AN ABSTRACT OF THE THESIS OF

RAI-YUN LEE for the degree of Master of Science

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Title: STABILITY OF ORAL LIQUID CIMETIDINE HCl AND FUROSEMIDE REPACKAGED IN UNIT DOSE CONTAINERS AT VARIOUS TEMPERATURES

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Oral liquid cimetidine HCl or furosemide were repackaged into unit dose containers (both plastic(polypropylene) oral syringes and glass vials) to yield a concentration of 60 mg/ml or 10 mg/ml respectively. Samples of 1 ml were stored in plastic oral syringes and glass vials at 4°C, 25°C, 44°C, 60°C and 76°C over 0 to 180 days. Drug concentration remaining after storage was determined by high performance liquid chromatography. Long term stabilities of cimetidine HCl or furosemide at lower temperatures were predicted using the Arrhenius equation.

Results indicate, under the conditions tested, that oral liquid cimetidine HCl or furosemide can be stored in either plastic oral syringes or glass vials for at least 180 days at 4°C (refrigerated) and 25°C (room temperature) with less than 10 percent loss in potency. Storage of

liquid cimetidine HCl or furosemide in either plastic oral syringes or glass vials at elevated temperatures adversely affects the stability and shelf-life of both drugs. No significant statistical difference was observed for storage of liquid cimetidine HCl or furosemide in plastic oral syringes and glass vials at refrigerated temperature (4^{o}C) or room temperature (25^{o}C) ($p>0.05$). Degradation appeared to be a zero-order process for cimetidine HCl and a first-order process for furosemide. From the Arrhenius equation the data indicate that cimetidine HCl or furosemide in oral liquid dosage forms probably would be stable at 4^{o}C and 25^{o}C for long term storage.

Stability of Oral Liquid Cimetidine HCl and Furosemide Repackaged in Unit Dose Containers at Various Temperatures

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INTRODUCTION

The pharmacist is concerned with the stability of drugs and factors that enchance or retard the rate of degradation of drug products. It has been shown that the stability of a pharmaceutical product is influenced by many factors such as container selection, exposure to air, light, moisture, final drug concentration, other chemical ingredients and temperature.[1,2] Determining drug stability and effects of the drug's dosage form on stability is necessary to assure a desired therapeutic concentration will be achieved when the drug is administered to a patient.

Generally, the formulation of a product is such that sufficient care has been taken that during preparation, and packaging, the product is stable. However, when the product is purchased by the pharmacist, repackaging of the product into a new container may occur. When a product is repackaged the conditions of storage are different from the original storage conditions which the manufacturer approved. Transfer of drugs such as insulin, gentamycin sulfate and penicillin V potassium from the original container to a unit-dose container can have deleterious effects on stability of these drugs.[2,3,4] It is important to take into account the nature of the drug repackaged, characteristics of the package and storage

conditions[5] to which the drug may be subjected to assure drug will be suitably stable for its anticipated storage time prior to use.

The stability of cimetidine HCl oral solution or furosemide oral solution were studied. Rosenberg et al. reported that cimetidine HCl in solution is visually and chemically stable for at least one week at ambient temperature[6] with frequently prescribed large-volume parenteral fluids in glass or polyvinyl chloride containers. Stability studies of furosemide solutions at room temperature (24°C) as well as higher temperatures (45°C, 65°C, 85°C) at various pH values and with different vehicles have been done.[7] Furosemide is unstable in acidic media and sucrose sugar solution but very stable in basic media at 65°C.

Cimetidine is a new, potent, H2-receptor antangonist. Furosemide is a potent diuretic agent. Both are widely used drugs which are commonly repackaged in plastic or glass unit dose containers by hospital pharmacists. Although information exists concerning advantages of repackaging in plastic or glass containers,[5,8,9] no specific stability data are available for oral liquid cimetidine HCl or furosemide repackaged in these containers.

Time and money could be saved if oral liquid preparations of cimetidine HCl or furosemide were

repackaged in unit dose containers and dispensed as needed. The purpose of this investigation was to determine the effect of temperature on stability of oral liquid cimetidine HCl or furosemide repackaged in plastic oral syringes and glass vials.

EXPERIMENTAL

Materials:

Analytical grade chemicals were used without further purification. Deionized water was used throughout the study. Methanol was analytical grade reagent.[a] Oral liquid cimetidine HCl[b] was obtained from SKSF Lab Co. and furosemide[c] was obtained from HOECHST-ROUSSEL Pharmaceuticals Inc. The internal standard was tyramine HCl[d] for cimetidine HCl and propyl paraben[e] for furosemide. Both were purchased commercially.

Sample preparation and storage:

Commercial oral liquid cimetidine HCl (label claim 60mg/ml, pH=5.8) and furosemide (label claim 10 mg/ml, pH=8.0) were used for this study. Both were repackaged into unit dose plastic oral syringes[f] and glass vials[g] (1 ml was placed in each container, capped and coded) and stored at a constant temperature, [4°C, 25°C, 44°C, 60°C, 76°C(± 1°C)] in enclosed compartments to prevent exposure to light and varying moisture conditions. Two hundred and ten unit dose containers were repackaged of each type. Each temperature contained 42 unit dose containers of each type.

Analytical Method:

Cimetidine HCl---A high performance liquid chromatography system[h] with a C18 column[i] was used to

analyze cimetidine HCl concentrations. The mobile phase for cimetidine HCl analysis was composed of 50% v/v acetonitrile-water[j] and 0.1% ammonium hydroxide.[k] The uv dector was generally set at a sensitivity of 1.0. All samples were analyzed at room temperature.

Samples of cimetidine HCl were assayed for initial concentration immediately after repackaging. Six unit dose packages from each type of container were withdrawn from five different temperatures at 5, 10, 20, 30, 60, 90, and 180 days for analysis of drug concentration.

One ml samples of cimetidine HCl in each type of container were transfered to a volumetric flask and diluted to 50 ml with distilled water. To a 0.5 ml diluted cimetidine HCl sample, an equal volume internal standard was added. This mixture was mixed well by vortexing. Five μl of this solution was then injected into the HPLC.

Furosemide---A high performance liquid chromatography system[l] with a C18 column was used to analyze furosemide concentrations. The mobile phase for furosemide analysis was composed of 40% v/v acetonitrile-water and 0.5% acetic acid.[m] The uv dector was set at a sensitivity of 0.5.

Samples of furosemide were assayed for initial concentration immediately after repackaging. Six unit dose packages from each type of container were withdrawn from five different temperatures at 5, 10, 20, 30, 60, 90, and 180 days for analysis of drug concentration.

One ml samples of furosemide in each type of container were transfered to a volumetric flask and diluted to 10 ml with methanol. To a 0.5 ml diluted furosemide sample, an equal volume internal standard was added. This mixture was mixed well by vortexing. Five μl of this solution was then injected into the HPLC.

RESULTS

Part I: Oral liquid cimetidine HCl studies

The data obtained for stability of cimetidine HCl in plastic oral syringes and glass vials at 25°C, 44°C, 60°C and 76°C are presented in Table I, Figure 1 and Figure 2. Linear regression correlation coefficients indicate there is a good linear relationship between time(days) and concentration for each set of data. Cimetidine HCl degradation appeared to follow a zero-order process under the conditions studied.

Dependence of Rate of degradation on Temperature

An increase in temperature usually causes a marked increase in the rate of a reaction. For a reaction in solution, a rough generalization is that the rate is doubled by a rise in temperature of 10°C.[10,11] However, in order to increase accuracy of prediction of the stability of a drug product at low temperatures, the Arrhenius relationship is used.[10,11]

The Arrhenius equation may be written as

$$K = Ae^{-Ea/RT}$$

K is degradation rate constant, A is a constant known as the frequency or collision factor, Ea is the activation energy of the molecules having energy Ea in excess, i. e. there may be many collision complexes in existence at a

given time, but only those with the energy Ea or higher are capable of forming product directly. A plot of lnK vs. the reciprocal of absolute temperature should result in a straight line with the slope equal to -Ea/R and the intercept equal lnA, if the above equation describes the reaction.

The rate constants for chemical degradation at lower temperatures can be predicted for zero-order process using the Arrhenius equation.[12,13] Stability of cimetidine HCl in plastic oral syringes and glass vials at lower temperatures was predicted using the Arrhenius equation.[12,13] Arrhenius plots for degradation rate-temperature relationships for these data are shown in Figure 3 and Figure 4.

The natural logrithm of the rate constant(lnK) is inversely proportional to absolute temperature(see Figures 3&4). By determining the rate constants for cimetidine HCl at 25°C, 44°C, 60°C, 76°C and by plotting lnK versus absolute temperature, the rate constant for lower temperatures can be predicted. Rate constants determined for cimetidine HCl at 25°C, 44°C, 60°C, 76°C along with a predicted rate constant for 4°C and predicted time for loss of 10 percent potency at 4°C and 25°C are shown in Table II. The Arrhenius equation predicts a long-term stability for cimetidine HCl at refrigerated temperature and room temperature.

Data presented in Table I indicate cimetidine HCl repackaged in either plastic oral syringes or glass vials retained more than 90 percent of label claim(54 mg/ml) after storage for 180 days at refrigerated temperature(4°C) and room temperature(25°C). However, storage at 76°C in either container resulted in loss of more than 10 percent after 10 days.

A factorial experimental design[14] was used to analyze the data. F-tests were performed at 5 percent significance level for these analysis.[14] Data presented show there was a greater loss of drug concentration in unit dose containers as temperature increased. Loss of drug concentration at different temperatures was statistically significant. No significant statistical difference was found when cimetidine HCl is repackaged in plastic oral syringes and glass vials stored at 4°C and also at 25°C over the designated time($P>0.05$). But a significant statistical difference in drug concentration for cimetidine HCl was observed between plastic oral syringes and glass vials when stored at temperatures above room temperature. Degradation rate was faster in plastic oral syringes than glass vials at higher temperatures.

Part II: Oral liquid furosemide studies

Mean concentrations of oral liquid furosemide after repackaging in unit dose containers and storage for the

specific times under different temperatures are given in Table III.

