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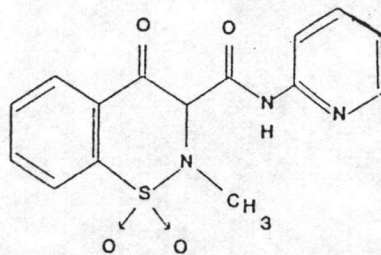
**APPENDICES**

**Appendix 1**

Description of Piroxicam and Nicotinamide

**PIROXICAM**

An off-white to light tan or light yellow, odourless powder. It forms a monohydrate that is yellow. (Reynolds, 1989) .



C<sub>15</sub> H<sub>13</sub> N<sub>3</sub> O<sub>4</sub> S = 331.4

**Chemical name** : 4-Hydroxy-2-methyl-N-(2-pyridyl) -2H -1, 2 - benzothiazine - 3 - carboxamide 1, 1-dioxide.

**Solubilities** : very slightly soluble in water, dilute acid and most organic solvents; slightly soluble in alcohol and aqueous alkaline solution.

**Adverse Effects** : Gastro-intestinal disturbances are the commonest side-effects. Peptic ulceration and gastro-intestinal bleeding have been reported. Other side-effects which have been reported include headache, dizziness, blurred vision, tinnitus, and oedema.

**Absorption and Fate** : Piroxicam is well absorbed from the gastro-intestinal tract. It is metabolized in the liver by hydroxylation and conjugation with glucuronic acid and excreted predominantly in the urine with smaller amounts in the feces. Less than 5% of the dose is excreted unchanged.

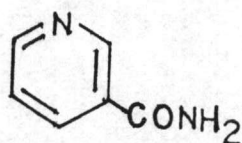


Piroxicam is extensively bound to plasma proteins (about 99%) and has a long plasma half-life of approximately 50 hours.

Uses and Administration : Piroxicam has analgesic, anti-inflammatory, and antipyretic properties. It is used in rheumatic disorders in a usual dose by mouth of 20 mg daily in single or divided doses with a range of 10 to 30 mg daily. In acute musculoskeletal conditions, an initial dose of 40 mg daily may be given for 2 days followed by 20 mg daily for 1 to 2 weeks.

### NICOTINAMIDE

A white, crystalline powder, odorless or nearly so, and has a bitter taste, solutions are neutral to litmus paper, melt between 128 and 131°. (Mc. Evoy, 1989; Reynolds, 1989; Zografis, 1990)



C<sub>6</sub> H<sub>6</sub> N<sub>2</sub> O (122.13)

Chemical Name : Pyridine-3-carboxamide.

Solubility : 1 in 1 of water, 1 in 10 of boiling water, 1 in 1.5 of alcohol, and 1 in 10 of glycerol, slightly soluble in chloroform and ether. A 5% solution in water has a pH 6 to 7.5. A 4.49% solution is iso-osmotic with serum.

Incompatible : with alkaline and mineral acids.

Adverse Effect : does not cause vasodilation like nicotinic acid.

Uses : Nicotinamide and nicotinic acid, the form which occurs naturally in the body, are water-soluble vitamin B substances which are converted to nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). These coenzymes are involved in electron

transfer reaction in the respiratory chain. Nicotinic acid and nicotinamide are used in the treatment and prevention of nicotinic acid deficiency. Nicotinamide is preferred as it does not cause vasodilation. They are usually given by mouth, the preferred route, but may also be administered by the intramuscular route or by slow intravenous administration. Doses of up to 500 mg daily doses have been recommended.

APPENDIX 2

Stability Data of Piroxicam Injection

## Stability data of formulation No.1

Time (day)	Concentration of piroxicam (ng/ml)								
	45° C			55° C			65° C		
	1	2	3	1	2	3	1	2	3
0	19.368	19.913	19.993	19.368	19.913	19.993	19.368	19.913	19.993
12	19.207	19.128	19.634	19.004	19.558	19.213	18.702	18.853	19.432
19	19.245	18.941	19.494	18.812	19.309	18.791	18.642	18.699	19.051
26	19.146	18.848	19.297	18.728	19.154	18.681	18.913	18.534	18.898
46	17.979	18.623	18.796	18.336	18.758	18.534	17.512	17.550	18.029
60	17.986	18.503	18.541	17.866	18.453	18.235	17.225	17.251	17.652
81	17.968	18.023	18.256						

Equation of drug remaining as function of time of  
formulation No. 1

45° C	run 1 :	Conc = 19.4549 - 0.0216	time :	r <sup>2</sup> = 0.8397
		: ln Conc = 2.9685 - 0.0012	time :	r <sup>2</sup> = 0.8389
	run 2 :	Conc = 19.5179 - 0.0190	time :	r <sup>2</sup> = 0.8659
		: ln Conc = 2.9715 - 0.0010	time :	r <sup>2</sup> = 0.8758
	run 3 :	Conc = 19.9032 - 0.0218	time :	r <sup>2</sup> = 0.9843
		: ln Conc = 2.9913 - 0.0011	time :	r <sup>2</sup> = 0.9869
55° C	run 1 :	Conc = 19.3224 - 0.0232	time :	r <sup>2</sup> = 0.9816
		: ln Conc = 2.9617 - 0.0012	time :	r <sup>2</sup> = 0.9809
	run 2 :	Conc = 19.8346 - 0.0236	time :	r <sup>2</sup> = 0.9873
		: ln Conc = 2.9878 - 0.0012	time :	r <sup>2</sup> = 0.9896
	run 3 :	Conc = 19.5906 - 0.0251	time :	r <sup>2</sup> = 0.8080
		: ln Conc = 2.9750 - 0.0013	time :	r <sup>2</sup> = 0.8175
65° C	run 1 :	Conc = 19.3706 - 0.0359	time :	r <sup>2</sup> = 0.9066
		: ln Conc = 2.9648 - 0.0019	time :	r <sup>2</sup> = 0.9076
	run 2 :	Conc = 19.6148 - 0.0422	time :	r <sup>2</sup> = 0.9543
		: ln Conc = 2.9772 - 0.0023	time :	r <sup>2</sup> = 0.9621
	run 3 :	Conc = 19.9032 - 0.0390	time :	r <sup>2</sup> = 0.9908
		: ln Conc = 2.9918 - 0.0012	time :	r <sup>2</sup> = 0.9932

## Stability data of formulation No.2

Time (day)	Concentration of piroxicam (mg/ml)								
	45° C			55° C			65° C		
	1	2	3	1	2	3	1	2	3
0	18.720	18.946	19.131	18.720	18.946	19.131	18.720	18.946	19.131
12	18.548	18.697	18.997	18.355	18.596	18.721	18.623	18.464	18.585
19	18.697	18.558	18.676	18.152	18.219	18.513	18.264	17.977	17.779
26	18.743	18.656	18.739	17.954	18.395	18.234	17.587	17.466	17.271
46	18.376	18.213	18.212	17.352	17.381	17.543	16.559	16.531	16.619
60	18.152	18.070	18.321	16.554	16.766	17.152	15.872	15.787	15.550
81	18.011	18.131	18.235						

Equation of drug remaining as function of time of  
formulation No. 2

45° C run 1 : Conc = 18.7931 - 0.0094 time : r<sup>2</sup> = 0.8564  
          : ln Conc = 2.9336 - 0.0005 time : r<sup>2</sup> = 0.8579  
run 2 : Conc = 18.8434 - 0.0108 time : r<sup>2</sup> = 0.8700  
          : ln Conc = 2.9362 - 0.0006 time : r<sup>2</sup> = 0.8711  
run 3 : Conc = 19.0256 - 0.0118 time : r<sup>2</sup> = 0.8298  
          : ln Conc = 2.9458 - 0.0006 time : r<sup>2</sup> = 0.8308

55° C run 1 : Conc = 18.7923 - 0.0347 time : r<sup>2</sup> = 0.9807  
          : ln Conc = 2.9346 - 0.0020 time : r<sup>2</sup> = 0.9757  
run 2 : Conc = 19.0316 - 0.0361 time : r<sup>2</sup> = 0.9628  
          : ln Conc = 2.9473 - 0.0020 time : r<sup>2</sup> = 0.9603  
run 3 : Conc = 19.1240 - 0.0334 time : r<sup>2</sup> = 0.9985  
          : ln Conc = 2.9518 - 0.0018 time : r<sup>2</sup> = 0.9988

65° C run 1 : Conc = 19.0093 - 0.0517 time : r<sup>2</sup> = 0.9696  
          : ln Conc = 2.9474 - 0.0030 time : r<sup>2</sup> = 0.9686  
run 2 : Conc = 18.9838 - 0.0536 time : r<sup>2</sup> = 0.9954  
          : ln Conc = 2.9460 - 0.0031 time : r<sup>2</sup> = 0.9957  
run 3 : Conc = 19.0669 - 0.0581 time : r<sup>2</sup> = 0.9746  
          : ln Conc = 2.9505 - 0.0034 time : r<sup>2</sup> = 0.9769



**Stability data of formulation No.3**

Time (day)	Concentration of piroxicam (mg/ml)								
	45° C			55° C			65° C		
	1	2	3	1	2	3	1	2	3
0	19.257	19.044	19.582	19.257	19.044	19.582	19.257	19.044	19.582
12	18.922	18.806	19.342	19.153	18.767	19.353	19.187	18.984	19.325
19	18.742	18.698	19.232	18.936	18.508	18.874	19.101	18.833	19.026
26	18.597	18.599	19.119	17.998	18.030	18.395	18.737	18.065	18.788
46	18.393	18.411	18.984	17.653	17.561	17.917	17.648	17.890	17.776
60	18.241	18.330	18.825	17.467	17.300	17.686	16.224	16.011	16.078
81	18.189	18.062	18.607						

Equation of drug remaining as function of time of  
formulation No. 3

45° C	run 1	Conc = 19.0621 - 0.0127 time	r <sup>2</sup> = 0.8904
		: ln Conc = 2.9478 - 0.0007 time	r <sup>2</sup> = 0.8951
	run 2	Conc = 18.9548 - 0.0112 time	r <sup>2</sup> = 0.9725
		: ln Conc = 2.9422 - 0.0006 time	r <sup>2</sup> = 0.9745
	run 3	Conc = 19.4894 - 0.0112 time	r <sup>2</sup> = 0.9723
		: ln Conc = 2.9699 - 0.0006 time	r <sup>2</sup> = 0.9744
55° C	run 1	Conc = 19.3275 - 0.0338 time	r <sup>2</sup> = 0.8848
		: ln Conc = 2.9621 - 0.0018 time	r <sup>2</sup> = 0.8877
	run 2	Conc = 19.0316 - 0.0306 time	r <sup>2</sup> = 0.9701
		: ln Conc = 2.9467 - 0.0017 time	r <sup>2</sup> = 0.9724
	run 3	Conc = 19.5472 - 0.0336 time	r <sup>2</sup> = 0.9475
		: ln Conc = 2.9734 - 0.0018 time	r <sup>2</sup> = 0.9514
65° C	run 1	Conc = 19.7559 - 0.0514 time	r <sup>2</sup> = 0.9005
		: ln Conc = 2.9866 - 0.0029 time	r <sup>2</sup> = 0.8907
	run 2	Conc = 19.4314 - 0.0476 time	r <sup>2</sup> = 0.8465
		: ln Conc = 2.9697 - 0.0027 time	r <sup>2</sup> = 0.8344
	run 3	Conc = 19.9663 - 0.0566 time	r <sup>2</sup> = 0.9222
		: ln Conc = 2.9977 - 0.0032 time	r <sup>2</sup> = 0.9079

