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APPENDICES

Appendix A

Calibration Curve

The concentration versus absorbance of diclofenac sodium in methanol at 280 nm, 0.1 N HCl acid at 276.5 nm and in phosphate buffer pH 6.8 at 276.5 nm are presented in Table 26 - 28. The standard curve of diclofenac sodium in these mediums are illustrated in Figures 60-62

Table 26 Absorbance of diclofenac sodium in methanol determined at 280 nm

Concentration (μg/ml)	Absorbance (SD)*
0	0
5	0.267 (0.001)
10	0.527 (0.003)
15	0.792 (0.001)
20	1.048 (0.002)
25	1.309 (0.003)

*Standard deviation from three determinations

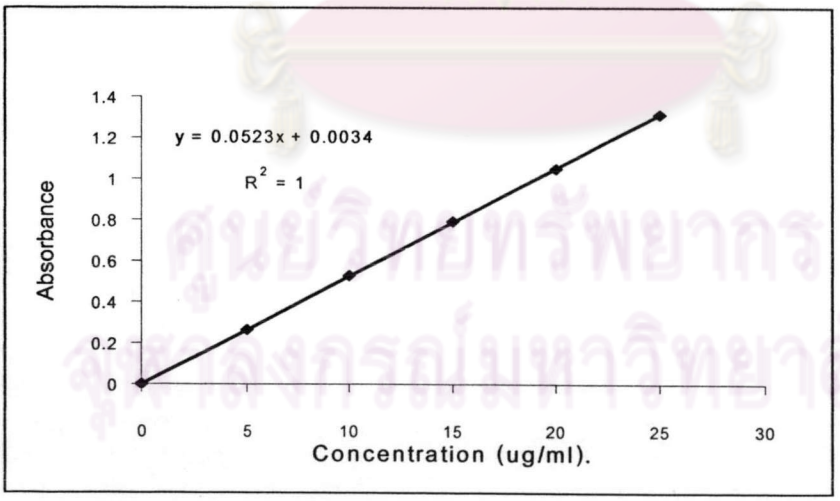

Figure 60 Calibration curve of diclofenac sodium in methanol at 280 nm

Table 27 Absorbance of diclofenac sodium in 0.1 N HCl acid determined at 276.5 nm

Concentration (μg/ml)	Absorbance (SD)*
0	0
5	0.153 (0.002)
10	0.301 (0.001)
15	0.457 (0.001)
20	0.611 (0.003)
25	0.768 (0.002)

* Standard deviation from three determinations

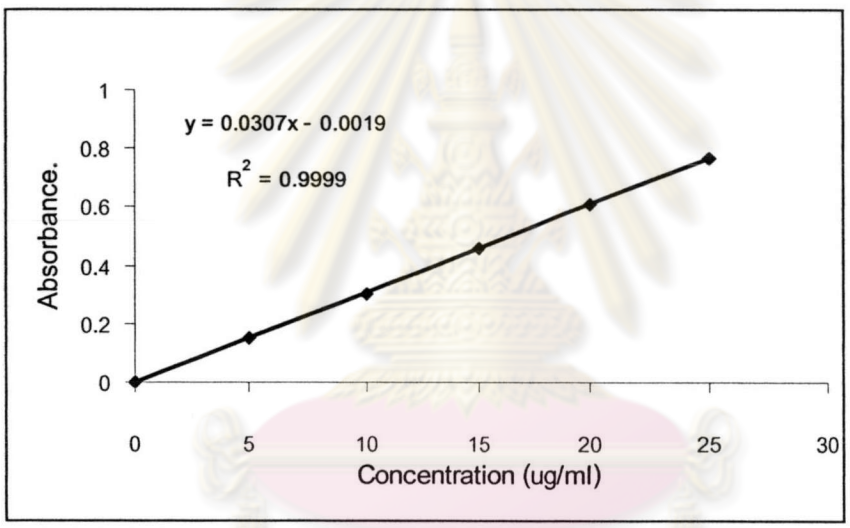

Figure 61 Calibration curve of diclofenac sodium in 0.1 N HCl at 276.5 nm

Table 28 Absorbance of diclofenac sodium in phosphate buffer pH 6.8 determined at 276.5 nm

