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## **APPENDICES**

## Appendix A

### Preformulation of Free Film Formulations

**Table 21** Mechanical Properties of free films from various formulations.

Formulations	Specimen Number	Thickness (mm)	Stress at Ultimate (MPa)	% Strain at Auto. Break (%)	Modulus (AutYoung) (MPa)	Toughness (MPa)
<i>F0</i>	1	0.065	76.43	9.51	965.0	3.683
	2	0.075	66.26	9.51	816.0	3.252
	3	0.065	76.51	10.16	914.4	3.979
	4	0.065	76.86	10.01	942.0	3.914
	5	0.065	76.35	10.34	936.8	4.218
	6	0.065	76.38	12.00	824.9	4.941
	<b>Mean:</b>	0.067	74.80	10.26	899.83	4.00
	<b>SD:</b>	0.004	4.19	0.92	63.64	0.57
<i>F1</i>	1	0.105	68.09	81.91	443.04	44.60
	2	0.110	71.34	85.81	464.14	46.72
	3	0.108	70.04	84.25	455.70	45.87
	4	0.095	79.59	95.74	517.84	52.13
	5	0.090	87.19	148.73	622.00	41.08
	6	0.094	83.91	143.13	598.59	39.53
	<b>Mean:</b>	0.100	76.69	106.59	516.89	44.99
	<b>SD:</b>	0.008	7.97	30.88	77.08	4.47
<i>F2</i>	1	0.077	25.47	22.73	182.9	3.625
	2	0.131	14.97	14.98	112.4	1.186
	3	0.098	19.77	14.53	150.6	1.528
	4	0.106	18.51	15.88	128.8	1.545
	5	0.100	19.62	19.81	118.5	2.135
	6	0.094	20.87	18.19	134.1	2.058
	<b>Mean:</b>	0.101	19.87	17.69	137.9	2.013
	<b>SD:</b>	0.018	3.42	3.19	25.7	0.866
<i>F3</i>	1	0.135	14.53	21.02	89.1	1.812
	2	0.079	21.04	59.21	106.3	9.105
	3	0.086	16.01	27.24	118.6	2.904
	4	0.065	19.69	42.06	144.7	5.853
	5	0.098	20.01	28.90	131.3	3.919
	6	0.083	23.63	20.39	166.4	2.987
	<b>Mean:</b>	0.091	19.15	33.14	126.1	4.430
	<b>SD:</b>	0.024	3.34	14.98	27.6	2.661



**Table 21** Mechanical Properties of free films from various formulations.

Formulations	Specimen Number	Thickness (mm)	Stress at Ultimate (MPa)	% Strain at Auto. Break (%)	Modulus (AutYoung) (MPa)	Toughness (MPa)
<i>F4</i>	1	0.127	15.44	18.91	106.4	1.752
	2	0.163	0.23	41.44	73.0	3.381
	3	0.131	0.27	31.26	95.7	2.535
	4	0.089	16.96	35.26	142.4	4.556
	5	0.109	0.55	37.15	86.6	3.709
	6	0.104	0.52	35.26	95.3	3.057
	<b>Mean:</b>	0.121	5.66	33.22	99.9	3.165
	<b>SD:</b>	0.026	8.18	7.75	23.6	0.968
<i>F5</i>	1	0.110	0.21	20.70	124.1	1.994
	2	0.122	12.19	19.81	91.9	1.521
	3	0.120	13.00	20.94	96.9	1.751
	4	0.113	15.39	20.96	103.8	1.976
	5	0.125	0.17	25.98	80.1	2.110
	6	0.118	0.30	24.11	96.5	2.348
	<b>Mean:</b>	0.118	6.88	22.08	98.9	1.950
	<b>SD:</b>	0.006	7.36	2.41	14.7	0.286
<i>F6</i>	1	0.099	10.40	22.30	94.8	1.587
	2	0.082	6.67	26.04	69.2	1.198
	3	0.084	8.95	28.18	79.2	1.734
	4	0.077	9.15	19.94	92.7	1.267
	5	0.119	0.26	26.01	98.6	2.479
	6	0.113	12.91	39.84	91.5	3.633
	<b>Mean:</b>	0.096	8.06	27.05	87.7	1.983
	<b>SD:</b>	0.018	4.33	6.93	11.2	0.929
<i>F7</i>	1	0.100	0.80	36.27	104.2	3.215
	2	0.119	0.61	30.46	100.5	2.719
	3	0.109	0.44	31.08	114.5	2.981
	4	0.118	0.21	22.82	85.5	1.356
	5	0.093	0.09	29.03	99.9	2.100
	6	0.094	0.05	35.63	60.4	1.602
	<b>Mean:</b>	0.106	0.37	30.88	94.2	2.329
	<b>SD:</b>	0.012	0.30	4.90	19.0	0.760
<i>F8</i>	1	0.090	27.42	26.20	395.8	2.350
	2	0.114	22.34	24.18	361.6	1.743
	3	0.107	28.60	29.16	360.4	2.754
	4	0.103	27.18	31.10	371.8	2.934
	5	0.114	23.26	29.26	301.2	2.292
	6	0.095	20.18	25.96	319.8	1.661

**Table 21** Mechanical Properties of free films from various formulations.

Formulations	Specimen Number	Thickness (mm)	Stress at Ultimate (MPa)	% Strain at Auto. Break (%)	Modulus (AutYoung) (MPa)	Toughness (MPa)
	<b>Mean:</b>	0.104	24.83	27.64	351.77	2.29
	<b>SD:</b>	0.010	3.37	2.60	34.90	0.52
<i>F9</i>	1	0.087	n/a*	n/a*	n/a*	n/a*
	2	0.094	n/a*	n/a*	n/a*	n/a*
	3	0.117	n/a*	n/a*	n/a*	n/a*
	4	0.126	n/a*	n/a*	n/a*	n/a*
	5	0.090	n/a*	n/a*	n/a*	n/a*
	6	0.100	n/a*	n/a*	n/a*	n/a*
	<b>Mean:</b>	0.102	n/a*	n/a*	n/a*	n/a*
<b>SD:</b>	0.016	n/a*	n/a*	n/a*	n/a*	
<i>F10</i>	1	0.091	n/a*	n/a*	n/a*	n/a*
	2	0.097	n/a*	n/a*	n/a*	n/a*
	3	0.085	n/a*	n/a*	n/a*	n/a*
	4	0.091	n/a*	n/a*	n/a*	n/a*
	5	0.084	n/a*	n/a*	n/a*	n/a*
	6	0.103	n/a*	n/a*	n/a*	n/a*
	<b>Mean:</b>	0.092	n/a*	n/a*	n/a*	n/a*
<b>SD:</b>	0.007	n/a*	n/a*	n/a*	n/a*	