## Stability data of formulation No.4

Time (day)	Concentration of piroxicam (µg/ml)								
	45° C			55° C			65° C		
	1	2	3	1	2	3	1	2	3
0	19.242	19.304	19.139	19.242	19.304	19.231	19.242	19.304	19.139
12	19.198	19.248	18.979	19.227	19.219	19.139	18.541	18.470	18.754
19	19.093	19.140	18.903	18.850	19.017	18.990	18.182	18.270	18.620
26	19.005	19.033	18.880	18.730	18.753	18.772	18.137	18.063	17.953
46	18.894	18.939	18.761	18.534	18.537	18.510	17.770	17.838	17.658
60	18.764	18.853	18.519	18.336	18.431	18.456	16.265	16.262	16.284
81	18.659	18.638	18.499						

Equation of drug remaining as function of time of  
formulation No. 4

45° C	run 1 :	Conc = 19.2419 - 0.0075	time :	r <sup>2</sup> = 0.9812
		: ln Conc = 2.9571 - 0.0004	time :	r <sup>2</sup> = 0.9819
	run 2 :	Conc = 19.3025 - 0.0080	time :	r <sup>2</sup> = 0.9792
		: ln Conc = 2.9603 - 0.0004	time :	r <sup>2</sup> = 0.9795
	run 3 :	Conc = 19.0904 - 0.0080	time :	r <sup>2</sup> = 0.9489
		: ln Conc = 2.9493 - 0.0004	time :	r <sup>2</sup> = 0.9494
55° C	run 1 :	Conc = 19.2497 - 0.0158	time :	r <sup>2</sup> = 0.9240
		: ln Conc = 2.9576 - 0.0008	time :	r <sup>2</sup> = 0.9267
	run 2 :	Conc = 19.3041 - 0.0157	time :	r <sup>2</sup> = 0.9416
		: ln Conc = 2.9605 - 0.0008	time :	r <sup>2</sup> = 0.9431
	run 3 :	Conc = 19.2365 - 0.0142	time :	r <sup>2</sup> = 0.9512
		: ln Conc = 2.9569 - 0.0008	time :	r <sup>2</sup> = 0.9522
65° C	run 1 :	Conc = 19.1770 - 0.0425	time :	r <sup>2</sup> = 0.9008
		: ln Conc = 2.9555 - 0.0024	time :	r <sup>2</sup> = 0.8922
	run 2 :	Conc = 19.2895 - 0.0444	time :	r <sup>2</sup> = 0.9037
		: ln Conc = 2.9615 - 0.0025	time :	r <sup>2</sup> = 0.8947
	run 3 :	Conc = 19.2803 - 0.0446	time :	r <sup>2</sup> = 0.9301
		: ln Conc = 2.9611 - 0.0025	time :	r <sup>2</sup> = 0.9215

**Stability data of formulation No.5**

Time (day)	Concentration of piroxicam (mg/ml)								
	45° C			55° C			65° C		
	1	2	3	1	2	3	1	2	3
0	19.337	19.055	19.641	19.337	19.055	19.641	19.337	19.055	19.641
12	18.372	19.035	19.412	19.169	18.705	18.796	17.888	18.062	17.778
19	18.851	18.529	18.699	18.759	18.476	18.708	17.429	17.541	17.506
26	18.147	18.038	18.635	18.240	18.199	18.301	17.426	17.414	17.191
46	18.027	18.859	17.806	17.808	17.672	17.901	16.704	16.815	16.891
60	17.838	17.569	17.775	17.484	17.344	17.745	16.702	16.343	16.392
81	17.296	17.420	17.738						

Equation of drug remaining as function of time of  
formulation No. 5

45° C	run 1	: Conc = 19.0139 - 0.0214 time	: r <sup>2</sup> = 0.8441
		: ln Conc = 2.9455 - 0.0012 time	: r <sup>2</sup> = 0.8523
	run 2	: Conc = 19.0417 - 0.0196 time	: r <sup>2</sup> = 0.6738
		: ln Conc = 2.9470 - 0.0011 time	: r <sup>2</sup> = 0.6779
	run 3	: Conc = 19.4168 - 0.0255 time	: r <sup>2</sup> = 0.8506
		: ln Conc = 2.9664 - 0.0014 time	: r <sup>2</sup> = 0.8552
55° C	run 1	: Conc = 19.3583 - 0.0328 time	: r <sup>2</sup> = 0.9556
		: ln Conc = 2.9638 - 0.0018 time	: r <sup>2</sup> = 0.9586
	run 2	: Conc = 19.0254 - 0.0288 time	: r <sup>2</sup> = 0.9949
		: ln Conc = 2.9464 - 0.0016 time	: r <sup>2</sup> = 0.9963
	run 3	: Conc = 19.3192 - 0.0296 time	: r <sup>2</sup> = 0.8999
		: ln Conc = 2.9613 - 0.0016 time	: r <sup>2</sup> = 0.9088
65° C	run 1	: Conc = 18.6408 - 0.0390 time	: r <sup>2</sup> = 0.7882
		: ln Conc = 2.9252 - 0.0022 time	: r <sup>2</sup> = 0.8048
	run 2	: Conc = 18.6594 - 0.0413 time	: r <sup>2</sup> = 0.9259
		: ln Conc = 2.9270 - 0.0024 time	: r <sup>2</sup> = 0.9381
	run 3	: Conc = 18.7763 - 0.0445 time	: r <sup>2</sup> = 0.7733
		: ln Conc = 2.9323 - 0.0025 time	: r <sup>2</sup> = 0.7955

## Stability data of formulation No.6

Time (day)	Concentration of piroxicam (mg/ml)								
	45° C			55° C			65° C		
	1	2	3	1	2	3	1	2	3
0	19.005	19.245	19.761	19.005	19.245	19.761	19.005	19.245	19.761
12	18.425	19.027	19.567	18.803	19.143	19.367	18.523	19.138	18.751
19	18.710	19.006	19.413	18.480	18.973	19.256	18.419	18.659	18.372
26	18.613	18.902	19.304	18.003	18.761	18.851	17.798	18.083	17.632
46	18.491	18.761	19.152	18.348	17.881	18.354	17.342	17.573	17.186
60	18.271	18.386	18.945	17.075	17.346	17.652	16.012	16.544	16.751
81	18.174	18.279	18.854						

Equation of drug remaining as function of time of  
formulation No. 6

45° C	run 1 :	Conc = 18.9381 - 0.0102	time :	r <sup>2</sup> = 0.9683
	:	ln Conc = 2.9413 - 0.0005	time :	r <sup>2</sup> = 0.9699
	run 2 :	Conc = 19.2213 - 0.0121	time :	r <sup>2</sup> = 0.9655
	:	ln Conc = 2.9562 - 0.0006	time :	r <sup>2</sup> = 0.9652
	run 3 :	Conc = 19.6733 - 0.0111	time :	r <sup>2</sup> = 0.9568
	:	ln Conc = 2.9794 - 0.0006	time :	r <sup>2</sup> = 0.9591
55° C	run 1 :	Conc = 19.0662 - 0.0349	time :	r <sup>2</sup> = 0.9735
	:	ln Conc = 2.9488 - 0.0019	time :	r <sup>2</sup> = 0.9749
	run 2 :	Conc = 19.4793 - 0.0339	time :	r <sup>2</sup> = 0.9604
	:	ln Conc = 2.9705 - 0.0019	time :	r <sup>2</sup> = 0.9574
	run 3 :	Conc = 19.8045 - 0.0343	time :	r <sup>2</sup> = 0.9857
	:	ln Conc = 2.9869 - 0.0018	time :	r <sup>2</sup> = 0.9832
65° C	run 1 :	Conc = 19.1271 - 0.0470	time :	r <sup>2</sup> = 0.9495
	:	ln Conc = 2.9534 - 0.0027	time :	r <sup>2</sup> = 0.9409
	run 2 :	Conc = 19.4438 - 0.0455	time :	r <sup>2</sup> = 0.9599
	:	ln Conc = 2.9694 - 0.0025	time :	r <sup>2</sup> = 0.9568
	run 3 :	Conc = 19.3760 - 0.0479	time :	r <sup>2</sup> = 0.9232
	:	ln Conc = 2.9649 - 0.0026	time :	r <sup>2</sup> = 0.9339



## Stability data of formulation No.7

Time (day)	Concentration of piroxicam (ng/ml)								
	45° C			55° C			65° C		
	1	2	3	1	2	3	1	2	3
0	19.346	19.604	19.951	19.346	19.604	19.951	19.346	19.604	19.951
12	19.270	19.479	19.585	19.012	19.408	19.344	18.865	18.321	19.625
19	19.203	19.405	19.479	18.754	19.229	18.983	18.657	18.955	19.350
26	19.168	19.334	19.219	18.354	18.659	18.778	18.214	18.201	18.732
46	18.832	19.159	18.918	17.823	17.977	18.457	17.245	17.572	17.745
60	18.690	18.989	18.862	17.326	17.519	17.389	16.232	16.635	16.654
81	18.561	18.583	18.765						

Equation of drug remaining as function of time of  
formulation No. 7

45° C	run 1 :	Conc = 19.3818 - 0.0107	time :	r <sup>2</sup> = 0.9755
	:	ln Conc = 2.9645 - 0.0006	time :	r <sup>2</sup> = 0.9758
	run 2 :	Conc = 19.6380 - 0.0119	time :	r <sup>2</sup> = 0.9743
	:	ln Conc = 2.9777 - 0.0006	time :	r <sup>2</sup> = 0.9718
	run 3 :	Conc = 19.6781 - 0.0130	time :	r <sup>2</sup> = 0.9191
	:	ln Conc = 2.9796 - 0.0007	time :	r <sup>2</sup> = 0.9212
55° C	run 1 :	Conc = 19.3597 - 0.0340	time :	r <sup>2</sup> = 0.9927
	:	ln Conc = 2.9641 - 0.0019	time :	r <sup>2</sup> = 0.9931
	run 2 :	Conc = 19.7446 - 0.0372	time :	r <sup>2</sup> = 0.9756
	:	ln Conc = 2.9839 - 0.0020	time :	r <sup>2</sup> = 0.9755
	run 3 :	Conc = 19.8489 - 0.0379	time :	r <sup>2</sup> = 0.9468
	:	ln Conc = 2.9892 - 0.0020	time :	r <sup>2</sup> = 0.9442
65° C	run 1 :	Conc = 19.4970 - 0.0517	time :	r <sup>2</sup> = 0.9866
	:	ln Conc = 2.9728 - 0.0029	time :	r <sup>2</sup> = 0.9808
	run 2 :	Conc = 19.7519 - 0.0504	time :	r <sup>2</sup> = 0.9746
	:	ln Conc = 2.9853 - 0.0028	time :	r <sup>2</sup> = 0.9730
	run 3 :	Conc = 20.2005 - 0.0561	time :	r <sup>2</sup> = 0.9791
	:	ln Conc = 3.0085 - 0.0031	time :	r <sup>2</sup> = 0.9735

