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APPENDIX

Table 3 Crystal Forms Obtained by Crystallization of Cimetidine by Different Procedures

Solvent	Solute/ Solvent ratio	Conditions*	Crystalline form	Melting Point °C	Characteristic IR bands, cm^{-1}, KBr spectra	Percentage** Yield
acetonitrile	2g/60 ml	1	A	139-142	1205[a], 1155[a], 1020, 800 760	83
water	2g/30 ml	2	B	142-145	1220, 1180[b], 1110, 1050 650	83

*condition 1 : warm to 60°C, set aside at room temperature, collect precipitate after 6 hours

condition 2 : heat to 90°C, set aside at room temperature, collect precipitate after 3-4 weeks

**Mean values from 5 times

(a) Characteristic bands of form A

(b) Sharp band characteristic of form B

Table 4 Relationship Between Content of Cimetidine Polymorph B and Absorbance Ratio at $\frac{1205}{1180}$ in the Standard Mixtures.

content (per cent)	Absorbance Ratio at $\frac{1205}{1180}$*
pure A	3.21 ± 0.40
5.00	2.83 ± 0.30
10.0	2.31 ± 0.28
15.0	1.95 ± 0.02
20.0	1.71 ± 0.02
25.0	1.40 ± 0.01
30.0	1.21 ± 0.03
35.0	1.05 ± 0.04
40.0	0.86 ± 0.02
45.0	0.75 ± 0.01
50.0	0.61 ± 0.01
55.0	0.60 ± 0.01
60.0	0.48 ± 0.01
65.0	0.40 ± 0.01
70.0	0.30 ± 0.01
75.0	0.25 ± 0.01
80.0	0.20 ± 0.02
85.0	0.13 ± 0.02
90.0	0.04 ± 0.01
95.0	0.03 ± 0.01
pure B	0.01 ± 0.01

Mean values of 3 nujol mulls and at least 5 separate runs on a single mull

Table 5 Relationship Between Content of Cimetidine Polymorph B and Absorbance Ratio at $\frac{1205}{1180}$ in Formula I

Content (per cent)	Absorbance Ratio at $\frac{1205}{1180}$*
pure A	4.65 ± 0.60
5.00	3.74 ± 0.23
10.0	2.90 ± 0.30
15.0	2.42 ± 0.09
20.0	2.08 ± 0.04
25.0	1.68 ± 0.03
30.0	1.36 ± 0.04
35.0	1.10 ± 0.02
40.0	0.88 ± 0.02
50.0	0.58 ± 0.03
60.0	0.30 ± 0.02
70...100	could not be calculated

*Mean values of 3 nujol mulls and at least 5 separate runs on a single mull.

Table 6 Precision and Accuracy of Infrared Determination of Cimetidine Polymorph B in the Standard Mixtures

Per cent added / Per cent found*	5.00 % B form		10.0 % B form		15.0 % B form	
	1**	2***	1	2	1	2
1	4.50	4.00	10.0	10.0	15.0	15.0
2	4.00	4.00	9.50	10.0	14.5	15.0
3	5.00	5.00	8.00	8.50	13.5	14.0
4	3.50	3.50	10.0	10.0	15.0	15.0
5	5.00	5.00	9.50	10.0	15.0	15.5
6	5.00	5.00	9.00	9.50	13.5	14.0
7	4.00	3.50	9.00	9.50	14.0	14.0
8	3.50	3.50	10.0	10.0	15.0	15.0
9	5.00	4.50	9.50	10.0	15.0	15.0
10	6.00	5.50	10.5	11.0	16.0	16.0
Mean	4.55	4.35	9.50	9.80	14.6	14.8
SD	0.80	0.75	0.71	0.63	0.78	0.67
RSD, %	17.6	17.2	7.47	6.43	5.34	4.53
relative error, %	-9.00	-13.0	-5.00	-2.00	-2.67	-1.33

*The results represent means of at least 5 separate runs.

**1 The results from the nonlinear standard curve I Fig. 15

***2 The results from the linear standard curve I Fig. 16

Table 7 Precision and Accuracy of Infrared Determination of Cimetidine Polymorph B in Formula I

Per cent added / Per cent found*	5 % B form		10 % B form		15 % B form	
	1**	2***	1	2	1	2
1	4.00	4.50	10.5	10.5	14.0	13.5
2	3.50	4.00	9.50	10.0	14.5	14.0
3	5.00	5.00	9.50	10.0	14.0	13.5
4	6.00	6.00	10.0	10.0	14.5	14.0
5	3.50	4.00	10.0	10.0	15.0	14.0
6	5.00	5.00	11.0	11.0	13.0	13.5
7	4.50	5.00	9.00	9.50	14.0	13.5
8	4.00	4.50	11.0	11.0	14.0	13.5
9	3.50	4.00	10.0	10.0	15.0	14.5
10	5.00	5.00	9.50	10.0	13.0	13.0
Mean	4.40	4.70	10.0	10.2	14.1	13.7
SD	0.84	0.63	0.67	0.48	0.66	0.42
RSD %	19.1	13.4	6.70	4.70	4.68	3.08
relative error %	-12.0	-6.00	-0.0	-2.00	-6.27	-8.66

* The results represent means of at least 5 separate runs

** 1. The results from the nonlinear standard curve II Fig. 19

*** 2. The results from the linear standard curve II Fig. 20.

Table 8 Infrared Determination of Cimetidine Polymorph B Content in the Commercial Raw Materials and Their Respective Tablet Formulations

Source (raw material)	% B found**	Source (tablet)	% B found**
1	0	1	***
2	0	2	***
3	0	3	***
4	0	4	***
5	13.0	5	12.0
6	0	6	***
7	0	7	***
8	0	8	***
9	0	9	***
10	0	10	***

*

**Mean values of 3 nujol mulls and at least 5 separate runs on a single mull.

***No band appeared at 1180 cm^{-1}

Table 9 Infrared Determination of Cimetidine Polymorph B Content in the Experimentally Formulated Tablets

Determination	formular II % found*	formula III % found*
1	10.5	10.0
2	10.0	11.0
3	10.0	10.0

*The results represent means of at least 5 separate runs

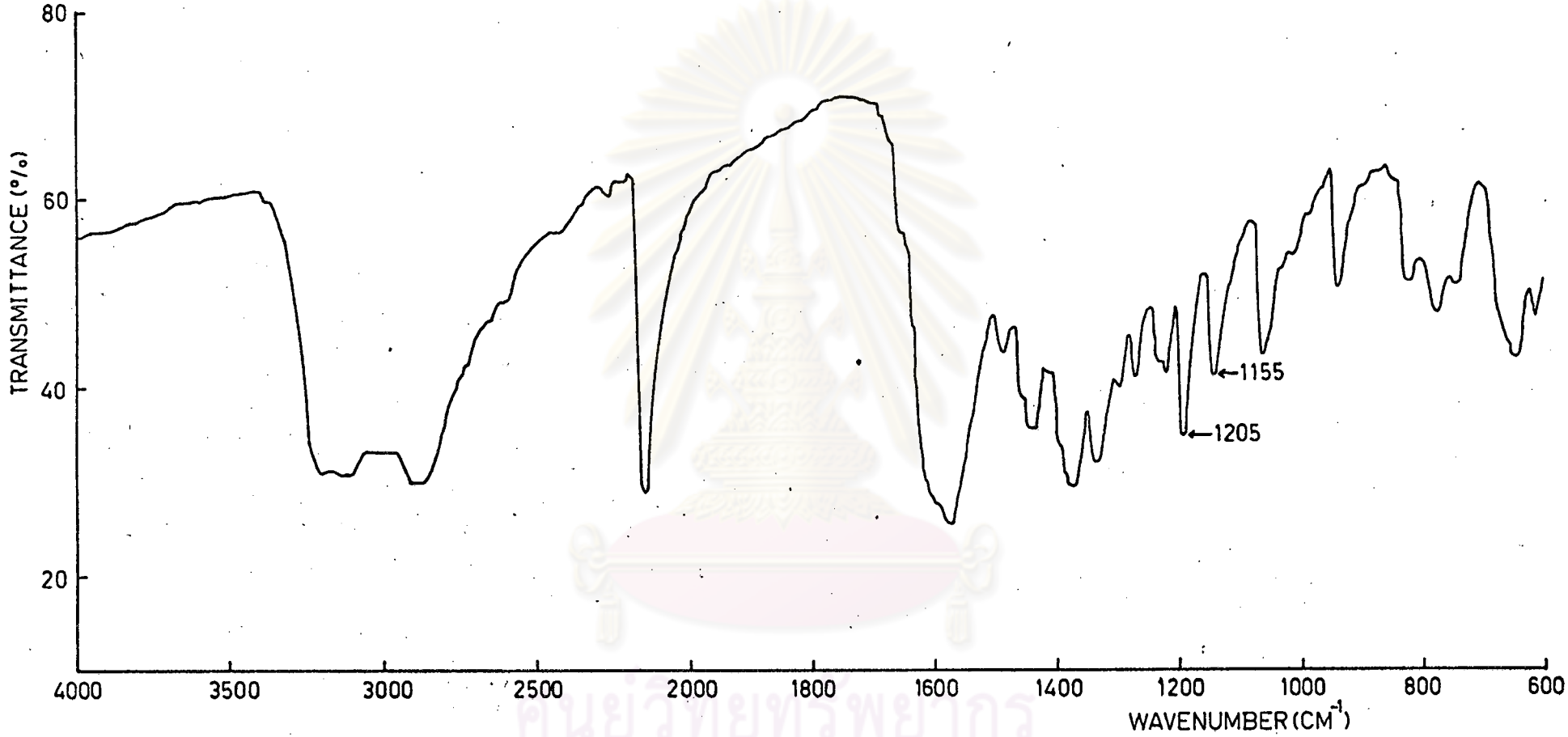

Fig. 6(a) The IR spectrum of crystalline polymorph A (Potassium bromide disc)

