CHAPTER III

RESULTS

1. Determination of The Crystallinity by X-Ray Diffractometer.

The X-Ray diffraction pattern of crystalline powder of diazepam in the absence of diluents was presented in Figure 5. The dominant peak intensity appeared at 9.5°, 11.0°, 13.6°, 17.5°, 18.9°, 22.8°, 24.4°, 26.6° and 29.7° in the term of 2θ angle.

1.1 Diazepam-Mannitol Mixture

1.1.1 1:20 Diazepam-Mannitol Mixture

a) Simple Blending Method

Mannitol produced its owns characteristic X-Ray diffraction pattern as shown in Figure 6. The dominant peak intensity appeared at 10.5°, 11.5°, 14.6°, 16.8°, 18.9°, 20.5°, 21.2°, 21.7°, 23.4°, 26.0°, 28.3° and 29.5° in the term of 2θ angle. The X-Ray diffraction pattern of 1:20 ratio of diazepam in mannitol mixture shown in Figure 8, demonstrated the superposition of the patterns of diazepam and mannitol. Each component contributed its own pattern with an intensity proportional to the amount presented in the mixture. The diazepam diffraction peak could be clearly seen at 9.5°, 17.5° and 22.8° in the term of 2θ angle of the diffraction pattern of the mixture.

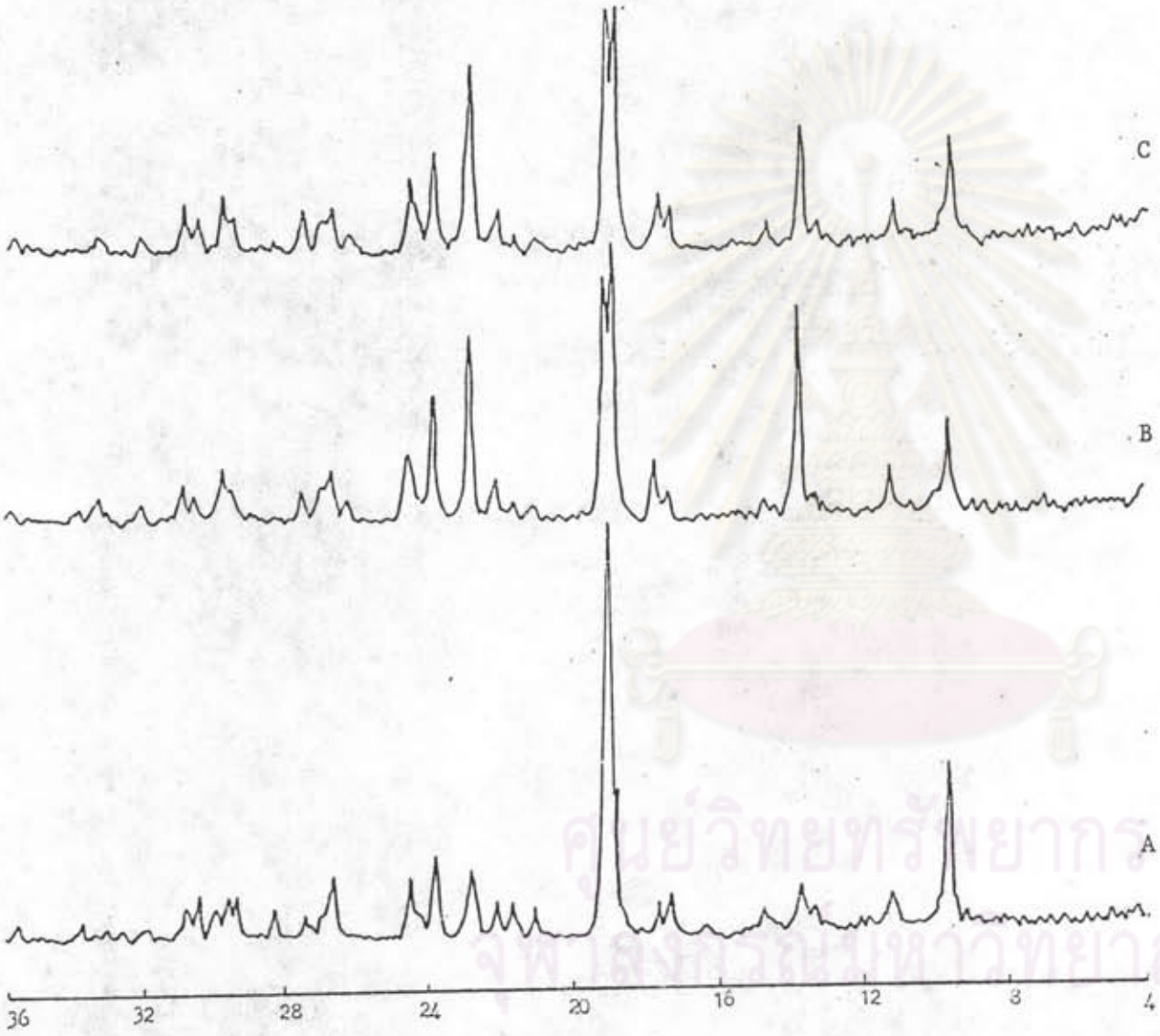

Figure: 5

X-Ray diffraction patterns

of diazepam

A: diazepam crystals

B: mill for 10 hours

C: mill for 20 hours

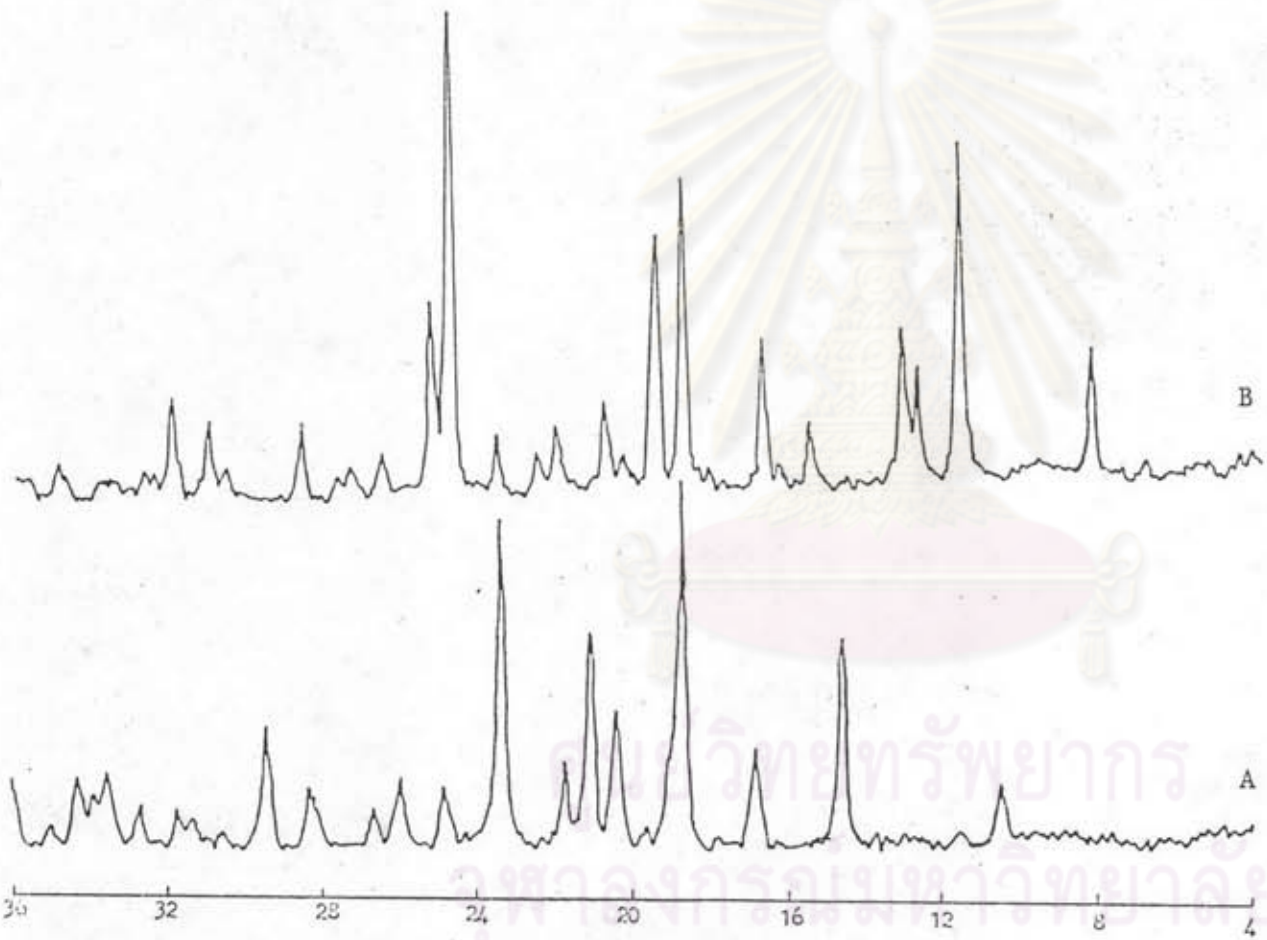

Figure: 6

X-Ray diffraction patterns

of

A: mannitol

B: sucrose

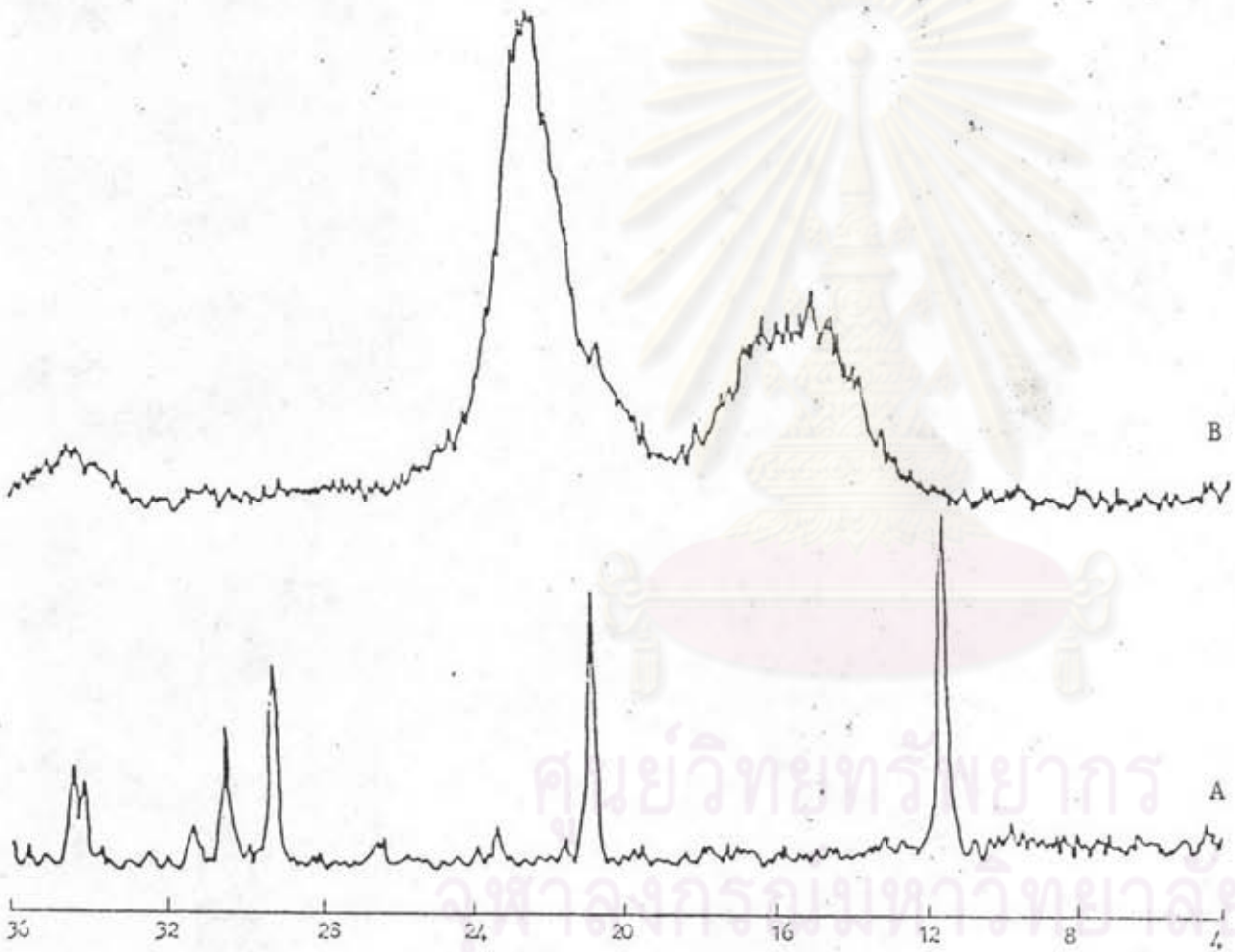

Figure: 7

X-Ray diffraction patterns

of

A: dibasic calcium phosphate

B: microcrystalline cellulose

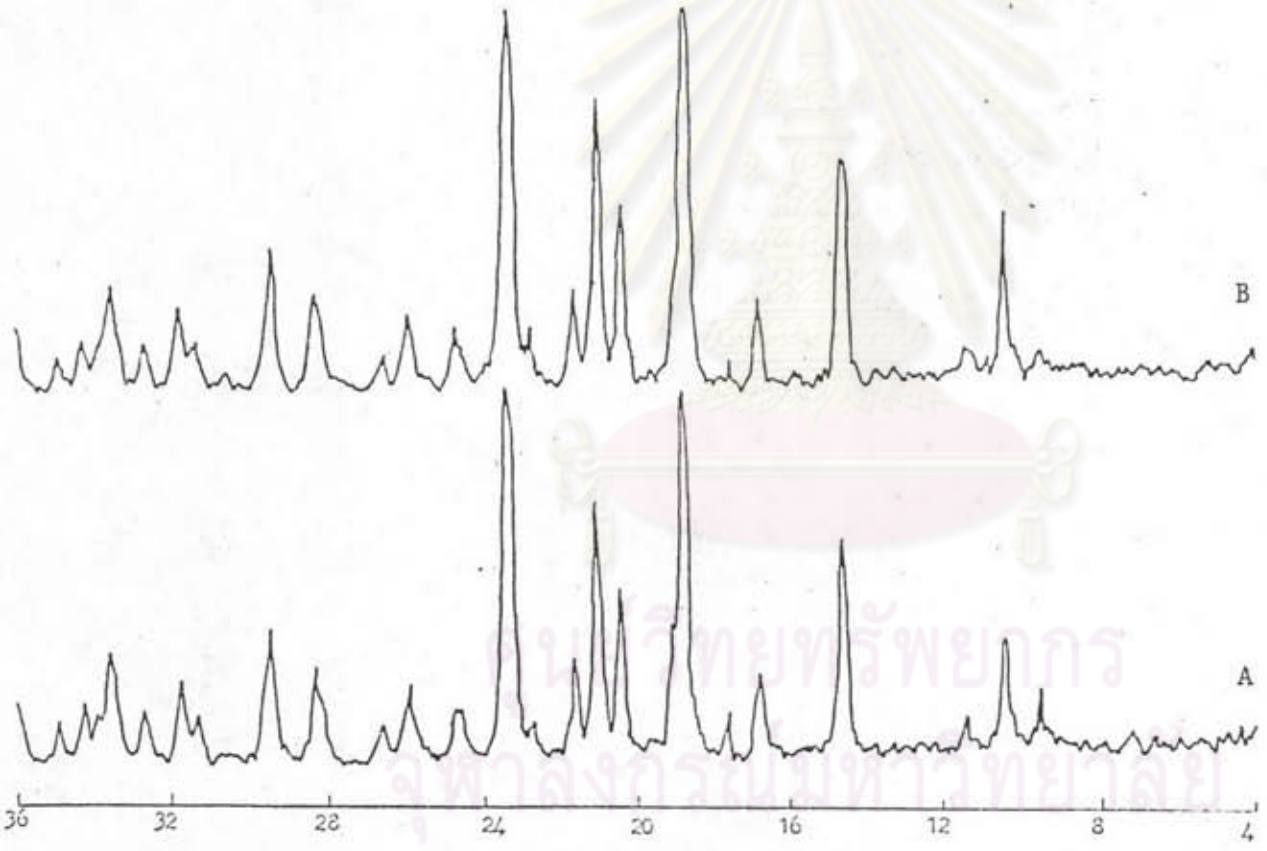

Figure: 8

X-Ray diffraction patterns of the mixtures of diazepam in mannitol at the ratio of 1:20 prepared by

A: simple blending method

B: solvent deposition method

b) Solvent Deposition Method

X-Ray diffraction pattern of 1:20 ratio of diazepam in mannitol mixture prepared by solvent deposition method was shown in Figure 8. It consisted of the superposition of the patterns of diazepam and mannitol- the radiation diffracted by diazepam crystals (the diazepam peaks) and mannitol crystals (the mannitol peaks). The diazepam peaks could be observed markly at 9.5°, 17.5°, and 22.8° in the term of 2θ angle of the diffraction pattern of the mixtures

c) Ball Milling Method

In case of grinding the 1:20 ratio of diazepam in mannitol mixture, the X-Ray diffraction pattern of the mixtures were determined at the 10 hour and 20 hour grinding as shown in Figure 9. After 10 hour grinding the diazepam peaks could be observed at 9.5° in the term of 2θ angle. After 20 hours grinding the diazepam peaks were disappeared in the diffraction pattern of the mixtures.

1.1.2) 1:10 Diazepam-Mannitol Mixture.

a) Simple Blending Method

The X-Ray diffraction pattern of 1:10 ratio of diazepam in mannitol mixture prepared by simple blending method was shown in Figure 10. The X-Ray diffraction pattern of the mixtures showed the superposition of the diffration pattern of diazepam and mannitol. The diazepam diffraction peaks increased in intensity comparing to 1:20 ratio of diazepam in mannitol mixture prepared by the same method.

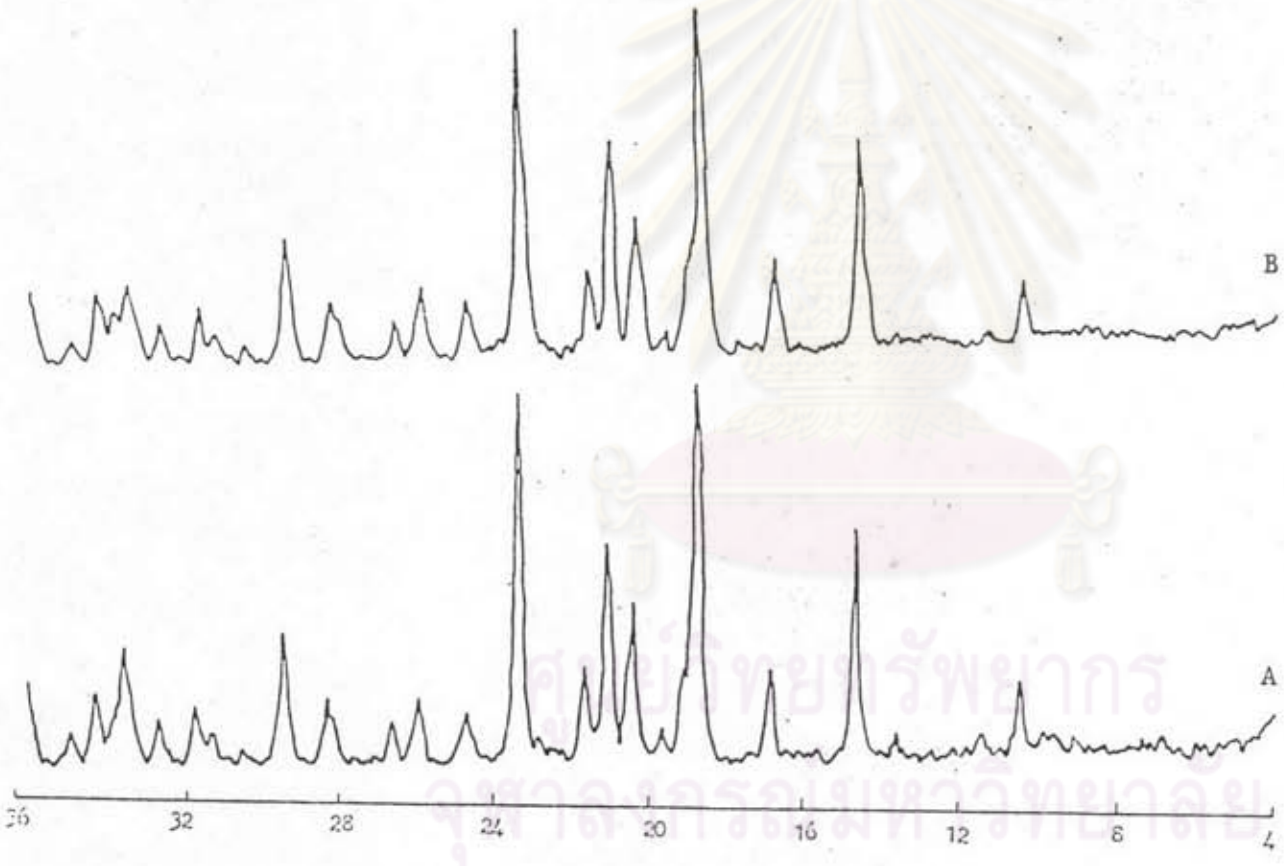

Figure: 9

X-Ray diffraction patterns of the mixtures of diazepam in mannitol at the ratio of 1:20 prepared by ball-milling method

A: mill for 10 hours

B: mill for 20 hours

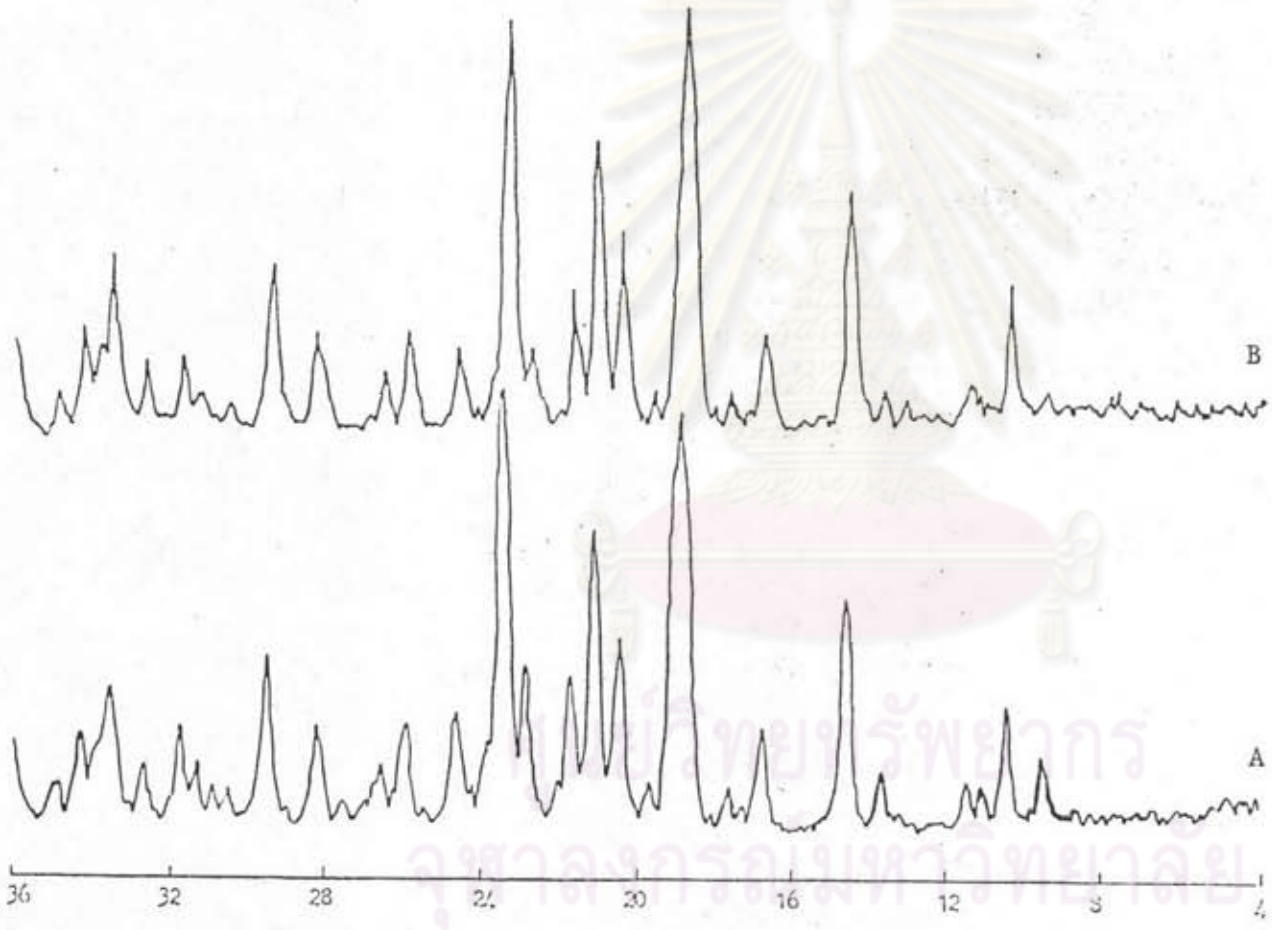

Figure: 10

X-Ray diffraction patterns of the mixtures of diazepam in mannitol at the ratio of 1:10 prepared by

A: simple blending method

B: solvent deposition method

The diazepam diffraction peaks could be clearly seen at 9.5°, 11.0°, 17.5° and 22.8° in the term of 2θ angle of the diffraction pattern of the mixture.

b) Solvent Deposition Method

The X-Ray diffraction pattern of 1:10 ratio of diazepam in mannitol mixture prepared by solvent deposition method was similar to the X-Ray diffraction pattern of 1:20 ratio of diazepam in mannitol mixture prepared by the same method, but the peaks intensity of diazepam at 9.5°, 17.5° and 22.8° in the term of 2θ angle markly increased as shown in Figure 10.

c) Ball Milling Method

In case of grinding the 1:10 ratio of diazepam in mannitol mixture, the X-Ray diffraction pattern of the mixtures was determined at the 10 hour, 20 hour and 30 hour grinding. After 10 hour grinding the diazepam diffraction peaks could be observed at 9.5°, 17.5° and 22.8° in the term of 2θ angle of the diffraction pattern of the mixtures. After 20 hour grinding the diazepam diffraction peaks decreased in their intensities. After 30 hour grinding the diazepam diffraction peaks were disappeared. The diazepam diffraction peaks were decreased in intensity with the increasing grinding time and were disappeared after 30 hour grinding as shown in Figure 11.

