CHAPTER III

RESULTS

The mean particle size of paracetamol and additives determined by microscopic method are given in Table 4.

The Beer's plot of the standard absorbance-concentration curve of paracetamol was constructed over a range of 0.25 to 2.5 mg %. The slope of regression line is 0.65 per mg % (the data are listed in Table 10).

Solubility of Paracetamol

Fig. 6 shows the typical concentration time curve for solubility determination of paracetamol by using the method of Nogami et al.[18] Concentrations at specific time interval were determined over a period of 2 hours and the dissolution data are listed in Table 11. Consequently the concentration time curve was used to construct a finite difference diagram as shown in Fig. 7 in order to elucidate the solubility of drug, C_1 and C_2 represent the concentrations at time t and t + 15 minutes respectively. Regression analysis of the linear plot was performed which yielded estimated solubility of paracetamol in 0.1 N HCl at 37° of 26.1 mg/ml.

Table 4. Surface Volume Mean Diameter of Drug and Additives Determined by Microscopic Method.

Materials	Surface-Volume Mean Diameter in μm
Paracetamol	68.59
Lactose	61.71
Talc	22.19
Magnesium Stearate	<5
Microcrystalline Cellulose	31.81
Corn Starch	15.4

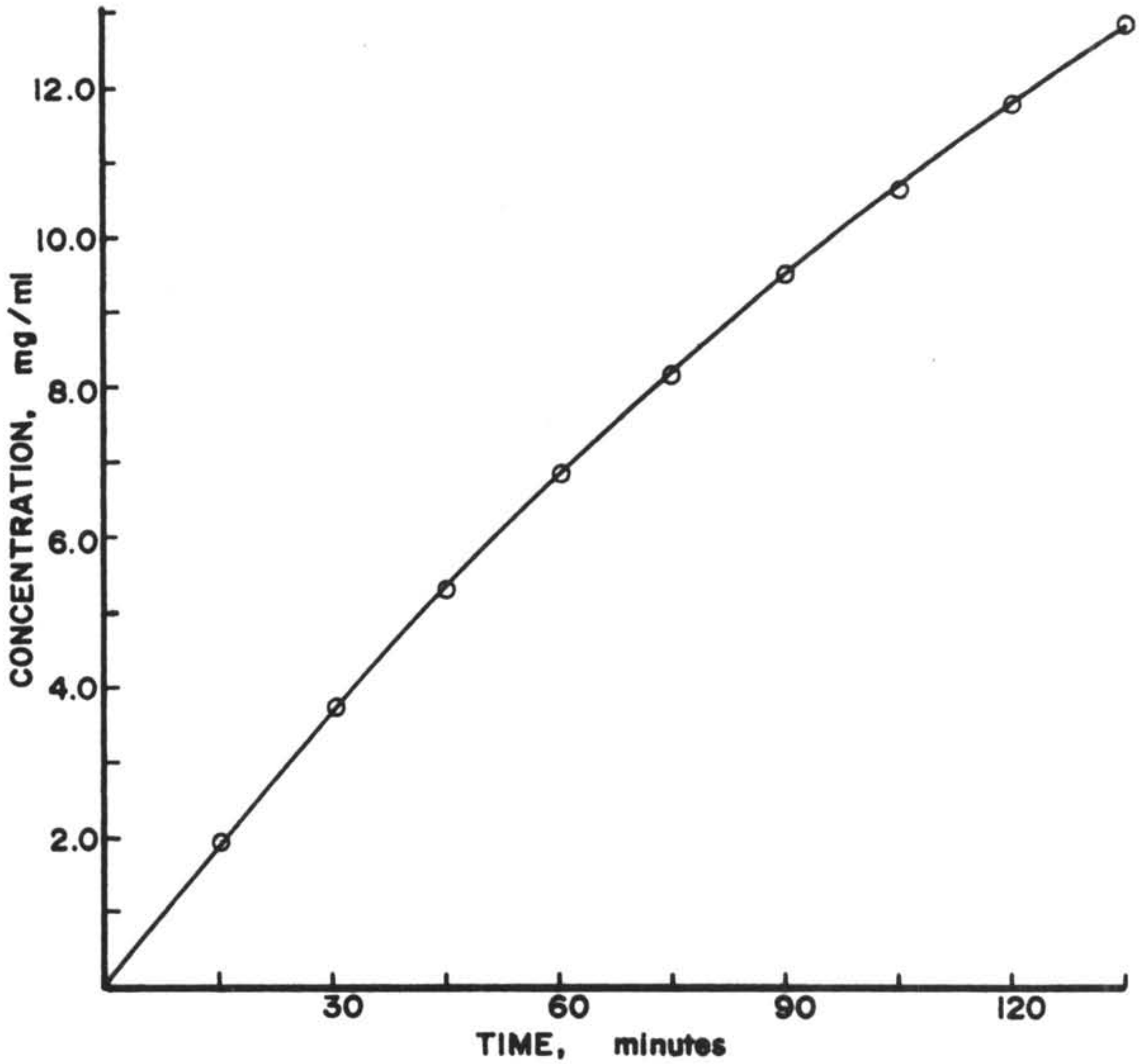