## **Appendix B**

### **Formulation Development of DTZ HCl TDDS**

#### **Spectrophotometric Analysis of DTZ HCl**

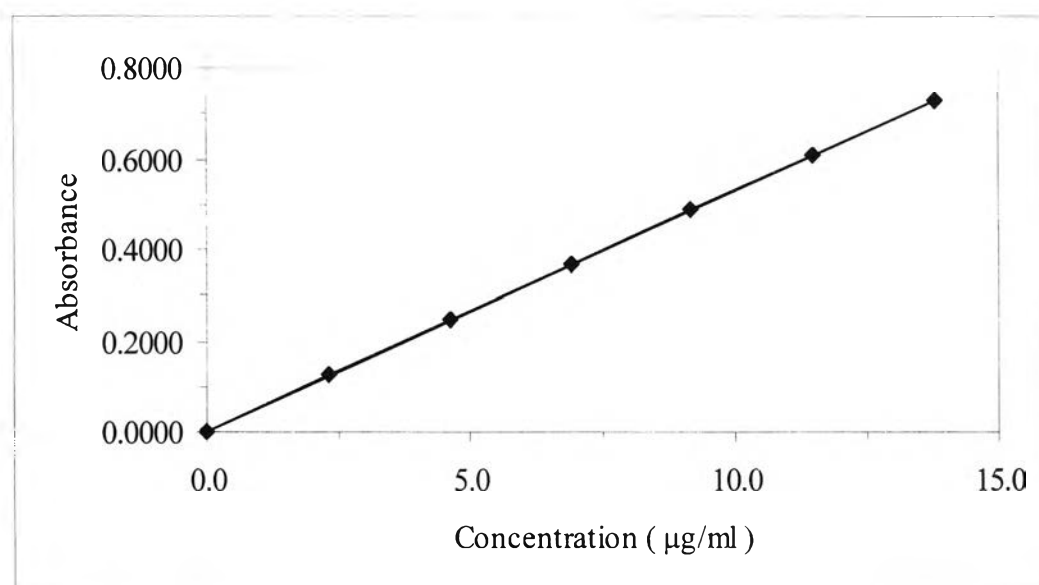
An ultraviolet absorption spectrum of DTZ HCl in DI water was obtained using a Jasco V-530, UV/VIS spectrophotometer. It was performed by scanning the UV absorption within the wavelength range of 350-200 nm at an ambient condition. The absorption spectrum was characterized by maxima at approximately 205 nm and 236 nm. The absorbance value at 236 nm was read and the corresponding DTZ HCl concentration was calculated from the calibration curve. The calibration curve of DTZ HCl in DI water was plotted between the concentration of drug as a function of absorbance. The concentration versus absorbance of DTZ HCl is presented in Table 22. A typical calibration plot showed a linear relationship between the absorbance and DTZ HCl concentration. The calibration curve of DTZ HCl after regression analysis is illustrated in Figure B1.

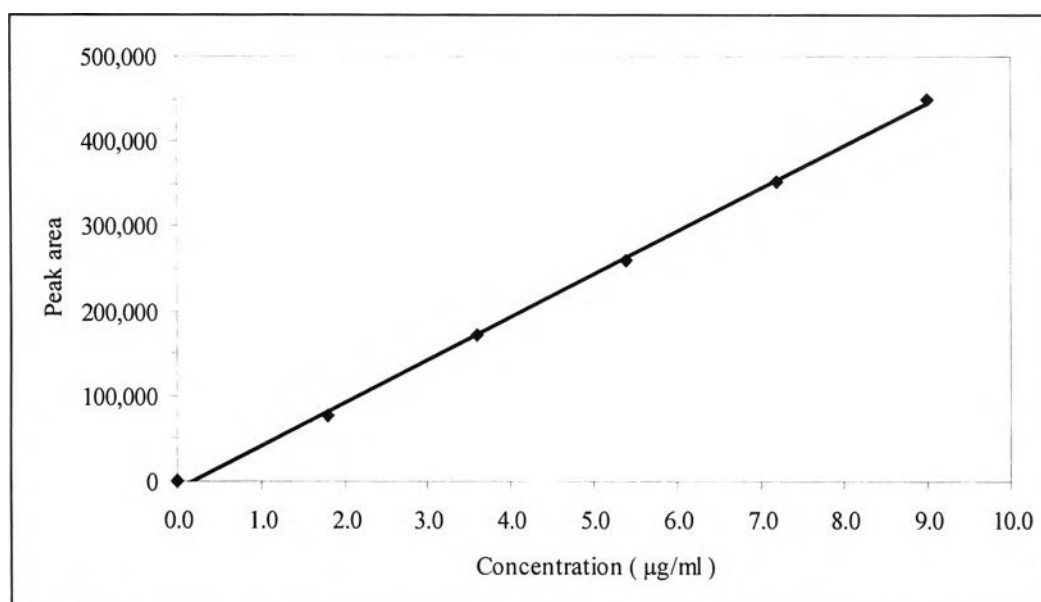
#### **HPLC Analysis of DTZ HCl**

Concentrations of DTZ HCl in the samples were obtained by a reversed phase HPLC as described in 2.1.3. The mobile phase was filtered through a 0.45  $\mu\text{m}$  membrane filter and then degassed by sonication for 30 min prior to use. The concentration versus peak area of DTZ HCl with HPLC method at 240 nm is presented in Table 23 and showed a linear relationship with the coefficient of determination 0.999. The standard curve of DTZ HCl after regression analysis was illustrated in Figure B2; it was repeated prior to every course of the analysis.

