of smaller particles formed	P_2
F : Particle fragmentation	F_2 : Fragmentation of smaller particles formed	

[a] Here not including particle rearrangement.
[b] Representing materials with low concentrations of crystal defects, pores and flaws.
[c] Representing materials with high concentration of defects.
[d] Utilizing, for example, porosity pressure functions.

order or homogeneous structure, with low concentrations of crystal defects, pores and flaws. The expected mechanisms are in the sequence, firstly by elastic, plastic deformation and particle fragmentation in finally if the stress is high enough. However, in pharmaceutical materials which consist of aggregates of primary particles or of highly porous particles, these secondary particles, show brittle during the initial loading and produce a large number of smaller discrete particles, with negligible deformation ability. These small particles would then deform elastic and/or plastic deformation as compaction load is increased. Therefore, some problems have been reported when using Heckel analysis to describe of the mechanisms involved in the compression of such pharmaceutical materials. Firstly, an initial fragmentation will give a deviation from the straight line and secondly, it is difficult to distinguish between elastic and plastic

deformation as obtained from the slope of the straight line of the profile. To solve this problem, the compression cycle could be divided into three parts as in Figure 6-1. In phase I that the applied pressure is low, the porosity reduction could be enhanced by particle fragmentation. The curvature of the plot could be evaluated and expressed as the correlation coefficient (CC) and then serve as a tool to quantify the fragmentation tendency. At higher pressure in phase II, elastic and/or plastic deformation are the dominating mechanisms and could be determined by the reciprocal of the slope (P_y). This P_y reflects the plasticity of the material and a low value indicates a high degree of plastic deformation. Owing to this value is the combination of plastic and elastic deformation therefore the elastic materials would result in a false low P_y value. The increase in porosity as given from decompression intercept in part III was then calculated and used to examine the contribution of plastic deformation during phase II.

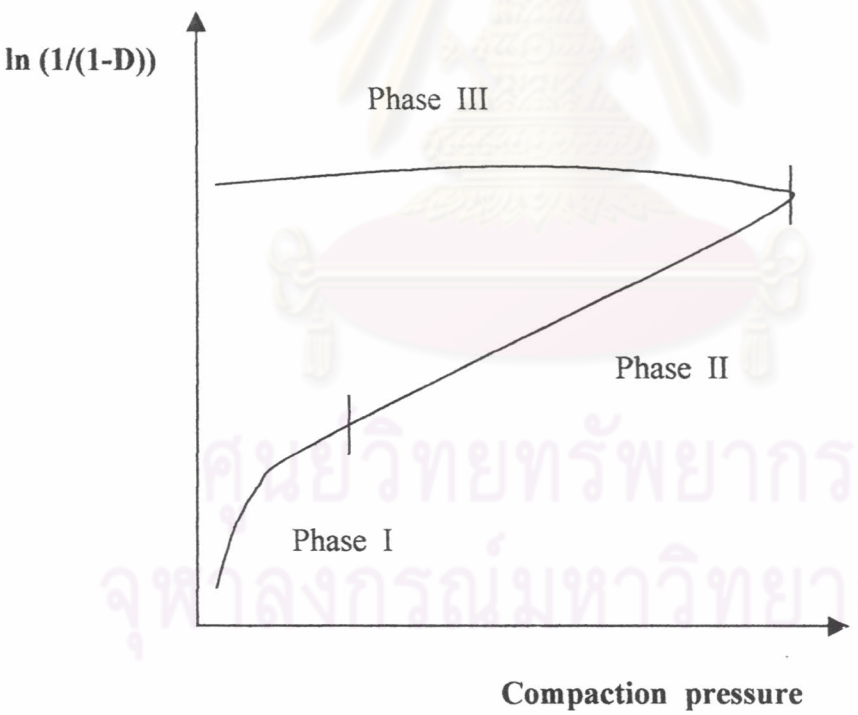


Figure 6-1 Three main phases of compression cycle.

Materials and Methods

Materials

Microcrystalline cellulose	(Vivapur®101, Lot No. 5610102917, J. Rettenmaier & Söhne, Germany)
Spray dried rice starch	(Eratab®, Lot No. T440219, Erawan Pharmaceutical Research & Laboratory Co., Ltd., Thailand)
Agglomerated lactose	(Tablettose® 80, Lot No. L0021A4003, Meggle GMBH, Germany)
Coprocessed of 75% lactose monohydrate and 25% cellulose	(Cellactose® 80, Lot No. L0016A4901, Meggle GMBH, Germany)
Paracetamol	(Lot No. 0100484, Anqiu Lu'an Pharmaceutical Co., Ltd., China)
Hydrochlorothiazide	(Lot No. 20020110, Huzhou Konch Pharmaceutical Co., Ltd., China)
Isoniazid	(Lot No. 0270312)
Talcum	(China)
Magnesium stearate	(Lot No. MAF 05/360, Italy)
Hydrochloric acid	(Mallinckrodt, AR grade, USA)
Sodium hydroxide	(Lot No. B131198214, Merck, Germany)
Absolute ethanol	(Mallinckrodt, AR grade, USA)
Deionized water	

Methods

1. **Effect of Magnesium Stearate Concentration on the Compressibility**

Direct compression diluent (Vivapur®101, Eratab®, Tablettose®, Cellactose® and RS/MCC which is composite particles of rice starch and MCC in the ratio of 7 : 3) was weighed and mixed with magnesium stearate which had been screened through 80

mesh sieve. The concentration of the lubricant used was 0.25, 0.5, 0.75, 1.0, 1.5 % w/w of the diluent. The diluent (300 g per batch) and lubricant were mixed in plastic bag for 5 minutes before tabletting. The powder was compressed on a 9.5 mm die and flat-face with beveled edge using an instrumented single punch tabletting machine (Model EKO, Korsch Pressen GMBH, Germany) as shown in Figure 6-2 to 6-3. Tabletting rate and tablet weight were 20 tablets per minute and 250 mg, respectively. Compression forces used in this study were 3, 5, 7 and 9 kN for Eratab®, Tablettose®, Cellactose® and RS/MCC tablets and 1, 3, 5 and 7 kN were used for Vivapur®101 tablets.

2. Evaluation of Dilution Potential Study

Paracetamol was sieved to break agglomerated particles by 40 mesh sieve before using in the preparations. The drug was weighed in an increment of 5, 10, 15, 20, 25, 30 and 35% of the batch size (300 g) and mixed with each direct compression diluent in plastic bag for 10 minutes. Talcum and magnesium stearate (both were sieved through 80 mesh screen) in the concentration of 3% and 0.75%, respectively, were added and additionally mixed for another 5 minutes. The condition and equipment used for tabletting were the same as described in 1.

3. Preparation of Tablet Products

3.1 Preparation of Isoniazid Tablets

The compositions of isoniazid (INH) tablets is shown in Table 6-2 and 1500 tablets per batch were prepared. INH was screened to break agglomerated particles by 40 mesh sieve. Talcum and magnesium stearate were sieved through 80 mesh sieve before weighing.

INH and various direct compression diluents were weighed and mixed in plastic bag for 10 minutes. Talcum and magnesium stearate were added and mixed for another 5 minutes. The resulting powder was compressed using instrumented single punch tabletting machine. The compression force of each direct compression diluents was adjusted to obtain the hardness of approximately 40-50 N. During compression,

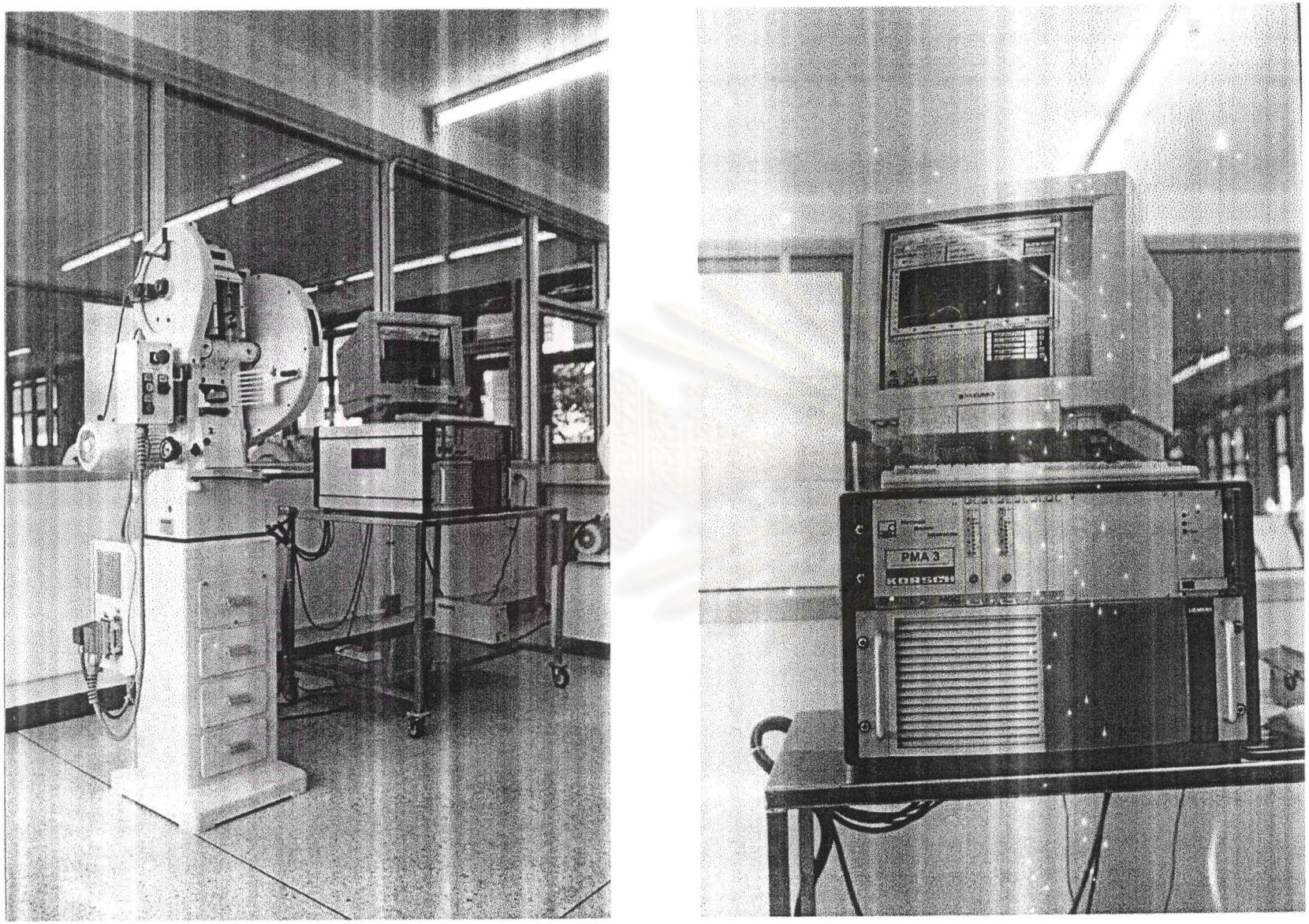


Figure 6-2 Instrumented single punch tabletting machine.

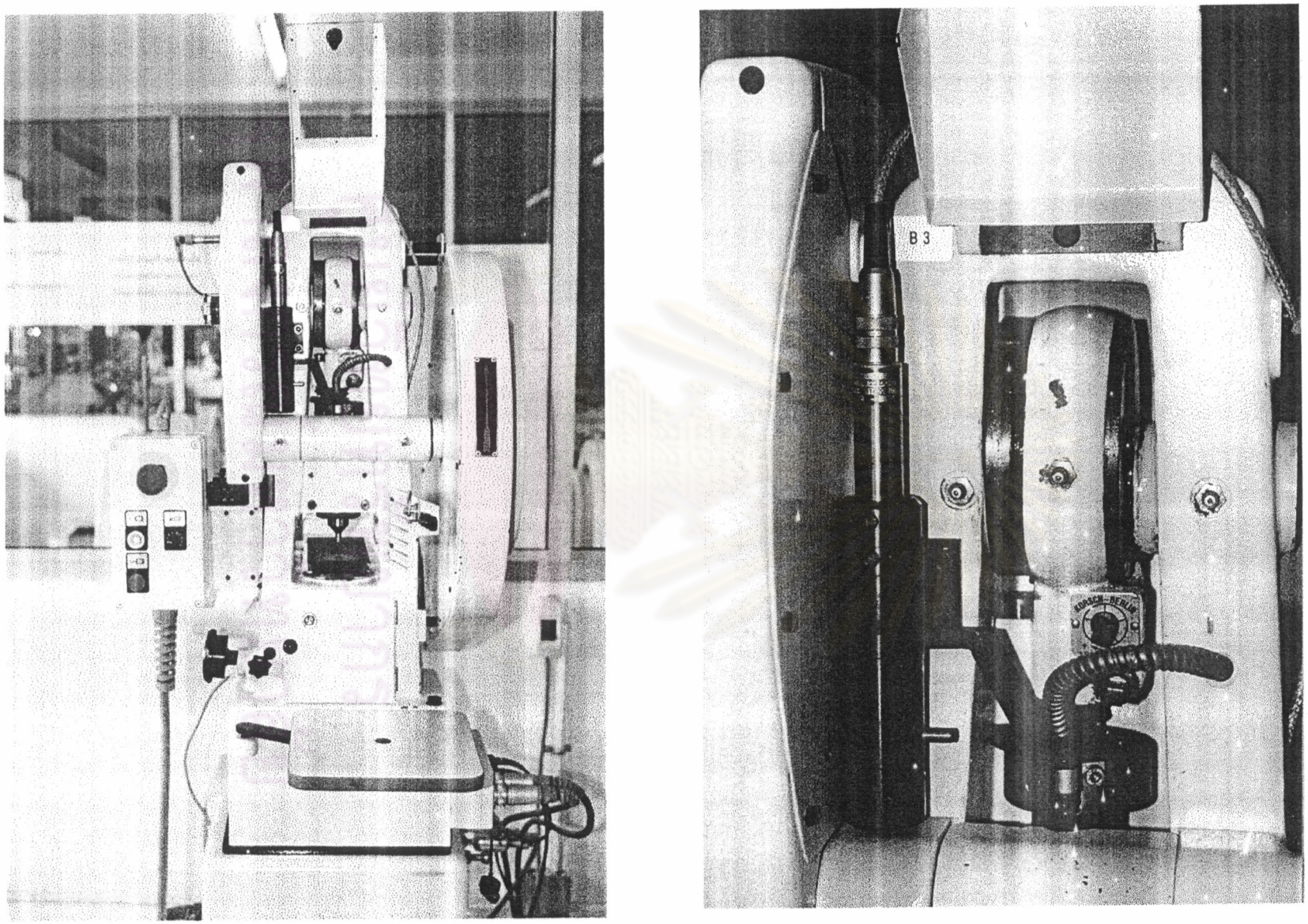


Figure 6-3 Instrumented single punch tabletting machine (indicated strain guage and upper punch displacement measuring device).

Table 6-2 The compositions of Isoniazid tablets.

Ingredients	Quantity (mg/tablet)
Isoniazid	50
Direct compression diluent[1]	200
Talcum	3%
Magnesium stearate	0.75%

Note: 1 = Vivapur®101, Eratab®, Cellactose®, or RS/MCC.

Table 6-3 The compositions of Hydrochlorothiazide tablets.

