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Appendices

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## Appendix A

### Preparation of Reagents

#### 1. 0.1 N Hydrochloric Acid

Dilute 8.5 mL of hydrochloric acid (HCl) with water to 1000 mL

#### 2. pH 6.8 Phosphate Buffer

Dissolve 27.22 g of monobasic potassium phosphate ( $\text{KH}_2\text{PO}_4$ ) in water and dilute to 1000 mL (= 0.2 M  $\text{KH}_2\text{PO}_4$ )

↓  
Dissolve 8 g of sodium hydroxide (NaOH) in water and dilute to 1000 mL (= 0.2 M NaOH)

↓  
Place 50 mL of 0.2 M  $\text{KH}_2\text{PO}_4$  in a 200-mL volumetric flask

↓  
Add 22.4 mL of 0.2 M NaOH, mix well

↓  
Add water to volume

### 3. 10 % w/v Zinc Sulfate

Dissolve 10 g of anhydrous zinc sulfate ( $\text{ZnSO}_4$ ) in water and dilute to 100 mL.

### 4. 0.01 M Sodium Acetate Buffer pH 4.0

Dissolve 0.8204 g of anhydrous sodium acetate ( $\text{CH}_3\text{COONa}$ ) in water

↓  
Adjust pH to 4.0 with glacial acetic acid

↓  
Transfer to 1000-mL volumetric flask and adjust to volume with water

↓  
Filter through 0.45  $\mu\text{m}$  membrane filter

### 5. Mobile Phase

Mobile phase composes of acetonitrile and 0.01 M sodium acetate buffer in the ratio of 1 : 9. It must be freshly prepared.

Mix 100 mL of acetonitrile (HPLC grade) with 900 mL of 0.01 M sodium acetate buffer pH 4.0

↓



↓  
Filter through 0.45  $\mu\text{m}$  membrane filter  
↓  
Degas using a sonicator for about 30 minutes



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## Appendix B

### Calibration Curve

The UV absorbance at specific wavelength for each of standard concentrations of theophylline in 0.1 N HCl and pH 6.8 phosphate buffer are presented in Table 34 and 35 respectively. The typical calibration curve obtained by regression analysis of these data are illustrated in Fig. 21 and 22 respectively.

The peak area ratio at various standard theophylline concentrations in rabbit plasma and the according calibration curve are shown in Table 36 and Figure 23 respectively.

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**Table 34** Absorbance of Theophylline in 0.1 N HCl at 268.5 nm

Concentration (mcg/mL)	Absorbance
4.00	0.212
6.00	0.318
8.00	0.428
10.00	0.532
12.00	0.640
14.00	0.740

Coefficient of determination = 0.9999 ;  $y = 0.000574 + 0.0531x$

(y = absorbance ; x = concentration)

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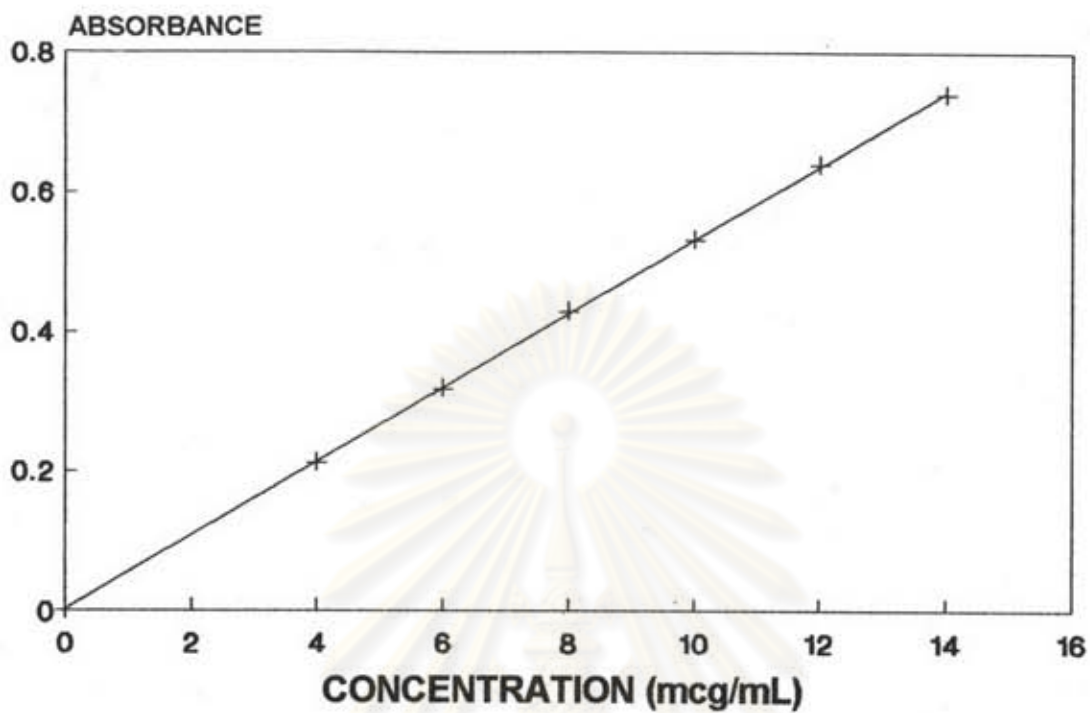
**Table 35** Absorbance of Theophylline in pH 6.8 buffer at 270.3 nm