**Table 22** Absorbance of DTZ HCl in DI water determined at 236 nm.

Concentration ( $\mu\text{g/ml}$ )	Absorbance
0.0	0.0000
2.3	0.1252
4.6	0.2442
6.9	0.3667
9.2	0.4888
11.5	0.6084
13.8	0.7300
$r^2$	1.0000
<b>Y-intercept</b>	0.0018
<b>Slope</b>	0.0528

**Figure 57** Calibration curve of DTZ HCl in DI water.



**Figure 58** Calibration curve of DTZ HCl from HPLC method.

**Table 23** Peak area of diltiazem hydrochloride with HPLC method at 240 nm.

Concentration (µg/ml)	Peak area
0.0	0
1.8	75,833
3.6	171,445
5.4	258,199
7.2	352,572
9.0	449,663

**Table 24** Diltiazem hydrochloride content in various films formulations.

Formulations	Content (mg/g)						Mean	SD
	1	2	3	4	5	6		
A1 (10:0)	158.3	170.5	145.5	158.7	153.4	166.7	158.9	9.0
A4 (8:2)	172.6	163.5	157.7	171.8	178.0	172.5	169.3	7.4
A5 (6:4)	143.1	153.1	157.8	159.8	148.1	161.5	153.9	7.2
A8 (4:6)	161.2	176.7	147.7	175.1	171.9	180.8	168.9	12.3
A9 (2:8)	135.7	136.0	142.5	135.4	147.3	136.6	138.9	4.9
A41* (IPM)	157.5	138.1	156.1	138.6	154.0	147.5	148.6	8.7
A42* (IPP)	146.0	131.8	134.3	133.5	136.7	128.5	135.1	6.0
A43* (NMP)	141.2	140.3	146.9	142.7	138.6	144.3	142.3	3.0
A44* (OA)	134.1	141.4	137.9	134.8	133.1	134.8	136.0	3.1
A45* (PEG)	151.2	152.5	153.4	154.8	155.0	158.4	154.2	2.5
A46* (PG)	146.3	146.9	148.7	148.0	150.2	149.3	148.2	1.5
A47* (Tw)	140.5	140.7	141.3	142.8	142.1	146.4	142.3	2.2

\* 8:2, HPMC:EC films with 30%DBP and 10% enhancer.

**Table 25** Percent moisture uptake of films containing diltiazem hydrochloride and various ratios of HPMC and EC.

Formulations	% Moisture Uptake						Mean	SD
	1	2	3	4	5	6		
A1 (10:0)	55.4	50.0	46.2	45.8	41.9	49.5	48.1	4.6
A4 (8:2)	32.7	33.3	24.6	30.9	29.8	25.9	29.5	3.6
A5 (6:4)	18.5	16.5	22.1	21.5	20.9	10.5	18.3	4.4
A8 (4:6)	16.2	7.8	17.0	16.1	17.6	15.5	15.0	3.6
A9 (2:8)	10.7	16.5	9.3	13.7	10.5	8.8	11.6	3.0
A10 (0:10)	1.7	0.8	4.0	3.1	2.3	5.1	2.8	1.6

**Table 26** Percent moisture uptake of 8:2 HPMC:EC films containing diltiazem hydrochloride and various types of enhancers.

Formulations	% Moisture Uptake						Mean	SD
	1	2	3	4	5	6		
<i>A4</i>	32.7	33.3	24.6	30.9	29.8	25.9	29.5	3.6
<i>A41</i> (IPM)	34.5	34.6	37.6	36.2	39.1	33.3	35.9	2.2
<i>A42</i> (IPP)	21.3	22.3	23.3	26.4	23.1	26.1	23.8	2.1
<i>A43</i> (NMP)	25.4	32.0	29.2	29.7	35.8	33.1	30.9	3.6
<i>A44</i> (OA)	30.2	35.0	33.6	36.4	33.6	30.4	33.2	2.5
<i>A45</i> (PEG)	37.7	31.7	41.2	36.0	28.3	34.2	34.9	4.5
<i>A46</i> (PG)	27.1	29.7	31.1	30.4	27.9	31.7	29.6	1.8
<i>A47</i> (Tw)	36.2	38.8	36.3	42.1	37.1	36.6	37.8	2.3

**Table 27** Absorbance of films containing diltiazem hydrochloride and various ratios of HPMC and EC.

Formulations	Absorbance						Mean	SD
	1	2	3	4	5	6		
<i>A1</i> (10:0)	0.0620	0.0640	0.0626	0.0622	0.0605	0.0644	0.0626	0.0014
<i>A4</i> (8:2)	0.0615	0.0614	0.0630	0.0592	0.0627	0.0608	0.0614	0.0014
<i>A5</i> (6:4)	0.0619	0.0607	0.0599	0.0606	0.0614	n/a*	0.0609	0.0008
<i>A8</i> (4:6)	0.0609	0.0607	0.0602	0.0603	0.0606	0.0591	0.0603	0.0006
<i>A9</i> (2:8)	0.0605	0.0628	0.0578	0.0575	0.0591	0.0606	0.0597	0.0020
<i>A10</i> (0:10)	0.0652	0.0614	0.0680	0.0711	0.0602	0.0660	0.0653	0.0041

\*n/a (not available)

**Table 28** Absorbance of 8:2 HPMC:EC films containing diltiazem hydrochloride and various types of enhancers.

Formulations	Absorbance						Mean	SD
	1	2	3	4	5	6		
<i>A4</i>	0.0615	0.0614	0.0630	0.0592	0.0627	0.0608	0.0614	0.0014
<i>A41</i> (IPM)	0.0648	0.0662	0.0663	0.0649	0.0696	0.0702	0.0670	0.0023
<i>A42</i> (IPP)	0.0615	0.0634	0.0701	0.0672	0.0678	0.0671	0.0662	0.0031
<i>A43</i> (NMP)	0.0616	0.0688	0.0619	0.0640	0.0650	0.0627	0.0640	0.0027
<i>A44</i> (OA)	0.0620	0.0666	0.0608	0.0642	0.0709	0.0661	0.0651	0.0036
<i>A45</i> (PEG)	0.0634	0.0615	0.0645	0.0646	0.0639	0.0639	0.0636	0.0011
<i>A46</i> (PG)	0.0689	0.0721	0.0717	0.0699	0.0660	0.0679	0.0694	0.0023
<i>A47</i> (Tw)	0.0770	0.0782	0.0736	0.0803	0.0702	0.0740	0.0756	0.0036



