CHAPTER IV

RESULTS AND DISCUSSION

The results can be divided into two main sections, first section describes the development of the matrices and in vitro evaluation. Second section reports the in vivo testing of selected formulations.

1. Formulation development and in vitro evaluation

Gliclazide matrix was compressed into tablets by direct compression method (using HPMC or xanthan gum polymer). Weight of tablet was approximately 150 mg.

1.1 Weight variation, hardness, thickness and friability

The average weight variation of tablet, hardness, thickness and friability of each formulation were summarized in Table 5. The tablet weight of gliclazide matrix was in the range of 146-154 mg. Since the acceptable limit of weight variation conforming to USP 24 is in the range of average weight $\pm$ 7.5% (139 - 161 mg), The weight variations of all formulations passed the specification. The hardness was varied from 5.46 to 7.02 kp. This result indicated that the hardness of matrix could be controlled within a predetermined range (5-7 kp).

The thickness was average about 2.76-3.15 mm. The variation of thickness of the matrix might be caused by the differences in powder properties such as bulk density and particle size. The friability of tablet containing 20% HPMC, 40% HPMC, 60% HPMC, 5% XG, 7% XG, and 9% XG were 0.37, 0.41, 0.35, 0.49, 0.57 and 0.52

%, respectively. The weight losses of all formulations were in the acceptance criteria that were less than 1% of the weight of the tablets being tested (USP 24). This referred that the hardness of tablet was suitable.

1.2 Disintegration time

Results of disintegration of all formulations are shown in Table 5. It was found that the disintegration times of all formulations were more than 60 minutes. The comparative disintegration of HPMC and XG formulations was slightly different. The six tablets of HPMC formulation left residual masses on the perforated plate, whereas residual mass of a few tablets of XG formulation were seen on the perforated plate (about two tablets from six tablets).

1.3 Drug content

Percent drug content of gliclazide matrix in each formulation is presented in Table 5. The average drug contents were in the limits of 95.0-105.0 % labeled amount and conformed general specifications as specified in the BP 2002.

1.4 Dissolution profile of gliclazide matrix

Each formulation was studied for dissolution profile in two media, 0.1 N HCl and phosphate buffer pH 6.8. The interference of additives in the matrix on drug absorbance measurement was observed. The blank tablet containing no gliclazide was prepared. The objective of the dissolution studies of blank tablet was to verify specificity of the method for quantitative analysis of drug release. It shows no interference of the wavelength measured in 0.1 N HCl and phosphate buffer pH 6.8 (Figure 23 of the Appendix B).

Table 5 Physical properties of gliclazide matrix containing various amounts of HPMC or xanthan gum.

Formulation		Physical properties of gliclazide matrix					
		Average weight mg (SD) (n=20)	Hardness kp (SD) (n=20)	Thickness mm (SD) (n=10)	Friability % (n=20)	Disintegration time min. (n=6)	% Drug content (n=20)
HPMC K4M	% polymer						
F1	20%	148.45(2.54)	6.71(0.50)	2.99(0.03)	0.37	>60 min.	97.56%
F2	40%	150.86(1.85)	6.94(0.48)	3.12(0.03)	0.41	>60 min.	100.21%
F3	60%	148.37(2.38)	7.02(0.38)	3.08(0.04)	0.35	>60 min.	98.49%
Xanthan gum	% polymer						
F4	5%	148.78(3.23)	5.86(0.59)	2.78(0.02)	0.49	>60 min.	99.64%
F5	7%	149.60(2.85)	5.46(0.47)	2.81(0.03)	0.57	>60 min.	102.81%
F6	9%	151.20(2.40)	6.97(0.52)	2.84(0.03)	0.52	>60 min.	100.95%

1.4.1 <u>Effect of polymer concentration on gliclazide release</u>

1.4.1.1 HPMC concentration on release characteristics of the gliclazide matrix tablets.

The release profiles of HPMC matrix in 0.1 N HCl and phosphate buffer pH 6.8 are shown in Figures 4 and 5, respectively. The drug release rate was influenced by the polymer concentration of the matrix. An increase in concentration of HPMC polymer from 20% to 60% exhibited a decline in the drug release rate.

1.4.1.2 Xanthan gum concentration on release characteristics of the gliclazide matrix tablets.

The effect of different XG concentration on gliclazide release are shown in Figures 6 (in 0.1 N HCl) and Figure 7 (in phosphate buffer pH 6.8). An increase in concentration of XG polymer from 5% to 9% exhibited a decline in the drug release rate.

Increasing the concentration of HPMC or XG polymer resulted in slower rate and extent of release of the drug from the tablet. This might be due to an augmentation of polymer chain entanglement in hydrated gel layer around the matrix comprising higher polymer content. This resulted in a more concentrated gel and increased gel tortuosity. As a result, the diffusion path became more convoluted and thus the diffusion rate decreased. Furthermore, a strong protective gel-barrier would be less susceptible to erosion, resulting in decreased drug release.
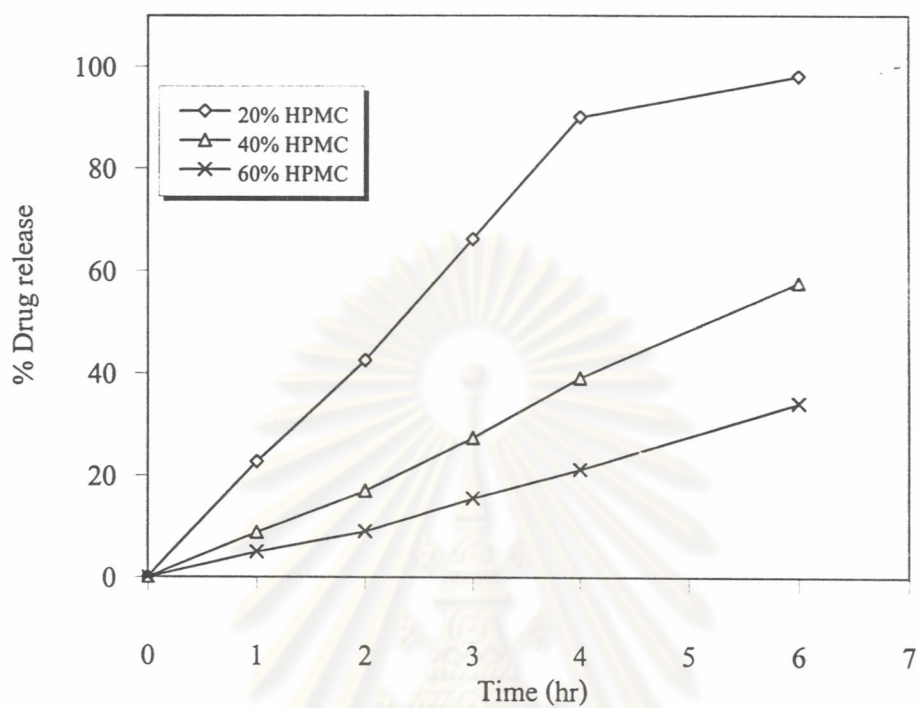
Figure 4 Dissolution profiles of gliclazide matrices containing various HPMC concentrations in 0.1 N HCl.

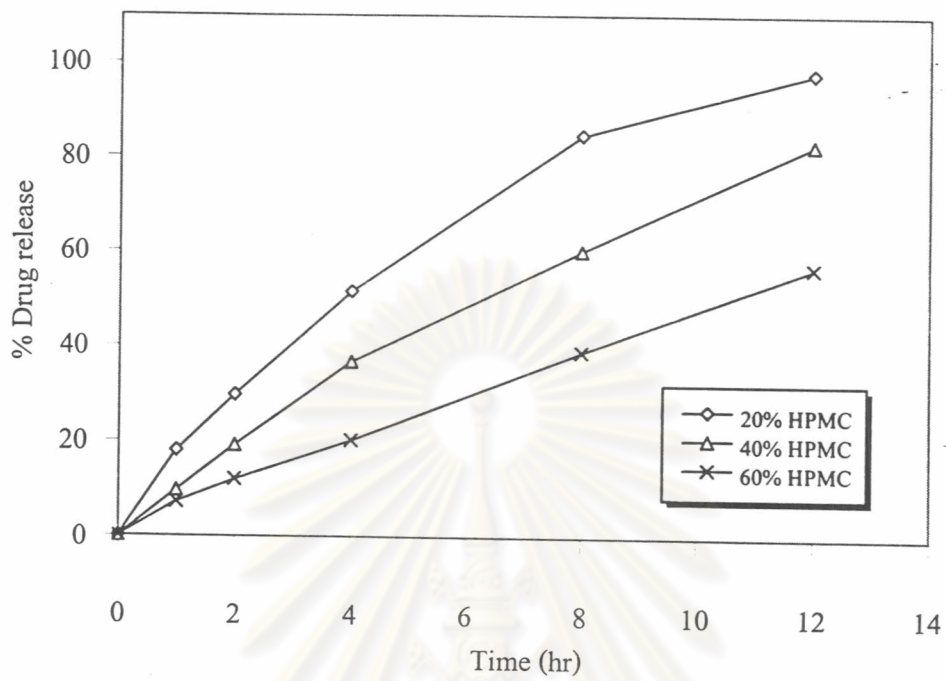**Figure 5** Dissolution profiles of gliclazide matrices containing various HPMC

concentrations in phosphate buffer pH 6.8.