Concentration (μg/ml)	Absorbance (SD)*
0	0
5	0.131 (0.003)
10	0.260 (0.002)
15	0.390 (0.001)
20	0.521 (0.001)
25	0.644 (0.002)

* Standard deviation from three determinations

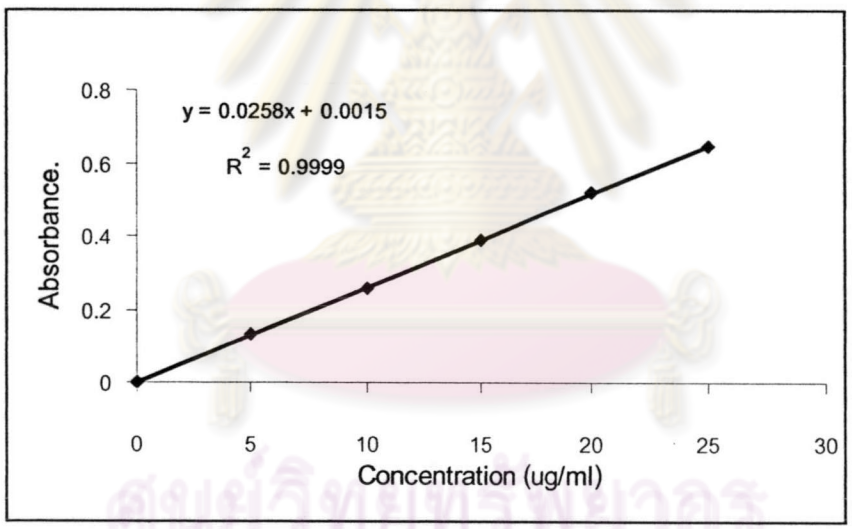

Figure 62 Calibration curve of diclofenac sodium in phosphate buffer pH 6.8 at 276.5 nm.

Appendix B

The physical properties of diclofenac sodium powder mixtures and granules

Table 29 The compressibility parameters of different diclofenac sodium powders after compression.

Process	Compressibility	Hardness
1) Untreated diclofenac sodium powder	+	2.8, 3, 2.6, 3, 3.2, 3, 2.8, 2.8, 3, 3
2) Diclofenac Sodium Powders was milled with mortar and pestle for 3 minutes	+	2.6, 3, 3, 3, 2.8, 3.2, 2.6, 3, 3.2, 3.2
3) Sieved diclofenac sodium powders through #30 mesh	+	3, 3.2, 3, 2.8,3, 2.8, 3, 3, 3.2, 2.8

O : could not compression + : could compression

Table 30 Some physical properties of diclofenac sodium microtablets containing various diluents.

Formulation	Flow Rate (g/s)	Angle of Repose (^{0})	%Friability	Hardness (kp) (Mean)
D1	13.30, 13.65, 13.40, 13.26, 13.50, 13.23	20.27, 20.35, 20.30	0.538 %	3.0, 3.0, 2.8, 2.8, 3.0, 2.8, 3.0, 2.3, 2.8, 2.8
D2	No flow	56.37, 57.01, 56.44	-	UNCOMPRESSIBLE
D3	18.67, 18.52, 18.49, 18.53, 18.31, 18.27	15.28, 15.23, 15.30	0.552 %	2.5, 2.8, 3.0, 2.8, 2.8, 3.0, 3.2, 2.7, 2.8, 3.0
D4	No flow	54.54, 54.68, 54.37	-	UNCOMPRESSIBLE
D5	No flow	55.64 , 55.23, 55.50	-	UNCOMPRESSIBLE

Table 31 The physical properties of powder mixtures and granules at the dose of 4.2 mg per microtablet

