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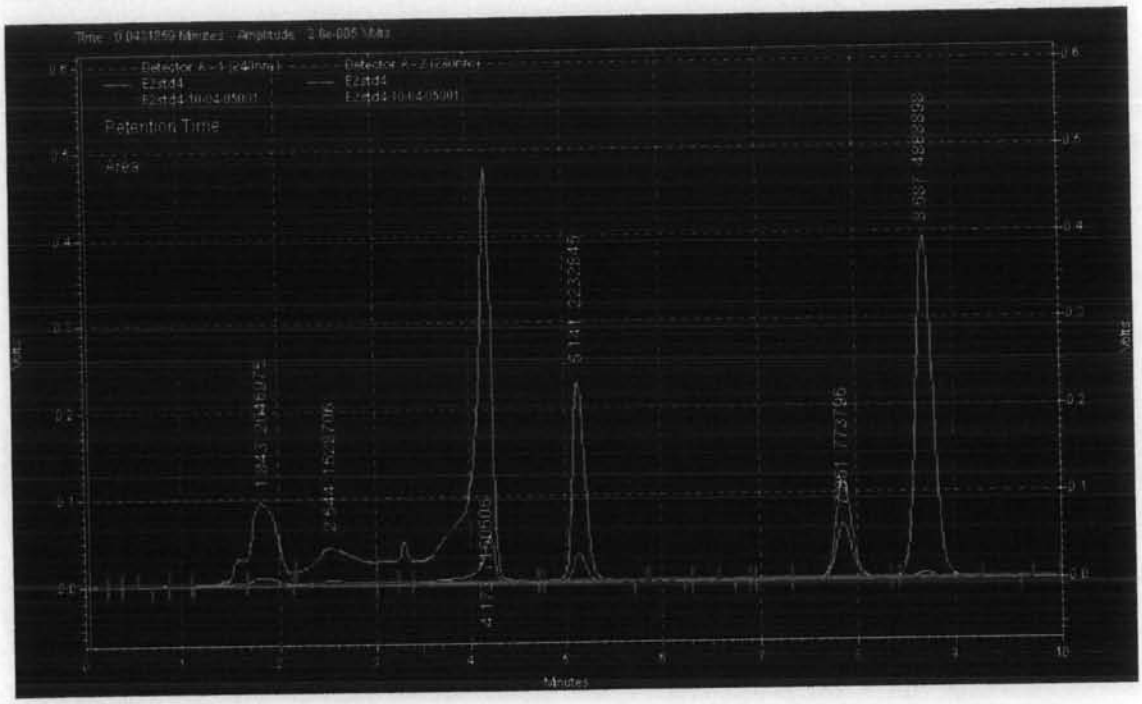
APPENDICES

APPENDIX A

Chromatogram of 17β-Estradiol and Norethindrone

Chromatogram of E_2 and NET obtained from HPLC Analysis with Dual Wavelength Measurement Mode



Retention time of E_2 was 7.86 min. Peak area of E_2 was measured at 280 nm.

Retention time of NET is 8.86 min Peak area of E_2 was measured at 240 nm.

APPENDIX B

Percent Amount of Drug Release and Daily Rate of Drug Release

Percent Amount of E_2 Released from Geomatrix® Implant Using Eudragit® RS as Release Controlling Agent

Formulation code	Time (d)	√Time (√d)	%E_2 released		ln (%E_2 remained)
			Mean*	SD	
10-E_2	0	0	0	0	4.60
	0.04	0.20	0.95	0.28	4.60
	1	1.00	12.74	0.96	4.47
	3	1.73	41.11	2.57	4.08
	5	2.24	66.52	4.85	3.50
	7	2.65	72.60	3.41	3.31
	9	3.00	72.92	3.34	3.30
	14	3.74	72.94	3.34	3.30
20-E_2	0	0	0	0	4.60
	0.04	0.20	4.042	6.02	4.56
	1	1.00	14.76	7.18	4.44
	3	1.73	42.84	6.78	4.04
	5	2.24	71.99	6.87	3.31
	7	2.65	83.36	8.45	2.81
	9	3.00	83.93	8.62	2.78
	14	3.74	83.96	8.63	2.78
30-E_2	0	0	0	0	4.60
	0.04	0.20	0.34	0.20	4.60
	1	1.00	9.28	0.83	4.51
	3	1.73	39.78	1.21	4.10
	5	2.24	71.50	0.95	3.35
	7	2.65	82.87	2.86	2.84
	9	3.00	83.51	3.02	2.80
	14	3.74	83.56	3.05	2.80

