CHAPTER III

RESULTS AND DISCUSSION

Phase solubility analysis

The solubilities of indomethacin and piroxicam in various concentrations of aqueous solution of β-cyclodextrin were presented in Table 14 and Fig. 3. They were observed that concentrations of indomethacin and piroxicam increased with the increasing concentrations of β-cyclodextrin. Phase solubility diagrams of both indomethacin and piroxicam were classified as type A. An apparent solubility constant (K_c), assuming the formation of 1:1 complex in solution of indomethacin and piroxicam are 264 M^{-1} and 184 M^{-1} respectively. The moderate solubility constants indicate a fairly adjustment of guest molecule inside the cavity of β-cyclodextrin. The increase in solubility of indomethacin and piroxicam in the present of β-cyclodextrin were shown in Table 15. The solubilities of indomethacin and piroxicam in approximately 14 x 10^{-3} M β-cyclodextrin solution increased about 5.8 and 3.9 times, respectively, comparing to the solubility of each pure component. The increase in solubility with the addition of β-cyclodextrin is generally considered to be mainly due to the formation of inclusion complex (Hamada, et al. 1975). The solubilities of indomethacin and piroxicam in water (S_0) is 2.453 x 10^{-5} M (≈ 0.8 mg %) and 2.339 x 10^{-5} M (≈ 0.7 mg%), respectively.

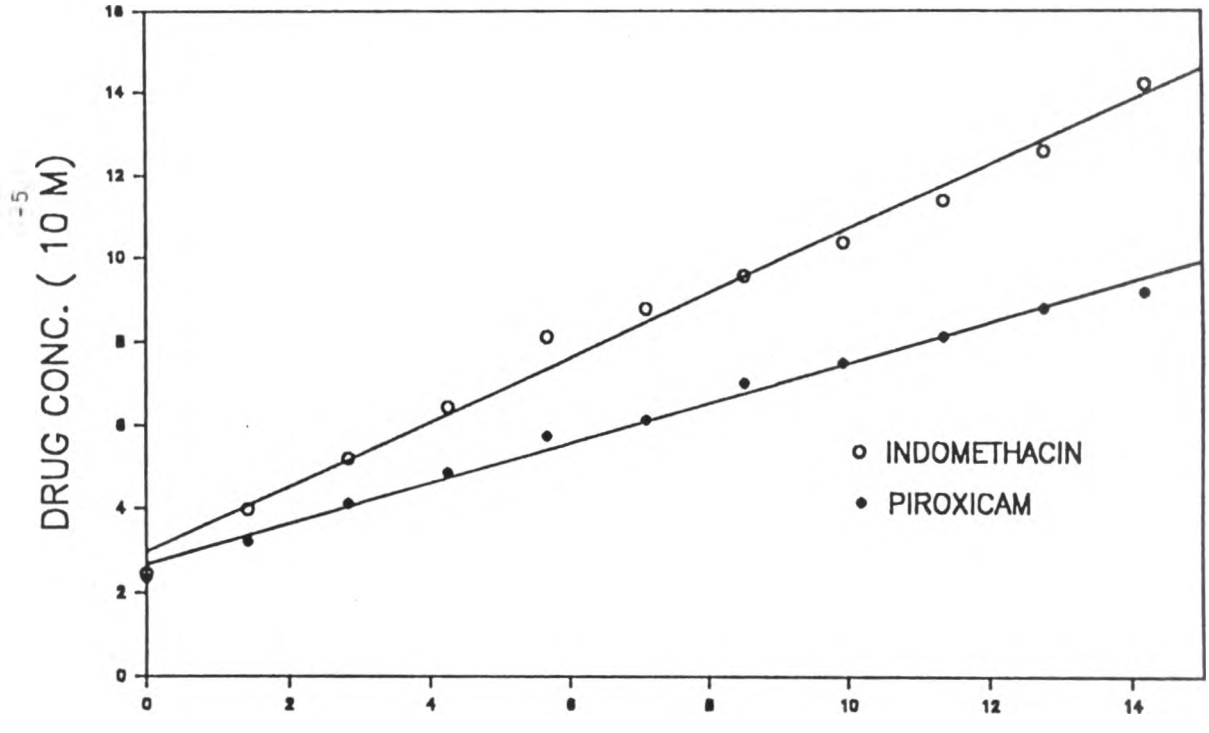


Fig 3 Phase solubility curves of indomethacin-β-cyclodextrin and piroxicam-β-cyclodextrin inclusion complexes in aqueous solution at 35±1 °C

Table 14 Solubility determinations of indomethacin and piroxicam in various concentrations of aqueous solution β-cyclodextrin (at 35 ±1 °C, controlled temperature water bath)

conc. of β-cd ($x10^{-3}$M)	conc. of indomethacin ($x10^{-5}$ M)	conc. of piroxicam ($x10^{-5}$ M)
0	2.453 (≅ 0.8 mg%)	2.339 (≅ 0.7 mg%)
1.418	3.975	3.217
2.837	5.169	4.122
4.256	6.445	5.738
7.092	8.786	6.128
8.511	9.561	7.034
9.930	10.365	7.507
11.348	11.385	8.134
12.766	12.577	8.803
14.185*	14.200	9.193

* solubility limit of β-cyclodextrin

Table 15 Apparent solubility constant (K_C) and type of phase solubility curve in aqueous solution of β-cyclodextrin at 35±1 °C

drug	$K_C(M^{-1})$	type	Increase of solubility*	S_o (M)
indomethacin	264	A	5.8 time	$2.453x10^{-5}$
piroxicam	180	A	3.9 time	$2.339x10^{-5}$

*Increase of solubility was calculated when using maximum concentration of β-cyclodextrin about 14.185×10^{-3} M (1.8 % w/w)

Characterization of Wet Kneaded Mixtures

1. Scanning Electron Microscope

Shape, size and surface of the wet kneaded mixtures were observed and photomicrographed by electron microscope. The ground drugs, the physical mixtures and the freeze-dried inclusion complexes were investigated and compared. Scanning electron microscope showed that β-cyclodextrin was in irregular crystals (Fig 4B). Indomethacin ground drugs are irregular plate and prism with different size (Fig 4A). In the wet kneaded mixtures of indomethacin and β-cyclodextrin, small particles of indomethacin adhered on the surface of β-cyclodextrin (Fig 4C, D). In the physical mixtures, crystals sizes of indomethacin were relatively larger than those in the wet kneaded mixtures (Fig 4E). Small and flake like particles were observed in the photomicrographs of the freeze-dried indomethacin-βcyclodextrin inclusion complex (Fig 4G, H). In piroxicam-β-cyclodextrin systems, piroxicam from Hong Kong, had crystals size larger than those from Italy (Fig 5B). Piroxicam manufactured in Italy, had uniformly small crystals and micronized size. (Fig 5A) Piroxicam in the wet kneaded mixtures, using the source from Italy were adhered on the surface of β-cyclodextrin (Fig 5C, D). The photomicrographs of the physical mixtures of piroxicam-β-cyclodextrin showed the dispersion of piroxicam on the surface of β-cyclodextrin (Fig 5E, F). In freeze-dried piroxicam-β-cyclodextrin inclusion complex, small plate-like particles were observed (Fig 5G, H).

Photomicrographs showed that wet kneading process affected the agglomeration and aggregation of indomethacin and piroxicam powder.

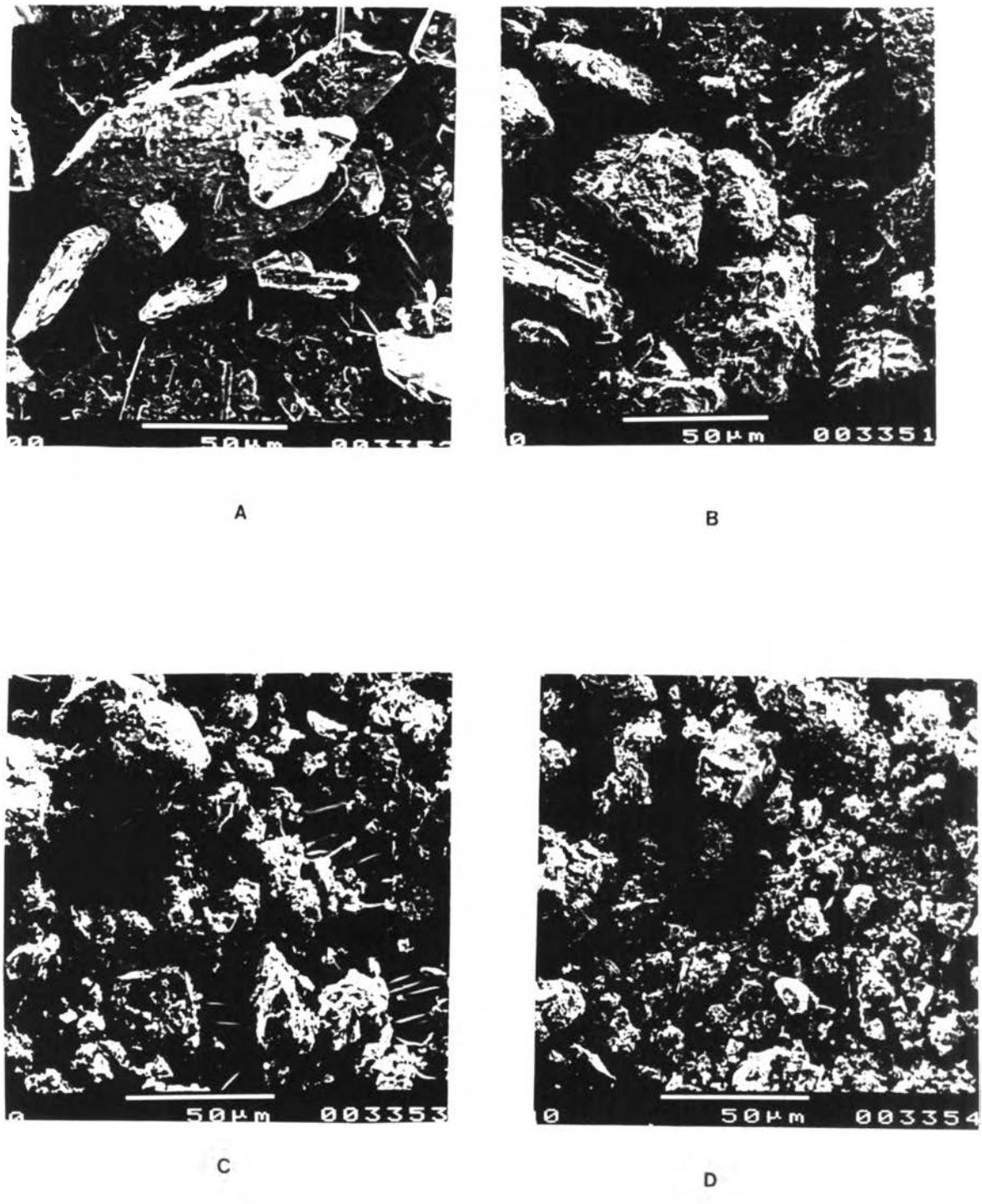


Fig 4 Photomicrograph of Indomethacin-β-Cyclodextrin Systems

A indomethacin

B β-cyclodextrin

C wet kneaded mixture 1:1 molar ratio

D wet kneaded mixture 1:2 molar ratio

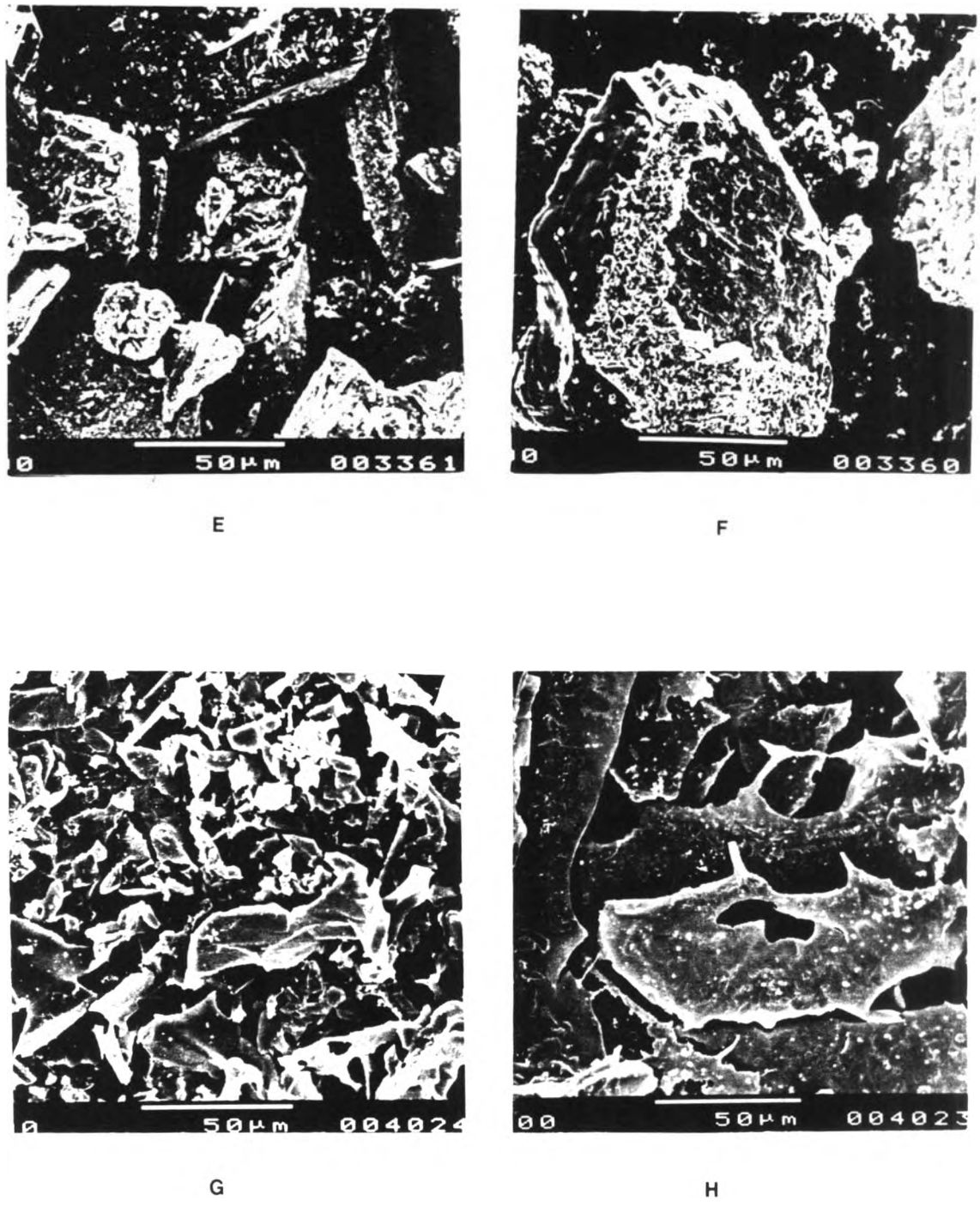


Fig 4 (cont.) Photomicrograph of Indomethacin-β-Cyclodextrin Systems

E physical mixture 1:1 molar ratio

F wet kneaded mixture 1:2 molar ratio kneaded in water bath 60 °C

G freeze-dried inclusion complex 1:1 molar ratio

H freeze-dried inclusion complex 1:2 molar ratio

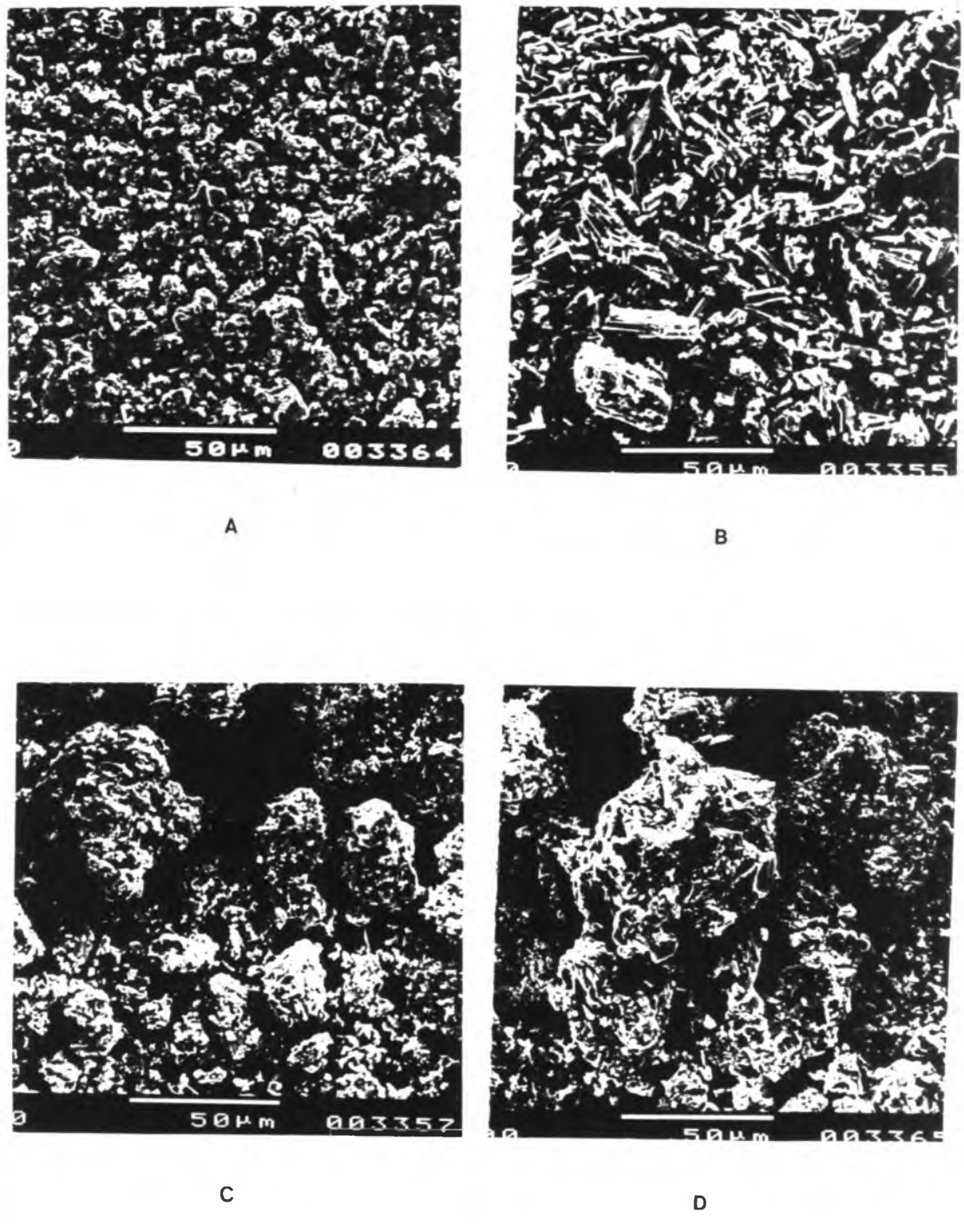
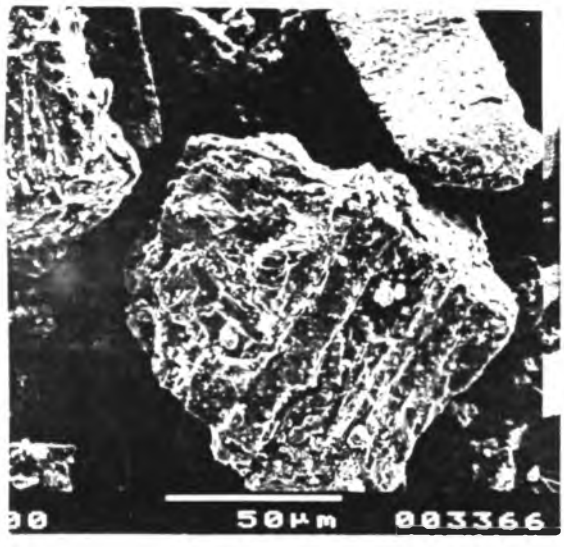


Fig 5 Photomicrograph of Piroxicam-β-Cyclodextrin Systems (piroxicam from Italy)