Concentration (mcg/mL)	Absorbance
4.02	0.225
6.02	0.336
8.03	0.452
10.04	0.560
12.05	0.672
14.06	0.781

Coefficient of determination = 0.9999 ;  $y = 0.00152 + 0.0556x$

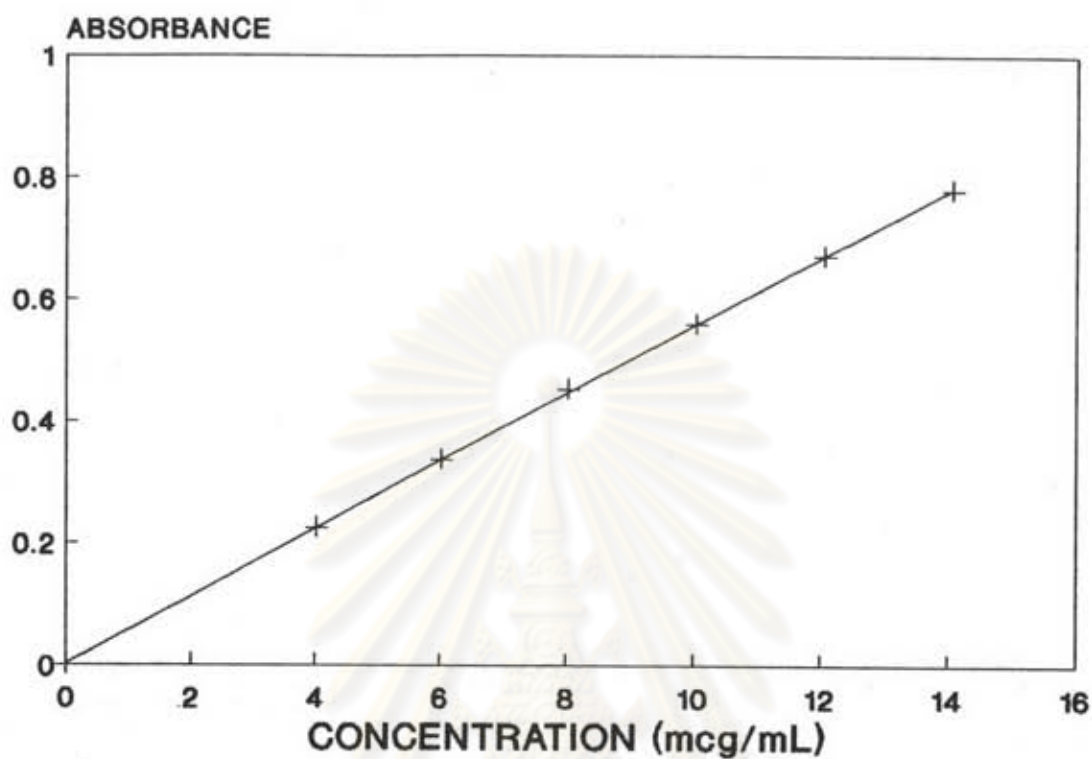
(y = absorbance ; x = concentration)

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**Figure 21** Typical Calibration Curve of Theophylline in 0.1 N HCl at 268.5 nm