Ingredients	Quantity (mg/tablet)
Hydrochlorothiazide	50
Direct compression diluent[1]	200
Talcum	3%
Magnesium stearate	0.75%

Note: 1 = Vivapur®101, Eratab®, Cellactose®, or RS/MCC.

tablets were sampled at the beginning, middle and final of the tabletting process to determined weight variation, hardness, thickness and diameter of the tablets.

3.2 Preparation of Hydrochlorothiazide Tablets

The compositions of hydrochlorothiazide (HCTZ) tablets is shown in Table 6-3 and 1500 tablets per batch size was prepared. HCTZ was screened by using 40 mesh sieve. Talcum and magnesium stearate were sieved through 80 mesh sieve.

HCTZ, direct compression diluents, talcum and magnesium stearate were weighed as indicated in Table 6-3. The procedure for preparation was the same as that of isoniazid tablets.

4. Evaluation of Tablets

4.1 Hardness, Thickness, Diameter, % Friability, and Disintegration Time

Hardness, Thickness, and Diameter were determined by tablet hardness tester. Percent friability and disintegration time were evaluated by Roche Friabilator and USP disintegration apparatus, respectively. The number of samples and condition were the same as previously described in chapter III.

4.2 Tensile Strength of Tablets

Tablet tensile strength (Ts) was calculated from the following equation (Fell and Newton, 1970).

$$Ts = 2F / \pi D T$$

where F(N) is the crushing force that diametrically tested by tablet hardness tester, D(cm) and T(cm) are the diameter and thickness of the tablet, respectively. The results reported are the average of ten determinations.

4.3 Percent Porosity of Tablets

Tablet porosity (ε) was calculated from the tablet weight (W), tablet volume (V) which was calculated from the measured tablet diameter and thickness, and true density of the powder (ρ) using the following equation.

$$\% \varepsilon = (1 - (W / V\rho)) * 100$$

The diameter and thickness of the tablets were examined by tablet hardness tester. True density was determined by helium pycnometer (Ultrapycnometer, Quantachrome, USA).

4.4 Assay of the Preparations

4.4.1 Assay of Isoniazid Tablets

Twenty tablets were ground to powder and transferred an accurately weighed, equivalent to 50 mg of INH , into 100 ml volumetric flask. 80 ml of deionized water was added, swirled for 30 minutes and adjusted to volume with deionized water. The preparation was filtered with 0.45 μm cellulose acetate membrane. The first 10 ml portion of the filtrate was discarded. 2 ml of the filtrate was pipetted and adjusted with 0.1 N HCl to 100 ml volumetric flask. The absorbance of sample was determined by ultraviolet visible spectrophotometer (JASCO V-530, JASCO, Japan) at the maximum wavelength of 265 nm, using 0.1 N HCl as blank. The quantity of INH in the sample was calculated from the absorbance concentration curve. The drug content was determined in triplicate (Weecharangsan, 1995).

The placebo preparations (without INH) of each DC diluents were subjected to determination the absorbance at 265 nm. The procedure was the same as the assay of INH tablets. Each sample was scanned at the wavelength 200-600 nm and no absorbance peak was found during this wavelength range (Appendix 2).

4.4.2 Calibration Curve of Isoniazid

INH 52.8 mg was accurately weighed in 100 ml volumetric flask. 0.1 N HCl was added, swirled to dissolve the drug and adjusted to volume for using as stock solution. The stock solution was pipetted and adjusted with 0.1 N HCl to obtain final concentration of 5.28, 10.56, 15.84, 21.12, 26.40 and 31.68 μg/ml. The absorbances of INH were measured at the maximum wavelength of 265 nm (Appendix 3), using 0.1 N HCl as blank. The absorbances and concentrations were calculated and fitted to the regression equation of $Y = 0.0373X + 0.0006$ with the coefficient of determination (r^2) equal to 0.9999 (see appendix 4-5).

4.4.3 Assay of Hydrochlorothiazide Tablets

Twenty tablets were ground to powder. The powder, equivalent to 50 mg of HCTZ, was accurately weighed and transferred to 100 ml volumetric flask. 50 ml of 0.1 N NaOH was added, and kept swirling for 30 minutes. The sample was adjusted to volume with 0.1 N NaOH and filtered with 0.45 μm cellulose acetate membrane, discarded the first 10 ml. The 1 ml filtrate was pipetted and adjusted with 0.1 N NaOH to 100 ml. The absorbance was measured by Ultraviolet Visible Spectrophotometer at 272 nm, using 0.1 N NaOH as the blank. HCTZ quantity was calculated from the absorbance concentration curve. Each sample was determined in triplicate (Weecharangsan, 1995).

The placebo preparations were evaluated for the absorbance at 272 nm. The procedure was the same as the assay of HCTZ tablets. Each sample was scanned at the wavelength of 200-600 nm and no absorbance peak was found in this wavelength range (Appendix 6).

4.4.4 Calibration Curve of Hydrochlorothiazide

Accurately weighed and placed 29.5 mg of HCTZ in 100 ml volumetric flask. Added 0.1 N NaOH to disslove and adjust the volume to be used as stock solution. The solution was pipetted in to volumetric flask and adjusted with 0.1 N NaOH to obtain the final concentration of 2.95, 5.90, 8.85, 11.80, 14.75 and 17.70 μg/ml. The absorbance was measured at 272 nm (Appendix 7), using 0.1 N NaOH as blank solution. The absorbance concentration profile was calculated to fit the linear regression equation of $Y = 0.05189X + 0.00178$ with the coefficient of determination (r^2) = 0.9999 (see Appendix 8-9).

4.5 Dissolution Study

4.5.1 INH Tablets

Dissolution studies of INH tablets were conducted using USP dissolution test apparatus (Hanson Research SR2, USA). Nine hundred millilitres of 0.1 N HCl was used as dissolution medium, which was maintained at 37 ° ± 0.5 °C. One INH

tablet was placed in the basket, which was rotated at the speed of 100 rpm. Ten millilitres of the samples were withdrawn at 3, 6, 9, 12, 15, 18, 20, 25, 30 and 45 minutes and filtered by using 0.45 μm cellulose acetate membrane, discard the first 2 ml. The filtrate was diluted to obtain appropriate concentration and measured the absorbance at 265 nm by using UV-VIS spectrophotometer. INH dissolved at various times interval was calculated from the absorbance concentration curve. Ten millilitres of fresh medium were replaced after each withdrawal of the sample to maintain a constant volume of dissolution medium.

The absorbance concentration curve of INH in 0.1 N HCl was performed the same as indicated in 4.4.2.

4.5.2 HCTZ Tablets

Dissolution studies of HCTZ tablets were performed using USP dissolution test apparatus. Nine hundred millilitres of 0.1 N HCl was used as dissolution medium, which was maintained at 37 ° ± 0.5 °C. The basket containing one tablet was rotated at 100 rpm. Ten millilitres of sample was withdrawn by syringe at 2, 5, 10, 15, 20, 25, 30,40, 50 and 60 minutes. The sample was filtered by using 0.45 μm cellulose acetate membrane, discard the first 2 ml. The filtrate was diluted to achieve appropriate concentration and measured the absorbance at 270 nm by UV-VIS spectrophotometer. HCTZ dissolved at various time intervals were calculated from the absorbance concentration curve. Ten millilitres of fresh medium was replaced after each withdrawal of the sample to maintain a constant volume of dissolution medium.

The standard curve of HCTZ in 0.1 N HCl was constructed as follow. HCTZ was accurately weighed (20.1 mg) in 100 ml volumetric flask. 5 ml of absolute ethanol was used to dissolve the drug. 0.1 N HCl was added and adjusted to volume for use as stock solution. The solution was pipetted to obtain the final concentration of 2.01, 4.02, 6.03, 8.04, 10.05 and 12.06 μg/ml. The absorbances were measured at 270 nm (Appendix 10), using 0.1 N HCl as the blank. The absorbance concentration profile was calculated to the linear fit regression equation of $Y = 0.0674X + 0.0017$ with the coefficient of determination (r^2) = 0.9999 (see Appendix 11-12).

5. Determination of True Density

True density of Vivapur®101, Eratab®, Tablettose®, Cellactose® and RS/MCC were determined using ultrapycnometer (Quantachrome, USA). Samples were dried at 105 °C for 6 hours before testing. Helium gas at pressure 20 psi was used to determine true density of the sample. The experimental temperature during the test was around 26.6° to 27.0°C. The obtained data was made from five determinations.

6. Volume Reduction Machanism of Direct Compression Diluent

Each direct compression diluents were mixed with 0.75% w/w magnesium stearate, which was passed through 80 mesh sieve screen, in plastic bag for 5 minutes. The powder was subjected to compression using flat-faced punch with beveled edge and die (9.5 mm in diameter), which was equipped to instrumented single punch tabletting machine. The speed of the machine and tablet weight were 20 tablets per minute and 200 mg, respectively. The maximum compression force was 9 kN. For one compression cycle, the applied force and upper punch displacement were determined and recorded at 7 ms intervals by using the Pharmapress Measuring and Analysis System (PMA-Programme, version 03.03g, Korsch, Germany). The sampling of each direct compression diluents was done for 6 cycles.

Heckel Plots of Various DC Diluents

The compaction behavior of various DC diluents was evaluated by Heckel analysis. From the upper punch displacement and true density of each DC diluents were used to calculate the relative density which is used with the compression force to construct Heckel plot as the following equation.

$$\ln (1/(1-D)) = KP + A$$

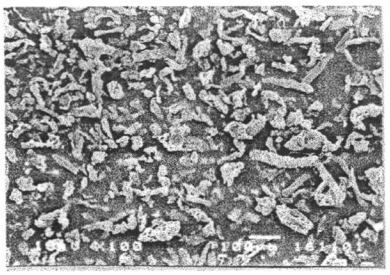
where D is the relative density of the tablet, P is the applied pressure, A is the constant to describe densification of the particles and K is slope of linear portion of the plot and used to measure the ability of the compact to deform plastically.

Results and Discussion

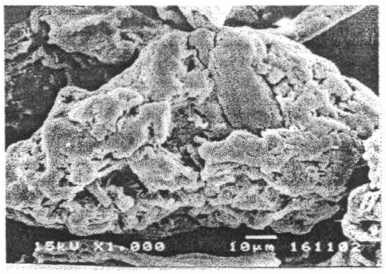
Compression characteristics of composite particles of rice starch and MCC (RS/MCC) were investigated in comparison with various direct compression diluents e.g. Vivapur®, Eratab®, Tablettose®, and Cellactose®. SEM photomicrographs of various DC diluents are illustrated in Figure 6-4. Vivapur® is the fiber-like shape while Eratab® and RS/MCC are spherical-shape particles. Tablettose® and Cellactose® are irregular in shape. Cellactose® is aggregated particles of cellulose and lactose while Tablettose® is only the aggregated particles of lactose particles produced by fluidized bed granulator. Particle size distribution and physical properties of various DC diluents powder are shown in Table 6-4 and Table 6-5, respectively. The order of particle size is as follow: Cellactose® > Tablettose® > Vivapur® > Eratab® > RS/MCC. Percent LOD of Eratab® was the highest (10.62%) and that of Vivapur® and RS/MCC were 5.55% and 6.76%, respectively. Tablettose® and Cellactose® were the lowest value. The flow property of various DC diluents are in the following order : Eratab® ≈ RS/MCC >Tablettose® ≈ Cellactose® > Vivapur®. This was due to the particle shape of the powder. The more spherical shape of the particles, the higher flowability of the powder might be.

1. Effect of Magnesium Stearate Concentration on Compressibility

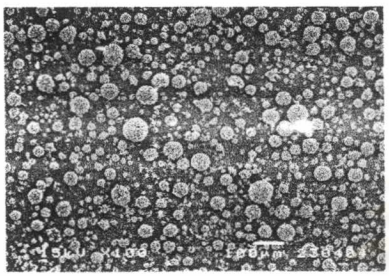
Magnesium stearate at various concentrations from 0.25% to 1.5% was mixed with the various DC diluents to study the effect of the lubricant concentrations on the physical properties of the tablets. Tablettose® and Cellactose® occurred binding in the die during compression when the amount of magnesium stearate was lower than 0.5% while Vivapur®, RS/MCC, and Eratab® could be compressed without that problem. This was due to the self lubricating property of the starch and cellulose in which magnesium stearate can be used at lower than 0.5% w/w (Manudhane, 1969; Small & Augsburger, 1978; Omray, 1986; Staniforth et al., 1989; Bos, 1992). The physical properties of tablets prepared from different DC diluents with various magnesium stearate concentrations and compression forces are shown in Tables 6-6 to 6-10 and Figures 6-5 to 6-8. Increasing the compression force resulted in higher tensile strength while lower percent porosity and % friability. In the case of Vivapur®, RS/MCC, and Eratab®, when



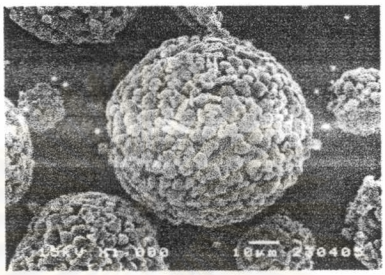
Vivapur® X 100



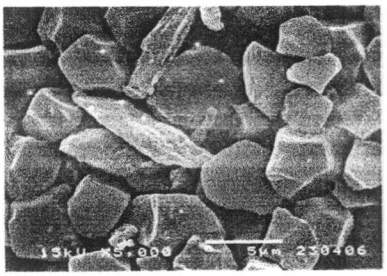
Vivapur® X 1000



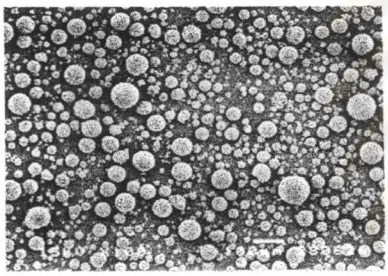
RS/MCC X 100



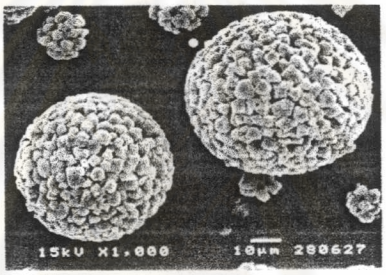
RS/MCC X 1000



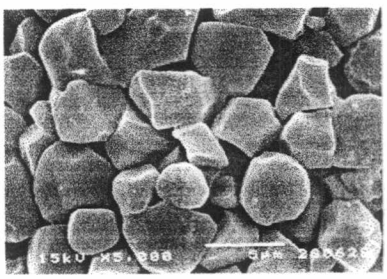
RS/MCC X 5000



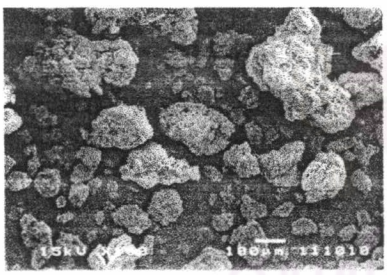
Eratab® X 100



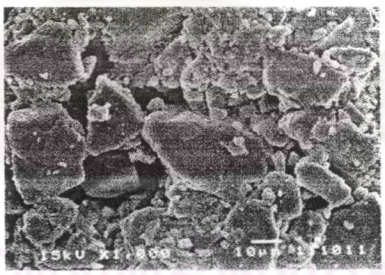
Eratab® X 1000



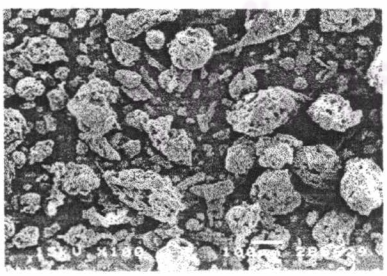
Eratab® X 5000



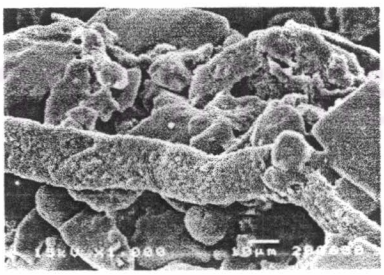
Tablettose® X 100



Tablettose® X 1000



Cellactose® X 100



Cellactose® X 1000

Figure 6-4 SEM photomicrographs of various DC diluents.