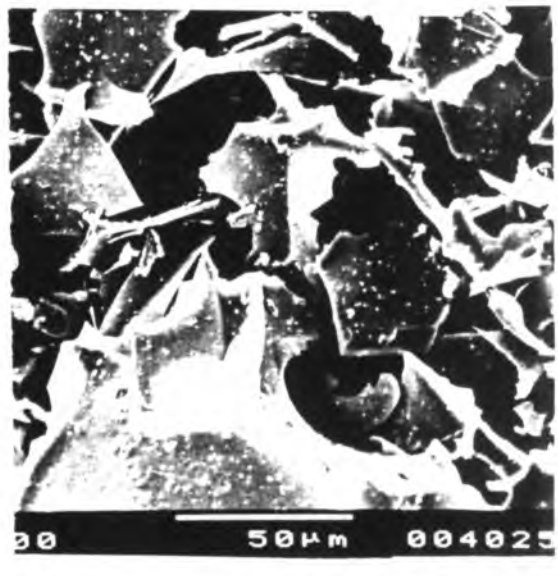
A piroxicam from Italy
B piroxicam from Hong Kong
C wet kneaded mixture 1:1 molar ratio
D wet kneaded mixture 1:2 molar ratio



E

F

G



H

Fig 5(cont.) Photomicrograph of Piroxicam-β-Cyclodextrin Systems (piroxicam from Italy)

E physical mixture 1:1 molar ratio
F physical mixture 1:2 molar ratio
G freeze-dried inclusion complex 1:1 molar ratio
H freeze-dried inclusion complex 1:2 molar ratio

2 Infrared Spectrophotometer.

Infrared spectra of indomethacin-β-cyclodextrin systems were shown in Fig 6. Indomethacin showed two distinct absorptions at 1690 and 1710 cm^{-1} which were assigned to stretching vibration of carbonyl groups COO and NCO, respectively. These bands could be observed in the wet kneaded mixtures as well as in the physical mixtures. The infrared spectra of the wet kneaded mixtures showed no chemical change comparing to the physical mixtures. The spectra of indomethacin-β-cyclodextrin wet kneaded mixtures were simply the summation of the spectra of two components. There were no evidence of complexation between indomethacin and β-cyclodextrin. The absorption bands characteristics of indomethacin were unaffected in the wet kneading process. In the freeze dried indomethacin-β-cyclodextrin inclusion complex, absorption spectra at 1690 cm^{-1} was disappeared due to either the formation of inclusion complex or the effect of the more intensity spectra of β-cyclodextrin. The spectrum change caused by functional group of indomethacin is interacted with β-cyclodextrin. Infrared spectra of piroxicam-β-cyclodextrin system were shown in Fig 7. Spectra of piroxicam from two sources, Italy and Hong Kong were different. Piroxicam from Italy showed absorption spectra of NH^-, OH^- stretching at 3390 cm^{-1} while piroxicam from Hong Kong showed absorptions at 3390, 3335 cm^{-1} which indicated the existing of two polymorphic forms (Fig 8). The spectra of the wet kneaded mixtures and the physical mixtures of piroxicam and β-cyclodextrin showed no chemical modification. The principal peak of piroxicam at 1573 cm^{-1} was disappeared in the freeze-dried piroxicam-β-cyclodextrin inclusion complex.

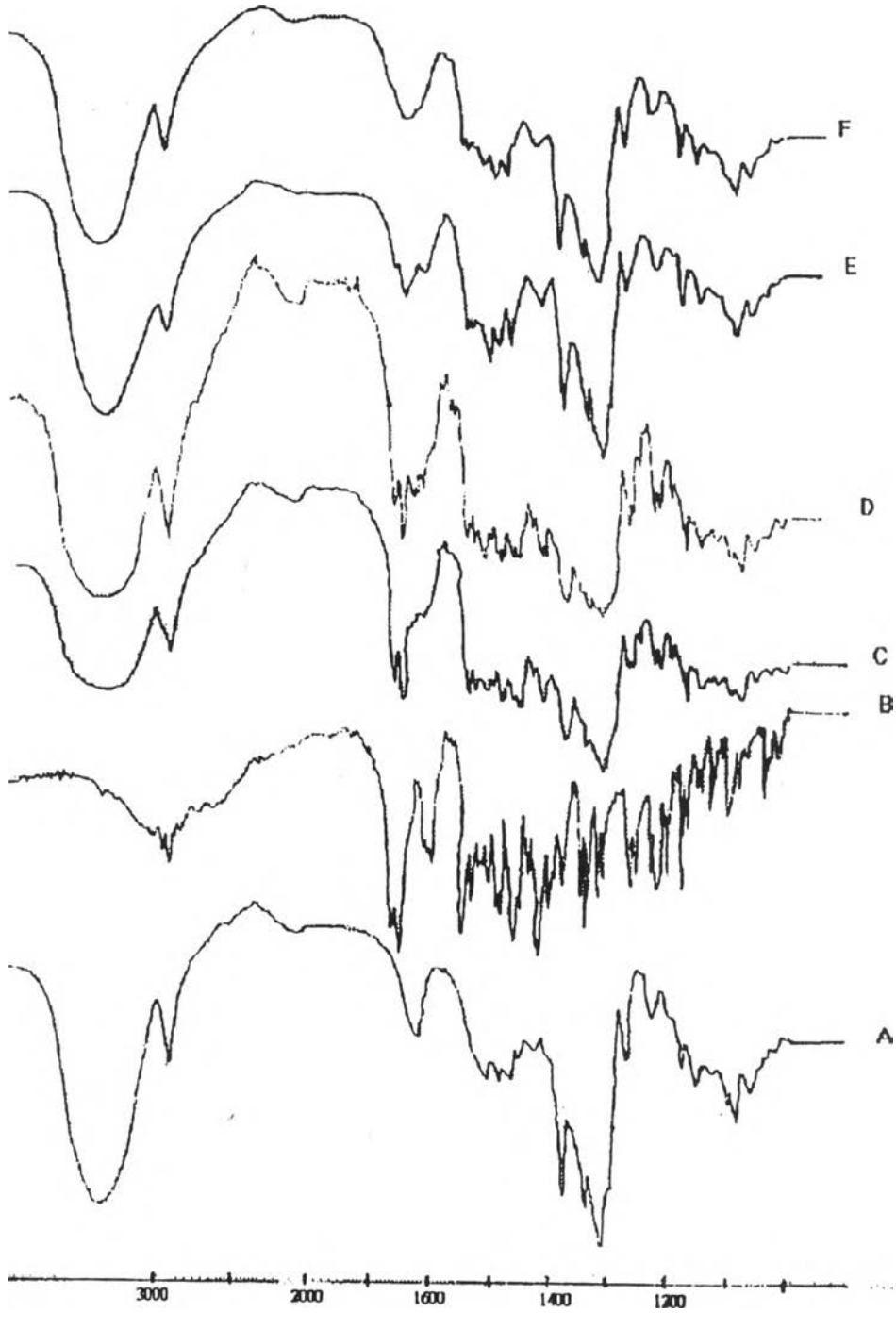


Fig 6 Infrared spectra of Indomethacin-β-Cyclodextrin Systems

A β-cyclodextrin
B indomethacin
C ind-β-cd wet kneaded mixture
D ind-β-cd physical mixture 1:1 molar ratio
E ind-β-cd inclusion complex 1:1 molar ratio
F ind-β-cd inclusion complex 1:2 molar ratio

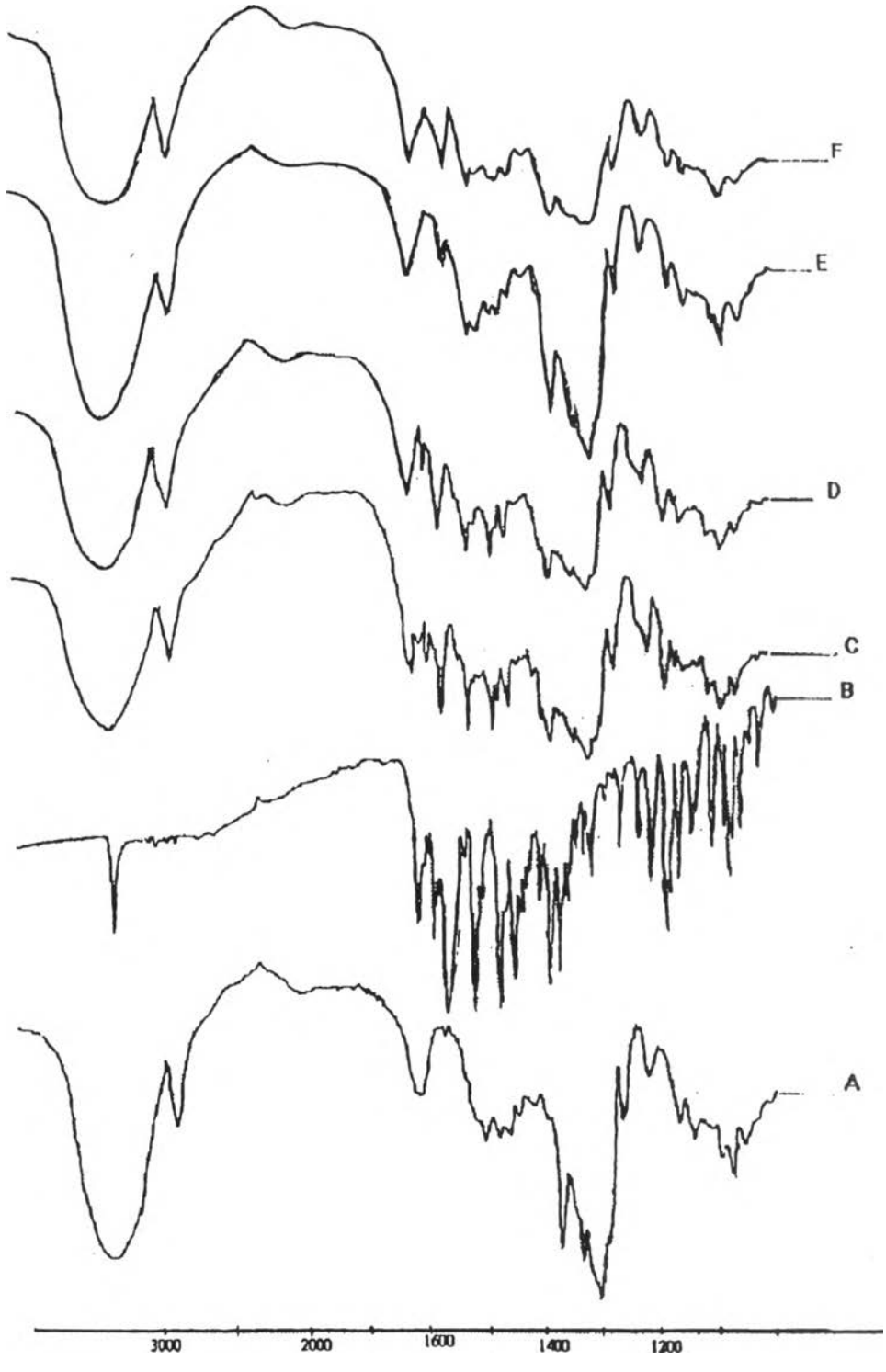


Fig 7 Infrared spectra of Piroxicam-β-Cyclodextrin Systems (piroxicam from Italy)

A β-cyclodextrin
B piroxicam
C pir-β-cd wet kneaded mixture
D pir-β-cd physical mixture 1:1 molar ratio
E pir-β-cd inclusion complex 1:1 molar ratio
F pir-β-cd inclusion complex 1:2 molar ratio

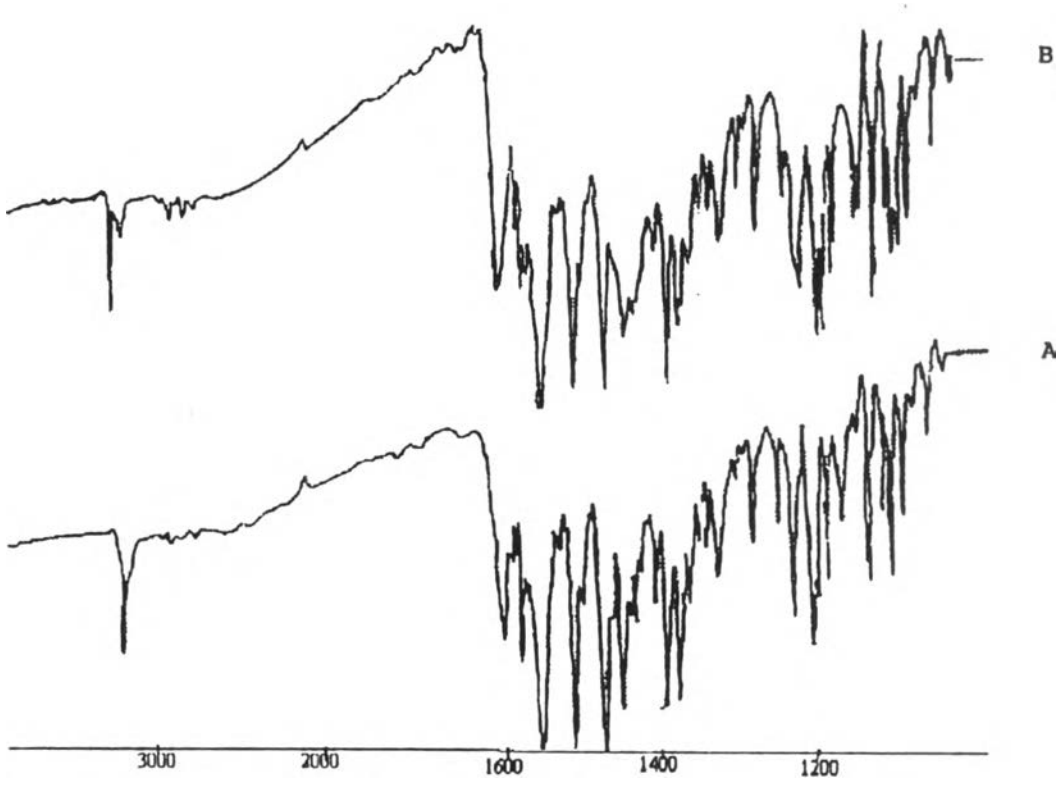


Fig 8 Infrared spectra of Piroxicam

A piroxicam (from Italy)

B piroxicam (from Hong Kong))

The infrared spectra of both indomethacin-β-cyclodextrin systems, and piroxicam β-cyclodextrin systems showed that there were no significant chemical modification of drugs and β-cyclodextrin occured during wet kneading process.

3 Differential Scanning Calorimetry

Thermograms of indomethacin-β-cyclodextrin systems were shown in Fig 9. Endothermic peak of β-cyclodextrin at about 100°C was due to the evaporation of water in β-cyclodextrin molecule. Indomethacin displayed one endothermic peak at 160°C which indicated polymorphic form 1. In the physical mixtures and the wet kneaded mixtures, thermograms showed two characteristic endothermic peaks at 100 °C and 160 °C corresponding to β-cyclodextrin and indomethacin respectively. A small endothermic peak occurred at 213 °C in the wet kneaded mixtures indicated some interactions between indomethacin and β-cyclodextrin. This interaction might create a new complex which could be the inclusion complex. The melting peak of indomethacin in the freeze-dried inclusion complex 1:1 molar ratio was shifted to higher temperature at about 208°C and was totally disappeared in the inclusion complex 1:2 molar ratio. Thermograms of piroxicam-β-cyclodextrin systems were shown in Fig 10 and 11. Thermogram of piroxicam from Italy, showed one endothermic peak at 202 °C. Thermogram of piroxicam from Hong Kong showed two endothermic peaks, the major peak at 202°C and a small endothermic peak at 195 °C which indicated the exist of two polymorphic forms. Thermograms of the wet kneaded mixtures, using the source from Italy, showed endothermic peaks at 100°C, 202°C and a small peak at 206°C.

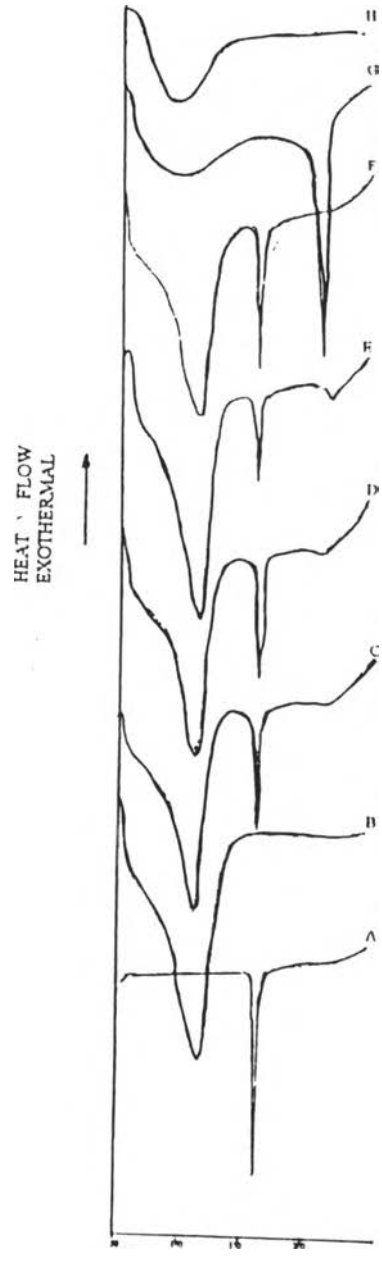


Fig 9 DSC curves of Indomethacin-β Cyclodextrin Systems

A indomethacin
B β-cyclodextrin
C ind-β-cd wet kneaded mixture 1:1 molar ratio
D ind-β-cd wet kneaded mixture 1:1 molar ratio (at 60 °C water bath)
E ind-β-cd wet kneaded mixture 1:2 molar ratio
F ind-β-cd physical mixture 1:1 molar ratio
G ind-β-cd inclusion complex 1:1 molar ratio
H ind-β-cd inclusion complex 1:2 molar ratio

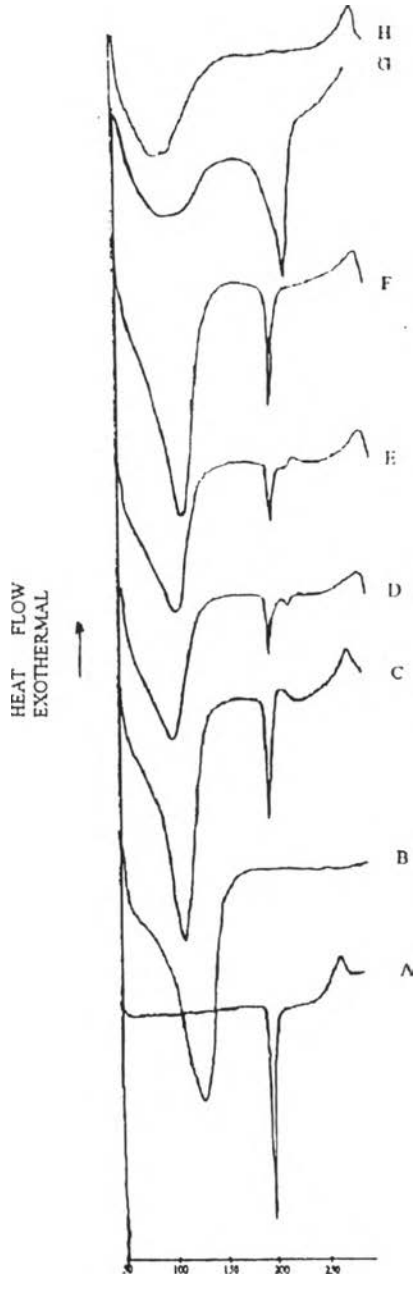


Fig 10 DSC curves of Piroxicam-β-Cyclodextrin Systems (piroxicam from Italy)

A piroxicam
B β-cyclodextrin
C pir-β-cd wet kneaded mixture 1:1 molar ratio
D pir-β-cd wet kneaded mixture 1:2 molar ratio
E pir-β-cd wet kneaded mixture 1:1 molar ratio (at 60 °C water bath)
F pir-β-cd physical mixture molar ratio 1:1
G pir-β-cd inclusion complex molar ratio 1:1
H pir-β-cd inclusion complex molar ratio 1:2