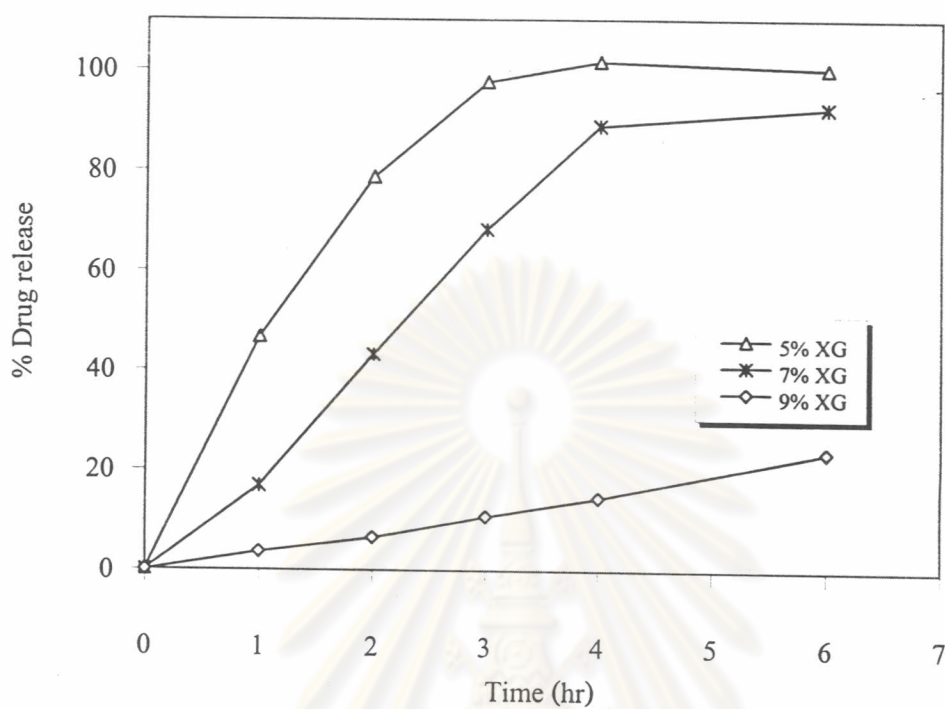**Figure 6** Dissolution profiles of gliclazide matrices containing various XG

concentrations in 0.1 N HCl.

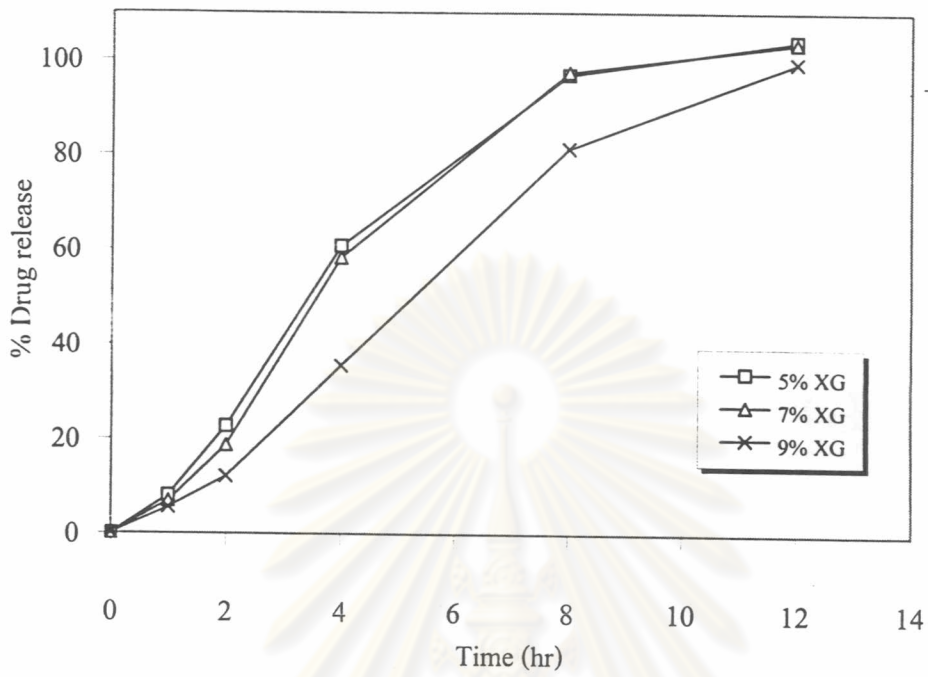**Figure 7** Dissolution profiles of gliclazide matrices containing various XG

concentrations in phosphate buffer pH 6.8.

The comparative dissolution profile of HPMC and XG formulations was slightly different. This experiment indicates that XG (7%) can be used in very small quantity (approximately 1/3 of HPMC) to achieve a similar controlled release profile of HPMC (20%). This result is consistent with previous report (Vinny and Joel, 1993).

1.4.2 Effect of pH of the dissolution medium on gliclazide release

The effect of dissolution medium pH on the gliclazide release from tablet formulation was studied. Dissolution profiles of HPMC formulation and xanthan gum formulation are shown in Figures 8 and 9, respectively. The drug release was slightly higher in 0.1 N HCl, compared with phosphate buffer pH 6.8. This result could be explained in terms of drug and diluent solubilities in the dissolution medium. Gliclazide is a weak acid (pKa = 5.8), it should be more soluble in phosphate buffer pH 6.8 higher than in 0.1 N HCl. However, diluent in formulation might play a more important role on drug release rate. Insoluble diluent might cause the occurrence of non-uniformity of the gel layer around the matrix. In case of dibasic calcium phosphate, when dissolution medium penetrated into the matrix, the insoluble dibasic calcium phosphate particles caused the discontinuous gel layer. Consequently, the matrix erosion caused by the slow dissolution of dibasic calcium phosphate in 0.1 N HCl solution and the gel layer destruction might cause the faster drug release rate of dibasic calcium phosphate matrix containing HPMC or XG polymer.

The release profiles of commercial product in 0.1 N HCl and phosphate buffer pH 6.8. are shown in Figures 10 and 11, respectively. The drug release rate was influenced by dissolution medium pH. The drug release was slightly higher in 0.1 N HCl, compared with phosphate buffer pH 6.8. The gliclazide release should be more soluble in phosphate buffer pH 6.8 higher than in 0.1 N HCl. However, the formulation might play a more important role on drug release rate such as polymer or diluent.
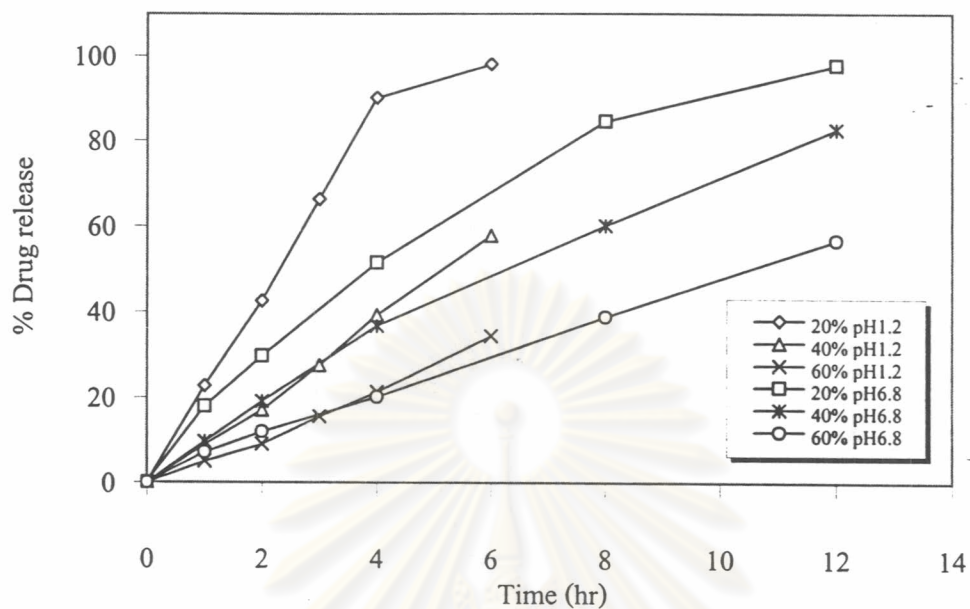
Figure 8 Effect of pH of dissolution medium on the release of gliclazide matrices
containing various HPMC.

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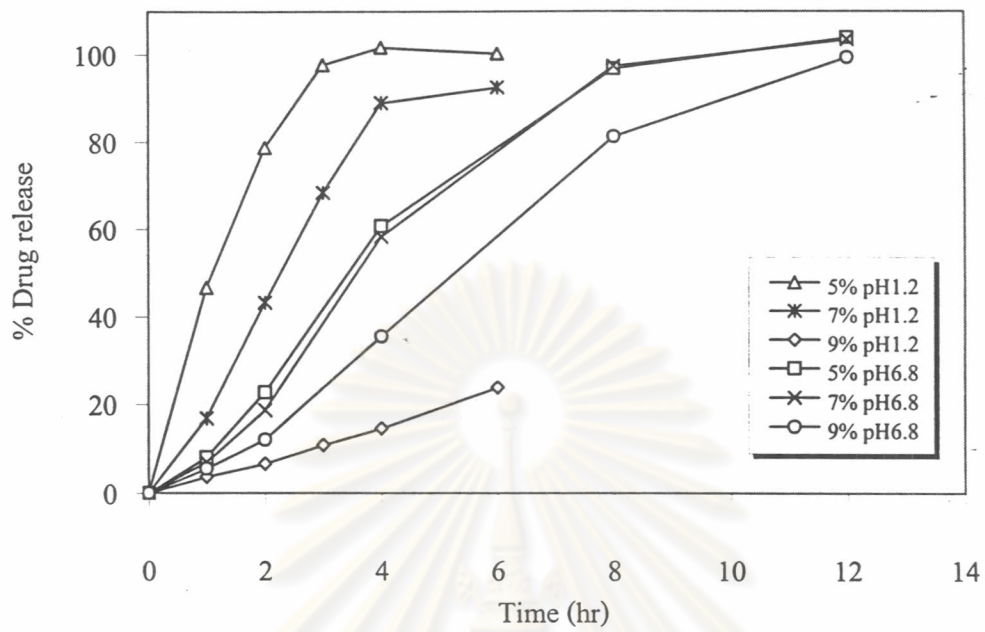
Figure 9 Effect of pH of dissolution medium on the release of gliclazide matrices
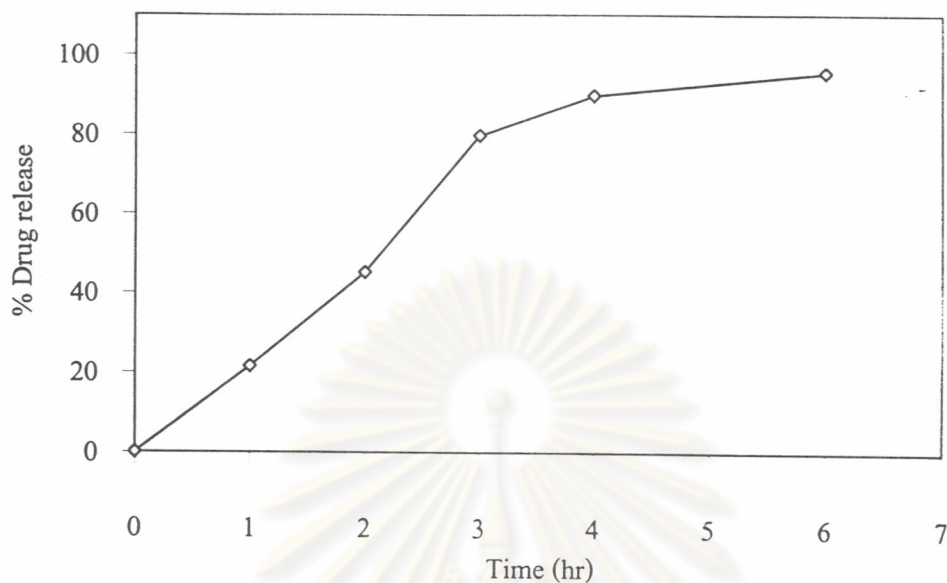containing various XG.

