# Chapter Three

# Results

## 1. The Optimum Conditions of the Fluidized Bed Granulator

Before proceeding with the preparation of sugar-starch granules, preliminary investigation of fluidized bed granulation process was carried out by the trial and error method. During the feasibility trial, the batch sizes of 400 g were used and air flap setting at $30^{o}$ was found to attain proper fluidization of powders. Several process variables were varied, i.e., inlet air temperature, binder solution spraying rate, nozzle pressure, concentration of binder solution and concentration of binder in granule. On the basis of these preliminary investigations, the process conditions as shown in Table 1 were suitable to prepare the powdered sugar-tapioca starch granules with various type of binders.

## 2. Physical Properties of Powdered Sugar-Tapioca Starch-PVP Granules.

### 2.1 Particle Size Distribution

The particle size distribution of the granules are given in Table 2. It is apparent from the data that particle size of granules increased with

Table 1 Summary of the Conditions of Fluidized Bed Granulator Used in Preparation of Granules with Various Type of Binders

| Type of Binders | Conditions | | | | |
|---|---|---|---|---|---|
| | Inlet Air Temperature (°C) | Binder Solution Spraying Rate (ml/min) | Nozzle Pressure (bar) | % Binder in Formula | % Binder Solution Concentration |
| PVP | 50 | 7.5 | 1.5 | 2.0 | 5.0 |
| Gelatin | 50 | 5.0 | 2.0 | 2.0 | 10.0 |
| Methyl-cellulose | 45 | 5.0 | 2.0 | 1.0 | 3.0 |
| Tapioca Starch | 50 | 5.0 | 2.0 | 1.0 | 2.0 |

Fixed Conditions : Batch Size 400 g

Air Flap 30

Table 2 Particle Size Distribution of Sugar-Starch-PVP Granules

| Formula | Composition of Sugar:Starch | % Retained on Seive Size (μm) | | | | | |
|---|---|---|---|---|---|---|---|
| | | 425 | 250 | 180 | 150 | 125 | 106 |
| 1 | 10 : 90 | 3.82 | 8.52 | 24.68 | 62.98 | - | - |
| 2 | 20 : 80 | 1.97 | 5.12 | 11.99 | 25.16 | 44.66 | 11.10 |
| 3 | 30 : 70 | 1.87 | 27.31 | 39.75 | 16.48 | 14.59 | - |
| 4 | 40 : 60 | 5.15 | 46.00 | 38.47 | 7.20 | 3.18 | - |
| 5 | 50 : 50 | 2.53 | 44.59 | 37.82 | 11.88 | 3.18 | - |
| 6 | 60 : 40 | 11.10 | 26.90 | 39.34 | 13.02 | 9.64 | - |
| 7 | 70 : 30 | 4.12 | 51.61 | 35.94 | 8.28 | - | - |
| 8 | 80 : 20 | 29.65 | 52.38 | 16.54 | 1.53 | - | - |
| 9 | 90 : 10 | 54.07 | 39.35 | 6.58 | - | - | - |

increase of the amount of sugar in the granule formula.

### 2.2 Density and Percent Compressibility

Bulk, tap, and true density and percent compressibility values of sugar-starch-PVP granules are given in Table 3. Relative low bulk and tap density were obtained with all granule formulations. The bulk density ranged from 0.3 to 0.4 g/ml. Formula 5 shows a lowest bulk and tap density. True density of granules in each formula was similar. The differnce in percent compressibility were within the range of 15.6-34.4 % and it appeared that the percent campressibitliy of the granules increased with the increase in the amount of starch in the formula.

### 2.3 Moisture Content

The results of moisture content of granules are shown in Table 3. It should be pointed out that the percent moisture content of granules increased with increase of the percent of tapioca starch in the formula. The moisture content was varied within the range of 1-7 %.

### 2.4 Flowability

As it is shown in Table 3, only the flow rate of granules from formula 4-9 could be measured. The flow rate of the other granule formula were unable to be determined by the flowmeter. The granule from these formulations had tendency to blockage the orifice of the

Table 3 Density, % Compressibility, Moisture Content, and Flowability of Sugar-Starch-PVP Granules

| Formula | Density (g/ml) Bulk | Tap | True | Compressibility (%) | Moisture Content (%) | Flowability Rate (g/sec) | $r^2$ |
|---|---|---|---|---|---|---|---|
| 1 | 0.35 (0.01) | 0.51 (0.01) | 1.50 (0.01) | 32.4 (0.9) | 7.1 (0.2) | - | - |
| 2 | 0.42 (0.00) | 0.64 (0.00) | 1.50 (0.01) | 34.3 (0.0) | 6.1 (0.1) | - | - |
| 3 | 0.31 (0.00) | 0.40 (0.00) | 1.51 (0.03) | 22.5 (0.0) | 5.4 (0.1) | - | - |
| 4 | 0.33 (0.01) | 0.42 (0.01) | 1.49 (0.01) | 21.4 (0.5) | 5.0 (0.1) | 7.8 (0.51) | 0.997 |
| 5 | 0.29 (0.01) | 0.39 (0.01) | 1.47 (0.01) | 25.6 (0.4) | 3.9 (0.1) | 6.8 (0.38) | 0.998 |
| 6 | 0.38 (0.00) | 0.50 (0.01) | 1.54 (0.01) | 24.0 (1.0) | 3.2 (0.1) | 8.7 (0.60) | 0.998 |
| 7 | 0.33 (0.01) | 0.42 (0.00) | 1.54 (0.01) | 21.4 (1.0) | 2.8 (0.1) | 7.7 (0.58) | 0.997 |
| 8 | 0.40 (0.00) | 0.49 (0.01) | 1.56 (0.03) | 18.3 (0.0) | 2.1 (0.1) | 9.5 (0.70) | 0.997 |
| 9 | 0.43 (0.01) | 0.51 (0.01) | 1.54 (0.02) | 15.6 (0.2) | 1.4 (0.1) | 9.7 (0.44) | 0.999 |

Means of three determinations with standard deviation in parentheses.

The flow rate of granules from formula 1-3 could not be measured.

$r^2$ = Correlation coefficient.

flowmeter during the test. The flow rate values were determined from the slope of the linear plot between amount of granules flew versus times where $r^2$ was the correlation coefficient derived from the plot. It could be seen from $r^2$ that the granules in formula 4-9 are characterized as good flowability (the linear correlation coefficient, $r^2$,> 0.99). The experimental data are shown in Appendix C.

### 2.5 Compressional Force-Hardness Profile

Relationship between compressional force and hardness of compacts of sugar-starch-PVP granules are presented in Table 4 and Figure 7. It was appeared that the effect of compressional force on tablet hardness was as expected, which increased with increasing compressional force.

### 2.6 Compressional Force-Disintegration Profile

The relationship between compressional force and disintegration time are shown in Table 5 and Figure 8. The granules were compacted without addition of any tablet adjuvants especially disintegrant. The compacts disintegrated within 3-5 minutes at the compressional force between 1000 upto 1600 lbs. The disintegration time of the compacts were not substantially changed with the increase of compressional force as compared with increase of hardness with the pressure as shown in Figure 7. In

Table 4 Relationship between Compressional Forces and Hardness of Compacts Prepared from Sugar-Starch-PVP Granules

| | Hardness (Kp) | | | |
|---|---|---|---|---|
| | Compressional Forces (lbs) | | | |
| Formula | 1000 | 1200 | 1400 | 1600 |
| 1 | 8.12 (2.99) | 14.05 (2.92) | 15.01 (0.56) | 16.96 (0.58) |
| 2 | 6.15 (2.13) | 11.51 (0.82) | 14.03 (0.70) | 15.28 (4.47) |
| 3 | 6.56 (1.34) | 11.51 (0.99) | 14.03 (0.66) | 15.28 (0.51) |
| 4 | 13.78 (1.01) | 19.02 (0.93) | >20 - | >20 - |
| 5 | 11.05 (0.66) | 13.46 (0.60) | 15.47 (0.57) | 16.48 (0.53) |
| 6 | 8.12 (0.31) | 12.47 (0.28) | 14.11 (0.39) | 13.40 (2.48) |
| 7 | 10.46 (1.27) | 12.98 (0.68) | 13.76 (0.80) | 15.06 (0.26) |
| 8 | 8.38 (1.94) | 11.38 (0.37) | 12.45 (0.06) | 13.32 (0.55) |
| 9 | 5.60 (0.72) | 8.12 (0.45) | 10.02 (0.34) | 11.17 (0.38) |

Means of four determinations with standard deviation in parentheses.

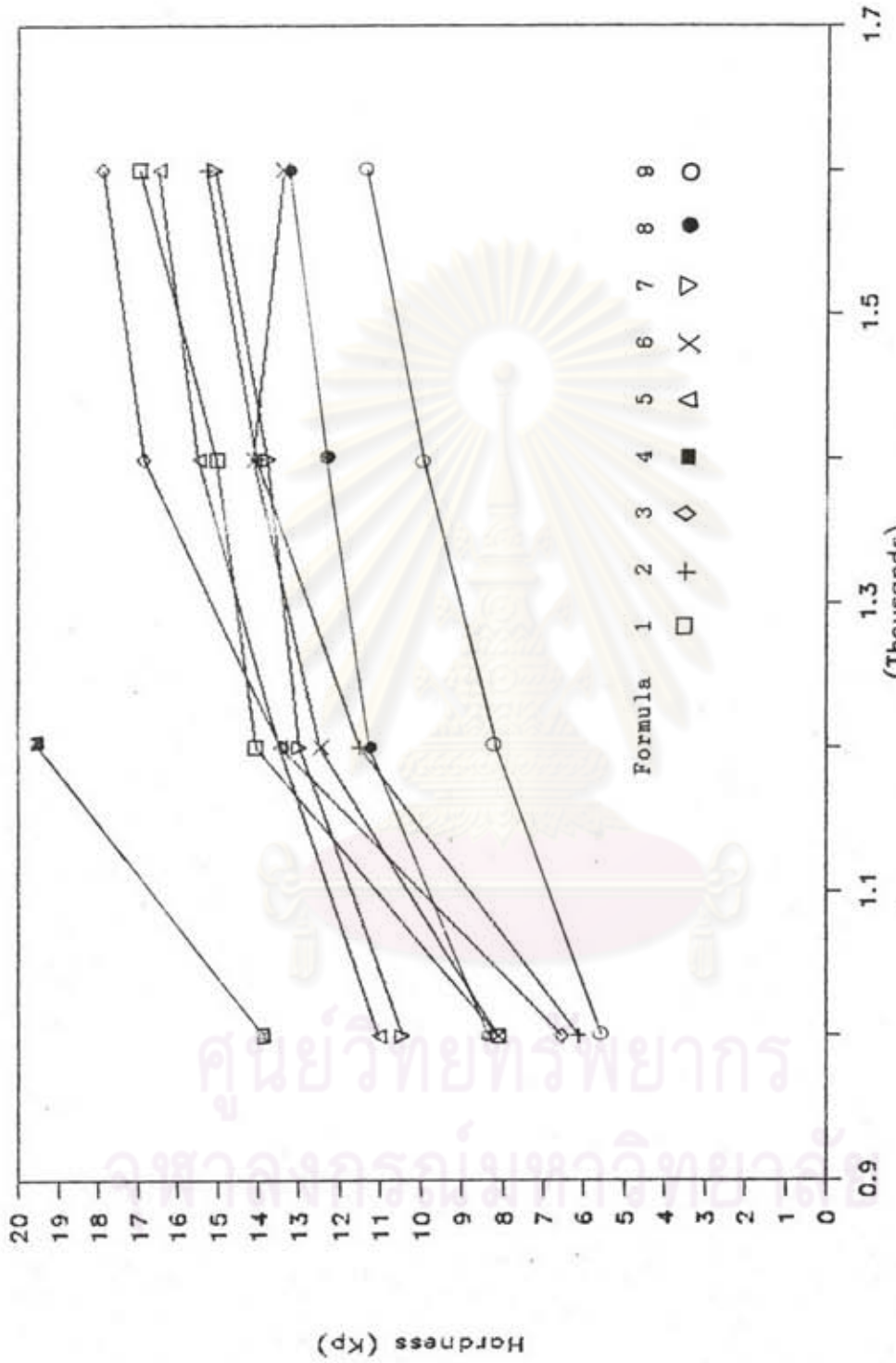


Figure 7 Compressional Force-Hardness Profiles of Compacts Prepared from Sugar-Starch-PVP Granules

Table 5 Relationship between Compressional Forces and Disintegration Time of Compacts Prepared from Sugar-Starch-PVP Granules

| Formula | Disintegration Time (min) | | | |
|---|---|---|---|---|
| | Compressional Forces (lbs) | | | |
| | 1000 | 1200 | 1400 | 1600 |
| 1 | 2.52 (0.22) | 3.32 (0.56) | 3.18 (0.68) | 4.48 (0.89) |
| 2 | 2.55 (0.57) | 5.61 (2.04) | 3.65 (0.67) | 5.09 (2.24) |
| 3 | 4.03 (1.39) | 3.10 (0.58) | 5.26 (2.34) | 4.62 (2.31) |
| 4 | 3.85 (1.65) | 4.59 (2.54) | 3.98 (1.13) | 3.72 (0.91) |
| 5 | 3.09 (0.43) | 3.24 (0.06) | 3.20 (0.22) | 3.43 (0.23) |
| 6 | 3.22 (1.42) | 3.38 (0.08) | 3.24 (0.04) | 3.13 (0.05) |
| 7 | 3.05 (0.02) | 3.26 (0.07) | 3.30 (0.10) | 3.31 (0.34) |
| 8 | 2.44 (0.13) | 2.76 (0.06) | 2.90 (0.06) | 3.03 (0.06) |
| 9 | 2.53 (0.08) | 3.28 (0.07) | 3.68 (0.09) | 3.91 (0.10) |

Means of six determinations with standard deviation in parentheses.

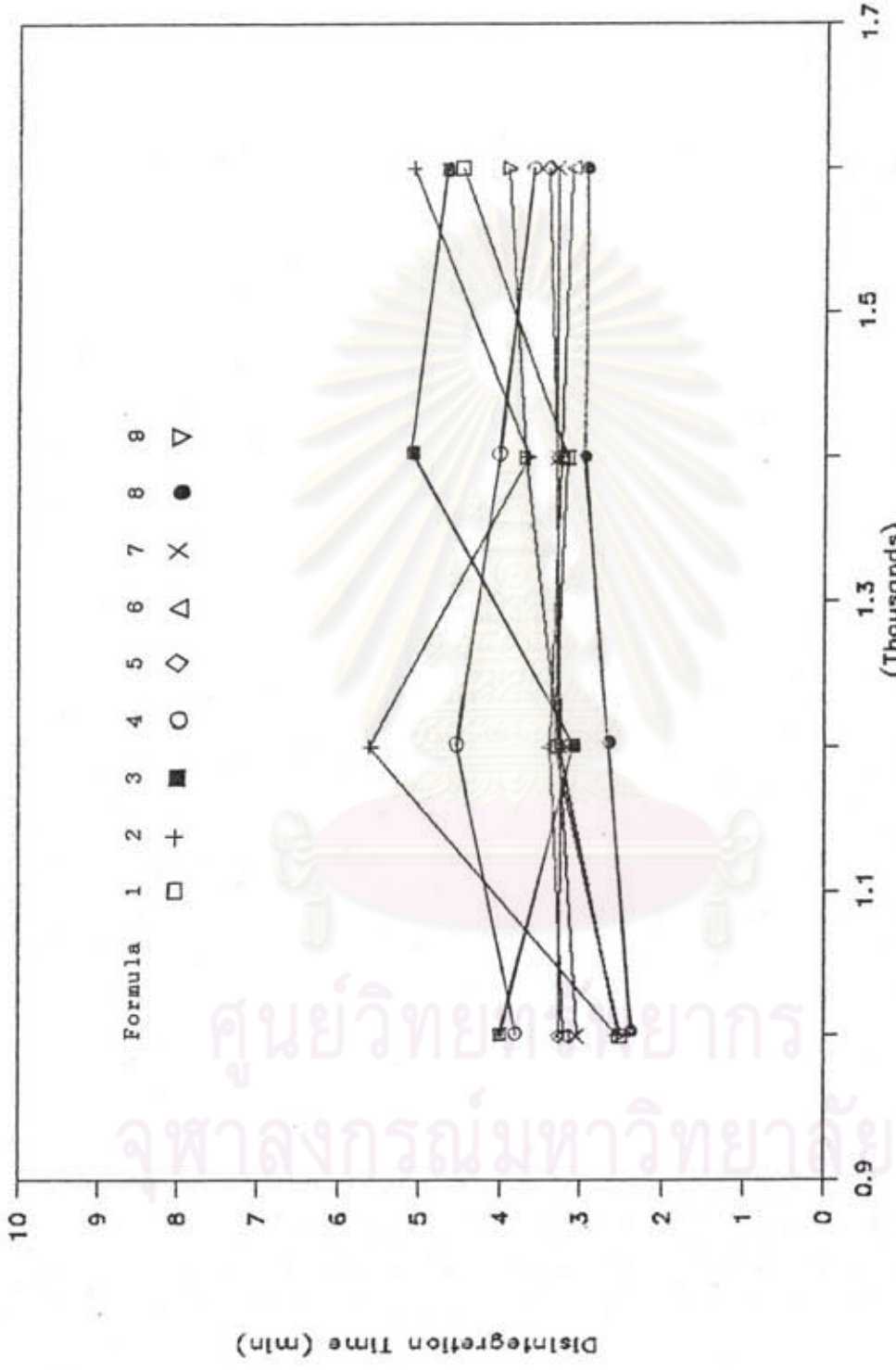


Figure 8 Compressional Force-Disintegration Profiles of Compacts Prepared from Sugar-Starch-PVP Granules

addition, very slightly increasing in disintegration time were observed in formula 5 to 9 when the compacts were compressed at high compressional forces.

2.7 **Tabletting Properties of Powdered Sugar-Tapioca Starch-PVP Granules.**

Table 6 presents weight variation, hardness, disintegration time, friability, and thickness of the sugar-starch-PVP tablets. Formula 3 to 9 provided the tablet weight with low percent coefficient of variation (less than 0.6 %). However, the tablets made from all granulations exhibited good weight variation within the requirements of USP standard.

The tablets were compressed to a required hardness about 4 Kp. The granules from formula 5 to 8 gave the low variation in hardness while formula 1 shows the highest variation in hardness.

Tablets were compressed without addition of disintegrant. It can be seen that disintegration time of all tablet formula were less than 5 minutes. However, the tablets prepared from the high amount of sugar gave lower variation in disintegration time.

The friability test was performed by rotating in Roche Friabilator for 15 minutes in stead of 4 minutes as this time period was not long enough to detect the weight loss after the test. The tablets prepared from high amount of tapioca starch show lower percent

Table 6 Tabletting Properties of Sugar-Starch-PVP Granules

| Formula | Weight Variation (mg) Mean (S.D.) | % C.V. | Hardness (Kp) Mean (S.D.) | % C.V. | D.T.[a] (min) Mean (S.D.) | % C.V. | Friability % Mean (S.D.) | Thickness (mm) Mean (S.D.) | % C.V. |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 295.6 (5.94) | 2.01 | 3.41 (1.84) | 53.66 | 3.08 (0.14) | 7.45 | 0.43 (0.06) | 3.79 (0.05) | 1.31 |
| 2 | 290.4 (4.56) | 1.51 | 2.43 (0.66) | 27.16 | 2.39 (0.13) | 8.18 | 0.93 (0.10) | 3.87 (0.01) | 0.25 |
| 3 | 298.2 (1.54) | 0.52 | 3.94 (0.56) | 14.21 | 2.56 (0.17) | 9.66 | 0.83 (0.08) | 3.97 (0.01) | 0.25 |
| 4 | 302.5 (1.10) | 0.36 | 3.68 (0.40) | 10.87 | 3.21 (0.15) | 7.46 | 1.04 (0.08) | 4.16 (0.01) | 0.24 |
| 5 | 303.1 (1.06) | 0.35 | 4.25 (0.11) | 2.59 | 3.47 (0.05) | 2.20 | 1.21 (0.06) | 3.90 (0.01) | 0.25 |
| 6 | 304.3 (1.81) | 0.59 | 3.72 (0.25) | 6.72 | 3.58 (0.09) | 3.78 | 1.50 (0.15) | 3.86 (0.01) | 0.26 |
| 7 | 291.4 (1.06) | 0.36 | 4.18 (0.29) | 6.94 | 3.56 (0.02) | 0.85 | 1.67 (0.26) | 3.79 (0.01) | 0.26 |
| 8 | 287.3 (1.56) | 0.52 | 4.93 (0.26) | 5.27 | 4.09 (0.02) | 0.80 | 1.23 (0.03) | 3.77 (0.01) | 0.26 |
| 9 | 295.7 (1.22) | 0.41 | 5.44 (0.80) | 14.70 | 4.47 (0.03) | 1.04 | 0.44 (0.04) | 3.69 (0.04) | 1.08 |

[a] = Disintegration time

friability as can be seen from Table 6.

Tablet thickness are also shown in Table 6. Mean values and standard deviation are given together with percent coefficient of variation. It was abserved that only formula 1 and 9 obtained percent coefficient of variation slightly higher than 1.0 %.

**3. Physical Properties of Powdered Sugar-Tapioca Starch-Gelatin Granules.**

**3.1 Particle Size Distribution**

The particle size distribution of the granules are shown in Table 7. The results indicated that the granule formulation which contained high proportion of tapioca starch content gave higher amount of fine granules than those formula which contained high proportion of sugar. As it has been seen in the table, 27.2 % of formula 1 and 36.73 % of formula 2 passed through seive size of 75 $\mu$m.

**3.2 Density and Percent Compressibility**

Bulk, tap, and true density of the sugar-starch-gelatin granules are given in Table 8. Formula 8 shows a greater bulk density (0.54 g/ml) and tap density (0.71 g/ml). Tendency of increase in bulk and tap density of the granules with the higher proportion of sugar in the formula was observed. The true density of granules in all formula were similar, ranging from 1.45-1.58 g/ml.

Table 7 Particle Size Distribution of Sugar-Starch-Gelatin Granules

| | % Retained on Sieve Size (μm) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Formula | 250 | 180 | 150 | 125 | 106 | 90 | 75 | PAN |
| 1 | 3.84 | 4.76 | 6.68 | 13.66 | 10.41 | 18.59 | 14.86 | 27.20 |
| 2 | 6.60 | 4.71 | 6.22 | 11.14 | 12.36 | 10.83 | 11.41 | 36.73 |
| 3 | 7.66 | 6.83 | 7.46 | 12.78 | 18.23 | 31.91 | 13.47 | 1.66 |
| 4 | 3.34 | 7.67 | 8.17 | 13.54 | 14.10 | 8.66 | 44.52 | - |
| 5 | 5.91 | 12.16 | 13.33 | 14.94 | 11.38 | 22.80 | 19.48 | - |
| 6 | 4.32 | 12.66 | 12.40 | 11.73 | 12.57 | 22.60 | 23.72 | - |
| 7 | 5.47 | 11.75 | 9.81 | 10.41 | 10.71 | 22.25 | 29.60 | - |
| 8 | 7.04 | 14.63 | 13.35 | 11.96 | 14.43 | 15.87 | 22.72 | - |
| 9 | 8.04 | 17.21 | 17.51 | 13.04 | 13.13 | 16.42 | 14.65 | - |

The composition of sugar and starch in each formula are the same as in Table 2.

Table 8 Density, % Compressibility, Moisture Content, and Flowability of Sugar-Starch-Gelatin Granules

| Formula | Density (g/ml) Bulk | Tap | True | Compressibility (%) | Moisture Content (%) | Flowability Rate (g/sec) | $r^2$ |
|---|---|---|---|---|---|---|---|
| 1 | 0.33 (0.00) | 0.49 (0.00) | 1.45 (0.01) | 32.6 (0.6) | 6.9 (0.3) | - | - |
| 2 | 0.39 (0.00) | 0.58 (0.00) | 1.55 (0.30) | 32.7 (0.0) | 6.5 (0.5) | - | - |
| 3 | 0.44 (0.00) | 0.65 (0.00) | 1.54 (0.02) | 32.3 (0.5) | 5.6 (0.3) | - | - |
| 4 | 0.46 (0.00) | 0.67 (0.00) | 1.53 (0.02) | 31.3 (0.0) | 5.7 (0.1) | - | - |
| 5 | 0.40 (0.00) | 0.59 (0.02) | 1.55 (0.02) | 32.2 (1.6) | 3.8 (0.2) | - | - |
| 6 | 0.43 (0.00) | 0.61 (0.00) | 1.57 (0.01) | 29.5 (0.0) | 3.6 (0.1) | - | - |
| 7 | 0.49 (0.00) | 0.68 (0.00) | 1.55 (0.02) | 27.9 (0.3) | 3.1 (0.5) | - | - |
| 8 | 0.54 (0.00) | 0.71 (0.00) | 1.57 (0.02) | 23.9 (0.9) | 1.9 (0.4) | - | - |
| 9 | 0.49 (0.00) | 0.62 (0.00) | 1.58 (0.06) | 20.9 (0.4) | 1.1 (0.2) | 7.5 (0.15) | 0.999 |

Means of three determinations with standard deviation in parentheses.

The flow rate of granules from formula 1-8 could not be measured.

$r^2$ = Correlation coefficient

Percent compressibility values seemed to decrease when high concentration of sugar incorporated in the granule formulations.

### 3.3 Moisture Content

The results of moisture content are presented in Table 8. It was found that percent moisture content in the granules proportionally increaed with increasing in the amount of the starch. Granules of formula 1 showed the highest percentage of moisture content (6.9 %), while granules from formula 9 had the lowest moisture content (1.1 %).

### 3.4 Flowability

As it is shown in Table 8, only the flow rate of granules from formula 9 could be measured. It could be seen from the data that the granules in formula 9 is characterized as good flowability (The correlation coefficient , $r^2$, > 0.99). The experimental data of flowability are shown in Appendix D.

### 3.5 Compressional Force-Hardness Profile

The hardness of sugar-starch-gelatin compacts after compressed at different compressional forces are given in Table 9 and Figure 9. As expected, the hardness of compacts increased with increasing the compressional forces, but the lower trend of increase in hardness than

Table 9 Relationship between Compressional Forces and Hardness of Compacts Prepared from Sugar-Starch-Gelatin Granules

| | Hardness (Kp) | | | |
|---|---|---|---|---|
| | Compressional Forces (lbs) | | | |
| Formula | 1000 | 1200 | 1400 | 1600 |
| 1 | 4.87 (0.39) | 6.68 (1.51) | 7.41 (1.03) | 8.87 (1.18) |
| 2 | 6.70 (0.57) | 8.98 (0.53) | 10.47 (0.92) | 11.51 (0.85) |
| 3 | 7.76 (1.05) | 10.02 (0.32) | 8.83 (0.54) | 13.52 (1.40) |
| 4 | 7.70 (0.65) | 10.70 (0.95) | 9.41 (1.57) | 15.15 (2.13) |
| 5 | 8.48 (0.45) | 13.40 (0.37) | 16.50 (0.78) | 19.35 (0.39) |
| 6 | 5.11 (0.53) | 7.18 (1.01) | 7.28 (0.94) | 10.38 (0.97) |
| 7 | 7.37 (0.36) | 10.18 (0.53) | 10.17 (1.19) | 13.11 (0.99) |
| 8 | 5.37 (0.61) | 6.97 (0.49) | 7.71 (0.42) | 9.27 (0.30) |
| 9 | 6.48 (0.33) | 7.83 (0.50) | 7.31 (0.35) | 8.63 (0.85) |

Means of four determinations with standard deviation in parentheses.

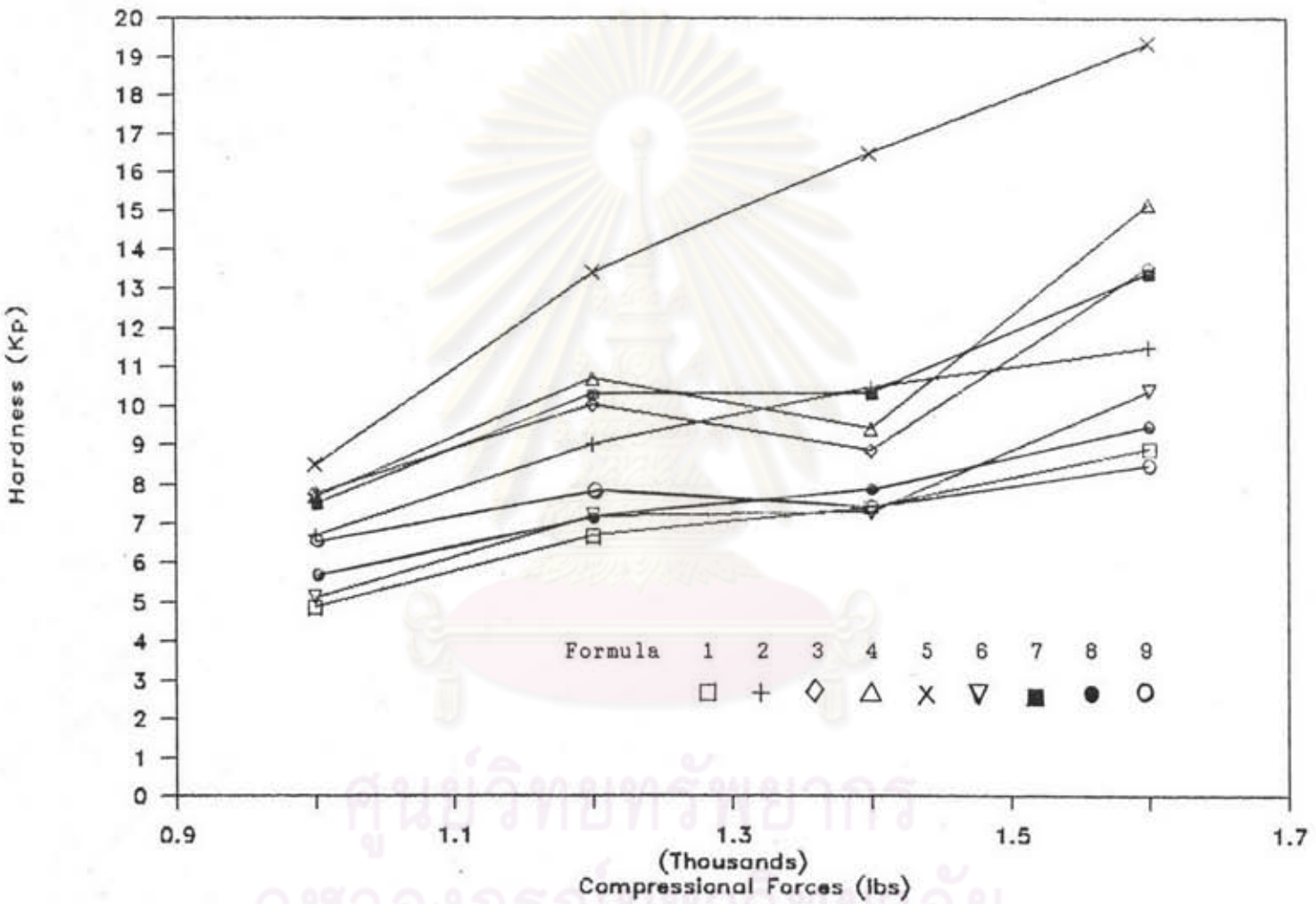


Figure 9 Compressional Force-Hardness Profiles of Compacts Prepared from Sugar-Starch-Gelatin Granules

those of sugar-starch-PVP granules were found.

### 3.6 Compressional Forces-Disintegration Profile

The relationships between compressional force and disintegration time of sugar-starch-gelatin compacts are shown in Table 10 and Figure 10. In general, disintegration time of compacts were not substantially changed with compressional force, i.e. , disintegrated within 3-5 minutes. However, the formula 1, 2 and 3 which had higher proportion of tapioca starch appeared to give fluctuation of disintegration time in comparing with those contain lower content of tapioca starch.

### 3.7 Tabletting Properties of Powdered Sugar-Tapioca Starch-Gelatin Granules

Table 11 presents weight variation, hardness, disintegration time, friability, and thickness of the tablets. Tablets of 300 mg were compressed to the hardness about 4 Kp. As can be seen from the data, weight variation of the tablets prepared from all granule formulations met the requirement of USP standard.

Hardness of the tablets produced ranged from 3.73 to 5.68 Kp and tablets disintegrated within less than 4 minutes in all granule formulations. The coefficient of variations of tablet hardness and tablet disintegration time are also shown in Table 11.

It was apparent that friability of sugar-

Table 10 Relationship between Compressional Forces and Disintegration Time of Compacts Prepared from Sugar-Starch-Gelatin Granules

| | Disintegration Time (min) | | | |
|---|---|---|---|---|
| | Compressional Forces (lbs) | | | |
| Formula | 1000 | 1200 | 1400 | 1600 |
| 1 | 3.08 (0.70) | 3.82 (1.33) | 4.56 (0.95) | 3.47 (0.95) |
| 2 | 5.32 (2.92) | 3.96 (2.40) | 5.25 (2.83) | 4.21 (0.48) |
| 3 | 3.54 (0.17) | 4.71 (2.84) | 4.07 (0.48) | 3.91 (0.60) |
| 4 | 3.04 (0.29) | 3.19 (0.40) | 3.29 (0.14) | 3.56 (0.62) |
| 5 | 3.22 (0.17) | 3.40 (0.07) | 3.71 (0.17) | 3.52 (0.04) |
| 6 | 2.90 (0.07) | 3.06 (0.13) | 3.31 (0.15) | 3.06 (0.28) |
| 7 | 3.03 (0.12) | 3.17 (0.13) | 3.15 (0.12) | 3.27 (0.10) |
| 8 | 3.11 (0.92) | 3.09 (0.06) | 3.61 (0.11) | 3.46 (0.06) |
| 9 | 2.91 (0.18) | 3.17 (0.07) | 3.25 (0.04) | 3.39 (0.06) |

Means of six determinations with standard deviation in parentheses.