Figure 6. Dissolution behavior of paracetamol under non-sink condition as a function of time in 50 ml of 0.1 N HCl at 37° from a disk 1.5 cm in diameter compressed at 10,000 lb(4,464.3 kg) rotating at 200 rpm.

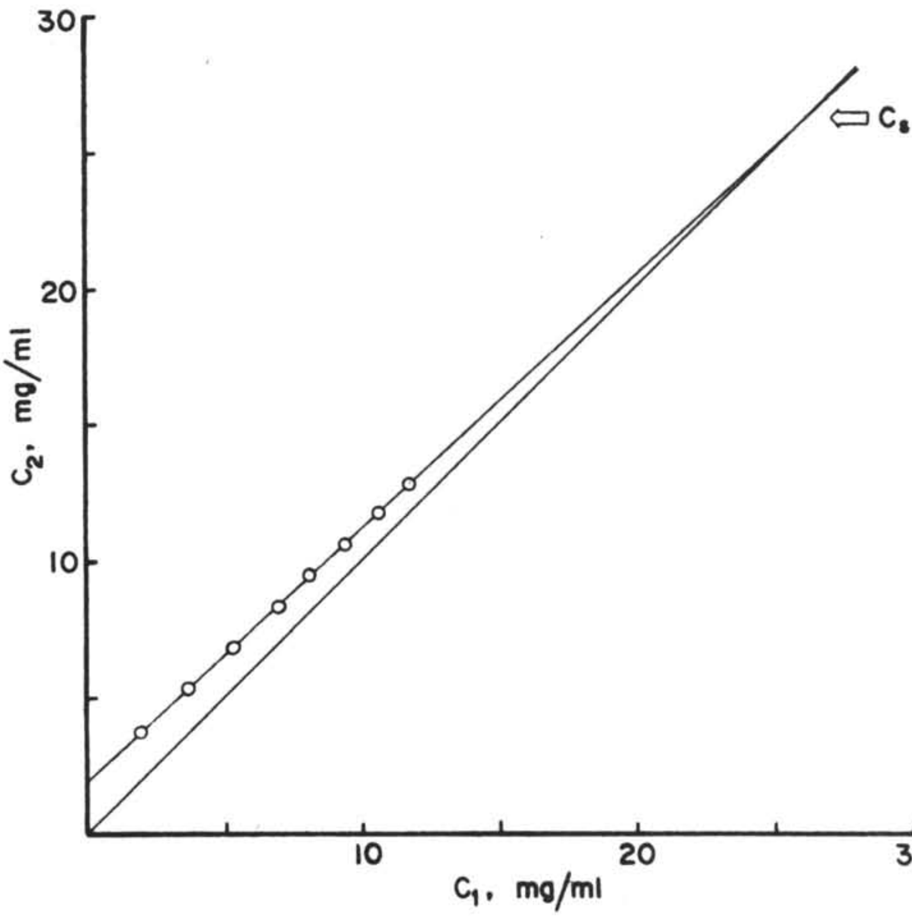

Figure 7. **Finite difference diagram for dissolution of paracetamol plotted in accordance with Fig. 6 Key: C_1, concentration at time t; C_2, concentration at time t+15; —o— , C_2 versus C_1; and ——, C_1=C_2.**

Studies on the Dissolution Behaviors of Paracetamol

The estimation of paracetamol solubility indicated that under experimental condition concentration of bulk solution did not exceed 15 % of saturated solution. Therefore, sink condition could be applied in our calculation of the dissolution rates of paracetamol.

The dissolution behaviors of paracetamol from the constant surface area under sink condition, by using compression die assembly are shown in Fig. 8 (see data in Table 12).

The plot of the amount dissolved as a function of time were correct to the origin and linear regression line analysis by least squares fitted method was applied. The intrinsic dissolution rate of paracetamol could be calculated from the slope of regression line divided by the surface area of the disk (0.61 cm^2). From the experimental results, it was seen that the increase in compressional forces showed no significant effect on the change of intrinsic dissolution rate.