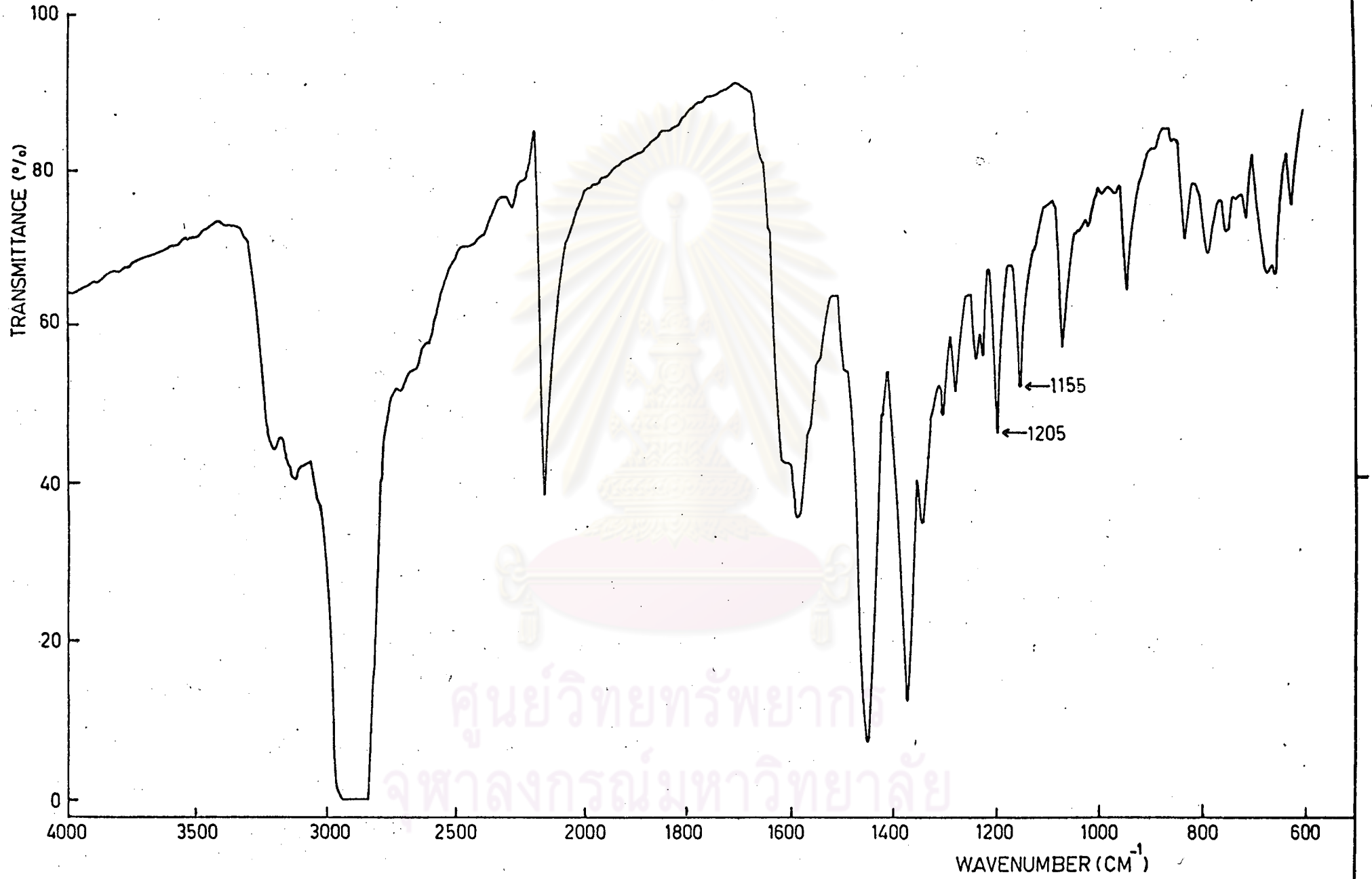

Fig. 6(b) The IR spectrum of crystalline polymorph A (nujol mull)

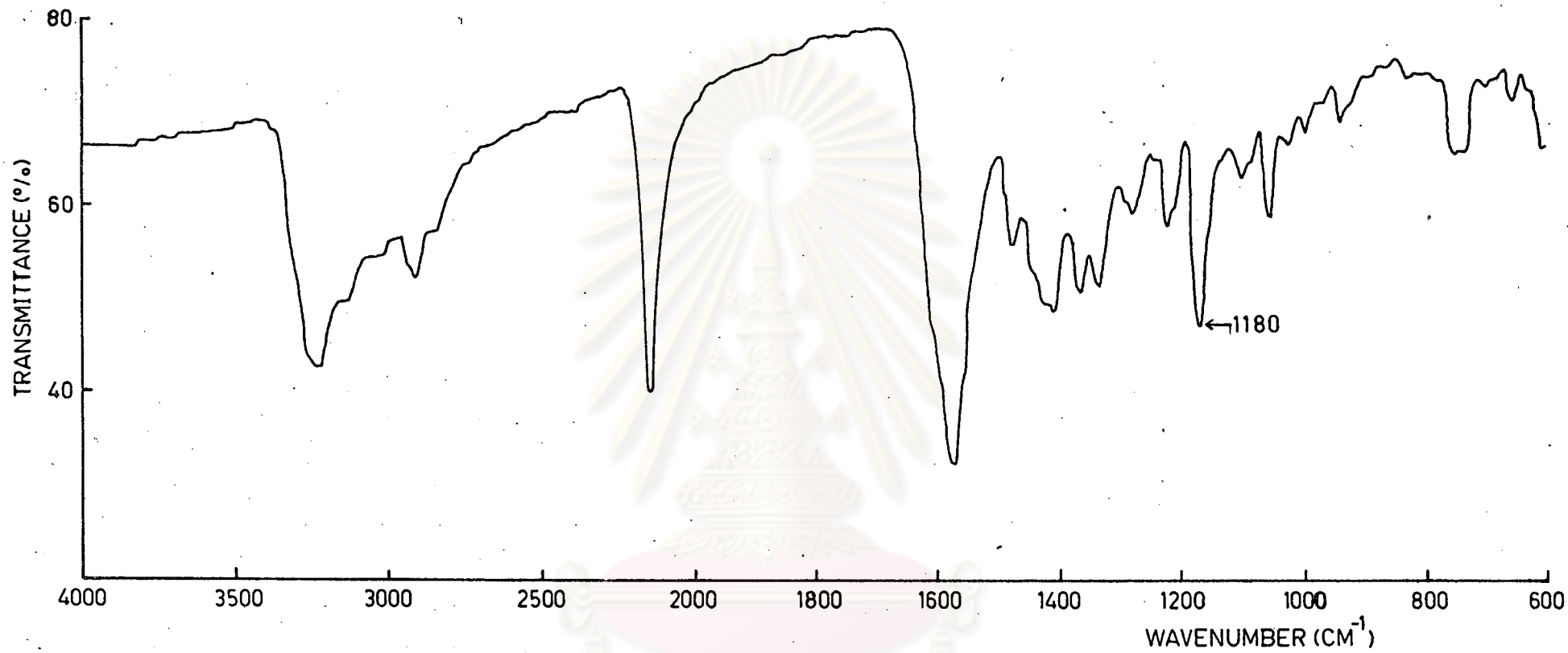

Fig. 7(a) The IR spectrum of crystalline polymorph B (potassium bromide disc)

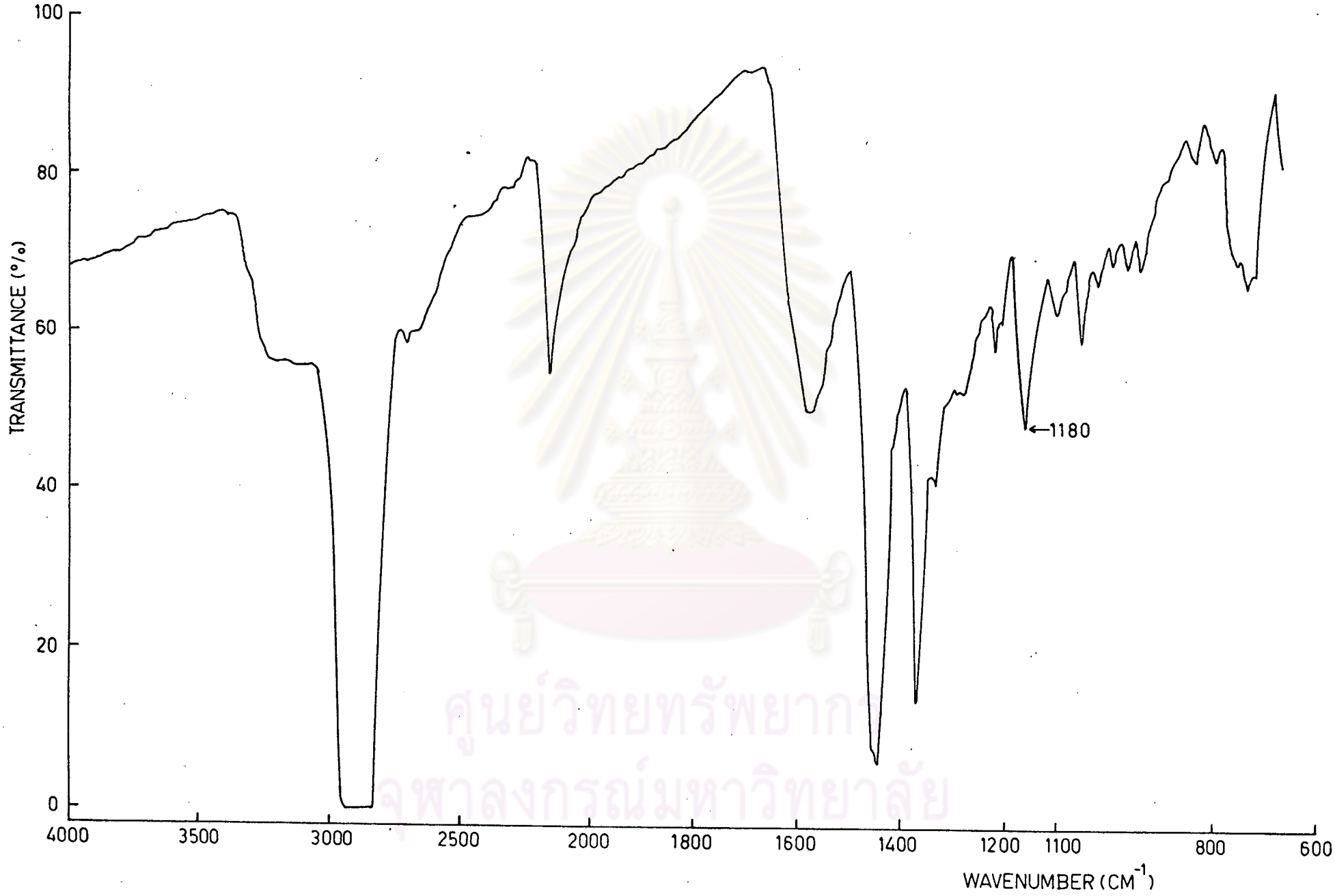

Fig.. 7(b) The IR spectrum of crystalline polymorph B (nujol mull)