*Mean of three determinations (%)

Daily rate of E_2 Released from Geomatrix® Implant Using Eudragit® RS as Release Controlling Agent

Time (d)	10-E_2		20-E_2		30-E_2	
	E_2 daily release rate (mcg/d)		E_2 daily release rate (mcg/d)		E_2 daily release rate (mcg/d)	
	Mean*	SD	Mean*	SD	Mean*	SD
0	0	0	0	0	0	0
1	54.80	3.26	41.42	7.74	31.19	5.14
3	63.30	4.24	53.84	5.45	53.27	2.45
5	56.56	4.59	53.64	3.28	52.72	2.83
7	13.60	5.46	20.73	5.11	18.86	2.84
9	0.69	0.33	1.03	0.50	1.08	0.35
14	0.02	0.01	0.02	0.02	0.03	0.01

*Mean of three determinations

Percent Amount of NET Released from Geomatrix® Implant Using Eudragit® RS as Release Controlling Agent

Formulation code	Time (d)	√Time (√d)	%NET released		ln (%NET remained)
			Mean*	SD	
30-NET	0	0	0	0	4.60
	1	1.00	6.82	1.09	4.53
	3	1.73	23.98	2.60	4.33
	5	2.24	40.73	2.87	4.08
	7	2.65	56.05	4.10	3.78
	9	3.00	69.48	4.10	3.41
	14	3.74	88.77	3.36	2.42
	21	4.58	98.66	0.38	0.29
40-NET	0	0	0	0	4.60
	1	1.00	7.96	0.29	4.52
	3	1.73	24.37	0.40	4.33
	5	2.24	38.21	1.15	4.12
	7	2.65	51.36	0.70	3.88
	9	3.00	64.24	0.55	3.58
	14	3.74	83.48	1.15	2.80
	21	4.58	97.71	0.93	0.83
50-NET	0	0	0	0	4.60
	1	1.00	9.27	0.88	4.51
	3	1.73	24.98	2.27	4.32
	5	2.24	39.02	2.42	4.11
	7	2.65	51.15	2.65	3.89
	9	3.00	64.05	2.96	3.58
	14	3.74	83.46	2.57	2.81
	21	4.58	97.89	1.21	0.75

*Mean of three determinations (%)

Daily rate of NET Released from Geomatrix® Implant Using Eudragit® RS as Release Controlling Agent

Time (d)	30-NET		40-NET		50-NET	
	NET daily release rate (mcg/d)		NET daily release rate (mcg/d)		NET daily release rate (mcg/d)	
	Mean*	SD	Mean*	SD	Mean*	SD
0	0	0	0	0	0	0
1	135.25	22.27	135.12	20.37	184.29	18.46
3	162.54	9.58	133.03	16.04	150.10	19.55
5	159.30	9.10	111.85	8.94	133.93	7.61
7	145.06	7.44	107.99	28.03	115.61	6.48
9	127.78	8.76	104.15	8.58	123.09	7.03
14	73.46	6.72	62.30	6.08	73.96	1.99
21	27.16	9.74	33.07	5.07	39.25	3.48

*Mean of three determinations

Percent Amount of NET Released from Matrix Implant and Geomatrix® Implant Using Various Types of Polymers Used in the Components

