REFERENCES

1. Seubert, J., Pohlke,R. and Loebich, F. "Synthesis and Properties of Praziquantel, a Novel Broad Spectrum Anthelmintic with Excellent Activity against Schistosomes and Cestodes" Experientia 33(1977): 1036-1037.

2. Kranz, O. "Biltricide" Drug Made in Germany 24(1981): 39-47.

3. Andrew, P., Thomas, H., Pohlke, R. and seubert, J. "Praziquantel" Medicinal Reserch Reviews. 3(1983): 147-200.

4. Groll, E. "Praziquantel" Advances in Pharmacology and Chemotherapy 20(1984): 219-237.

5. Viyanant, V. "Opisthorchiasis in Thailand, A Review" J. Parasit. Trop. Med. Ass. Thailand 4(1981): 87-106.

6. Bunnag, D. and Co-workers "*Opisthorchis viverini*: Clinical Experience with Praziquantel in Hospital for Topical Diseases" Arzneim-Forsch/Drug Res. 34(II), (1984): 1173-1174.

7. Supanvanich, K., Supanvanish, S. and Mana ruchi, A. "Treatment of Opisthorchiasis with Praziquantel" J. Pub. Heth. Thailand. 12(1982): 124.

8. Supanvanich, S., Supanvanich, K. and Pawabut, P. "Field Trial of Praziquantel in Human Opisthorchiasis in Thailand" Southeast Asian J. Trop. Med. Pub. Hlth. 12(1981): 598-602.

9. Pungpak, S., Bunnag, D. and Harinasuta, T. "Studies on the Chemotherapy of Human Opisthorchiasis: Effective Dose of Praziquantel in Heavy Infection" Southeast Asian J. Trop. Med. Pub. Heth. 16(1985): 248-252.

10. Bunnag, D. and Harinasuta, T. "Studies on the Chemotherapy of Human Opisthorchiasis III Minimum Effective Doses of Praziquantel" Southeast Asian J. Trop. Med. Pub. Hlth. 12(1981): 413-417.

11. Vivatanasesth, P., Sornmani, S., Sohelp, F.P., Impand, P., Sitabatra, P., Preuksaraj, S. and Harinasuta, C. "Mass Treatment of Opisthorchiasis in Northeast Thailand" Southeast Asian J. Trop. Med. Pub. Hlth. 13(1982): 609-613.

12. Tawatsin, A., Sirisha, S., Vajrasthira S., Bunnag, D. and Harinasuta, T. "Evaluation of Selected Anthelmintic Compounds for Activity against *Opisthorchis viverrini*" Tropenmed. Parasit. 35(1984): 85-90

13. Leopold, G., Ungethum, W., Groll, E., Diekmann, H.W., Nowak, H. and Wegner, D.H.G. "Clinical Pharmacology in Normal Volunteers of Praziquantel, a New Drug aginst Schistosomes and Cestodes" Eur. J. Clin. Pharm. 14(1978): 281-291.

14. Buhring, K.U., Diekmann, H., Muller, H., Garbe, A. and Nowak, H. "Metabolism of Praziquantel in Man" Eur. J. Drug Metab. Pharmacokin. 3(1978): 179-190.

15. Patzchke, K., Putter, J., Wagner, L.A., Horster, F.A. and Diekmann H.W. "Serum Concentrations and Renal Excretion in Humans after Oral Administration of Praziquantel-results of three determination methods" Eur. J. Drug Metab. Pharmacokin. 3(1979): 149-156.

16. Putter, J. and Held, F. "Quantitative Studies on the Ocurrence of Praziquantel in Milk and Plasma of Lactating Woman" Eur. J. Drug Metab. Pharmacokin. 4(1979): 193-198.

17. American Pharmaceutical Association, The Biavailability of Drug Products cumulative Edi., American Pharmaceutical Association Inc., New York, 1978.

18. Merck Index 10 ed., PP. 7612 Merck & co, Inc., Rahway, N.J., U.S.A., 1983.

19. Pax, R., Bennett, J.L. and Fetterer, R. "A Benzodiazepine Derivative and Praziquantel: Effect on Musculature of *Schistosoma mansoni and Schistosoma japanicum*" Naunyn-Schmiedeberg's Arch. Pharm. 304(1978): 309

20. Mehlhorn, H., Becker, B., Andrew, P., Thomas, H. and Frenkel, J.K. "In Vivo and in Vitro Experiment on the Effect of Praziquantel on *Schistosoma mansoni*, A Light and Electron Microscopic study" Arzneim-Forsch/Drug Res. 31(1981): 544-554.

21. Aehlhon, H., Kojima, S., Rim, H.J., Ruenwongsa, P., Andrews, P. Thomas, H. and Bunnag, D. "Ultrastructural Investigations on the Effects of Praziquantel on Human Trematodes from Asia: *Clonorchis sinensis, Metagsnimus yokogawai, Opisthorchis viverini, Paragonimus westermani and Schistosoma japanicum*" Arzneim-Forsch/Drug Res. 33(1983): 91-98.

22. Andrews, P. "A Summary of Efficacy of Praziquantel against Schistosomes in Animal Experiments and Notes on its Mode of Action" Arzneim-Forsch/Drug Res. 31(1981): 538-41.

23. Ruenwongsa, P., Hutadilok, N. and Yuthavong, Y. "Stimulation of Ca^{++} Uptake in the Human Liver Fluke *Opisthorchis viverrini* by Praziquantel" Life Sc. 32(1983): 2529-2534

24. Frohberg, H. and Scheneking, M.S. "Toxicological Profile of Praziquantel, a New Drug against Cestode and Schistosome Infection, as compared to some other Schistosomicides" Arzneim-Forsch/Drug Res. 31(1981): 555-565.

25. Steiner, K., Garbe, A., Diekmann, H.W. and Nourak, H. "The fate of praziquantel in the organism I. Pharmacokinetics in animals" Eur. J. Drug Metab. Pharmacokin. 2(1976): 85-95.

26. Steiner, K. and Garbe, A. "The Fate of Praziquantel in the Organism II Distribution in rats" Eur. J. Drug Metab. Pharmacokin. 2(1976): 97-106.

27. Diekmann, H.W. and Buhring, K.U. "The Fate of Praziquantel in the Organism III Metabolism in Rat, Beagle, Dog and Rhesus Monkey" Eur. J. Drug Metab. Pharmacokin. 2(1976) : 107-112.

28. Shao, H-Sheng and Co-workers in Jiangsu Inst. Nucl. Med., Woxi, Peop. Rep. China "Absorption, Distribution and Excretion of [^{14}C] Praziquantel in Animals" Chung-kuo Yoo Li Hsuch Pao 2(1981): 49-54.

29. Davis, A. and Wegner, D.H.G. "Multicentre Trials of Praziquantel in Human Schistosomiasis: Design and Techniques" WHO (Bulletin) 57(1979): 767-771.

30. Davis, A., Biles, J.E. and Ulrich, A.M. "Initial Experiences with Praziquantel in the Treatment of Human Infection due to *Schistosoma hematobium*" WHO [Bulletin] 57(1979): 773-779.

31. Ishizaki, T., Kamo, E., and Bochme, K. "Double-Blind Studies of Tolerance to Praziquantel in Japanese patients with *Schistosoma japanicum* Infection" WHO [Bulletin] 57(1979) : 781-791.

32. Katz, N., Rocha, R.S. and Claves, A. "Preliminary Trials with Praziquantel in Human Infection due to *Schistosoma mansoni*" WHO [Bulletin] 57(1979): 781-785.

33. Rim, Hom-Jong and Kwang-Sa Yoo "Chemotherapeutic Effect of Praziquantel [EMBAY 8440] in the Treatment of *Clonorchis sinensis*" Univ. Med. J. (Korea) 16(1979): 459-470.

34. Loscher, T., Northdurft, H.D., Prufer, L., Von Sonnenburg, F. and Lang, W. "Praziquantel in Clonorchiasis and Opisthorchiasis" Tropenmed. Parasitol. 32(1981): 234-236.

35. Rim, Hom-Jong "Paraqonimiasis: Experimental and Clinical Experience with Praziquantel in Korea" Arzneim-Forsch./Drug Res. 34(1984): 1197-1203.

36. Groll, E. "Praziquantel for Cestode Infection in Man" Acta Trop. 37(1980): 293.

37. Schenone, H. "Praziquantel in the Treatment of *Hymenolepsis nana* Infection in children" Am. J. Trop. Hyp. 29(1980): 320.

38. Botero, D. and Castano, D. "Treatment of Cysticerosis with Praziquantel in Colombia" Am. J. Trop. Med. Hyg. 31 (1982): 810.

39. British Pharmacopoeia 1973 pp. 459-460. London Her Magesty's Stationary Office, 1973.

40. British Pharmacopoeia 1980, Vol II pp. 727-729, A 113-119, London Her Magesty's Stationary Office, 1980.

41. Yuan, Xibing. "Derivative Spectroscopic Assay of Praziquantel Tablets" Yaown Fenxi Zazhi 5(1985): 120-121.

42. The United State Pharmacopoeia 21 th rev. pp. 1242-1245, 1424, United States Pharmacopoeial Convention, Inc., Rockville, Md., 1985.

43. Neter, J. and Wasserman, W. Applied Linear Statistical Models pp. 21, Richard D. Irwin, Inc., Home wood, I.L., 1974.

44. Anderson-Bell ABSTAT^{tm}User Manual Release 3.0 pp. 1-93, Anderson-Bell, Canon City, 1981.

45. Xiao, S.H., Catto, B.A. and Webster, L.T. "Quantitative Determination of Praziquantel in serum by high-performance liquid chromatography" J. Chromatogr. 275(1933) : 127-132.

46. Metzler, C.M., and Weiner, D.L. PCNONLIN Nonlinear Estimation Program V01-A Statistical Consultants, Inc., 1984.

47. Kaplan, S.A. "Biopharmaceutics in the Preformulation Stages of Drug Development" in Current Concepts in the Pharmaceutical Sciences : Dosage Form Design and Bioavailability (Swarbrik, J. ed.) pp. 1-30, Lea & Febiger, Philadelphia, 1973.

48. Pernarowski, M. "Dissolution Methodology" Dissolution Technology (Leeson, L.S. and Carstensen, J.T. eds.) pp. 58-105., The Industrial Pharmaceutical Technology section of the Academy of Pharmaceutical Science, Washington, D.C., 1974.

49. Shargel, L. and Yu, A.B.C. Applied Biopharmaceutics and Pharmacokinetics. pp. 85-101, Appleton-Century-Crafts, New York, 1980.

50. Lin, Y.J. and Chien, Y.W. Oral Drug Bioavailability Variations, Limitations, and Control in Control Drug Bioavailability Vol.3 (Smolen, V.F.ed.) pp. 1-64, Wiley-Interscience Publication, John Wiley & Sons, New York, 1985.

51. Tawatsin, A., Sirisha, S., Vajrasthira S., Bunnag, D. and Harinasuta, T. "Evaluation of Selected Anthelmintic Compounds for Activity against *Opisthorchis viverrini*" Tropenmed. Parasit. 35(1984): 85-90

52. Wagner, J.G. Biopharmaceutics and Relevant Pharmacokinetics pp. 121-125, Drug Intelligence Publications, Hamilton, Ill., 1971.

53. Mason, R.D., Lind, D.A., and Marchal, W.G., Statistics An Introduction, pp. 368-395, Harcourt Brace Jovanovich, Inc., New York, 1983.

54. Winter, M.E, Katcher, B.S. and Koda-Kimble, M.A. Basic Clinical Pharmacokinetics pp. 203, Applied Therapeutics, Inc., Spokane, W.A., 1980.