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Flow rate (g/sec)	Angle of repose (x °)	Moisture content (%)
DLHC	0.32, 0.35, 0.34	0.36,0.38 , 0.40	9.52, 9.60, 9.89	No flow	38.21,38.29, 38.46	1.87
DLEC	0.38, 0.36, 0.33	0.42, 0.44, 0.41	7.91, 7.95, 8.01	No flow	37.12, 37.25, 37.33	1.75
DSHC	0.33, 0.35, 0.38	0.38, 0.41, 0.40	14.28, 14.30, 14.25	No flow	39.08, 38.98, 39.01	2.00
DSEC	0.33, 0.35, 0.32	0.37, 0.39, 0.41	10.00, 11.20, 12.30	No flow	38.26 , 38.32, 38.14	1.90
WGHCL	0.28, 0.30, 0.35	0.32, 0.38, 0.33	12.5, 13.01, 12.89	18.24 ,18.25, 18.30, 18.29, 18.27, 18.32	27.12 , 27.25, 27.09	2.14
WGHCH	0.30, 0.32 ,0.31	0.35, 0.36, 0.34	13.28, 13.29, 13.30	15.41, 15.49, 15.32, 15.42, 15.55, 15.23	30.02 , 30.18, 30.22	2.32
WGEC	0.28, 0.30, 0.29	0.31, 0.33, 0.32	9.09, 9.11, 9.10	25.21, 25.26, 25.31, 25.14, 25.20, 25.30	25.18 , 25.22, 25.09	2.01

Table 32 The physical properties of powder mixtures and granules at dose 3 mg per microtablet

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Flow rate (g/sec)	Angle of repose (x °)	Moisture content (%)
DHC	0.36, 0.30, 0.31	0.38, 0.35 ,0.36	7.03, 7.15, 7.23	11.72 , 11.53, 11.66, 11.40, 11.27, 11.28	34.01, 34.15, 34.05	2.09
DEC	0.33, 0.34, 0.32	0.36, 0.38 0.37	6.72, 6.75, 6.73	13.49 , 13.53, 13.37, 13.25, 13.41, 13.27	32.14, 32.19, 32.08	1.85
WHCL	0.50, 0.57, 0.52	0.63, 0.61, 0.65	19.12, 19.25, 19.15	17.65 , 17.59, 17.32, 17.41, 17.22, 17.30	26.64, 26.53, 26.60	3.50
WHCH	0.39, 0.31, 0.33	0.47, 0.48, 0.46	20.00, 22.04, 21.13	14.37, 14.25, 14.50, 14.50, 14.02, 14.10	29.75, 29.78, 29.85	3.16
WECL	0.56, 0.58, 0.53	0.67, 0.69, 0.65	13.49, 13.54, 13.78	25.21, 25.27, 25.32, 25.16, 25.24, 25.19	22.45, 22.56, 22.48	2.63
WECH	0.46, 0.45, 0.49	0.53, 0.55, 0.59	16.64, 16.80, 16.78	23.46 , 23.52, 23.33, 23.24, 23.29, 23.12	24.78, 24.85, 24.90	2.75

Table 33 The angle of repose of the granules (Gordon et al., 1990)

Angle of repose (x °)	Flowability
25.30	Good flow
30-38	Fair flow
38.45	Very fair flow
45-55	Poor flow
55-70	Very poor flow
> 70	Very very poor flow

Table 34 Particle size distribution of powder mixtures and granules of diclofenac sodium

Formulation	% Weight Retained on Sieve Size					
	250 μm	180 μm	150 μm	125 μm	106 μm	pan
DLHC	9.24, 9.26	86.89, 87.01	1.68, 1.70	0.73, 0.76	0.39, 0.42	1.12, 1.14
DLEC	23.56, 23.64	72.77, 72.98	1.09, 1.18	0.76, 0.82	0.56, 0.64	0.79, 0.83
DSHC	2.48, 2.50	77.12, 77.19	5.45, 5.52	11.62,11.58	0.73, 0.71	1.48, 1.57
DSEC	13.86, 13.94	60.86, 60.97	11.91,11.85	7.46, 7.42	1.85, 1.94	1.88, 1.90
WGHCL	0.74, 0.76	2.40, 2.55	17.28, 17.20	21.02, 21.09	10.22, 10.05	45.94, 46.01
WGHCH	0.82, 0.75	8.15, 8.26	7.38, 7.15	7.51, 7.63	6.73, 6.64	72.57, 73.01
WGEC	27.04, 26.99	21.04, 21.28	37.16, 37.31	16.22, 16.47	0.46, 0.42	0.44, 0.39
DHC	10.52, 10.68	72.73, 73.14	11.36, 11.04	1.79, 1.62	1.57, 1.50	1.86, 1.81
DEC	10.56, 10.68	64.67, 65.26	18.88, 17.25	3.13, 3.04	0.39, 0.26	1.03, 0.92
WHCL	4.58, 4.32	23.11, 22.91	37.14, 36.95	19.33, 18.87	16.56, 16.63	0.17, 0.19
WHCH	18.88, 17.11	14.92, 15.07	10.68, 10.84	7.74, 8.02	8.52, 8.69	42.46, 43.20
WECL	27.68, 28.02	21.24, 21.03	44.42, 44.36	5.18, 5.10	0.60, 0.65	0.96, 0.98
WECH	22.98, 23.04	24.58, 24.46	31.66, 31.79	10.72, 10.55	0.34, 0.40	0.60, 0.71