Formulation code	Time (d)	√Time (√d)	%NET released		ln (%NET remained)
			Mean*	SD	
ERS-B-ERL-C	0	0	0	0	4.60
	0.04	0.20	0.14	0.03	4.60
	1	1.00	42.50	40.03	3.74
	2	1.41	82.71	16.77	1.98
	3	1.73	96.22	4.84	0.54
	5	2.24	99.76	0.03	-1.43
ERL-B-ERL-C	0	0	0	0	4.60
	0.04	0.20	1.37	1.13	4.59
	1	1.00	47.58	10.28	3.94
	2	1.41	94.75	1.32	1.64
	3	1.73	99.96	0.005	-3.20
ERL-B-ERS-C	0	0	0	0	4.60
	0.04	0.20	0	0	4.60
	1	1.00	6.70	3.40	4.54
	2	1.41	16.18	3.24	4.43
	3	1.73	24.47	3.42	4.32
	5	2.24	38.26	3.64	4.12
	7	2.65	51.25	3.18	3.88
	14	3.74	79.43	2.32	3.02
	21	4.58	94.06	1.17	1.78
	28	5.29	99.56	0.16	-0.82
ERS-B-ERS-C	0	0	0	0	4.60
	0.04	0.20	0	0	4.60
	1	1.00	6.65	0.38	4.54
	2	1.41	13.30	0.71	4.46
	3	1.73	20.48	1.09	4.38
	5	2.24	34.26	2.15	4.18
	7	2.65	46.37	2.29	3.95
	14	3.74	75.29	1.59	3.21
	21	4.58	91.77	0.94	2.11
	28	5.29	98.92	0.25	0.07
ERS-C	0	0	0	0	4.60
	0.04	0.20	0	0	4.60
	1	1.00	8.83	0.42	4.51
	2	1.41	16.12	0.85	4.43
	3	1.73	22.78	1.16	4.35
	5	2.24	35.83	2.19	4.16
	7	2.65	47.64	2.25	3.96
	14	3.74	74.65	1.64	3.23
	21	4.58	90.08	1.23	2.30
	28	5.29	97.96	0.72	0.71

*Mean of three determinations (%)

Daily rate of NET Released from Matrix Implant and Geomatrix® Implant Using Various Types of Polymers Used in the Components

Time (d)	ERS-B-ERL-C		ERL-B-ERL-C		ERL-B-ERS-C		ERS-B-ERS-C		ERS-C	
	NET daily release rate (mcg/d)		NET daily release rate (mcg/d)		NET daily release rate (mcg/d)		NET daily release rate (mcg/d)		NET Daily release rate (mcg/d)	
	Mean*	SD	Mean*	SD	Mean*	SD	Mean*	SD	Mean*	SD
0	0	0	0	0	0	0	0	0	0	0
0.04	116.92	35.79	1070.20	837.89	0	0	0	0	0	0
1	1470.73	1346.17	1604.52	414.19	263.75	141.90	268.79	9.04	367.25	20.84
2	1405.36	1043.79	1573.95	386.08	352.95	22.74	257.61	8.20	290.64	21.61
3	463.99	413.36	175.94	63.72	308.89	18.86	278.37	8.13	265.61	24.63
5	59.29	79.59	#	#	256.93	14.34	266.89	13.23	260.12	28.62
7	#	#	#	#	241.84	8.95	234.68	4.04	235.27	7.43
14	#	#	#	#	149.81	6.01	160.36	10.10	153.74	1.93
21	#	#	#	#	77.66	3.34	91.39	5.97	87.84	2.34
28	#	#	#	#	29.14	4.05	39.67	5.02	44.86	2.56

*Mean of three determinations
#not determined

Amount Percent of E_2 Released from Implant Using Eudragit® RS as Release Controlling Agent

Formulation code	Time (d)	√Time (√d)	%E_2 released		ln (%E_2 remained)
			Mean*	SD	
1-E_2	0	0	0	0	4.60
	0.04	0.20	3.32	0.99	4.57
	1	1.00	41.50	2.08	4.07
	2	1.41	61.35	11.08	3.63
	3	1.73	63.72	12.69	3.55
2-E_2	0	0	0	0	4.60
	0.04	0.20	4.02	1.86	4.56
	1	1.00	54.62	0.24	3.82
	2	1.41	85.89	1.27	2.64
	3	1.73	86.18	1.34	2.62

*Mean of three determinations (%)

