CHAPTER IV

RESULTS AND DISCUSSION

Titrations of eight weak acidic compounds were conducted in aqueous solvent (0.1 M KCl in Distilled deionized water) and mixed solvent (40%v/v ethanol/water). The end point volumes obtained from Gran's method were used to determine the percentage purities of these weak acidic compounds. These results were then compared with that obtained from standard titration methods as described in USP XXI. To determine whether there was a statistical difference between these results, the t test was employed at 99% confidence level.

Titration in Aqueous System

Titration of eight weak acidic compounds in aqueous solvent could be divided into two groups. One group was composed of weak acids which showed no precipitation during the course of titrations. The other group was weak acids whose unionized forms had limited solubilities and precipitated during the course of titrations.

1. Weak acids which showed no precipitation during the course of titrations.

Compounds in this group were potassium hydrogenphthalate, phenylpropanolamine HCl and pseudoephedrine HCl.

a. Potassium hydrogenphthalate

This compound is generally employed as a primary standard substance for standardization of sodium hydroxide solution. It is a moderately weak acid with the dissociation constant of 4×10^{-6}. The titration curve of potassium hydrogenphthalate in aqueous solvent (Figure 2) showed a well-defined inflection point at the equivalence region. Therefore conventional methods in potentiometric end point determination such as methods based on the shape of titration curve and differential methods would give accurate and reproducible end point volumes. Based on the end point volumes, the average percentage purity was $100.1 \pm 0.3\%$ (by using parallel tangents method in this study).

Figure 3 showed a V plot shape of Gran plot for the titration of potassium hydrogenphthalate with sodium hydroxide. The curvature at the beginning of the plot (Gran plot which was uncorrected for autoprotolysis of water, this would be called V plot throughout this paper), was probably partly due to high concentration of hydronium

ion and hence, the assumption that $\frac{VN}{Vo+V} >> [H+] - [OH-]$ was not valid. Less curvature was obtained when G plot (corrected for autoprotolysis of water) was employed. However, the curvature at the beginning of the plot did not affect end point determination which was gained from the linear region of the plot.

Table 3 illustrated average end point volumes of four different potassium hydrogenphthlate solutions which were obtained by Gran plots. The end point volumes obtained from G plot differred from that which obtained from V plot by only ± 0.01 ml. This corresponded to difference in percentage purity of only ± 0.38%. It indicated that for the titration of potassium hydrogen-phthalate, autoprotolysis of water did not significantly affect extrapolated value of this end point volume. This result was due to pH range of titration data which was selected for extrapolated line. In this study, the selected pH range was between 5 - 7, hence, hydronium concentration and hydroxide concentration were much smaller than $\frac{VN}{Vo+V}$ as assumed for the V plot.

The average percentage purity calculated from end point volumes (obtained from G plot and V plot) were 99.86 ± 0.4% and 99.48 ± 0.4%, respectively. These values were not significantly different from the average percentage purity obtained from the conventional method (100.1 ± 0.3%, using parallel tangents method to determine end point volumes from potentiographs). Gran plot of the

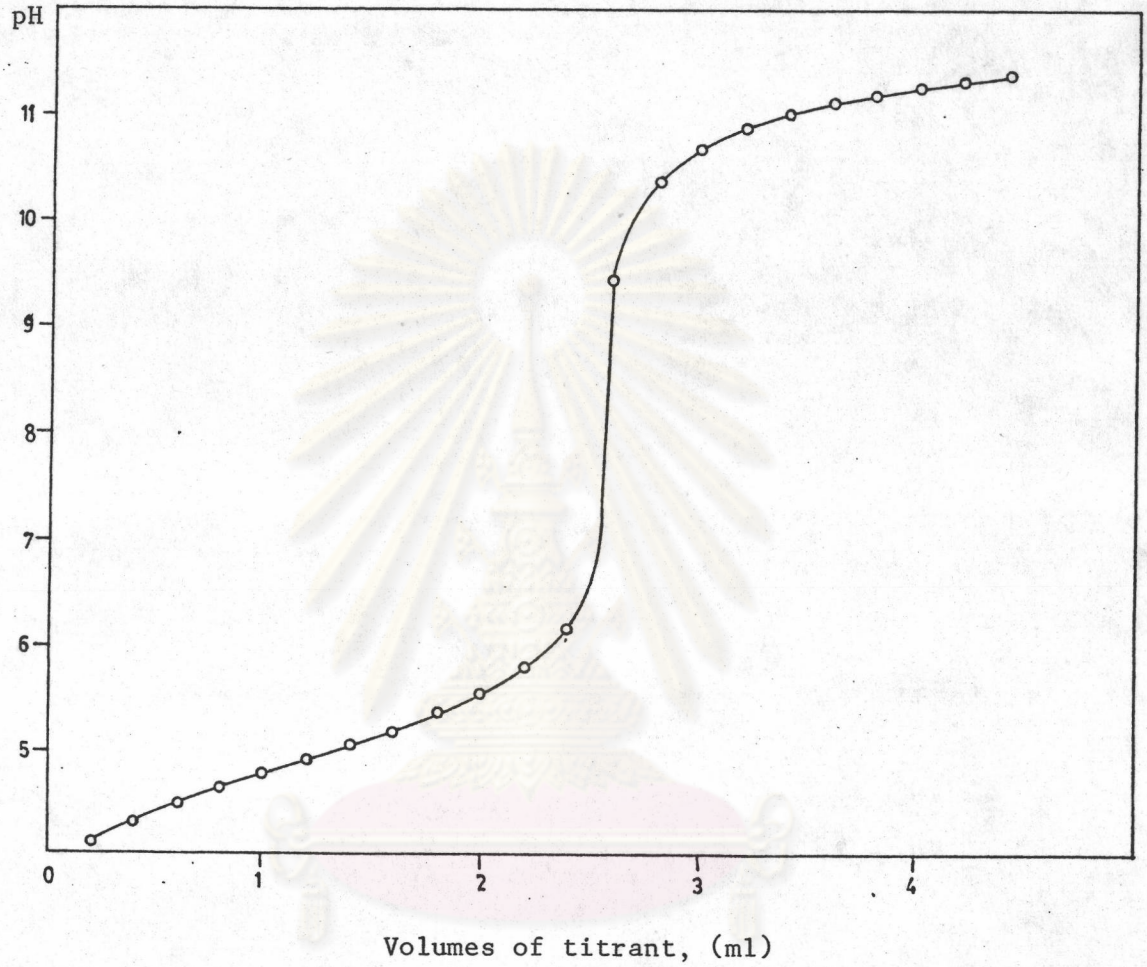

Figure 2 Titration curve of Potassium hydrogenphthalate in 0.1M KCl

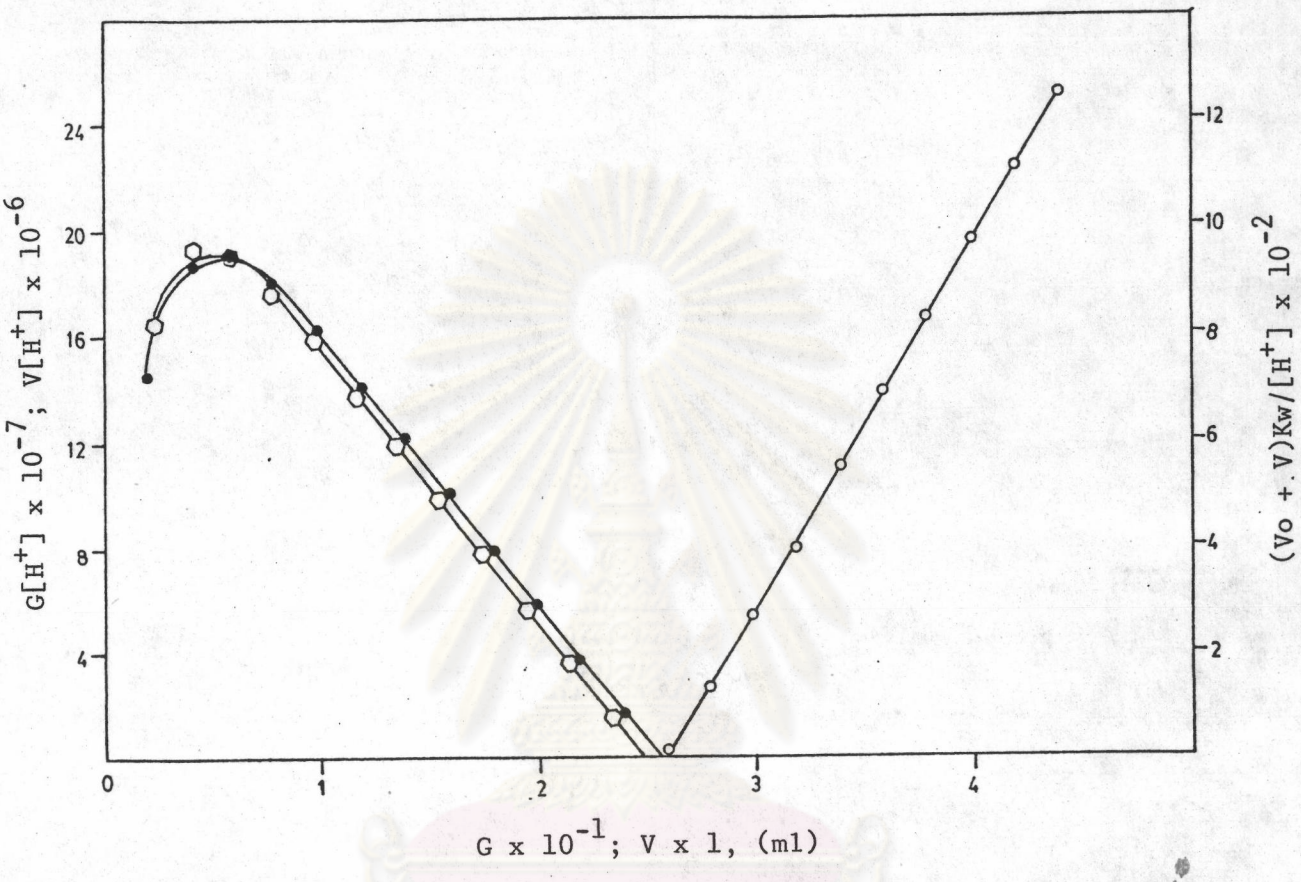

Figure 3 Gran plot for the titration of Potassium hydrogenphthalate in 0.1M KCl with sodium hydroxide; G plot (⬡), V plot (●), and Va plot (○)