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**Figure 22** Typical Calibration Curve of Theophylline in pH 6.8 Buffer at 270.3 nm

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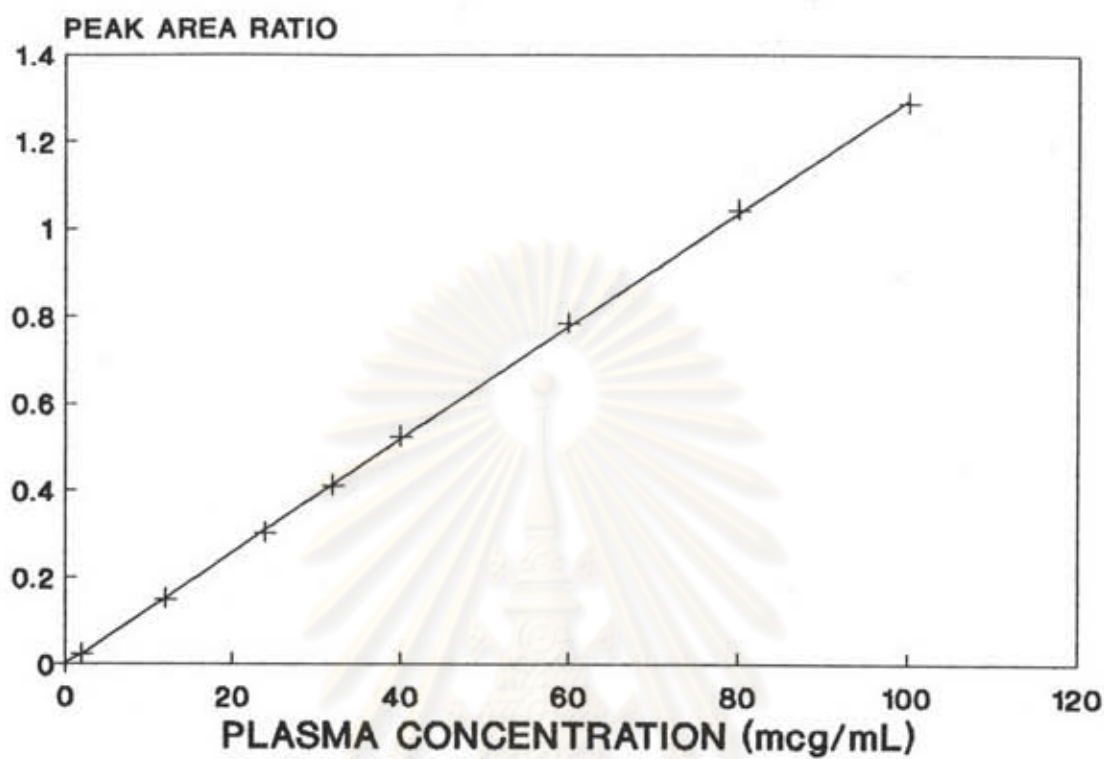
**Table 36** Peak Area Ratio of Theophylline to  $\beta$ -Hydroxyethyltheophylline in Rabbit Plasma

Concentration (mcg/mL)	Peak Area Ratio
2	0.022
12	0.150
24	0.302
32	0.410
40	0.524
60	0.784
80	1.044
100	1.290

Coefficient of determination = 0.9999 ;  $y = -0.0032 + 0.0130x$

(y = peak area ratio ; x = plasma concentration)

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**Figure 23** Typical Calibration Curve of Theophylline in Rabbit Plasma

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## Appendix C

### Dissolution Data

The cumulative percentage of drug dissolved from theophylline sustained-release tablets prepared by wet granulation, spray drying, fluidized-bed coating and from commercial products, Theo-Dur<sup>®</sup> and Nuelin<sup>®</sup>, are presented in Tables 37-51.

Dissolution rate constant (Kd) for tablet of individual product is obtained from the slope of the plot between the logarithm of amount of undissolved theophylline against the corresponding time, For example, dissolution rate constant of Theo-Dur<sup>®</sup> is calculated as follows.