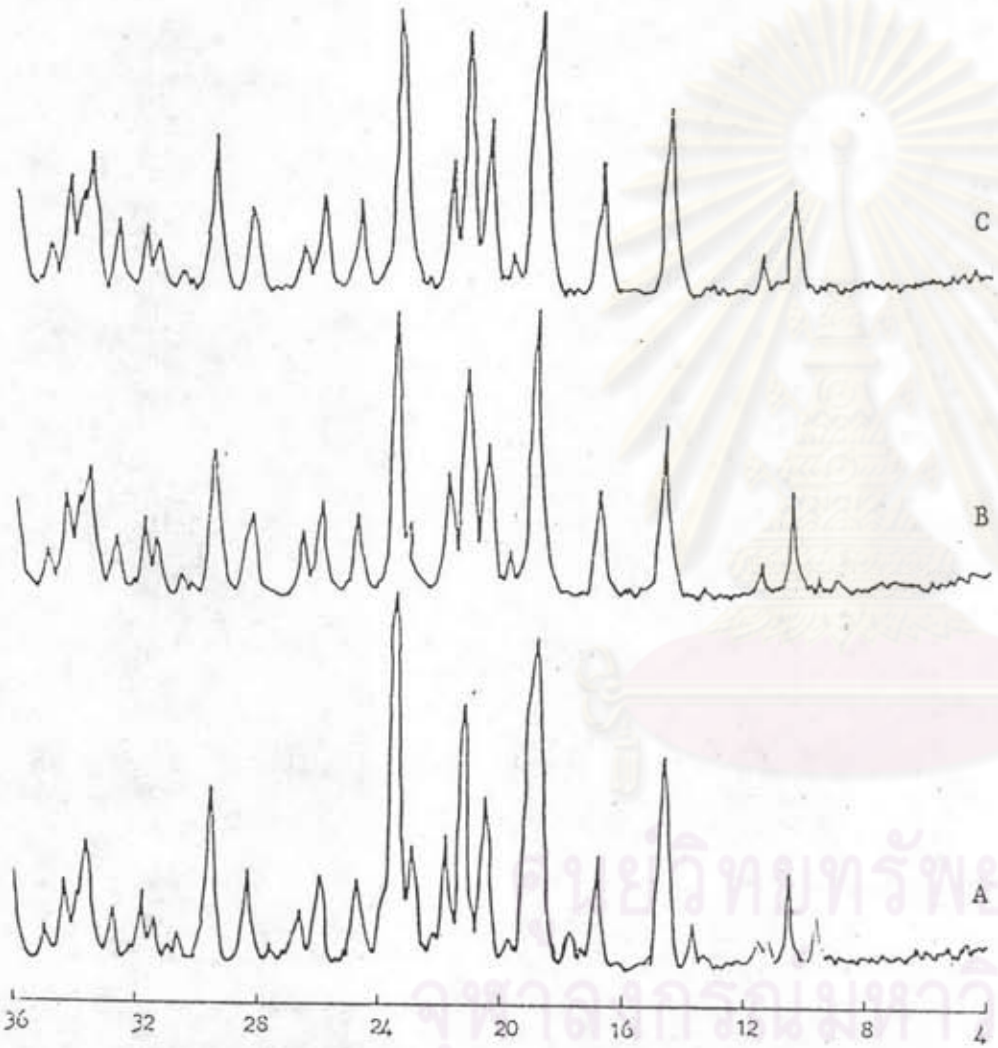

Figure: 11

X-Ray diffraction patterns of the mixtures of diazepam in mannitol at the ratio of 1:10 prepared by ball-milling method

A: mill for 10 hours

B: mill for 20 hours

C: mill for 30 hours

1.1.3 1:5 Diazepam-Mannitol Mixture

a) Simple Blending Method

The X-Ray diffraction pattern of the 1:5 ratio of diazepam in mannitol mixture prepared by simple blending method showed the superposition of the pattern of diazepam and mannitol. The diazepam diffraction peaks increased in intensity comparing to 1:10 ratio of diazepam in mannitol mixture prepared by the same method. The diazepam diffraction peaks could be observed markly at 9.5°, 11.0°, 17.5° and 22.8° in the term of 2θ angle of the diffraction pattern of the mixtures as shown in Figure 12.

b) Solvent Deposition Method

The X-Ray diffraction pattern of 1:5 ratio of diazepam in mannitol mixture prepared by solvent deposition method was similar to the X-Ray diffraction pattern of 1:10 ratio of diazepam in mannitol mixtures prepared by the same method, but the peaks intensity of diazepam at 9.5°, 11.0°, 17.5° and 22.8° in the term of 2θ angle markly increased as shown Figure 12.

c) Ball Milling Method

The X-Ray diffraction pattern of 1:5 ratio of diazepam in mannitol mixture was determined at 20 hour, 40 hour and 60 hour grinding. After 20 hour and 40 hour grinding the diazepam diffraction peaks at 9.5°, 11.0°, 17.5° and 22.8° in the term of 2θ angle were remained in the diffraction pattern of the mixtures. After 60 hour

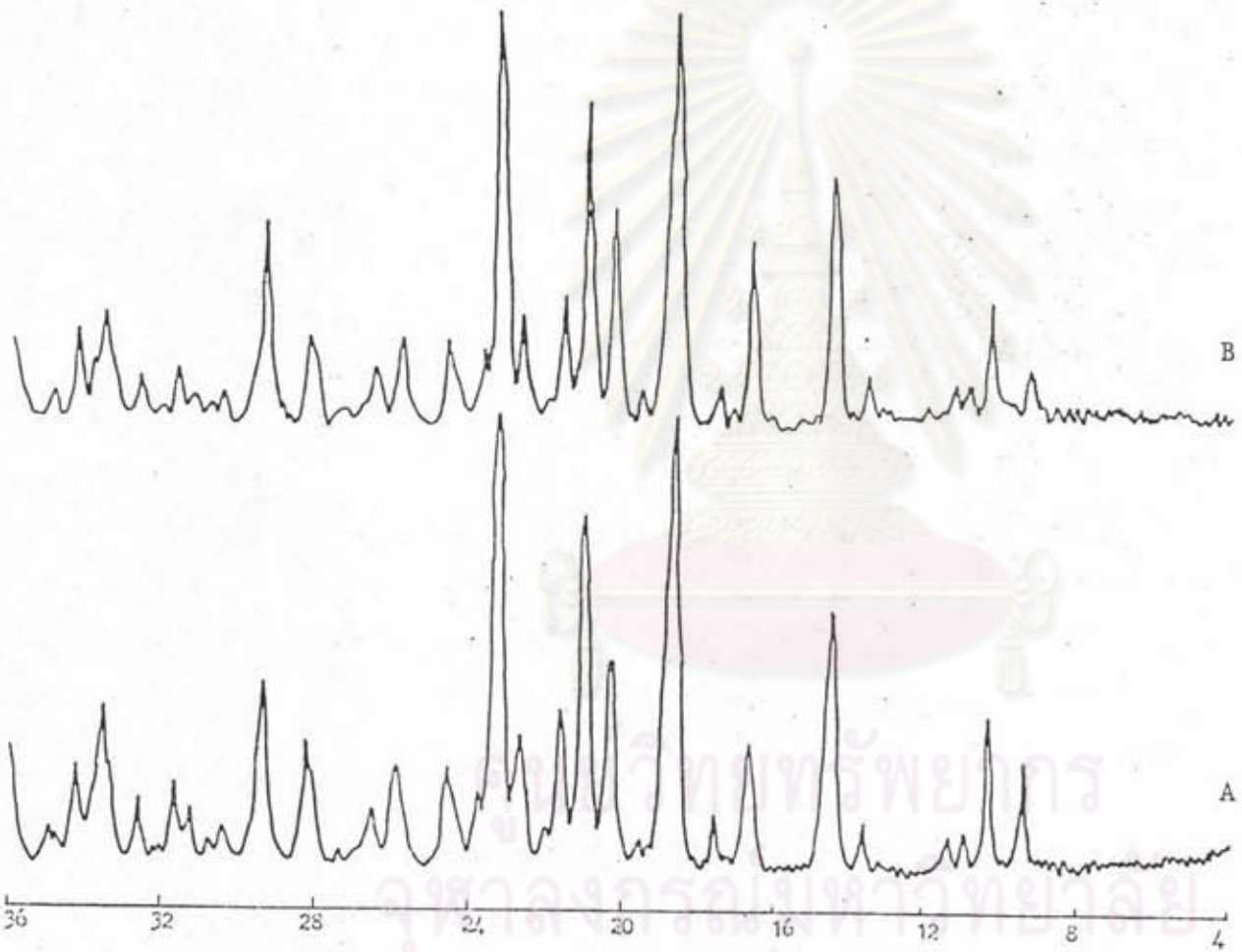

Figure: 12

X-Ray diffraction patterns of the mixtures of diazepam in mannitol at the ratio 1:5 prepared by

A: simple blending method

B: solvent deposition method

grinding, the diazepam diffraction peaks at 9.5° and 17.5° in the term of 2θ angle were remained in the diffraction pattern of the mixtures. It is likely that the crystalline portions of diazepam were remained in the ground mixtures as shown in Figure 13.

1.2 Diazepam-Sucrose Mixture

1.2.1 1:20 Diazepam-Sucrose Mixture

a) Simple Blending Method

The characteristic X-Ray diffraction pattern of sucrose was presented in Figure 6. The diffraction peak intensity appeared obviously, at 8.4°, 11.8°, 12.8°, 13.2°, 15.6°, 16.4°, 16.8°, 18.9°, 19.6°, 20.4°, 20.8° 22.0°, 22.4° and 24.9° in the term of 2θ angle. The X-Ray diffraction patterns of 1:20 ratio of diazepam in sucrose mixture showed the superposition of the patterns of diazepam and sucrose. Each components contributed its own pattern with an intensity proportional to the amount present in the mixtures. The diazepam diffraction peaks could be observed at 9.5°, 11.0°, in the term of 2θ angle of the diffraction pattern of the mixture as shown in Figure 14.

b) Solvent Deposition Method

The X-Ray diffraction pattern of 1:20 ratio of diazepam in sucrose mixture prepared by solvent deposition method was shown in Figure 13. It consisted of the superposition of the patterns of diazepam and sucrose - the radiation diffracted by diazepam crystals

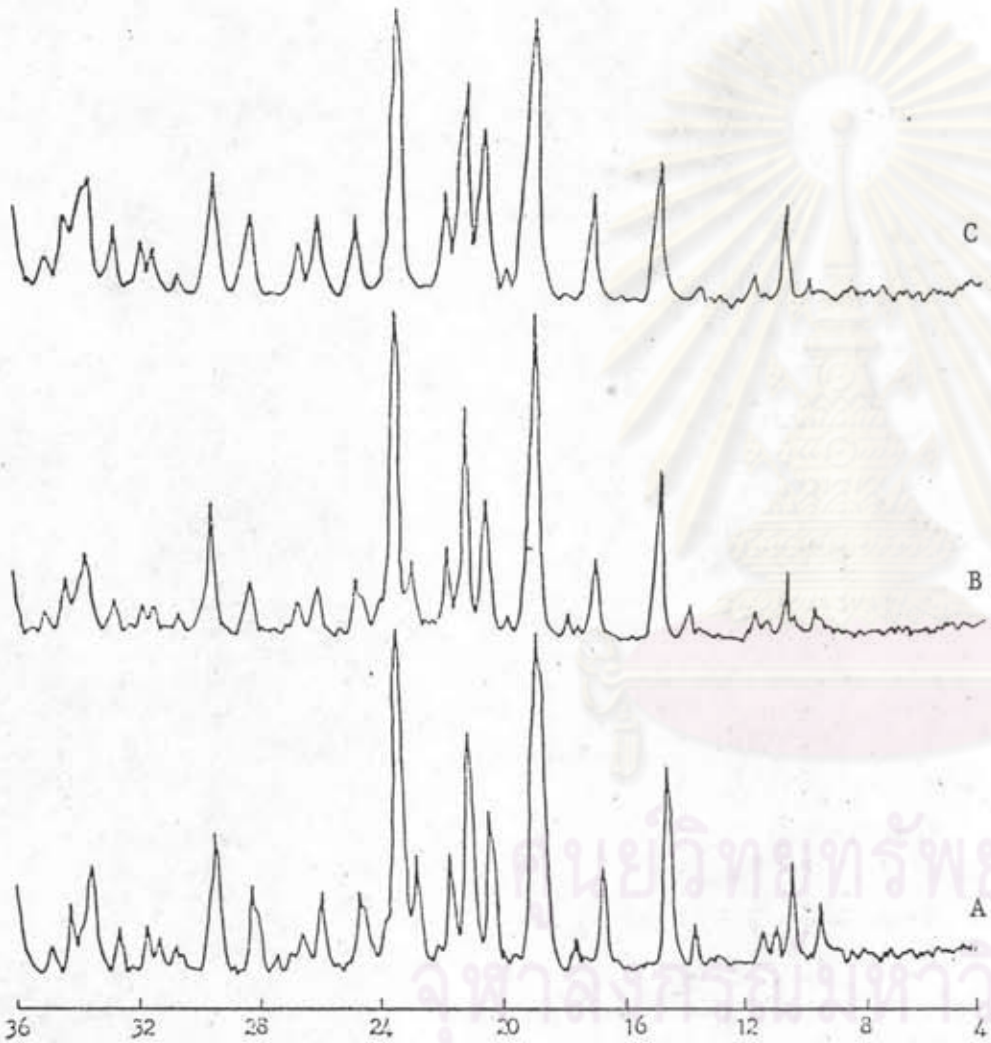

Figure: 13

X-Ray diffraction patterns of the mixtures of diazepam in mannitol at the ratio of 1:5 prepared by ball-milling method

A: mill for 20 hours

B: mill for 40 hours

C: mill for 60 hours

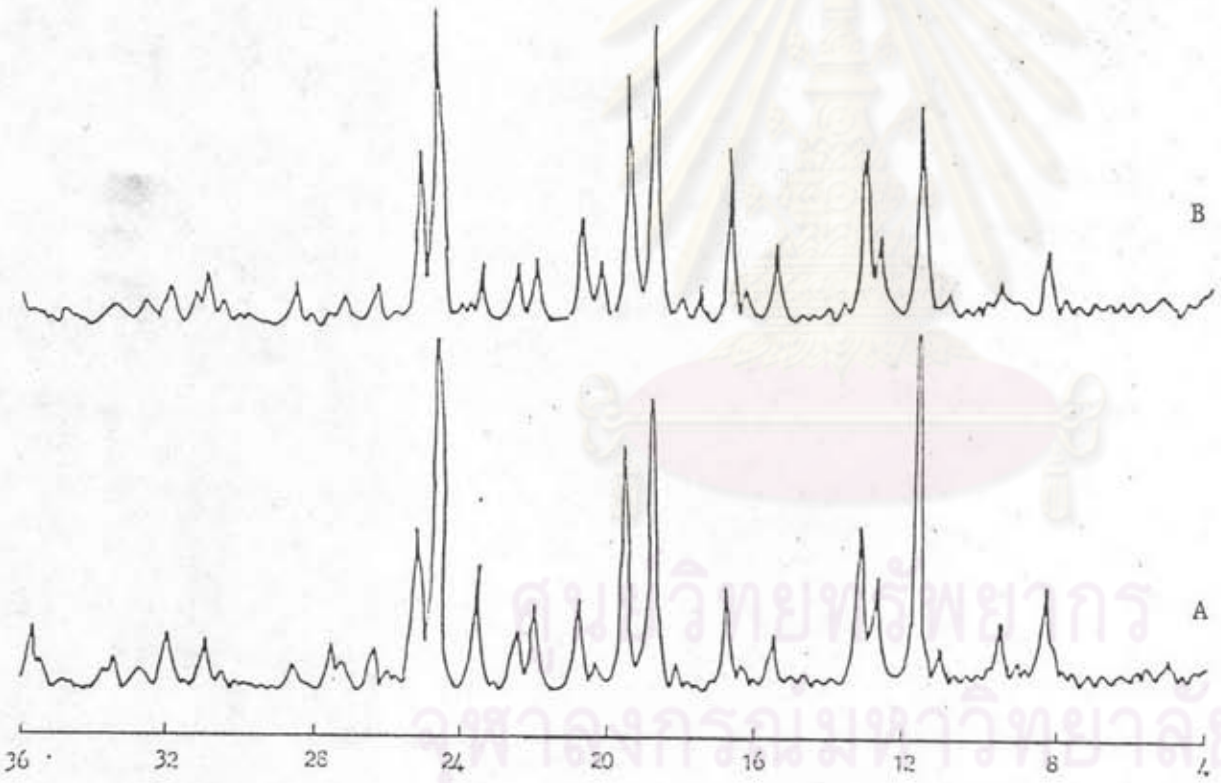

Figure: 14

X-Ray diffraction patterns of the mixtures of diazepam in sucrose at the ratio of 1:20 prepared by

A: simple blending method

B: solvent deposition method

(the diazepam peaks) and sucrose crystals (the sucrose peaks). The diazepam peaks could be observed markly at 9.5°, 11.0° in term of 2θ angle of the diffraction pattern of the mixture as shown in Figure 14.

c) Ball Milling Method

The X-Ray diffraction pattern of 1:20 ratio of diazepam in sucrose mixture was determined at 10 hour and 20 hour grinding. After 10 hour grinding the diazepam diffraction peaks were still remained at 9.5° in the term of 2θ angle. After 20 hour grinding the diazepam diffraction peaks were disappered in the diffraction pattern of the mixtures as shown in Figure 15.

1.2.2 1:10 Diazepam-Sucrose Mixture

a) Simple Blending Method

The X-Ray diffraction pattern of 1:10 ratio of diazepam in sucrose mixture prepared by simple blending method showed the superposition of the diffraction pattern of diazepam and sucrose. The increasing of diazepam diffraction peaks intensity comparing to 1:20 ratio of diazepam in sucrose mixtures prepared by the same method, was observed at 9.5°,11.0°,13.6° in term of 2θ angle of the diffraction pattern of the mixture as shown in Figure 16.

b) Solvent Deposition Method

The X-Ray diffraction pattern of 1:10 ratio of diazepam in sucrose mixture prepared by solvent deposition method was similar to

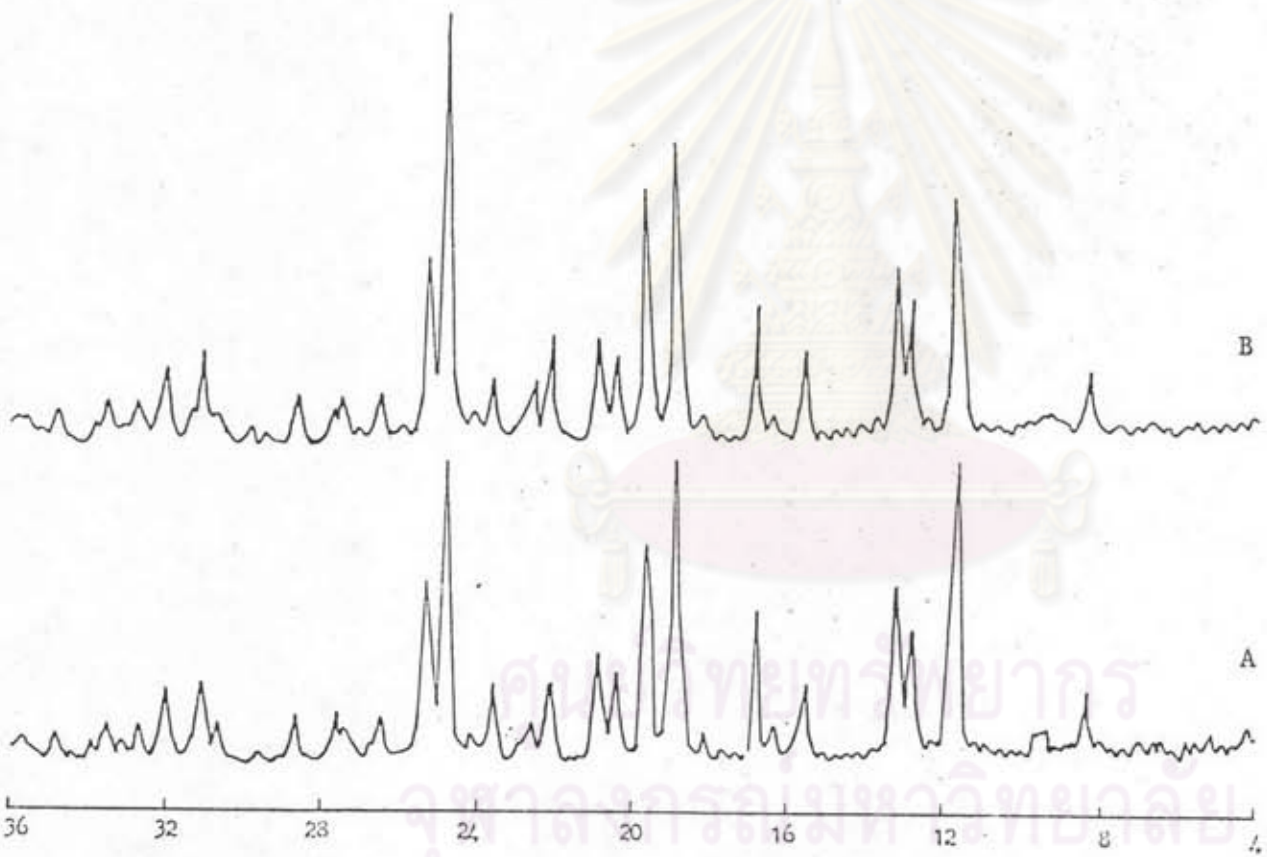

Figure: 15

X-Ray diffraction patterns of the mixtures of diazepam in sucrose at the ratio of 1:20 prepared by ball-milling method