Table 3 Average End Point Volumes by Gran's Method for the Titration of Potassium hydrogenphthalate in 0.1M KCl with 0.09730N NaOH

Experiment	Wt. of sample (mg)	End point volumes (ml) Method 1	Method 2	Method 3
A	51.20	2.58 ± 0.01	2.57 ± 0.01	2.59 ± 0.01
B	51.22	2.57 ± 0.01	2.56 ± 0.01	2.58 ± 0.01
C	51.14	2.56 ± 0.01	2.55 ± 0.01	2.58 ± 0.01
D	50.96	2.57 ± 0.00	2.56 ± 0.01	2.58 ± 0.01

Note: (a) average from three parallel titrations

(b) method 1 obtained from the plot of G[H+] versus G

method 2 " " V[H+] " V

method 3 " " (Vo+V)Kw/[H+] " V

titration data after equivalence point also yielded percentage purity (100.4 ± 0.2%) which was statistically same as values obtained from the conventional method, G plot and V plot (Gran plot using titration data prior to equivalence point).

The advantages of Gran's method over the conventional methods were as followed :

1. Simplicity. The end point volume was obtained by extrapolation of linear line which was easier than using some geometrical constructions in order to fix the end point volume of sigmoid curve or drawing the first and second derivatives of titration curves.

2. Rapidness. The end point determination by Gran plot would be faster than the conventional methods since Gran plot needed fewer titration data for evaluation and measurements of titration data need not be made close to equivalence point. Therefore, incompleteness of reaction or instability of measurement which caused slow equilibrium of electrode and titration solution could be avoided (41). Moreover, preliminary estimation of equivalence point was not necessary for Gran plot method.

3. Accuracy. The linear line drawn by Gran plot would serve as an estimate of the accuracy of the data, any point which deviated greatly from the linear line would obviously be an error and should be deleted

from end point determination. However, under reasonable care with good laboratory technics, all points should lie on the linear extrapolated line.

b. Phenylpropanolamine HCl

This compound is a very weak acid with the dissociation constant of 4×10^{-10}. The titration curve of phenylpropanolamine HCl in aqueous solvent illustrated a poorly-defined inflection point in the region of equivalence point (Figure 4). Hence, the conventional methods were not recommended to determine end point volumes (1, 2). The small pH change of each increment of titrant at equivalence region made it impossible to gain accurate and reproducible end point volume from the methods based on sigmoid form of titration curve. For the differential methods (first and second derivative methods), fluctuated curves would be obtained if incomplete reaction near equivalence region occurred. Hence, these methods would not yield correct end point volumes. Thus, in determining percentage purity of phenylpropanolamine HCl, the non-aqueous titration method was usually employed and yielded the result with good accuracy and reproducibility (100.3 ± 0.1%).

Gran's method, end point volumes were usually resulted from titration data which were not close to equivalence region so that the problem of small pH change and incomplete reaction in the vicinity of equiva-

lence point would be avoided. However, titration data near equivalence could be employed in the end point determination by Gran's method if they still lay on tne linear extrapolated line.

Table 4 showed average end point volume obtained by Gran plots (G plot, V plot and the plot of titration data after equivalence point). The V plot gave end point volumes of which the average percentage purity was an overestimate value (102.0 ± 0.8%) which was statistically different from standard method (100.3 ± 0.1%). This result was due to the curvature at equivalence region for V plot. By employing G plot, less curvature was obtained (Figure 5) and average end point volumes were more accurate and reproducible (Table 4). The percentage purity based on these values was 100.2 ± 0.3%. The difference between average percentage purities obtained from standard non-aqueous method and G plot was not statistically different. Gran plot of titration data after equivalence point yielded percentage purity of 99.83 ± 0.4% which was also statistically identical to those of non-aqueous method and G plot of titration data prior to equivalence point.

c. Pseudoephedrine HCl

This is the weakest acid in this study which has dissociation constant of 1×10^{-10}. Titration curve of this compound in aqueous solvent showed no noticeable inflection point at equivalence point (Figure 6).