The dissolution rates of paracetamol as determined from the binary mixtures containing various concentration of additives are presented in Table 5. The disks were compressed at 2,000 lb (892.9 kg), 3,000 lb (1,339.2 kg), and 4,000 lb (1,785.7 kg) respectively.

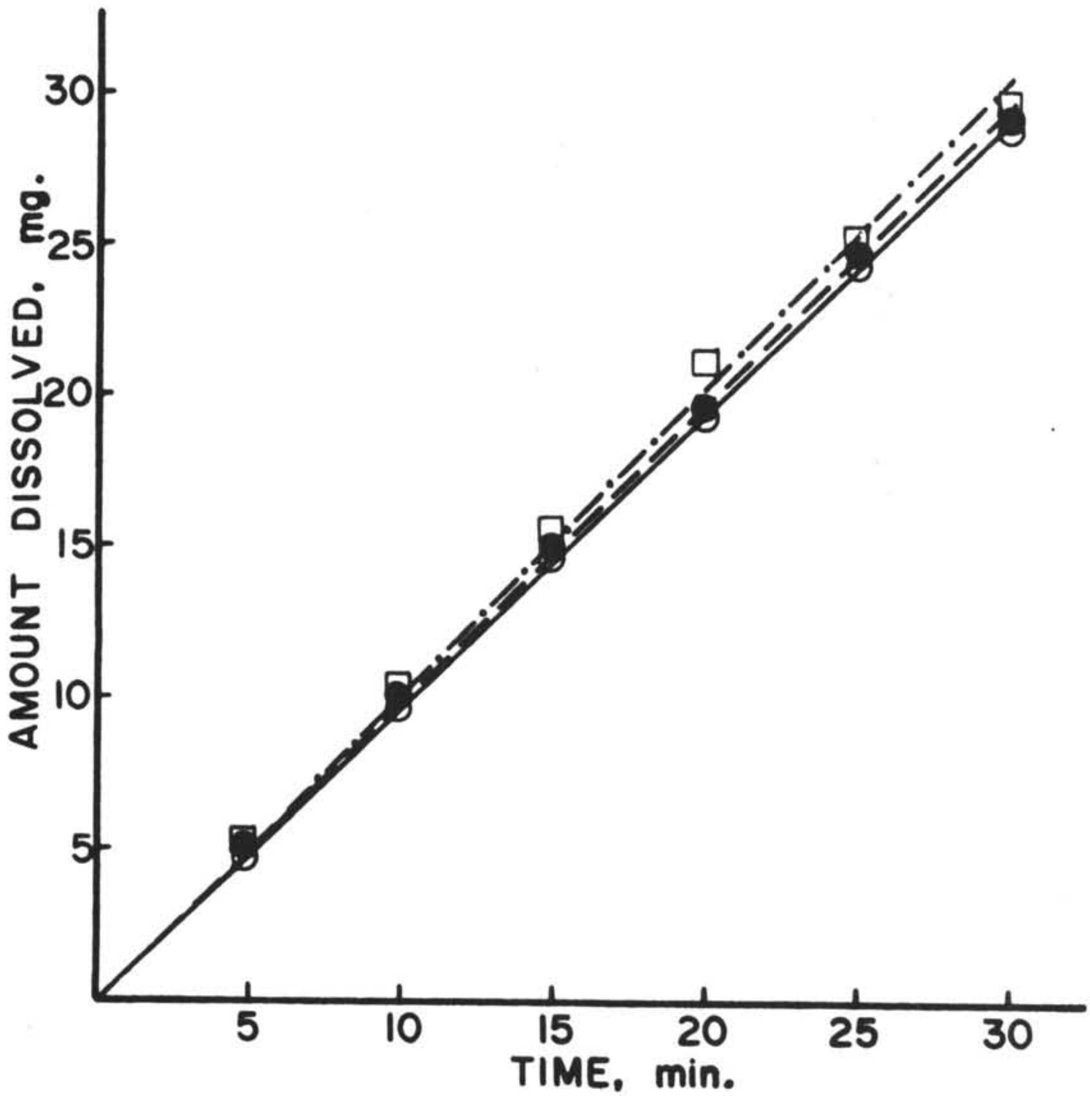

Figure 8. Dissolution behaviors of paracetamol under sink condition at various compressional force in 250 ml of 0.1 N HCl at 37° rotating at 50 rpm using compression die assembly. Key: ○—○ , 2,000 lb; ●- -● , 3,000 lb; □-·-·-□, 4,000 lb.

