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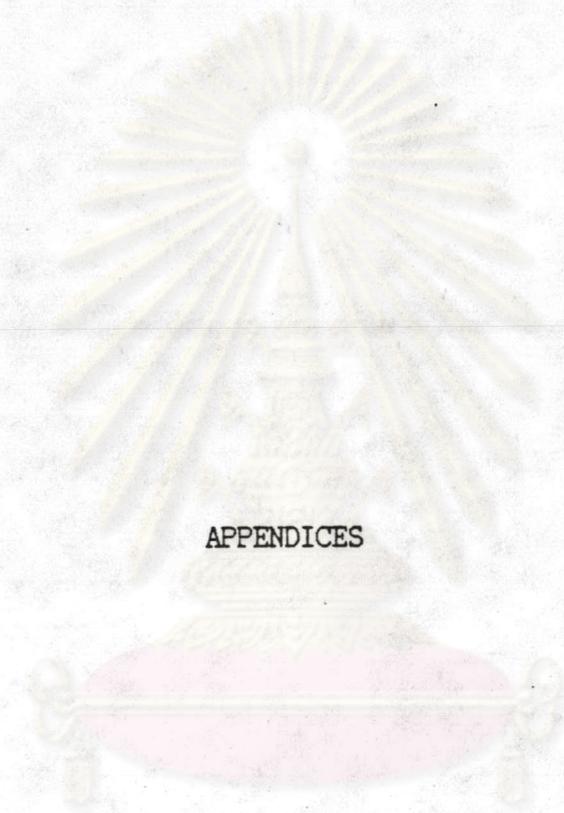
APPENDICES

APPENDIX

A   Test Products

B   Determination of Furosemide Content in Tablets

C   Preparation of Phosphate Buffer pH 5.8

D   Standard Curve Determination

E   One-Way Analysis of Variance, Multiple Comparison, Friedman's Test and Wilcoxon Rank Sum Test Using a Computerized Statistical Program SPSS

F   Average Percent Furosemide Dissolved in Dissolution Medium from 13 Commercial Brands at Various Times

G   Pharmacokinetic Analysis by Using The PCNONLIN Nonlinear Estimation Program

H   Clinical Response from 8 Subjects after Oral Administration of 40 mg of 4 Different Brands of Furosemide Tablets

APPENDIX A

Table 8   Test Products Information

Code	Brand name	Manufacturers	Mfg Date	Batch no.
A	Lasix[R]	Hoechst Thai Ltd.	11-17-86	30 L 6
B	Diusil[R]	Silom Medical Co. Ltd.	27-2-84	840201
C	Furetic[R]	Siam Pharmaceutical Co. Ltd.	11-12-86	20PL172
D	Difu[R]	Seng Thai	10-86	82986
E	Dirine[R]	Atlantic Trading Co. Ltd.	8-9-86	860219
F	Diurine[R]	Thavatchai Pharmaceutical	28-1-86	901
G	Fluidsemide[R]	Nida Pharma	2-87	874015
H	Furetic[R]	Ashford	12-83	T312107
I	Furex[R]	Siegfried	4-10-80	212998995
J	Furozide[R]	ANH	8-12-86	861202
K	Fusesian[R]	Asian Pharmaceutical Ltd. Part	4-85	T5074
L	Impugan[R]	Dumex Ltd.	22-8-84	C417102
M	Nildema[R]	Great Eastern Drug Co. Ltd	28-7-86	60703151

Determination of Furosemide Content in Tablets (29)

Prepare a standard furosemide solution by dissolving about 10 mg of standard furosemide, accurately weighed, in 6.0 ml of 0.1 N sodium hydroxide in a 25 ml volumetric flask, and diluting with water to volume. Dilute 2.0 ml of this solution quantitatively with 0.02 N sodium hydroxide to obtain a standard solution having a known concentration of about 8 µg/ml.

Calculate the quantity, in mg, of $C_{12}H_{11}ClN_2O_5S$ in tablets by the formula 5C (Au/As), in which C is the concentration, in µg/ml, of standard furosemide solution, and Au and As are the absorbances of the solution from tablets and the standard solution, respectively.

APPENDIX C

<u>Preparation of Phosphate Buffer pH 5.8</u>

    1. Preparation of 0.2 M Monobasic Potassium Phosphate

    27.22 g of monobasic potassium phosphate was dissolved in water and made to volume 1,000 ml.

    2. Preparation of 0.2 M Sodium Hydroxide

    8.0 g of sodium hydroxide was dissolved in water and made to volume 1,000 ml.

    3. 250 ml of 0.2 M monobasic potassium phosphate was mixed with 18 ml of 0.2 M sodium hydroxide and sufficient water to make 1,000 ml. The resulting solution was adjusted with 0.2 M sodium hydroxide or 0.2 M hydrochloric acid to a pH of 5.8 $\pm$ 0.05.

APPENDIX D

Standard Curve Determination

      The typical standard curves data for furosemide concentration in phosphate buffer pH 5.8 and in human plasma are presented in Table 10-11 and Figure 7a, and b, respectively.
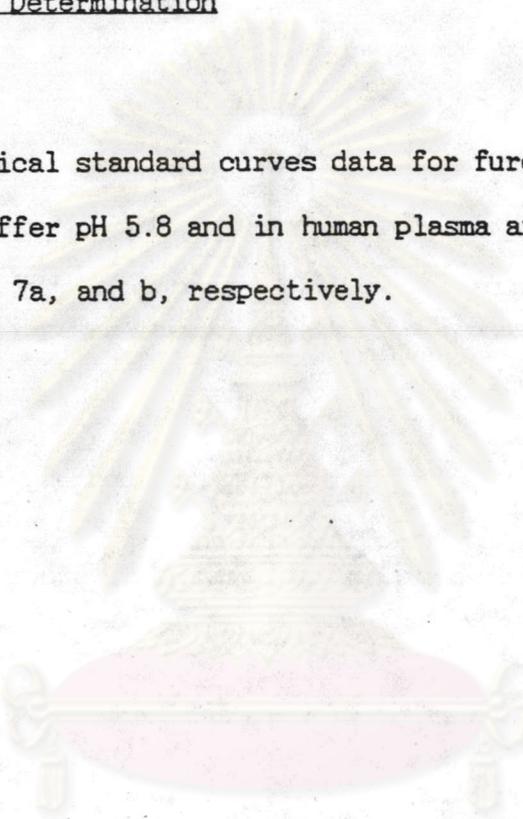
Table 10 Typical Standard Curve Data for Furosemide Concentrations

in Phosphate Buffer pH 5.8 Estimated Using Linear Regression[a]

Standard No.	Conc. (µg/ml)	Absorbance at 271 nm	Inversely estimated[b] concentration(µg/ml)	%Theory[c]
1	4.472	0.243	4.449	99.51
2	6.707	0.369	6.836	101.93
3	7.825	0.419	7.784	99.47
4	8.943	0.481	8.958	100.17
5	10.061	0.538	10.038	99.77
6	11.179	0.598	11.175	99.96
7	13.414	0.712	13.334	99.39
8	15.651	0.830	15.569	99.48
9	17.886	0.959	18.013	100.71
			Mean	99.94
			S.D.	0.83
			C.V.[d]	0.83%

a. $r^2 = 0.999$

b. Inversely estimated concentration $= \dfrac{Absorbance - 8.148 \times 10^{-3}}{5.279 \times 10^{-2}}$

c. %Theory $= \dfrac{Inversely\ estimated\ concentration}{known\ concentration} \times 100$

d. C.V. $= \dfrac{S.D.}{Mean} \times 100$

Table 11   Typical Standard Curve Data for Furosemide Concentrations

in Human Plasma Estimated   Using Linear Regression[a]