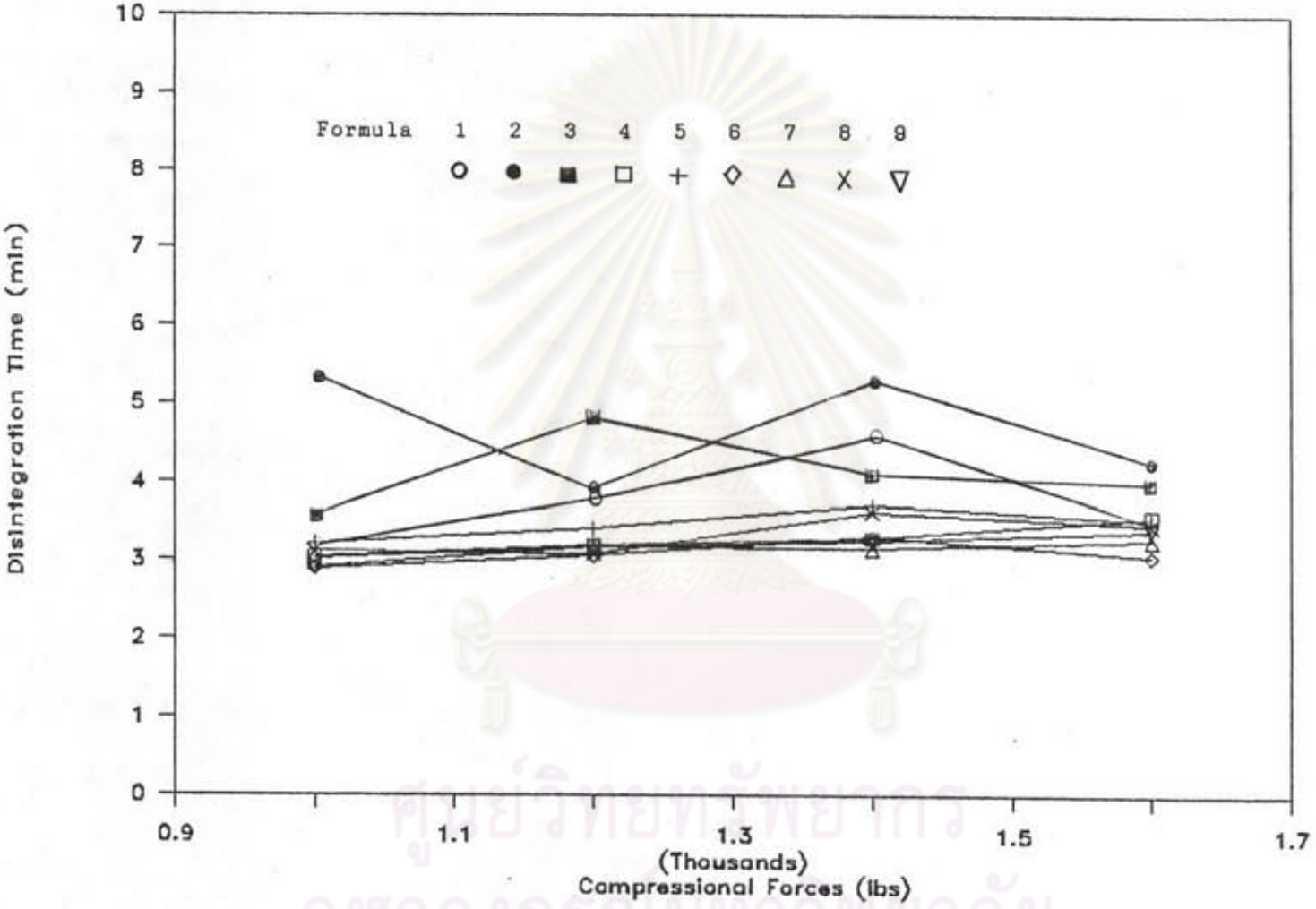


Figure 10 Compressional Force-Disintegration Profiles of Compacts Prepared from Sugar-Starch-Gelatin Granules

Table 11 Tabletting Properties of Sugar-Starch-Gelatin Granules

| Formula | Weight Variation (mg) Mean (S.D.) | % C.V. | Hardness (Kp) Mean (S.D.) | % C.V. | D.T.[a] (min) Mean (S.D.) | % C.V. | Friability % Mean (S.D.) | Thickness (mm) Mean (S.D.) | % C.V. |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 284.1 (1.47) | 0.51 | 4.32 (0.38) | 8.79 | 6.01 (1.71) | 28.51 | 0.27 (0.03) | 3.87 (0.01) | 0.25 |
| 2 | 299.4 (1.61) | 0.53 | 4.08 (0.45) | 11.03 | 3.36 (0.35) | 10.51 | 0.94 (0.06) | 4.07 (0.01) | 0.25 |
| 3 | 298.5 (1.84) | 0.61 | 3.73 (0.35) | 9.38 | 3.24 (0.24) | 7.60 | 1.10 (0.08) | 3.97 (0.01) | 0.25 |
| 4 | 296.7 (2.58) | 0.86 | 3.65 (0.71) | 19.45 | 3.45 (0.09) | 2.65 | 1.62 (0.08) | 3.96 (0.01) | 0.25 |
| 5 | 297.1 (2.50) | 0.84 | 3.90 (0.24) | 6.15 | 2.96 (0.03) | 1.12 | 2.02 (0.06) | 3.97 (0.01) | 0.25 |
| 6 | 304.7 (2.01) | 0.65 | 4.90 (0.38) | 7.75 | 3.58 (0.08) | 2.27 | 1.78 (0.05) | 3.98 (0.01) | 0.25 |
| 7 | 298.7 (3.88) | 1.29 | 4.67 (0.40) | 8.56 | 3.41 (0.11) | 3.32 | 2.00 (0.16) | 3.87 (0.01) | 0.25 |
| 8 | 297.7 (1.38) | 0.46 | 5.10 (0.36) | 7.05 | 3.65 (0.04) | 1.32 | 2.20 (0.03) | 3.75 (0.01) | 0.26 |
| 9 | 301.4 (2.14) | 0.71 | 5.68 (0.38) | 6.69 | 3.84 (0.14) | 3.68 | 2.30 (0.14) | 3.75 (0.01) | 0.26 |

[a] = Disintegration time

starch-gelatin granule tablets increased with increasing the amount of sugar in the granule. A maximum value is 2.30 % for formula 9.

The thickness of tablets were expressed in mean, standard deviation, and percent coefficient of variation. As can be seen, the variation in tablet thickness were relatively low in all nine granule formula.

**4. Physical Properties of Powdered Sugar-Tapioca Starch Methylcellulose Granules**

**4.1 Particle Size Distribution**

The sugar-starch granules prepared using methylcellulose as a binder exhibited wide particle size distribution in comparing with the granules using PVP or gelatin as binders (Table 12).

**4.2 Density and Percent Compressibility**

Table 13 shows bulk, tap, and true density and percent compressibility of sugar-starch-methylcellulose granules. Sugar-starch-methylcellulose granules of all formula appeared to possess higher bulk and tap density than those of sugar-starch-PVP and sugar-starch-gelatin granules. It is appeared that the true density of granules were similar among nine granule formulations.

Table 12 Particle Size Distribution of Sugar-Starch-Methylcellulose Granules

| | % Retained on Seive Size (µm) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Formula | 250 | 180 | 150 | 125 | 106 | 90 | 75 | PAN |
| 1 | 1.04 | 3.63 | 91.15 | 4.18 | - | - | - | - |
| 2 | 2.66 | 5.89 | 12.05 | 22.27 | 10.27 | 42.77 | 4.09 | - |
| 3 | 2.85 | 7.37 | 10.28 | 13.41 | 15.24 | 20.77 | 30.08 | - |
| 4 | 8.96 | 12.99 | 12.69 | 11.31 | 13.61 | 11.00 | 17.88 | 11.56 |
| 5 | 15.39 | 22.70 | 20.04 | 11.48 | 12.04 | 10.42 | 7.93 | - |
| 6 | 4.57 | 11.25 | 11.44 | 17.05 | 35.27 | 9.12 | 11.30 | - |
| 7 | 9.32 | 14.73 | 14.69 | 14.02 | 16.59 | 8.20 | 14.60 | 7.85 |
| 8 | 4.63 | 12.70 | 14.03 | 14.44 | 18.66 | 17.00 | 18.54 | - |
| 9 | 23.04 | 20.93 | 16.50 | 10.84 | 11.05 | 10.24 | 7.40 | - |

The composition of sugar and starch in each formula are the same as in Table 2.

Table 13 Density, % Compressibility, Moisture Content, and Flowability of Sugar-Starch-Methylcellulose Granules

| Formula | Density (g/ml) Bulk | Tap | True | Compressibility (%) | Moisture Content (%) | Flowability Rate (g/sec) | $r^2$ |
|---|---|---|---|---|---|---|---|
| 1 | 0.47 (0.00) | 0.71 (0.00) | 1.48 (0.01) | 33.8 (0.0) | 6.3 (0.7) | - | - |
| 2 | 0.49 (0.00) | 0.70 (0.00) | 1.50 (0.01) | 30.0 (0.0) | 6.2 (0.2) | - | - |
| 3 | 0.47 (0.01) | 0.65 (0.00) | 1.52 (0.01) | 27.6 (1.0) | 5.6 (0.3) | - | - |
| 4 | 0.48 (0.00) | 0.62 (0.00) | 1.49 (0.01) | 22.5 (0.0) | 4.6 (0.2) | 7.8 (0.42) | 0.999 |
| 5 | 0.45 (0.00) | 0.55 (0.00) | 1.51 (0.01) | 18.1 (0.0) | 3.8 (0.2) | 8.8 (0.39) | 0.999 |
| 6 | 0.56 (0.00) | 0.73 (0.00) | 1.53 (0.00) | 23.2 (0.3) | 3.1 (0.1) | - | - |
| 7 | 0.59 (0.00) | 0.74 (0.00) | 1.54 (0.00) | 20.2 (0.0) | 2.6 (0.1) | 6.1 (0.30) | 0.998 |
| 8 | 0.60 (0.00) | 0.80 (0.00) | 1.52 (0.00) | 25.0 (0.3) | 1.8 (0.1) | - | - |
| 9 | 0.58 (0.00) | 0.69 (0.00) | 1.56 (0.00) | 15.9 (0.3) | 1.0 (0.0) | 12.1 (0.67) | 0.999 |

Means of three determinations with standard deviation in parentheses.

The flow rate of granules from formula 1-3,6,8 could not be measured.

$r^2$ = Correlation coefficient

### 4.3 Moisture Content

Percent moisture content of sugar-starch-methylcellulose granules are given in Table 13. The percent moisture content decreased in relation to the decrease of amount of the tapioca starch in the granule formulations. The values were within the range of 1-6.3 %.

### 4.4 Flowability

Flowability test of formula 1-3, 6, 8 were unsuccessful. Only the flow rate of formula 4, 5, 7 and 9 could be determined as shown in Table 13 which are characterized as good flowability (the correlation coefficient , $r^2 > 0.99$). The experimental data are shown in Appendix E.

### 4.5 Compressional Force-Hardness Profile

It was observed that under the conditions in this study, compacts prepared from sugar-starch-methylcellulose granules were softer than those prepared using sugar-starch-PVP and sugar-starch-gelatin granules (Table 14 and Figure 11). At the compressional force of 1000 lbs, the compacts made from granules of formula 2-4 were too soft to be measured by the hardness tester.

### 4.6 Compressional Force-Disintegration Profile

Table 15 and Figure 12 show the relationships between compressional force and disintegration time of compacts prepared from sugar-starch-methylcellulose

Table 14 Relationship between Compressional Forces and Hardness of Compacts Prepared from Sugar-Starch-Methylcellulose Granules

| Formula | Hardness (Kp) Compressional Forces (lbs) 1000 | 1500 | 2000 | 2500 |
|---|---|---|---|---|
| 1 | 2.11 (0.07) | 4.58 (0.26) | 5.57 (0.10) | 7.05 (0.29) |
| 2 | - - | 3.45 (0.43) | 5.23 (0.37) | 6.18 (0.42) |
| 3 | - - | 2.32 (0.36) | 5.71 (1.57) | 7.32 (0.34) |
| 4 | - - | 4.76 (0.45) | 7.91 (0.27) | 8.68 (0.50) |
| 5 | 3.95 (0.41) | 5.72 (0.50) | 8.83 (0.56) | 11.45 (0.53) |
| 6 | 3.66 (0.61) | 6.53 (0.29) | 8.86 (0.30) | 11.85 (0.81) |
| 7 | 4.06 (0.57) | 6.45 (0.29) | 8.35 (0.23) | 10.48 (0.64) |
| 8 | 3.08 (0.67) | 5.82 (0.86) | 11.83 (0.44) | 13.05 (0.69) |
| 9 | 4.97 (0.21) | 7.77 (0.70) | 11.93 (1.09) | 14.42 (0.38) |

Means of four determinations with standard deviation in parentheses.

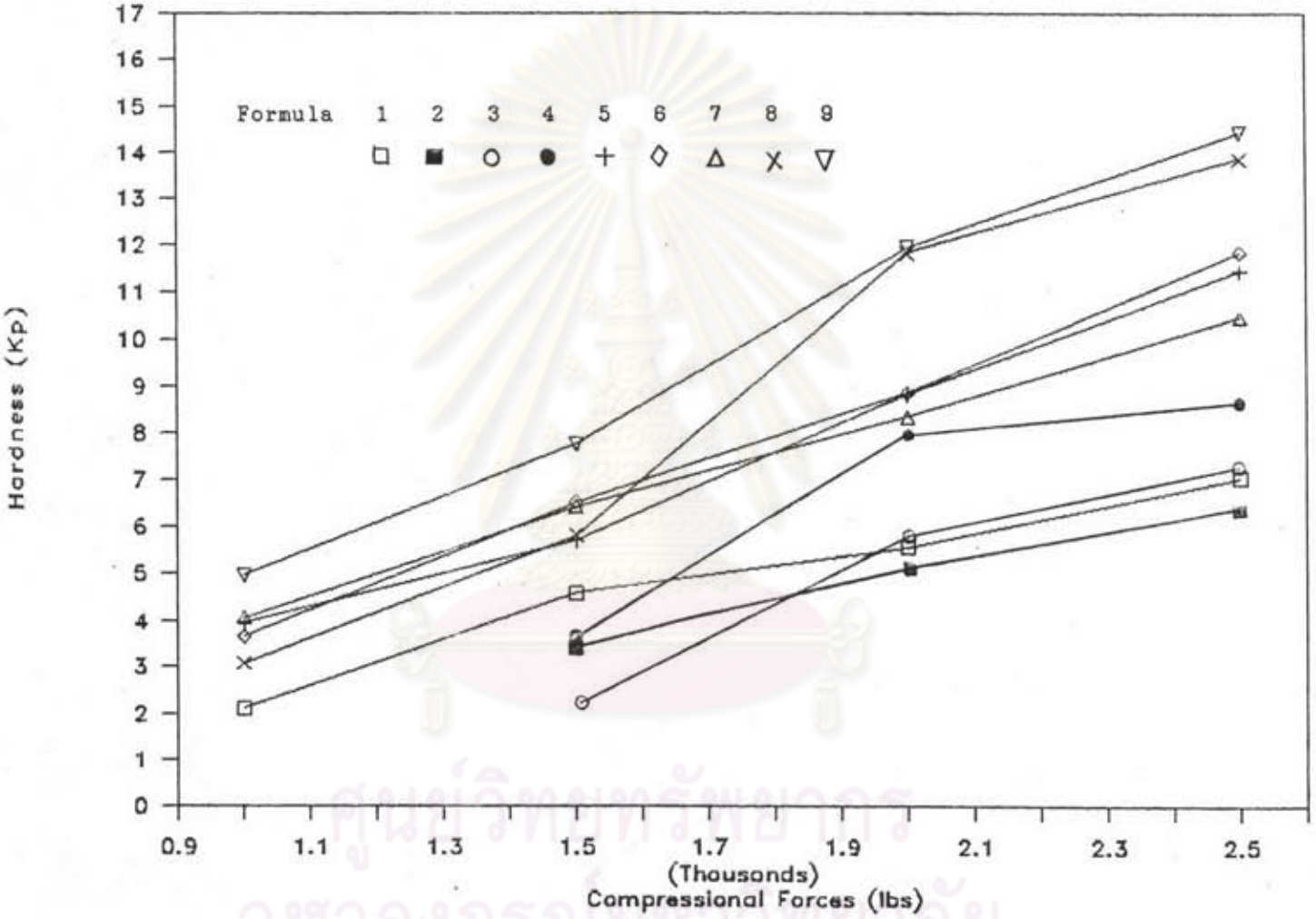


Figure 11 Compressional Force-Hardness Profiles of Compacts Prepared from Sugar-Starch-Methylcellulose Granules

Table 15 Relationship between Compressional Forces and Disintegration Time of Compacts Prepared from Sugar-Starch-Methylcellulose Granules

| | Disintegration Time (min) | | | |
|---|---|---|---|---|
| | Compressional Forces (lbs) | | | |
| Formula | 1000 | 1500 | 2000 | 2500 |
| 1 | 9.81 (1.07) | 12.36 (1.72) | 16.39 (1.10) | 15.92 (1.09) |
| 2 | 6.54 (0.55) | 12.97 (3.22) | 16.41 (2.52) | 12.67 (2.38) |
| 3 | 6.43 (0.83) | 9.66 (1.71) | 22.11 (0.97) | 16.71 (3.46) |
| 4 | 12.40 (2.90) | 15.50 (4.32) | 18.13 (3.67) | 18.03 (4.33) |
| 5 | 11.66 (2.02) | 12.67 (2.60) | 16.44 (5.23) | 16.48 (5.65) |
| 6 | 11.30 (2.41) | 8.89 (1.81) | 13.73 (4.60) | 13.67 (4.29) |
| 7 | 9.40 (4.69) | 8.52 (2.70) | 14.21 (5.03) | 13.80 (6.22) |
| 8 | 11.94 (4.28) | 11.37 (3.28) | 10.48 (2.49) | 13.28 (2.98) |
| 9 | 6.90 (2.03) | 6.60 (1.30) | 9.40 (2.99) | 11.00 (3.39) |

Means of six determinations with standard deviation in parentheses.

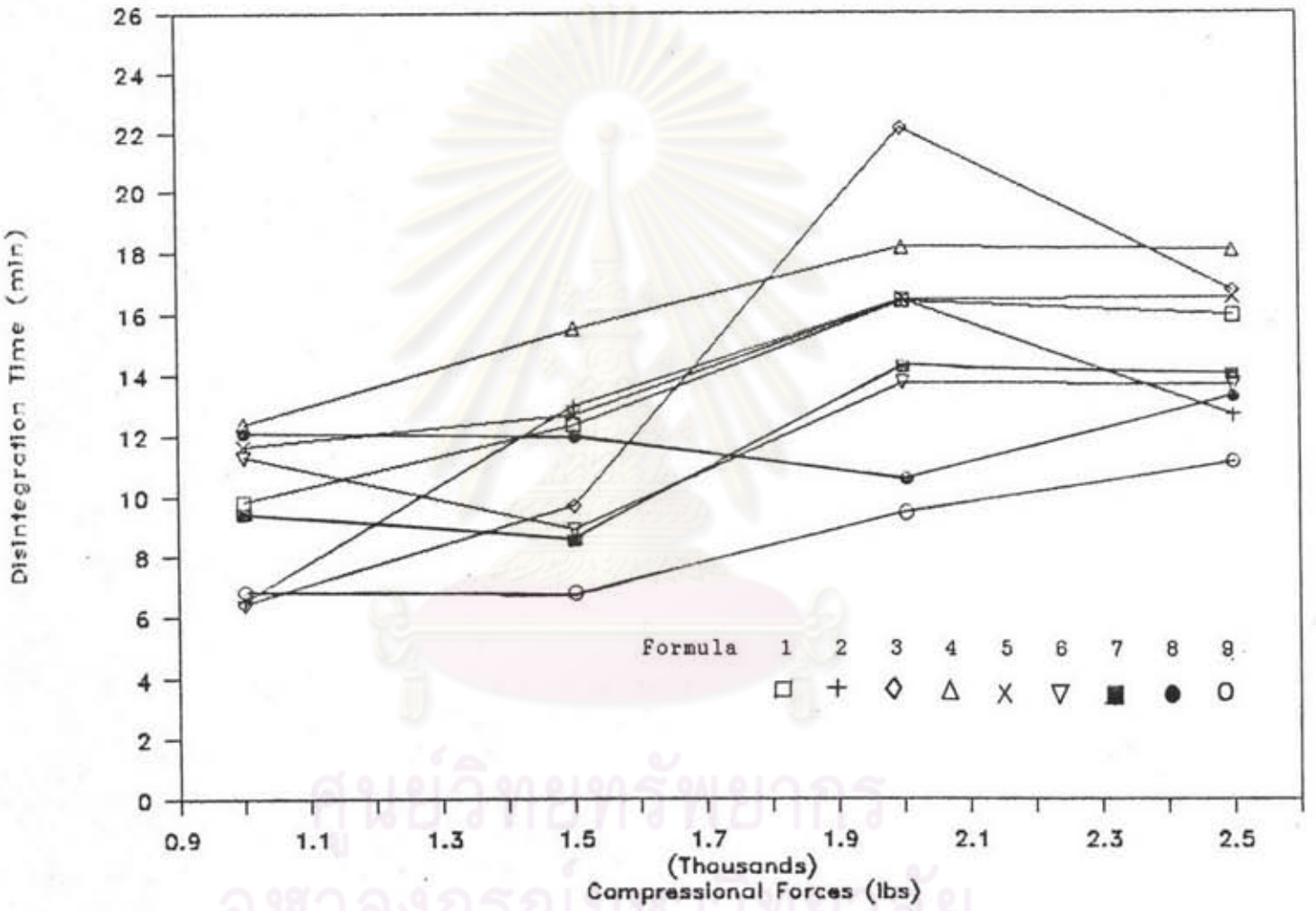


Figure 12 Compressional Force-Disintegration Profiles of Compacts Prepared from Sugar-Starch-Methylcellulose Granules

granules. The results indicate that disintegration time of the compacts were longer than those of the compacts made from sugar-starch-PVP and sugar-starch-gelatin granules at the same level of compressional forces.

**4.7 Tabletting Properties of Powdered Sugar-Tapioca Starch-Methylcellulose Granules**

Table 16 shows weight variation, hardness, disintegration time, friability and thickness of the tablets prepared from sugar-starch-methylcellulose granules. All granule formulations gave low coefficient of variation in tablet weight and were within the USP requirement even if the formula 2, 3, 6, 8 showed unsatisfactory flowabilily when they were subjected to the flowability test.

Values of mean, standard deviation and percent coefficient of variation of tablet hardness are also shown in the Table 16. The variation of tablet hardness among nine formula were different ranging from 3.69 to 25.52 % and no relationship was observed.

Disintegration time of tablets prepared by sugar-starch-methylcellulose granules were longer than those of sugar-starch-PVP and sugar-starch-gelatin granules when compressed to the same hardness level. The data also show that the tablets from formula 9 gave lowest percent coefficient of variation of disintegration time

Table 16 Tabletting Properties of Sugar-Starch-Methylcellulose Granules

| Formula | Weight Variation (mg) Mean (S.D.) | % C.V. | Hardness (Kp) Mean (S.D.) | % C.V. | D.T.[a] (min) Mean (S.D.) | % C.V. | Friability % Mean (S.D.) | Thickness (mm) Mean (S.D.) | % C.V. |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 300.0 (2.81) | 0.94 | 2.33 (0.30) | 12.87 | 8.35 (0.36) | 4.23 | 1.50 (0.19) | 3.76 (0.03) | 0.79 |
| 2 | 294.5 (1.42) | 0.48 | 3.91 (0.32) | 8.18 | 11.55 (1.32) | 11.08 | 1.23 (0.16) | 3.67 (0.01) | 0.27 |
| 3 | 295.9 (2.26) | 0.76 | 4.00 (0.44) | 11.00 | 12.10 (3.25) | 26.76 | 1.42 (0.05) | 3.69 (0.02) | 0.54 |
| 4 | 302.3 (1.24) | 0.41 | 4.49 (0.24) | 5.34 | 12.50 (2.29) | 17.84 | 1.44 (0.08) | 3.74 (0.01) | 0.26 |
| 5 | 303.3 (0.93) | 0.31 | 4.19 (0.32) | 7.63 | 11.07 (1.30) | 11.73 | 1.56 (0.06) | 3.77 (0.01) | 0.26 |
| 6 | 297.1 (1.92) | 0.64 | 3.62 (0.50) | 13.81 | 10.39 (0.86) | 8.07 | 2.19 (0.11) | 3.70 (0.01) | 0.26 |
| 7 | 299.9 (2.29) | 0.76 | 3.33 (0.85) | 25.52 | 9.28 (0.64) | 6.81 | 2.33 (0.16) | 3.70 (0.01) | 0.26 |
| 8 | 297.2 (1.14) | 0.38 | 3.86 (0.76) | 19.69 | 10.48 (1.32) | 12.23 | 2.88 (0.15) | 3.70 (0.01) | 0.26 |
| 9 | 306.5 (0.92) | 0.30 | 4.79 (0.19) | 3.69 | 9.18 (0.08) | 0.86 | 2.71 (0.24) | 3.73 (0.01) | 0.26 |

[a] = Disintegration time

among nine formula.

Friability of tablets prepared from sugar-starch-methylcellulose granules appeared to increase with increasing the amount of the sugar in the formula. Friability of the tablets were higher than 2 % when the composition of sugar in formula larger than 50 % (formula 5).

Values of mean, standard deviation and percent coefficient of variation of tablet thickness are shown in Table 16. It is appeared that the variation of tablet thickness were not excess 1.0 % in all nine formula.

**5. Physical Properties of Powdered Sugar-Tapica Starch-Tapioca Starch (Binder) Granules.**

**5.1 Particle Size Distribution**

Table 17 presents particle size distribution of sugar-starch-granules using tapioca starch as a binder. It is apparent from the data that the larger granule sizes were obtained when granule contained high proportion of sugar. High percentage of larger granules collected on large seive size in all formula as compared with sugar-starch-PVP, sugar-starch-gelatin, and sugar-starch-methylcellulose granules.

**5.2 Density and Percent Compressibility**

Bulk, tap, and true density and percent

Table 17 Particle Size Distribution of Sugar-Starch-Starch Granules

| Formula | % Retained on Seive Size (µm) | | | | | |
|---|---|---|---|---|---|---|
| | 425 | 250 | 180 | 150 | 125 | 106 |
| 1 | 5.88 | 23.57 | 27.01 | 21.62 | 21.92 | - |
| 2 | 10.03 | 18.19 | 21.83 | 39.94 | 10.01 | - |
| 3 | 19.05 | 30.79 | 21.71 | 13.76 | 12.61 | 2.08 |
| 4 | 30.83 | 24.00 | 20.99 | 20.71 | 3.47 | - |
| 5 | 22.24 | 42.52 | 24.44 | 7.32 | 3.48 | - |
| 6 | 64.85 | 28.47 | 4.96 | 1.72 | - | - |
| 7 | 35.44 | 38.78 | 15.58 | 5.61 | 1.73 | 2.86 |
| 8 | 25.37 | 49.56 | 16.71 | 4.15 | 1.60 | 2.61 |
| 9 | 50.34 | 38.07 | 8.85 | 1.02 | 1.72 | - |

The copmposition of sugar and starch in each formula are the same as in Table 2.

Table 18 Density, % Compressibility, Moisture Content, and Flowability of Sugar-Starch-Starch Granules

| Formula | Density (g/ml) Bulk | Tap | True | Compressibility (%) | Moisture Content (%) | Flowability Rate (g/sec) | $r^2$ |
|---|---|---|---|---|---|---|---|
| 1 | 0.39 (0.00) | 0.51 (0.00) | 1.49 (0.01) | 23.5 (1.0) | 6.5 (0.1) | 6.3 (0.33) | 0.999 |
| 2 | 0.40 (0.00) | 0.54 (0.00) | 1.50 (0.02) | 25.9 (0.0) | 6.3 (0.0) | - | - |
| 3 | 0.45 (0.00) | 0.57 (0.00) | 1.46 (0.03) | 21.1 (1.0) | 5.1 (0.1) | 8.6 (0.49) | 0.999 |
| 4 | 0.58 (0.00) | 0.76 (0.00) | 1.45 (0.02) | 23.7 (0.3) | 4.7 (0.1) | - | - |
| 5 | 0.40 (0.00) | 0.52 (0.01) | 1.48 (0.03) | 23.1 (1.3) | 3.2 (0.0) | 10.0 (0.44) | 0.999 |
| 6 | 0.48 (0.00) | 0.58 (0.00) | 1.49 (0.01) | 17.2 (0.6) | 3.2 (0.1) | 10.1 (0.48) | 0.999 |
| 7 | 0.49 (0.00) | 0.59 (0.00) | 1.52 (0.00) | 16.9 (0.3) | 2.9 (0.1) | 11.1 (0.54) | 0.998 |
| 8 | 0.46 (0.00) | 0.57 (0.00) | 1.52 (0.01) | 19.3 (0.2) | 1.9 (0.0) | 10.0 (0.28) | 0.999 |
| 9 | 0.47 (0.01) | 0.56 (0.00) | 1.46 (0.06) | 16.1 (0.6) | 1.3 (0.1) | 10.4 (0.64) | 0.997 |

Means of three determinations with standard deviation in parentheses.

The flow rate of granules from formula 2,4 could not be measured.

$r^2$ = Correlation coefficient

compressibility are given in Table 18. Tendency of low percent compressibility values of sugar-starch-starch granules was obtained where sugar content in granule increased. True density, however, do appear similar for all nine formula.

### 5.3 Moisture Content

The percent moisture content of the granules were related to the amount of starch in the same manner as described before. This mean that the moisture content of the granules increased with increasing the proportion of starch in the formula.

### 5.4 Flowability

Flow rate of formula 2 and 4 could not be measured due to the granules had tendency to blockage the orifice of flowmeter during the test. It appeared from the data that flow rate of the granules contained high amount of sugar gave better flow rate than those of sugar-tapioca-PVP, sugar-starch-gelatin, and sugar-starch-methylcellulose granules. In addition, formula 1, 3, 5 to 9 are characterized as good flowability (The correlation coefficient, $r^2$, > 0.99). The experimental data are presented in Appendix F.

### 5.5 Compressional Force-Hardness Profile

Table 19 and Figure 13 show the compressional

Table 19 Relationship beteen Compressional Forces and Hardness of Compacts Prepared from Sugar-Starch-Starch Granules

| | Hardness (Kp) | | | |
|---|---|---|---|---|
| | Compressional Forces (lbs) | | | |
| Formula | 1000 | 1400 | 2000 | 2500 |
| 1 | 5.00 (1.11) | 8.43 (0.20) | 11.82 (0.21) | 14.37 (0.92) |
| 2 | 1.95 (0.41) | 6.57 (0.53) | 9.08 (0.28) | 11.47 (0.38) |
| 3 | 4.75 (0.40) | 7.52 (0.32) | 6.88 (0.40) | 12.52 (0.96) |
| 4 | 2.37 (0.24) | 6.91 (0.12) | 8.28 (0.71) | 12.65 (0.99) |
| 5 | 4.77 (0.10) | 9.32 (0.14) | 9.75 (0.08) | 14.63 (0.22) |
| 6 | 3.75 (0.59) | 7.66 (0.21) | 7.93 (0.56) | 12.96 (0.59) |
| 7 | 4.02 (0.10) | 7.17 (0.34) | 8.25 (0.66) | 13.20 (0.52) |
| 8 | 3.56 (0.27) | 5.86 (0.09) | 10.95 (1.60) | 11.83 (2.21) |
| 9 | 3.58 (0.34) | 5.81 (0.43) | 8.86 (0.61) | 14.58 (0.94) |

Means of four determinations with standard deviation in parentheses.

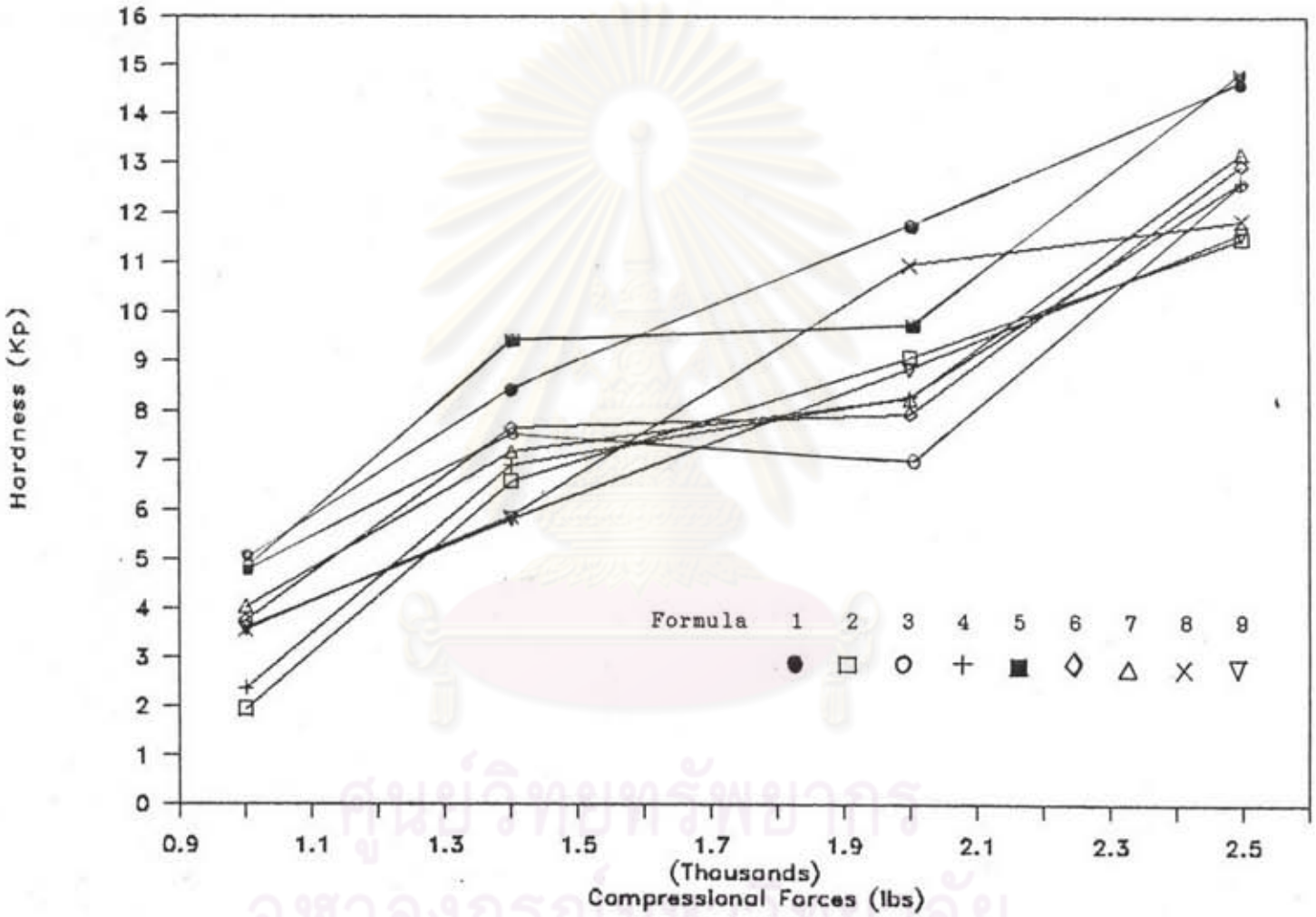


Figure 13 Compressional Force-Hardness Profiles of Compacts Prepared from Sugar-Starch-Starch Granules

characteristics of sugar-starch-starch granules. It was seen that the effect of compressional forces on tablet hardness was as expected, it was increased with increasing compressional forces.