## Stability data of formulation No.8

Time (day)	Concentration of piroxicam (ng/ml)								
	45° C			55° C			65° C		
	1	2	3	1	2	3	1	2	3
0	19.462	19.756	19.154	19.462	19.756	19.154	19.462	19.756	19.154
12	19.239	19.666	18.994	19.173	19.524	18.878	18.974	18.966	18.724
19	19.252	19.533	18.910	18.940	19.335	18.760	18.443	18.639	18.432
26	19.029	19.337	18.869	18.638	18.802	18.618	18.023	18.291	18.163
46	18.956	19.281	18.628	18.319	18.570	18.215	17.538	17.791	17.413
60	18.862	18.995	18.504	18.100	18.461	17.966	16.529	16.688	16.408
81	18.776	18.906	18.449						

Equation of drug remaining as function of time of  
formulation No. 8

45° C	run 1 :	Conc = 19.3644 - 0.0081	time :	r <sup>2</sup> = 0.9059
	:	ln Conc = 2.9635 - 0.0004	time :	r <sup>2</sup> = 0.9084
	run 2 :	Conc = 19.7358 - 0.0109	time :	r <sup>2</sup> = 0.9523
	:	ln Conc = 2.9826 - 0.0006	time :	r <sup>2</sup> = 0.9533
	run 3 :	Conc = 19.1009 - 0.0090	time :	r <sup>2</sup> = 0.9619
	:	ln Conc = 2.9498 - 0.0005	time :	r <sup>2</sup> = 0.9631
55° C	run 1 :	Conc = 19.3951 - 0.0229	time :	r <sup>2</sup> = 0.9697
	:	ln Conc = 2.9653 - 0.0012	time :	r <sup>2</sup> = 0.9724
	run 2 :	Conc = 19.6992 - 0.0229	time :	r <sup>2</sup> = 0.9074
	:	ln Conc = 2.9808 - 0.0012	time :	r <sup>2</sup> = 0.9096
	run 3 :	Conc = 19.1335 - 0.0197	time :	r <sup>2</sup> = 0.9988
	:	ln Conc = 2.9517 - 0.0011	time :	r <sup>2</sup> = 0.9992
65° C	run 1 :	Conc = 19.4283 - 0.0466	time :	r <sup>2</sup> = 0.9756
	:	ln Conc = 2.9684 - 0.0026	time :	r <sup>2</sup> = 0.9747
	run 2 :	Conc = 19.6197 - 0.0466	time :	r <sup>2</sup> = 0.9696
	:	ln Conc = 2.9782 - 0.0026	time :	r <sup>2</sup> = 0.9685
	run 3 :	Conc = 19.2525 - 0.0443	time :	r <sup>2</sup> = 0.9822
	:	ln Conc = 2.9595 - 0.0025	time :	r <sup>2</sup> = 0.9761

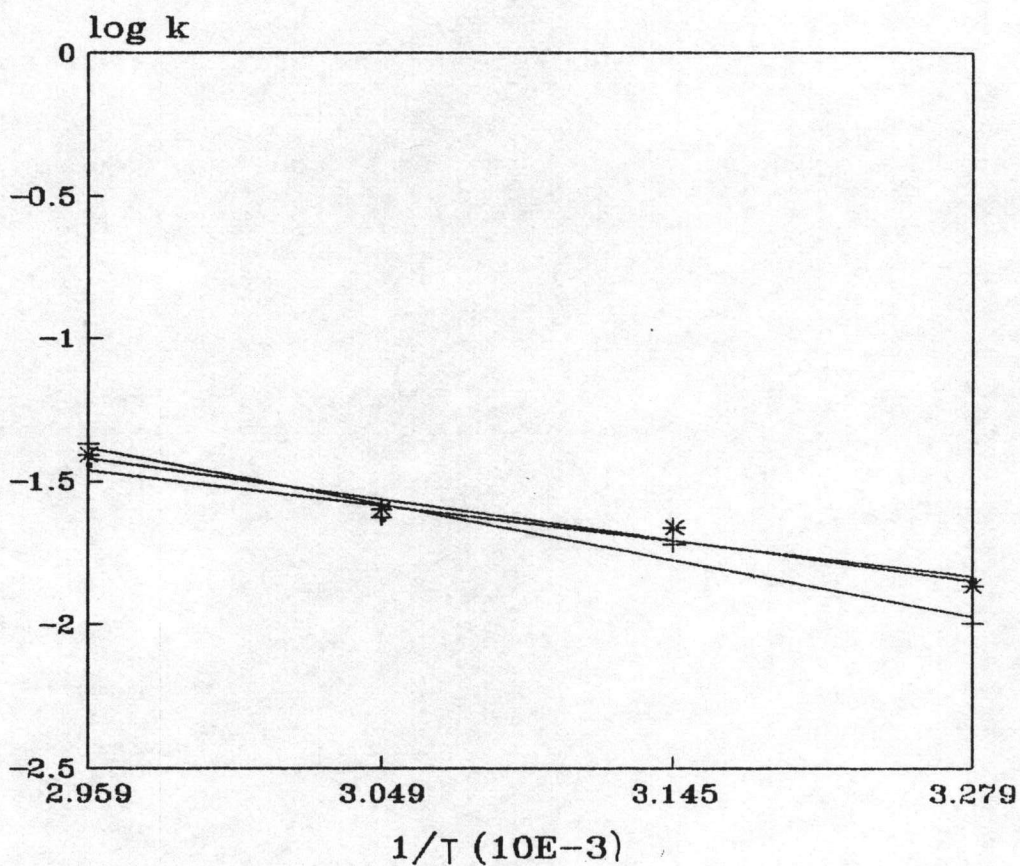
## Stability data of innovator's product.

Time (day)	Concentration of piroxicam (mg/ml)								
	45° C			55° C			65° C		
	1	2	3	1	2	3	1	2	3
0	20.054	20.369	20.222	20.054	20.369	20.222	20.054	20.369	20.222
20	19.943	20.186	20.045	19.820	19.959	19.650	19.528	19.748	19.882
34	19.807	20.002	19.946	19.708	19.674	19.392	18.408	18.334	18.488
41	19.767	19.947	19.864	19.575	19.652	19.256	18.270	18.415	18.253
48	19.686	19.861	19.755	19.353	19.547	19.183	18.012	18.973	18.199
55	19.622	19.813	19.774	19.273	19.528	19.133	17.852	18.173	18.028
62	19.585	19.783	19.691	19.189	19.491	19.033	17.512	17.290	17.332
76	19.458	19.858	19.658	18.905	19.124	18.990	16.916	16.908	16.958

Equation of drug remaining as function of time of  
Innovator's product.

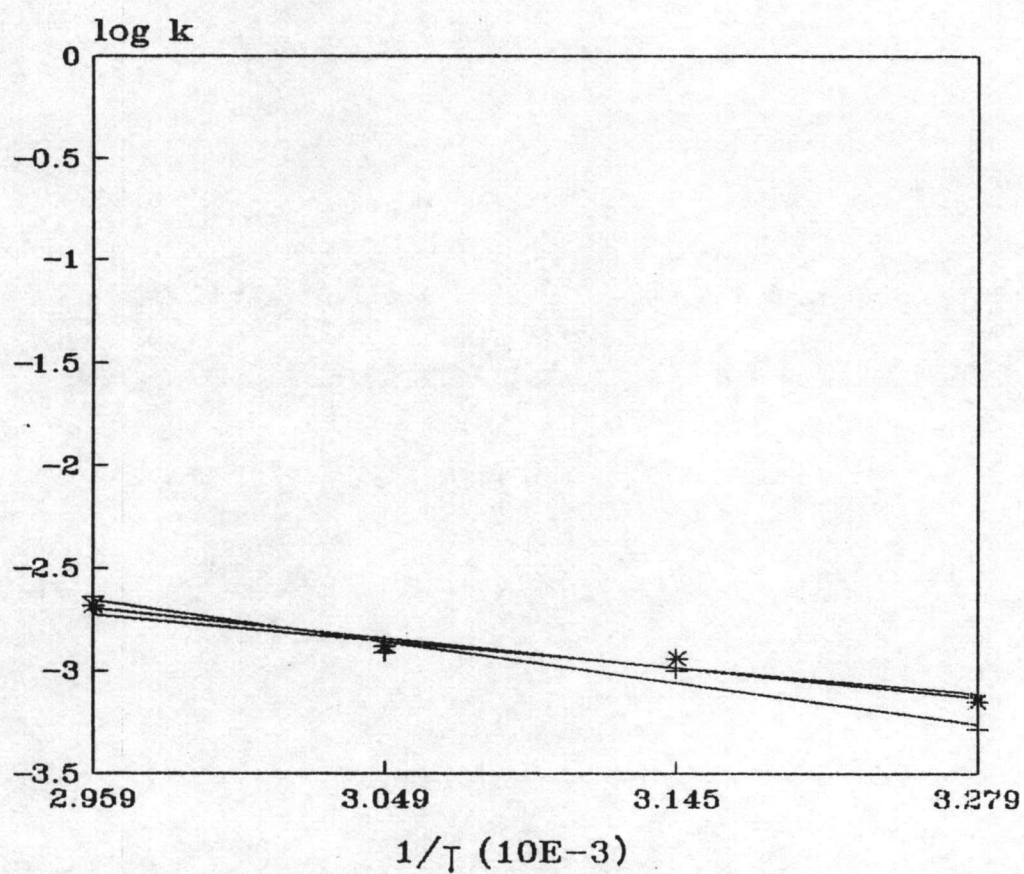
45° C	run 1 :	Conc =	20.0779 - 0.0080	time :	r <sup>2</sup> =	0.9927
		: ln Conc =	2.9997 - 0.0004	time :	r <sup>2</sup> =	0.9923
	run 2 :	Conc =	20.3068 - 0.0079	time :	r <sup>2</sup> =	0.8633
		: ln Conc =	3.0109 - 0.0004	time :	r <sup>2</sup> =	0.8635
	run 3 :	Conc =	20.1990 - 0.0078	time :	r <sup>2</sup> =	0.9656
		: ln Conc =	3.0057 - 0.0004	time :	r <sup>2</sup> =	0.9661
55° C	run 1 :	Conc =	20.1268 - 0.0153	time :	r <sup>2</sup> =	0.9729
		: ln Conc =	3.0024 - 0.0008	time :	r <sup>2</sup> =	0.9708
	run 2 :	Conc =	20.2912 - 0.0148	time :	r <sup>2</sup> =	0.9567
		: ln Conc =	3.0104 - 0.0008	time :	r <sup>2</sup> =	0.9575
	run 3 :	Conc =	20.0365 - 0.0162	time :	r <sup>2</sup> =	0.9135
		: ln Conc =	2.9976 - 0.0008	time :	r <sup>2</sup> =	0.9180
65° C	run 1 :	Conc =	20.0908 - 0.0422	time :	r <sup>2</sup> =	0.9781
		: ln Conc =	3.0023 - 0.0023	time :	r <sup>2</sup> =	0.9798
	run 2 :	Conc =	20.4258 - 0.0452	time :	r <sup>2</sup> =	0.8859
		: ln Conc =	3.0195 - 0.0024	time :	r <sup>2</sup> =	0.8817
	run 3 :	Conc =	20.3389 - 0.0457	time :	r <sup>2</sup> =	0.9509
		: ln Conc =	3.0149 - 0.0025	time :	r <sup>2</sup> =	0.9527