Daily rate of E_2 Released from Geomatrix® Implant Using Eudragit® RS as Release Controlling Agent

Time (d)	1-E_2		2-E_2	
	E_2 daily release rate (mcg/d)		E_2 daily release rate (mcg/d)	
	Mean*	SD	Mean*	SD
0	0	0	0	0
0.04	320.61	57.02	280.06	99.24
1	164.43	27.50	156.41	16.78
2	77.85	41.48	92.18	3.96
3	9.52	9.84	0.85	1.20

*Mean of three determinations

APPENDIX C

Examination of the Difference Among Rates of NET Release Obtained from Different Formulations

ANOVA for the Release Rate of NET among Different Formulations

Explore

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
RATE	9	100.0%	0	.0%	9	100.0%

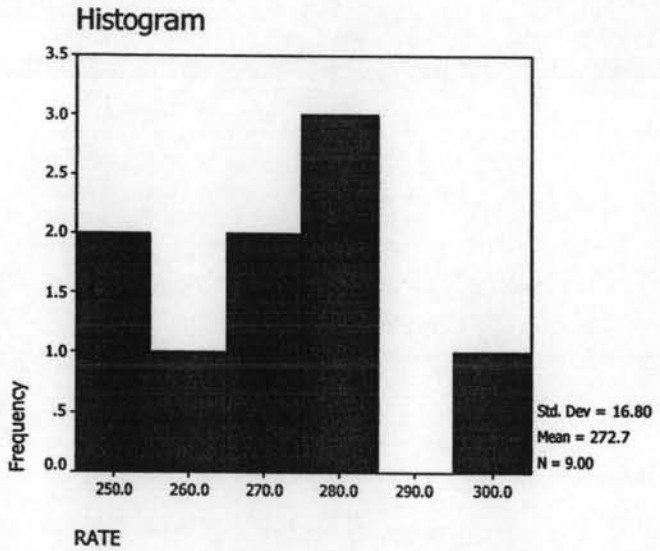
Tests of Normality

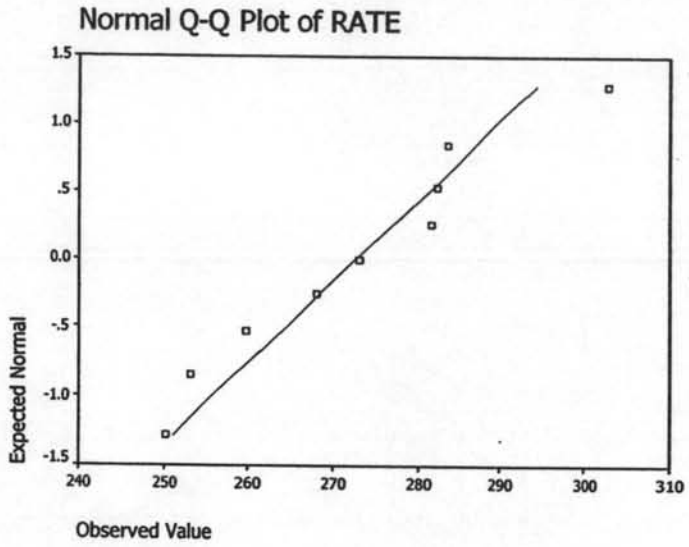
	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
RATE	.153	9	.200*	.954	9	.732

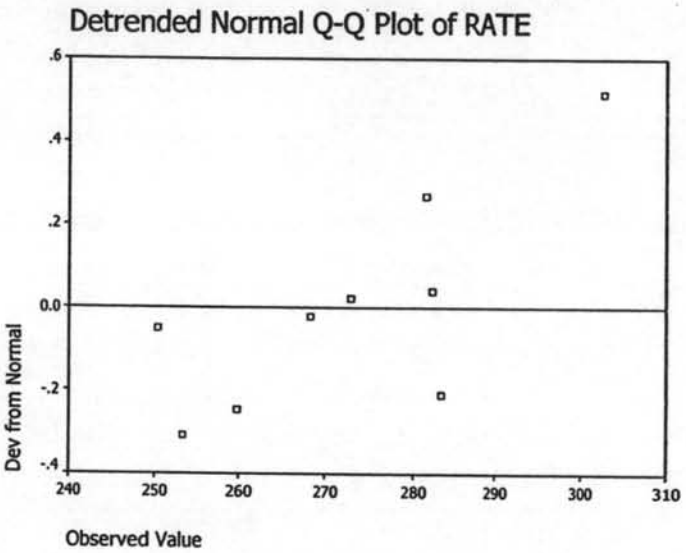
*. This is a lower bound of the true significance.