Table 5. Effect of Concentration of Additives on Intrinsic Dissolution Rate of Paracetamol from Paracetamol-Additive Mixtures Compressed at 2,000, 3,000, and 4,000 lb Using Compression Die Assembly.

Composition	Dissolution Rate, mg/min/cm^2		
	2,000 lb	3,000 lb	4,000 lb
D*	1.59	1.62	1.67
D + 10 % Lactose	1.42	1.42	1.51
D + 20 % Lactose	1.43	1.45	1.49
D + 30 % Lactose	1.42	1.42	1.49
D + 10 % Microcrystalline Cellulose.	1.14	1.12	1.15
D + 20 % Microcrystalline Cellulose	0.88	0.79	0.74
D + 30 % Microcrystalline Cellulose	0.76	0.61	0.58
D + 0.5 % Magnesium Stearate	1.36	1.34	1.35
D + 1 % Magnesium Stearate	1.12	1.13	1.12
D + 3 % Magnesium Stearate	0.87	0.88	0.86
D + 5 % Magnesium Stearate	0.78	0.79	0.78
D + 1 % Talc	1.46	1.44	1.45
D + 3 % Talc	1.31	1.29	1.30
D + 5 % Talc	1.20	1.22	1.18
D + 7 % Talc	1.16	1.15	1.15
D + 1 % Starch(in Paste 10 % w/w)	1.10	1.06	1.09
D + 2 % Starch(in Paste 10 % w/w)	0.82	0.82	0.81
D + 3 % Starch(in Paste 10 % w/w)	0.75	0.74	0.76

D* = Paracetamol

Table 5. (Continued) Effect of Concentration of Additives on Intrinsic Dissolution Rate of Paracetamol from Paracetamol-Additive Mixtures Compressed at 2,000, 3,000, and 4,000 lb Using Compression Die Assembly.

Composition	Dissolution Rate, mg/min/cm^2		
	2,000 lb	3,000 lb	4,000 lb
D* + 4 % Starch (in Paste 10 % w/w)	0.70	0.71	0.70
D + 3 % PVP** (in Solution)	-	1.52	1.51
D + 4 % PVP (in Solution)	-	1.51	1.50
D + 5 % PVP (in Solution)	-	1.48	1.49
D + 3 % PVP (Dry adding)	-	1.53	1.51
D + 4 % PVP (Dry adding)	-	1.50	1.52
D + 5 % PVP (Dry adding)	-	1.52	1.51

D* = Paracetamol

PVP** = Polyvinylpyrrolidone

The dissolution rates were obtained by using the data from Table 13-19 in calculation.

The presence of lactose in the compressed disk had only slight effect on intrinsic dissolution rate of the drug. Fig. 9 shows relation between the dissolution rate and the concentration of lactose at various compressional force. The increase of the amount of lactose from 10 to 30 % did not alter the dissolution rate significantly.

The influence of microcrystalline cellulose on the intrinsic dissolution rate of paracetamol is shown in Fig. 10. The rate of dissolution of paracetamol was lowered by the pressence of microcrystalline cellulose in the compressed disk. An increase of concentration of microcrystalline cellulose resulted in a further reduction of dissolution rate. It appeared from the curves that the compressional forces affected the intrinsic dissolution rate of paracetamol from the mixtures containing 20 and 30 % microcrystalline cellulose which may lead to a conclusion that the interaction between varying amounts of microcrystalline cellulose and compressional force existed.

The effect of magnesium stearate and talc on tablet formulation are shown in Fig. 11 and Fig. 12, respectively. An increase in the amounts of magnesium stearate produced a markedly change in the dissolution rate. But talc behaved differently from magnesium stearate, that the dissolution rate gradually