Table 6-4 Particle size distribution of various DC diluents.

DC diluents	D (v, 0.1) (μm) average (SD)	D (v, 0.5) (μm) average (SD)	D (v, 0.9) (μm) average (SD)	Span = (D90 – D10) / D50 average (SD)
Vivapur®	24.25 (0.12)	69.05 (0.91)	142.77 (5.17)	1.72 (0.05)
RS/MCC	18.49 (0.55)	52.60 (0.34)	95.56 (2.26)	1.47 (0.05)
Eratab®	19.20 (0.71)	62.21 (1.40)	116.45 (3.44)	1.56 (0.02)
Tablettose®	60.54 (2.95)	202.88 (2.90)	411.08 (21.4)	1.73 (0.10)
Cellactose®	68.83 (1.74)	214.51 (2.53)	371.61 (2.10)	1.41 (0.02)

Table 6-5 Physical properties of powder of various DC diluents.

DC diluents	LOD (%) average (SD)	Angle of Repose (degree) average (SD)	Angle of Spatula (degree) average (SD)	Bulk Density (g/ml) average (SD)	Packed Density (g/ml) average (SD)	Compressibility (%) average (SD)	Cohesion (%) average (SD)	Flowability index average (SD)
Vivapur®	5.55 (0.35)	39.5 (0.75)	64.7 (1.27)	0.298 (0.00)	0.442 (0.00)	32.58 (0.60)	0.0 (0.01)	52.5 (1.73)
RS/MCC	6.76 (0.20)	34.6 (2.89)	59.5 (1.27)	0.427 (0.00)	0.521 (0.01)	17.92 (0.22)	6.2 (0.01)	69.0 (0.87)
Eratab®	10.62 (0.29)	33.2 (1.76)	55.5 (2.90)	0.543 (0.00)	0.624 (0.00)	13.03 (0.40)	12.3 (0.00)	70.0 (0.00)
Tablettose®	1.34 (0.12)	36.6 (1.07)	59.3 (1.79)	0.549 (0.00)	0.718 (0.00)	23.50 (0.22)	47.2 (0.01)	57.2 (1.76)
Cellactose®	2.65 (0.31)	39.6 (1.59)	57.3 (2.04)	0.414 (0.00)	0.528 (0.00)	21.53 (0.50)	45.3 (0.00)	57.0 (0.00)

Table 6-6 Effect of magnesium stearate concentration on tensile strength, %friability, %porosity, and disintegration time of Vivapur® tablets.

MgSt (%)	CF (kN)	Tensile strength (N/cm^2) average (SD)	Friability (%)	Porosity (%) average (SD)	DT (min) average (SD)
0.25	1	61.8 (3.95)	0.24	48.8 (0.59)	10.08 (1.79)
	3	237.9 (8.73)	0.06	33.8 (0.37)	> 60*
	5	413.4 (10.81)	0.00	26.2 (0.47)	> 60
	7	550.4 (17.21)	0.00	21.1 (0.28)	> 60
0.50	1	63.0 (1.45)	0.23	48.5 (0.66)	13.69 (1.50)
	3	237.4 (10.56)	0.06	34.1 (0.28)	> 60*
	5	408.1 (9.42)	0.00	25.7 (0.42)	> 60
	7	548.3 (8.44)	0.00	21.3 (0.78)	> 60
0.75	1	56.6 (2.87)	0.30	49.3 (0.84)	8.54 (1.43)
	3	233.7 (7.97)	0.14	33.2 (0.21)	> 60*
	5	389.1 (16.31)	0.02	25.8 (0.35)	> 60
	7	520.7 (16.83)	0.00	20.9 (0.35)	> 60
1.00	1	65.1 (2.78)	0.28	46.4 (0.26)	12.35 (2.60)
	3	214.1 (10.33)	0.18	34.1 (0.34)	> 60*
	5	382.3 (17.00)	0.04	23.7 (0.39)	> 60
	7	498.0 (14.32)	0.00	20.2 (0.82)	> 60
1.50	1	38.7 (1.62)	1.37	46.1 (0.20)	5.69 (0.76)
	3	155.3 (5.00)	0.25	29.9 (0.16)	35.00 (12.17)
	5	285.9 (7.75)	0.06	22.7 (0.29)	> 60*
	7	374.3 (9.06)	0.02	19.1 (0.31)	> 60

Note : * = small pieces of tablet remained in the basket after disintegration test

Table 6-7 Effect of magnesium stearate concentration on tensile strength, %friability, %porosity, and disintegration time of RS/MCC tablets.

MgSt (%)	CF (kN)	Tensile strength (N/cm^2) average (SD)	Friability (%)	Porosity (%) average (SD)	DT (min) average (SD)
0.25	3	50.2 (1.53)	3.86	40.0 (0.08)	1.65 (0.19)
	5	134.7 (4.51)	0.34	32.1 (0.27)	1.63 (0.15)
	7	247.4 (6.83)	0.22	25.6 (0.24)	1.60 (0.25)
	9	333.0 (9.16)	0.20	21.5 (0.25)	1.96 (0.29)
0.50	3	44.1 (1.66)	2.58	41.9 (0.11)	1.89 (0.22)
	5	117.5 (8.39)	0.32	33.7 (0.60)	1.95 (0.11)
	7	198.3 (6.61)	0.28	28.7 (0.16)	1.92 (0.19)
	9	304.4 (14.48)	0.16	23.6 (0.32)	2.24 (0.22)
0.75	3	35.73 (1.11)	2.42	41.4 (0.16)	2.04 (0.14)
	5	102.2 (19.2)	0.51	32.5 (0.17)	1.85 (0.40)
	7	176.9 (4.23)	0.35	27.1 (0.28)	1.65 (0.24)
	9	274.1 (5.26)	0.26	22.2 (0.45)	2.06 (0.12)
1.00	3	18.1 (4.36)	3.93	40.2 (0.17)	1.79 (0.22)
	5	86.0 (2.27)	0.83	33.2 (0.30)	1.74 (0.18)
	7	141.9 (4.76)	0.30	28.6 (0.23)	1.81 (0.16)
	9	219.0 (5.08)	0.26	24.0 (0.40)	1.83 (0.15)
1.50	3	*	5.58	*	2.17 (0.21)
	5	60.4 (2.37)	1.51	30.0 (0.23)	1.93 (0.37)
	7	116.5 (4.30)	0.47	27.8 (0.24)	1.88 (0.32)
	9	189.3 (5.34)	0.28	23.4 (0.36)	1.97 (0.37)

Note : * = soft tablet was formed and could not be measured by hardness tester

Table 6-8 Effect of magnesium stearate concentration on tensile strength, %friability, %porosity, and disintegration time of Eratab® tablets.

MgSt (%)	CF (kN)	Tensile strength (N/cm^2) average (SD)	Friability (%)	Porosity (%) average (SD)	DT (min) average (SD)
0.25	3	38.2 (2.53)	1.82	39.0 (0.18)	1.69 (0.16)
	5	93.2 (5.79)	0.22	31.0 (0.17)	1.80 (0.10)
	7	138.3 (9.16)	0.20	26.1 (0.32)	1.87 (0.11)
	9	192.4 (10.46)	0.10	23.6 (0.40)	1.72 (0.43)
0.50	3	43.7 (1.86)	1.59	38.5 (0.11)	1.64 (0.15)
	5	90.5 (7.11)	0.20	29.4 (0.43)	1.78 (0.10)
	7	121.7 (10.30)	0.14	24.3 (0.26)	1.80 (0.05)
	9	160.7 (12.67)	0.10	20.5 (0.18)	1.95 (0.26)
0.75	3	15.9 (4.66)	4.06	39.3 (0.26)	1.83 (0.13)
	5	71.7 (2.39)	0.76	30.4 (0.17)	1.83 (0.10)
	7	108.0 (6.18)	0.38	25.6 (0.40)	1.98 (0.15)
	9	129.9 (7.09)	0.30	22.5 (0.15)	1.98 (0.18)
1.00	3	16.83 (7.11)	3.71	37.6 (0.12)	1.87 (0.12)
	5	47.5 (9.15)	1.33	31.4 (0.23)	1.84 (0.20)
	7	84.7 (3.92)	0.55	27.2 (0.18)	2.05 (0.11)
	9	114.2 (7.72)	0.36	24.1 (0.13)	2.03 (0.20)
1.50	3	*	**	*	1.66 (0.13)
	5	27.2 (10.2)	2.04	32.0 (0.31)	1.85 (0.19)
	7	78.7 (1.64)	0.93	26.2 (0.18)	2.13 (0.20)
	9	101.7 (2.47)	0.56	23.1 (0.22)	1.99 (0.10)

Note : * = soft tablet was formed and could not be measured by hardness tester

** = all tablets were broken after testing

Table 6-9 Effect of magnesium stearate concentration on tensile strength, %friability, %porosity, and disintegration time of Tablettose® tablets.

MgSt (%)	CF (kN)	Tensile strength (N/cm^2) average (SD)	Friability (%)	Porosity (%) average (SD)	DT (min) average (SD)
0.50	3	*	*	*	5.36 (0.93)
	5	19.5 (5.31)	**	22.3 (0.57)	9.40 (0.87)
	7	25.3 (4.43)	**	20.4 (0.55)	9.08 (1.58)
	9	56.4 (14.2)	**	18.1 (0.38)	10.97 (1.17)
0.75	3	*	*	*	18.64 (0.77)
	5	18.4 (4.03)	**	22.5 (0.33)	19.87 (0.62)
	7	28.9 (11.80)	**	20.3 (0.55)	20.13 (1.42)
	9	47.9 (15.53)	18.03	18.6 (0.54)	18.43 (1.52)
1.00	3	*	*	*	16.18 (1.56)
	5	16.4 (1.55)	**	23.5 (0.36)	17.21 (1.07)
	7	26.5 (4.00)	***	19.5 (0.23)	19.47 (1.80)
	9	48.4 (12.17)	11.1	17.9 (0.54)	20.46 (2.37)
1.50	3	*	*	*	35.23 (2.45)
	5	15.9 (0.66)	**	21.0 (0.48)	33.59 (4.47)
	7	24.0 (3.45)	**	19.7 (0.82)	32.73 (2.54)
	9	47.8 (10.18)	**	17.6 (0.31)	35.61 (2.83)

Note : * = soft tablet was formed and could not be measured by hardness tester

** = all tablets were broken after testing

*** = 1 tablet was broken after testing

Table 6-10 Effect of magnesium stearate concentration on tensile strength, %friability, %porosity, and disintegration time of Cellactose® tablets.

MgSt (%)	CF (kN)	Tensile strength (N/cm^2) average (SD)	Friability (%)	Porosity (%) average (SD)	DT (min) average (SD)
0.50	3	40.9 (1.40)*	2.90	34.2 (0.15)	0.16 (0.02)
	5	79.8 (3.21)*	0.15	29.1 (0.59)	0.19 (0.01)
	7	125.5 (7.01)*	0.02	25.5 (1.37)	0.26 (0.02)
	9	**	**	**	**
0.75	3	34.2 (1.99)	2.64	35.2 (0.38)	0.19 (0.02)
	5	77.1 (5.14)	0.21	29.4 (0.34)	0.20 (0.02)
	7	116.7 (4.15)	0.18	24.8 (0.33)	0.25 (0.02)
	9	155.5 (8.24)	0.15	22.2 (0.48)	0.38 (0.01)
1.00	3	40.3 (1.77)	1.20	33.3 (0.22)	0.19 (0.01)
	5	85.1 (4.40)	0.31	27.7 (0.78)	0.19 (0.01)
	7	118.6 (3.76)	0.19	23.6 (0.83)	0.24 (0.01)
	9	171.4 (6.34)	0.10	20.8 (0.78)	0.36 (0.02)
1.50	3	29.5 (2.56)	2.25	33.0 (0.19)	1.37 (0.59)
	5	76.1 (3.20)	0.19	27.2 (0.45)	0.56 (0.08)
	7	119.9 (6.41)	0.04	22.9 (0.37)	0.50 (0.03)
	9	156.6 (10.12)	0.04	20.4 (0.20)	0.65 (0.04)

Note : * = binding in the die occurred during tabletting

** = could not be measured because of excessive binding in the die occurred during tabletting

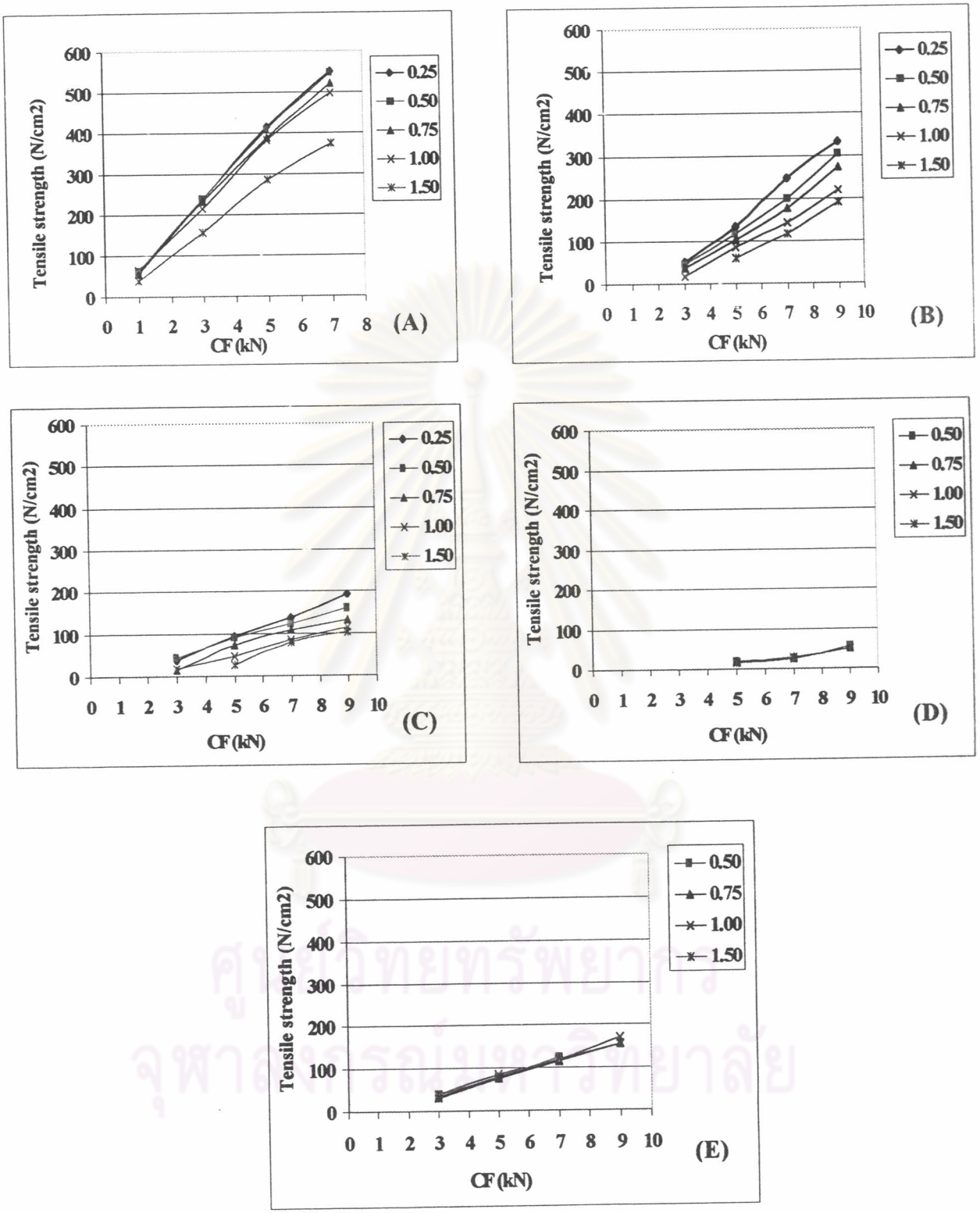


Figure 6-5 Effect of magnesium stearate concentration on compression force - tensile strength profile of various DC tablets ; (A) : Vivapur®, (B) : RS/MCC, (C) : Eratab®, (D) : Tablettose®, and (E) : Cellactose®.