55. Gibaldi, M., Perrier, D. "Method of Residuals." Drugs and the Pharmaceutical Sciences : Pharmacokinetics. 2d.ed., revised and expanded. pp. 433-444. Marcel Dekker, Inc., New York and Basel, 1982.

56. Rawland, M. and Tozer, T.N. Clinical Pharmacokinetics : Concepts and Applications pp. 288-289. Lea & Febiger, Philadelphia, 1980.

57. Gibaldi, M. and Perrier, D. One Compartment Model in Pharmacokinetics (Swarbrick,J.ed.) pp. 1-43, Marcel Dekker Inc., New York, 1975.

APPENDIX

APPENDIX A

Opisthorchiasis in Thailand (5)

Liver fluke infection in Thailand is caused by *Opisthorchis viverini*. The worms reside in the biliary passage of man. They are found mostly in all provinces of Northeast of Thailand and some limitted provinces of North of Thailand where the people have the habit of consuming raw fish. *Bithynia* snails and fresh water *Cyprinoid* fishes are intermediate hosts (see Life Cycle in Figure 7). The pathogenesis is due to the mechanical irritation caused by the flukes and some toxic substances produced by them. The clinical manifestation of the infection range from asyptomatic to severe mal-norichment, cirrhosis of liver and malignant neoplasm of biliary system and liver. Praziquantel, a single dose of 40 mg/kg , is chosen for the treatment and control of the disease in the endemic area. Opisthorchiasis is considered a major public health problem in Thailand since about 7 millions of Thai people are suffering from this disease at the present time.

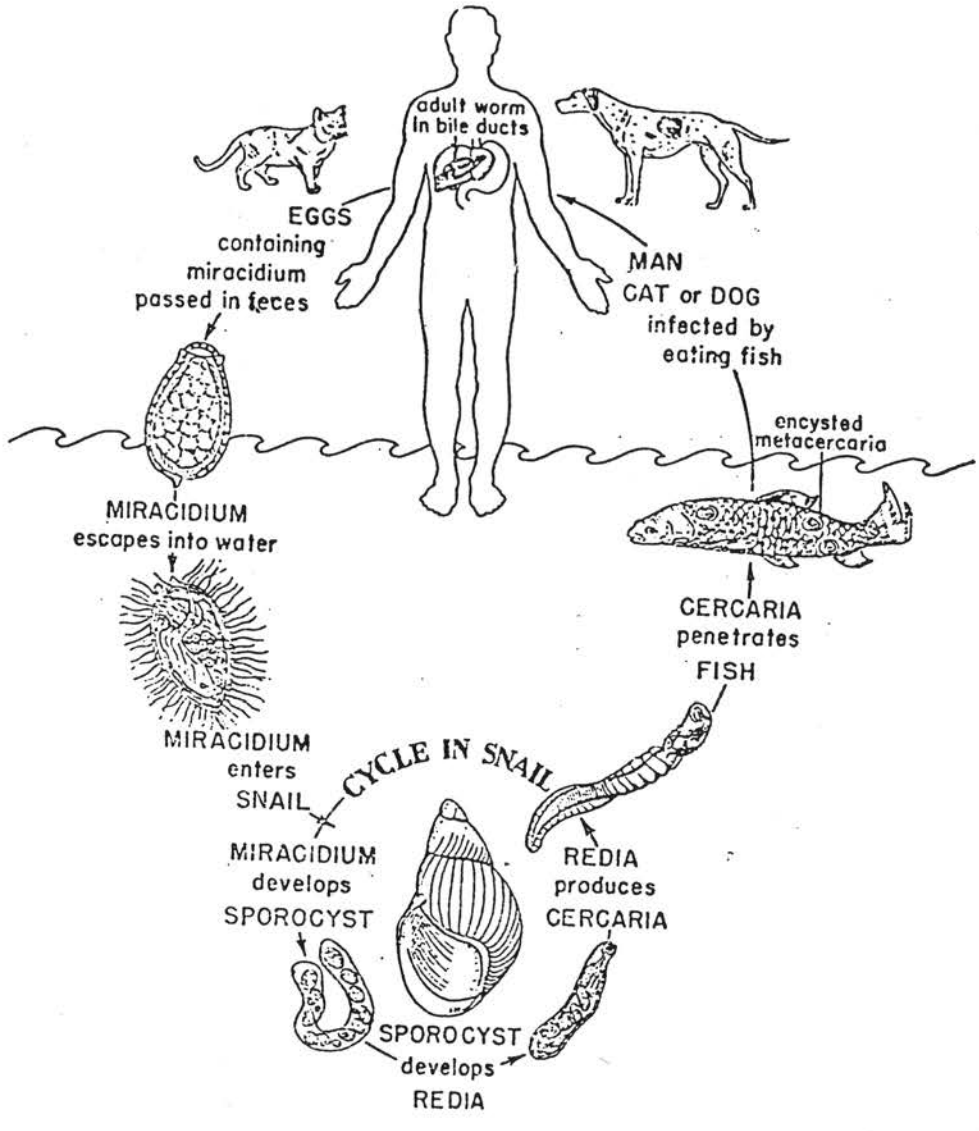


Figure 7 Life Cycle of *Opisthorchis viverrini*

APPENDIX B

Test Products

Code	Brand name	Manufacturers	Mtd. date	Batch no.
A	Biltricide[R]	Bayer AG[a]	9-4-84	301 A
B	Pontel[R]	Biolab Co.,Ltd.	7-9-84	409127
C	Praquantel[R]	Atlantic Laboratories Corp.	12-3-85	850077 F/C
D	Z-Queen[R]	Pond Chemical Thailand	3-5-85	805-205
E	Sequantel[R]	Chankit Trading Ltd., Part.	16-3-85	07285
F	Pratez[R]	Berlin Pharmaceutical Industry Ltd.,Part.	19-11-84	840068

[a]Bayer Thai Co.,Ltd. is its distributor in Thailand.

APPENDIX C

Standard Curve Determination

The typical standard curves and data for praziquantel concentrations in absoluted alcohol, simulated gastric fluid without enzyme (pH 1.2), simulated intestinal intestinal fluid without emzyme (pH 7.5), and human serum are presented in Tables8-11 and Figures8-11, respectively. The correlation coeffcient of the fit to the straight line were highly significant (r^2= 0.997, 0.999, 0.999 and 0.999, respectively).

Table 8 Typical Standard Curve Data for Praziquantel Concentrations in Absolute Ethanol Estimated using Linear Regression[1]

Standard No.	Concentration[a] (μg/ml)	Absorbance at λ 264	Inversely estimated[2] concentration (μg/ml)	% Theory[3]
1	700	0.784	697	99.6
2	600	0.665	591	98.5
3	500	0.575	510	102.0
4	400	0.467	414	103.5
5	300	0.332	293	97.7
6	200	0.222	195	97.5
			Mean	99.8
			S.D.	2.45
			C.V.[4]	2.45 %

1. $r^2 = 0.997$, $A = 3.886 \times 10^{-3}$, $B = 1.119 \times 10^{-3}$ ($y = A + Bx$)

2. Inversely estimated concentration = $(\text{Absorbance} - 3.886 \times 10^{-3})/1.119 \times 10^{-3}$

3. $\% \text{ Theory} = \frac{\text{Inversely estimated concentration}}{\text{Known concentration}} \times 100$

4. Coefficient of variation = $\frac{\text{S.D.}}{\text{Mean}} \times 100$

a. Each value represents the average of duplicate samples.

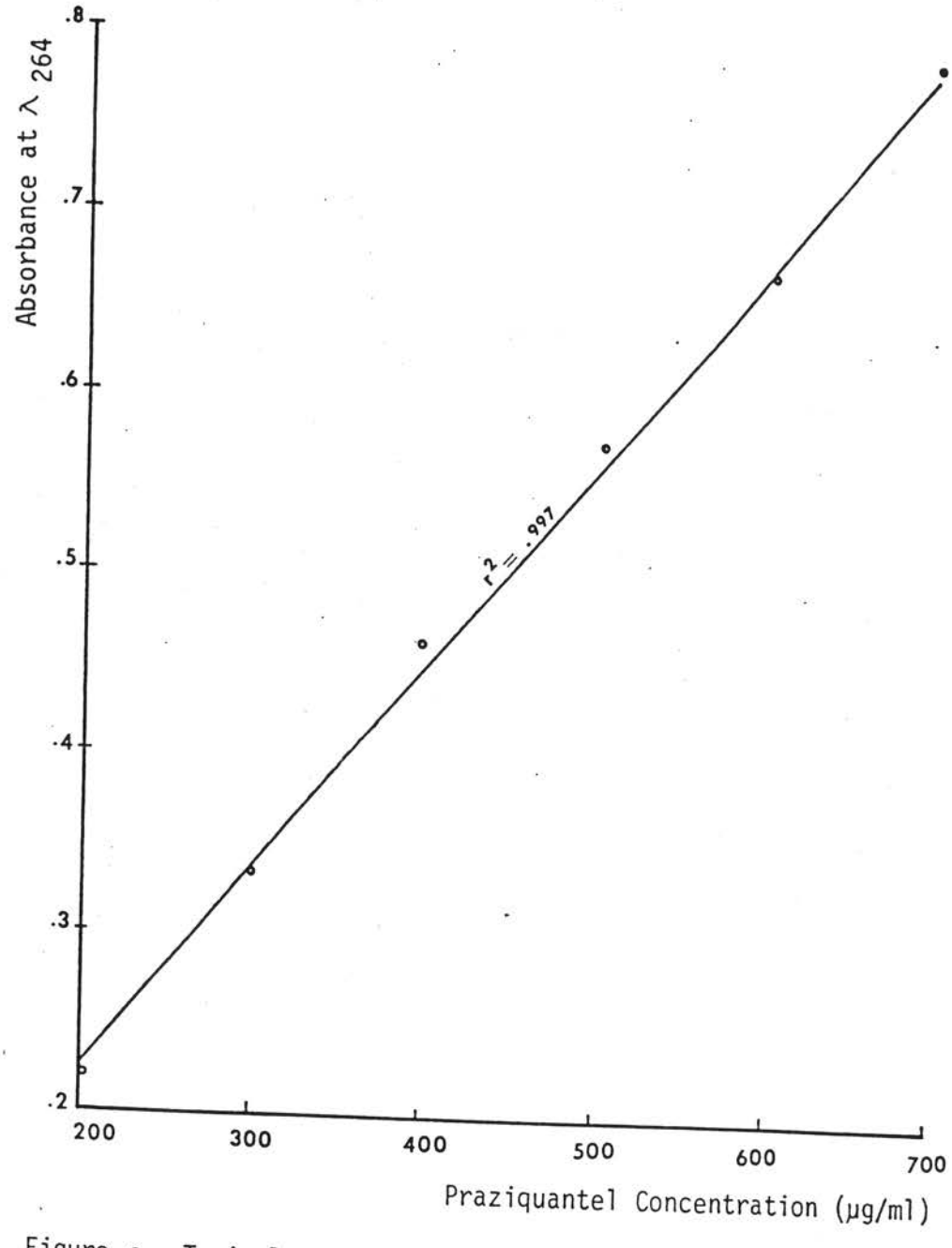


Figure 8 · Typical standard curve for praziquantel concentration in absolute ethanol.