### 5.6 Compressional Force-Disintegration Profile

The relationship between compressional force and disintegration time are shown in Table 20 and Figure 14. Disintegration time of the compacts was longer than those of the compacts prepared from sugar-starch-PVP and sugar-starch-gelatin granules especially when high amount of starch incorporated into the granules. Tablets from all granule formulations exhibited disintegration time between 10-20 minutes except tablets from formula 8 and 9 disintegrated within less than 10 minutes.

### 5.7 Tabletting Properties of Powdered Sugar-Tapioca Starch-Tapioca Starch (Binder) Granules

Table 21 shows weight variation, hardness, disintegration time, friability, and thickness of the tablets prepared by sugar-starch-starch granules. All tablet formulations exhibited low percent coefficient of weight variation within the USP requirement.

The tablets were compressed to hardness about 4 Kp. As can be seen from the data, formula 8 showed the lowest value of variation (3.58 %).

The disintegration time of tablets prepared

Table 20 Relationship between Compressional Forces and Disintegration Time of Compacts Prepared from Sugar-Starch-Starch Granules

| Formula | Disintegration Time (min) | | | |
|---|---|---|---|---|
| | Compressional Forces (lbs) | | | |
| | 1000 | 1500 | 2000 | 2500 |
| 1 | 15.69 (1.54) | 16.46 (1.90) | 19.58 (2.52) | 16.38 (2.14) |
| 2 | 11.63 (0.78) | 11.73 (1.92) | 14.17 (2.28) | 13.81 (3.74) |
| 3 | 18.78 (2.75) | 21.26 (1.95) | 19.38 (1.91) | 19.98 (1.29) |
| 4 | 14.13 (4.06) | 17.86 (5.07) | 20.73 (2.63) | 18.60 (4.47) |
| 5 | 17.30 (3.16) | 20.18 (3.03) | 18.41 (7.53) | 19.41 (5.09) |
| 6 | 13.91 (3.73) | 12.29 (4.17) | 18.53 (4.80) | 20.36 (4.41) |
| 7 | 8.05 (3.79) | 10.34 (4.28) | 9.00 (3.57) | 15.66 (5.54) |
| 8 | 5.21 (0.89) | 7.38 (2.46) | 8.37 (2.01) | 9.05 (2.54) |
| 9 | 6.45 (3.02) | 7.67 (2.48) | 6.41 (0.79) | 6.17 (0.18) |

Means of six determinations with standard deviation in parentheses.

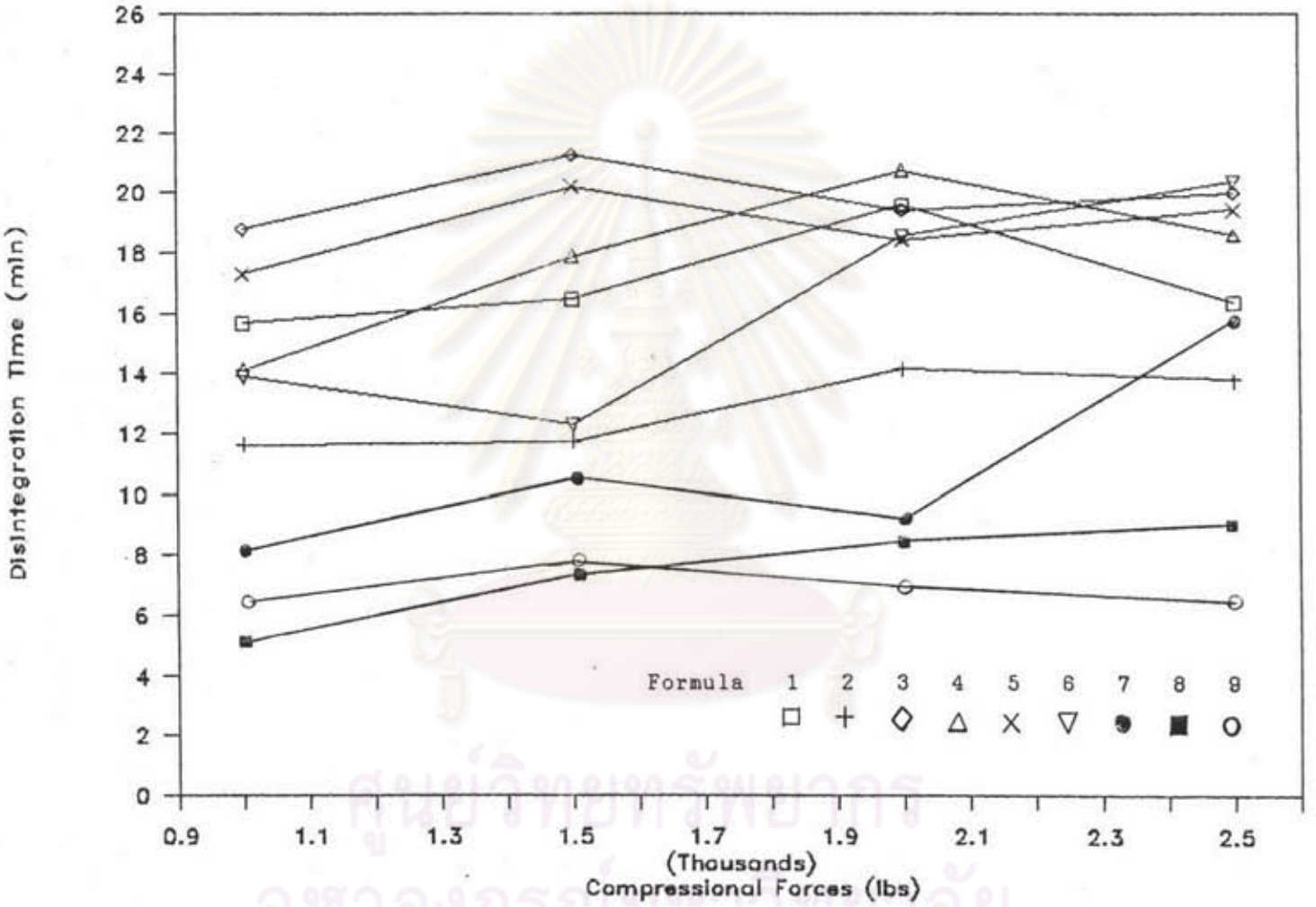


Figure 14 Compressional Force-Disintegration Profiles of Compacts Prepared from Sugar-Starch-Starch Granules

Table 21 Tabletting Properties of Sugar-Starch-Starch Granules

| Formula | Weight Variation (mg) Mean (S.D.) | % C.V. | Hardness (Kp) Mean (S.D.) | % C.V. | D.T.[a] (min) Mean (S.D.) | % C.V. | Friability % Mean (S.D.) | Thickness (mm) Mean (S.D.) | % C.V. |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 311.7 (0.66) | 0.21 | 2.89 (0.54) | 18.68 | 16.18 (0.21) | 1.31 | 0.84 (0.06) | 4.16 (0.01) | 0.24 |
| 2 | 307.8 (1.76) | 0.57 | 3.47 (0.39) | 11.24 | 13.46 (2.11) | 15.37 | 0.64 (0.09) | 4.00 (0.01) | 0.25 |
| 3 | 306.5 (0.94) | 0.31 | 3.96 (0.23) | 5.81 | 25.06 (0.98) | 3.93 | 0.62 (0.07) | 3.95 (0.01) | 0.25 |
| 4 | 291.1 (2.25) | 0.77 | 3.18 (0.48) | 15.09 | 18.00 (2.47) | 13.75 | 1.00 (0.17) | 3.77 (0.01) | 0.26 |
| 5 | 307.1 (0.97) | 0.31 | 3.83 (0.20) | 5.22 | 11.55 (0.95) | 8.01 | 1.40 (0.06) | 3.98 (0.01) | 0.25 |
| 6 | 300.0 (2.14) | 0.71 | 5.17 (0.38) | 7.35 | 8.47 (0.54) | 6.17 | 1.10 (0.10) | 3.80 (0.01) | 0.26 |
| 7 | 305.6 (2.14) | 0.70 | 4.60 (0.31) | 6.74 | 9.34 (1.24) | 12.95 | 1.86 (0.16) | 3.90 (0.01) | 0.25 |
| 8 | 309.3 (1.24) | 0.40 | 5.02 (0.18) | 3.58 | 7.51 (0.49) | 6.30 | 2.00 (0.13) | 3.87 (0.01) | 0.25 |
| 9 | 322.8 (5.56) | 1.72 | 8.63 (1.14) | 13.21 | 7.03 (0.48) | 6.92 | 1.54 (0.11) | 3.90 (0.02) | 0.51 |

[a] = Disintegration time

from sugar-starch-starch granules were faster when the proportion of sugar in granules increased. High variation in tablet disintegration times were observed among nine formula.

It appeared from the data that, tablet friability incrased when high concentration of sugar incorporated in granule formulation. The friability were within the range of 0.6 to 2.0 % as shown in the Table 21.

Values of mean, standard deviation and percent coefficient of variation of tablet thickness are also shown in Table 21. As from the data, very low variation are observed.

It can be concluded from the data in sections 2-5 that the granule formulations of sugar-starch-PVP, sugar-starch-methylcellulose, sugar-starch-gelatin and sugar-starch-starch which gave satisfactory granule and tablet properties are formula number 5, 9, 5 and 8, respectively. These formula were selected to prepare the granules for further physical stability studies. The criteria in selecting these formulations were discussed in Chapter Four.

Electronphotomicrographs of selected granule formula are shown in Figure 15-18. It was seen that the starch grains adhere to the sugar particles to form the granules. More irregular surface and shape of the granules were observed in the formula which contained high

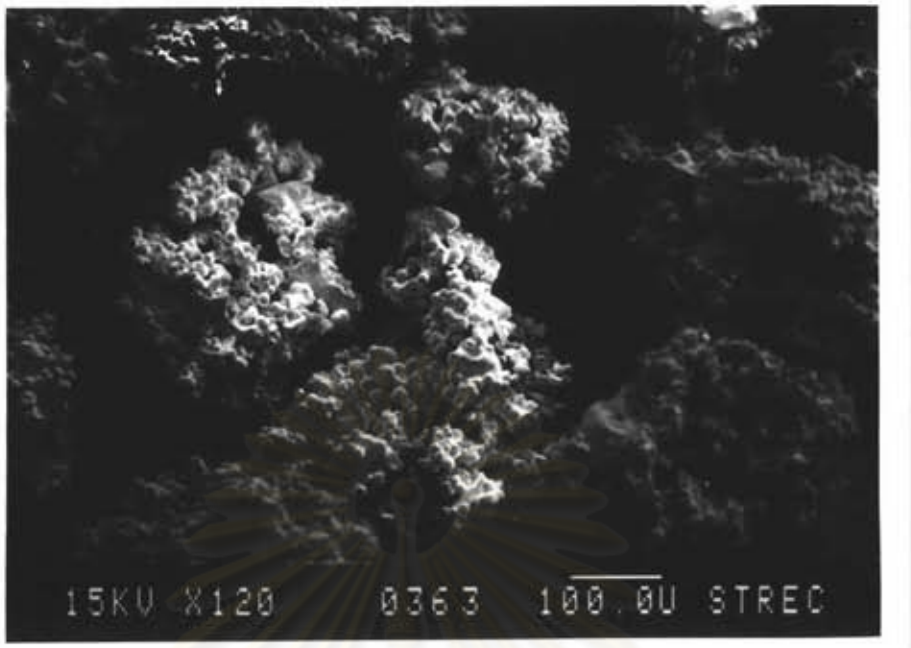


Figure 15 Electronphotomicrograph of Granules Prepared from Selected Sugar-Starch-PVP Granule Formulation (Formula 5)


Figure 16 Electronphotomicrograph of Granules Prepared from Selected Sugar-Starch-Gelatin Granule Formulation (Formula 5)

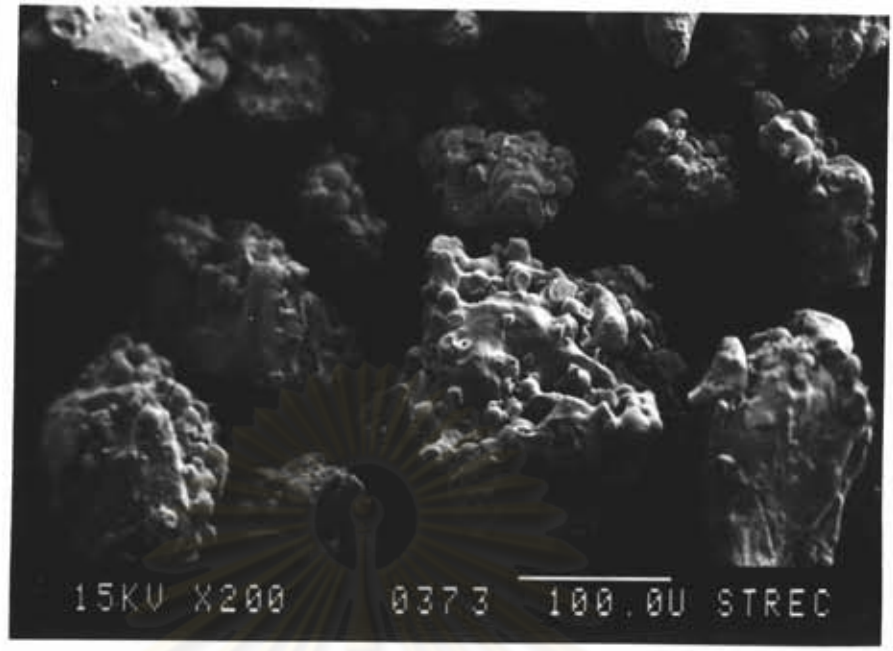


Figure 17 Electronphotomicrograph of Granules Prepared from Selected Sugar-Starch-Methylcellulose Granule Formulation. (Formula 9)

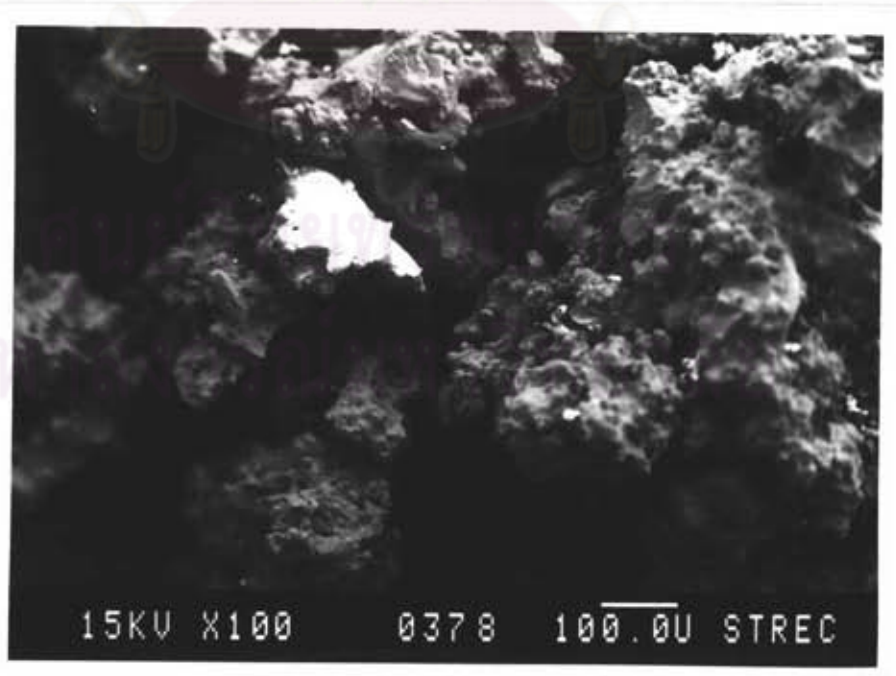


Figure 18 Electronphotomicrograph of Granules Prepared from Selected Sugar-Starch-Starch Granule Formulation (Formula 8)

proportion of starch than those granules composed of high content of sugar.

6. **Compressional Force-Hardness and Compressional Force-Disintegration Profile of Tablets Prepared from Selected Granule Formulations and Commercial Direct Compressible Diluents**

The effect of compressional force on hardness and disintegration time of compacts prepared from selected sugar-starch granule formulations without addition of disintegrant were observed together with the hardness and disintegration profiles of commercial direct compressible diluents as illustrated in Figures 19-20. The direct compressible diluents employed in these comparative investigations were as follows : Starch 1500$^{R}$ , Emdex$^{R}$ , Tabfine$^{R}$ , Tablettose$^{R}$ , and Emcompress$^{R}$.

It is no doubt that sugar-starch compacts should exhibit better hardness profile due to binding property enhancements of the binders in the formulations. Only compacts of sugar-starch-methylcellulose granules and sugar-starch-starch granules showed lower hardness profiles than those of Emdex$^{R}$ but better than of other direct compressible diluents. It was interesting that compacts of sugar-starch mixtures had the high hardness profiles but they were disintegrated in shorter time period (3-4 min). The compressional force very slightly

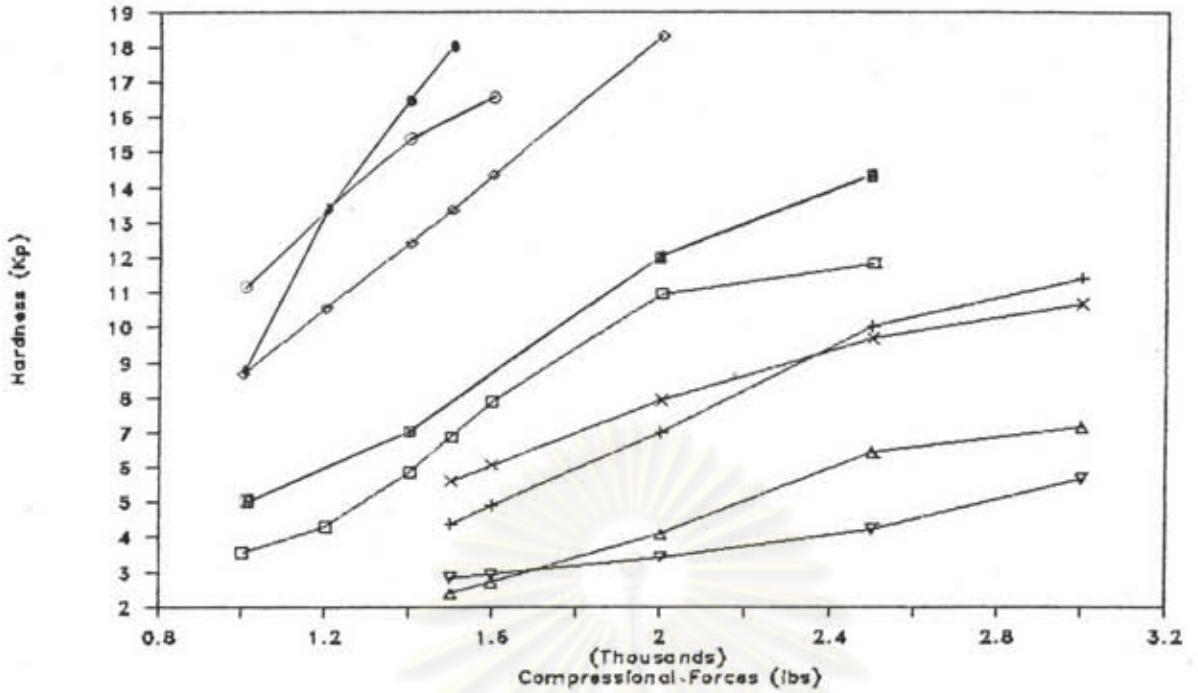


Figure 19 Compressional Force-Hardness Profiles of Compacts Prepared from Selected Granule Formulations and Five Commercial Direct Compressible Diluents
Key : + Starch 1500 ▽ Emcompress △ Tablettose
× Tabfine ◇ Emdex ○ S-S-P⊘
● S-S-G⊘ ■ S-S-M⊘ □ S-S-T⊘
(⊘ : These abbreviations are the same as in Table 22)

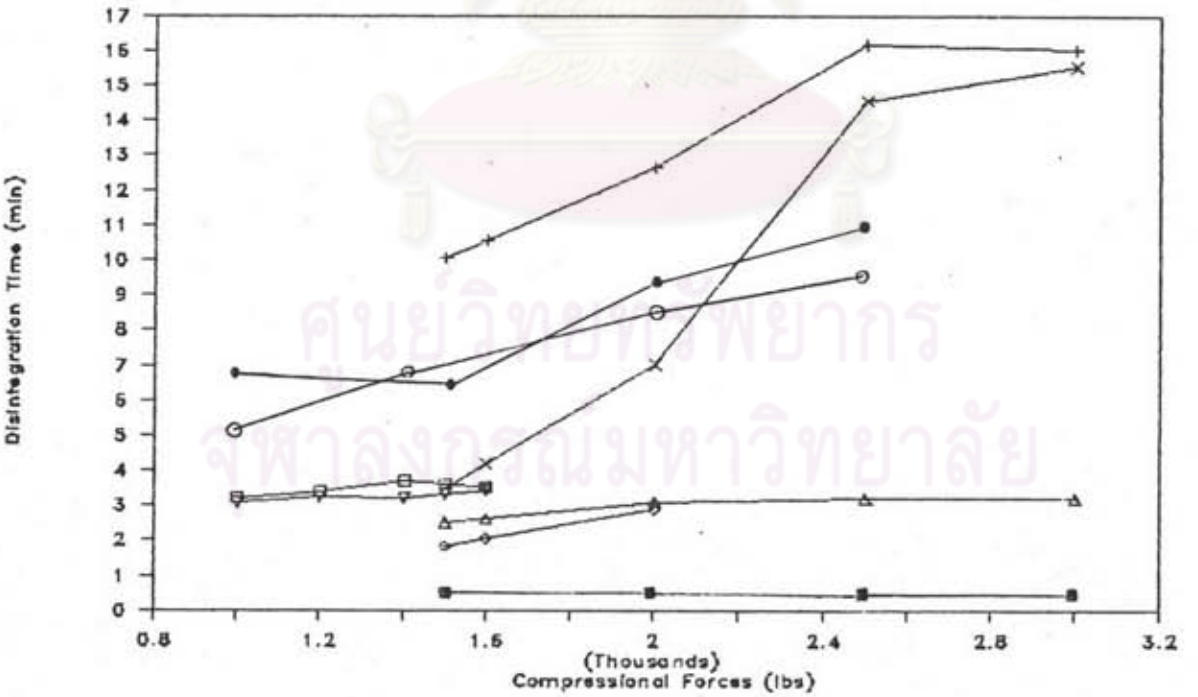


Figure 20 Compressional Force-Disintegration Profiles of Compacts Prepared from Selected Granule Formulations and Five Commercial Direct Compressible Diluents
Key : + Starch 1500 × Emcompress ■ Tablettose
△ Tabfine ◇ Emdex ▽ S-S-P⊘
□ S-S-G⊘ ● S-S-M⊘ ○ S-S-T⊘
(⊘ : These abbreviations are the same as in Table 22)

affected disintegration of sugar-starch-PVP and sugar-starch-gelatin compacts as little change in profiles were exhibited (Figure 20). But disintegration time of sugar-starch-methylcellulose and sugar-starch-starch compacts increased with increasing compressional forces.

**7. Aging Study of Diazepam and Chlorpheniramine Maleate Tablets**

The granules employed in this part of experiment were prepared according to the procedures and conditions of the fluidized bed granulator as described in section 2.2 of Chapter Two and Table 1,respectively. The method of preparing diazepam and chlorpheniramine maleate have been described previously in section 2.8 and 2.9.

**Content Uniformity**

Tablets were determined individually for content uniformity of diazepam and chlorpheniramine maleate before aging study. The results are shown in Tables 22 and 23. Diazepam and chlorpheniramine maleate tablets prepared using sugar-starch-PVP, sugar-starch-gelatin, and sugar-starch-methylcellulose granules were within the limits of USP standard whereas tablets prepared from sugar-starch-starch granules did not met the compendial requirement.

Table 22 Content Uniformity of Diazepam Tablets Prepared Using all Types of Granules

| Sample Number | % Drug in Tablet | | | |
|---|---|---|---|---|
| | Types of Granules | | | |
| | S-S-P[d] | S-S-G[e] | S-S-M[f] | S-S-T[g] |
| 1 | 105.6 | 100.7 | 95.2 | 124.2 |
| 2 | 105.2 | 95.6 | 99.1 | 110.7 |
| 3 | 105.0 | 96.7 | 105.4 | 91.6 |
| 4 | 97.2 | 97.8 | 104.6 | 92.4 |
| 5 | 96.6 | 100.0 | 99.1 | 90.2 |
| 6 | 95.1 | 97.5 | 95.5 | 97.4 |
| 7 | 95.6 | 100.2 | 104.1 | 118.7 |
| 8 | 99.0 | 99.4 | 101.5 | 101.7 |
| 9 | 95.8 | 98.0 | 100.0 | 128.1 |
| 10 | 103.7 | 94.6 | 99.7 | 118.9 |
| $\bar{X}$ (S.D.) | 99.8 (4.4) | 98.0 (2.0) | 100.4 (3.5) | 107.3 (14.4) |
| %C.V. | 4.4 | 2.0 | 3.5 | 13.4 |

d = Sugar=Starch=PVP

e = Sugar=Starch=Gelatin

f = Sugar=Starch=Methylcellulose

g = Sugar=Starch=Starch

Table 23 Content Uniformity of Chlorpheniramine Maleate Tablets Prepared Using all Types of Granules

| Sample Number | % Drug in Tablet | | | |
|---|---|---|---|---|
| | Types of Granules | | | |
| | S-S-P[d] | S-S-G[e] | S-S-M[f] | S-S-T[g] |
| 1 | 101.5 | 99.4 | 105.1 | 93.7 |
| 2 | 98.7 | 95.4 | 107.9 | 99.1 |
| 3 | 99.0 | 97.6 | 108.6 | 117.5 |
| 4 | 100.4 | 94.5 | 109.4 | 104.8 |
| 5 | 99.1 | 93.3 | 112.4 | 108.8 |
| 6 | 99.2 | 95.9 | 100.2 | 92.3 |
| 7 | 99.1 | 96.3 | 109.8 | 91.8 |
| 8 | 94.0 | 94.1 | 104.4 | 91.9 |
| 9 | 99.6 | 94.4 | 103.9 | 106.2 |
| 10 | 98.8 | 96.4 | 108.0 | 114.2 |
| $\bar{X}$ | 98.9 | 95.7 | 106.9 | 101.0 |
| (S.D.) | (1.9) | (1.8) | (3.5) | (9.6) |
| %C.V. | 1.9 | 1.9 | 3.3 | 9.4 |

d = Sugar=Starch=PVP

e = Sugar=Starch=Gelatin

f = Sugar=Starch=Methylcellulose

g = Sugar=Starch=Starch

**Weight Variation**

The results of weight variation of diazepam and chlorpheniramine maleate tablets prepared from sugar-starch-PVP, sugar-starch-gelatin, sugar-starch-methyl cellulose, and sugar-starch-starch granules after storage for 3 months under various conditions are shown in Tables 24-27.

Statistically significant differences in tablet weigh occurred for both diazepam and chlorpheniramine maleate tablets using sugar-starch-PVP granules ($\alpha$= 0.01, Table 24). There was an initial increase in tablet weight during the first month. No obviously change in weight of tablet was observed After the first month. Great difference was found at the storage condition of 75 % R.H. Weight variation of diazepam and chlorpheniramine maleate tablets prepared from sugar-starch-gelatin granules after storage for 3 months under various conditions were shown in Table 25. There were statistically significant changes in weight of diazepam tablets stored at room condition, 51 and 75 % R.H. while significant changes were observed at 51 and 75 % R.H. for chlorpheniramine maleate tablets. However, slight change of tablet weight was found at low humid conditions.

Effect of storage conditions on weight variation of diazepam and chlorpheniramine maleate tablets prepared

Table 24 Effect of Aging on Weight Variation of Diazepam(DZP) and Chlorpheniramine Maleate(CPM) Tablets Prepared from Sugar-Starch-PVP Granules After Storage for 3 Months under Various Conditions

| Conditions of Storage | Month | DZP Weight Variation (mg) Mean±S.D. | DZP F-value | CPM Weight Variation (mg) Mean±S.D. | CPM F-value |
|---|---|---|---|---|---|
| Room Storage | 0 | 121.9±0.7 | | 123.5±1.2 | |
| | 1 | 124.4±0.8 | * | 126.0±1.1 | * |
| | 2 | 124.5±0.6 | 53.74 | 126.1±1.0 | 27.64 |
| | 3 | 124.5±0.7 | | 126.2±0.9 | |
| 32% R.H. | 0 | 121.2±1.0 | | 123.1±0.8 | |
| | 1 | 122.4±1.0 | * | 124.4±0.9 | * |
| | 2 | 122.4±1.0 | 6.48 | 124.5±0.9 | 11.56 |
| | 3 | 122.5±1.1 | | 124.6±0.9 | |
| 51% R.H. | 0 | 121.7±1.1 | | 123.5±1.0 | |
| | 1 | 124.4±1.0 | * | 126.1±1.0 | * |
| | 2 | 124.5±1.1 | 34.02 | 126.2±1.0 | 28.26 |
| | 3 | 124.5±0.8 | | 126.0±1.3 | |
| 75% R.H. | 0 | 121.9±0.9 | | 123.3±1.6 | |
| | 1 | 126.8±0.9 | * | 128.4±1.1 | * |
| | 2 | 127.1±1.0 | 121 | 128.6±1.1 | 73.99 |
| | 3 | 126.7±1.0 | | 128.2±1.3 | |

* = Statistically significant difference ( $\alpha$ =0.01)

Table 25 Effect of Aging on Weight Variation of Diazepam(DZP) and Chlorpheniramine Maleate(CPM) Tablets Prepared from Sugar-Starch-Gelatin Granules after Storage for 3 Months under Various Conditions

| Conditions of Storage | Month | DZP Weight Variation (mg) Mean±S.D. | DZP F-value | CPM Weight Variation (mg) Mean±S.D. | CPM F-value |
|---|---|---|---|---|---|
| Room Storage | 0 | 121.1±1.4 | | 120.2±1.4 | |
| | 1 | 122.3±1.4 | * | 120.4±1.7 | |
| | 2 | 122.8±1.3 | 6.15 | 121.2±1.4 | 2.83 |
| | 3 | 122.9±1.4 | | 121.3±1.3 | |
| 32% R.H. | 0 | 121.5±1.7 | | 120.6±1.4 | |
| | 1 | 122.1±1.7 | | 121.2±1.3 | |
| | 2 | 122.1±1.7 | 0.47 | 121.3±1.3 | 1.40 |
| | 3 | 122.1±1.9 | | 121.4±1.3 | |
| 51% R.H. | 0 | 121.0±1.9 | | 121.0±1.0 | |
| | 1 | 123.1±1.8 | * | 123.0±1.1 | * |
| | 2 | 123.0±1.8 | 6.33 | 123.1±1.0 | 19.07 |
| | 3 | 123.0±1.8 | | 123.1±1.1 | |
| 75% R.H. | 0 | 121.2±1.2 | | 120.7±1.3 | |
| | 1 | 125.3±1.4 | * | 124.9±1.6 | * |
| | 2 | 125.5±1.4 | 42.63 | 125.0±2.3 | 30.39 |
| | 3 | 125.4±1.4 | | 124.8±1.3 | |

* = Statistically significant difference ( $\alpha$ =0.01)

Table 26 Effect of Aging on Weight Variation of Diazepam(DZP) and Chlorpheniramine Maleate(CPM) Tablets Prepared from Sugar-Starch-Methylcellulose Granules after Storage for 3 Months under Various Conditions

| Conditions of Storage | Month | DZP Weight Variation (mg) Mean±S.D. | DZP F-value | CPM Weight Variation (mg) Mean±S.D. | CPM F-value |
|---|---|---|---|---|---|
| Room Storage | 0 | 119.9±1.1 | | 122.1±1.0 | |
| | 1 | 119.9±1.2 | | 122.1±1.1 | |
| | 2 | 120.0±1.0 | 0.02 | 122.2±1.0 | 0.14 |
| | 3 | 120.0±1.2 | | 122.2±1.0 | |
| 32% R.H. | 0 | 119.7±1.1 | | 121.9±1.0 | |
| | 1 | 119.7±1.0 | | 121.8±0.8 | |
| | 2 | 119.6±1.0 | 0.07 | 121.8±0.9 | 0.18 |
| | 3 | 119.6±1.1 | | 121.8±0.9 | |
| 51% R.H. | 0 | 119.4±1.0 | | 122.2±0.9 | |
| | 1 | 119.6±1.0 | | 122.5±0.8 | |
| | 2 | 119.6±1.0 | 0.10 | 122.5±0.9 | 0.29 |
| | 3 | 119.6±1.1 | | 122.5±0.9 | |
| 75% R.H. | 0 | 119.6±1.1 | | 122.2±0.8 | |
| | 1 | 120.3±1.2 | | 123.0±0.9 | * |
| | 2 | 120.0±1.4 | 1.58 | 123.1±0.8 | 4.13 |
| | 3 | 120.4+1.3 | | 122.9+0.7 | |

* = Statistically significant difference ($\alpha$ =0.01)

Table 27 Effect of Aging on Weight Variation of Diazepam(DZP) and Chlorpheniramine Maleate(CPM) Tablets Prepared from Sugar-Starch-Starch Granules after Storage for 3 Months under Various Conditions

| Conditions of Storage | Month | DZP Weight Variation (mg) Mean±S.D. | DZP F-value | CPM Weight Variation (mg) Mean±S.D. | CPM F-value |
|---|---|---|---|---|---|
| Room Storage | 0 | 122.4±1.4 | | 122.8±1.5 | |
| | 1 | 122.8±1.5 | | 123.2±1.6 | |
| | 2 | 122.8±1.4 | 0.58 | 123.3±1.5 | 0.37 |
| | 3 | 122.9±1.3 | | 123.3±1.7 | |
| 32% R.H. | 0 | 122.3±1.3 | | 123.3±1.3 | |
| | 1 | 122.3±1.1 | | 123.4±1.3 | |
| | 2 | 122.3±1.0 | 0.00 | 123.4±1.3 | 0.12 |
| | 3 | 122.2±1.0 | | 123.4±1.4 | |
| 51% R.H. | 0 | 122.0±1.1 | | 122.6±1.9 | |
| | 1 | 122.6±1.1 | | 123.2±1.8 | |
| | 2 | 122.6±1.2 | 1.23 | 123.3±1.8 | 0.58 |
| | 3 | 122.6±1.4 | | 123.2±1.7 | |
| 75% R.H. | 0 | 122.2±1.4 | | 123.2±2.2 | |
| | 1 | 123.7±1.4 | * | 124.8±1.8 | |
| | 2 | 123.7±1.5 | 4.84 | 125.0±1.8 | 3.82 |
| | 3 | 123.5±1.3 | | 124.9±1.9 | |

* = Statistically significant difference ($\alpha$=0.01)

from sugar-starch-methylcellulose granules are presented in Table 26. Only chlorpheniramine maleate tablets stored at 75 % R.H. present statistically significant change in weight.