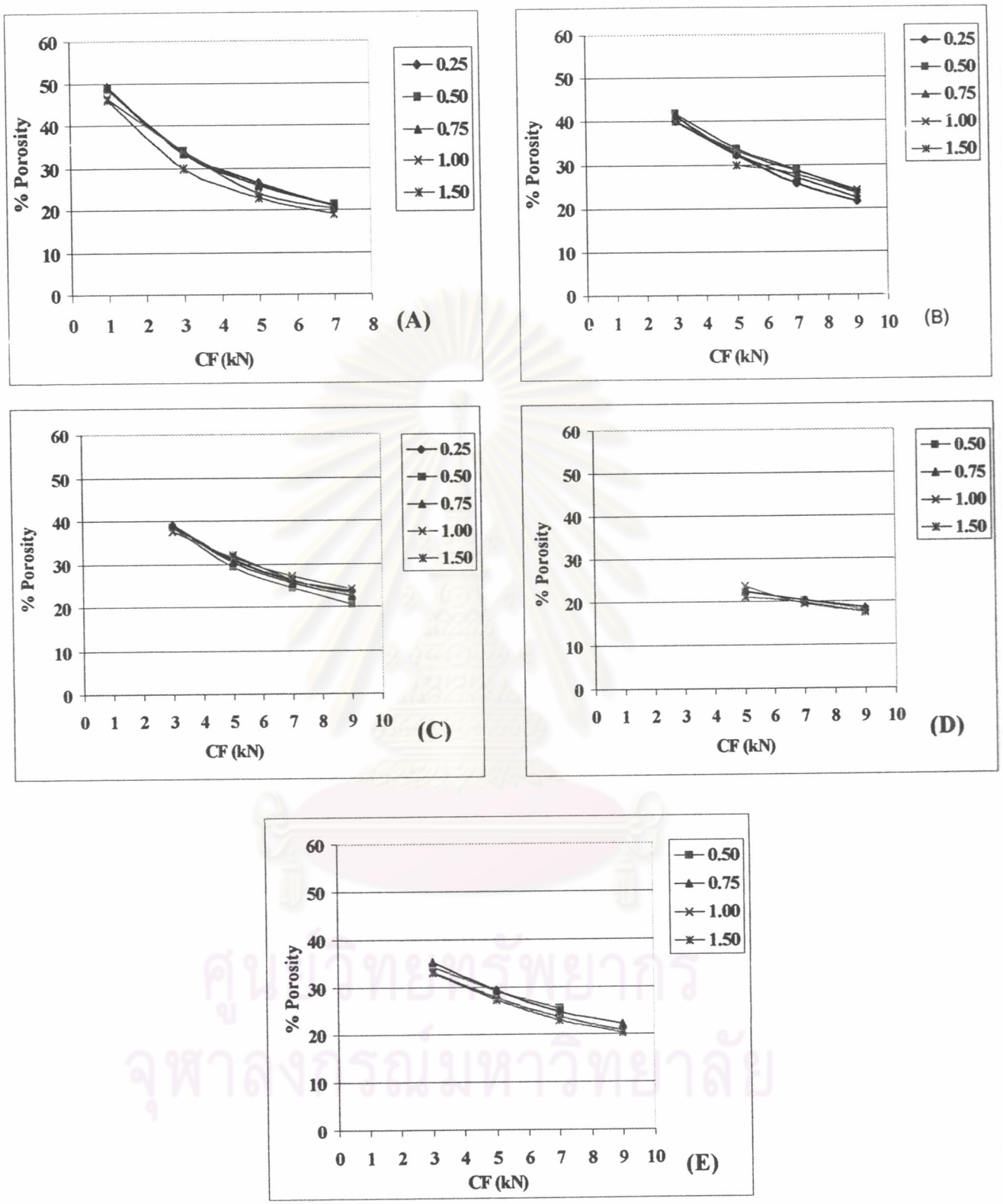


Figure 6-6 Effect of magnesium stearate concentration on compression force - % porosity profile of various DC tablets ; (A) : Vivapur®, (B) : RS/MCC, (C) : Eratab®, (D) : Tablettose®, (E) : Cellactose®.

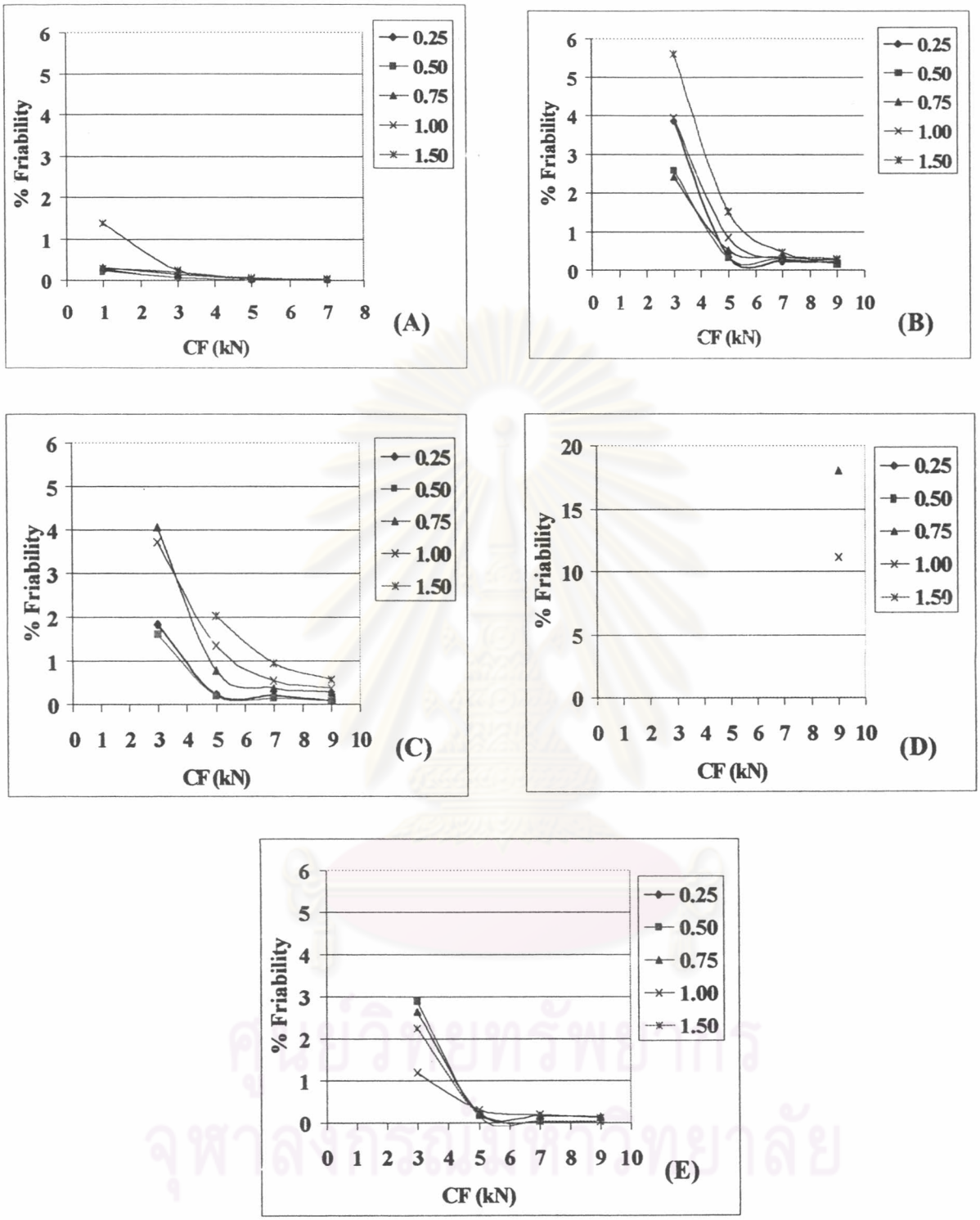


Figure 6-7 Effect of magnesium stearate concentration on compression force - % friability profile of various DC tablets ; (A) : Vivapur®, (B) : RS/MCC, (C) : Eratab®, (D) : Tablettose®, and (E) : Cellactose®.

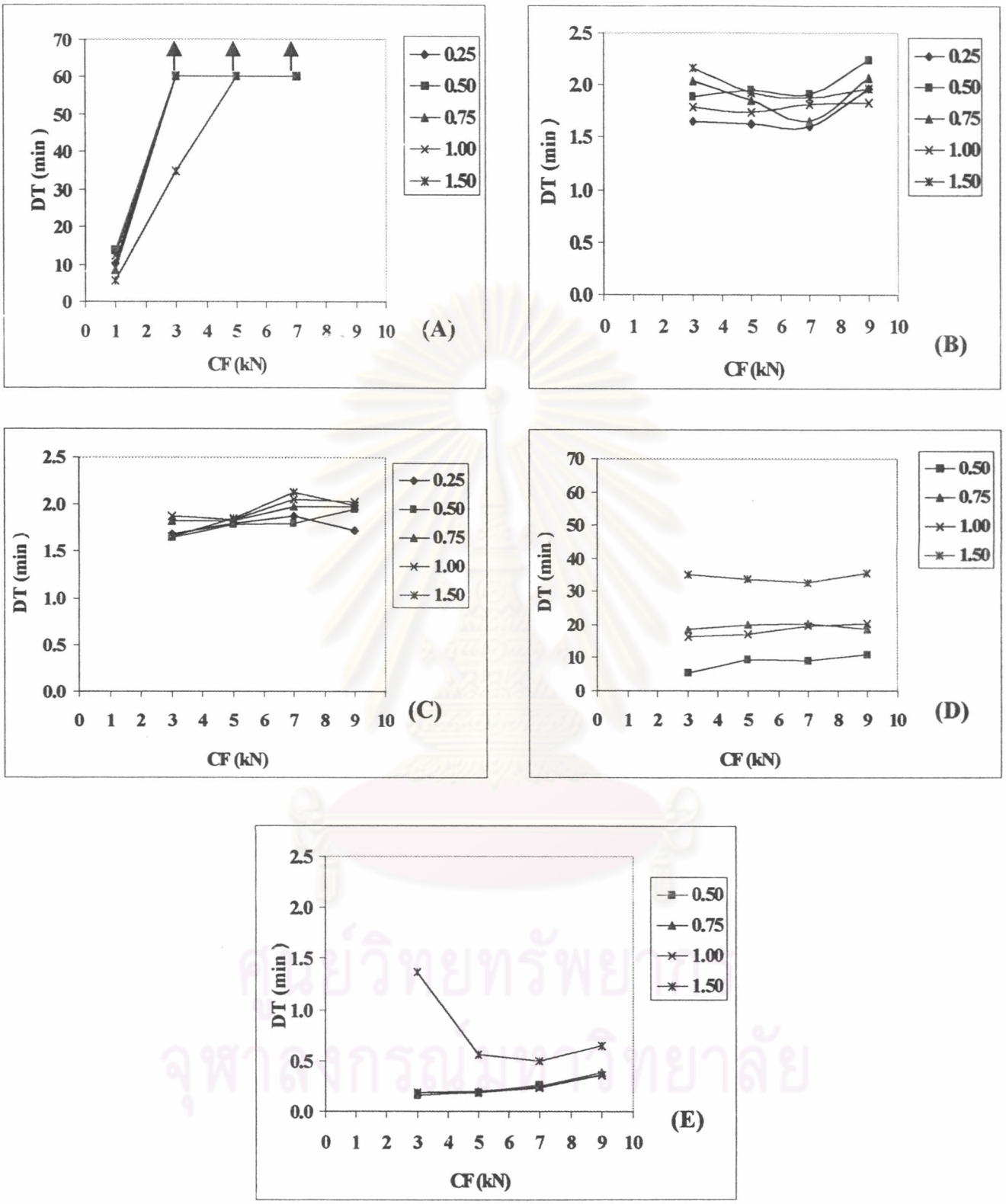


Figure 6-8 Effect of magnesium stearate concentration on compression force - disintegration time profile of various DC tablets ; (A) : Vivapur®, (B) : RS/MCC, (C) : Eratab® , (D) : Tablettose®, and (E) : Cellactose®. (The arrow sign in (A) indicates DT is longer than 60 min.)

lubricant concentration was increased, the tensile strength of tablets was reduced. Bolhuis, Smallenbreak, and Lerk (1981) indicated that magnesium stearate have a strong negative effect on binding properties of tablet excipients. The phenomenon is caused by the formation of lubricant film interfering with particle binding. The lubricant film is a result of adhesion to the substrate of magnesium stearate molecules, which are sheared off mechanically from the magnesium stearate crystal during mixing. This formation of such a hydrophobic film is not only dramatically decrease the particle bonding but also reduce the wettability of the powder mix. Therefore, increasing magnesium stearate in the preparation would reduce the tensile strength of the compact. However, tensile strength of Tablettose® and Cellactose® tablets did not affect by the magnesium stearate level. This can be explained by the nature of the materials when subjected to compression. Cellulose and starch exhibit plastic deformation during compression while lactose has brittle fracture deformation (Paronen and Juslin, 1983; Nystrom and Duberg, 1993). Plastic deformation creates less new surface that is accounted for bonding than brittle deformation. Magnesium stearate that covers on the surface would then hinder and/or reduce the bonding of the particles. Therefore, plastic deformation materials are sensitive to magnesium stearate concentration. The more magnesium stearate concentration, the more reduction in the tensile strength observed for plastic deformation materials. However, more new surface of brittle fracture materials can be produce after compression, then very little change in tensile strength of the compact resulted. Disintegration times of Vivapur® and Tablettose® tablets increased when magnesium stearate level was increased. This is due to the hydrophobic property of magnesium stearate, which reduce the wettability of the materials. Although their disintegration times were deteriorated by lubricant, the mechanisms of disintegration of these two materials are different. Vivapur® is water insoluble material but it has rapid-water absorption property that can draw fluids into its tablet by capillary attraction, swells upon contact, and thus acts as its own disintegrating agent (Mendes and Roy, 1978). Tablettose® is water soluble then its disintegration occurred by dissolution especially at the surface when in contact with the medium. During the test, the tablets eroded and tablets became smaller and smaller when the test is progressed. Then the higher amount

of magnesium stearate, the longer disintegration time was obtained. However, the highest disintegration time of Vivapur® tablets due to the strongest of the compact. In the case of RS/MCC, Eratab®, and Cellactose® tablets, it should be noted that their disintegration times did not influenced by the compression force and the lubricant level. These results are the same as the previous studies (Bos, 1992; Weecharangsan, 1995; Mitrevej, 1996). RS/MCC and Eratab® are starch based materials that composed of mainly rice starch aggregates. These starch aggregate particles had high porosity to enhance water absorption into tablets by cappillary action and then promote the disintegration time of the tablets. When compare RS/MCC tablets with Eratab® tablets, their disintegration time values were not different although RS/MCC gave the higher tablets strength than Eratab®. This was due to MCC in composite particles of RS/MCC that would act as a disintegrant and reduce the disintegration time of tablets. Tablets prepared from tablettose® and Cellactose® gave different disintegration times although they are lactose-based excipient. Tablettose® tablets had longer disintegration time than Cellactose® tablets although they had the lower hardness. Moreover, disintegration time was prolonged with increasing lubricant concentration. This is because of the pattern of disintegration of the materials. Moreover, Cellactose® is coprocessed excipient which is composed of 25% cellulose which would act as a disintegrant and gave the shorter disintegration time than Tablettose® tablets which was composed of only lactose. From the results above, the incorporation of cellulose in the composite particles would raise the tablet strength and also help promote disintegration time of prepared tablets.