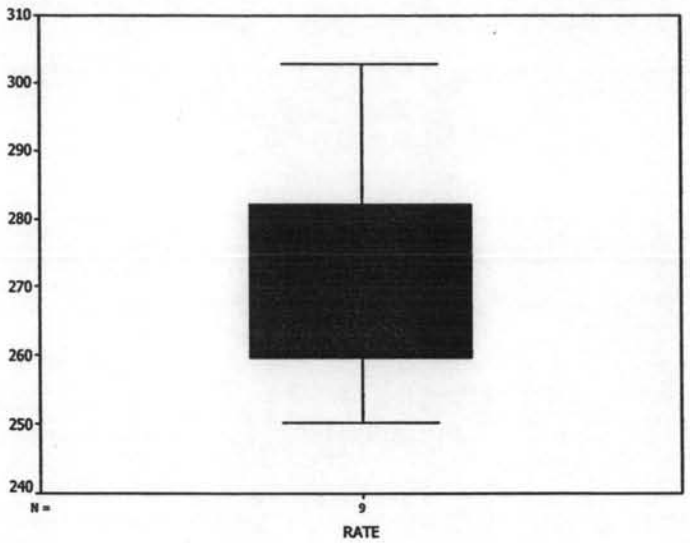
a. Lilliefors Significance Correction

RATE




Normal Q-Q Plot of RATE
Expected Normal
1.5
1.0
.5
0.0
-.5
-1.0
-1.5
240
250
260
270
280
290
300
310
Observed Value


Detrended Normal Q-Q Plot of RATE
Dev from Normal
.6
.4
.2
0.0
-.2
-.4
240
250
260
270
280
290
300
310
Observed Value



Oneway Analysis of Variance

Descriptives

RATE

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
ERL-B-ERS-C	3	278.43381	26.507193	15.303935	212.58629	344.28132	250.270	302.895
ERS-B-ERS-C	3	266.93305	6.736287	3.889197	250.19919	283.66692	259.705	273.037
ERS-C	3	272.68192	16.790035	9.693731	230.97316	314.39068	253.324	283.282
Total	9	272.68293	16.801151	5.600384	259.76842	285.59743	250.270	302.895