Table 9 Typical Standard Curve Data for Praziquantel Concentrations in simulated gastric fluid without enzyme (pH 1.2) Estimated Using Linear Regression[1]

Standard No.	Concentration (µg/ml)	Absorbance at λ 264	Inversely estimated[2] concentration (µg/ml)	% Theory
1	300	0.377	299	99.7
2	270	0.341	270	100.0
3	240	0.303	239	99.6
4	210	0.268	211	100.5
5	180	0.227	178	98.9
6	150	0.198	154	102.7
7	120	0.161	124	103.3
8	90	0.117	88	97.8
9	60	0.080	58	96.7
10	30	0.043	29	96.7
			Mean	99.6
			S.D.	2.23
			C.V.	2.24 %

1. $r^2 = 0.999$, $A = 7.733 \times 10^{-3}$, $B = 1.235 \times 10^{-3}$

2. Inversely estimated concentration = (Absorbance - 7.733×10^{-3})/1.235×10^{-3}

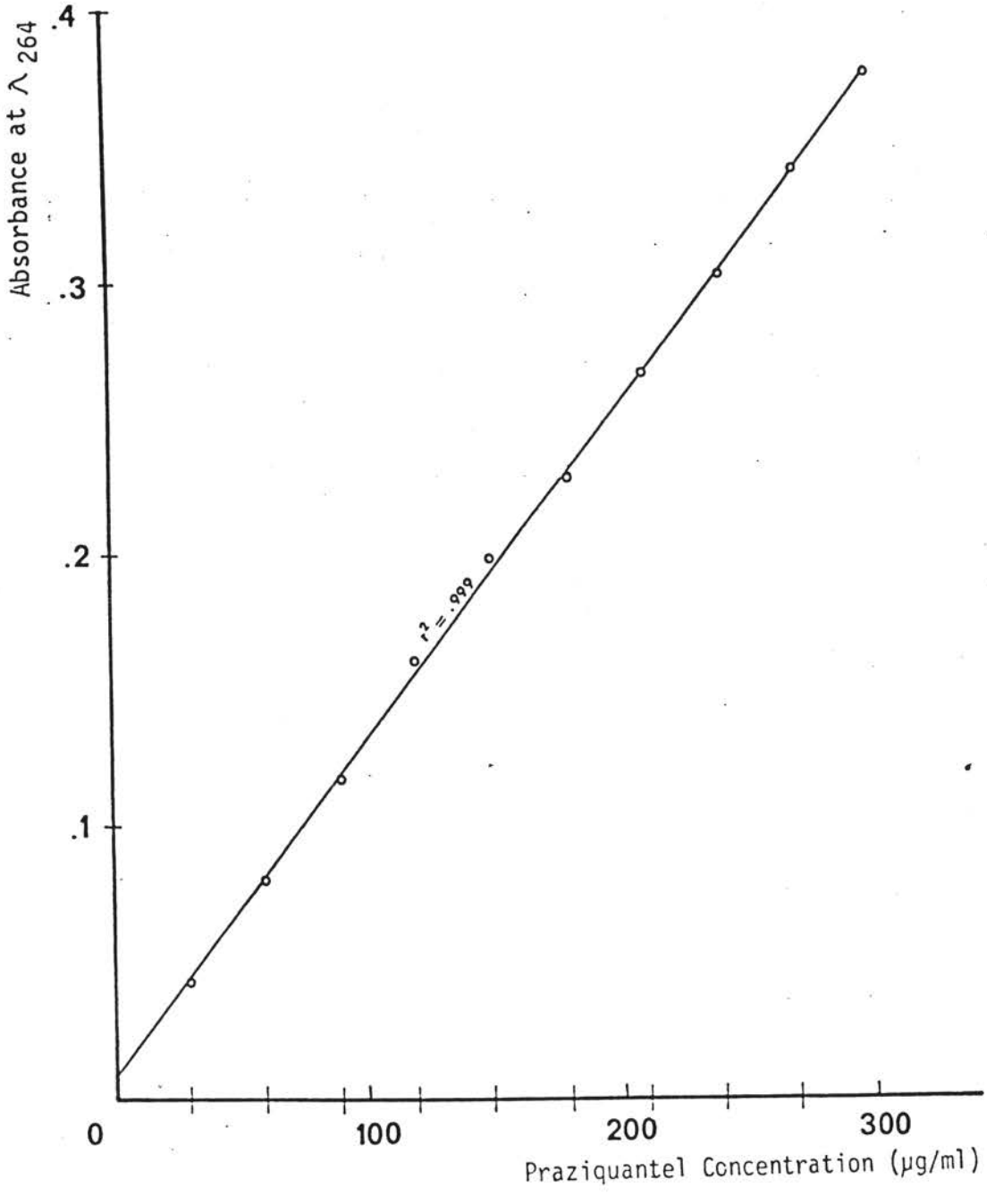


Figure 9 Typical standard curve for praziquantel concentration in simulated gastric fluid without enzyme (pH 1.2).

Table 10 Typical Standard Curve Data for Praziquantel Concentrations in simulated intestinal fluid without enzyme (pH 7.5) Estimated using Linear Regression[1]

Standard No.	Concentration (μg/ml)	Absorbance at λ 264	Inverselyestimated[2] concentration (μg/ml)	% Theory
1	200	0.248	203	101.5
2	192	0.233	191	99.5
3	184	0.225	184	100.0
4	176	0.217	177	100.6
5	168	0.205	167	99.4
6	160	0.195	159	99.4
7	152	0.188	153	100.6
8	144	0.175	142	98.6
9	136	0.166	134	98.5
10	128	0.157	127	99.2
11	120	0.151	122	101.7
12	100	0.126	101	101.0
13	80	0.102	80	100.0
14	60	0.078	60	100.0
15	40	0.054	40	100.0
16	20	0.030	20	100.0
			Mean	100.0
			S.D.	0.90
			C.V.	0.90 %

1. $r^2 = 0.999$, $A = 6.220 \times 10^{-3}$, $B = 1.190 \times 10^{-3}$

2. Inversely estimated concentration = (Absorbance - 6.220×10^{-3})/1.190×10^{-3}

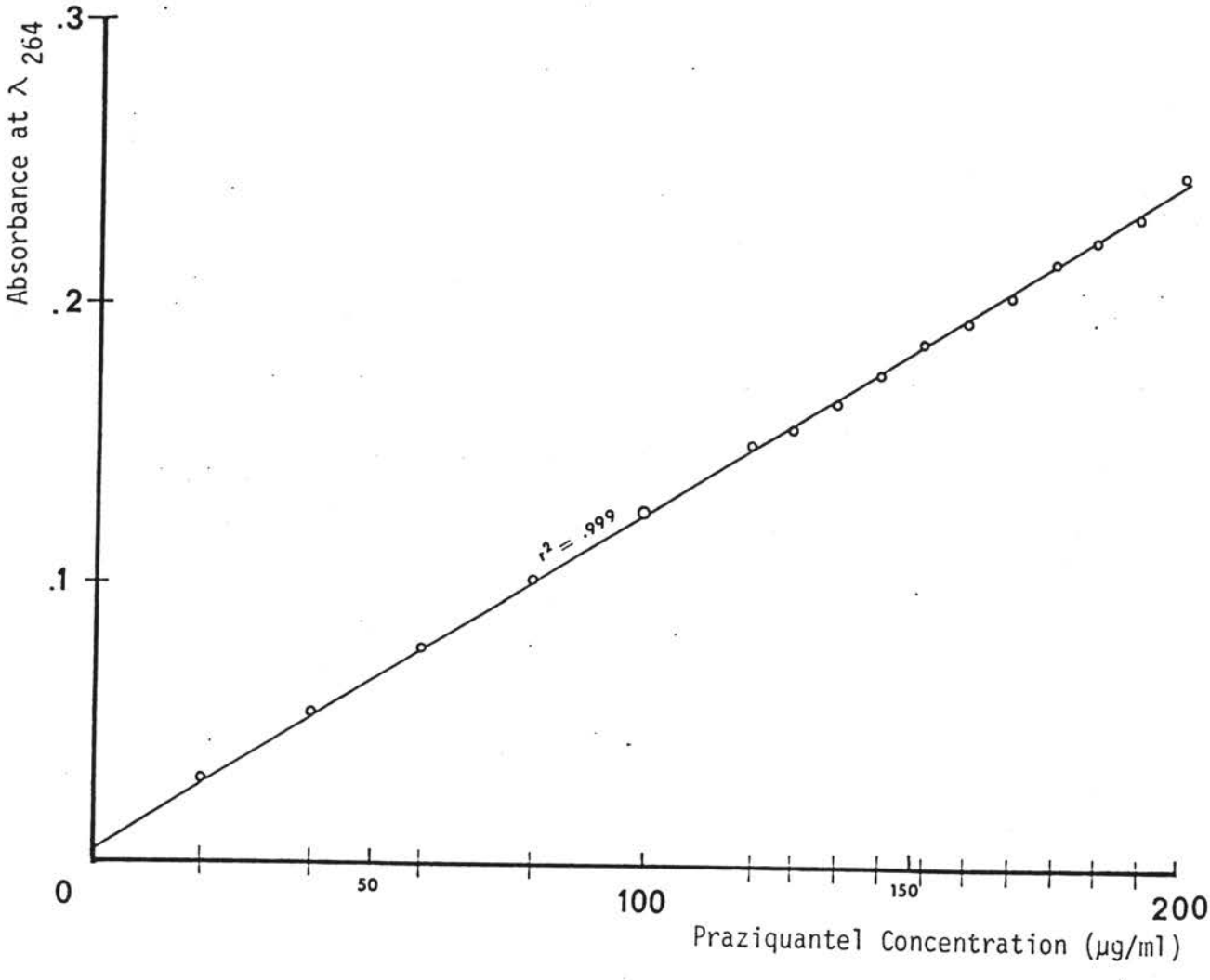


Figure 10 Typical standard curve for praziquantel concentration in simulated intestinal fluid without enzyme (pH 7.5).

Table 11 Typical Standard Curve Data for Praziquantel Concentrations in Human Serum Estimated Using Linear Regression[1]

Standard No.	Concentration (μg/ml)	Peak area PZQ^{*}/IS^{**} ratio	Inversely estimated[2] concentration (μg/ml)		% Theory
1	0.05	0.0878	0.040		80.0
2	0.1	0.1736	0.105		105.0
3	0.5	0.6944	0.502		100.4
4	1.0	1.3294	0.986		98.6
5	1.5	2.0632	1.545		103.0
6	2.0	2.6253	1.973		98.6
7	2.5	3.3168	2.500		100.0
8	3	3.9730	3.000		100.0
				Mean	98.2
				S.D.	7.67
				C.V.	7.81 %