In comparing the compressibility properties of various DC diluents, their compression tensile strength profiles were evaluated by calculating slope and coefficient of determination (r^2), using linear regression analysis. Those values are exhibited in Table 6-11. If the material gave high tensile strength with low compression force, high slope was obtained. From calculated slope, Vivapur® had the highest compressibility property then RS/MCC. Cellactose® and Eratab® have likely compressibility property while Tablettose® was the lowest. Increasing lubricant concentration resulted in reduction of compressibility of the material as indicated by lowering slope value. Since

Table 6-11 Effect of magnesium stearate concentration on slope and coefficient of determination (r^2) of regression analysis of compression tensile strength profiles of various DC diluents.

DC diluents	% MgSt	Slope	r^2
Vivapur®	0.25	82.07	0.997
	0.50	81.33	0.998
	0.75	77.39	0.996
	1.00	73.35	0.995
	1.50	56.87	0.995
RS/MCC	0.25	48.06	0.997
	0.50	43.09	0.992
	0.75	39.49	0.992
	1.00	32.93	0.997
	1.50	32.23	0.994
Eratab®	0.25	25.39	0.999
	0.50	19.11	0.994
	0.75	18.92	0.961
	1.00	16.47	0.998
	1.50	18.63	0.954
Tablettose®	0.50	9.23	0.865
	0.75	7.37	0.973
	1.00	8.00	0.957
	1.50	7.98	0.925
Cellactose®	0.50	21.15	0.998
	0.75	20.18	0.999
	1.00	21.34	0.993
	1.50	21.26	0.997

compressibility of Tablettose® and Cellactose® were not affected by lubricant concentration, theirs slope values remained the same as increasing magnesium stearate level.

2. Evaluation of Dilution Potential Study

Paracetamol was used to study the dilution potential of DC diluents because of its poor compressibility. Dilution potential or carrying capacity is " the amount of active drug (s) which the diluent can successfully carry in the direct compression technique" (Czeisler and Perlman, 1991). To determine the effect of drug content on the compressibility of various DC diluents, paracetamol in the preparation was increased with an increment of 5 % until the physical properties of tablets were not acceptable or the flowability problem has arise. Because of the poor flowabiltiy of Vivapur® , talcum at 3 % w/w was necessary to be added as glidant in its formulation and all of other DC diluents. The physical properties of tablets are presented in Tables 6-12 to 6-16 and Figure 6-9 to 6-12. An increasing of drug concentration in the formulation resulted in the reduction of tablet strength and disintegration time while increasing % porosity and % friability. This is due to paracetamol has poor compressibility that would reduced the compressibility of the diluents. The higher the drug content was, the lower tablet strength resulted. From this part of experiment, the dilution potential of DC diluents investigated might be ranked in the following order: Vivapur® > RS/MCC > Eratab® ≥ Cellactose® >> Tablettose® (for example at drug content of 10 %w/w, see Figure 6-13). Although Vivapur® has the highest compressibility, the tablets containing the drug powder more than 35% could not be produced because flowability problem occured. Dilution potential of Tablettose® was lowest because it has the poorest compressibility. The dilution potential of Tablettose® was less than 5% and although increasing in the compression force in the formulation of drug content at 5 % w/w, the reasonable compact was not achieved. Disintegration time of Vivapur®, RS/MCC, and Eratab® tablets were reduced when increasing drug content, this is due to the reduction of the tensile strength of tablets. Disintegration time of RS/MCC and Eratab® tablets were

Table 6-12 Effect of drug content on tensile strength, %friability, %porosity, and disintegration time of Vivapur® tablets at different compression force.

Drug (%)	CF (kN)	Tensile strength (N/cm^2) average (SD)	Friability (%)	Porosity (%) average (SD)	DT (min) average (SD)
10	1	35.1 (3.39)	0.91	49.8 (0.62)	6.02 (1.47)
	3	160.4 (7.01)	0.04	34.2 (0.57)	36.72 (10.58)
	5	299.3 (8.36)	0.00	25.7 (0.61)	> 60
	7	396.9 (22.49)	0.02	21.2 (0.37)	> 60
15	1	45.2 (3.10)	0.76	45.0 (0.44)	5.44 (1.17)
	3	148.3 (5.99)	0.10	32.4 (0.54)	15.30 (2.50)
	5	266.0 (12.19)	0.06	24.6 (0.32)	29.50 (6.10)
	7	368.6 (16.82)	0.06	19.0 (0.50)	> 60
20	1	33.68 (2.56)	1.51	47.4 (0.55)	4.55 (1.53)
	3	118.4 (7.84)	0.22	35.2 (0.69)	21.15 (2.14)
	5	218.7 (6.80)	0.14	27.9 (0.40)	22.26 (4.49)
	7	306.3 (10.53)	0.08	23.4 (0.36)	> 60
25	1	31.54 (1.94)	1.84	45.9 (0.40)	2.42 (0.65)
	3	115.2 (5.83)	0.12	33.5 (0.61)	7.43 (2.17)
	5	205.4 (9.07)	0.04	26.6 (0.43)	24.62 (15.23)
	7	286.4 (7.72)	0.06	22.4 (0.35)	> 60*
30	1	22.7 (2.74)	4.44	47.4 (0.71)	1.34 (0.47)
	3	97.1 (5.16)	0.25	34.2 (0.59)	6.59 (2.51)
	5	173.9 (6.19)	0.14	28.0 (0.57)	28.28 (4.94)
	7	244.8 (8.52)	0.10	23.7 (0.46)	20.35 (6.57)**
35	1	21.6 (3.06)	4.86	45.7 (0.80)	1.44 (0.26)
	3	77.8 (6.48)	0.32	35.0 (0.48)	6.92 (2.11)
	5	149.1 (5.47)	0.01	28.9 (0.19)	18.25 (5.07)
	7	215.4 (8.39)	0.04	24.7 (0.29)	18.32 (7.43)

Note : * = small pieces of tablet remained in the basket after disintegration test

** = average from 5 tablets, one tablet remained some small pieces in the basket

Table 6-13 Effect of drug content on tensile strength, %friability, %porosity, and disintegration time of RS/MCC tablets at different compression force.

Drug (%)	CF (kN)	Tensile strength (N/cm^2) average (SD)	Friability (%)	Porosity (%) average (SD)	DT (min) average (SD)
10	3	46.3 (1.68)	2.56	38.3 (0.22)	2.00 (0.12)
	5	98.3 (6.65)	0.34	32.2 (0.14)	1.95 (0.19)
	7	169.9 (5.02)	0.20	27.0 (0.25)	1.71 (0.43)
	9	232.9 (9.58)	0.08	20.6 (0.25)	2.02 (0.39)
15	3	39.4 (1.24)	3.27	37.1 (0.29)	1.91 (0.13)
	5	89.1 (2.37)	0.42	30.4 (0.26)	2.02 (0.19)
	7	144.6 (5.94)	0.16	25.9 (0.41)	1.51 (0.37)
	9	202.5 (3.94)	0.06	22.0 (0.46)	1.99 (0.19)
20	3	32.9 (1.16)	4.47	37.5 (0.31)	1.40 (0.11)
	5	79.0 (4.43)	0.88	31.1 (0.38)	1.59 (0.14)
	7	134.3 (6.31)	0.36	26.0 (0.70)	1.47 (0.23)
	9	186.5 (10.27)	0.22	22.7 (0.41)	1.68 (0.40)
25	3	18.5 (6.12)	6.97	39.2 (0.23)	1.49 (0.07)
	5	59.1 (2.84)	1.67	31.8 (0.27)	1.52 (0.10)
	7	102.6 (3.94)	0.44	27.7 (0.46)	1.61 (0.25)
	9	147.5 (8.34)	0.22	25.3 (0.36)	1.65 (0.16)
30	3	13.62 (5.50)	7.20	39.1 (0.28)	1.18 (0.12)
	5	49.6 (3.51)	2.09	33.3 (0.39)	1.41 (0.12)
	7	95.7 (2.60)	0.60	25.8 (0.27)	1.44 (0.14)
	9	138.7 (2.36)	0.24	25.1 (0.43)	1.27 (0.42)
35	3	*	**	*	1.27 (0.07)
	5	36.9 (7.14)	3.37	33.6 (0.38)	1.19 (0.21)
	7	73.8 (3.32)	1.18	29.4 (0.37)	1.28 (0.23)
	9	112.3 (5.85)	0.46	25.2 (0.55)	1.11 (0.32)

Note : * = soft tablet was formed and could not be measured by hardness tester

** = 9 tablets were broken after testing

Table 6-14 Effect of drug content on tensile strength, %friability, %porosity, and disintegration time of Eratab® tablets at different compression force.

Drug (%)	CF (kN)	Tensile strength (N/cm^2) average (SD)	Friability (%)	Porosity (%) average (SD)	DT (min) average (SD)
10	3	38.2 (1.70)	2.91	37.0 (0.18)	1.53 (0.11)
	5	74.7 (3.33)	0.77	30.6 (0.56)	1.66 (0.19)
	7	127.3 (7.77)	0.38	25.8 (0.24)	1.85 (0.13)
	9	171.1 (5.28)	0.32	22.9 (0.22)	1.92 (0.17)
15	3	18.8 (7.08)	4.93	36.8 (0.57)	1.67 (0.07)
	5	65.0 (2.52)	0.92	30.0 (0.20)	1.91 (0.15)
	7	109.5 (3.00)	0.30	26.4 (0.23)	1.84 (0.10)
	9	137.3 (3.93)	0.28	21.3 (0.50)	1.95 (0.16)
20	3	5.81 (9.54)	**	37.4 (0.37)	1.45 (0.17)
	5	59.2 (3.37)	1.45	30.0 (0.38)	1.77 (0.13)
	7	93.3 (3.28)	0.28	25.7 (0.41)	1.80 (0.19)
	9	122.0 (6.67)	0.24	22.6 (0.50)	1.79 (0.14)
25	3	*	**	*	1.49 (0.07)
	5	46.6 (2.34)	2.29	31.1 (0.32)	1.64 (0.17)
	7	79.0 (2.35)	0.40	26.7 (0.74)	1.70 (0.20)
	9	108.3 (3.90)	0.24	23.1 (0.35)	1.66 (0.19)
30	3	*	**	*	1.31 (0.10)
	5	47.2 (2.14)	2.62	32.3 (0.33)	1.55 (0.11)
	7	73.9 (3.89)	0.76	28.2 (0.26)	1.59 (0.13)
	9	110.5 (2.75)	0.41	24.7 (0.45)	1.65 (0.23)
35	3	*	**	*	1.23 (0.17)
	5	21.4 (3.96)	4.14	32.7 (0.26)	1.55 (0.11)
	7	59.5 (4.32)	1.45	28.3 (0.20)	1.64 (0.14)
	9	85.7 (4.24)	0.70	24.8 (0.32)	1.54 (0.15)

Note : * = soft tablet was formed and could not be measured by hardness tester

** = some tablets were broken after testing

Table 6-15 Effect of drug content on tensile strength, %friability, %porosity, and disintegration time of Tablettose® tablets at different compression force.

Drug (%)	CF (kN)	Tensile strength (N/cm^2) average (SD)	Friability (%)	Porosity (%) average (SD)	DT (min) average (SD)
5	3	*	**	*	6.73 (2.19)
	5	18.7 (2.40)	**	20.5 (0.25)	13.86 (2.23)
	7	26.7 (3.98)	**	19.0 (0.38)	17.10 (1.70)
	9	42.9 (13.93)	**	16.9 (0.30)	20.94 (1.00)
10	3	*	**	*	1.22 (0.40)
	5	17.9 (1.27)	**	20.9 (0.28)	7.56 (2.81)
	7	23.4 (3.50)	**	19.0 (0.31)	15.30 (1.93)
	9	33.0 (3.18)	**	17.5 (0.23)	16.42 (2.88)

Note : * = soft tablet was formed and could not be measured by hardness tester

** = some tablets were broken after testing

Table 6-16 Effect of drug content on tensile strength, %friability, %porosity, and disintegration time of Cellactose® tablets at different compression force.