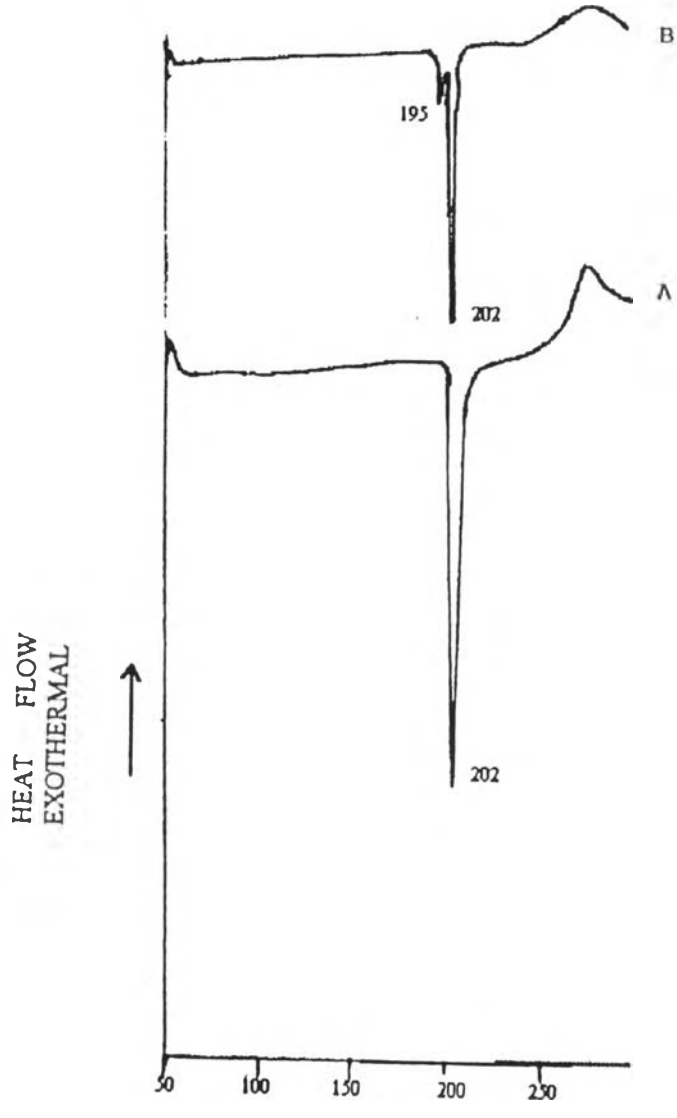


Fig 11 DSC curves of Piroxicam

A piroxicam (from Italy)

B piroxicam (from Hong Kong)

The evidences were the same as indomethacin-β-cyclodextrin systems. The melting peak of piroxicam in the freeze-dried inclusion complex 1:1 molar ratio was shifted to higher temperature at 221°C and endothermic peak of piroxicam disappeared in the inclusion complex 1:2 molar ratio. The disappearance of melting peak or the shift of melting peak to higher temperature indicated that some interaction had occurred between piroxicam and β-cyclodextrin. This type of interaction might lead to the formation of inclusion complex. The inclusion complexes of both indomethacin-β-cyclodextrin and piroxicam-β-cyclodextrin could be formed using freeze-dried process, but could be hardly formed in the wet kneaded process. Most molecules of indomethacin and piroxicam still existed in the free state and dispersed between β-cyclodextrin molecules.

4. X-ray Diffractometer

X-ray diffraction patterns of both indomethacin-β-cyclodextrin systems and piroxicam-β-cyclodextrin systems were observed. (Fig 12 and 13) Diffractograms of the wet kneaded mixtures of both indomethacin and piroxicam with β-cylcodextrin were simply the superposition of each component pattern. The results from X-ray diffraction showed that there were no phase transition between crystalline state and amorphous state. It appeared that no drug degradation or no new drug compound occured during wet kneading process. The wet kneaded mixtures still existed in the crystalline state.

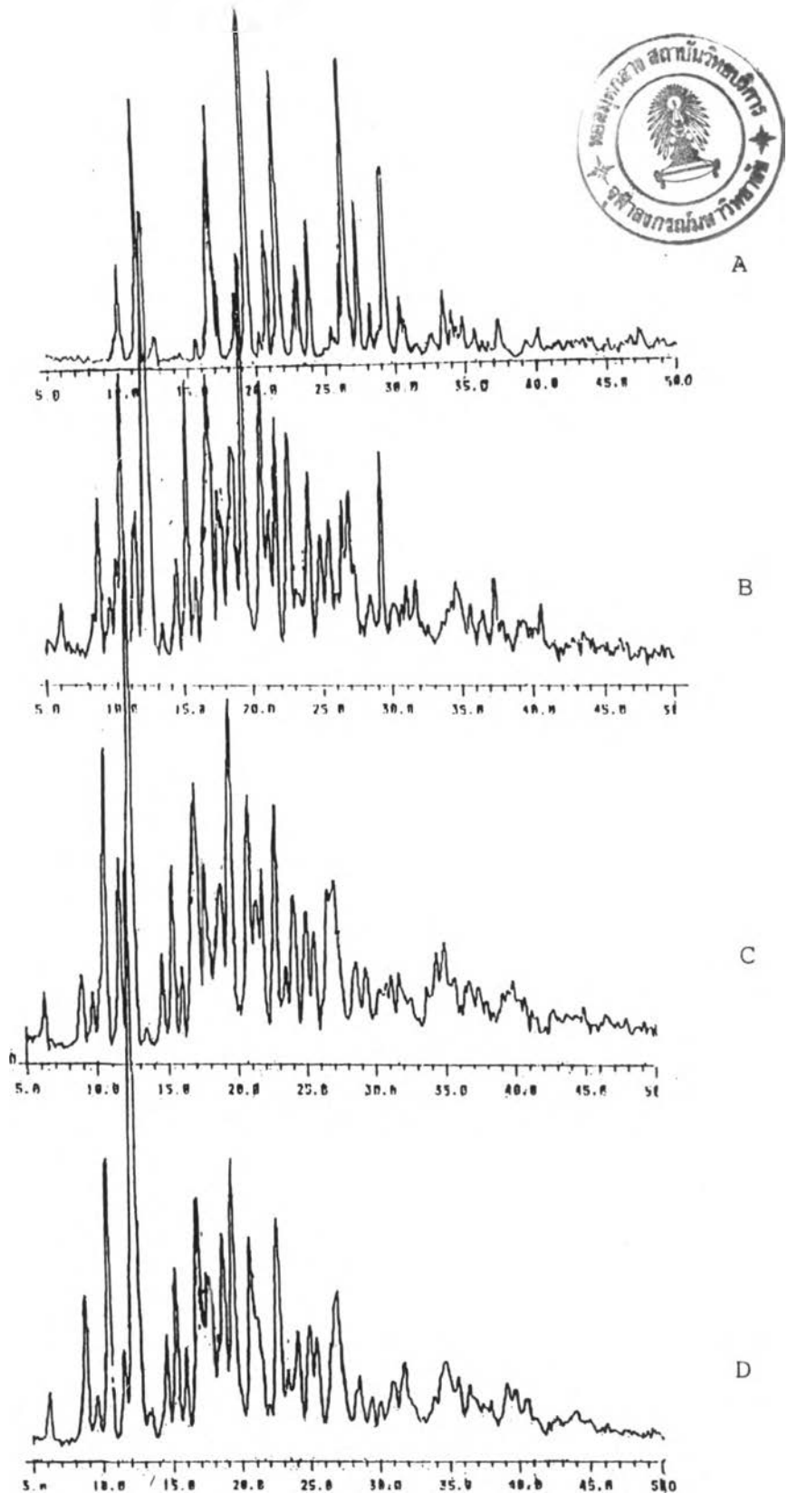


Fig 12 X-Ray Diffractograms of Indomethacin-β-Cyclodextrin Systems
A indomethacin
B indomethacin-β-cyclodextrin physical mixture 1:1 molar ratio
C indomethacin-β-cyclodextrin physical mixture 1:1 molar ratio
D β-cyclodextrin

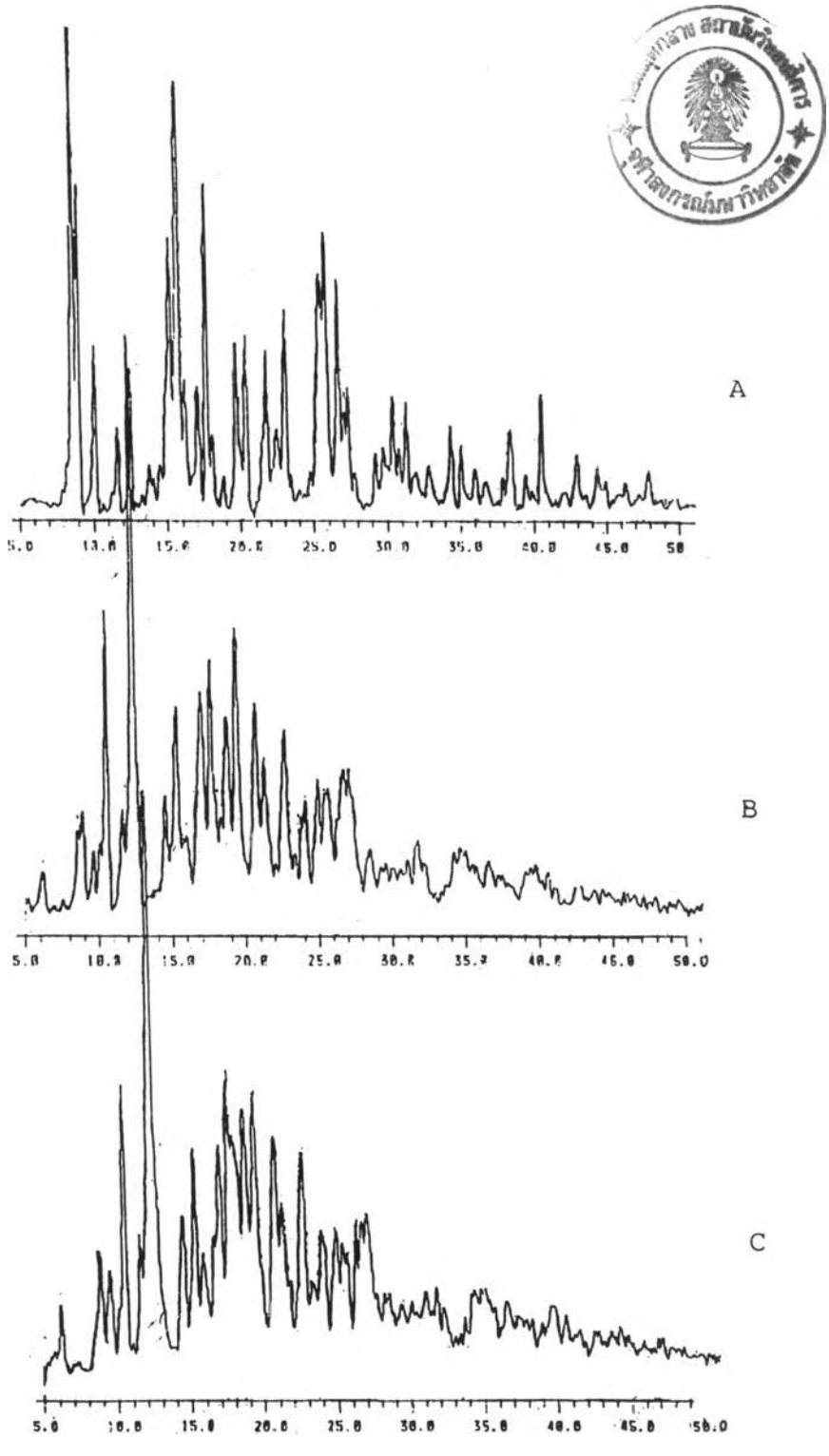


Fig 13 X-Ray Diffractograms of Piroxicam-β-Cyclodextrin Systems
A piroxicam
B piroxicam-β-cyclodextrin wet kneaded mixture 1:1 molar ratio
C piroxicam-β-cyclodextrin physical mixture 1:1 molar ratio

5. Wettability

Wettability is able to improve the dissolution behavior of drugs. The method used in this experiment is an upward migration of water through the sample packed in a small glass column. The degree of wettability is as follows :

wet kneaded mixture > physical mixture > ground drug (indomethacin, piroxicam).

Tablets and Capsules Evaluations

The evaluations on the properties and contents of indomethacin capsules and piroxicam tablets were shown in Table 16 and 17

Table 16 Physical Evaluations of Indomethacin Capsules

R_X	weight variation (mg) mean ± SD	content % la	Disintegration (minute)
I-1	240.6 ± 4.38	109.65	3.5
I-2	254.9 ± 5.35	109.42	4.1
I-3	265.9 ± 4.75	104.46	4.3
I-4	234.2 ± 2.38	112.62	5.0
I-5	214.5 ± 3.90	113.41	4.1
I-6	224.2 ± 2.68	104.03	3.7
I-7	257.2 ± 2.15	108.00	2.5
I-8	274.1 ± 8.77	97.51	4.3
I-9	229.6 ± 3.48	107.09	3.3
I-10	237.5 ± 2.92	107.56	3.0
I-11	268.3 ± 3.53	107.65	4.5

Table 16 (cont) Physical Evaluations of Indomethacin Capsules

R_X	weight variation (mg) mean ± SD	content % la	Disintegration (minute)
I-12	263.3 ± 3.63	104.05	3.7
I-13	220.9 ± 3.00	108.17	3.3
I-14	277.4 ± 3.92	100.81	2.8
I-15	305.4 ± 5.69	107.52	3.1
I-16	280.8 ± 6.87	106.13	3.3
I-17	278.8 ± 6.15	102.48	4.0
I-18	283.9 ± 5.77	101.89	3.9
I-19	285.2 ± 6.91	103.69	3.7
I-20	262.9 ± 5.01	92.53	4.5
I-21	282.1 ± 5.16	103.64	4.5
I-22	294.2 ± 4.62	104.58	3.3
I-23	269.3 ± 5.75	105.18	2.9
I-24	279.1 ± 3.55	95.98	4.4
I-25	262.6 ± 4.06	95.66	5.1
I-26	265.7 ± 7.67	94.86	5.0
I-27 (powder)	284.7 ± 4.47	102.51	4.3
I-27 (solution)	291.5 ± 5.01	101.03	4.7
I-28	303.6 ± 6.01	97.04	5.3
I-29	299.3 ± 7.16	97.92	4.4
I-30	309.4 ± 6.83	97.73	4.7

Table 17 Physical Evaluations of Piroxicam Tablets (piroxicam from Italy)

R_x	weight variation (mg) mean ± SD	content % la	Hardness (Kp)	Friability (% loss)	Disintegration (minute)
P-1	298.0 ± 6.86	97.31	3.82	0.62	4.0
P-2	296.3 ± 4.93	92.89	4.51	0.44	4.0
P-3	322.3 ± 1.19	103.64	3.23	0.58	4.0
P-4	298.1 ± 3.54	96.55	4.73	1.03	4.0
P-5	319.6 ± 6.10	104.02	4.05	0.66	4.2
P-6	307.7 ± 6.11	95.59	3.30	0.82	3.3
P-7	313.0 ± 6.30	98.41	3.71	0.94	2.4
P-8	337.3 ± 6.53	114.26	5.10	0.67	3.5
P-9	305.2 ± 7.10	105.95	4.92	1.10	5.2
P-10	323.4 ± 4.51	108.59	2.73	1.62	5.1
P-11	324.0 ± 2.13	112.36	2.72	1.13	4.2
P-12	312.0 ± 6.61	108.89	3.73	0.72	4.3
P-13	288.3 ± 6.33	99.61	4.87	0.53	4.0
P-14	318.7 ± 6.32	110.94	5.11	1.12	5.1
P-15	304.9 ± 3.32	110.67	3.75	0.85	4.3
P-16	304.5 ± 8.15	105.95	3.64	0.73	6.0
P-17	303.3 ± 7.75	104.70	5.20	0.95	5.3
P-18	309.1 ± 2.28	105.46	4.15	0.82	7.5
P-19	307.3 ± 8.01	105.04	3.73	1.10	4.0
P-20	306.5 ± 7.21	110.90	3.51	0.71	3.5
P-21	299.3 ± 4.83	105.26	3.72	0.88	5.3
P-22	303.0 ± 7.03	104.62	6.21	0.95	5.2

Table 17(cont.) Physical Evaluations of Piroxicam Tablets (piroxicam from Italy)

R_X	weight variation(mg) mean ± SD	content % la	Hardness (Kp)	Friability (% loss)	Disintegration (minute)
P-23	308.7 ± 1.12	102.28	4.65	1.21	5.4
P-24	300.5 ± 4.92	102.60	6.03	0.58	3.2
P-25	290.0 ± 6.79	108.94	3.20	0.87	4.1
P-26	296.5 ± 4.69	110.67	3.40	0.93	4.2
P-27	303.5 ± 3.71	101.50	4.40	1.02	4.5
P-28	301.1 ± 5.79	102.5	3.53	0.85	5.0

The physical evaluations of piroxicam tablets which were prepared from piroxicam from Hong Kong

R_X	weight variation (mg) mean ± SD	content %.la	Hardness (Kp)	Friability (% loss)	Disintegration (minute)
P-1	300.3 ± 5.12	98.95	4.47	0.75	5.1
P-13	298.9 ± 2.55	96.17	3.25	0.95	4.3
P-25	291.7 ± 6.21	98.75	3.60	0.58	4.5
P-27	297.9 ± 1.33	98.75	2.90	1.12	3.9
P-28	308.1 ± 5.13	96.50	3.71	0.87	3.9

Dissolution of Indomethacin Capsules

Dissolution profiles of indomethacin capsules were preparing from wet kneaded mixtures were shown in Fig 14-21. Dissolution data of these capsules could be found in appendices 1-2. Dissolution profile of commercial indomethacin capsules (Indocid) was studied as innovator.

The times required for 85 % of indomethacin to be dissolved were shown in Table 18.

Table 18 Time for 85% labeled amount of indomethacin dissolved

R_X	T 85% dissolved (minutes)
I_1-I_3	10 - 17.5
I_4-I_6	9 - 18.8
I_7-I_9	9.5 - 15
I_{10}-I_{13}	9.5 - 23.2*
I_{14}-I_{16}	9.5 - 18.6
I_{17}-I_{19}	9.1 - 13.2
I_{20}-I_{22}	12.0 - 17.7
I_{23}	> 20*
I_{24}-I_{26}	13.9 - 20
I_{27} - I_{30}	> 20
indocid	12.7

*USP XXII requires for dissolution of indomethacin must not less than 80 % (Q) dissolved in 20 minutes.

Dissolution of all formulas prepared from wet kneaded mixtures met the USP XXII requirement except formulas I-10 and I-23. The wet kneading process could affect the crystallinity of indomethacin and β-cyclodextrin. Moreover β-cyclodextrin powder bed could easily disperse and wet by dissolution medium. Indometahcin molecules were dispersed in the networks of β-cyclodextrin molecules. The enhancement in dissolution could be attributed to the reduction in particle size and the

increase in wettability. In the formulas I-10 and I-23, the wet kneading procedure had been done at higher temperature and small volume of water were used as solvent. They took about 20 minutes and 15 minutes for I-10 and I-23 respectively for the wet kneading process. The mixtures changed from slurry suspension to harden paste in a short time which might due to the volatility of water. Indomethacin might cause aggregation and was not completely dispersed on β-cyclodextrin surface. These effects caused lower dissolution.

The ranks of dissolution of indomethacin capsules were as follows :

wet kneaded mixtures > sodium lauryl sulfate > physical mixtures > ground indomethacin capsules.

The dissolution of all formulations of indomethacin capsules, not preparing from the wet kneaded mixtures, failed the USP XXII requirement (Fig 22-23). The indomethacin capsules using sodium lauryl sulfate solution had higher dissolution than those using sodium lauryl sulfate in the powder form. (Fig 22) The results implied that sodium lauryl sulfate in solution form was more powerful dispersing agent than the powder form. Ground indomethacin capsules exhibited slowest dissolution due to the aggregation of fine particles of ground indomethacin. In addition lactose used in the ground indomethacin capsules might decrease the dissolution of indomethacin. Lactose needs so much liquid to be dissolved thus there is not enough liquid left to dissolve drug particles. The capsules prepared from physical mixtures gave rise to better dissolution than the use of ground drug with lactose due to less aggregation of indomethacin powder.