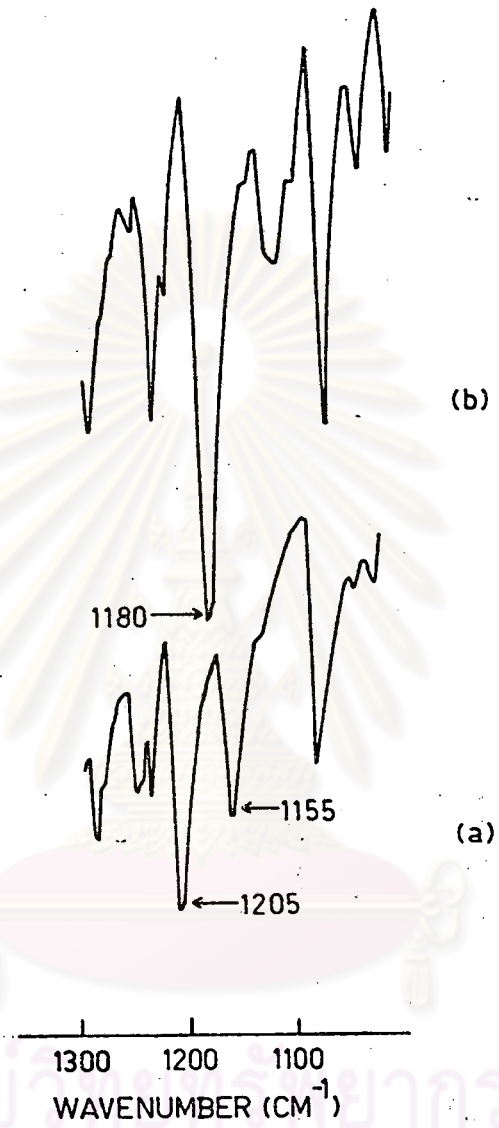

Fig. 8 The IR spectra of cimetidine polymorphs A(a) and B(b) in the range of 1300 to 1000 cm^{-1} in nujol

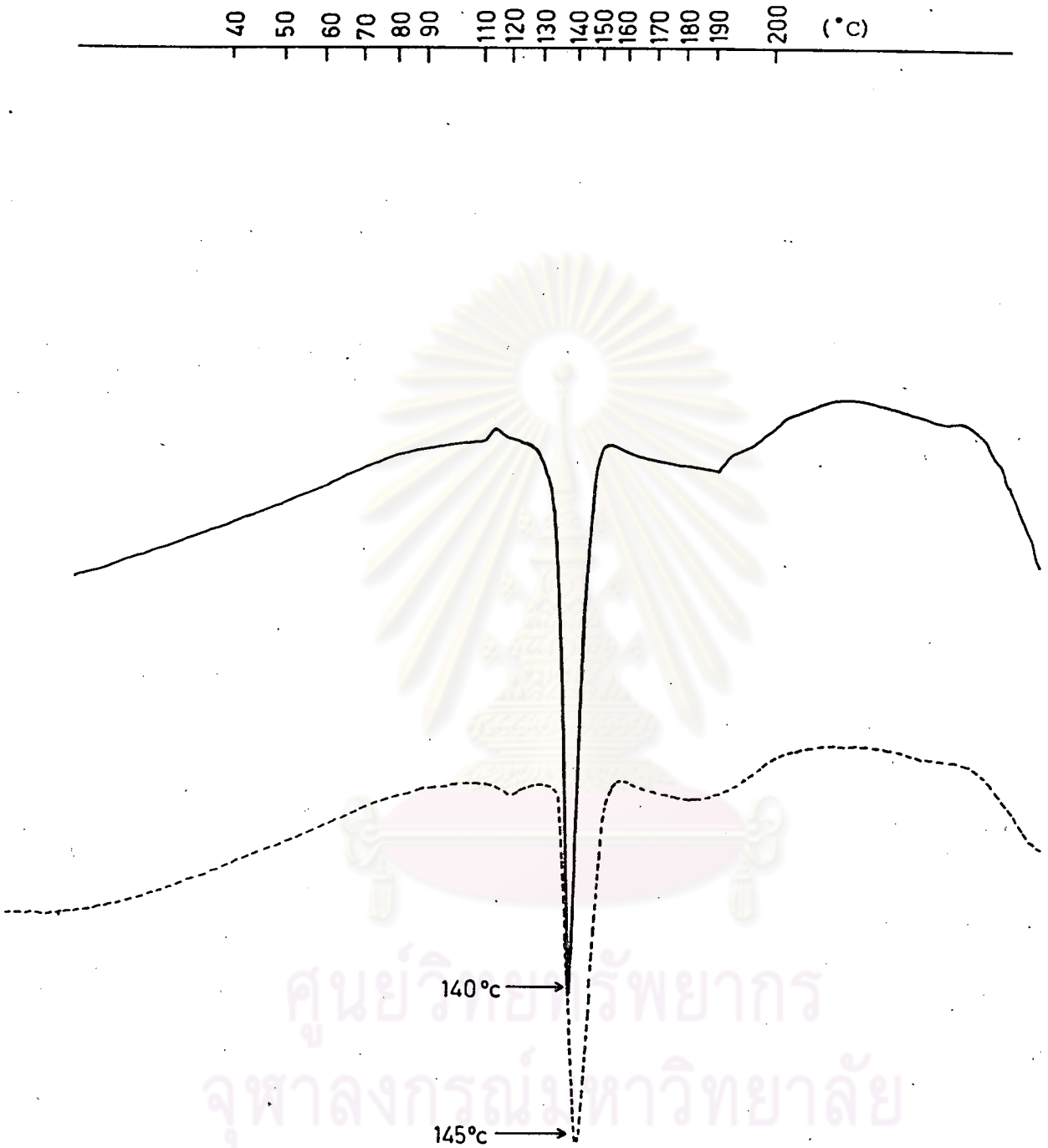

Fig. 9 Differential thermal analysis (DTA) curves of cimetidine forms A(-) and B(....)
Atmosphere air, seal cell

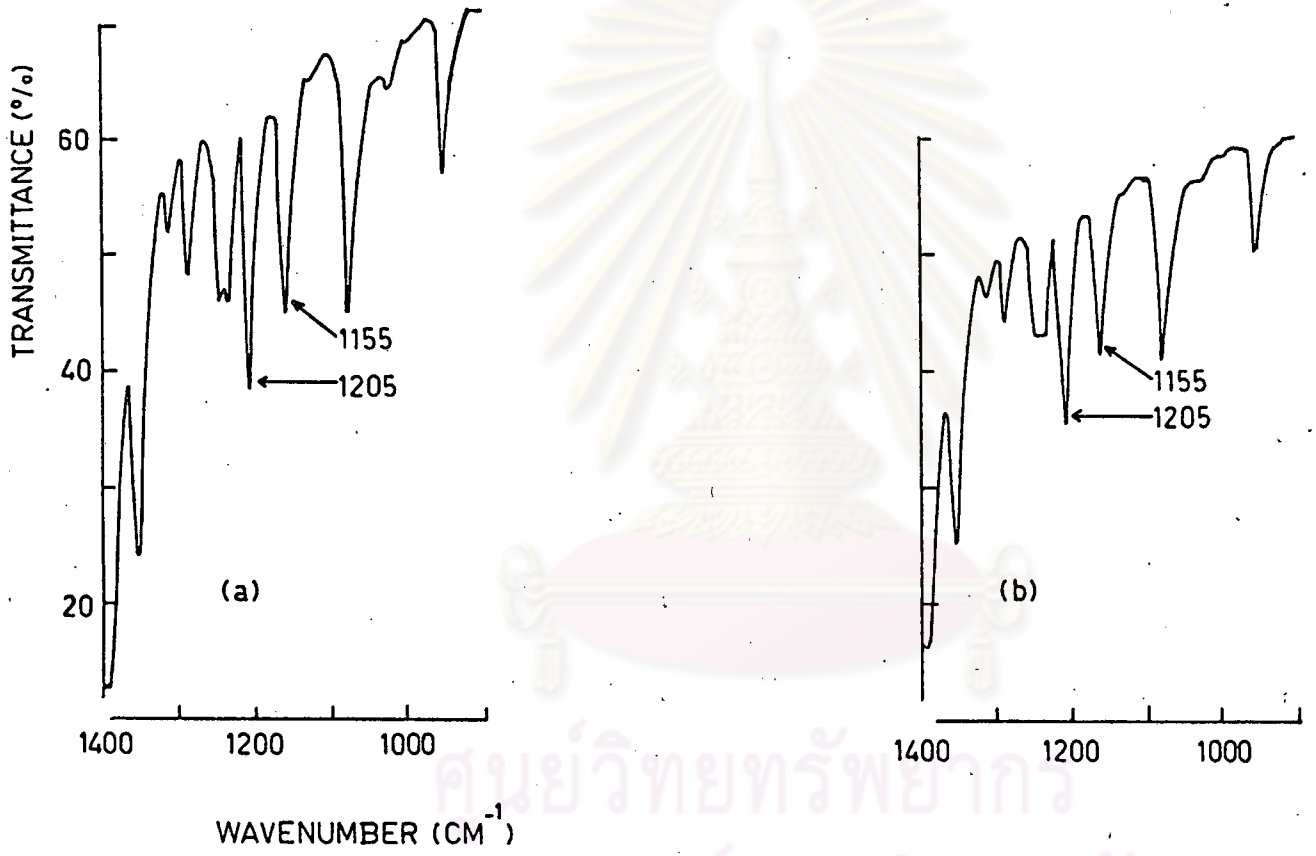

Fig. 10 The IR spectra of polymorph A during the manual grinding in an agate mortar (potassium bromide disc)