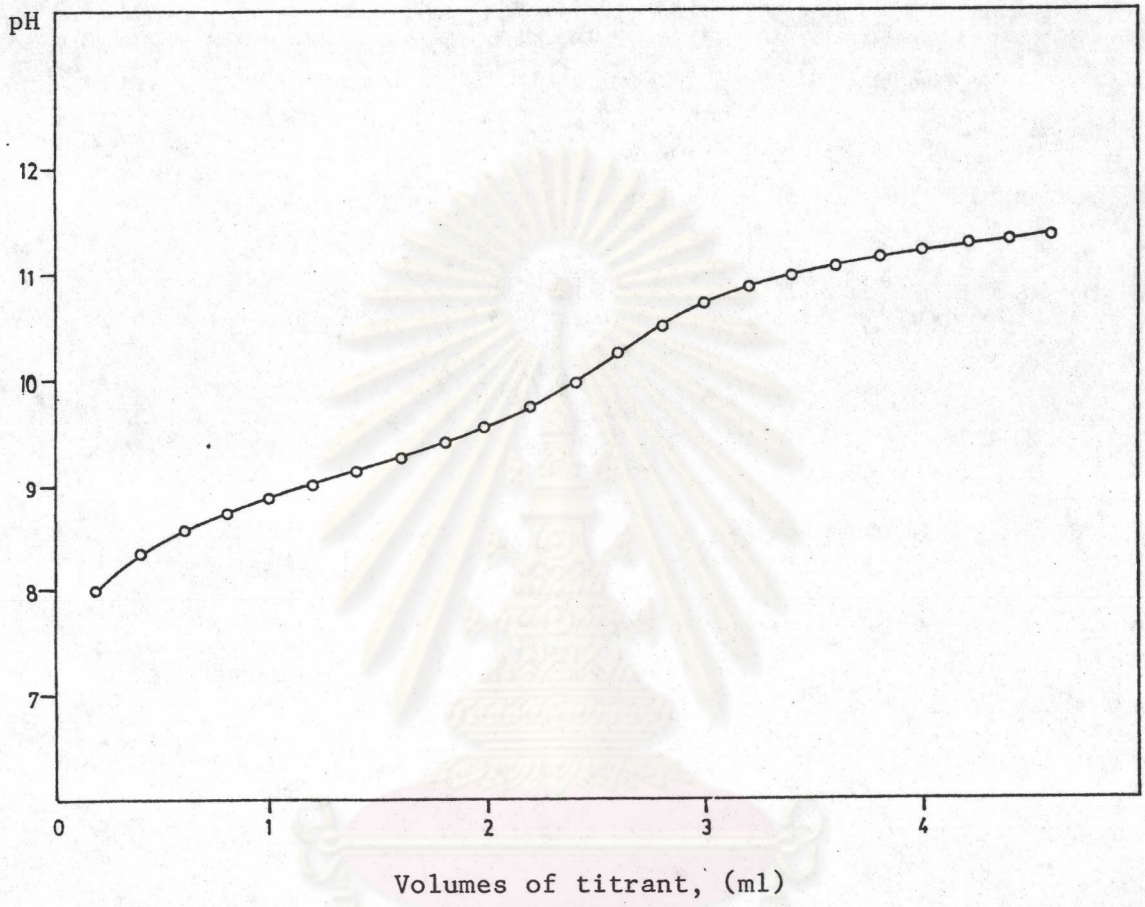

Figure 4 Titration curve of Phenylpropanolamine HCl in 0.1M KCl

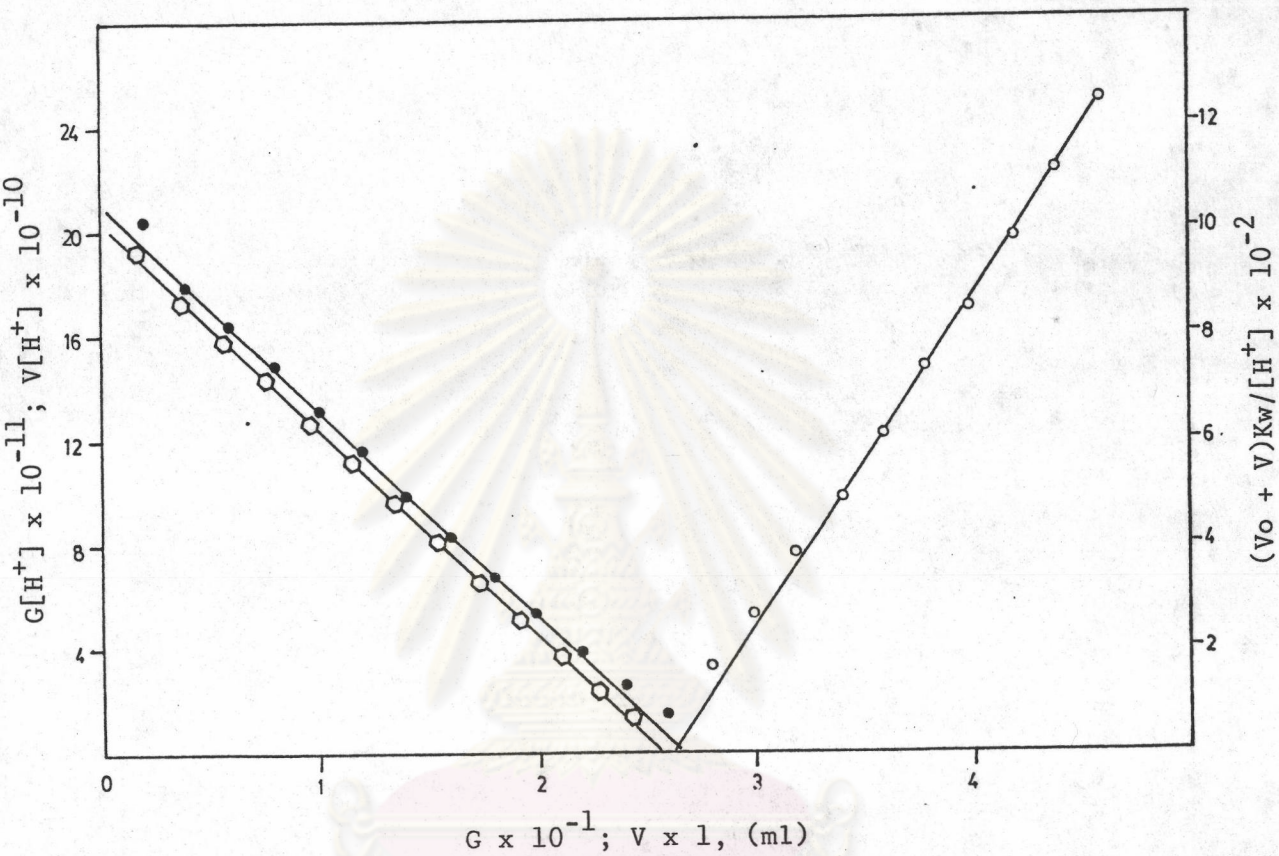

Figure 5 Gran plot for the titration of Phenylpropanolamine HCl in 0.1M KCl with sodium hydroxide; G plot (⬡), V plot (●) and Va plot (○)

Table 4 Average End Point Volumes by Gran's Method for the Titration of Phenylpropanolamine HCl in 0.1 M KCl with 0.09730N NaOH

Experiment	Wt. of sample (mg)	End point volumes (ml) Method 1	Method 2	Method 3
A	47.64	2.62 ± 0.02	2.65 ± 0.02	2.60 ± 0.02
B	47.28	2.59 ± 0.01	2.63 ± 0.01	2.60 ± 0.01
C	47.16	2.58 ± 0.01	2.63 ± 0.01	2.57 ± 0.00
D	47.24	2.60 ± 0.03	2.67 ± 0.01	2.58 ± 0.01

Note : (a) average from three parallel titrations

(b) method 1 obtained from the plot of $G[H^+]$ versus G

method 2 " " $V[H^+]$ " V

method 3 " " $(Vo+V)Kw/[H^+]$ " V

Therefore, it was not possible to determine end point volumes by the conventional methods especially the method based on sigmoid curve. Thus, percentage purity of pseudoephedrine HCl should be determined by non-aqueous titration method which yielded excellent value of 99.98 ± 0.3%.

Gran's method should be advantageously employed for end point determination of pseudoephedrine HCl in aqueous solvent as the same reason for that of phenyl propanolamine HCl. In this case, the correction for autoprotolysis of water was still important for Gran's method since V plot showed profound curvature at equivalence region (Figure 7). This resulted in an highly overestimation of percentage purity value of this compound (106.7 ± 1.0%) while G plot gave portions of linear lines which extrapolation to X-axis yielded accurate and reproducible end point volumes (Table 5). The percentage purity calculated from these values (from G plot) was 100.2 ± 0.5% which was statistically same as that of non-aqueous titration method.

Gran plot from titration data after equivalence point gave an erroneous result (95.71 ± 0.7%).
The reason was that the curvature of the titration line was large and only few titration data were useful as the measured pHs which were higher than 11 should be avoided due to alkaline error of glass electrode which could occur especially in the high concentration of potassium chloride solution. In this condition glass electrode would falsely

