CHAPTER 4

Results

4.1 Tranexamic acid patch preparations

The hydrogel preparations of formulae M35, M38 and J33 observed at 24 hours after preparation (day 1) at room temperature were homogeneous, fairly tough and flexible. The data of their appearances in addition to adhesion time are shown in Table 4.1

Table 4.1 The appearances of different hydrogel formulations.

Formula	Appearance
M35	Clear gel, slight flexibility, poor adhesion, approximate skin adhesion time, 1 hour
M38	White turbid gel, good flexibility, good adhesion, approximate skin adhesion time, 2 hours
J33	Clear gel, very good flexibility, good adhesion, approximate skin adhesion, 5 hours

4.2 The pH measurement

The pH data of hydrogel patches in various formulae are shown in table 4.2. The range of pH was approximately 3-7.

4.3 Spectrofluorimetric determination of tranexamic acid

4.3.1 Assay validation

The validation method was expressed in terms of accuracy and precision, linearity,

selectivity and limit of detection. The results are shown by the following titles;

Table 4.2 pH of tranexamic acid hydrogel patch formulations.

Formula	pH measured on first day of storage			
	1st	2nd	3rd	Average pH
M35	6.716	6.701	6.681	6.699
M38	6.751	6.700	6.787	6.746
J33	5.126	5.149	5.248	5.174
P1	3.936	3.931	3.943	3.937
P4	3.013	3.019	3.059	3.030
P7	6.247	6.560	6.387	6.398
P8	6.569	6.648	6.660	6.626
P9	5.325	5.370	5.330	5.342
P10	5.364	5.401	5.405	5.390
P11	5.436	5.435	5.434	5.435

4.3.1.1 Accuracy and precision of tranexamic acid analysis method

The accuracy and precision of tranexamic acid were investigated from a calibration curve (figure 4.1). This method was validated from the intra-day and inter-day of determination that is shown in table 4.3. A linear relationship between tranexamic concentration and fluorescence intensity was observed in the range of 8.4-84.0 mg/ml with an equation of inter-day investigation as follows:

Fluorescence intensity = 27.961 Tranexamic acid conc. + 163.39

The coefficient of determination (R^2) was 0.9996. The accuracy and precision of tranexamic acid calibration curve are shown in table 1. The accuracy of this method was in the range of 96.34-101.81% and the precision (%RSD) was below 1.85% and was independent of concentrations.

4.3.1.2 Examination of derivatization stability

The stability of derivatization reaction of 50.4 μg/ml tranexamic acid standard solution with NDA/CN^- , and drug-reagent reaction comparing with the reaction of NDA/CN^- alone (reagent blank) are shown in figure 4.2.

Table 4.3 Accuracy and precision of tranexamic acid calibration curve.

Nominal conc. (μg/ml)	Estimated conc. (μg/ml) (mean ± SD)	Accuracy (Estimated/Nominal)x 100	Precision (%RSD)
Intra-day (n=5)			
8.4	8.49 ± 0.13	101.11	0.92
16.8	16.19 ± 0.13	96.34	0.57
33.6	34.08 ± 0.47	101.44	1.18
50.4	51.52 ± 0.08	102.23	0.14
67.2	66.67 ± 0.22	99.21	0.30
84.0	83.73 ± 0.13	99.67	0.14
Inter-day (n=5)			
8.4	8.34 ± 0.17	99.34	1.17
16.8	16.81 ± 0.42	100.04	1.84
33.6	32.92 ± 0.72	97.98	1.85
50.4	51.31 ± 0.41	101.81	0.71
67.2	67.62 ± 1.19	100.63	1.62
84.0	83.39 ± 0.37	99.27	0.41

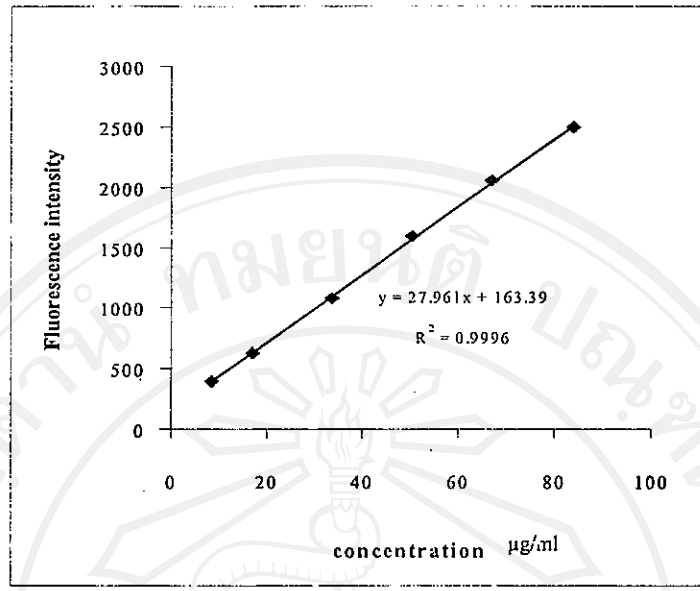

Figure 4.1 Calibration curve of tranexamic acid.

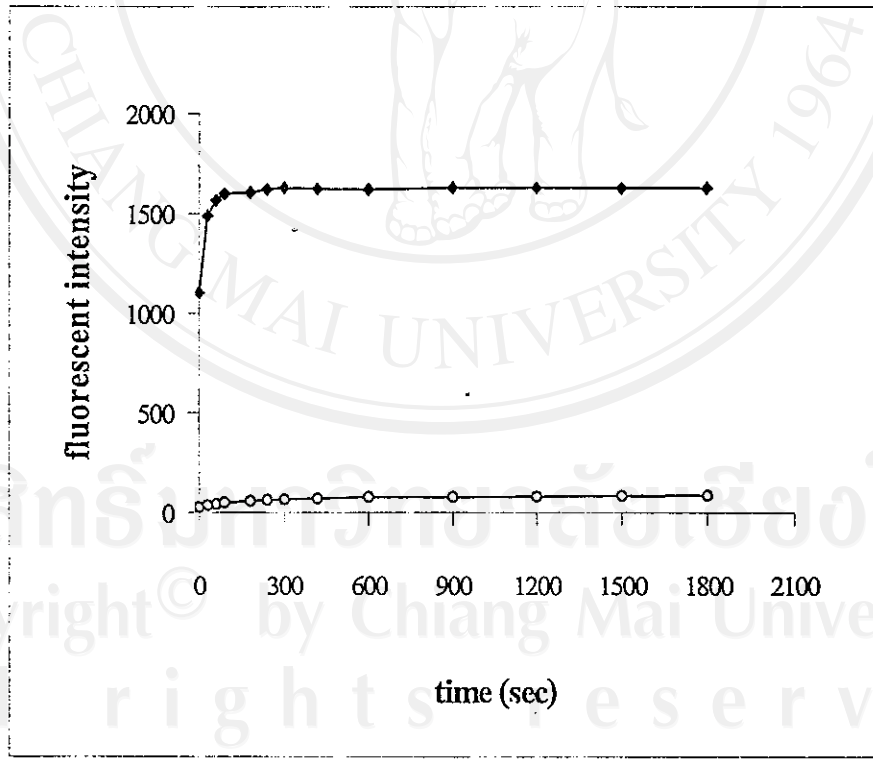

Figure 4.2 Fluorescence intensities investigated by derivatization of 50.4 µg/ml tranexamic acid standard solution (♦) and reagent blank (○).

4.3.1.3 Limit of detection of tranexamic acid determination

The lowest concentration of tranexamic acid that can be detected by this method was 4.2 μg/ml (table 4.4). The average intensity (n=5) of reagent blank was used to compare in a signal-to-noise ratio. It was found that this concentration exhibited an average fluorescent intensity approximately three times more than that from the reagent blank. Thus, the signal-to-noise ratio was 3:1.

Table 4.4 Limit of detection of tranexamic acid.

(The average intensity of reagent blank was 60.74)

Concentration (μg/ml)	Average intensity	SD	%RSD
4.2	190.6	3.09	1.62

4.3.2 Fluorescence spectra of NDA reacted with tranexamic acid

Tranexamic acid standard solution in a concentration of 33.6 μg/ml was derivatized with NDA in presence of cyanide ion. The derivative was measured and scanned by spectrofluorometer. Figure 4.3 shows the fluorescence spectra consisting of emission and excitation spectra.

4.4 Quantitative analysis of tranexamic acid in hydrogels

4.4.1 Examination of gel base influence

Tranexamic acid content in standard solution was converted from the intensities and compared with the drug content from spiking and sample solutions. It was found that the drug contents of formulae M35s and J33s prepared by spiking method were significantly less than the standard solution (84.0 μg/ml tranexamic acid in PBS), (Anova, Tukey, $P<0.05$). the hydrogel samples of formulas M35, M38 and J33 showed the same drug content comparing with the drug content in standard solution.

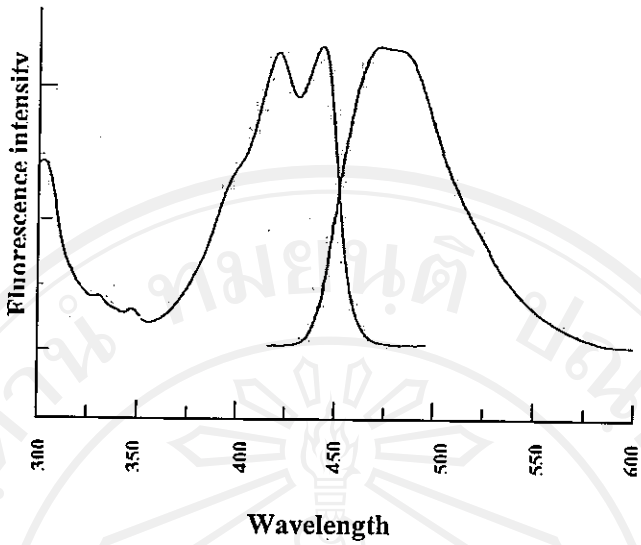

Figure 4.3 The fluorescence spectra of tranexamic acid derivatized with NDA.