Time (hr)	A*	100-A	log (100-A)	r
0.25	4.94	95.06	1.978	
0.50	7.61	92.39	1.966	
0.751	9.64	90.36	1.956	
1	11.70	88.30	1.946	
2	16.08	83.92	1.924	
3	18.40	81.60	1.912	
4	22.42	77.58	1.890	-0.96
5	27.48	72.52	1.860	
6	33.52	66.48	1.823	
7	43.72	56.28	1.750	
8	52.89	47.11	1.673	
10	64.63	35.37	1.549	
12	75.74	24.26	1.385	

\*A = % Drug Dissolved

$$\log (100 - A) = 2.025 - 0.046 (\text{Time})$$

$$\text{Therefore ; } Kd = 0.046$$



**Table 37** Cumulative Percent Release of Theophylline from Sustained-release Tablets with 5 % Methocel E4M in 0.1 N HCl

Time (hr)	Cumulative % Drug Released			
	1	2	3	Mean (SD)
0.25	5.87	7.24	7.32	6.58(0.81)
0.50	10.31	12.31	13.05	11.89(1.42)
0.75	13.63	17.06	17.46	16.05(2.10)
1	17.54	21.21	21.62	20.12(2.25)
2	30.02	35.53	35.66	33.74(3.22)
3	42.45	49.70	46.86	46.34(3.65)
4	54.16	62.36	57.92	58.15(4.10)
6	71.96	79.74	72.89	74.86(4.25)
9	93.51	96.57	91.24	93.77(2.67)
12	99.42	101.07	98.13	99.54(1.47)

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**Table 38** Cumulative Percent Release of Theophylline from Sustained-release Tablets with 5 % Methocel E4M in pH 6.8 Buffer

Time (hr)	Cumulative % Drug Released			
	1	2	3	Mean (SD)
0.25	6.43	6.10	5.66	6.06(0.39)
0.50	10.19	10.02	9.31	9.84(0.47)
0.75	12.94	12.91	12.19	12.68(0.42)
1	15.24	15.45	14.73	15.14(0.37)
2	21.31	21.85	21.67	21.61(0.27)
3	25.73	27.53	27.73	27.00(1.10)
4	29.67	32.08	33.04	31.60(1.74)
6	36.58	40.97	41.83	39.79(2.82)
9	45.28	50.66	50.44	48.79(3.04)
12	51.08	56.17	56.93	54.73(3.18)

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**Table 39** Cumulative Percent Release of Theophylline from Sustained-release Tablets with 7 % Methocel E4M in 0.1 N HCl

Time (hr)	Cumulative % Drug Released			
	1	2	3	Mean (SD)
0.25	6.61	6.44	6.13	6.39(0.24)
0.50	11.08	10.94	10.40	10.81(0.36)
0.75	14.61	14.83	13.81	14.42(0.54)
1	17.33	18.29	16.75	17.46(0.78)
2	28.50	29.30	26.95	28.25(1.19)
3	39.73	38.71	36.07	38.17(1.89)
4	50.85	48.13	45.36	48.11(2.74)
6	68.06	63.85	59.79	63.90(4.14)
9	86.78	81.78	72.45	80.34(7.27)
12	97.48	91.46	83.79	90.91(6.86)

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**Table 40** Cumulative Percent Release of Theophylline from Sustained-release Tablets with 7 % Methocel E4M in pH 6.8 Buffer

Time (hr)	Cumulative % Drug Released			
	1	2	3	Mean (SD)
0.25	5.18	5.06	5.60	5.28(0.28)
0.50	8.52	8.41	9.58	8.84(0.65)
0.75	11.10	10.96	12.63	11.56(0.93)
1	13.30	13.25	15.23	13.93(1.13)
2	19.20	18.77	21.14	19.70(1.26)
3	23.67	23.01	25.34	24.00(1.20)
4	27.54	27.10	29.44	28.03(1.24)
6	30.31	33.13	35.81	33.08(2.75)
9	41.91	40.49	43.74	42.05(1.63)
12	49.65	48.34	52.58	50.19(2.17)

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**Table 41** Cumulative Percent Release of Theophylline from Sustained-release Tablets with 10 % Methocel E4M in 0.1 N HCl

