CHAPTER III

RESULTS

The results of the studies will be summarized in the following order :

1. Preformulation of Drug Reservoirs for Diclofenac Diethylamine
   - 1.1 Determination of Drug Solubility
   - 1.2 Effect of Various Solvents on the Physical Change at Accelerated Condition
   - 1.3 Effect of Various pH Values of Buffer Solutions on the Physical Change at Accelerated Condition
   - 1.4 Stability Study of Drug in Gelling Agents at Accelerated Condition
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   - 2.1 *In-vitro* Evaluation of Voltaren® emulgel
     - 2.1.1 *In-vitro* Drug Release of Voltaren® emulgel in patch
     - 2.1.2 *In-vitro* Skin Permeation of Voltaren® emulgel in patch
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   - 2.3 *In-vivo* Evaluation of Diclofenac Diethylamine-TDS Formulations

1. Preformulation of Drug Reservoirs for Diclofenac Diethylamine

1.1 Determination of Drug Solubility

The equilibrium solubilities of DD in different solvents at 37±1°C are listed in Table 4. The rank order of solubility was : benzyl alcohol > N,N-dimethyl acetamide > ethyl alcohol > isopropyl alcohol > propylene glycol > polyethylene glycol 400, respectively.

Table 4 Solubility of Diclofenac Diethylamine at 37±1°C.

Solvents	Solubilities (mg/ml)
Benzyl alcohol	297
N,N-dimethyl acetamide	264
Ethyl alcohol	135
Isopropyl alcohol	64
Propylene glycol	49
Polyethylene glycol 400	22

1.2 Effect of Solvents on the Physical Change at Accelerate Condition

In this section, prescreening the effects of solvents on the physical stability of DD were obtained. Drug was added to various solvents, at 1.16 %w/w concentration. The accelerated samples were kept at 45±2°C for 1 month. The result in color change was compared as illustrated in Figure 14.

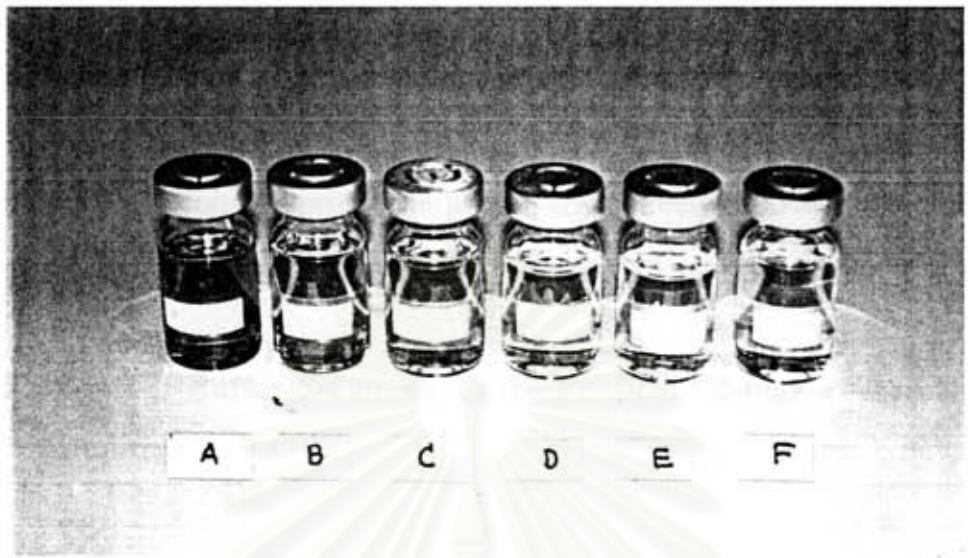

Figure 14 Color change of 1.16 %w/w diclofenac diethylamine in various solvents after storage at 45±2°C for 1 month (A=polyethylene glycol 400, B=benzyl alcohol, C=N,N-dimethyl acetamide, D=isopropyl alcohol, E=ethyl alcohol, F=propylene glycol).

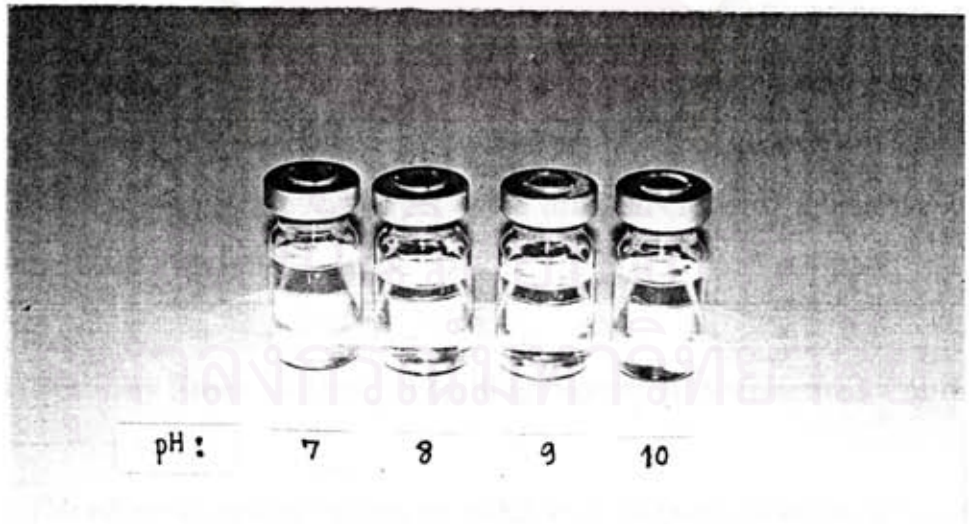

Figure 15 Color change of 1.16 %w/w diclofenac diethylamine in buffer solution at pH values of 7, 8, 9, and 10 after storage at 45±2°C for 1 month.

It was found that degree of intensity for color changing of 1.16 %w/w DD in various solvents after storage at 45±2°C for 1 month were in the order of polyethylene glycol 400 > benzyl alcohol > N,N-dimethyl acetamide > isopropyl alcohol > ethyl alcohol ~ propylene glycol, respectively. However, no change were observed for ethyl alcohol and propylene glycol.

1.3 Effect of Buffer Solutions on the Physical Change at Accelerated Condition

Because of the complex mixtures that may occur in dosage forms, many kinds of drug decomposition reactions are possible. Prescreening the effect of pH values on the physical change of DD solution at pH values of 6, 7, 8, 9, and 10, after storage at 45±2°C up to 1 month were studied as illustrated in Figure 15.

It was found that degree of color change intensity of 1.16 %w/w DD in buffer solutions after storage at 45±2°C for 1 month were in the order of pH 10~ pH 9 > pH 8 > pH 7, respectively. The result indicated that no change was observed at pH 7. However, at pH 6 the drug precipitated immediately after mixing.

1.4 Stability Study of Drug in Gelling Agents at Accelerated Condition

The effect of gelling agents on stability of DD were studied, according to formulas in Table 3. Drug was added to various gelling agents, at 1.16 %w/w concentration. The accelerated samples were kept at 45±2°C for 4 months. The results in color change were compared as illustrated in Figures 16-19.

Figure 16 Color change of 1.16 %w/w diclofenac diethylamine in various gelling agents after incubating at 45±2°C for 1 month.

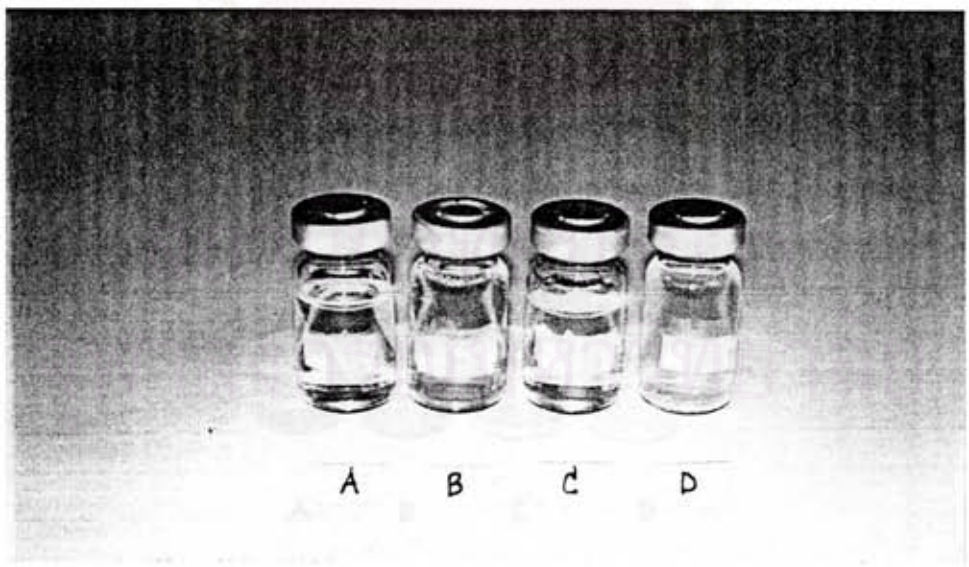

Figure 17 Color change of 1.16 %w/w diclofenac diethylamine in various gelling agents after incubating at 45±2°C for 2 months.