4.4.2 Tranexamic acid content in hydrogels

Drug content in the preparation was measured on the first day of storage. Table 4.5 shows the tranexamic acid content measured by sampling from the patches compared with spiking method. Table 4.6, figures 4.4, 4.5 and 4.6 show that the drug remained in tranexamic acid patches in 3 storage conditions (4 °C, room temperature and 45°C). The drug content from the hydrogel patches that are stored at 4 °C and 45°C conditions were first measured on 30th day.

Table 4.5 Tranexamic acid content in hydrogel patch preparations in the first day of storage comparing with spiking method measurement.

Formula	Drug in analytes (μg/ml)	% Drug recovery	% Drug content
M35s	82.49	98.20	4.12 ±0.04
M38s	83.15	98.99	4.16 ± 0.05
J33s	81.87	97.46	4.09 ± 0.04
M35	83.00	98.81	4.15 ± 0.02
M38	82.85	98.63	4.14 ± 0.05
J33	83.26	99.12	4.16 ± 0.03

Table 4.6 Tranexamic acid content of tranexamic acid patches in various storage conditions.

Day of storage	% Tranexamic acid remained of three formulas in various storage conditions								
	M35			M38			J33		
	4 °C	RT[a]	45°C	4 °C	RT[a]	45°C	4 °C	RT[a]	45°C
1	-	4.15 ± 0.02	-	-	4.14± 0.05	-	-	4.16± 0.03	-
30	4.18± 0.03	4.18± 0.01	4.02± 0.02*	4.15± 0.03	4.18± 0.01	3.82± 0.01*	4.15± 0.02	4.19± 0.01	4.18± 0.01
60	4.06± 0.04*	4.15± 0.04	4.02± 0.02*	4.30± 0.13*	4.21± 0.01	4.15± 0.02*	4.05± 0.02*	4.17± 0.01	4.64± 0.02*
90	4.18± 0.03	4.20± 0.05	4.18± 0.04	4.31± 0.08*	4.18± 0.03	3.94± 0.04*	4.14± 0.01	4.05± 0.12	4.03± 0.03*
120	4.39± 0.09*	4.14± 0.05	4.28± 0.02*	4.36± 0.09*	3.88± 0.02*	4.33± 0.02*	4.38± 0.09*	3.89± 0.15*	4.32± 0.02

a = Room temperature (29°C)

* = Significantly different from the drug content on day1 at 95% confident (ANOVA, Tukey tests, $P < 0.05$)

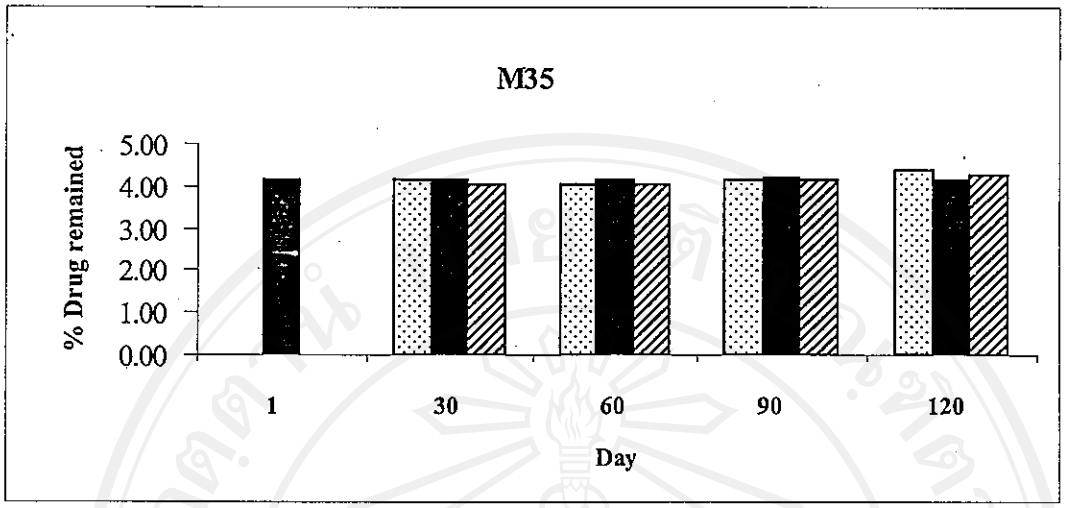

Figure 4.4 % Drug remained in hydrogel formula M35 stored in 4°C (⊡) , room temperature (■) and 45°C (▨).

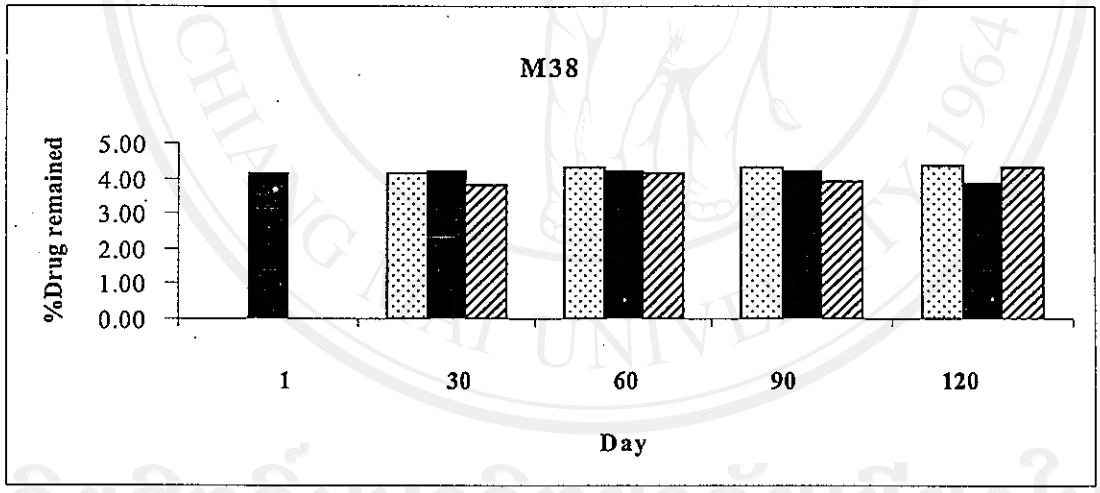

Figure 4.5 % Drug remained in hydrogel formula M38 stored in 4°C (⊡) , room temperature (■) and 45°C (▨).

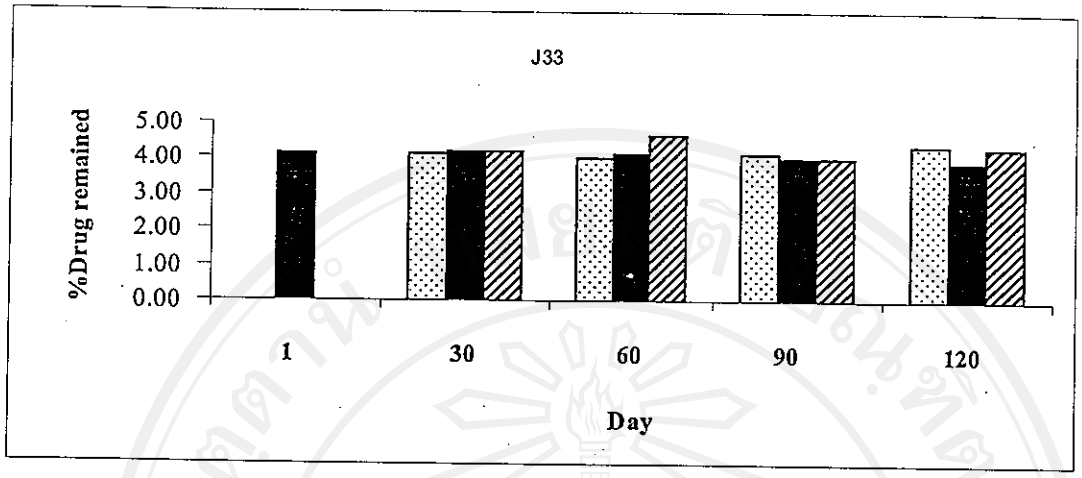

Figure 4.6 % Drug remained in hydrogel formula J33 stored in 4°C ( ), room temperature ( ) and 45°C ( ).

4.4.3 Release study of tranexamic acid from the hydrogels

Formula J33 was examined for its reproducibility. Table 4.7 shows 3 series of tranexamic acid releasing from the hydrogel of J33 patches. The standard deviations of these series were below 1.44. The release profiles (figure 4.7) were significantly indifferent (95% confidence, Repeated measurement, Tukey tests).

Table 4.7 Reproducibility of formula J33 exhibited as % tranexamic acid released.

Time (min)	% Released			% Average released	SD
	1st	2nd	3rd		
10	4.43	4.30	4.09	4.27	0.17
20	8.65	8.60	7.82	8.36	0.46
30	12.66	11.69	10.91	11.75	0.87
60	17.20	19.75	18.03	18.33	1.30
120	29.36	30.54	27.67	29.19	1.44
180	34.01	34.72	33.69	34.14	0.53

The one-day patches prepared with different gelling agents were investigated in term of % released shown in table 4.8 and their release profiles are shown in figure 4.8. Formula M35 was prepared with HPMC E4M, M38 was prepared with HPMC E4M and acrylax® 1061, while formula J33 was prepared with HPMC E50 and carbopol® 980 NF. Table 4.9 shows the % released for these three patch formulas investigated on the 120th day of storage. Their release profiles are shown in figures 4.9, 4.10 and 4.11.