(a) 1 minute (b) 10 minutes

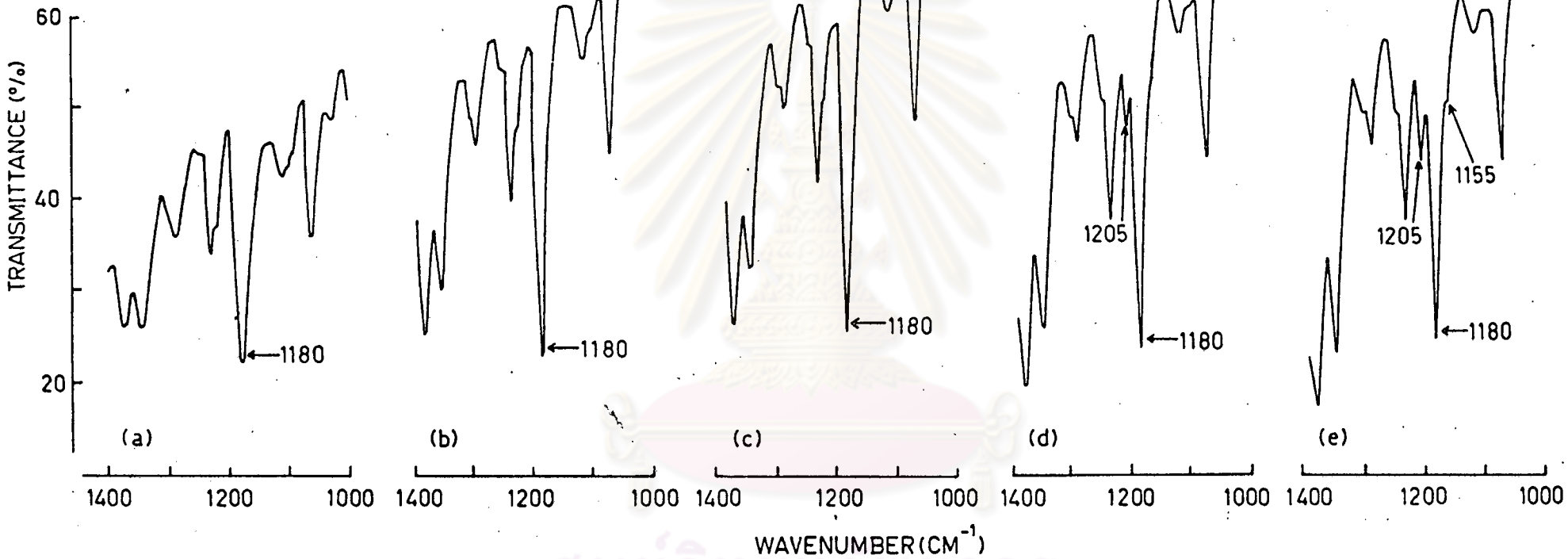

Fig. 11 The IR spectra of polymorph B during the manual grinding in an agate mortar (potassium bromide disc)

(a) 1 minute (b) 3 minutes (c) 5 minutes

(d) 7 minutes (e) 10 minutes

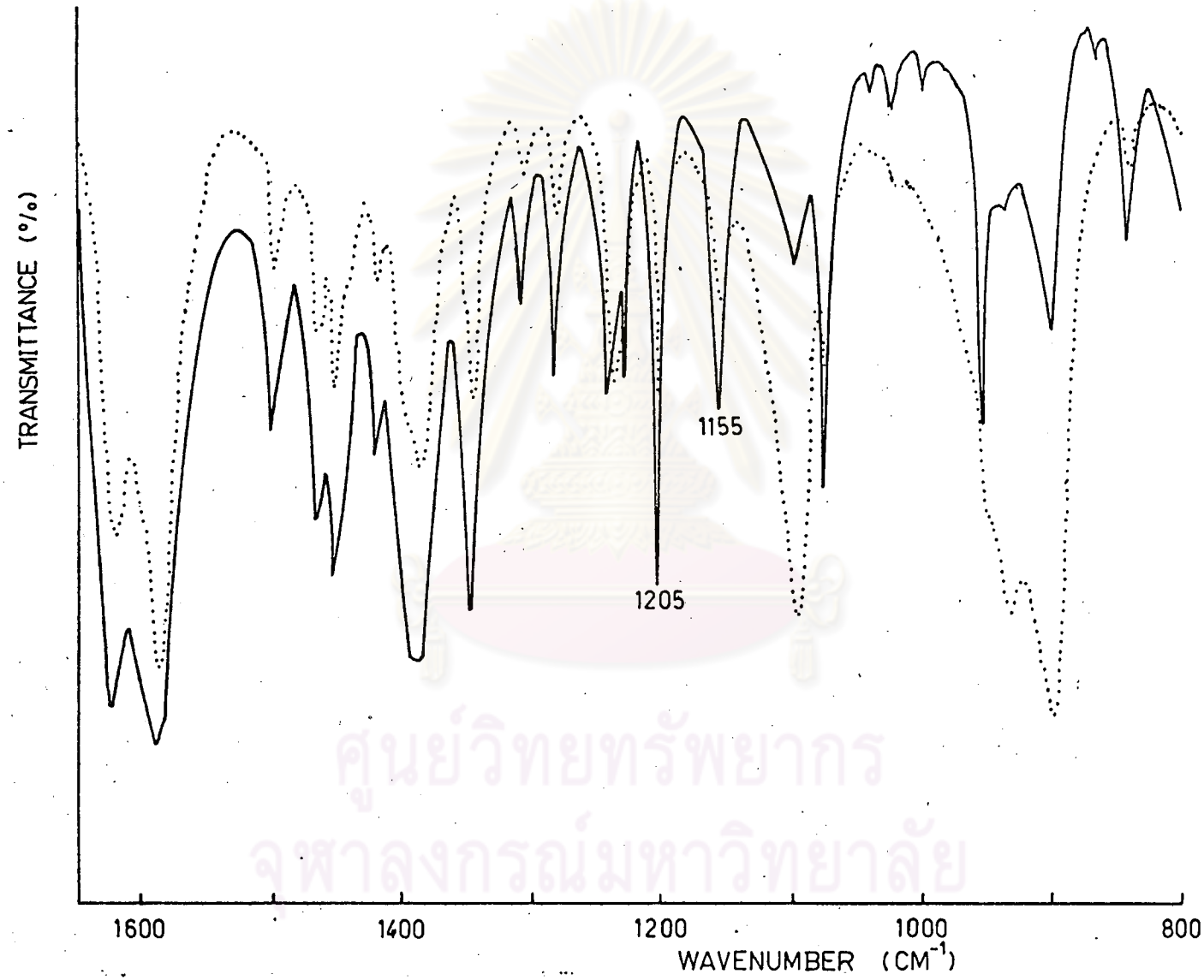

Fig. 12 The IR spectra of polymorph A during grinding in the vibration grinder (potassium bromide disc)
(——) 1 minute (.....) 4 minutes

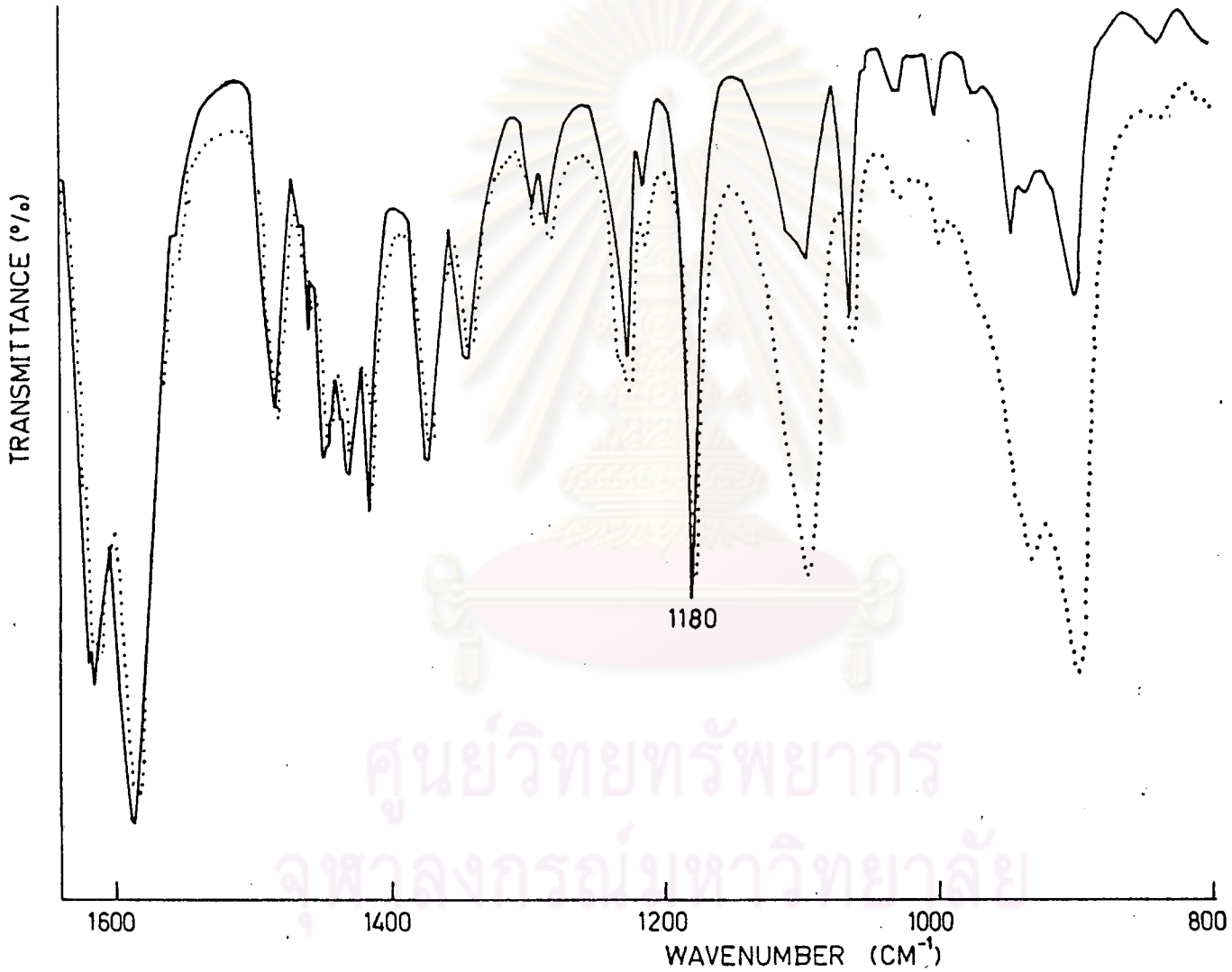

Fig. 13 The IR spectra of polymorph B during grinding in vibration grinder (potassium bromide disc)