Time (hr)	Cumulative % Drug Released			
	1	2	3	Mean (SD)
0.25	5.74	5.67	5.00	5.47(0.41)
0.50	9.68	9.54	8.20	9.14(0.82)
0.75	12.61	12.64	10.81	12.02(1.05)
1	15.54	15.71	13.59	14.95(1.18)
2	24.04	23.52	20.42	22.66(1.96)
3	30.46	28.53	26.09	28.36(2.19)
4	35.97	32.78	31.46	33.40(2.32)
6	43.44	41.25	40.16	41.62(1.67)
9	53.45	51.13	52.42	52.33(1.16)
12	64.08	61.53	62.71	62.77(1.28)

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**Table 42** Cumulative Percent Release of Theophylline from Sustained-release Tablets with 10 % Methocel E4M in pH 6.8 Buffer

Time (hr)	Cumulative % Drug Released			
	1	2	3	Mean (SD)
0.25	5.54	4.93	5.31	5.26(0.31)
0.50	9.23	7.84	8.25	8.44(0.71)
0.75	12.08	10.14	10.44	10.89(1.04)
1	14.57	12.15	12.54	13.09(1.30)
2	20.96	17.72	17.83	18.84(1.84)
3	26.20	21.57	22.23	23.33(2.50)
4	29.33	25.44	25.45	26.74(2.24)
6	35.69	31.67	31.69	33.02(2.32)
9	43.08	38.71	38.72	40.17(2.52)
12	49.63	46.11	44.81	46.85(2.49)

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**Table 43** Cumulative Percent Release of Theophylline from Sustained-release Tablets with 20 % Lactose in 0.1 N HCl

Time (hr)	Cumulative % Drug Released			
	1	2	3	Mean (SD)
0.25	6.76	6.30	5.14	6.07(0.83)
0.50	12.19	10.80	9.00	10.66(1.60)
0.75	17.83	15.09	12.35	15.09(2.74)
1	22.75	19.20	15.53	19.16(3.61)
2	37.93	32.49	26.24	32.22(5.85)
3	50.17	42.03	35.47	42.56(7.36)
4	59.54	52.15	43.39	51.69(8.08)
6	74.52	66.75	56.13	65.80(9.23)
9	88.31	82.85	70.26	80.47(9.26)
12	96.74	90.83	81.58	89.72(7.64)

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**Table 44** Cumulative Percent Release of Theophylline from Sustained-release Tablets with 20 % Lactose in pH 6.8 Buffer

Time (hr)	Cumulative % Drug Released			
	1	2	3	Mean (SD)
0.25	6.74	6.19	6.98	6.64(0.40)
0.50	11.06	9.97	9.86	10.30(0.66)
0.75	14.31	12.77	12.64	13.24(0.93)
1	17.21	15.34	15.02	15.86(1.18)
2	24.77	22.94	21.85	23.19(1.48)
3	30.67	29.33	29.93	29.98(0.67)
4	37.80	35.36	32.95	35.37(2.42)
6	44.11	46.55	41.73	44.13(2.41)
9	53.39	59.00	50.89	54.43(4.15)
12	64.46	72.18	61.62	66.09(5.46)

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**Table 45** Cumulative Percent Release of Theophylline from Sustained-release Tablets with 20 % Lactose Tested by pH Change Method

Time (hr)	Cumulative % Drug Released						
	1	2	3	4	5	6	$\bar{x}$ (SD)
0.25	5.01	6.40	6.71	5.44	5.70	6.32	5.93(0.65)
0.50	9.91	10.93	12.08	10.30	10.51	10.77	10.75(0.74)
0.75	12.33	15.41	17.35	12.59	13.44	15.13	14.38(1.94)
1	17.83	19.75	20.85	18.12	18.49	19.35	19.06(1.14)
2	26.41	28.85	30.88	26.66	27.02	28.16	28.00(1.69)
3	32.88	35.42	38.77	33.36	34.28	35.32	35.00(2.11)
4	37.97	42.82	45.75	38.80	40.74	41.96	41.34(2.84)
5	44.22	48.78	51.56	45.33	48.28	51.17	48.22(2.98)
6	49.53	54.87	58.47	49.36	52.36	54.79	53.23(3.52)
7	53.90	60.22	63.25	53.80	56.61	60.19	58.00(3.84)
8	57.44	64.59	66.89	57.98	59.77	63.93	61.77(3.90)
10	62.38	69.26	71.93	62.66	65.22	69.17	66.77(3.93)
12	66.54	75.23	76.54	67.36	70.26	74.55	71.75(4.28)