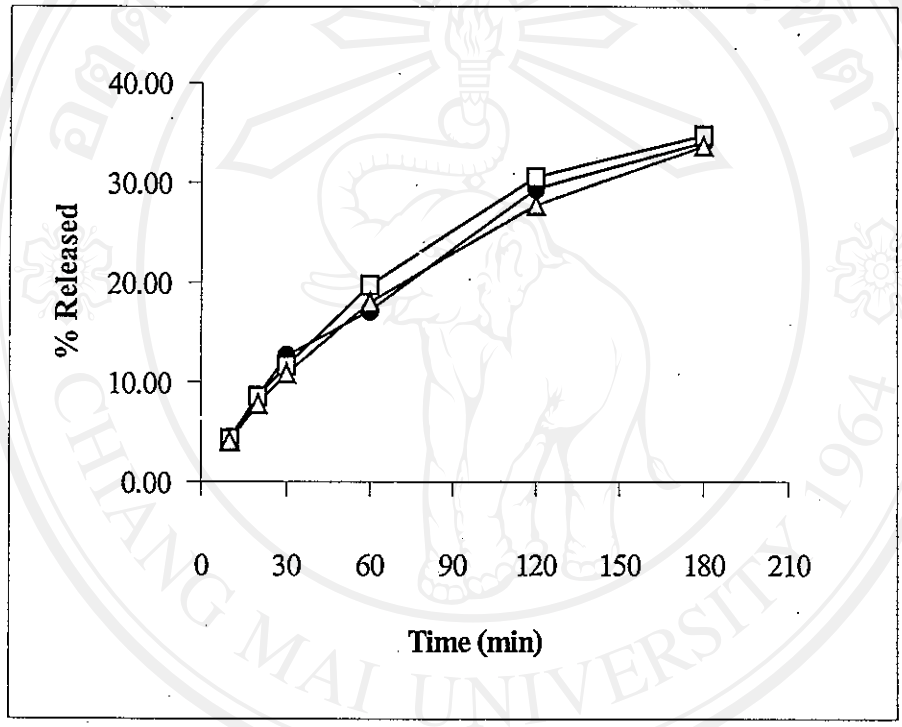

Figure 4.7 Triplicate release profiles of tranexamic acid from formula J33 ; 1st profile (●), 2nd profile (□), 3rd profile (Δ).

Table 4.8 Release of tranexamic acid from the hydrogels prepared with different gelling agents on the first day of storage.

Time (min)	% Release (day 1)		
	M35	M38	J33
10	8.12 ± 0.65	3.46 ± 0.63	4.27 ± 0.17
20	14.21 ± 0.92	12.03 ± 2.53	8.36 ± 0.46
30	19.74 ± 0.76	16.09± 2.28	11.75 ± 0.87
60	31.54 ± 0.78	20.02 ± 3.43	18.33 ± 1.30
120	44.59 ± 2.19	28.34 ± 3.19	29.19 ± 1.44
180	49.88 ± 3.95	30.83 ± 5.14	34.14 ± 0.53

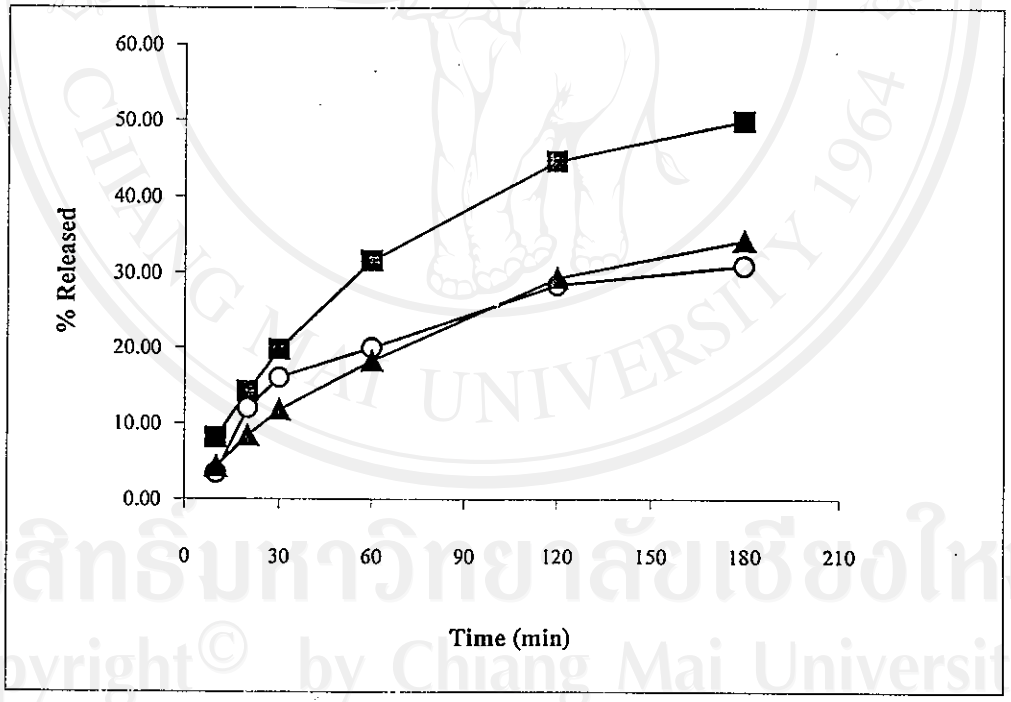

Figure 4.8 Release profiles of tranexamic acid from the hydrogels on the first day of storage; formula M35 (■), M38 (○) and J33 (▲).

Table 4.9 Release of tranexamic acid from the hydrogels on the first day of room temperature storage and the 120th day of 3 storage conditions ; 4 °C , Room temperature (RT) and 45°C.

Time (min)	% Released of three formulas of tranexamic acid in various storage conditions											
	M35				M38				J33			
	Day 1	4 °C	RT	45°C	Day 1	4 °C	RT	45°C	Day 1	4 °C	RT	45°C
10	8.12 ± 0.65	4.39 ± 0.65	8.19 ± 1.13	6.33 ± 1.50	3.46 ± 0.63	4.80 ± 1.64	8.12 ± 0.27	6.55 ± 0.65	4.27 ± 0.17	3.47 ± 0.87	6.72 ± 1.51	4.58 ± 0.88
20	14.21±10.92	8.64 ± 0.36	13.52 ± 1.61	11.61 ± 2.41	12.03 ± 2.53	8.39 ± 3.23	13.93 ± 0.44	10.83 ± 1.71	8.36 ± 0.46	7.04 ± 2.47	10.35 ± 0.93	8.48 ± 1.58
30	19.74 ± 0.76	10.75 ± 0.75	17.46 ± 2.44	12.99 ± 2.61	16.09 ± 2.28	10.94 ± 3.19	17.12 ± 1.71	13.99 ± 3.61	11.75 ± 0.87	9.80 ± 1.66	12.65 ± 1.87	11.43 ± 2.51
60	31.54 ± 0.78	18.50 ± 1.14	23.11 ± 2.25	21.29 ± 2.91	20.02 ± 3.43	19.11 ± 3.72	24.95 ± 2.65	23.94 ± 3.85	18.33 ± 1.30	16.62 ± 0.95	17.28 ± 0.94	17.62 ± 2.89
120	44.59 ± 2.19	29.11 ± 1.44	33.87 ± 1.98	34.92 ± 2.47	28.34 ± 3.19	27.95 ± 1.91	31.30 ± 2.81	31.79 ± 3.51	29.19 ± 1.44	28.64 ± 1.12	24.91 ± 2.85	30.69 ± 2.43
180	49.88 ± 3.95	33.64 ± 0.77	38.40 ± 2.11	40.42 ± 1.78	30.83 ± 5.14	31.65 ± 1.53	36.69 ± 3.49	35.72 ± 4.09	34.14 ± 0.53	33.87 ± 1.83	32.23 ± 3.41	36.64 ± 3.42

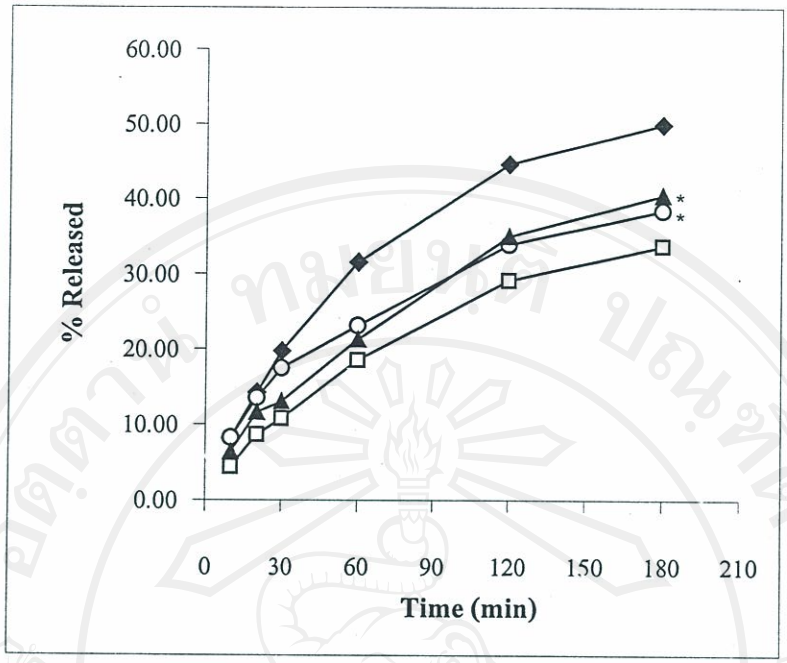

Figure 4.9 Release profiles of tranexamic acid from hydrogel formula M35 on first day of storage (♦) and three profiles investigated from 120th day of various storage conditions; 4 °C (□), room temperature (O) and 45°C (▲).