## Appendix C

### An Evaluation of DTZ HCl TDDS

**Table 29** Percent release of diltiazem hydrochloride from films containing various ratios of HPMC and EC in DI water.

Formulations	Time (hours)	% Drug Release						Mean	SD	Log % drug remained
		1	2	3	4	5	6			
<i>A1</i> 10:0	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.00
	0.5	36.50	64.68	54.61	59.97	34.08	54.00	50.64	12.53	1.69
	1	55.12	80.66	72.03	75.36	48.87	70.07	67.02	12.33	1.52
	2	73.27	89.35	83.10	85.44	64.67	81.23	79.51	9.02	1.31
	3	80.89	92.38	87.08	90.19	71.78	84.83	84.53	7.43	1.19
	4	91.35	93.86	88.98	94.11	75.66	88.30	88.71	6.83	1.05
	6	93.69	98.62	93.68	99.79	80.28	93.40	93.24	6.93	0.83
	8	99.90	101.38	94.69	98.75	81.71	94.33	95.13	7.15	0.69
	12	101.47	105.90	99.87	105.11	86.55	99.80	99.78	6.98	-
<i>A4</i> 8:2	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.00
	0.5	39.74	40.45	41.22	38.72	40.35	58.15	43.10	7.42	1.76
	1	64.21	63.30	63.47	62.76	59.93	74.62	64.71	5.07	1.55
	2	78.22	79.02	80.10	78.31	78.07	82.54	79.38	1.72	1.31
	3	79.88	82.55	83.05	82.00	80.13	83.86	81.91	1.60	1.26
	4	83.53	84.43	86.82	85.29	85.83	85.07	85.16	1.13	1.17
	6	97.51	95.00	93.11	91.93	93.10	84.90	92.59	4.25	0.87
	8	95.55	94.52	94.74	95.21	94.62	87.92	93.76	2.89	0.79
	12	103.15	101.28	100.46	101.91	103.16	89.93	99.98	5.04	-
<i>A5</i> 6:4	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.00
	0.5	24.23	34.05	34.30	34.32	34.98	27.01	31.48	4.63	1.84
	1	41.19	53.81	54.00	53.28	53.98	38.45	49.12	7.26	1.71
	2	64.03	72.75	72.48	73.04	72.02	60.21	69.09	5.54	1.49
	3	75.28	78.06	78.32	78.74	77.91	70.03	76.39	3.35	1.37
	4	81.22	80.51	80.68	81.34	80.10	74.52	79.73	2.59	1.31
	6	89.85	88.32	89.69	89.40	88.89	79.53	87.61	4.00	1.09
	8	95.85	90.88	91.17	91.52	89.63	82.90	90.33	4.21	0.99
	12	96.82	92.02	93.76	93.41	92.62	85.93	92.43	3.59	0.88

**Table 29** Percent release of diltiazem hydrochloride from films containing various ratios of HPMC and EC in DI water (continue).

Formulations	Time (hours)	% Drug Release								Log % drug remained
		1	2	3	4	5	6	Mean	SD	
<i>A8</i>	0	0	0	0	0	0	0	0	0	2.00
4:6	0.5	19.74	23.74	25.10	26.11	23.86	17.40	22.66	3.37	1.89
	1	35.01	40.30	42.29	43.21	40.63	29.27	38.45	5.32	1.79
	2	57.76	64.30	66.85	66.97	64.68	48.89	61.57	7.06	1.58
	3	68.82	74.31	76.99	76.80	75.18	58.71	71.80	7.07	1.45
	4	74.35	79.84	81.98	81.09	79.99	64.49	76.96	6.66	1.36
	6	79.48	83.82	86.44	85.67	84.34	71.30	81.84	5.70	1.26
	8	82.23	86.89	88.48	88.36	87.72	74.79	84.74	5.40	1.18
	12	85.51	89.33	91.70	91.70	90.26	79.41	87.98	4.78	1.08
<i>A9</i>	0	0	0	0	0	0	0	0	0	2.00
2:8	0.5	6.40	5.40	6.00	5.69	4.50	5.34	5.55	0.65	1.98
	1	13.91	10.95	12.99	11.52	14.33	11.20	12.49	1.46	1.94
	2	28.80	23.95	27.01	24.62	30.17	21.33	25.98	3.29	1.87
	3	40.34	34.50	38.87	36.94	42.44	30.50	37.26	4.30	1.80
	4	48.06	42.86	47.07	45.92	50.17	38.46	45.42	4.18	1.74
	6	59.90	55.89	59.99	59.36	62.54	52.73	58.40	3.50	1.62
	8	68.57	65.55	69.85	68.70	72.24	68.82	68.95	2.16	1.49
	12	82.75	80.43	86.54	82.58	89.74	92.63	85.78	4.71	1.15
<i>A10</i>	0	0	0	0	0	0	0	0	0	2.00
0:10	0.5	0.39	0.43	0.43	0.52	0.28	0.30	0.39	0.09	2.00
	1	0.61	0.66	0.65	0.71	0.51	0.52	0.61	0.08	2.00
	2	0.94	1.02	1.06	1.04	0.85	0.79	0.95	0.11	2.00
	3	1.11	1.19	1.29	1.29	1.03	1.00	1.15	0.12	1.99
	4	1.29	1.44	1.49	1.43	1.23	1.15	1.34	0.14	1.99
	6	1.58	1.71	1.80	1.76	1.53	1.48	1.64	0.13	1.99
	8	1.63	1.82	1.94	1.90	1.73	1.67	1.78	0.12	1.99
	12	2.38	2.56	2.61	2.45	2.20	2.15	2.39	0.19	1.99

**Table 30** Percent release of diltiazem hydrochloride from films of HPMC containing various types of plasticizers in DI water.

Formulations	Time (hours)	% Drug Release						Mean	SD	Log % drug remained
		1	2	3	4	5	6			
<i>A2</i>	0	0	0	0	0	0	0	0	0	2.00
DEP	0.5	26.63	25.43	30.31	17.36	22.30	20.51	23.76	4.64	1.88
	1	35.14	33.96	43.93	26.96	33.41	29.69	33.85	5.80	1.82
	2	45.72	45.46	60.73	41.43	52.49	43.00	48.14	7.24	1.71
	3	53.39	53.91	67.28	50.34	63.55	51.73	56.70	6.97	1.64
	4	61.35	60.78	72.90	58.49	72.81	59.38	64.28	6.71	1.55
	6	71.95	70.50	81.61	65.79	83.28	71.46	74.10	6.84	1.41
	8	80.36	78.71	89.05	75.49	92.81	79.64	82.68	6.71	1.24
	12	94.89	92.14	102.99	89.73	97.66	94.13	95.26	4.63	0.68
<i>A3</i>	0	0	0	0	0	0	0	0	0	2.00
TEC	0.5	36.46	55.53	19.01	26.13	27.21	18.46	30.47	13.92	1.84
	1	47.17	69.85	26.14	38.50	42.18	33.46	42.88	15.06	1.76
	2	60.02	82.47	42.66	54.14	62.75	61.06	60.52	13.02	1.60
	3	68.58	88.01	53.28	61.77	73.25	79.48	70.73	12.42	1.47
	4	74.61	94.20	61.25	67.19	81.69	90.08	78.17	12.89	1.34
	6	80.94	99.79	69.35	73.29	86.47	99.74	84.93	12.94	1.18
	8	85.09	104.86	72.75	80.56	90.76	100.67	89.12	12.18	1.04
	12	93.07	109.16	74.68	83.18	91.63	102.66	92.40	12.54	0.88

**Table 31** Percent release of diltiazem hydrochloride from films of HPMC:EC 6:4 containing various types of plasticizers in DI water.