1. $r^2 = 0.999$, $A = 3.582 \times 10^{-2}$, $B = 1.312 \times 10^{-3}$

2. Inversely estimated concentration = $(\text{Absorbance} - 3.582 \times 10^{-2})/1.312 \times 10^{-3}$

* Praziquantel

** Internal Standard

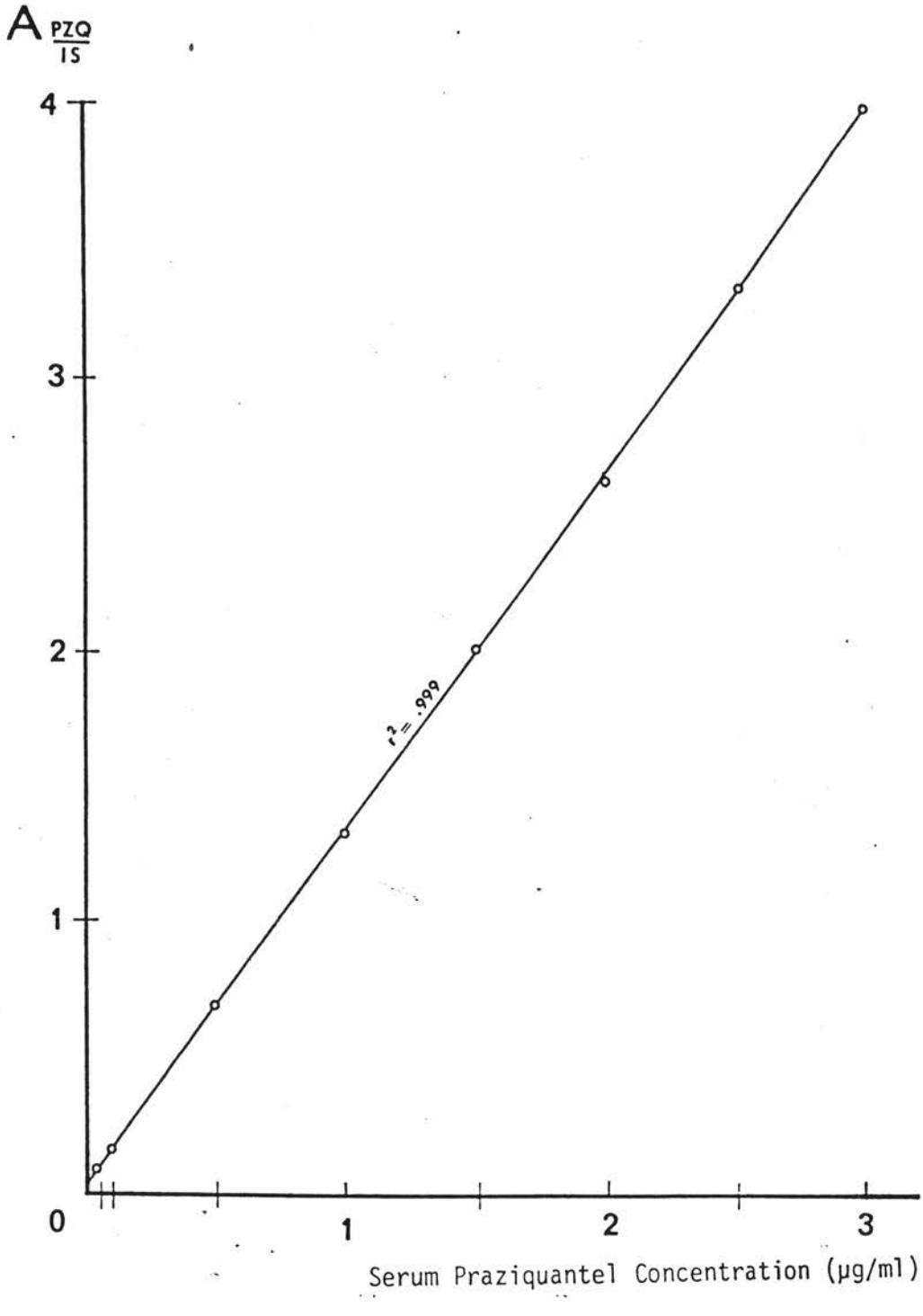


Figure 11 Typical standard curve for praziquantel concentration in human serum.

APPENDIX D

Preparation of dissolution media (42)

a. Simulated gastric fluid without enzyme (pH 1.2)

2.0 g of sodium chloride was dissolved in 7.0 ml of hydrochloric acid and suffcient water to make 1,000 ml. This test solution had a pH of about 1.2

b. Simulated intestinal fluid without enzyme (pH 7.5)

6.8 g of monobasic potassium phosphate was dissolved in 250 ml of water, mixed, and 190 ml of 0.2 N sodium hydroxide and 400 ml of water was added. The resulting solution was adjusted with 0.2 N sodium hydroxide to a pH of 7.5 ± 0.1 , and diluted with water to 1,000 ml.

APPENDIX E

One-way Analysis of Variance and Student't-Test Using a Computerized Statistical Program ABSTAT

Percentile of the F- Distribution

$d.f._{5,30}$ $F_{0.95} = 2.53$

$d.f._{3,28}$ $F_{0.95} = 2.95$

Percentile of the t- Distribution

$d.f._{10}$	$t_{0.95} = 1.8125$	$d.f._{5}$	$t_{0.95} = 2.5706$
$d.f._{14}$	$t_{0.95} = 1.7613$	$d.f._{7}$	$t_{0.95} = 2.3646$
(one-side test)		(two-side test)	

```
                Welcome to ABSTAT
                  RELEASE 3.0x

MEMORY AVAILABLE IS xxxxx. WITH ROOM FOR xxxx VALUES.  {CP/M-80 only}

                  COPYRIGHT 1981, 1982
                ANDERSON-BELL COMPANY

     you may type "?" for HELP at any prompt

The following commands will display names of commands available
in each of the following catagories.  All commands must be
entered in UPPER CASE.

DATA   - Data manipulation
STAT   - Statistical analysis
GRAPH  - Graphic functions
REPORT - Report writing
MISC   - Miscellaneous: QUIT, HELP, COMM, MISS, etc.

WHICH COMMAND?
```

Figure 12 The output of one-way analysis of variance and student't-test using a computerized statistical program ABSTAT

```
    VARIABLES:
CASE          1 A          2 B          3 C          4 D          5 E          6 F
   1       9.50000      6.00000      26.5000      56.0000      5.50000      20.6000
   2       8.00000      4.50000      24.5000      58.0000      11.0000      20.6000
   3       9.00000      5.00000      20.5000      76.0000      11.0000      21.5000
   4       10.0000      4.50000      24.5000      58.0000      5.00000      27.0000
   5       7.00000      4.50000      24.0000      75.0000      3.50000      21.0000
   6       9.00000      7.00000      24.5000      77.0000      6.50000      21.5000

WHICH COMMAND? ANOV1*
WHICH VARIABLES?
*

                    *** 1 WAY ANALYSIS OF VARIANCE ***

      SAMPLE                SIZE          MEAN        STD DEV
       1 A                     6       8.75000       1.08397
       2 B                     6       5.25000       1.03682
       3 C                     6       24.0833       1.96002
       4 D                     6       66.6667       10.2697
       5 E                     6       7.08333       3.18460
       6 F                     6       22.8333       2.90975

                    DEGREES OF          SUM OF        MEAN OF
SOURCE OF VARIANCE    FREEDOM          SQUARES       SQUARES        F TEST
AMONG SAMPLES               5          16065.6       3213.11       148.108
WITHIN REPLICATIONS        30          650.833       21.6944
TOTAL                      35          16716.4

                    *** STUDENT'S T STATISTICS ***

VARIABLES:
 1 A          0.00000
 2 B         -7.00000      0.00000
 3 C          17.7714      23.7697      0.00000
 4 D          13.2038      14.9885      8.99598      0.00000
 5 E         -1.22169      1.29817     -9.13046     -13.6132      0.00000
 6 F          15.8422      14.1678     -1.13519     -8.80589      7.33352
              0.00000
                1 A          2 B          3 C          4 D          5 E
                6 F

DEGREES OF FREEDOM =     5

WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: A,B

FOR VARIABLES:    1 A
      AND         2 B

T STATISTIC =       5.21749
DEGREES OF FREEDOM =    10

WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: A,C

FOR VARIABLES:    1 A
      AND         3 C

T STATISTIC =      -15.3078
DEGREES OF FREEDOM =    10

WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: A,D

FOR VARIABLES:    1 A
      AND         4 D

T STATISTIC =      -12.5408
DEGREES OF FREEDOM =    10

WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: A,E

FOR VARIABLES:    1 A
      AND         5 E

T STATISTIC =       1.10783
DEGREES OF FREEDOM =    10

WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: A,F

FOR VARIABLES:    1 A
      AND         6 F

T STATISTIC =      -10.1418
DEGREES OF FREEDOM =    10
```

Figure 12 (cont): Output of ANOVA and Student't-Test for Disintegration Time

```
VARIABLES:
CASE          1 A          2 B          3 C          4 D          5 E          6 F
  1        35.5000      36.7300      22.7500      2.89000      30.8400      31.5800
  2        35.0100      38.9400      23.8000      2.40000      30.8400      31.2100
  3        34.8900      36.9800      22.2600      2.15000      30.2300      30.6600
  4        35.5000      38.5700      24.1000      2.76000      30.9700      31.0900
  5        35.2600      39.0600      23.8600      2.40000      31.5800      31.3400
  6        35.3800      38.6900      25.0800      2.76000      30.7200      31.2100

WHICH COMMAND? ANOV1*
WHICH VARIABLES?
*

                    *** 1 WAY ANALYSIS OF VARIANCE ***

SAMPLE          SIZE        MEAN        STD DEV
 1 A               6      35.2567      .256489
 2 B               6      38.1617      1.03002
 3 C               6      23.6417      1.00555
 4 D               6      2.56000      .285727
 5 E               6      30.8633      .435370
 6 F               6      31.1717      .326032

SOURCE OF VARIANCE     DEGREES OF FREEDOM     SUM OF SQUARES     MEAN OF SQUARES     F TEST
AMONG SAMPLES                   5              5001.93            1000.39          2386.28
WITHIN REPLICATIONS            30              12.5767            .419224
TOTAL                          35              5014.51

WHICH COMMAND? PAIRT*
WHICH VARIABLES?
*

                    *** STUDENT'S T STATISTICS ***

VARIABLES:
 1 A      0.00000
 2 B      6.77677     0.00000
 3 C     -30.6645    -56.1096     0.00000
 4 D     -790.432    -80.6172    -55.8057     0.00000
 5 E     -27.0607    -21.3616     19.2534     148.586      0.00000
 6 F     -41.5090    -16.6015     19.1994     293.610      2.25058
          0.00000
            1 A         2 B          3 C          4 D          5 E
            6 F

DEGREES OF FREEDOM =    5

WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: A,B

FOR VARIABLES:   1 A
      AND        2 B

T STATISTIC =       -6.11959
DEGREES OF FREEDOM =    10

WHICH COMMAND? A,C
INVALID COMMAND: A,C

WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: A,C

FOR VARIABLES:   1 A
      AND        3 C

T STATISTIC =        25.0272
DEGREES OF FREEDOM =    10

WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: A,D

FOR VARIABLES:   1 A
      AND        4 D

T STATISTIC =        190.415
DEGREES OF FREEDOM =    10

WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: A,E

FOR VARIABLES:   1 A
      AND        5 E

T STATISTIC =        19.4413
DEGREES OF FREEDOM =    10

WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: A,F

FOR VARIABLES:   1 A
      AND        6 F

T STATISTIC =        22.0195
DEGREES OF FREEDOM =    10
```

Figure 12 (cont): Output of ANOVA and Student't Test for Dissolution Rate at pH 1.2

```
   VARIABLES:
CASE          1 A          2 B          3 C          4 D          5 E          6 F
   1       27.5800      29.8500      32.5200      2.76000      27.5800      25.0600
   2       27.5800      29.8500      34.3700      7.93000      27.5800      24.6700
   3       27.2100      30.4800      32.6500      7.50000      28.0900      24.6900
   4       26.9600      29.6000      33.1400      5.66000      28.3400      25.3200
   5       27.7100      30.2300      33.3900      14.3500      27.5800      24.3100
   6       27.2100      29.8500      32.9000      5.78000      28.0900      24.5600

WHICH COMMAND? ANOV1*
WHICH VARIABLES?
*

                    *** 1 WAY ANALYSIS OF VARIANCE ***

      SAMPLE                SIZE          MEAN        STD DEV
       1 A                     6       27.3750       .290844
       2 B                     6       29.9767       .318601
       3 C                     6       33.1617       .671518
       4 D                     6       7.33000       5.89219
       5 E                     6       27.8767       .337560
       6 F                     6       24.7683       .362955

                      DEGREES OF        SUM OF        MEAN OF
SOURCE OF VARIANCE     FREEDOM         SQUARES       SQUARES        F TEST
AMONG SAMPLES                5         2505.23       501.046       187.519
WITHIN REPLICATIONS         30         80.1592       2.67197
TOTAL                       35         2585.39

WHICH COMMAND? PAIRT*
WHICH VARIABLES?
*

                  *** STUDENT'S T STATISTICS ***

VARIABLES:
 1 A              0.00000
 2 B              17.3280      0.00000
 3 C              22.3052      9.71765      0.00000
 4 D             -13.0068     -14.8396     -17.3150      0.00000
 5 E              1.96263     -10.2243     -15.1596      12.5617      0.00000
 6 F             -11.0391     -20.7555     -24.3333      10.2492     -20.6113
                  0.00000
                    1 A          2 B          3 C          4 D          5 E
                    6 F

DEGREES OF FREEDOM =     5

WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: A,D

FOR VARIABLES:    1 A
      AND         2 B

T STATISTIC =       -13.4855
DEGREES OF FREEDOM =    10


WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: A,C

FOR VARIABLES:    1 A
      AND         3 C

T STATISTIC =       -17.6817
DEGREES OF FREEDOM =    10


WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: A,D

FOR VARIABLES:    1 A
      AND         4 D

T STATISTIC =        11.4839
DEGREES OF FREEDOM =    10


WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: A,E

FOR VARIABLES:    1 A
      AND         5 E

T STATISTIC =       -2.51756
DEGREES OF FREEDOM =    10


WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: A,F

FOR VARIABLES:    1 A
      AND         6 F

T STATISTIC =        12.5319
DEGREES OF FREEDOM =    10
```