A: mill for 10 hours

B: mill for 20 hours

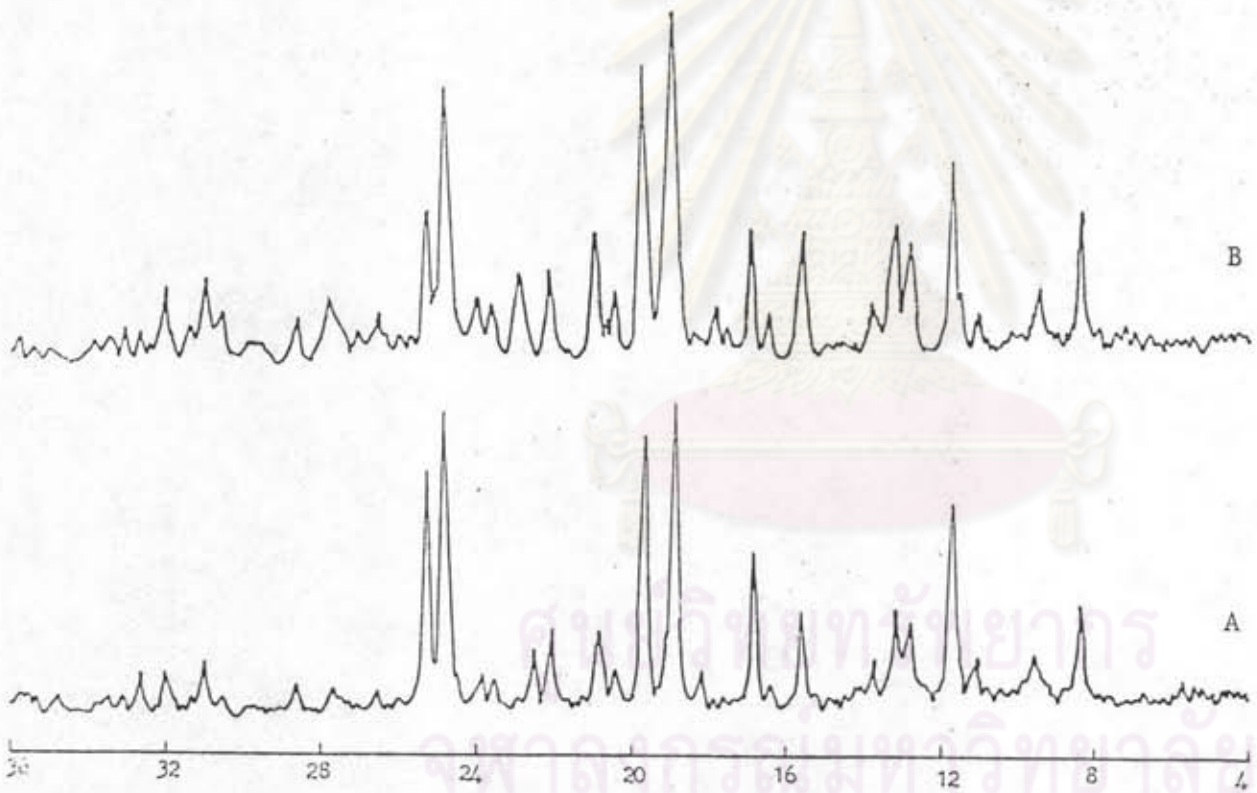

Figure: 16

X-Ray diffraction patterns of the mixtures of diazepam in sucrose at the ratio of 1:10 prepared by

A: simple blending method

B: solvent deposition method

the X-Ray diffraction pattern of 1:20 ratio of diazepam in sucrose mixture prepared by the same method, but the peaks intensity of diazepam at 9.5° and 11.0° in the term of 2θ angle slightly increased. The diazepam diffraction peak at 13.6° in the term of 2θ angle was also observed as shown in Figure 16.

c) Ball Milling Method

The X-Ray diffraction pattern of the 1:10 ratio of diazepam in sucrose mixture was determined after 10 hour, 20 hour, and 30 hour grinding. The diazepam diffraction peaks could be observed at 9.5°, 11.0° in the term of 2θ angle after 10 hour and 20 hour grinding. After 30 hour grinding the diazepam diffraction peaks were disappeared. According to grinding process, the diazepam diffraction peaks were decreased in intensity when the grinding time increased and disappeared after 30 hour grinding as shown in Figure 17.

1.2.3 1:5 Diazepam-Sucrose Mixture

a) Simple Blending Method

The X-Ray diffraction pattern of the 1:5 ratio of diazepam in sucrose mixture prepared by simple blending method showed the superposition of the pattern of diazepam and sucrose. The diazepam diffraction peaks increased intensity comparing to 1:10 ratio of diazepam in sucrose mixture prepared by the same method. The diazepam diffraction peaks could be observed at 9.5°, 11.0° and 13.6° in the term of 2θ angle of the diffraction pattern of the mixtures as shown in Figure 18.

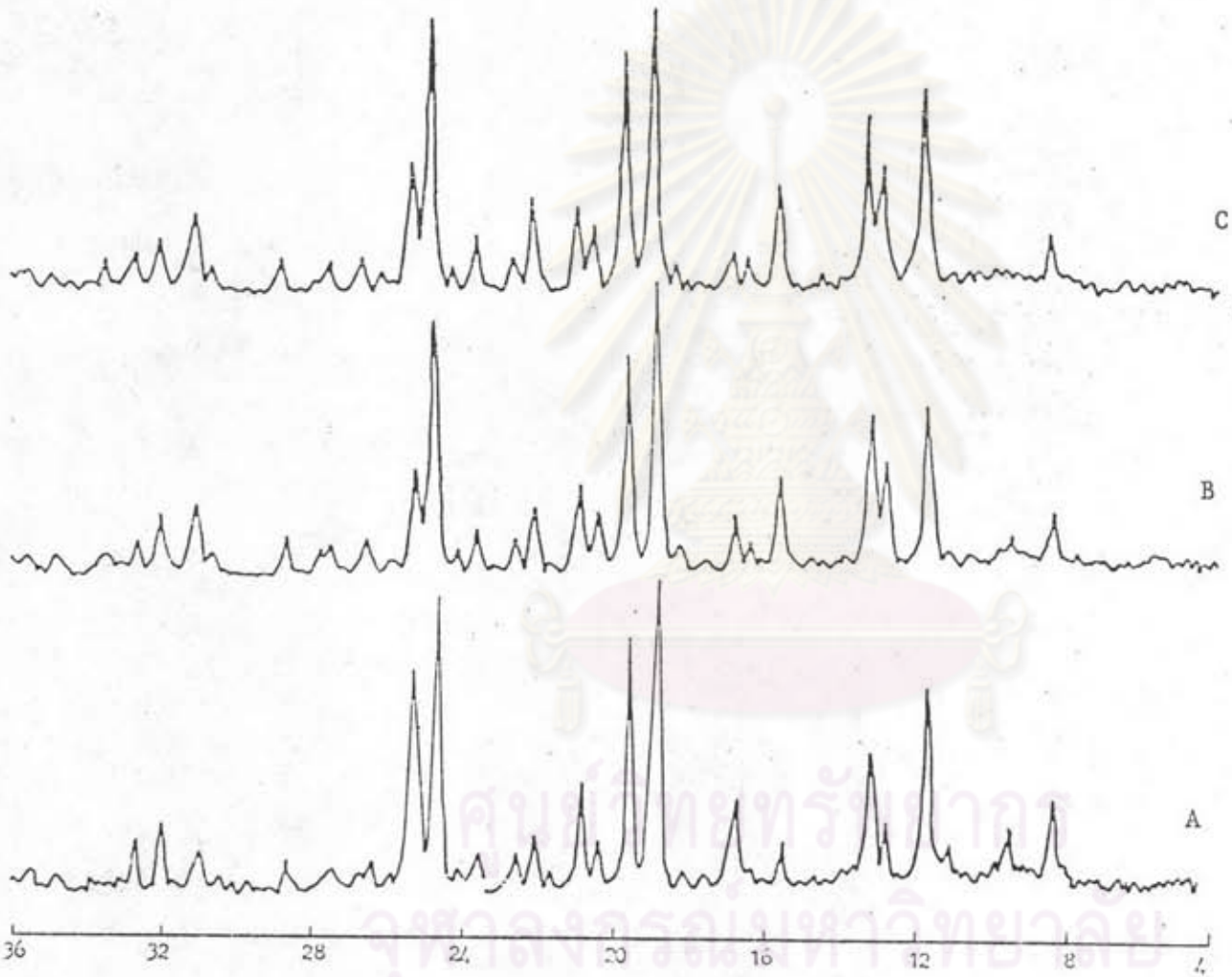

Figure: 17

X-Ray diffraction patterns of the mixtures of diazepam in sucrose at the ratio of 1:10 prepared by ball-milling method

A: mill for 10 hours

B: mill for 20 hours

C: mill for 30 hours

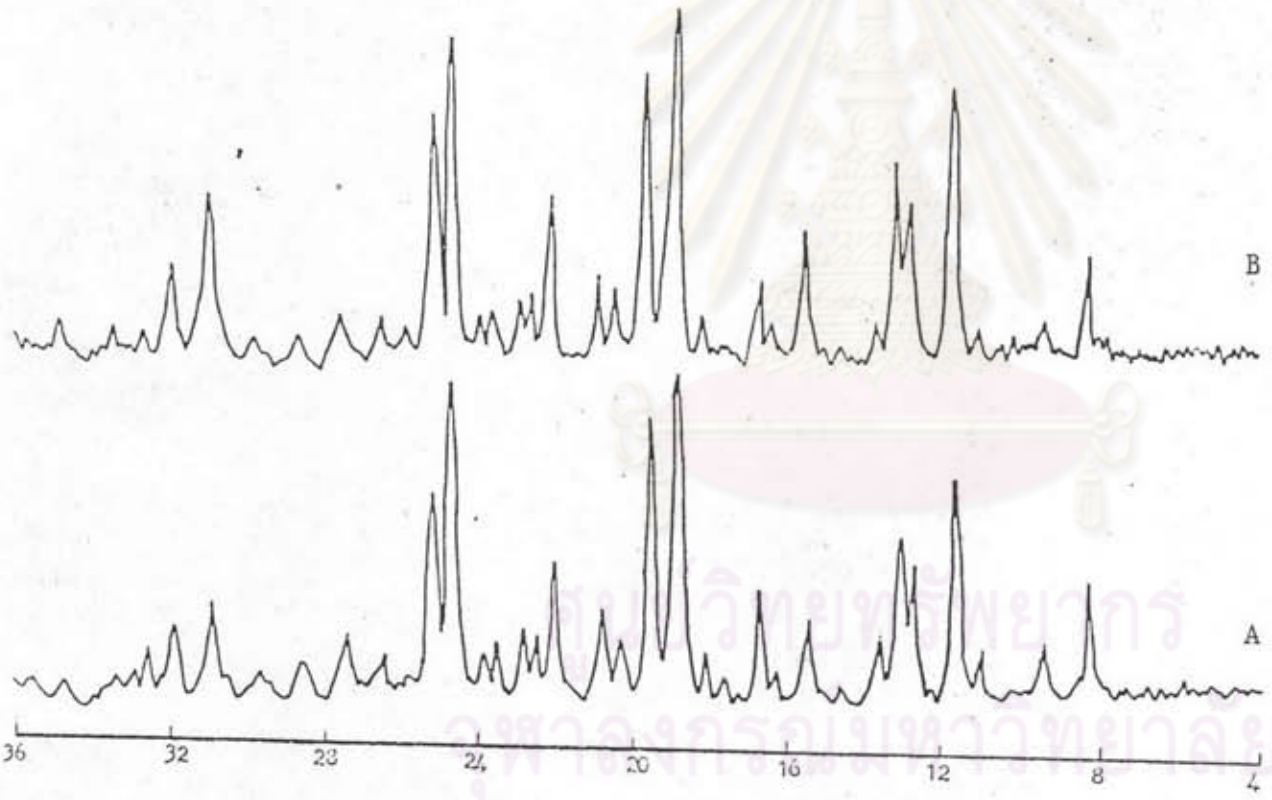

Figure: 18

X-Ray diffraction patterns of the mixtures of diazepam in sucrose at the ratio of 1:5 prepared by

A: simple blending method

B: solvent deposition method

b) Solvent Deposition Method

The X-Ray diffraction pattern of 1:5 ratio of diazepam in sucrose mixture prepared by solvent deposition method was similar to the X-Ray diffraction pattern of 1:10 ratio of diazepam in sucrose mixture prepared by the same method, but the peaks intensity of diazepam at 9.5°and 11.0° in the term of 2θ angle markly increased as shown in Figure 18.

c) Ball Milling Method

The X-Ray diffraction pattern of 1:5 ratio of diazepam in sucrose mixture was determined at 20 hour, 40 hour and 60 hour grinding. The diazepam diffraction peaks at 9.5°, 11.0° and 13.6° in the term of 2θ angle were remained in the diffraction pattern of the mixtures after 60 hour grinding as shown in Figure 19. It was seemed to be that the crystalline portions of diazepam were remained in the ground mixtures.

1.3 Diazepam- Dibasic calcium phosphate

1.3.1 1:20 Diazepam- Dibasic calcium phosphate Mixture

a) Simple Blending Method

Dibasic calcium phosphate produced its own characteristic X-Ray diffraction pattern as presented in Figure 7. The dominant peaks intensity appeared at 11.6°, 21.0°, 29.3°, 30.5°, 31.3°, 34.2° and 34.4° in the term of 2θ angle. The X-Ray diffraction pattern of 1:20 ratio of diazepam in Dibasic calcium phosphate mixture showed

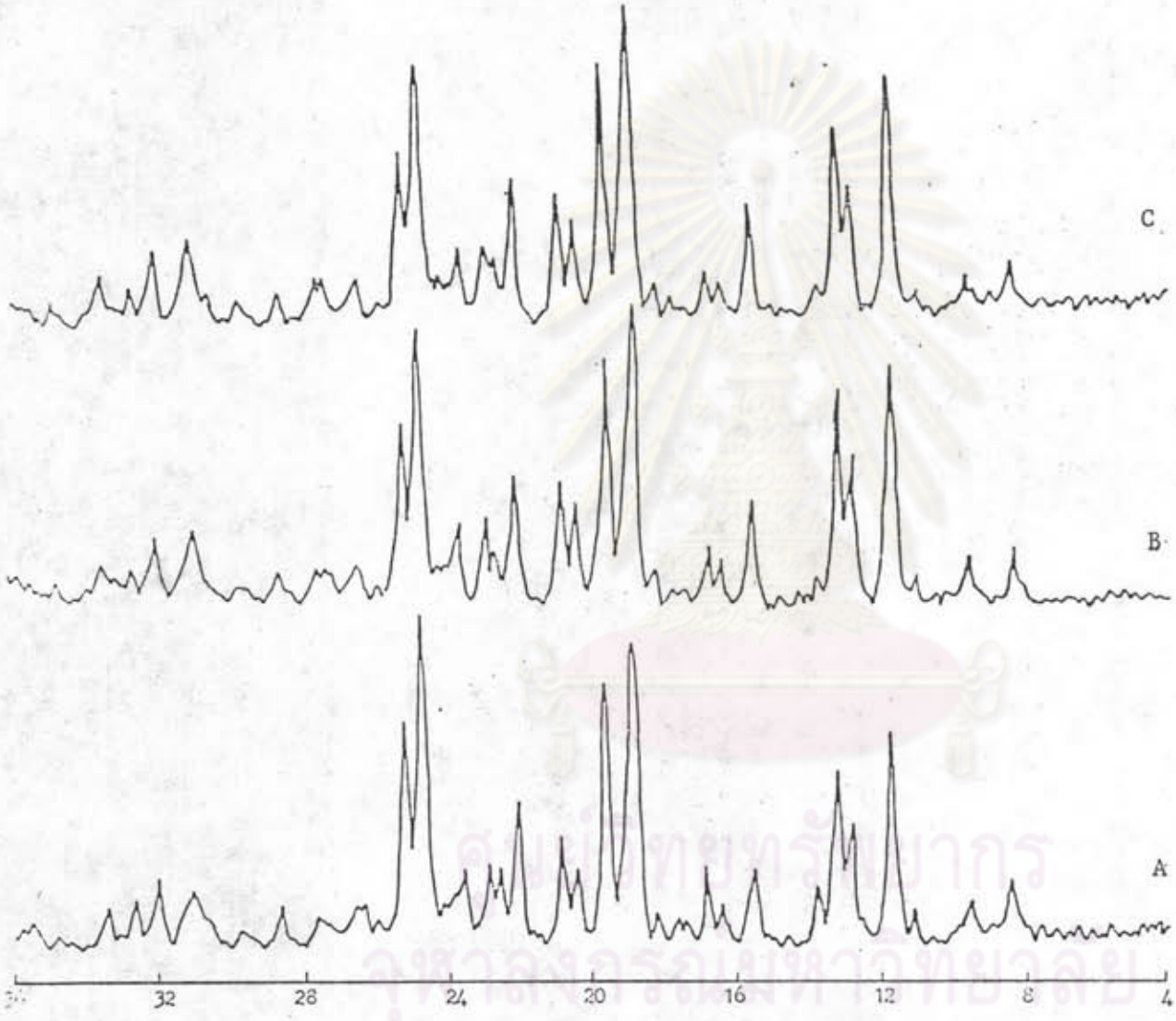

Figure: 19

X-Ray diffraction patterns of the mixtures of diazepam in sucrose at the ratio of 1:5 prepared by ball-milling method

A: mill for 20 hours

B: mill for 40 hours

C: mill for 60 hours

the superposition of the patterns of diazepam and dibasic calcium phosphate. Each components contributed its own pattern with an intensity proportional to the amount present in the mixtures. The diazepam diffraction peaks could be observed at 9.5°and 18.9°in the term of 2θ angle of the diffraction pattern of the mixtures as shown in Figure 20.

b) Solvent Deposition Method

X-Ray diffraction pattern of 1:20 ratio of diazepam in dibasic calcium phosphate mixture prepared by solvent deposition method was shown in Figure 20. It consisted of the superposition of the diazepam diffraction peaks and dibasic calcium phosphate diffraction peaks. The diazepam diffraction peaks could be observed obviously at 9.5° and 18.9° in term of 2θ angle of the diffraction pattern of the mixtures as shown in Figure 20.

c) Ball Milling Method

Effect of grinding on crystallinity of diazepam in diazepam - dibasic calcium phosphate mixture was determined after 10 hour and 15 hour grinding. After 10 hour grinding, the diazepam diffraction peaks could be observed at 9.5° and 18.9° in the term of 2θ angle of the diffraction pattern of the mixtures. After 15 hour grinding the diazepam diffraction peaks could not be observed in the diffraction pattern of the mixtures as shown in Figure 21.

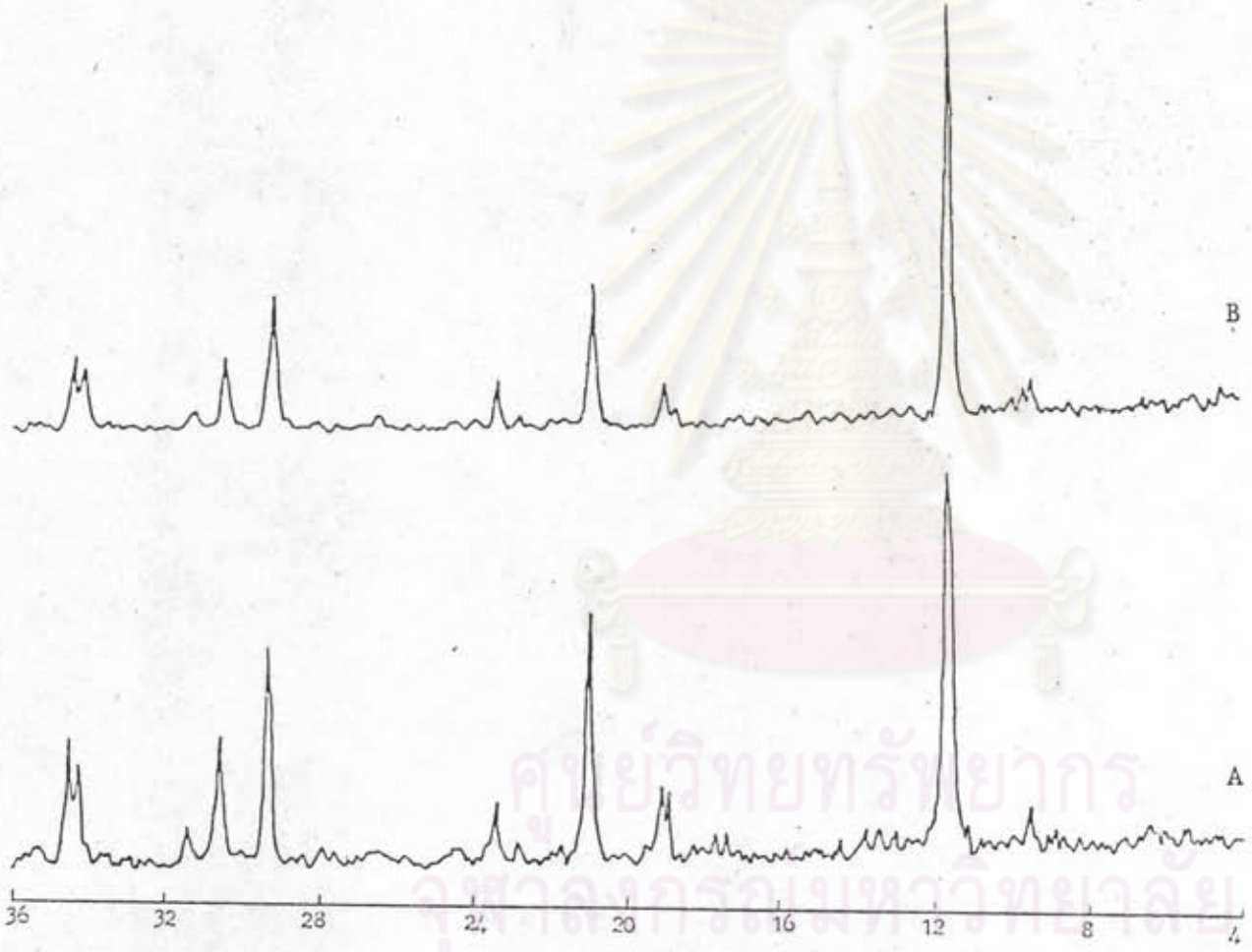

Figure: 20

X-Ray diffraction patterns of the mixtures of diazepam in dibasic calcium phosphate at the ratio of 1:20 prepared by