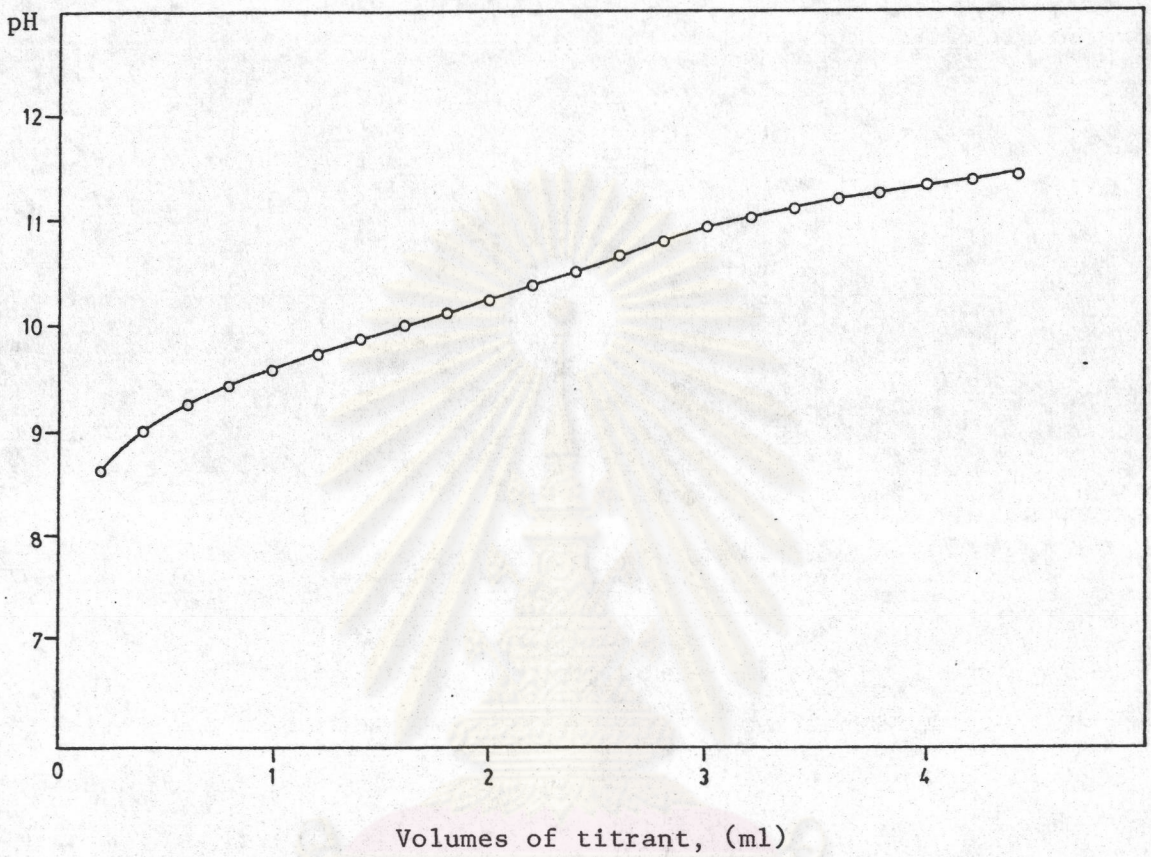

Figure 6 Titration curve of Psuedoephedrine HCl in 0.1M KCl

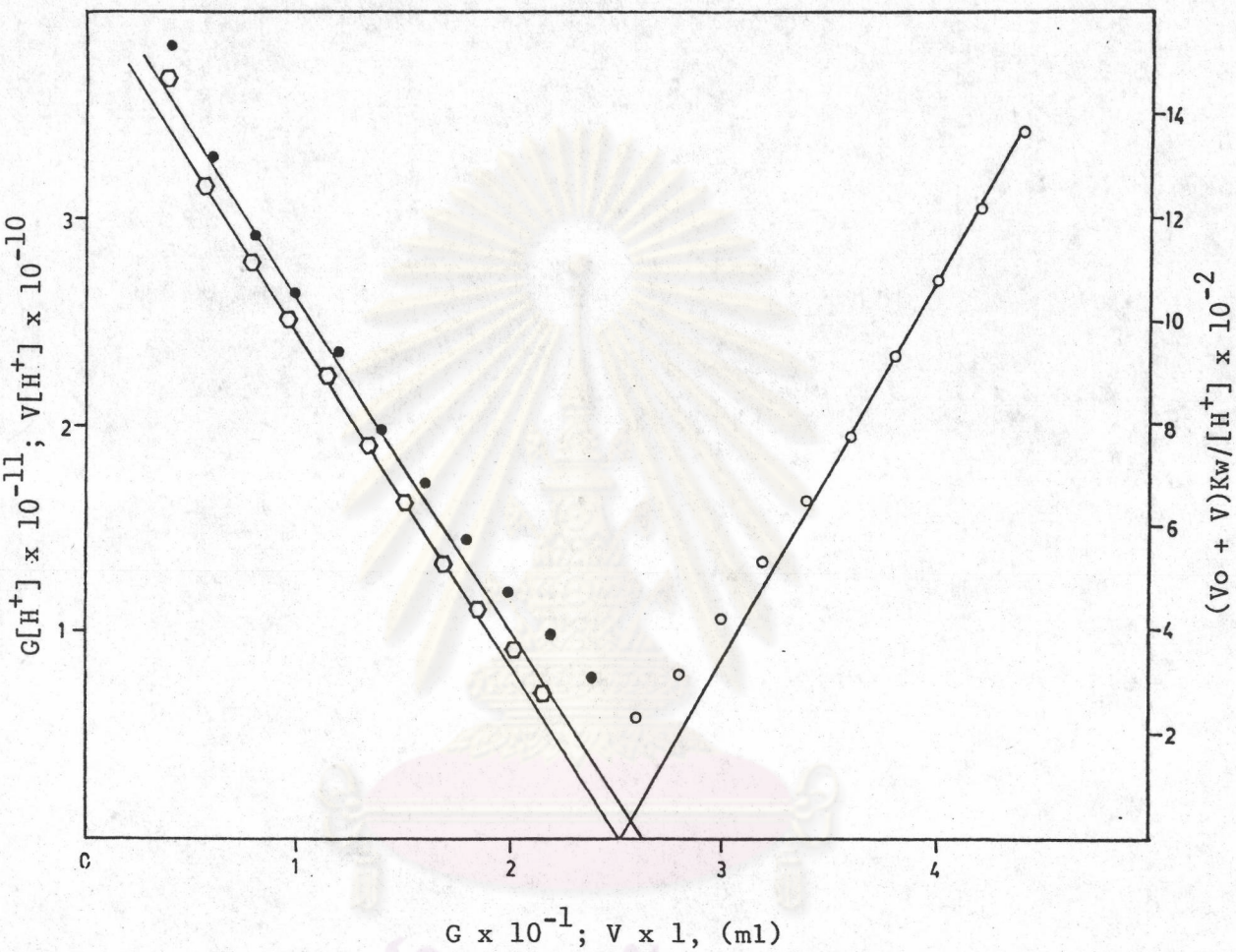

Figure 7 Gran plot for the titration of Pseudoephedrine HCl in 0.1M KCl with sodium hydroxide; G plot (⬡), V plot (●) and Va plot (○)

Table 5 Average End Point Volumes by Gran's Method for the Titration of Pseudoephedrine HCl in 0.1M KCl with 0.09730N NaOH

Experiment	Wt. of sample (mg)	End point volumes (ml) Method 1	Method 2	Method 3
A	50.74	2.58 ± 0.02	2.76 ± 0.01	2.50 ± 0.03
B	50.64	2.60 ± 0.01	2.76 ± 0.01	2.45 ± 0.04
C	51.04	2.61 ± 0.00	2.80 ± 0.01	2.48 ± 0.02
D	51.40	2.60 ± 0.00	2.76 ± 0.01	2.51 ± 0.04

Note: (a) average from three parallel titrations

(b) method 1 obtained from the plot of G[H+] versus G

method 2 " " V[H+] " V

method 3 " " (Vo+V)Kw/[H+] " V

measured some of the Na^+ ion in the solution for hydronium ion. Therefore, actual pH should be higher than what was measured.

2. Weak acids which unionized products precipitated during the course of titrations

This group was composed of triprolidine HCl, diphenhydramine HCl, dextromethorphan HBr, quinine sulfate and chlorpheniramine maleate. Precipitations occurred because of low solubilities in water of their conjugate bases.

If there were precipitations during acid-base titrations, conventional methods for potentiometric end point determinations would yield erroneous results because titrations of these weak acids would show asymmetrical titration curves. In the region of initial precipitation, supersaturation would occur and fine particles of the precipitate could redissolve again. Since pH values were altered according to the changes of buffering system of [B] and [HB^+], the variable [B] in the region of initial precipitation caused erroneous measured pH values.

Gran's method was exploited for determining end point volumes of acid-base titrations which involved precipitations. According to new equilibrium dissociations after unionized conjugate bases had precipitated, new Gran plots were obtained as described in equations 62 and 63. They still yielded V plot shapes and end point volumes could be determined by extrapolation to X-axis. Those five

compounds which employed Gran's method were discussed as followed :

a. Triprolidine HCl

This compound has the dissociation constant of 3×10^{-7}. Its conjugate base, triprolidine, had sparing solubility in water and began to precipitate after 0.6 ml of sodium hydroxide standard solution had been added. At this point the pH of the solution was found to decrease as illustrated in the titration curve (Figure 8).

Table 6 showed average end point volumes obtained from Gran plots (V plot, G plot and the plot of titration data after equivalence point). Gran plot curves were shown in Figure 9. The percentage purity of triprolidine HCl based on end point volumes of V plot was 99.63 ± 0.2% which was statistically significantly higher from that of standard non-aqueous titration (98.49 ± 0.6%), while percentage purity from G plot was 99.02 ± 0.3% and did not differed statistically from that of non-aqueous method. Therefore, autoprotolysis of water should be taken into account for the Gran plot in determination of percentage purities (or end point volumes).

Employing titration data after equivalence point, Gran plot yielded end point volumes of which percentage purity was 98.92 ± 0.2%. The t test at 99% confidence level indicated the statistically indifference of this