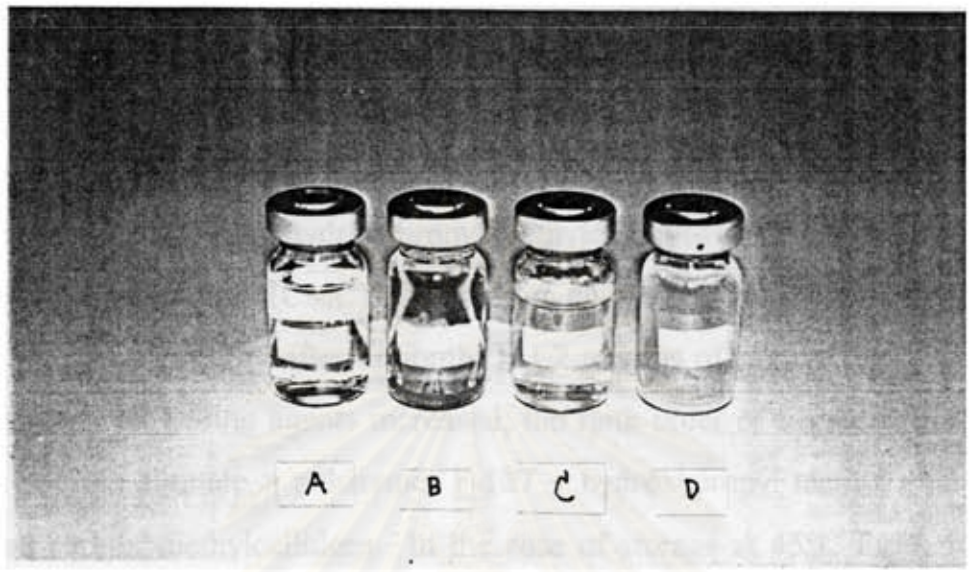

Figure 18 Color change of 1.16 %w/w diclofenac diethylamine in various gelling agents after incubating at 45±2°C for 3 months.

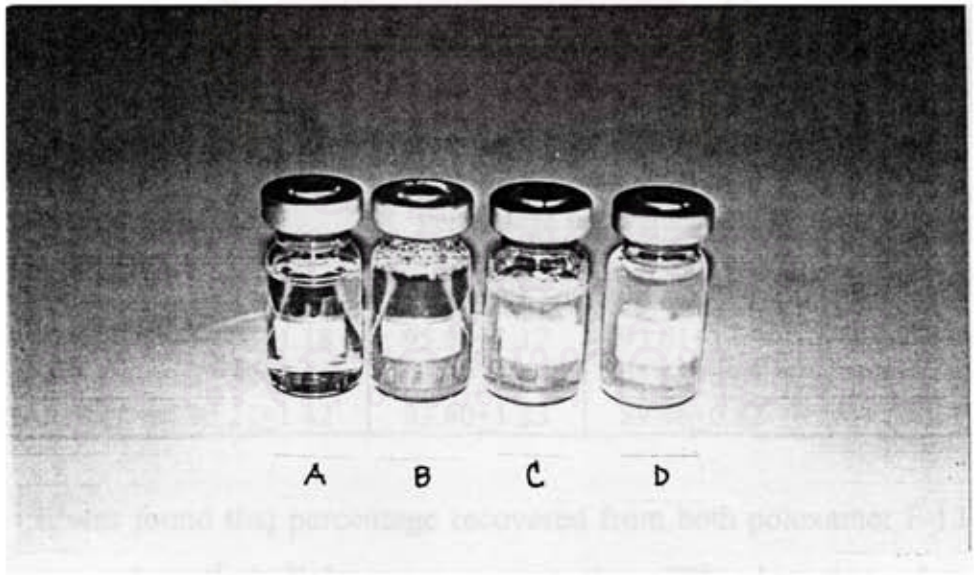

Figure 19 Color change of 1.16% w/w diclofenac diethylamine in various gelling agents after incubating at 45±2°C for 4 months.

Remark : A = poloxamer F-127, B = hydroxypropyl methylcellulose, C = sodium carboxymethylcellulose, D = sodium alginate.

As illustrated in Figure 16, after incubating diclofenac diethylamine in various gelling agents at 45±2°C for 1 month, no change was observed for poloxamer -F127 (PLX), hydroxypropyl methylcellulose (HPMC), and sodium carboxymethylcellulose (CMC). For sodium alginate (SALG) the increasing in color intensity appeared after 1 month. At 2 months of storage, the degree of intensity for all gelling agents increased, the rank order of degree of intensity was : sodium alginate > poloxamer F-127 ~ hydroxypropyl methylcellulose ~ sodium carboxymethylcellulose. In the case of storage at 45°C for 3 months and 4 months, the rank order of degree of intensity was the same : sodium alginate > sodium carboxymethylcellulose > poloxamer F-127 ~ hydroxypropyl methylcellulose.

Table 4 Percentage recover of diclofenac diethylamine in various gelling agents after incubating at 45±2°C for 4 months analyzed by HPLC method (n=3).

Gelling agents	Percentage recovered±SD			
	1 mth	2 mths	3 mths	4 mths
PLX	98.85±0.48	98.60±0.62	97.81±0.44	96.06±1.58
HPMC	97.68±1.18	95.56±1.17	93.61±1.09	91.76±0.91
CMC	97.58±0.94	94.47±1.36	91.68±0.62	88.39±0.83
SALG	96.21±1.42	93.80±1.33	89.46±0.82	87.25±1.31

It was found that percentage recovered from both poloxamer F-127 and hydroxypropyl methylcellulose were more than 90%, but that of sodium carboxymethylcellulose and sodium alginate were lower, after the incubation of

4 months. The lower limit of percentage recovered in USP for diclofenac is not less than 90.0%.

2. Evaluation of Diclofenac Diethylamine-TDS Formulations

The *in-vitro* release and skin permeation results, which used shed snake skin, of Voltaren® emulgel, Voltaren® emulgel patch, and 23 formulas are summarized in Tables 16-21.

2.1 *In-vitro* Evaluation of Voltaren® emulgel

2.1.1 *In-vitro* Drug Release of Voltaren® emulgel in patch

The *in-vitro* drug release studies of the drug from Voltaren® emulgel in patches were carried out. The drug release results are presented in Table 16. The average cumulative amount of drug release is given in Table 6. A typical release-time profile is shown in Figure 20.

2.1.2 *In-vitro* Skin Permeation of Voltaren® emulgel in patch

The *in-vitro* skin permeation studies of the drug from Voltaren® emulgel in patches were carried out. The skin permeation results are presented in Table 17. The average accumulative amount of drug permeation is given in Table 6. A typical permeation-time profile in shown is Figure 21.

Table 6 Average cumulative release and permeation of diclofenac diethylamine per surface area (mg/cm^2) from Voltaren® emulgel (VE) via skin as compared to Voltaren® emulgel in patch (VE patch) via skin, (n=6).

Time (hrs)		Cumulative release ± SD	Cumulative skin permeation ± SD	
		VE patch	VE patch	VE
0		0	0	0
0.5		0.352±0.175	0.005±0.005	0.003±0.005
1		0.472±0.205	0.006±0.005	0.006±0.006
2		0.695±0.205	0.007±0.004	0.011±0.016
3		0.882±0.202	0.008±0.004	0.016±0.023
4		1.041±0.183	0.008±0.004	0.022±0.026
5		1.186±0.184	0.008±0.004	0.023±0.026
6		1.251±0.149	0.009±0.005	0.026±0.029
8		1.354±0.081	0.011±0.007	0.034±0.028
10		1.460±0.125	0.014±0.009	0.043±0.031
12		1.545±0.221	0.016±0.013	0.055±0.031
Zero order	r^2	0.992*	0.962	0.992
	intercept	0.292*	0.005	0.002
	slope	0.186*	0.001	0.004
First order	r^2	0.999*	0.882	0.992
	intercept	0.237*	0.002	0.006
	slope	-0.072*	0.000	0.000
Higuchi's plot	r^2	0.997*	0.902	0.960
	intercept	-0.065*	0.001	-0.013
	slope	0.552*	0.004	0.018

Remark : * calculate from time range of 0.5-5 hours.