A: simple blending method

B: solvent deposition method

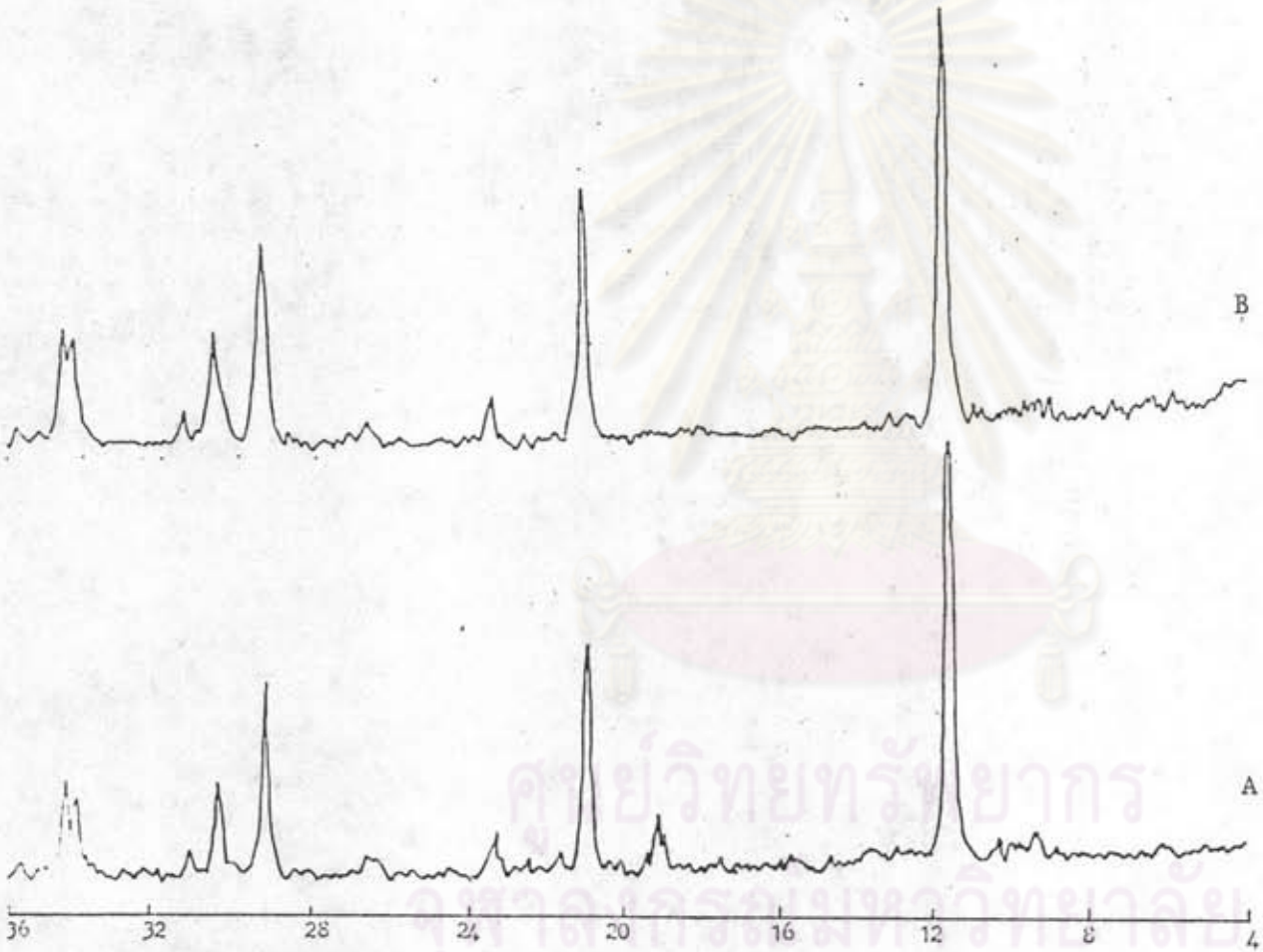

Figure: 21

X-Ray diffraction patterns of the mixtures of diazepam in dibasic calcium phosphate at the ratio of 1:20 prepared by ball-milling method

A: mill for 10 hours

B: mill for 15 hours

1.3.2 1:10 Diazepam - Dibasic calium phosphate Mixture

a) Simple Blending Method

The X-Ray diffraction pattern of 1:10 ratio of diazepam in dibasic calcium phosphate mixture prepared by simple blending method was observed. The X-Ray diffraction pattern of the mixtures showed the superposition of the diffraction pattern of diazepam and dibasic calcium phosphate. The diazepam diffraction peaks appeared at 9.5° and 18.9° in the term of 2θ angle of the diffraction pattern of the mixtures as shown in Figure 22.

b) Solvent Deposition Method

The X-Ray diffraction pattern of 1:10 ratio of diazepam in dibasic calcium phosphate mixture prepared by solvent deposition method was similar to the X-Ray diffraction pattern of 1:20 ratio of diazepam in dibasic calcium phosphate mixture prepared by the same method. The diazepam diffraction peaks appeared at 9.5° and 18.9° in term of 2θ angle of the diffraction pattern of the mixtures as shown in Figure 22.

c) Ball Milling Method

Effect of grinding on crystallinity of diazepam in 1:10 ratio of diazepam-dibasic calcium phosphate mixture was determined after 10 hour, 20 hour and 30 hour grinding. After 10 hour grinding, the diazepam diffraction peaks could be observed at 9.5° and 18.9° in term of 2θ angle of the diffraction pattern of the mixtures. After 20 hour grinding the diazepam diffraction peaks decreased in their

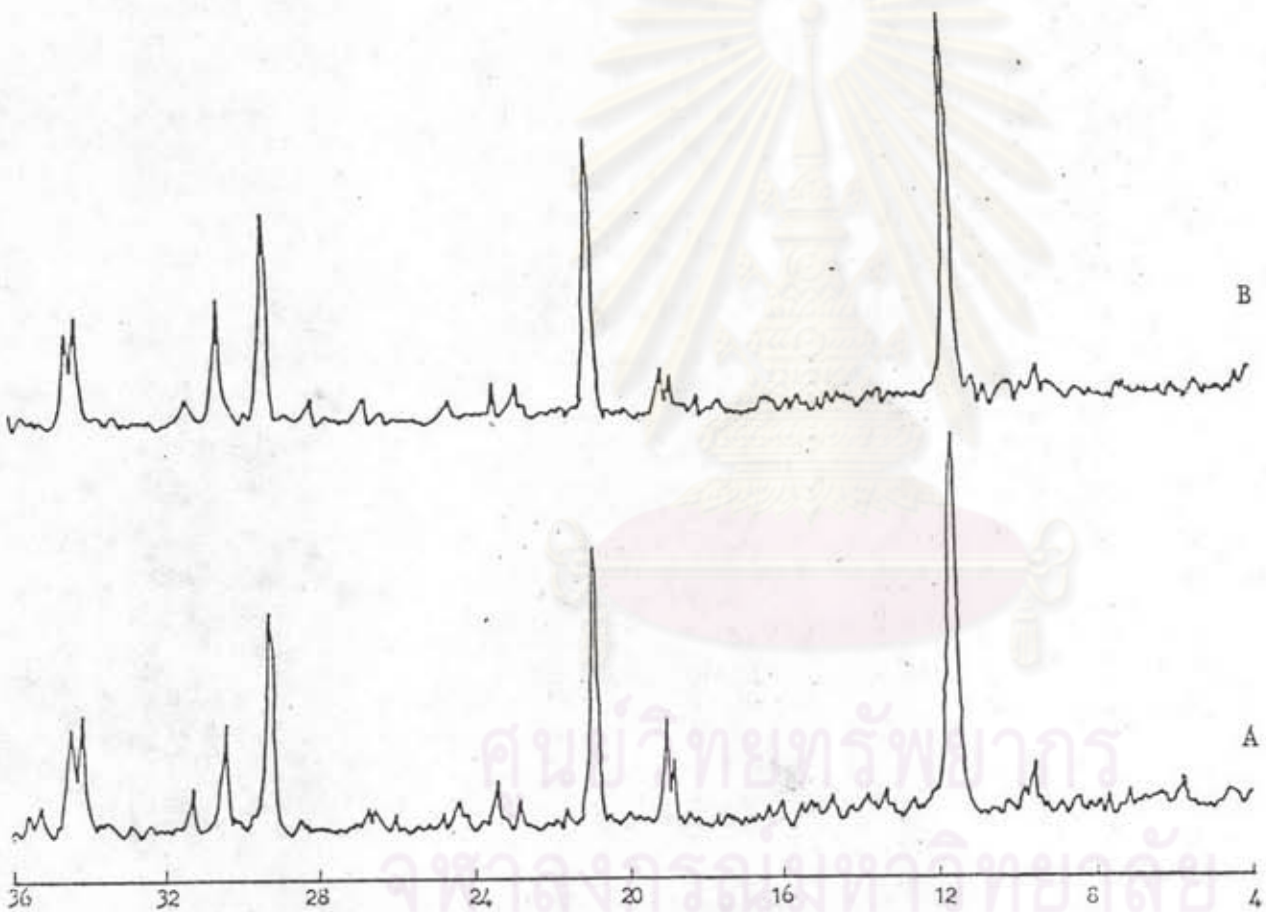

Figure: 22

X-Ray diffraction patterns of the mixtures of diazepam in dibasic calcium phosphate at the ratio of 1:10 prepared by

A: simple blending method

B: solvent deposition method

intensities. After 30 hour grinding the diazepam diffraction peaks were disappeared. The diazepam diffraction peaks were decreased in intensity with the increasing of grinding time and were disappeared after 30 hour grinding as shown in Figure 23.

1.3.3 1:5 Diazepam - Dibasic calcium phosphate Mixture

a) Simple Blending Method

The X-Ray diffraction pattern of the 1:5 ratio of diazepam in dibasic calcium phosphate mixture prepared by simple blending method showed the superposition of the diffraction pattern of diazepam and dibasic calcium phosphate. The diazepam diffraction peaks increased in intensity comparing to 1:10 ratio of diazepam in dibasic calcium phosphate mixtures prepared by the same method. The diazepam diffraction peak could be observed markly at 9.5° and 18.9° in the term of 2θ angle of the diffraction pattern of the mixtures as shown in Figure 24.

b) Solvent Deposition Method

The X-Ray diffraction pattern of 1:5 ratio of diazepam in dibasic calcium phosphate mixture prepared by solvent deposisiton method was similar to the X-Ray diffraction patterns of 1:10 ratio of diazepam in dibasic calcium phosphate mixtures prepared by the same method, but the peak intensity of diazepam at 9.5° and 18.9° in the term of 2θ angle markly increased as shown in Figure 24.

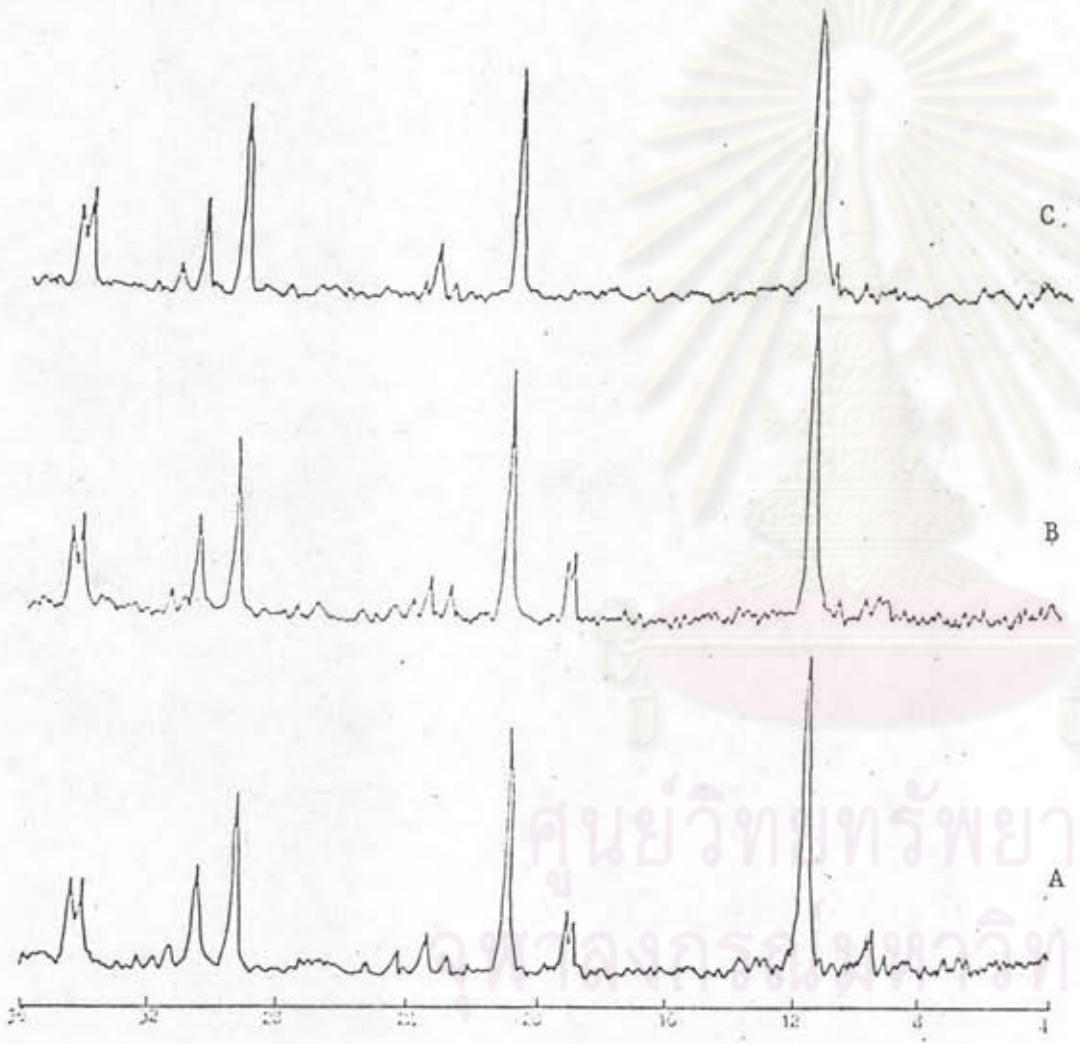

Figure: 23

X-Ray diffraction patterns of the mixtures of diazepam in dibasic calcium phosphate at the ratio of 1:10 prepared by ball-milling method

A: mill for 10 hours

B: mill for 20 hours

C: mill for 30 hours

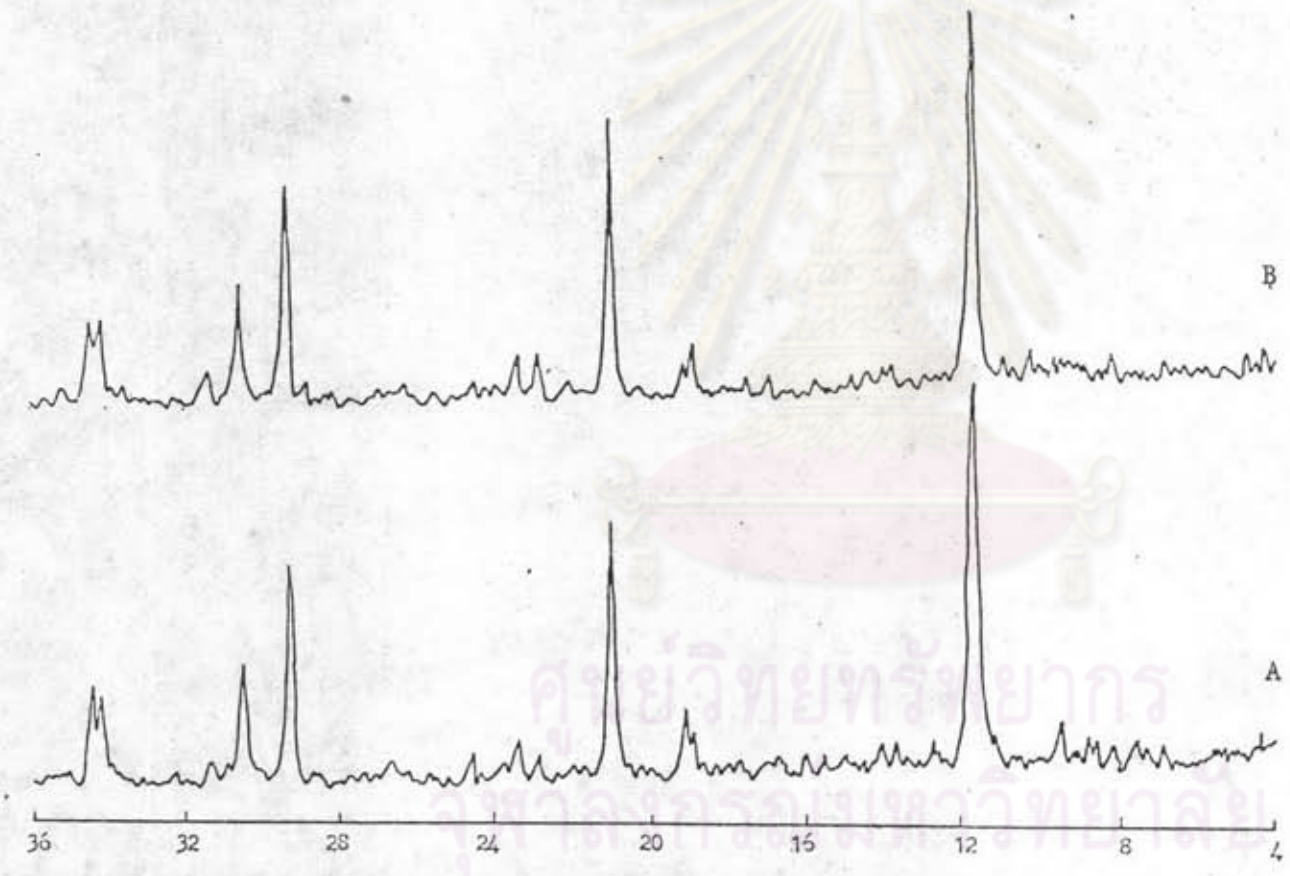

Figure: 24

X-Ray diffraction patterns of the mixtures of diazepam in dibasic calcium phosphate at the ratio of 1:5 prepared by

A: simple blending method

B: solvent deposition method

c) Ball Milling Method

The X-Ray diffraction pattern of 1:5 ratio of diazepam in dibasic calcium phosphate mixture was determined at 20 hour, 40 hour and 60 hour grinding. The diazepam diffraction peaks at 9.5° and 18.9° in the term of 2θ angle were remained in the diffraction pattern of the mixtures as shown in Figure 25. It was seemed to be that the crystalline portions of deazepam were remained in the ground mixtures.

1.4 Diazepam - Microcrystalline cellulose Mixture

1.4.1 1:20 Diazepam - Microcrystalline cellulose Mixture

a) Simple Blending Method

The X-Ray diffraction pattern of microcrystalline cellulose is presented in Figure 7. It consisted of diffraction pattern of crystalline portion of microcrystalline cellulose and the diffuse background due to amorphous portion of microcrystalline cellulose. The X-Ray diffraction pattern of 1:20 ratio of diazepam in microcrystalline cellulose mixture showed the superposition of the patterns of diazepam and microcrystalline cellulose. The diazepam diffraction peak could be observed at 18.9° in the term of 2θ angle of the diffraction pattern of the mixtures as shown in Figure 26.

b) Solvent Deposition Method

The X-Ray diffraction of 1:20 ratio of diazepam in microcrystalline cellulose mixture prepared by solvent deposition method was presented in Figure 26. It consisted of diffraction patterns of

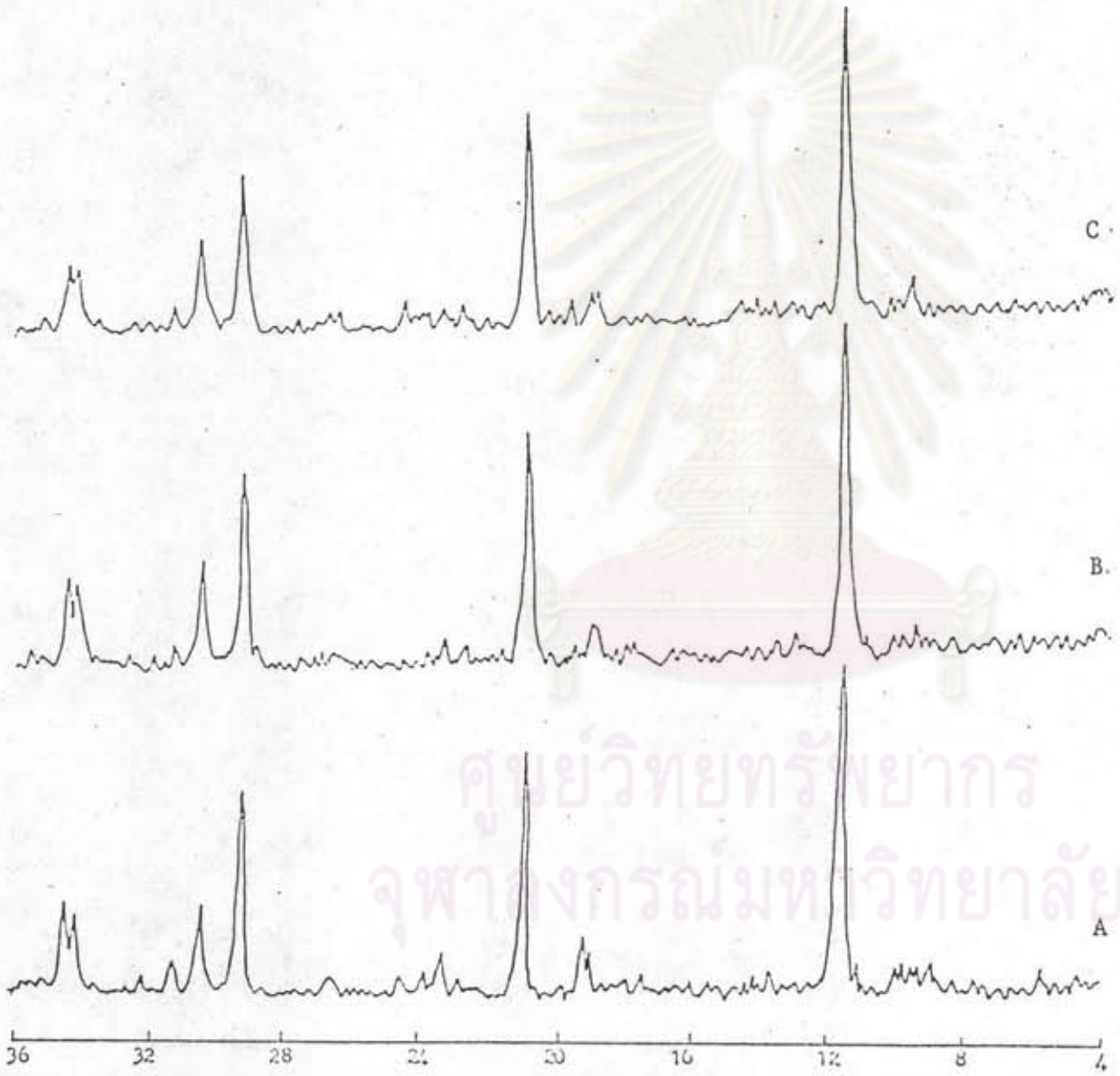

Figure: 25

X-Ray diffraction patterns of the mixtures of diazepam in dibasic calcium phosphate at the ratio of 1:5 prepared by ball-milling method

A: mill for 20 hours

B: mill for 40 hours

C: mill for 60 hours

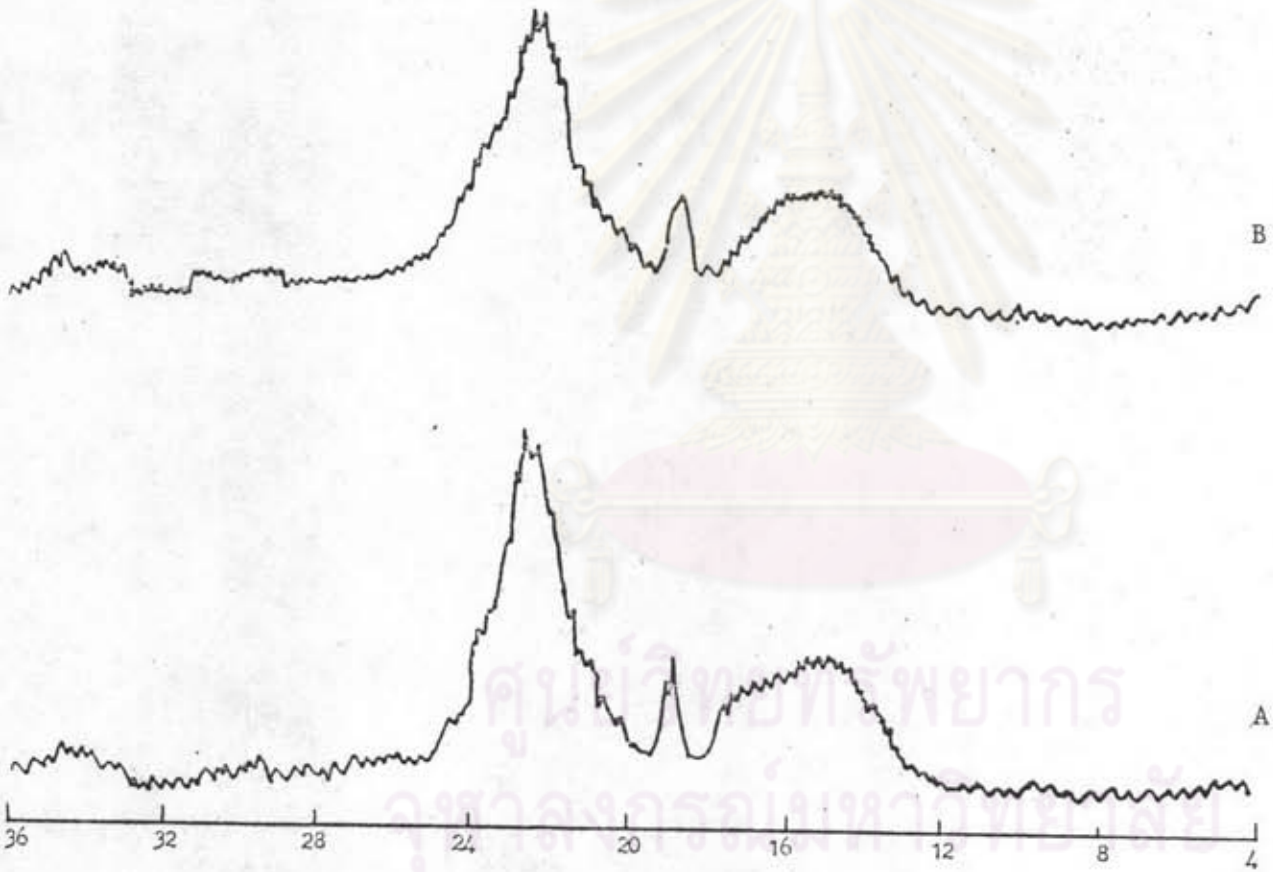

Figure: 26

X-Ray diffraction patterns of the mixtures of diazepam in microcrystalline cellulose at the ratio of 1:20 prepared by

A: simple blending method

B: solvent deposition method

diazepam, diffraction patterns of crystalline portion of microcrystalline cellulose and the diffuse background due to amorphous portions of microcrystalline cellulose. The diazepam diffraction peak appeared at 18.9° in the term of 2θ angle of the diffraction pattern of the mixtures as shown in Figure 26.

c) Ball Milling Method

The X-Ray diffraction pattern of 1:20 ratio of diazepam in microcrystalline cellulose mixture was determined at 10 hour, 20 hour grinding. After 10 hour grinding, the diazepam diffraction peak decreased in intensity, but still remained at 18.9° in term of 2θ angle of the diffraction pattern of the mixtures. After 20 hour grinding the diazepam peaks were disappeared in the diffraction pattern of the mixtures as shown in Figure 27.