No statistically significant change in weight variation of diazepam and chlorpheniramine maleate tablets made from sugar-starch-starch granules stored at various conditions was observed except diazepam tablets stored at 75 % R.H. (Table 27) .

**Hardness**

The results of tablet hardness of diazepam and chlorpheniramine maleate tablets prepared from all type of granules after storage for 3 months under various conditions are shown in Tables 28-31 and Figures 21-28. There was statistically significant difference in diazepam tablet hardness occurred at the storage condition of 75 % R.H. and significant difference of chlorpheniramine maleate tablet hardness was found at 51 and 75 % R.H. ($\alpha$=0.01). Deteriorated effect of the moisture was shown at the 75 % R.H. level at which the hardness of tablets decreased from 6 to 2 Kp. The hardness of tablets under other storage conditions remained unchange (Table 28 and Figures 21-22).

Table 28 Effect of Aging on Hardness of Diazepam(DZP) and Chlorpheniramine Maleate(CPM) Tablets Prepared from Sugar-Starch-PVP Granules after Storage for 3 Months under Various Conditions

| Conditions of Stoage | Month | DZP Hardness (Kp) Mean±S.D. | DZP F-value | CPM Hardness (Kp) Mean±S.D. | CPM F-value |
|---|---|---|---|---|---|
| Room Storage | 0 | 6.37±0.45 | | 5.79±0.18 | |
| | 1 | 5.92±0.35 | | 6.20±0.34 | |
| | 2 | 6.10±0.52 | 1.66 | 5.94±0.24 | 3.43 |
| | 3 | 5.97±0.59 | | 5.97±0.34 | |
| 32% R.H. | 0 | 6.37±0.45 | | 5.79±0.18 | |
| | 1 | 6.03±0.21 | | 6.20±0.28 | |
| | 2 | 6.23±0.28 | 1.39 | 6.17±0.28 | 3.90 |
| | 3 | 6.14±0.51 | | 6.22±0.46 | |
| 51% R.H. | 0 | 6.37±0.45 | | 5.79±0.18 | |
| | 1 | 6.50±0.45 | | 6.59±1.02 | * |
| | 2 | 6.99±0.56 | 3.08 | 7.19±0.32 | 7.93 |
| | 3 | 6.74±0.50 | | 6.81±0.75 | |
| 75% R.H | 0 | 6.37±0.45 | | 5.79±0.18 | |
| | 1 | 3.27±0.30 | * | 2.62±0.15 | * |
| | 2 | 2.67±0.25 | 314 | 2.20±0.33 | 466 |
| | 3 | 2.41±0.25 | | 1.51±0.37 | |

* = Statistically significant difference ($\alpha$=0.01)

Table 29 Effect of Aging on Hardness of Diazepam(DZP) and Chlorpheniramine Maleate(CPM) Tablets Prepared from Sugar-Starch-Gelatin Granules after Storage for 3 Months under Various Conditions

| Conditions of Storage | Month | DZP Hardness (Kp) Mean±S.D. | DZP F-value | CPM Hardness (Kp) Mean±S.D. | CPM F-value |
|---|---|---|---|---|---|
| Room Storage | 0 | 6.20±0.57 | | 6.04±0.39 | |
| | 1 | 5.96±0.38 | | 6.21±0.67 | |
| | 2 | 6.35±0.41 | 1.35 | 6.24±0.57 | 0.67 |
| | 3 | 6.48±0.89 | | 5.84±1.02 | |
| 32% R.H. | 0 | 6.20±0.57 | | 6.04±0.39 | |
| | 1 | 6.51±0.56 | | 6.32±0.47 | |
| | 2 | 6.35±0.62 | 0.70 | 6.25±0.37 | 1.43 |
| | 3 | 6.49±0.42 | | 6.42±0.46 | |
| 51% R.H | 0 | 6.20±0.57 | | 6.04±0.39 | |
| | 1 | 6.02±0.26 | | 5.78±0.39 | |
| | 2 | 6.38±0.77 | 1.08 | 6.03±0.50 | 1.26 |
| | 3 | 5.94±0.66 | | 5.67±0.75 | |
| 75% R.H. | 0 | 6.20±0.57 | | 6.04±0.39 | |
| | 1 | 4.51±0.29 | * | 4.17±0.21 | * |
| | 2 | 4.07±0.30 | 75.42 | 3.68±0.30 | 160 |
| | 3 | 3.66±0.38 | | 3.40±0.24 | |

* = Statistically significant difference ($\alpha$ =0.01)

Table 30 Effect of Aging on Hardness of Diazepam(DZP) and Chlorpheniramine Maleate(CPM) Tablets Prepared from Sugar-Starch-Methylcellulose Granules after Sorage for 3 Months under Various Conditions

| Conditions of Storage | Month | DZP Hardness (Kp) Mean±S.D. | DZP F-value | CPM Hardness (Kp) Mean±S.D. | CPM F-value |
|---|---|---|---|---|---|
| Room Storage | 0 | 6.84±0.44 | | 7.04±0.28 | |
| | 1 | 6.66±0.44 | | 6.18±0.66 | * |
| | 2 | 6.98±0.62 | 0.94 | 5.81±0.55 | 13.38 |
| | 3 | 6.59±0.76 | | 6.79±0.32 | |
| 32% R.H. | 0 | 6.84±0.44 | | 7.04±0.28 | |
| | 1 | 6.48±0.45 | | 6.79±0.33 | * |
| | 2 | 6.33±0.60 | 2.25 | 5.99±1.07 | 5.67 |
| | 3 | 6.77±0.48 | | 6.42±0.33 | |
| 51% R.H. | 0 | 6.84±0.44 | | 7.04±0.28 | |
| | 1 | 6.30±0.56 | | 5.98±0.50 | * |
| | 2 | 6.52±0.35 | 3.60 | 5.73±0.65 | 10.43 |
| | 3 | 6.14±0.60 | | 5.62±0.91 | |
| 75% R.H. | 0 | 6.84±0.44 | | 7.04±0.28 | |
| | 1 | 5.61±0.39 | * | 4.90±0.42 | * |
| | 2 | 4.91±0.44 | 55.38 | 4.66±0.33 | 100 |
| | 3 | 4.65±0.36 | | 4.09±0.53 | |

* = Statistically significant difference ( $\alpha$ = 0.01)

Table 31 Effect of Aging on Hardness of Diazepam(DZP) and Chlorpheniramine Maleate(CPM) Tanlets Prepared from Sugar-Starch-Starch Granules after Storage for 3 Months under Various Conditions

| Conditions of Storage | Month | DZP Hardness (Kp) Mean±S.D. | DZP F-value | CPM Hardness (Kp) Mean±S.D. | CPM F-value |
|---|---|---|---|---|---|
| Room Storage | 0 | 6.64±0.58 | | 7.01±0.65 | |
| | 1 | 6.13±0.92 | | 7.30±0.69 | |
| | 2 | 6.61±0.35 | 1.53 | 7.92±0.84 | 2.37 |
| | 3 | 6.12±0.95 | | 7.42±0.89 | |
| 32% R.H. | 0 | 6.64±0.58 | | 7.01±0.65 | |
| | 1 | 6.40±0.68 | | 7.20±0.45 | |
| | 2 | 6.30±0.29 | 1.47 | 7.29±1.38 | 0.24 |
| | 3 | 6.06±0.84 | | 7.37±1.41 | |
| 51% R.H. | 0 | 6.64±0.58 | | 7.01±0.65 | |
| | 1 | 5.82±0.58 | | 6.38±1.13 | |
| | 2 | 5.69±0.92 | 3.54 | 6.74±0.85 | 2.88 |
| | 3 | 5.86±0.60 | | 5.98±0.57 | |
| 75% R.H. | 0 | 6.64±0.58 | | 7.01±0.65 | |
| | 1 | 5.39±0.41 | * | 5.23±0.55 | * |
| | 2 | 4.84±0.71 | 25.81 | 4.85±0.62 | 36.47 |
| | 3 | 4.24±0.77 | | 4.24±0.64 | |

* = Statistically significant difference ($\alpha$=0.01)

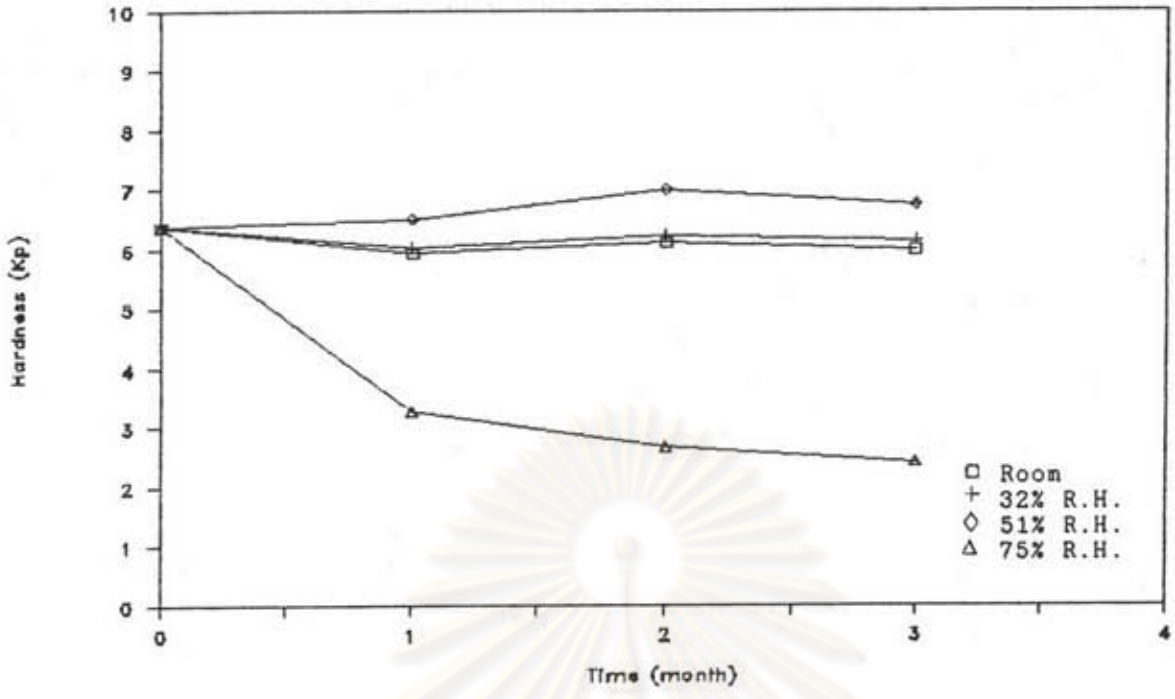


Figure 21 Effect of Aging on Hardness of Diazepam Tablets Prepared from Sugar-Starch-PVP Granules after Storage for 3 Months under Various Conditions

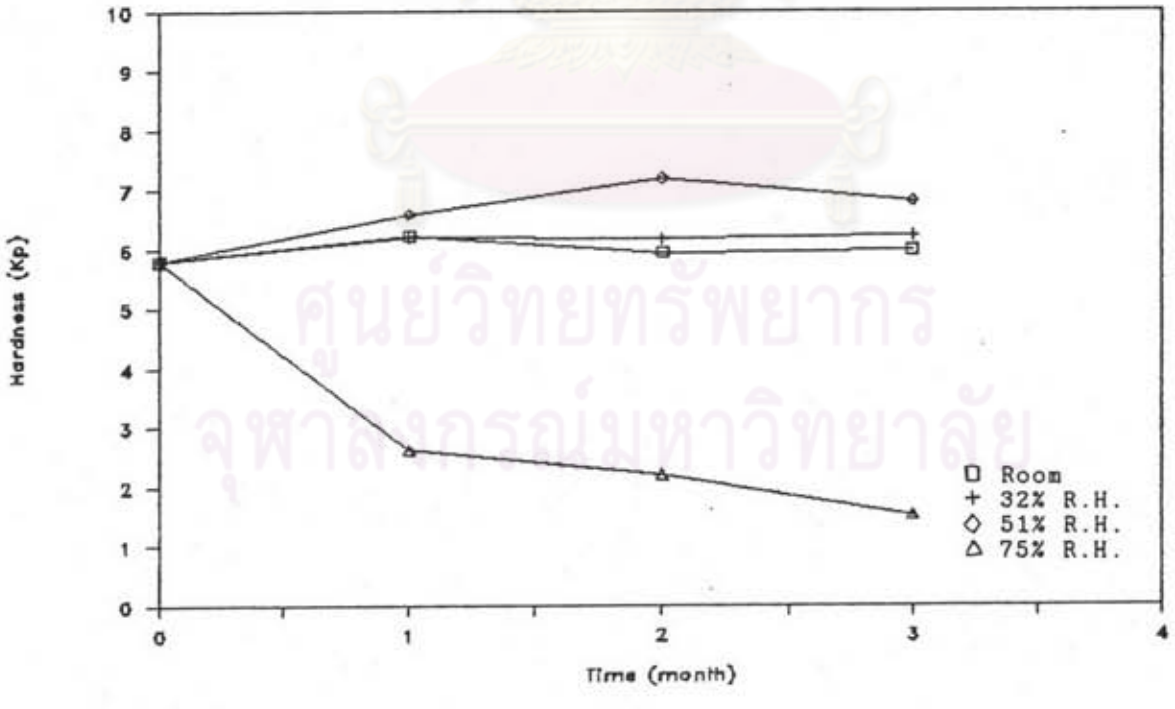


Figure 22 Effect of Aging on Hardness of Chlorpheniramine Maleate Tablets Prepared from Sugar-Starch-PVP Granules after Storage for 3 Months under Various Conditions

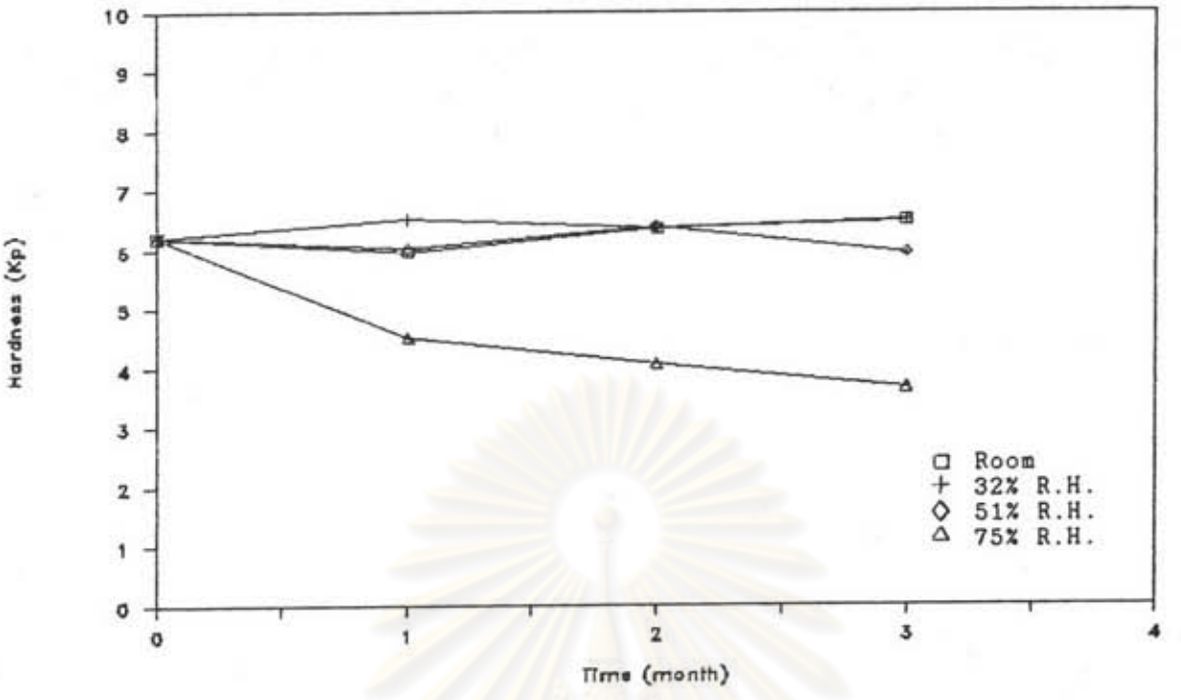


Figure 23 Effect of Aging on Hardness of Diazepam Tablets Prepared from Sugar-Starch-Gelatin Granules after Storage for 3 Months under Various Conditions

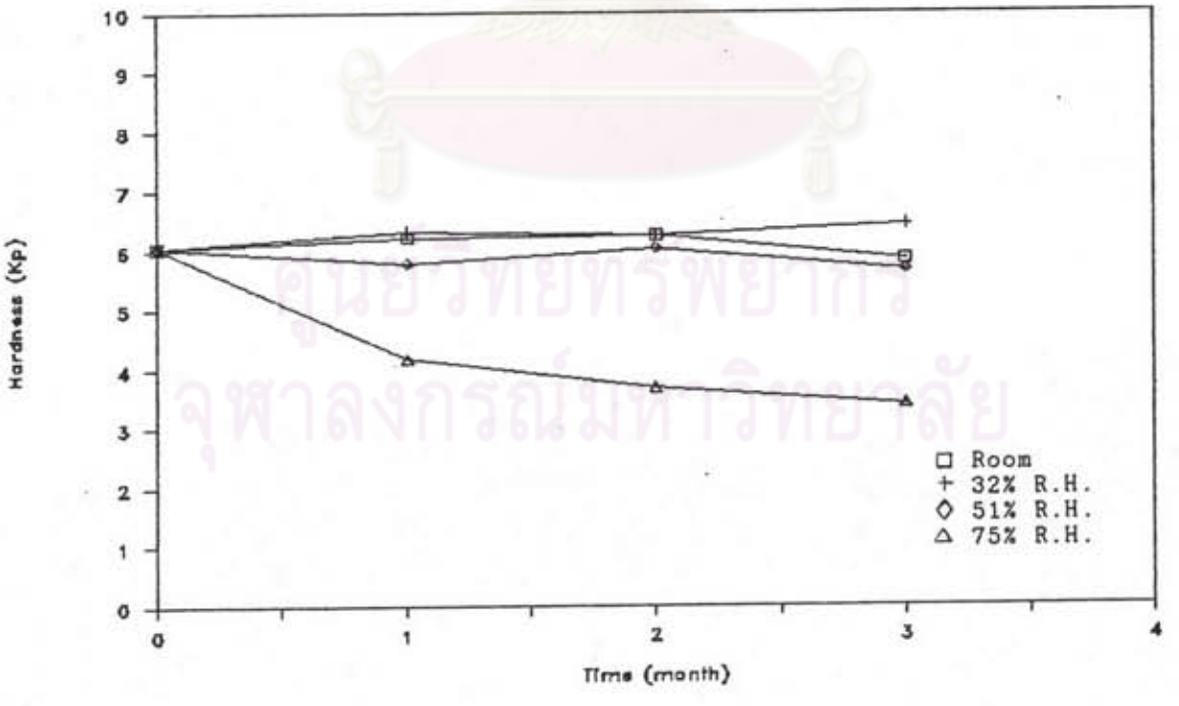


Figure 24 Effect of Aging on Hardness of Chlorpheniramine Maleate Tablets Prepared from Sugar-Starch-Gelatin Granules after Storage for 3 Months under Various Conditions

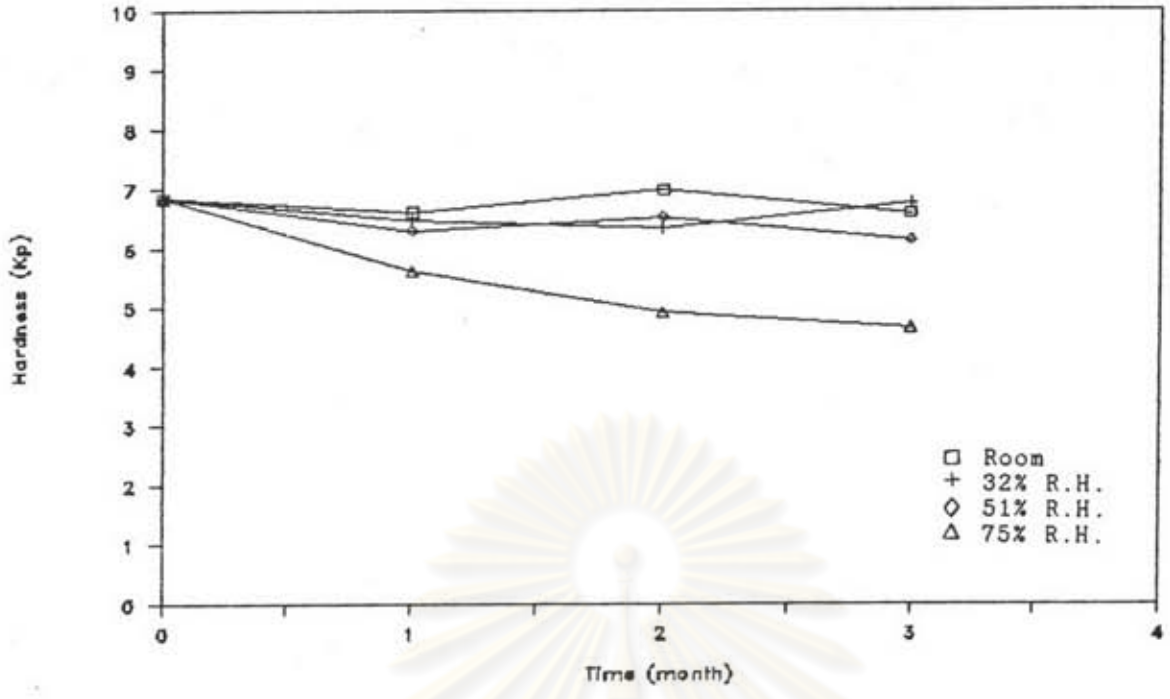


Figure 25 Effect of Aging on Hardness of Diazepam Tablets Prepared from Sugar-Starch-Methylcellulose Granules after Storage for 3 Months under Various Conditions

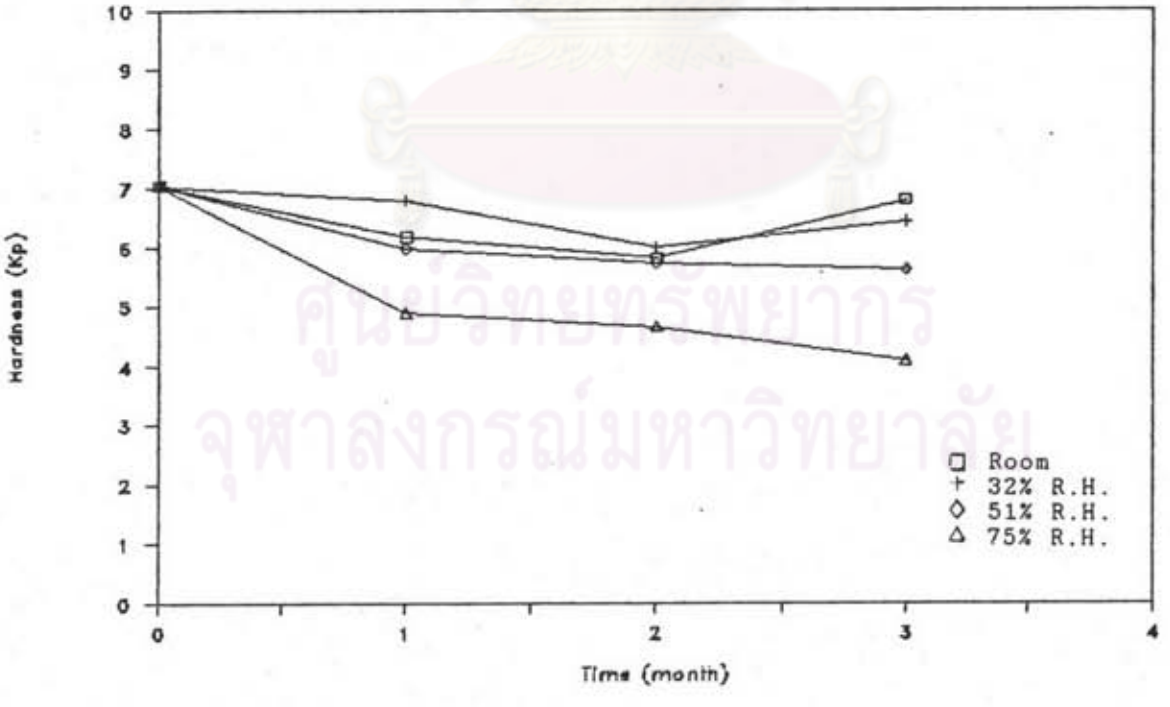


Figure 26 Effect of Aging on Hardness of Chlorpheniramine Maleate Tablets Prepared from Sugar-Starch-Methyl-cellulose Granules after Storage for 3 Months under Various Conditions

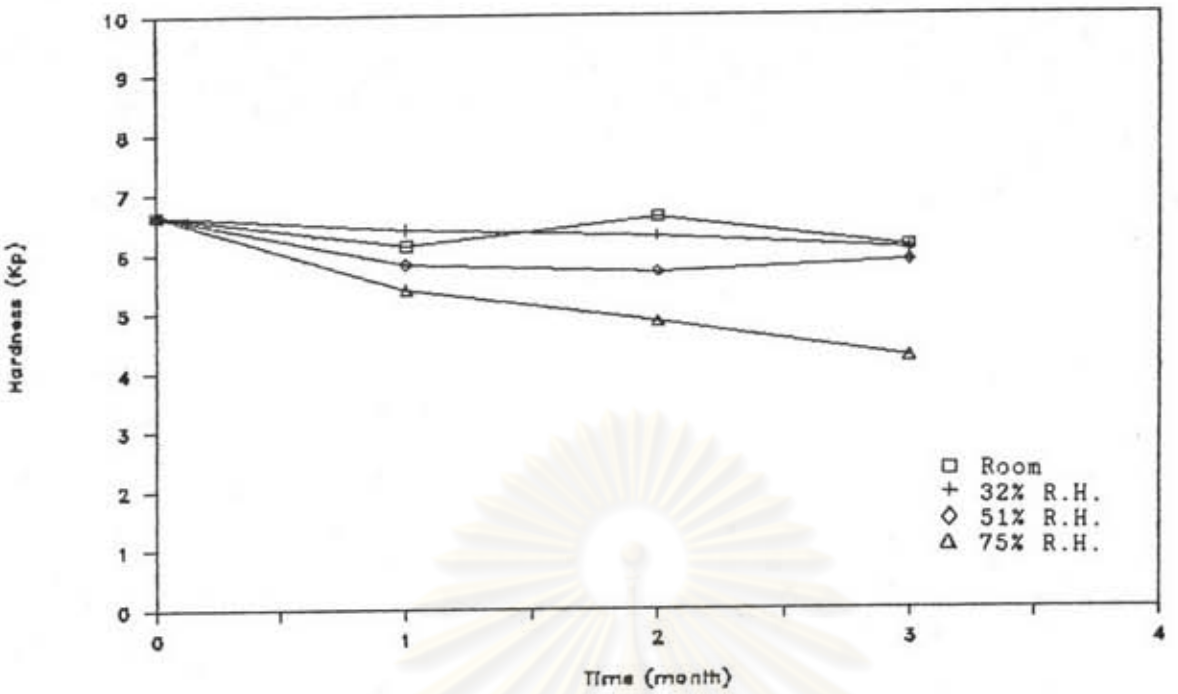


Figure 27 Effect of Aging on Hardness of Diazepam Tablets Prepared from Sugar-Starch-Starch Granules after Storage for 3 Months under Various Conditions

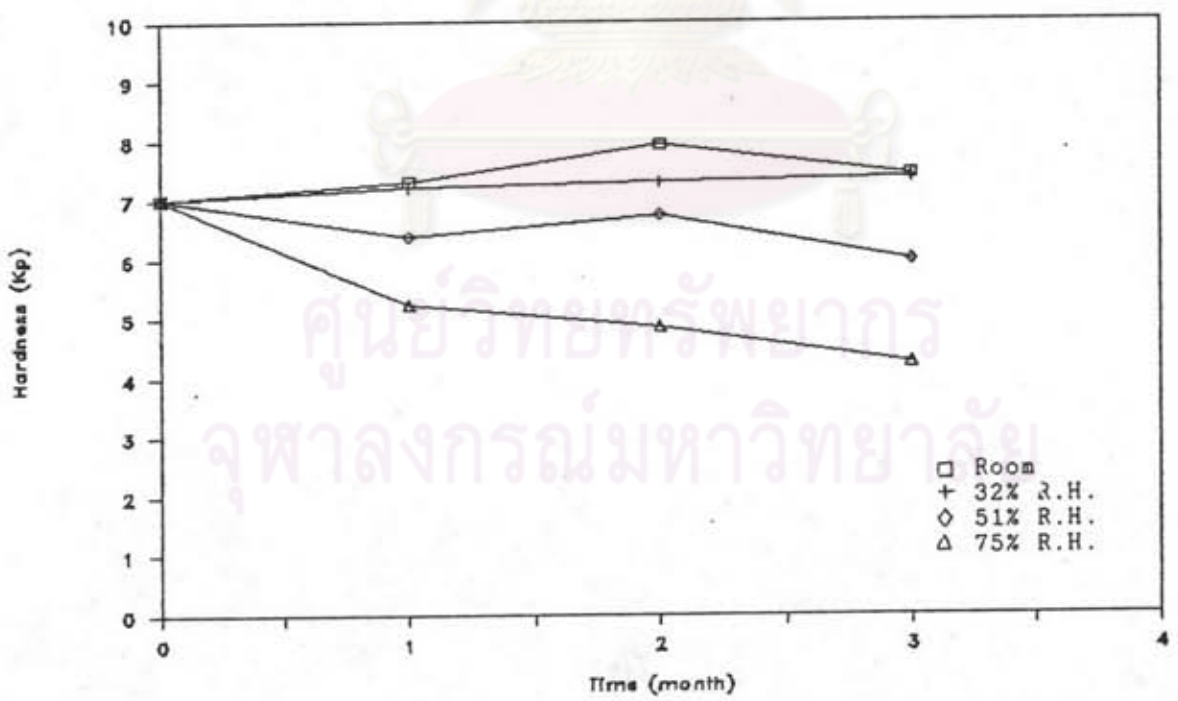


Figure 28 Effect of Aging on Hardness of Chlorpheniramine Maleate Tablets Prepared from Sugar-Starch-Starch Granules after Storage for 3 Months under Various Conditions

Diazepam and chlorpheniramine maleate tablets prepared from sugar-starch-gelatin granules showed statistically significant decrease in hardness only at the storage relative humidy of 75 % as shown in Table 29 and Figures 23-24. Initial pronounced decrease in tablet hardness was seen during the first month.

Table 30 and Figures 25-26 show the hardness of tablets made from sugar-starch-methylcellulose granules after storage for 3 months under various conditions. It could be seen that chlorpheniramine maleate tablets at all storage conditions show statistically significant difference in hardness after storage for 3 months but only slight change was observed. Significant difference of diazepam tablet hardness was noted at 75 % R.H. storage condition. The reduction of tablet hardness was slightly observed in comparing with those prepared from sugar-starch-PVP granules.

Diazepam and chlorpheniramine maleate tablets made from sugar-starch-starch granules exhibit statistically significant difference only at 75 % R.H. storage. However, the slight reduction of tablet hardness was observed in comparing with those of sugar-starch-PVP granules (Table 31 and Figures 27-28).