* = Significant difference at 95% confidence (Repeated measurement, Tukey tests)

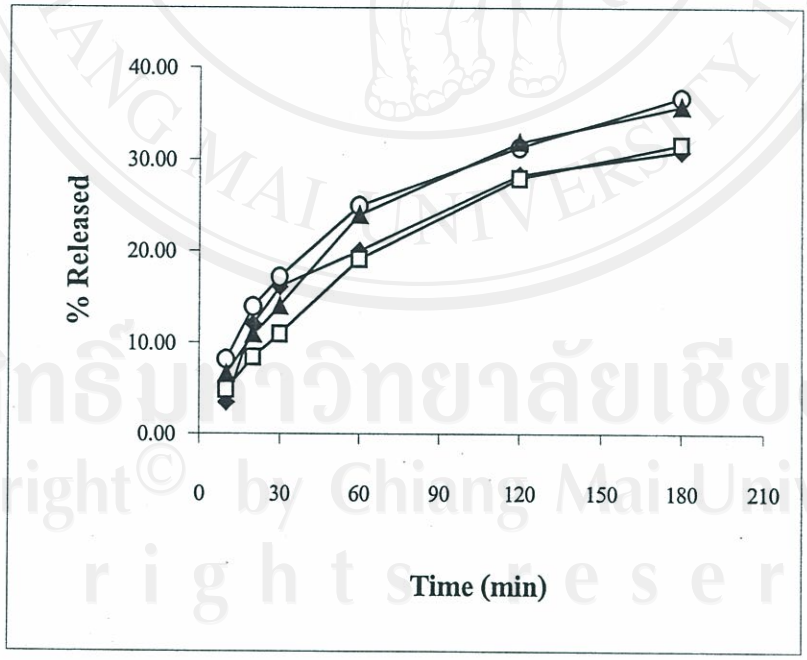

Figure 4.10 Release profiles of tranexamic acid from hydrogel formula M38 on first day of storage (♦) and three profiles investigated from 120th day of various storage condition; 4 °C (□), room temperature (O) and 45°C (▲).

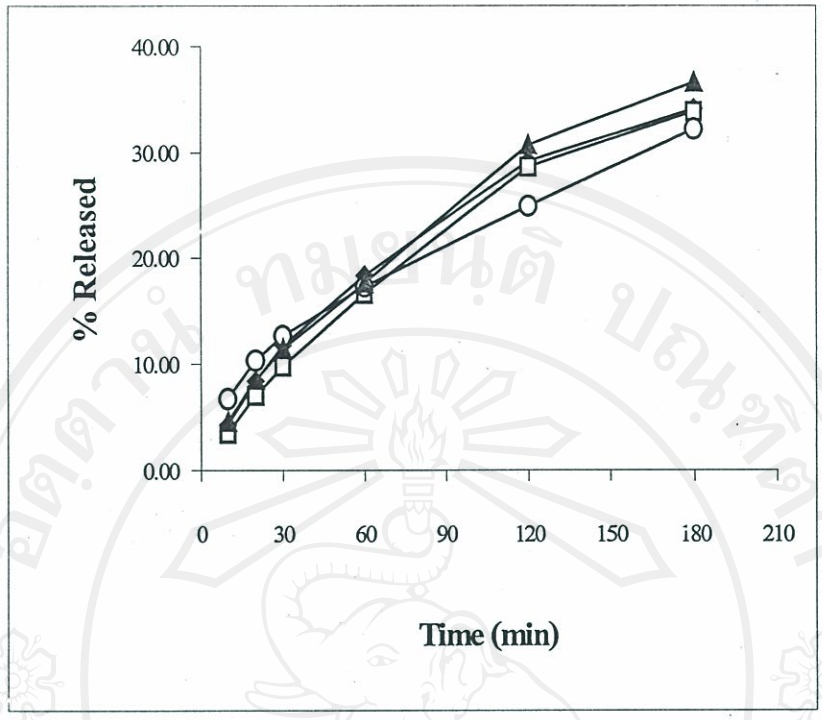

Figure 4.11 Release profiles of tranexamic acid from hydrogel formula J33 on first day of storage (♦) and three profiles investigated from 120th day of various storage condition; 4 °C (□), room temperature (O) and 45°C (▲).

4.4.4 Release study of tranexamic acid patches with releasing accelerants

Percentage released of tranexamic patches in formula M35 and its related formulae consisted of a releasing accelerant, lactic acid, are shown in table 4.10 and their release profiles are shown in figure 4.12. Both of P1 and P4, which contained lactic acid at 4.76 and 9.09 %w/w respectively, released lower than M35, a control formula.

Table 4.11 shows the data of percentage released of M35 and the presence of N-methylpyrrolidone (NMP) in its related formulas. It was found that tranexamic acid and NMP in the ratio of 1:1 as in formula P7 released more than those of control formula and formula with drug: NMP ratio of 1:2 as in formula P8.

Table 4.10 Release of tranexamic acid from formula M35 and the formulae containing lactic acid (P1 and P4).

Time (min)	% Released		
	M35	P1	P4
10	8.12 ± 0.65	4.33 ± 1.43	4.91 ± 1.09
20	14.21 ± 0.92	8.72 ± 0.51	7.00 ± 0.83
30	19.74 ± 0.76	11.87 ± 0.25	8.27 ± 0.60
60	31.54 ± 0.78	20.18 ± 1.08	11.87 ± 0.92
120	44.59 ± 2.19	27.78 ± 1.80	25.78 ± 5.62
180	49.88 ± 3.95	37.28 ± 1.12	34.46 ± 4.07

Table 4.11 Release of tranexamic acid from formula M35 and the formulae containing NMP (P7 and P8).

Time (min)	% Released		
	M35	P7	P8
10	8.12 ± 0.65	8.51 ± 0.95	7.00 ± 1.83
20	14.21 ± 0.92	14.30 ± 0.32	10.87 ± 1.31
30	19.74 ± 0.76	20.62 ± 0.99	16.55 ± 1.58
60	31.54 ± 0.78	32.83 ± 0.63	25.90 ± 2.15
120	44.59 ± 2.19	48.81 ± 0.53	37.25 ± 0.79
180	49.88 ± 3.95	59.22 ± 0.75	45.52 ± 1.85

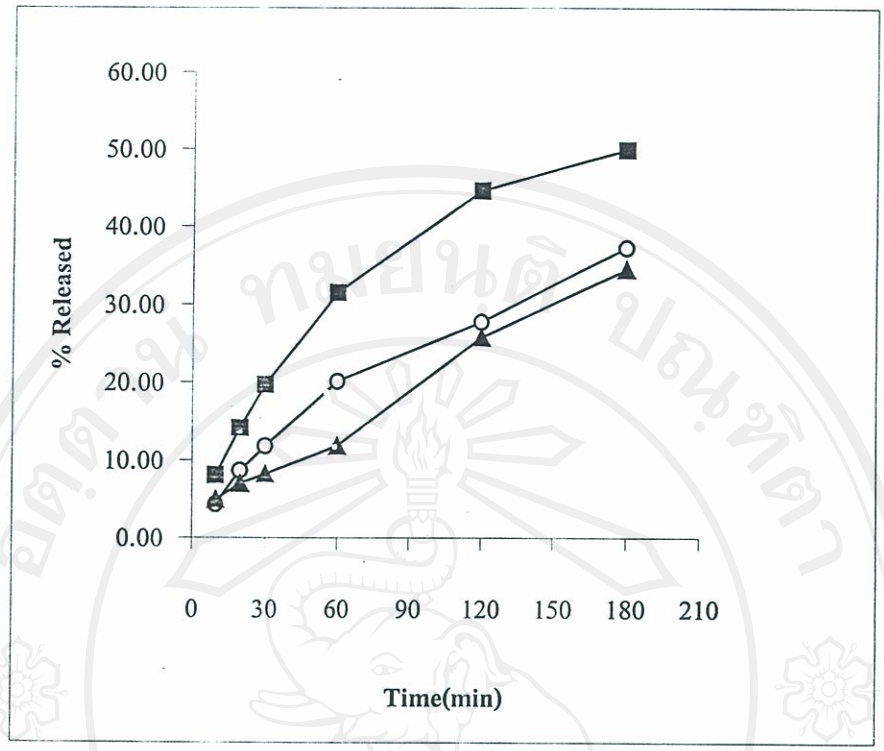

Figure 4.12 Release profiles of tranexamic acid from hydrogel formula M35 (■)and the formulas with lactic acid; P1 (○)and P4 (▲).