Drug (%)	CF (kN)	Tensile strength (N/cm^2) average (SD)	Friability (%)	Porosity (%) average (SD)	DT (min) average (SD)
10	3	31.9 (1.36)	3.23	32.6 (0.33)	0.17 (0.01)
	5	57.5 (2.55)	0.63	28.0 (0.22)	0.23 (0.02)
	7	92.0 (3.53)	0.27	24.1 (0.29)	0.30 (0.07)
	9	117.3 (3.65)	0.20	22.1 (0.20)	0.34 (0.02)
15	3	23.7 (1.76)	5.80	33.9 (0.22)	0.20 (0.02)
	5	50.4 (1.54)	0.90	28.7 (0.36)	0.24 (0.05)
	7	80.1 (1.90)	0.49	25.2 (0.16)	0.31 (0.03)
	9	108.6 (3.46)	0.36	22.6 (0.20)	0.38 (0.03)
20	3	*	8.36	*	0.21 (0.02)
	5	47.5 (1.39)	1.56	27.6 (0.36)	0.29 (0.06)
	7	75.0 (2.02)	0.52	24.5 (0.23)	0.38 (0.05)
	9	97.5 (3.67)	0.39	22.6 (0.17)	0.52 (0.07)
25	3	*	**	*	0.24 (0.01)
	5	44.7 (1.54)	1.51	28.9 (0.51)	0.42 (0.07)
	7	70.7 (2.68)	0.58	25.4 (0.34)	0.50 (0.12)
	9	93.7 (3.87)	0.32	23.4 (0.23)	0.68 (0.08)
30	3	*	**	*	0.25 (0.03)
	5	42.1 (2.37)	2.03	29.1 (0.26)	0.37 (0.04)
	7	62.6 (1.59)	0.74	26.5 (0.54)	0.58 (0.16)
	9	85.7 (2.13)	0.40	24.5 (0.25)	0.90 (0.21)
35	3	*	**	*	0.31 (0.03)
	5	35.9 (1.06)	3.03	29.8 (0.12)	0.36 (0.05)
	7	54.2 (2.59)	1.21	26.7 (0.20)	0.73 (0.15)
	9	71.5 (2.42)	0.62	25.3 (0.19)	1.06 (0.49)

Note : * = could not be measured because of binding in the die occurred during tabletting

** = some tablets were broken after testing

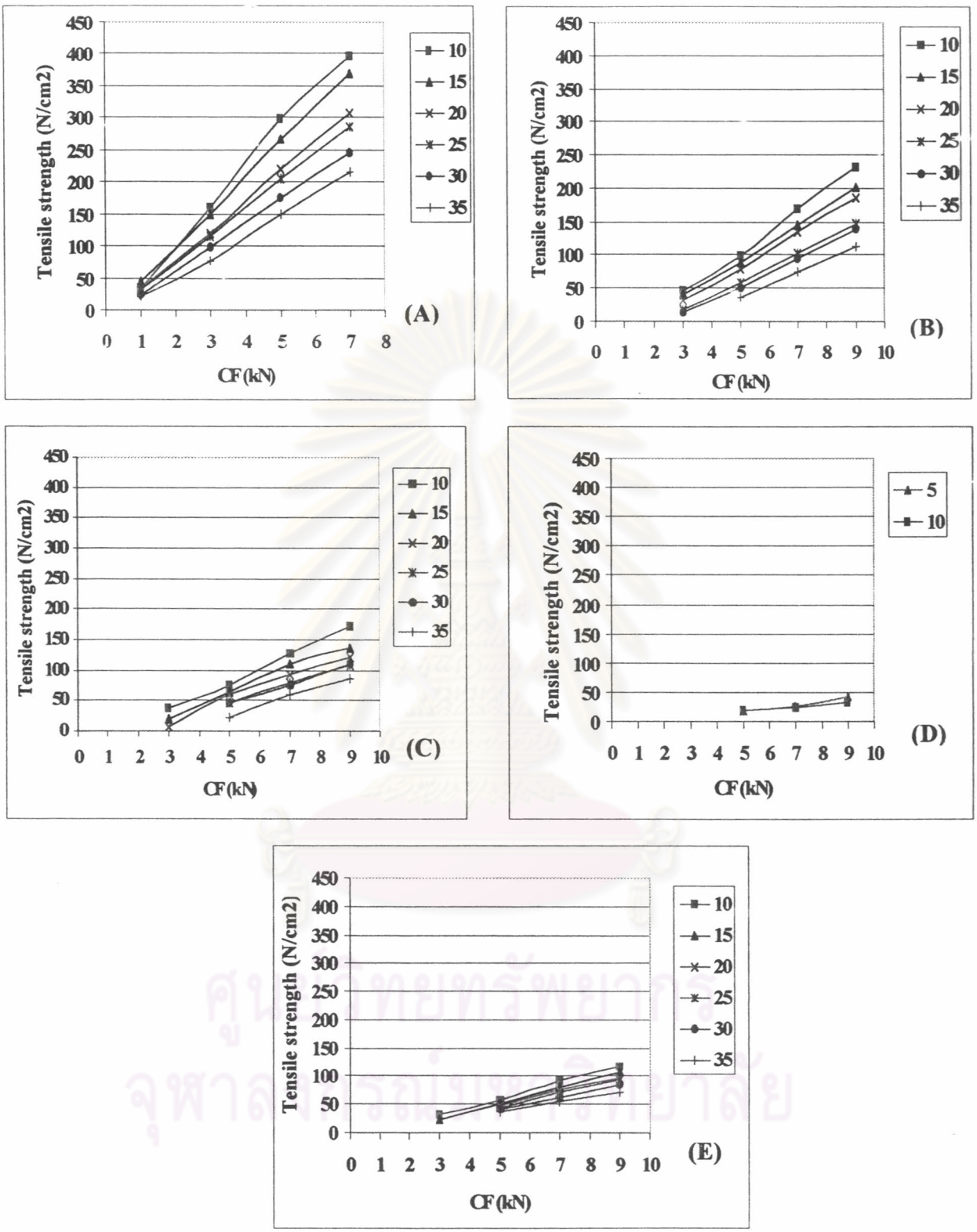


Figure 6-9 Effect of drug concentration on compression forces - tensile strength profile of various DC diluents ; (A) : Vivapur®, (B) : RS/MCC, (C) : Eratab®, (D) : Tablettose®, and (E) : Cellactose®.

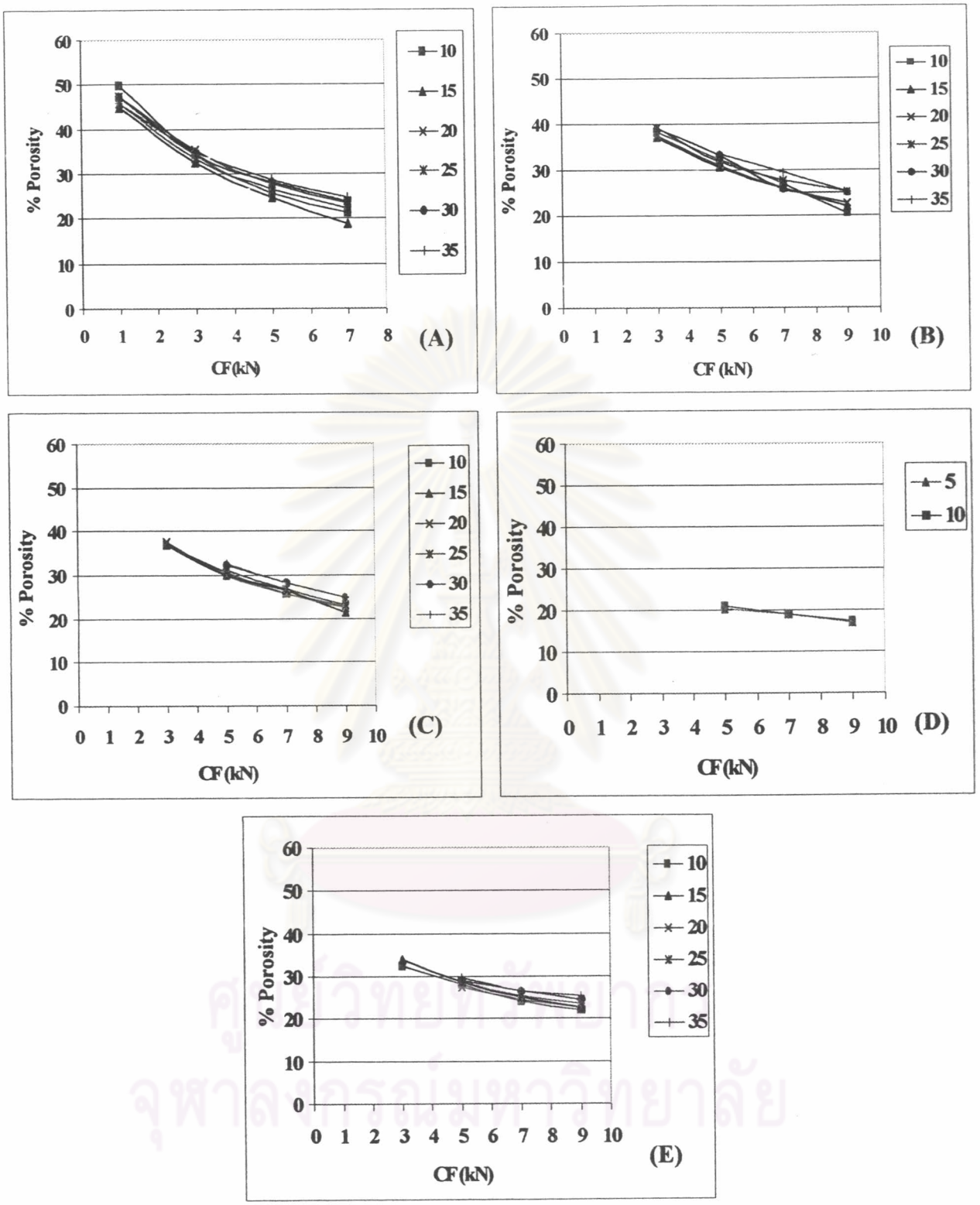


Figure 6-10 Effect of drug concentration on compression forces - % porosity profiles of various DC diluents ; (A) : Vivapur®, (B) : RS/ MCC, (C) : Eratab®, (D) : Tablettose®, and (E) : Cellactose®.

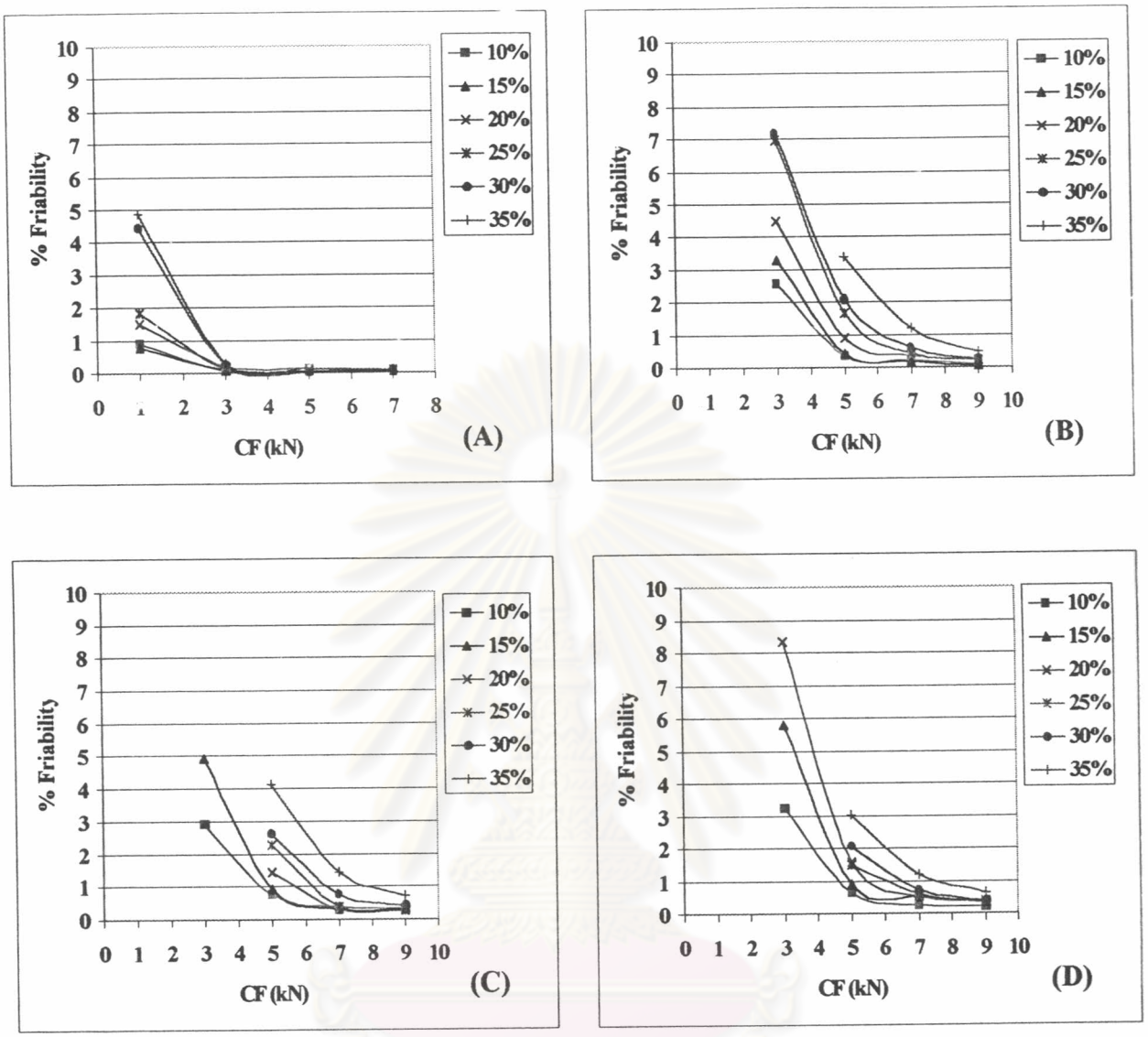


Figure 6-11 Effect of drug concentration on compression forces - % friability profiles of various DC diluents ; (A) : Vivapur®, (B) : RS/ MCC, (C) : Eratab®, and (D) : Cellactose®.

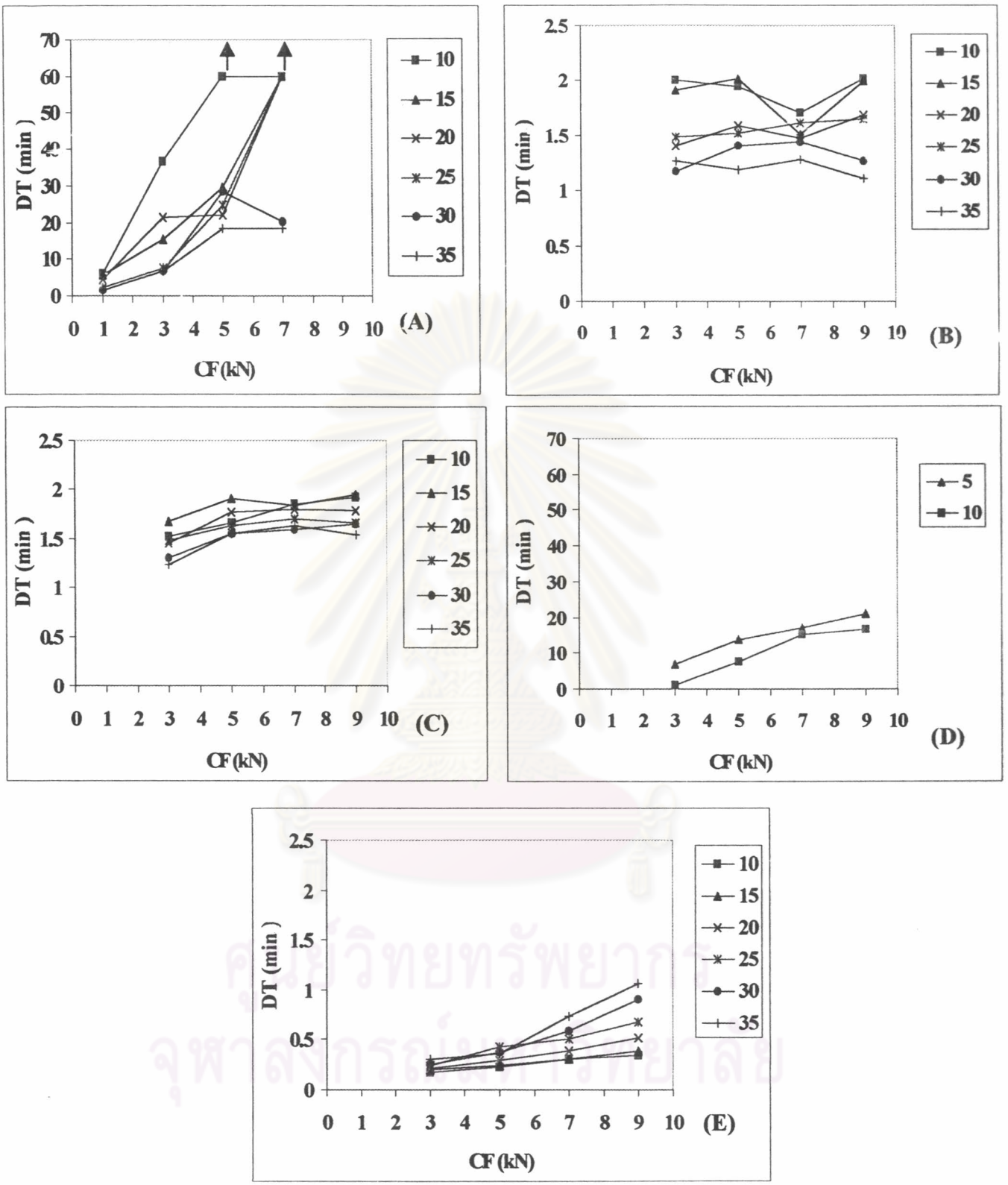
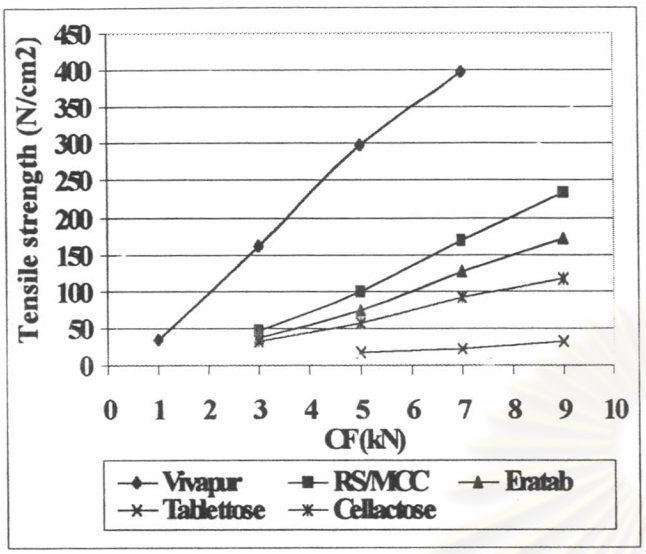
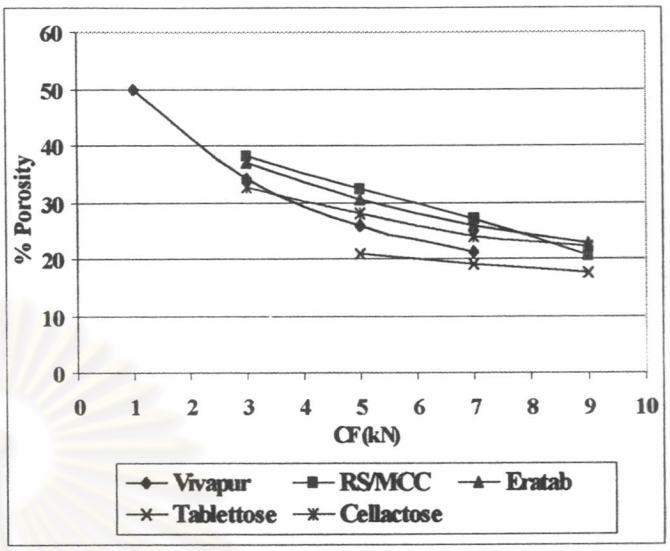