Arrhenius plot of  $\log k$  against  $1/T$   
formula No1 (Zero-order reaction)



Key : —•— Series 1    —+— Series 2    —\*— Series 3

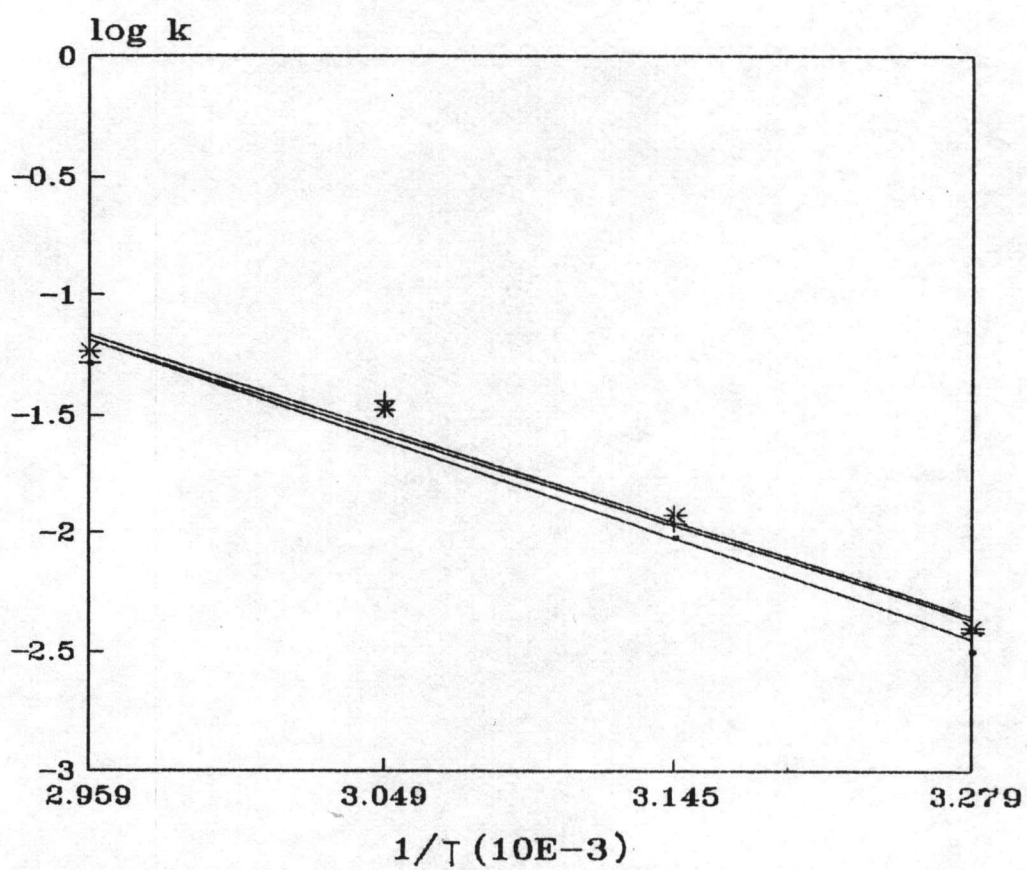
Arrhenius plot of  $\log k$  against  $1/T$   
Formula No1 (First order reaction)



Key : —•— Series 1    —+— Series 2    —\*— Series 3

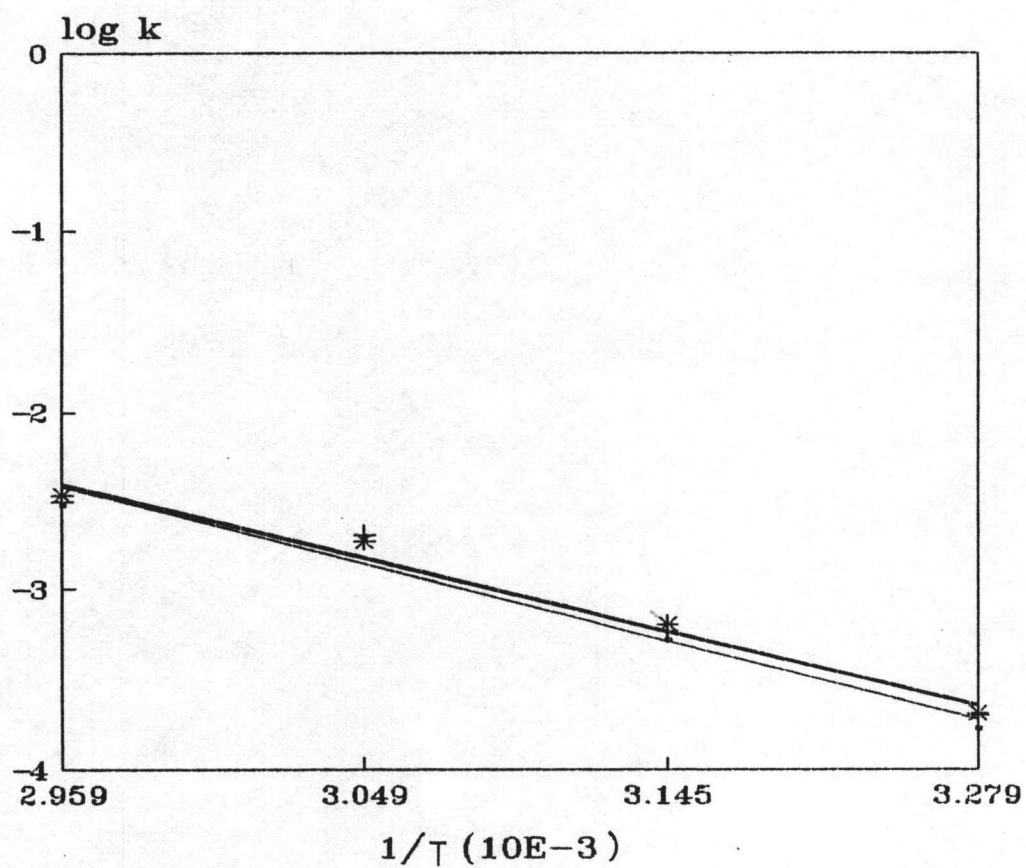


Arrhenius plot of  $\log k$  against  $1/T$   
formula No2 (Zero-order reaction)



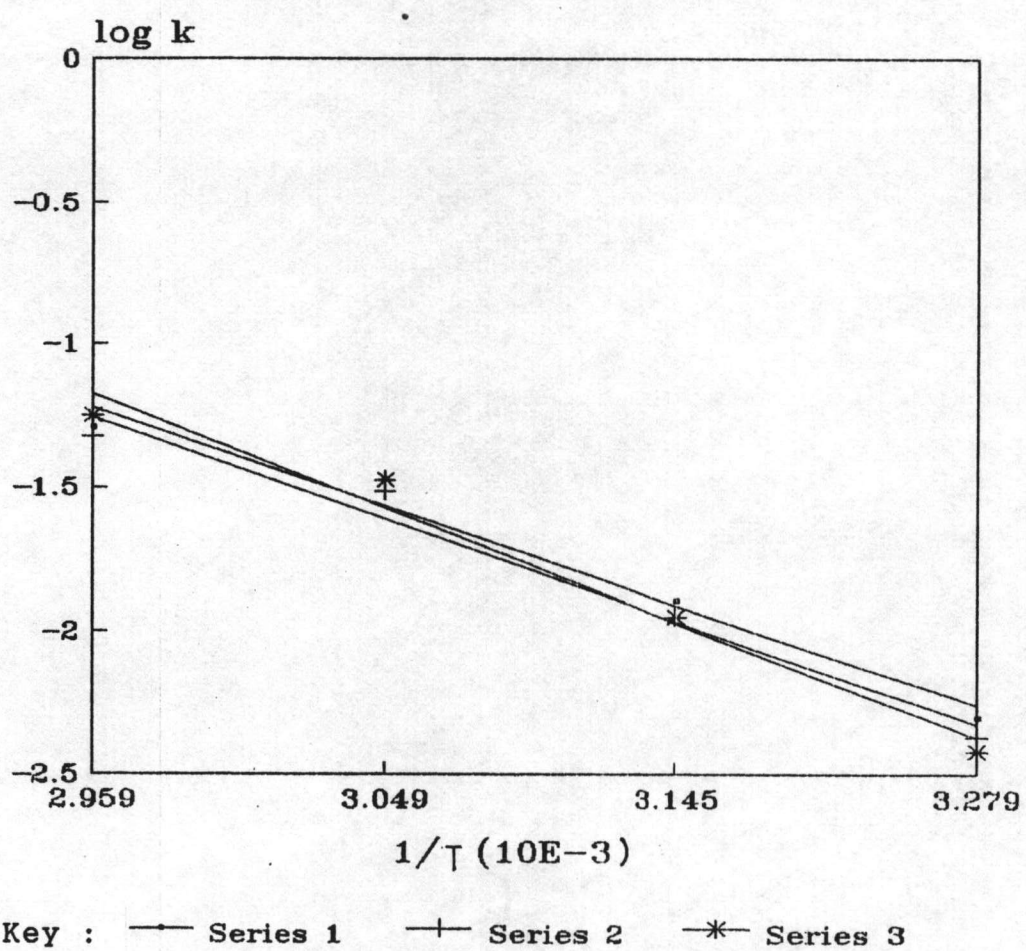
Key : —•— Series 1    —+— Series 2    —\*— Series 3

Arrhenius plot of log k against  $1/T$   
Formula No2 (First order reaction)