**Disintegration Time**

The results of disintegration time of diazepam and chlorpheniramine maleate tablets prepared using sugar-starch-PVP, sugar-starch-gelatin, sugar-starch-methyl cellulose, and sugar-starch-starch granules after storage for 3 months under various conditions are given in Tables 32-35. Little increase in disintegration time of diazepam tablets prepared using sugar-starch-PVP granules from 4 to 5 minutes was found at storage condition of 75 % R.H.( $\alpha$ = 0.01). No change of tablet disintegration time was found at the other storge conditions (Table 32).

Disintegration time of diazepam and chlorpheniramine maleate tablets prepared from sugar-starch-gelatin granules show no statistically significant difference at all storage conditions except diazepam tablets which stored at 75 % R.H. exhibited little increase in disintegration time as shown in Table 33.

It appeared from Table 34 that diazepam and chlorpheniramine maleate tablets prepared using sugar-starch-methylcellulose granules showed a little decrease in disintegration time at all storage conditions but statistically significant difference of tablets was found only at room storage and relative humidity of 32 %.

Table 32 Effect of Aging on Disintegration Time of Diazepam(DZP) and Chlorpheniramine Maleate(CPM) Tablets Prepared from Sugar-Starch-PVP Granules after Storage for 3 Months under Various Conditions

| Conditions of Storage | Month | DZP D.T.[A] (min) Mean±S.D. | DZP F-value | CPM D.T.[A] (min) Mean±S.D. | CPM F-value |
|---|---|---|---|---|---|
| Room Storage | 0 | 3.91±0.36 | | 3.57±0.30 | |
| | 1 | 3.90±0.13 | | 3.57±0.35 | |
| | 2 | 4.00±0.62 | 0.29 | 4.45±1.40 | 1.89 |
| | 3 | 4.10±0.36 | | 4.44±1.01 | |
| 32% R.H. | 0 | 3.91±0.36 | | 3.57±0.30 | |
| | 1 | 3.59±0.39 | | 3.86±0.41 | |
| | 2 | 4.56±1.33 | 2.20 | 3.83±0.69 | 0.25 |
| | 3 | 3.68±0.09 | | 3.77±0.91 | |
| 51% R.H. | 0 | 3.91±0.36 | | 3.57±0.30 | |
| | 1 | 3.59±0.19 | | 3.51±0.68 | |
| | 2 | 3.86±0.31 | 0.83 | 3.38±0.03 | 0.51 |
| | 3 | 3.79±0.52 | | 3.69±0.43 | |
| 75% R.H. | 0 | 3.91±0.36 | | 3.57±0.30 | |
| | 1 | 4.68±0.88 | * | 3.29±0.29 | |
| | 2 | 5.20±0.35 | 6.49 | 4.39±0.33 | 3.90 |
| | 3 | 5.11±0.49 | | 4.38±1.28 | |

* = Statistically significant difference ( $\alpha$ =0.01)

A = Disintegration time

Table 33 Effect of Aging on Disintegration Time of Diazepam(DZP) and Chlorpheniramine Maleate(CPM) Tablets Prepared from Sugar-Starch-Gelatin Granules after Storage for 3 Months under Various Conditions

| Conditions of Storage | Month | DZP D.T.[A] (min) Mean±S.D. | DZP F-value | CPM D.T.[A] (min) Mean±S.D. | CPM F-value |
|---|---|---|---|---|---|
| Room Storage | 0 | 3.46±0.25 | | 3.35±0.27 | |
| | 1 | 3.00±0.08 | | 3.48±0.25 | |
| | 2 | 4.19±1.48 | 2.61 | 3.85±1.06 | 0.95 |
| | 3 | 3.37±0.08 | | 3.91±0.77 | |
| 32% R.H. | 0 | 3.46±0.25 | | 3.35±0.27 | |
| | 1 | 3.34±0.22 | | 3.41±0.41 | |
| | 2 | 3.37±0.19 | 4.86 | 3.75±1.42 | 0.56 |
| | 3 | 3.76±0.16 | | 3.19±0.27 | |
| 51% R.H. | 0 | 3.46±0.25 | | 3.35±0.27 | |
| | 1 | 3.08±0.15 | | 3.72±1.30 | |
| | 2 | 3.26±0.17 | 2.45 | 3.94±1.86 | 0.71 |
| | 3 | 4.10±1.33 | | 3.05±0.08 | |
| 75% R.H. | 0 | 3.46±0.25 | | 3.35±0.27 | |
| | 1 | 3.07±0.29 | * | 3.28±0.40 | |
| | 2 | 3.89±0.35 | 13.07 | 4.68±1.86 | 2.91 |
| | 3 | 4.10±0.31 | | 4.32±0.57 | |

* = Statistically significant difference ( $\alpha$=0.01)

A = Disintegration time

Table 34 Effect of Aging on Disintegration Time of Diazepam(DZP) and Chlorpheniramine Maleate(CPM) Tablets Prepared from Sugar-Starch-Meyhylcellulose Granules after Storage for 3 Months under Various Conditions

| Conditions of Storage | Month | DZP D.T.[A] (min) Mean±S.D. | DZP F-value | CPM D.T.[A] (min) Mean±S.D. | CPM F-value |
|---|---|---|---|---|---|
| Room Storage | 0 | 9.43±0.30 | | 7.49±0.42 | |
| | 1 | 9.04±0.87 | * | 6.64±0.30 | |
| | 2 | 8.75±0.30 | 11.73 | 7.04±1.80 | 1.39 |
| | 3 | 7.74±0.33 | | 6.47±0.22 | |
| 32% R.H. | 0 | 9.43±0.30 | | 7.49±0.42 | |
| | 1 | 9.27±0.27 | * | 6.99±0.20 | * |
| | 2 | 9.85±0.34 | 68.89 | 6.72±0.18 | 9.34 |
| | 3 | 7.42±0.33 | | 6.87±0.28 | |
| 51% R.H. | 0 | 9.43±0.30 | | 7.49±0.42 | |
| | 1 | 9.13±0.52 | | 7.55±0.21 | |
| | 2 | 8.53±0.62 | 2.65 | 6.86±0.47 | 2.72 |
| | 3 | 8.83±0.76 | | 7.31±0.69 | |
| 75% R.H. | 0 | 9.43±0.30 | | 7.49±0.42 | |
| | 1 | 8.80±1.09 | | 6.83±0.93 | |
| | 2 | 9.35±0.82 | 1.22 | 7.23±0.22 | 1.55 |
| | 3 | 8.87±0.32 | | 7.25±0.57 | |

* = Statistically significant difference ( $\alpha$ =0.01)

A = Disintegration time

Table 35 Effect of Aging on Disintegration Time of Diazepam(DZP) and Chlorpheniramine Maleate(CPM) Tablets Prepared from Sugar-Starch-Starch Granules after Storage for 3 Months under Various Conditions

| | | DZP | | CPM | |
|---|---|---|---|---|---|
| Conditions of Storage | Month | D.T.[A] (min) Mean±S.D. | F-value | D.T.[A] (min) Mean±S.D. | F-value |
| Room Storage | 0 | 6.96±0.15 | | 7.59±1.92 | |
| | 1 | 6.40±0.18 | * | 6.76±0.23 | |
| | 2 | 7.68±0.46 | 20.28 | 6.29±0.28 | 1.76 |
| | 3 | 6.86±0.24 | | 6.80±0.35 | |
| 32% R.H. | 0 | 6.96±0.15 | | 7.59±1.92 | |
| | 1 | 6.47±0.30 | * | 6.83±0.23 | |
| | 2 | 8.76±0.54 | 42.43 | 6.74±0.31 | 1.18 |
| | 3 | 7.18±0.36 | | 6.61±0.24 | |
| 51% R.H. | 0 | 6.96±0.15 | | 7.59±1.92 | |
| | 1 | 6.63±0.24 | * | 7.89±1.65 | |
| | 2 | 7.46±0.38 | 23.47 | 6.64±0.14 | 1.25 |
| | 3 | 9.31±1.11 | | 6.84±0.55 | |
| 75% R.H. | 0 | 6.96±0.15 | | 7.59±1.92 | |
| | 1 | 8.37±0.24 | * | 6.64±0.28 | * |
| | 2 | 9.46±1.09 | 14.51 | 7.24±0.57 | 7.65 |
| | 3 | 9.99±1.29 | | 8.35±0.71 | |

* = Statistically significant difference ($\alpha$=0.01)

A = Disintegration time

Inconsistent change in disintegration time of stored diazepam tablets prepared from sugar-starch-starch granules was observed (Table 35). Statistically significant difference in diazepam and chlorpheniramine maleate tablet disintegration times was seen under all storage conditions and at 75 % R.H., respectively.

**Friability**

Friability of diazepam and chlorpheniramine maleate tablets prepared from all type of granules after storage for 3 months under various conditions are shown in Table 36. Significant increase in friability of tablets prepared from sugar-starch-PVP and sugar-starch-gelatin granules was observed at the storage conditions of 51 and 75 % R.H. during the first month. But all of the friability values were less than 0.5 % . In contrast, the friability of tablets prepared from sugar-starch-methylcellulose and sugar-starch-starch granules did not substantial change at all of the storage conditions during the storage period.

**Thickness**

The results of thickness of diazepam and chlorpheniramine maleate tablets prepared from all type of granules after storage for 3 months under various conditions are given in Tables 37-40. Statistically

Table 36 Effect of Aging on Friability of Diazepam(DZP) and Chlorpheniramine Maleate(CPM) Tablets Prepared from all Types of Storage Granules after Storage for 3 Months under Various Conditions

| Conditions of Storage | Month | % Friability | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Type of Granules | | | | | | | |
| | | S-S-P[a] | | S-S-G[b] | | S-S-M[c] | | S-S-T[d] | |
| | | DZP | CPM | DZP | CPM | DZP | CPM | DZP | CPM |
| Room Storage | 0 | <0.1 | <0.1 | <0.1 | <0.1 | 0.26 | 0.22 | 0.18 | 0.15 |
| | 1 | <0.1 | <0.1 | <0.1 | <0.1 | 0.26 | 0.28 | 0.20 | 0.15 |
| | 2 | <0.1 | <0.1 | <0.1 | <0.1 | 0.23 | 0.25 | 0.12 | 0.13 |
| | 3 | <0.1 | <0.1 | <0.1 | <0.1 | 0.23 | 0.28 | 0.18 | 0.23 |
| 32% R.H. | 0 | <0.1 | <0.1 | <0.1 | <0.1 | 0.26 | 0.22 | 0.18 | 0.15 |
| | 1 | <0.1 | <0.1 | <0.1 | <0.1 | 0.25 | 0.27 | 0.18 | 0.20 |
| | 2 | <0.1 | <0.1 | <0.1 | 0.13 | 0.27 | 0.25 | 0.21 | 0.20 |
| | 3 | <0.1 | <0.1 | <0.1 | <0.1 | 0.24 | 0.24 | 0.17 | 0.17 |
| 51% R.H. | 0 | <0.1 | <0.1 | <0.1 | <0.1 | 0.26 | 0.22 | 0.18 | 0.15 |
| | 1 | <0.1 | 0.14 | <0.1 | 0.19 | 0.27 | 0.25 | 0.25 | 0.21 |
| | 2 | 0.10 | <0.1 | 0.13 | 0.10 | 0.24 | 0.27 | 0.21 | 0.18 |
| | 3 | 0.17 | 0.17 | 0.18 | 0.18 | 0.18 | 0.26 | 0.20 | 0.21 |
| 75% R.H. | 0 | <0.1 | <0.1 | <0.1 | <0.1 | 0.26 | 0.22 | 0.18 | 0.15 |
| | 1 | 0.35 | 0.36 | 0.35 | 0.40 | 0.32 | 0.39 | 0.32 | 0.32 |
| | 2 | <0.1 | 0.38 | 0.47 | 0.46 | 0.34 | 0.36 | 0.28 | 0.34 |
| | 3 | 0.28 | 0.27 | 0.34 | 0.35 | 0.30 | 0.31 | 0.29 | 0.27 |

[a] = Sugar-Starch-PVP

[b] = Sugar-Starch-Gelatin

[c] = Sugar-Starch-Methylcellulose

[d] = Sugar-Starch-Starch

Table 37 Effect of Aging on Thickness of Diazepam(DZP) and Chlorpheniramine Maleate(CPM) Tablets Prepared from Sugar-Starch-PVP Granules after Storage for 3 Months under Various Conditions

| Conditions of Storage | Month | DZP Thickness (mm) Mean±S.D. | DZP F-value | CPM Thickness (mm) Mean±S.D. | CPM F-value |
|---|---|---|---|---|---|
| Room Storage | 0 | 2.74±0.01 | | 2.75±0.03 | |
| | 1 | 2.83±0.01 | * | 2.85±0.01 | * |
| | 2 | 2.82±0.01 | 138 | 2.84±0.02 | 42.41 |
| | 3 | 2.83±0.01 | | 2.84±0.02 | |
| 32% R.H. | 0 | 2.70±0.02 | | 2.75±0.01 | |
| | 1 | 2.75±0.02 | * | 2.79±0.02 | * |
| | 2 | 2.76±0.02 | 12.00 | 2.80±0.01 | 13.73 |
| | 3 | 2.76±0.02 | | 2.79±0.02 | |
| 51% R.H. | 0 | 2.72±0.02 | | 2.75±0.01 | |
| | 1 | 2.83±0.03 | * | 2.87±0.00 | * |
| | 2 | 2.83±0.02 | 40.39 | 2.86±0.02 | 81.09 |
| | 3 | 2.82±0.03 | | 2.85±0.02 | |
| 75% R.H. | 0 | 2.73±0.03 | | 2.71±0.03 | |
| | 1 | 2.91±0.02 | * | 2.96±0.03 | * |
| | 2 | 2.94±0.02 | 135 | 2.98±0.03 | 166 |
| | 3 | 2.92±0.02 | | 2.96±3.0 | |

* = Statistically significant difference ($\alpha$=0.01)

Table 38 Effect of Aging on Thickness of Diazepam(DZP) and Chlorpheniramine Maleate(CPM) Tablets Prepared from Sugar-Starch-Gelatin Granules after Storage for 3 Months under Various Conditions

| Conditions of Storage | Month | DZP Thickness (mm) Mean±S.D. | DZP F-value | CPM Thickness (mm) Mean±S.D. | CPM F-value |
|---|---|---|---|---|---|
| Room Storage | 0 | 2.75±0.02 | | 2.73±0.02 | |
| | 1 | 2.80±0.02 | * | 2.76±0.02 | |
| | 2 | 2.79±0.03 | 9.85 | 2.76±0.02 | 3.15 |
| | 3 | 2.79±0.02 | | 2.76±0.03 | |
| 32% R.H. | 0 | 2.74±0.03 | | 2.74±0.02 | |
| | 1 | 2.76±0.03 | | 2.77±0.02 | * |
| | 2 | 2.78±0.03 | 3.48 | 2.77±0.01 | 7.48 |
| | 3 | 2.76±0.02 | | 2.75±0.02 | |
| 51% R.H. | 0 | 2.75±0.03 | | 2.74±0.01 | |
| | 1 | 2.83±0.03 | * | 2.83±0.01 | * |
| | 2 | 2.83±0.04 | 13.52 | 2.83±0.02 | 88.90 |
| | 3 | 2.84±0.03 | | 2.82±0.01 | |
| 75% R.H. | 0 | 2.75±0.03 | | 2.74±0.02 | |
| | 1 | 2.92±0.01 | * | 2.94±0.02 | * |
| | 2 | 2.94±0.02 | 92.43 | 2.94±0.02 | 214 |
| | 3 | 2.94±0.04 | | 2.93±0.01 | |

* = Statistically significant difference ( $\alpha$=0.01)

Table 39 Effect of Aging on Thickness of Diazepam(DZP) and Chlorpheniramine Maleate(CPM) Tablets Prepared from Sugar-Starch-Methylcellulose Granules after Storage for 3 Months under Various Conditions

| Conditions of Storage | Month | DZP Thickness (mm) Mean±S.D. | DZP F-value | CPM Thickness (mm) Mean±S.D. | CPM F-value |
|---|---|---|---|---|---|
| Room Storage | 0 | 2.61±0.01 | | 2.67±0.02 | |
| | 1 | 2.61±0.02 | | 2.68±0.01 | |
| | 2 | 2.61±0.01 | 1.48 | 2.66±0.02 | 2.04 |
| | 3 | 2.60±0.02 | | 2.66±0.02 | |
| 32% R.H. | 0 | 2.59±0.02 | | 2.65±0.01 | |
| | 1 | 2.61±0.01 | | 2.67±0.01 | |
| | 2 | 2.59±0.01 | 3.47 | 2.65±0.02 | 2.84 |
| | 3 | 2.58±0.01 | | 2.65±0.02 | |
| 51% R.H. | 0 | 2.59±0.01 | | 2.66±0.01 | |
| | 1 | 2.61±0.01 | | 2.68±0.01 | * |
| | 2 | 2.61±0.01 | 2.27 | 2.68±0.01 | 5.37 |
| | 3 | 2.60±0.01 | | 2.68±0.01 | |
| 75% R.H. | 0 | 2.60±0.02 | | 2.66±0.01 | |
| | 1 | 2.63±0.01 | * | 2.72±0.01 | * |
| | 2 | 2.63±0.01 | 8.39 | 2.71±0.01 | 22.53 |
| | 3 | 2.62±0.02 | | 2.70±0.03 | |

* = Statistically significant different ($\alpha$=0.01)

Table 40 Efect of Aging on Thickness of Diazepam(DZP) and Chlorpheniramine Maleate(CPM) Tablets Prepared from Sugar-Starch-Starch Granules after Storage for 3 Months under Various Conditions

| Conditions of Storage | Month | DZP Thickness (mm) Mean±S.D. | DZP F-value | CPM Thickness (mm) Mean±S.D. | CPM F-value |
|---|---|---|---|---|---|
| Room Storage | 0 | 2.66±0.03 | | 2.68±0.03 | |
| | 1 | 2.68±0.03 | | 2.70±0.03 | |
| | 2 | 2.67±0.03 | 1.29 | 2.68±0.03 | 0.75 |
| | 3 | 2.66±0.03 | | 2.69±0.04 | |
| 32% R.H. | 0 | 2.67±0.02 | | 2.68±0.02 | |
| | 1 | 2.66±0.01 | | 2.70±0.03 | |
| | 2 | 2.66±0.02 | 1.63 | 2.70±0.02 | 1.48 |
| | 3 | 2.65±0.02 | | 2.68±0.02 | |
| 51% R.H. | 0 | 2.66±0.02 | | 2.67±0.02 | |
| | 1 | 2.67±0.02 | | 2.70±0.04 | |
| | 2 | 2.69±0.02 | 2.77 | 2.69±0.02 | 1.90 |
| | 3 | 2.66±0.02 | | 2.69±0.02 | |
| 75% R.H. | 0 | 2.66±0.02 | | 2.68±0.02 | |
| | 1 | 2.71±0.02 | * | 2.76±0.03 | * |
| | 2 | 2.71±0.02 | 5.92 | 2.75±0.03 | 8.01 |
| | 3 | 2.69±0.04 | | 2.73±0.03 | |

* = Statistically significant difference ($\alpha$=0.01)

significant differences in tablet thickness prepared from sugar-starch-PVP granules occurred at all storage conditions especially at the 75 % R.H. ($\alpha = 0.01$). It is observed that there was an initial increase in tablet thickness during the first month, and remained unchange after that (Table 37).

Table 38 revealed that there were statistically significant difference in thickness of diazepam and chlorpheniramine maleate tablets made from sugar-starch-gelatin granules stored at all the storage conditions except diazepam and chlorpheniramine maleate tablets stored at 32 % R.H. and room condition, respectively. It could be seen from the data that there were an initial increase in tablet thickness during the first month form the statistically significant different data.

Effect of aging an the thickness of tablets prepared using sugar-starch-methylcellulose granules are shown in Table 39. The results indicated the statistically significant difference in chlorpheniramine maleate tablet thickness under the storage of 51 and 75 % R.H. Significant increase in diazepam tablet thickness was observed at 75 % R.H. However, sligh increase in tablet thickness from the initial values was observed.

Diazepam and chlorpheniramine maleate tablets made from sugar-starch-starch granules stored at 75 % R.H.

exhibit statistically significant difference in thickness after storage for 3 months. The results are shown in table 40 .

**Dissolution of Diazepam Tablets**

The dissolution behaviors of diazepam tablets prepared from sugar-starch-PVP, sugar-starch-gelatin, sugar-stach-methylcellulose, and sugar-starch-starch granules after storage for 3 months under various conditions are shown in Figures 29-44 (the experimental data are presented in Appendices G-J). The dissolutions of freshly prepared tablets using sugar-starch-PVP and sugar-starch-gelatin granules exhibited 100 % diazepam release within 20 and 15 minutes, respectively (Figures 29-36). This means that their dissolutions met the USP requirement (85 % diazepam dissolved within 30 minutes). The dissolutions were still within the compendial limit and remained unchange after storage for 3 months under various conditions although slight difference in dissolution profiles could be seen for the dissolution rate of diazepam tablets prepared from sugar-starch-PVP granules at the storage conditions of 32 and 51 % R.H.

It could be seen from Figures 37-44 that freshly prepared diazepam tablets using sugar-starch-methyl cellulose and sugar-starch-starch granules did not meet

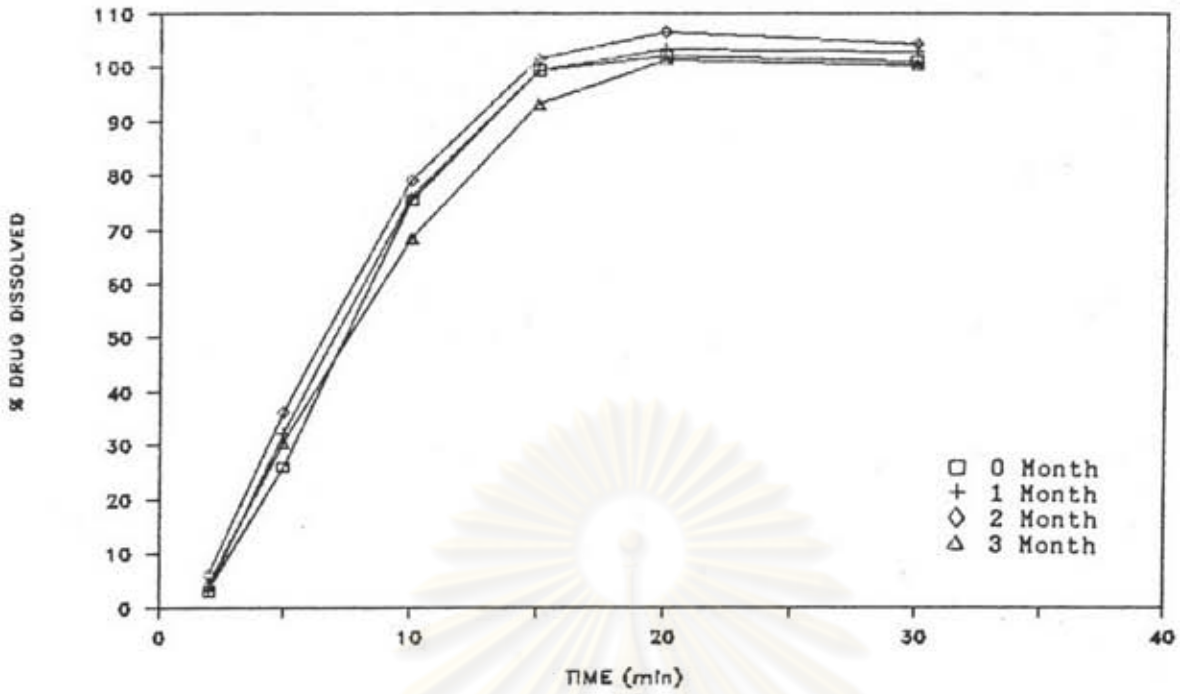


Figure 29 Effect of Aging on Dissolution of Diazepam Tablets Prepared from Sugar-Starch-PVP Granules after Storage for 3 Months at Room Condition

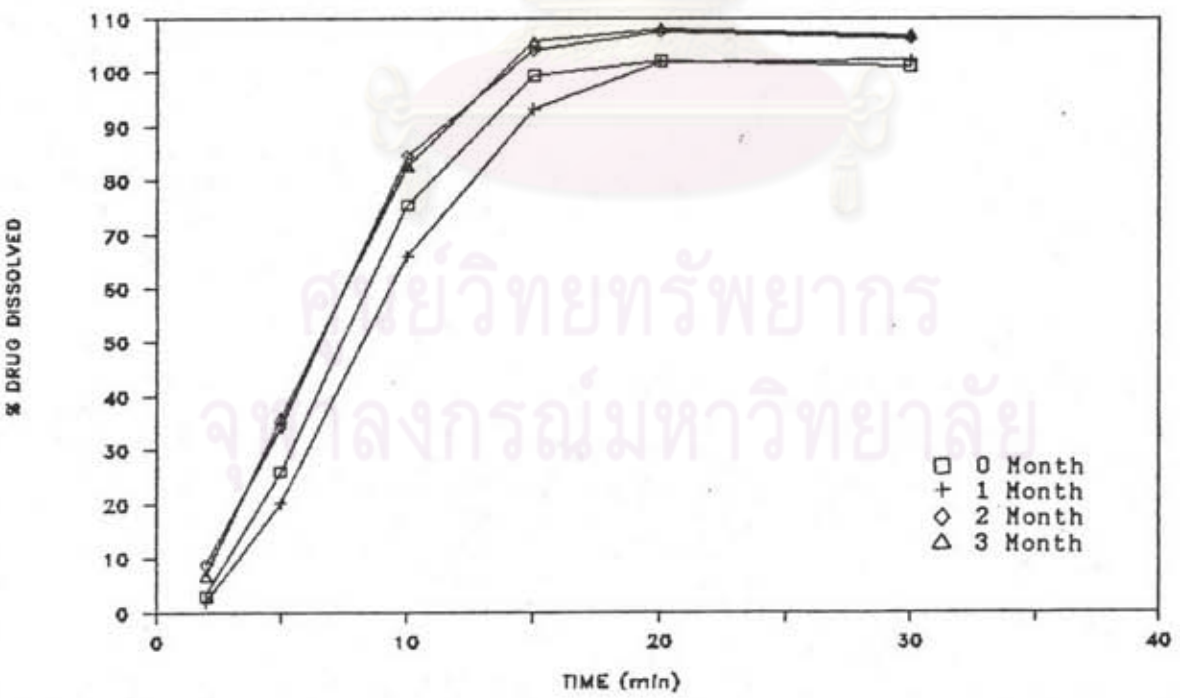


Figure 30 Effect of Aging on Dissolution of Diazepam Tablets Prepared from Sugar-Starch-PVP Granules after Storage for 3 Months at 32 % R.H.

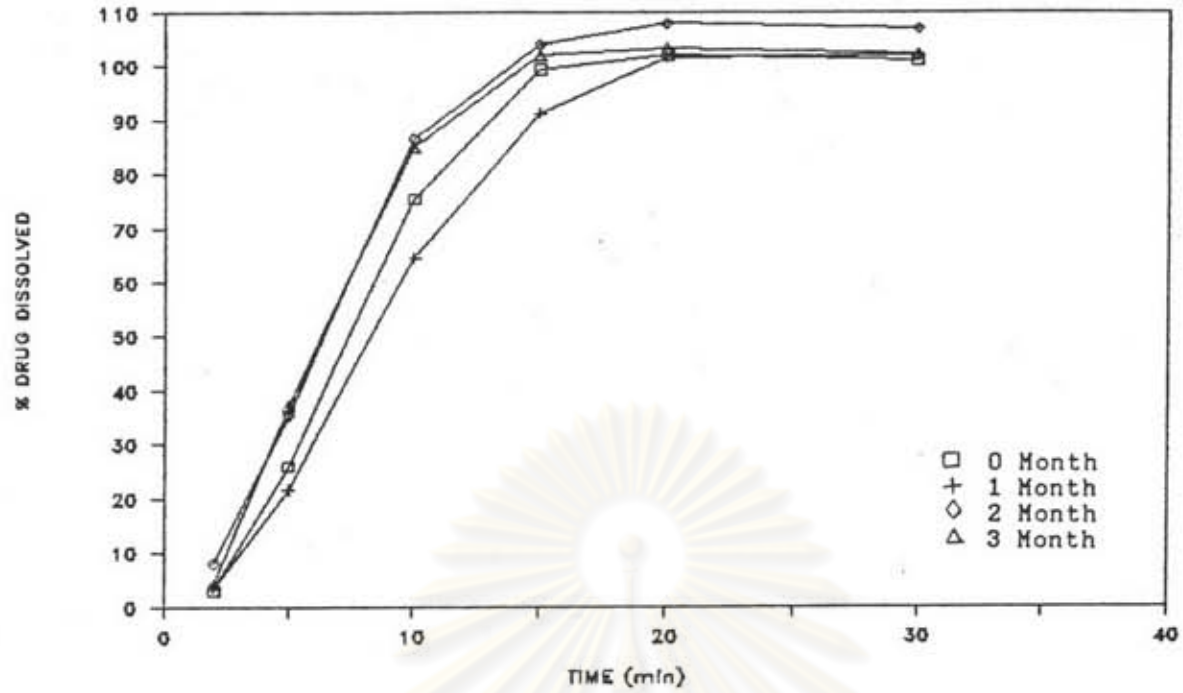


Figure 31 Effect of Aging on Dissolution of Diazepam Tablets Prepared from Sugar-Starch-PVP Granules after Storage for 3 Months at 51 % R.H.

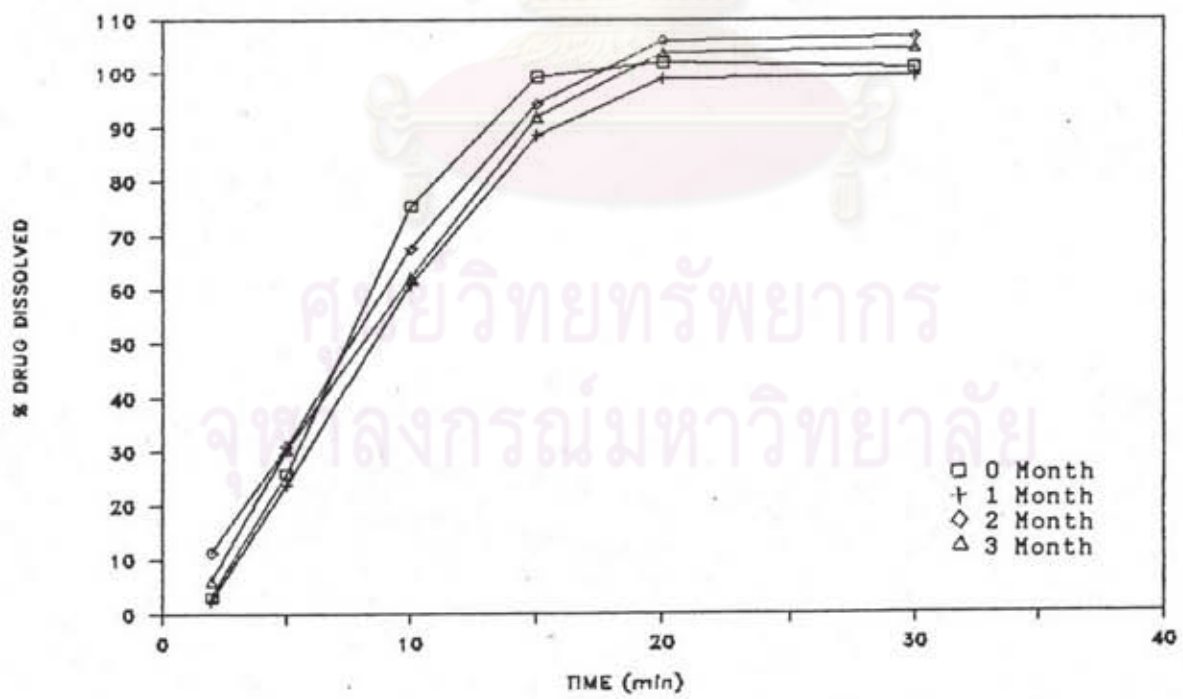


Figure 32 Effect of Aging on Dissolution of Diazepam Tablets Prepared from Sugar-Starch-PVP Granules after Storage for 3 Months at 75 % R.H.