(—) 1 minute, (....) 4 minutes

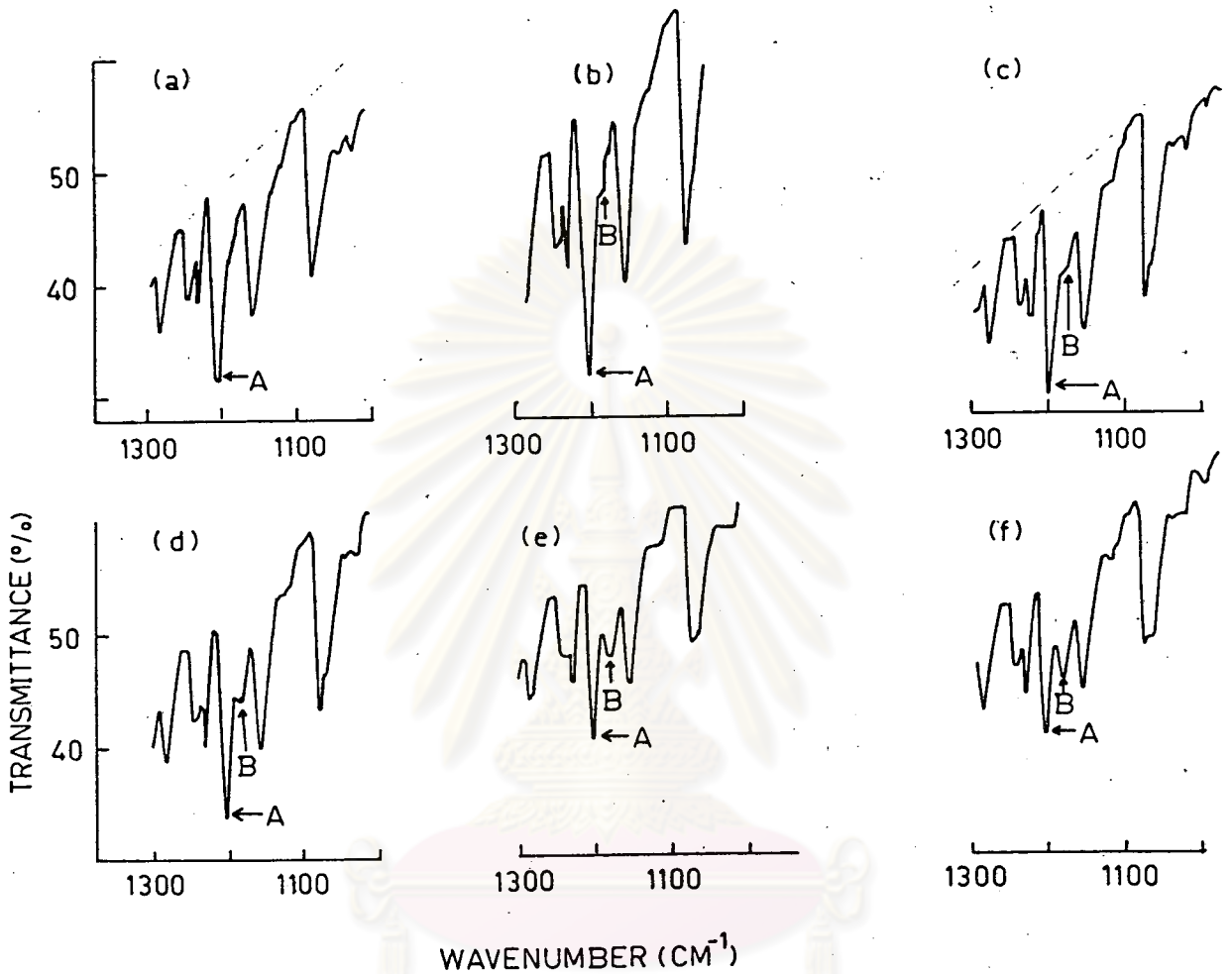

Fig. 14 The IR spectra of cimetidine polymorphs A and B and their mixtures in the range of 1300-1000 cm^{-1}, in nujol
The bands at 1205 cm^{-1} (form A) and 1180 cm^{-1} (form B) are marked with arrows.

(a) pure A (b) B 5.00 % (c) B 10.0 %

(d) B 15.0 % (e) B 20.0 % (f) B 25.0 %

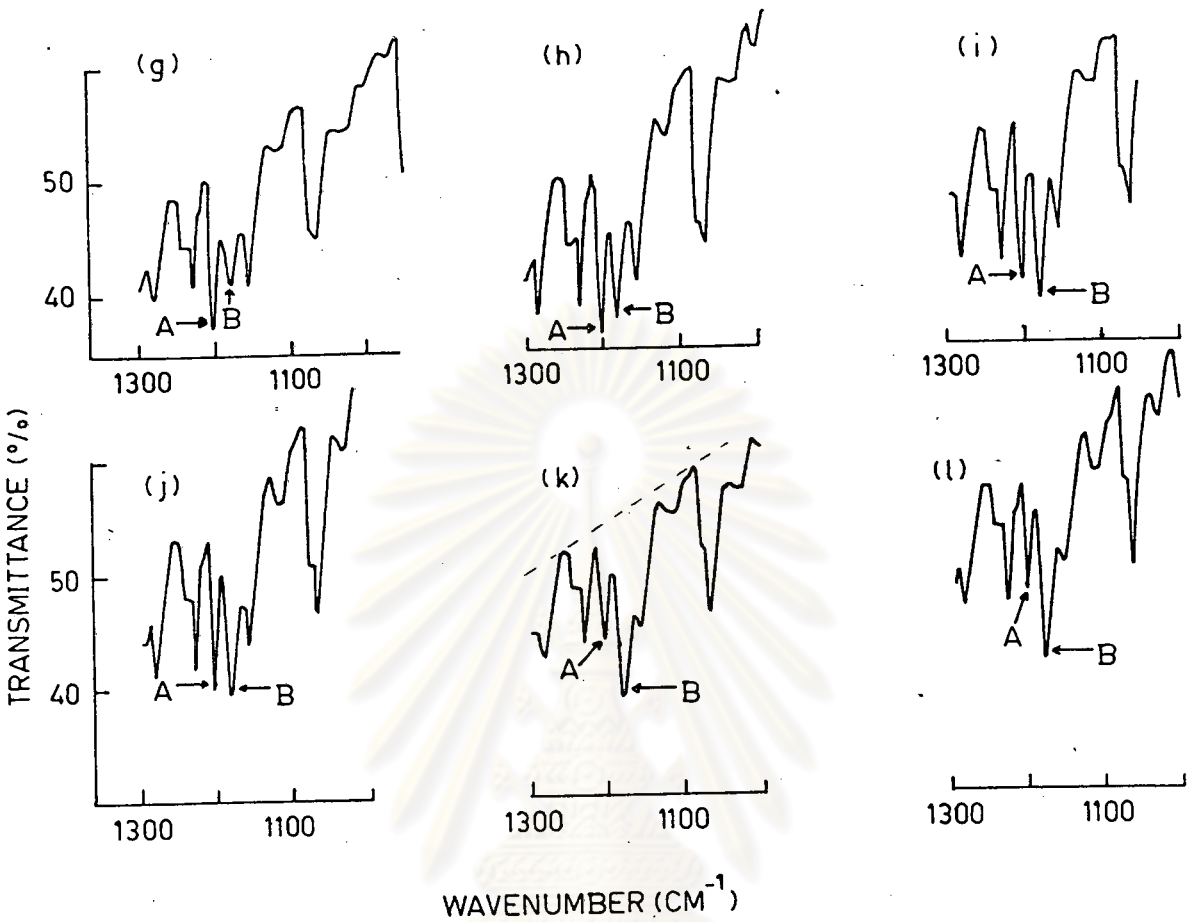

Fig. 14 (continue) The IR spectra of cimetidine polymorphs A and B and their mixtures in the range of 1300-1000 cm^{-1}, in nujol The bands at 1205 cm^{-1} (form A) and 1180 cm^{-1} (form B) are marked with arrows.