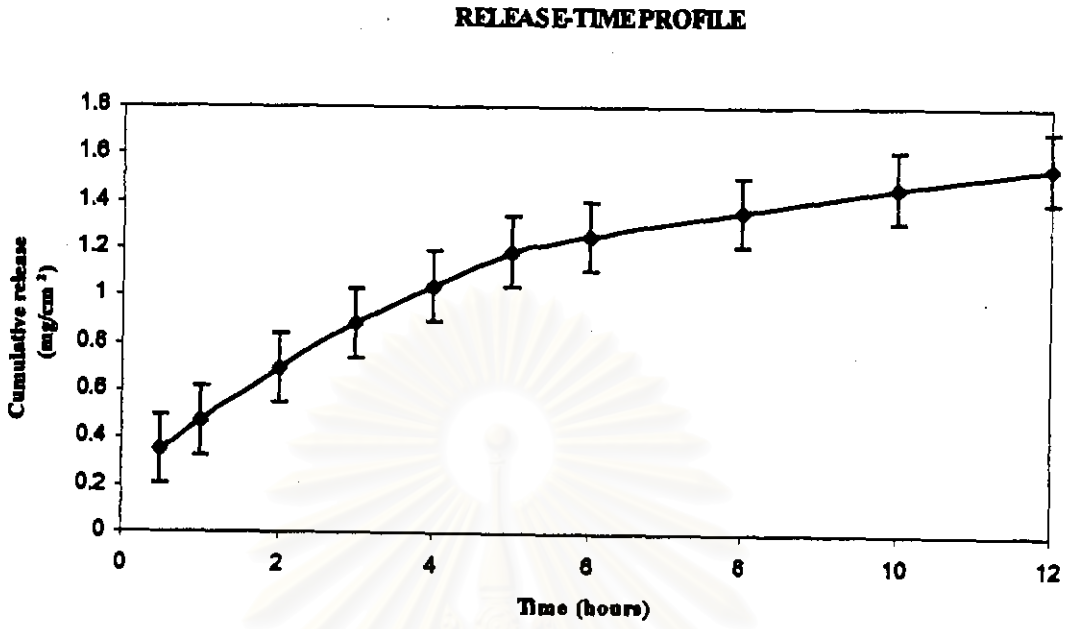

Figure 20 Average release-time profile of Voltaren® emulgel in patch, (n=10).

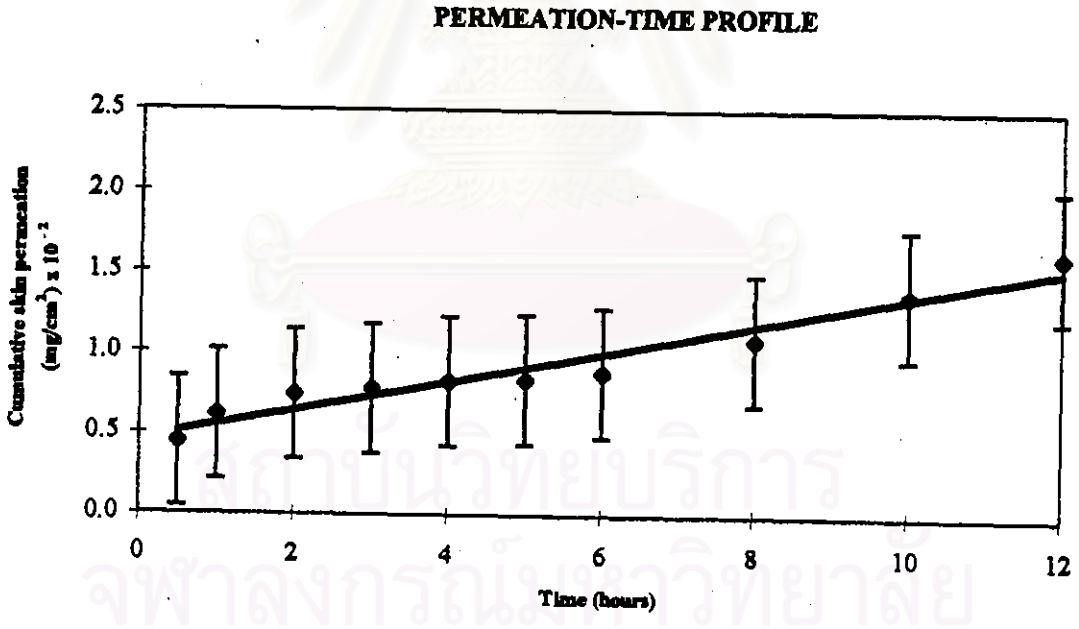

Figure 21 Zero order plot of permeation-time profile of Voltaren® emulgel in patch via shed snake skin, (r^2=0.962, intercept=0.005, slope=0.001, n=11).

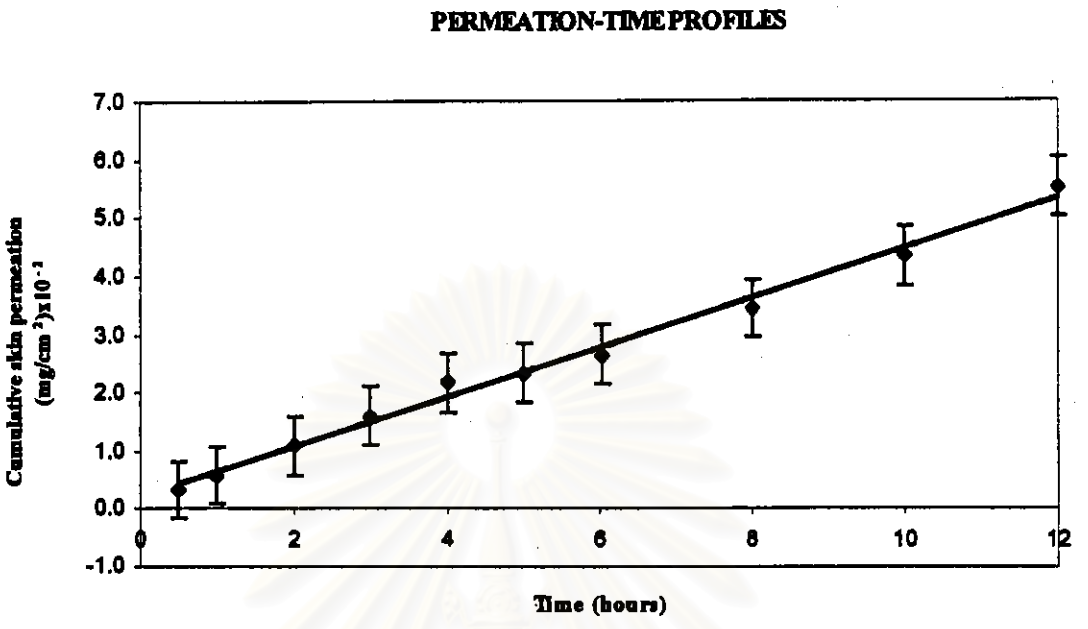

Figure 22 Zero order plot of permeation-time profile of Voltaren® emulgel via shed snake skin, (r^2=0.992, intercept=0.002, slope=0.004, n=6).

2.1.3 *In-vitro* Direct Skin Permeation of Voltaren® emulgel

The *in-vitro* skin permeation studies of the drug from Voltaren® emulgel were carried out. The skin permeation results are presented in Table 18. The average cumulative amount of drug permeation is given in Table 6. A typical permeation-time profile is shown in Figure 22.

The drug release-time profile from Voltaren® emulgel in patch indicated that the initial release kinetic of drug (from 0.5-5 hrs) seemed to be either a first order kinetic or followed a Higuchi's model. The skin permeation-time profiles from Voltaren® emulgel in patch and Voltaren® emulgel under careful consideration, sustained the permeation of DD over 12 hours. The skin permeation kinetics of both Voltaren® emulgel in patch and Voltaren® emulgel seemed to be a zero order kinetic.

2.2 *In-vitro* Evaluation of Diclofenac Diethylamine-TDS Formulations

This experiment was conducted to fabricate DD transdermal drug delivery system by using different solvents and gelling agents as drug carriers.

2.2.1 *In-vitro* Drug Release of Diclofenac Diethylamine-TDS Formulations

The influence of drug concentrations and gelling agents on the *in-vitro* release of the drug through membrane were carried out. The drug release results in propylene glycol and various gelling agents are presented in Table 19. The average cumulative amount of DD release are given in Tables 7-11.

The drug release with the same concentration from various solvents does not indicate the same release rate. A typical release time profiles depicting the effect of drug and gelling agents concentrations are shown in Figures 23-31.

The drug release-time profiles of Formulas #1-3 indicated that the initial release kinetic seemed to be a first order kinetic.

The drug release-time profiles of Formulas #4-8 indicated that the initial drug release kinetic seemed to follow the Higuchi's model.

The drug release-time profiles of Formulas #9-13 indicated that the initial drug release kinetic seemed to be either a first order kinetic or the Higuchi's model.

Table 7 The average cumulative amount of diclofenac diethylamine release per surface area (mg/cm^2) from diclofenac diethylamine-TDS in propylene glycol, (n=3).