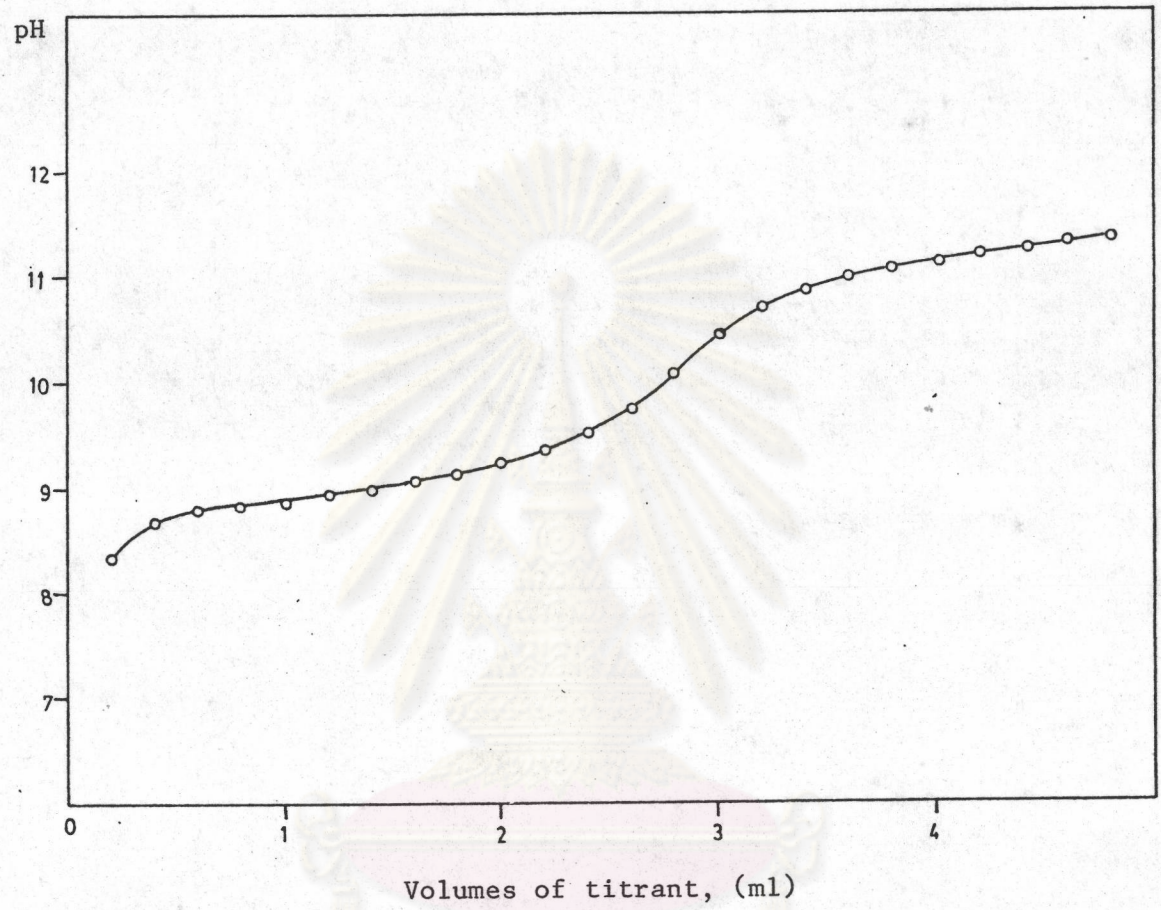

Figure 8 Titration curve of Triprolidine HCl in 0.1M HCl

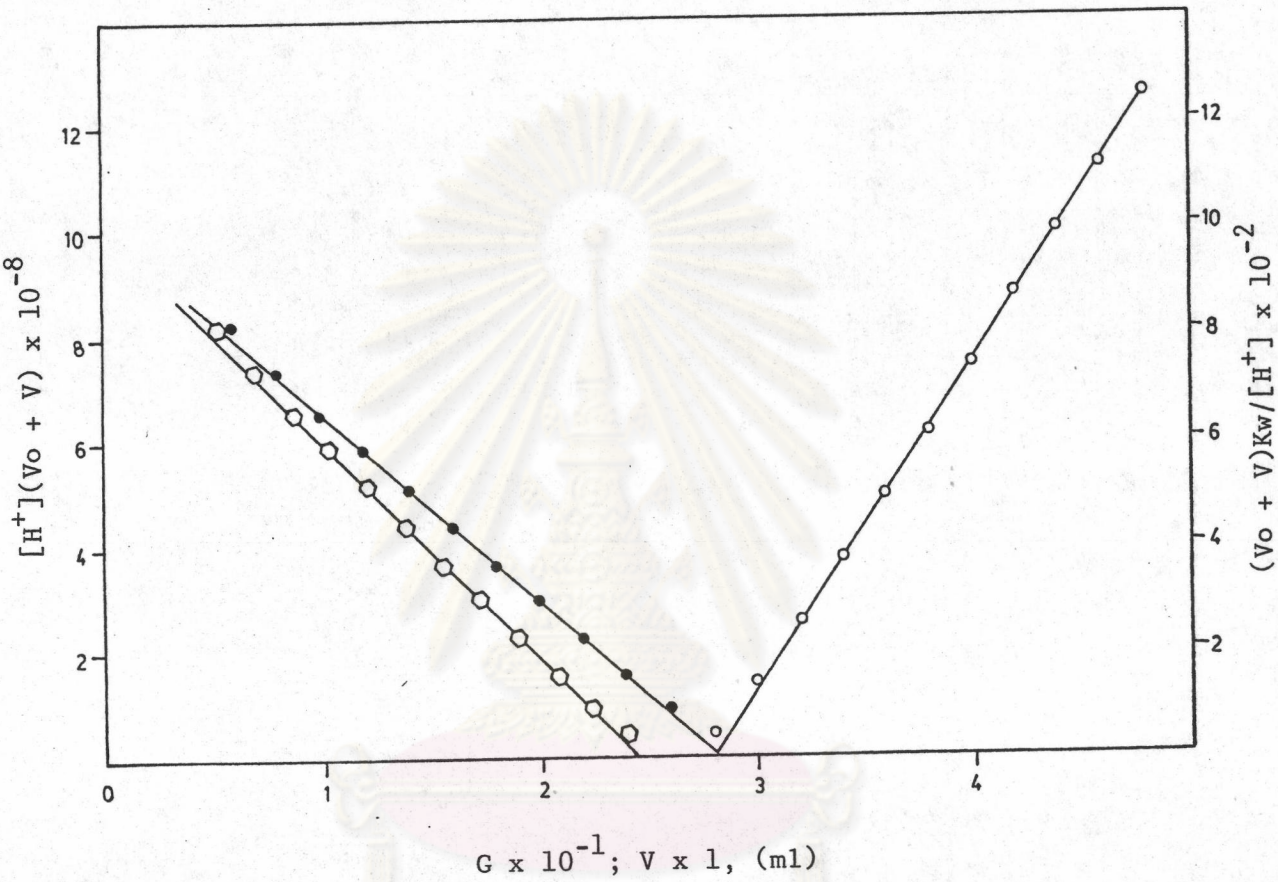

Figure 9 Gran plot for the titration of Triprolidine HCl in 0.1M KCl with sodium hydroxide; G plot (⬡), V plot (●) and Va plot (○)

Table 6 Average End Point Volumes by Gran's Method for the Titration of Triprolidine HCl in 0.1M KCl with 0.08737N NaOH

Experiment	Wt. of sample (mg)	End point volumes (ml) Method 4	Method 5	Method 3
A	82.54	2.80 ± 0.01	2.82 ± 0.01	2.81 ± 0.01
B	81.56	2.79 ± 0.01	2.80 ± 0.01	2.78 ± 0.01
C	81.72	2.78 ± 0.00	2.80 ± 0.01	2.78 ± 0.01
D	81.40	2.77 ± 0.01	2.79 ± 0.01	2.76 ± 0.02

Note: (a) average from three parallel titrations

(b) method 4 obtained from the plot of [H+](Vo+V) versus G

method 5 " " [H+](Vo+V) " V

method 3 " " (Vo+V)Kw/[H+] " V

value from that of non-aqueous method and G plot. Hence, for triprolidine HCl, only G plot and the plot of titration data after equivalence point were found to give satisfactory results.

b. Diphenhydramine HCl

The dissociation constant of this compound was 1×10^{-9}. Its conjugate base began to precipitate out of solution after 0.8 ml of titrant was added to the solution. Titration curve of diphenhydramine HCl in aqueous was shown in Figure 10.

Table 7 showed values of end point volumes which were obtained by Gran plot methods. The V plot shape for Gran plots of this compound was shown in Figure 11. The V plot yielded end point values which when calculated in term of percentage purity was 100.2 ± 0.2%. This was statistically same as percentage purity obtained from G plot (100.1 ± 0.2%).

Gran plot of titration data after equivalence point also yielded percentage purity of 100.2 ± 0.4% which was statistically identical to that of V plot and G plot. All three plots of Gran methods (V plot, G plot and the plot of titration data after equivalence point) could be employed to determine end point volumes which gave percentage purity with the same degree of accuracy and reproducibility as that of standard non-aqueous method (99.73 ± 0.1%).