The kinetics of furosemide degradation in plastic oral syringes and glass vials were evaluated at various temperatures. Figure 5 and Figure 6 are typical plots of the natural logarithm of the concentration of furosemide in mg/ml vs. time (day) at 25°C, 44°C, 60°C and 76°C.

This highly linear relationship between natural logarithm of concentration and time suggest an apparent first order degradation of furosemide under the conditions studied, i. e. the rate of change per unit of time is proportional to the first power of the concentration of the compound. First order rate constants were determined using linear regression.

The stability of furosemide in plastic oral syringes and glass vials at lower temperatures was also predicted using the Arrhenius equation.[12,13] Arrhenius plots for degradation rate-temperature relationships for these data are shown in Figure 7 and Figure 8.

The natural logarithm of the rate constant(lnK) is inversely proportional to absolute temperature(see Figures 7&8). By determining the rate constants for a drug at 25°C, 44°C, 60°C, 76°C and by plotting lnK versus absolute temperature, the rate constant for lower temperatures can be predicted. Rate constants determined for furosemide at 25°C, 44°C, 60°C, 76°C along with predicted rate constant

for 4°C and predicted time for loss of 10 percent potency at 4°C and 25°C are shown in Table IV. The Arrhenius equation predicts a long-term stability at refrigerated temperature and room temperature.

The data presented in Table III indicate furosemide repackaged in either plastic oral syringes or glass vials still retained more than 90 percent of its label claim(9 mg/ml) after 180 days of storage at refrigerated temperature(4°C) and room temperature(25°C). Storage at 76°C in either container resulted in loss of more than 10 percent of drug content after 10 days. Additionally, increasing temperature increased degradation rate.

A factorial experimental design[14] was used to analyze the data. F-tests were performed at 5 percent significance level for these analysis. The data presented show there was a greater loss of drug concentration in unit dose container as temperature increased. No significant statistical difference was found for furosemide repackaged in plastic oral syringes and glass vials stored at 4°C and also 25°C over the study time ($p>0.05$). But a significant statistical difference in drug concentration for furosemide was observed between plastic oral syringes and glass vials when stored at temperature above room temperature. Degradation rate was faster in plastic oral syringes than glass vials at higher temperatures.

DISCUSSION

The results indicate the degradation rate is dramatically decreased by storing at lower temperatures for both cimetidine HCl and furosemide. No significant statistical difference was observed when either cimetidine HCl or furosemide is stored in plastic oral syringes and glass vials at $4^{\circ}C$ and also $25^{\circ}C$ over the designated time. Degradation rates of cimetidine HCl and furosemide were faster in plastic oral syringes than glass vials at all temperatures studied.

Repackaging of cimetidine HCl and furosemide in either plastic oral syringes or glass vials and stored at elevated temperature adversely affects the stability and shelf-life of both drugs. The loss of drug can be statistically significant if the temperature is raised. Less than 90 percent of label claim will be retained after 10 days storage at $76^{\circ}C$ for both drugs in either container. However, more than 90 percent of label claim is still retained after 180 days when stored at $4^{\circ}C$ and $25^{\circ}C$ for both drug in each container. The loss of drug is increased significantly with increasing temperature for both cimetidine HCl and furosemide.

The Arrhenius equation provides a quick estimation of the long-term stability of the drug. Predicted rate constant for cimetidine HCl at $4^{\circ}C$ is 1.68×10^{-3} and

1.69×10^{-3} and predicted time for loss of 10 percent potency at 4°C is 3577 days and 3556 days for glass vials and plastic oral syringes respectively. At 25°C the predicted time for 10 percent loss of potency is 332 days and 317 days for glass vials and plastic oral syringes respectively. Predicted rate constant for furosemide at 4°C is 1.39×10^{-5} and 1.77×10^{-5} and predicted time for loss of 10 percent potency at 4°C is 7553 days and 5932 days for glass vials and plastic oral syringes respectively. At 25°C the predicted time for 10 percent loss of potency is 608 days and 475 days for glass vials and plastic oral syringes respectively. Long-term stability can be obtained in either plastic oral syringes or glass vials at 4°C and 25°C.

CONCLUSION

Oral liquid cimetidine HCl or furosemide may be repackaged in either plastic oral syringes or glass vials and stored at lower temperatures (4°C, 25°C) for up to 180 days with less than 10 percent loss of potency. There is no significant statistical difference for cimetidine HCl and furosemide stored in either plastic oral syringes or glass vials at 4°C and also 25°C over designated study time. This is not true at higher temperatures. The degradation rate were faster in plastic oral syringes than in glass vials. Storing both drugs above room temperature is undesirable. Data obtained from cimetidine HCl and furosemide stability study and the Arrhenius equation indicate oral liquid cimetidine HCl and furosemide would probably be stable for much longer periods at lower temperatures.

Table I- Mean Concentration of Cimetidine HCl (mg/ml) Remaining After Repackaging and Storage at Various Conditions
(Data Given as Mean Concentration of Six Samples ± One Standard Deviation; Label Claim 60 mg/ml)

Days	Plastic Oral Syringes					Glass Vials				
	4°C	25°C	44°C	60°C	76°C	4°C	25°C	44°C	60°C	76°C
0	60.1±1.4	60.1±1.4	60.1±1.4	60.1±1.4	60.1±1.4	60.1±1.4	60.1±1.4	60.1±1.4	60.1±1.4	60.1±1.4
5	59.7±0.6	59.4±1.0	59.4±1.0	58.3±0.6	47.3±1.8	59.8±0.7	59.4±0.5	59.4±0.8	55.1±1.3	49.1±1.0
10	59.5±0.6	58.7±0.8	57.6±1.2	50.2±1.4	40.0±0.8	59.6±0.7	59.2±1.2	58.5±1.1	52.7±1.1	42.5±0.9
20	59.2±0.5	58.4±0.5	56.0±1.5	44.8±0.9	28.1±0.5	59.3±1.3	59.0±0.8	58.0±1.2	43.5±1.1	26.9±0.5
30	58.7±0.5	58.3±0.6	55.1±0.6	37.2±0.6	12.0±0.9	59.0±1.0	58.5±0.5	57.3±0.5	38.0±0.6	15.5±0.6
60	58.3±0.8	57.6±1.0	52.2±1.2	####[a]	####[a]	58.6±0.6	58.2±0.5	53.1±1.4	####[a]	####[a]
90	57.8±0.6	57.1±0.6	49.9±0.8	####[a]	####[a]	58.1±0.5	57.5±0.5	50.6±2.0	####[a]	####[a]
180	57.4±0.7	56.1±0.5	42.0±0.8	####[a]	####[a]	57.5±0.5	56.2±0.6	44.6±1.2	####[a]	####[a]

[a] ####No sample taken

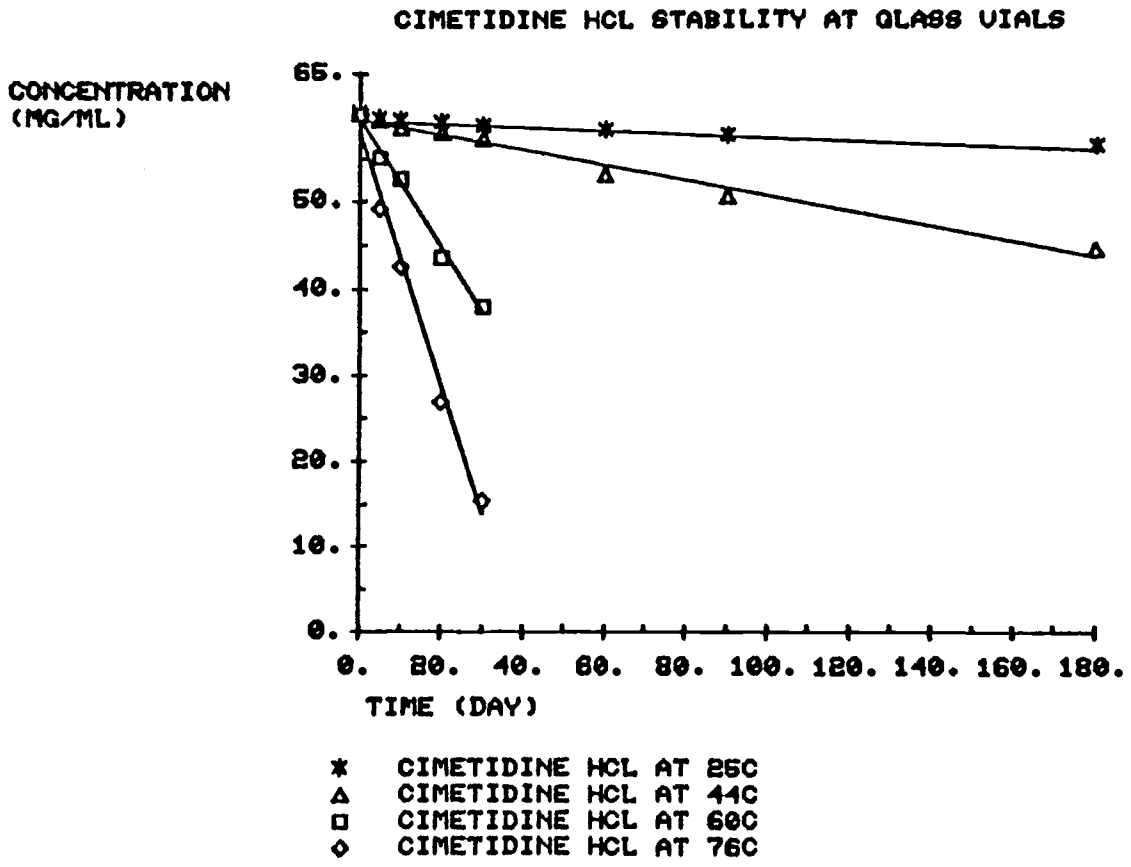

Figure 1- Apparent zero-order plots for the degradation of cimetidine HCl in glass vials at 25°C, 44°C, 60°C and 76°C