Figure 10 Dissolution profiles of gliclazide matrices containing commercial product in 0.1 N HCl.
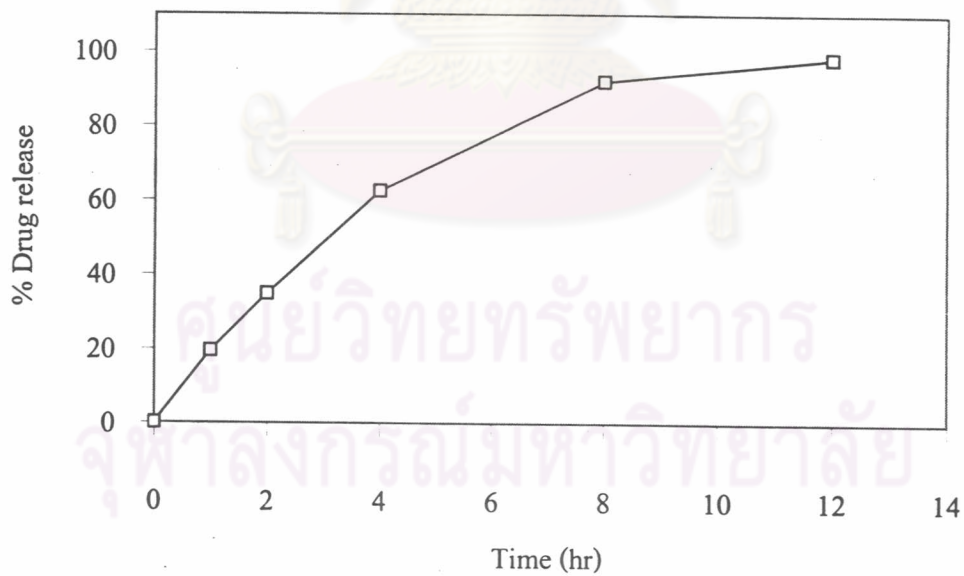

Figure 11 Dissolution profiles of gliclazide matrices containing commercial product in phosphate buffer pH 6.8.

In order to select the appropriate formulation for investigating the drug release property in pH change medium, the following criteria were considered.

1. The suitable formulation should produce sufficient sustained release. The drug release rate should not be rapid or too slow.

2. The suitable formulation should be similar to commercial product, the f_2 value of the two profiles is not less than 50 and the f_1 value is not more than 15(percentage amounts of gliclazide from matrices containing commercial product is shown in Table 45 of the Appendix D.

HPMC formulation

A test batch dissolution consisting of 20% HPMC (F1) was considered similar to that of the commercial product than other formulations in 0.1 N HCl ($f_2$value =59.95, $f_1$value = 5.99) and in phosphate buffer pH 6.8 (f_2 value = 59.32, $f_1$value = 8.38).

Xanthan gum formulation

A test batch dissolution consisting of 7% XG (F5) was considered similar to that of the commercial product than other formulations in 0.1 N HCl ($f_2$value =61.76, $f_1$value = 6.60) and in phosphate buffer pH 6.8 (f_2 value = 50.06, $f_1$value = 14.23).

According to the above criteria, the formulation containing 20% HPMC (F1) and 7% XG (F5) were chosen for investigating drug release property in pH change medium.

1.4.3 Dissolution study of gliclazide matrix in pH change medium

In order to simulate the environment of the gastro-intestinal tract, the dissolution test was carried out by using pH change dissolution method. The drug release study was performed by using 0.1 N HCl solution as the dissolution medium in the first 2 hours. After that phosphate buffer pH 6.8 solution was used as the dissolution medium. The drug release study was performed for 12 hours.

The dissolution profiles in pH change medium of tablet with two types of polymer (20% HPMC and 7 % XG) and commercial product are shown in Figure 12. The drug release rate in 0.1 N HCl solution at the first 2 hours of dissolution test was faster than that in phosphate buffer pH 6.8 solution at the last 10 hours of dissolution test. This might be due to an augmentation of the erosion rate in hydrated gel layer around the matrix. Drug release from the XG matrix was slightly faster in 0.1 N HCl, due to more rapid initial surface erosion. After hydration of the gum, drug release was essentially pH-independent.

The f_2 and f_1 values for test batch compared to the commercial product is given in Table 48 of the Appendix D. A test batch dissolution consisting of 20% HPMC was considered similar to that of the commercial product (f_2 value = 51.11, the f_1 value = 9.81). A test batch dissolution consisting of 7% XG was considered similar to that of the commercial product (f_2 value = 59.53, f_1 value = 8.32).

The formulation 1 (20% HPMC) and 5 (7% XG) were considered to be similar to the commercial product. A single dose of each formulation was administered to rabbits. Pharmacokinetic parameters of gliclazide were studied after an oral administration of gliclazide tablets in rabbits.
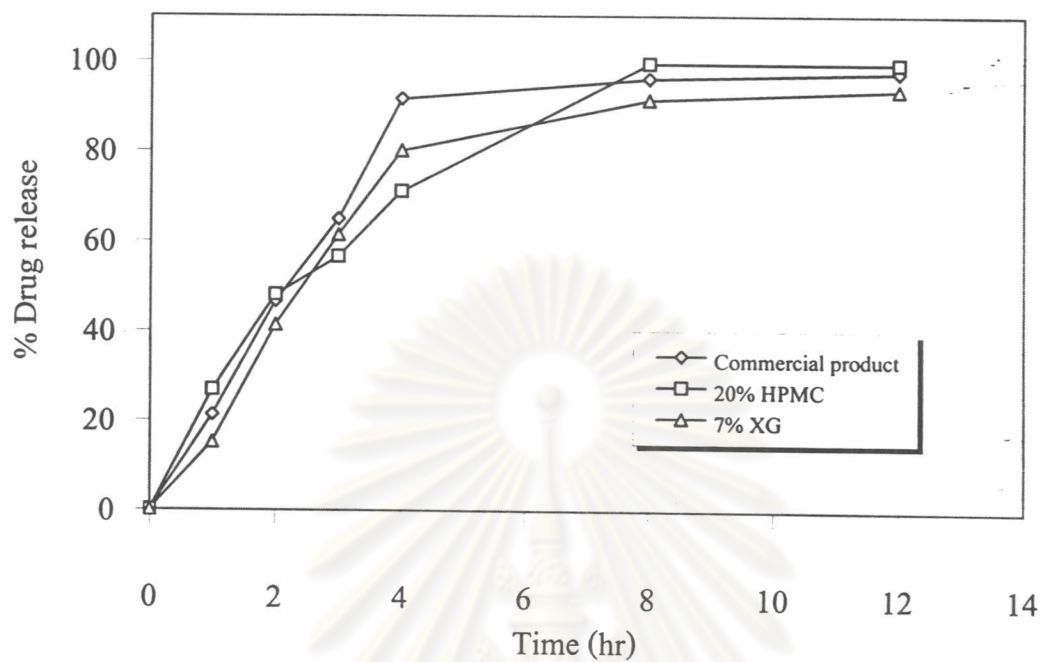
Figure 12 Comparison of gliclazide release between 20% HPMC, 7% XG

matrices and commercial product in pH change method.

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The photograph of the dissolution study by pH change method

Figures 13, 14 and 15 display the photographs of 20% HPMC, 7% XG matrix and commercial product during the course of dissolution test by pH change method. The experiments were performed at the time intervals of 1, 2, 3, 4, 8 and 12 hours. In hydrophilic matrix systems, the polymer at the surface of the matrices swells initially during dissolution test to generate an outer viscous gel layer. This phase is then sequentially followed by matrix bulk hydration, swelling and erosion.

Release model analysis in pH change medium

Release data for the first four hours of gliclazide matrix using 20% HPMC and 7% XG and commercial product were plotted based on Higuchi, zero order and first order equations. The coefficients of determination (r^2) of all plots are presented in Table 6. The main mechanism of gliclazide release matrix using 20% HPMC and 7% XG were Higuchi diffusion model while commercial product followed zero order model.