Standard No.	Conc. (μg/ml)	Peak Height F^1/IS^2 ratio	Inversely estimated[b] concentration(μg/ml)	%Theory
1	0.207	0.202	0.209	101.12
2	0.311	0.291	0.308	99.01
3	0.518	0.458	0.492	94.99
4	0.622	0.589	0.637	102.42
5	0.829	0.750	0.814	98.25
6	1.036	0.993	1.082	104.48
7	1.554	1.402	1.534	98.69
			Mean	99.99
			S.D.	3.11
			C.V.	3.11 %

a. $r^2 = 0.997$

b. Inversely estimated concentration $= \dfrac{\text{Peak height ratio} - 1.211 \times 10^{-2}}{9.063 \times 10^{-1}}$

1. Furosemide

2. Internal Standard
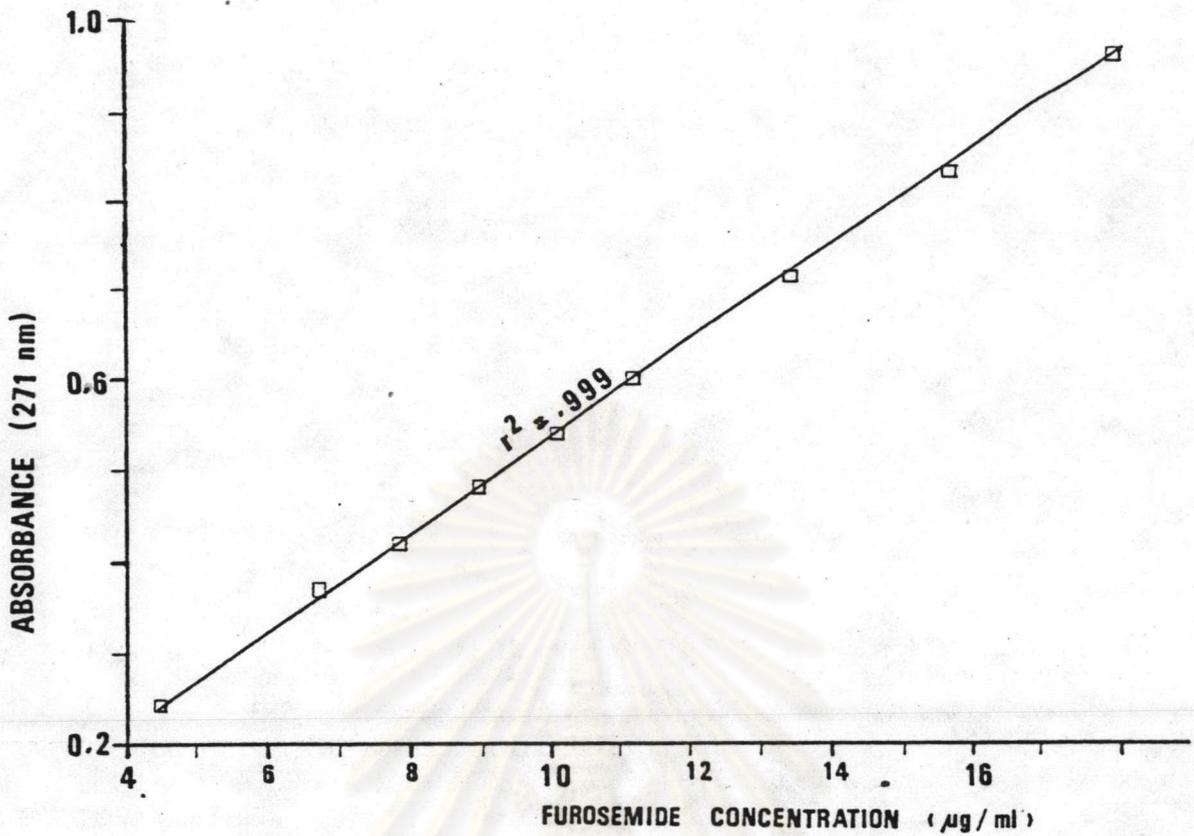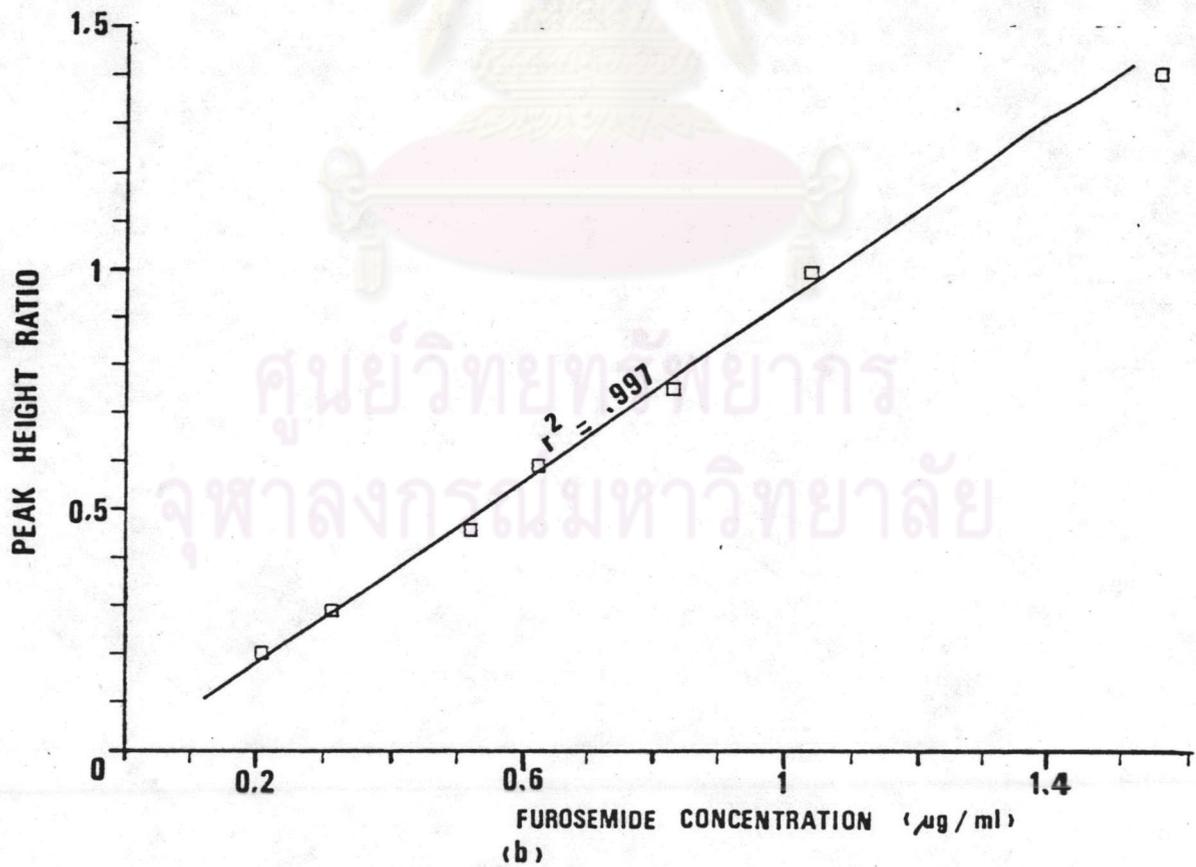
Figure 7 Typical Standard Curve for Furosemide Concentration

(a) in Dissolution Medium ,(b) in Human Plasma

APPENDIX E

The Output from The Statistical Program SPSS

- - - - - - - - - O N E W A Y - - - - - - - - - -

Variable SOV % dissolved at 30 min

By Variable BN

Analysis of Variance

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	12	44202.8015	3683.5668	80.7789	0.0
Within Groups	65	2964.0403	45.6006		
Total	77	47166.8418			

- - - - - - - - - O N E W A Y - - - - - - - - - -

Variable SOV
By Variable BN

Multiple Range Test

Tukey-HSD Procedure
Ranges for the .050 level -

        4.86   4.86   4.86   4.86   4.86   4.86   4.86   4.86   4.86   4.86
        4.86   4.86

The ranges above are table ranges.
The value actually compared with Mean(J)-Mean(I) is..
      4.7750 * Range * Sqrt(1/N(I) + 1/N(J))