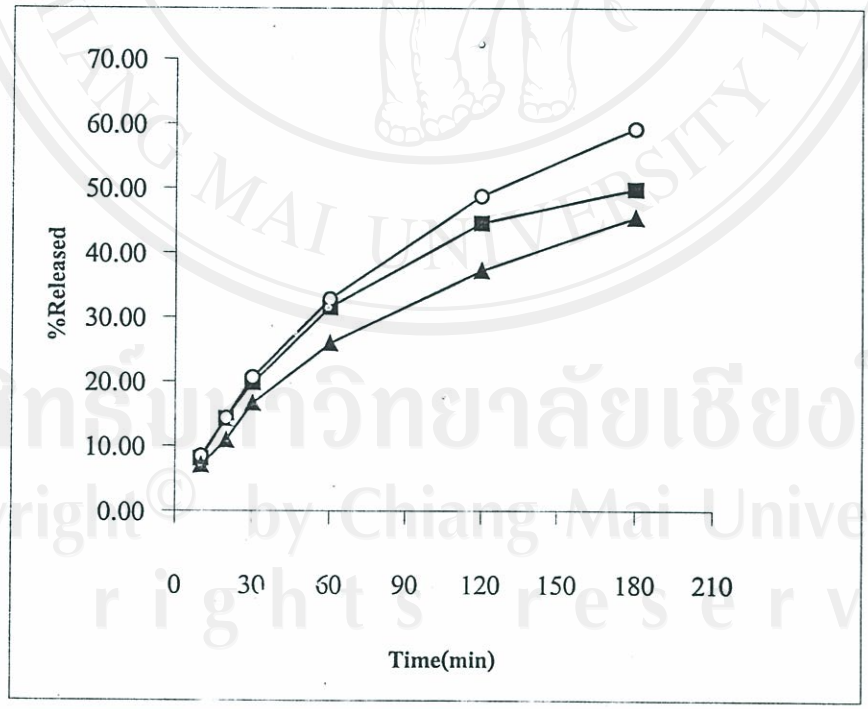

Figure 4.13 Release profiles of tranexamic acid from hydrogel formula M35 (■)and the formulas with NMP; P7 (○)and P8 (▲).

The comparison between a control formula (J33) and three related formulas in presence of NMP is shown in table 4.12 and the tranexamic acid release profiles are shown in figure 4.14. It was found that all formulas consisted of NMP provided more tranexamic acid release than a control formula, particularly formula P9 (amount ratio of drug: NMP = 1:2) had highest release.

Table 4.12 Release of tranexamic acid from formula J33 and the formulae with NMP (P9, P10 and P11).

Time (min)	% Released			
	J33	P9	P10	P11
10	4.27 ± 0.17	7.19 ± 2.08	4.57 ± 1.15	4.31 ± 0.52
20	8.36 ± 0.46	12.02 ± 0.92	9.14 ± 0.48	8.58 ± 0.98
30	11.75 ± 0.87	16.67 ± 0.72	11.62 ± 0.36	13.84 ± 0.58
60	18.33 ± 1.30	28.07 ± 1.29	21.52 ± 0.95	25.36 ± 0.38
120	29.19 ± 1.44	44.28 ± 1.90	34.99 ± 1.91	36.31 ± 1.38
180	34.14 ± 0.53	53.11 ± 3.75	49.55 ± 1.96	45.13 ± 1.58

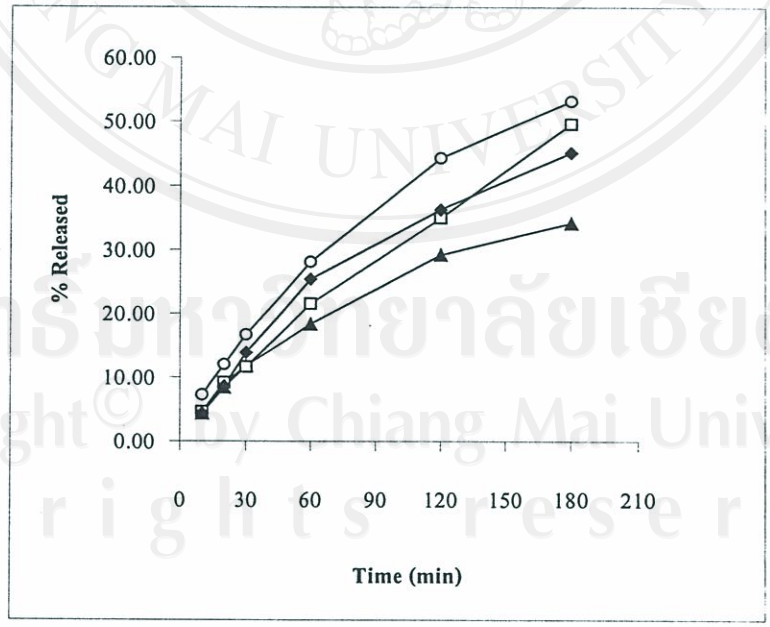

Figure 4.14 Release profiles of tranexamic acid from hydrogel formula J33 (▲) and the formulas with NMP; P9 (○), P10 (□) and P11(◆).

4.4.5 Examination of first order kinetics of tranexamic acid release

The % tranexamic acid released was plotted with the square root of time in Higuchi relation. The similar slopes of the repeated profiles were obtained from the reproducibility study of J33 (figure 4.15). All release profiles of J33 were first order kinetics as seen from the linear relationships between % tranexamic acid and the square root of time. The highest of the drug from hydrogel M35 corresponded with the highest slope in figure 4.16. The similar slopes of J33 release profiles are also shown in day1 and day120 release comparison (figure 4.17).

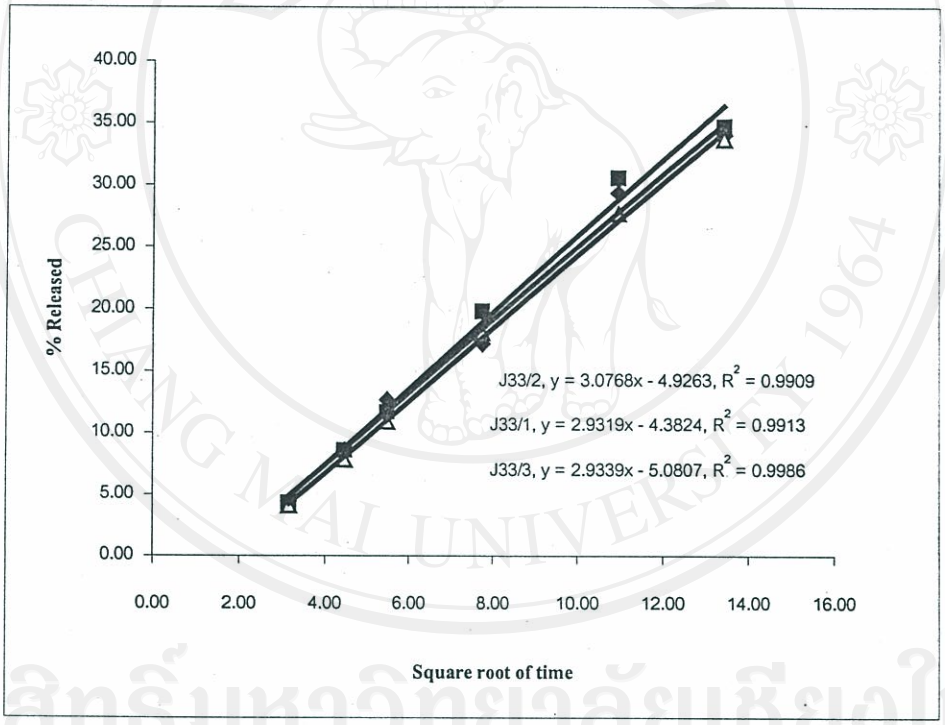

Figure 4.15 Higuchi plot of tranexamic acid released from hydrogel formula J33, the repeated profiles; 1st (♦), 2nd (■)and 3rd (△).

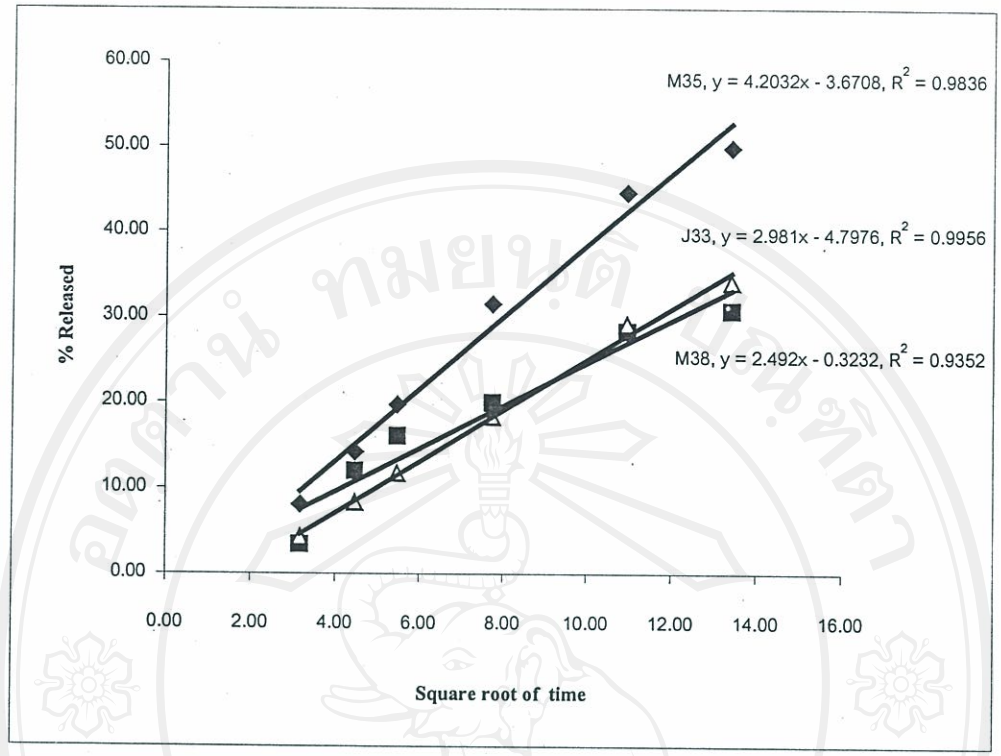

Figure 4.16 Higuchi plot of tranexamic acid released from hydrogels on day1; M35 (♦), M38 (■)and J33 (△).