From comparative plot of dissolution profile in Fig 23, it was shown that both physical mixtures in 1:1 and 1:2 molar ratio of indomethacin : β-cyclodextrin had better dissolution profiles than that of ground indomethacin capsules.

It is evident that the dissolution of indomethacin capsules prepared from the wet kneaded mixtures of indomethacin-β-cyclodextrin was significantly better than that of the ground indomethacin powder as shown in the dissolution profiles in Fig 24-25. Indomethacin capsules prepared from the wet kneaded mixtures dissolved more than 85 % labeled amount within 20 minutes while only 14 % of indomethacin ground drug and 50-60 % indomethacin capsules prepared from the physical mixtures were dissolved within the same period of time. The capsules prepared from the wet kneaded mixtures, Rx I-1, Rx I-14 had approximately 7 and 6 times respectively higher dissolution than the ground indomethacin powder. The ground indomethacin capsules (Rx I-30) had approximately 3 times higher dissolution than ground indomethacin. The additions of both β-cyclodextrin and lactose improved dissolution behavior but β-cyclodextrin was more effective because molecules of indomethacin could be released simultaneously from the mixtures

Effect of Aging on Dissolution of Indomethacin Capsules

The formulations of interesting indomethacin capsules, I-1, I-4, I-7, I-13, I-14, I-22 I-23, I-27, I-29 and I-30, were studied for aging effect. The dissolution profiles were shown in Fig 26-30. After aging, at both room temperature and 45 °C/ 75 % relative humidity, the dissolution of indomethacin capsules decreased due to the effect of gelatin shell. On storage in loosely closed bottles at both room temperature and 45 °C/ 75 % relative humidity, gelatin shell absorbed moisture from both environment

and powder bed. When gelatin shell was in contact with the dissolution medium, it distorted and did not appear to break down readily. The gelatin capsules remained as a pasty mass and occluded powder bed which caused slow release of indomethacin. The dissolutions of storage indomethacin capsules were lower than the initial values.

Test for Stability of Indomethacin Capsules

After aging for 3 months at room temperature and at 45 °C/ 75 % relative humidity. The stability of indomethacin capsules was tested using high performance liquid chromatography. The chromatograms were shown in Fig 31. The retention times of both standard indomethacin and indomethacin in the wet kneaded mixture were the same at 3.1 minutes, and that of piroxicam internal standard was 1.8 minutes. The retention times of the degradation products of indomethacin were 1.2 and 1.7 minutes. The β-cyclodextrin did not interfere with UV absorption of indomethacin at 240 nm. After aging at both room temperature and at 45 ° C/ 75% relative humidity, the chromatograms showed no traces of degradation products.

Dissolution of Piroxicam Tablets

Dissolution profiles of piroxicam tablets were shown in Fig 32-40. Dissolution profile of commercial piroxicam tablets (Feldene) was studied comparatively. Times required for 80 % of piroxicam dissolved from various formulations were shown in Table 19. The dissolution data these tablets could be found in appendices 3 and 4.

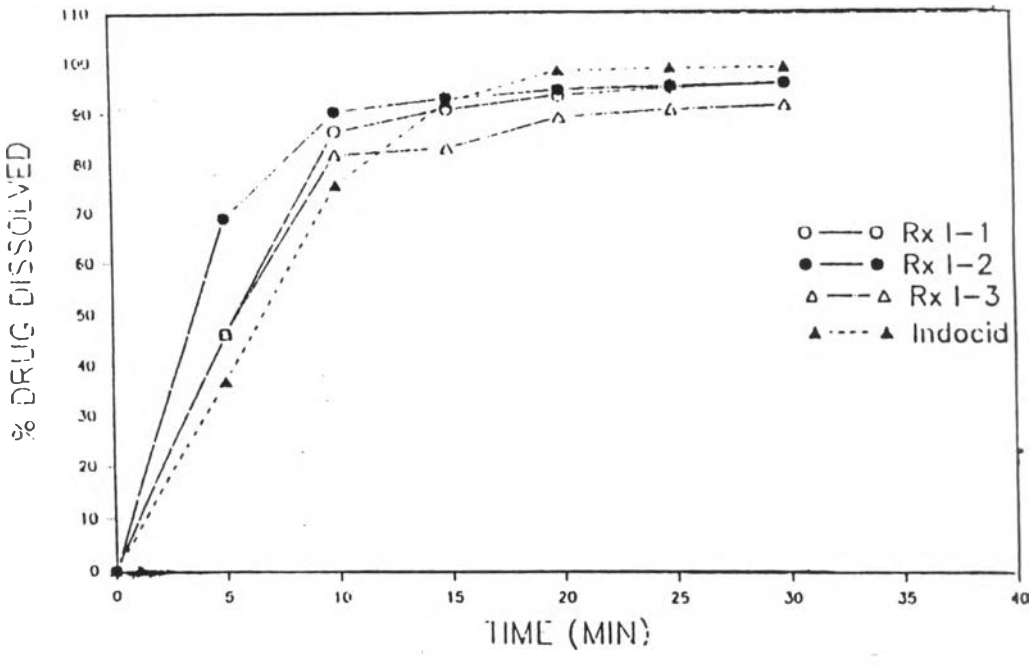


Fig 14 Dissolution profiles of indomethacin capsules prepared in the condition of ind : β-cd 1:1 molar ratio, 50 % w/w water with different kneading times 30, 60 and 90 minutes.

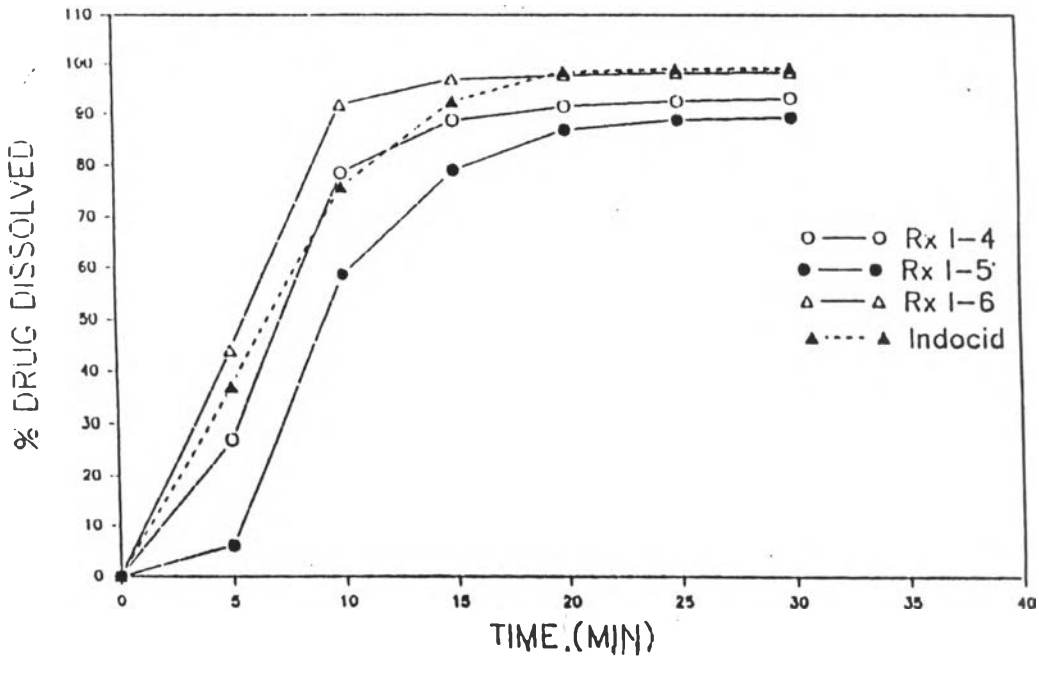


Fig 15 Dissolution profiles of indomethacin capsules prepared in the condition of ind : β-cd 1:1 molar ratio, 100%w/w water with different kneading times 30, 60 and 90 minutes

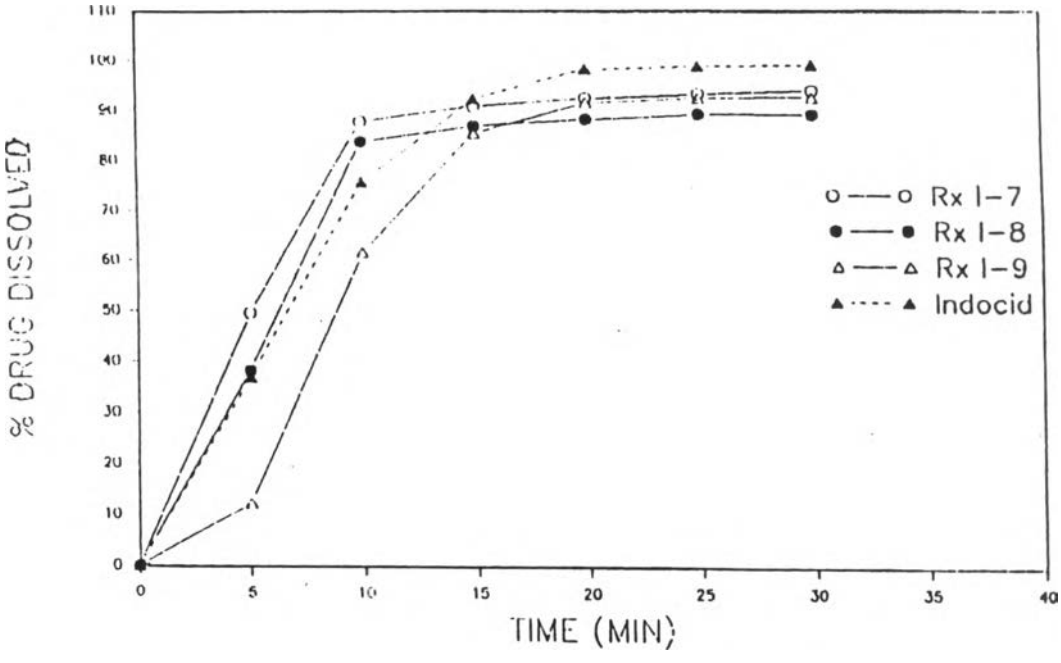


Fig 16 Dissolution profiles of indomethacin capsules prepared in the condition of ind : β-cd 1:1 molar ratio, 150 % w/w water with different kneading times 30, 60 and 90 minutes

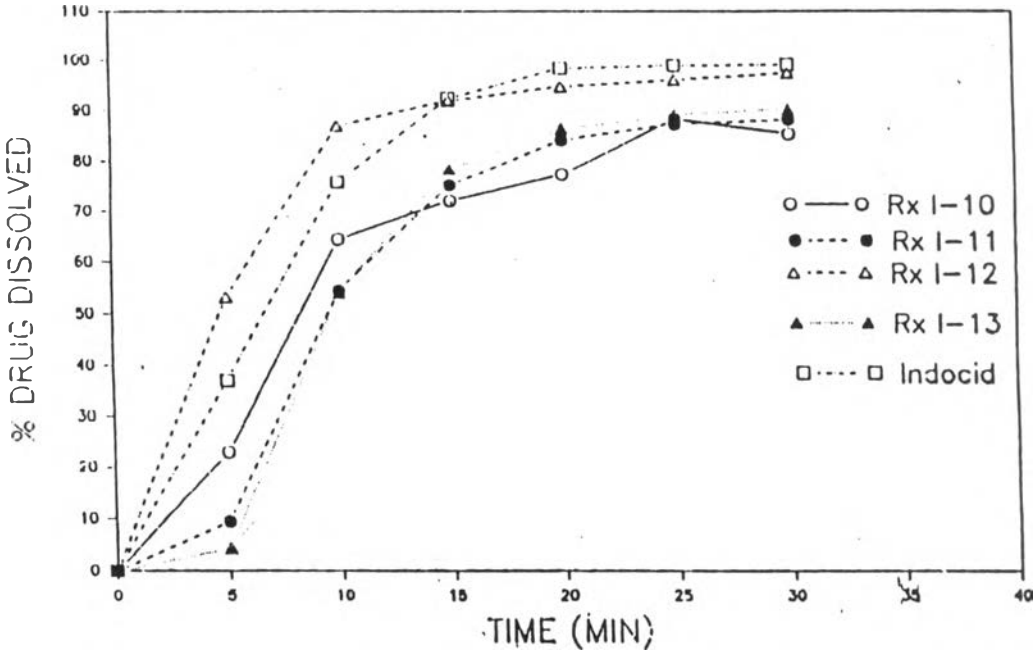


Fig 17 Dissolution profiles of indomethacin capsules prepared in the condition of ind : β-cd 1:1 molar ratio, 50, 100 and 150 % w/w water, kneaded at water bath 60 °C with different kneading times

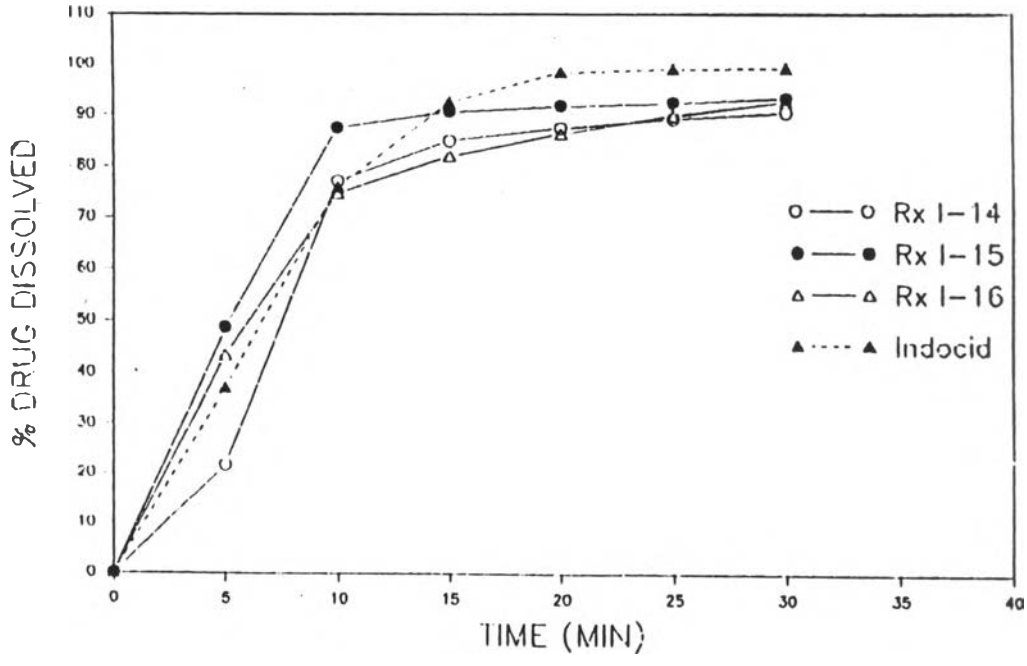


Fig 18 Dissolution profiles of indomethacin capsules prepared in the condition of ind : β-cd 1:2 molar ratio, 50 % w/w water with different kneading times 30, 60 and 90 minutes

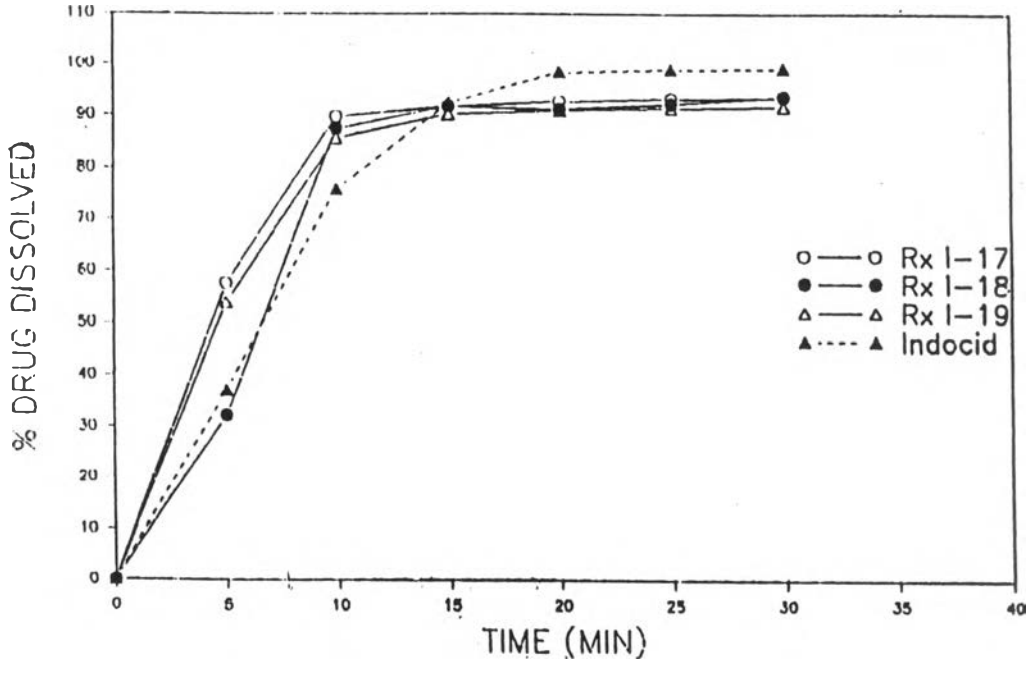


Fig 19 Dissolution profiles of indomethacin capsules prepared in the condition of ind : β-cd 1:2 molar ratio, 100%w/w water, with different kneading times 30, 60 and 90 minutes

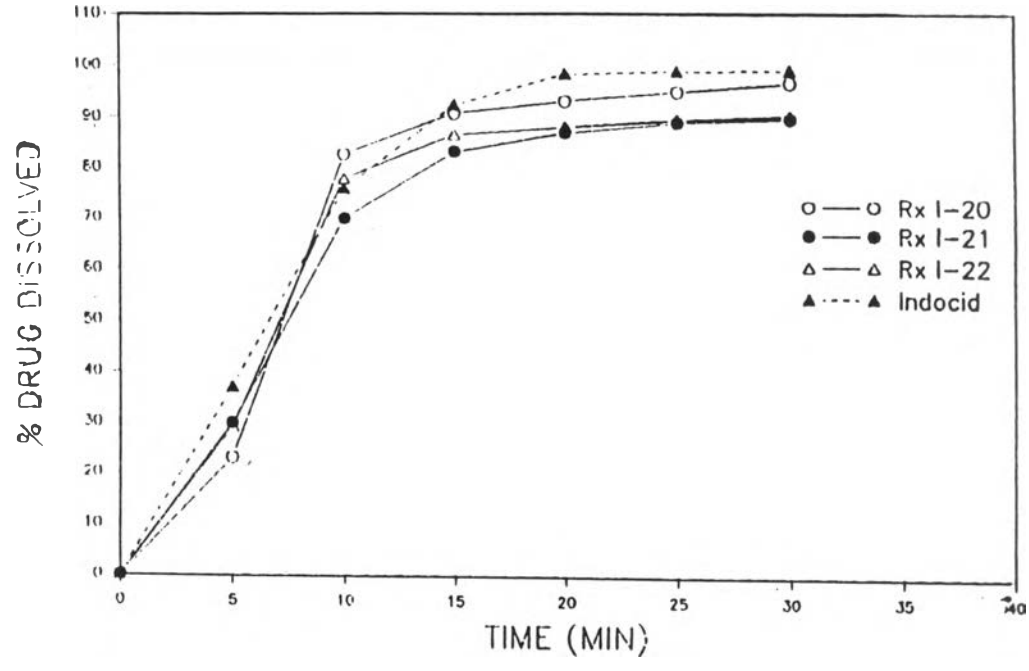


Fig 20 Dissolution profiles of indomethacin capsules prepared in the condition of ind : β-cd 1:2 molar ratio, 100 % w/w water with different kneading times 30, 60 and 90 minutes.