(g) B 30.0 % (h) B 35.0 % (i) B 40.0 %

(j) B 45.0 % (k) B 50.0 % (l) B 55.0 %

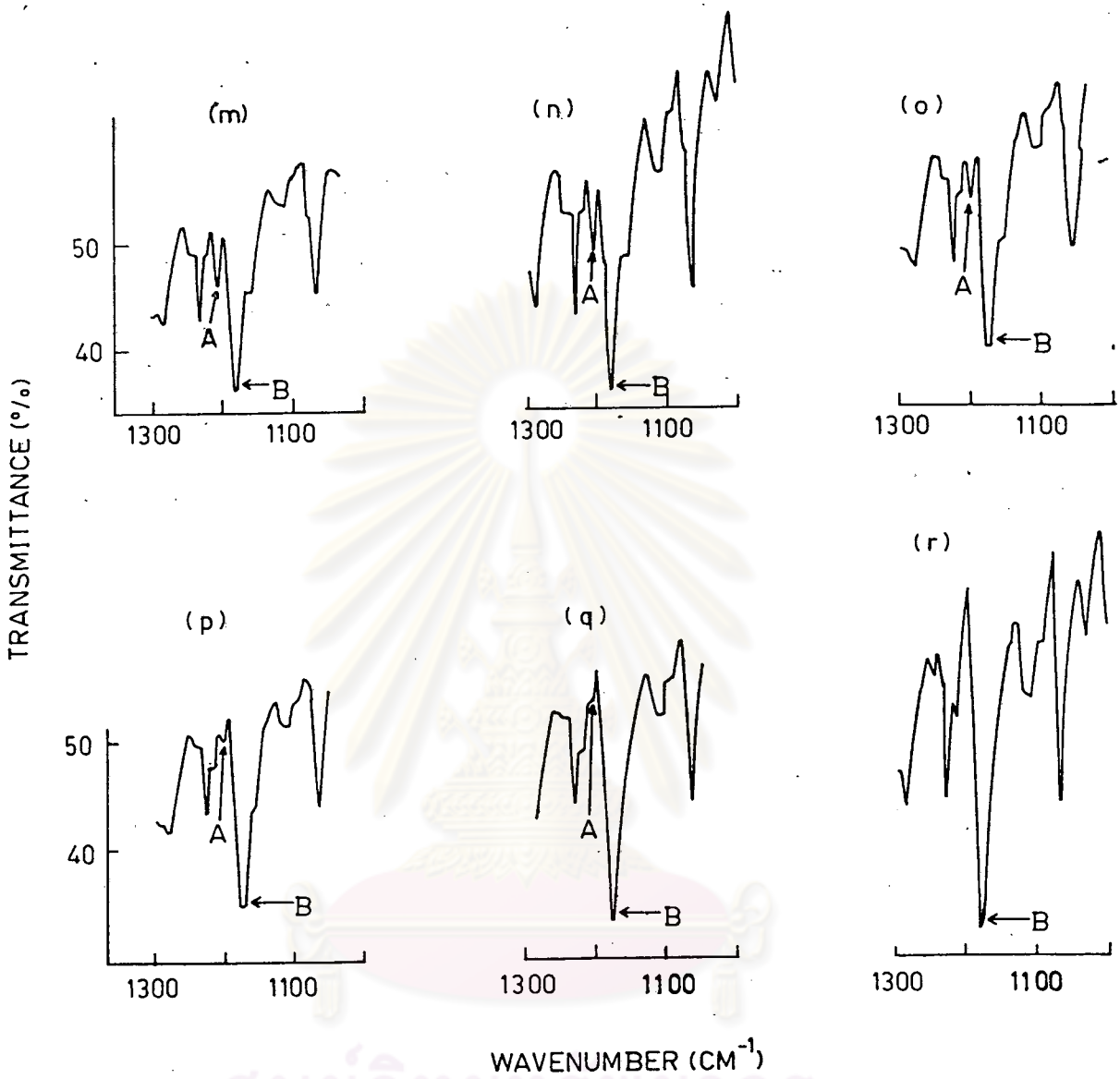

Fig. 14 (continue) The IR spectra of cimetidine polymorphs A and B and their mixtures in the range of 1300-1000 cm^{-1}, in nujol The bands at 1205 cm^{-1} (form A) and 1180 cm^{-1} (form B) are marked with arrows.

(m) B 60 % (n) B 65 % (o) B 70 %

(p) B 80 % (q) B 90 % (r) pure B

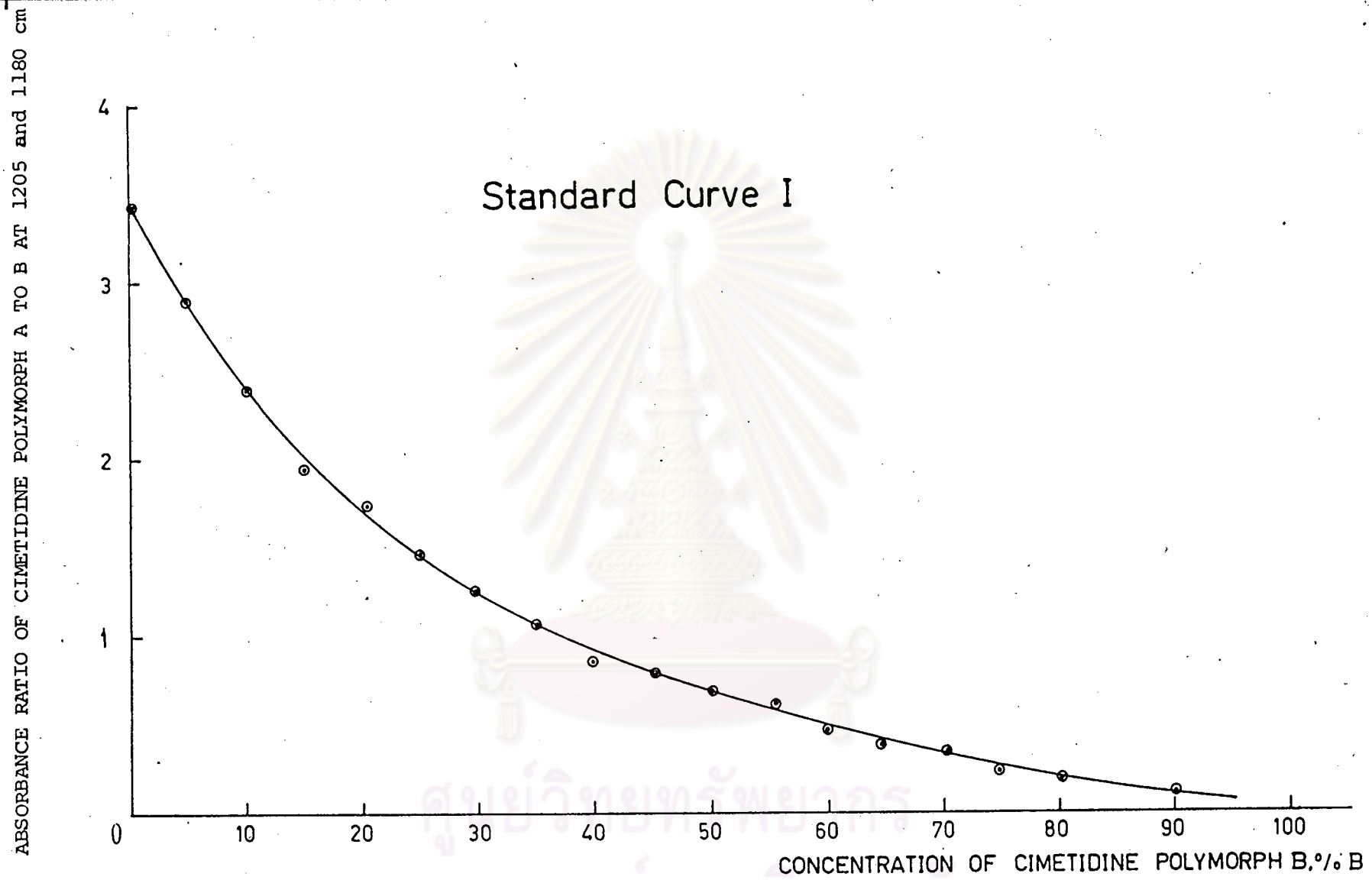

Fig. 15 Absorbance ratios of cimetidine polymorph A to polymorph B versus the contents of polymorph B in the mixtures (nujol mull technique)

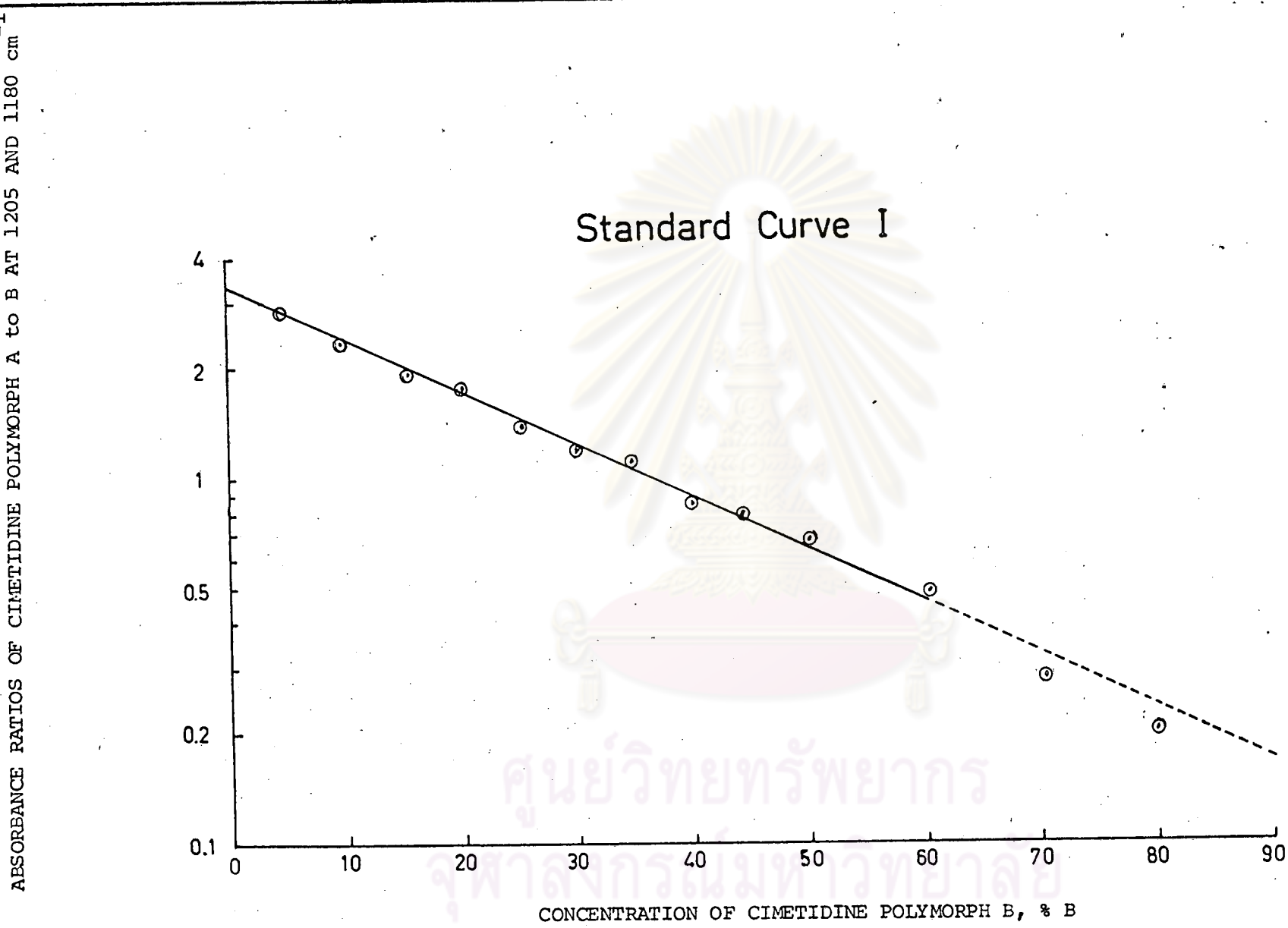

Fig. 16 The natural logarithm of the absorbance ratios of cimetidine polymorph A to polymorph B versus the contents of polymorph B in the mixtures (nujol mull technique)