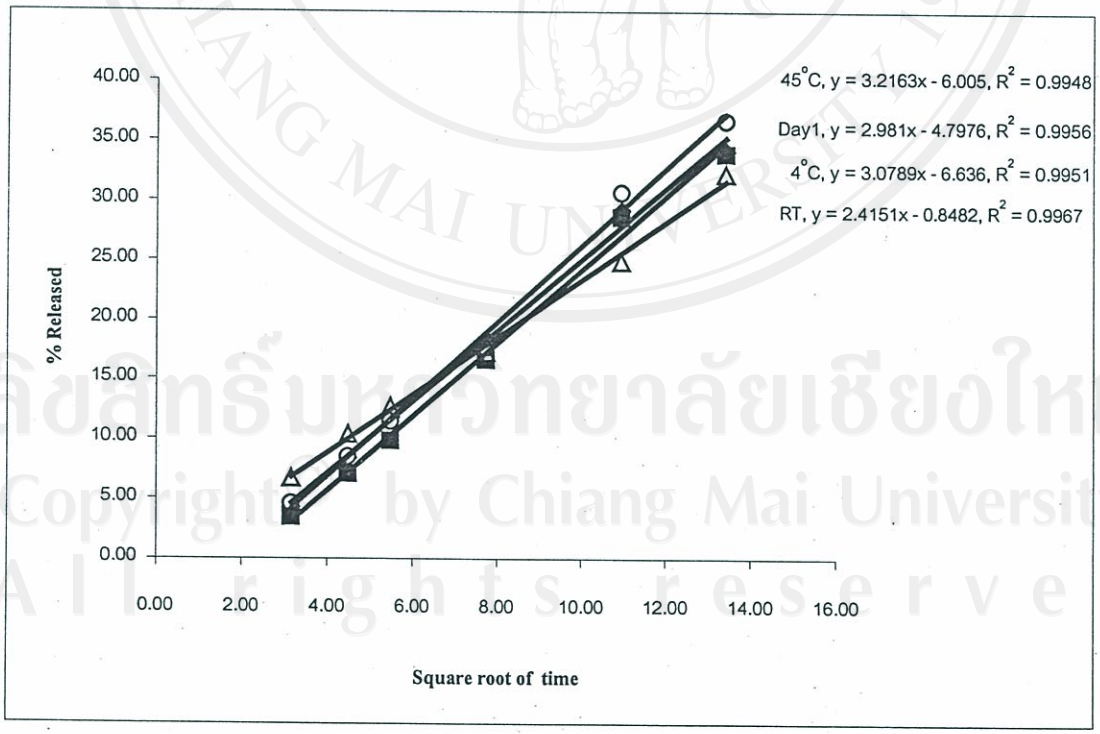

Figure 4.17 Higuchi plot of tranexamic acid released from hydrogel formula J33 on day1 (♦), day120/4°C (■), day120/RT (△) and day120/45°C (O).

4.5 Stability evaluations

The formulae M35, M38 and J33 were observed for their appearance and skin adhesion time on the first day of storage at room temperature (table 4.1) and on the 120th day of storage at 4 °C, room temperature and 45°C as shown in table 4.13. The appearance of all formulas are photographically shown in figures 4.15 – 4.26. For adhesive property evaluation of tranexamic hydrogel patches, the data are presented in two parameters that are an average distance of the metal ball stopping on a patch (table 4.14) and friction coefficient (table 4.15, figures 4.27, 4.28). Comparisons of the friction coefficient of formulae M35, M38 and J33 between a group of hydrogels stored in laminated aluminum foil and zip-locked plastic bags are shown in figures 4.29, 4.30 and 4.31 respectively. Additionally, tables 4.16 – 4.18 show the summarized physical/chemical properties of the patches investigated for the content, appearance, thickness, adhesion time and release data of formulae M35, M38 and J33 respectively.

Table 4.13 The observed data of tranexamic acid hydrogel patches on 120th day of storage.

Formula	Patches observed on 120th day		
	4 °C	Room temperature	45°C
M35	Clear gel, exuded, flattened, fair adhesion, approximate skin adhesion time; 1 hour	Clear gel , slightly dry, lack of adhesive property, approximate skin adhesion time; half-hour.	Dry gel, very poor adhesion, approximate skin adhesion time; 10 minutes.
M38	White turbid gel, slightly exuded, fair adhesion, approximate skin adhesion time; 2 hours	White turbid gel, less flexibility, slightly dry, approximate skin adhesion time; half-hour	Distinctly dry, flexibility lost, flakes on surface of the gel, no skin adhesion.
J33	Gel appearance was same as the first day of observation, approximate skin adhesion time; 5 hours.	Gel appearance was same as the first day of observation, approximate skin adhesion time; 5 hours.	The colour of gel changed to light yellow, good flexibility and adhesion, approximate skin adhesion time; 4 hours.

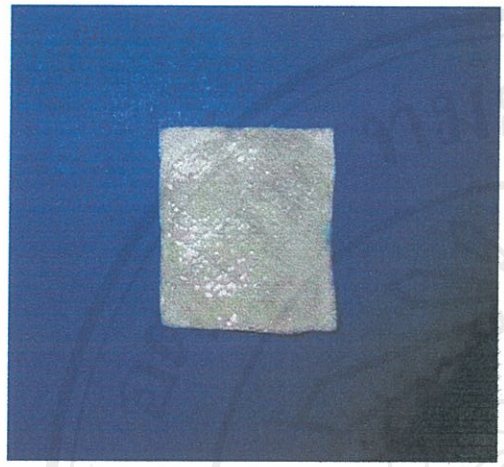

Figure 4.18 Formula M35 patch, One-day stored at RT.

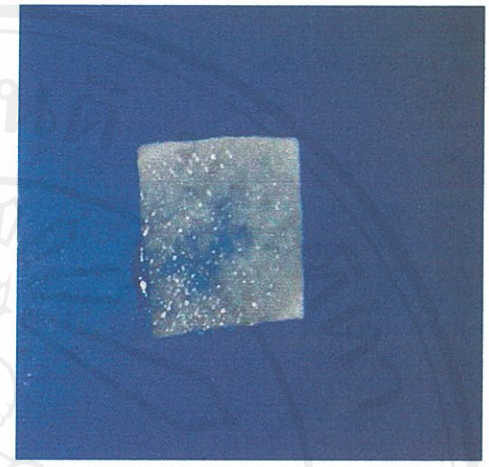

Figure 4.19 Formula M35 patch, 120 days-stored at 4°C.

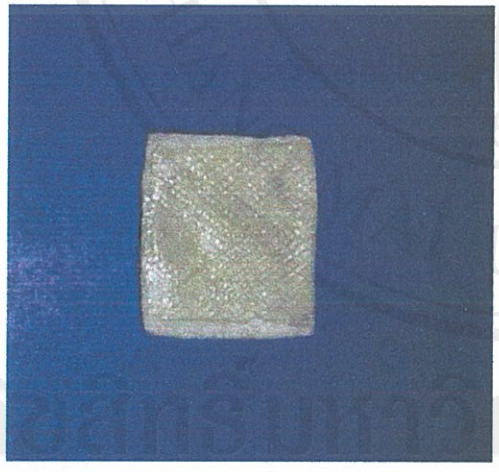

Figure 4.20 Formula M35 patch, 120 days-stored at RT.

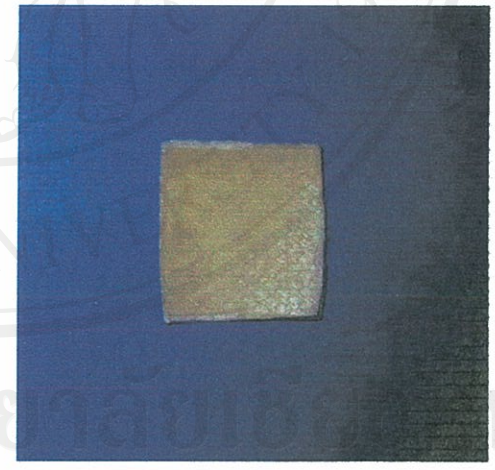

Figure 4.21 Formula M35 patch, 120 days-stored at 45°C.

Figure 4.22 Formula M38 patch,
One-day stored at RT.

Figure 4.23 Formula M38 patch,
120 days-stored at 4°C.

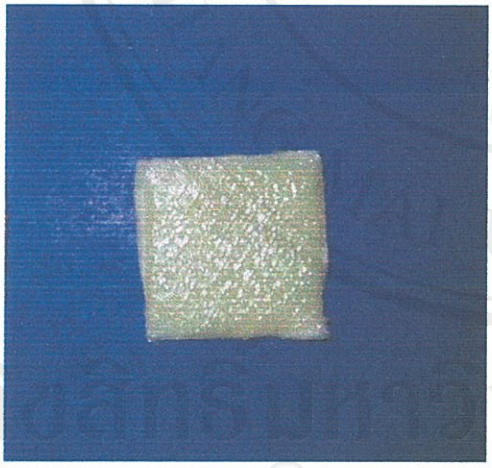

Figure 4.24 Formula M38 patch,
120 days-stored at RT.