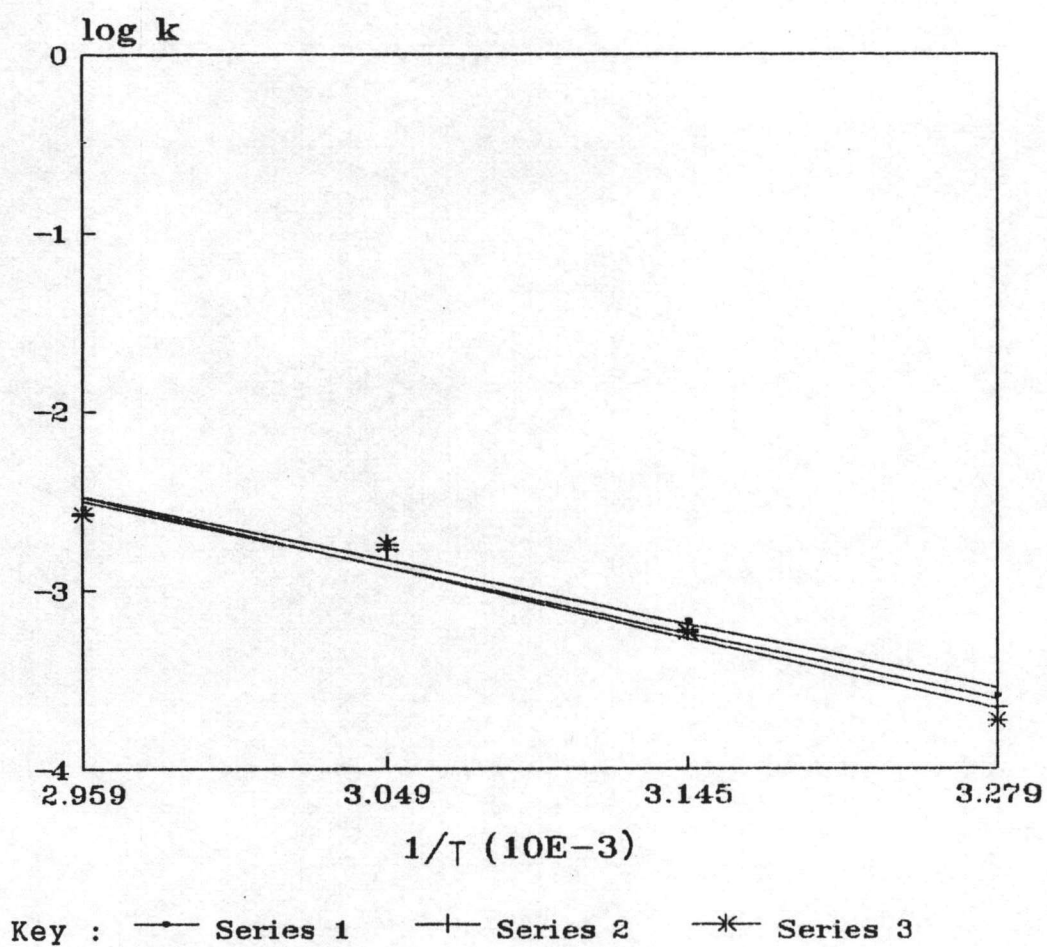


Key : —●— Series 1    —+— Series 2    —\*— Series 3

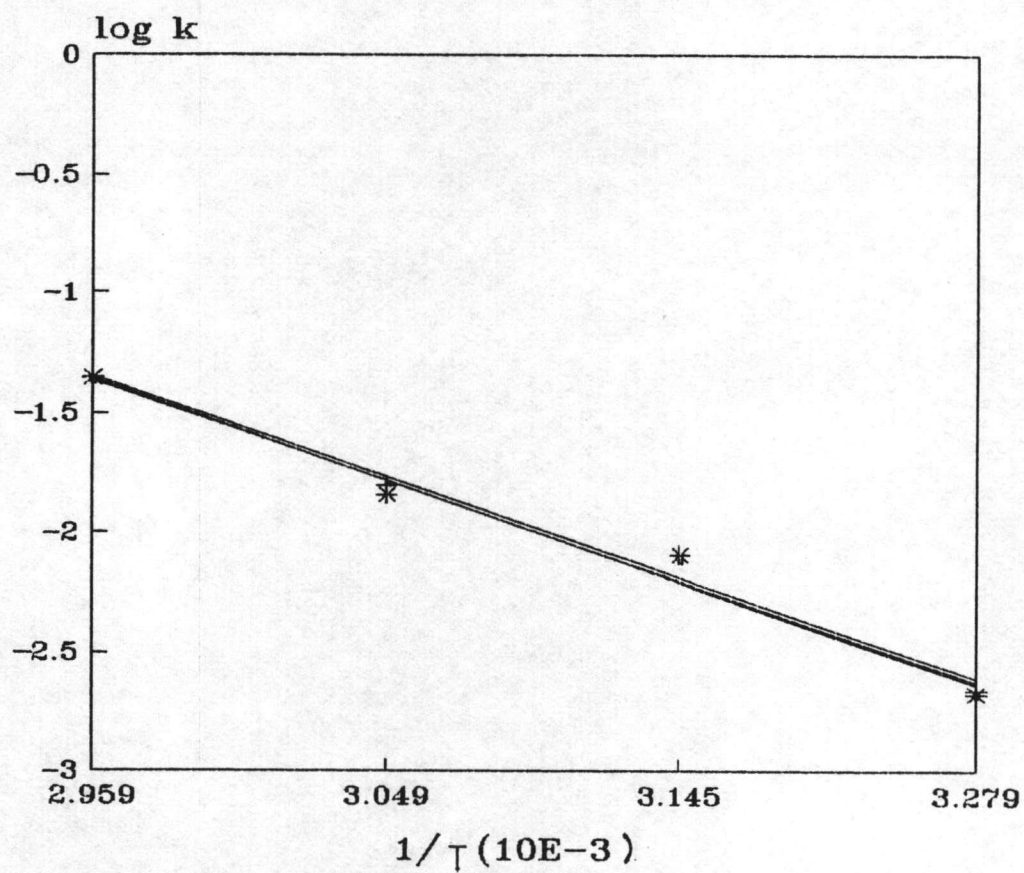
Arrhenius plot of  $\log k$  against  $1/T$   
formula No3 (Zero-order reaction)



Arrhenius plot of  $\log k$  against  $1/T$   
Formula No3 (First order reaction)

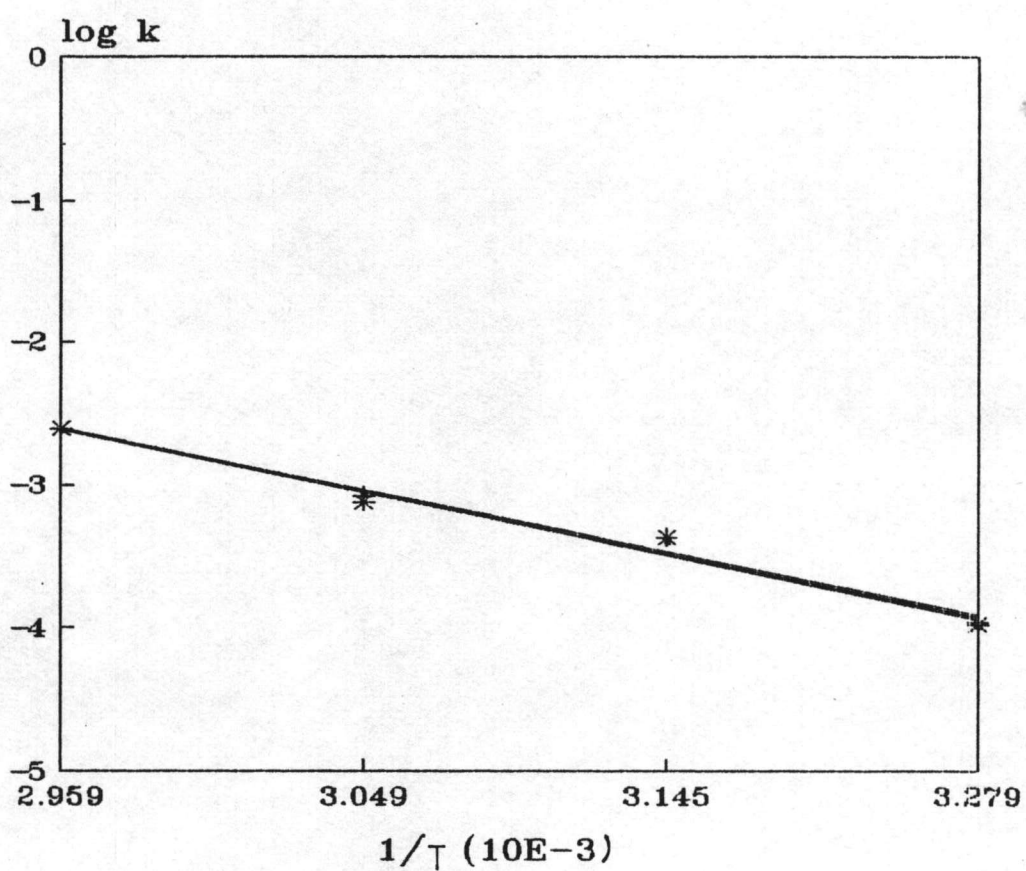


Arrhenius plot of  $\log k$  against  $1/T$   
formula No4 (Zero-order reaction)



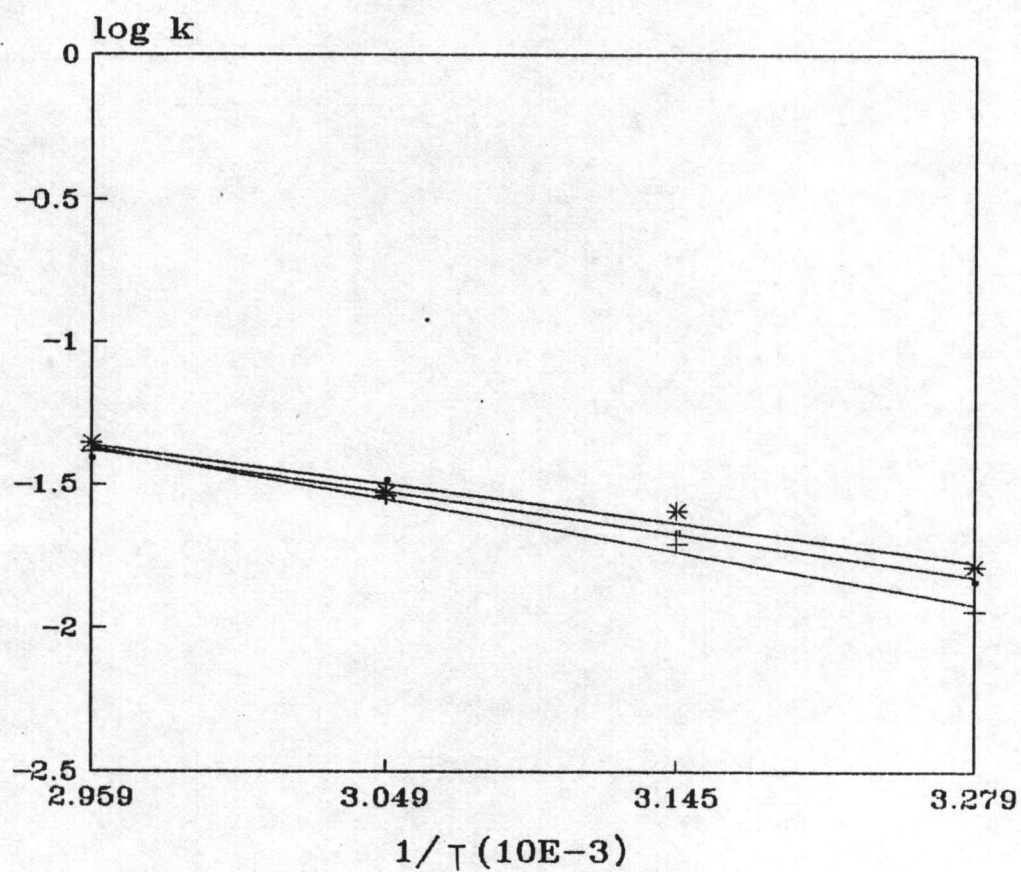
Key :  $\leftarrow$  Series 1     $\leftarrow$  Series 2     $\leftarrow$  Series 3