The dissolution rate constants (Kd) of 20% HPMC and 7% XG were reported in Table 7. It was calculated from the slope of the respective plots (see Figure 16 a). The average Kd of 7% XG higher than 20% HPMC. Table 8 shows that there were statistically significant difference ($p < 0.05$) among Kd values of 20% HPMC versus 7% XG.
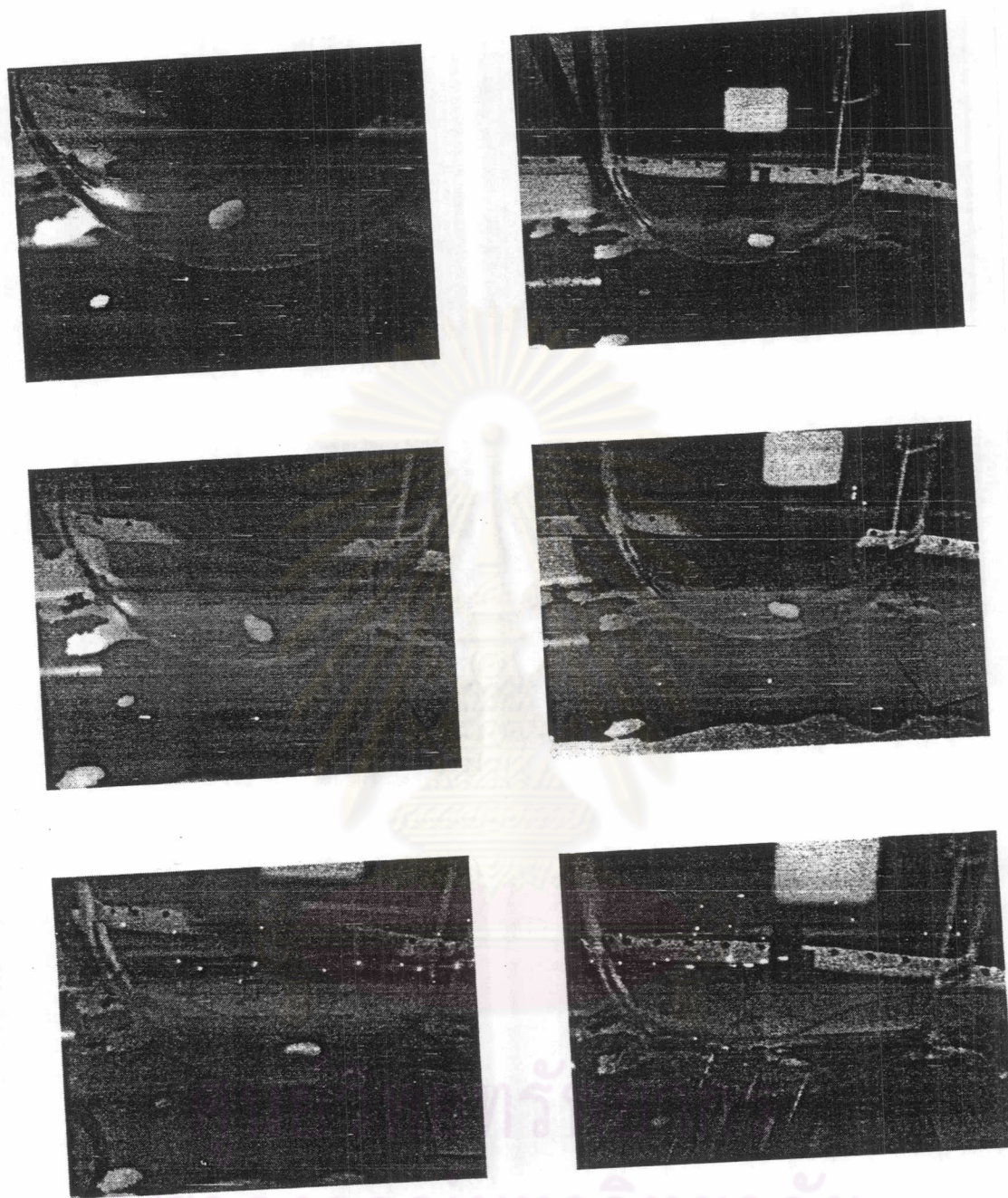
Figure 13 Photograph of the progressive dissolution of HPMC formulation of gliclazide matrix tablets by pH change method.

Figure 14 Photograph of the progressive dissolution of xanthan gum formulation of gliclazide matrix tablets by pH change method.
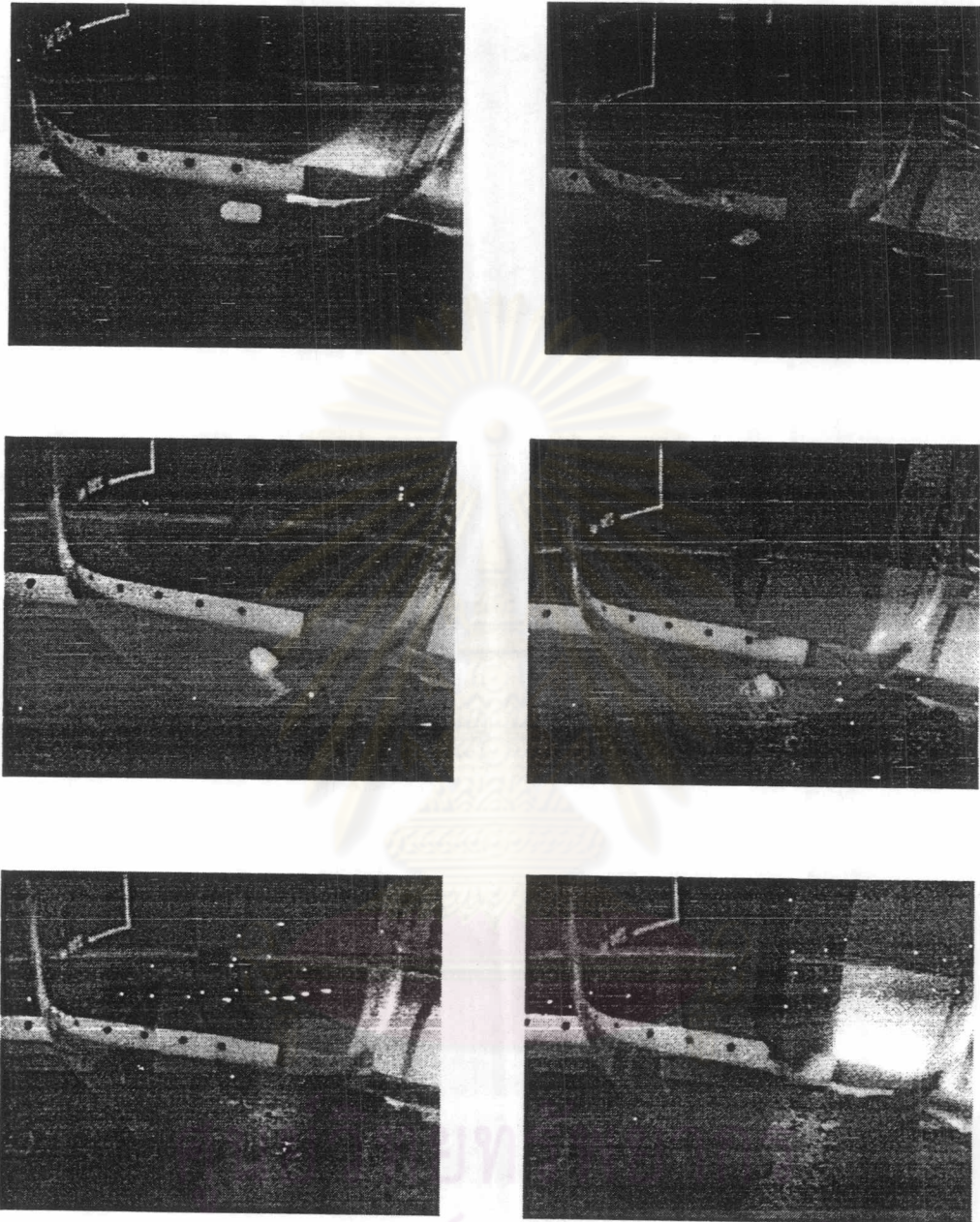
Figure 15 Photograph of the progressive dissolution of commercial product of gliclazide matrix tablets by pH change method.
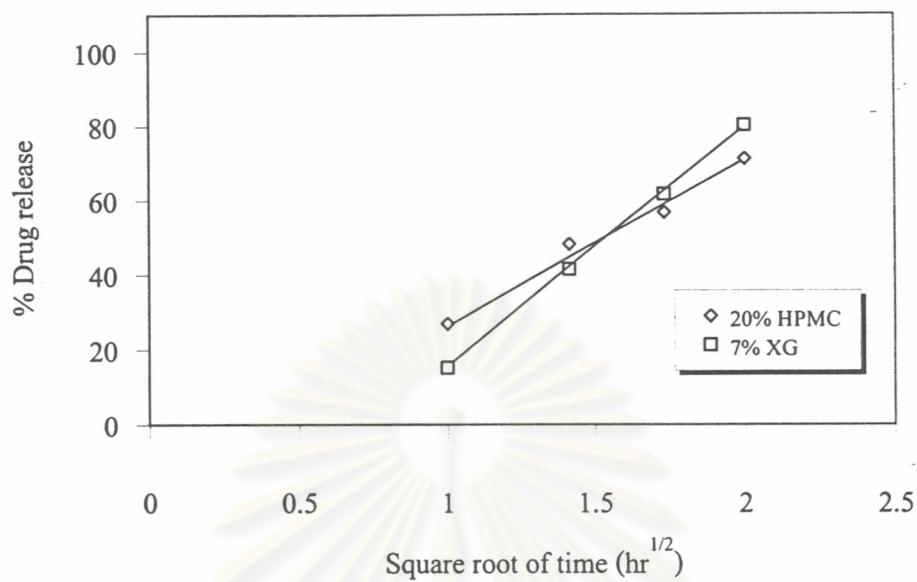
Figure 16 a. Higuchi plot of gliclazide release between 20% HPMC and 7% XG

matrices in pH change method.
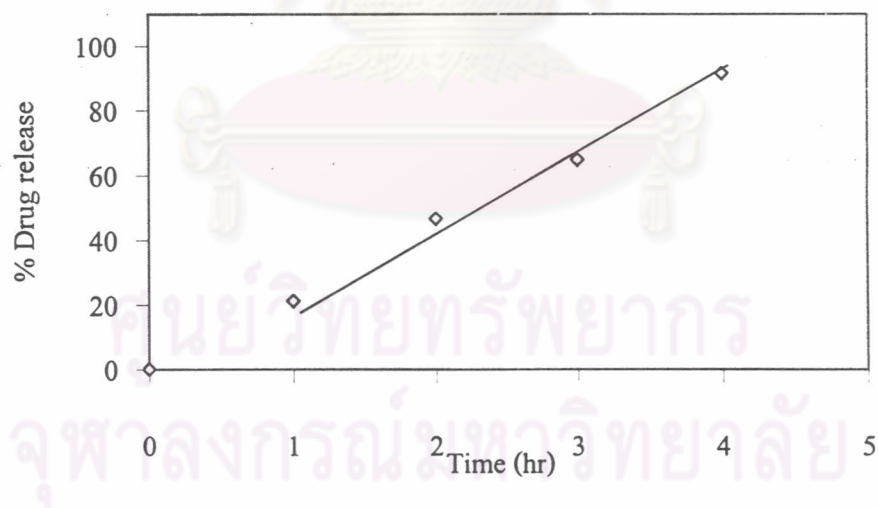
b. Zero order plot of gliclazide release of commercial product in

pH change method.

Table 6 The coefficient of determination (r^2) of 20% HPMC, 7% XG and commercial product.

Formulation	Higuchi r^2	Zero order r^2	First order r^2
20 %HPMC	0.9931	0.9859	0.9904
7 % XG	0.9998	0.9967	0.9899
Commercial product	0.9925	0.9977	0.9432

Table 7 Dissolution rate constant (Kd) of HPMC, xanthan gum and commercial product formulation of gliclazide matrix tablets.