Formulations	Time (hours)	% Drug Release						Mean	SD	Log % drug remained
		1	2	3	4	5	6			
<i>A6</i>	0	0	0	0	0	0	0	0	0	2.00
DEP	0.5	12.31	18.63	17.02	9.16	21.01	14.36	15.42	4.34	1.93
	1	19.40	28.15	26.29	28.39	25.98	24.15	25.39	3.32	1.87
	2	26.54	37.13	34.06	37.79	31.94	35.02	33.75	4.12	1.82
	3	32.83	43.28	40.82	43.24	35.28	43.44	39.82	4.63	1.78
	4	46.72	49.96	49.76	52.01	41.89	55.81	49.36	4.73	1.70
	6	55.50	54.33	55.35	57.23	47.58	64.31	55.72	5.37	1.65
	8	64.63	61.51	69.27	64.29	58.75	74.34	65.46	5.59	1.54
	12	71.74	65.77	78.90	71.07	70.21	78.48	72.70	5.09	1.44
<i>A7</i>	0	0	0	0	0	0	0	0	0	2.00
TEC	0.5	26.37	22.35	39.57	33.01	20.85	41.56	30.62	8.80	1.84
	1	40.83	33.69	59.81	50.15	33.18	64.23	46.98	13.24	1.72
	2	61.70	54.09	79.75	78.62	51.12	85.42	68.45	14.64	1.50
	3	70.63	63.98	85.37	85.08	61.29	92.37	76.45	12.86	1.37
	4	75.45	69.31	87.71	87.35	66.10	94.18	80.02	11.34	1.30
	6	80.74	75.96	90.31	87.99	70.87	94.29	83.36	9.02	1.22
	8	83.43	78.84	93.43	88.56	73.69	95.56	85.59	8.50	1.16
	12	88.80	84.35	98.01	89.71	77.73	98.82	89.57	8.06	1.02

**Table 32** Cumulative skin permeation of diltiazem hydrochloride per surface area ( $\text{mg}/\text{cm}^2$ ) from films containing various ratios of HPMC and EC.

Formulations	Time (hours)	Cumulative skin permeation ( $\text{mg}/\text{cm}^2$ )									
		1	2	3	4	5	6	7	8	Mean	SD
<i>A1</i> (10:0)	0	0	0	0	0	0	0	0	0	0	0
	1	0.01	0.02	0.02	0.02	0.04	0.01	0.01	0.01	0.02	0.01
	2	0.06	0.07	0.12	0.12	0.13	0.02	0.04	0.05	0.08	0.04
	3	0.16	0.17	0.26	0.24	0.27	0.05	0.12	0.18	0.18	0.07
	4	0.29	0.23	0.37	0.35	0.43	0.11	0.26	0.37	0.30	0.10
	6	0.53	0.45	0.57	0.54	0.73	0.27	0.60	0.71	0.55	0.15
	8	0.73	0.62	0.72	0.69	0.93	0.48	0.98	1.02	0.77	0.19
	12	0.94	0.77	0.90	0.89	1.20	0.77	1.52	1.39	1.05	0.29
<i>A4</i> (8:2)	0	0	0	0	0	0	0	0	0	0	0
	1	0.01	0.02	0.02	0.01	0.02	0.01	0.02	0.02	0.02	0.01
	2	0.04	0.11	0.10	0.05	0.13	0.07	0.02	0.10	0.08	0.04
	3	0.11	0.27	0.19	0.15	0.29	0.17	0.05	0.23	0.18	0.08
	4	0.20	0.43	0.35	0.27	0.43	0.30	0.11	0.39	0.31	0.11
	6	0.42	0.74	0.63	0.49	0.67	0.50	0.27	0.65	0.54	0.16
	8	0.64	0.96	0.84	0.69	0.85	0.70	0.49	0.90	0.76	0.15
	12	0.92	1.22	1.07	0.97	1.09	0.97	0.93	1.25	1.05	0.13
<i>A5</i> (6:4)	0	0	0	0	0	0	-	-	-	0	0
	1	0.01	0.02	0.02	0.03	0.04	-	-	-	0.02	0.01
	2	0.10	0.09	0.02	0.03	0.04	-	-	-	0.06	0.04
	3	0.31	0.18	0.04	0.05	0.05	-	-	-	0.13	0.12
	4	0.44	0.28	0.06	0.07	0.05	-	-	-	0.18	0.17
	6	0.72	0.47	0.07	0.13	0.08	-	-	-	0.29	0.29
	8	0.94	0.63	0.17	0.22	0.13	-	-	-	0.42	0.35
	12	1.18	0.83	0.34	0.39	0.31	-	-	-	0.61	0.38

**Table 33** Cumulative skin permeation of diltiazem hydrochloride per surface area ( $\text{mg}/\text{cm}^2$ ) from films of HPMC:EC 8:2 containing various ratios of enhancers.

Formulations	Time (hours)	Cumulative skin permeation ( $\text{mg}/\text{cm}^2$ )						
		1	2	3	4	5	Mean	SD
<i>A41</i>	0	0	0	0	0	-	0	0
IPM	1	0.01	0.01	0.01	0.00	-	0.01	0.01
	2	0.14	0.06	0.09	0.05	-	0.08	0.04
	3	0.42	0.24	0.28	0.22	-	0.29	0.09
	4	0.71	0.43	0.48	0.41	-	0.51	0.14
	6	1.29	0.87	0.97	0.86	-	1.00	0.20
	8	1.82	1.35	1.46	1.40	-	1.51	0.21
	12	2.64	2.14	2.18	2.32	-	2.32	0.22
<i>A42</i>	0	0	0	0	0	-	0	0
IPP	1	0.04	0.01	0.01	0.00	-	0.01	0.02
	2	0.30	0.08	0.09	0.04	-	0.13	0.12
	3	0.74	0.28	0.29	0.12	-	0.36	0.27
	4	1.22	0.49	0.51	0.20	-	0.60	0.43
	6	2.16	0.95	0.95	0.43	-	1.12	0.73
	8	2.91	1.49	1.40	0.68	-	1.62	0.93
	12	4.18	2.40	2.21	1.15	-	2.48	1.26
<i>A43</i>	0	0	0	0	0	-	0	0
NMP	1	0.00	0.00	0.01	0.00	-	0.00	0.00
	2	0.01	0.01	0.02	0.03	-	0.02	0.01
	3	0.05	0.04	0.06	0.11	-	0.06	0.03
	4	0.12	0.10	0.11	0.19	-	0.13	0.04
	6	0.35	0.27	0.28	0.44	-	0.33	0.08
	8	0.63	0.51	0.50	0.72	-	0.59	0.11
	12	1.24	1.07	1.05	1.33	-	1.17	0.13
<i>A44</i>	0	0	0	0	0	0	0	0
OA	1	0.00	0.00	0.00	0.01	0.00	0.00	0.00
	2	0.02	0.02	0.01	0.04	0.01	0.02	0.01
	3	0.07	0.07	0.05	0.09	0.03	0.06	0.02
	4	0.13	0.15	0.11	0.15	0.08	0.12	0.03
	6	0.19	0.27	0.20	0.29	0.14	0.22	0.06
	8	0.25	0.40	0.29	0.47	0.21	0.32	0.11
	12	0.77	1.13	0.84	0.96	0.77	0.89	0.15