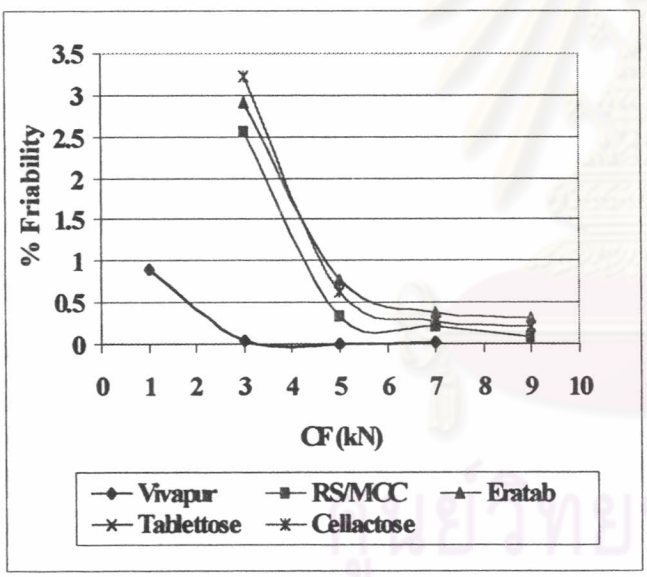
Figure 6-12 Effect of drug concentration on compression forces - disintegration time profiles of various DC diluents ; (A) : Vivapur®, (B) : RS/ MCC, (C) : Eratab®, (D) : Tablettose®, and (E) : Cellactose®.
(The arrow sign in (A) indicates DT is longer than 60 minutes.)



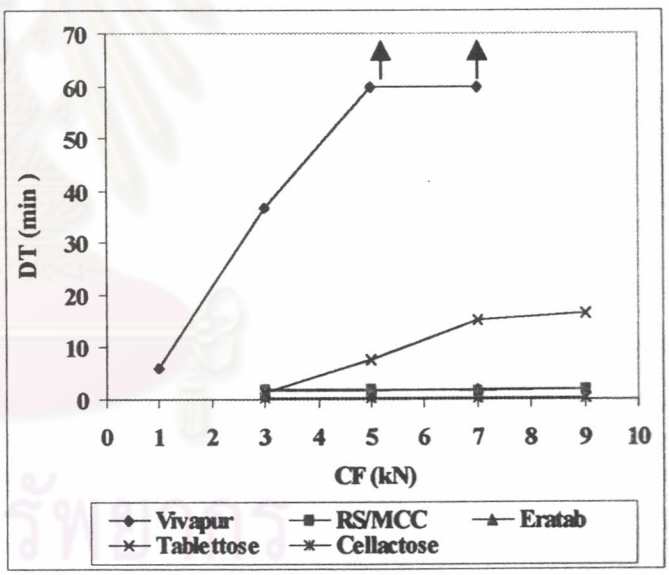
(A)



(B)



(C)



(D)

Figure 6-13 Compression tensile strength profiles (A), compression % porosity profiles (B) , compression % friability profiles (C), and compression disintegration time profiles (D) of tablets prepared from various diluents when incorporated with 10% paracetamol.

(The arrow sign in (D) indicates DT is longer than 60 minutes.)

not affected by the compression force while that of other diluents tablets had the tendency to increase. Disintegration time of Tablettose® tablets increased with an increasing of the compression force. These are due to the higher tablet strength and the hydrophobicity property of the drug that is practically insoluble in water that reduced the wettability of the excipient which disintegration pattern is occurred by dissolution. Disintegration times of Cellactose® tablets were also affected by the drug concentration but they were slightly increased with an increase of compression force.

3. Preparation of Tablet Products

INH and HCTZ were chosen as the model drugs to represent water soluble and slightly soluble, respectively, to prepare tablet formulations. These two drugs at 20%w/w were mixed with various DC diluents, talcum, and magnesium stearate and tabletting by direct compression. The disintegrant was not included in these formulations by the purpose to observe only the diluents effect. Owing to the lowest dilution potential of Tablettose®, this diluent was excluded in this part of study. During compression, tablets were sampling at the beginning, the middle and the final period of the tabletting. The hardness target was set around 40 – 50 N and the compression force used in the production was also recorded. Physical properties of INH and HCTZ tablets are presented in Table 6-17 and 6-18, respectively. The hardness of INH and HCTZ tablets was in the range 47.0 to 52.2 N and 46.0 to 54.9 N, respectively. The compression force employed to prepare both of drug tablets was lowest in formulation containing Vivapur®. The compression forces to prepare RS/MCC containing formulations was lower than for those of Eratab®. However, the formulation of Cellactose® required the highest compression force in tabletting. This is because Vivapur® possesses the highest compressibility and then it uses low compression force in the production than the others. When comparing between RS/MCC and Cellactose®, which have nearly same proportion of cellulose, RS/MCC gave the higher compressibility properties than Cellactose®. % Friability of all formula was in the acceptable range that is less than 1%. Disintegration time of the all formulations disintegrated within 10 minutes and could be ranked in the following order: Vivapur® > Eratab® > RS/MCC® > Cellactose®.

Table 6-17 Physical properties of INH tablets made from various DC diluent.

DC Diluent	CF (kN)	Sampling	Weight Variation (mg) average (SD)	Diameter (mm) average (SD)	Thickness (mm) average (SD)	Hardness (N) average (SD)	Friability (%)	DT (min) average (SD)
		I	262.24 (1.84)	9.51 (0.00)	3.49 (0.01)	52.1 (2.08)	0.15	4.56 (2.03)
Vivapur®	2.1 - 2.3	II	262.20 (1.90)	9.51 (0.00)	3.51 (0.01)	50.8 (1.75)	0.19	5.70 (2.07)
		III	259.72 (1.48)	9.51 (0.00)	3.48 (0.01)	51.7 (1.42)	0.41	5.44 (2.11)
		I	258.15 (0.69)	9.56 (0.00)	3.34 (0.01)	47.4 (1.58)	0.50	2.14 (0.27)
RS/MCC	5.3 - 5.5	II	261.63 (0.84)	9.55 (0.01)	3.36 (0.00)	48.7 (1.57)	0.48	2.25 (0.18)
		III	259.65 (0.75)	9.56 (0.00)	3.35 (0.01)	47.0 (0.82)	0.40	2.35 (0.22)
		I	262.01 (0.39)	9.53 (0.01)	3.02 (0.00)	50.8 (1.32)	0.58	2.71 (0.17)
Eratab®	6.8 - 7.0	II	261.63 (0.38)	9.54 (0.01)	3.03 (0.01)	52.2 (1.99)	0.44	2.56 (0.17)
		III	258.95 (0.31)	9.54 (0.00)	2.95 (0.01)	49.5 (1.58)	0.43	2.78 (0.24)
		I	258.76 (1.05)	9.51 (0.00)	2.91 (0.01)	49.0 (2.79)	0.19	0.39 (0.03)
Cellactose®	8.3 - 8.5	II	266.50 (2.78)	9.52 (0.00)	3.00 (0.04)	49.7 (1.64)	0.15	0.42 (0.01)
		III	260.79 (0.98)	9.52 (0.00)	2.94 (0.00)	47.3 (1.64)	0.27	0.42 (0.02)

Note : I = first sampling

II = second sampling

III = third sampling

Table 6-18 Physical properties of HCTZ tablets made from various DC diluent.

DC Diluent	CF (kN)	Sampling	Weight Variation (mg) average (SD)	Diameter (mm) average (SD)	Thickness (mm) average (SD)	Hardness (N) average (SD)	Friability (%)	DT (min) average (SD)
		I	260.58 (2.20)	9.51 (0.00)	3.55 (0.01)	46.0 (2.40)	0.17	5.94 (1.24)
Vivapur®	2.0 - 2.2	II	261.71 (1.19)	9.51 (0.00)	3.53 (0.01)	49.0 (2.49)	0.21	6.87 (3.52)
		III	260.78 (1.66)	9.51 (0.00)	3.54 (0.01)	47.5 (2.12)	0.31	5.82 (1.12)
		I	258.97 (1.26)	9.56 (0.00)	3.28 (0.01)	47.8 (2.57)	0.62	1.58 (0.15)
RS/MCC	5.3 - 5.5	II	261.30 (0.73)	9.55 (0.00)	3.30 (0.01)	49.8 (2.53)	0.53	1.49 (0.21)
		III	261.13 (0.59)	9.55 (0.00)	3.26 (0.01)	49.7 (1.42)	0.49	1.57 (0.24)
		I	260.70 (0.43)	9.52 (0.00)	2.99 (0.01)	51.3 (2.54)	0.13	1.79 (0.06)
Eratab®	7.9 - 8.1	II	260.50 (0.78)	9.52 (0.00)	2.98 (0.01)	53.0 (1.89)	0.08	1.92 (0.26)
		III	260.90 (0.72)	9.52 (0.00)	2.99 (0.01)	53.1 (2.28)	0.04	1.89 (0.08)
		I	262.28 (1.17)	9.51 (0.00)	2.80 (0.03)	53.9 (1.91)	0.15	0.51 (0.11)
Cellactose®	9.5 - 9.7	II	260.76 (0.91)	9.51 (0.01)	2.78 (0.01)	54.8 (1.87)	0.06	0.51 (0.09)
		III	263.75 (0.45)	9.51 (0.01)	2.81 (0.02)	54.9 (1.91)	0.04	0.42 (0.06)

Note : I = first sampling

II = second sampling

III = third sampling

3.1 Drug Content of Tablets Products

INH and HCTZ tablets were subjected to assay for drug contents. Data are shown in Table 6-19. The placebo tablets was found to give no interference of absorbance peak in the wavelength of 400-600 nm which used to determine the amount of drug in assayed solution (see Appendix 2 and 6). Percent content of INH and HCTZ tablets were between 96.41 – 103.07% and 100.45 – 101.78%, repectively. This results were complied the USP 24 requirement that % drug content of INH and HCTZ tablets were in the range of 90 – 110%.

3.2 Dissolution of INH and HCTZ Tablets

Dissolution profiles of INH and HCTZ tablets are depicted in Figure 6-14. In the case of INH tablets, Cellactose® gave higher dissolution rate than RS/MCC and Vivapur® while Eratab® gave the slowest initial dissolution rate. This is due to the disintegration properties of cellulose that occurred by uptake of water into the tablet by means of capillary pores, which subsequently disrupts interparticulate bonding and breaks the tablet to small pieces to increase surface area. INH is water soluble, therefore, the more surface area contacting the medium, the more dissolution rate would occur. Cellactose® is lactose-based filler, which is soluble in water. This would make the more hydrophilicity of the surroundings drug particles and leaded to give the highest dissolution rate than the others. However, all formulations released INH nearly 100% within less than 15 minutes and met the USP 24 requirement that not less than 80% (Q) of the labeled amount of INH should dissolved in 45 minutes. In the case of HCTZ tablets, Cellactose® also gave the highest dissolution rate then RS/MCC and Eratab® while Vivapur® presented the slowest dissolution rate. This is explained by the properties of drug and excipients. Cellactose® is the lactose – based filler, and water soluble and lead to make more hydrophilicity of the system comprised slightly soluble drug than the others diluents, which are insoluble excipients. Moreover, the lower disintegration time as the result from the effect of cellulose in this coprocessed excipient would promote higher dissolution rate. Although RS/MCC and Eratab® are starch-based filler that are not soluble in water, they have good disintegration properties and could

Table 6-19 Percent drug content of INH and HCTZ tablets.