(*) Denotes pairs of groups significantly different at the .050 level

- - - - - - - - - O N E W A Y - - - - - - - - - -

Variable SOV
(Continued)

```
                        G G G G G G G G G G G G G
                        r r r r r r r r r r r r r
                        p p p p p p p p p p p p p
                        1       1           1 1
        Mean    Group   2 1 3 3 5 4 2 7 9 0 1 8 6

        7.5018  Grp12
       22.8107  Grp 1   *
       22.8875  Grp 3   *
       40.4833  Grp13   * * *
       43.6235  Grp 5   * * *
       59.8345  Grp 4   * * * * *
       60.3200  Grp 2   * * * * *
       62.1427  Grp 7   * * * * *
       64.1868  Grp 9   * * * * *
       72.8803  Grp10   * * * * *
```

Figure 8   The Output from The Statistical Program SPSS

:Brand A (Grp4), Brand B (Grp11), Brand C (Grp1), Brand D (Grp12),
Brand E (Grp7), Brand F (Grp9), Brand G (Grp10), Brand H (Grp2),
Brand I (Grp8), Brand J (Grp3), Brand K (Grp5), Brand L (Grp6), and
Brand M (Grp13).

```
--------------------------------------------------------------------
Page  10                        SPSS/PC+                    4/5/88
           - - - - - - - - - O N E W A Y - - - - - - - - - -

        Variable  SOV
        (Continued)


                            G G G G G G G G G G G G
                            r r r r r r r r r r r r
                            p p p p p p p p p p p p
                            1 1             1 1
         Mean     Group     2 1 3 3 5 4 2 7 9 0 1 8 6

       74.4673   Grp11     * * * * * * *
       76.5427   Grp 8     * * * * * * * *         ->x
       92.0357   Grp 6     * * * * * * * * * * * * *
--------------------------------------------------------------------
Page  11                        SPSS/PC+                    4/5/88

        Homogeneous Subsets    (Subsets of groups, whose highest and lowest means
                                do not differ by more than the shortest
                                significant range for a subset of that size)


SUBSET  1

Group      Grp12
Mean       7.5018
- - - - - - - - - -

SUBSET  2

Group      Grp 1      Grp 3
Mean       22.8107    22.8875
- - - - - - - - - - - - - -

SUBSET  3

Group      Grp13      Grp 5
Mean       40.4833    43.6235
- - - - - - - - - - - - - -
--------------------------------------------------------------------
Page  12                        SPSS/PC+                    4/5/88
SUBSET  4

Group      Grp 4      Grp 2      Grp 7      Grp 9      Grp10
Mean       59.8345    60.3200    62.1427    64.1868    72.8803
- - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -

SUBSET  5

Group      Grp 7      Grp 9      Grp10      Grp11
Mean       62.1427    64.1868    72.8803    74.4673
- - - - - - - - - - - - - - - - - - - -

SUBSET  6

Group      Grp 9      Grp10      Grp11      Grp 8
Mean       64.1868    72.8803    74.4673    76.5427
- - - - - - - - - - - - - - - - - - - -

SUBSET  7

Group      Grp 6
Mean       92.0357
- - - - - - - - - -
--------------------------------------------------------------------
Page  13                        SPSS/PC+                    4/5/88

This procedure was completed at 16:36:28
```

Figure 8 (cont)The Output from The Statistical Program SPSS for % Dissolved at
          30 min.

```
--------------------------------------------------------------------------------
Page    7                                SPSS/PC+                Tmax    4/7/88

-.- - - - Friedman Two-way ANOVA


    Mean Rank    Variable

        2.38     V1
        2.50     V2
        2.50     V3
        2.63     V4

        Cases         Chi-Square          D.F.     Significance
          8             .1500              3           .9852

--------------------------------------------------------------------------------
Page    8                                SPSS/PC+                        4/7/88

This procedure was completed at 10:22:14

***** WORKSPACE allows for      4414 cases for NPAR TESTS *****

--------------------------------------------------------------------------------
Page    9                                SPSS/PC+                        4/7/88

- - - - - Wilcoxon Matched-pairs Signed-ranks Test

    V1
with V2


    Mean Rank    Cases

        4.25        4   - Ranks (V2 Lt V1)
        4.75        4   + Ranks (V2 Gt V1)
                    0     Ties  (V2 Eq V1)
                    -
                    8     Total

        Z =    -.1400           2-tailed P =   .8886

--------------------------------------------------------------------------------
Page   10                                SPSS/PC+                        4/7/88

- - - - - Wilcoxon Matched-pairs Signed-ranks Test

    V1
with V3


    Mean Rank    Cases

        5.67        3   - Ranks (V3 Lt V1)
        3.80        5   + Ranks (V3 Gt V1)
                    0     Ties  (V3 Eq V1)
                    -
                    8     Total

        Z =    -.1400           2-tailed P =   .8886

--------------------------------------------------------------------------------
```

Figure 8   The Output from The Statistical Program SPSS for Tmax

:Brand A (V1), Brand B (V2), Brand C (V3), and Brand D (V4)

- - - - - Wilcoxon Matched-pairs Signed-ranks Test

```
      V1
with V4


    Mean Rank    Cases

        4.75         4    - Ranks (V4 Lt V1)
        4.25         4    + Ranks (V4 Gt V1)
                     0      Ties  (V4 Eq V1)
                     -
                     8      Total

        Z =    -.1400           2-tailed P =   .8886
```

- - - - - Wilcoxon Matched-pairs Signed-ranks Test

```
      V2
with V3


    Mean Rank    Cases

        3.40         5    - Ranks (V3 Lt V2)
        6.33         3    + Ranks (V3 Gt V2)
                     0      Ties  (V3 Eq V2)
                     -
                     8      Total

        Z =    -.1400           2-tailed P =   .8886
```

- - - - - Wilcoxon Matched-pairs Signed-ranks Test

```
      V2
with V4


    Mean Rank    Cases

        5.00         3    - Ranks (V4 Lt V2)
        4.20         5    + Ranks (V4 Gt V2)
                     0      Ties  (V4 Eq V2)
                     -
                     8      Total

        Z =    -.4201           2-tailed P =   .6744
```

- - - - - Wilcoxon Matched-pairs Signed-ranks Test

```
      V3
with V4


    Mean Rank    Cases

        4.00         4    - Ranks (V4 Lt V3)
        5.00         4    + Ranks (V4 Gt V3)
                     0      Ties  (V4 Eq V3)
                     -
                     8      Total

        Z =    -.2801           2-tailed P =   .7794
```

Figure 8 (cont)The Output from The Statistical Program SPSS for Tmax

---

Page 21   SPSS/PC+   *Cmax* 4/7/88

- - - - - Friedman Two-way ANOVA

    Mean Rank   Variable

        2.00   V1
        2.06   V2
        3.00   V3
        2.94   V4

        Cases   Chi-Square   D.F.   Significance
          8   4.2875   3   .2364

Page 22   SPSS/PC+   4/7/88

This procedure was completed at 10:38:28

***** WORKSPACE allows for   4414 cases for NPAR TESTS *****

Page 23   SPSS/PC+   4/7/88

- - - - - Wilcoxon Matched-pairs Signed-ranks Test

      V1
with V2

    Mean Rank   Cases

        4.50   4   - Ranks (V2 Lt V1)
        4.50   4   + Ranks (V2 Gt V1)
                     0   Ties (V2 Eq V1)
                     -
                     8   Total

        Z =   0.0   2-tailed P = 1.0000

Page 24   SPSS/PC+   4/7/88

- - - - - Wilcoxon Matched-pairs Signed-ranks Test

      V1
with V3

    Mean Rank   Cases

        3.50   2   - Ranks (V3 Lt V1)
        4.83   6   + Ranks (V3 Gt V1)
                     0   Ties (V3 Eq V1)
                     -
                     8   Total

        Z =   -1.5403   2-tailed P = .1235

Page 25   SPSS/PC+   4/7/88

- - - - - Wilcoxon Matched-pairs Signed-ranks Test

      V1
with V4

    Mean Rank   Cases

        4.25   2   - Ranks (V4 Lt V1)
        4.58   6   + Ranks (V4 Gt V1)
                     0   Ties (V4 Eq V1)
                     -
                     8   Total