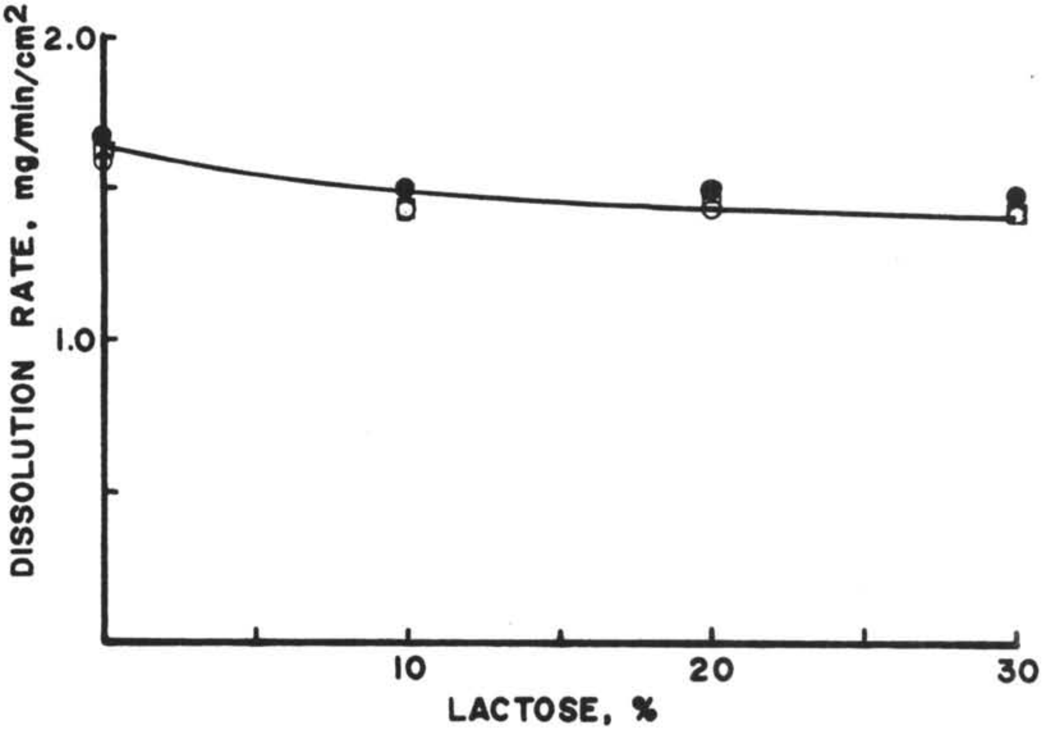

Figure 9. Effect of concentration of lactose and compressional force on dissolution rate of paracetamol from paracetamol-lactose mixture. Key: ○ , 2,000 lb; □ , 3,000 lb; ● , 4,000 lb.

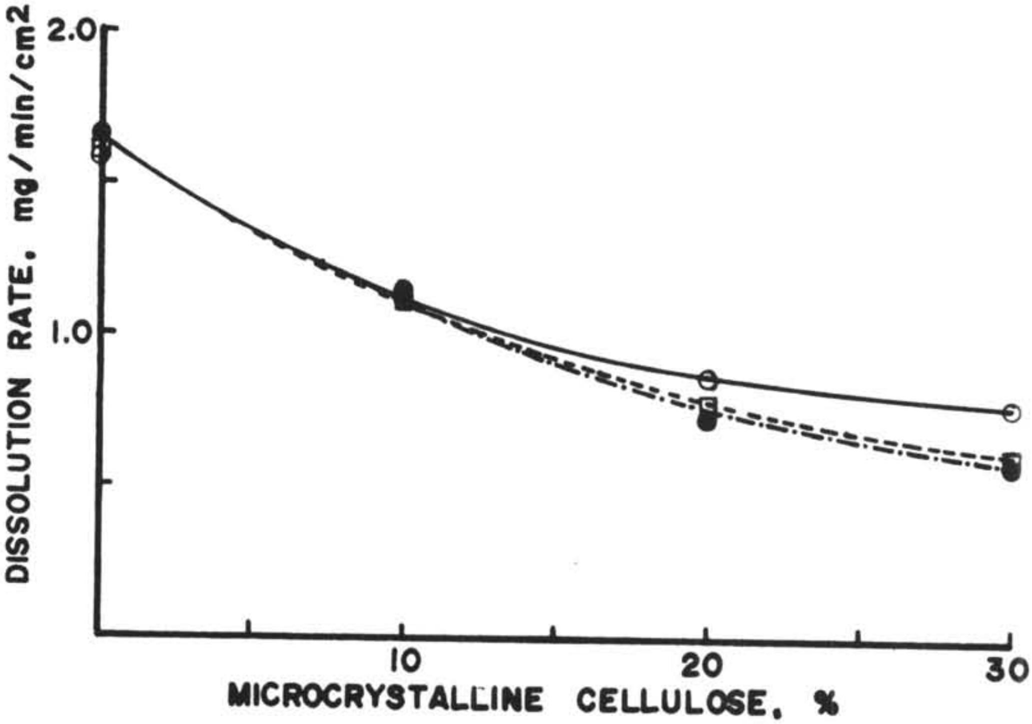

Figure 10. Effect of concentration of microcrystalline cellulose and compressional force on dissolution rate of paracetamol from paracetamol-microcrystalline cellulose mixture. Key: —○— , 2,000 lb;---□--- , 3,000 lb;-·-○-·-, 4,000 lb.