**Table C5** Cumulative skin permeation of diltiazem hydrochloride per surface area ( $\text{mg}/\text{cm}^2$ ) from films of HPMC:EC 8:2 containing various ratios of enhancers (continue).

Formulations	Time (hours)	Cumulative skin permeation ( $\text{mg}/\text{cm}^2$ )						
		1	2	3	4	5	Mean	SD
<i>A45</i>	0	0	0	0	0	-	0	0
PEG	1	0.01	0.03	0.01	0.00	-	0.01	0.01
	2	0.03	0.11	0.06	0.03	-	0.06	0.04
	3	0.08	0.24	0.11	0.06	-	0.13	0.08
	4	0.14	0.40	0.19	0.11	-	0.21	0.13
	6	0.27	0.78	0.36	0.25	-	0.41	0.25
	8	0.42	1.24	0.57	0.49	-	0.68	0.38
	12	0.82	2.20	1.18	1.47	-	1.42	0.59
<i>A46</i>	0	0	0	0	0	0	0	0
PG	1	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	2	0.01	0.01	0.04	0.02	0.03	0.02	0.01
	3	0.03	0.05	0.11	0.07	0.08	0.07	0.03
	4	0.08	0.12	0.20	0.12	0.17	0.14	0.05
	6	0.14	0.20	0.29	0.29	0.29	0.24	0.07
	8	0.21	0.30	0.40	0.40	0.40	0.34	0.09
	12	0.70	0.92	0.94	0.73	1.18	0.90	0.19
<i>A47</i>	0	0	0	0	0	-	0	0
Tw	1	0.02	0.01	0.01	0.02	-	0.02	0.01
	2	0.23	0.15	0.14	0.21	-	0.18	0.05
	3	0.53	0.29	0.29	0.44	-	0.39	0.12
	4	0.78	0.51	0.51	0.89	-	0.67	0.20
	6	1.22	0.81	0.97	1.42	-	1.11	0.27
	8	1.55	1.14	1.37	1.79	-	1.46	0.28
	12	2.00	1.56	1.90	2.25	-	1.93	0.28

### Preparation of Phosphate Buffer Saline, pH 7.4

The 0.02 M phosphate buffer saline (PBS, pH 7.4) was prepared as follows.

<i>Stock solution 1</i>		<i>Stock solution 2</i>	
<b>Rx</b>		<b>Rx</b>	
Sodium phosphate dibasic anhydrous,		Sodium phosphate monobasic monohydrate,	
Na <sub>2</sub> HPO <sub>4</sub> (anhydrous)	14.2 g	NaH <sub>2</sub> PO <sub>4</sub> ·H <sub>2</sub> O	13.8 g
Sodium chloride, NaCl	42.5 g	Sodium chloride, NaCl	42.5 g
DI water to make 500 ml		DI water to make 500 ml	

Stock solutions of 0.2 M mono- and disodium phosphate in 8.5% sodium chloride solutions were prepared and then, make 1:10 dilution separately. Finally, the pH of *Diluted solution 1* was adjusted to 7.4 with *Diluted solution 2* using pH meter.



## Appendix D

### Data in Statistical Processes

#### D1. Thickness of free film formulations at various ratios of HPMC and EC (data from Table 7)

- Kruskal-Wallis one way analysis of variance on ranks

<b>Group</b>	<b>Median</b>	<b>25%</b>	<b>75%</b>	<b>H</b>	<b>P</b>	<b>Results*</b>
<i>F1</i> (10:0)	0.1000	0.0940	0.108	12.574	0.028	S
<i>F2</i> (8:2)	0.0990	0.0940	0.106			
<i>F5</i> (6:4)	0.119	0.113	0.122			
<i>F8</i> (4:6)	0.105	0.0950	0.114			
<i>F9</i> (2:8)	0.0970	0.0900	0.117			
<i>F10</i> (0:10)	0.0910	0.0850	0.097			

\* There are significant differences when  $p < 0.05$ ,  
S = Significance, NS = Non-significance

All pairwise multiple comparison procedures (Dunnett's method) :

<b>Comparison</b>	<b>Diff of Ranks</b>	<b>p</b>	<b>q'</b>	<b>P&lt;0.05</b>
<i>F10</i> vs <i>F5</i>	126.000	6	3.452	Yes
<i>F1</i> vs <i>F5</i>	81.500	5	2.672	Yes
<i>F2</i> vs <i>F5</i>	79.000	4	3.225	Yes
<i>F9</i> vs <i>F5</i>	79.000	3	4.272	Yes
<i>F8</i> vs <i>F5</i>	63.500	2	5.084	Yes

**D2. UTS of free film formulations at various ratios of HPMC and EC (data from Table 7)**

- Kruskal-Wallis one way analysis of variance on ranks

Group	Median	25%	75%	H	P	Results*
<i>F2</i> (8:2)	19.695	18.510	20.870	13.205	0.001	S
<i>F5</i> (6:4)	6.245	0.210	13.000			
<i>F8</i> (4:6)	25.220	22.340	27.420			

\* There are significant differences when  $p < 0.05$ ,  
S = Significance, NS = Non-significance

All pairwise multiple comparison procedures (Dunnett's method) :

Comparison	Diff of Ranks	p	q'	P<0.05
<i>F5</i> (6:4) vs <i>F2</i> (8:2)	38.000	3	2.055	No
<i>F8</i> (4:6) vs <i>F2</i> (8:2)	29.000	2	2.322	No Test Needed

**D3. Percentage of elongation at break of free film formulations at various ratios of HPMC and EC (data from Table 7).**

- Kruskal-Wallis one way analysis of variance on ranks

Group	Median	25%	75%	H	P	Results*
<i>F2</i> (8:2)	17.035	14.980	19.810	12.612	0.002	S
<i>F5</i> (6:4)	20.950	20.700	24.110			
<i>F8</i> (4:6)	27.680	25.960	29.260			