1.4.2 1:10 Diazepam - Microcrystalline cellulose Mixture

a) Simple Blending Method

The X-Ray diffraction pattern of 1:10 ratio of diazepam in microcrystalline cellulose mixture prepared by simple blending method was shown in Figure 28. It consisted of diffraction patterns of diazepam, diffraction patterns of crystalline portion of microcrystalline cellulose and the diffuse background due to amorphous partions of microcrystalline cellulose. The diazepam diffraction peaks appeared at 9.5°, 11.0°, 13.6° and 18.9° in the term of 2θ angle of the diffraction pattern of the mixtures as shown in Figure 28.

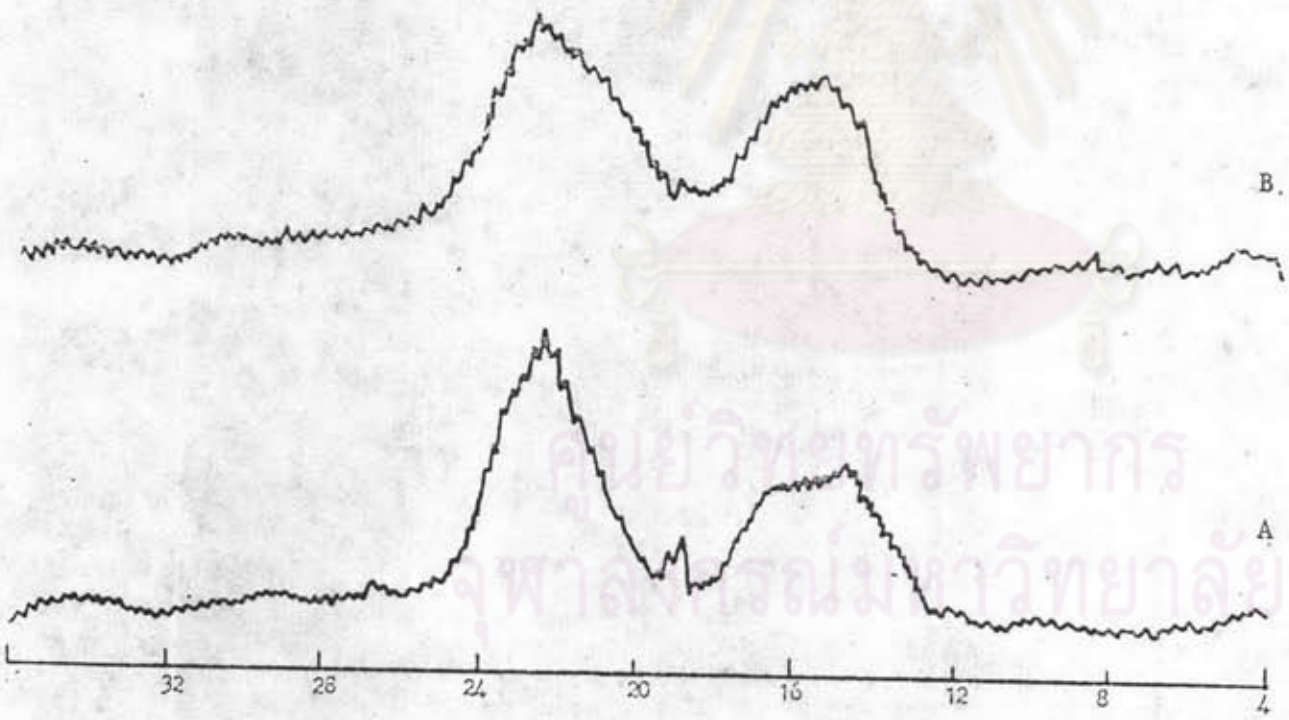

Figure: 27

X-Ray diffraction patterns of the mixtures of diazepam in microcrystalline cellulose at the ratio of 1:20 prepared by ball-milling method

A: mill for 10 hours

B: mill for 20 hours

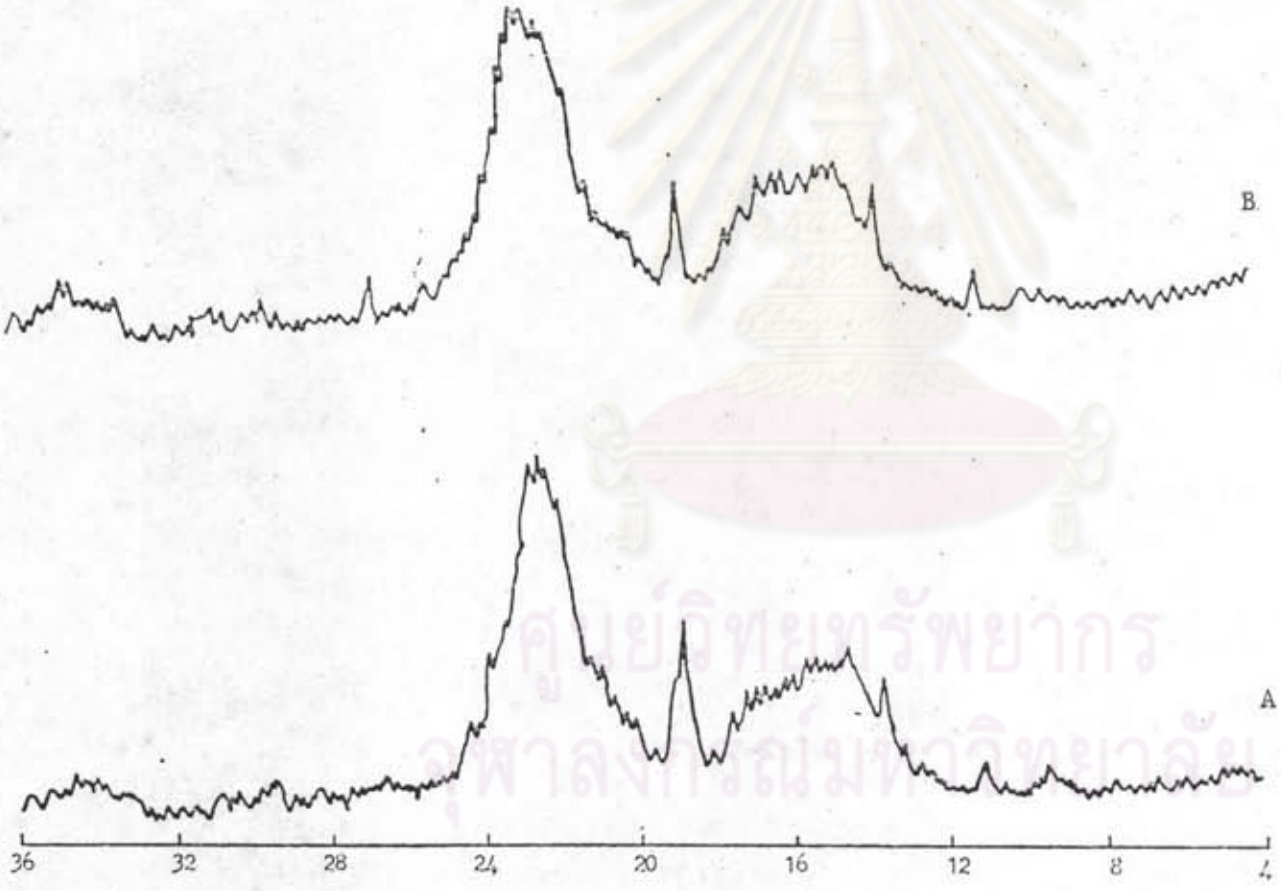

Figure: 26

X-Ray diffraction patterns of the mixtures of diazepam in microcrystalline cellulose at the ratio of 1:10 prepared by

A: simple blending method

B: solvent deposition method

b) Solvent Deposition Method

The X-Ray diffraction pattern of 1:10 ratio of diazepam in microcrystalline cellulose mixture prepared by solvent deposition method was similar to the X-Ray diffraction pattern of 1:20 ratio of diazepam in microcrystalline cellulose mixtures prepared by the same method. The diazepam diffraction peaks appears at 9.5°, 11.0°, 13.6°, 18.9° and 26.6° in the term of 2θ angle of the diffraction pattern of the mixtures as shown in Fifure 28.

c) Ball Milling Method

The change of crystallinity of diazepam in 1:10 ratio of diazepam - microcrystalline cellulose mixture was determined after 10 hour, 20 hour and 30 hour grinding. After 10 hour grinding the diazepam diffraction peaks could be observed at 11.0°, 13.6° and 18.9° in the term of 2θ angle of the diffraction pattern of the mixtures. After 20 hour grinding the diazepam diffraction peaks appeared at 13.6° and 18.9° in the term of 2θ angle of the diffraction pattern of the mixtures and decreased in their tensities. After 30 hour grinding the diazepam diffraction peaks were disappeared as shown in Figure 29.

1.4.3 1:5 Diazepam - Microcrystalline cellulose Mixture

a) Simple Blending Method

The X-Ray diffraction pattern of 1:5 ratio of diazepam in microcrystalline cellulose mixture prepared by simple blending method

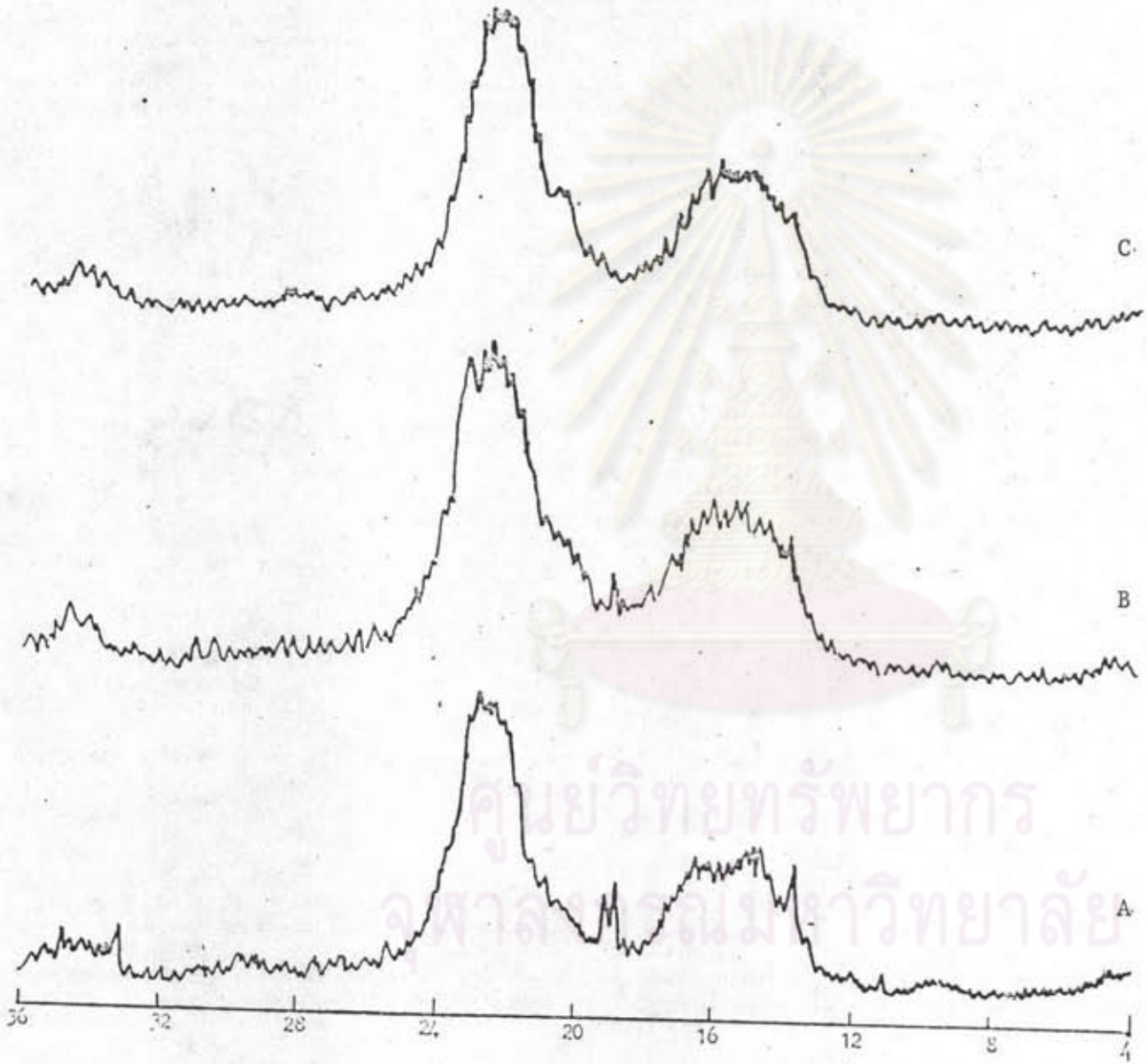

Figure: 29

X-Ray diffraction patterns of the mixtures of diazepam in microcrystalline cellulose at the ratio of 1:10 prepared by

A: mill for 10 hours

B: mill for 20 hours

C: mill for 30 hours

was similar to the X-Ray diffraction pattern of 1:10 ratio of diazepam in microcrystalline cellulose mixture prepared by the same method, but the peaks intensity of diazepam at 9.5°, 11.0° 13.6° and 18.9° slightly increased and the diazepam diffraction peaks at 24.4°, 26.6° and 29.7° in the term of 2θ angle markly appeared as shown in Figure 30.

b) Solvent Deposition Method

The X-Ray diffraction pattern of 1:5 ratio of diazepam in microcrystalline cellulose mixture prepared by solvent deposition method was similar to the X-Ray diffraction pattern of 1:10 ratio of diazepam in microcrystalline cellulose mixture prepared by the same method, but the peak intensity of diazepam at 9.5°, 11.0°, 13.6°, 18.9° and 26.6° slightly increased and the diazepam diffraction peak at 29.7° in the term of 2θ angle appeared as shown in Figure 30.

c) Ball Milling Method

The change of crystallinity of diazepam in 1:5 ratio of diazepam in microcrystalline cellulose mixture was determined after 20 hour, 40 hour and 60 hour grinding. After 60 hour grinding, the diazepam diffraction peaks at 9.5°, 11.0°, 13.6° and 18.9° in the term of 2θ angle were remained in the diffraction pattern of the mixtures as shown in Figure 31. It was likely that the crystalline portions of diazepam were remained in the ground mixtures.

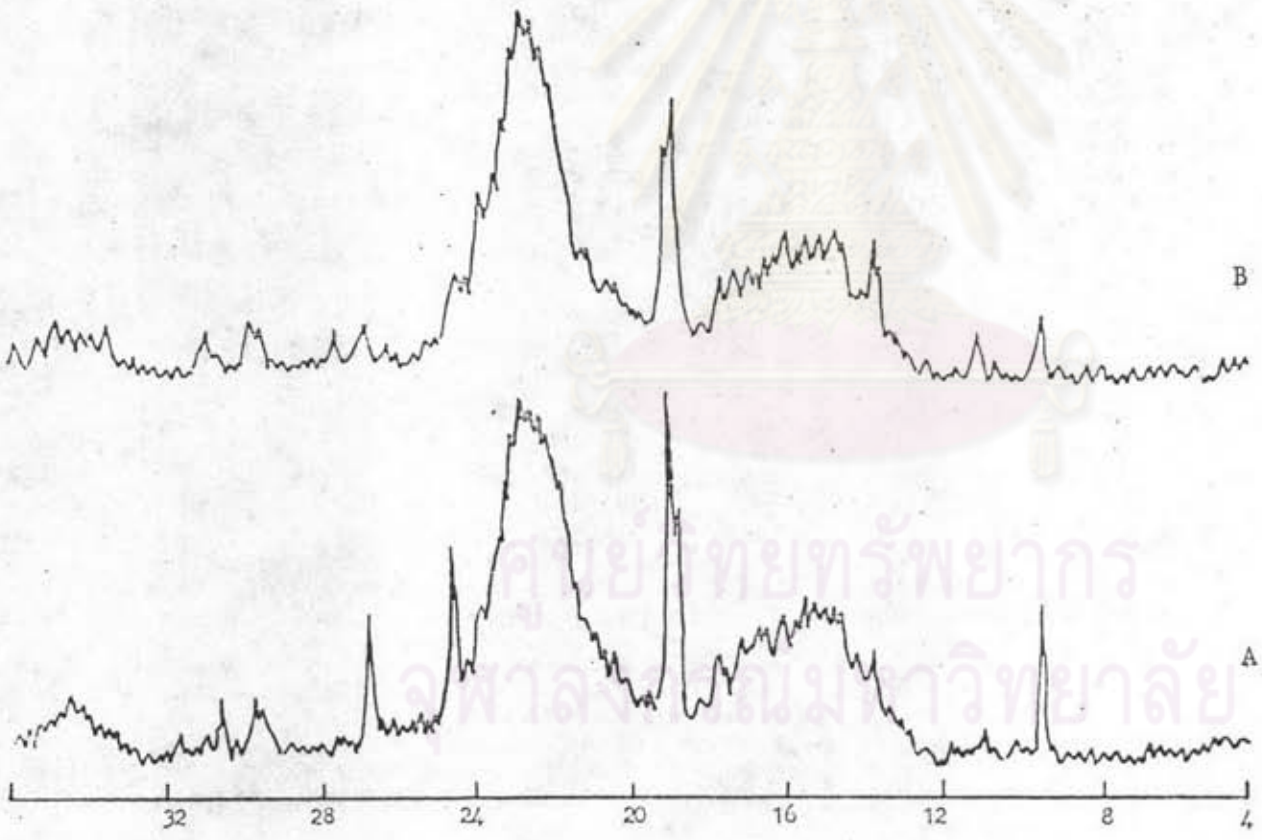

Figure: 30

X-Ray diffraction patterns of the mixtures of diazepam in microcrystalline cellulose at the ratio of 1:5 prepared by

A: simple blending method

B: solvent deposition method

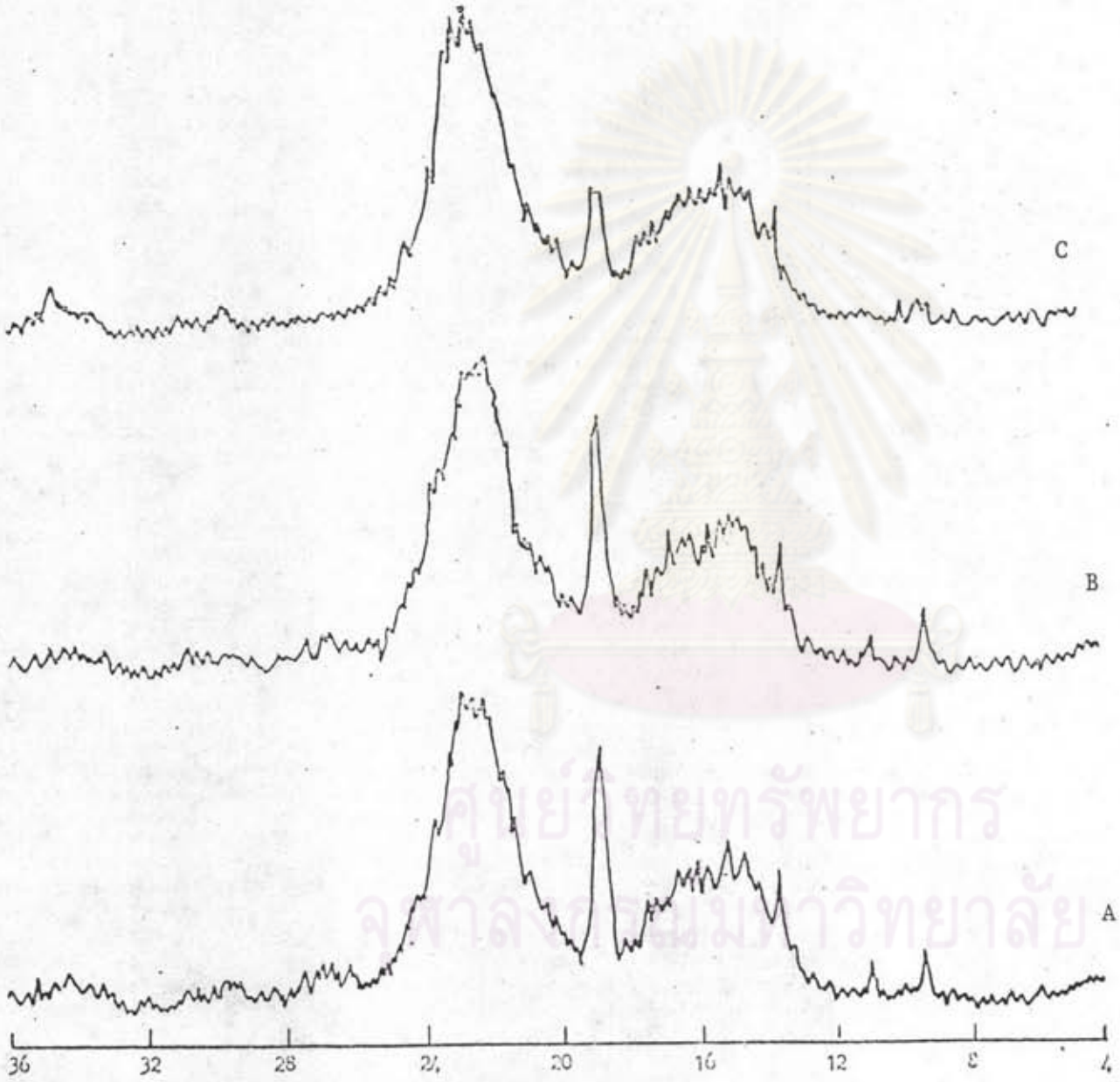

Figure: 31

X-Ray diffraction patterns of the mixtures of diazepam in microcrystalline cellulose at the ratio of 1:5 prepared by ball-milling method

A: mill for 20 hours

B: mill for 40 hours

C: mill for 60 hours

2. Determination of The Specific Surface Area of the Diluents by Fisher Sub-Sieve Sizer

The specific surface area of four diluents; mannitol, sucrose, dibasic calcium phosphate and microcrystalline cellulose were determined by Fisher Sub-Sieve Sizer which operating on the air-peameability principle. The results were summerized in table 15.