Figure 12 (cont): Output of ANOVA and Student't Test for Dissolution Rate at pH 7.5

```
VARIABLES:
CASE          1 A          2 B          3 C          4 D
  1        1.22600      1.44100      1.42500      .987000
  2        .727000      .691000      .548000      .240000
  3        1.76400      1.24800      .985000      1.01200
  4        2.15700      2.53500      1.30500      1.62700
  5        2.04900      1.55100      1.37600      1.20900
  6        1.72300      1.64800      1.62800      1.38000
  7        1.34800      1.64600      1.17000      .921000
  8        1.91600      2.34000      1.53800      .678000

WHICH COMMAND? ANOV1*
WHICH VARIABLES?

                *** 1 WAY ANALYSIS OF VARIANCE ***

SAMPLE          SIZE          MEAN          STD DEV
1 A                8          1.61375       .480733
2 B                8          1.62500       .585481
3 C                8          1.24688       .347379
4 D                8          1.00675       .425724

SOURCE OF VARIANCE    DEGREES OF FREEDOM    SUM OF SQUARES    MEAN OF SQUARES    F TEST
AMONG SAMPLES                  3               2.17209           .724030        3.30681
WITHIN REPLICATIONS           28               6.13063           .218951
TOTAL                         31               8.30272

WHICH COMMAND? PAIRT*
WHICH VARIABLES?

                *** STUDENT'S T STATISTICS ***

VARIABLES:
1 A          0.00000
2 B      8.40672E-002      0.00000
3 C         -2.79604      -2.42127       0.00000
4 D         -5.31163      -3.58565      -1.98337       0.00000
              1 A           2 B           3 C           4 D

DEGREES OF FREEDOM =  7

WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: A,B

FOR VARIABLES:   1 A
      AND        2 B

T STATISTIC = -3.92904E-002
DEGREES OF FREEDOM =  14

WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: A,C

FOR VARIABLES    1 A
      AND        3 C

T STATISTIC =      1.63657
DEGREES OF FREEDOM =  14

WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: A,D

FOR VARIABLES:   1 A
      AND        4 D

T STATISTIC =      2.50097
DEGREES OF FREEDOM =  14

WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: B,C

FOR VARIABLES:   2 B
      AND        3 C

T STATISTIC =      1.46953
DEGREES OF FREEDOM =  14

WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: B,D

FOR VARIABLES:   2 B
      AND        4 D

T STATISTIC =      2.25962
DEGREES OF FREEDOM =  14

WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: C,D

FOR VARIABLES:   3 C
      AND        4 D

T STATISTIC =      1.15623
DEGREES OF FREEDOM =  14
```

Figure 12 (cont): Output of ANOVA and Student't Test for $C_{p\ max}$

```
VARIABLES:
CASE          1 A          2 B          3 C          4 D
  1        1.92000      1.07000      1.65000      2.60000
  2        3.02000      2.79000      3.22000      4.44000
  3        1.59000      1.87000      1.88000      2.72000
  4         .860000      .820000     1.42000      1.32000
  5        2.31000      2.66000      2.55000      2.67000
  6        1.85000      2.09000      1.47000      1.82000
  7        1.98000      1.23000      2.73000      4.14000
  8        1.91000      1.23000      1.78000      2.75000
WHICH COMMAND? ANOV1#
WHICH VARIABLES?

                *** 1 WAY ANALYSIS OF VARIANCE ***

SAMPLE          SIZE        MEAN        STD DEV
1 A                8      1.93000      .609731
2 B                8      1.72000      .746177
3 C                8      2.13750      .617732
4 D                8      2.80750      1.04890

SOURCE OF VARIANCE    DEGREES OF FREEDOM    SUM OF SQUARES    MEAN OF SQUARES    F TEST
AMONG SAMPLES                  3              5.32605           1.77535         2.94668
WITHIN REPLICATIONS           28              16.8755           .602696
TOTAL                         31              22.2016

WHICH COMMAND? PAIRT#
WHICH VARIABLES?
#

                *** STUDENT'S T STATISTICS ***

VARIABLES:
1 A          0.00000
2 B         -1.20260      0.00000
3 C          1.24500      1.78140      0.00000
4 D          3.60991      2.98035      2.98505      0.00000
                1 A          2 B          3 C          4 D
DEGREES OF FREEDOM =    7

WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: A,B

FOR VARIABLES:   1 A
      AND        2 B

T STATISTIC =        .576448
DEGREES OF FREEDOM =    14

WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: A,C

FOR VARIABLES:   1 A
      AND        3 C

T STATISTIC =       -.632506
DEGREES OF FREEDOM =    14

WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: A,D

FOR VARIABLES:   1 A
      AND        4 D

T STATISTIC =      -1.91358
DEGREES OF FREEDOM =    14

WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: B,C

FOR VARIABLES:   2 B
      AND        3 C

T STATISTIC =      -1.14002
DEGREES OF FREEDOM =    14

WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: B,D

FOR VARIABLES:   2 B
      AND        4 D

T STATISTIC =      -2.23492
DEGREES OF FREEDOM =    14

WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: C,D

FOR VARIABLES:   3 C
      AND        4 D

T STATISTIC =      -1.45623
DEGREES OF FREEDOM =    14
```

Figure 12 (cont): Output of ANOVA and Student't Test for t_{max}

```
   VARIABLES:
CASE          1 A          2 B          3 C          4 D
  1        4.82410      4.11890      3.33030      2.74770
  2        3.19090      3.08140      3.12650      1.13670
  3        5.54680      3.23630      3.60300      3.64330
  4        5.28750      5.21640      3.84020      3.02880
  5        4.12720      3.71300      4.30430      3.80810
  6        5.41620      5.52330      4.32140      4.15040
  7        4.29090      4.10650      4.33910      4.01240
  8        5.95440      6.20100      4.41110      3.20800

WHICH COMMAND? ANOV1*
WHICH VARIABLES?
*

                *** 1 WAY ANALYSIS OF VARIANCE ***

      SAMPLE                SIZE          MEAN       STD DEV
       1 A                     8       4.82975       .910436
       2 B                     8       4.40710      1.12597
       3 C                     8       3.90004       .507422
       4 D                     8       3.37430      1.03631

                    DEGREES OF      SUM OF       MEAN OF
SOURCE OF VARIANCE    FREEDOM       SQUARES      SQUARES      F TEST
AMONG SAMPLES               3       6.48783      2.16261     3.69020
WITHIN REPLICATIONS        28       23.9968       .857030
TOTAL                      31       33.4847

WHICH COMMAND? PAIRT*
WHICH VARIABLES?
*

                *** STUDENT'S T STATISTICS ***

VARIABLES:
 1 A          0.00000
 2 B         -1.46055      0.00000
 3 C         -3.10151     -1.56137      0.00000
 4 D         -4.34145     -2.52050     -2.13805      0.00000
                1 A          2 B          3 C          4 D

DEGREES OF FREEDOM =    7

WHICH COMMAND? MDIFF*
WHICH 2 VARIABLES: A,B

FOR VARIABLES:    1 A
      AND         2 B

T STATISTIC =        .772142
DEGREES OF FREEDOM =    14


WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: A,C

FOR VARIABLES:    1 A
      AND         3 C

T STATISTIC =       2.33485
DEGREES OF FREEDOM =    14

WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: A,D
FOR VARIABLES:    1 A
      AND         4 D

T STATISTIC =       2.79155
DEGREES OF FREEDOM =    14


WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: B,C

FOR VARIABLES:    2 B
      AND         3 C

T STATISTIC =       1.06519
DEGREES OF FREEDOM =    14

WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: B,D

FOR VARIABLES:    2 B
      AND         4 D

T STATISTIC =       1.78575
DEGREES OF FREEDOM =    14


WHICH COMMAND? MDIFF
WHICH 2 VARIABLES: C,D

FOR VARIABLES:    3 C
      AND         4 D

T STATISTIC =       1.22818
DEGREES OF FREEDOM =    14
```

Figure 12 (cont): Output of ANOVA and Student't Test for $[AUC]_0^{\infty}$

APPENDIX F

Table12 Physiological Characteristics of the Subjects

Subject No.	Age (yr)	Height (cm)	Weight (kg)	Surface area[a] (m^2)
1	19	168	47.6	1.51
2	23	163	53.0	1.55
3	20	170	53.7	1.61
4	19	170	57.5	1.66
5	19	170	58.4	1.67
6	21	168	59.0	1.66
7	20	170	59.6	1.69
8	20	169	60.5	1.70
range	19-23	163-170	47.6-60.5	1.51-1.70
mean	20.1	168.5	56.2	1.63
S.D.	1.4	2.4	4.4	0.07

a. Nomogram for Calculating the Body Surface Area of Adults (54).

APPENDIX F

Table 13 Biochemical Laboratory Results

Test	Expected Range	Units	Results Subject 1	2	3	4	5	6	7	8
Na+	135-147	mmol/L	140	142	139	142	142	140	144	142
K+	3.6-4.6	mmol/L	4.1	4.1	4.5	4.4	4.9	4.9	4.4	4.2
CI^-	101-111	mmol/L	109	102	102	102	104	105	107	106
CO_2	23-31	mmol/L	23	26	27	25	25	23	22	23
A.P.	40-105	U/L	98	39	81	138	95	97	92	147
LDH	140-310	U/L	244	209	243	246	249	290	260	271
SGOT	5-40	U/L	23	20	24	23	18	23	20	39
SGPT	5-35	U/L	16	17	10	15	15	10	7	25
CPK	10-170	U/L	178	122	211	157	233	206	131	136
T.P.	66-84	U/L	75.9	74.2	79.7	73.5	81.8	77.7	82.3	84.9
ALB	42-52	g/L	48.8	43.6	43.5	43.5	46.7	49.9	44.5	50.5
Ca++	8.8-10.0	mg/dl	9.4	8.6	9.6	9.1	9.2	9.5	9.1	9.8
IN.P.	3.3-4.6	mg/dl	4.0	3.8	3.3	4.4	3.8	3.7	4.0	3.0
GLUOX	60-95	mg/dl	79	79	72	72	86	77	80	80
BUN	7-17	mg/dl	9	11	9	10	10	8	9	8
CREA	0.6-1.2	mg/dl	0.8	1.0	0.8	0.9	1.1	1.1	1.1	0.6
U.A.	4.4-8.1	mg/dl	5.2	4.6	5.2	7.3	5.4	5.5	6.2	4.8
CHOLENZ	110-270	mg/dl	101	207	178	152	180	216	162	250
T.BILI	0.2-1.2	mg/dl	0.8	0.6	0.5	0.9	0.8	0.6	1.2	1.4
D.BILI	0.1-0.5	mg/dl	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.3

APPENDIX G

Pharmacokinetic Analysis by Using the PCNONLIN Nonlinear Estimation Program

Previous study (15), it was proposed that the time course of praziquantel in serum for each subject could be well described by a one-compartment open model with first-order absorption, first order elimination and the lagtime. (as shown in Figure 13 and Equation 1)

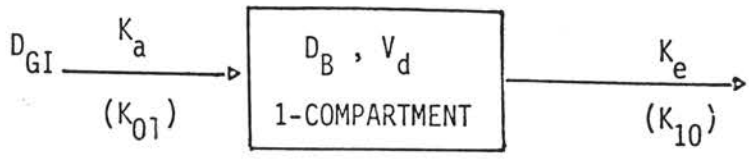


Figure 13 Diagram of one-compartment open model with first-order absorption, first-order elimination and the lag time.

$$C_t = \frac{K_a FD}{V_d(K_a - K_e)} \left[e^{-K_e(t - t_0)} - e^{-K_a(t - t_0)} \right] \quad \text{Eq. 1}$$

Where C_t is the serum concentration at time t, F is the fraction of the dose, D, to be absorbed, V_d is the drug distribution volume in body, K_a and K_e are the first-order rate constants for absorption and elimination respectively, and t_o or T_{lag} is the lag time.