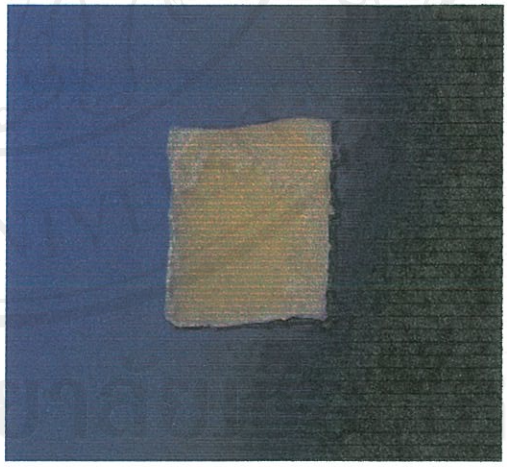

Figure 4.25 Formula M38 patch,
120 days-stored at 45°C.

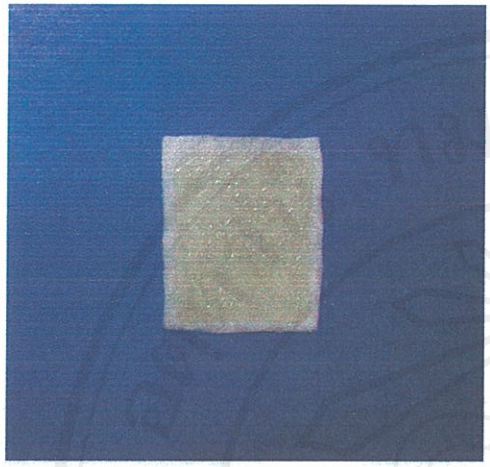

Figure 4.26 Formula J33 patch,
One-day stored at RT.

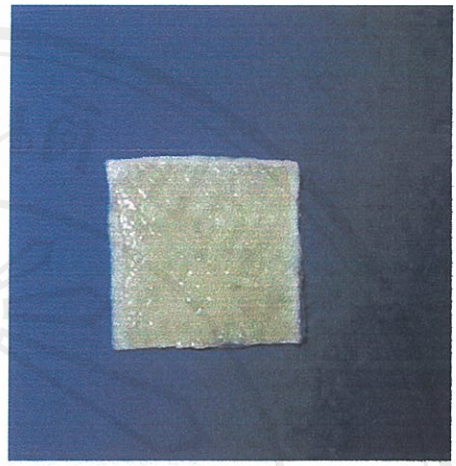

Figure 4.27 Formula J33 patch,
120 days-stored at 4°C.

Figure 4.28 Formula J33 patch,
120 days-stored at RT.

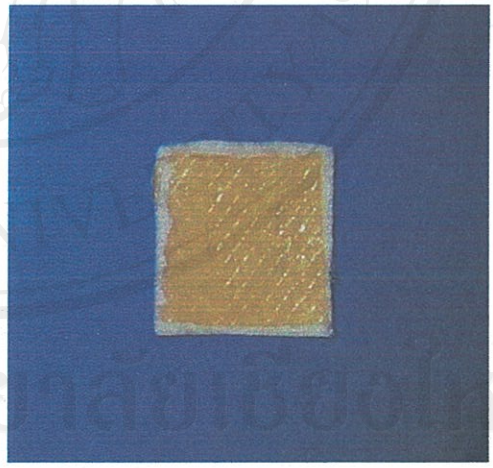

Figure 4.29 Formula J33 patch,
120 days-stored at 45°C.

Table 4.14 The average distance of rolling ball measured on the surface of patches.

Storage condition	Day	Average distance (cm)					
		Patches in aluminum foils			Patches in plastic bags		
		M35	M38	J33	M35	M38	J33
Room Temp.	1	2.1	1.8	1.4	2.1	1.8	1.4
	3	1.9	1.8	1.4	2.3	2.0	1.3
	7	1.9	1.9	1.4	2.6	2.3	1.5
	14	2.2	2.1	1.2	2.7	2.4	1.5
	28	2.4	2.1	1.3	2.7	2.4	1.6
	60	2.5	2.0	1.3	2.7	2.4	1.4
	90	2.5	2.0	1.4	x	x	1.5
	120	2.6	2.3	1.4	x	x	x
4 °C	120	2.6	2.9	1.2	x	x	x
45°C	120	2.8	x	1.6	x	x	x

X = Unable to measure

Table 4.15 Friction coefficient (μ) of the patch surfaces.

Condition of storage	Day	Friction coefficient (μ)					
		Patches in aluminum foils			Patches in plastic bags		
		M35	M38	J33	M35	M38	J33
Room Temp.	1	0.50	0.58	0.74	0.50	0.58	0.74
	3	0.55	0.58	0.74	0.45	0.52	0.80
	7	0.55	0.55	0.74	0.40	0.45	0.69
	14	0.47	0.50	0.87	0.39	0.43	0.69
	28	0.43	0.50	0.80	0.39	0.43	0.65
	60	0.42	0.52	0.80	0.39	0.43	0.74
	90	0.41	0.53	0.76	x	x	0.69
	120	0.40	0.45	0.74	x	x	x
4 °C	120	0.40	0.36	0.87	x	x	x
45°C	120	0.37	x	0.65	x	x	x

X = Unable to measure

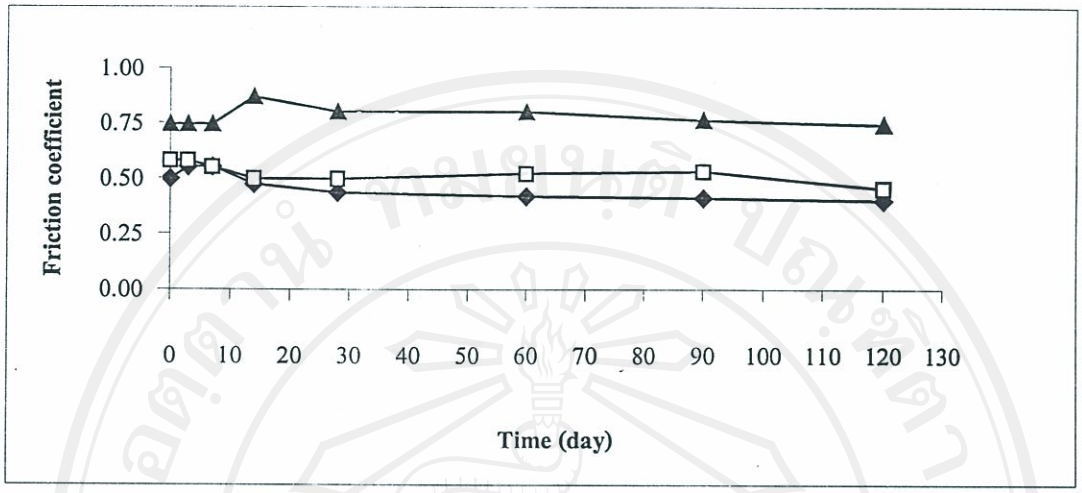

Figure 4.30 The friction coefficient (μ) on the patch surfaces; formula M35 (♦), M38 (□) and J33 (▲), stored in laminated aluminum foils at room temperature.

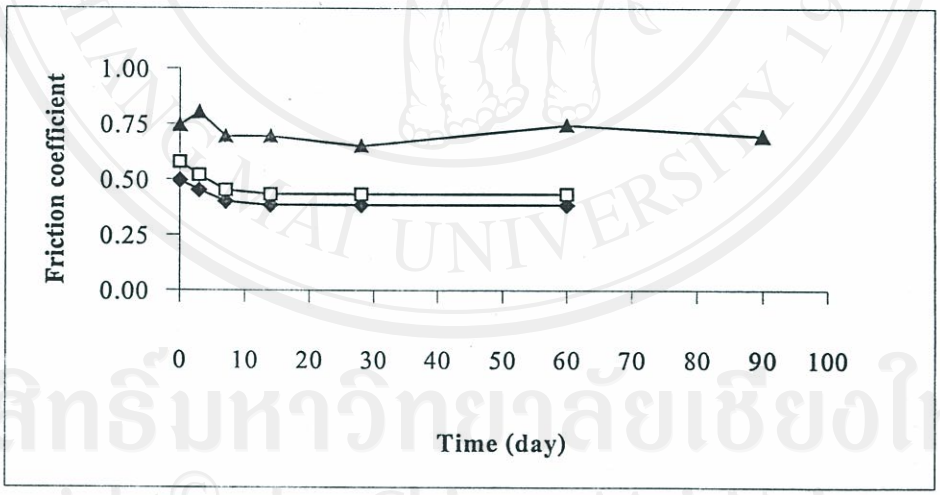

Figure 4.31 The friction coefficient (μ) on the patch surfaces; formula M35 (♦), M38 (□) and J33 (▲), stored in zip-locked plastic bags at room temperature.