3. Properties of Diazepam Capsules

3.1 Weight Variation of Diazepam Capsules

The average weight and standard deviation of diazepam capsules were shown in table 17. Each formula of diazepam capsules possessed the weight variation in the limit of USP standard (64).

3.2 Disintegration Time of Diazepam Capsules

The disintegration time of diazepam capsules in 0.1.N. HCl maintained at 37±2° as the immersion fluid were shown in table 18. The disintegration time of each formulations was the mean value of 6 determinations. There was slightly difference in the disintegration time of each formulation. The average disintegration time of all formula was between 1.50 - 3.33 minutes.

3.3 Percent Labeled Amount of Diazepam Capsules.

The percent labeled amount of diazepam capsules in each formulation were shown in table 19. The percent labeled amount of each formulations was the mean value of 2 determinations.

Table: 15

The Specific surface area of four diluents;

mannitol, sucrose, dibasic calcium phosphate ($Ca\ HPO_4$)

and microcrystalline cellulose (Avicel)

Sample	mannitol	sucrose	$Ca\ HPO_4$	Avicel
Weight of Sample (g) (equal to true density)	1.52[a]	1.60[b]	1.76[c]	1.55[d]
Porosity	0.496	0.425	0.414	0.665
Particle size (um)	9.0	20.4	11.5	10.5
Specific surface area (m^2/gm)	0.44	0.18	0.29	0.37

[a]taken from, Martha Windholz "The Merck index" tenth edition Merck & Co., INC 1983.

[b]taken from, Alfred N. Martin, James Swarbrick, Arthur cammarate "Physical pharmacy" Lea & Febiger 1970, page 487.

[c]Calculate from experimental data (table 16).

[d]taken from Avicel [R] pH, FMC corporation and Asahi Chemical Co., Ltd Technical data , page 4.

Table: 16

True density of dibasic calcium phosphate

Experimental Data

Weight	Experiment	
	I	II
pycnometer (g)	17.0000	17.000
pycnometer + water (g)	27.0010	26.9987
pycnometer + sample (g)	17.9662	18.0090
pycnometer + sample + water(g)	27.4171	27.4420
True density (g/c.c.)	1.76	1.78
Average True density (g/c.c.)	1.77	

Table: 17 Average weight of Diazepam Capsules.

Formula No.	Average weight ± S.D. (mg)	Formula No.	Average weight ± S.D. (mg)
0	85.12 ± 2.10	25	104.6 ± 2.2
1	125.5 ± 3.2	26	105.1 ± 1.6
2	126.0 ± 4.8	27	106.1 ± 2.9
3	124.8 ± 3.6	28	105.0 ± 1.0
4	127.6 ± 2.4	29	104.3 ± 1.7
5	124.6 ± 3.0	30	105.1 ± 1.0
6	125.2 ± 1.7	31	104.6 ± 1.6
7	126.1 ± 2.3	32	106.6 ± 2.2
8	124.8 ± 3.0	33	96.1 ± 2.1
9	123.9 ± 2.7	34	95.1 ± 3.1
10	126.6 ± 2.8	35	94.8 ± 2.8
11	125.0 ± 2.1	36	95.1 ± 3.0
12	127.0 ± 3.0	37	94.6 ± 2.1
13	126.0 ± 1.0	38	95.6 ± 3.1
14	124.9 ± 2.6	39	96.0 ± 3.2
15	125.0 ± 3.0	40	94.6 ± 3.6
16	126.1 ± 4.1	41	95.1 ± 4.0
17	104.8 ± 2.6	42	96.3 ± 2.9
18	105.2 ± 1.9	43	95.6 ± 3.2
19	106.3 ± 2.1	44	94.7 ± 2.1
20	105.6 ± 3.2	45	95.3 ± 3.1
21	105.1 ± 1.9	46	96.2 ± 2.1
22	104.8 ± 2.1	47	94.8 ± 3.4
23	105.2 ± 3.1	48	95.0 ± 3.7
24	106.3 ± 1.9		

Table: 18 Disintegration time of Diazepam Capsules.

Formula No.	Disintegration time (min) ± S.D.	Formula No.	Disintegration time (min)
0	2.67 ± 0.10	25	2.00 ± 0.04
1	3.33 ± 0.04	26	2.17 ± 0.13
2	2.41 ± 0.18	27	2.19 ± 0.14
3	3.18 ± 0.07	28	1.67 ± 0.10
4	2.08 ± 0.06	29	1.86 ± 0.16
5	2.12 ± 0.16	30	1.50 ± 0.12
6	2.58 ± 0.19	31	2.12 ± 0.18
7	3.10 ± 0.11	32	3.12 ± 0.20
8	1.90 ± 0.20	33	2.80 ± 0.18
9	2.00 ± 0.15	34	1.96 ± 0.21
10	2.50 ± 0.04	35	2.16 ± 0.18
11	2.67 ± 0.11	36	3.10 ± 0.09
12	1.50 ± 0.21	37	1.98 ± 0.03
13	2.20 ± 0.31	38	2.10 ± 0.26
14	2.50 ± 0.19	39	2.56 ± 0.12
15	3.12 ± 0.16	40	3.09 ± 0.03
16	2.16 ± 0.08	41	2.11 ± 0.09
17	3.10 ± 0.06	42	3.01 ± 0.11
18	2.91 ± 0.16	43	2.81 ± 0.26
19	3.10 ± 0.11	44	3.10 ± 0.06
20	2.10 ± 0.07	45	2.84 ± 0.24
21	1.96 ± 0.19	46	1.60 ± 0.12
22	2.17 ± 0.31	47	2.16 ± 0.19
23	3.11 ± 0.14	48	3.20 ± 0.13
24	2.60 ± 0.08		

Table: 19 Percent labeled Amount of Diazepam Capsules.

Formula No.	Percent labeled Amount*	Formula No.	Percent labeled Amount*
0	99.56	25	101.58
1	98.76	26	99.12
2	101.33	27	101.33
3	99.20	28	98.76
4	100.50	29	99.56
5	99.28	30	98.73
6	100.52	31	100.50
7	101.85	32	99.28
8	99.08	33	98.76
9	100.48	34	101.85
10	100.22	35	101.18
11	100.17	36	97.90
12	100.58	37	100.77
13	97.90	38	101.87
14	98.28	39	102.12
15	100.77	40	101.50
16	100.97	41	100.16
17	101.87	42	99.18
18	100.76	43	101.12
19	99.08	44	99.00
20	99.97	45	98.28
21	100.21	46	101.61
22	101.00	47	99.26
23	99.12	48	100.10
24	101.85		

*Mean of two determinations.

3.4 Dissolution Time of Diazepam Capsules

The dissolution time of diazepam capsules that used as a comparative parameter in the differentiation of diazepam capsule formulations in this study was the time required for 85% of diazepam to dissolve and read from the dissolution profiles. The results were shown in table 20-45.

3.4.1 The Effects of Dispersion Methods on The Dissolution Time of Diazepam Capsules.

The effects of three dispersion methods: simple blending, solvent deposition and ball milling were studied.

Formula 0, 1 to 8, 17 to 24, 33 to 40, were prepared by simple blending method. Formula 13 to 16, 29 to 32 and 45 to 48 were prepared by solvent deposition method. Formula 9 to 12, 25 to 28 and 41 to 44 were prepared by ball milling method.

The dissolution profiles of all formulations were presented in Figure: 32-43.

According to the diazepam capsule formula, using mannitol as diluent in preparing the 1:20 ratio of diazepam-diluent mixtures, there was distinct difference in the dissolution profiles of diazepam capsule formula 0, 1, 5, 9, 13 prepared by different dispersion method as shown in Figure 32. The dissolution time of the diazepam capsule formula was ranked as follow 0$\rangle$ 1$\rangle$ 13$\rangle$ 5$\rangle$ 9. Formula 0 was the control formula, prepared in the absence of mannitol. Formula

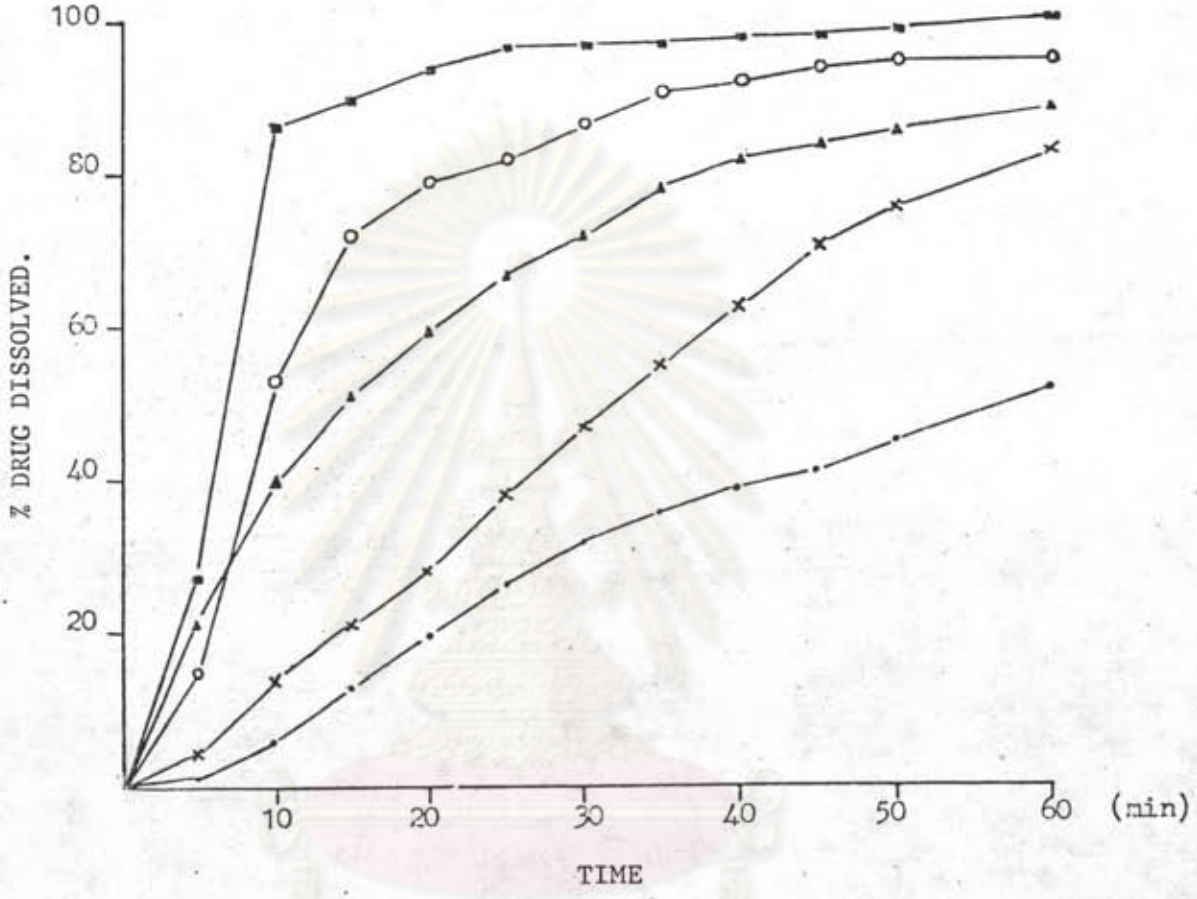

Figure: 32 Dissolution Profiles of Diazepam Capsules, Formula 0, 1, 5, 9, 13 (1:20 Diazepam-Mannitol Capsules)

Key. —•— Formula 0, control

—×— Formula 1, unmilled, simple blending

—▲— Formula 13, solvent deposition

—o— Formula 5, milled, simple blending

—■— Formula 9, ball milling

1, 5, 13, 9, the diazepam-mannitol mixtures were prepared by simple blending method of unmilled diazepam, simple blending method of milled diazepam, solvent deposition method of diazepam and ball-milling method of diazepam in 20-fold of mannitol, respectively. It was found that ball-milling method gave the shorter dissolution time than solvent deposition method and simple blending method. According to simple blending method, simple blending method of milled diazepam gave the shorter dissolution time than simple blending method of unmilled diazepam. And it was found that solvent deposition method gave the shorter dissolution time than simple blending method of unmilled diazepam.

According to the diazepam capsule formula, using mannitol as diluent in preparing the 1:10 ratio of diazepam-diluent mixtures (Formula 17, 21, 25, 29), there was a significant difference in the dissolution profiles among the diazepam capsule formulas (Formula 17, 21, 25, 29) prepared by different dispersion method as shown in Figure 33. The dissolution time of the diazepam capsule formulas was ranked as follow: 0 $\rangle$ 17 $\rangle$ 29 $\rangle$ 21 $\rangle$ 25. Formula 0 was the control formula, prepared in the absence of mannitol. Formula 17, 21, 29, 25, the diazepam-mannitol mixtures were prepared by simple blending method of unmilled diazepam, simple blending method of milled diazepam, solvent deposition method of diazepam and ball-milling method of diazepam in 10-fold of mannitol, respectively. It was found that ball milling method gave the shorter dissolution time than solvent deposition method and simple blending method. According to simple blending method, simple blending method of milled diazepam gave the shorter dissolution

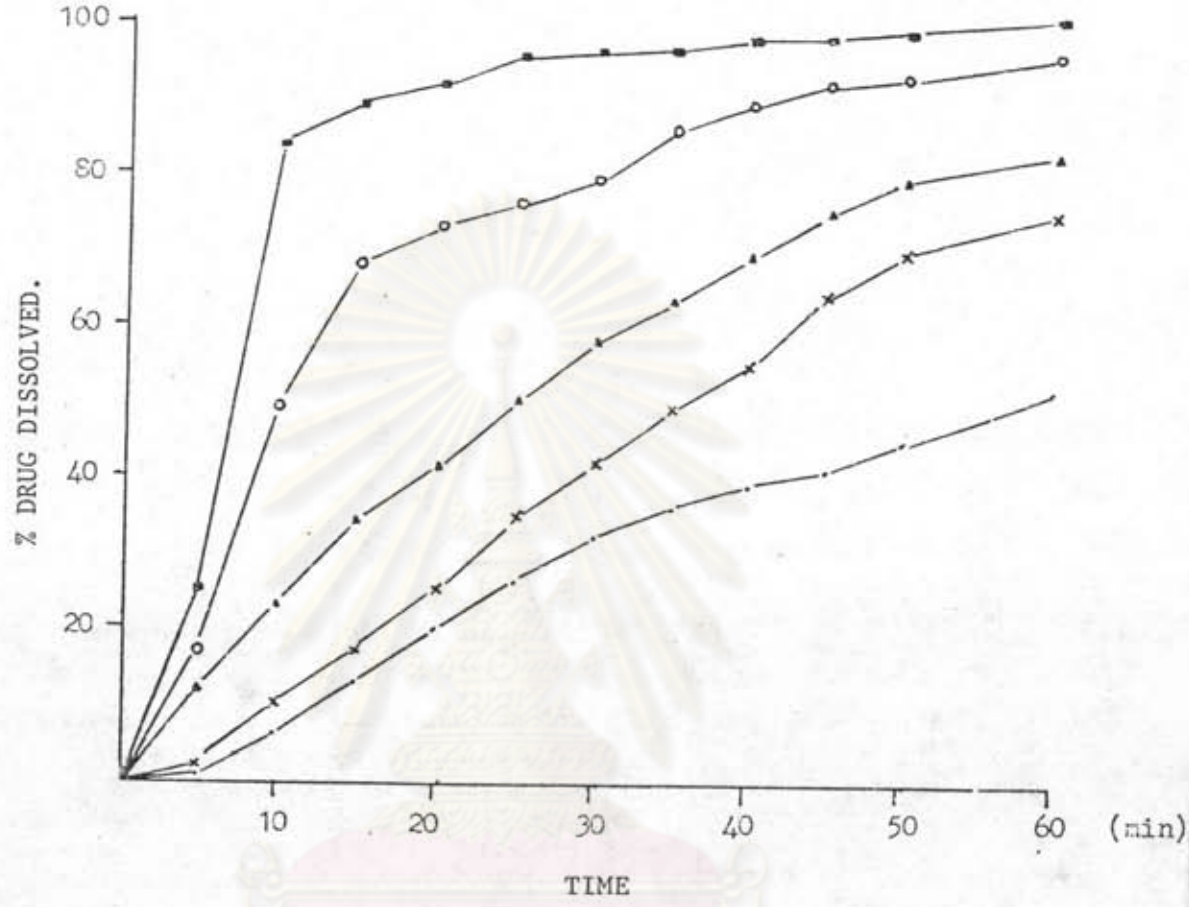

Figure: 33 Dissolution Profiles of Diazepam Capsules, Formula 0, 17, 21, 25, 29 (1:10 Diazepam - Mannitol Capsules)

Key. —•— Formula 0, control

—×— Formula 17, unmilled, simple blending

—▲— Formula 29, solvent deposition

—o— Formula 21, milled, simple blending

—▪— Formula 25, ball milling

time than simple blending method of unmilled diazepam. And it was found that solvent deposition method gave the shorter dissolution time than simple blending method of unmilled diazepam.

According to the diazepam capsule formula, using mannitol as diluent in preparing the 1:5 ratio of diazepam-diluent mixtures (Formula 33, 37, 41, 45), there was a significant difference in the dissolution profiles among the diazepam capsule formulas (Formula 33, 37, 41, 45) prepared by difference dispersion methods as shown in Figure 34. The dissolution time of the diazepam capsule formulas was ranked, as follow: 0 $\rangle$ 33 $\rangle$ 45 $\rangle$ 37 $\rangle$ 41. Formula 0 was the control formula prepared in the absence of mannitol. Formula 33, 37, 45, 41 the diazepam-mannitol mixtures were prepared by simple blending method of unmilled diazepam, simple blending method of milled diazepam, solvent deposition method of diazepam and ball-milling method of diazepam in 5-fold of mannitol, respectively. It was found that ball milling method gave the shorter dissolution than solvent deposition method and simple blending method. According to simple blending method, simple blending method of milled diazepam gave the shorter dissolution time than simple blending method of unmilled diazepam. And it was found that solvent deposition method gave the shorter dissolution time than simple blending method of unmilled diazepam.

According to the diazepam capsule formula, using sucrose as diluent in preparing the 1:20 ratio of diazepam-diluent mixtures, there was a difference in the dissolution profiles among the diazepam capsule

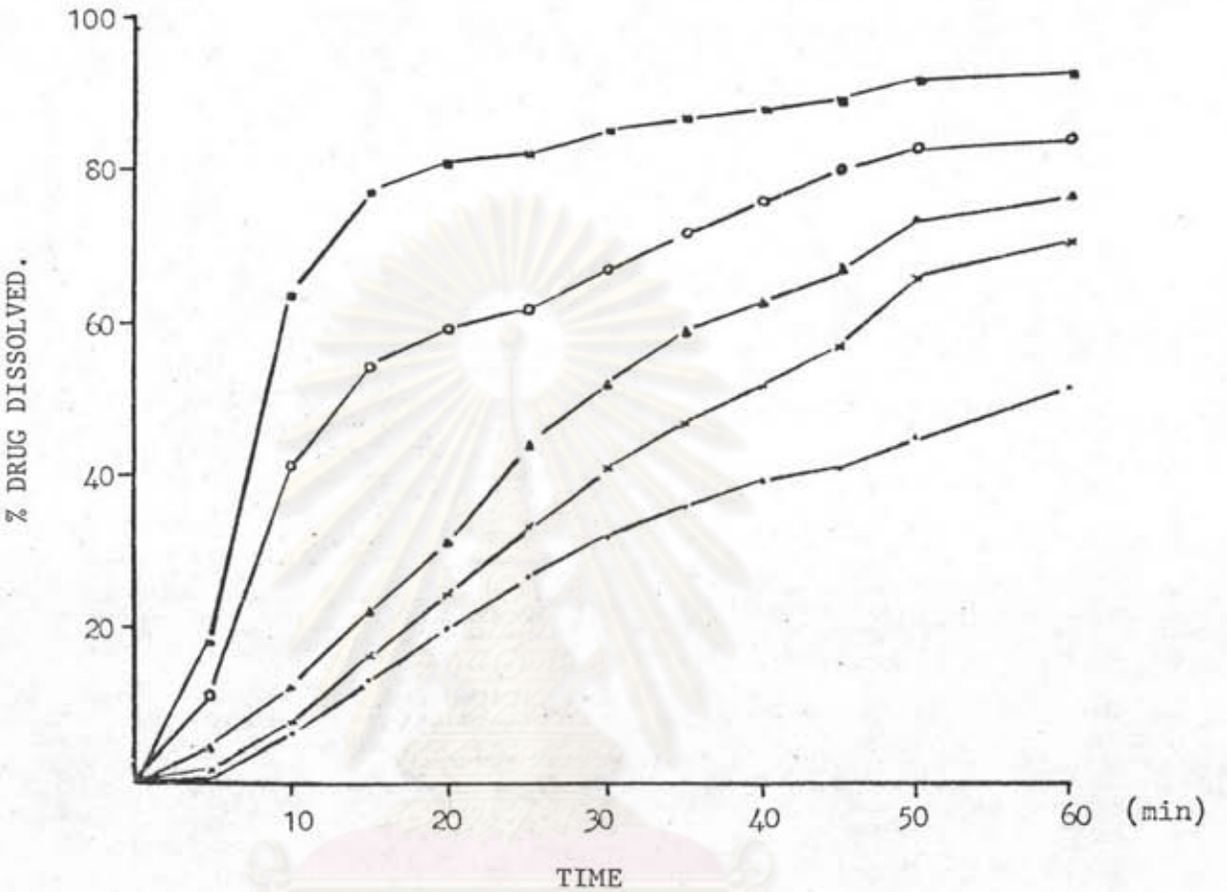

Figure: 34 Dissolution Profiles of Diazepam Capsules, Formula 0, 33, 37, 41, 45 (1:5 Diazepam-Mannitol Capsules)

Key. —•— Formula 0, control

—×— Formula 33, unmilled, simple blending

—▲— Formula 45, solvent deposition

—o— Formula 37, milled, simple blending

—■— Formula 41, ball milling

formulas (Formula 2, 6, 10, 14) prepared by different dispersion methods as shown in Figure 35. The dissolution time of the diazepam capsule formula was ranked as follow: 0 > 2 > 14 > 6 > 10. Formula 0 was the control formula, prepared in the absence of sucrose. Formula 2, 6, 14, 10 the diazepam-sucrose mixtures were prepared by simple blending method of unmilled diazepam, simple blending method of milled diazepam, solvent deposition method of diazepam and ball-milling method of diazepam in 20-fold of sucrose, respectively. It was found that ball-milling method gave the shorter dissolution time than solvent deposition method and simple blending method. According to simple blending method, simple blending method of milled diazepam gave the shorter dissolution time than simple blending method of unmilled diazepam. And it was found that solvent deposition method gave the shorter dissolution time than simple blending method of unmilled diazepam.