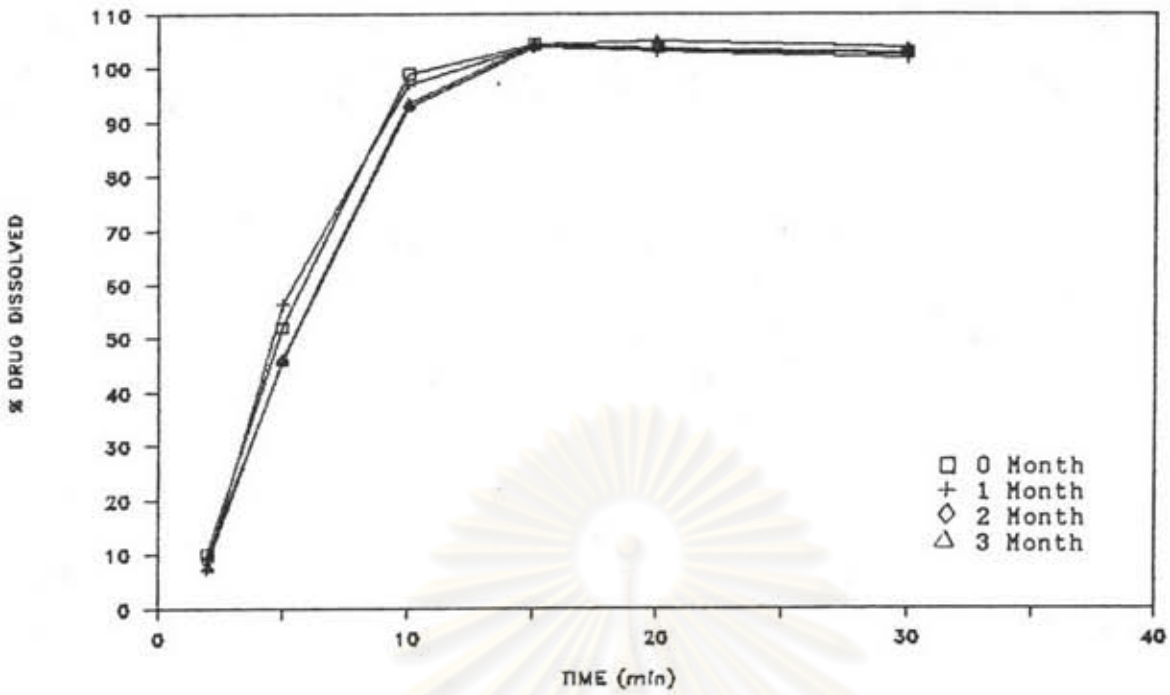


Figure 33 Effect of Aging on Dissolution of Diazepam Tablets Prepared from Sugar-Starch-Gelatin Granules after Storage for 3 Months at Room Condition

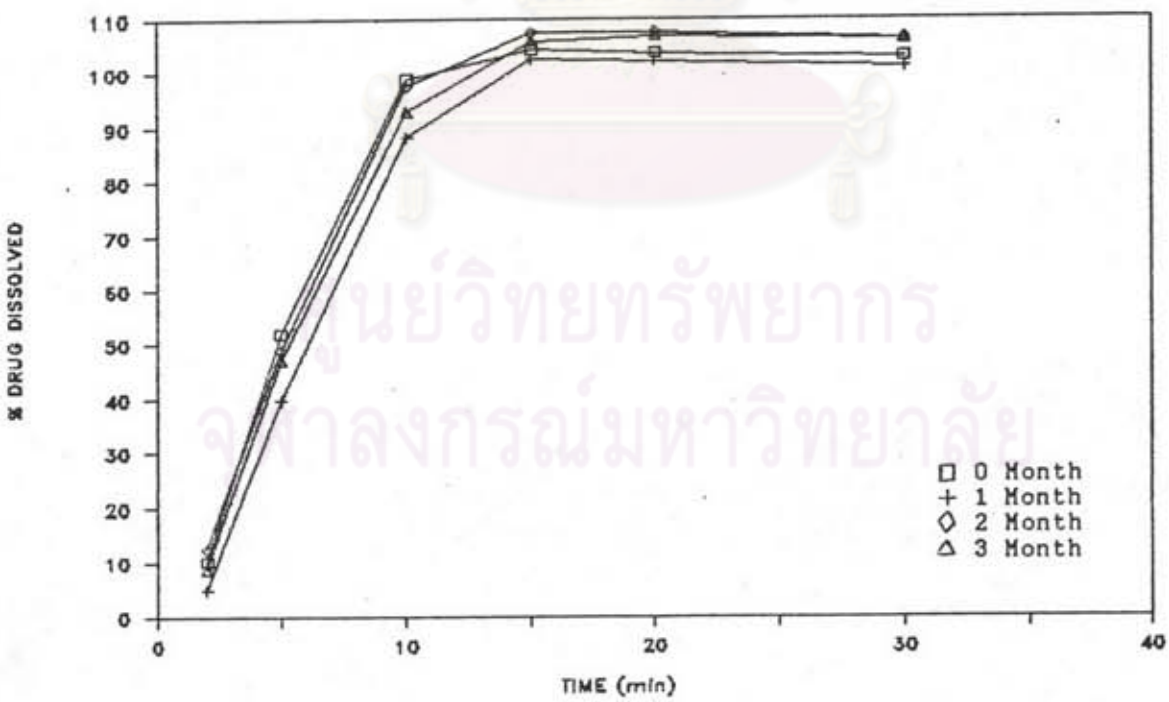


Figure 34 Effect of Aging on Dissolution of Diazepam Tablets Prepared from Sugar-Starch-Gelatin Granules after Storage for 3 Months at 32 % R.H.

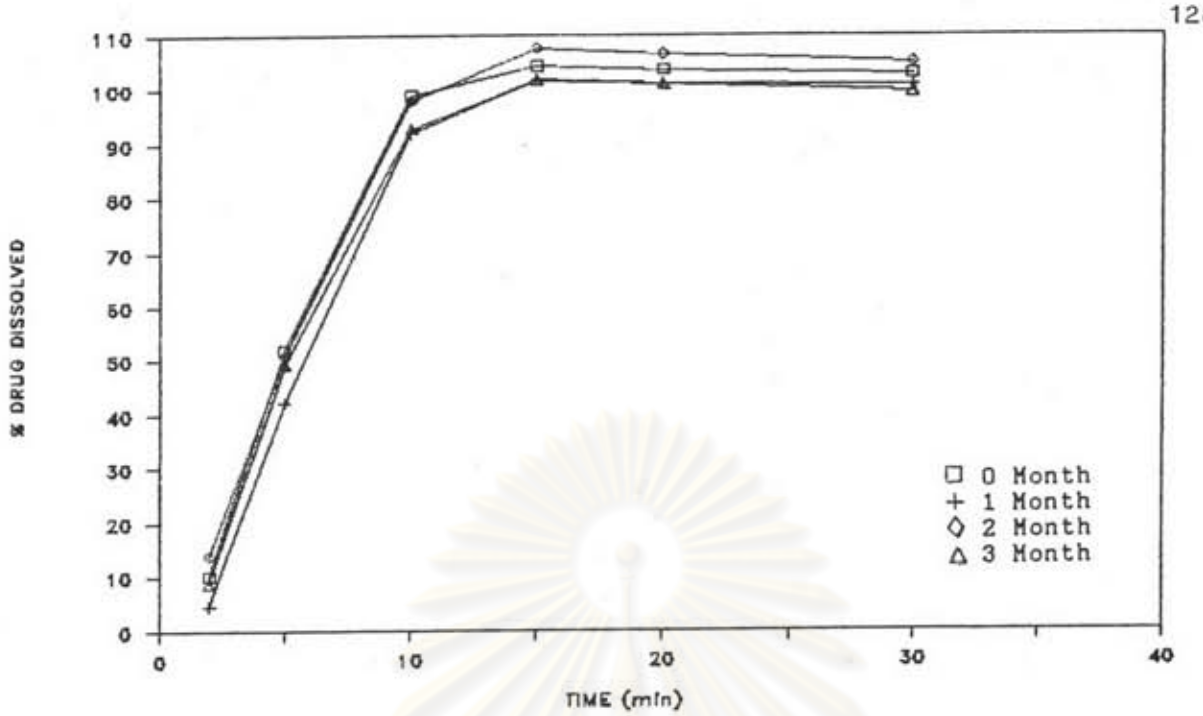


Figure 35 Effect of Aging on Dissolution of Diazepam Tablets Prepared from Sugar-Starch-Gelatin Granules after Storage for 3 Months at 51 % R.H.


Figure 36 Effect of Aging on Dissolution of Diazepam Tablets Prepared from Sugar-Starch-Gelatin Granules after Storage for 3 Months at 75 % R.H.

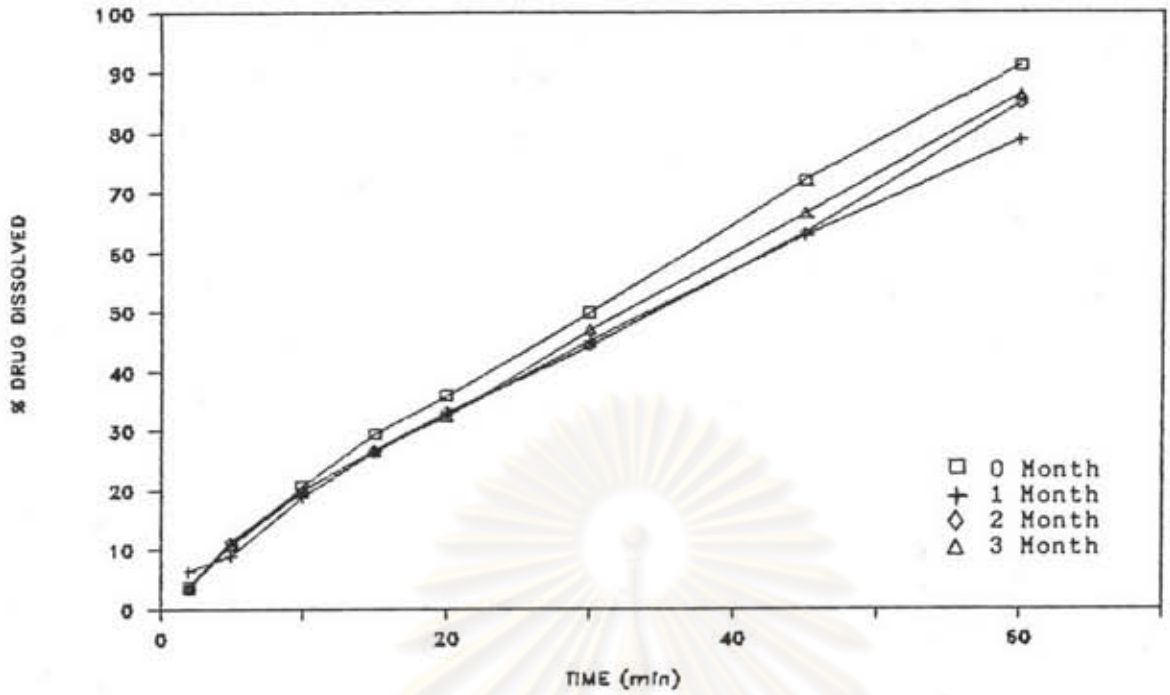


Figure 37 Effect of Aging on Dissolution of Diazepam Tablets Prepared from Sugar-Starch-Methylcellulose Granules after Storage for 3 Months at Room Condition

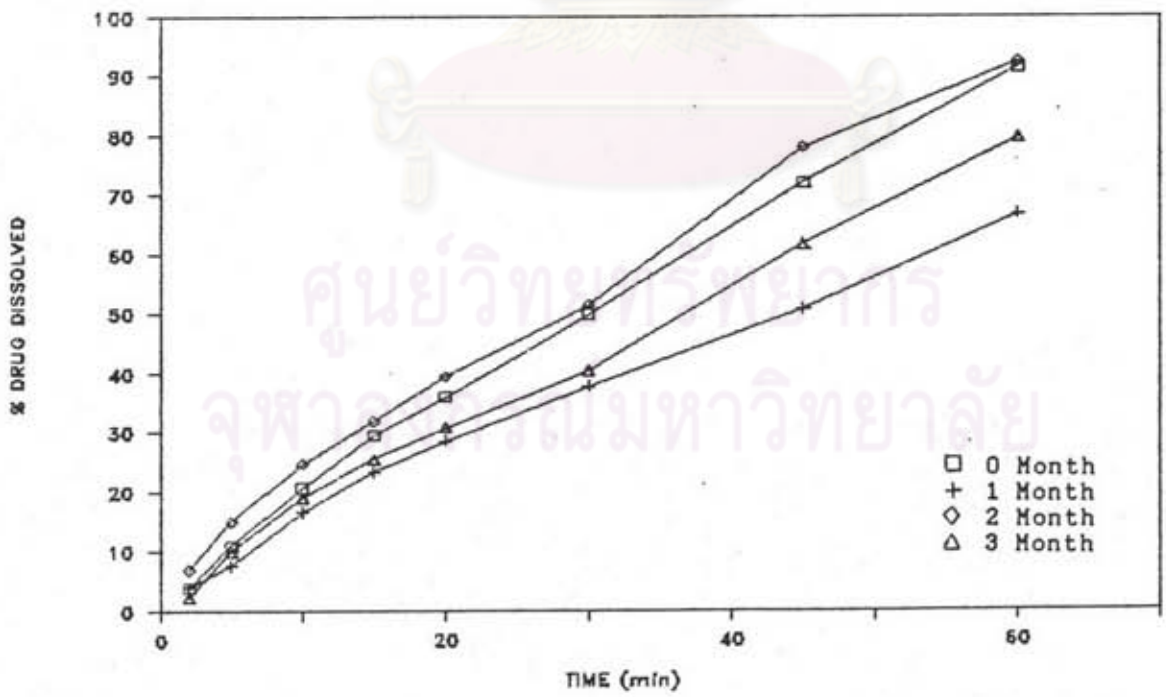


Figure 38 Effect of Aging on Dissolution of Diazepam Tablets Prepared from Sugar-Starch-Methylcellulose Granules after Storage for 3 Months at 32 % R.H.

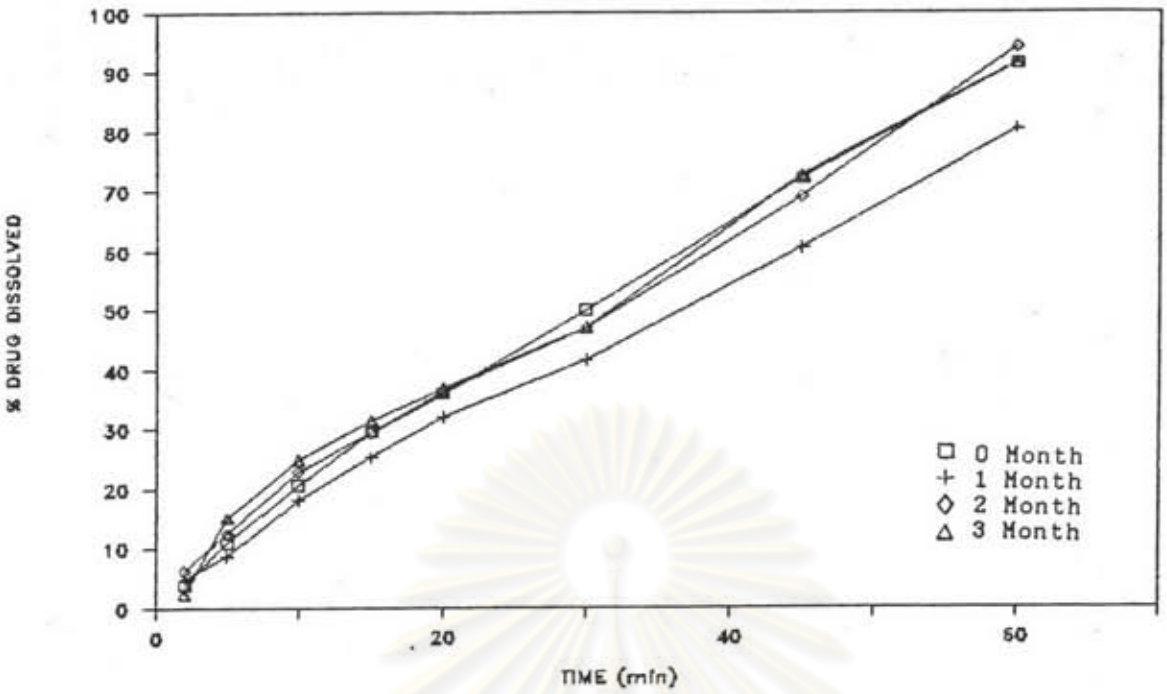


Figure 39 Effect of Aging on Dissolution of Diazepam Tablets Prepared from Sugar-Starch-Methylcellulose Granules after Storage for 3 Months at 51 % R.H.

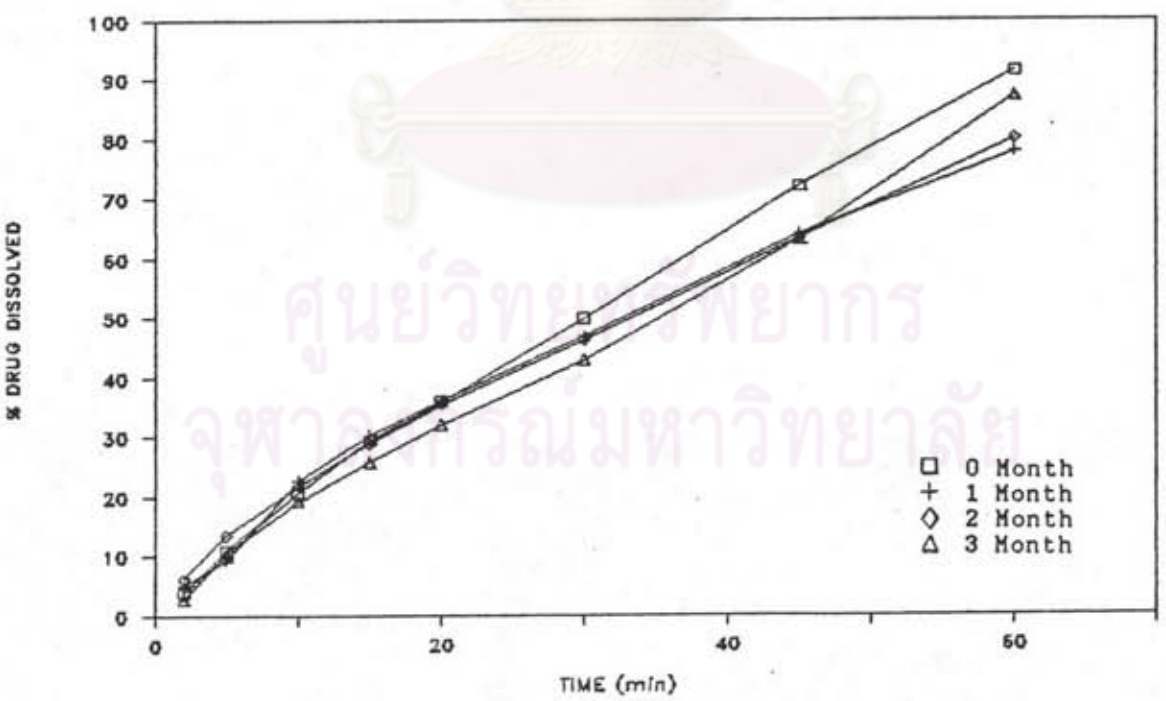


Figure 40 Effect of Aging on Dissolution of Diazepam Tablets Prepared from Sugar-Starch-Methylcellulose Granules after Storage for 3 Months at 75 % R.H.

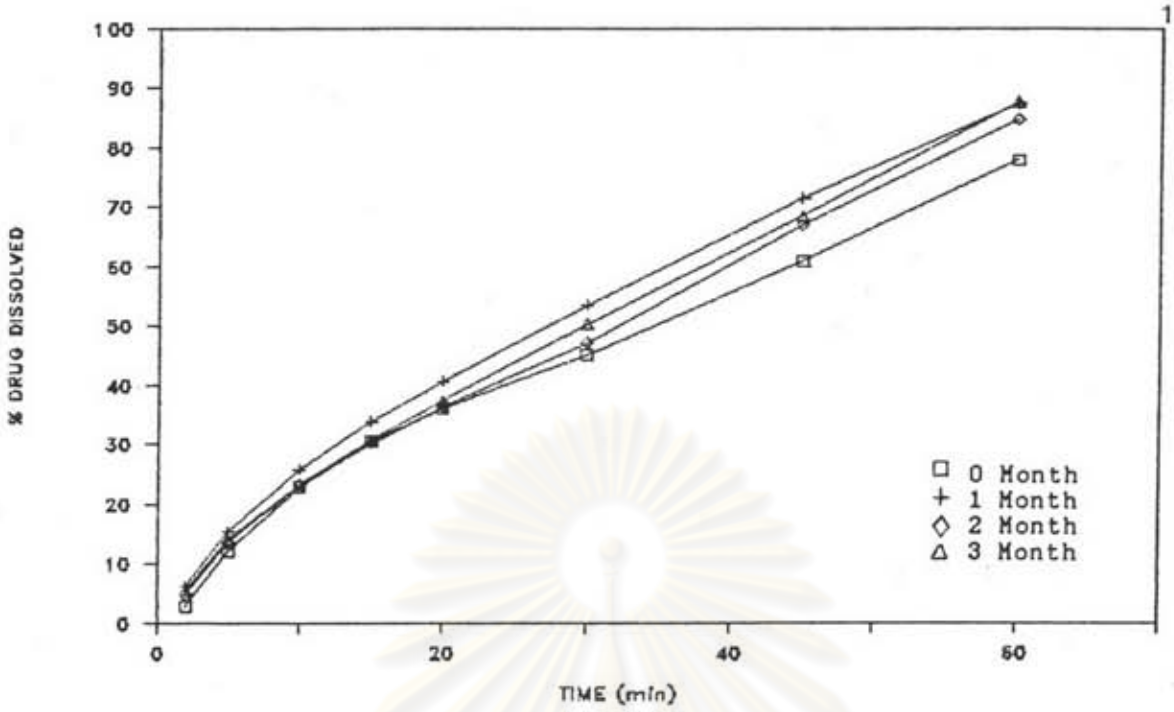


Figure 41 Effect of Aging on Dissolution of Diazepam Tablets Prepared from Sugar-Starch-Starch Granules after Storage for 3 Months at Room Condition

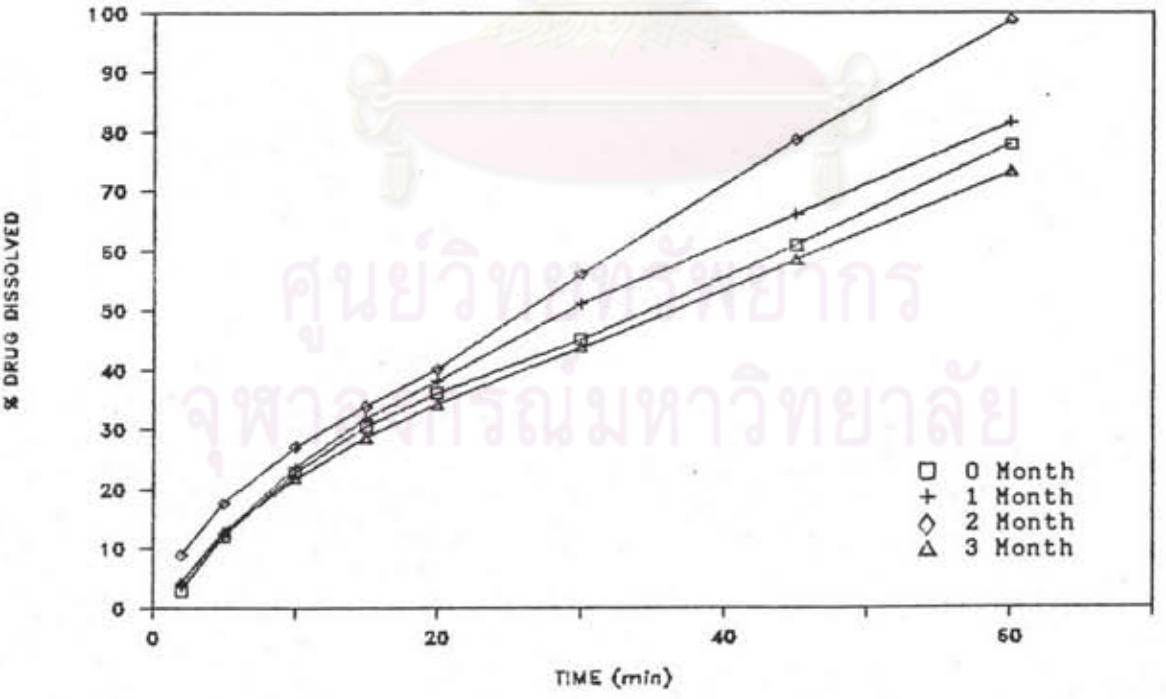


Figure 42 Effect of Aging on Dissolution of Diazepam Tablets Prepared from Sugar-Starch-Starch Granules after Storage for 3 Months at 32 % R.H.

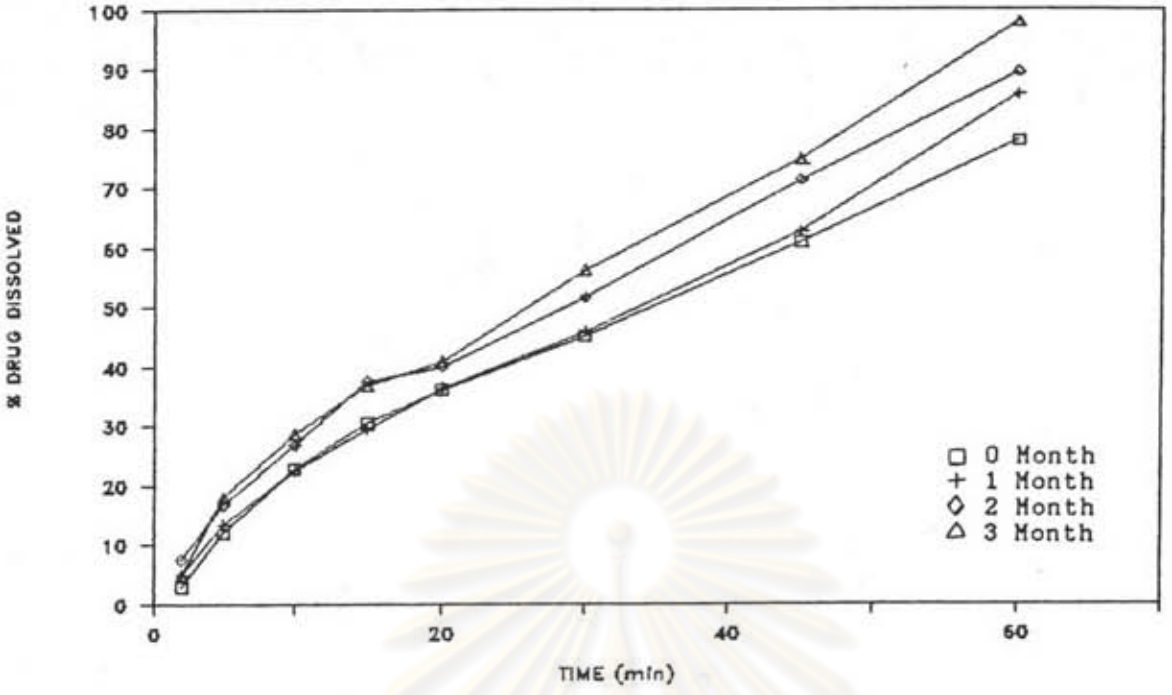


Figure 43 Effect of Aging on Dissolution of Diazepam Tablets Prepared from Sugar-Starch-Starch Granules after Storage for 3 Months at 51 % R.H.

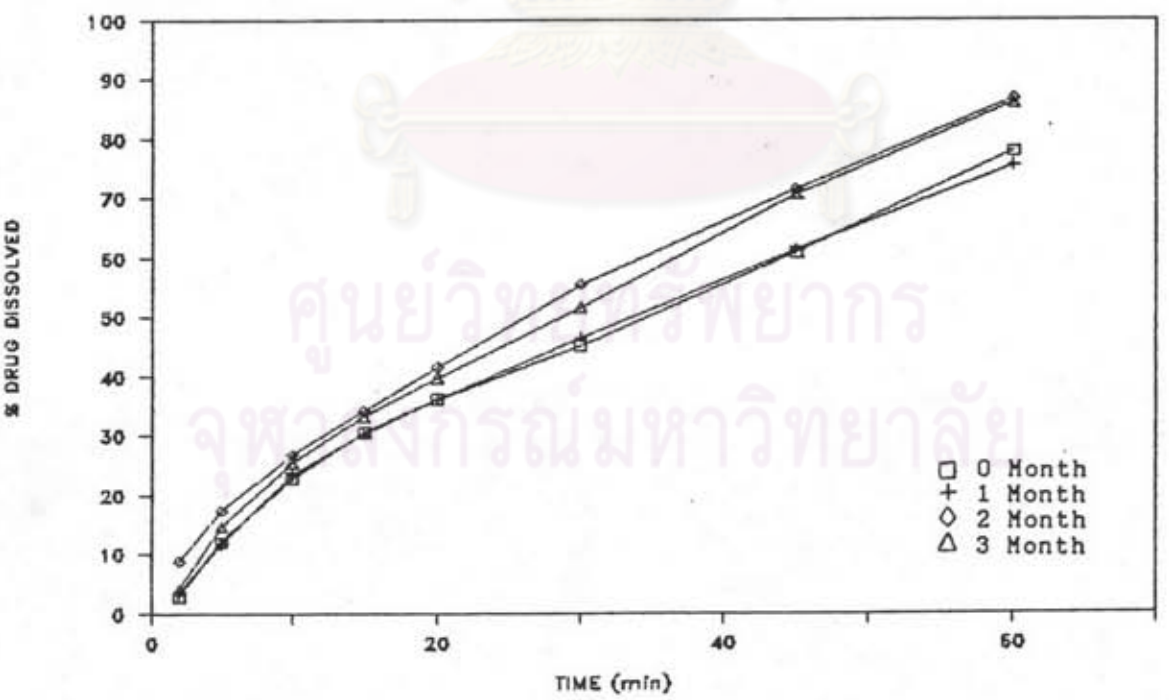


Figure 44 Effect of Aging on Dissolution of Diazepam Tablets Prepared from Sugar-Starch-Starch Granules after Storage for 3 Months at 75 % R.H.

the USP requirement for dissolution. After storage, tablets made from sugar-starch-methylcellulose granules at various conditions for 3 months showed decreasing in dissolution rates while those tablets prepared using sugar-starch-starch granules seemed to increase slightly in dissolution. However, the dissolution of diazepam tablets prepared using these two types of granules after storage for 3 months at all conditions did not meet the USP specification. Their dissolutions were within the range of 50-74 % of diazepam release at 30 minutes.

**Dissolution of Chlorpheniramine Maleate Tablets**

Figures 45-60 illustrate the dissolution behaviors of chlorpheniramine maleate tablets made from sugar-starch-PVP, sugar-starch-gelatin, sugar-starch-methylcellulose, and sugar-starch-starch granules after storage for 3 months under various conditions (the experimental data are presented in Appendices K-N). At the initial time of storage, the dissolution of tablets made from sugar-starch-PVP and sugar-starch-gelatin exhibited 100 % chlorpheniramine maleate release within 30 minutes which complied with the USP specification (75 % chlorpheniramine maleate dissolved within 45 minutes). Although the dissolution of these tablet formulations after storage for 3 months under various conditions yielded 100 % chlorpheniramine maleate release within the

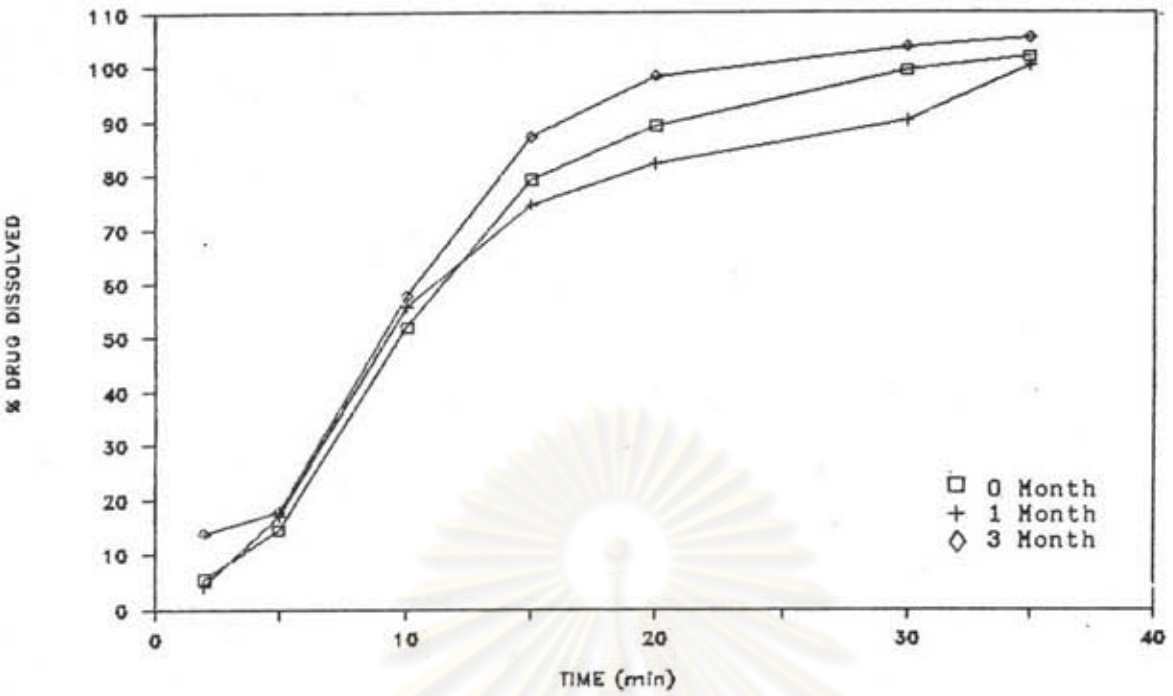


Figure 45 Effect of Aging on Dissolution of Chlorpheniramine Maleate Tablets Prepared from Sugar-Starch-PVP Granules after Storage for 3 Months at Room Condition

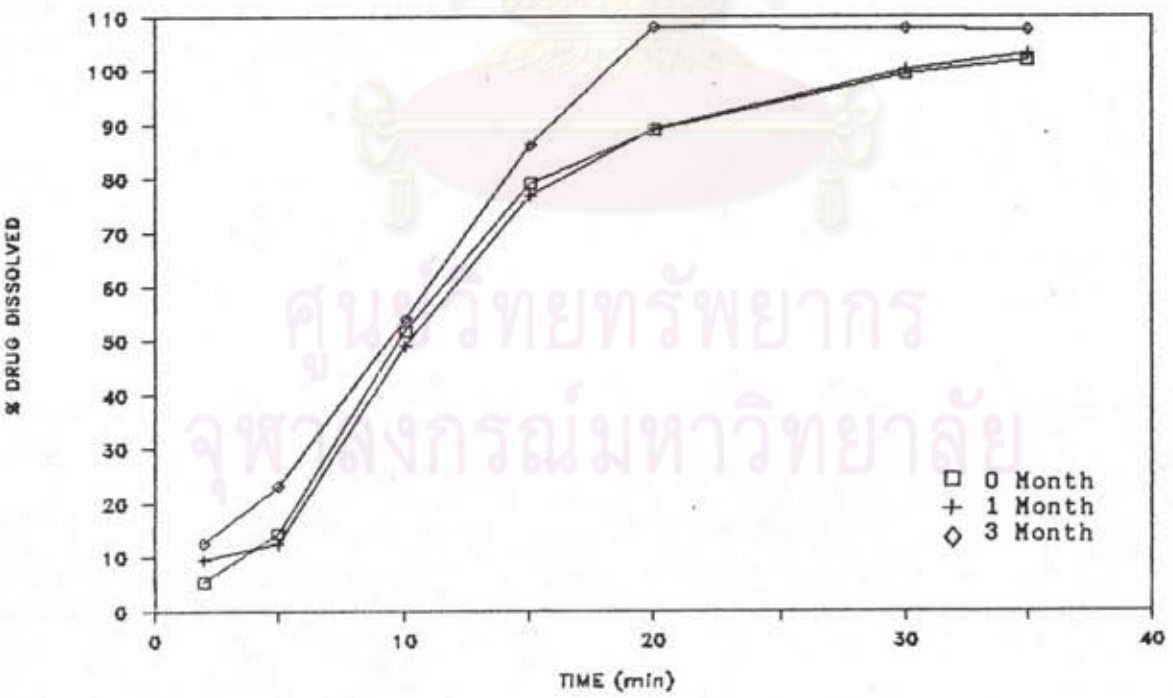


Figure 46 Effect of Aging on Dissolution of Chlorpheniramine Maleate Tablets Prepared from Sugar-Starch-PVP Granules after Storage for 3 Months at 32 % R.H.