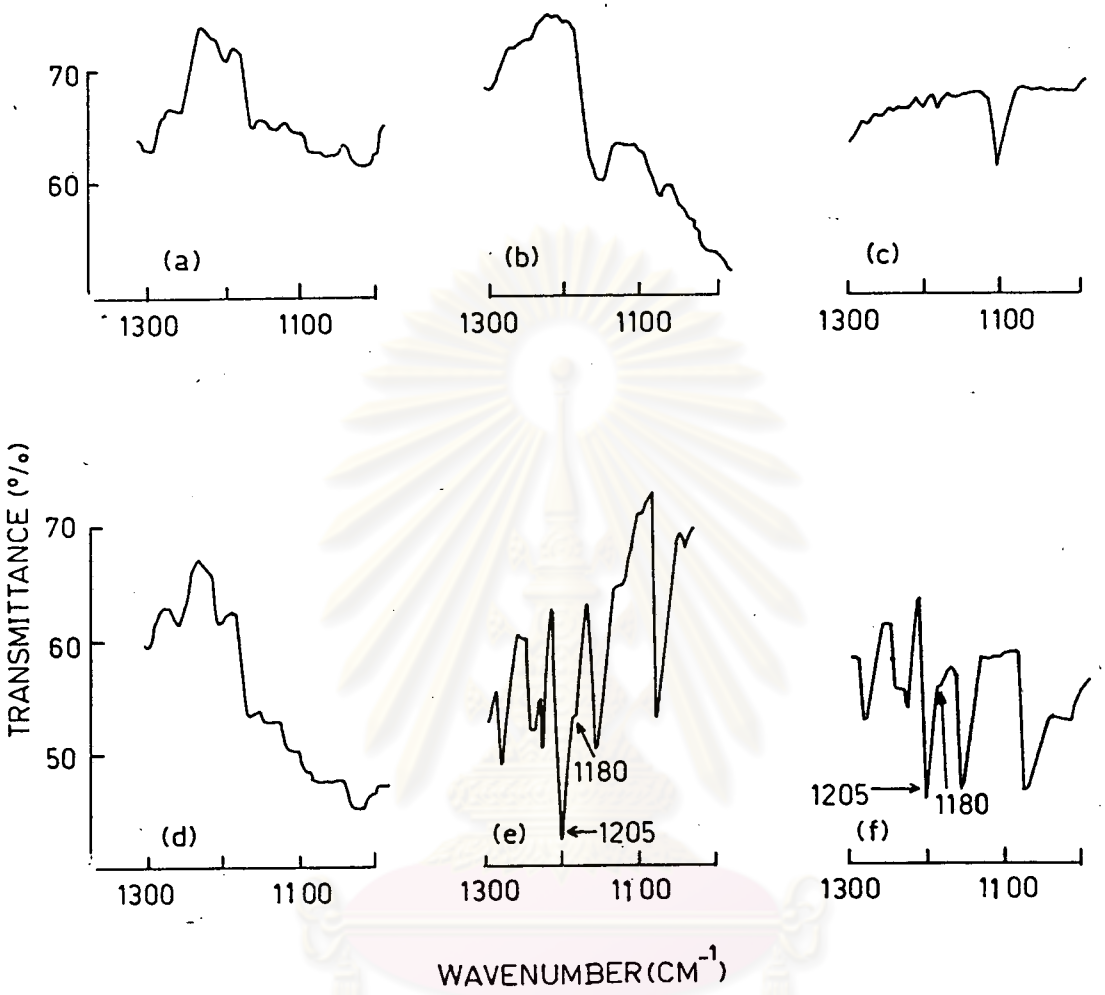

Fig. 17 The IR spectra of lactose (a), corn starch (b) magnesium stearate (c), base of formula I (d), raw material of sample 5(e) and sample 5 (f) in the range of 1300-1000 cm^{-1} in nujol. The bands at 1205 cm^{-1}(form A) and 1180 cm^{-1}(form B) are marked with arrows

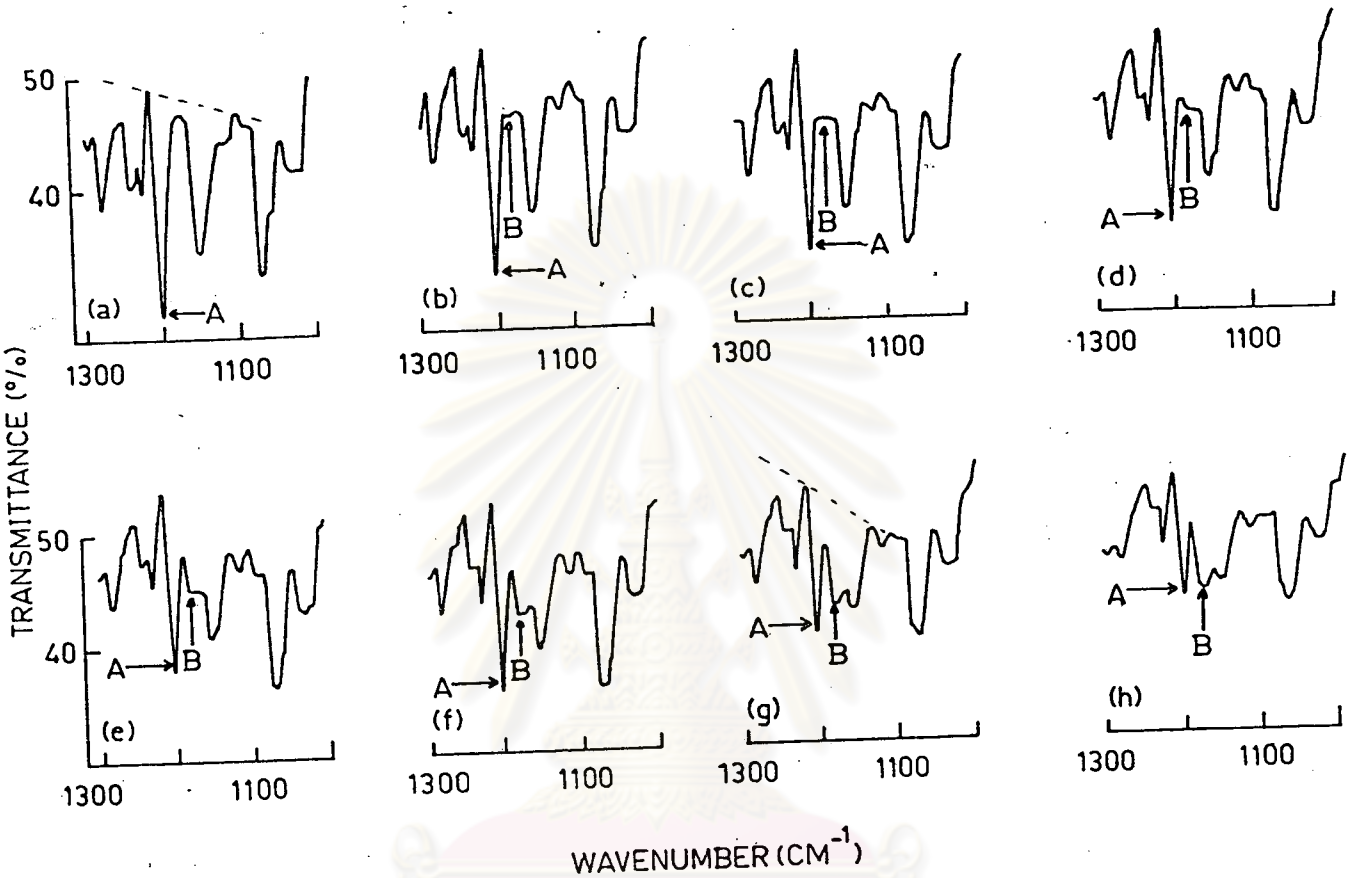

Fig. 18 The IR spectra of a series of mixtures containing various proportions of polymorphs A and B in tablet formula I in the range of 1300-1000 cm^{-1} in nujol

The bands at 1205 cm^{-1} (form A) and 1180 cm^{-1} (form B) are marked with arrows

(a)	pure A	(b)	B 5.0 %
(c)	B 10.0 %	(d)	B 15.0 %
(e)	B 20.0 %	(f)	B 25.0 %
(g)	B 30.0 %	(h)	B 35.0 %