Formulation	Average dissolution rate constant Kd (SD)	Release model
20 % HPMC	42.66 (2.03) % hr$^{-1/2}$	Higuchi
7% Xanthan gum	64.69 (1.92) % hr$^{-1/2}$	Higuchi
Commercial product	22.91 (0.14) % hr^{-1}	Zero

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Table 8 Comparison of dissolution rate constant (Kd) between HPMC and

xanthan gum of gliclazide matrix tablets.

Formulation	t-value (Calculated)	p-value (Calculated)	Statistical significance
HPMC versus xanthan gum	13.644	<0.001	S

$t_{(0.975, 10)}$

S = Significant difference at P < 0.05

NS = Not significant difference at P > 0.05

2. In vivo evaluation

Thirty milligram of gliclazide matrix tablets with 20% HPMC or 7% XG as matrix forming agent and commercial product were used for in vivo comparative studies.

2.1 Determination of gliclazide concentrations in plasma

The chromatograms of deprotenized rabbit plasma were shown in Figure 17, with and without gliclazide, and an aqueous mixture of gliclazide and methyl 4-hydroxybenzoate (internal standard). Blank rabbit plasma shows no peaks in the region of gliclazide or internal standard. Chromatogram of internal standard and gliclazide were separated at the retention time of about 4.3 minutes and about 7.2 minutes, respectively. The entire chromatogram was generated within 8 minutes.

The method of analysis was validated by determining the accuracy, within run and between run precision. Results were accessible in Appendix C. Accuracy in term of percent recovery for all concentrations were between 96.00 - 106.40%. Within run and between run precision expressed as percent coefficient of variations were 5.48 - 8.45% and 6.72 - 8.74%, respectively. The calibration curve of peak area ratio of gliclazide to methyl 4-hydroxybenzoate versus plasma gliclazide concentrations was linear cover all concentration tested with the coefficient of determination of 0.9997 as shown in Table 39 and Figure 26 (Appendix C).

The plasma concentration of gliclazide at each sampling time interval up to 24 hours after oral administration of 30 mg gliclazide matrix tablet of 20% HPMC, commercial product, 7% XG and commercial product formulation are shown in Tables 9, 10,11 and 12 and Figures 18, 19,20 and 21, respectively. The plots indicated that the
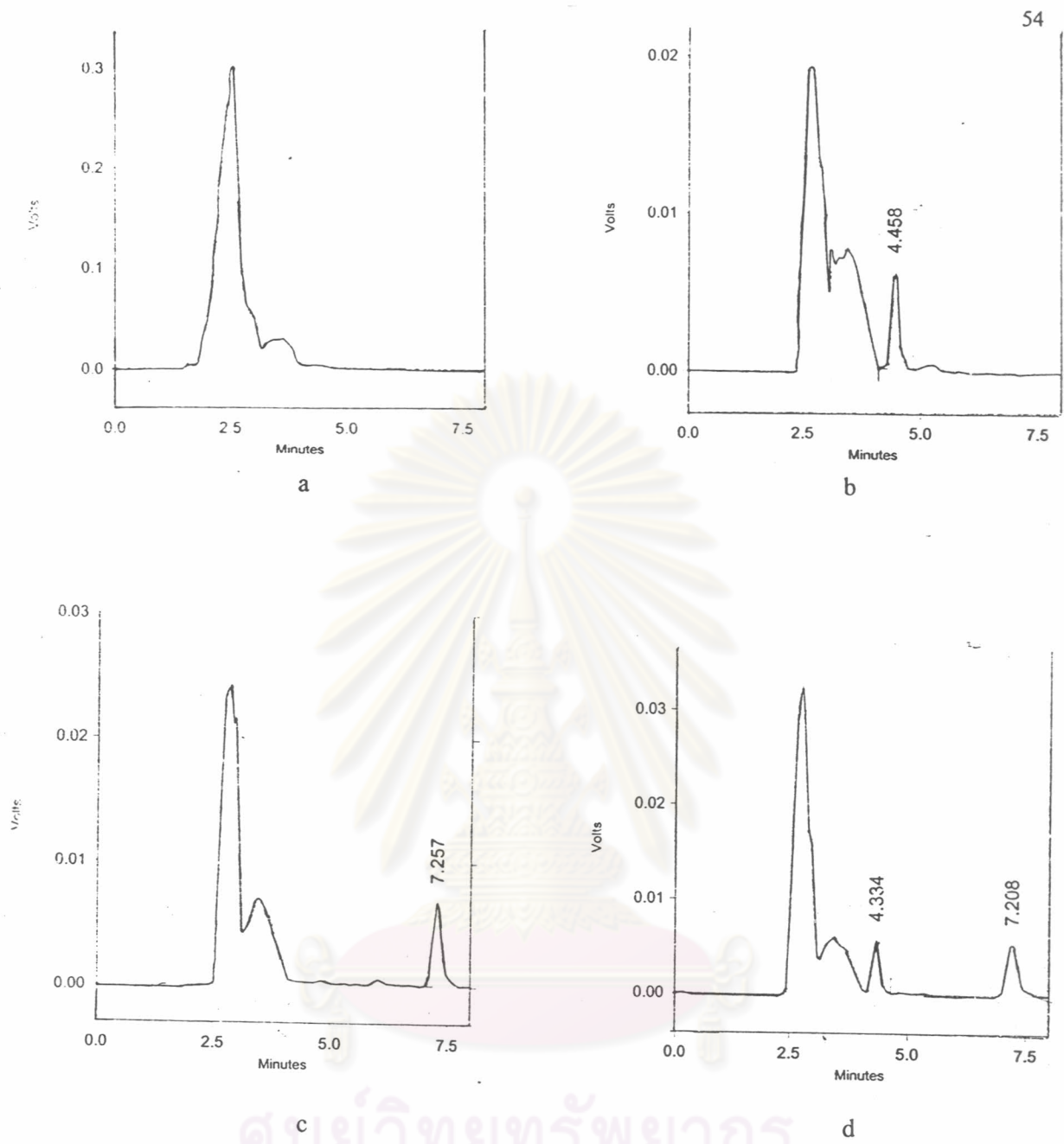
Figure 17 High performance liquid chromatogram of :

    a. Blank rabbit plasma

    b. Spiked plasma with internal standard

    c. Gliclazide spiked plasma

    d. Gliclazide spiked plasma and internal standard in mobile phase

concentrations of the drug were fluctuated among rabbits given the same formulation. Comparison of the mean plasma gliclazide-concentration profile of 20% HPMC, 7% XG and commercial product formulations is illustrated in Figure 22.

2.2 Pharmacokinetic analysis

Generally, pharmacokinetic study is used to characterize the bioavailability of pharmaceutical formulation after administration. This may be viewed as a bioassay that assesses transport of the drug substance from the formulation into the systemic circulation. The relevant pharmacokinetic parameters derived from plasma concentration-time data are as follows:

2.2.1 Peak plasma concentration (C_{max})

This parameter is generally used to indicate the intensity of action of a drug product. The average peak plasma concentration of gliclazide for 20% HPMC, commercial product, 7% XG and commercial product were 13.948 ± 1.560, 13.625 ± 0.922, 11.860 ± 0.814 and 10.921 ± 1.576 μg/ml, respectively, as shown in Tables 13 and 14. The C_{max} values from the formula with 20% HPMC appeared to be higher than that with 7% XG because different type of polymer in formulation affected absorption process. The C_{max} value of 20% HPMC and 7% XG were comparable to that of commercial product. Table 15 shows that there was statistically significant difference ($p < 0.05$) among C_{max} values of 20% HPMC versus 7% XG. However, C_{max} values of 20% HPMC and 7% XG versus commercial product were no statistically significant difference ($p > 0.05$).

Table 9 Plasma gliclazide concentration (μg/ml) from six subjects following oral administration of 30 mg gliclazide matrix tablets of HPMC formulation.

Subject No.	Time (hr.)									
	0.5	1	2	3	4	6	8	12	18	24
1	2.378	4.596	8.415	10.672	13.404	15.709	12.210	7.424	4.761	2.858
2	2.085	3.202	7.999	8.644	11.399	11.619	9.659	6.506	4.831	3.360
3	2.615	6.298	9.159	10.431	12.034	12.061	12.727	8.893	3.411	2.882
4	1.016	1.209	3.592	5.521	10.570	13.890	9.600	5.270	2.327	1.688
5	0.768	1.832	6.642	5.935	9.500	14.402	11.765	5.360	3.510	2.037
6	1.106	1.232	3.025	11.620	12.922	15.339	13.468	9.680	3.930	1.882
Mean	1.662	3.008	6.472	8.804	11.638	13.837	11.571	7.189	3.795	2.451
SD	0.791	2.114	2.590	2.573	1.462	1.683	1.608	1.825	0.939	0.671

Table 10 Plasma gliclazide concentration (μg/ml) from six subjects following oral administration of 30 mg
gliclazide matrix tablets of commercial product..

Subject No.	Time (hr.)									
	0.5	1	2	3	4	6	8	12	18	24
1	1.247	2.005	3.456	7.388	11.505	13.483	9.886	6.338	2.496	1.413
2	1.285	3.443	3.621	8.893	14.008	10.652	8.654	3.771	1.616	1.305
3	1.128	1.976	9.106	11.853	13.790	11.213	7.141	3.521	1.555	0.839
4	2.418	5.026	9.398	11.100	11.616	12.679	9.356	5.296	2.218	1.279
5	1.817	4.500	9.494	13.985	15.123	14.615	11.171	5.100	2.547	1.491
6	1.214	3.181	6.908	7.472	8.041	11.566	12.667	4.235	1.511	1.034
Mean	1.518	3.355	6.997	10.115	12.347	12.368	9.812	4.710	1.990	1.227
SD	0.504	1.254	2.842	2.641	2.543	1.504	1.933	1.065	0.485	0.245

Table 11 Plasma gliclazide concentration (μg/ml) from six subjects following oral administration of 30 mg gliclazide matrix tablets of xanthan gum formulation.