        Z =   -1.3303   2-tailed P = .1834

Figure 8   The Output from The Statistical Program SPSS for Cmax

Brand A (V1), Brand B (V2), Brand C (V3), and Brand D (V4)

- - - - - Wilcoxon Matched-pairs Signed-ranks Test

V2
with V3

    Mean Rank   Cases

        2.50   2   - Ranks (V3 Lt V2)
        5.17   6   + Ranks (V3 Gt V2)
                      0   Ties (V3 Eq V2)
                      -
                      8   Total

        Z =   -1.8204   2-tailed P = .0687

- - - - - Wilcoxon Matched-pairs Signed-ranks Test

V2
with V4

    Mean Rank   Cases

        4.50   2   - Ranks (V4 Lt V2)
        3.80   5   + Ranks (V4 Gt V2)
                      1   Ties (V4 Eq V2)
                      -
                      8   Total

        Z =   -.8452   2-tailed P = .3980

- - - - - Wilcoxon Matched-pairs Signed-ranks Test

V3
with V4

    Mean Rank   Cases

        4.75   4   - Ranks (V4 Lt V3)
        4.25   4   + Ranks (V4 Gt V3)
                      0   Ties (V4 Eq V3)
                      -
                      8   Total

        Z =   -.1400   2-tailed P = .8886

This procedure was completed at 10:38:36

Figure 8 (cont)The Output from The Statistical Program SPSS for Cmax

```
---------------------------------------------------------------------------
Page  35                         SPSS/PC+                      AUC  4/5/88
- - - - - Friedman Two-way ANOVA


    Mean Rank    Variable

        2.38     V1
        1.75     V2
        3.13     V3
        2.75     V4

        Cases         Chi-Square        D.F.      Significance
          8             4.9500            3           .1755

---------------------------------------------------------------------------
Page  36                         SPSS/PC+                           4/5/88

This procedure was completed at 15:50:33

   ***** WORKSPACE allows for    4414 cases for NPAR TESTS *****

---------------------------------------------------------------------------
Page  37                         SPSS/PC+                      AUC  4/5/88
- - - - - Wilcoxon Matched-pairs Signed-ranks Test

       V1
with V2


    Mean Rank    Cases

        5.40        5   - Ranks (V2 Lt V1)
        3.00        3   + Ranks (V2 Gt V1)
                    0   Ties  (V2 Eq V1)
                    -
                    8   Total

        Z =   -1.2603          2-tailed P =   .2076

---------------------------------------------------------------------------
Page  38                         SPSS/PC+                           4/5/88
- - - - - Wilcoxon Matched-pairs Signed-ranks Test

       V1
with V3


    Mean Rank    Cases

        2.67        3   - Ranks (V3 Lt V1)
        5.60        5   + Ranks (V3 Gt V1)
                    0   Ties  (V3 Eq V1)
                    -
                    8   Total

        Z =   -1.4003          2-tailed P =   .1614

---------------------------------------------------------------------------
Page  39                         SPSS/PC+                           4/5/88
- - - - - Wilcoxon Matched-pairs Signed-ranks Test

       V1
with V4


    Mean Rank    Cases

        6.00        3   - Ranks (V4 Lt V1)
        3.60        5   + Ranks (V4 Gt V1)
                    0   Ties  (V4 Eq V1)
                    -
                    8   Total

        Z =    0.0            2-tailed P = 1.0000

---------------------------------------------------------------------------
```

Figure 8   The Output from The Statistical Program SPSS for AUC

Brand A (V1), Brand B (V2), Brand C (V3), and Brand D (V4)

- - - - - Wilcoxon Matched-pairs Signed-ranks Test

      V2
with V3

    Mean Rank   Cases

       3.00   1 - Ranks (V3 Lt V2)
       4.71   7 + Ranks (V3 Gt V2)
                     0   Ties (V3 Eq V2)
                     -
                     8   Total

        Z = -2.1004   2-tailed P = .0357

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- - - - - Wilcoxon Matched-pairs Signed-ranks Test

      V2
with V4

    Mean Rank   Cases

       3.00   2 - Ranks (V4 Lt V2)
       5.00   6 + Ranks (V4 Gt V2)
                     0   Ties (V4 Eq V2)
                     -
                     8   Total

        Z = -1.6803   2-tailed P = .0929

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- - - - - Wilcoxon Matched-pairs Signed-ranks Test

      V3
with V4

    Mean Rank   Cases

       5.00   5 - Ranks (V4 Lt V3)
       3.67   3 + Ranks (V4 Gt V3)
                     0   Ties (V4 Eq V3)
                     -
                     8   Total

        Z = -.9802   2-tailed P = .3270

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This procedure was completed at 15:50:40
The raw data or transformation pass is proceeding
   8 cases are written to the uncompressed active file.

Figure 8 (cont)The Output from The Statistical Program SPSS for AUC

Table 12 Average Percent Furosemide Dissolved in Dissolution Medium
from 13 Commercial Brands at Various Times

Brand / Time(hr)	Percent Drug Dissolved												
	A	B	C	D	E	F	G	H	I	J	K	L	M
2	3.69	1.20	0.00	0.00	1.04	0.00	0.20	0.27	2.67	1.92	0.39	2.66	0.00
5	17.50	*	1.54	*	15.71	10.70	16.03	6.52	46.60	10.01	6.57	39.02	3.48
10	34.56	62.12	6.66	*	37.59	33.97	49.65	25.28	*	21.28	16.86	*	14.08
15	44.84	*	10.27	4.42	47.77	47.82	59.96	38.34	64.94	23.18	23.41	85.95	21.98
20	51.89	*	13.84	*	54.20	55.43	67.74	47.69	72.35	25.14	34.62	89.89	29.20
30	59.83	74.47	19.69	7.50	62.14	64.19	72.88	60.32	76.54	27.25	43.62	92.04	40.48
50	70.41	78.26	29.58	11.02	69.98	69.66	80.41	71.96	80.20	30.56	55.56	*	62.46
70	75.59	80.30	37.67	*	74.18	72.48	83.20	79.07	85.69	32.82	62.00	92.63	79.05
90	78.87	81.99	42.97	16.48	78.50	74.36	84.74	82.92	90.64	34.74	65.36	94.27	86.50
120	81.68	82.19	49.68	19.81	80.93	75.92	86.87	85.94	90.34	37.84	71.26	94.47	92.26
150	83.65	83.11	55.53	22.85	82.09	77.51	86.08	88.78	89.39	40.05	75.51	94.33	93.17
180	85.34	83.44	60.23	25.03	82.55	77.68	85.92	90.68	89.77	42.59	79.04	94.18	94.35
210	85.34	84.19	*	27.27	83.12	78.86	85.03	90.17	90.24	44.10	80.82	*	93.53
240	86.11	86.41	66.70	28.20	84.07	78.90	84.58	89.67	87.32	45.65	81.23	*	92.92
270	86.35	87.38	68.86	29.95	83.83	80.40	84.95	89.43	*	46.79	81.69	*	92.40

*. missing data

Pharmacokinetic Analysis by Using The PCNONLIN Nonlinear Estimation Program

From the plasma data of each subject, the time course of furosemide in plasma could be well described by a one-compartment open model with first-order absorption, first order elimination and the lag time. (Figure 9 and Equation 1)

$$D_{GI} \xrightarrow[\ (K_{01})\ ]{Ka} \boxed{\begin{array}{c} D_B \quad , \quad Vd \\ \text{1-compartment} \end{array}} \xrightarrow[\ (K_{10})\ ]{Ke}$$
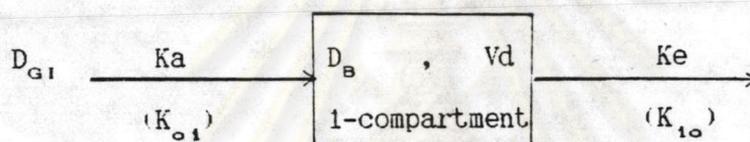
Figure 9 Diagram of One-Compartment Open Model with First-Order Absorption, First-Order Elimination and The Lag Time.

$$C_t = \frac{K_a FD}{Vd(Ka-Ke)} [e^{-Ke(t-to)} - e^{-Ka(t-to)}] \quad \text{Eq. 1}$$

Where C_t is the serum concentration at time t, F is the fraction of the dose, D, to be absorbed, Vd is the drug distribution volume in body, Ka and Ke are the first-order rate constants for absorption and elimination, respectively and to is the lag time.