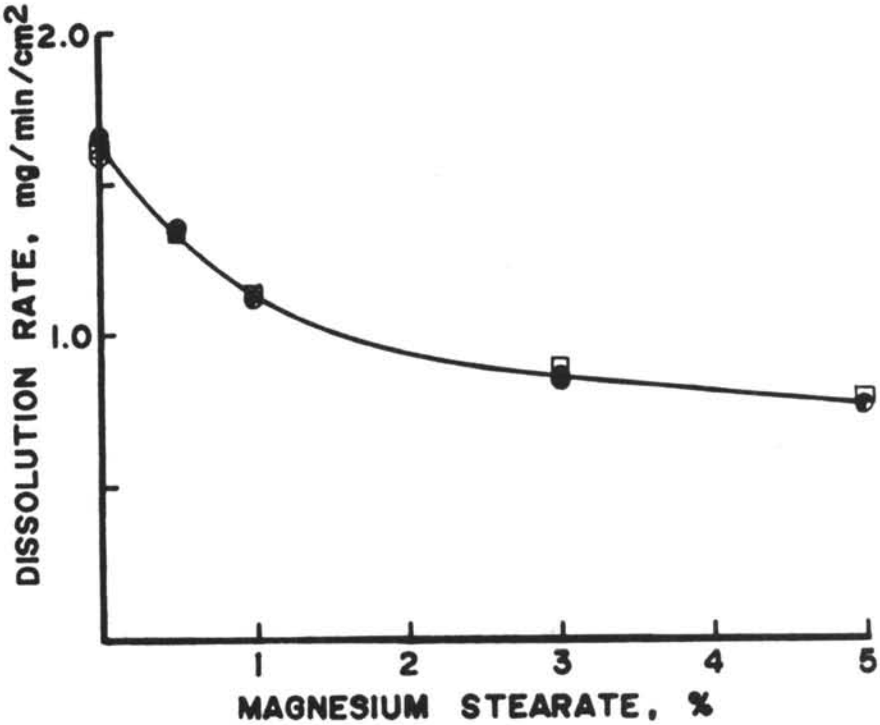

Figure 11. Effect of concentration of magnesium stearate and compressional force on dissolution rate of paracetamol from paracetamol-magnesium stearate mixture. Key: ○, 2,000 lb; □, 3,000 lb; ●, 4,000 lb.

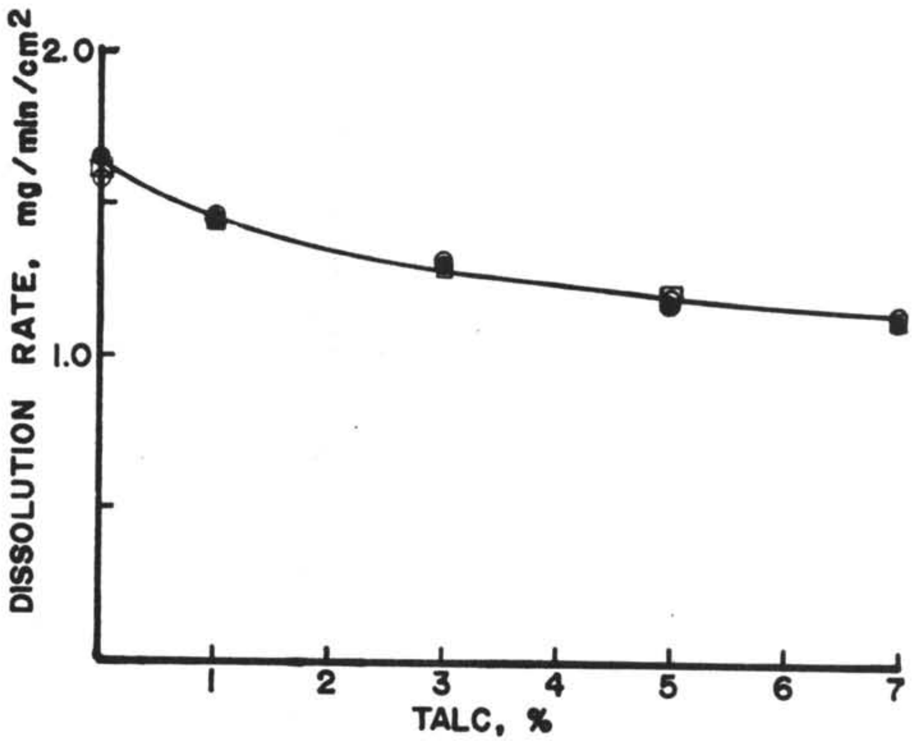

Figure 12. Effect of concentration of talc and compressional force on dissolution rate of paracetamol from paracetamol-talc mixture. Key: ○ , 2,000 lb; □ , 3,000 lb; ● , 4,000 lb.

decreased as the concentration of talc in the compressed disk increased. The compressional force exerted no influence on the intrinsic dissolution rate in both cases which indicated that no interaction had taken place in these two cases.