DC Diluent	INH tablets average (SD)	HCTZ tablets average (SD)
Vivapur®	100.66 (0.53)	100.96 (0.83)
RS/MCC	100.70 (0.35)	100.45 (0.99)
Cellactose®	96.41 (0.65)	101.78 (1.94)
Eratab®	103.07 (1.58)	101.31 (2.12)

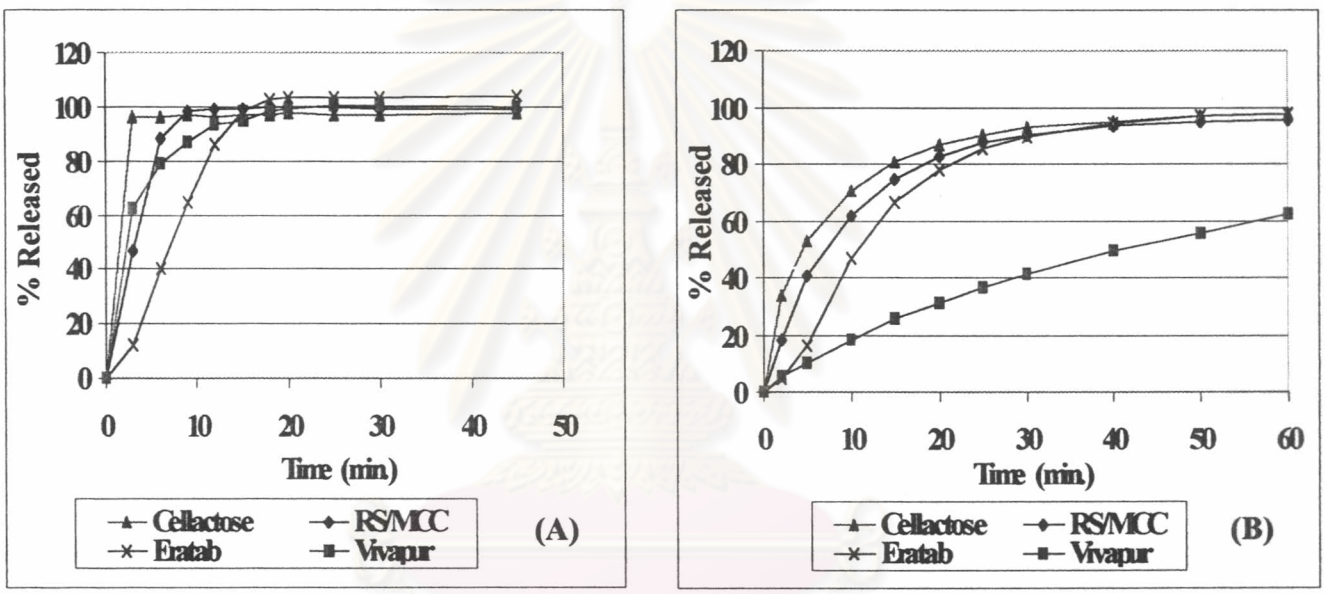


Figure 6-14 Dissolution profile of drug tablets made from various DC diluents ; (A): INH tablets, (B) : HCTZ tablets.

break easily into small particles when contacting to medium. However, Vivapur® tablets released only 60% in 60 minutes while the other DC diluents gave 60% released in less than 15 minutes which complied with the specification of USP 24 that not less than 60% (Q) of the labeled amount of HCTZ is dissolved in 60 minutes. This is because Vivapur® tablets disintegrated into the large particles than the starch – based filler and those large particles took longer time to further break into the smaller particles. Therefore, some drug particles would be trap in the fiber network of Vivapur® that led to slower and incomplete dissolution of HCTZ from the tablets. This result is the same as previous investigations that incomplete dissolution of drug, especially insoluble drug, is obtained in the formulation contained more than 80% MCC because of the physically entrapment or mechanical interlock of drug in MCC particles was occurred (Czeisler and Perlman, 1991; Shangraw, 1991).

4. Volume Reduction Mechanisms Study

Volume reduction mechanisms of RS/MCC and various DC diluents were determined and the physical properties of obtained tablets were presented in Table 6-20. The porosity-pressure function according to Heckel was calculated from the data of force and displacement-time profiles as presented in Figure 6-15 and true density as shown in Table 6-21. The relationship between the compression pressure and porosity of the tablet compact of various DC diluents were constructed and depicted in Figures 6-16 to 6-17. The curvature of phase I was calculated and the coefficient of determination (r^2) in the pressure range around 2 – 30 MPa, using linear regression analysis. The pressure interval around 20 – 80 MPa in phase II was used to calculate the r^2, the yield pressure, P_y (reciprocal of the slope K) and intercept. The data derived from Heckel plot were calculated and represented in Table 6-22. The r^2 from part I of Tablettose® and Cellactose® were lower than that of the other three excipients. Duberg and Nystrom (1986) have used this value as an indication of particle fragmentation, which a linear curve is obtained for non-fragmenting materials and the deviation from the linear curve (low value) indicated fragmentation of the particles. Then these low values reflected a higher degree of fragmentation than the other three DC diluents. Because Tablettose®

Table 6-20 Tablet properties of various DC diluents obtained from volume reduction mechanisms study.

DC Diluents	Weight Variation (mg) average (SD)	Hardness (N) average (SD)	Diameter (mm) average (SD)	Thickness (mm) average (SD)
Vivapur®	209.8 (1.06)	181.8 (9.87)	9.49 (0.00)	2.22 (0.01)
RS/MCC	200.5 (0.30)	150.6 (5.30)	9.52 (0.00)	2.27 (0.01)
Eratab®	197.2 (0.19)	106.8 (2.94)	9.50 (0.00)	2.28 (0.01)
Cellactose®	207.6 (0.71)	73.2 (4.42)	9.52 (0.01)	2.18 (0.01)
Tablettose®	203.9 (0.96)	29.3 (2.06)	9.54 (0.01)	2.24 (0.02)

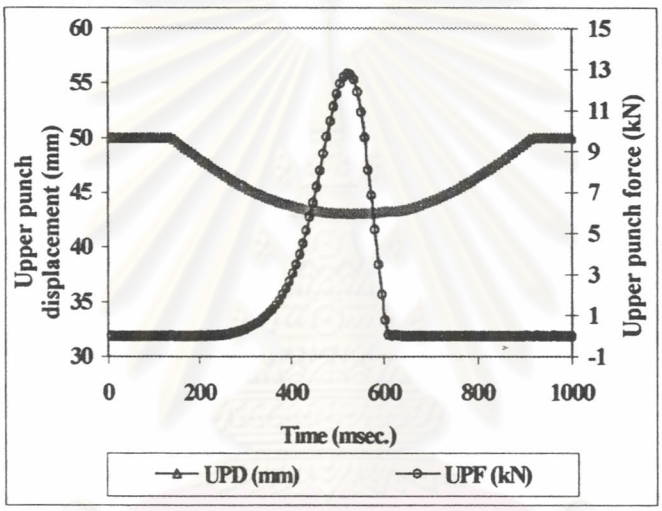


Figure 6-15 Upper punch force (UPF) and upper punch displacement (UPD)-time profiles obtained from instrumented tabletting machine.

Table 6-21 True density of various DC diluents.

DC Diluents	True Density (g/cm^3)					Average (SD)
	1	2	2	4	5	
Vivapur®	1.5950	1.5972	1.6038	1.6021	1.6016	1.5999 (0.002)
RS/MCC	1.5358	1.5388	1.5407	1.5450	1.5433	1.5407 (0.002)
Eratab®	1.5510	1.5483	1.5505	1.5488	1.5494	1.5496 (0.001)
Tablettose®	1.5274	1.5239	1.5210	1.5194	1.5197	1.5223 (0.002)
Cellactose®	1.5929	1.5884	1.5946	1.5986	1.5948	1.5938 (0.002)

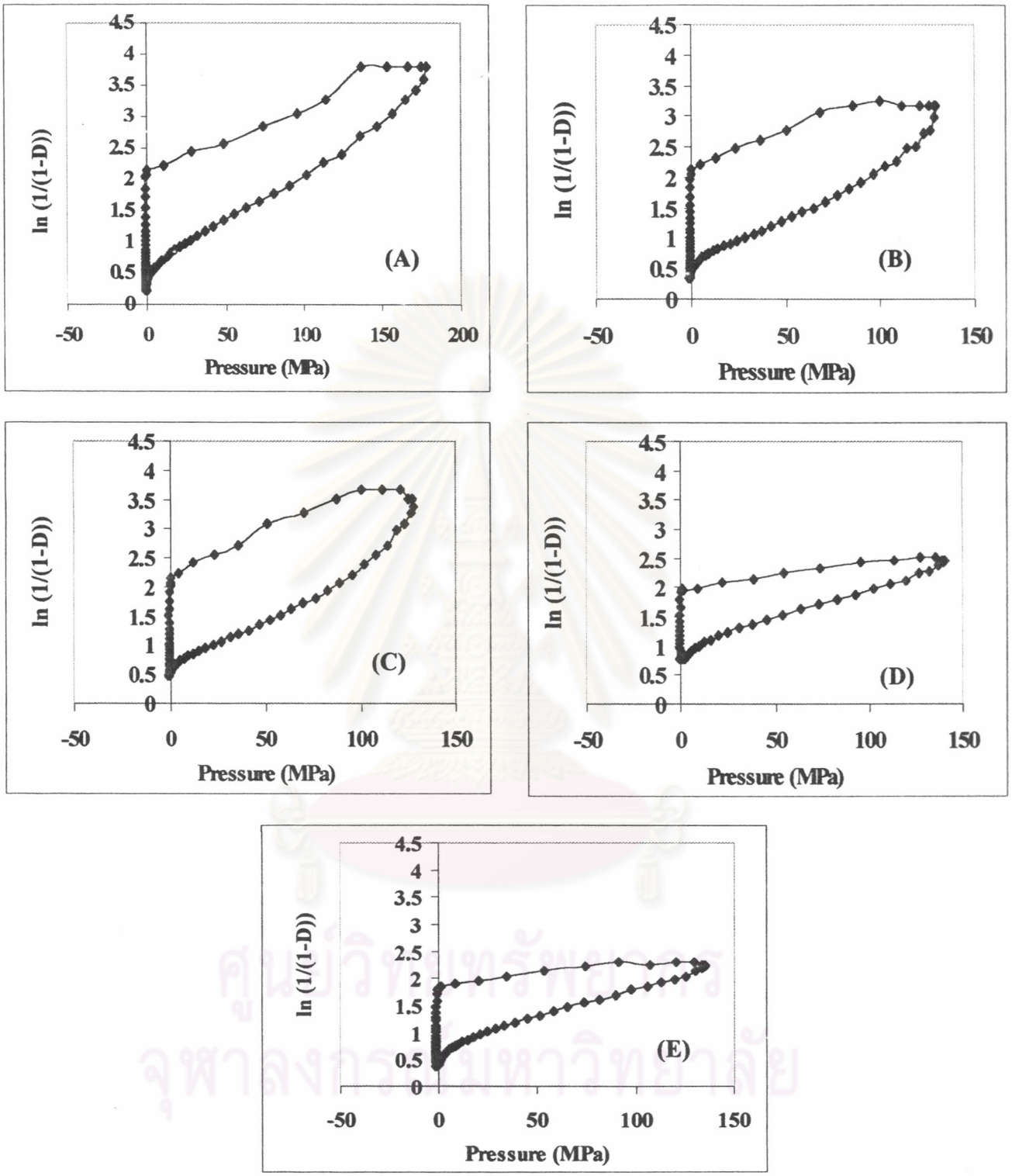


Figure 6-16 Heckel plot of various DC diluents ; (A) : Vivapur®, (B) : RS/MCC, (C) : Eratab®, (D) : Tablettose®, and (E) : Cellactose®.

Table 6-22 Data derived from Heckel plot of various DC diluents (Appendix 25-27).

DC Diluents	r^2 Phase I	r^2 Phase II	Intercept (A)	Slope (K) * 10^{-3}	Yield Pressure P_y (MPa)	D_A	D_O	D_B
Vivapur®	0.9867 (0.00)	0.9982 (0.00)	0.6347 (0.01)	14.6 (0.00)	68.64 (2.25)	0.4699 (0.00)	0.2102 (0.00)	0.2598 (0.01)
RS/MCC	0.9829 (0.00)	0.9953 (0.00)	0.5980 (0.01)	15.5 (0.00)	64.62 (1.60)	0.4500 (0.01)	0.3060 (0.00)	0.1441 (0.01)
Eratab®	0.9849 (0.00)	0.9976 (0.00)	0.6434 (0.00)	15.3 (0.00)	65.58 (0.60)	0.4745 (0.00)	0.3859 (0.00)	0.0886 (0.00)
Tablettose®	0.9648 (0.00)	0.9966 (0.00)	1.0146 (0.02)	9.8 (0.00)	101.74 (2.25)	0.6374 (0.01)	0.5380 (0.01)	0.0994 (0.01)
Cellactose®	0.9712 (0.00)	0.9962 (0.00)	0.7719 (0.00)	10.6 (0.00)	94.26 (2.68)	0.5379 (0.00)	0.3169 (0.00)	0.2210 (0.00)

Table 6-23 Decompression intercept and porosity of various DC diluents.

DC Diluents	Decompression Intercept average (SD)	Porosity average (SD)
Vivapur®	2.194 (0.11)	0.112 (0.01)
RS/MCC	2.013 (0.05)	0.134 (0.01)
Eratab®	1.993 (0.01)	0.136 (0.00)

and Cellactose® are lactose-based filler then the fragmentation would predominate in the first portion of the compression. P_y values of various DC diluents were ranked in the following order: Tablettose® > Cellactose® > Vivapur® > Eratab® ≈ RS/MCC. Due to P_y value has been used to indicate the plasticity of the material and lower P_y value reflects higher degree of plastic deformation. These data indicated that Vivapur®, RS/MCC and Eratab® had the higher plastic deformation than Cellactose® and Tablettose®. This high plastic deformation of particles would lead to the high tensile strength of the tablet (as indicated in Table 6-20) because of an increasing of the contact area between the particles under load (Takeuchi et al., 1987). However, only P_y value could not explain the tablet strength of Vivapur®, RS/MCC and Eratab®. This may be due to in phase II, elastic and/or plastic deformation are the dominating mechanisms in some materials especially elastic materials and this deformation might contained elastic component which would lead to a false low P_y value. Elastic properties in decompression curve of Heckel plot results in an increase in porosity and could be important for the compactibility of powders. Tablets with high strength could not be produced from elastic materials due to bonding could be broken by the elastic expansion during compact ejection. Only particles with a strong bond type, or a large number of bonds will remain the sufficient bonds that maintain compact strength after ejection. The decompression intercept and porosity obtained from part III of Vivapur®, RS/MCC, and Eratab® are presented in Table 6-23. RS/MCC and Eratab® gave higher porosity than Vivapur® and this might be resulted from the elastic component of starch-based filler that lower the bonding of the compact. However, the compaction behavior between RS/MCC and Eratab® could not be clearly explained by Heckel analysis. This might be due to the determination of bonding from this analysis come from the bulk behavior of the compact that is not totally correct. Duberg et al. (1993) indicated the bonding surface area and bonding mechanisms used for interparticulate attraction are also important of the compact strength. Therefore, the characterization of these factors is required for more investigation in detail.

Conclusion

1. Tablet tensile strength : compression force-tensile strength profile of tablets containing RS/MCC was higher than Eratab® and Cellactose® but inferior to Vivapur®.

2. Effect of lubricant : RS/MCC is sensitive to alkaline stearate like the other starch–based filler and cellulose–based filler. The higher lubricant quantity in the formulation is, the more reducing in tablet tensile strength. However, the disintegration time of RS/MCC was not influenced by the compression force used (3 – 9 kN) and lubricant level used (0.25 – 1.5 %w/w).

3. Dilution potential study : RS/MCC gave higher dilution potential than Eratab® and Cellactose® but lower than that of Vivapur®. Tablettose® gave the lowest dilution potential and it can not produce the acceptable tablets even at the low drug concentration (5%w/w).

4. Production of tablet products : Tablets formulations utilizing RS/MCC diluents used the lower compression force than Eratab® and Cellactose® and exhibited shorter disintegration time than Vivapur®. Dissolution of INH and HCTZ using RS/MCC are comparable to those used Cellactose® as diluent, however, slightly higher than those of Eratab®. The tablets of two drugs made from RS/MCC released nearly 100 % within 45 minutes and 60 minutes for INH and HCTZ, respectively, and complied with the specification of USP 24. Moreover, in the case of slightly soluble drug tablets (HCTZ tablets), RS/MCC gave more complete dissolution than Vivapur®.

5. Volume reduction mechanisms: RS/MCC, Eratab®, and Vivapur® gave higher plastic deformation than lactose-based diluents (Tablettose® and Cellactose®). However, starch-based diluents had higher elastic expansion than Vivapur® and this might be lead to obtain lower strength compact than that of Vivapur®.