Appendix C

Percentage of Drug Release, Release Rate Release Rate Against Amount and Reciprocal of Amount

Table 35 Percentage of diclofenac sodium release from commercial product in pH change method.

Formulation	Time (hrs)	Time^0.5	Mean*	SD	Log % drug remain
Voltaren SR 75 mg	0	0.00	0.00	0.00	4.61
	0.5	0.71	0.92	0.05	4.60
	1	1.00	1.00	0.02	4.60
	1.5	1.22	1.18	0.02	4.59
	2	1.41	1.32	0.04	4.59
	2.5	1.58	3.69	0.09	4.57
	3	1.73	5.85	0.14	4.54
	3.5	1.87	8.96	0.36	4.51
	4	2.00	11.44	0.10	4.48
	5	2.24	16.45	0.06	4.43
	6	2.45	20.58	0.39	4.37
	7	2.65	24.78	0.43	4.32
	8	2.83	28.49	0.40	4.27
	9	3.00	31.27	0.29	4.23
	10	3.16	36.62	0.08	4.15
	11	3.32	39.72	0.23	4.10
	12	3.46	44.82	2.17	4.01
	20	4.47	63.88	0.42	3.59
	21	4.58	66.88	0.38	3.50
	22	4.69	71.52	0.19	3.35
	23	4.80	74.22	0.35	3.25
	24	4.90	75.22	0.12	3.21

- *Mean of three determinations (%)

Table 36 Percentage of diclofenac sodium release from microtablets formulation WHCL in capsule size NO. 2 containing hydroxypropylmethylcellulose in pH change method.

Formulation	DS:HPMC	Time (hrs)	Time^0.5	Mean*	SD	Log%Drug Remained
WHCL	Low content	0	0.00	0.00	0.00	4.61
		0.5	0.71	1.59	0.11	4.59
		1	1.00	1.70	0.21	4.59
		1.5	1.22	1.84	0.34	4.59
		2	1.41	2.02	0.41	4.58
		2.5	1.58	7.10	0.76	4.53
		3	1.73	11.82	1.33	4.48
		3.5	1.87	15.48	0.83	4.44
		4	2.00	19.48	1.09	4.39
		5	2.24	25.41	1.58	4.31
		6	2.45	30.84	2.11	4.24
		7	2.65	34.74	1.08	4.18
		8	2.83	38.47	0.95	4.12
		9	3.00	43.94	5.87	4.03
		10	3.16	47.34	3.42	3.96
		11	3.32	50.17	3.18	3.91
		12	3.46	53.15	3.08	3.85
		20	4.47	64.01	1.92	3.58
		21	4.58	66.43	1.25	3.51
		22	4.69	65.98	1.19	3.53
		23	4.80	65.73	0.55	3.53
		24	4.90	66.26	0.61	3.52

- Mean of three determinations (%)

Table 37 Percentage of diclofenac sodium release from microtablets formulation WHCH in capsule size NO. 2 containing hydroxypropylmethylcellulose in pH change method.