The inital estimates of the parameters (Vd, Ka, Ke, t_o) used with PCNONLIN program were obtained by graphic procedure using the method of residuals (36).

69

For example, the data set from Table 3 for brand D in subject no 2 was chosen. Plot C_t versus t on a semilogarithmic scale and use the method of residuals to determine Ka and Ke (Figure 10, Table 13). Values of 6.3 and 3.56 were y-intercepts 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 :

$$Ke = \frac{\ln 3.56 - \ln 0.24}{3} = 0.9 \text{ hr.}^{-1}$$

as well as the Ka

$$Ka = \frac{\ln 6.3 - \ln 0.33}{1} = 2.94 \text{ hr.}^{-1}$$

The lag time, ie., the time at the point of intersection of the two residual lines on the X-axis. Thus, to was found to be 0.3 hr.

Vd is calculated by Equation 2

$$Vd = \frac{FD}{Ke \ [AUC]_0^\infty} \qquad \text{Eq. 2}$$

Where $[AUC]_0^\infty$, calculated by the trapezoidal rule (37), was 2.177 hr.μg/ml. Since D = 40 mg and F = 1 (assuming that absorption is complete)

$$\text{Therefore, } Vd = \frac{1 \times 40}{0.9 \times 2.117} = 20.9 \text{ Lit}$$

Table 13   Stripping Biexponentials from Plasma Data of Subject no. 2

Following a Single Oral Dose of Brand D (38)

Time (hr)	Cobs (µg/ml)	Ct [a]	R_1 [b]	$\widehat{R}_1$ [c]	Cestimate [d]	$\dfrac{Cest}{Cobs} \times 100$
0	0.00	3.56	3.56	6.3	-2.74	–
0.5	0.76	2.27	1.51	1.45	0.82	107.9
1.0	1.13	1.45	0.32	0.33	1.12	99.1
1.5	0.92	0.92	0.00	0.08	0.84	91.3
2.0	0.59	0.59	0.00	0.02	0.57	96.6
2.5	0.38	0.38	0.00	0.004	0.38	98.9
3.0	0.24	0.24	0.00	0.0009	0.24	100.0

Mean = 98.97

SD = 7.003

CV = 7.08%

a. $Ct = 3.5\,e^{-0.9t}$

b. $R_1 = Ct - Cobs$

c. $\widehat{R}1 = 6.3\,e^{-2.94t}$

d. $Cestimate = 3.56\,e^{-0.9t} - 6.3\,e^{-2.94t}$
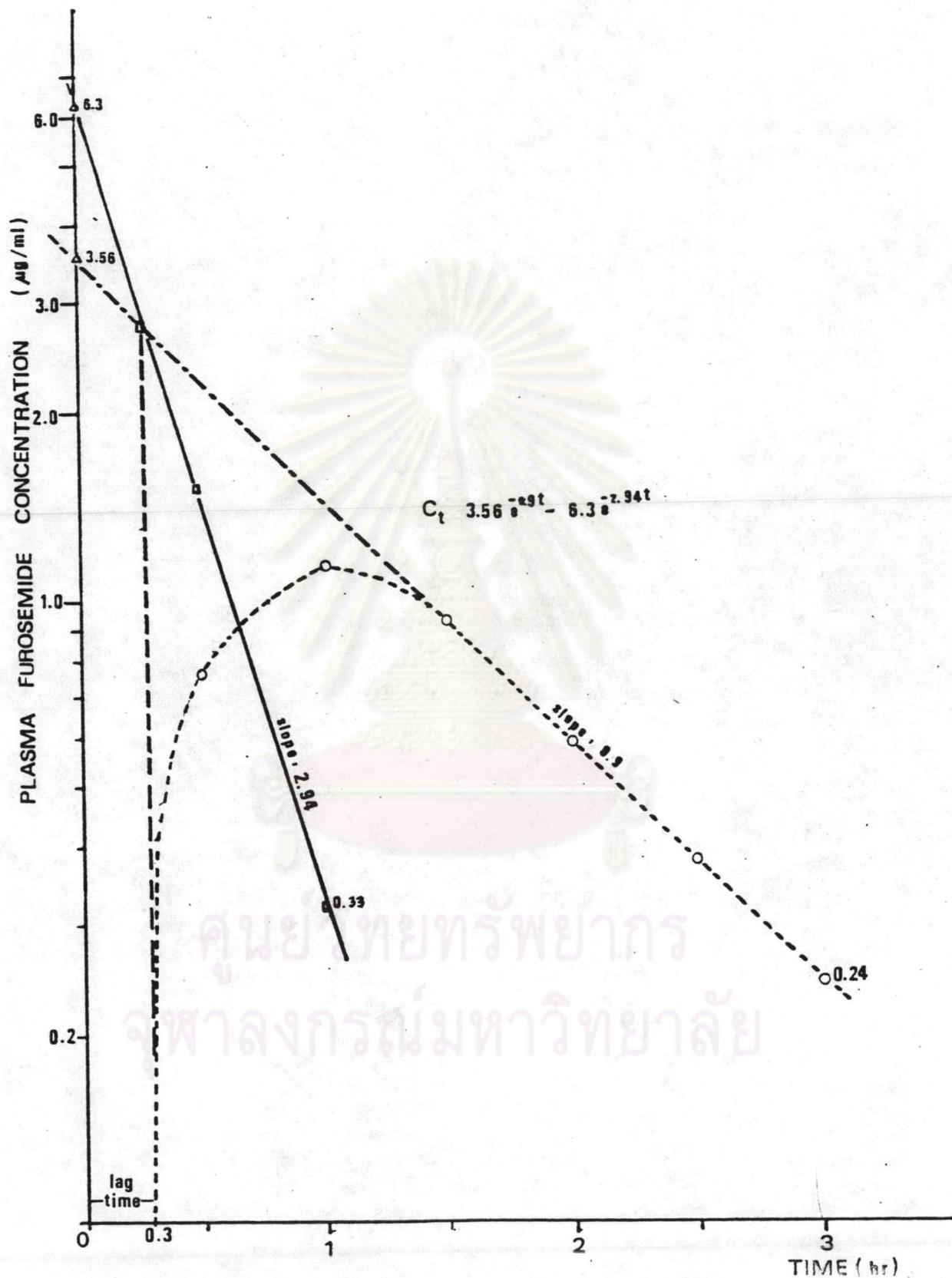
Figure 10 Graphical Technique of Calculating Estimated Parameters in

Plasma Data by The Method of Residual

The final estimation of 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 shown in Figure 11 and Table 4.
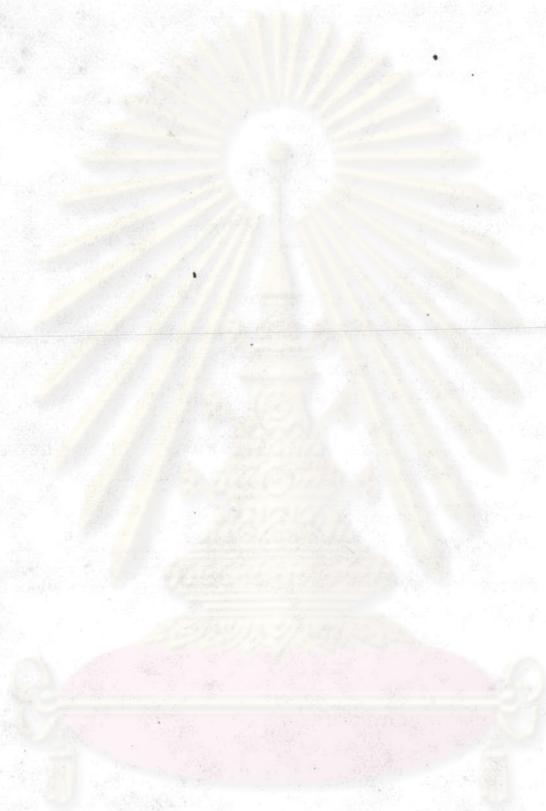
PCNONLIN NONLINEAR ESTIMATION PROGRAM V01-3