\* There are significant differences when  $p < 0.05$ ,  
S = Significance, NS = Non-significance

All pairwise multiple comparison procedures (Dunnett's method) :

Comparison	Diff of Ranks	p	q'	P<0.05
<i>F8</i> (4:6) vs <i>F2</i> (8:2)	65.500	3	3.542	Yes
<i>F5</i> (6:4) vs <i>F2</i> (8:2)	29.000	2	2.322	Yes

**D4. Young's modulus of free film formulations at various ratios of HPMC and EC (data from Table 7).**

- Kruskal-Wallis one way analysis of variance on ranks

Group	Median	25%	75%	H	P	Results*
<i>F1</i> (10:0)	490.990	455.700	598.590	21.147	<0.001	S
<i>F2</i> (8:2)	131.450	118.500	150.600			
<i>F5</i> (6:4)	96.700	91.900	103.800			
<i>F8</i> (4:6)	361.000	319.800	371.800			

\* There are significant differences when  $p < 0.05$ ,  
S = Significance, NS = Non-significance

All pairwise multiple comparison procedures (Dunnett's method) :

Comparison	Diff of Ranks	p	q'	P<0.05
<i>F5</i> (6:4) vs <i>F8</i> (4:6)	70.000	4	2.858	Yes
<i>F2</i> (8:2) vs <i>F8</i> (4:6)	38.000	3	2.055	No
<i>F1</i> (10:0) vs <i>F8</i> (4:6)	36.000	2	2.882	No Test Needed

**D5. Toughness of free film formulations at various ratios of HPMC and EC (data from Table 7).**

- Kruskal-Wallis one way analysis of variance on ranks

Group	Median	25%	75%	H	P	Results*
<i>F2</i> (8:2)	1.801	1.528	2.135	2.00	0.368	NS
<i>F5</i> (6:4)	1.985	1.751	2.110			
<i>F8</i> (4:6)	2.321	1.743	2.754			

\* There are significant differences when  $p < 0.05$ ,  
S = Significance, NS = Non-significance

**D6. Thickness of free film formulations of HPMC and EC with various plasticizers** (data from Table 8)

- Kruskal-Wallis one way analysis of variance on ranks (8:2, HPMC:EC films)

<b>Group</b>	<b>Median</b>	<b>25%</b>	<b>75%</b>	<b>H</b>	<b>P</b>	<b>Results*</b>
<i>F2</i> (DBP)	0.0990	0.0940	0.106	4.492	0.106	NS
<i>F3</i> (DEP)	0.0845	0.0790	0.0980			
<i>F4</i> (TEC)	0.118	0.104	0.131			

\* There are significant differences when  $p < 0.05$ ,  
S = Significance, NS = Non-significance

- Kruskal-Wallis one way analysis of variance on ranks (6:4, HPMC:EC films)

<b>Group</b>	<b>Median</b>	<b>25%</b>	<b>75%</b>	<b>H</b>	<b>P</b>	<b>Results*</b>
<i>F5</i> (DBP)	0.119	0.113	0.122	6.523	0.038	S
<i>F6</i> (DEP)	0.0915	0.0820	0.113			
<i>F7</i> (TEC)	0.105	0.0940	0.118			

\* There are significant differences when  $p < 0.05$ ,  
S = Significance, NS = Non-significance

All pairwise multiple comparison procedures (Dunnett's method) :

<b>Comparison</b>	<b>Diff of Ranks</b>	<b>p</b>	<b>q'</b>	<b>P&lt;0.05</b>
<i>F6</i> (DEP) vs <i>F5</i> (DBP)	46.000	3	2.487	Yes
<i>F7</i> (TEC) vs <i>F5</i> (DBP)	32.000	2	2.562	Yes

**D7. UTS of free film formulations of HPMC and EC with various plasticizers**  
(data from Table 8)

- Kruskal-Wallis one way analysis of variance on ranks (8:2, HPMC:EC films)

<b>Group</b>	<b>Median</b>	<b>25%</b>	<b>75%</b>	<b>H</b>	<b>P</b>	<b>Results*</b>
<i>F2</i> (DBP)	19.695	18.510	20.870	8.433	0.015	S
<i>F3</i> (DEP)	19.850	16.010	21.040			
<i>F4</i> (TEC)	0.535	0.270	15.440			

\* There are significant differences when  $p < 0.05$ ,  
S = Significance, NS = Non-significance

All pairwise multiple comparison procedures (Dunnett's method) :

<b>Comparison</b>	<b>Diff of Ranks</b>	<b>p</b>	<b>q'</b>	<b>P&lt;0.05</b>
<i>F4</i> (TEC) vs <i>F3</i> (DEP)	46.000	3	2.487	Yes
<i>F2</i> (DBP) vs <i>F3</i> (DEP)	1.000	2	0.0801	No

- Kruskal-Wallis one way analysis of variance on ranks (6:4, HPMC:EC films)

<b>Group</b>	<b>Median</b>	<b>25%</b>	<b>75%</b>	<b>H</b>	<b>P</b>	<b>Results*</b>
<i>F5</i> (DBP)	6.245	0.210	13.000	4.610	0.100	NS
<i>F6</i> (DEP)	9.050	6.670	10.400			
<i>F7</i> (TEC)	0.325	0.0900	0.610			

\* There are significant differences when  $p < 0.05$ ,  
S = Significance, NS = Non-significance

**D8. Percentage of elongation at break of free film formulations of HPMC and EC with various plasticizers (data from Table 8)**

- Kruskal-Wallis one way analysis of variance on ranks (8:2, HPMC:EC films)

Group	Median	25%	75%	H	P	Results*
<i>F2</i> (DBP)	17.035	14.980	19.810	9.039	0.011	S
<i>F3</i> (DEP)	28.070	21.020	42.060			
<i>F4</i> (TEC)	35.260	31.260	37.150			

\* There are significant differences when  $p < 0.05$ ,  
S = Significance, NS = Non-significance

All pairwise multiple comparison procedures (Dunnett's method) :

Comparison	Diff of Ranks	p	q'	P<0.05
<i>F4</i> (TEC) vs <i>F3</i> (DEP)	46.000	3	2.487	Yes
<i>F2</i> (DBP) vs <i>F3</i> (DEP)	1.000	2	0.0801	No

- Kruskal-Wallis one way analysis of variance on ranks (6:4, HPMC:EC films)