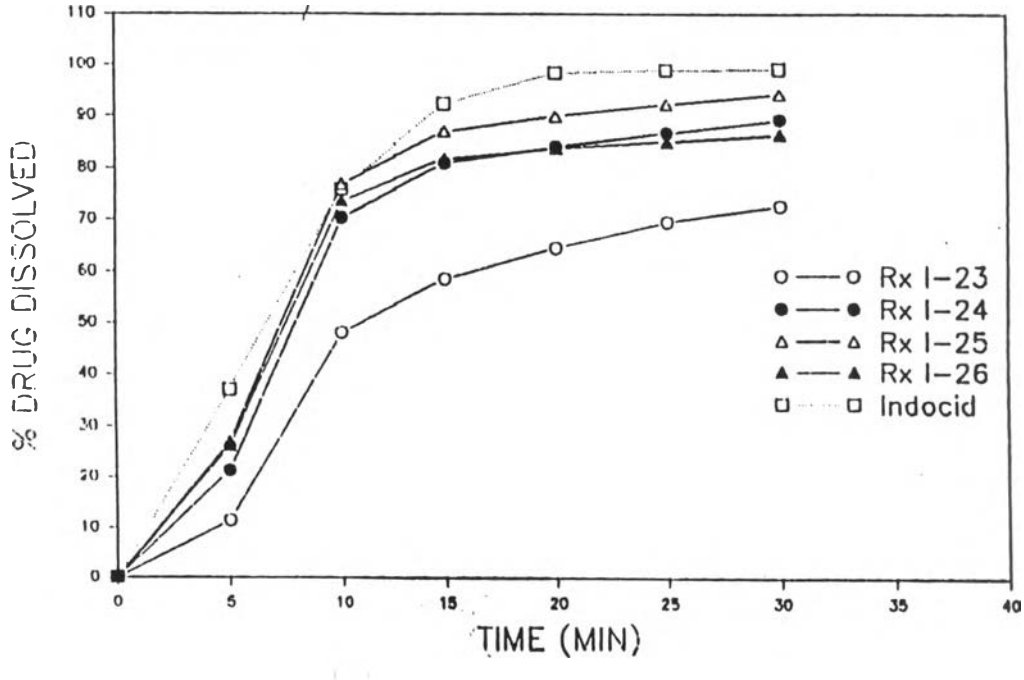


Fig 21 Dissolution profiles of indomethacin capsules prepared in the condition of ind : β-cd 1:2 molar ratio, 50, 100. 150 % w/w water, kneaded at water bath 60 °C with different kneading times

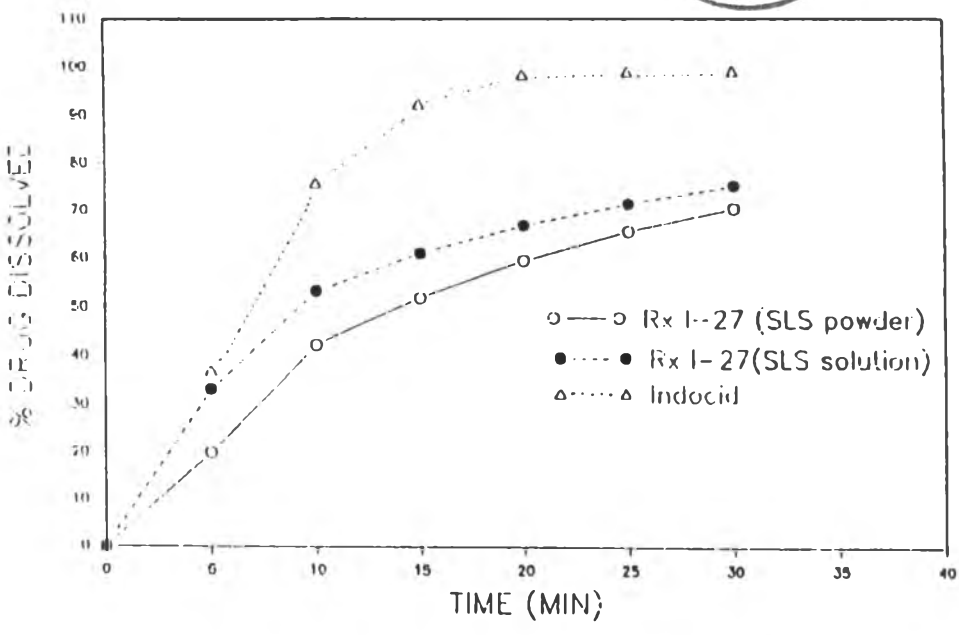


Fig 22 Dissolution profiles of indomethacin capsules prepared from the ground indomethacin mix with 1 % w/w sodium lauryl sulfate

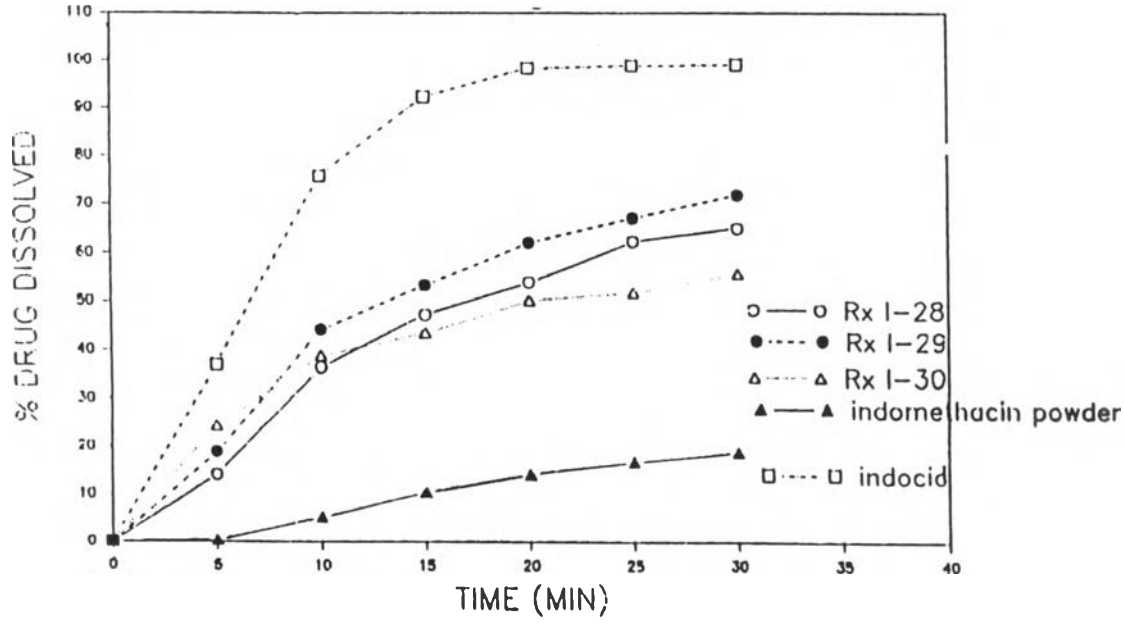


Fig 23 Dissolution profiles of indomethacin capsules prepared from the physical mixtures of ind : β-cd 1:1, 1:2 molar ratio and mix with lactose

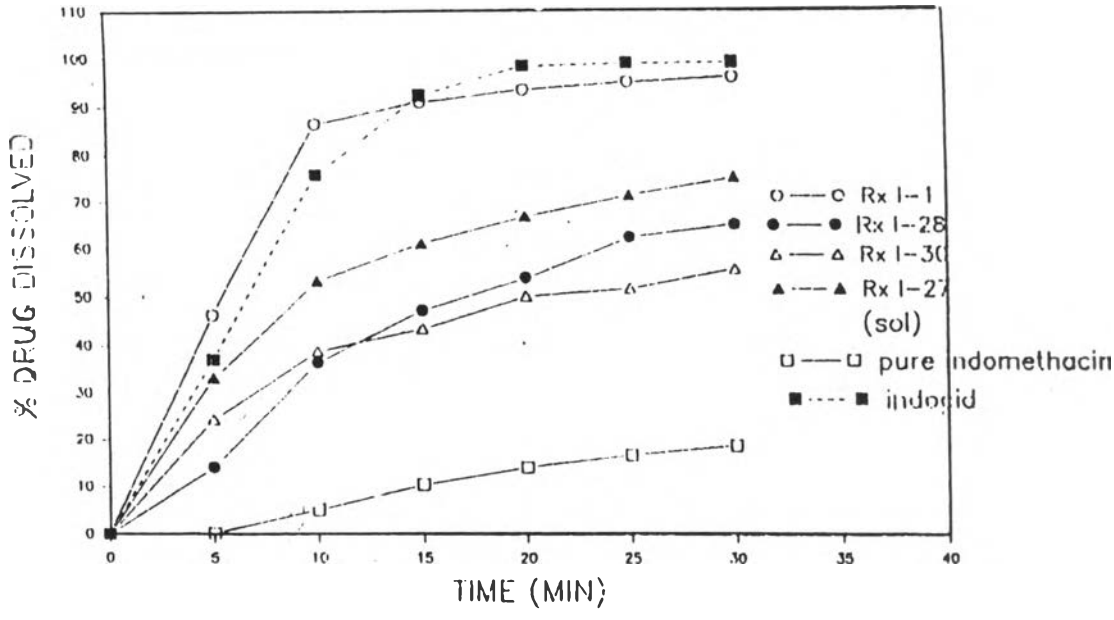


Fig 24 Dissolution profiles of indomethacin capsules. Comparative plot between wet kneaded mixture 1:1 molar ratio, physical mixture 1:1 molar ratio, mix with lactose and using 1 % w/w sodium lauryl sulfate (in solution form)

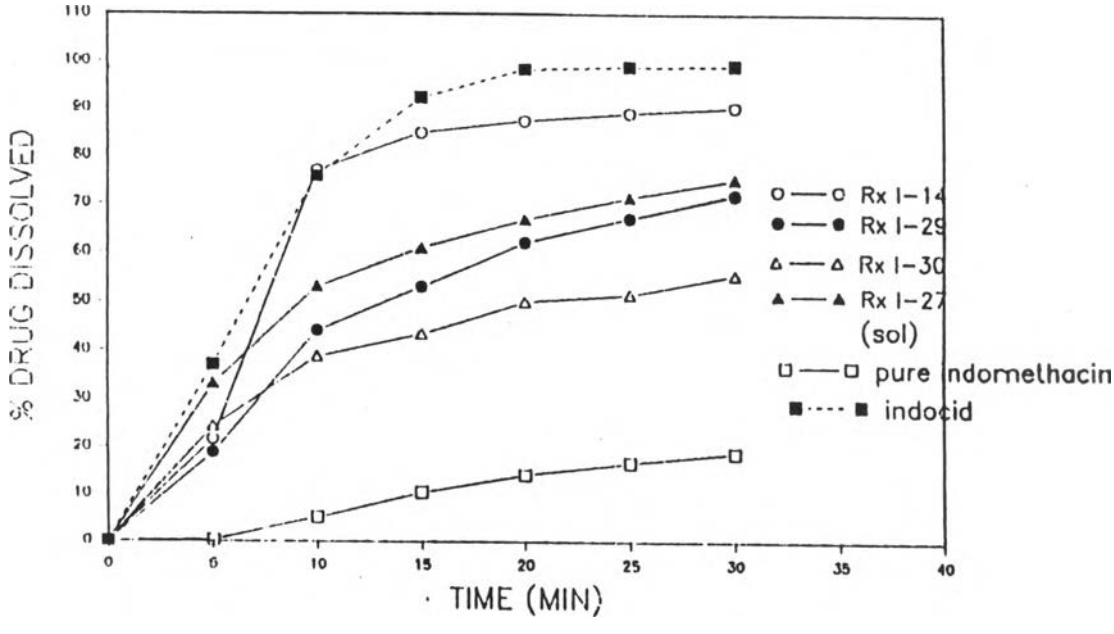


Fig 25 Dissolution profiles of indomethacin capsules. Comparative plot between wet kneaded mixture 1:2 molar ratio, physical mixture 1:2 molar ratio, mix with lactose and using 1 % w/w sodium lauryl sulfate (in solution form)

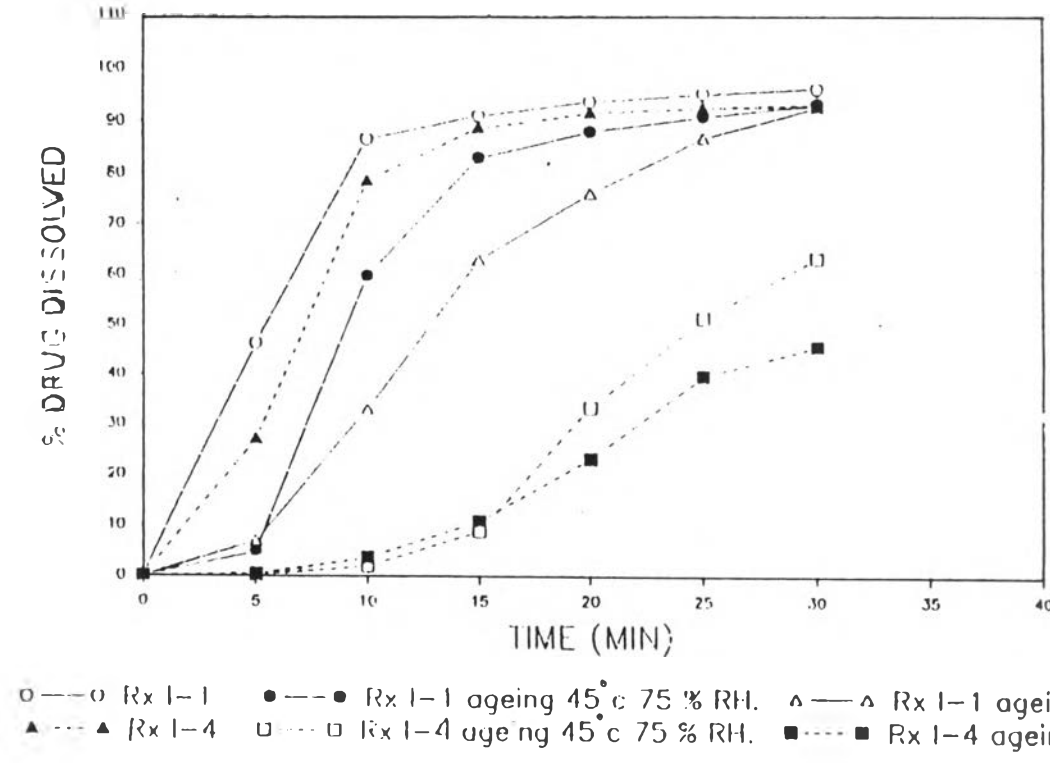


Fig 26 Dissolution profiles of indomethacin capsules,aging for 3 months (ind : β-cd 1:1 molar ratio, 50, 100 % w/w water wet kneading 30 minutes.)

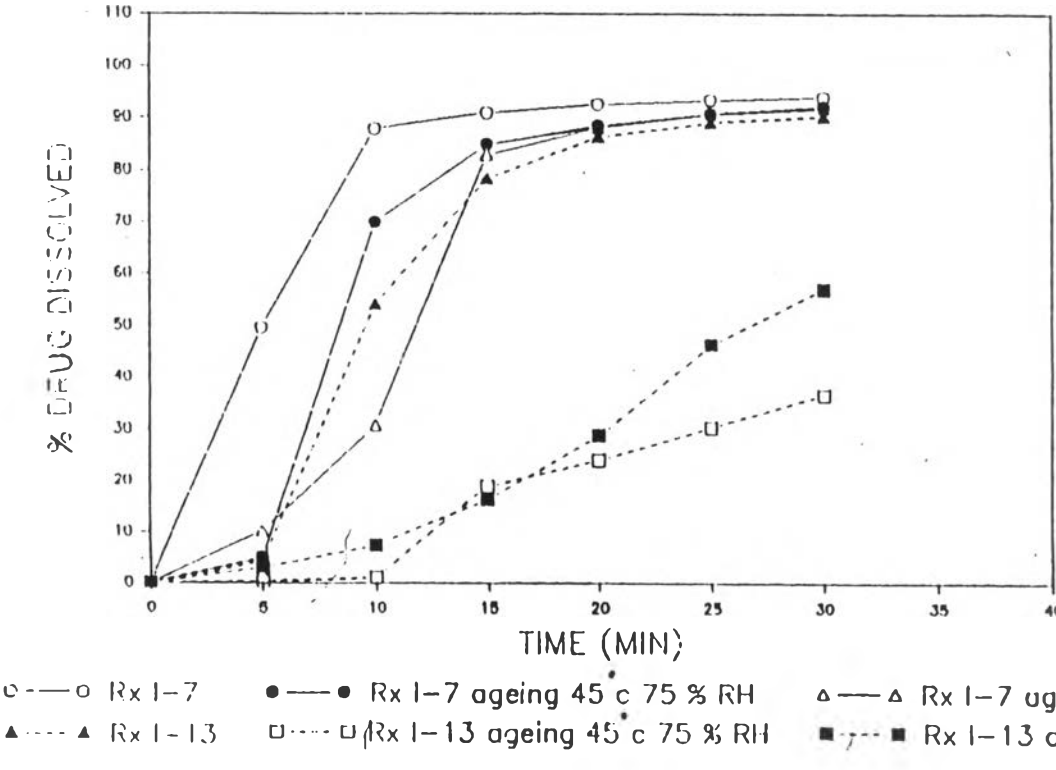


Fig 27 Dissolution profiles of indomethacin capsules,aging for 3 months (ind : β-cd 1: 1 molar ratio 150 % w/w water wet kneading 30 minutes., kneading at ambient temperature and water bath 60 C °

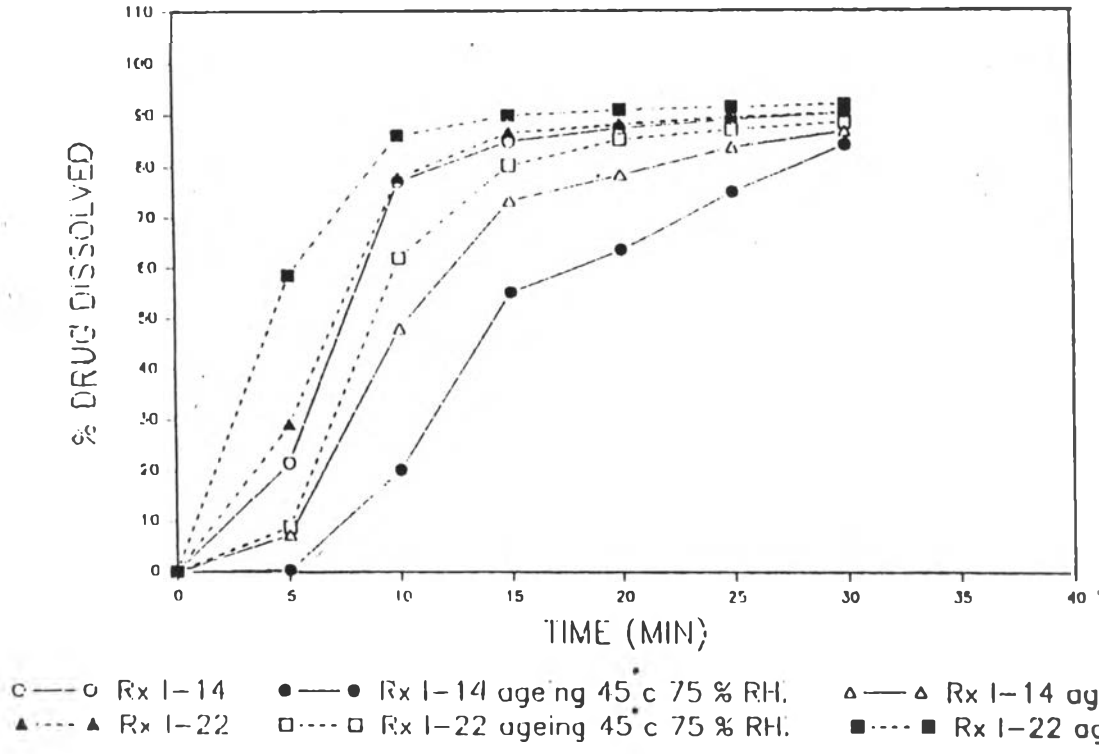


Fig 28 Dissolution profiles of indomethacin capsules,aging for 3 months (ind : β-cd 1:2 molar ratio 50 % w/w water wet kneading 30 minutes, 150 % w/w water, wet kneading 90 minutes