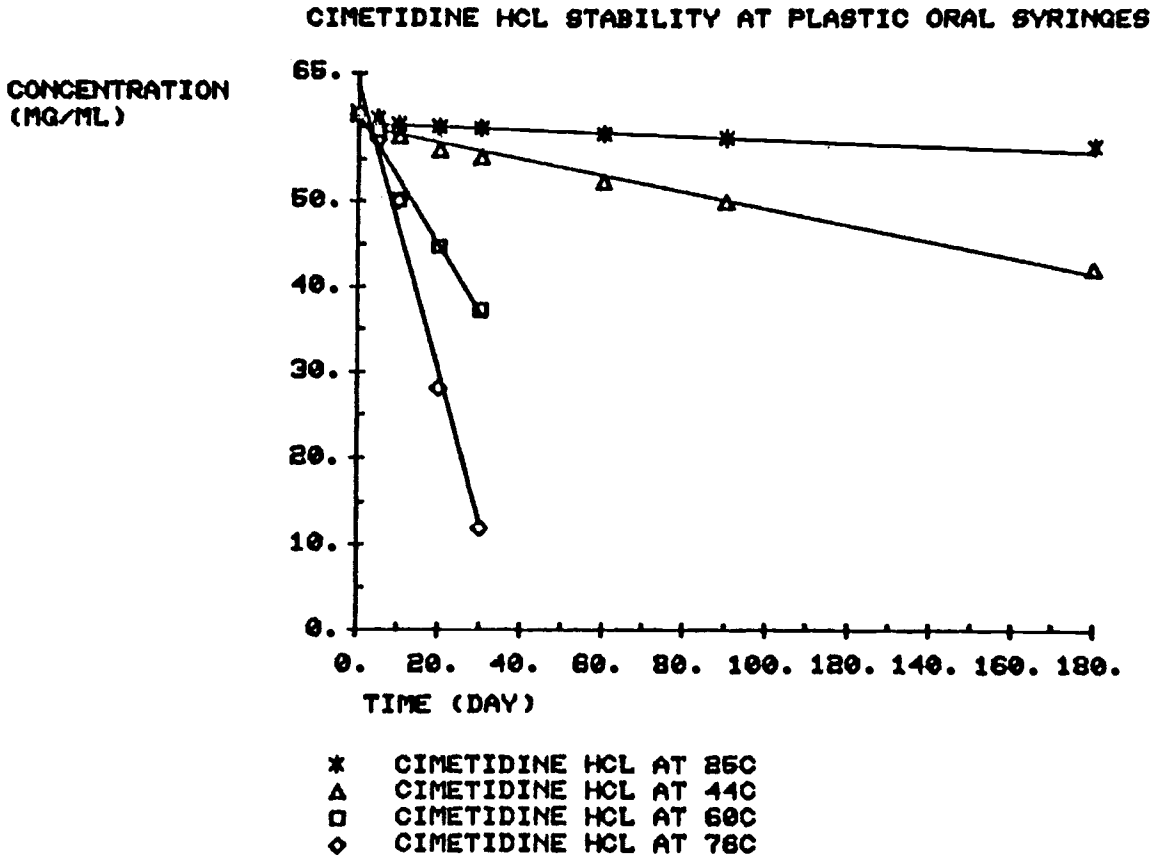

Figure 2- Apparent zero-order plots for the degradation of cimetidine HCl in plastic oral syringes at 25°C, 44°C, 60°C, and 76°C

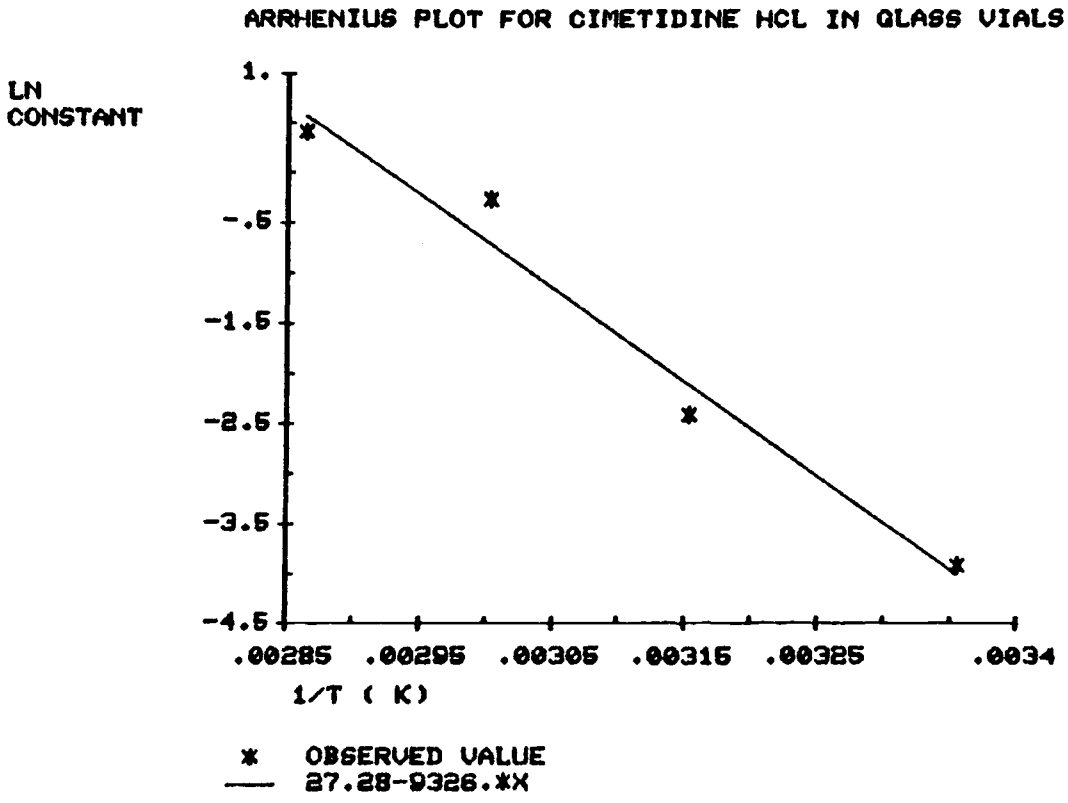

Figure 3- Arrhenius plot of apparent zero-order rate constants for degradation of cimetidine HCl in glass vials at 25°C, 44°C, 60°C and 76°C

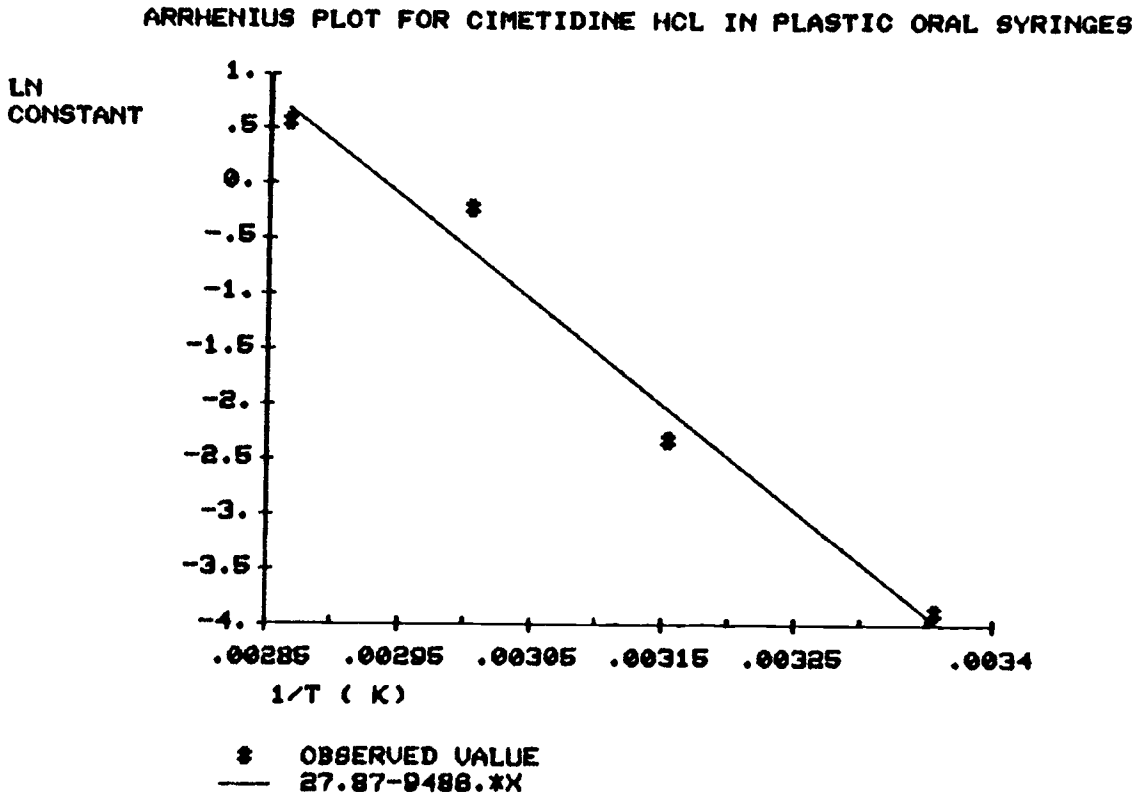

Figure 4- Arrhenius plot of apparent zero-order rate constants for degradation of cimetidine HCl in plastic oral syringes at 25°C, 44°C, 60°C and 76°C

Table II- Cimetidine HCl degradation rate constant and predicted time for 10 percent loss in potency

Container	K_{76}[a]	K_{60}[b]	K_{44}[c]	K_{25}[d]	K_4[e]	$t_{10\%}$[f]	$t_{10\%}$[g]
Glass Vials	1.47_{-2} ($\pm 8 \times 10^{-2}$)	0.74_{-2} ($\pm 4 \times 10^{-2}$)	0.088_{-3} ($\pm 5 \times 10^{-3}$)	0.019_{-3} ($\pm 2 \times 10^{-3}$)	0.00168	332 days	3577 days
Plastic Oral Syringes	1.71 (± 0.13)	0.78_{-2} ($\pm 7 \times 10^{-2}$)	0.097_{-3} ($\pm 6 \times 10^{-3}$)	0.020_{-3} ($\pm 3 \times 10^{-3}$)	0.00169	317 days	3556 days

[a]Degradation rate constant(mg/mlxday) at 76°C, calculated.

[b]Degradation rate constant(mg/mlxday) at 60°C, calculated.