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                          1-606-252-3890

LISTING OF INPUT COMMANDS

```
MODEL 4,'NLIN2.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
FNAMES '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
S(4)=TMAX
S(5)= (D/V)*DEXP(-K10*(TMAX-TLAG))
END
EOM
CONS 40
INIT 18, 2.25, .39, .27
NOBS 7
DATA
BEGI
```

Figure 11 The Output of Fitting Data to Model 4 (one-compartment model
-first order input and output, including a lag time) of
The PCNONLIN Library

PCNONLIN NONLINEAR ESTIMATION PROGRAM

ITERATION	WEIGHTED SS	VOLUME	K01	K10	TLAG
0	.467703E-01	18.00	2.250	.3900	.2700
1	.102773E-02	17.66	2.141	1.052	.2775
2	.699205E-03	16.86	2.020	1.113	.2749
3	.691465E-03	16.86	2.024	1.121	.2752

CONVERGENCE ACHIEVED
RELATIVE CHANGE IN WEIGHTED SUM OF SQUARES LESS THAN .000100

3	.691464E-03	16.86	2.023	1.121	.2752

PCNONLIN NONLINEAR ESTIMATION PROGRAM

PARAMETER	ESTIMATE	STANDARD ERROR	95% CONFIDENCE LIMITS		
VOLUME	16.855015	2.429064	9.122137	24.587392	UNIVARIATE
			2.111179	31.598851	PLANAR
K01	2.023463	.449273	.593213	3.453714	UNIVARIATE
			-.703514	4.750441	PLANAR
K10	1.121292	.175906	.561210	1.681194	UNIVARIATE
			.053497	2.188707	PLANAR
TLAG	.275214	.020440	.210144	.340284	UNIVARIATE
			.151149	.399279	PLANAR

PCNONLIN NONLINEAR ESTIMATION PROGRAM

CORRELATION MATRIX OF THE ESTIMATES

```
1.00000
 .93925  1.00000
-.99715  -.93750  1.00000
 .83834   .53507  -.81977  1.00000
```

EIGENVALUES OF (A TRANSPOSE A) MATRIX

NUMBER	EIGENVALUE
1	5.993
2	1.377
3	.5389E-01
4	.3761E-04

PCNONLIN NONLINEAR ESTIMATION PROGRAM

SUMMARY OF NONLINEAR ESTIMATION

FUNCTION 1

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZED RESIDUAL
.0000	.0000	.0000	.0000	1.000	.0000	.0000
.5000	.7600	.7594	.6477E-03	1.000	.1518E-01	.4268E-01
1.000	1.128	1.134	-.5504E-02	1.000	.1482E-01	-.3625
1.500	.9130	.9016	.1640E-01	1.000	.1131E-01	1.080
2.000	.5390	.6072	-.1823E-01	1.000	.1006E-01	-1.201
2.500	.3810	.3803	.7062E-03	1.000	.9353E-02	.4852E-01
3.000	.2370	.2293	.7670E-02	1.000	.1199E-01	.5052

CORRECTED SUM OF SQUARED OBSERVATIONS = .940363
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = .940363
SUM OF SQUARED RESIDUALS =   .691464E-03
SUM OF WEIGHTED SQUARED RESIDUALS = .691464E-03
S = .151818E-01 WITH   3 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = 1.00

Figure 11 (cont) The Output of Fitting Data to Model 4

PCNONLIN NONLINEAR ESTIMATION PROGRAM

SUMMARY OF ESTIMATED SECONDARY PARAMETERS

PARAMETER	ESTIMATE	STANDARD ERROR
AUC	2.116640	.036146
K01-HL	.342555	.075982
K10-HL	.618218	.096895
TMAX	.929580	.017248
CMAX	1.139460	.016730

PCNONLIN NONLINEAR ESTIMATION PROGRAM

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

**: ARE CALCULATED POINTS, OOO ARE OBSERVED POINTS
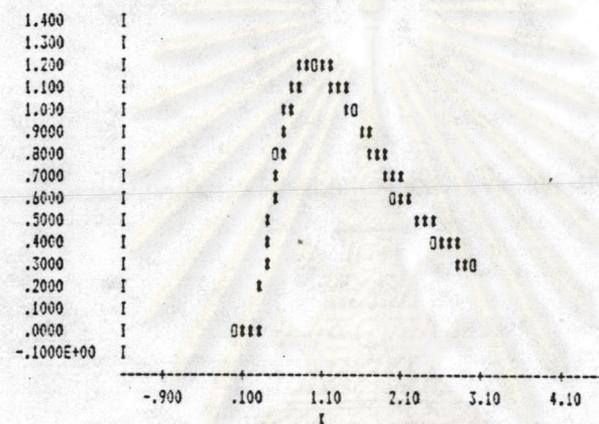
PCNONLIN NONLINEAR ESTIMATION PROGRAM

FUNCTION 1
PLOT OF OBSERVED Y VS. CALCULATED Y
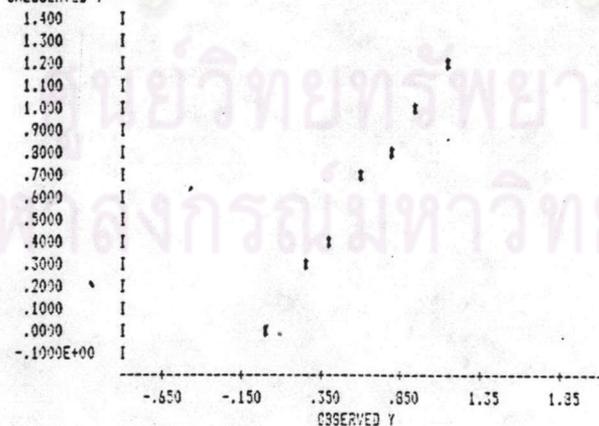

Figure 11 (cont) The Output of Fitting Data to Model 4

```
PCNONLIN NONLINEAR ESTIMATION PROGRAM

FUNCTION 1
PLOT OF CALCULATED Y VS. RESIDUAL


RESIDUAL
 .4000E-01   I
 .3500E-01   I
 .3000E-01   I
 .2500E-01   I
 .2000E-01   I                                        t
 .1500E-01   I
 .1000E-01   I                        t
 .5000E-02   I                    t        t
 .0000       I    ------------t------------------------------
-.5000E-02   I                                    t
-.1000E-01   I
-.1500E-01   I                            t
-.2000E-01   I
-.2500E-01   I
-.3000E-01   I
-.3500E-01   I
             ----+--------+--------+--------+--------+--------+--
              -.550   -.500E-01  .450     .950    1.45    1.95
                              CALCULATED Y
```
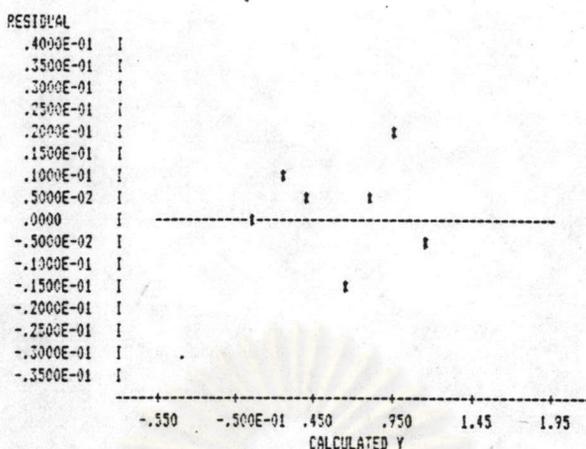
```
PCNONLIN NONLINEAR ESTIMATION PROGRAM

FUNCTION 1
PLOT OF X VS. RESIDUAL Y


RESIDUAL
 .8000E-01   I
 .7000E-01   I
 .6000E-01   I
 .5000E-01   I
 .4000E-01   I
 .3000E-01   I
 .2000E-01   I                    t
 .1000E-01   I          t               t    t
 .0000       I    --------t--------t---------------
-.1000E-01   I                        t
-.2000E-01   I
-.3000E-01   I
-.4000E-01   I
-.5000E-01   I
-.6000E-01   I
-.7000E-01   I
             ----+--------+--------+--------+--------+--------+--
              -.900    .100    1.10    2.10    3.10    4.10
                                 t
```
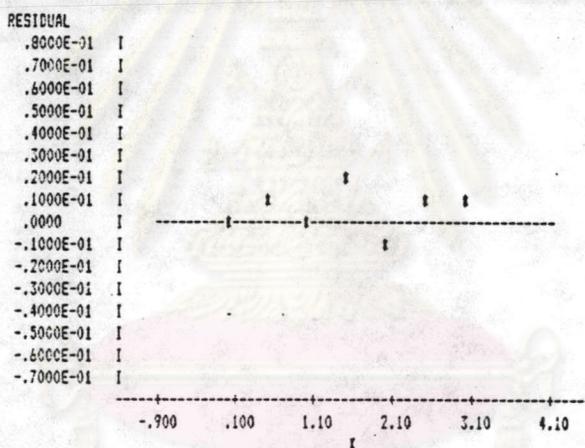
```
PCNONLIN NONLINEAR ESTIMATION PROGRAM V01-3

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                    1-606-252-3390



LISTING OF INPUT COMMANDS

FINI


NORMAL ENDING
```