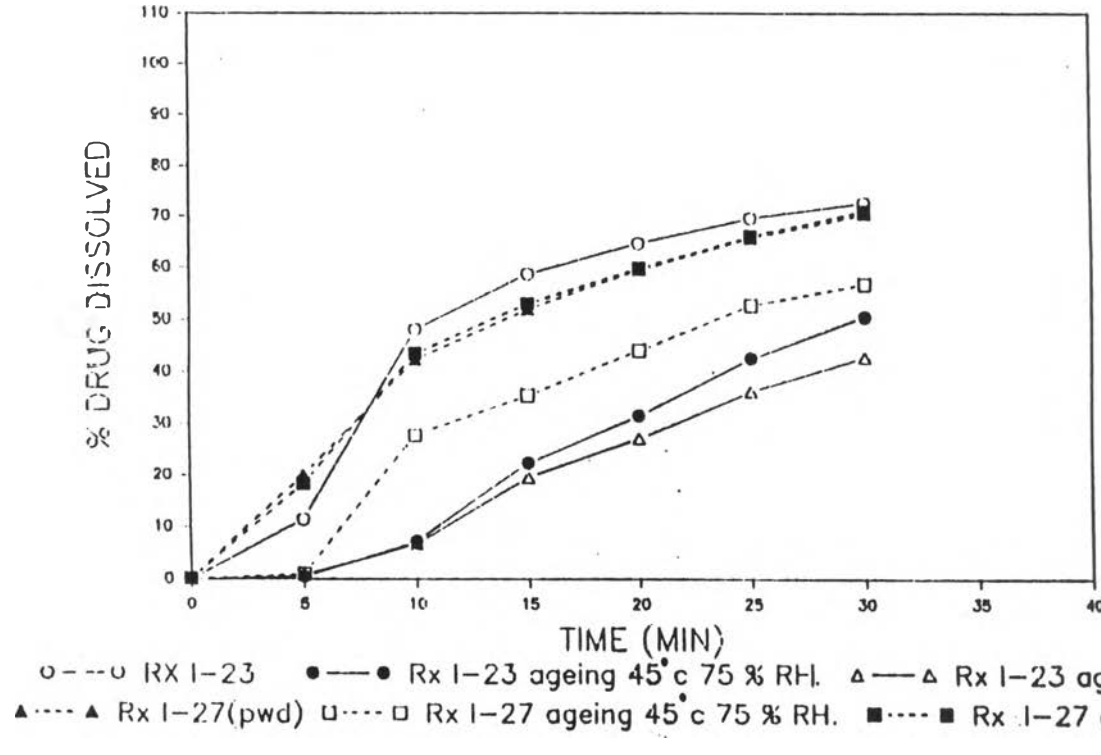


Fig 29 Dissolution profiles of indomethacin capsules,aging for 3 months (ind : β-cd 1:2 molar ratio, 50 % w/w water kneading at water bath 60 C°, 15 minutes and using 1% w/w sodium lauryl sulfate in powder form

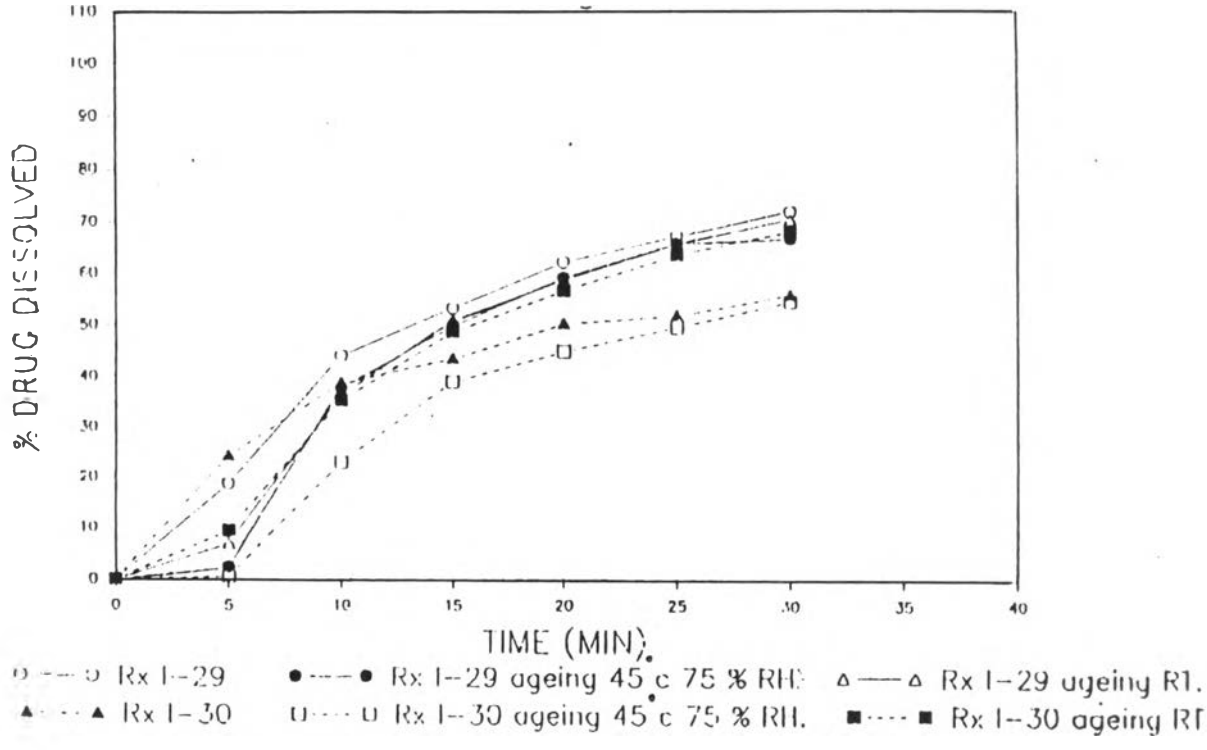


Fig 30 Dissolution profiles of indomethacin capsules, aging for 3 months (ind : β-cd physical mixture 1:2 molar ratio and mix with lactose

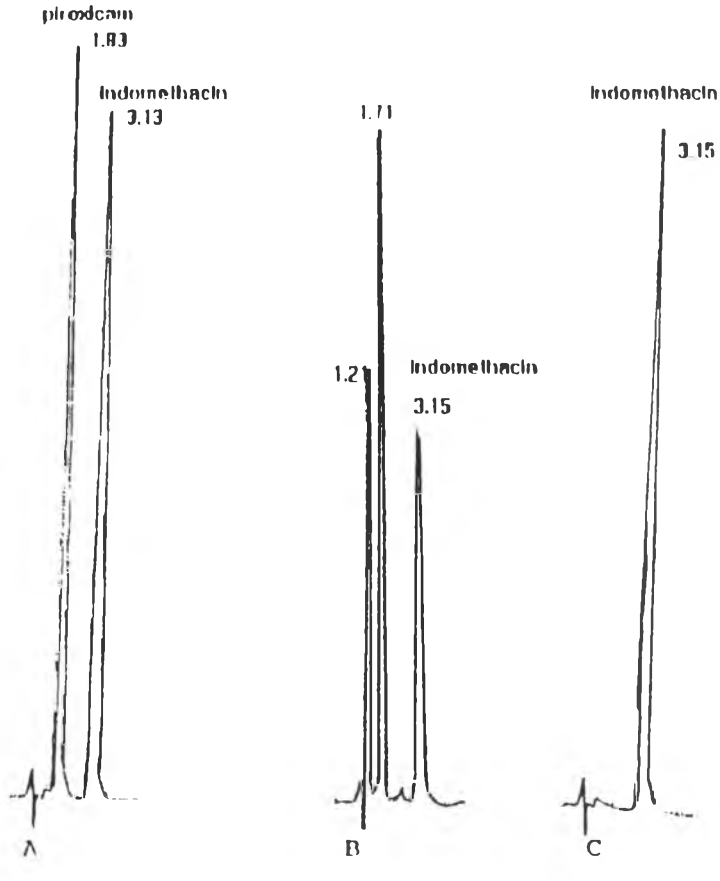


Fig 31 HPLC chromatograms of indomethacin

A standard indomethacin with piroxicam internal standard

B indomethacin and its degradation products

C indomethacin-β-cyclodextrin wet kneaded mixture

Table 19 Times for 80 % labeled amount of piroxicam dissolved

R_X	T 80% dissolved (minutes)
P1 - P3	9.6 - 12.5
P4 - P6	8.3 - 9.8
P7 - P9	9.8 - 11.8
P10 - P12	9.8 - 11.4
P13 - P14	10.0
P15 - P17	9.8 - 12.8
P18 - P20	12.8
P21 - P24	10.0 - 17.0
P25 - P26	13.6 - 19.0
P27	22.4
P28	> 45
feldene	30.4

*USP XXII requires for dissolution of piroxicam must not less than 75 % (Q) dissolved in 45 minutes.

All formulas prepared from piroxicam, from Italy, had dissolution met the USP XXII requirement except the formula, Rx P-28, which prepared from the ground piroxicam using starch and lactose as additives. The dissolutions of other formulas were enhanced by either the effect of sodium lauryl sulfate or β-cyclodextrin. Although the piroxicam, from Italy had much effective surface area, the dissolution of Rx P-28 was still lower than the requirement. The use of β-cyclodextrin in both physical mixtures and wet kneaded mixtures significantly enhanced dissolution.

The ranks of dissolution of piroxicam tablets were as follows :

wet kneaded mixtures > physical mixtures ≅ Sodium lauryl sulfate > ground piroxicam tablets.

Comparative studied of dissolution profiles of piroxicam tablets using raw material from different sources were shown in Fig 41, 44-45. The dissolution profiles of piroxicam tablets, using piroxicam from Hong Kong, were lower than those of the formulations using piroxicam from Italy. Although β-cyclodextrin and sodium lauryl sulfate could enhance the dissolution, the dissolution of piroxicam tablets using piroxicam from Hong Kong was still lower than the USP requirement. Comparative amounts of piroxicam dissolved within 45 minutes were shown in Table 20.

Table 20 Comparative study of dissolution of piroxicam tablets prepared from two sources of raw material.

Rx	% piroxicam dissolved at T= 45 minutes	
	source	
	Hong Kong	Italy
P-1	72.3	94.7
P-13	73.4	86.7
P-25	72.4	97.3
P-27	68.8	90.3
P-28	67.1	79.0

Fig 42 and 43 showed that the dissolution profiles of piroxicam tablets prepared from physical mixtures of piroxicam : β-cyclodextrin 1: 1 and 1:2 molar ratio were similar to those of the tablets adding 1 % w/w

sodium lauryl sulfate. The remarkable enhancement in the dissolution rate of wet kneaded mixtures with β-cyclodextrin was considered to be caused mainly by such effects on the wettability of the kneaded mixtures and the active surface area. The wet kneading process might promote dissolution of piroxicam by providing means for the surface of fine drug particles to closely contact with β-cyclodextrin. It is of interest that wet kneading process is available in practice by virtue of the simple and efficient preparation for simple productions. The procedure was expected to become a valuable tool for solubilizing various practically insoluble drugs.

Effect of Aging on Dissolution of Piroxicam Tablets

Aging at both room temperature and accelerated condition (45°C/ 75% relative humidity) have little effect on dissolution of piroxicam tablets. The dissolution profiles of formulas tested still met the USP XXII requirement. Aging at 45°C/ 75% relative humidity had lower dissolution than aging at room temperature. On storage, moisture was one of the factor influenced the changes of dissolution behavior. Moisture and heat can retard the dissolution of the tablets. (Fig 46-49)

Test for Stability of Piroxicam Tablets

The chromatograms from high performance liquid chromatography were shown in Fig 50. The chromatograms showed no evidence of degradation products. The retention times of piroxicam, the standard and the piroxicam in the wet kneaded mixture, were the same at 2.85 minutes, while that of indomethacin internal standard was

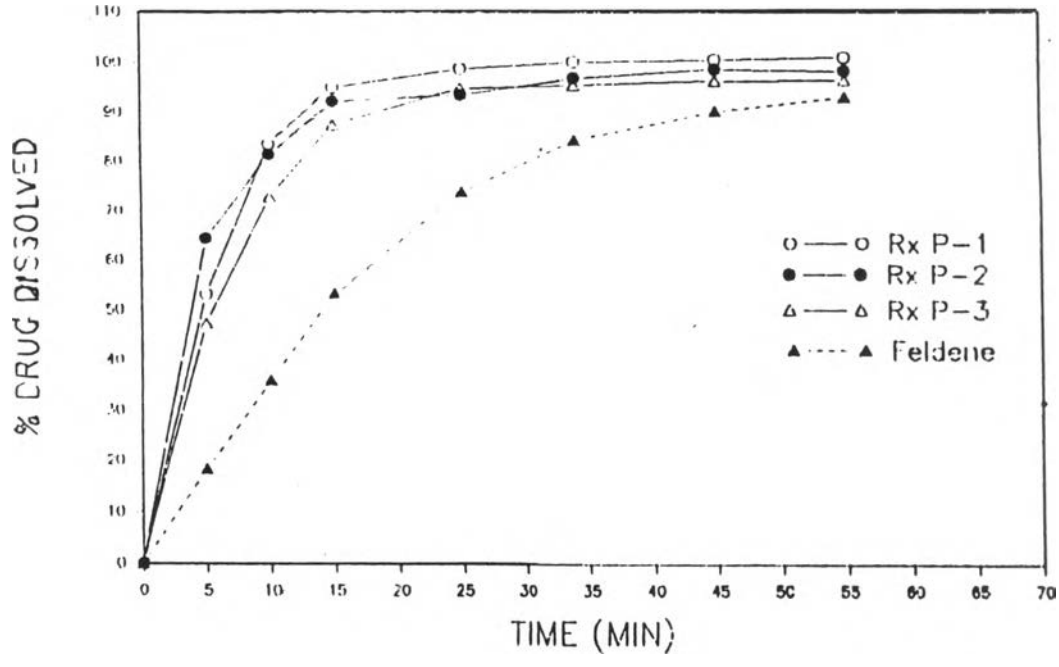


Fig 32 Dissolution profiles of piroxicam tablets (piroxicam from Italy) prepared in the condition of pir: β-cd 1:1 molar ratio, 50 % w/w water, with different kneading times 30, 60 and 90 minutes.

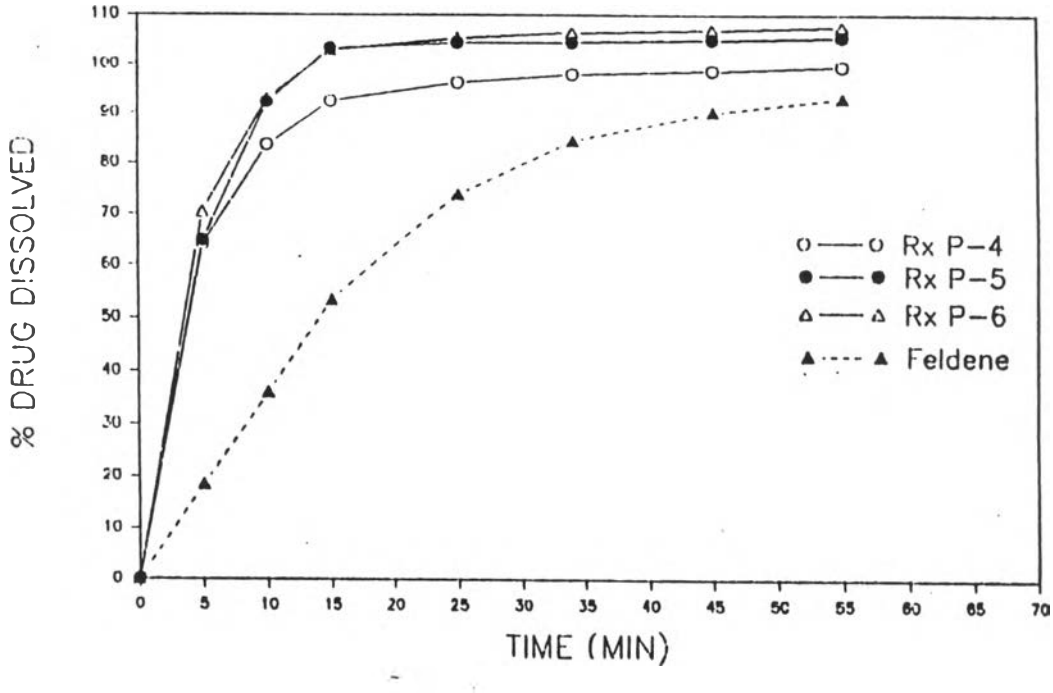


Fig 33 Dissolution profiles of piroxicam tablets (piroxicam from Italy) prepared in the condition of pir : β-cd 1:1 molar ratio, 100 % w/w water, with different kneading times 30, 60 and 90 minutes.

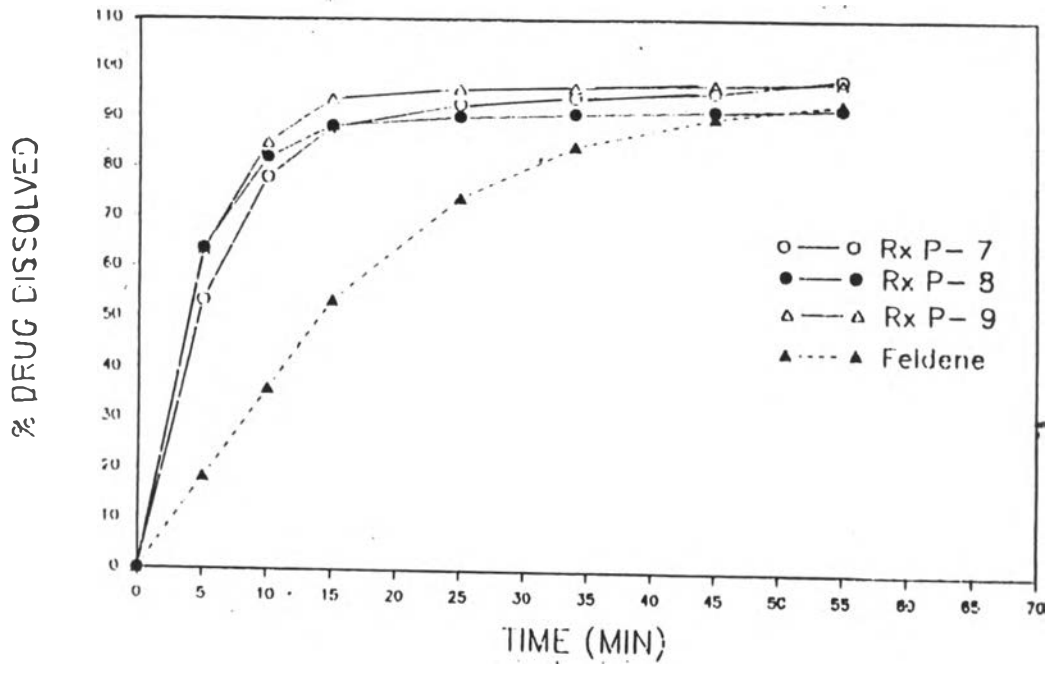


Fig 34 Dissolution profiles of piroxicam tablets (piroxicam from Italy) prepared in the condition of pir: β-cd 1:1 molar ratio, 150 % w/w water, with different kneading times 30, 60 and 90 minutes.