**Table 46** Cumulative Percent Release of Theophylline from Sustained-release Tablets with 30 % Lactose (Product E) Tested by pH Change Method

Time (hr)	Cumulative % Drug Released						
	1	2	3	4	5	6	$\bar{x}$ (SD)
0.25	7.22	5.90	6.97	7.34	5.92	5.75	6.52(0.74)
0.50	12.52	10.59	12.55	12.32	10.28	10.14	11.40(1.18)
0.75	17.11	14.92	17.73	17.45	14.09	14.41	15.95(1.65)
1	21.49	18.75	22.51	22.17	18.41	18.12	20.24(2.02)
2	36.23	32.22	38.38	38.27	31.77	31.76	34.77(3.22)
3	45.36	41.52	48.51	47.54	41.40	41.29	44.27(3.30)
4	51.22	47.14	53.63	53.41	46.38	46.48	49.71(3.45)
5	56.04	51.28	60.08	58.45	50.63	50.84	54.55(4.19)
6	60.24	55.65	63.55	62.86	54.96	55.77	58.84(3.87)
7	63.94	58.52	67.67	67.78	58.23	58.36	62.42(4.64)
8	67.12	61.13	70.06	70.71	62.05	62.46	65.59(4.26)
10	72.74	67.12	76.10	77.30	67.38	69.00	71.61(4.44)
12	82.03	74.09	82.85	86.21	75.70	78.41	79.88(4.62)

**Table 47** Cumulative Percent Release of Theophylline from Sustained-release Tablets with 40 % Lactose Tested by pH Change Method

Time (hr)	Cumulative % Drug Released						
	1	2	3	4	5	6	$\bar{x}$ (SD)
0.25	8.75	8.95	8.55	8.86	7.93	9.03	8.68(0.40)
0.50	14.71	14.99	14.14	14.88	13.94	15.53	14.70(0.58)
0.75	20.10	20.90	19.14	20.50	19.22	21.46	20.22(0.92)
1	25.88	26.51	24.18	26.28	24.85	26.57	25.71(0.98)
2	44.77	48.40	42.94	46.36	43.84	46.37	45.45(1.99)
3	57.56	60.93	58.39	61.02	56.88	62.12	59.48(2.15)
4	68.23	73.35	68.86	71.29	64.75	72.38	69.81(3.17)
5	80.57	87.39	83.79	84.80	82.82	88.60	84.66(2.96)
6	91.40	95.02	92.75	95.79	92.98	96.24	94.03(1.93)
7	98.64	100.93	99.73	104.14	103.34	101.21	101.33(2.09)
8	100.12	103.77	104.18	104.43	103.76	103.79	103.34(1.60)
10	103.49	103.12	103.53	102.84	104.59	102.32	103.32(0.77)
12	108.10	106.37	106.38	107.57	107.45	108.67	107.42(0.92)



**Table 48** Cumulative Percent Release of Theophylline from Sustained-release Tablets Prepared by Spray Drying (Product C)

Time (hr)	Cumulative % Drug Released						
	1	2	3	4	5	6	$\bar{x}$ (SD)
0.25	7.10	7.27	6.64	7.61	7.47	7.86	7.32(0.43)
0.50	12.73	13.30	11.99	13.53	13.25	14.24	13.17(0.76)
0.75	18.43	19.45	17.23	19.54	18.94	19.66	18.88(0.93)
1	24.12	25.10	22.97	25.16	24.53	25.22	24.52(0.87)
2	38.73	40.11	39.85	40.79	39.42	40.01	39.82(0.69)
3	45.30	46.84	45.72	47.07	46.94	45.33	46.20(0.84)
4	52.62	53.20	52.07	53.10	52.65	51.24	52.48(0.73)
5	57.92	57.30	56.27	58.18	58.71	56.20	57.43(1.03)
6	60.96	63.06	61.48	61.33	61.97	61.96	61.79(0.73)
7	65.02	66.28	66.90	66.83	67.23	67.21	66.58(0.84)
8	70.54	71.54	71.62	71.28	71.67	70.03	71.11(0.68)
10	76.37	76.69	77.32	77.24	78.32	75.17	76.85(1.06)
12	82.90	83.37	81.54	83.92	82.42	81.70	82.64(0.94)