The initial estimates of the parameters (V_d, K_a, K_e, T_{lag}) used with PCNONLIN nonlinear estimation program were obtained by graphic procedure using the method of residuals. (55).

For example, The data set from Table 3 for Brand C in subject No. 1 was chosen. We plotted C_t versus t on a semilogarithmic graph paper and use the method of residuals to determine K_a and K_e(see Figure 14 and Table 14). Values of 11.8 and 5.8 were the intercepts on the y axis after extrapolation of the residual and terminal lines for absorption and elimination, respectively.

The slope of the terminal portion of the curve was calculated as follow :

$$K_e = \frac{\ln 5.8 - \ln 0.02}{8} = \frac{1.76 - (-3.91)}{8} = 0.71 \ hr^{-1}$$

as well as the K_a

$$K_a = \frac{\ln 11.8 - \ln 0.1}{2.5} = \frac{2.47 - (-2.30)}{2.5} = 1.91 \ hr^{-1}$$

The lag time (T_{lag}), that is the time at the point of intersection of the two residual lines on the x axis. Thus, T_{lag} was found to be 0.60 hr.

V_d is calculated with the following Equation 2

$$V_d = \frac{FD}{K_e[AUC]_o^{\infty}} \qquad \text{Eq. 2}$$

Where $[AUC]_o^{\infty}$, calculated directly by the trapezoidal rule(56), would be 3,6665 $\mu g.hr.ml^{-1}$. Since D = 40 mg/Kg and F = 1 (assuming that absorption is complete)

Therefore , $Vd = \frac{1 \times 40}{0.71 \times 3.6665} = 15.36 \quad L/kg$

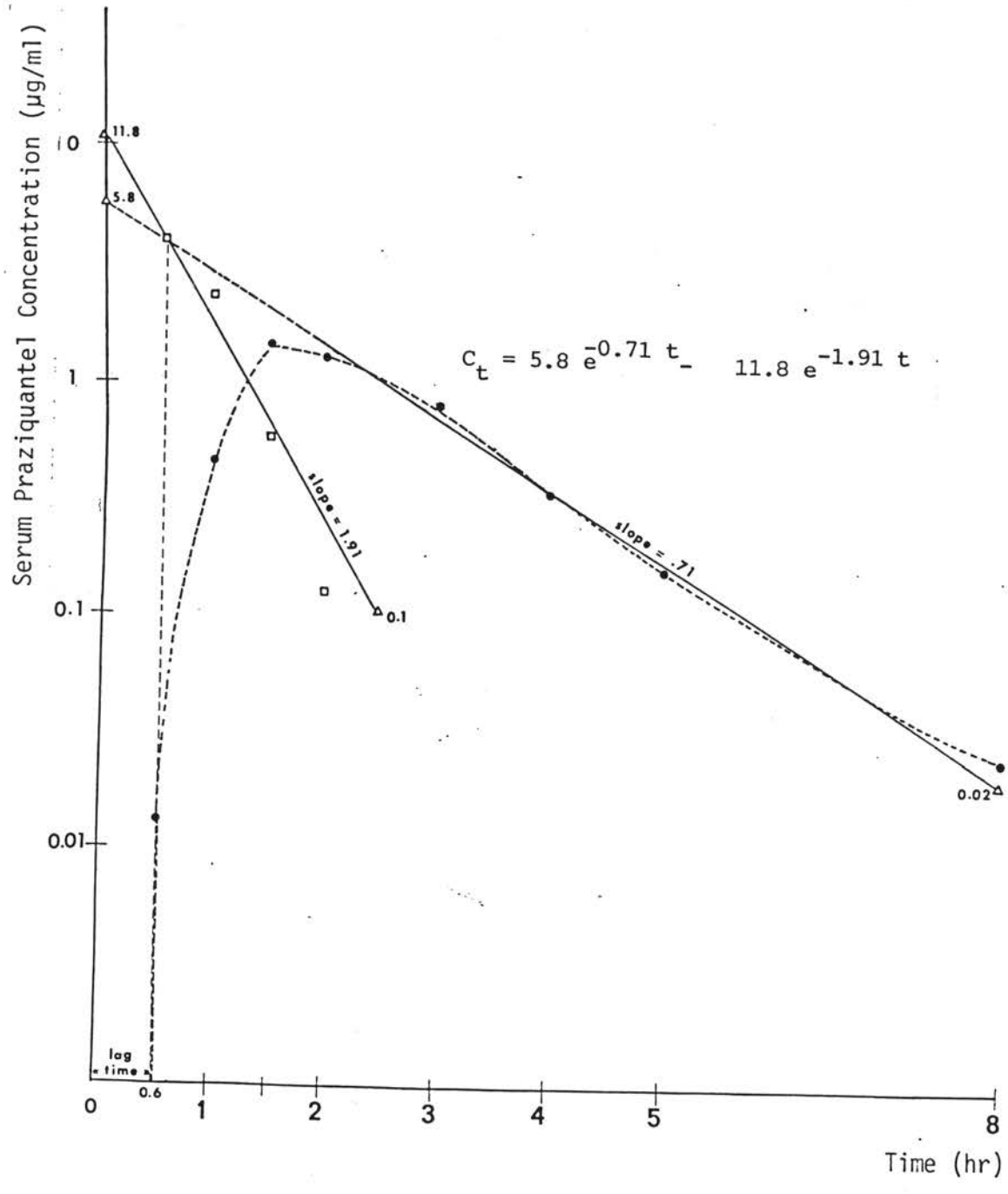


Figure 14 Graphical technique of calculating estimated pharmacokinetic parameters in the serum praziquantel cancentration-time curve by the method of residuals.

Table 14 Stripping Biexponentials from Set of the Serum Praziquantel Concentrations in Subject no.1 Following a Single Oral Dose (40 mg/kg) of Brand C (57)

t(hr)	C_{obs}(μg/ml)	$\hat{C}_t = 5.8e^{-0.71t}$	$R_1 = \hat{C}_t - C_{obs}$	$R_1 = 11.8e^{-1.91t}$	$C_{pred} = \hat{C}_t - R_1$	$\frac{Cpred}{C_{obs}} \times 100$
0	0	5.80	5.80	11.80	-6.00	100.0
0.5	0.133	4.07	3.94	4.54	-0.47	100.0
1.0	0.467	2.85	2.38	1.75	1.10	235.5
1.5	1.417	2.00	0.58	0.66	1.34	94.4
2.0	1.282	1.40	0.12	0.25	1.15	89.8
3.0	0.806	0.69	-	0.04	0.65	80.6
4.0	0.340	0.34	-	0.01	0.33	97.0
5.0	0.162	0.17	-	0	0.17	104.9
8.0	0.026	0.02	-	0	0.02	76.9

Mean = 108.8

SD = 48.4

CV = $\frac{48.4}{108.8} \times 100$

= 44.5 %

The final estimated of the parameters were obtained by repeatedly entering the computed parameter values as initial estimation until the values were stabilized. Results obtained from the computer analysis of the estimated pharmacokinetic parameters were showed in Figure 15,16 and Table 5 .

```
PCNONLIN NONLINEAR ESTIMATION PROGRAM V01-E

****  COPYRIGHT 1984,1985  ****
FOR INFORMATION CONTACT - STATISTICAL CONSULTANTS INC.
                          1-606-252-3890


 LISTING OF INPUT COMMANDS

 model 3,'nlin.lib'
 MODEL 3
 REMARK  ONE COMPARTMENT MODEL - FIRST ORDER INPUT AND OUTPUT
 REMA
 REMA   NO.    PARAMETER      CONSTANT       SECONDARY PARM.
 REMA   ---    ---------      --------       ---------------
 REMA   1       VOLUME          DOSE             AUC
 REMA   2        K01                          K01 HALF LIFE
 REMA   3        K10                          K10 HALF LIFE
 REMA   4                                        TMAX
 REMA   5                                        CMAX
 REMA*****************************************************************
 REMA           I-------------------I
 REMA           I                   I
 REMA   K01 --> I   COMPARTMENT  1   I  ---> K10
 REMA           I                   I
 REMA           I-------------------I
 REMA*****************************************************************
 COMM
 NPARM 3
 NCON 1
 NSEC 5
 PNAMES 'VOLUME', 'K01', 'K10'
 SNAMES 'AUC', 'K01-HL', 'K10-HL', 'TMAX', 'CMAX'
 END
 TEMP
 D=CON(1)
 V=P(1)
 K01=P(2)
 K10=P(3)
 T=X
 END
 FUNC1
 COEF=D*K01/(V*(K01-K10))
 F=COEF*(DEXP(-K10*T)-DEXP(-K01*T))
 END
 SECO
 S(1)=D/V/K10
 S(2)=-DLOG(.5)/K01
 S(3)=-DLOG(.5)/K10
 TMAX=(DLOG(K01/K10)/(K01-K10))
 S(4)=TMAX
```

Figure 15 The output of example 1-fitting data to Model 3 (one compartment model - first order input and output) of the PCNONLIN Library

```
S(5)=(D/V)*DEXP(-K10*TMAX)
END
EOM
cons 40
init 15.36,1.91,0.71
nobs 8
data
begin

PCNONLIN NONLINEAR ESTIMATION PROGRAM

ITERATION WEIGHTED SS     VOLUME      K01         K10
    0      2.61025         15.36      1.910       .7100
    1      2.02922         15.43      1.537       .7185
    2      1.26540         15.49      1.071       .6972
    3      .809050         15.51      .6736       .6410
    4      .790655         15.51      .6087       .5959
    5      .790278         15.51      .6075       .6034

CONVERGENCE ACHIEVED
RELATIVE CHANGE IN WEIGHTED SUM OF SQUARES LESS THAN    .000100
    5      .790274         15.46      .6054       .6055

PCNONLIN NONLINEAR ESTIMATION PROGRAM



***   WARNING   ***
MATRIX OF PARTIAL DERIVATIVES IS NOT OF FULL RANK OR
IS ILL-CONDITIONED.  PARAMETER ESTIMATES AND THEIR
ASSOCIATED STANDARD ERRORS SHOULD BE INTERPRETED
WITH CAUTION.


 PARAMETER  ESTIMATE       STANDARD        95% CONFIDENCE LIMITS
                             ERROR
VOLUME        15.459607  119635.537393 -307513.022361  307543.941575 UNIVARIATE
                                       -498781.198303  498812.117517 PLANAR

K01            .605401    4679.941509  -12029.392869   12030.603671 UNIVARIATE
                                       -19511.483019   19512.693821 PLANAR

K10            .605529    4685.697237  -12044.188096   12045.399155 UNIVARIATE
                                       -19535.480258   19536.691317 PLANAR


PCNONLIN NONLINEAR ESTIMATION PROGRAM


*** CORRELATION MATRIX OF THE ESTIMATES ***

 1.00000
 1.00000   1.00000
-1.00000  -1.00000   1.00000
```