Incorporation of starch paste into tablet formulation resulted in drastical change of the dissolution rate of paracetamol even only small quantities were added (Fig. 13). The amounts of corn starch as indicated in the figure are the amount presented in the paste of 10 % w/w concentration which were mixed with the drugs. However, these seemed to be no effect exerted by varying of compressional forces.

In the case of polyvinylpyrrolidone, we were unable to obtain any data from the compressed disks which contained in their formulations 1-2 % of polyvinylpyrrolidone. The main obstacle was due to the rapid disintegration of the disks. The estimation of dissolution rates were done only in the cases when the disks contained 3,4 and 5 % of polyvinylpyrrolidone. The compressional forces of 3,000 and 4,000 lb were used because of 2,000 lb the disk also disintegrated rapidly.

At each concentration of polyvinylpyrrolidone (Fig. 14), the dissolution rate is essentially constant and nearly equal to the intrinsic dissolution rate of the pure drug. The change of compressional forces did not affected the dissolution rate.

Polyvinylpyrrolidone is sometimes added dry and blended

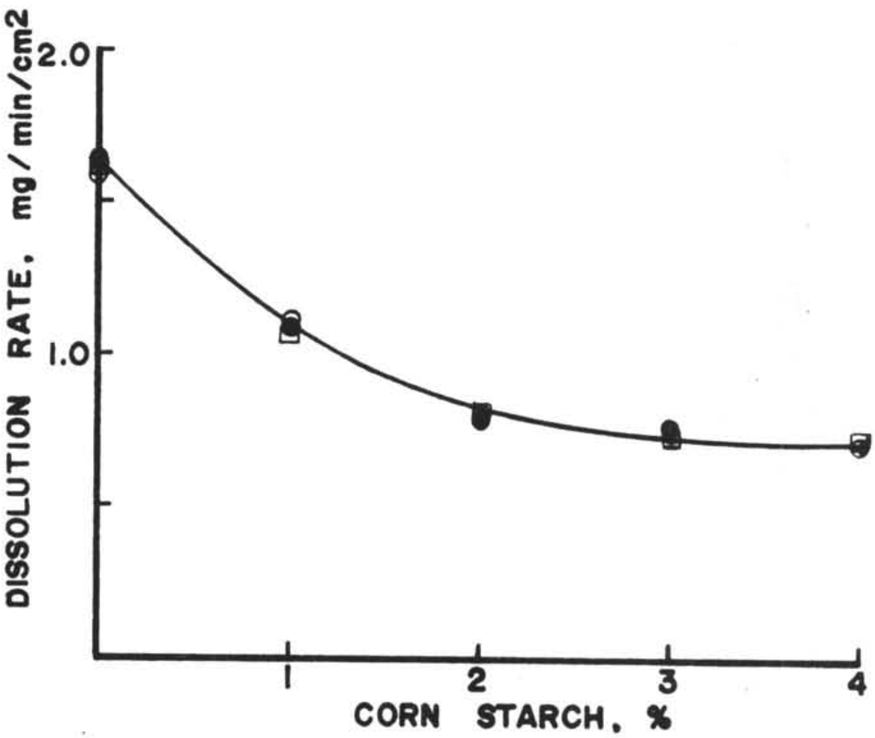

Figure 13. Effect of concentration of 10 % w/w starch paste and compressional force on dissolution rate of paracetamol from paracetamol-starch paste mixture. Key: ○ , 2,000 lb; □ , 3,000 lb; ● , 4,000 lb.