Time (hrs)		Cumulative release ± SD		
		Formula #1	Formula #2	Formula #3
0		0	0	0
0.5		1.150±0.509	0.672±0.468	0.711±0.475
1		1.429±0.382	1.215±0.594	1.203±0.613
2		1.523±0.293	1.702±0.317	1.988±0.374
3		1.625±0.174	1.989±0.214	2.482±0.382
4		1.635±0.168	2.216±0.203	2.815±0.304
5		1.673±0.113	2.355±0.203	2.946±0.294
6		1.681±0.114	2.387±0.199	2.984±0.290
8		1.698±0.106	2.430±0.199	3.135±0.268
10		1.718±0.111	2.447±0.196	3.186±0.264
12		1.738±0.120	2.456±0.196	3.210±0.262
Zero order*	r^2	0.761	0.907	0.928
	intercept	1.253	0.784	0.734
	slope	0.098	0.351	0.499
First order*	r^2	0.871	0.986	0.983
	intercept	-0.155	0.373	0.539
	slope	-0.096	-0.133	-0.123
Higuchi's plot*	r^2	0.861	0.951	0.982
	intercept	0.309	0.059	-0.282
	slope	1.038	1.078	1.522

Remark : * calculate from time range of 0.5-5 hours.

Table 8 The average cumulative amount of diclofenac diethylamine release per surface area (mg/cm^2) from diclofenac diethylamine-TDS in poloxamer F-127, (n=3).

Time (hrs)		Cumulative release ± SD				
		Formula #4	Formula #5	Formula #6	Formula #7	Formula #8
0		0	0	0	0	0
0.5		0.527±0.030	0.436±0.035	1.270±0.188	0.664±0.055	0.494±0.033
1		0.826±0.045	0.685±0.048	1.779±0.158	0.931±0.076	0.654±0.029
2		1.219±0.065	1.044±0.074	2.293±0.190	1.365±0.097	1.032±0.038
3		1.376±0.068	1.262±0.079	2.712±0.219	1.583±0.109	1.319±0.040
4		1.456±0.072	1.403±0.078	2.841±0.208	1.798±0.110	1.512±0.042
5		1.485±0.073	1.553±0.085	2.979±0.210	1.987±0.121	1.703±0.040
6		1.506±0.066	1.666±0.083	3.063±0.214	2.151±0.116	1.899±0.053
8		1.532±0.054	1.855±0.087	3.303±0.212	2.570±0.118	2.066±0.056
10		1.565±0.048	2.021±0.066	3.549±0.190	2.883±0.115	2.240±0.053
12		1.572±0.042	2.044±0.065	3.563±0.179	2.892±0.107	2.307±0.060
Zero order*	r^2	0.841	0.948	0.899	0.961	0.980
	intercept	0.620	0.442	1.369	0.648	0.412
	slope	0.204	0.241	0.365	0.286	0.272
First order*	r^2	0.918	0.978	0.961	0.984	0.993
	intercept	0.142	0.402	0.425	0.517	0.546
	slope	-0.112	-0.057	-0.103	-0.051	-0.043
Higuchi's plot*	r^2	0.930	0.992	0.967	0.996	0.997
	intercept	0.183	-0.043	0.612	0.078	-0.114
	slope	0.637	0.731	1.122	0.865	0.814

Remark : * calculate from time range of 0.5-5 hours.

Table 9 The average cumulative amount of diclofenac diethylamine release per surface area (mg/cm^2) from diclofenac diethylamine-TDS in hydroxypropyl methylcellulose, (n=3).

Time (hrs)		Cumulative release ± SD				
		Formula #9	Formula #10	Formula #11	Formula #12	Formula #13
0		0	0	0	0	0
0.5		0.028±0.003	0.593±0.046	1.842±0.119	1.058±0.053	0.886±0.042
1		0.129±0.011	1.041±0.067	2.436±0.122	1.775±0.068	1.528±0.050
2		0.302±0.023	1.632±0.068	2.988±0.135	2.374±0.084	2.156±0.067
3		0.457±0.034	1.890±0.069	3.163±0.134	2.932±0.088	2.391±0.069
4		0.541±0.035	2.185±0.072	3.303±0.137	3.109±0.087	2.618±0.067
5		0.673±0.037	2.242±0.071	3.374±0.139	3.163±0.076	2.693±0.061
6		0.750±0.038	2.334±0.072	3.395±0.131	3.165±0.073	2.744±0.052
8		0.997±0.045	2.461±0.070	3.409±0.111	3.186±0.071	2.785±0.051
10		1.140±0.049	2.494±0.063	3.433±0.105	3.194±0.071	2.815±0.047
12		1.246±0.047	2.514±0.061	3.442±0.103	3.204±0.071	2.859±0.045
Zero order*	r^2	0.985	0.907	0.819	0.872	0.855
	intercept	-0.010	0.669	2.050	1.235	1.079
	slope	0.141	0.359	0.310	0.452	0.374
First order*	r^2	0.994	0.972	0.931	0.948	0.927
	intercept	0.295	0.389	0.291	0.463	0.462
	slope	-0.039	-0.124	-0.132	-0.138	-0.088
Higuchi's plot*	r^2	0.997	0.971	0.913	0.949	0.939
	intercept	-0.282	-0.073	1.381	0.285	0.284
	slope	0.421	1.103	0.971	1.397	1.162

Remark : * calculate from time range of 0.5-5 hours.

Table 10 The average cumulative amount of diclofenac diethylamine release per surface area (mg/cm^2) from diclofenac diethylamine-TDS in sodium carboxymethylcellulose, (n=3).

Time (hrs)		Cumulative release ± SD				
		Formula #14	Formula #15	Formula #16	Formula #17	Formula #18
0		0	0	0	0	0
0.5		0.044±0.009	0.249±0.039	1.674±0.293	1.504±0.219	1.147±0.151
1		0.155±0.028	0.473±0.062	2.455±0.372	2.056±0.261	1.789±0.201
2		0.416±0.067	0.939±0.108	3.060±0.341	2.734±0.278	2.559±0.223
3		0.578±0.077	1.230±0.119	3.267±0.353	2.987±0.258	2.788±0.210
4		0.717±0.081	1.479±0.118	3.318±0.323	3.047±0.226	2.903±0.194
5		0.815±0.084	1.702±0.115	3.398±0.300	3.080±0.199	2.955±0.176
6		0.926±0.086	1.788±0.109	3.424±0.270	3.109±0.177	2.999±0.151
8		0.992±0.071	1.976±0.117	3.468±0.238	3.116±0.175	3.026±0.146
10		1.068±0.071	2.119±0.116	3.494±0.209	3.126±0.173	3.070±0.125
12		1.154±0.071	2.126±0.115	3.498±0.206	3.133±0.173	3.078±0.124
Zero order*	r^2	0.972	0.977	0.756	0.793	0.801
	intercept	0.005	0.179	1.993	1.716	1.388
	slope	0.174	0.323	0.336	0.330	0.375
First order*	r^2	0.990	0.998	0.883	0.866	0.880
	intercept	0.295	0.457	0.296	0.347	0.410
	slope	-0.052	-0.077	-0.141	-0.106	-0.104
Higuchi's plot*	r^2	0.996	0.998	0.865	0.895	0.901
	intercept	-0.337	-0.452	1.247	0.994	0.571
	slope	0.522	0.967	1.066	1.039	1.179

Remark : * calculate from time range of 0.5-5 hours.

Table 11 The average cumulative amount of diclofenac diethylamine release per surface area (mg/cm^2) from diclofenac diethylamine-TDS in sodium alginate, (n=3).

Time (hrs)		Cumulative release ± SD				
		Formula #19	Formula #20	Formula #21	Formula #22	Formula #23
0		0	0	0	0	0
0.5		0.290±0.041	1.288±0.174	1.528±0.208	1.017±0.104	0.368±0.042
1		0.575±0.062	1.873±0.200	2.757±0.302	2.082±0.194	0.763±0.071
2		1.109±0.082	2.277±0.184	3.617±0.324	2.851±0.210	1.384±0.101
3		1.356±0.086	2.411±0.161	3.803±0.302	3.103±0.197	1.928±0.120
4		1.572±0.072	2.419±0.158	3.855±0.288	3.215±0.165	2.399±0.129
5		1.731±0.061	2.436±0.144	3.895±0.275	3.272±0.154	2.657±0.115
6		1.748±0.060	2.441±0.139	3.919±0.265	3.307±0.144	2.851±0.108
8		1.794±0.044	2.459±0.140	3.925±0.263	3.352±0.122	3.052±0.101
10		1.804±0.031	2.466±0.134	3.934±0.259	3.394±0.111	3.067±0.100
12		1.810±0.026	2.477±0.121	3.963±0.255	3.412±0.102	3.074±0.093
Zero order	r^2	0.942	0.698	0.686	0.748	0.980
	intercept	0.288	1.550	2.087	1.456	0.251
	slope	0.317	0.220	0.447	0.439	0.516
First order	r^2	0.996	0.793	0.933	0.871	0.998
	intercept	0.327	0.134	0.381	0.420	0.607
	slope	-0.198	-0.113	-0.323	-0.131	-0.099
Higuchi's plot	r^2	0.988	0.817	0.807	0.858	0.998
	intercept	-0.351	1.049	1.065	0.479	-0.753
	slope	0.961	0.705	1.437	1.394	1.543

Remark : * calculate from time range of 0.5-5 hours.