[c]Degradation rate constant(mg/mlxday) at 44°C, calculated.

[d]Degradation rate constant(mg/mlxday) at 25°C, calculated.

[e]Degradation rate constant(mg/mlxday) at 4°C, predicted.

[f]Time in days predicted for product to loss 10% potency at 25°C.

[g]Time in days predicted for product to loss 10% potency at 4°C.

Table III- Mean Concentration of Furosemide (mg/ml) Remaining After Repackaging and Storage at Various Conditions
(Data Given as Mean Concentration of Six Samples ± One Standard Deviation; Label Claim 10 mg/ml)

Days	Plastic Oral Syringes				
	4^0C	25^0C	44^0C	60^0C	76^0C
0	10.14±0.20	10.14±0.20	10.14±0.20	10.14±0.20	10.14±0.20
5	10.12±0.08	10.00±0.08	9.83±0.19	9.18±0.11	8.79±0.20
10	10.07±0.17	9.97±0.21	9.62±0.16	8.87±0.10	7.62±0.10
20	9.99±0.21	9.92±0.20	9.52±0.20	8.28±0.18	6.45±0.09
30	9.96±0.14	9.89±0.05	9.40±0.07	7.22±0.19	4.87±0.07
60	9.90±0.14	9.81±0.17	9.21±0.12	4.89±0.15	####[a]
90	9.84±0.18	9.78±0.09	9.04±0.13	####[a]	####[a]
180	9.77±0.05	9.63±0.11	7.96±0.05	####[a]	####[a]

Days	Glass Vials				
	4^0C	25^0C	44^0C	60^0C	76^0C
0	10.14±0.20	10.14±0.20	10.14±0.20	10.14±0.20	10.14±0.20
5	10.07±0.18	10.05±0.17	9.90±0.09	9.87±0.14	9.59±0.22
10	10.06±0.20	10.04±0.13	9.87±0.08	9.39±0.09	8.69±0.09
20	10.05±0.18	10.03±0.17	9.86±0.13	8.86±0.15	7.35±0.10
30	10.03±0.20	9.99±0.24	9.70±0.15	8.17±0.12	6.01±0.08
60	10.02±0.07	9.96±0.03	9.46±0.18	6.23±0.19	3.30±0.06
90	9.97±0.11	9.92±0.08	9.16±0.16	####[a]	####[a]
180	9.91±0.20	9.76±0.10	8.40±0.15	####[a]	####[a]

[a] ####No sample taken

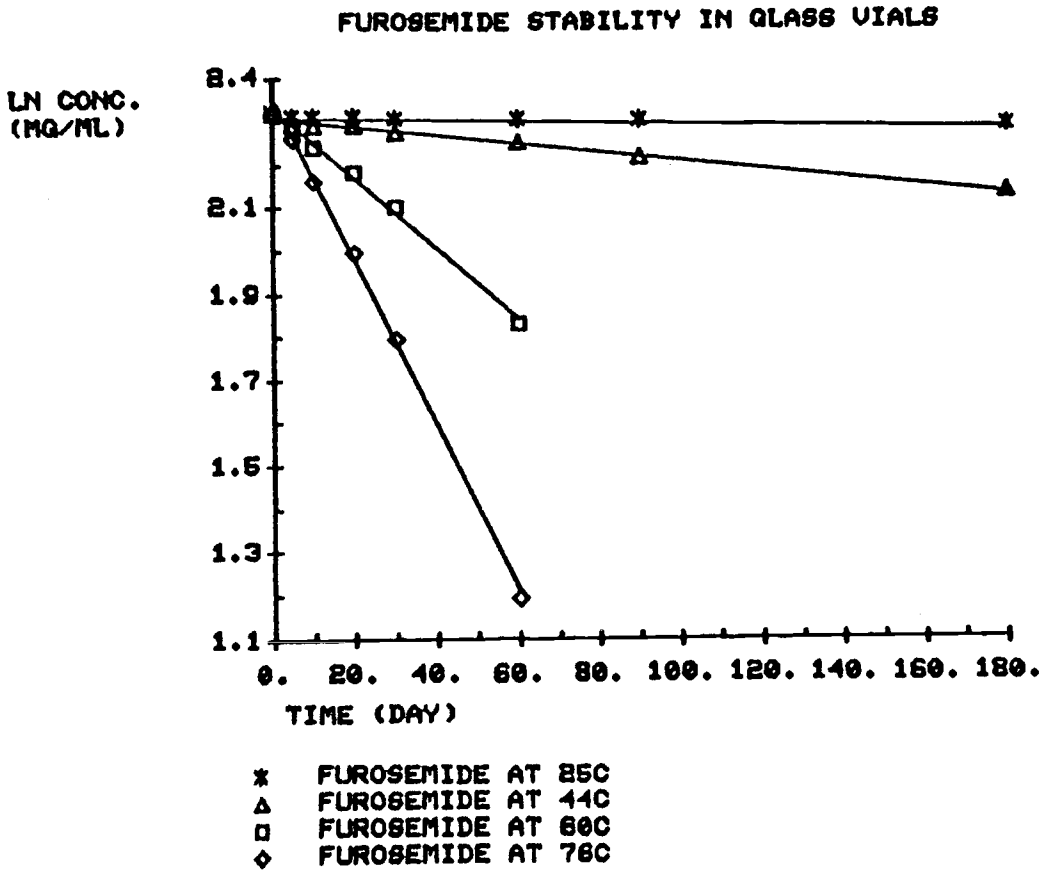

Figure 5 - Apparent first-order plots for the degradation of furosemide in glass vials at 25°C, 44°C, 60°C and 76°C

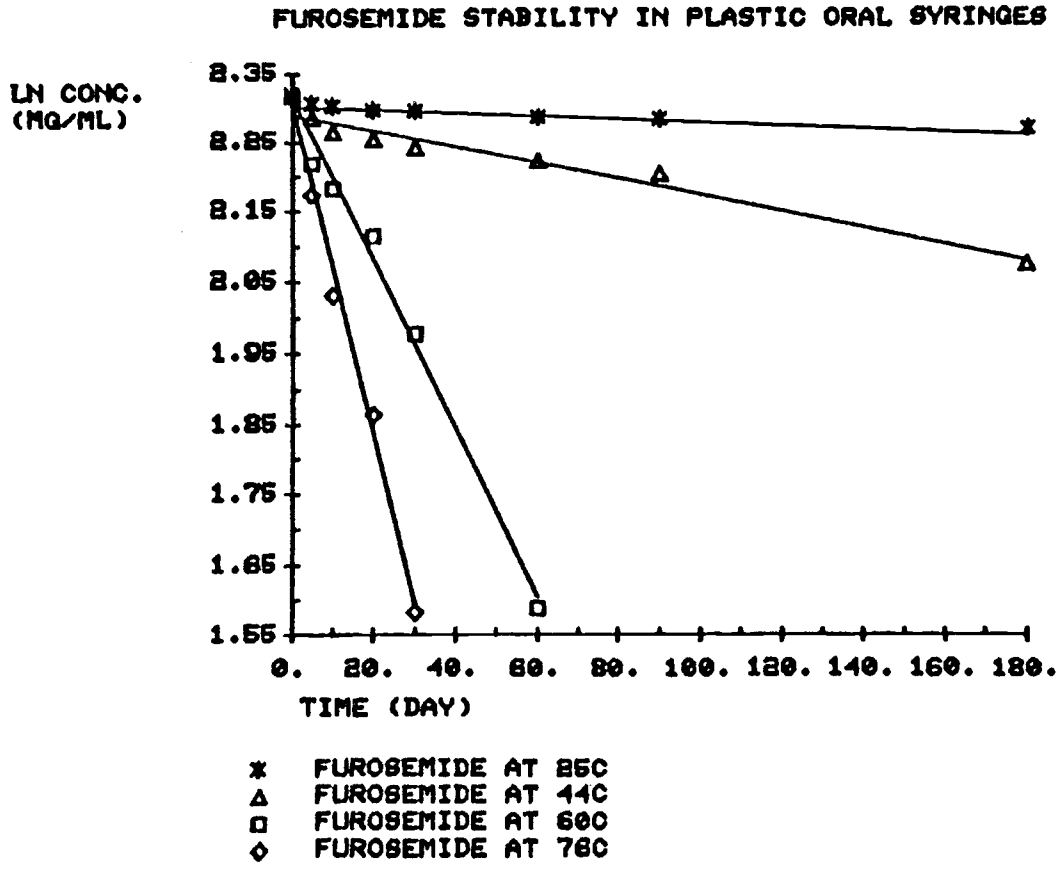

Figure 6 - Apparent first-order plots for the degradation of furosemide in plastic oral syringes at 25°C, 44°C 60°C and 76°C

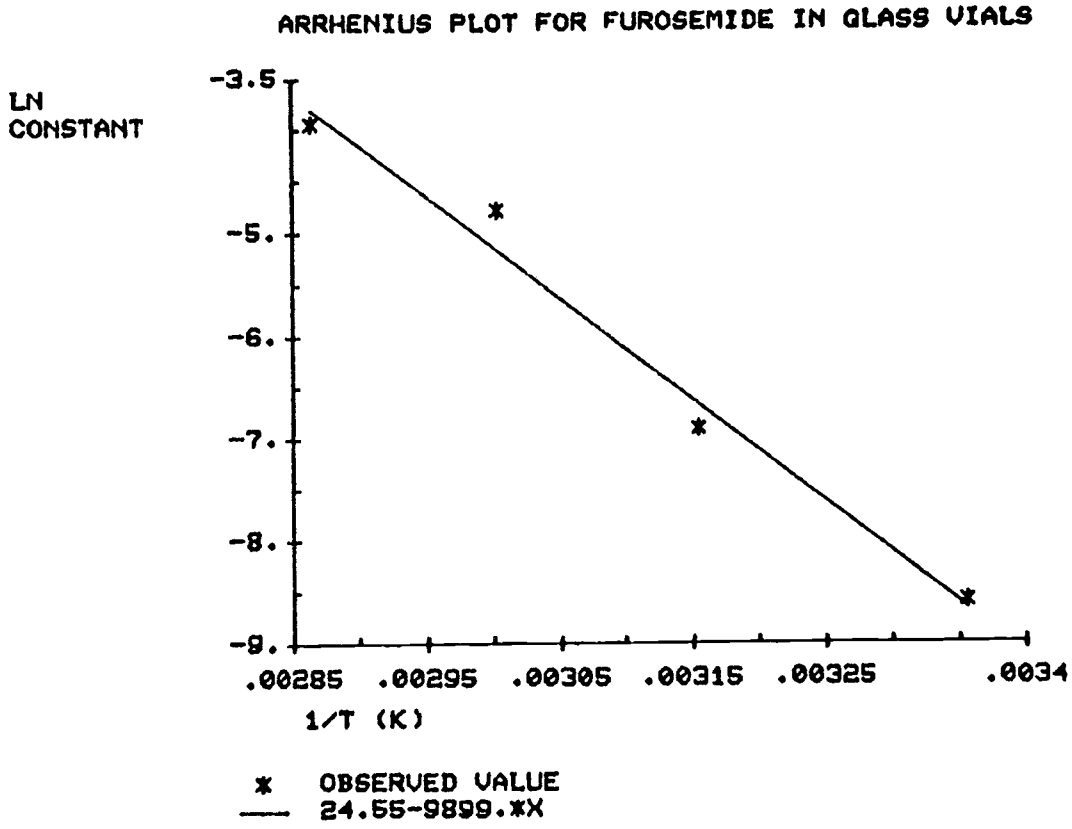

Figure 7 - Arrhenius plot of apparent first-ofder rate constants for degradation of furosemide in glass vials at 25°C, 44°C, 60°C and 76°C