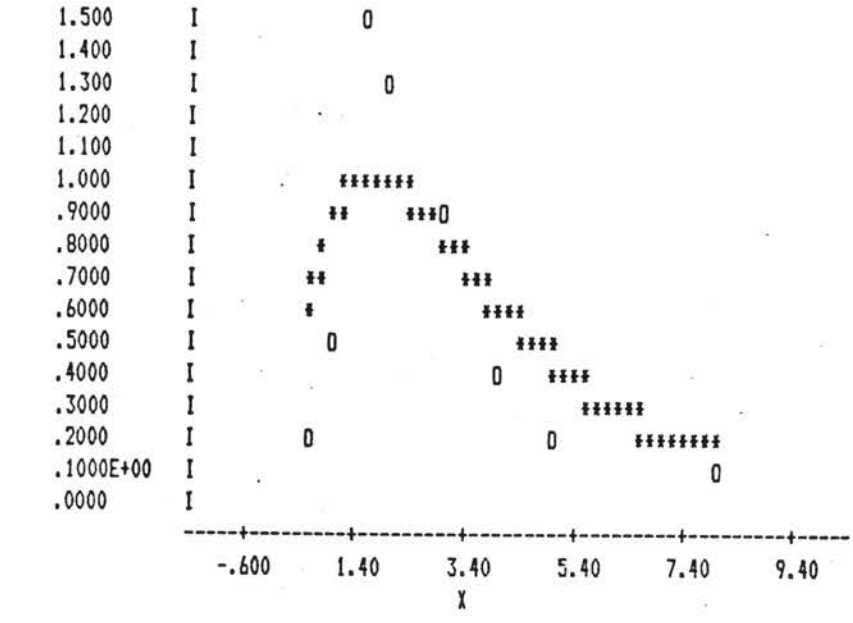
Figure 15 (cont): Output for fitting Model 3

```
*** EIGENVALUES OF (A TRANSPOSE A) MATRIX ***
 NUMBER      EIGENVALUE
    1         5.738
    2         2.390
    3         .1101E-10

PCNONLIN NONLINEAR ESTIMATION PROGRAM


*** SUMMARY OF NONLINEAR ESTIMATION ***


 FUNCTION  1

    X      OBSERVED     CALCULATED   RESIDUAL      WEIGHT    SD-YHAT   STANDARIZED
           Y            Y                                             RESIDUAL
.5000      .1330        .5786       -.4456         1.000     .2575      -1.121
1.000      .4670        .8550       -.3880         1.000     .2451      -.9759
1.500      1.415        .9475        .4675         1.000     .2119       1.176
2.000      1.282        .9333        .3487         1.000     .2257       .8770
3.000      .8060        .7641        .4186E-01     1.000     .2415       .1053
4.000      .3400        .5561       -.2161         1.000     .2242      -.5436
5.000      .1620        .3794       -.2174         1.000     .2527      -.5469
8.000      .2600E-01    .9872E-01   -.7272E-01     1.000     .2820      -.1829

CORRECTED SUM OF SQUARED OBSERVATIONS =  1.99291
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS =  1.99291
SUM OF SQUARED RESIDUALS =          .790274
SUM OF WEIGHTED SQUARED RESIDUALS =  .790274
S =  .397561     WITH     5 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .834


PCNONLIN NONLINEAR ESTIMATION PROGRAM

SUMMARY OF ESTIMATED SECONDARY PARAMETERS


PARAMETER        ESTIMATE        STANDARD
                                   ERROR

AUC              4.272936        2.162470
K01-HL           1.144939     8841.898527
K10-HL           1.144696     8849.020421
TMAX             1.651623        6.959329
CMAX              .951746         .212548

PCNONLIN NONLINEAR ESTIMATION PROGRAM

FUNCTION  1
```

Figure 15 (cont): Output for fitting Model 3

PLOT OF X VS. OBSERVED Y AND CALCULATED Y

*** ARE CALCULATED POINTS, OOO ARE OBSERVED POINTS



PCNONLIN NONLINEAR ESTIMATION PROGRAM

FUNCTION 1
PLOT OF OBSERVED Y VS. CALCULATED Y

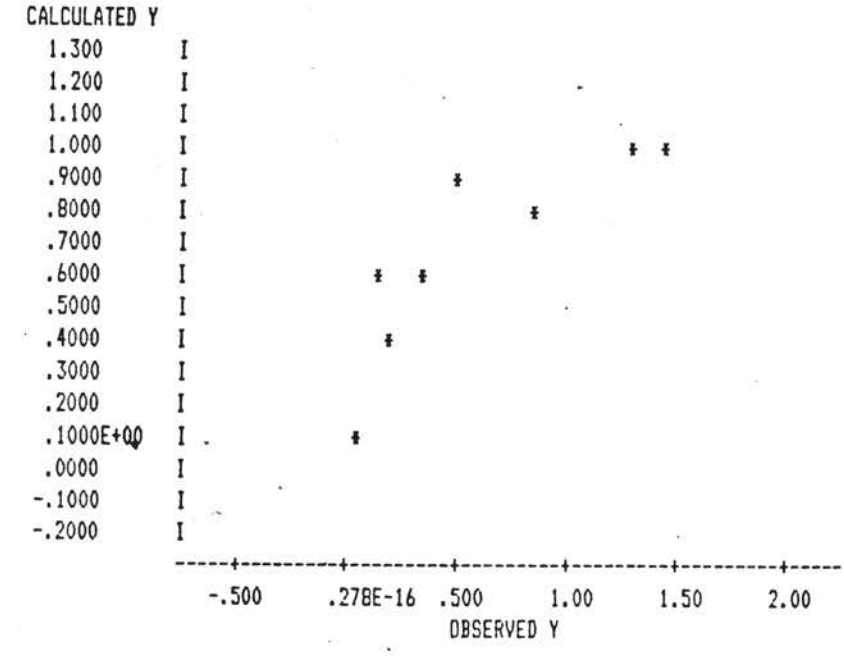
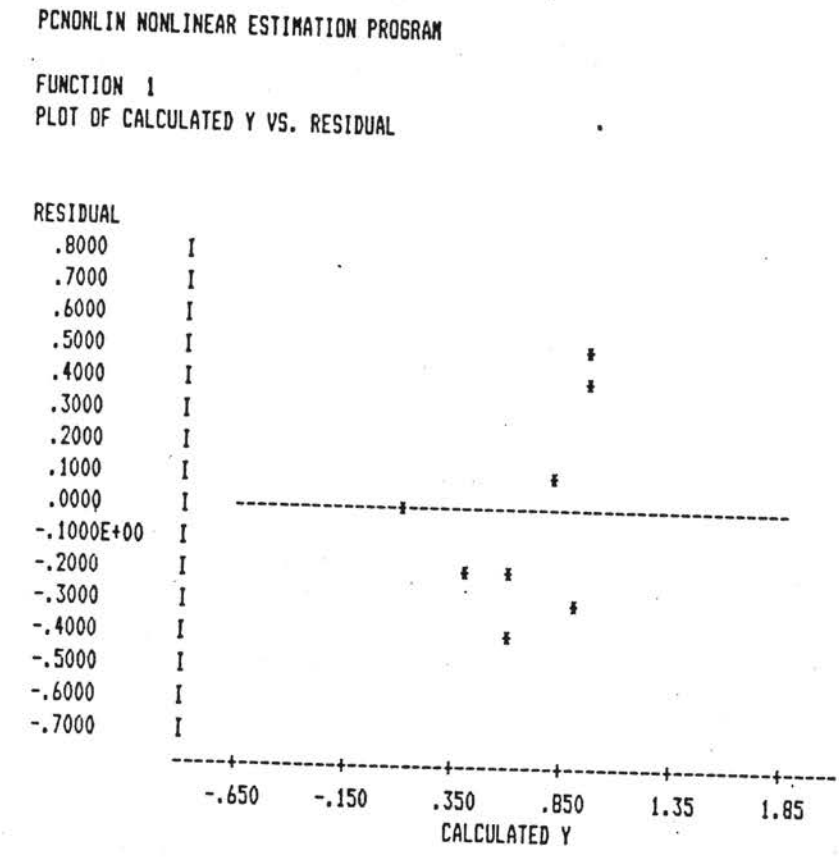


Figure 15 (cont): Output fitting Model 3



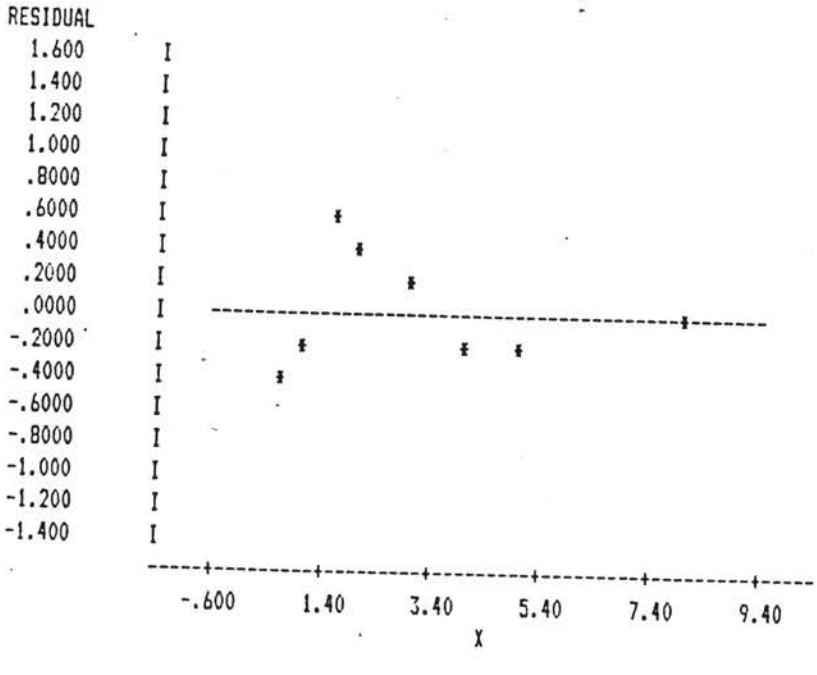


Figure 15 (cont): Output fitting Model 3

```
PCNONLIN NONLINEAR ESTIMATION PROGRAM V01-E

****  COPYRIGHT 1984,1985  ****
FOR INFORMATION CONTACT - STATISTICAL CONSULTANTS INC.
                          1-606-252-3890


LISTING OF INPUT COMMANDS

finish


NORMAL ENDING
```