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**Table 49** Cumulative Percent Release of Theophylline from Sustained-release Tablets Prepared by Fluidized-bed Coating (Product D)

Time (hr)	Cumulative % Drug Released						
	1	2	3	4	5	6	$\bar{x}$ (SD)
0.25	2.81	2.45	2.67	3.93	2.25	2.50	2.77(0.60)
0.50	7.21	7.80	7.66	8.38	5.29	6.80	7.19(1.07)
0.75	11.24	11.46	11.72	12.38	10.29	10.75	11.31(0.73)
1	14.73	14.91	15.81	15.88	13.81	14.56	14.95(0.79)
2	26.69	27.14	26.75	25.98	23.95	25.21	25.95(1.20)
3	35.77	34.27	35.08	32.82	34.06	36.18	34.70(1.23)
4	42.50	40.82	41.85	38.67	42.50	43.61	41.66(1.73)
5	47.34	45.60	46.70	43.66	48.59	49.28	46.86(2.05)
6	52.35	49.85	51.38	47.35	54.25	55.37	51.76(2.93)
7	56.30	53.79	54.46	52.14	58.54	59.34	55.76(2.81)
8	59.16	57.09	58.47	55.02	61.44	63.38	59.09(3.00)
10	64.74	62.52	65.66	60.45	68.38	71.27	65.50(3.91)
12	70.89	67.58	70.33	64.82	73.06	75.17	70.31(3.72)

**Table 50** Cumulative Percent Release of Theophylline from Theo-Dur®

Time (hr)	Cumulative % Drug Released						
	1	2	3	4	5	6	$\bar{x}$ (SD)
0.25	4.94	4.80	5.02	4.06	5.45	4.28	4.76(0.51)
0.50	7.61	7.26	7.66	6.15	7.89	6.55	7.19(0.69)
0.75	9.64	9.21	9.84	7.66	9.81	8.35	9.08(0.89)
1	11.70	11.19	11.99	9.58	11.65	10.15	11.04(0.96)
2	16.08	15.62	16.31	13.66	15.29	14.58	15.26(0.99)
3	18.40	17.62	19.93	16.50	17.42	17.49	17.89(1.17)
4	22.42	21.15	25.86	19.58	19.80	22.05	21.81(2.29)
5	27.48	29.64	35.79	24.91	23.65	27.23	28.12(4.30)
6	33.52	37.54	43.83	31.58	31.19	34.02	35.28(4.76)
7	43.72	44.93	51.59	38.39	36.91	42.92	43.08(5.22)
8	52.89	54.98	58.73	44.48	42.12	54.26	51.24(6.49)
10	64.63	68.47	71.65	63.51	54.41	69.77	65.41(6.20)
12	75.74	81.10	81.29	76.51	65.87	81.72	77.04(6.05)

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**Table 51** Cumulative Percent Release of Theophylline from Nuclin®

Time (hr)	Cumulative % Drug Released						
	1	2	3	4	5	6	$\bar{x}$ (SD)
0.25	8.06	8.19	7.68	8.23	8.13	8.16	8.08(0.20)
0.50	12.34	12.51	11.83	12.82	12.78	12.38	12.44(0.36)
0.75	15.87	15.94	15.46	16.31	15.94	16.07	15.93(0.28)
1	19.10	19.24	18.55	19.24	18.97	18.83	18.99(0.27)
2	26.73	26.94	26.18	27.08	26.67	26.60	26.70(0.31)
3	33.54	33.93	34.18	36.14	36.91	34.97	34.94(1.33)
4	43.05	43.31	45.24	48.25	49.93	45.13	45.82(2.74)
5	53.90	55.34	57.14	60.95	64.97	54.57	57.81(4.32)
6	66.37	64.06	68.72	72.29	76.72	64.19	68.72(4.99)
7	71.86	68.31	78.21	83.80	84.51	72.68	76.56(6.68)
8	79.22	74.18	85.76	91.87	91.60	79.55	83.70(7.23)
10	87.74	84.94	94.48	98.19	97.44	87.76	91.76(5.65)
12	97.76	94.14	100.33	100.99	100.07	96.00	98.22(2.73)

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## Biography

Mr. Chaichana Techawatcharatep was born on February 14, 1969 in Bangkok. He got his degree, Bachelor of Science in Pharmacy, with honors in 1991 from Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand.



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