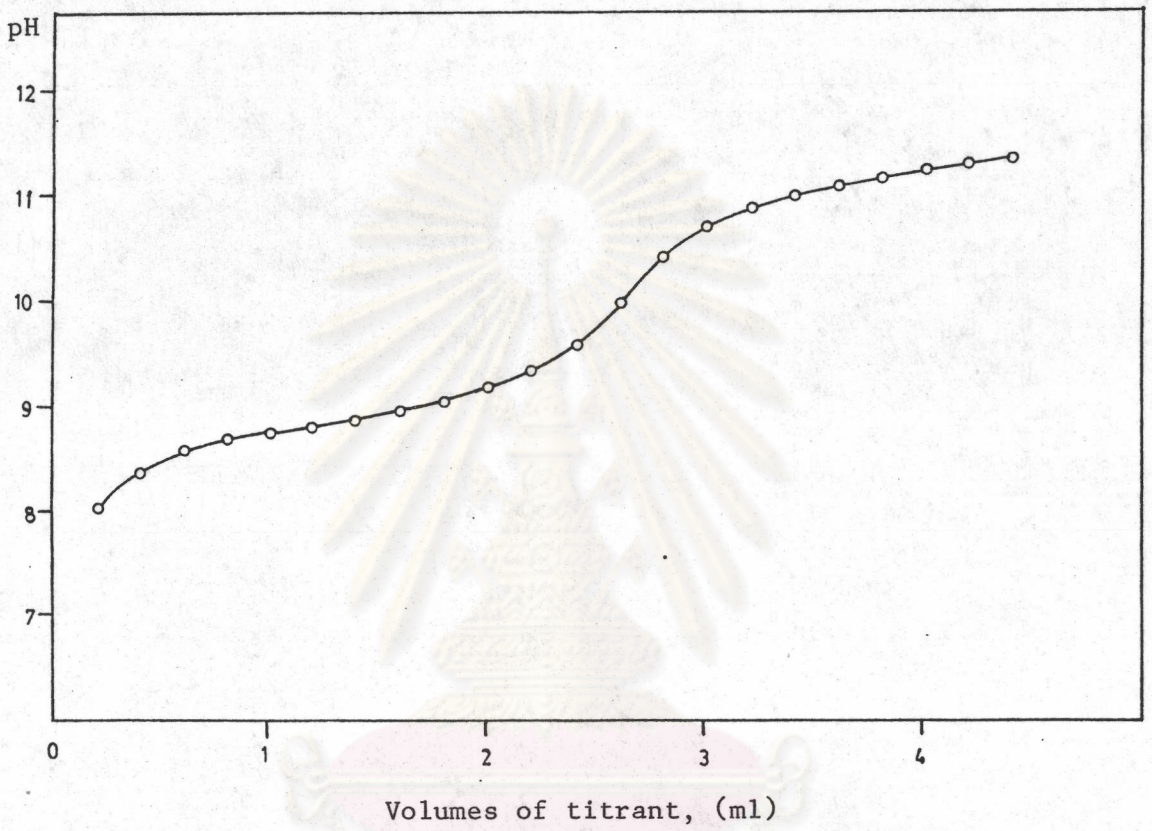

Figure 10 Titration curve of Diphenhydramine HCl in 0.1M KCl

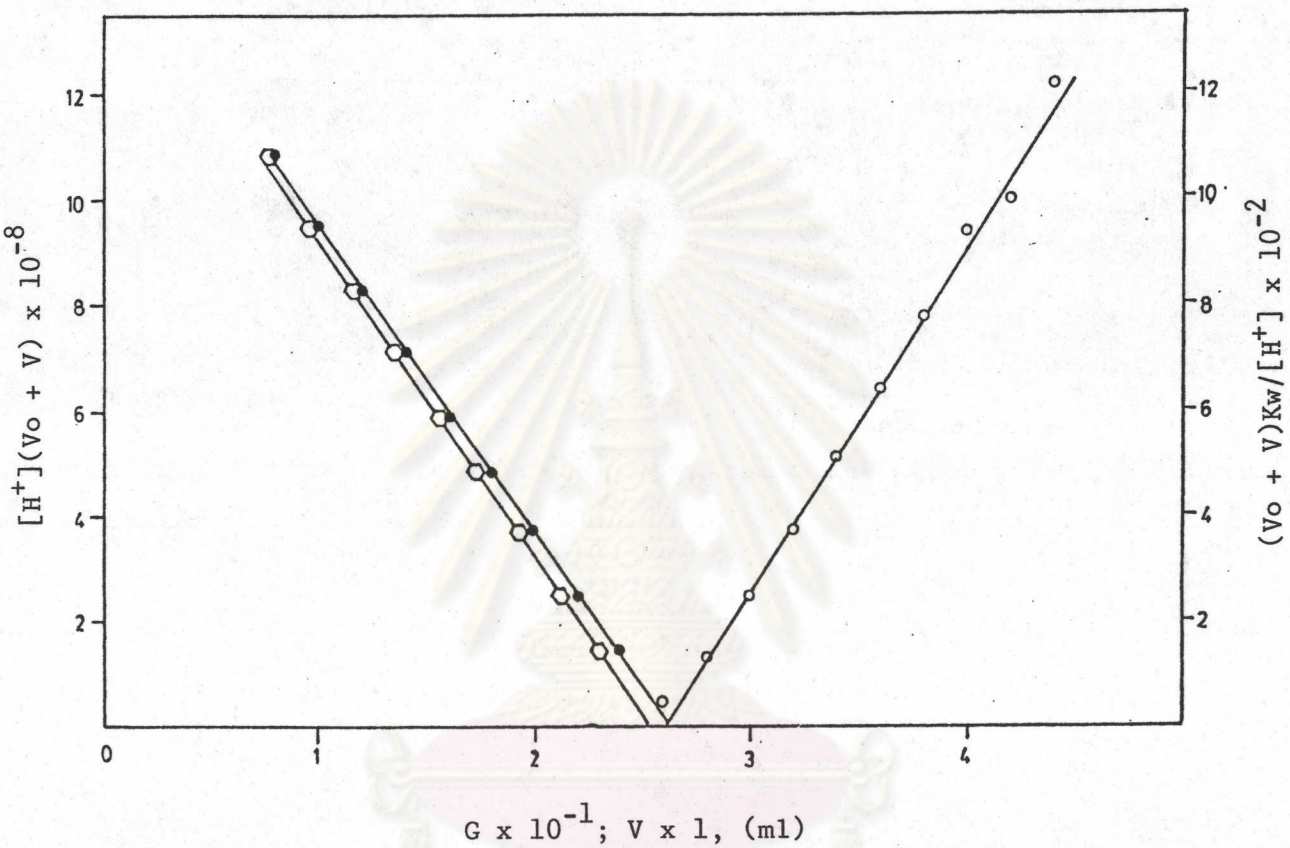

Figure 11 Gran plot for the titration of Diphenhydramine HCl in 0.1M KCl with sodium hydroxide; G plot (⬡), V plot (●) and Va plot (○)

Table 7 Average End Point Volumes by Gran's Method for the Titration of Diphenhydramine HCl in 0.1M KCl with 0.09730N NaOH

Experiment	Wt. of sample (mg)	End point volumes (ml) Method 4	Method 5	Method 3
A	73.36	2.59 ± 0.01	2.59 ± 0.01	2.60 ± 0.01
B	74.78	2.63 ± 0.01	2.64 ± 0.01	2.63 ± 0.01
C	73.30	2.59 ± 0.01	2.59 ± 0.01	2.59 ± 0.01
D	73.90	2.60 ± 0.02	2.60 ± 0.02	2.60 ± 0.01

Note: (a) average from three parallel titrations

(b) method 4 obtained from the plot of $[H^+](V_o+V)$ versus G

method 5 " " $[H^+](V_o+V)$ " V

method 3 " " $(V_o+V)K_w/[H^+]$ " V

c. Dextromethorphan HBr

This weak acid has dissociation constant of 5×10^{-9}. Precipitation occured after about 0.8 ml of titrant was added to the titrated solution. Titration curve for this compound was shown in Figure 12. The pattern of the titration curve was similar to that of triprolidine HCl and diphenhydramine HCl.

The average end point volumes obtained from Gran plot were shown in Table 8. The Gran plot curves were shown in Figure 13. The non linear lines were obtained from V plot and G plot because there was influence of solubility of the precipitate (33) which was very fine and could redissolve during the stirrer on. Hence, [B] in equation 55 which was assumed for a constant value was not valid and Gran plot prior to equivalence point would yield erroneous end point volumes (104.8 ± 0.9%, 102.0 ± 0.4% for V plot and G plot, respectively) as standard non-aqueous method yielded 99.97 ± 0.1%.

In the alkaline region of titration, Gran plot was not affected by the precipitation. The titration was as if we were titrating a blank solution. The pH values recorded were direct results of sodium hydroxide volumes of which were added to the titrated solution. Thus, extrapolation to X-axis of the linear line from Gran plot would yield accurate and reproducible end point volumes. The percentage purity based on these end point