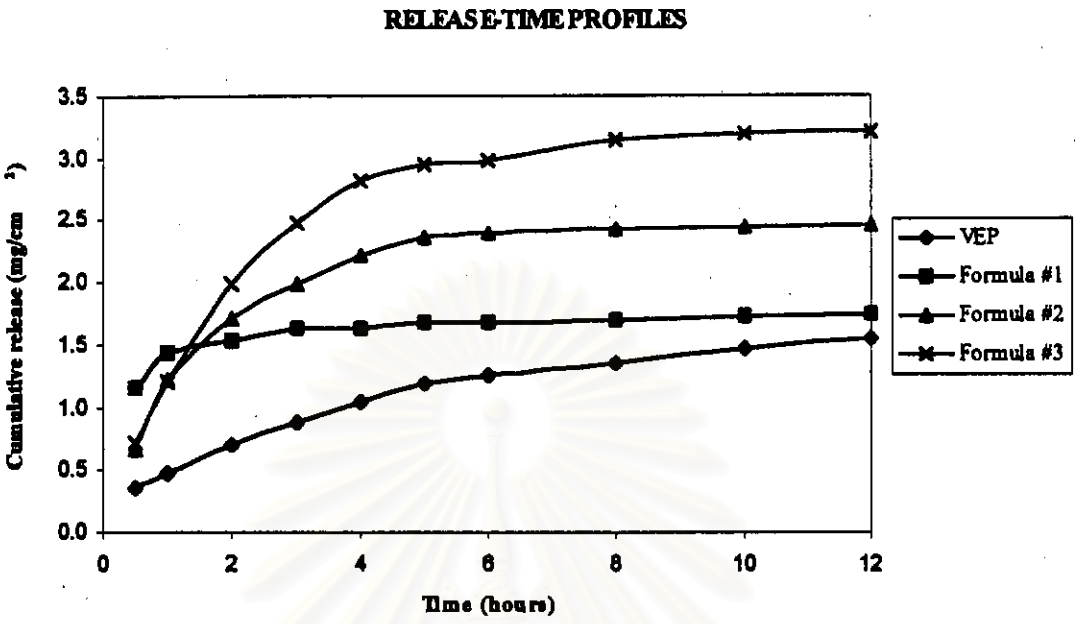

Figure 23 Effect of drug concentrations on average release-time profiles of diclofenac diethylamine-TDS (Formulas #1-3), (n=3).

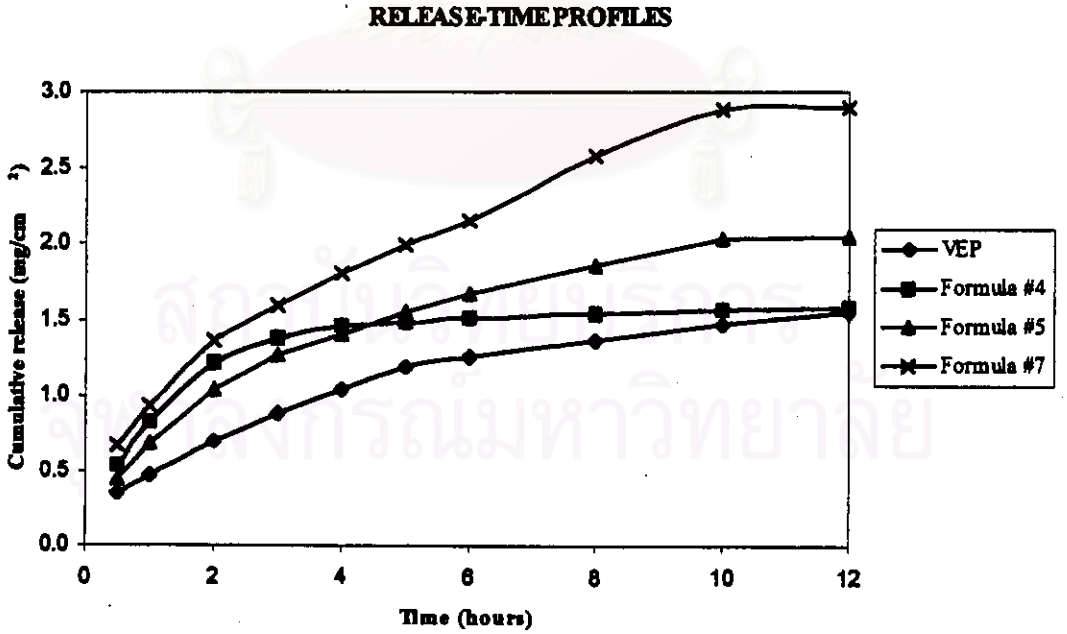

Figure 24 Effect of drug concentrations on average release-time profiles of diclofenac diethylamine-TDS (Formulas #4,5,7), (n=3).

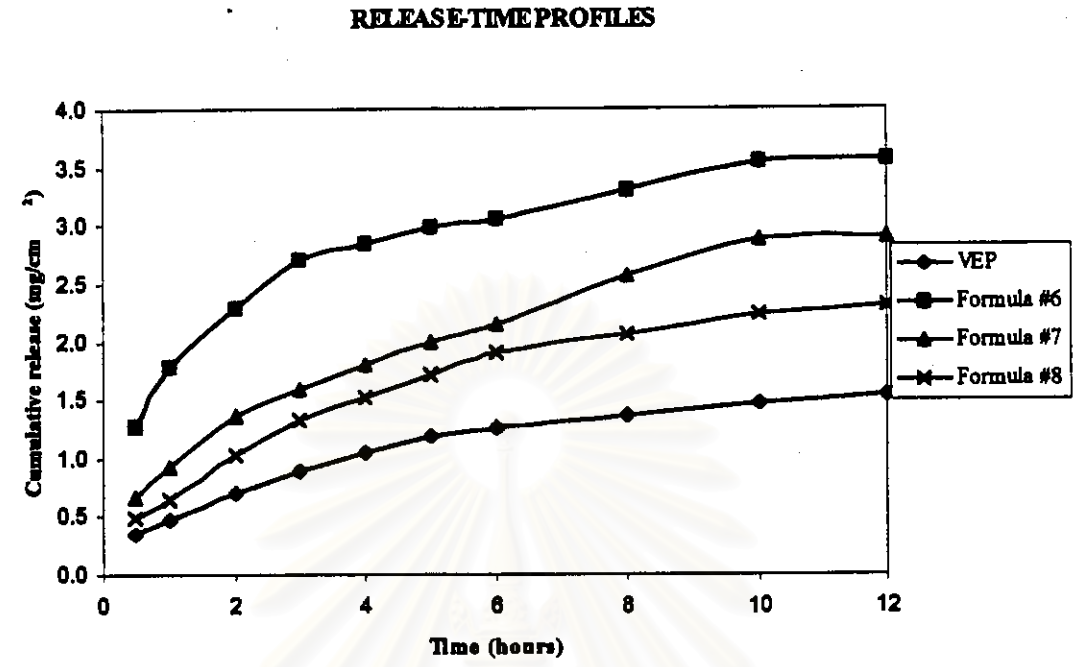

Figure 25 Effect of poloxamer F127 concentration on average release-time profiles of diclofenac diethylamine-TDS (Formulas #6-8), (n=3).

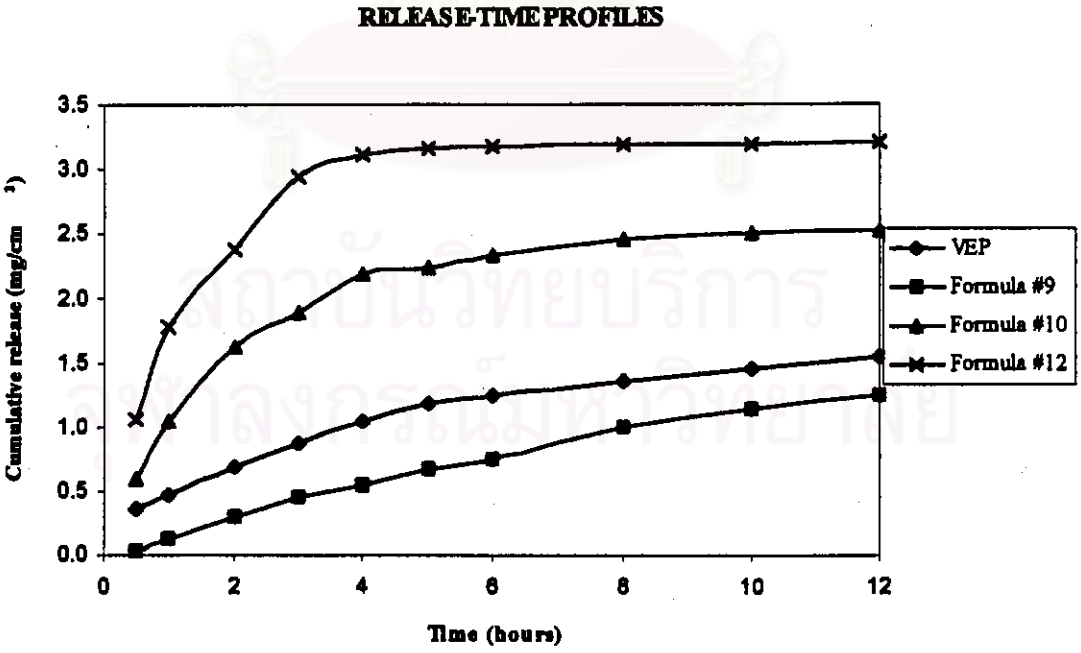

Figure 26 Effect of drug concentrations on average release-time profiles of diclofenac diethylamine-TDS (Formulas #9,10,12), (n=3).