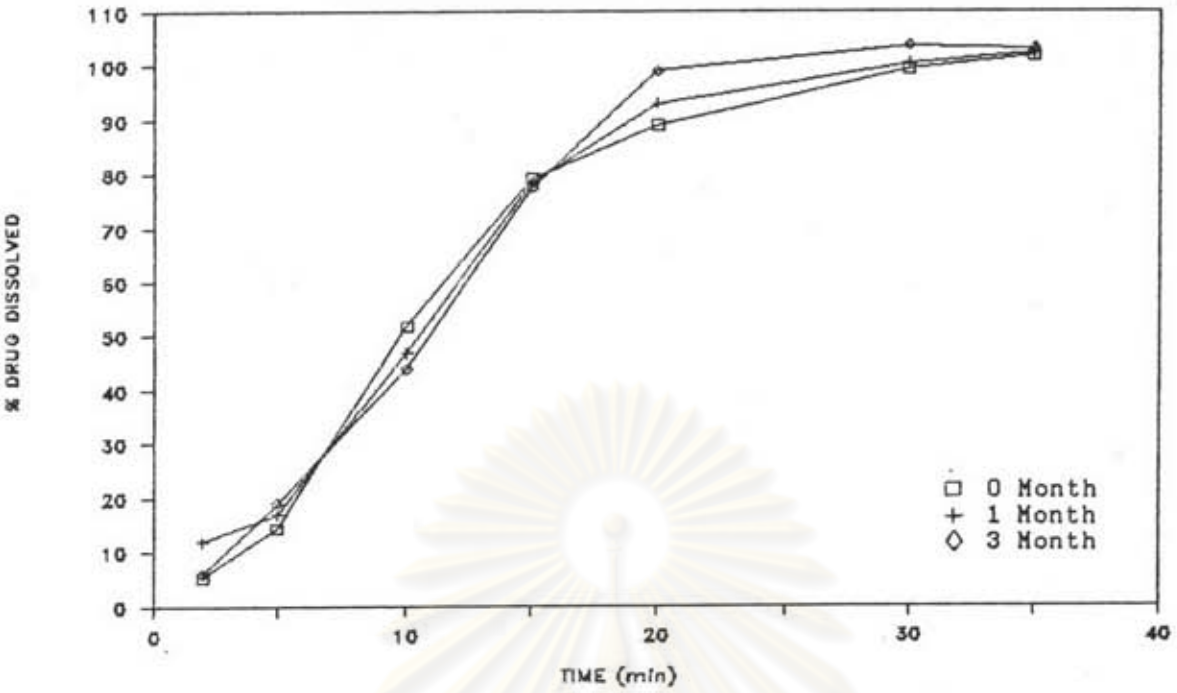


Figure 47 Effect of Aging on Dissolution of Chlorpheniramine Maleate Tablets Prepared from Sugar-Starch-PVP Granules after Storage for 3 Months at 51 % R.H.

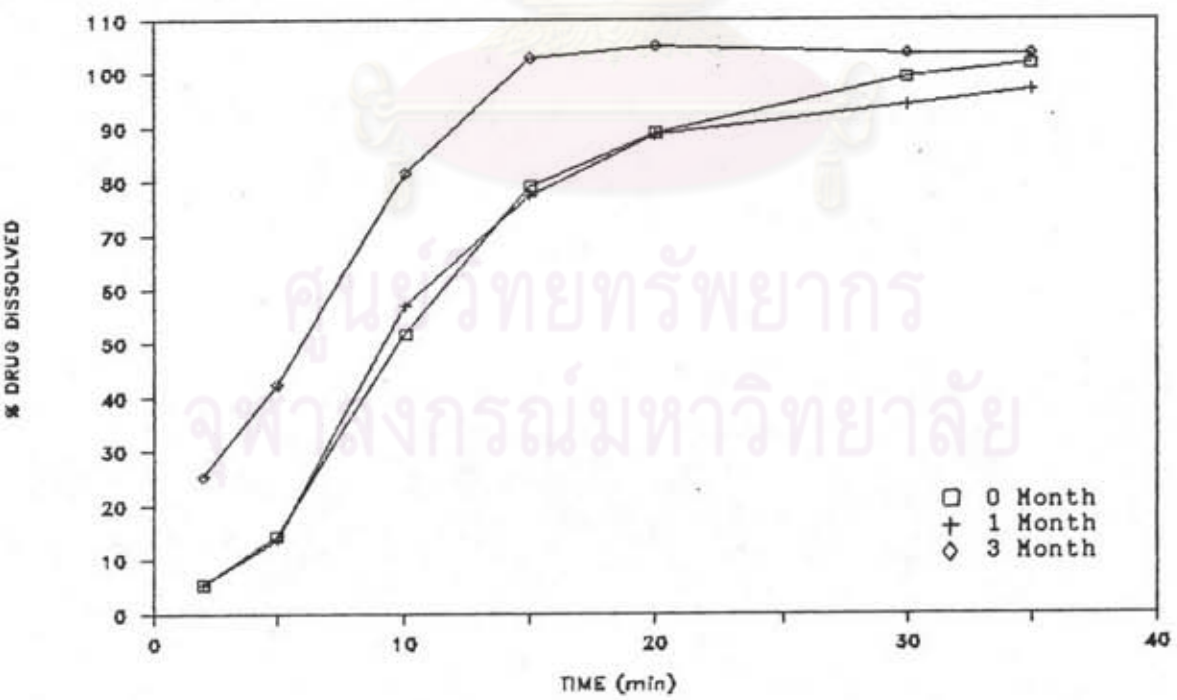


Figure 48 Effect of Aging on Dissolution of Chlorpheniramine Maleate Tablets Prepared from Sugar-Starch-PVP Granules after Storage for 3 Months at 75 % R.H.

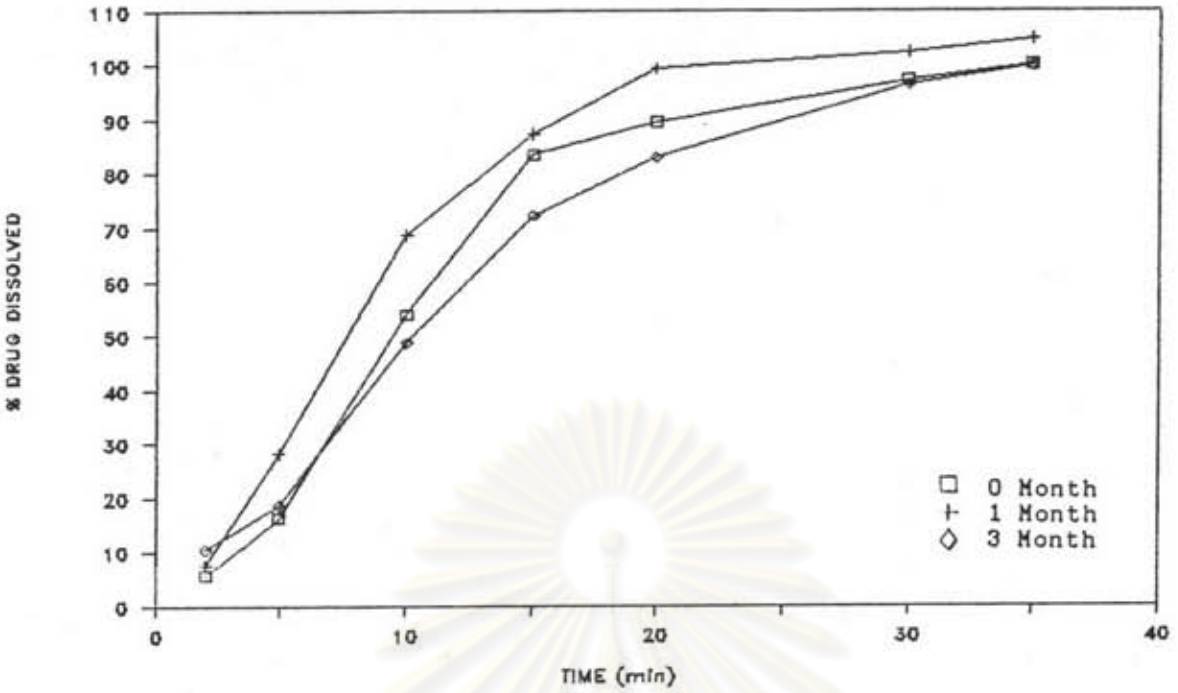


Figure 49 Effect of Aging on Dissolution of Chlorpheniramine Maleate Tablets Prepared from Sugar-Starch-Gelatin Granules after Storage for 3 Months at Room Condition

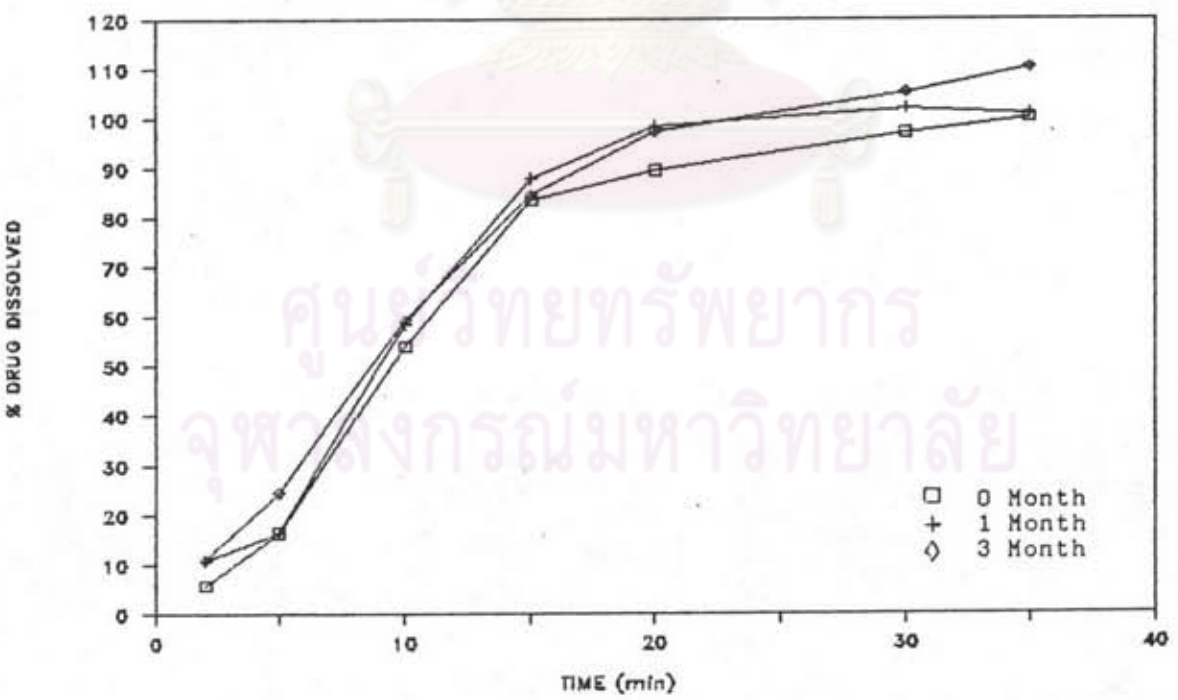


Figure 50 Effect of Aging on Dissolution of Chlorpheniramine Maleate Tablets Prepared from Sugar-Starch-Gelatin Granules after Storage for 3 Months at 32 % R.H.

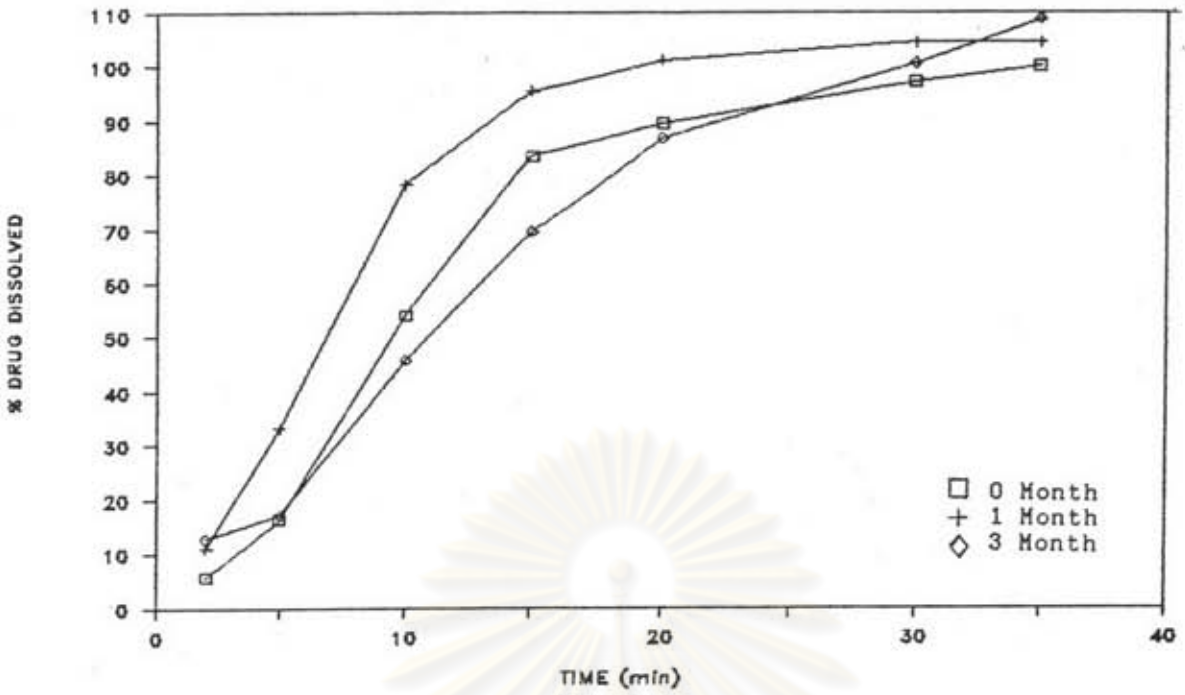


Figure 51 Effect of Aging on Dissolution of Chlorpheniramine Maleate Tablets Prepared from Sugar-Starch-Gelatin Granules after Storage for 3 Months at 51 % R.H.

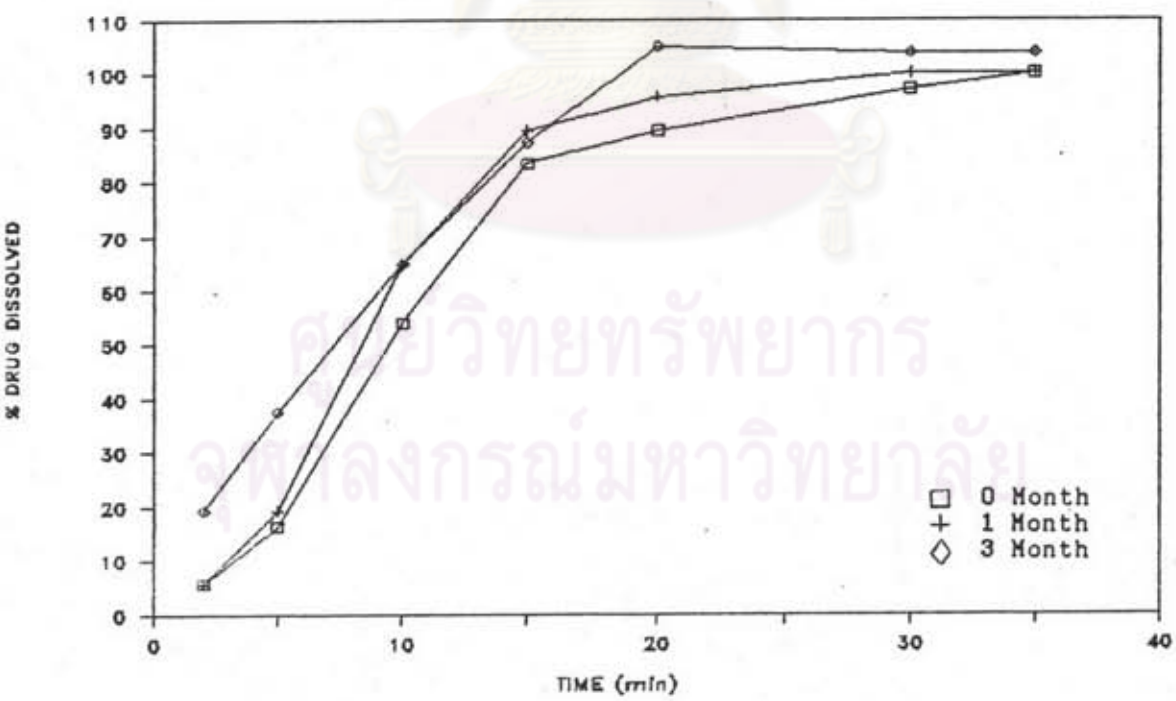


Figure 52 Effect of Aging on Dissolution of Chlorpheniramine Maleate Tablets Prepared from Sugar-Starch-Gelatin Granules after Storage for 3 Months at 75 % R.H.

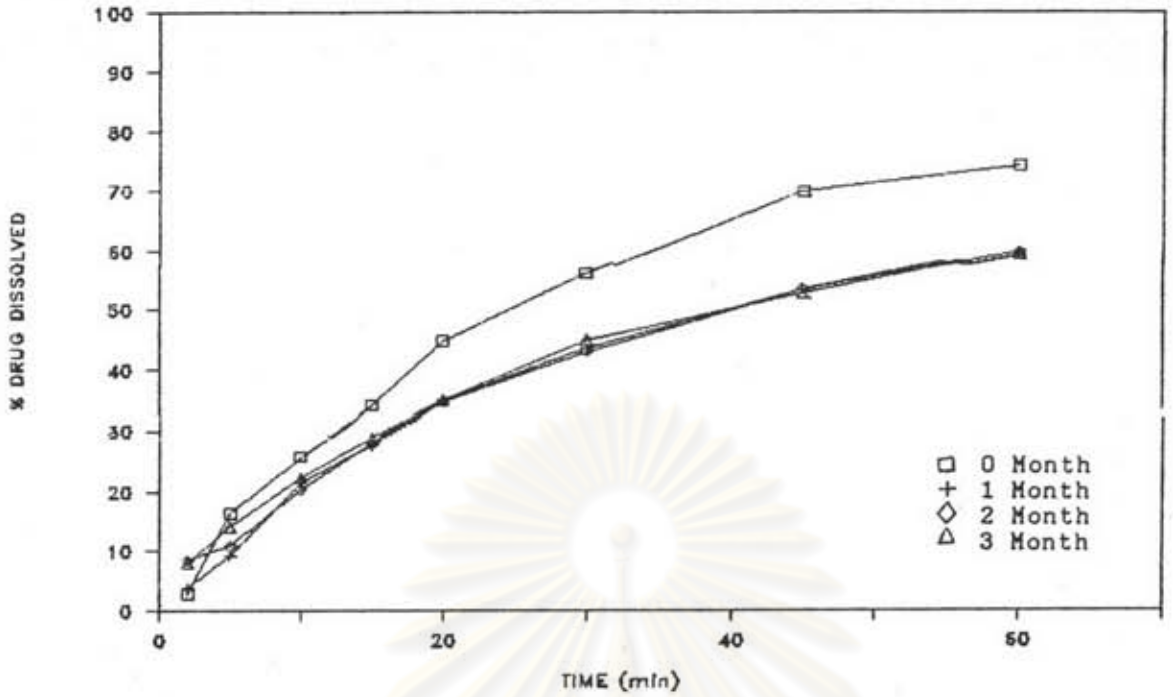


Figure 53 Effect of Aging on Dissolution of Chlorpheniramine Maleate Tablets Prepared from Sugar-Starch-Methylcellulose Granules after Storage for 3 Months at Room Condition

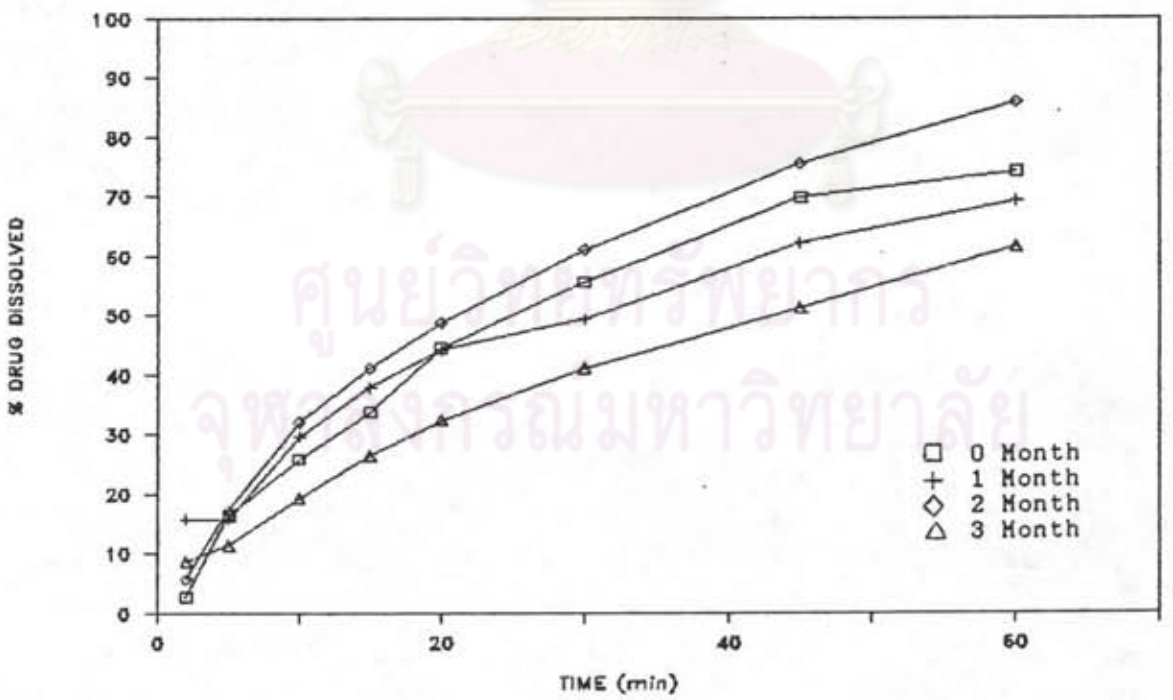


Figure 54 Effect of Aging on Dissolution of Chlorpheniramine Maleate Tablets Prepared from Sugar-Starch-Methylcellulose Granules after Storage for 3 Months at 32 % R.H.

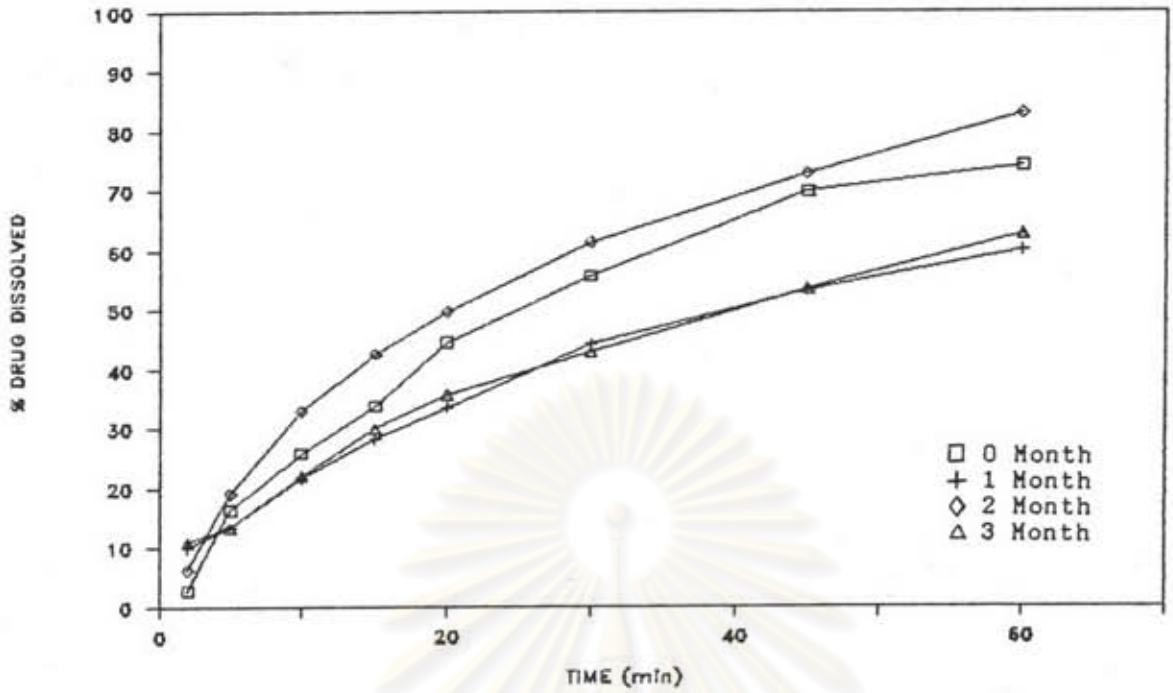


Figure 55 Effect of Aging on Dissolution of Chlorpheniramine Maleate Tablets Prepared from Sugar-Starch-Methylcellulose Granules after Storage for 3 Months at 51 % R.H.

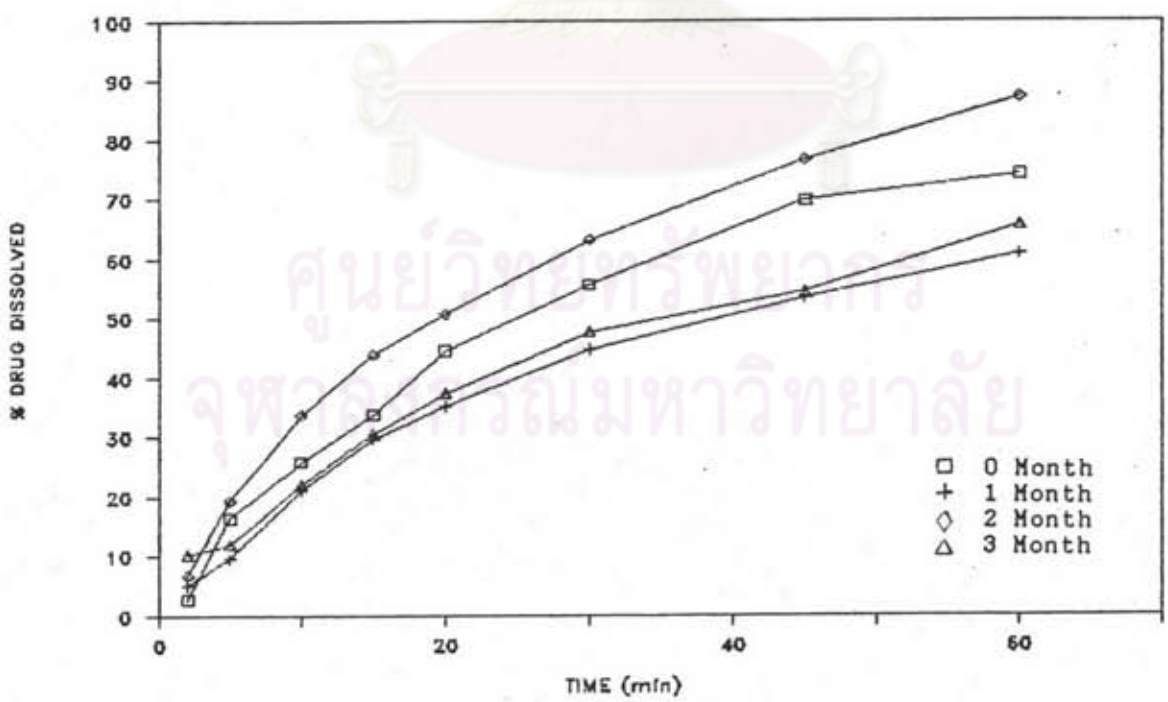


Figure 56 Effect of Aging on Dissolution of Chlorpheniramine Maleate Tablets Prepared from Sugar-Starch-Methylcellulose Granules after Storage for 3 Months at 75 % R.H.

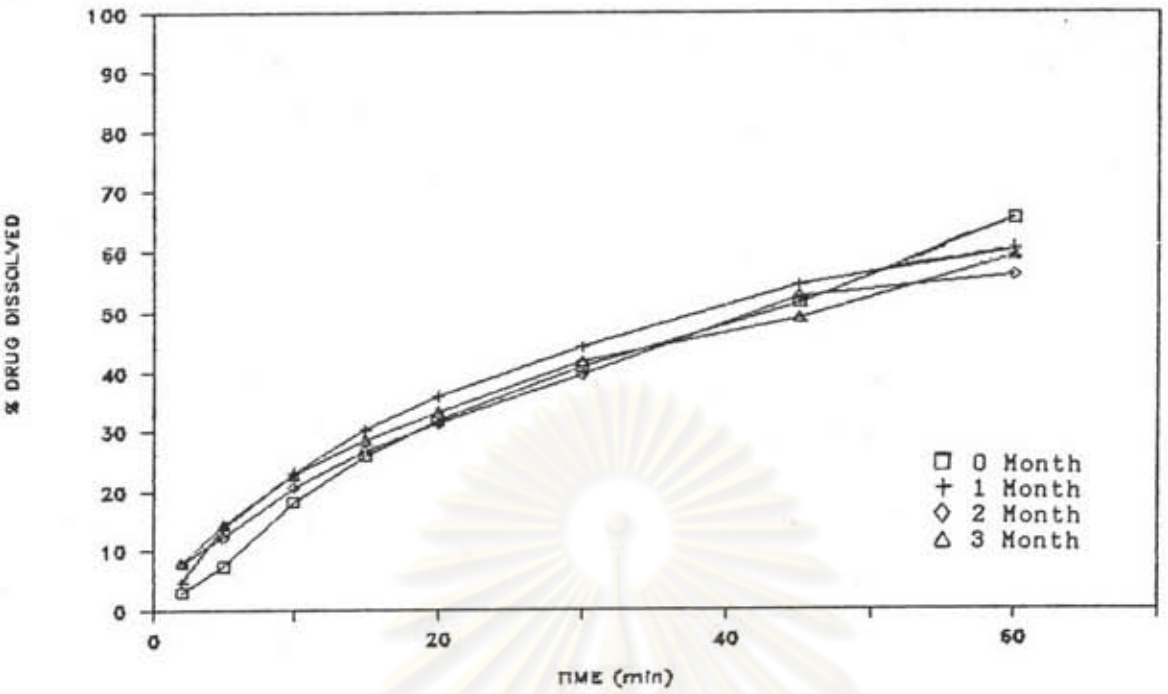


Figure 57 Effect of Aging on Dissolution of Chlorpheniramine Maleate Tablets Prepared from Sugar-Starch-Starch Granules after Storage for 3 Months at Room Condition

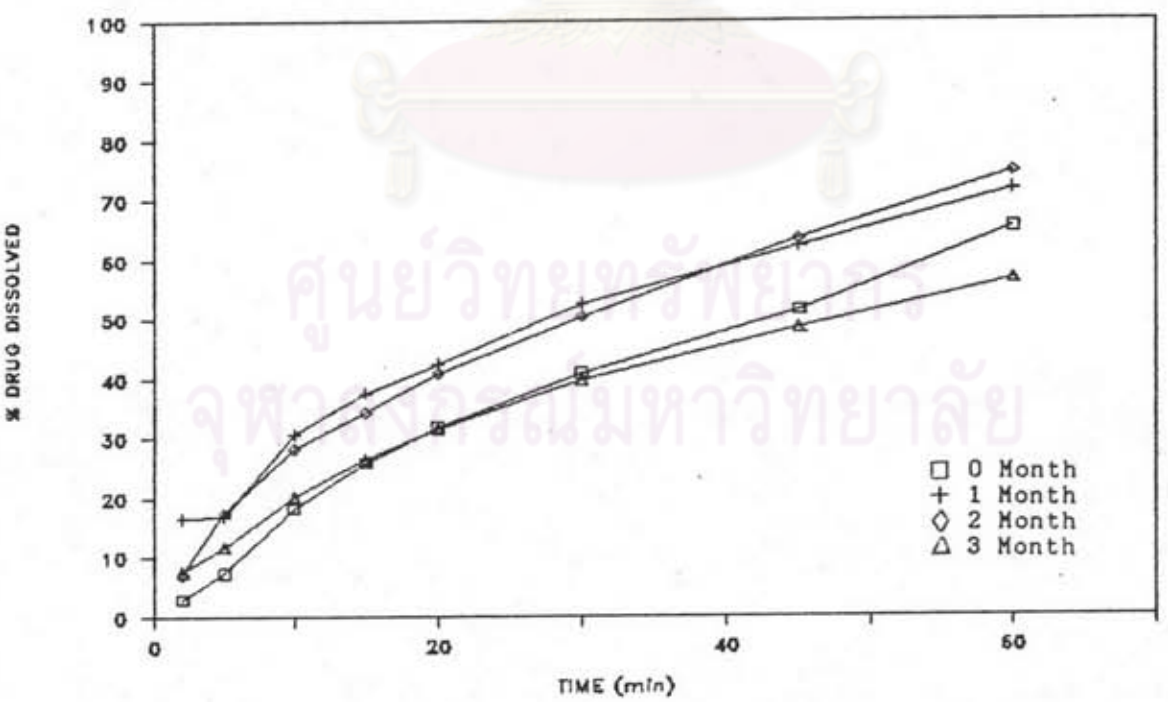


Figure 58 Effect of Aging on Dissolution of Chlorpheniramine Maleate Tablets Prepared from Sugar-Starch-Starch Granules after Storage for 3 Months at 32 % R.H.