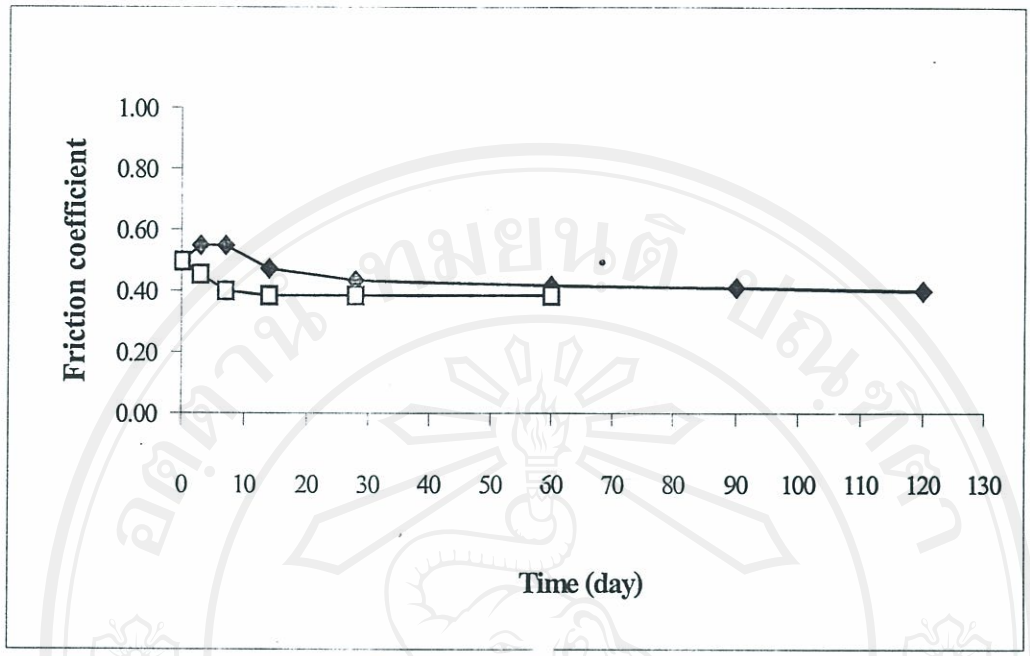

Figure 4.32 Comparison of friction coefficient of hydrogel formula M35 stored in laminated aluminum foils (◆) and zip-locked plastic bags (□).

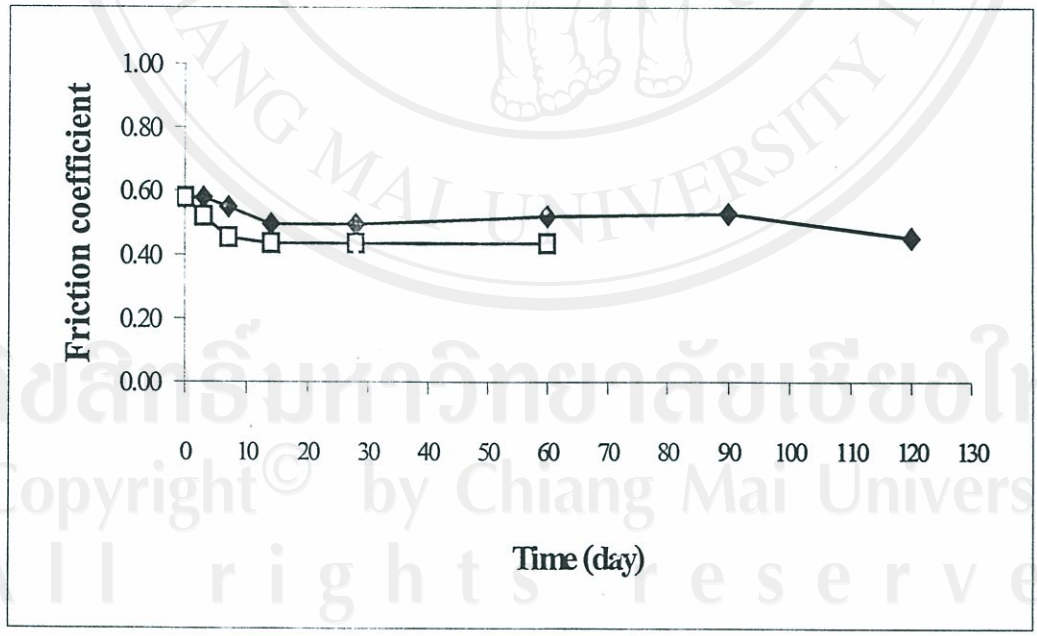

Figure 4.33 Comparison of friction coefficient of hydrogel formula M38 stored in laminated aluminum foils (◆) and zip-locked plastic bags (□).

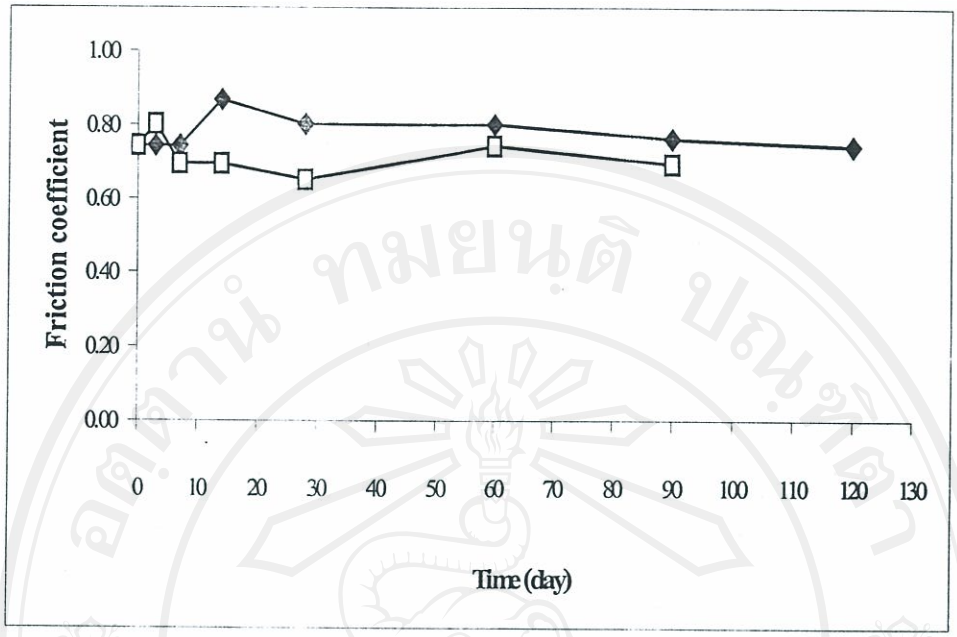

Figure 4.34 Comparison of friction coefficient of hydrogel formula J33 stored in laminated aluminum foils (◆) and zip-locked plastic bags (□).

Table 4.16 The quality of M35 patches examined on 1st and 120th day of storage.

Quality of M35	Day 1	Day 120		
	RT	4 °C	RT	45°C
% Drug content	4.15	4.39	4.14	4.28
Thickness (mm.)	1.95	0.97	1.92	1.81
Adhesive time (min)	60	60	30	10
Friction efficiency (μ)	0.50	0.40	0.40	0.37
Appearance	fair	poor	mediocre	poor
Drug releasing	D1 > RT > 45°C > 4°C			

Table 4.17 The quality of M38 patches examined on 1st and 120th day of storage.

Quality of M38	Day 1	Day 120		
	RT	4 °C	RT	45°C
% Drug content	4.14	4.36	3.88	4.33
Thickness (mm.)	2.08	1.89	1.92	1.35
Adhesive time (min)	120	120	30	-
Friction efficiency (μ)	0.58	0.36	0.45	-
Appearance	fair	poor	fair	poor
Drug releasing	RT = 45°C > D1 = 4°C			

Table 4.18 The outcomes of J33 patches examined on 1st and 120th day of storage.

Outcomes of J33	Day 1	Day 120		
	RT	4 °C	RT	45°C
% Drug content	4.16	4.38	3.89	4.32
Thickness (mm.)	2.05	2.06	1.77	1.87
Adhesive time (min)	300	300	300	240
Friction efficiency (μ)	0.74	0.87	0.74	0.65
Appearance	good	good	good	fair
Drug releasing	45°C > D1 = 4°C > RT			

4.6 Irritation test

The skin irritation test of hydrogel patch preparations was reported. The data of 24 hours occlusion are shown in table 4.19. The patch formula of J33 caused no redness or itchiness to the volunteers. Other three formulas in presence of NMP caused an irritation in some volunteer. Table 4.20 shows the results of irritation test after 24 hours of patch occlusion (day1) and 24 hours after patch removal (day2).

Table 4.19 The irritation test of tranexamic acid hydrogel patches observed within 24 hours.

No.	Sex	Age (years)	Approximate time of an itchiness had begun (hours)					Itchiness comparison between the formulae*
			control	J33	P9	P10	P11	
1	F	25	N	N	1	1.5	7.5	P9 >P10 >P11
2	F	26	N	N	1	5	6.5	P9 >P10 >P11
3	F	29	N	N	4	4.5	7.5	P9 >P10 >P11
4	M	24	N	N	7	7.5	N	P9 >P10 >P11
5	F	39	N	N	N	N	N	-
6	F	20	N	N	6.5	N	1.5	P11 >P9 >P10
7	M	21	N	N	N	N	N	-
8	M	25	N	N	N	N	N	-
9	F	54	N	N	N	N	N	-

F = female, M = male, N = neither redness nor itchiness

* Evaluated by each volunteer

Table 4.20 The visual scoring evaluation on 24 hours after patches occlusion (day1) and 24 hours after patches removal (day2).

No.	Sex	Age (years)	Visual scoring evaluation on 24 hours after patches occlusion (day1)					Visual scoring evaluation on 24 hours after patches removal (day2)				
			control	J33	P9	P10	P11	control	J33	P9	P10	P11
1	F	25	0	0	?	?	0	0	0	?	0	0
2	F	26	0	0	1	1	?	0	0	?	?	0
3	F	29	0	0	1	?	?	0	0	?	?	0
4	M	24	0	0	1	?	?	0	0	1	?	0
5	F	39	0	0	0	0	0	0	0	0	0	0
6	F	20	0	0	?	0	?	0	0	0	0	0
7	M	21	0	0	0	0	0	0	0	0	0	0
8	M	25	0	0	0	0	0	0	0	0	0	0
9	F	54	0	0	0	0	0	0	0	0	0	0

F = female, M = male

visual scores;

0 = No reaction

? = Very weak erythema or scaling

1 = Mild erythema or scaling across most of the patch test area

2 = Distinct erythema and/or oedema

3 = Erythema and oedema spreading outside the test area