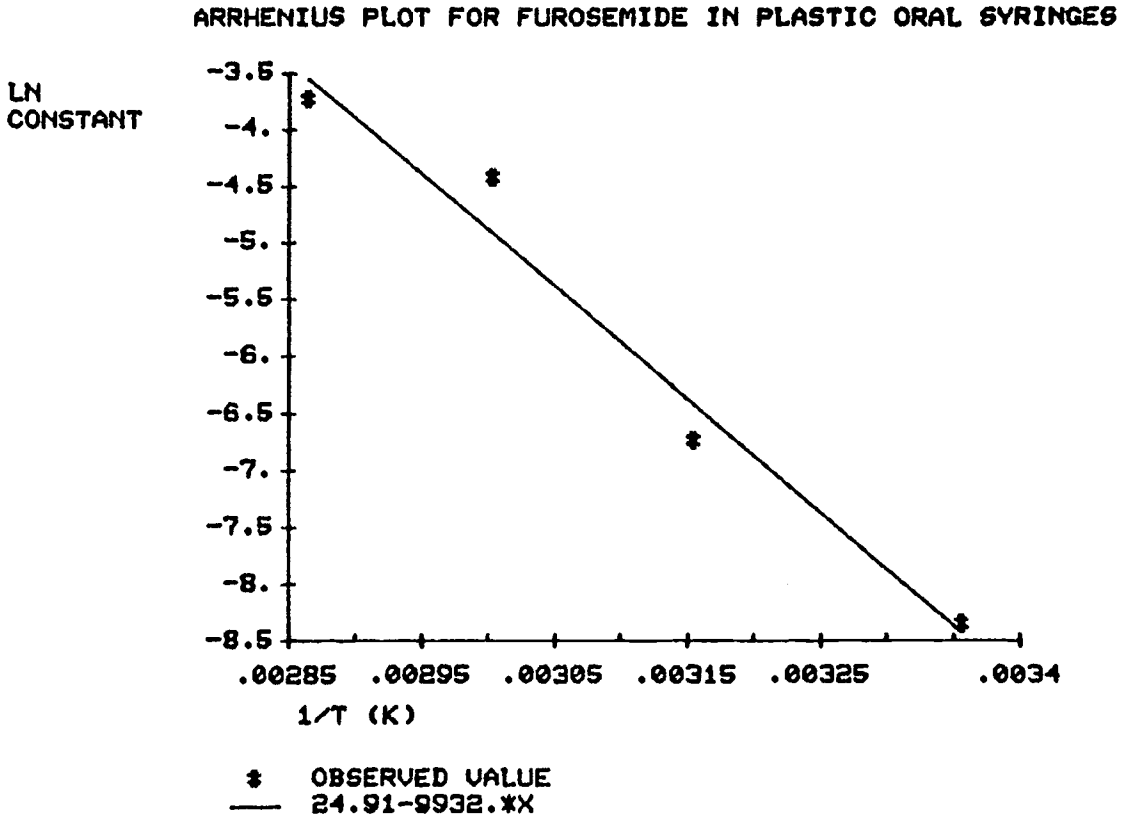

Figure 8 - Arrhenius plot of apparent first-order rate constants for degradation of furosemide in plastic oral syringes at 25°C, 44°C, 60°C and 76°C

Table IV- Furosemide degradation rate constant and predicted time for 10 percent loss in potency

Container	K_{76}[a]	K_{60}[b]	K_{44}[c]	K_{25}[d]	K_{4}[e]	$t_{10\%}$[f]	$t_{10\%}$[g]
Glass Vials	1.89×10^{-2} ($\pm 5 \times 10^{-4}$)	8.13×10^{-3} ($\pm 3 \times 10^{-4}$)	9.84×10^{-4} ($\pm 4 \times 10^{-5}$)	1.81×10^{-4} ($\pm 2 \times 10^{-5}$)	1.39×10^{-5}	608 days	7553 days
Plastic Oral Syringes	2.35×10^{-2} ($\pm 1 \times 10^{-3}$)	1.17×10^{-2} ($\pm 6 \times 10^{-4}$)	1.17×10^{-3} ($\pm 1 \times 10^{-4}$)	2.35×10^{-4} ($\pm 4 \times 10^{-5}$)	1.77×10^{-5}	475 days	5932 days

[a] Degradation rate constant(day^{-1}) at 76°C, calculated.

[b] Degradation rate constant(day^{-1}) at 60°C, calculated.

[c] Degradation rate constant(day^{-1}) at 44°C, calculated.

[d] Degradation rate constant(day^{-1}) at 25°C, calculated.

[e] Degradation rate constant(day^{-1}) at 4°C, predicted.

[f] Time in days predicted for product to loss 10% potency at 25°C.

[g] Time in days predicted for product to loss 10% potency at 4°C.

FOOTNOTES

a. Methanol 'Baker analyzed reagent', J. T. Baker Chemical Co., Phillipsburg, N.J. 08865, Lot number 134602.

b. Tagamet (Cimetidine) HCl liquid, SKSF Lab Co., Carolina, P.R. 00630, (Subsidary of SmithKline Corporation), Lot numbers 21T14 and X20T14.

c. Lasix (Furosemide) oral solution, HOECHST-ROUSSEL Pharmaceuticals Inc., Somerville, N.J. 08876, Lot numbers 680040 and 680031.

d. Tyramine HCl, Aldrich Chemical Company, Inc., Milwaukee WIS 53233 Lot number 011787.

e. Propyl paraben, City Chemical Corporation, New York, N.Y. 10011.

f. Bexa Corporation, Northbrook, IL. 60062, 5 ml amber syringes (Polyproplyene)

g. Wheaton Scientific, Millville, N.J. 08332, 15 ml amber vials.

h. uBondpak C18 (methanol-water), Water Associates Inc., Milford, Massachusett 01757.

i. HPLC: water association chromatography pump; model- M-6000; dector: uv-vis; wavelength- 228 nm; model- 635 LC; recorder: model- 285; 16 inches/hr. flow rate: 2.5 ml/min; sensitivity: 1.0; pressure: 3000psi. Water Associates Inc., Milford, Massachusett 01757.

j. Acetonitrile, J. T. Baker Chemical Co., Phillipsburg, N.J. 08865.

k. Ammonium hydroxide, J. T. Baker Chemical Co., Phillipsburg, N.J. 08865, Lot number 606148.

l. HPLC: water association chromatography pump; model- M-6000; detector: uv-vis; wavelength- 280 nm; model- 635 LC; recorder: model- 285; 16 inches/hr. flow rate: 2.0 ml/min; sensitivity: 0.5; pressure: 2500psi; Water Associates Inc., Milford, Massachusett 01757.

m. Acetic acid, J. T. Baker Chemical Co., Phillipsburg, N.J. 08865 Lot number 609863.

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APPENDIX

(Detailed Analysis)

Materials

Structures of cimetidine and furosemide are shown in Figure 1.

Preparation of standard curve

Standard solutions with known concentrations of cimetidine HCl and a constant concentration of tyramine HCl (internal standard) in distilled water were accurately prepared. The concentration of cimetidine HCl ranged from 1.6 mg/ml to 0.2 mg/ml. The concentration of the internal standard was 4.8 mg/ml.

Standard solutions with known concentrations of furosemide and a constant concentration of propyl paraben (internal standard) in methanol were also accurately prepared. The concentration of furosemide ranged from 1.2 mg/ml to 0.25 mg/ml. The concentration of the internal standard was 3 mg/ml.

The peak height ratio of cimetidine HCl and furosemide were plotted vs. their known concentrations and the intercepts, slopes and correlation coefficients(r) of these standard curves determined.

Chromatogram and standard curve

Figure 2 shows a typical HPLC chromatograms for determination of cimetidine HCl concentration. Both cimetidine HCl and internal standard peaks involved in this study separate nicely and no other absorbance occurs

in either the region of drug peak or internal standard peak. The cimetidine peak height was eluted at two minutes and internal standard was eluted at eight minutes.

Peak height ratios of cimetidine HCl and internal standard were related to their concentration. Parabolic regression was performed to determine the standard curve (Fig 3). Data of four standard curves prepared on different days during the experiment was summerized in Table I. Inversely estimated concentrations from each individual standard curve and pooled data are listed in Table II.

Figure 4 shows a typical HPLC chromatograms for determination of furosemide concentration. Both furosemide and internal standard peak involved in this study separated nicely. There is a small peak from oral liquid (not in standard solution) appearing before furosemide peak but not in the region of drug peak or internal standard. The furosemide peak was eluted at three minutes and internal standard was eluted at six minutes.