According to the diazepam-capsule formula, using sucrose as diluent in preparing the 1:10 ratio of diazepam-diluent mixtures, there was a different in the dissolution profiles among the diazepam capsule formulas (Formula 18, 22, 26, 30) prepared by different dispersion methods as shown in Figure 36. The dissolution time of the diazepam-capsule formulas was ranked as follow: 0 > 18 > 30 > 22 > 26 . Formula 0 was the control formula prepared in the absence of sucrose. Formula 18, 22, 30, 26 the diazepam-sucrose mixtures were prepared by simple blending method of unmilled diazepam, simiple blending method of milled diazepam, solvent deposition method of diazepam and ball-milling method of diazepam in 10-fold of sucrose, respectively. It was found that

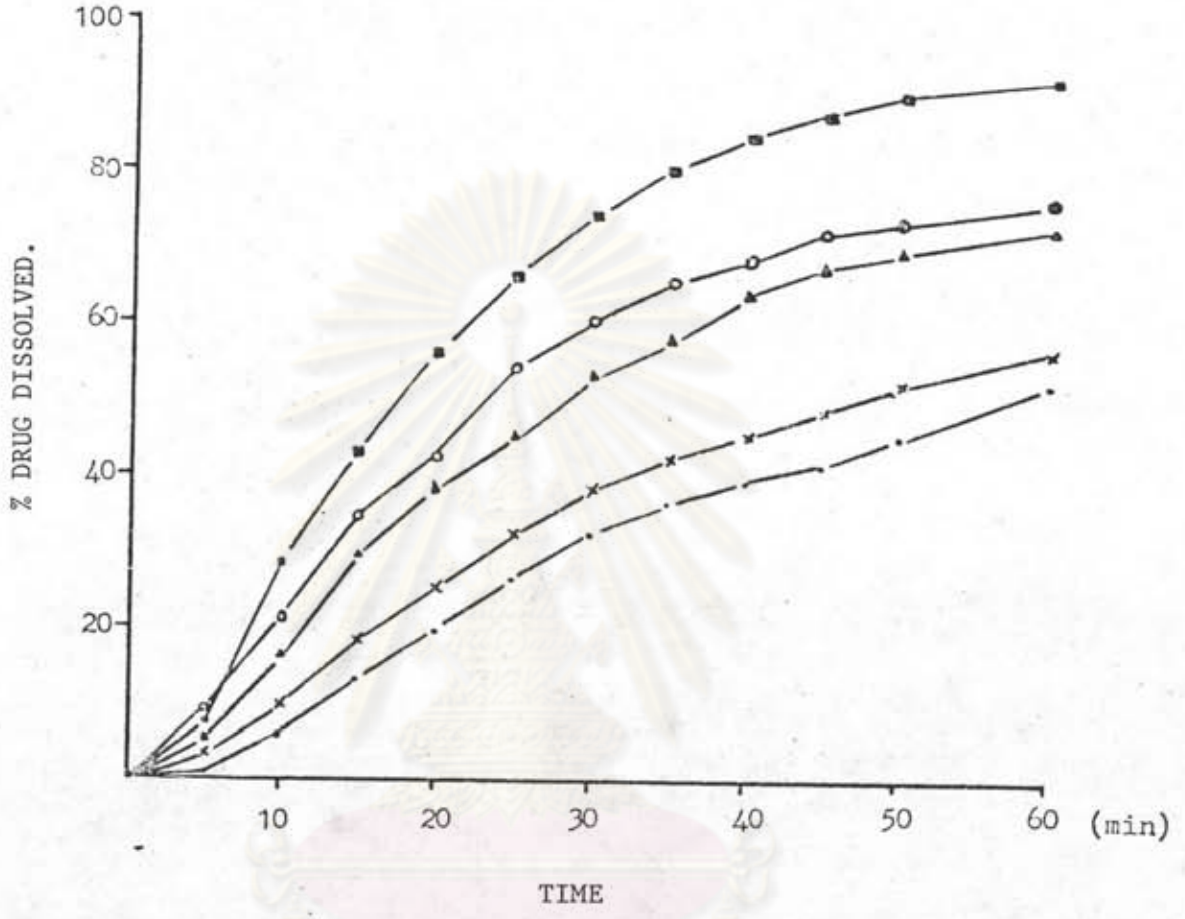

Figure: 35 Dissolution Profiles of Diazepam Capsules, Formula 0, 2, 6, 10, 14 (1:20 Diazepam-Sucrose Capsules)

Key. —•— Formula 0, control

—×— Formula 2, unmilled, simple blending

—▲— Formula 14, solvent deposition

—○— Formula 6, milled, simple blending

—▪— Formula 10, ball milling

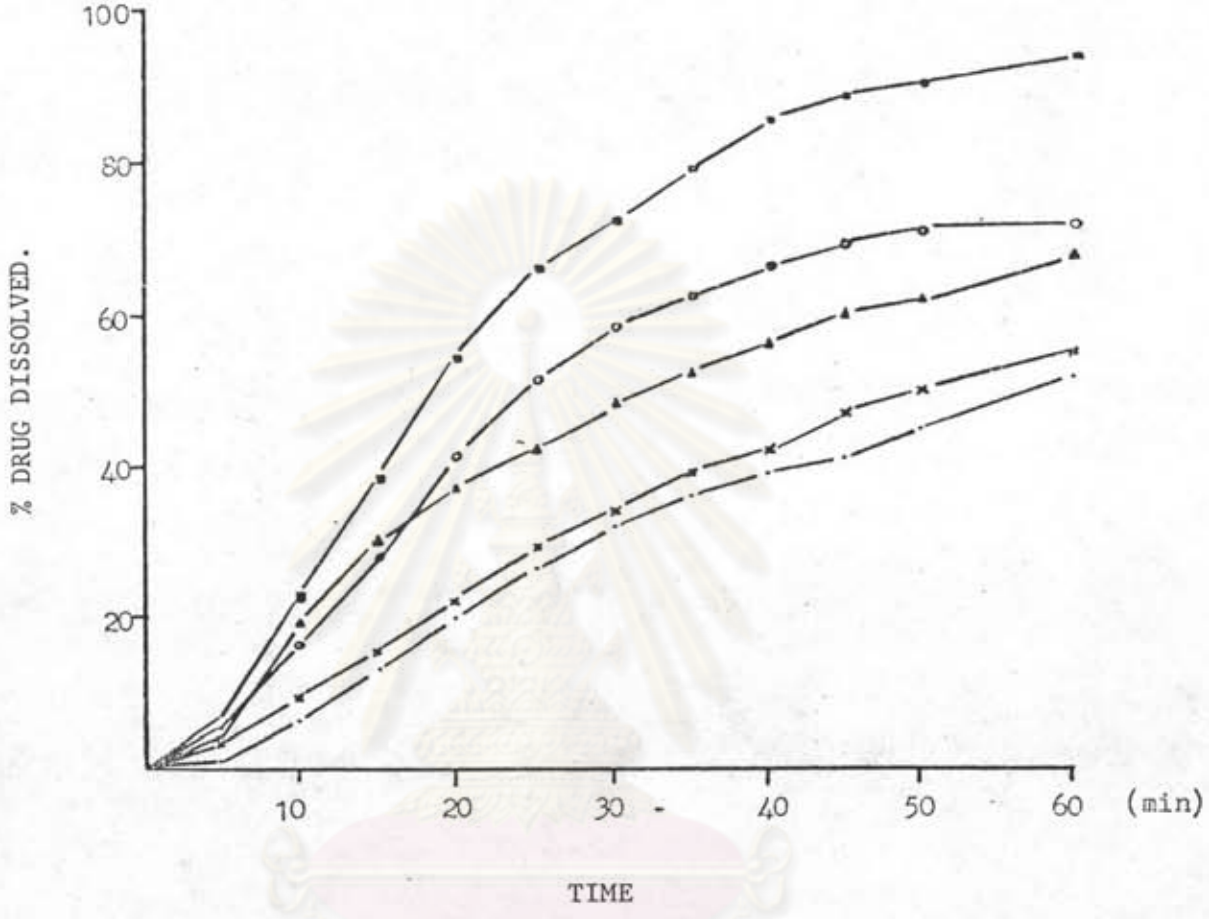

Figure: 36 Dissolution Profiles of Diazepam Capsules, Formula 0, 18, 22, 26, 30 (1:10 Diazepam-Sucrose Capsules)

Key. —•— Formula 0, control

—×— Formula 18, unmilled, simple blending

—▲— Formula 30, solvent deposition

—o— Formula 22, milled, simple blending

—•— Formula 26, ball milling

ball-milling method gave the shorter dissolution time than solvent deposition method and simple blending method. According to simple blending method, simple blending method of milled diazepam gave the shorter dissolution time than simple blending method of unmilled diazepam. And it was found that solvent deposition method gave the shorter dissolution time than simple blending method of unmilled diazepam.

According to the diazepam-capsule formula, using sucrose as diluent in preparing the 1:5 ratio of diazepam-diluent mixtures, there was a different in the dissolution profiles among the diazepam capsule formulas (Formula 34, 38, 42, 46), prepared by different dispersion methods as shown in Figure 37. Formula 0 was the control formula, prepared in the absence of sucrose. Formula 34, 38, 46, 42 the diazepam-sucrose mixtures were prepared by simple blending method of unmilled diazepam, simple blending method of milled diazepam, solvent deposition method of diazepam and ball-milling method of diazepam in 5-fold of sucrose, respectively. The dissolution time of the diazepam-capsule formula was ranked as follow: 34 $\rangle$ 46 $\rangle$ 38 $\rangle$ 42. There was slightly difference in the dissolution profiles between formula 0 and formula 34. Among three dispersion methods, ball-milling method gives the shorter dissolution time than solvent deposition method and simple blending method. According to simple blending method, simple blending method of milled diazepam gave the shorter dissolution time than simple blending method of unmilled diazepam. And it was found that solvent deposition method gave the shorter dissolution time than simple blending method of unmilled diazepam.

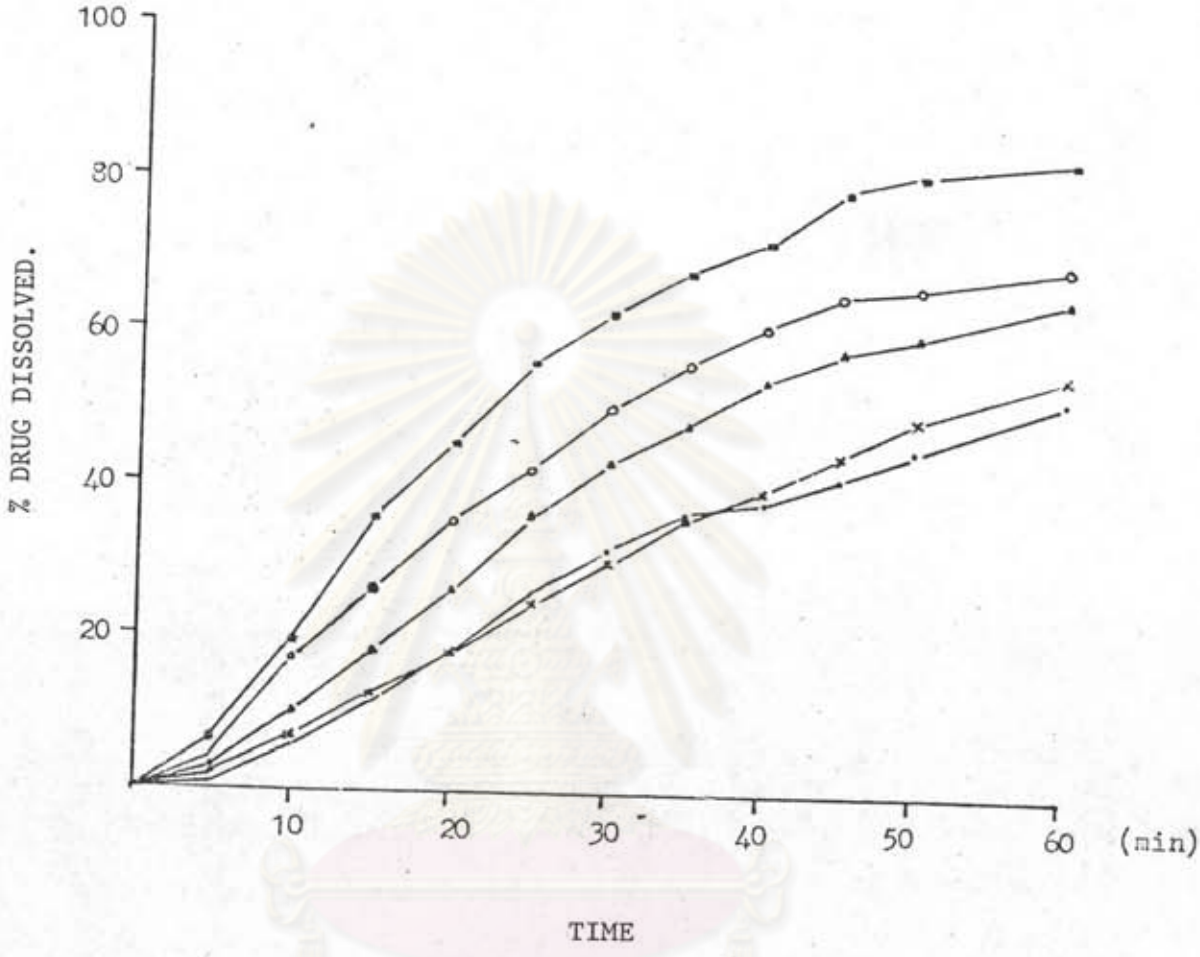

Figure: 37 Dissolution Profiles of Diazepam Capsules, Formula 0, 34, 38, 42, 46 (1:5 Diazepam-Sucrose Capsules)

Key. —•— Formula 0, control

—×— Formula 34, unmilled, simple blending

—▲— Formula 46, solvent deposition

—o— Formula 38, milled, simple blending

—■— Formula 42, ball milling

According to the diazepam capsule formula, using dibasic calcium phosphate as diluent in preparing the 1:20 ratio of diazepam-diluents mixtures, there was a differrence in the dissolution profiles among the diazepam capsule formulas (Formula 3, 7, 11, 15) prepared by different dispersion methods, as shown in Figure 38. The dissolution time of the diazepam capsule formulas was ranked as follow: 0 > 3 > 15 > 7 > 11. Formula 0 was the control formula, prepared in the absence of dibasic calcium phosphate. Formula 3, 7, 15, 11 the diazepam-dibasic calcium phosphate mixtures were prepared by simple blending method of unmilled diazepam, simple blending method of milled diazepam, solvent deposition method of diazepam and ball-milling method of diazepam in 20-fold of dibasic calcium phosphate, respectively. It was found that ball-milling method gave the shorter dissolution time than solvent deposition method and simple blending method. According to simple blending method, simple blending method of milled diazepam gave the shorter dissolution time than simple blending method of unmilled diazepam. And it was found that solvent deposition method gave shorter dissolution time than simple blending method of unmilled diazepam.

According to the diazepam capsule formula, using dibasic calcium phosphate as diluent in preparing the 1:10 ratio of diazepam-diluent mixtures, there was a difference in the dissolution profiles among the diazepam capsule formulas (Formula 19, 23, 27, 31) prepared by different dispersion method as shown in Figure 39. The dissolution time of the diazepam capsule formula was ranked as follow: 0 > 19 31 > 23 > 27. Formula 0 was the control formula, prepared in the absence

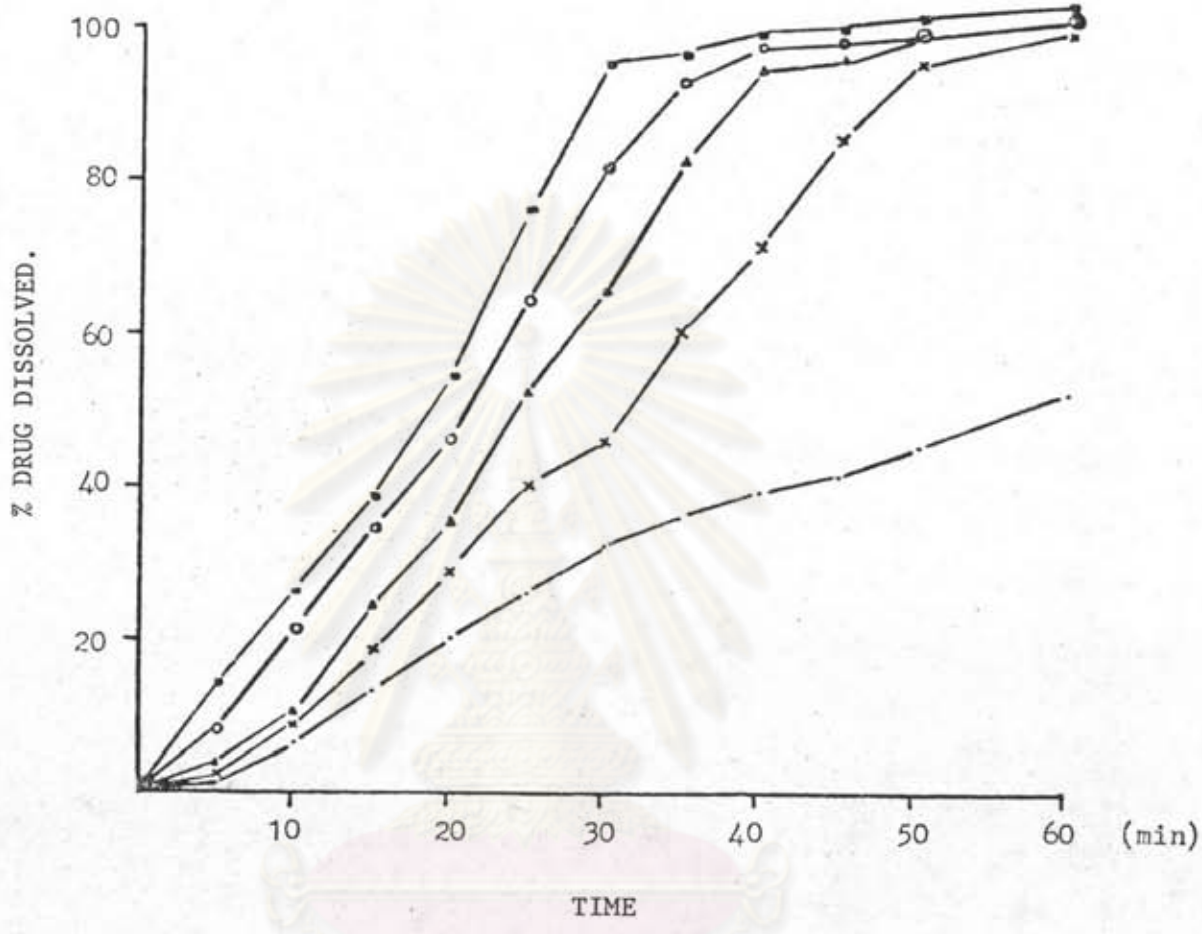

Figure: 38 Dissolution Profiles of Diazepam Capsules, Formula 0, 3, 7, 11, 15 (1:20 Diazepam-Dibasic calcium Phosphate Capsules)

Key. —•— Formula 0, control

—×— Formula 3, unmilled, simple blending

—▲— Formula 15, solvent deposition

—o— Formula 7, milled, simple blending

—▪— Formula 11, ball milling

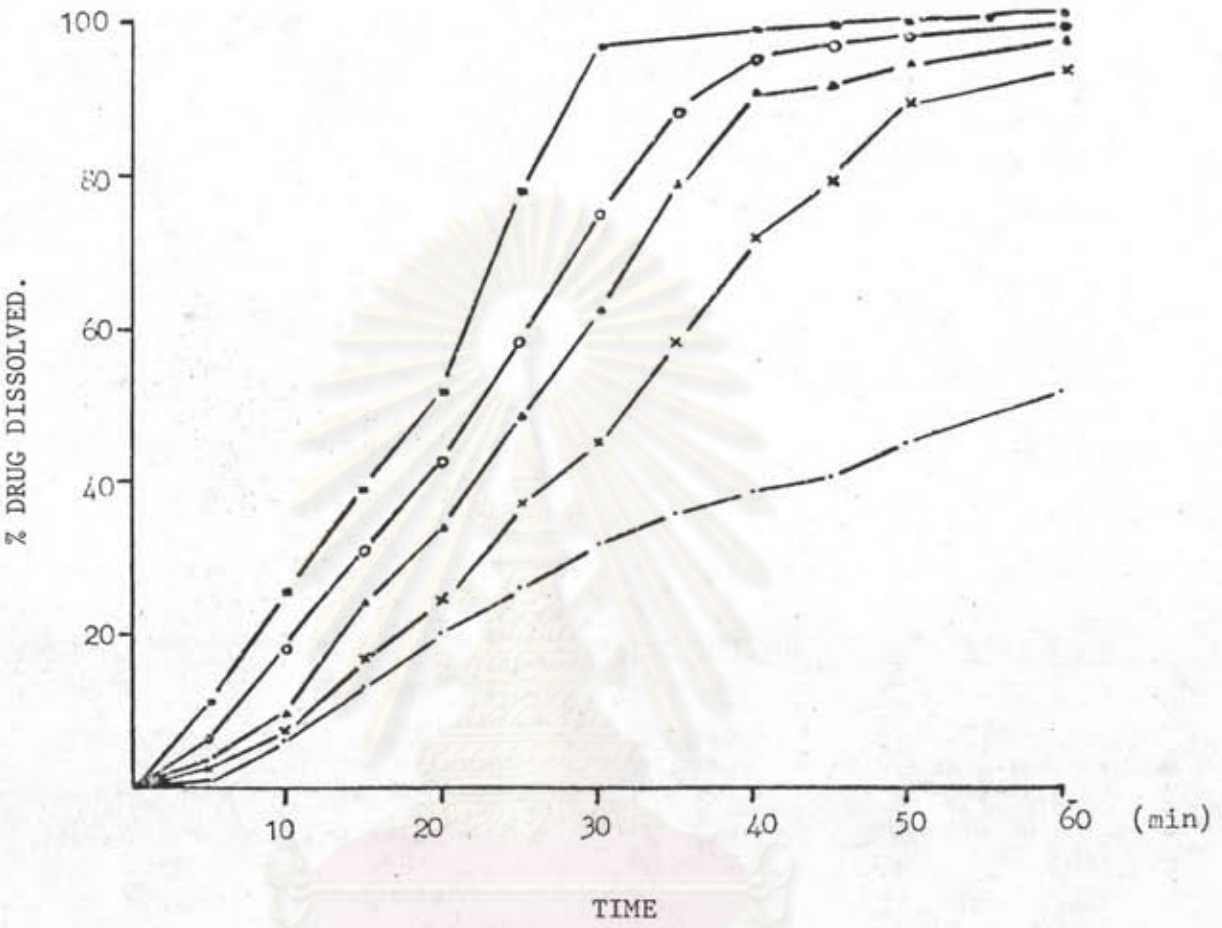

Figure: 39 Dissolution Profiles of Diazepam Capsules, Formula 0, 19, 23, 27, 31 (1:10 Diazepam-Dibasic Calcium Phosphate Capsules)

Key. —•— Formula 0, control

—×— Formula 19, unmilled, simple blending

—▲— Formula 31, solvent deposition

—o— Formula 23, milled, simple blending

—•— Formula 27, ball milling

of dibasic calcium phosphate. Formual 19, 23, 31, 27 the diazepam-dibasic calcium phosphate mixtures were prepared by simple blending method of unmilled diazepam, simple blending method of milled diazepam, solvent deposition method of diazepam and ball-milling method of diazepam in 10-fold of dibasic calcium phosphate, respectively. It was found that ball-milling method gave the shorter dissolution time than solvent deposition method and simple blending method. According to simple blending method, simple blending method of milled diazepam gave the shorter dissolution time than simple blending method of unmilled diazepam. And it was found that solvent deposition method gave the shorter dissolution time than simple blending method of unmilled diazepam.