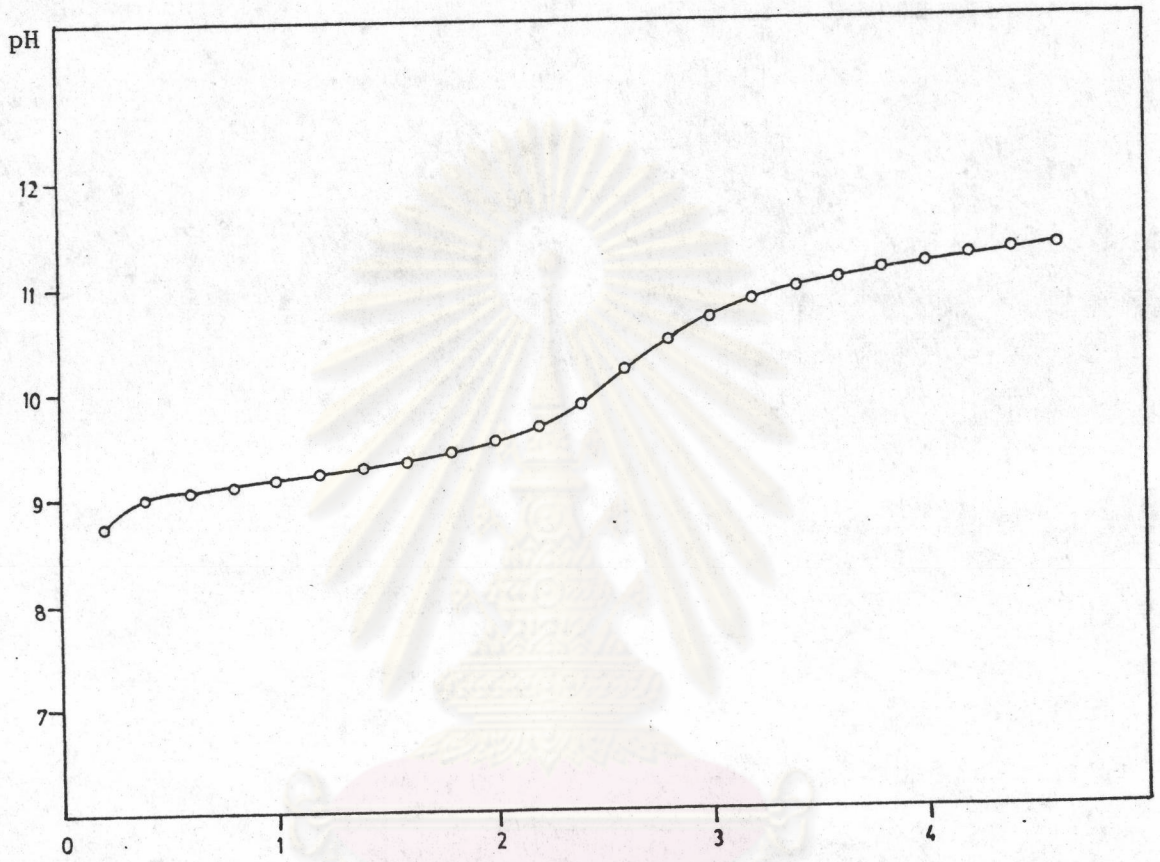

Figure 12 Titration cruve of Dextromethorphan HBr in 0.1M KCl

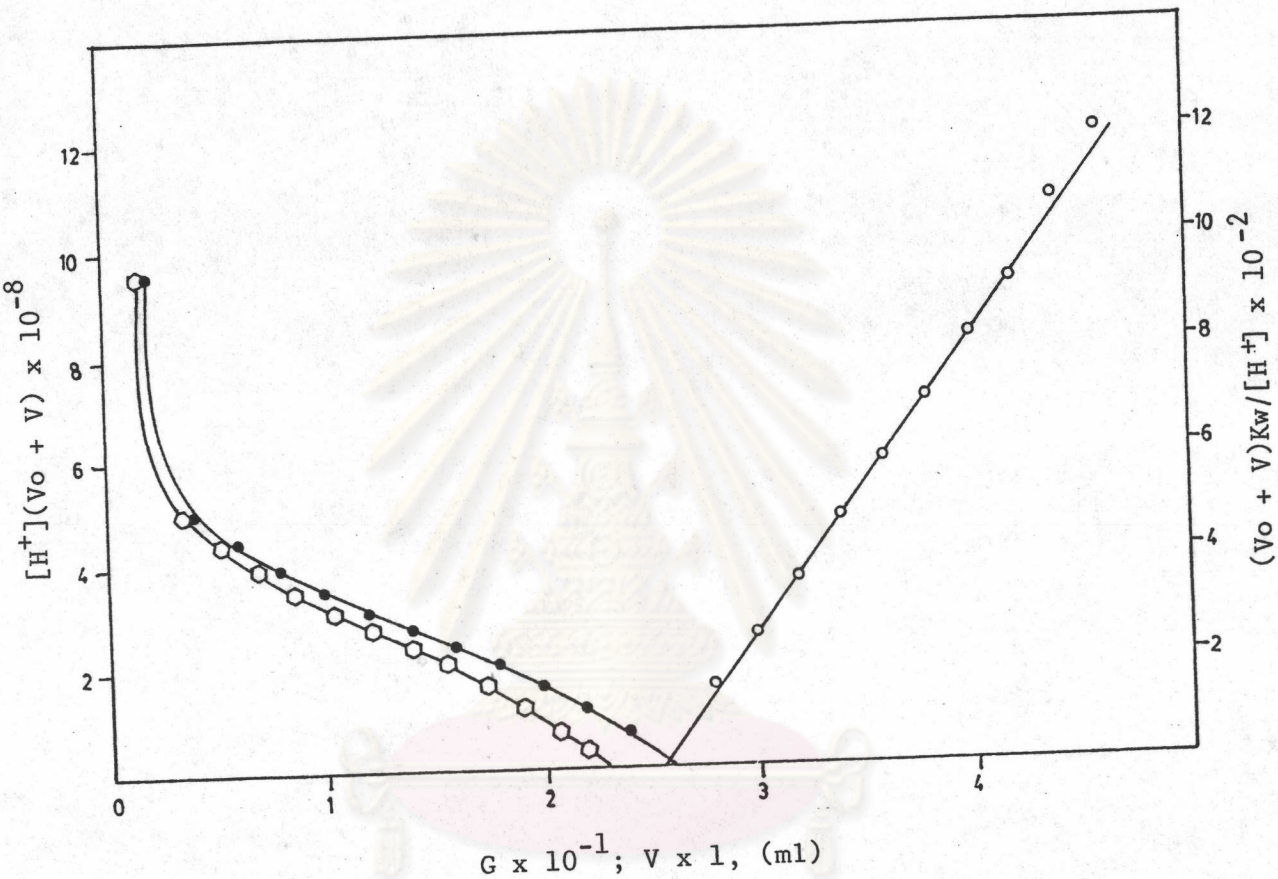

Figure 13 Gran plot for the titration of Dextromethorphan HBr in 0.1M KCl with sodium hydroxide; G plot (⬡), V plot (●) and Va plot (○)

Table 8 Average End Point Volumes by Gran's Method for the Titration of Dextrometorphan HBr in 0.1M KCl with 0.08737N NaOH

Experiment	Wt. of sample (mg)	End point volumes (ml) Method 4	Method 5	Method 3
A	84.26	2.67 ± 0.01	2.75 ± 0.01	2.60 ± 0.01
B	84.76	2.67 ± 0.01	2.76 ± 0.01	2.61 ± 0.01
C	89.52	2.81 ± 0.01	2.87 ± 0.01	2.77 ± 0.01
D	87.96	2.77 ± 0.01	2.84 ± 0.01	2.72 ± 0.02

Note: (a) average from three parallel titrations

(b) method 4 obtained from the plot of $[H^+](V_o+V)$ versus G

method 5 " " $[H^+](V_o+V)$ " V

method 3 " " $(V_o+V)K_w/[H^+]$ " V

volumes was 99.90 ± 0.9% which was equivalencent to that of standard method.

d. Quinine sulfate

This compound has dissociation constant of 2×10^{-9}. Titration curve was shown in Figure 14. During the course of titration, this compound yielded a light and bulky precipitate which differed from triprolidine, diphenhydramine and dextromethorphan. The precipitate could interfere the pH measurement during the course of titration because it deposited on the membrane of glass electrode and hence ion-exchange at the membrane would be altered from an ordinary condition. This resulted erroneous pH values. It was difficult to clean the electrode while the titration was in process without affecting the concentration of ions in the titration solution.

Gran plot (V plot, G plot and the plot of titration data after equivalence, Figure 15) yielded end point volumes as shown in Table 9. All of these values when calculated in percentage purities were 100.8 ± 0.5%, 100.6 ± 0.4% and 100.7 ± 0.5%, respectively. However, all these values were statistically different from the percentage purity of standard method (97.94 ± 0.5%). This discrepency would be due to effect of the precipitate coating the electrode.