Test of Homogeneity of Variances

RATE

Levene Statistic	df1	df2	Sig.
2.042	2	6	.211

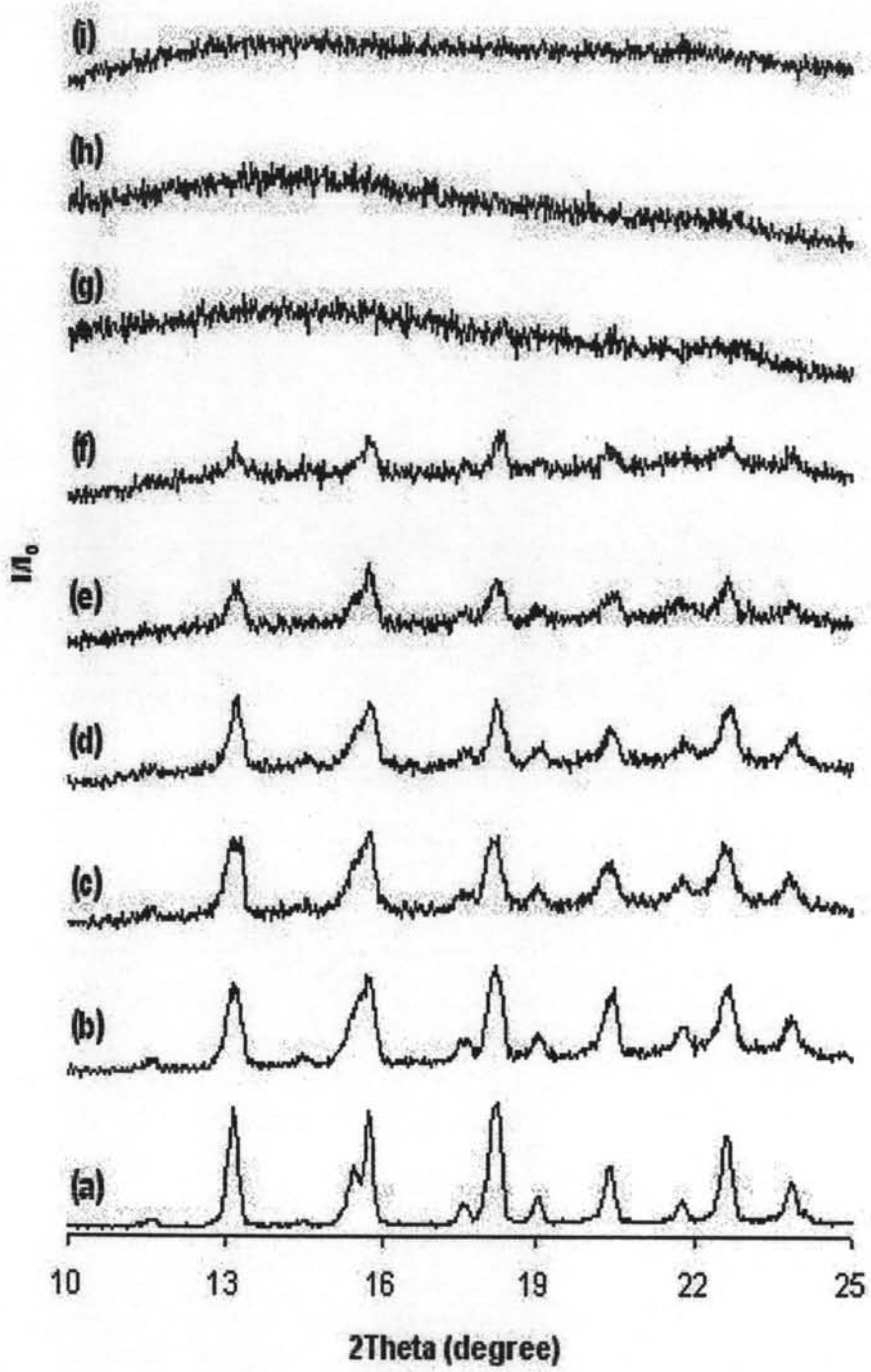
ANOVA

RATE

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	198.401	2	99.201	.289	.759
Within Groups	2059.828	6	343.305		
Total	2258.229	8			

APPENDIX D

XRPD Pattern of E_2 in ERS Physical Mix



X-ray powder diffraction patterns of physical mixes containing E_2 at different weight percent: (a) E_2; (b) 75 % E_2; (c) 50 % E_2; (d) 30 % E_2; (e) 20 % E_2; (f) 10 % E_2; (g) 2 % E_2; (h) 1 % E_2; (i) ERS

VITA

Miss Chutima Wiranidchapong was born on March 26, 1971 in Bangkok, Thailand. She received the Bachelor of Science (Pharmacy) in 1993 from the Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand. Since graduation, she worked as a hospital pharmacist in Government Hospital, Ministry of Health, Loei, Thailand. In 1995, she entered the Master's degree program at the Faculty of Graduated Studies, Mahidol University, Bangkok, Thailand and received the Master of Science in Pharmacy (Pharmaceutics) in 1997 and became a faculty member at the Faculty of Pharmacy, Srinakharinwirot University, Nakorn-nayok, Thailand. She entered the Doctoral program in Pharmaceutics at Chulalongkorn University in 2002 under the supports by the Ministry of Education, Thai Government and the Thailand Research Fund-Master Research Grant.