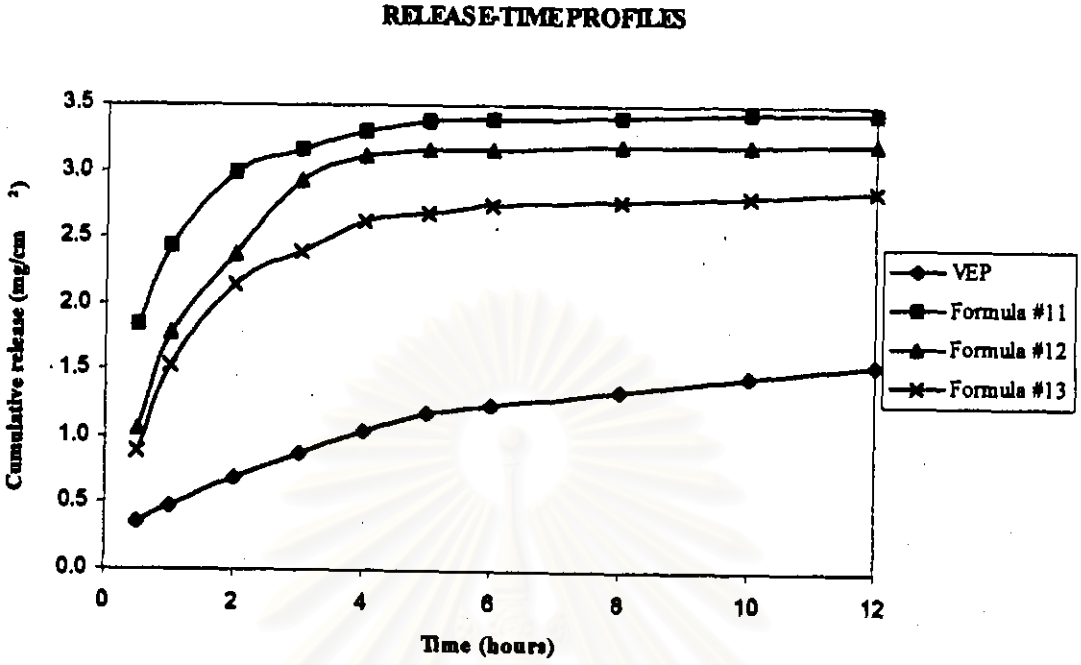

Figure 27 Effect of hydroxypropyl methylcellulose concentrations on average release-time profiles of diclofenac diethylamine-TDS (Formulas #11-13), (n=3).

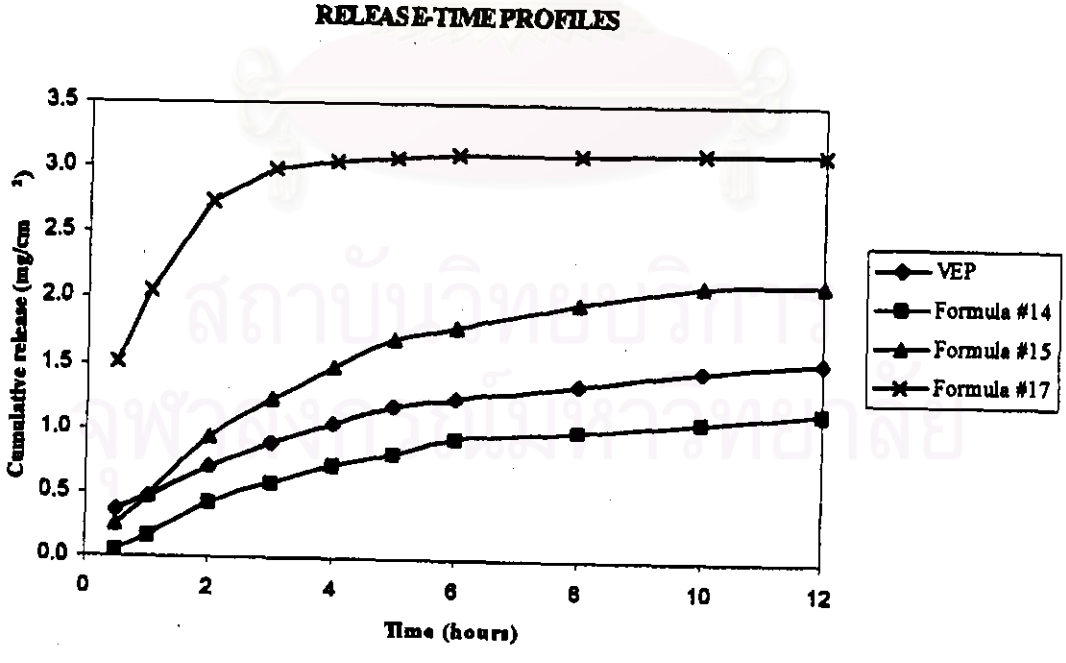

Figure 28 Effect of drug concentrations on average release-time profiles of diclofenac diethylamine-TDS (Formulas #14,15,17), (n=3).

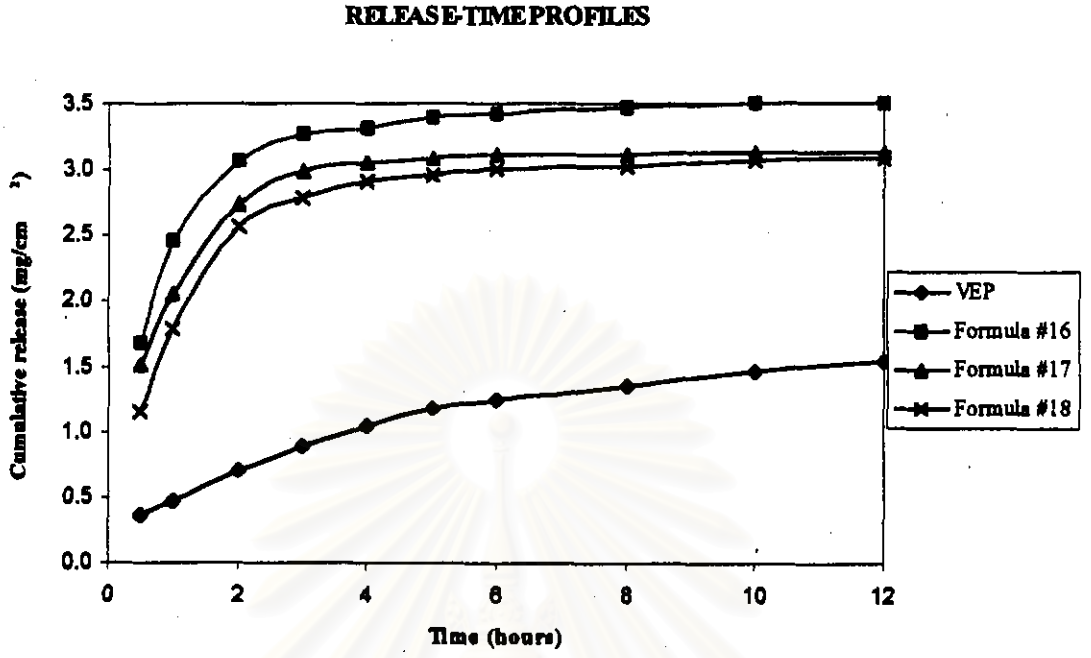

Figure 29 Effect of sodium carboxymethylcellulose concentrations on average release-time profiles of diclofenac diethylamine-TDS (Formulas #16-18), (n=3).

Figure 30 Effect of drug concentrations on average release-time profiles of diclofenac diethylamine-TDS (Formulas #19-21), (n=3).

Figure 31 Effect of sodium alginate concentrations on average release-time profiles of diclofenac diethylamine-TDS (Formulas #21-23), (n=3).

The drug release-time profiles of Formulas #14-18 also indicated that the initial drug release kinetic seemed to be either a first order kinetic or the Higuchi's model.

The drug release-time profiles #19-23 indicated that the initial drug release kinetic seemed to be either a first order kinetic or the Higuchi's model, too.

For propylene glycol and every gelling agents, it was found that the drug concentration was directly proportional to the release rate, while the correlation of the gelling agent concentration and the release rate was the opposite.