Formulation	DS:HPMC	Time (hrs)	Time^0.5	Mean*	SD	Log%Drug Remained
WHCH	High content	0	0.00	0.00	0.00	4.61
		0.5	0.71	1.68	0.00	4.59
		1	1.00	1.94	0.13	4.59
		1.5	1.22	2.60	0.25	4.58
		2	1.41	4.14	0.06	4.56
		2.5	1.58	6.04	0.47	4.54
		3	1.73	9.86	0.53	4.50
		3.5	1.87	13.46	0.84	4.46
		4	2.00	17.24	1.21	4.42
		5	2.24	21.67	1.29	4.36
		6	2.45	26.38	1.14	4.30
		7	2.65	30.03	2.05	4.25
		8	2.83	33.54	2.00	4.20
		9	3.00	35.62	2.11	4.16
		10	3.16	39.32	2.84	4.11
		11	3.32	40.57	3.21	4.08
		12	3.46	42.74	3.44	4.05
		20	4.47	56.39	3.23	3.78
		21	4.58	59.71	2.07	3.70
		22	4.69	59.95	1.97	3.69
		23	4.80	60.29	2.37	3.68
		24	4.90	60.72	1.93	3.67

* Mean of three determinations (%)

Table 38 Percentage of diclofenac sodium release from microtablets formulation WECL in capsule size NO. 2 containing ethylcellulose in pH change method.

Formulation	DS:EC	Time (hrs)	Time^0.5	Mean*	SD	Log%Drug Remained
WECL	Low content	0	0.00	0.00	0.00	4.61
		0.5	0.71	1.90	0.10	4.59
		1	1.00	2.17	0.14	4.58
		1.5	1.22	2.65	0.08	4.58
		2	1.41	3.03	0.02	4.57
		2.5	1.58	18.64	2.40	4.40
		3	1.73	29.19	3.12	4.26
		3.5	1.87	39.78	3.75	4.10
		4	2.00	49.03	0.51	3.93
		5	2.24	60.43	3.66	3.68
		6	2.45	67.01	3.49	3.50
		7	2.65	72.11	1.92	3.33
		8	2.83	77.35	3.45	3.12
		9	3.00	80.84	3.98	2.95
		10	3.16	85.25	4.04	2.69
		11	3.32	86.35	4.21	2.61
		12	3.46	88.10	3.27	2.48
		20	4.47	90.89	3.55	2.21
		21	4.58	92.13	3.04	2.06
		22	4.69	94.15	2.44	1.77
		23	4.80	93.83	2.55	1.82
		24	4.90	94.10	2.50	1.78

* Mean of three determinations (%)

Table 40 Percentage of diclofenac sodium release from microtablets formulation WHCL1 in capsule size NO. 1 containing ethylcellulose in pH change method.

Formulation	DS:HPMC	Time (hrs)	Time^0.5	Mean*	SD	Log%Drug Remained
WHCL1	Low content	0	0.00	0.00	0.00	4.61
		0.5	0.71	1.21	0.24	4.59
		1	1.00	1.38	0.28	4.59
		1.5	1.22	1.62	0.14	4.59
		2	1.41	1.67	0.10	4.59
		2.5	1.58	6.63	0.20	4.54
		3	1.73	11.58	0.25	4.48
		3.5	1.87	15.72	0.26	4.43
		4	2.00	19.06	0.20	4.39
		5	2.24	24.10	0.10	4.33
		6	2.45	30.03	0.26	4.25
		7	2.65	34.72	0.13	4.18
		8	2.83	39.31	0.14	4.11
		9	3.00	44.95	0.50	4.01
		10	3.16	48.95	0.29	3.93
		11	3.32	52.70	0.30	3.86
		12	3.46	55.36	0.30	3.80
		20	4.47	68.70	0.40	3.44
		21	4.58	70.94	0.82	3.37
		22	4.69	72.85	0.62	3.30
		23	4.80	74.57	0.49	3.24
		24	4.90	75.84	0.30	3.18

- *Mean of three determinations (%)

Table 41 The release rate of commercial product of diclofenac sodium in pH change method.

Mean Time	Release Rate (%/hours)
	Voltaren SR 75 mg
0.25	0.00
0.75	1.84
1.25	0.16
1.75	0.36
2.25	0.28
2.75	4.74
3.25	4.32
3.75	6.22
4.5	2.48
5.5	5.01
6.5	4.13
7.5	4.20
8.5	3.71
9.5	5.35
10.5	3.10
11.5	5.10
16	2.38
20.5	3.00
21.5	4.64
22.5	2.70
23.5	1.00
23.5	1.00

Table 42 The release rate of diclofenac sodium microtablets from formulation WHCL, WHCH and WHCL1 in pH change method.