Subject No.	Time (hr.)									
	0.500	1.000	2.000	3.000	4.000	6.000	8.000	12.000	18.000	24.000
1	1.385	1.646	4.736	11.059	12.467	8.959	5.858	5.109	2.122	1.437
2	1.095	1.681	2.737	3.792	8.316	10.750	7.299	5.852	4.368	2.404
3	1.027	1.376	6.184	7.348	9.465	11.082	8.382	4.700	2.018	1.198
4	0.894	0.963	1.735	3.868	12.841	11.458	6.596	3.360	1.395	1.156
5	0.910	1.120	1.960	4.030	11.790	9.240	7.480	3.110	1.200	1.050
6	1.100	1.884	3.793	9.399	12.231	10.945	9.725	4.479	1.584	1.803
Mean	1.069	1.445	3.524	6.583	11.185	10.406	7.557	4.435	2.114	1.508
SD	0.178	0.355	1.725	3.169	1.846	1.042	1.361	1.044	1.160	0.515

Table 12 Plasma gliclazide concentration (μg/ml) from six subjects following oral administration of 30 mg gliclazide matrix tablets of commercial product.

Subject No.	Time (hr.)										
	0.5	1	2	3	4	6	8	12	18	24
1	1.098	2.977	4.995	6.375	7.824	10.696	6.518	4.140	1.683	1.104
2	1.085	3.114	4.094	7.136	10.619	9.398	4.730	4.031	2.002	1.686
3	1.036	3.014	4.004	6.085	7.164	9.743	9.971	5.975	1.866	1.286
4	1.430	1.550	2.390	3.660	5.490	10.700	12.700	3.900	1.400	1.070
5	0.970	1.400	2.730	4.310	6.690	8.090	8.750	3.660	1.740	1.210
6	0.920	1.810	3.790	6.370	7.700	12.790	7.840	3.000	1.320	0.920
Mean	1.090	2.311	3.667	5.656	7.581	10.236	8.418	4.118	1.669	1.213
SD	0.180	0.805	0.957	1.356	1.711	1.581	2.771	0.996	0.264	0.264

Figure 18 Plasma gliclazide concentration-time profiles from 6 subjects
after oral administration of 20% HPMC formulation.

Figure 19 Plasma gliclazide concentration-time profiles from 6 subjects
after oral administration of commercial product.

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Figure 20 Plasma gliclazide concentration-time profiles from 6 subjects

after oral administration of 7 % XG formulation.

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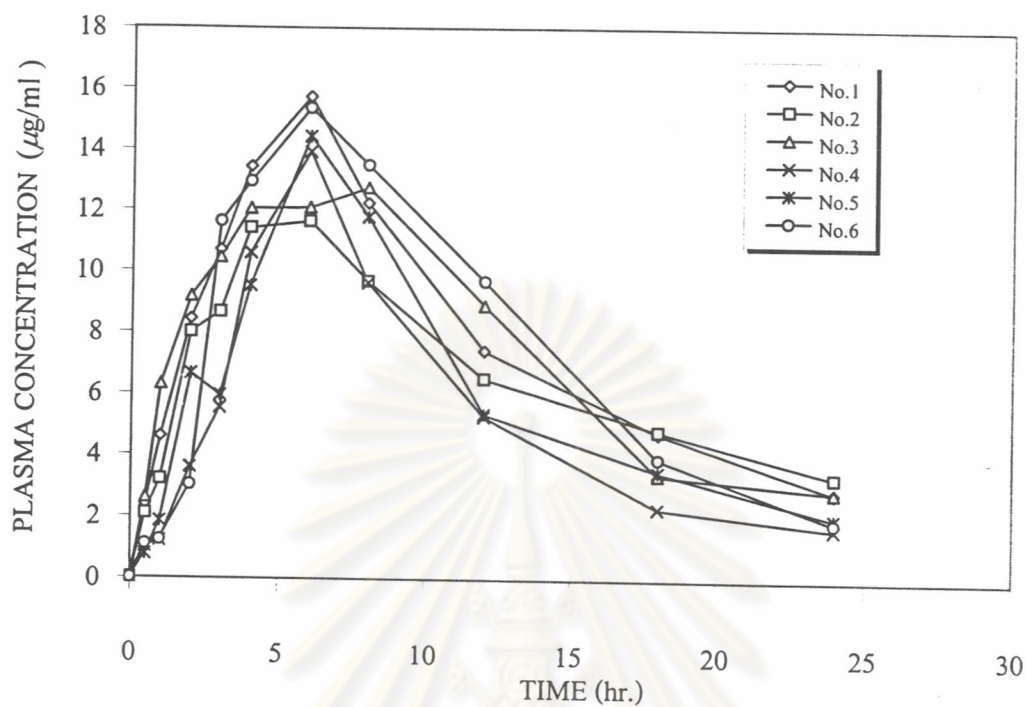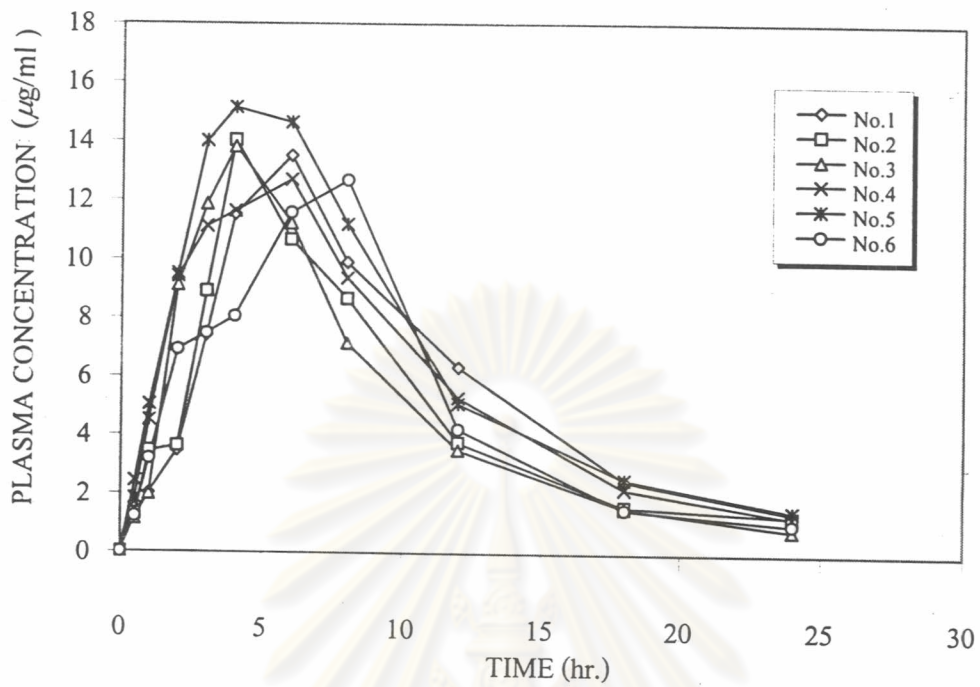
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Figure 21 Plasma gliclazide concentration-time profiles from 6 subjects
after oral administration of commercial product.
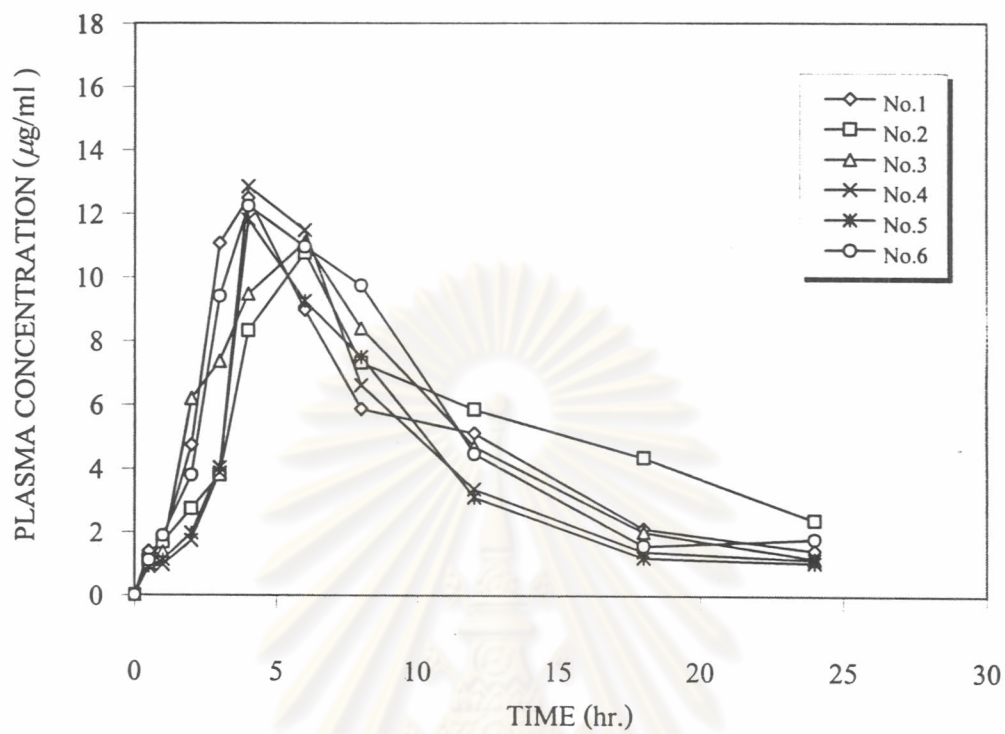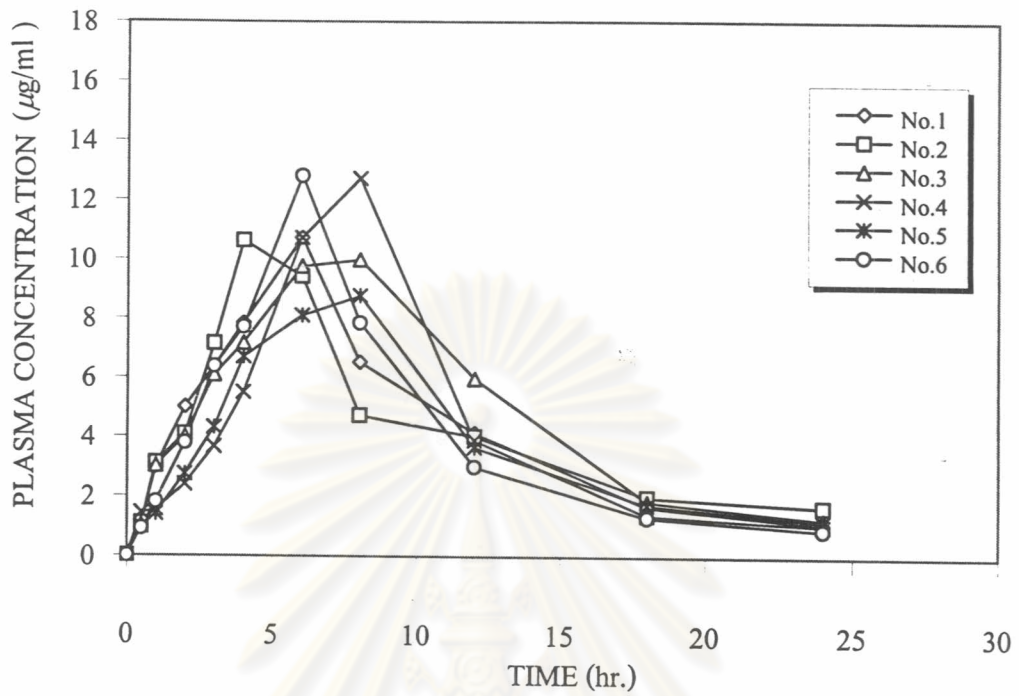
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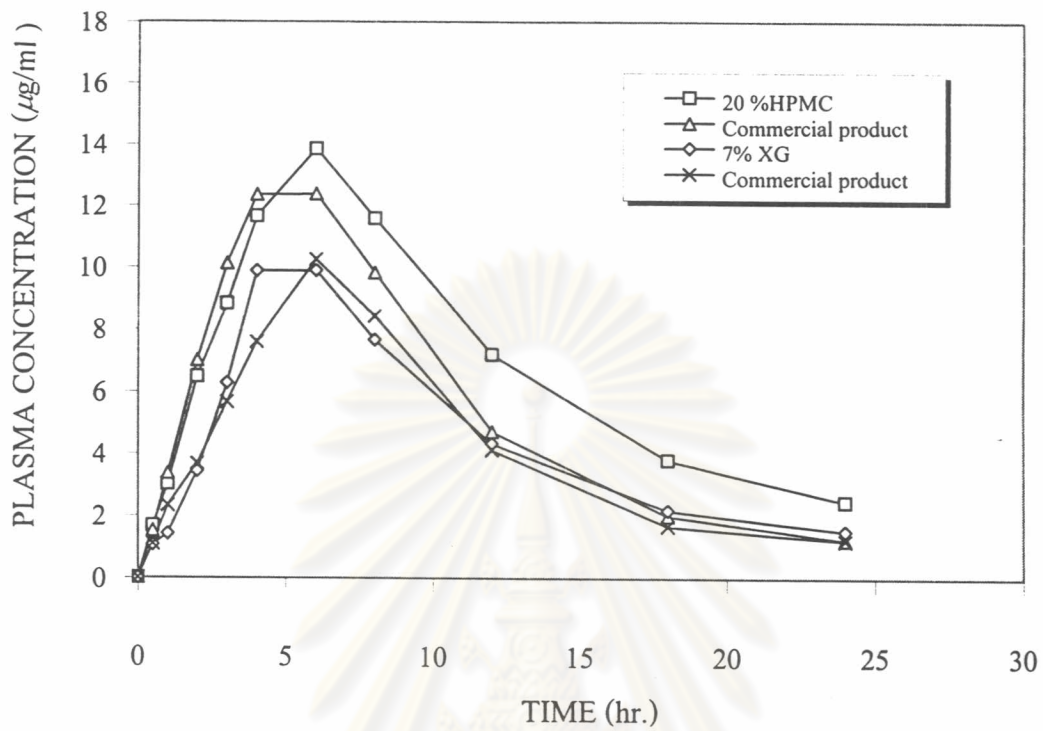
Figure 22 Average plasma gliclazide concentration-time profiles between
20% HPMC, 7 % XG and commercial product formulation.