Arrhenius plot of  $\log k$  against  $1/T$   
Formula No4 (First order reaction)



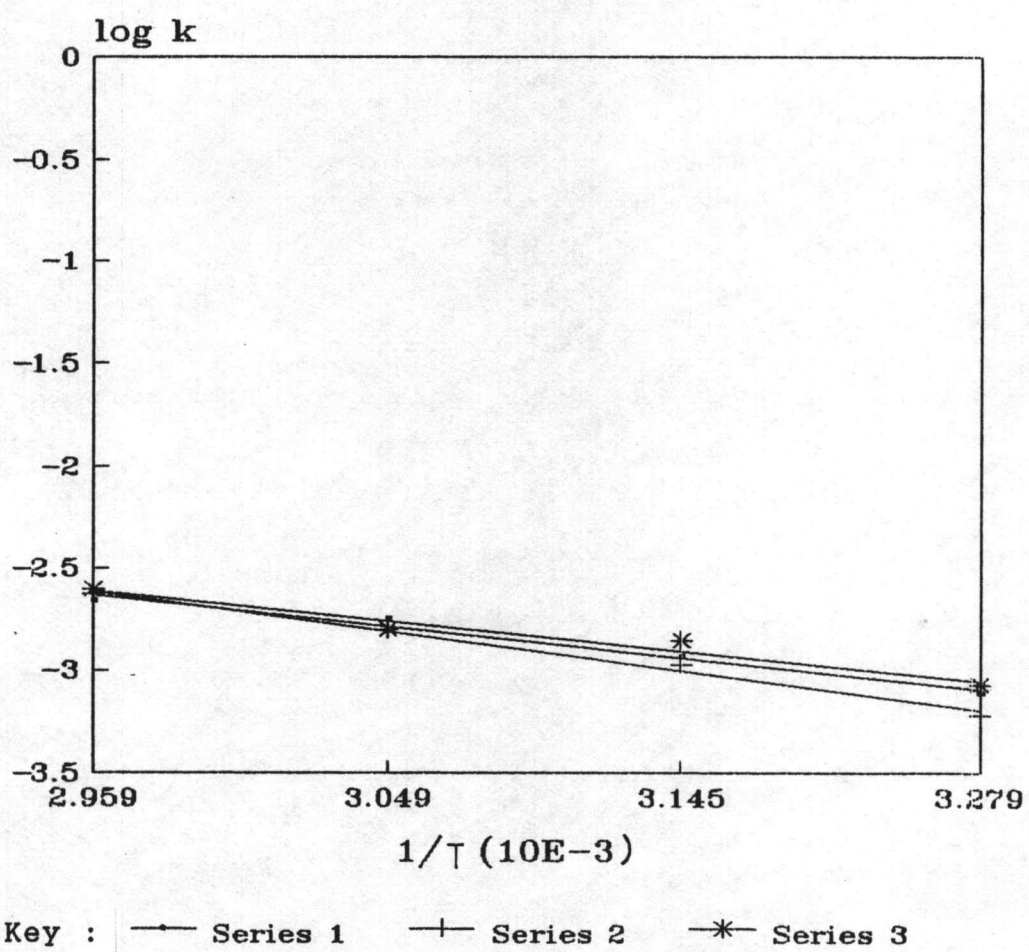
Key : —●— Series 1    —+— Series 2    —\*— Series 3

Arrhenius plot of  $\log k$  against  $1/T$   
formula No5 (Zero-order reaction)



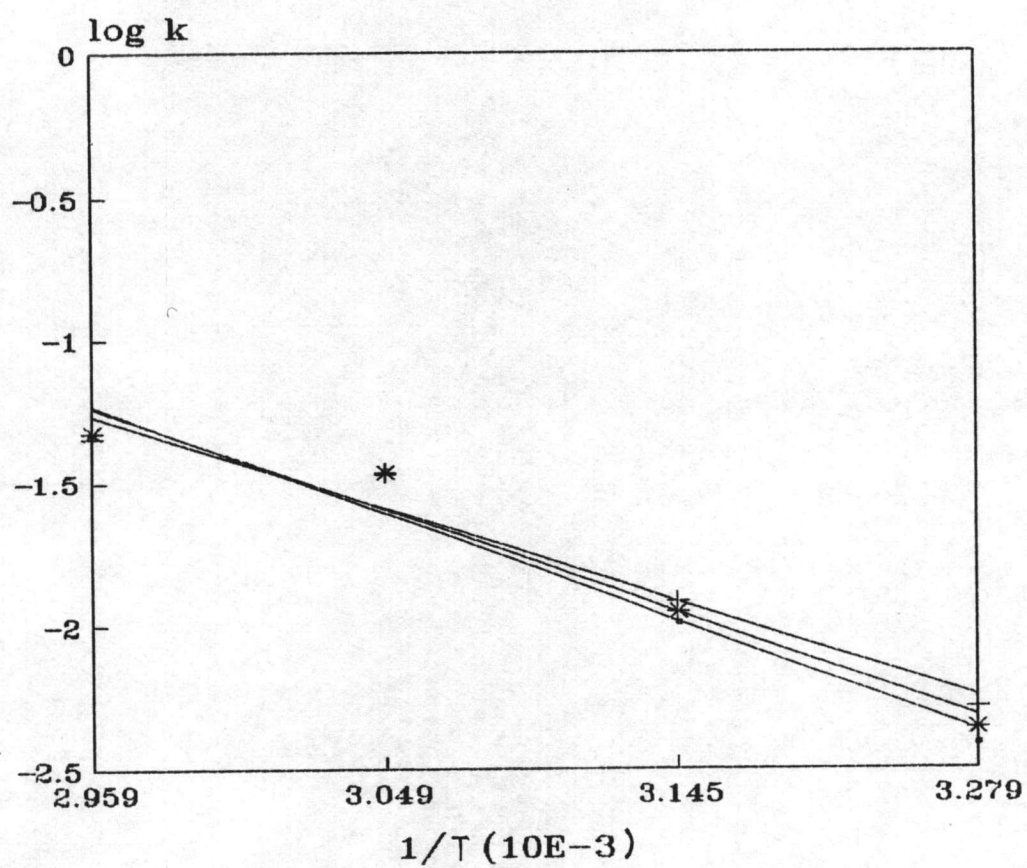
Key : — Series 1    + Series 2    \* Series 3

Arrhenius plot of  $\log k$  against  $1/T$   
Formula No5 (First order reaction)



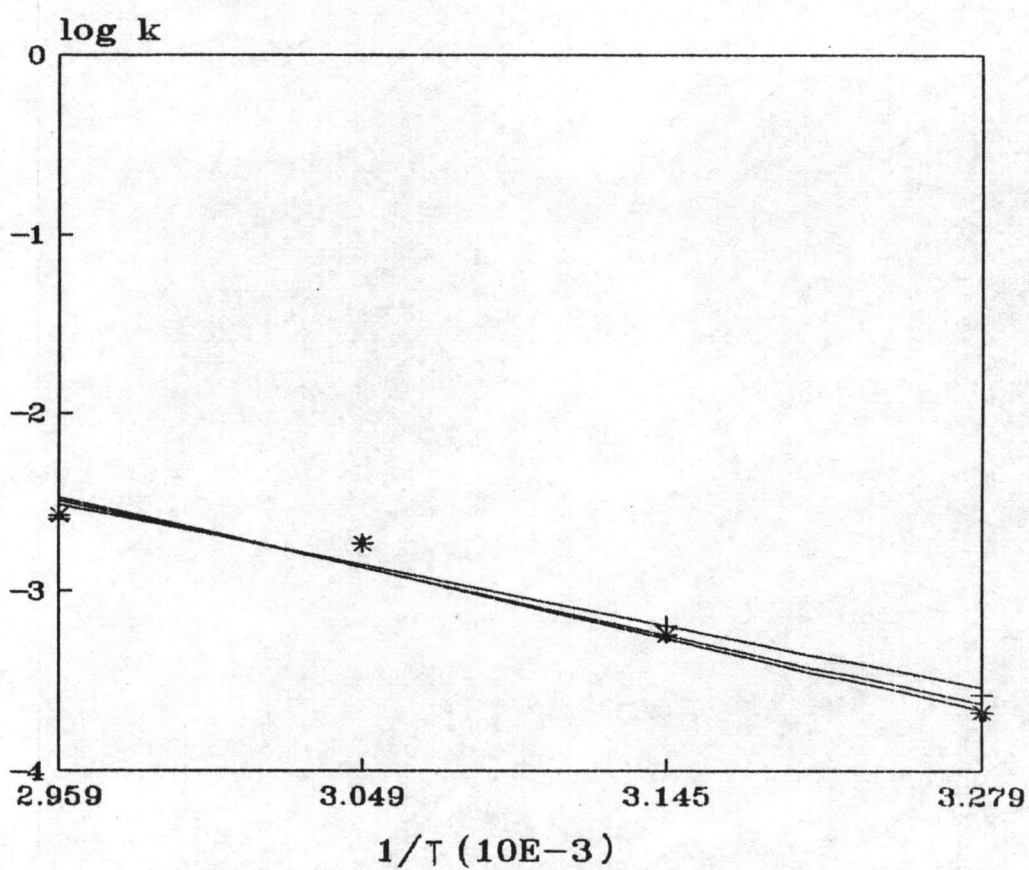


Arrhenius plot of  $\log k$  against  $1/T$   
formula No6 (Zero-order reaction)