Peak height ratios of furosemide and internal standard were directly related to their concentration. Linear regression was performed to determine the standard curve. A typical standard curve for furosemide is shown in Figure 5. Data of four standard curves prepared on different days during the experiment are summerized in

Table III. Inversely estimated concentrations from each individual standard curve and pooled data are listed in Table IV.

Statistical analysis

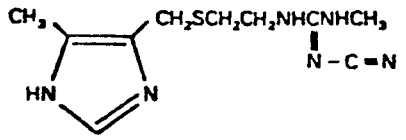
Table V-XII are computer output of the linear regression of concentration on time for cimetidine HCl in two kinds of containers at four different temperatures. The correlation coefficient (r) was acceptable for each line (range -0.96 to -0.99 and -0.92 to -0.99 for glass vials and plastic oral syringes respectively) to assume linearity.

Table XIII-XX are computer output of the linear regression of natural logarithm of the concentration on time for furosemide in two kinds of container at four different temperatures. The correlation coefficient (r) was acceptable for each line (range -0.96 to -0.99 and -0.94 to -0.99 for glass vials and plastic oral syringes respectively) to assume linearity.

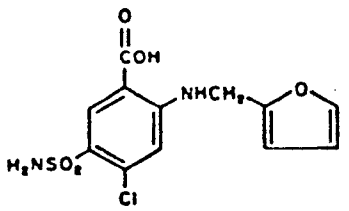
Table XXI and XXII are summary of results of Arrhenius plots for furosemide and cimetidine HCl in glass vials and plastic oral syringes.

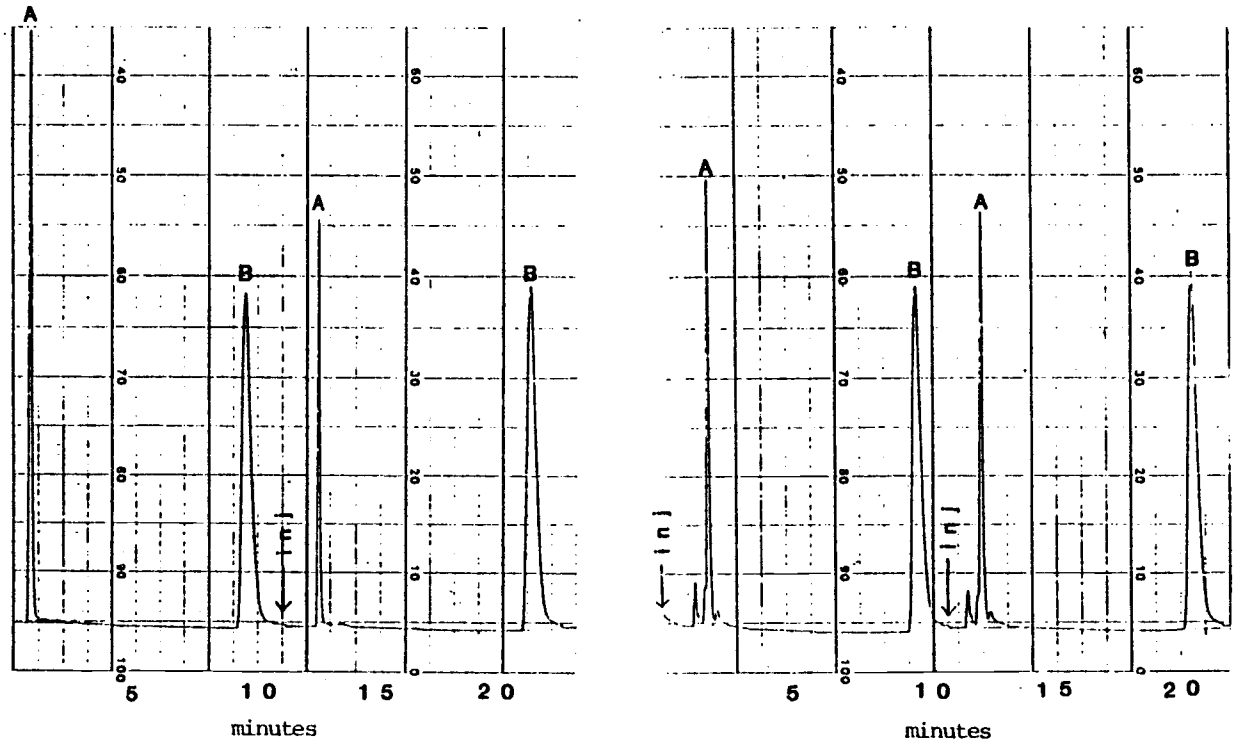
Figure 1- Structures of cimetidine and furosmeide

Cimetidine



FUROSEMIDE
[Lasix]





[a]chromatogram from standard solution

[b]chromatogram from sample solution

Figure 2- Typical chromatogram to show separation of cimetidine and internal standard
A: cimetidine, B: internal standard (tyramine HCl)

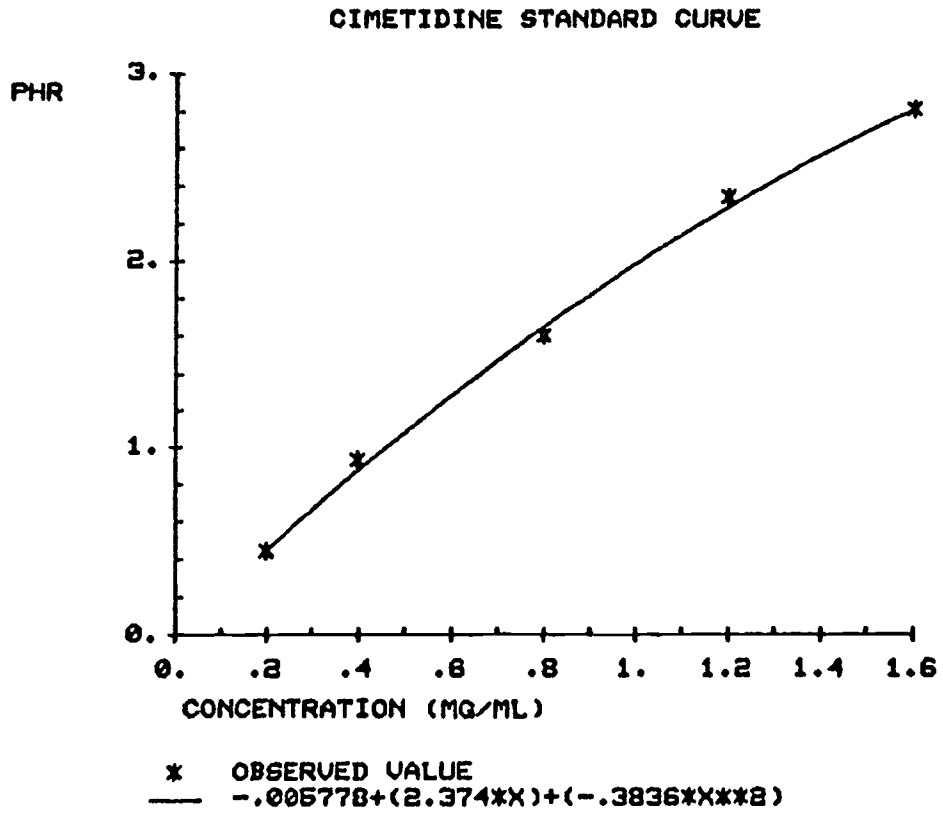


Figure 3- Typical standard curve for cimetidine HCl

Table I- Peak height ratios for four standard curves of Cimetidine

	conc.(mg/ml)	PHR(7/2)	PHR(7/6)	PHR(7/12)	PHR(7/13)
Std1	0.2	0.4507	0.4386	0.4878	0.4861
Std2	0.4	0.9346	0.9231	0.9639	0.9571
Std3	0.8	1.6753	1.5922	1.7333	1.7361
Std4	1.2	2.2065	2.3333	2.2113	2.3140
Std5	1.6	2.5626	2.7984	2.4776	2.6939

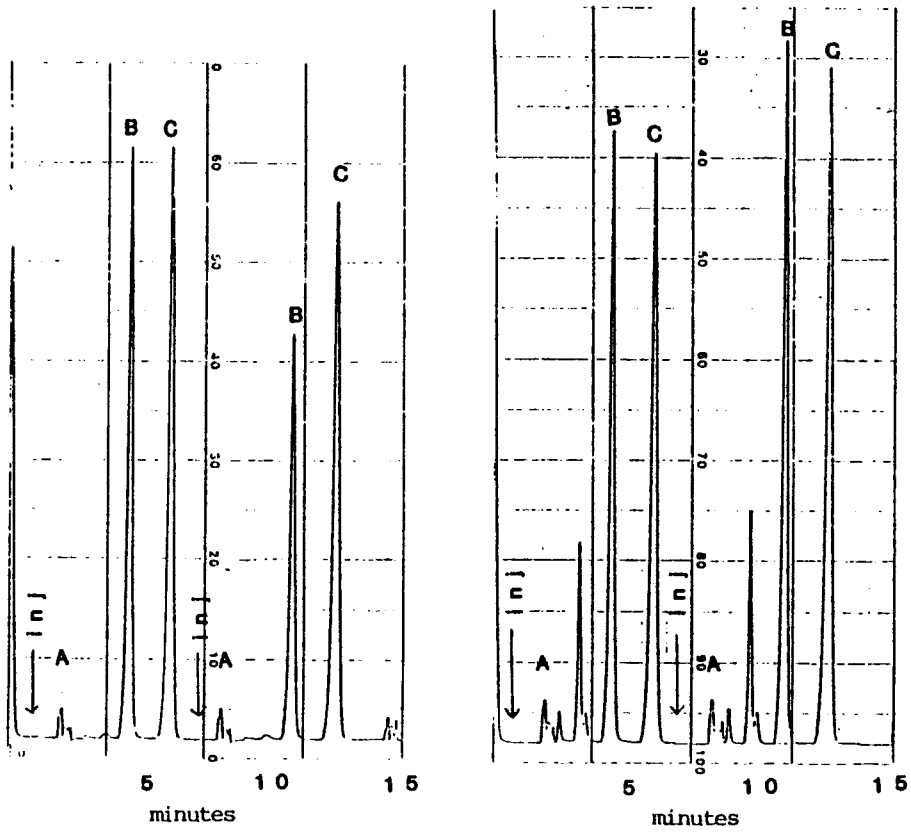
Table II- Inversely estimated concentrations of individual Standard curve data of Cimetidine