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2.2.2 <u>Time to peak plasma concentration</u> (t_{max})

This parameter is generally used to indicate the onset of drug action. The time to peak plasma concentration of gliclazide of each formulation is presented in Tables 16 and 17. The average times for 20% HPMC, commercial product, 7% XG and commercial product were 6.333 ± 0.816, 5.333 ± 1.633, 4.667 ± 1.033 and 6.667 ± 1.633 hours, respectively. It implied that the drug release from 7% XG was as fast as and more rapidly absorbed into the systemic circulation than those observed from 20% HPMC and commercial product. Table 18 shows that there was statistically significant difference ($p < 0.05$) among t_{max} values of 20% HPMC versus 7% XG. However, there were no statistically significant difference ($p > 0.05$) among t_{max} values of 20% HPMC and 7% XG versus commercial product.

2.2.3 <u>Area under the plasma concentration-time curve</u> (AUC)

This parameter is generally used to indicate the total amount of drug absorbed into the systemic circulation and becomes available at the site of action.

2.2.3.1 AUC$_{gliclazide-24}$

The average AUC$_{gliclazide-24}$ for 20% HPMC, commercial product, 7% XG and commercial product were 0.164 ± 0.023, 0.132 ± 0.016, 0.112 ± 0.014 and 0.103 ± 0.009 mg-hr/ml, respectively as shown in Tables 19 and 20. The tablet with 20% HPMC exhibited the maximum extent of drug absorption. Table 21 shows that there was statistically significant difference ($p < 0.05$) among values AUC$_{gliclazide-24}$ of 20% HPMC versus 7% XG. However, AUC$_{gliclazide-24}$ values of 20% HPMC and 7% XG versus commercial product were no statistically significant difference ($p > 0.05$).

2.2.3.2 AUC_0^∞

The average AUC_0^∞ for 20% HPMC, commercial product, 7% XG and commercial product were 0.208 ± 0.044, 0.150 ± 0.017, 0.138 ± 0.008 and 0.129 ± 0.019 mg-hr/ml, respectively as shown in Tables 22 and 23. Table 24 shows that there was statistically significant difference ($p < 0.05$) among AUC_0^∞ values of 20% HPMC versus 7% XG. However, there were no statistically significant difference ($p > 0.05$) between AUC_0^∞ values of 20% HPMC and 7% XG versus commercial product.

2.2.4 Other pharmacokinetic parameters (Ka, Ke and $t_{1/2}$)

2.2.4.1 Absorption rate constant (Ka)

The average absorption rate constants for matrix of 20% HPMC, commercial product, 7% XG and commercial product were 0.947 ± 0.609, 0.815 ± 0.310, 0.842 ± 0.238, and 0.692 ± 0.132 hr^{-1}, respectively, as presented in Tables 25 and 26. Table 27 shows that There were no statistically significant difference ($p > 0.05$) among Ka values of the all formulations. The absorption rate of drug appeared to be independent of drug dissolution rate. Although 7% XG showed higher dissolution rate than 20% HPMC, the absorption rate constants for 20% HPMC and 7% XG were similar.

2.2.4.2 Elimination rate constant (Ke)

The average elimination rate constants for matrix of 20% HPMC, commercial product, 7% XG and commercial product were 0.073 ± 0.033, 0.081 ± 0.025, 0.061 ± 0.034 and 0.055 ± 0.015 hr^{-1}, respectively as presented in Tables 28 and 29. Table 30 shows that there were no statistically significant difference ($p > 0.05$) among Ke values of the all formulations.

Table 13 Peak plasma concentration (C_{max}) of gliclazide following oral administration of HPMC and commercial product.

Subject No.	C_{max} ($\mu g/ml$)	
	HPMC	Commercial product
1	15.709	13.483
2	11.619	14.008
3	12.727	13.790
4	13.890	12.679
5	14.402	15.123
6	15.339	12.667
Mean	13.948	13.625
SD	1.560	0.922

Table 14 Peak plasma concentration (C_{max}) of gliclazide following oral administration of XG and commercial product.

Subject No.	C_{max} ($\mu g/ml$)	
	Xanthan gum	Commercial product
1	12.467	10.696
2	10.750	10.619
3	11.082	9.971
4	12.841	12.700
5	11.790	8.750
6	12.231	12.790
Mean	11.860	10.921
SD	0.814	1.576

Table 15 Comparison of peak plasma concentration (C_{max}) of three formulations

of gliclazide matrix tablets.

Formulation	Mann-Whitney U test				Statistical
	U_{HPMC}	U_{XG}	U	U_0	significance
HPMC versus xanthan gum	5	31	5	6	S
(n_1=6, n_2=6)					
Formulation	Wilcoxon Singed Rank test				Statistical
	T^+	T^-	T	T_L	significance
HPMC versus commercial product	13	8	8	1	NS
(n =6)					
Xanthan gum versus commercial product	18	3	3	1	NS
(n =6)					

S = Significant difference at $P < 0.05$

NS = Not significant difference at $P > 0.05$

Table 16 Time to peak plasma concentration (t_{max}) of gliclazide following oral administration of HPMC and commercial product.

Subject No.	t_{max} (hr)	
	HPMC	Commercial product
1	6.000	6.000
2	6.000	4.000
3	8.000	4.000
4	6.000	6.000
5	6.000	4.000
6	6.000	8.000
Mean	6.333	5.333
SD	0.816	1.633

Table 17 Time to peak plasma concentration (t_{max}) of gliclazide following oral administration of XG and commercial product.

Subject No.	t_{max} (hr)	
	Xanthan gum	Commercial product
1	4.000	6.000
2	6.000	4.000
3	6.000	8.000
4	4.000	8.000
5	4.000	8.000
6	4.000	6.000
Mean	4.667	6.667
SD	1.033	1.633

Table 18 Comparison of time to peak plasma concentration (t_{max}) of three

formulations of gliclazide matrix tablets.

Formulation	Mann-Whitney U test				Statistical significance
	U_{HPMC}	U_{XG}	U	U_0	
HPMC versus xanthan gum	5	31	5	6	S
(n_1=6, n_2=6)					
Formulation	Wilcoxon Singed Rank test				Statistical significance
	T^+	T^-	T	T_L	
HPMC versus commercial product	8	2	2	<1	NS
(n =4)					
Xanthan gum versus commercial product	2.5	18.5	2.5	1	NS
(n =6)					

S = Significant difference at P < 0.05

NS = Not significant difference at P > 0.05

Table 19 Area under the plasma concentration-time curve 24 hr.$(AUC_{gliclazide-24})$ of gliclazide following oral administration of HPMC and commercial product.