Figure 15 (cont): Output fitting Model 3

```
PCNONLIN NONLINEAR ESTIMATION PROGRAM V01-E

****  COPYRIGHT 1984,1985  ****
FOR INFORMATION CONTACT - STATISTICAL CONSULTANTS INC.
                          1-606-252-3890


LISTING OF INPUT COMMANDS

MODEL 4,'NLIN.LIB'
MODEL 4
REMARK  ONE COMPARTMENT MODEL - FIRST ORDER INPUT AND OUTPUT
REMARK  INCLUDES A TIME LAG
REMA
REMA   NO.    PARAMETER      CONSTANT       SECONDARY PARM.
REMA   ---    ---------      --------       ---------------
REMA    1      VOLUME          DOSE             AUC
REMA    2        K01                          K01 HALF LIFE
REMA    3        K10                          K10 HALF LIFE
REMA    4       TLAG                             TMAX
REMA    5                                        CMAX
REMA*****************************************************************
REMA            I-------------------I
REMA            I                   I
REMA   K01  --> I   COMPARTMENT  1  I  ---> K10
REMA            I                   I
REMA            I-------------------I
REMA*****************************************************************
COMM
NPARM 4
NCON 1
NSEC 5
PNAMES 'VOLUME', 'K01', 'K10', 'TLAG'
SNAMES 'AUC', 'K01-HL', 'K10-HL', 'TMAX', 'CMAX'
END
TEMP
D=CON(1)
V=P(1)
K01=P(2)
K10=P(3)
TLAG=P(4)
COEF=D*K01/(V*(K01-K10))
T=X-TLAG
END
FUNC1
F=MAX(0,COEF*(DEXP(-K10*T)-DEXP(-K01*T)))
END
SECO
S(1)=D/V/K10
S(2)=-DLOG(.5)/K01
S(3)=-DLOG(.5)/K10
TMAX=(DLOG(K01/K10)/(K01-K10))+ TLAG
```

Figure 16 The output of example 1-fitting data to Model 4 (one compartment model - first order input and output includes a time lag) of the PCNONLIN Library

```
S(4)=TMAX
S(5)= (D/V)*DEXP(-K10*(TMAX-TLAG))
END
EOM
CONS 40
INIT 15.36,1.91,0.71,0.60
NOBS 8
DATA
BEGIN

PCNONLIN NONLINEAR ESTIMATION PROGRAM

ITERATION WEIGHTED SS     VOLUME     K01        K10        TLAG

    0      .551546         15.36      1.910      .7100      .6000

    1      .374827E-01     15.19      1.803      .7959      .8537

    2      .241435E-01     15.36      1.979      .7871      .8962

    3      .238494E-01     15.82      2.110      .7590      .8980

    4      .238418E-01     15.87      2.129      .7572      .8987

CONVERGENCE ACHIEVED
RELATIVE CHANGE IN WEIGHTED SUM OF SQUARES LESS THAN    .000100
    4      .238416E-01     15.89      2.133      .7561      .8988

PCNONLIN NONLINEAR ESTIMATION PROGRAM

PARAMETER  ESTIMATE       STANDARD        95% CONFIDENCE LIMITS
                          ERROR
VOLUME       15.885031     3.373144      6.519808     25.250254 UNIVARIATE
                                         -1.417616     33.187678 PLANAR

K01           2.132952      .853124       -.235669      4.501572 UNIVARIATE
                                         -2.243175      6.509079 PLANAR

K10            .756127      .192685        .221155      1.291100 UNIVARIATE
                                          -.232257      1.744512 PLANAR

TLAG           .898803      .030382        .814450       .983156 UNIVARIATE
                                          .742957      1.054648 PLANAR

PCNONLIN NONLINEAR ESTIMATION PROGRAM

*** CORRELATION MATRIX OF THE ESTIMATES ***

1.00000
 .95382   1.00000
```

Figure 16 (cont): Output for fitting Model 4

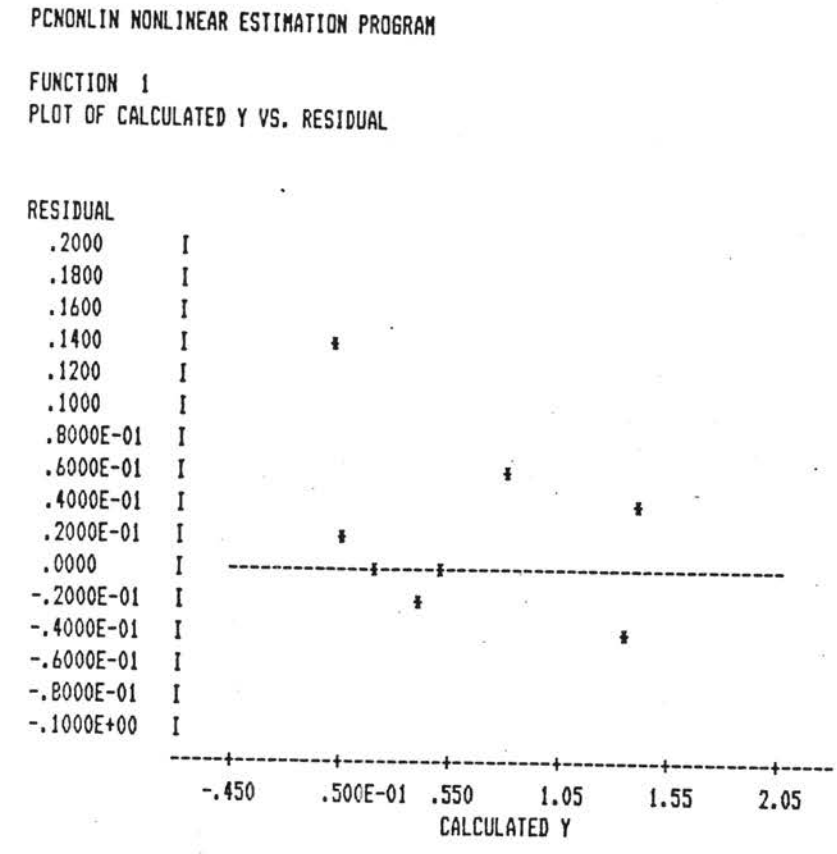
```
 -.97594   -.92431   1.00000
  .59964    .72041   -.55587   1.00000


*** EIGENVALUES OF (A TRANSPOSE A) MATRIX ***
 NUMBER      EIGENVALUE
    1          16.74
    2          3.409
    3          .9566E-01
    4          .4934E-03

PCNONLIN NONLINEAR ESTIMATION PROGRAM


*** SUMMARY OF NONLINEAR ESTIMATION ***


  FUNCTION   1

   X      OBSERVED     CALCULATED   RESIDUAL      WEIGHT   SD-YHAT     STANDARIZED
          Y            Y                                              RESIDUAL
.5000     .1330        .0000        .1330         1.000    .0000       1.723
1.000     .4670        .4700        -.2988E-02    1.000    .7713E-01   -.3870E-01
1.500     1.415        1.394        .2109E-01     1.000    .7356E-01   .2732
2.000     1.282        1.324        -.4205E-01    1.000    .6271E-01   -.5446
3.000     .8060        .7524        .5365E-01     1.000    .5605E-01   .6949
4.000     .3400        .3687        -.2871E-01    1.000    .5170E-01   -.3718
5.000     .1620        .1749        -.1294E-01    1.000    .5004E-01   -.1676
8.000     .2600E-01    .1817E-01    .7835E-02     1.000    .1518E-01   .1015

CORRECTED SUM OF SQUARED OBSERVATIONS =  1.99291
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS =  1.99291
SUM OF SQUARED RESIDUALS =           .238416E-01
SUM OF WEIGHTED SQUARED RESIDUALS =  .238416E-01
S =  .772036E-01 WITH     4 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .995


PCNONLIN NONLINEAR ESTIMATION PROGRAM

SUMMARY OF ESTIMATED SECONDARY PARAMETERS


PARAMETER        ESTIMATE        STANDARD
                                   ERROR

AUC              3.330252        .220904
K01-HL            .324971        .129850
K10-HL            .916707        .233373
TMAX             1.652023        .085626
CMAX             1.424715        .060430
```

Figure 16 (cont): Output for fitting Model 4

```
PCNONLIN NONLINEAR ESTIMATION PROGRAM

FUNCTION  1
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

*** ARE CALCULATED POINTS, OOO ARE OBSERVED POINTS

  1.500       I              O*
  1.400       I             ** *
  1.300       I             *  O**
  1.200       I             *    *
  1.100       I            *      *
  1.000       I                   **
  .9000       I            *      *O
  .8000       I                   **
  .7000       I                  **
  .6000       I            *       **
  .5000       I           O          **
  .4000       I                      O**
  .3000       I            *           ***
  .2000       I          O                 O****
  .1000E+00   I                                ***********O
  .0000       I          ***
              -----+---------+---------+---------+---------+---------+-----
                 -.600      1.40      3.40      5.40      7.40      9.40
                                        X
```

```
PCNONLIN NONLINEAR ESTIMATION PROGRAM

FUNCTION  1
PLOT OF OBSERVED Y VS. CALCULATED Y


CALCULATED Y
  1.500       I
  1.400       I                                        *  *
  1.300       I
  1.200       I
  1.100       I
  1.000       I
  .9000       I
  .8000       I                              *
  .7000       I
  .6000       I
  .5000       I                     *
  .4000       I                  *
  .3000       I
  .2000       I               *
  .1000E+00   I             *
  .0000       I               *
              -----+---------+---------+---------+---------+---------+-----
                 -.500     .278E-16   .500      1.00      1.50      2.00
                                      OBSERVED Y
```

Figure 16 (cont): Output for fitting Model 4



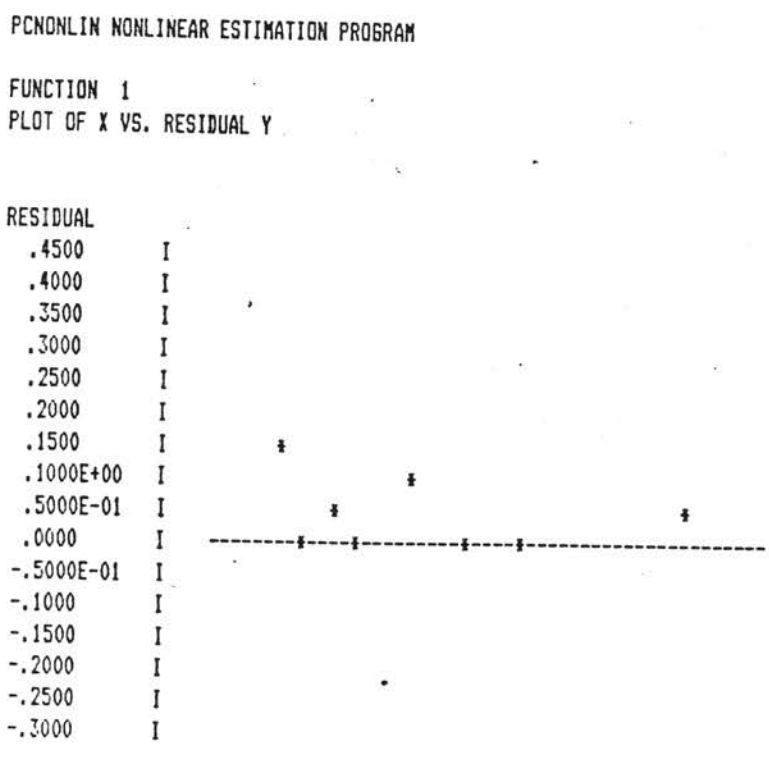


Figure 16 (cont): Output for fitting Model 4

```
-----+---------+---------+---------+---------+---------+-----
   -.600      1.40      3.40      5.40      7.40      9.40
                              X

PCNONLIN NONLINEAR ESTIMATION PROGRAM V01-E

****  COPYRIGHT 1984,1985  ****
FOR INFORMATION CONTACT - STATISTICAL CONSULTANTS INC.
                          1-606-252-3890


 LISTING OF INPUT COMMANDS

 FINISH


 NORMAL ENDING
```

Figure 16 (cont): Output for fitting Model 4

VITA

Name Mr. Suraphol Nathakarnkikool

Birth Date April 1, 1957

Education Bachelor of Science in Pharmacy in 1979 from the Faculty of Pharmacy, Chiangmai University, Chiangmai, Thailand.

Position Pharmacist in Department of Pharmacy, Phayao Hospital, Phayao, Thailand.