	Conc. (mg/ml)	Trial 1		Trial 2		Trial 3		Trial 4		Mean	
		Inv.Est.[a]	%Theory[b]	Inv.Est.	%Theory	Inv.Est.	%Theory	Inv.Est.	%Theory	Inv.Est.	%Theory
Std1	0.20	0.1951	97.5	0.1932	96.6	0.1991	99.6	0.1993	99.6	0.1967	98.4
Std2	0.40	0.4079	101.9	0.4197	104.9	0.3998	99.9	0.4012	100.3	0.4071	101.8
Std3	0.80	0.7982	99.8	0.7685	96.1	0.8073	100.9	0.8002	100.0	0.7935	99.2
Std4	1.20	1.1886	99.1	1.2295	102.5	1.1859	98.8	1.1987	99.9	1.2007	100.1
Std5	1.60	1.6098	100.6	1.5893	99.3	1.6165	101.0	1.6011	100.1	1.6042	100.3
											99.96

[a]Inversely estimated concentration

[b]%Theory=(inversely estimated concentration/known concentration)*100

C.V.=1.28%



[a]chromatogram from standard solution [b]chromatogram from sample solution

Figure 4- Typical chromatogram for separation of furosemide and internal standard
A: solvent, B: furosemide, C: internal standard (propyl paraben)

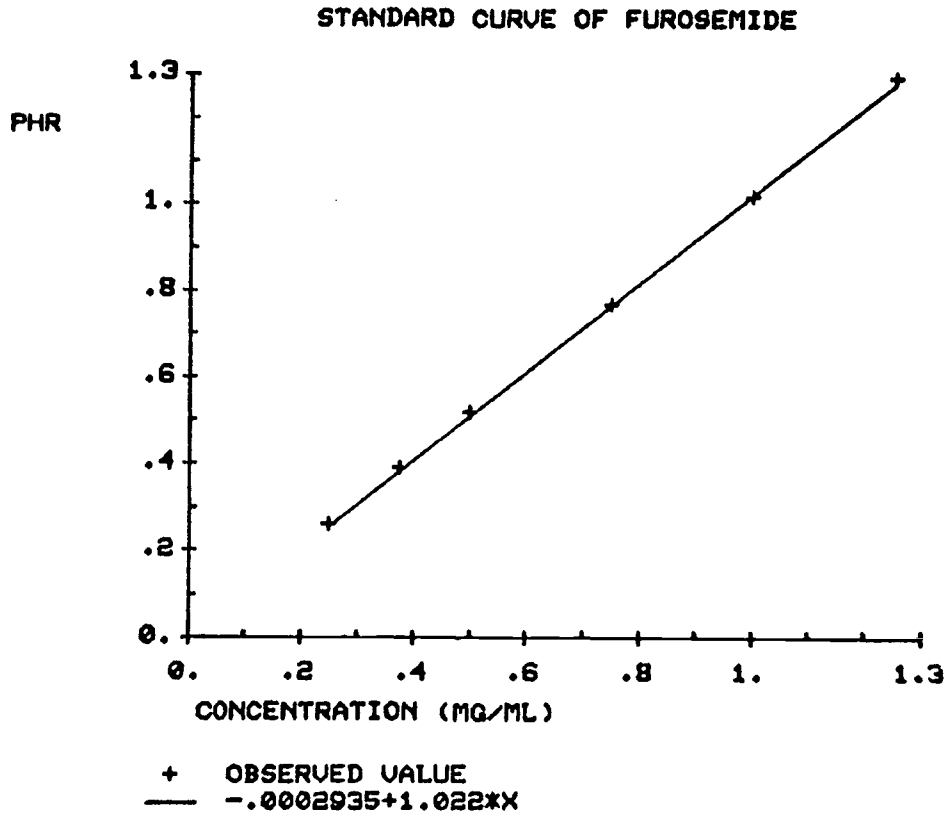


Figure 5- Typical standard curve for furosemide

Table III- Peak height ratios for four standard curves of furosemide

0 ROWNAME	1 CONC.(MG/ML)	2 PHR (7/14)	3 PHR (8/3)	4 PHR (8/7)	5 PHR (9/2)
1. STD1	.25	.2572	.2557	.256	.254
2. STD2	.375	.3763	.3852	.389	.3885
3. STD3	.5	.5477	.5141	.5042	.5018
4. STD4	.75	.79	.7626	.7663	.7566
5. STD5	1.	1.0134	1.01173	1.02531	1.0059
6. STD6	1.25	1.2917	1.2855	1.3059	1.2833

Table IV- Inversely estimated concentrations of individual standard curve data of Furosemide

	Conc. (mg/ml)	Trial 1		Trial 2		Trial 3		Trial 4		Mean	
		Inv.Est.[a]	%Theory[b]	Inv.Est.	%Theory	Inv.Est.	%Theory	Inv.Est.	%Theory	Inv.Est.	%Theory
Std1	0.25	0.2426	97.0	0.2504	100.1	0.2523	100.9	0.2531	101.2	0.2496	99.8
Std2	0.375	0.3589	95.7	0.3770	100.5	0.3842	102.4	0.3825	102.0	0.3756	100.2
Std3	0.50	0.5623	105.3	0.5031	100.6	0.4954	99.1	0.4926	98.5	0.5043	100.8
Std4	0.75	0.7629	101.7	0.7461	99.5	0.7413	98.8	0.7434	99.1	0.7485	99.8
Std5	1.00	0.9812	98.1	0.9898	99.0	0.9898	99.0	0.9913	99.1	0.9880	98.8
Std6	1.25	1.2530	100.0	1.2584	100.7	1.2619	101.0	1.2598	100.8	1.2583	100.7
											100.02

[a] Inversely estimated concentration

[b] %Theory=(inversely estimated concentration/known concentration)*100

C.V.=0.73%

Table V- Computer output for linear regression of cimetidine HCl concentration vs. time in glass vials at 25°C

NUMBER OF DATA POINTS = 8
CORRELATION COEFFICIENT R = -.9680859 R-SQUARED = .9371902
STANDARD DEVIATION OF REGRESSION = .3295819

PARAMETER TABLE

PARAMETER	FITTED VALUE	STANDARD DEVIATION	T-VALUE	SIG. LEV.
INTERCEPT	59.48576	.154116	385.9804	.0001
SLOPE	-.01933039	.002042997	-9.46178	.0001

ANALYSIS OF VARIANCE TABLE

SOURCE	SUM OF SQUARES	D.F.	MEAN SQUARE	F VALUE	SIG. LEV.
REGRESSION	9.723578	1.	9.723578	89.52658	.001
RESIDUAL	.6516664	6.	.1086111		

Table VI- Computer output for linear regression of cimetidine HCl concentration vs. time in glass vials at 44°C

NUMBER OF DATA POINTS = 8
CORRELATION COEFFICIENT R = -.9900683 R-SQUARED = .9802353
STANDARD DEVIATION OF REGRESSION = .8188033

PARAMETER TABLE

PARAMETER	FITTED VALUE	STANDARD DEVIATION	T-VALUE	SIG. LEV.
INTERCEPT	59.52137	.3829043	155.4471	.0001
SLOPE	-.08756006	.005075867	-17.25027	.0001

ANALYSIS OF VARIANCE TABLE

SOURCE	SUM OF SQUARES	D.F.	MEAN SQUARE	F VALUE	SIG. LEV.
REGRESSION	199.5035	1.	199.5035	297.5715	.0001
RESIDUAL	4.022633	6.	.6704388		

Table VII- Computer output for linear regression of cimetidine HCl concentration vs. time in glass vials at 60°C

NUMBER OF DATA POINTS = 5
CORRELATION COEFFICIENT R = -.9952636 R-SQUARED = .9905496
STANDARD DEVIATION OF REGRESSION = 1.007776

PARAMETER TABLE

PARAMETER	FITTED VALUE	STANDARD DEVIATION	T-VALUE	SIG. LEV.
INTERCEPT	59.51799	.7064353	84.25115	.0001
SLOPE	-.7420347	.04184562	-17.73267	.0004

ANALYSIS OF VARIANCE TABLE

SOURCE	SUM OF SQUARES	D.F.	MEAN SQUARE	F VALUE	SIG. LEV.
REGRESSION	319.357	1.	319.357	314.4477	.001
RESIDUAL	3.046837	3.	1.015612		

Table VIII- Computer output for linear regression of cimetidine HCl concentration vs. time in glass vials at 76°C

NUMBER OF DATA POINTS = 5
CORRELATION COEFFICIENT R = -.9949453 R-SQUARED = .9899162
STANDARD DEVIATION OF REGRESSION = 2.059025

PARAMETER TABLE

PARAMETER	FITTED VALUE	STANDARD DEVIATION	T-VALUE	SIG. LEV.
INTERCEPT	57.88919	1.443345	40.10767	.0001
SLOPE	-1.467219	.08549635	-17.16119	.0004

ANALYSIS OF VARIANCE TABLE

SOURCE	SUM OF SQUARES	D.F.	MEAN SQUARE	F VALUE	SIG. LEV.
REGRESSION	1248.585	1.	1248.585	294.5064	.001
RESIDUAL	12.71875	3.	4.239583		

Table VIIII- Computer output for linear regression of cimetidine HCl concentration vs. time in plastic oral syringes at 25°C

NUMBER OF DATA POINTS = 8
CORRELATION COEFFICIENT R = -.9330418 R-SQUARED = .870567
STANDARD DEVIATION OF REGRESSION = .5159889

PARAMETER TABLE

PARAMETER	FITTED VALUE	STANDARD DEVIATION	T-VALUE	SIG. LEV.
INTERCEPT	59.11339	.2412965	244.9823	.0001
SLOPE	-.02031999	.003198682	-6.352612	.0007

ANALYSIS OF VARIANCE TABLE

SOURCE	SUM OF SQUARES	D.F.	MEAN SQUARE	F VALUE	SIG. LEV.
REGRESSION	10.74457	1.	10.74457	40.35603	.001
RESIDUAL	1.597467	6.	.2662446		