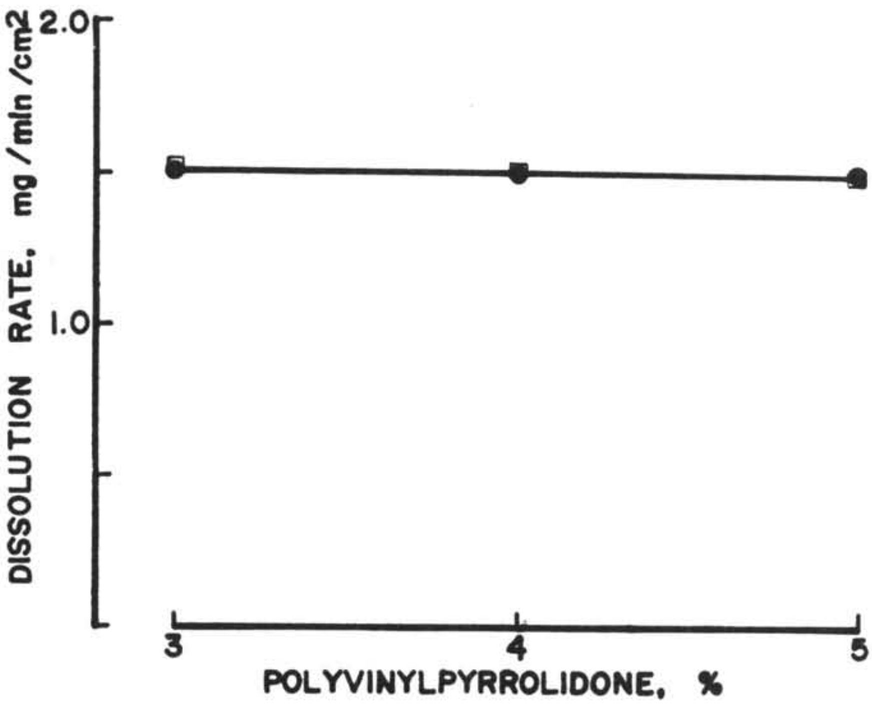

Figure 14. Effect of concentration of polyvinylpyrrolidone(in solution) and compressional force on dissolution rate of paracetamol from paracetamol-polyvinylpyrrolidone mixture. Key: □, 3,000 lb; ●, 4,000 lb.

with other components. They are then activated by the addition of solvent. Thus, the comparison between dry mixing prior to activate with water and in solution adding was conducted. According to the results shown in Table 5, it concluded that there were no difference between two methods.

The dissolution rate of paracetamol from the mixture of paracetamol and dry corn starch could not be determined because of the swelling of the starch which caused flaking. This made the total surface area of the solid mixture exposed to the dissolution medium to be altered.

The flaking of the disk did not occur when dry corn starch was mixed with paracetamol granules. However, in this instance, concentration of dry corn starch should not exceed 5 % of granules. As shown in Table 6, the dissolution rates of paracetamol as determined from the disks are independent of the concentrations of dry corn starch and compressional force at 2,000, 3,000, and 4,000 lb (see data in Table 20).

The influence caused by interaction between magnesium stearate and talc were studied by factorially designed experiments as shown in Table 7(see data in Table 21). The results of the analysis of variances are given in Table 8. The effects produced by interaction of magnesium stearate and talc were found to be non-significant.

In addition, by comparing the results in Table 6 and 7,

Table 6. Dissolution Rate of Paracetamol from Mixtures Containing Different Concentration of Dry Corn Starch Compressed at 2,000, 3,000, and 4,000 lb Using Compression Die Assembly.

	Dissolution Rate, mg/min/cm^2		
Concentration of Dry Corn Starch, %	2,000 lb	3,000 lb	4,000 lb
1	0.68	0.68	0.67
3	0.67	0.68	0.68
5	0.67	0.64	0.67

Table 7. The Effect of Lubricants in Combination of Talc and Magnesium Stearate on Intrinsic Dissolution Rate of Paracetamol by Factorially Designed Experiment.

Variables : Talc, Magnesium Stearate, Compressional Force

Response : Dissolution Rate, mg/min/cm^2

Levels : Two : High and Low

				Talc	
				Low(3 %)	high(5 %)
Compressional forces	Low(2,000 lb)	Magnesium Stearate	Low(0.3 %)	0.70	0.66
			High(1 %)	0.67	0.65
	High(3,000 lb)	Magnesium Stearate	Low(0.3 %)	0.70	0.67
			High(1 %)	0.69	0.66

Table 8. Analysis of Variance of a Factorial

Variance of	D.F.	Sum of Squares	Variances	F-ratio
Force	1	2.0×10^{-4}	2.0×10^{-4}	
Talc	1	1.8×10^{-3}	1.8×10^{-3}	
Magnesium Stearate	1	4.5×10^{-4}	4.5×10^{-4}	
Interaction	1	5.0×10^{-5}	5.0×10^{-5}	1.67*
Error	3	1.0×10^{-4}	3.3×10^{-5}	
Total	7	2.6×10^{-3}		

*critical F-values at the 5 % level is 10.13.

it is evident that the granule containing 3 % talc, 1 % magnesium stearate and the granule containing equal amount of lubricants with adding dry corn starch did not exhibited difference in dissolution rate. This mean that the addition of dry corn starch did not affected dissolution in this specific case.