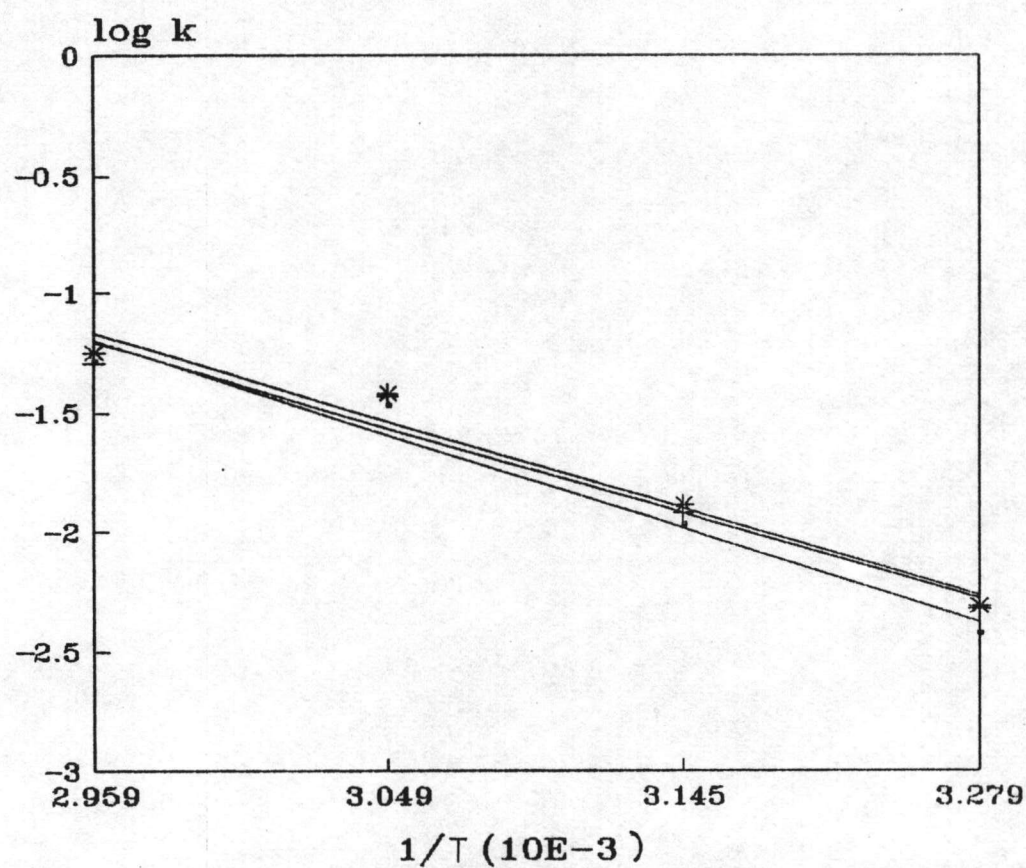
Key : — Series 1    + Series 2    \* Series 3

Arrhenius plot of log k against  $1/T$   
Formula No6 (First order reaction)



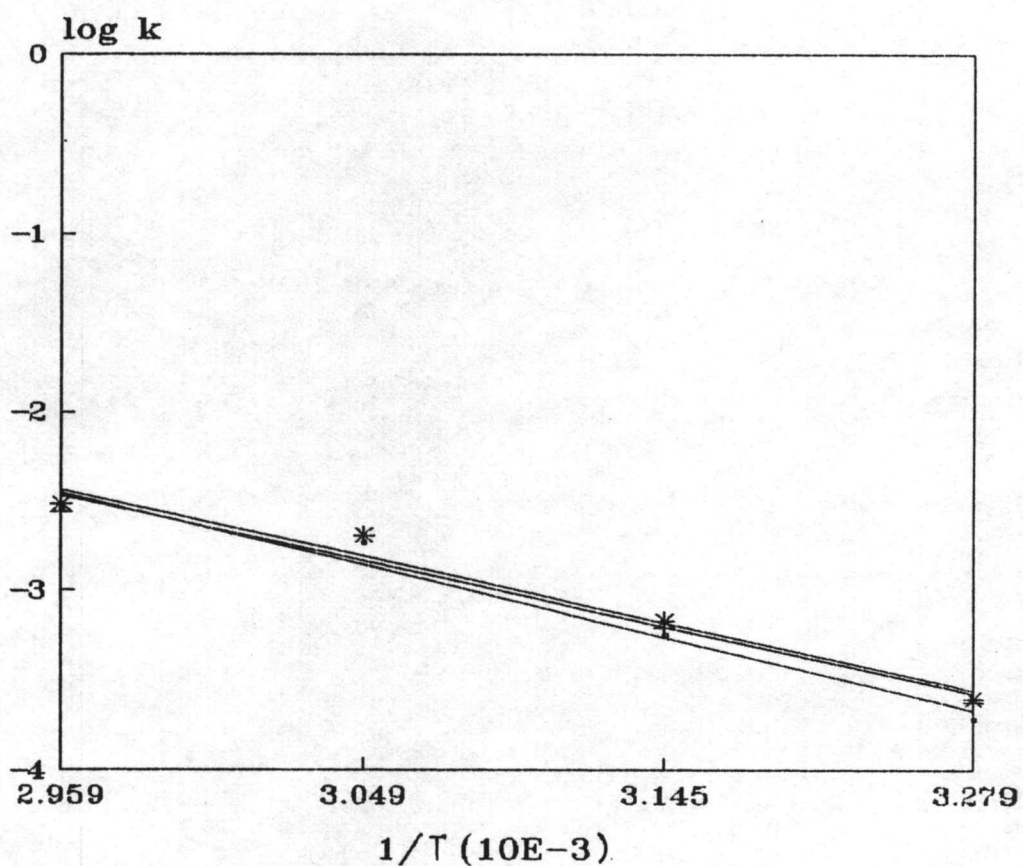
Key : —•— Series 1    —+— Series 2    —\*— Series 3

Arrhenius plot of  $\log k$  against  $1/T$   
formula No7 (Zero-order reaction)



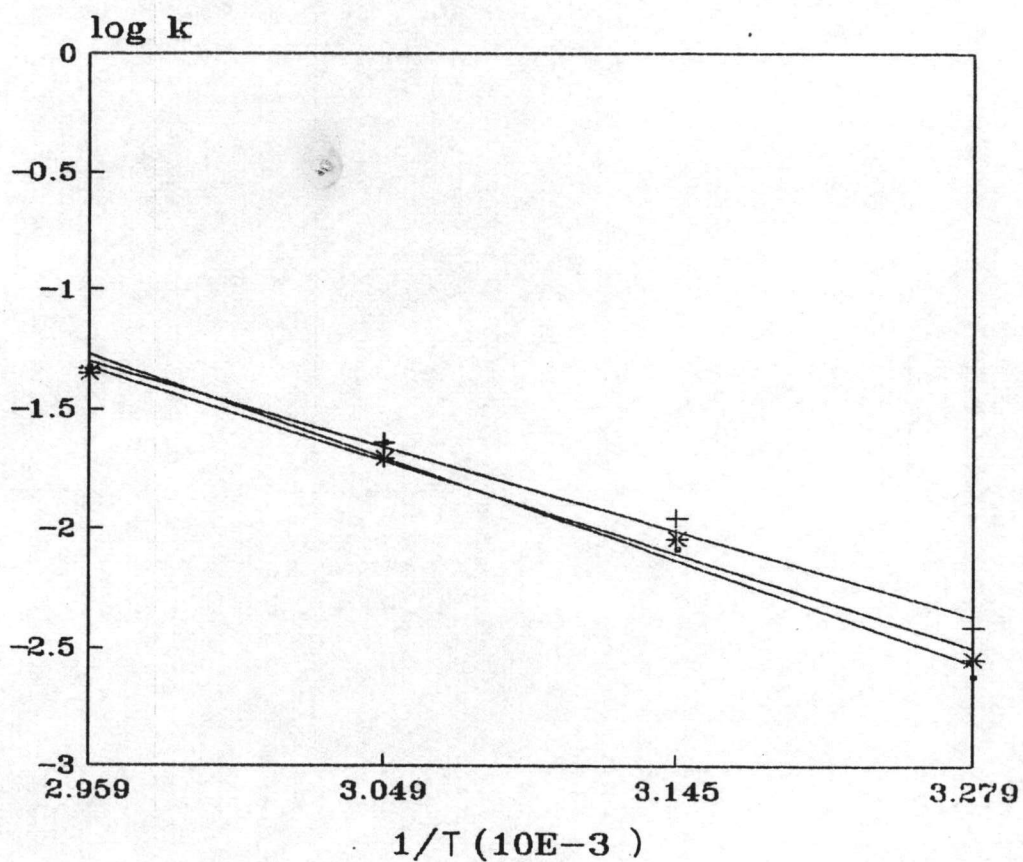
Key : —•— Series 1    —+— Series 2    —\*— Series 3

Arrhenius plot of log k against  $1/T$   
Formula No7 (First order reaction)



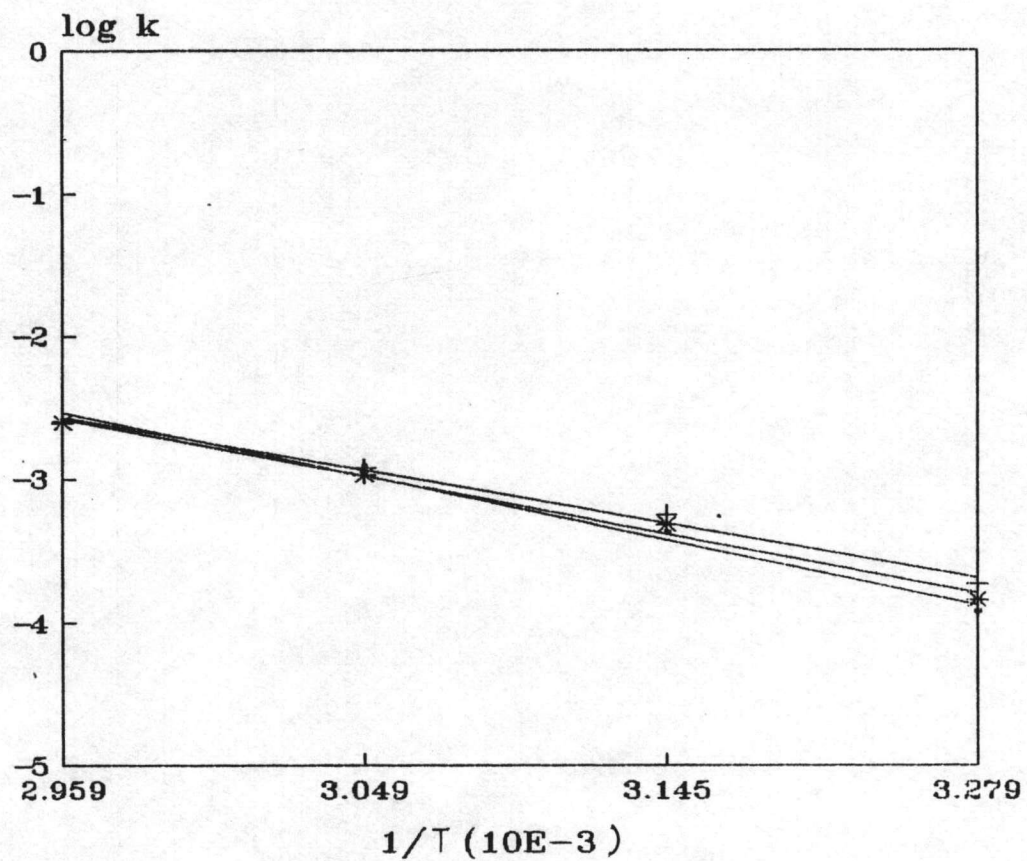
Key : —•— Series 1    —+— Series 2    —\*— Series 3