Table X- Computer output for linear regression of cimetidine HCl concentration vs. time in plastic oral syringes at 44°C

NUMBER OF DATA POINTS = 8
CORRELATION COEFFICIENT R = -.9890919 R-SQUARED = .9783028
STANDARD DEVIATION OF REGRESSION = .9486603

PARAMETER TABLE

PARAMETER	FITTED VALUE	STANDARD DEVIATION	T-VALUE	SIG. LEV.
INTERCEPT	58.8029	.4436305	132.5493	.0001
SLOPE	-.09672786	.005880868	-16.44789	.0001

ANALYSIS OF VARIANCE TABLE

SOURCE	SUM OF SQUARES	D.F.	MEAN SQUARE	F VALUE	SIG. LEV.
REGRESSION	243.4679	1.	243.4679	270.533	.0001
RESIDUAL	5.399738	6.	.8999564		

Table XI- Computer output for linear regression of cimetidine HCl concentration vs. time in plastic oral syringes at 60°C

NUMBER OF DATA POINTS = 5
CORRELATION COEFFICIENT R = -.9875232 R-SQUARED = .9752021
STANDARD DEVIATION OF REGRESSION = 1.73255

PARAMETER TABLE

PARAMETER	FITTED VALUE	STANDARD DEVIATION	T-VALUE	SIG. LEV.
INTERCEPT	60.26509	1.814491	49.6217	.0001
SLOPE	-.7813978	.07194022	-10.86177	.0017

ANALYSIS OF VARIANCE TABLE

SOURCE	SUM OF SQUARES	D.F.	MEAN SQUARE	F VALUE	SIG. LEV.
REGRESSION	354.138	1.	354.138	117.978	.00167
RESIDUAL	9.005188	3.	3.001729		

Table XII- Computer output for linear regression of cimetidine HCl concentration vs. time in plastic oral syringes at 76°C

NUMBER OF DATA POINTS = 5
CORRELATION COEFFICIENT R = -.9908429 R-SQUARED = .9817697
STANDARD DEVIATION OF REGRESSION = 3.833145

PARAMETER TABLE

PARAMETER	FITTED VALUE	STANDARD DEVIATION	T-VALUE	SIG. LEV.
INTERCEPT	63.66131	2.866385	28.08937	.0001
SLOPE	-1.706396	.134249	-12.71068	.0011

ANALYSIS OF VARIANCE TABLE

SOURCE	SUM OF SQUARES	D.F.	MEAN SQUARE	F VALUE	SIG. LEV.
REGRESSION	1688.837	1.	1688.837	161.5613	.00105
RESIDUAL	31.35968	3.	10.45323		

Table XIII- Computer output for linear regression of furosemide ln concentration vs. time in glass vials at 25°C

NUMBER OF DATA POINTS = 8
CORRELATION COEFFICIENT R = -.9650578 R-SQUARED = .9313366
STANDARD DEVIATION OF REGRESSION = .003230945

PARAMETER TABLE

PARAMETER	FITTED VALUE	STANDARD DEVIATION	T-VALUE	SIG. LEV.
INTERCEPT	2.309922	.001510916	1528.822	.0001
SLOPE	-.000180735	2.002905×10^{-5}	-9.023646	.0001

ANALYSIS OF VARIANCE TABLE

SOURCE	SUM OF SQUARES	D.F.	MEAN SQUARE	F VALUE	SIG. LEV.
REGRESSION	.0008495555	1.	.0008495555	81.3828	.001
RESIDUAL	6.263403×10^{-5}	6.	1.043901×10^{-5}		

Table XIV- Computer output for linear regression of furosemide ln concentration vs. time in glass vials at 44°C

NUMBER OF DATA POINTS = 8
CORRELATION COEFFICIENT R = -.9951629 R-SQUARED = .9903492
STANDARD DEVIATION OF REGRESSION = .006398717

PARAMETER TABLE

PARAMETER	FITTED VALUE	STANDARD DEVIATION	T-VALUE	SIG. LEV.
INTERCEPT	2.304935	.002992289	770.2916	.0001
SLOPE	-.0009842576	3.966648×10^{-5}	-24.81334	.0001

ANALYSIS OF VARIANCE TABLE

SOURCE	SUM OF SQUARES	D.F.	MEAN SQUARE	F VALUE	SIG. LEV.
REGRESSION	.02520934	1.	.02520934	615.7092	.0001
RESIDUAL	.0002456615	6.	4.094358×10^{-5}		

Table XV- Computer output for linear regression of furosemide ln concentration vs. time in glass vials at 60°C

NUMBER OF DATA POINTS = 6
CORRELATION COEFFICIENT R = -.9974213 R-SQUARED = .9948493
STANDARD DEVIATION OF REGRESSION = .01439663

PARAMETER TABLE

PARAMETER	FITTED VALUE	STANDARD DEVIATION	T-VALUE	SIG. LEV.
INTERCEPT	2.328907	.008467806	275.0307	.0001
SLOPE	-.008133073	.0002926028	-27.79561	.0001

ANALYSIS OF VARIANCE TABLE

SOURCE	SUM OF SQUARES	D.F.	MEAN SQUARE	F VALUE	SIG. LEV.
REGRESSION	.1601307	1.	.1601307	772.5963	.0001
RESIDUAL	.0008290522	4.	.000207263		

Table XVI- Computer output for linear regression of furosemide ln concentration vs. time in glass vials at 76°C

NUMBER OF DATA POINTS = 6
CORRELATION COEFFICIENT R = -.9987523 R-SQUARED = .9975062
STANDARD DEVIATION OF REGRESSION = .02331719

PARAMETER TABLE

PARAMETER	FITTED VALUE	STANDARD DEVIATION	T-VALUE	SIG. LEV.
INTERCEPT	2.34873	.01371469	171.2565	.0001
SLOPE	-.01895612	.0004739076	-39.9996	.0001

ANALYSIS OF VARIANCE TABLE

SOURCE	SUM OF SQUARES	D.F.	MEAN SQUARE	F VALUE	SIG. LEV.
REGRESSION	.8698889	1.	.8698889	1599.969	.0001
RESIDUAL	.002174765	4.	.0005436912		

Table XVII- Computer output for linear regression of furosemide ln concentration vs. time in plastic oral syringes at 25°C

NUMBER OF DATA POINTS = 8
CORRELATION COEFFICIENT R = -.9171814 R-SQUARED = .8411116
STANDARD DEVIATION OF REGRESSION = .006726342

PARAMETER TABLE

PARAMETER	FITTED VALUE	STANDARD DEVIATION	T-VALUE	SIG. LEV.
INTERCEPT	2.303297	.003145499	732.2518	.0001
SLOPE	-.0002350018	4.169746×10^{-5}	-5.635879	.0013

ANALYSIS OF VARIANCE TABLE

SOURCE	SUM OF SQUARES	D.F.	MEAN SQUARE	F VALUE	SIG. LEV.
REGRESSION	.001437046	1.	.001437046	31.76236	.00134
RESIDUAL	.000271462	6.	4.524367×10^{-5}		

Table XVIII- Computer output for linear regression of furosemide ln concentration vs. time in plastic oral syringes at 44°C

NUMBER OF DATA POINTS = 8
CORRELATION COEFFICIENT R = -.9780889 R-SQUARED = .956658
STANDARD DEVIATION OF REGRESSION = .0164621

PARAMETER TABLE

PARAMETER	FITTED VALUE	STANDARD DEVIATION	T-VALUE	SIG. LEV.
INTERCEPT	2.290105	.007698317	297.4818	.0001
SLOPE	-.001174399	.0001020507	-11.508	.0001

ANALYSIS OF VARIANCE TABLE

SOURCE	SUM OF SQUARES	D.F.	MEAN SQUARE	F VALUE	SIG. LEV.
REGRESSION	.03588964	1.	.03588964	132.4338	.001
RESIDUAL	.001626004	6.	.0002710006		

Table XVIIII- Computer output for linear regression of furosemide ln concentration vs. time in plastic oral syringes at 60°C

NUMBER OF DATA POINTS = 6
CORRELATION COEFFICIENT R = -.9948498 R-SQUARED = .9897267
STANDARD DEVIATION OF REGRESSION = .02948718

PARAMETER TABLE

PARAMETER	FITTED VALUE	STANDARD DEVIATION	T-VALUE	SIG. LEV.
INTERCEPT	2.310966	.01734378	133.2448	.0001
SLOPE	-.01176421	.000599309	-19.62962	.0001

ANALYSIS OF VARIANCE TABLE

SOURCE	SUM OF SQUARES	D.F.	MEAN SQUARE	F VALUE	SIG. LEV.
REGRESSION	.3350349	1.	.3350349	385.3217	.001
RESIDUAL	.003477976	4.	.0008694939		

Table XX- Computer output for linear regression of furosemide ln concentration vs. time in plastic oral syringes at 76°C

NUMBER OF DATA POINTS = 5
CORRELATION COEFFICIENT R = -.9956311 R-SQUARED = .9912814
STANDARD DEVIATION OF REGRESSION = .03063989

PARAMETER TABLE

PARAMETER	FITTED VALUE	STANDARD DEVIATION	T-VALUE	SIG. LEV.
INTERCEPT	2.29943	.02147809	107.0593	.0001
SLOPE	-.02349678	.001272252	-18.46865	.0003

ANALYSIS OF VARIANCE TABLE

SOURCE	SUM OF SQUARES	D.F.	MEAN SQUARE	F VALUE	SIG. LEV.
REGRESSION	.3202172	1.	.3202172	341.0909	.001
RESIDUAL	.002816409	3.	.000938803		

Table XXI- Summary of results of Arrhenius plots for furosemide in glass vials and plastic oral syringes

Container	Intercept	-slope=Ea/R	Ea(Kcal/mole)	r^2
Glass Vials	24.55	9899.16	19.66	0.983
Plastic Oral Syringes	24.91	9931.94	19.73	0.972

Table XXII- Summary of results of Arrhenius plots for cimetidine HCl in glass vials and plastic oral syringes

Container	Intercept	-slope=Ea/R	Ea(Kcal/mole)	r^2
Glass Vials	27.28	9325.69	18.52	0.974
Plastic Oral Syringes	27.87	9486.25	18.84	0.980