Figure 11 (cont) The Output of Fitting Data to Model 4

Clinical Response from 8 Subjects after Oral Administration of 40 mg of 4 Different Brands of Furosemide Tablets

Table **14** Urine Output from 8 Subjects Following Oral Administration of 4 Different Brands of Furosemide Tablets

Brand	Time(hr)	1	2	3	4	5	6	7	8	Mean	SD
					Subject no.						
A	0.50	1.13[a]	6.08	6.92	10.67	16.42	4.92	3.92	7.00	7.13[a]	4.65
	1.50	1.97	10.17	11.67	10.13	11.25	7.58	10.55	16.12	9.93	4.01
	2.50	6.08	4.25	3.67	5.67	3.75	5.58	2.83	3.92	4.47	1.16
	3.50	5.58	0.98	3.67	9.45	4.00	4.17	5.67	1.92	4.43	2.59
	4.50	2.13	0.92	2.58	6.00	4.42	2.17	1.57	3.50	2.91	1.66
	5.50	2.28	0.50	6.33	2.50	4.33	0.83	1.08	1.63	2.44	1.99
	Total	1151.00[b]	1374.00	2090.00	2665.00	2650.00	1515.00	1537.00	2045.00	1878.38[b]	575.55
B	0.50	0.83	9.70	8.00	10.33	9.03	10.20	2.93	8.17	7.40	3.55
	1.50	6.67	10.83	7.92	12.17	7.08	8.08	14.08	9.18	9.50	2.63
	2.50	6.92	6.43	12.33	6.42	7.33	5.42	6.92	2.50	6.78	2.72
	3.50	1.92	7.25	10.67	0.42	7.17	0.93	7.83	2.00	4.77	3.88
	4.50	0.58	3.25	7.08	8.00	4.00	0.60	12.75	3.17	4.93	4.13
	5.50	0.75	3.83	6.25	4.83	2.42	0.40	5.83	2.58	3.36	2.20
	Total	1060.00	2478.00	3135.00	2530.00	2222.00	1538.00	3021.00	1656.00	2205.00	733.73
C	0.50	2.75	4.42	13.08	2.58	11.58	6.17	13.92	7.15	7.71	4.58
	1.50	13.75	5.08	8.38	4.08	15.25	8.95	13.67	12.33	10.19	4.19
	2.50	6.58	10.25	8.47	2.42	9.57	12.42	6.83	10.42	8.37	3.08
	3.50	2.42	7.00	1.48	1.08	3.17	4.50	3.50	1.58	3.09	1.96
	4.50	4.25	2.67	5.25	0.48	7.75	1.07	4.92	0.42	3.35	2.64
	5.50	1.50	0.88	2.53	3.83	2.42	0.42	3.58	0.80	2.00	1.30
	Total	1875.00	1818.00	2352.00	869.00	2984.00	2011.00	2785.00	1962.00	2082.00	652.91
D	0.50	0.87	4.58	7.17	6.75	7.42	2.78	8.00	4.33	5.24	2.53
	1.50	1.63	5.00	9.47	7.50	7.17	15.50	15.17	13.42	9.36	5.00
	2.50	10.00	5.25	9.33	12.50	7.42	11.83	6.25	7.17	8.72	2.63
	3.50	5.17	2.08	2.50	10.33	4.75	3.50	1.75	3.17	4.16	2.77
	4.50	2.17	0.90	3.00	4.42	4.83	1.08	1.58	0.95	2.37	1.57
	5.50	1.20	0.85	5.42	1.42	4.25	0.57	1.25	0.48	1.93	1.85
	Total	1262.00	1120.00	2213.00	2575.00	2150.00	2116.00	2040.00	1771.00	1905.88	494.85

a. Urine output in ml/min
b. Urine output in 6 hr.(ml)

Table **15** Sodium Excretion from 8 Subjects after Oral Administration of
4 Different Brands of Furosemide Tablets

Brand	Time(hr)	Subject no. 1	2	3	4	5	6	7	8	Mean	SD
	0.50	0.220^{a}	0.377	0.526	0.224	1.034	0.413	0.282	0.476	0.444^{a}	0.479
	1.50	0.315	0.946	0.761	0.284	0.923	0.766	0.971	1.628	0.824	0.914
	2.50	0.670	0.417	0.422	0.295	0.364	0.603	0.448	0.473	0.462	0.469
A	3.50	0.720	0.117	0.359	0.955	0.376	0.583	0.159	0.192	0.433	0.478
	4.50	0.107	0.145	0.183	0.462	0.230	0.193	0.058	0.263	0.205	0.213
	5.50	0.094	0.064	0.120	0.138	0.032	0.080	0.078	0.031	0.080	0.080
	Total	127.560^{b}	123.960	142.260	141.480	177.540	158.580	119.760	183.780	146.865^{b}	24.270
	0.50	0.165	0.834	0.552	0.734	0.253	1.102	0.085	0.449	0.522	0.354
	1.50	0.713	1.235	0.459	1.205	0.318	0.905	0.709	0.514	0.757	0.337
	2.50	0.816	0.759	0.666	0.314	0.499	0.596	0.242	0.305	0.525	0.220
B	3.50	0.282	0.638	0.352	0.035	0.265	0.080	0.094	0.168	0.239	0.195
	4.50	0.066	0.273	0.205	0.176	0.160	0.053	0.102	0.127	0.145	0.074
	5.50	0.123	0.130	0.334	0.108	0.097	0.026	0.070	0.072	0.120	0.093
	Total	129.900	232.140	154.080	154.320	95.520	165.720	78.120	98.100	138.488	49.572
	0.50	0.270	0.141	0.877	0.276	0.544	0.672	0.459	0.822	0.508	0.270
	1.50	1.236	0.208	0.981	0.449	1.266	0.877	1.120	1.036	0.897	0.379
	2.50	0.718	1.251	0.576	0.239	0.469	1.267	0.581	1.094	0.774	0.384
C	3.50	0.297	0.301	0.105	0.107	0.168	0.464	0.123	0.157	0.215	0.123
	4.50	0.234	0.435	0.158	0.034	0.155	0.102	0.143	0.039	0.163	0.128
	5.50	0.101	0.146	0.142	0.077	0.034	0.037	0.143	0.079	0.095	0.046
	Total	171.360	148.920	170.340	70.920	158.160	205.140	154.140	193.620	159.075	40.519
	0.50	0.147	0.564	0.688	0.182	0.141	0.301	0.480	0.143	0.331	0.218
	1.50	0.101	0.640	0.843	0.150	0.509	1.349	1.047	1.208	0.731	0.465
	2.50	1.000	0.656	0.017	1.038	0.682	0.852	0.456	0.817	0.690	0.331
D	3.50	0.517	0.335	0.263	0.930	0.451	0.347	0.074	0.219	0.392	0.257
	4.50	0.301	0.145	0.195	0.688	0.227	0.099	0.043	0.123	0.228	0.202
	5.50	0.198	0.100	0.173	0.156	0.141	0.057	0.061	0.068	0.119	0.055
	Total	135.840	146.400	130.740	138.640	129.060	130.300	129.660	154.680	149.415	23.504

a. Na excretion in meq/min
b. Na excretion in 6 hr.(meq)