According to the diazepam capsule formula, using dibasic calcium phosphate as diluent in preparing the 1:5 ratio of diazepam-diluent mixtures, there were a difference in the dissolution profiles among the diazepam capsule formulas (Formula 35, 39, 43, 47) prepared by different dispersion methods as shown in Figure 40. The dissolution time of the diazepam capsule formulas were ranked as follow: 0 $\rangle$ 35 47 $\rangle$ 39 $\rangle$ 43. Formula 0 was the control formula, prepared in the absence of dibasic calcium phosphate. Formula 35, 39, 47, 43 the diazepam-dibasic calcium phosphate mixtures were prepared by simple blending method of unmilled diazepam, simple blending method of milled diazepam, solvent deposition method of diazepam and ball-milline method of diazepam in 5-fold of dibasic calcium phosphate, respectively. It was found that ball-milling method gave the shorter dissolution time than solvent deposition method and simple blending method. According to

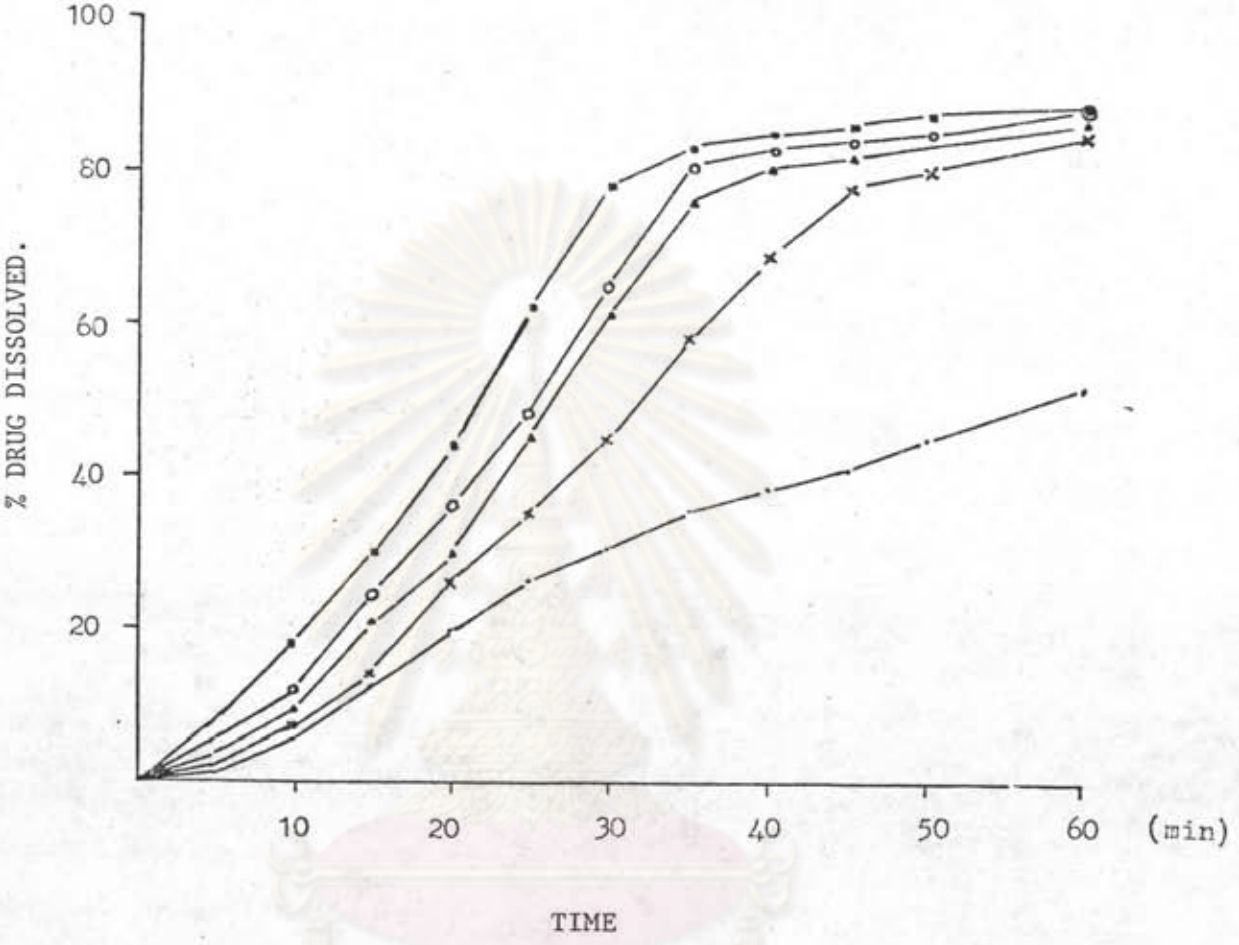

Figure: 40 Dissolution Profiles of Diazepam Capsules, Formula 0, 35, 39, 43, 47 (1:5 Diazepam-Dibasic Calcium Phosphote Capsules)

Key. —•— Formula 0, control

—×— Formula 35, unmilled, simple blending

—▲— Formula 47, solvent deposition

—○— Formula 39, milled, simple blending

—■— Formula 43, ball milling

simple blending method, simple blending method of milled diazepam gave the shorter dissolution time than simple blending method of unmilled diazepam. And it was found that solvent deposition method gave the shorter dissolution time than simple blending method of unmilled diazepam.

According to the diazepam capsule formula, using microcrystalline cellulose as diluent in preparing the 1:20 ratio of diazepam-diluent mixtures, there was a difference in the dissolution profiles among the diazepam-capsule formulas (Formula 4, 8, 12, 16) prepared by different dispersion methods as shown in Figure 41. The dissolution time of the diazepam capsule formula was ranked as follow: 0 $\rangle$ 4 16 $\rangle$ 8 $\rangle$ 12. Formula 0 was the control formula, prepared in the absence of microcrystalline cellulose. Formual 4, 8, 16, 12 the diazepam-microcrystalline cellulose mixturese were prepared by simple blending method of unmilled diazepam, simple blending method of milled diazepam, solvent deposition method of diazepam and ball-milling method of diazepam in 20-fold of microcrystalline cellulose, respectively. It was found that ball-milling method gave the shorter dissolution time than solvent deposition method and simple blending method. According to simple blending method, simple blending method of milled diazepam gave the shorter dissolution time than simple blending method of unmilled diazepam. And it was found that solvent deposition method gave the shorter dissolution time than simple blending method of unmilled diazepam.

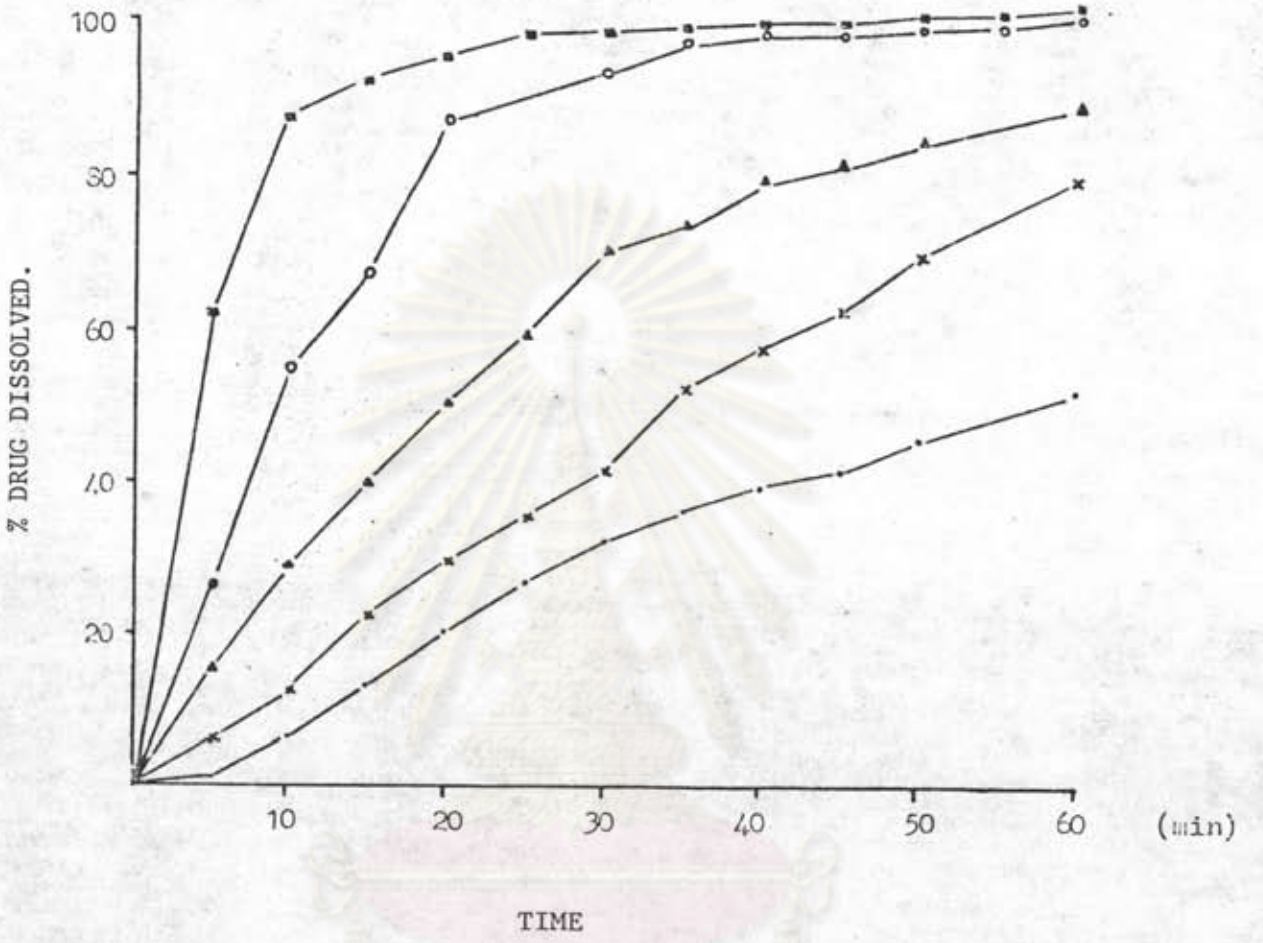

Figure: 41 Dissolution Profiles of Diazepam Capsules, Formula 0, 4, 8, 12, 16 (1:20 Diazepam-Microcrystalline cellulose Capsules)

Key. —•— Formula 0, control

—×— Formula 4, unmilled, simple blending

—▲— Formula 16, solvent deposition

—○— Formula 8, milled, simple blending

—▪— Formula 12, ball milling

According to the diazepam-capsule formula, using microcrystalline cellulose as diluent in preparing the 1:10 ratio of diazepam-diluent mixtures, there was a difference in the dissolution profiles among the diazepam-capsule formula (Formula 20, 24, 28, 32) prepared by different dispersion methods as shown in Figure 42. The dissolution time of the diazepam capsule formulas was ranked as follow: 0 $\rangle$ 20 32 $\rangle$ 24 $\rangle$ 28. Formula 0 was the control formula, prepared in the absence of microcrystalline cellulose. Formula 20, 24, 32, 28, the diazepam-microcrystalline cellulose mixtures were prepared by simple blending method of unmilled diazepam, simple blending method of milled diazepam, solvent deposition method of diazepam and ball-milling method of diazepam in 10-fold of microcrystalline-cellulose, respectively. It was found that ball-milling method gave the shorter dissolution time than solvent deposition method and simple blending method. According to simple blending method, simple blending method of milled diazepam gave the shorter dissolution time than simple blending method of unmilled diazepam. And it was found that solvent deposition method gave the shorter dissolution time than simple blending method of unmilled diazepam.

According to the diazepam capsule formula, using microcrystalline cellulose as diluent in preparing the 1:5 ratio of diazepam-diluent mixtures, there was a difference in the dissolution profiles among the diazepam capsule formulas (Formula 36, 40, 44, 48) prepared by different dispersion methods as shown in figure 43. The dissolution time of the diazepam capsule formula was ranked as follow: 0 $\rangle$ 36 48 $\rangle$ 40 $\rangle$ 44. Formula 0 was the control formula, prepared in the

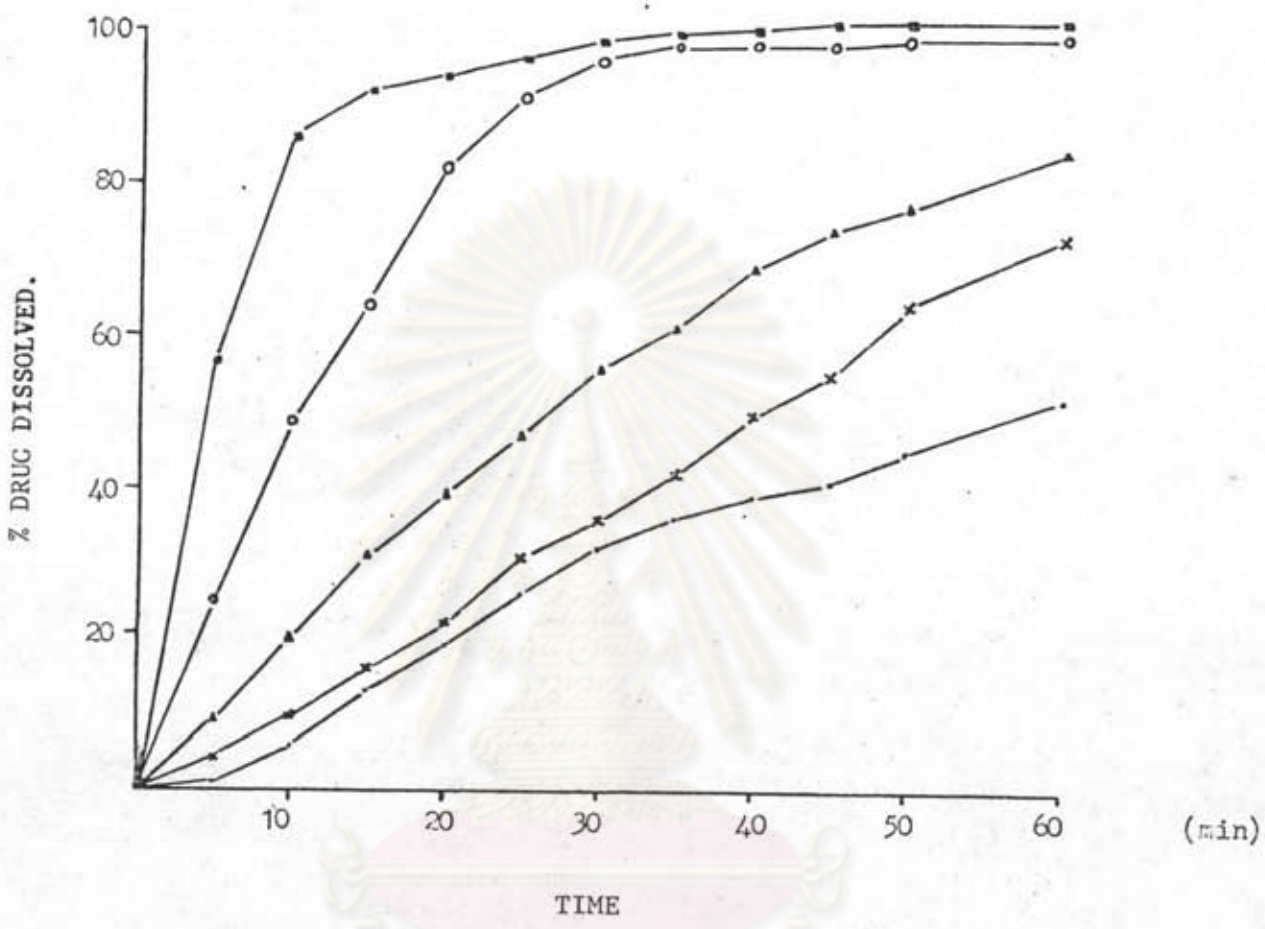

Figure: 42 Dissolution Profiles of Diazepam Capsules, Formula 0, 20, 24, 28, 32 (1:10 Diazepam-Microcrystalline cellulose Capsules)

Key. —•— Formula 0, control

—×— Formula 20, unmilled, simple blending

—▲— Formula 32, solvent deposition

—○— Formula 24, milled, simple blending

—■— Formula 28, ball milling

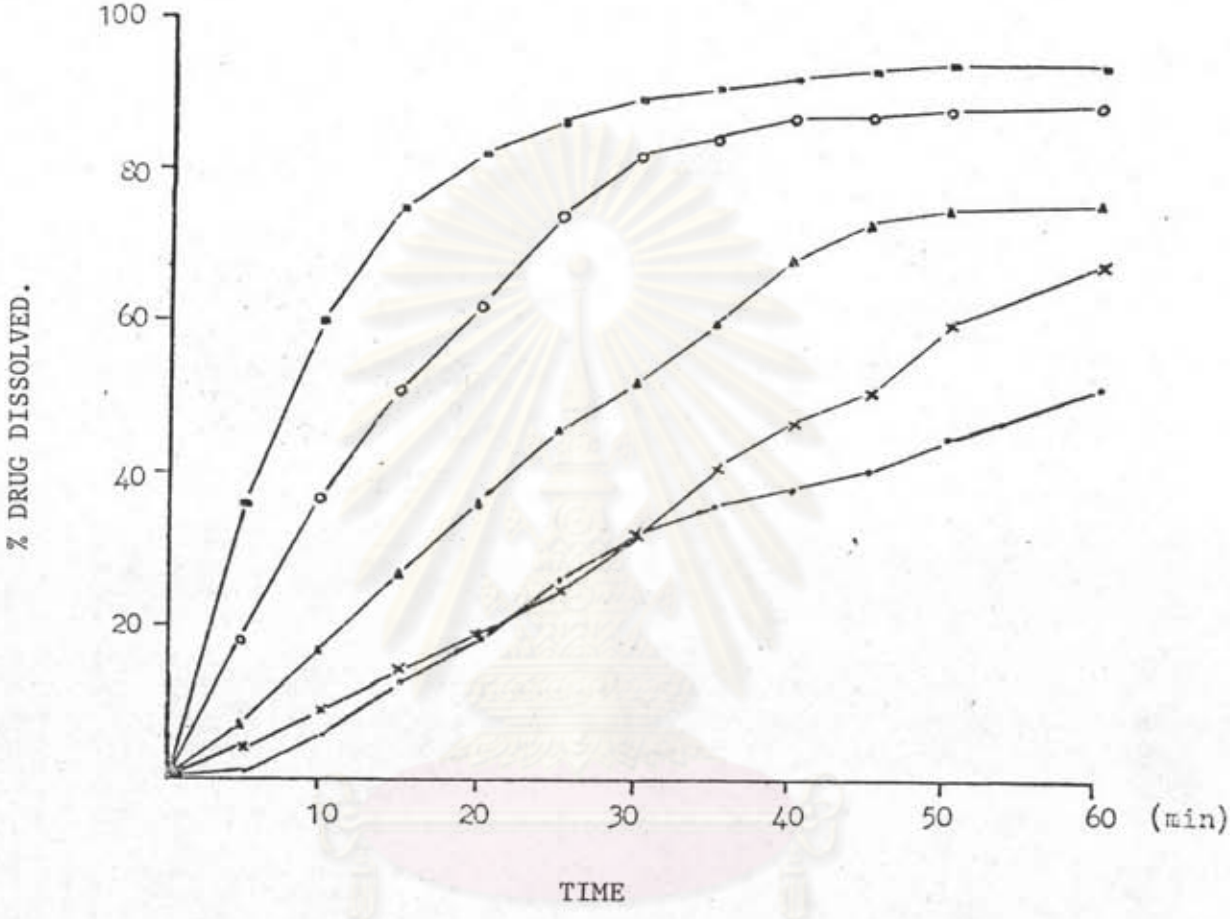

Figure: 43 Dissolution Profiles of Diazepam Capsules, Formula 0, 36, 40, 44, 48 (1:5 Diazepam-Microcrystalline cellulose Capsules)

Key. —•— Formula 0, control

—×— Formula 36, unmilled, simple blending

—▲— Formula 48, solvent deposition

—○— Formula 40, milled, simple blending

—■— Formula 44, ball milling

absence of microcrystalline cellulose. Formula 36, 40, 48, 44, the diazepam microcrystalline cellulose mixtures were prepared by simple blending method of unmilled diazepam, simple blending method of milled diazepam, solvent deposition method of diazepam and ball-milling method of diazepam in 5-fold of microcrystalline cellulose, respectively. It was found that ball-milling method gave the shorter dissolution time than solvent deposition method and simple blending method. According to simple blending method, simple blending method of milled diazepam gave the shorter dissolution time than simple blending method of unmilled diazepam. And it was found that solvent deposition method gave the shorter dissolution time than simple blending method of unmilled diazepam.

From the experimental data, it may be concluded as the following : Among three dispersion methods of diazepam in four diluents, used prepared the diazepam-diluent mixtures in different ratio, ball-milling method was likely to be the best way that gave the shortest dissolution time. In generally, solvent deposition methods gave the shorter dissolution than simple blending method, however simple blending methods of milled diazepam gave the shorter dissolution time than solvent deposition method in four diluents. Therefore, the dispersion methods that gave the shorter dissolution time were ordered as follow ball-milling method $<$ simple blending method of milled diazepam $<$ solvent deposition method $<$ simple blending method of unmill diazepam.

3.4.2 The Effects of Diluents on The Dissolution Time of Diazepam Capsules

In consideration of the effects of diluents on the dissolution time of diazepam capsules, the two groups of diluents had been included in this study : water-soluble diluent group and water-insoluble diluent group. Mannitol and sucrose were selected for water-soluble diluent. Dibasic calcium phosphate and microcrystalline cellulose were selected for water-insoluble diluents. According to table 45, the time required for 85 percent of diazepam to dissolve (t85%) and read from the dissolution profiles were used as comperative parameter in the comparison of the effects of diluents on the dissolution time of diazepam capsules. The time required for 85 percent of the labeled amount of diazepam to dissolve into solution is recommended to be limited not more than 45 minutes as suggested by USP XXI (64).

The diazepam capsule formulations using mannitol as diluent at 1:20 and 1:10 ratio of diazepam-diluent mixture prepared by simple blending method of milled diazepam (Formula 5, 21) and at 1:20, 1:10 and 1:5 ratio of diazepam-diluent mixtures prepared by ball milling method (Formula 9, 25, 41) were found that the t85% was not more than 45 minutes and met the requirement according to dissolution test of diazepam capsule (64). But the diazepam capsule formulations using mannitol as diluent at 1:20, 1:10 and 1:5 ratio of diazepam-diluent mixture prepared by simple blending method of unmilled diazepam (Formula 1, 17, 33) and solvent deposition method (Formula 13, 29, 45) were found that the t85% was more than 45 minutes and did not meet the requirement according to dissolution test of diazepam capsule (64).

The diazepam capsule formulation using mannitol as diluent at 1:5 ratio of diazepam-diluent mixture prepared by simple blending method of milled diazepam (Formula 27) also did not meet the requirement according to dissolution test of diazepam capsule (64).

The diazepam capsule formulation using sucrose as diluent at 1:20 and 1:10 ratio of diazepam-diluent mixture prepared by ball-milling method (Formula 10, 26) were found that the t85% was less than 45 minutes and met the requirement according to dissolution test of diazepam capsule (64). But the diazepam capsule formulation using sucrose as diluent at 1:5 ratio of diazepam-diluent mixture prepared by ball milling method (Formula 42) did not meet the requirement according to dissolution test of diazepam capsule (64). The other diazepam capsule formulations using sucrose as diluent at 1:20, 1:10 and 1:5 ratio of diazepam-diluent mixtures prepared by simple blending method of unmilled diazepam (Formula 2, 18, 34), simple blending method of milled diazepam (Formula 6, 22, 38) and solvent deposition method (Formula 14, 30, 46) also did not meet the requirement according to dissolution test of diazepam capsule (64).

The diazepam capsule formulations using dibasic calcium phosphate as diluent at 1:20 and 1:10 ratio of diazepam-diluent mixture prepared by simple blending method of milled diazepam (Formula 7, 23), solvent deposition method (Formula 15, 31) and ball milling method (Formula 11, 27) were found to meet the requirement according to dissolution test of diazepam capsule, but the another method, simple blending method of unmilled diazepam (Formula 3, 15) did not meet

the requirement according to dissolution test of diazepam capsule (64). The diazepam capsule formulation using dibasic calcium phosphate dihydtate as diluent at 1:5 ratio of diazepam-diluent mixture only prepared by ball milling method (Formula 43) was also found to meet the requirement according to dissolution test of diazepam capsule, but the other method, simple blending method of unmilled diazepam (Formula 31), simple blending method of milled diazepam (Formual 35) and solvent deposition method (Formula 39) did not meet the requirements according to dissolution test of diazepam capsule (64).

The diazepam capsule formulation using microcrystalline cellulose as diluent at 1:20, 1:10 and 1:5 ratio of diazepam-diluent mixture prepared by simple blending method of milled diazepam (Formula 8, 24, 40) and ball milling method (Formula 12, 28, 44) were found to meet the requirement according to dissolution test of diazepam capsule, but the other methods, simple blending of unmilled diazepam (4, 20, 36) and solvent deposition method (16, 32, 48) did not meet the requirement according to dissolution test of diazepam capsule (64).

From the experiment , it was likely that among the water-soluble diluent group, mannitol was found to release diazepam from diazepam capsules better than sucrose. When compared among the water-insoluble diluent group, the diazepam capsule formulation which prepared by simple blending method and ball milling method, microcrystalline cellulose gave the superior dissolution rate over the dibasic calcium phosphate, however the diazepam capsule formulations used dibasic calcium

phosphate as diluent prepared by solvent deposition method gave the superior dissolution rate over microcrystalline cellulose.

It was observed that the color of diazepam-dibasic calcium phosphate dihydrate mixture was changed from white to yellowish color after storage at room temperature for about two weeks , however the amount of diazepam in the mixture was not lowered. The change in color of diazepam-diluent mixture was not found in the other three diluents after storage at the same conditions.