Mean Time	Release Rate (%/hours)		
	Formulation WHCL	Formulation WHCH	Formulation WHCL1
0.25	0.00	0.00	0.00
0.75	3.18	3.36	2.42
1.25	0.22	0.52	0.34
1.75	0.28	1.32	0.48
2.25	0.36	3.08	0.10
2.75	10.16	3.80	9.92
3.25	9.44	7.64	9.90
3.75	7.32	7.20	8.28
4.5	4.00	3.78	3.34
5.5	5.93	4.43	5.04
6.5	5.43	4.71	5.93
7.5	3.90	3.65	4.69
8.5	3.73	3.51	4.59
9.5	3.40	3.70	4.00
10.5	2.83	1.25	3.75
11.5	2.98	2.17	2.66
16	1.36	1.71	1.67
20.5	1.42	3.32	2.24
21.5	0.55	0.24	1.91
22.5	0.01	0.34	1.72
23.5	0.27	0.43	1.27
23.5	0.27	0.43	1.27

Table 43 The release rate of diclofenac sodium microtablets from formulation WECL and WECH in pH change method.

Mean Time	Release Rate (%/hours)	
	Formulation WECL	Formulation WECH
0.25	0.00	0.00
0.75	3.80	2.28
1.25	0.54	0.48
1.75	0.96	0.18
2.25	0.76	0.16
2.75	31.22	24.94
3.25	21.10	20.06
3.75	21.18	8.66
4.5	9.25	5.24
5.5	11.40	7.65
6.5	6.58	6.34
7.5	5.10	6.54
8.5	5.24	4.96
9.5	4.41	3.86
10.5	1.10	5.13
11.5	1.75	5.54
16	0.35	0.84
20.5	1.24	1.47
21.5	1.02	2.25
22.5	0.68	0.08
23.5	0.27	0.30
23.5	0.27	0.30

Table 44 Values of rate, amount released and the corresponding reciprocal for the release of Voltaren SR 75 mg from pH change method

Formulation	dQ/dt	Q	1/Q
Voltaren SR 75 mg	0.00	0	0.0000
	1.84	0.92	1.0870
	0.16	1.00	1.0000
	0.36	1.18	0.8475
	0.28	1.32	0.7576
	4.74	3.69	0.2710
	4.32	5.85	0.1709
	6.22	8.96	0.1116
	2.48	11.44	0.0874
	5.01	16.45	0.0608
	4.13	20.58	0.0486
	4.20	24.78	0.0404
	3.71	28.49	0.0351
	5.35	31.27	0.0320
	3.10	36.62	0.0273
	5.10	39.72	0.0252
	2.38	44.82	0.0223
	3.00	63.88	0.0157
	4.64	66.88	0.0150
	2.70	71.52	0.0140
	1.00	74.22	0.0135
	1.00	75.22	0.0133

Table 45 Values of rate, amount released and the corresponding reciprocal for the release of formulation with hydroxypropylmethylcellulose from pH change method

Formulation	dQ/dt	Q	1/Q	Formulation	dQ/dt	Q	1/Q
WHCL	0.00	0.00	0.0000	WHCH	0.00	0.00	0.0000
	3.18	1.59	0.6289		3.36	1.68	0.5952
	0.22	1.70	0.5882		0.52	1.94	0.5155
	0.28	1.84	0.5435		1.32	2.60	0.3846
	0.36	2.02	0.4950		3.08	4.14	0.2415
	10.16	7.10	0.1408		3.80	6.04	0.1656
	9.44	11.82	0.0846		7.64	9.86	0.1014
	7.32	15.48	0.0646		7.20	13.46	0.0743
	4.00	19.48	0.0513		3.78	17.24	0.0580
	5.93	25.41	0.0394		4.43	21.67	0.0461
	5.43	30.84	0.0324		4.71	26.38	0.0379
	3.90	34.74	0.0288		3.65	30.03	0.0333
	3.73	38.47	0.0260		3.51	33.54	0.0298
	3.40	43.94	0.0228		3.70	35.62	0.0281
	2.83	47.34	0.0211		1.25	39.32	0.0254
	2.98	50.17	0.0199		2.17	40.57	0.0246
	1.36	53.15	0.0188		1.71	42.74	0.0234
	1.42	64.01	0.0156		3.32	56.39	0.0177
	0.55	65.43	0.0153		0.24	59.71	0.0167
	0.01	65.98	0.0152		0.34	59.95	0.0167
	0.27	65.99	0.0152		0.43	60.29	0.0166
	0.27	66.26	0.0151		0.43	60.72	0.0165