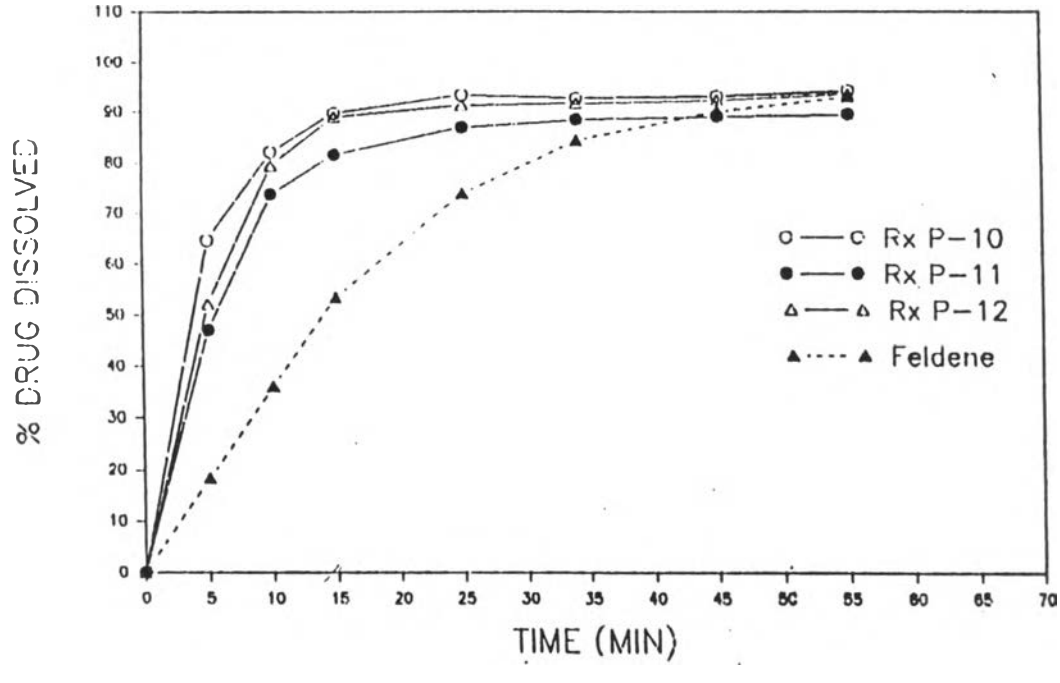


Fig 35 Dissolution profiles of piroxicam tablets (piroxicam from Italy) prepared in the condition of pir: β-cd 1:1 molar ratio, 50, 100, 150 % w/w water, kneaded at water bath 60 °C with different kneading times

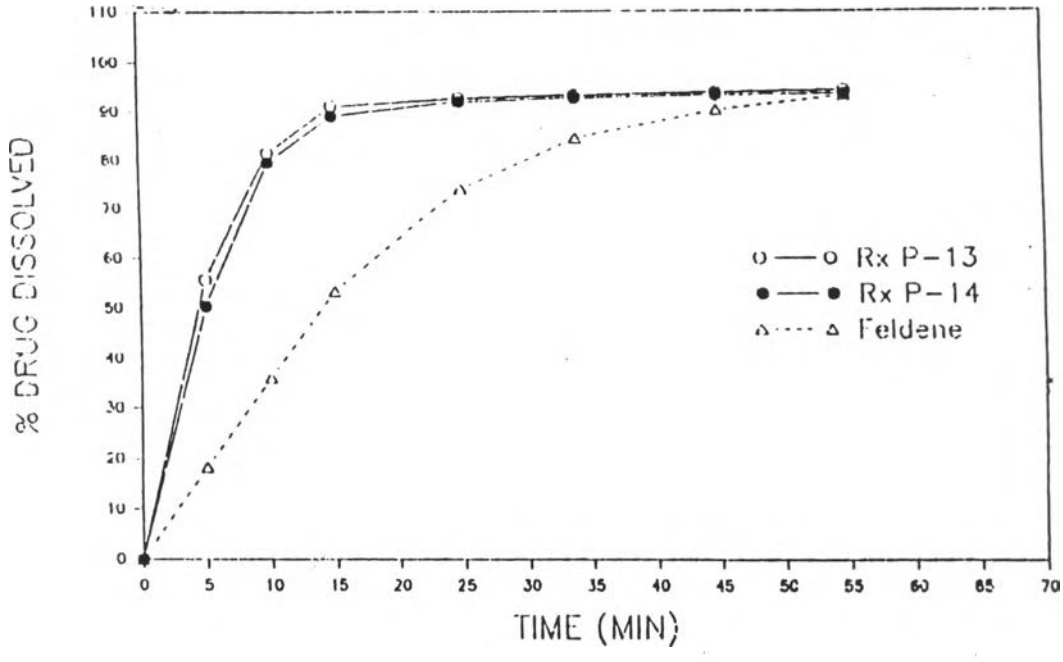


Fig 36 Dissolution profiles of piroxicam tablets (piroxicam from Italy) prepared in the condition of pir : β-cd 1:2 molar ratio, 50 % w/w water,with different kneading times 30 and 60 minutes

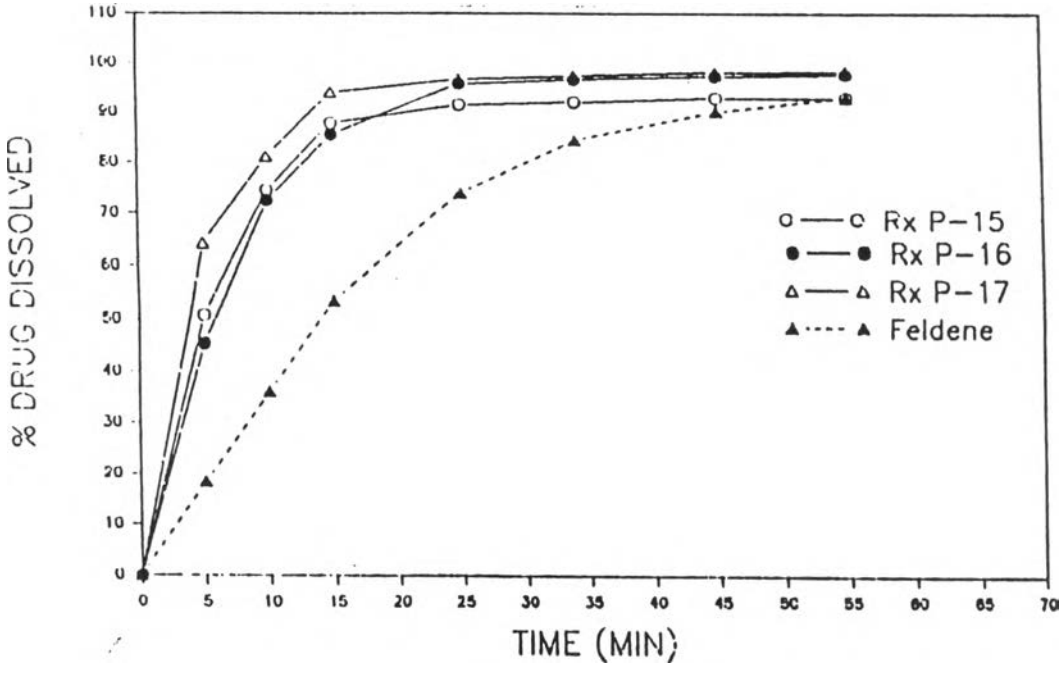


Fig 37 Dissolution profiles of piroxicam tablets (piroxicam from Italy) prepared in the condition of pir : β-cd 1:2 molar ratio, 100 % w/w water,with different kneading times 30, 60 and 90 minutes.

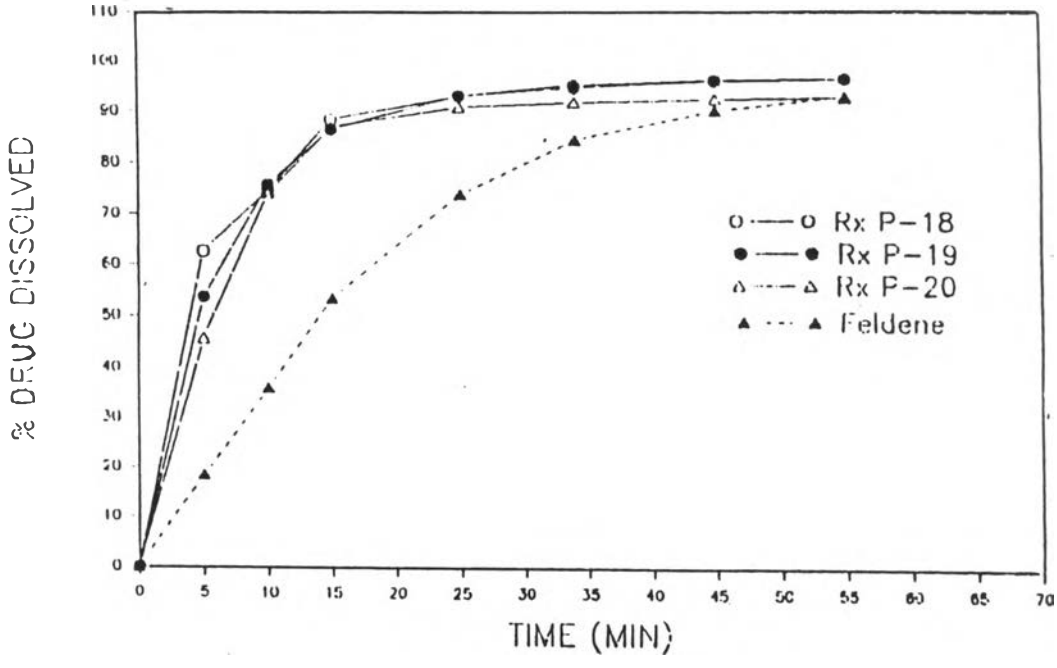


Fig 38 Dissolution profiles of piroxicam tablets (piroxicam from Italy) prepared in the condition of pir : β-cd 1:2 molar ratio, 150 % w/w water with different kneading times 30, 60 and 90 minutes.

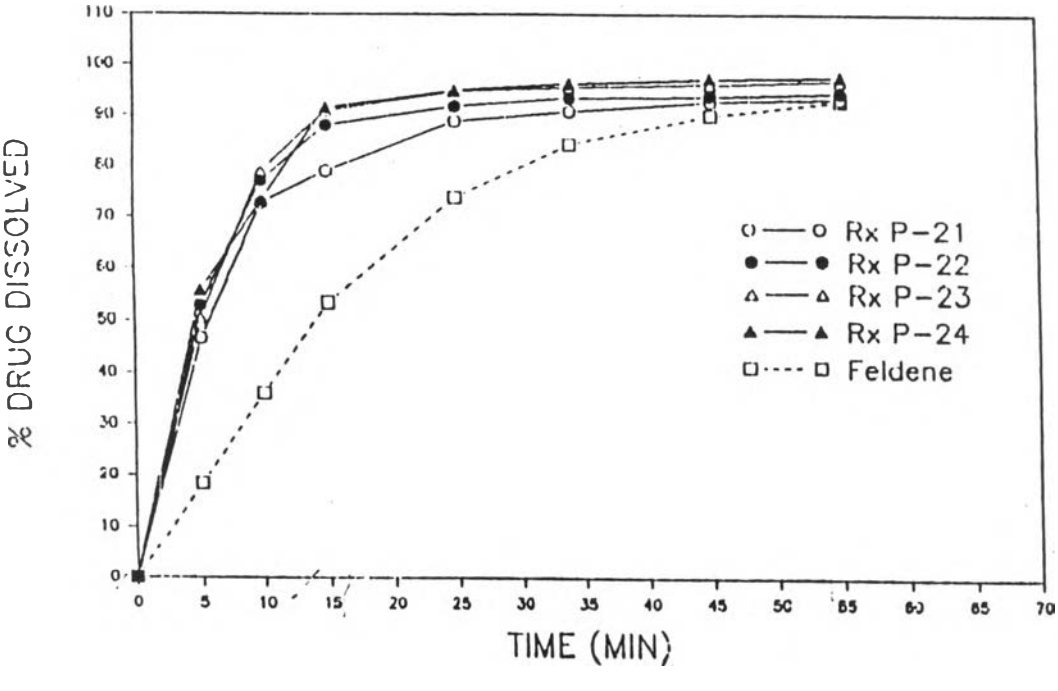


Fig 39 Dissolution profiles of piroxicam tablets (piroxicam from Italy) prepared in the condition of pir: β-cd 1:2 molar ratio, 50, 100 and 150 % w/w water, kneaded at water bath 60°C with different kneading times

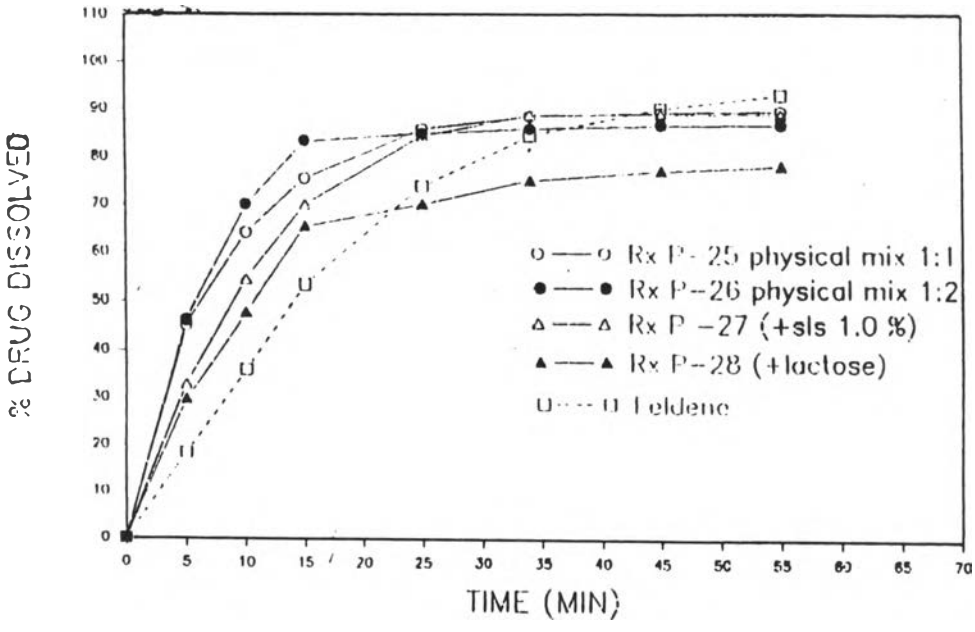


Fig 40 Dissolution profiles of piroxicam tablets (piroxicam from Italy) prepared from the physical mixtures of piroxicam : β-cd 1:1,1:2 molar ratio, 1% w/w sodium lauryl sulfate and mix with starch+lactose

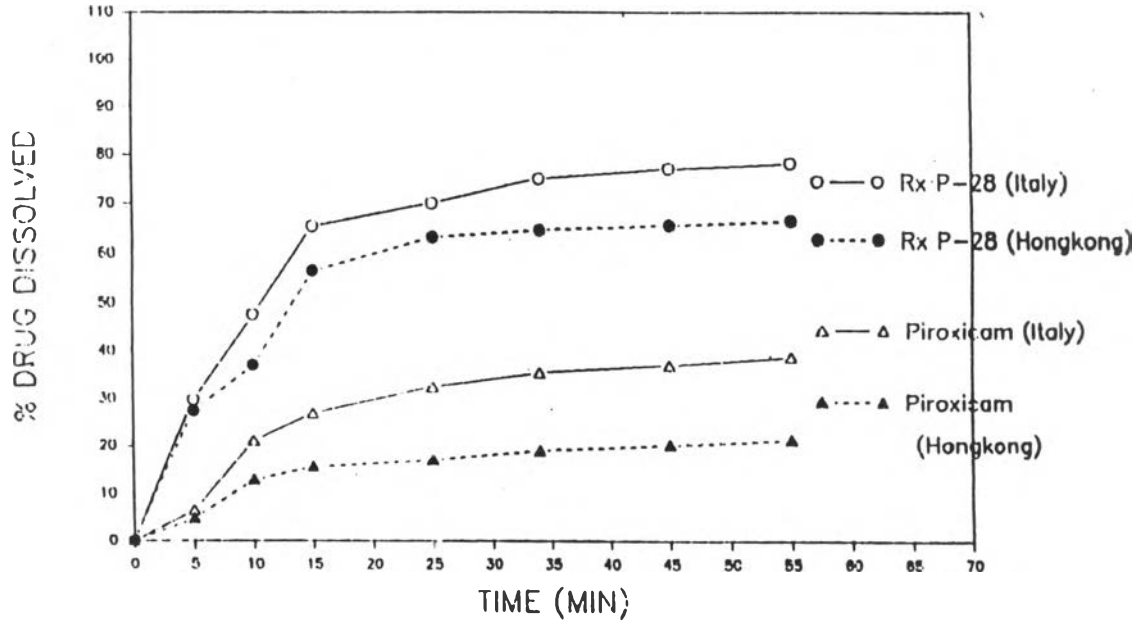


Fig 41 Dissolution profiles of piroxicam tablets (piroxicam from Italy and Hong Kong) using starch+lactose as diluents and piroxicam powder

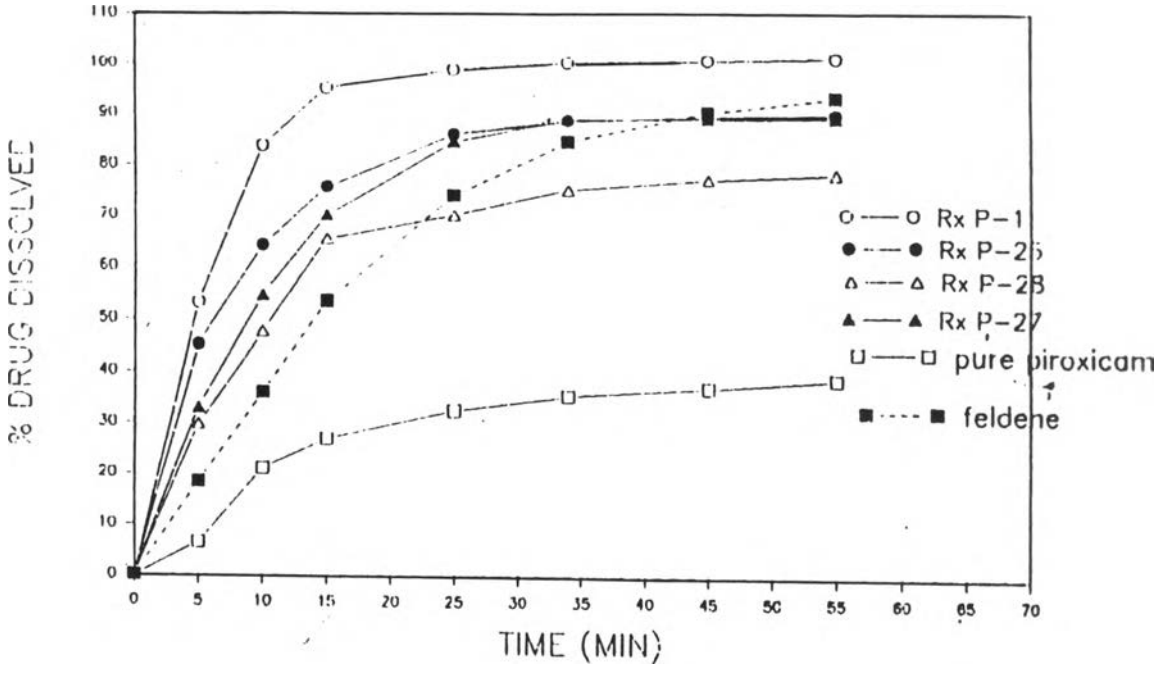


Fig 42 Dissolution profiles of piroxicam tablets.
Comparative plot between wet kneaded mixture 1:1 molar ratio, physical mixture 1:1 molar ratio, mix with starch+lactose and using 1 % w/w sodium lauryl sulfate

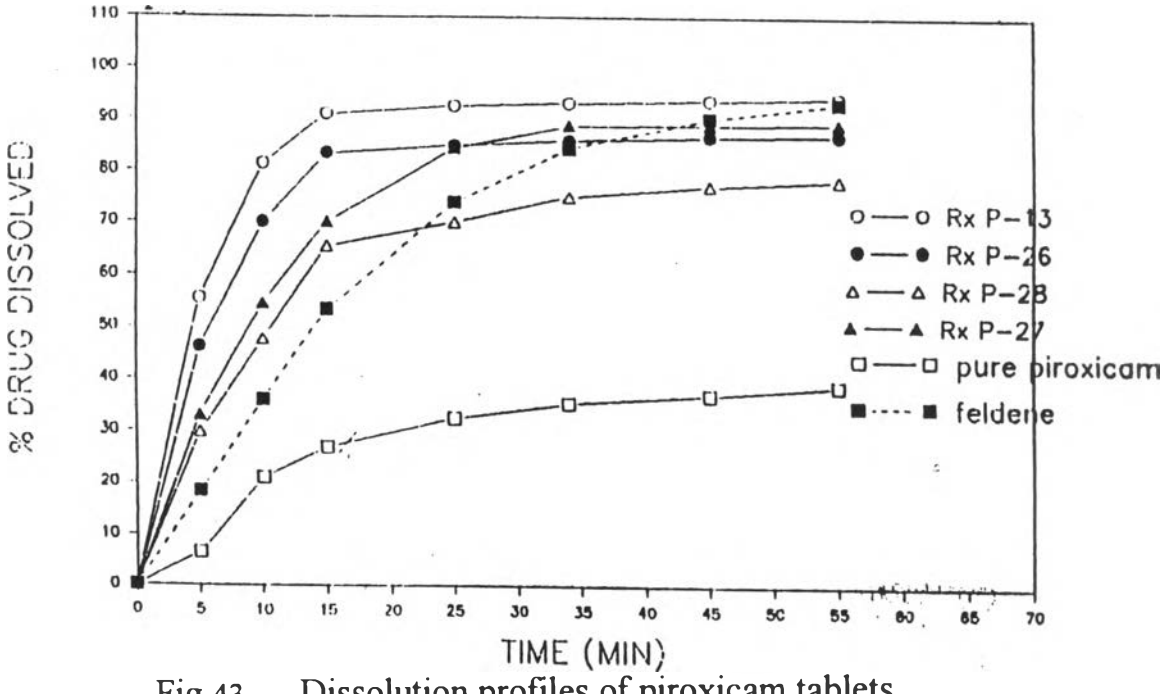


Fig 43 Dissolution profiles of piroxicam tablets.
Comparative plot between wet kneaded mixture 1:2 molar ratio, physical mixture 1:2 molar ratio, mix with starch+lactose and using 1 % w/w sodium lauryl sulfate