Subject No.	$AUC_{gliclazide-24}$ (mg-hr/ml)	
	HPMC	Commercial product
1	0.186	0.138
2	0.161	0.116
3	0.180	0.117
4	0.128	0.140
5	0.147	0.158
6	0.184	0.124
Mean	0.164	0.132
SD	0.023	0.016

Table 20 Area under the plasma concentration-time curve 24 hr.$(AUC_{gliclazide-24})$ of gliclazide following oral administration of XG and commercial product.

Subject No.	$AUC_{gliclazide-24}$ (mg-hr/ml)	
	Xanthan gum	Commercial product
1	0.115	0.101
2	0.127	0.100
3	0.116	0.118
4	0.097	0.107
5	0.092	0.093
6	0.122	0.098
Mean	0.112	0.103
SD	0.014	0.009

Table 21 Comparison of area under the plasma concentration-time curve 24 hr.

(AUC$_{\text{gliclazide-24}}$) of three formulations of gliclazide matrix tablets.

Formulation	Mann-Whitney U test				Statistical
	U_{HPMC}	U_{XG}	U	U_0	significance
HPMC versus xanthan gum	0	36	0	6	S
(n_1=6, n_2=6)					
Formulation	Wilcoxon Singed Rank test				Statistical
	T^+	T^-	T	T_L	significance
HPMC versus commercial product	18	3	3	1	NS
(n =6)					
Xanthan gum versus commercial product	15	6	6	1	NS
(n =6)					

S = Significant difference at P < 0.05

NS = Not significant difference at P > 0.05

Table 22 Area under the plasma concentration-time curve (AUC_0^{∞}) of gliclazide following oral administration of HPMC and commercial product.

Subject No.	AUC_0^{∞} (mg-hr/ml)	
	HPMC	Commercial product
1	0.220	0.152
2	0.217	0.152
3	0.282	0.125
4	0.160	0.154
5	0.169	0.175
6	0.200	0.140
Mean	0.208	0.150
SD	0.044	0.017

Table 23 Area under the plasma concentration-time curve (AUC_0^{∞}) of gliclazide following oral administration of XG and commercial product.

Subject No.	AUC_0^{∞} (mg-hr/ml)	
	Xanthan gum	Commercial product
1	0.137	0.116
2	0.151	0.161
3	0.130	0.139
4	0.136	0.131
5	0.137	0.113
6	*	0.114
Mean	0.138	0.129
SD	0.008	0.019

* = cannot be calculated

Table 24 Comparison of area under the plasma concentration-time curve

(AUC_0^{∞}) of three formulations of gliclazide matrix tablets.

Formulation	Mann-Whitney U test				Statistical
	U_{HPMC}	U_{XG}	U	U_0	significance
HPMC versus xanthan gum	0	30	0	4	S
$(n_1=6, n_2=5)$					
Formulation	Wilcoxon Singed Rank test				Statistical
	T^+	T^-	T	T_L	significance
HPMC versus commercial product	19.5	1.5	1.5	1	NS
(n =6)					
Xanthan gum versus commercial product	10	5	5	<1	NS
(n =5)					

S = Significant difference at P < 0.05

NS = Not significant difference at P > 0.05

2.2.4.3 Biological half-life ($t_{1/2}$)

The average half-life of gliclazide matrix using 20% HPMC, commercial product, 7% XG and commercial product were 11.818 ± 6.884, 9.779 ± 4.623, 15.787 ± 10.291 and 14.000 ± 5.593 hours, respectively as presented in Tables 31 and 32. Table 33 shows that there were no statistically significant difference ($p > 0.05$) among $t_{1/2}$ values of the all formulations.

All estimated pharmacokinetic parameters of gliclazide matrix tablet in rabbits after oral administration of three formulations were summarized in Table 34, 35 and 36. From this study, 20% HPMC formulation was dissimilar to 7% XG. However, 20% HPMC and 7% XG formulation were similar to commercial product. In this study, pharmacokinetic parameters among 20% HPMC versus 7% XG were statistically significant difference (see Table 34), it could be stated that the formulation tablets prepared using difference polymer may be lead to difference in terms of the rate and the extent of absorption in rabbits.

Table 25 Absorption rate constant (Ka) of gliclazide following oral administration of HPMC and commercial product.

Subject No.	Ka (hr^{-1})	
	HPMC	Commercial product
1	1.575	1.420
2	0.286	0.641
3	0.587	0.837
4	1.338	0.714
5	*	0.717
6	*	0.563
Mean	0.947	0.815
SD	0.609	0.310

* = cannot be calculated

Table 26 Absorption rate constant (Ka) of gliclazide following oral administration of XG and commercial product.

Subject No.	Ka (hr^{-1})	
	Xanthan gum	Commercial product
1	0.922	0.773
2	*	0.921
3	1.064	0.634
4	0.877	0.629
5	0.506	0.555
6	*	0.641
Mean	0.842	0.692
SD	0.238	0.132

* = cannot be calculated

Table 27 Comparison of absorption rate constant (Ka) of three formulations
of gliclazide matrix tablets.

Formulation	Mann-Whitney U test				Statistical
	U_{HPMC}	U_{XG}	U	U_0	significance
HPMC versus xanthan gum	7	9	7	1	NS
$(n_1=4, n_2=4)$					
Formulation	Wilcoxon Singed Rank test				Statistical
	T^+	T^-	T	T_L	significance
HPMC versus commercial product	5	5	5	<1	NS
(n =4)					
Xanthan gum versus commercial product	9	1	1	<1	NS
(n =4)					

S = Significant difference at $P < 0.05$

NS = Not significant difference at $P > 0.05$

Table 28 Elimination rate constant (Ke) of gliclazide following oral administration of HPMC and commercial product.

Subject No.	Ke (hr^{-1})	
	HPMC	Commercial product
1	0.085	0.096
2	0.060	0.037
3	0.028	0.104
4	0.053	0.092
5	0.090	0.090
6	0.122	0.064
Mean	0.073	0.081
SD	0.033	0.025

Table 29 Elimination rate constant (Ke) of gliclazide following oral administration of XG and commercial product.

Subject No.	Ke (hr^{-1})	
	Xanthan gum	Commercial product
1	0.064	0.071
2	0.099	0.028
3	0.088	0.062
4	0.030	0.045
5	0.023	0.061
6	*	0.060
Mean	0.061	0.055
SD	0.034	0.015

* = cannot be calculated

Table 30 Comparison of elimination rate constant (Ke) of three formulations of gliclazide matrix tablets.

Formulation	Mann-Whitney U test				Statistical significance
	U_{HPMC}	U_{XG}	U	U_0	
HPMC versus xanthan gum	13	17	13	4	NS
(n_1=6, n_2=5)					
Formulation	Wilcoxon Singed Rank test				Statistical significance
	T^+	T^-	T	T_L	
HPMC versus commercial product	6	9	6	<1	NS
(n =5)					
Xanthan gum versus commercial product	8	7	7	<1	NS
(n =5)					

S = Significant difference at P < 0.05

NS = Not significant difference at P > 0.05

Table 31 Biological half-life ($t_{1/2}$) of gliclazide following oral administration of HPMC and commercial product.

Subject No.	$t_{1/2}$ (hr)	
	HPMC	Commercial product
1	8.153	7.219
2	11.550	18.730
3	24.750	6.663
4	13.075	7.533
5	7.700	7.700
6	5.680	10.828
Mean	11.818	9.779
SD	6.884	4.623

Table 32 Biological half-life ($t_{1/2}$) of gliclazide following oral administration of XG and commercial product.

Subject No.	$t_{1/2}$ (hr)	
	Xanthan gum	Commercial product
1	10.828	9.761
2	7.000	24.750
3	7.875	11.177
4	23.100	15.400
5	30.130	11.361
6	*	11.550
Mean	15.787	14.000
SD	10.291	5.593

* = cannot be calculated

Table 33 Comparison of biological half-life ($t_{1/2}$) of three formulations of
gliclazide matrix tablets.

Formulation	Mann-Whitney U test				Statistical
	U_{HPMC}	U_{XG}	U	U_0	significance
HPMC versus xanthan gum	17	13	13	4	NS
(n_1=6, n_2=5)					
Formulation	Wilcoxon Singed Rank test				Statistical
	T^+	T^-	T	T_L	significance
HPMC versus commercial product	9	6	6	<1	NS
(n =5)					
Xanthan gum versus commercial product	9	6	6	<1	NS
(n =5)					

S = Significant difference at P < 0.05

NS = Not significant difference at P > 0.05

Table 34   Estimated pharmacokinetic parameters (Mean + S.D.)of gliclazide

from six rabbits following oral administration of gliclazide 30 mg

matrix tablets between HPMC and xanthan gum.

Parameters	Formulation		
	HPMC	Xanthan gum	Significance
Cmax	13.948(1.560)	11.860(0.814)	S
tmax	6.333(0.816)	4.667(1.033)	S
AUC_0^∞	0.208(0.044)	0.138(0.008)	S
Ka	0.947(0.609)	0.842(0.238)	NS
Ke	0.073(0.033)	0.061(0.034)	NS
$t_{1/2}$	11.818(6.884)	15.787(10.291)	NS

Table 35   Estimated pharmacokinetic parameters (Mean + S.D.) of gliclazide

from six rabbits following oral administration of gliclazide 30 mg

matrix tablets between HPMC and commercial product.

Parameters	Formulation		
	HPMC	Commercial product	Significance
Cmax	13.948(1.560)	13.625(0.922)	NS
tmax	6.333(0.816)	5.333(1.633)	NS
AUC_0^∞	0.208(0.044)	0.150(0.017)	NS
Ka	0.947(0.609)	0.815(0.310)	NS
Ke	0.073(0.033)	0.081(0.025)	NS
$t_{1/2}$	11.818(6.884)	9.779(4.623)	NS

Table 36   Estimated pharmacokinetic parameters (Mean + S.D.) of gliclazide from six rabbits following oral administration of gliclazide 30 mg matrix tablets between xanthan gum and commercial product.

Parameters	Formulation		
	Xanthan gum	Commercial product	Significance
Cmax	11.860(0.814)	10.921(1.576)	NS
tmax	4.667(1.033)	6.667(1.633)	NS
AUC_0^{∞}	0.138(0.008)	0.129(0.019)	NS
Ka	0.842(0.238)	0.692(0.132)	NS
Ke	0.061(0.034)	0.055(0.015)	NS
$t_{1/2}$	15.787(10.291)	14.000(5.593)	NS