Table **16** Chloride Excretion from 8 Subjects after Oral Administration of

4 Different Brands of Furosemide Tablets

Brand	Time(hr)	Subject no. 1	2	3	4	5	6	7	8	Mean	SD
A	0.5	0.280[a]	0.499	0.629	0.320	1.166	0.536	0.349	0.630	0.551[a]	0.283
	1.5	0.562	1.118	1.575	0.456	1.114	0.565	1.234	2.047	1.096	0.555
	2.5	0.791	0.527	0.546	0.408	0.439	0.826	0.541	0.560	0.580	0.151
	3.5	0.826	0.174	0.455	1.162	0.468	0.679	0.198	0.297	0.532	0.340
	4.5	0.124	0.164	0.243	0.642	0.278	0.251	0.061	0.462	0.278	0.170
	5.5	0.101	0.070	0.139	0.245	0.179	0.087	0.045	0.051	0.122	0.068
	Total	149.040[b]	163.120	215.220	193.980	217.840	194.750	148.080	242.820	189.608[b]	36.152
B	0.5	0.198	1.154	0.648	0.720	0.163	1.295	0.123	0.678	0.647	0.457
	1.5	0.867	1.538	0.538	1.545	0.361	1.083	0.775	0.690	0.927	0.436
	2.5	0.996	0.952	0.777	0.468	0.601	0.802	0.304	0.402	0.663	0.258
	3.5	0.335	0.798	0.416	0.057	0.308	0.134	0.133	0.244	0.303	0.233
	4.5	0.087	0.452	0.248	0.208	0.208	0.094	0.140	0.155	0.198	0.118
	5.5	0.161	0.179	0.606	0.103	0.116	0.039	0.093	0.080	0.175	0.181
	Total	159.840	305.580	193.980	198.060	105.420	206.220	74.080	134.940	174.765	67.762
C	0.5	0.336	0.186	1.021	0.346	0.672	0.759	0.343	1.015	0.610	0.314
	1.5	1.453	0.275	0.570	0.588	1.540	1.056	1.380	1.332	1.025	0.483
	2.5	0.875	1.425	0.694	0.357	0.574	1.478	0.759	1.635	0.975	0.473
	3.5	0.365	0.382	0.150	0.178	0.212	0.517	0.172	0.239	0.352	0.264
	4.5	0.289	0.493	0.179	0.077	0.163	0.161	0.138	0.064	0.196	0.139
	5.5	0.131	0.178	0.155	0.119	0.036	0.067	0.113	0.108	0.113	0.045
	Total	207.300	206.340	166.140	99.900	191.820	248.280	186.300	263.580	196.208	59.388
D	0.5	0.168	0.697	0.788	0.203	0.134	0.379	0.624	0.256	0.409	0.257
	1.5	0.145	0.740	1.013	0.180	0.609	1.659	1.274	1.597	0.902	0.587
	2.5	1.260	0.803	1.223	1.213	0.764	1.101	0.563	1.039	0.996	0.256
	3.5	0.682	0.406	0.340	1.157	0.532	0.431	0.116	0.393	0.507	0.308
	4.5	0.362	0.199	0.229	0.472	0.276	0.152	0.065	0.182	0.242	0.127
	5.5	0.199	0.142	0.179	0.238	0.166	0.081	0.062	0.072	0.142	0.065
	Total	170.160	179.220	226.260	207.780	148.360	228.180	162.240	212.340	191.680	30.348

a. Cl excretion in meq/min

b. Cl excretion after 6 hr.(meq)

Table **17** Potassium Excretion from 8 Subjects after Oral Administration
of 4 Different Brands of Furosemide Tablets

Brand	Time(hr)	1	2	3	4	5	6	7	8	Mean	SD
					Subject no.						
A	0.50	0.048[a]	0.079	0.042	0.075	0.099	0.084	0.051	0.070	0.069[a]	0.020
	1.50	0.033	0.081	0.093	0.122	0.079	0.076	0.074	0.161	0.090	0.038
	2.50	0.091	0.072	0.040	0.045	0.045	0.061	0.037	0.071	0.058	0.019
	3.50	0.050	0.040	0.037	0.095	0.040	0.075	0.040	0.052	0.054	0.021
	4.50	0.019	0.035	0.026	0.066	0.035	0.037	0.011	0.161	0.049	0.048
	5.50	0.013	0.018	0.032	0.045	0.026	0.029	0.017	0.021	0.026	0.010
	Total	15.540[b]	19.500	16.218	26.880	19.440	21.720	13.300	32.160	20.657[b]	6.136
B	0.50	0.021	0.126	0.056	0.070	0.632	0.163	0.024	0.098	0.149	0.201
	1.50	0.047	0.119	0.032	0.110	0.043	0.137	0.055	0.083	0.078	0.040
	2.50	0.069	0.090	0.043	0.058	0.051	0.125	0.021	0.053	0.064	0.032
	3.50	0.036	0.065	0.043	0.017	0.036	0.049	0.031	0.040	0.040	0.014
	4.50	0.018	0.039	0.021	0.040	0.032	0.043	0.026	0.032	0.031	0.009
	5.50	0.023	0.031	0.038	0.025	0.022	0.040	0.233	0.021	0.054	0.073
	Total	12.840	28.200	13.980	19.200	48.960	33.420	23.460	19.620	24.960	11.889
C	0.50	0.036	0.080	0.065	0.021	0.811	0.099	0.056	0.157	0.166	0.264
	1.50	0.083	0.041	0.042	0.045	0.107	0.045	0.068	0.099	0.066	0.027
	2.50	0.070	0.082	0.051	0.044	0.077	0.087	0.048	0.229	0.086	0.060
	3.50	0.041	0.070	0.015	0.030	0.041	0.063	0.023	0.035	0.040	0.018
	4.50	0.030	0.056	0.021	0.023	0.047	0.028	0.025	0.021	0.031	0.013
	5.50	0.020	0.027	0.018	0.027	0.015	0.019	0.050	0.022	0.025	0.011
	Total	16.800	21.360	12.720	11.400	65.880	20.460	16.500	33.780	24.863	17.957
D	0.50	0.032	0.046	0.036	0.041	0.371	0.042	0.048	0.095	0.089	0.116
	1.50	0.026	0.045	0.057	0.038	0.057	0.078	0.076	0.161	0.067	0.042
	2.50	0.070	0.053	0.065	0.075	0.059	0.059	0.050	0.108	0.067	0.018
	3.50	0.046	0.044	0.030	0.093	0.052	0.039	0.025	0.063	0.049	0.021
	4.50	0.033	0.032	0.024	0.053	0.048	0.023	0.027	0.049	0.036	0.012
	5.50	0.029	0.041	0.217	0.038	0.034	0.023	0.014	0.025	0.053	0.067
	Total	14.100	15.660	25.740	20.280	37.260	15.340	14.400	30.060	21.668	8.554

a. K excretion in meq/min
b. K excretion after 6 hr.(meq)

VITA

Miss Onoomar Poobrasert was born on May 13, 1964, in Tokyo, Japan. She graduated with Bachelor of Science in Pharmacy (second class honors) in 1986 from Faculty of Pharmacy, Mahidol University.