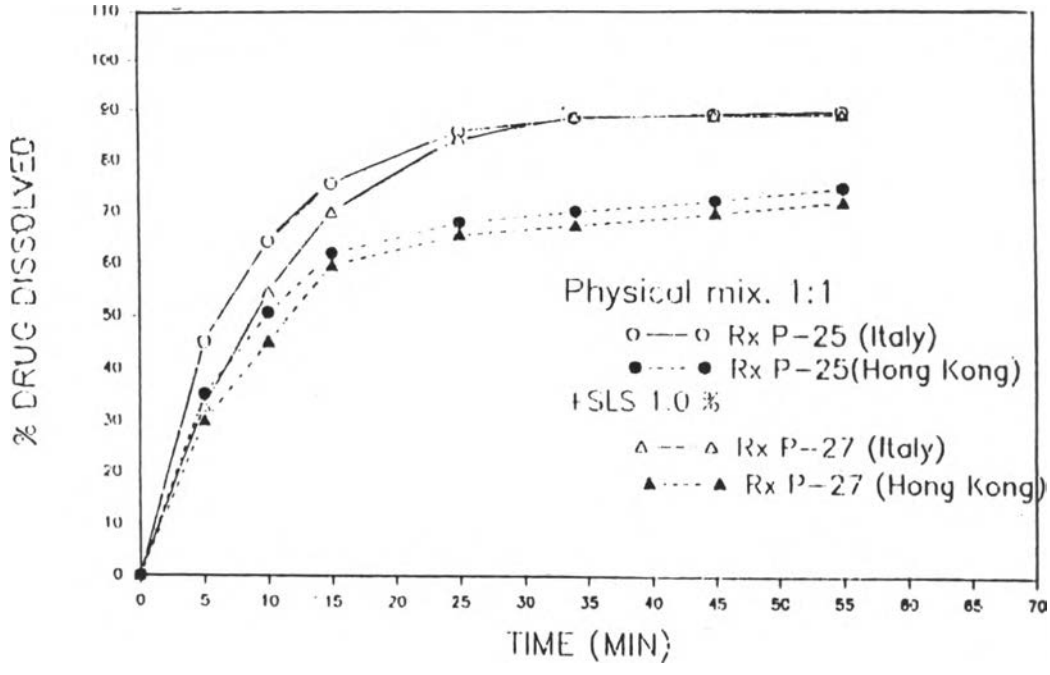


Fig 44 Dissolution profiles of piroxicam tablets (piroxicam from Italy and Hong Kong) prepared in the condition of pir : β-cd 1:1 molar ratio, 50 % w/w water with kneading time 30 minutes

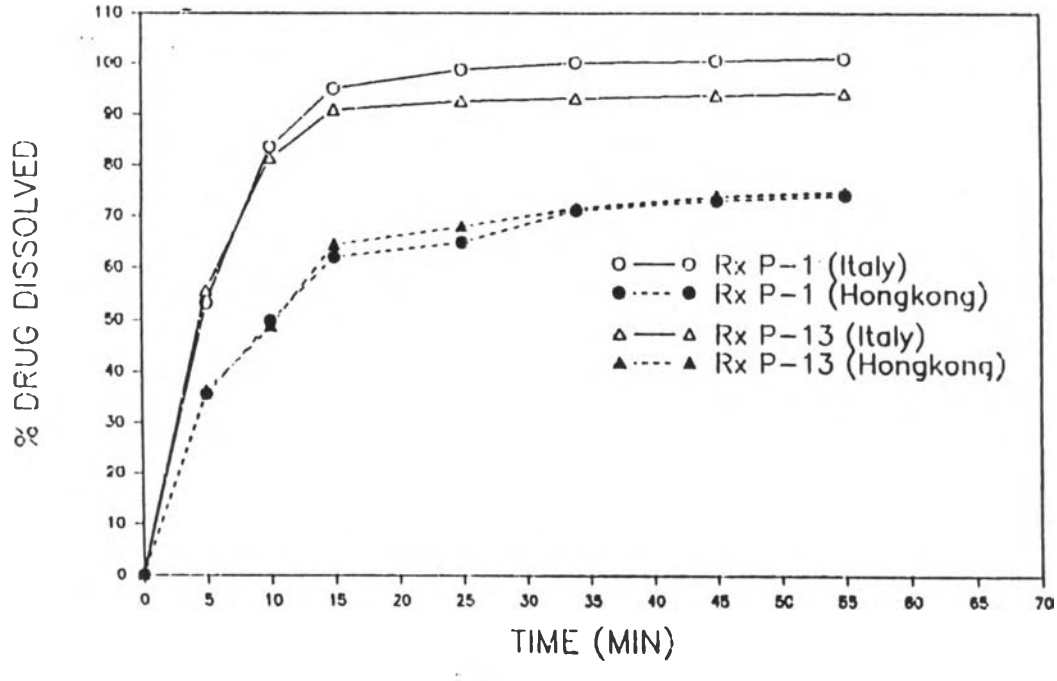


Fig 45 Dissolution profiles of piroxicam tablets (piroxicam from Italy and Hong Kong) prepared in the condition of physical mixture 1:2 molar ratio and using 1 % w/w sodium lauryl sulfate

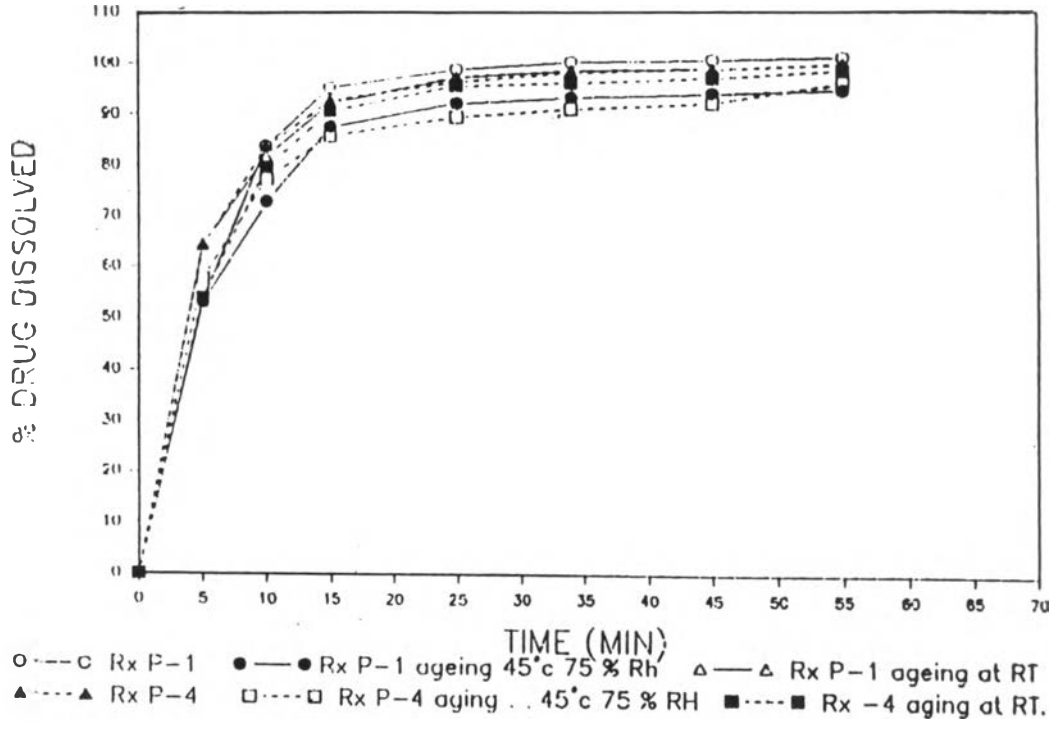


Fig 46 Dissolution profiles of piroxicam tablets (piroxicam from Italy, aging for 3 months (pir : β-cd 1:1 molar ratio, 50 and 100 % w/w water with kneading times 30 minutes.)

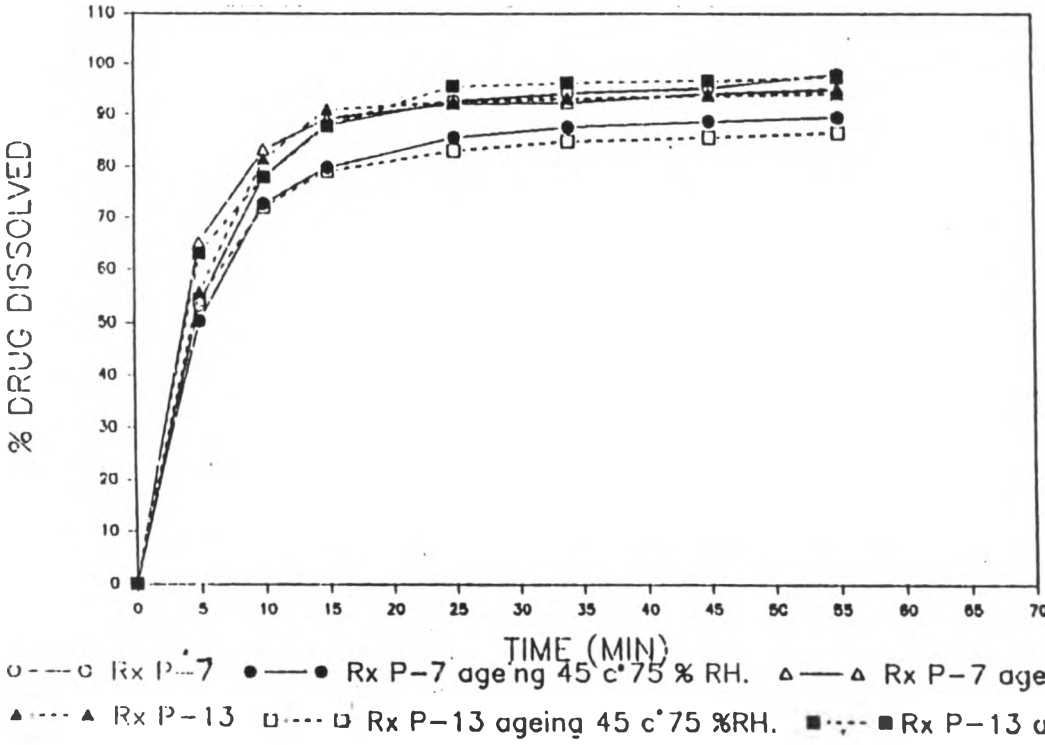


Fig 47 Dissolution profiles of piroxicam tablets (piroxicam from Italy, aging for 3 months, pir:β-cd 1:1 molar ratio, 150 % w/w water, pir:β-cd 1:2 molar ratio, 50 % w/w water with kneading times 30 minutes)

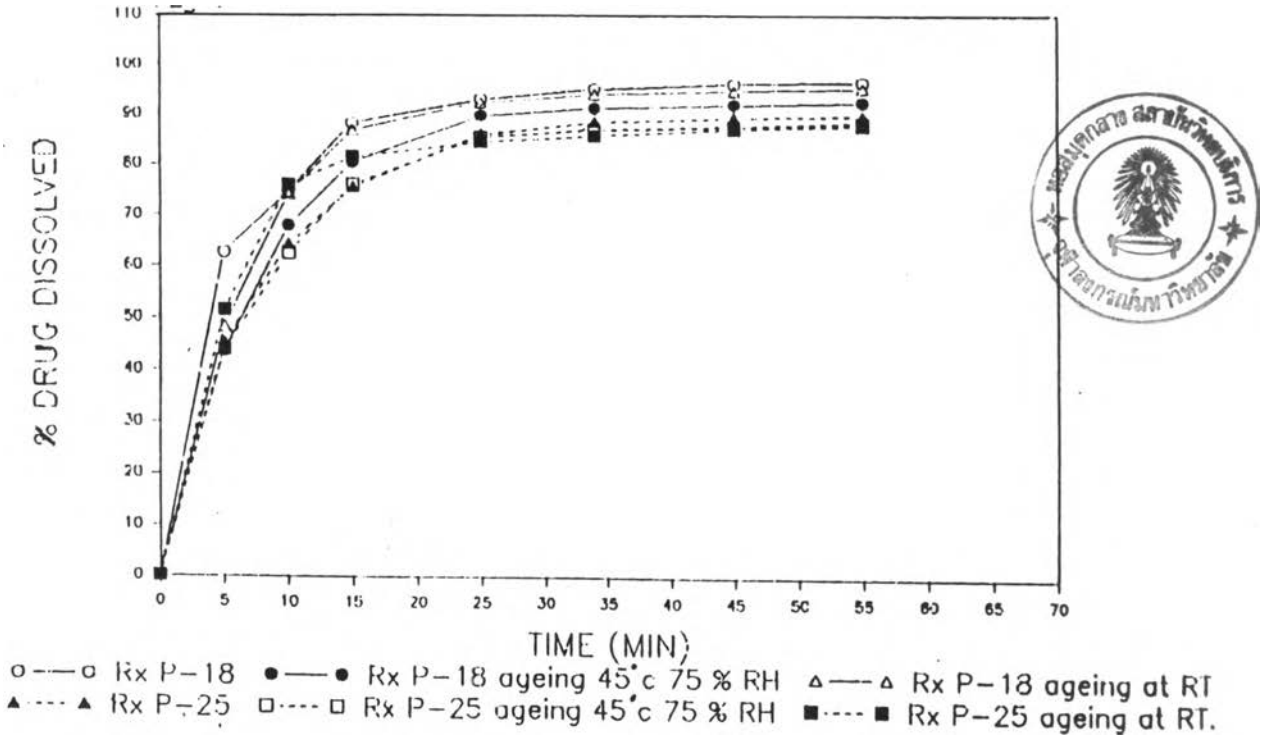


Fig 48 Dissolution profiles of piroxicam tablets (piroxicam from Italy, aging for 3 months, pir:β-cd 1:1 molar ratio, 150 % w/w water, pir:β-cd 1:2 ratio molar, 50 % w/w water with kneading times 30 minutes.)

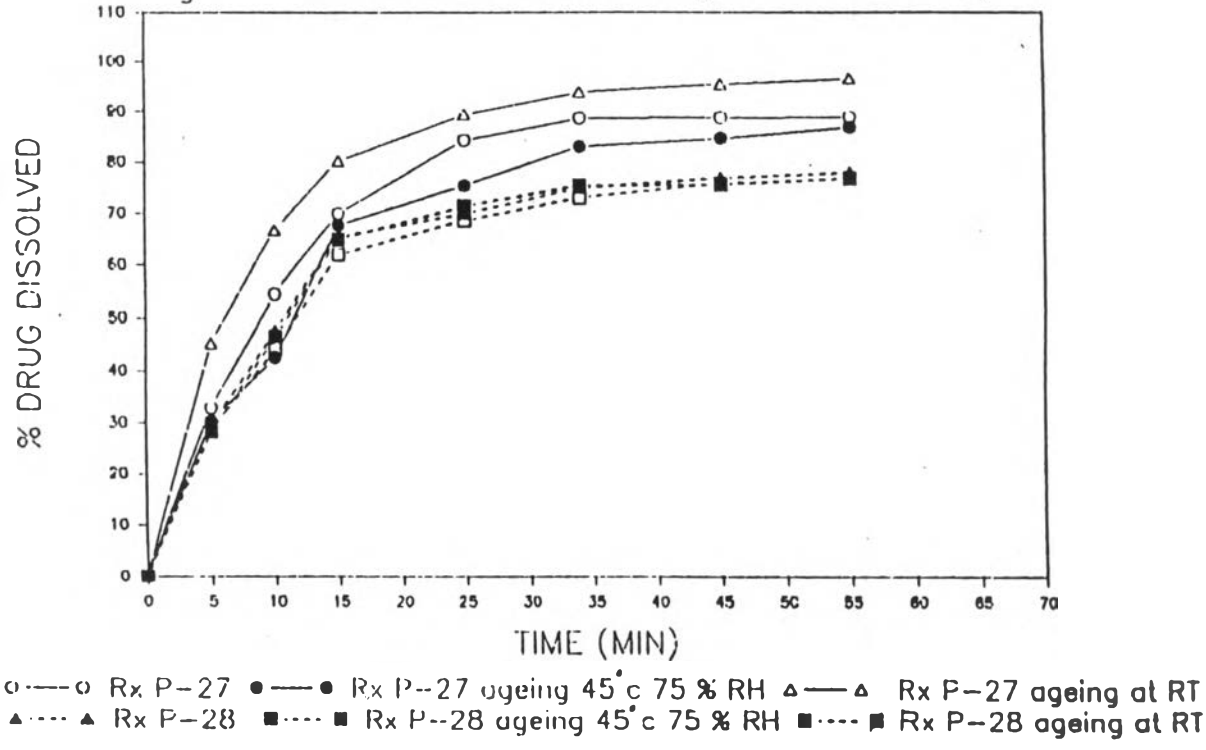


Fig 49 Dissolution profiles of piroxicam tablets (piroxicam from Italy, aging for 3 months, piroxicam mix with 1 % w/w sodium lauryl sulfate and piroxicam mix with starch+lactose

4.79 minutes. The β-cyclodextrin did not interfere with UV absorption of indomethacin at 254 nm. After aging at both room temperature and 45 °C/ 75% relative humidity, the chromatogram showed no traces of degradation products. Under the wet kneading process used in this experimental condition, no appreciable degradation of indomethacin and piroxicam were observed.

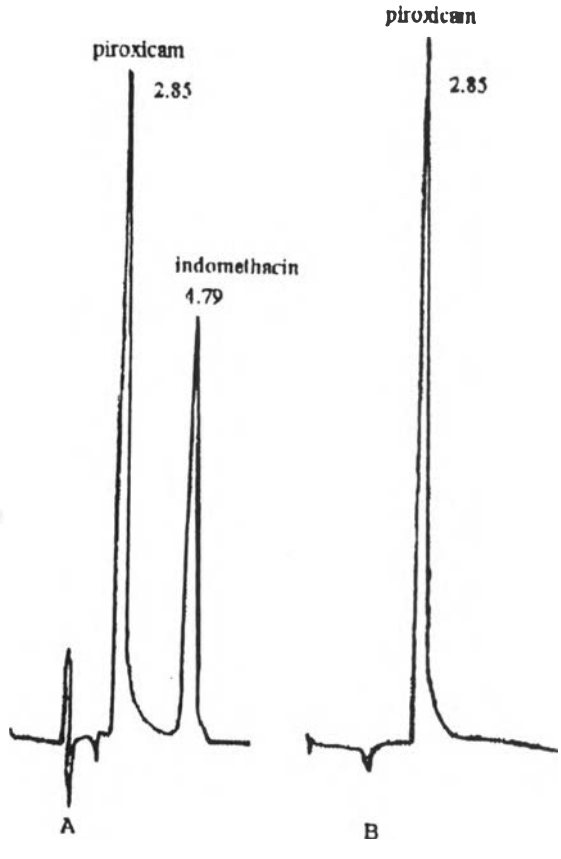


Fig 50 HPLC chromatograms of piroxicam
A piroxicam with indomethacin internal standard
B piroxicam β-cyclodextrin wet kneaded mixture