Group	Median	25%	75%	H	P	Results*
<i>F5</i> (DBP)	20.950	20.700	24.110	7.942	0.019	S
<i>F6</i> (DEP)	26.025	22.300	28.180			
<i>F7</i> (TEC)	30.770	29.030	35.630			

\* There are significant differences when  $p < 0.05$ ,  
S = Significance, NS = Non-significance

All pairwise multiple comparison procedures (Dunnett's method) :

Comparison	Diff of Ranks	p	q'	P<0.05
<i>F7</i> (TEC) vs <i>F5</i> (DBP)	52.000	3	2.812	Yes
<i>F6</i> (DEP) vs <i>F5</i> (DBP)	29.000	2	2.322	Yes

**D9. Young's modulus of free film formulations of HPMC and EC with various plasticizers (data from Table 8)**

- Kruskal-Wallis one way analysis of variance on ranks (8:2, HPMC:EC films)

<b>Group</b>	<b>Median</b>	<b>25%</b>	<b>75%</b>	<b>H</b>	<b>P</b>	<b>Results*</b>
<i>F2</i> (DBP)	131.450	118.500	150.600	5.474	0.065	NS
<i>F3</i> (DEP)	124.950	106.300	144.700			
<i>F4</i> (TEC)	95.500	86.600	106.400			

\* There are significant differences when  $p < 0.05$ ,  
S = Significance, NS = Non-significance

- Kruskal-Wallis one way analysis of variance on ranks (6:4, HPMC:EC films)

<b>Group</b>	<b>Median</b>	<b>25%</b>	<b>75%</b>	<b>H</b>	<b>P</b>	<b>Results*</b>
<i>F5</i> (DBP)	96.700	91.900	103.800	2.538	0.281	NS
<i>F6</i> (DEP)	92.100	79.200	94.800			
<i>F7</i> (TEC)	100.200	85.500	104.200			

\* There are significant differences when  $p < 0.05$ ,  
S = Significance, NS = Non-significance

**D10. Young's modulus of free film formulations of HPMC and EC with various plasticizers (data from Table 8)**

- Kruskal-Wallis one way analysis of variance on ranks (8:2, HPMC:EC films)

Group	Median	25%	75%	H	P	Results*
F2 (DBP)	1.801	1.528	2.135	5.719	0.057	NS
F3 (DEP)	3.453	2.904	5.853			
F4 (TEC)	3.219	2.535	3.709			

\* There are significant differences when  $p < 0.05$ ,  
S = Significance, NS = Non-significance

- Kruskal-Wallis one way analysis of variance on ranks (6:4, HPMC:EC films)

Group	Median	25%	75%	H	P	Results*
F5 (DBP)	1.985	1.751	2.110	1.298	0.523	NS
F6 (DEP)	1.660	1.267	2.479			
F7 (TEC)	2.410	1.602	2.981			

\* There are significant differences when  $p < 0.05$ ,  
S = Significance, NS = Non-significance

**D11. Average release time profile of diltiazem hydrochloride from the films containing various ratios of HPMC and EC (data from Table 15)**

- Kruskal-Wallis one way analysis of variance on ranks (time range of 0-12 hrs)

Group	Median	25%	75%	H	P	Results*
A1 (10:0)	84.250	71.462	88.248	5.981	0.201	NS
A4 (8:2)	92.460	82.390	94.972			
A5 (6:4)	94.330	84.055	95.980			
A8 (4:6)	94.660	86.850	96.557			
A9 (2:8)	91.340	71.235	94.828			

\* There are significant differences when  $p < 0.05$ ,  
S = Significance, NS = Non-significance



**D12. Average release time profile of diltiazem hydrochloride from the films of HPMC containing various types of plasticizers (data from Table 16)**

- Kruskal-Wallis one way analysis of variance on ranks (8:2, HPMC:EC films)

Group	Median	25%	75%	H	P	Results*
A1 (DBP)	84.500	62.900	93.675	2.864	0.239	NS
A2 (DEP)	56.700	31.300	76.250			
A3 (TEC)	70.700	39.800	85.950			

\* There are significant differences when  $p < 0.05$ ,  
S = Significance, NS = Non-significance

**D13. Average release time profile of diltiazem hydrochloride from 6:4, HPMC:EC films containing various types of plasticizers (data from Table 17)**

- Kruskal-Wallis one way analysis of variance on ranks (6:4, HPMC:EC films)

Group	Median	25%	75%	H	P	Results*
A5 (DBP)	76.400	44.700	88.275	2.801	0.247	NS
A6 (DEP)	49.400	22.900	67.300			
A7 (TEC)	76.500	42.900	83.950			

\* There are significant differences when  $p < 0.05$ ,  
S = Significance, NS = Non-significance

**D14. Average cumulative permeation of diltiazem hydrochloride from the films containing various ratios of HPMC and EC via pig ear skin from time range of 3-12 hours (data from Table 18)**

- Kruskal-Wallis one way analysis of variance on ranks

Group	Median	25%	75%	H	P	Results*
A1 (10:0)	0.550	0.270	0.840	2.185	0.335	NS
A4 (8:2)	0.540	0.277	0.833			
A5 (6:4)	0.290	0.167	0.467			

\* There are significant differences when  $p < 0.05$ ,  
S = Significance, NS = Non-significance

**D15. Average cumulative permeation of diltiazem hydrochloride from the films containing various ratios of HPMC and EC via pig ear skin from time range of 3-12 hours (data from Table 19)**

- Kruskal-Wallis one way analysis of variance on ranks

Group	Median	25%	75%	H	P	Results*
A4 (8:2)	0.540	0.277	0.833	8.051	0.045	S
A41 (IPM)	1.000	0.455	1.712			
A42 (IPP)	1.120	0.540	1.835			
A47 (Tw)	2.820	1.530	4.010			

\* There are significant differences when  $p < 0.05$ ,  
S = Significance, NS = Non-significance

All pairwise multiple comparison procedures (Dunnett's method) :

Comparison	Diff of Ranks	p	q'	P<0.05
A47 (Tw) vs A4	52.000	4	2.780	Yes
A42 (IPP) vs A4	25.000	3	1.768	No
A41 (IPM) vs A4	17.000	2	1.776	No Test Needed

## VITAE

Mr. Ekapol Limpongsa was born on January 3, 1972 in Nakornratchasima. He got his degree in Bachelor of Pharmacy in 1993 from Faculty of Pharmacy, Chiangmai University, Chiangmai, Thailand. He received his Master degree of Science in Industrial Pharmacy from Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand, in 1996. After the graduation, he has been working as a lecturer in the Faculty of Pharmaceutical Sciences, Khonkaen University, Khonkaen, Thailand.