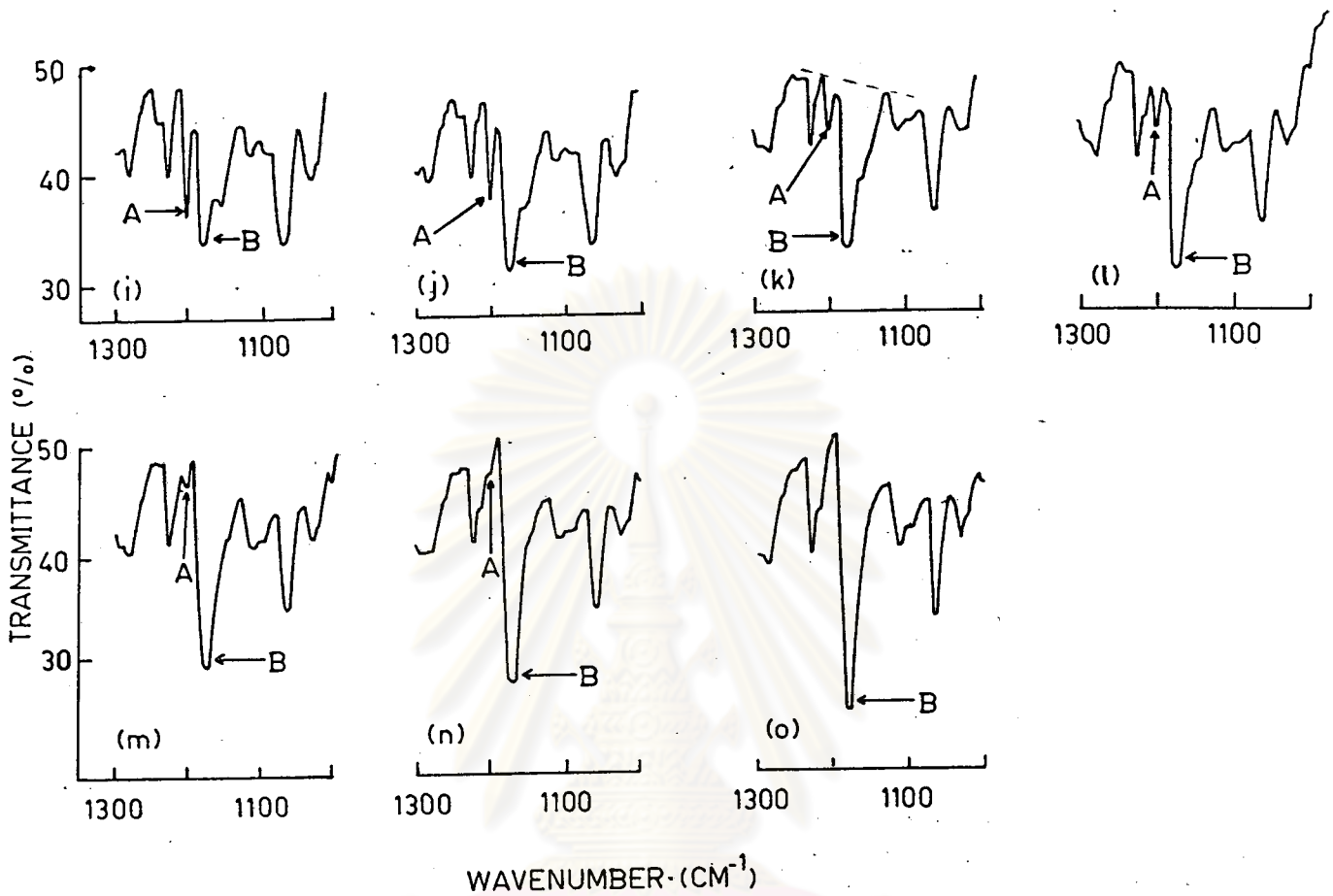

Fig. 18 The IR spectra of a series of mixtures containing various proportions of polymorphs A and B in tablet formula I in the range of 1300-1000 cm^{-1} in nujol

The bands at 1205 cm^{-1} (form A) and 1180 cm^{-1} (form B) are marked with arrows

(i) B 40.0 %
(j) B 50.0 %
(k) B 60.0 %
(l) B 70.0 %
(m) B 80.0 %
(n) B 90.0 %
(o) pure B

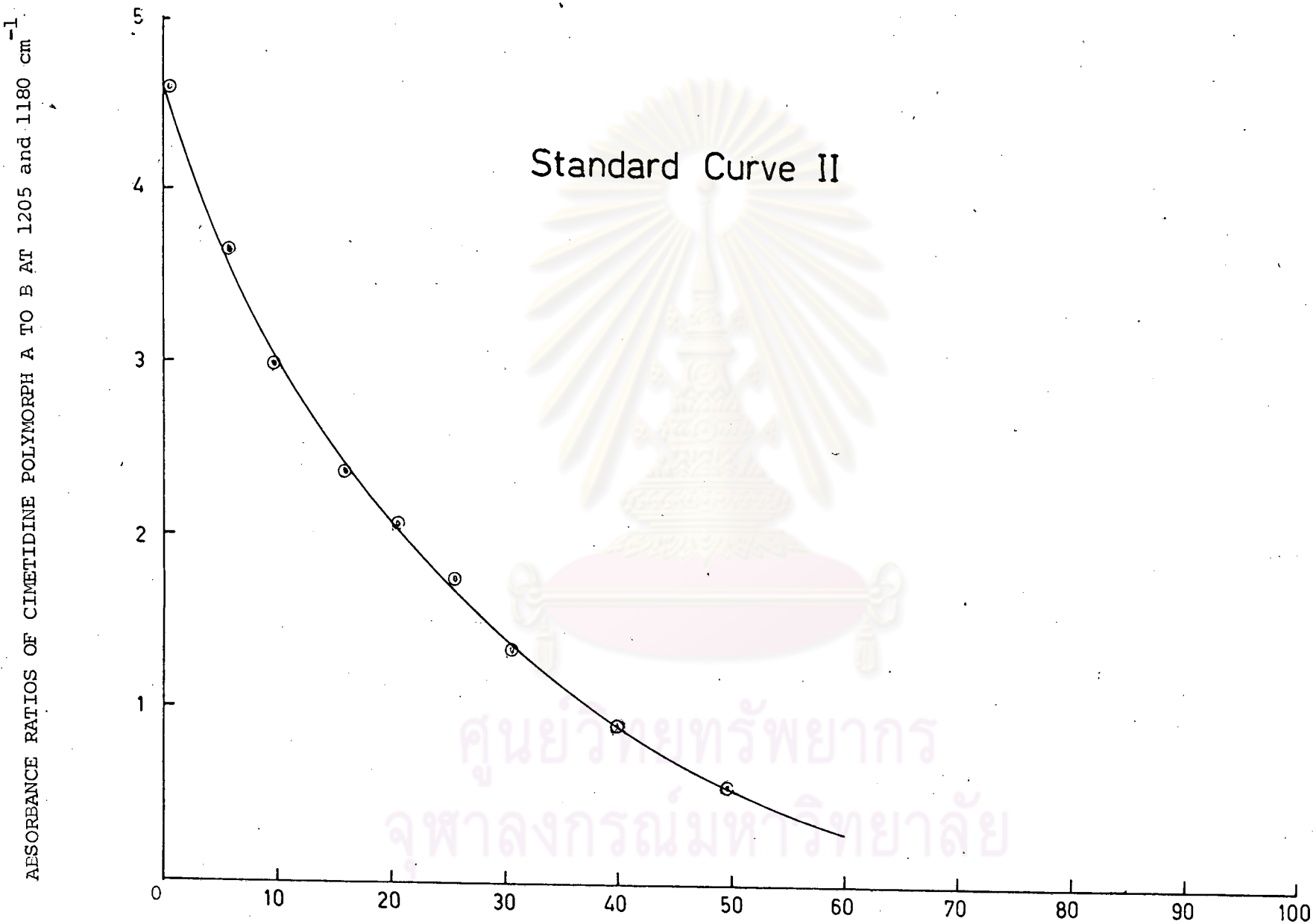

Fig. 19 Absorbance ratios of cimetidine polymorph A to polymorph B versus the contents of polymorph B in formula I (nujol mull technique)

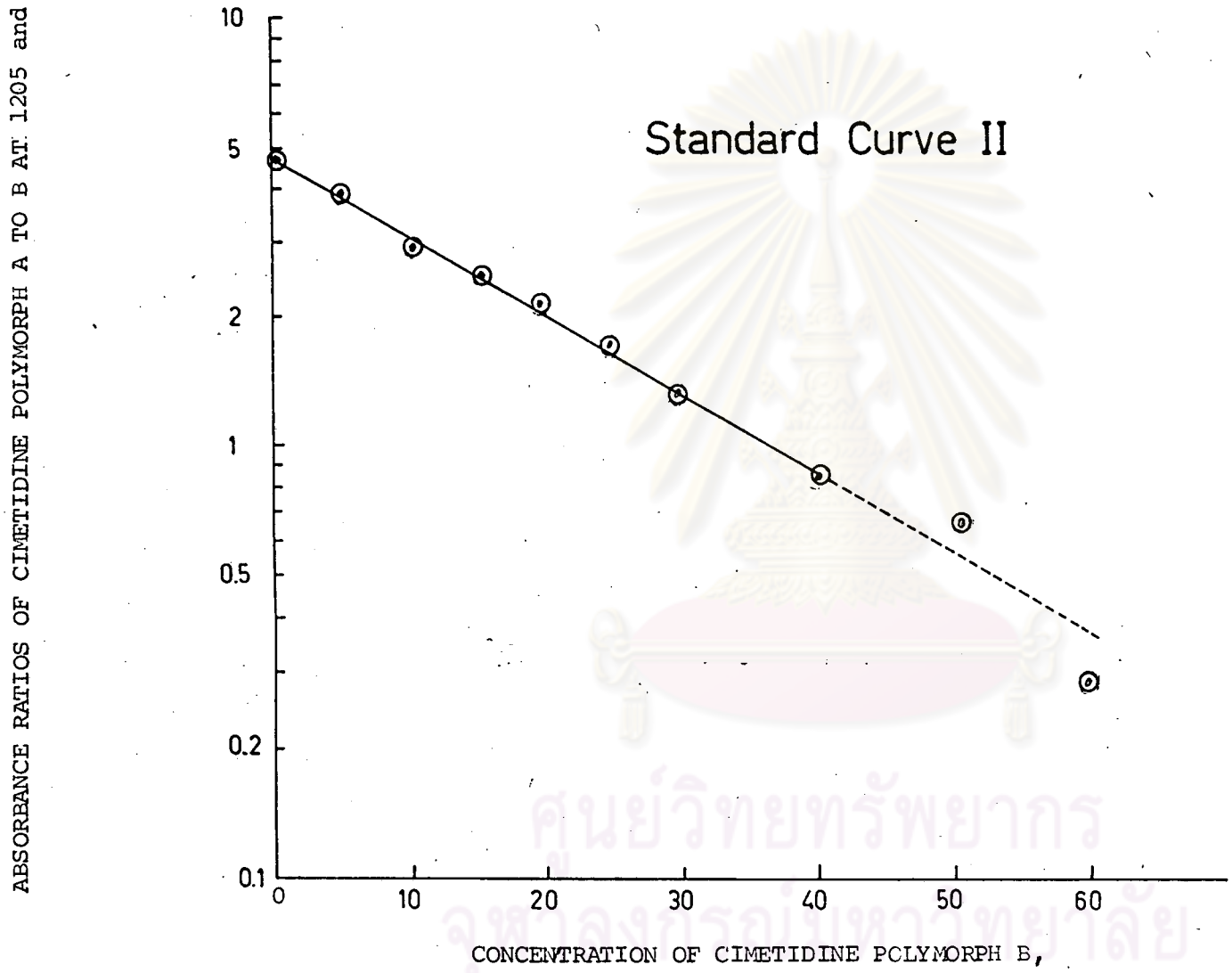

Fig. 20 The natural logarithm of the absorbance ratios of cimetidine polymorph A to polymorph B versus the contents of polymorph B in formula I (nujol mull technique)

VITAE

Miss Chantana Ungsukomutkul was born on the 10th June, 1955, graduated with a B.Sc. in Pharmacy from Chiangmai University in 1975, and is now working in Drug Analysis Division, Department of Medical Sciences, Ministry of Public Health.