Arrhenius plot of  $\log k$  against  $1/T$   
formula No8 (Zero-order reaction)



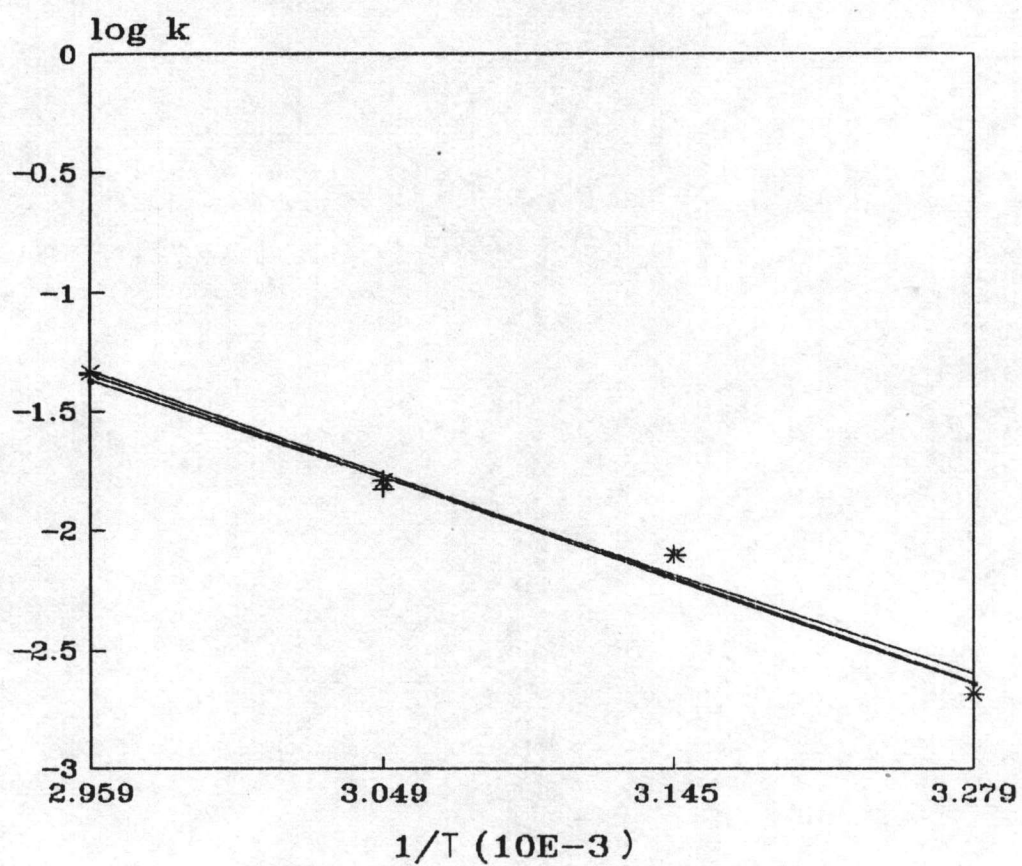
Key : —•— Series 1    —+— Series 2    —\*— Series 3

Arrhenius plot of  $\log k$  against  $1/T$   
Formula No8 (First order reaction)



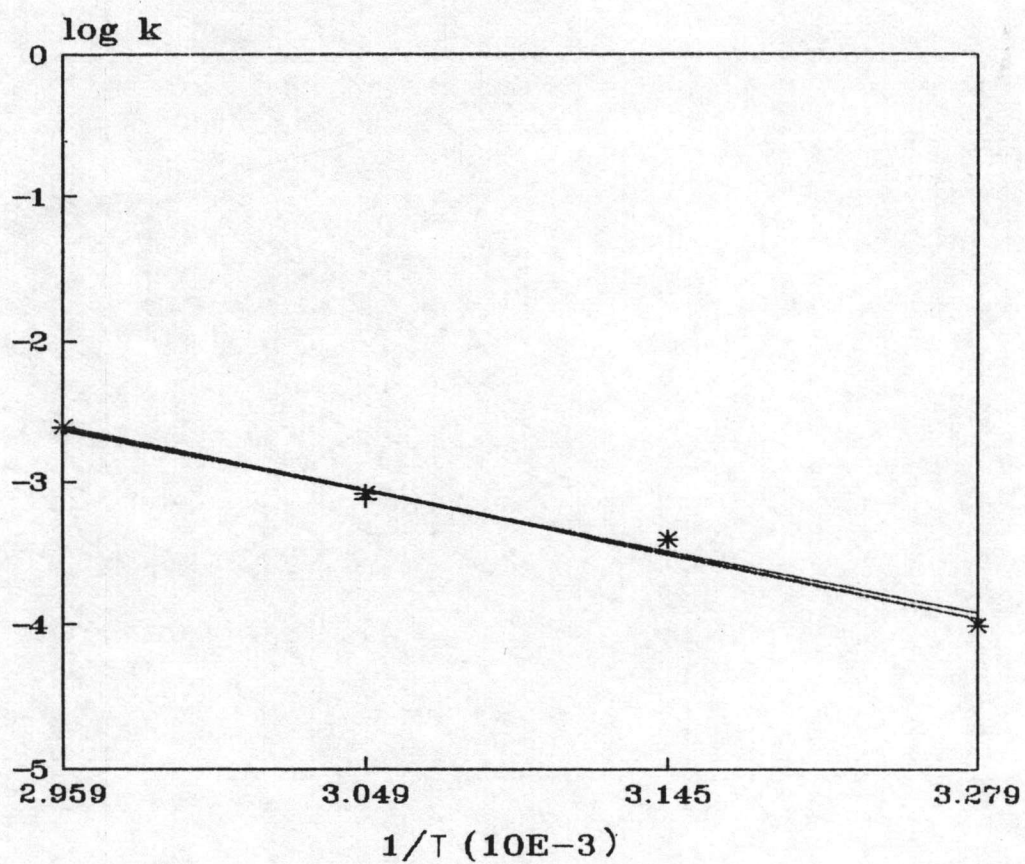
Key : — Series 1    + Series 2    \* Series 3

Arrhenius plot of  $\log k$  against  $1/T$   
Inovator formula (Zero-order reaction)



Key : —•— Series 1    —+— Series 2    —\*— Series 3

Arrhenius plot of  $\log k$  against  $1/T$   
Inovator formula (First order reaction)



Key : —•— Series 1    —+— Series 2    —\*— Series 3



**Appendix 3**

**Statistical Evaluation**

## 1. Simple linear regression and correlation

### 1.1 Least-Squares Estimation ( Milton and Arnol, 1990)

Recall from elementary algebra that the equation for a straight line is

$$Y_i = a + bx_i$$

Where "a" denotes the intercept, "b" the slope of regression line or regression coefficient

The parameters a and b are estimated by the method of least squares using equation as follow.

$$a = \bar{Y} - b\bar{X}$$

$$b = \frac{\sum_{i=1}^n (X_i - \bar{X})(Y_i - \bar{Y})}{\sum_{i=1}^n (X_i - \bar{X})^2}$$

$$\bar{X} = \frac{1}{n} \sum_{i=1}^n X_i$$

$$\bar{Y} = \frac{1}{n} \sum_{i=1}^n Y_i$$

## 1.2 Simple Correlation (Milton and Arnold, 1990)

The theoretical parameter used to measure the linear relationship between X and Y is the Pearson coefficient of correlation  $\rho$ . This parameter is defined by

$$\begin{aligned} \rho &= \frac{\text{Cov. (x, y)}}{\sigma_x \sigma_y} \\ &= \frac{\sum (X - u_x)(Y - u_y)}{\sqrt{\sum (X - u_x)^2 \sum (Y - u_y)^2}} \\ &= \frac{\sum_{i=1}^n (X_i - u_x)(Y_i - u_y)}{\sqrt{\sum_{i=1}^n (X_i - u_x)^2 \sum_{i=1}^n (Y_i - u_y)^2}} \end{aligned}$$

Estimator for  $\rho$

$$\hat{\rho} = r = \frac{\sum_{i=1}^n (X_i - \bar{X})(Y_i - \bar{Y})}{\sqrt{\sum_{i=1}^n (X_i - \bar{X})^2 \sum_{i=1}^n (Y_i - \bar{Y})^2}}$$

$$= \frac{n \sum XY - X \sum Y}{\sqrt{[n \sum X^2 - (\sum X)^2] [n \sum Y^2 - (\sum Y)^2]}}$$

## 2. Analysis of variance (One-Way classification) (Milton and Arnold, 1990)

### 2.1 ANOVA table for the one-way classification design with fixed effects.

Source of variation	Degress of freedom (DF)	Sum of Square (SS)	Mean Square (MS)	Expected mean square	F
Treatment or level	$k - 1$	$\frac{\sum_{i=1}^k T_i^2}{n_i} - \frac{T_{..}^2}{N}$ (SSTr)	$\frac{SSTr}{k - 1}$	$\sigma^2 + \sum_{i=1}^k \frac{n_i}{k - 1} \tau_i^2$	$\frac{MSTr}{MSE}$
Error or residual	$N - k$	Subtraction (SSE)	$\frac{SSE}{N - k}$	$\sigma^2$	
Total	$N - 1$	$\sum_{i=1}^k \sum_{j=1}^{n_i} Y_{ij}^2 - \frac{T_{..}^2}{N}$			

$$SSTot = \sum_{i=1}^k \sum_{j=1}^{n_i} Y_{ij}^2 - \frac{T_{..}^2}{N}$$

$$SS_{Tr} = \sum_{i=1}^k \frac{T_i^2}{n_i} - \frac{T_{..}^2}{N}$$

$$SS_E = SS_{Tot} - SS_{Tr}$$

### 2.2 Least Significant Different (LSD)

$$LSD(0.05) = t_{0.05} \sqrt{\frac{2MSE}{n}}$$

### 3. Comparison of two means

A t-test with the equation. (Milton and Arnold, 1990)

$$t = \frac{\bar{Y}_1 - \bar{Y}_2}{S(\bar{Y}_1 - \bar{Y}_2)}$$

S = Sample Standard Error

$$S = \sqrt{\frac{2S^2}{n}}$$

$$S^2 = \text{Pooled Sample Variance}$$

$$= \frac{(n_1 - 1) S_1^2 + (n_2 - 1) S_2^2}{(n_1 - 1) + (n_2 - 1)}$$

## VITA

Miss Chanida Pongsanguansin was born on March 14<sup>th</sup>, 1962, in Bangkok, Thailand. She received Bachelor of Science in Pharmacy in 1986 from Faculty of Pharmacy, Mahidol University, Bangkok, Thailand. Following graduation, she worked as a medical representative for two years, and then she has been worked with the Narcotics Analysis Division, Medical Sciences Department as a medical scientist before joining the Master's Degree programme in Pharmacy at Chulalongkorn University in 1990.