Table 46 Values of rate, amount released and the corresponding reciprocal for the release of formulation with ethylcellulose from pH change method

Formulation	dQ/dt	Q	1/Q	Formulation	dQ/dt	Q	1/Q
WECL	0.00	0.00	0.0000	WECH	0.00	0.00	0.0000
	3.80	1.90	0.5263		2.28	1.14	0.8772
	0.54	2.17	0.4608		0.48	1.38	0.7246
	0.96	2.65	0.3774		0.18	1.47	0.6803
	0.76	3.03	0.3300		0.16	1.55	0.6452
	31.22	18.64	0.0536		24.94	14.02	0.0713
	21.10	29.19	0.0343		20.06	24.05	0.0416
	21.18	39.78	0.0251		8.66	28.38	0.0352
	9.25	49.03	0.0204		5.24	33.62	0.0297
	11.40	60.43	0.0165		7.65	41.27	0.0242
	6.58	67.01	0.0149		6.34	47.61	0.0210
	5.10	72.11	0.0139		6.54	54.15	0.0185
	5.24	77.35	0.0129		4.96	59.11	0.0169
	4.41	80.84	0.0124		3.86	63.87	0.0157
	1.10	85.25	0.0117		5.13	67.73	0.0148
	1.75	86.35	0.0116		5.54	72.86	0.0137
	0.35	88.10	0.0114		0.84	78.4	0.0128
	1.24	90.89	0.0110		1.47	85.09	0.0118
	1.02	92.13	0.0109		2.25	86.56	0.0116
	0.68	93.15	0.0107		0.08	88.81	0.0113
	0.27	93.83	0.0107		0.30	88.89	0.0112
	0.27	94.10	0.0106		0.30	89.19	0.0112

Table 47 Values of rate, amount released and the corresponding reciprocal for the release of formulation with hydroxypropylmethylcellulose from pH-change method

Formulation	DQ/Dt	Q	1/Q
WHCL1	0.00	0.00	0.0000
	2.42	1.21	0.8264
	0.34	1.38	0.7246
	0.48	1.62	0.6173
	0.10	1.67	0.5988
	9.92	6.63	0.1508
	9.90	11.58	0.0864
	8.28	15.72	0.0636
	3.34	19.06	0.0525
	5.04	24.10	0.0415
	5.93	30.03	0.0333
	4.69	34.72	0.0288
	4.59	39.31	0.0254
	4.00	44.95	0.0222
	3.75	48.95	0.0204
	2.66	52.70	0.0190
	1.67	55.36	0.0181
	2.24	68.70	0.0146
	1.91	70.94	0.0141
	1.72	72.85	0.0137
	1.27	74.57	0.0134
	1.27	75.84	0.0132

Appendix D

Data in statistical processes

Table 48 The t-values of percentage drug release between Voltaren SR tablet and the sustained release DS microtablet (Formulation WHCL1) (degree of freedom = 21, data from Tables 44 and 47)

Acid stage

Product I	Product II	t-value*	Result**
Voltaren SR tablet	Formulation WHCL1 (DS microtablet with HPMC)	-1.479	NS

*If $\alpha = 0.05$, degree of freedom = 3
then critical values of t are ± 3.182
**S = significance
NS = non - significance

Buffer stage

Product I	Product II	t-value*	Result**
Voltaren SR tablet	Formulation WHCL1 (DS microtablet with HPMC)	-5.879	S

*If $\alpha = 0.05$, degree of freedom = 17
then critical values of t are ± 2.110
**S = significance
NS = non - significance

VITAE

Miss Tapanee Phueksuwan was born on October 6, 1974. She got her degree in Bacheler of Science in Pharmacy in 1997 from Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand. At that time, she proudly won a research reward which was related to any senior projects before graduation. Her research was Development of furosemide tablet It might be a great price prize before she finnished. After graduation, she has been employed by the Government Pharmaceutical Organization. In 2000, she entered the Master's Degree program in Manufacturing Pharmacy of Chulalongkorn University.