2.2.2 *In-vitro* Skin Permeation of Diclofenac Diethylamine-TDS Formulations

From previous studies, preformulation of diclofenac diethylamine in various gelling agents indicated that the drug was more stable in poloxamer F-127 and hydroxypropyl methylcellulose. From this reason, poloxamer F-127 and hydroxypropyl methylcellulose were selected as gelling agents for further study. The skin permeation results are summarized in Table 20 and Tables 12-13. The skin permeation profiles of the formulas compared to Voltaren® emulgel patch are shown in Figures 32-37 which obtained from correlation between cumulative skin permeation versus time (zero order kinetic), the logarithm of drug remained versus time (first order kinetic), and cumulative skin permeation versus square root of time (Higuchi's model), respectively.

The skin permeation-time profiles of all Formulas #6-8 and Formulas #11-13 indicated that the skin permeation kinetics seemed to follow the zero order. Moreover, in both gelling agents, poloxamer F-127 and hydroxypropyl methylcellulose, a higher gel concentration showed lower permeation rate (or slope), as found in the *in-vitro* drug release evaluation.

2.3 *In-vivo* Evaluation of Diclofenac Diethylamine-TDS Formulation

The anti-inflammatory activity of Voltaren® emulgel and diclofenac diethylamine-TDS on carrageenan-induced paw edema in rats are illustrated in Table 14.

Table 12 Average cumulative amount of diclofenac diethylamine skin permeation per surface area (mg/cm^2) from diclofenac diethylamine-TDS in poloxamer F-127, (n=6).

Time (hrs)		Cumulative skin permeation ± SD		
		Formula #6	Formula #7	Formula #8
0		0	0	0
0.5		0.008±0.002	0.008±0.002	0.008±0.002
1		0.009±0.002	0.008±0.002	0.008±0.003
2		0.009±0.002	0.009±0.002	0.008±0.003
3		0.010±0.002	0.009±0.002	0.009±0.004
4		0.010±0.003	0.009±0.002	0.009±0.004
5		0.010±0.003	0.009±0.002	0.009±0.003
6		0.011±0.002	0.010±0.003	0.009±0.003
8		0.014±0.002	0.012±0.003	0.010±0.003
10		0.017±0.003	0.014±0.003	0.012±0.004
12		0.020±0.003	0.016±0.004	0.014±0.002
Zero order	r^2	0.9253	0.9334	0.9092
	intercept	0.0067	0.0068	0.0071
	slope	0.0009	0.0007	0.0005
First order	r^2	0.8987	0.9170	0.8975
	intercept	0.0051	0.0051	0.0050
	slope	-0.00016	-0.00011	-0.00007
Higuchi's plot	r^2	0.8111	0.8166	0.7852
	intercept	0.0037	0.0045	0.0057
	slope	0.0037	0.0028	0.0019

Table 13 Average cumulative amount of diclofenac diethylamine skin permeation per surface area (mg/cm^2) from diclofenac diethylamine-TDS in hydroxypropyl methylcellulose, (n=6).

Time (hrs)		Cumulative skin permeation ± SD		
		Formula #11	Formula #12	Formula #13
0		0	0	0
0.5		0.012±0.002	0.011±0.004	0.011±0.003
1		0.013±0.003	0.012±0.004	0.011±0.003
2		0.014±0.003	0.012±0.003	0.011±0.003
3		0.015±0.003	0.012±0.004	0.011±0.003
4		0.015±0.003	0.012±0.003	0.011±0.003
5		0.015±0.003	0.012±0.004	0.011±0.003
6		0.016±0.003	0.013±0.004	0.012±0.004
8		0.017±0.003	0.014±0.004	0.012±0.004
10		0.019±0.004	0.015±0.004	0.013±0.004
12		0.021±0.004	0.016±0.004	0.013±0.003
Zero order	r^2	0.9733	0.9606	0.9412
	intercept	0.0120	0.0108	0.0105
	slope	0.0007	0.0004	0.0002
First order	r^2	0.9657	0.9530	0.9391
	intercept	0.0043	0.0045	0.0045
	slope	-0.00014	-0.00007	-0.00004
Higuchi's plot	r^2	0.9280	0.8682	0.8594
	intercept	0.0095	0.0095	0.0098
	slope	0.0029	0.0016	0.0009

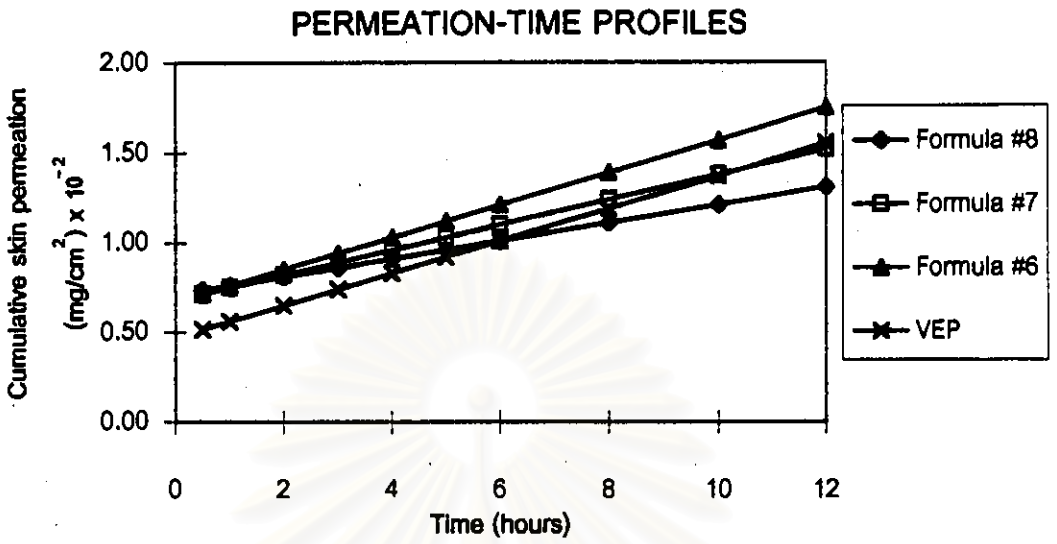

Figure 32 Zero order plot of skin permeation-time profiles of Formulas #6-8 compared to Voltaren® emulgel in patch (r^2=0.9253,0.9334,0.9092; intercept=0.0067,0.0068,0.0071; slope=0.0009,0.0007,0.0005, respectively, n = 6).

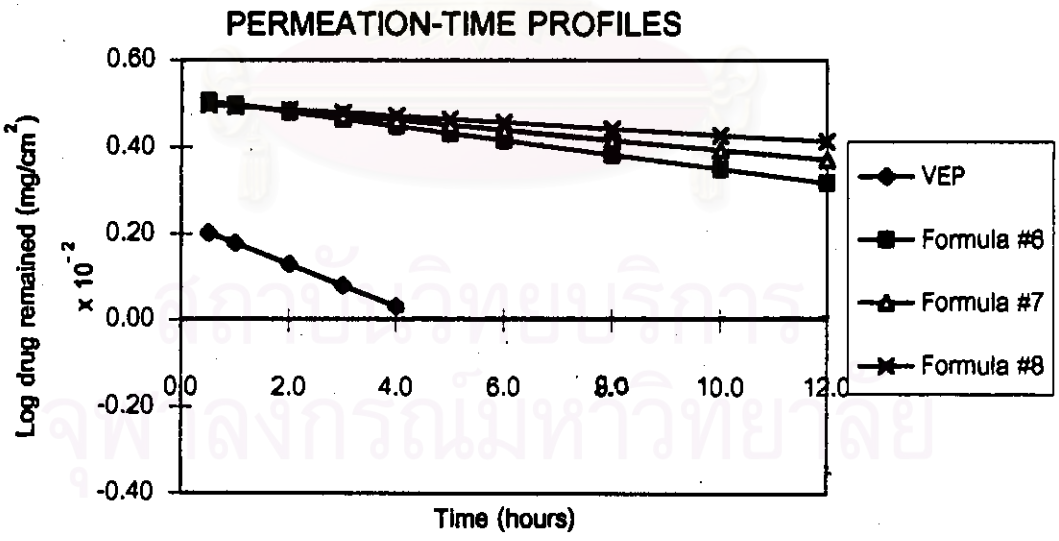

Figure 33 First order plot of logarithm of drug remaining-time profiles of Formulas #6-8 compared to Voltaren® emulgel in patch (r^2=0.8987,0.9170,0.8975; intercept=0.0051,0.0051,0.0050; slope=-0.00016,-0.00011,-0.00007; n=6).