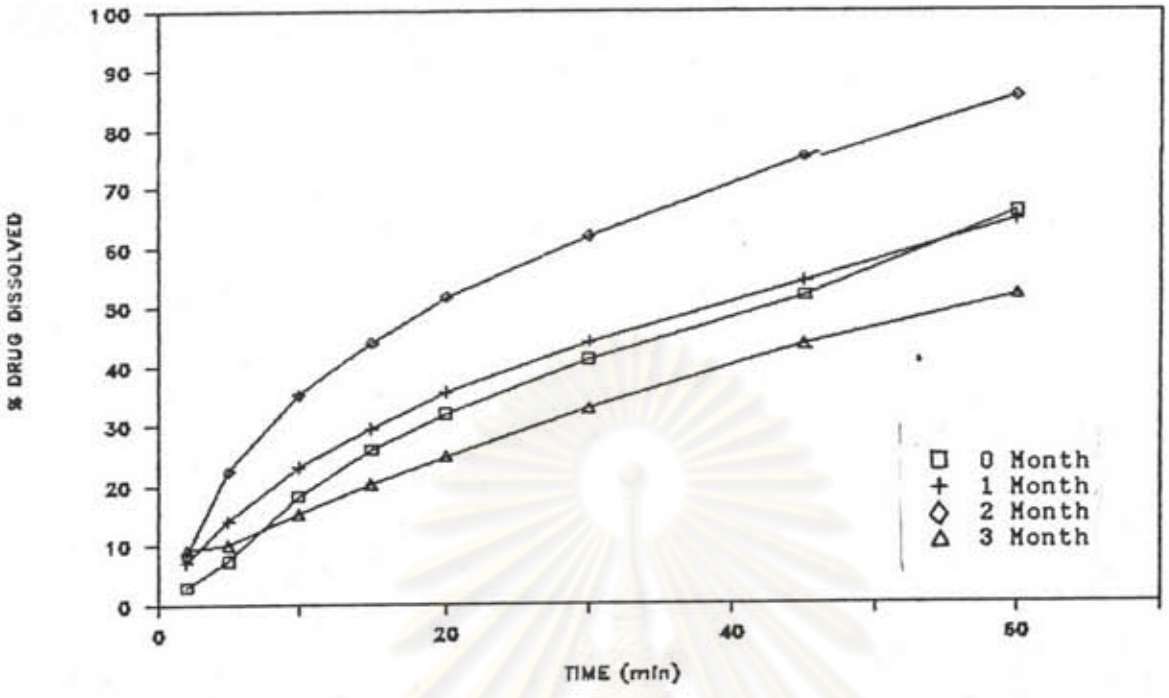


Figure 59 Effect of Aging on Dissolution of Chlorpheniramine Maleate Tablets Prepared from Sugar-Starch-Starch Granules after Storage for 3 Months at 51 % R.H.

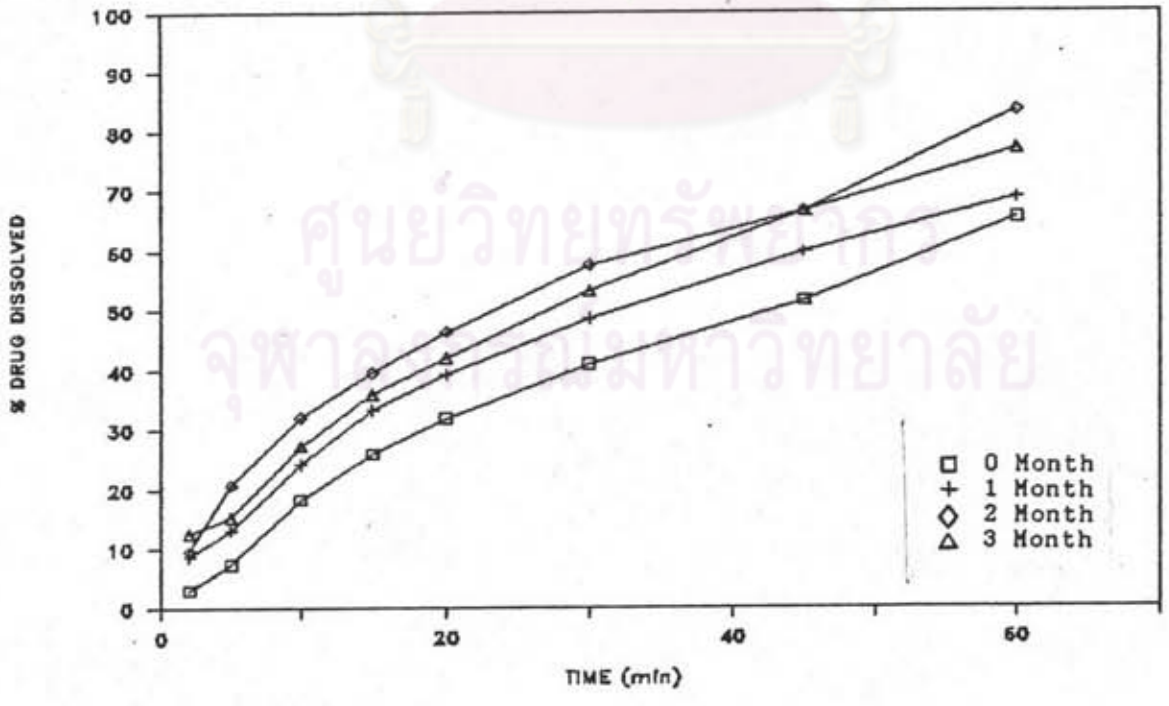


Figure 60 Effect of Aging on Dissolution of Chlorpheniramine Maleate Tablets Prepared from Sugar-Starch-Starch Granules after Storage for 3 Months at 75 % R.H.

same time but difference of the dissolution profiles among each month interval were observed as compared with those of diazepam tablets (Figures 45-52).

The chlorpheniramine maleate tablets made from sugar-starch-methylcellulose and sugar-starch-starch granules did not meet the USP requirement either at initial or after storage as shown in Figures 53-60. Their dissolutions were within the range of 43-74 % of chlorpheniramine maleate released at 45 minutes. Inconsistent change in dissolution of tablets made from these two types of granules were observed among each month interval of storage at all conditions.

8. **Physical Properties of Tablets Prepared from Storage Granules**

Tables 41 and 42 show weight variation, hardness, disintegration time, friability and thickness of diazepam and chlorpheniramine maleate tablets prepared from all types of granules after storage for 3 months at room conditions. Tablets prepared from all granule formulations taken at the end of first, second, and third month could be manufactured to required physical properties. The physical characteristics of tablets were comparable to those made from freshly prepared granules.

Table 41 Effect of Aging on the Physical Properties of Diazepam Tablets Prepared from all Types of Storage Granules

| Type of Granules | Month | Physical Properties | | | | |
|---|---|---|---|---|---|---|
| | | Weight Variation (mg) Mean±S.D. | Hardness (Kp) Mean±S.D. | D.T.[a] (min) Mean±S.D. | Friability (%) | Thickness (mm) Mean±S.D. |
| Sugar-Starch-PVP | 0 | 122.0±0.82 | 6.37±0.45 | 3.91±0.36 | <0.1 | 2.74±1.26 |
| | 1 | 122.5±0.80 | 5.66±0.22 | 3.74±0.25 | <0.1 | 2.76±1.70 |
| | 2 | 124.7±0.89 | 5.83±0.28 | 4.83±0.61 | <0.1 | 2.77±2.39 |
| | 3 | 121.9±1.16 | 6.18±0.40 | 4.01±0.37 | <0.1 | 2.73±2.01 |
| Sugar-Starch-Gelatin | 0 | 121.1±1.41 | 6.20±0.57 | 3.46±0.25 | <0.1 | 2.75±2.11 |
| | 1 | 125.6±1.30 | 6.58±0.22 | 3.48±0.19 | <0.1 | 2.84±2.58 |
| | 2 | 124.1±1.56 | 5.73±0.58 | 3.69±0.26 | <0.1 | 2.82±2.00 |
| | 3 | 118.3±1.85 | 6.11±0.54 | 3.19±0.27 | <0.1 | 2.69±1.87 |
| Sugar-Starch-Methyl cellulose | 0 | 119.9±1.16 | 6.84±0.44 | 9.43±0.30 | 0.26 | 2.61±0.68 |
| | 1 | 120.6±0.57 | 5.54±0.33 | 8.54±0.42 | 0.30 | 2.66±1.31 |
| | 2 | 119.6±0.88 | 6.04±0.52 | 8.60±0.31 | 0.16 | 2.62±1.15 |
| | 3 | 119.9±1.12 | 6.74±0.57 | 8.69±0.61 | 0.14 | 2.62±1.19 |
| Sugar-Starch-Starch | 0 | 122.4±1.50 | 6.64±0.58 | 6.96±0.15 | 0.18 | 2.66±3.45 |
| | 1 | 119.4±1.83 | 5.95±0.38 | 6.46±0.72 | 0.25 | 2.61±2.23 |
| | 2 | 120.3±1.16 | 5.69+0.23 | 7.26+0.43 | 0.12 | 2.66±2.11 |
| | 3 | 120.6±1.35 | 6.32±0.36 | 6.46±0.30 | 0.14 | 2.63±2.02 |

[a] = Disintegration time

Table 42 Effect of Aging on the Physical Properties of Chlopheniramine Maleate Tablets Prepared from all Types of Storage Granules

| Type of Granules | Month | Physical Properties: Weight Variation (mg) Mean±S.D. | Hardness (Kp) Mean±S.D. | D.T.* (min) Mean±S.D. | Friability (%) | Thickness (mm) Mean±S.D. |
|---|---|---|---|---|---|---|
| Sugar-Starch-PVP | 0 | 123.5±1.22 | 5.79±0.18 | 3.57±0.30 | <0.1 | 2.75±2.82 |
| | 1 | 122.9±0.76 | 5.77±0.26 | 3.15±0.27 | <0.1 | 2.75±2.00 |
| | 2 | 123.2±1.13 | 6.05±0.39 | 3.73±0.36 | <0.1 | 2.77±1.61 |
| | 3 | 120.8±0.96 | 5.78±0.34 | 3.73±0.41 | <0.1 | 2.71±1.84 |
| Sugar-Starch-Gelatin | 0 | 120.2±1.46 | 6.04±0.39 | 3.35±0.27 | <0.1 | 2.73±2.12 |
| | 1 | 120.9±1.03 | 6.43±0.41 | 3.47±0.41 | <0.1 | 2.72±1.25 |
| | 2 | 121.4±1.49 | 5.66±0.49 | 3.03±0.10 | <0.1 | 2.78±1.61 |
| | 3 | 120.1±1.42 | 5.76±0.69 | 3.08±0.28 | <0.1 | 2.77±1.52 |
| Sugar-Starch-Methyl cellulose | 0 | 122.1±1.06 | 7.04±0.28 | 7.49±0.42 | 0.22 | 2.67±2.37 |
| | 1 | 120.1±0.79 | 6.03±0.36 | 6.90±0.89 | 0.30 | 2.64±1.03 |
| | 2 | 119.8±0.87 | 6.32±0.51 | 6.97±0.29 | 0.16 | 2.61±1.05 |
| | 3 | 121.2±0.91 | 5.89±0.53 | 5.45±0.08 | 0.10 | 2.66±1.63 |
| Sugar-Starch-Starch | 0 | 122.8±1.58 | 7.01±0.65 | 7.59±1.92 | 0.15 | 2.68±3.43 |
| | 1 | 119.3±2.74 | 5.44±0.71 | 5.74±0.72 | 0.29 | 2.64±2.06 |
| | 2 | 122.7±1.74 | 5.94±0.56 | 7.03±0.19 | 0.08 | 2.70±1.64 |
| | 3 | 120.8±1.02 | 6.81±0.46 | 5.71±0.15 | 0.13 | 2.63±1.66 |

* = Disintegration time

**Dissolution of Diazepam Tablets**

The dissolution behaviors of diazepam tablets prepared using storage granules at room environment are illustrated in Figures 61-64 (the experimental data are presented in Appendix O). Dissolution of freshly prepared diazepam tablets using sugar-starch-PVP and sugar-starch-gelatin granules exhibited 100 % diazepam release within 20 and 15 minutes, respectively. The amount of drug released met the USP requirement (85 % of diazepam dissolved within 30 minutes). Dissolution of tablets prepared from storage granules at the end of 1, 2 and 3 month showed the same dissolution rate in accordance with freshly prepared tablets (Figures 61-62).

It could be seen from Figures 63-64 that freshly prepared tablets using sugar-starch-methylcellulose and sugar-starch-starch granules did not meet the USP specification for dissolution test. Little decrease in dissolutions was observed when diazepam tablets were compressed from sugar-starch-methylcellulose granules after storage for 1, 2, 3 months in comparing with initial results. This was in contrary with the dissolution behaviors of tablets made from sugar-starch-starch granules which slight increase in dissolutions were found. However, all of these tablets prepared from these two types of storage granules did not meet the USP requirement

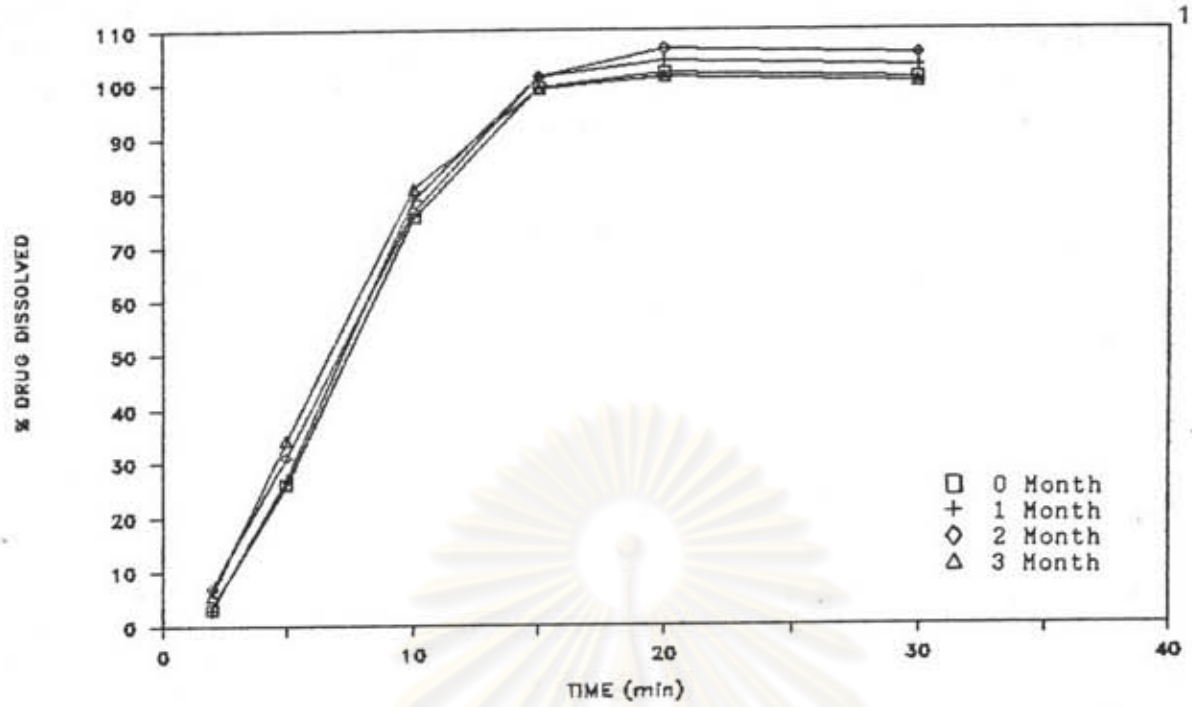


Figure 61 Effect of Aging on Dissolution of Diazepam Tablets Prepared from Storage Sugar-Starch-PVP Granules


Figure 62 Effect of Aging on Dissolution of Diazepam Tablets Prepared from Storage Sugar-Starch-Gelatin Granules

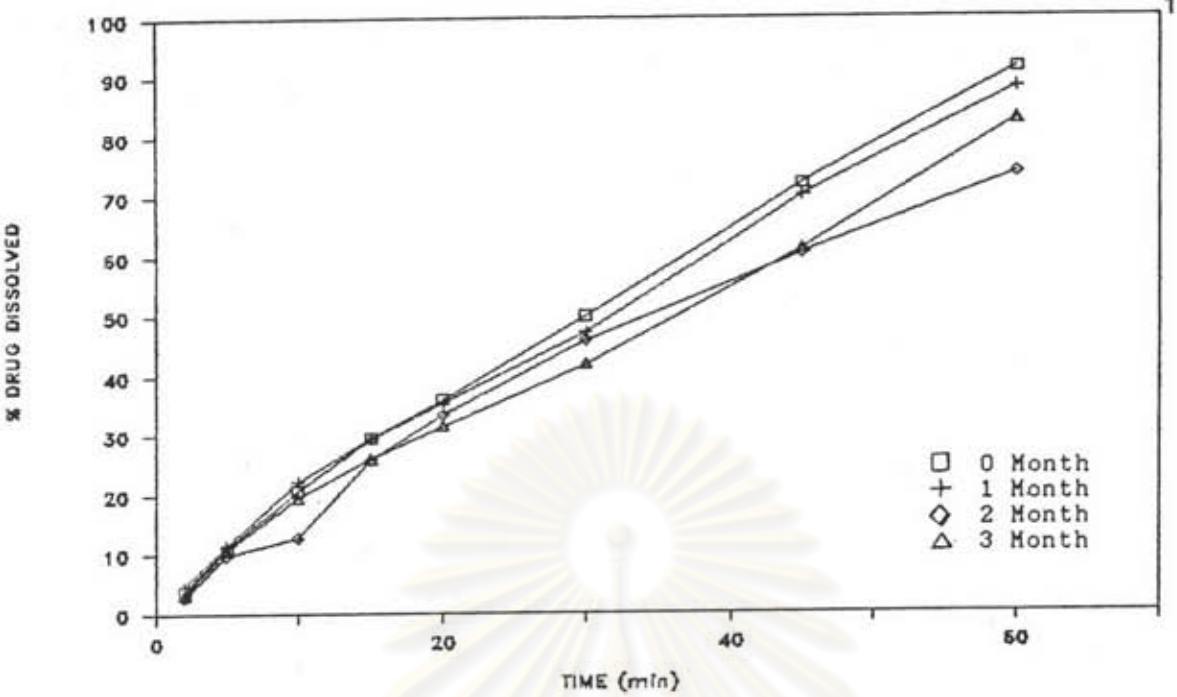


Figure 63 Effect of Aging on Dissolution of Diazepam Tablets Prepared from Storage Sugar-Starch-Methylcellulose Granules

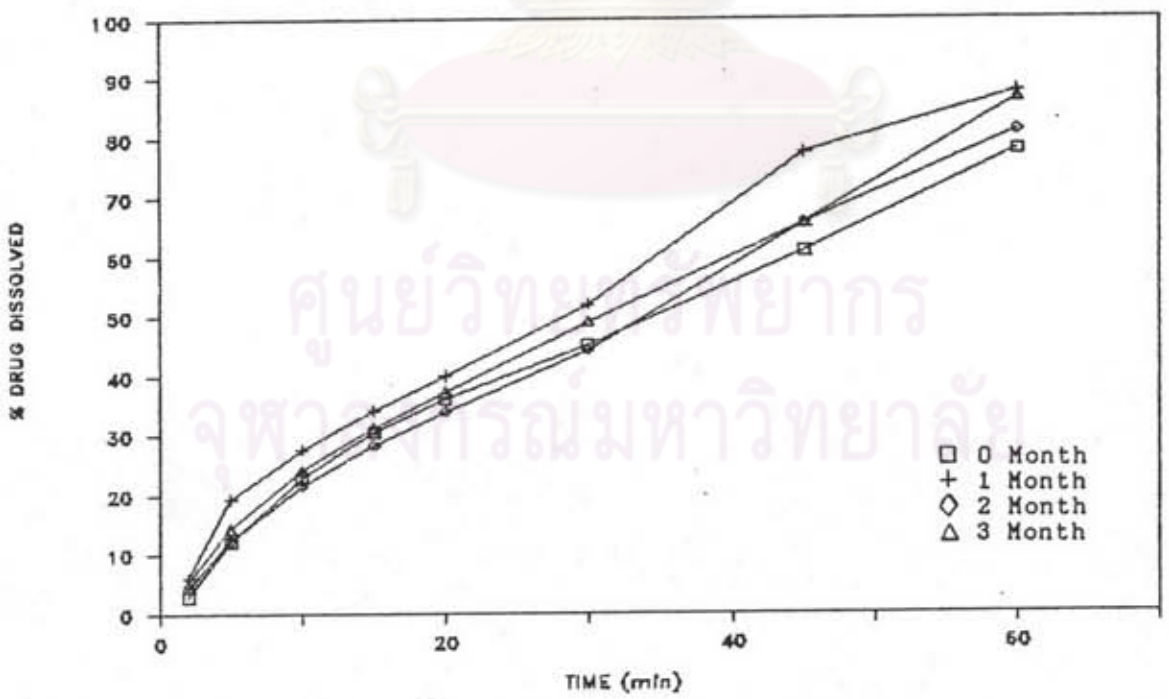


Figure 64 Effect of Aging on Dissolution of Diazepam Tablets Prepared from Storage Sugar-Starch-Starch Granules

for dissolution.

**Dissolution of Chlorpheniramine Maleate Tablets**

Figures 65-68 illustrate the dissolution behaviors of chlorpheniramine maleate tablets prepared from stored granules at room temperature (the experimental data are presented in Appendix P). At the initial time of storage, the dissolution of chlorpheniramine maleate tablets made from stored sugar-starch-PVP and sugar-starch-gelatin granules exhibited 100 % drug release within 30 minutes which met the USP specification (75 % chlorpheniramine maleate dissolved within 45 minutes, Figures 65-66). Although the dissolution of tablets prepared from storage granules yielded 100 % chlorpheniramine maleate released within the same time but difference in the dissolution profiles among the tablets prepared from storage granules at the end of first, second, and third month was observed.

The dissolution of chlorpheniramine maleate tablets prepared from sugar-starch-methylcellulose granules are shown in Figure 67. As has been shown, chlorpheniramine maleate released from freshly prepared tableds were about 70 % within 45 minutes which did not meet the USP specification. It has been seen that the reduction in dissolution rate of the tablets occurred with the time of storage.

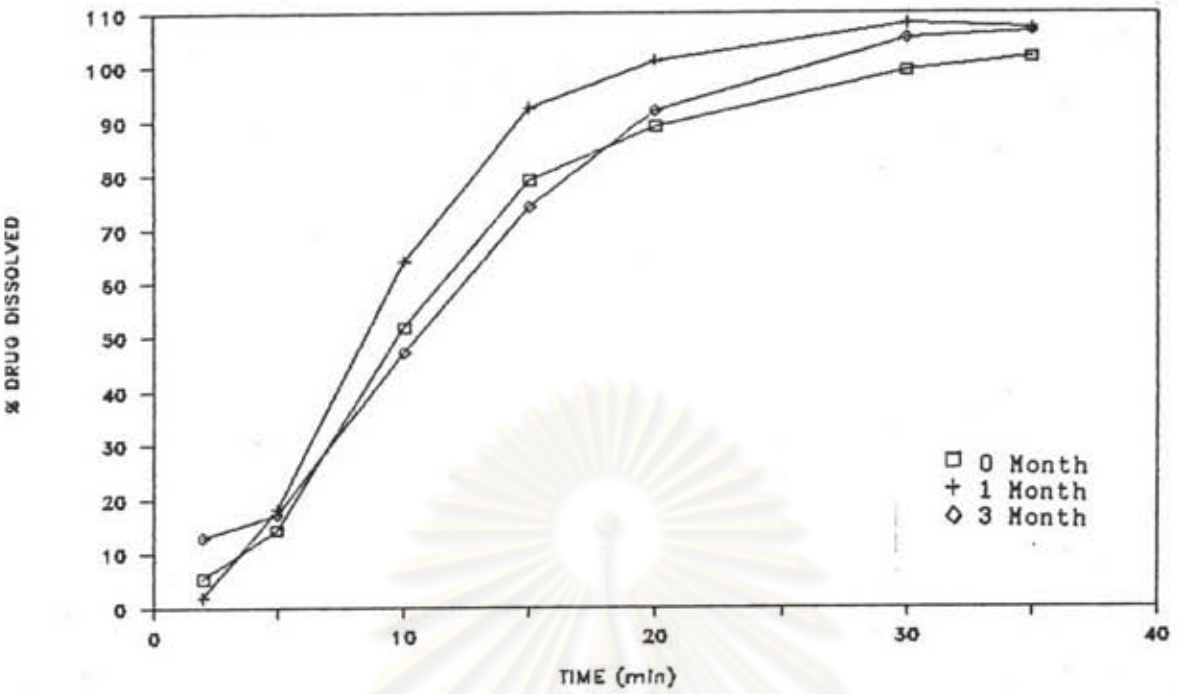


Figure 65 Effect of Aging on Dissolution of Chlorpheniramine Maleate Tablets Prepared from Storage Sugar-Starch-PVP Granules

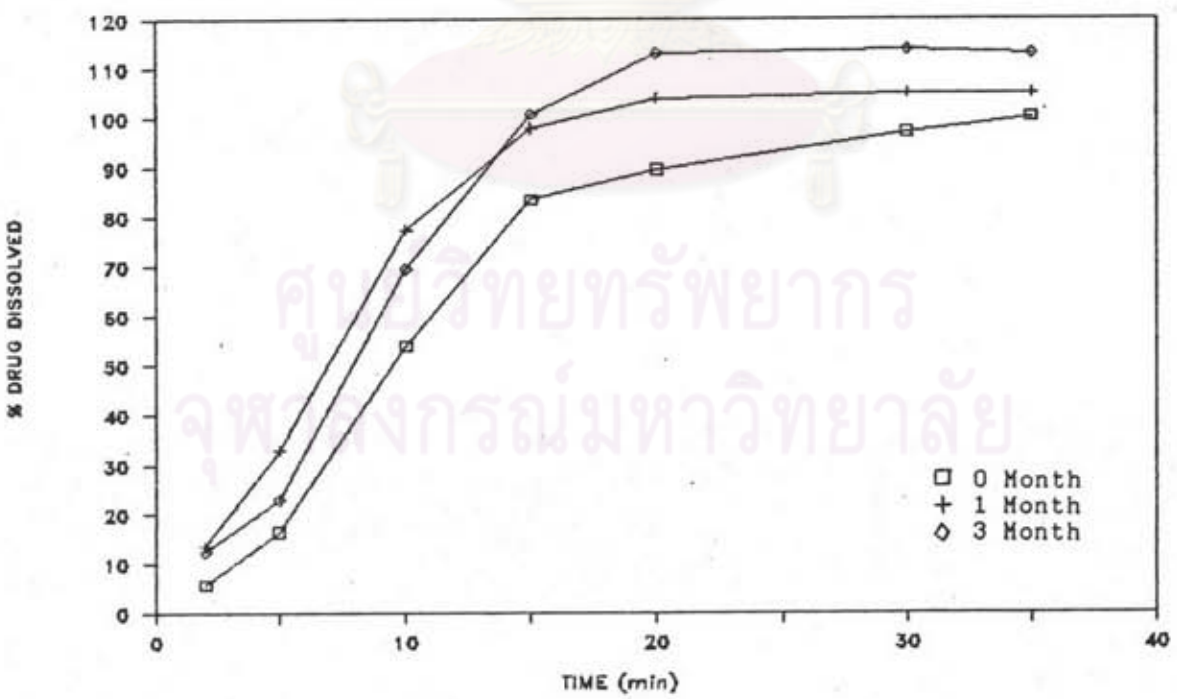


Figure 66 Effect of Aging on Dissolution of Chlorpheniramine Maleate Tablets Prepared from Storage Sugar-Starch-Gelatin Granules

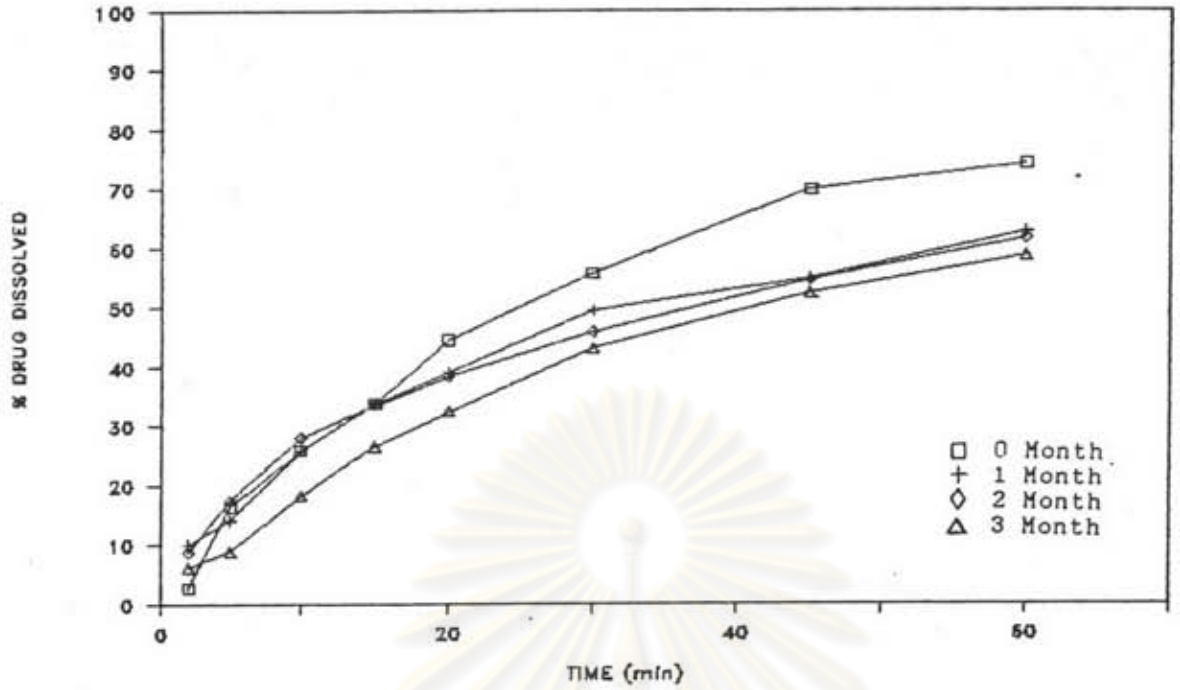


Figure 67 Effect of Aging on Dissolution of Chlorpheniramine Maleate Tablets Prepared from Storage Sugar-Starch-Methylcellulose Granules

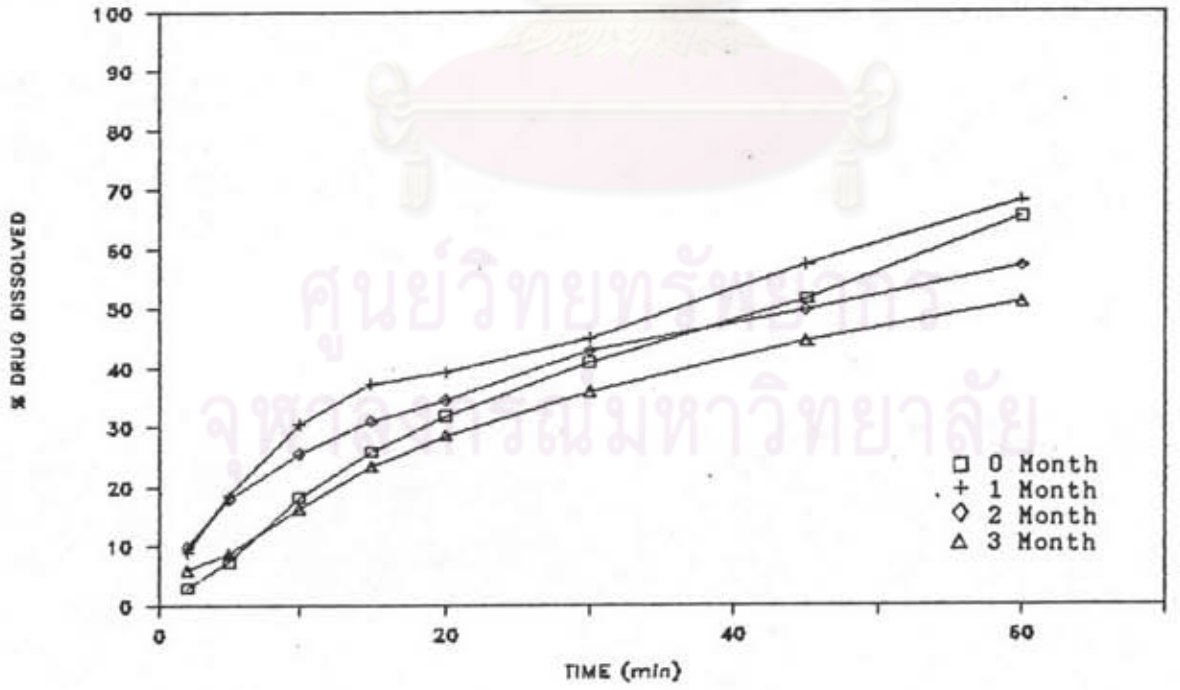


Figure 68 Effect of Aging on Dissolution of Chlorpheniramine Maleate Tablets Prepared from Storage Sugar-Starch-Starch Granules

Figure 68 illustrates the dissolution behaviors of chlorpheniramine maleate tablets made from sugar-starch-starch granules. Inconsistent change in dissolution of tablets among each month of storage could be found and their dissolutions did not meet the USP requirement.