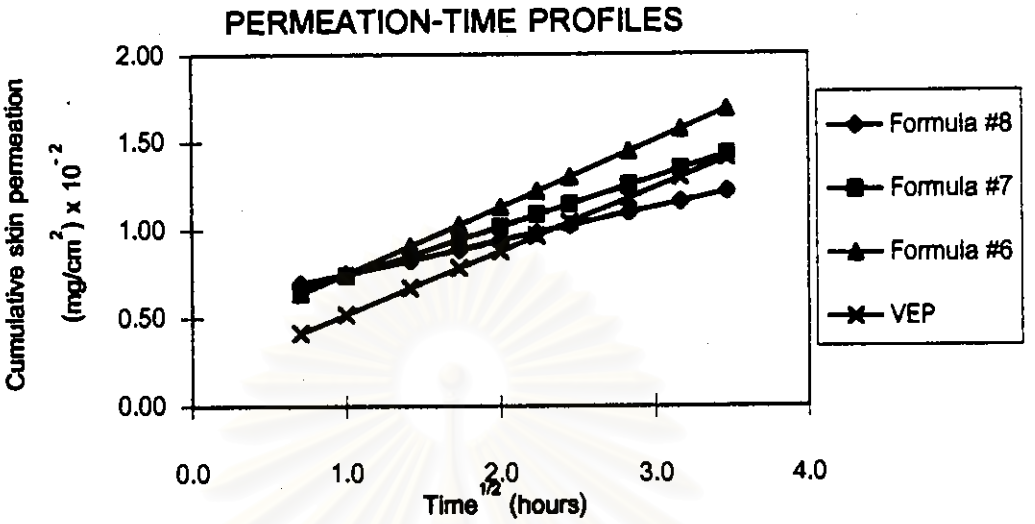

Figure 34 Higuchi plot of skin permeation-square root of time profiles of Formulas #6-8 compared to Voltaren® emulgel in patch, (r^2=0.8111,0.8166,0.7852; intercept=0.0037,0.0045,0.0057; slope=0.0037, 0.0028,0.0019; n=6).

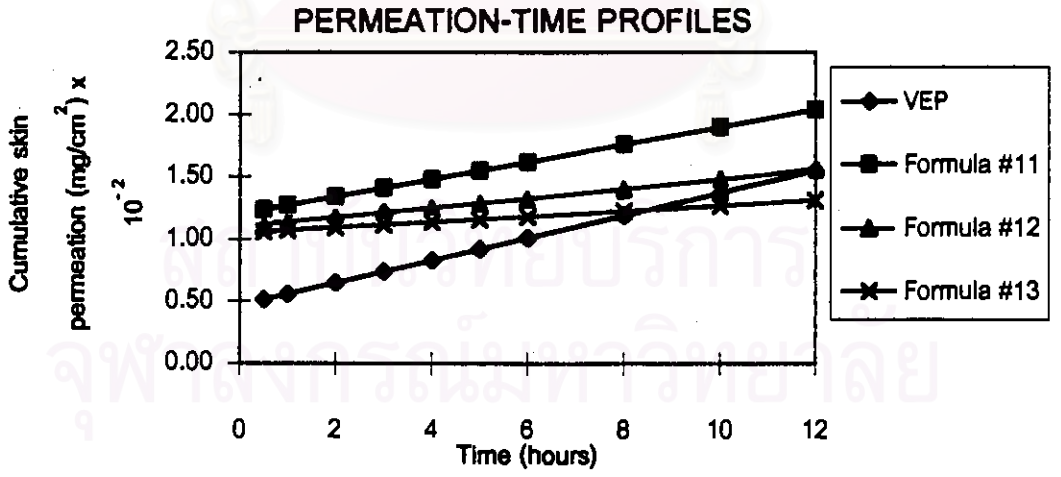

Figure 35 Zero order plot of skin permeation-time profiles of Formulas #11-13 compared to Voltaren® emulgel in patch, (r^2=0.9733,0.9606,0.9412; intercept=0.0120,0.0108,0.0105; slope=0.0007,0.0004,0.0002; n=6).

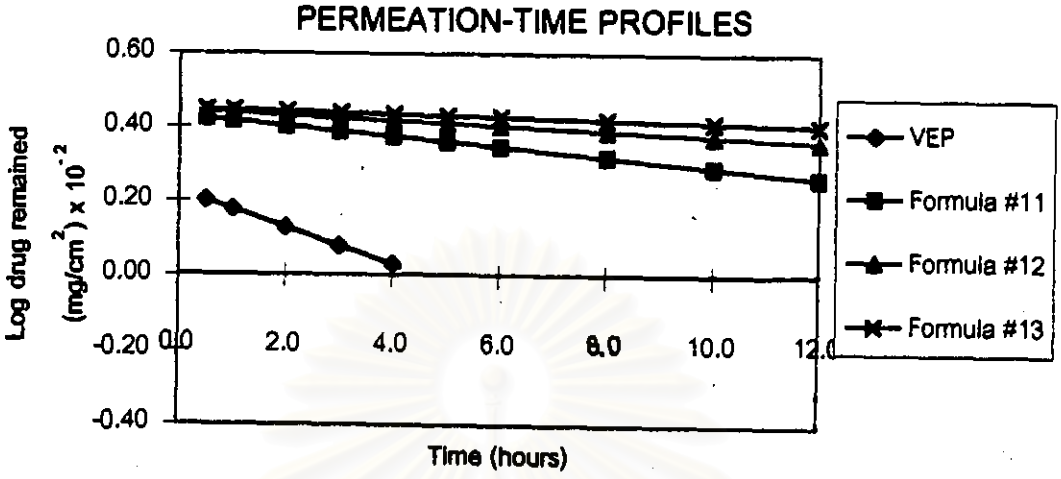

Figure 36 First order plot of logarithm of drug remaining-time profiles of Formulas #11-13 compared to Voltaren® emulgel in patch, (r^2=0.9657,0.9530,0.9391; intercept=0.0043,0.0045,0.0045; slope=-0.00014,-0.00007,-0.00004; n=6).

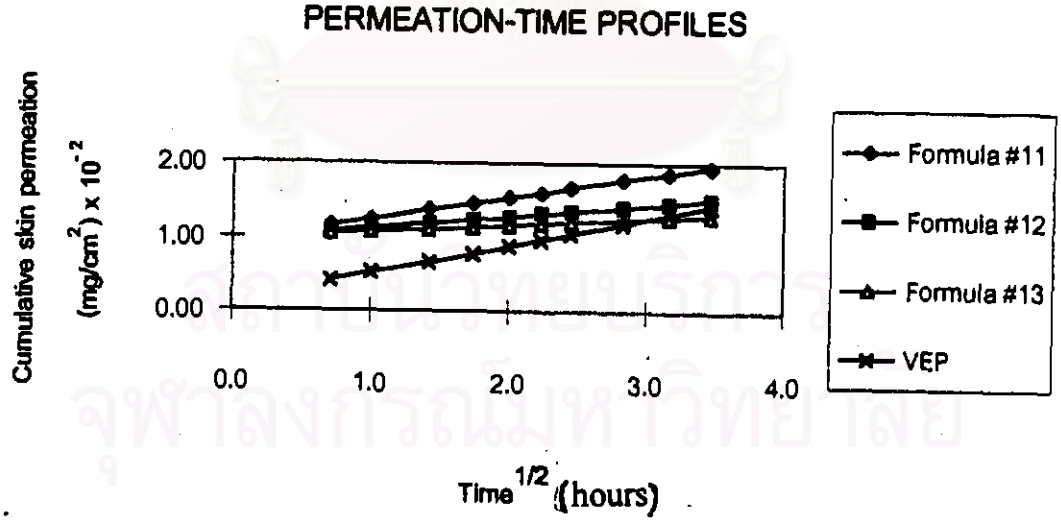

Figure 37 Higuchi plot of skin permeation-square root of time profiles of Formulas #11-13 compared to Voltaren® emulgel in patch, (r^2=0.9280,0.8682,0.8594; intercept=0.0095,0.0095,0.0098; slope=0.0029,0.0016,0.0009; n=6).

Table 14 Anti-inflammatory activity of Voltaren® emulgel and diclofenac diethylamine-TDS on carrageenan-induced paw edema in rats, (n=6).

	3 hour* application time			12 hours* application time		
	Mean	SD	%Inhibition	Mean	SD	%Inhibition
Control group	0.51	0.10	-	-	-	-
Voltaren group	0.34	0.15	34.82	0.44	0.29	14.72
Patch group	0.20	0.14	61.09	0.13	0.07	74.32

Remark : * patch or gel application time prior to the carrageenan injection.

The results from Table 14 were indicated that both dosage forms exhibited anti-inflammatory activity. The percentages of inhibition of paw volume of formulated patch were 61.09 and 74.32 after administered 3 and 12 hours, respectively. For the Voltaren® emulgel patch, the percentages of inhibition of paw volume were 34.82 and 14.72 after administered 3 and 12 hours, respectively. Hence, the formulated patch seemed to afford higher anti-inflammatory profile than that of Voltaren® emulgel following a transdermal application. From these dosage forms, the percentages of inhibition of paw volume administrated 12 hours were higher than administrated 3 hours. It indicated that the group which was placed the patch longer time got higher anti-inflammatory activity.