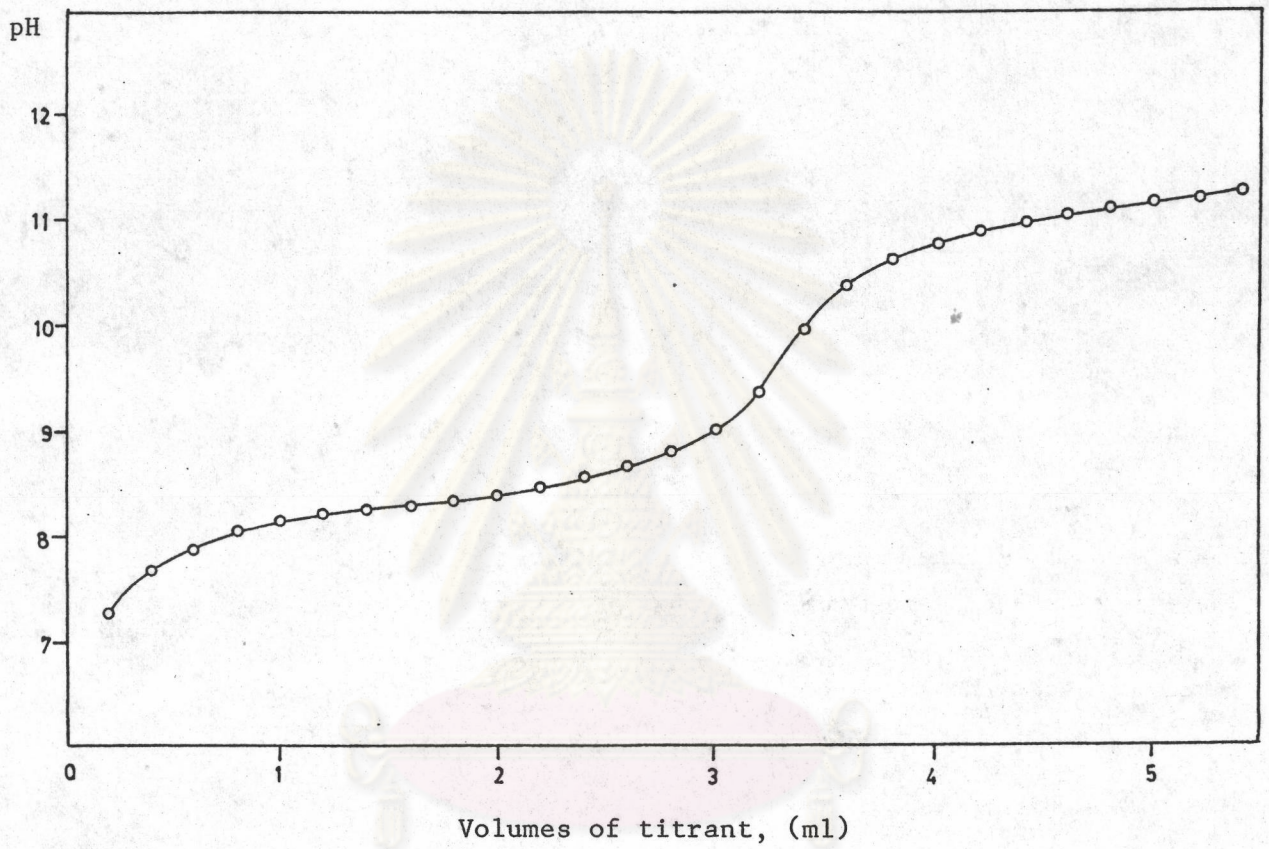

Figure 14 Titration curve of Quinine sulfate in 0.1M KCl

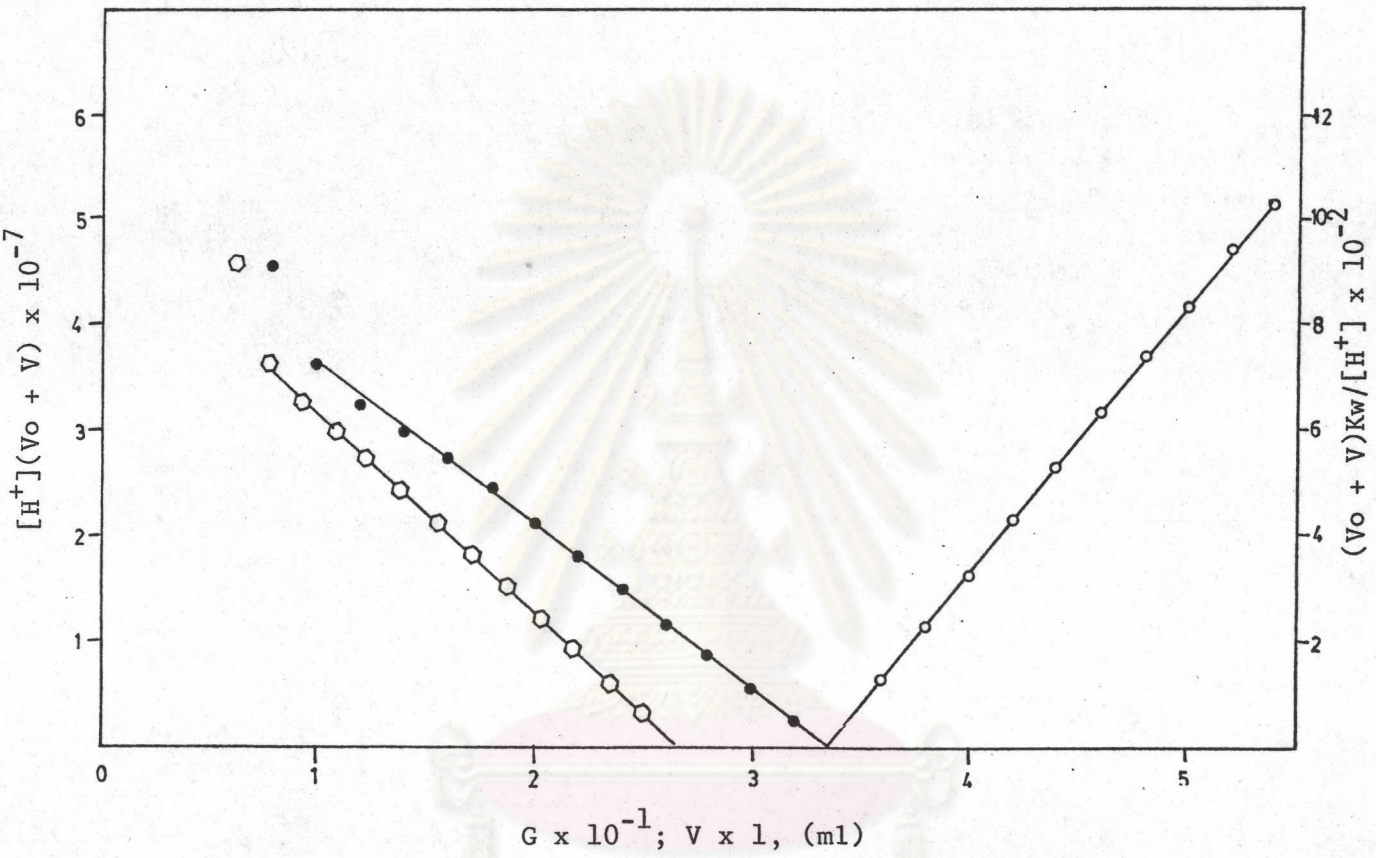

Figure 15 Gran plot for the titration of Quinine sulfate in 0.1M KCl with sodium hydroxide; G plot (⬡), V plot (●) and Va plot (○)

Table 9 Average End Point Volumes by Gran's Method for the Titration of Quinine sulfate in 0.1M KCl with 0.07835N NaOH

Experiment	Wt. of sample (mg)	End point volumes (ml) Method 4	Method 5	Method 3
A	98.68	3.41 ± 0.02	3.42 ± 0.02	3.40 ± 0.02
B	96.12	3.29 ± 0.01	3.29 ± 0.01	3.29 ± 0.01
C	98.76	3.39 ± 0.02	3.40 ± 0.02	3.42 ± 0.01
D	95.70	3.29 ± 0.01	3.30 ± 0.02	3.29 ± 0.01

Note: (a) average from three parallel titrations

(b) method 4 obtained from the plot of $[H^+](V_o+V)$ versus G

method 5 " " $[H^+](V_o+V)$ " V

method 3 " " $(V_o+V)K_w/[H^+]$ " V

e. Chlorpheniramine maleate

Titration curve of chlorpheniramine maleate illustrated two neutralizations (Figure 16). The first inflection point indicated the neutralization of the second proton of maleic acid ($Ka = 6 \times 10^{-7}$) and the second inflection point was the titration of protonated chlorpheniramine ($Ka = 6 \times 10^{-10}$).

Gran plots based on equations 42 and 52 were employed to determine the first end point volume as the difference between Ka of second proton of maleic acid and Ka of protonated of chlorpheniramine was high enough and thus would not interfere with each other. The average end point volume obtained from V plot and G plot were shown in Table 10 and Gran plot curves were illustrated in Figure 17. It was found that at the beginning of V plot the curvature also occurred for the same reason as in potassium hydrogenphthalate. Extrapolation from the linear region of V plot yielded end point volumes which percentage purity based on these values was 99.52 ± 0.1%. This is identical to the value obtained from G plot. These percentage purities were statistically equivalent to non-aqueous method (99.95 ± 0.2%).

To determine the second end point volume, Gran plot based on equations 51 and 53 were recommended. The plots should show linearity when the first end point volume, Ve_1, had already been known. An inflection was

observed at the point of initial precipitation (Figure 17). For this situation, a modified Gran plot equation must be derived from equation 55. The equations that were employed for end point determination were

$$[H+](Vo + V) = \frac{1\ Ka_2 NVe_2}{2[B]_c} - \frac{Ka_2 NG}{[B]_c} \qquad \text{Eq. 77}$$

and

$$[H+](Vo + V) = \frac{1\ Ka_2 NVe_2}{2[B]_c} - \frac{Ka_2 NV}{[B]_c} \qquad \text{Eq. 78}$$

Figure 17 showed the linear line of Gran plot based on equation 77 and 78. The average end point volumes from these plot were illustrated in Table 11. Percentage purities based on end point volumes of V plot and G plot were 101.1 ± 0.2% and 99.84 ± 0.2%, respectively. The V plot yielded overestimate values because titration data which were selected in V plot were in the region of high pH that there would be affecting of autoprotolysis of water.

Gran plot of titration data after equivalence point yielded end point volumes (Table 11) of which percentage purity was 99.36 ± 0.1%. Percentage purities based on second end point volumes (titration of protonated chlorpheniramine) which were obtained from G plot and the plot after equivalence was statistically identical to that obtained from non-aqueous method. Therefore, for the titration of chlorpheniramine maleate, the first and second

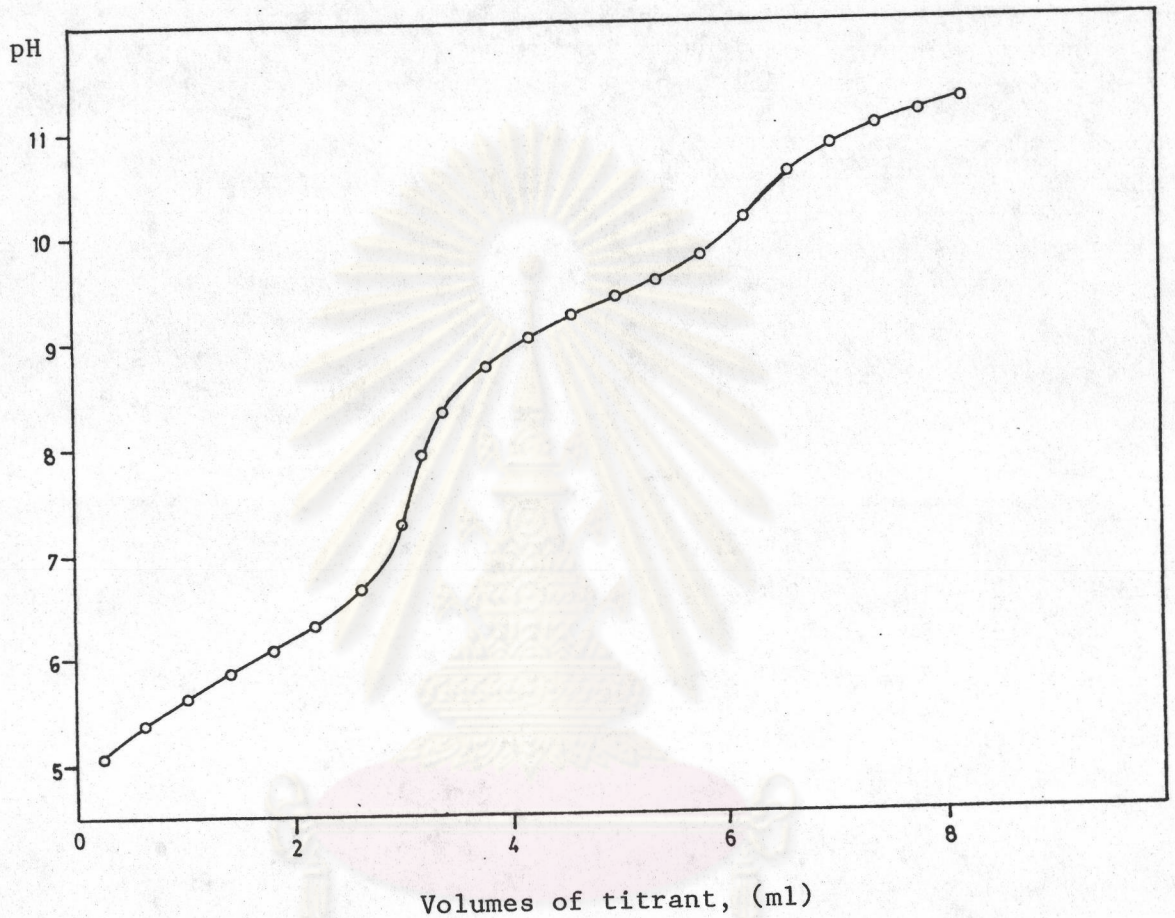

Figure 16 Titration curve of Chorpheniramine maleate in 0.1M KCl

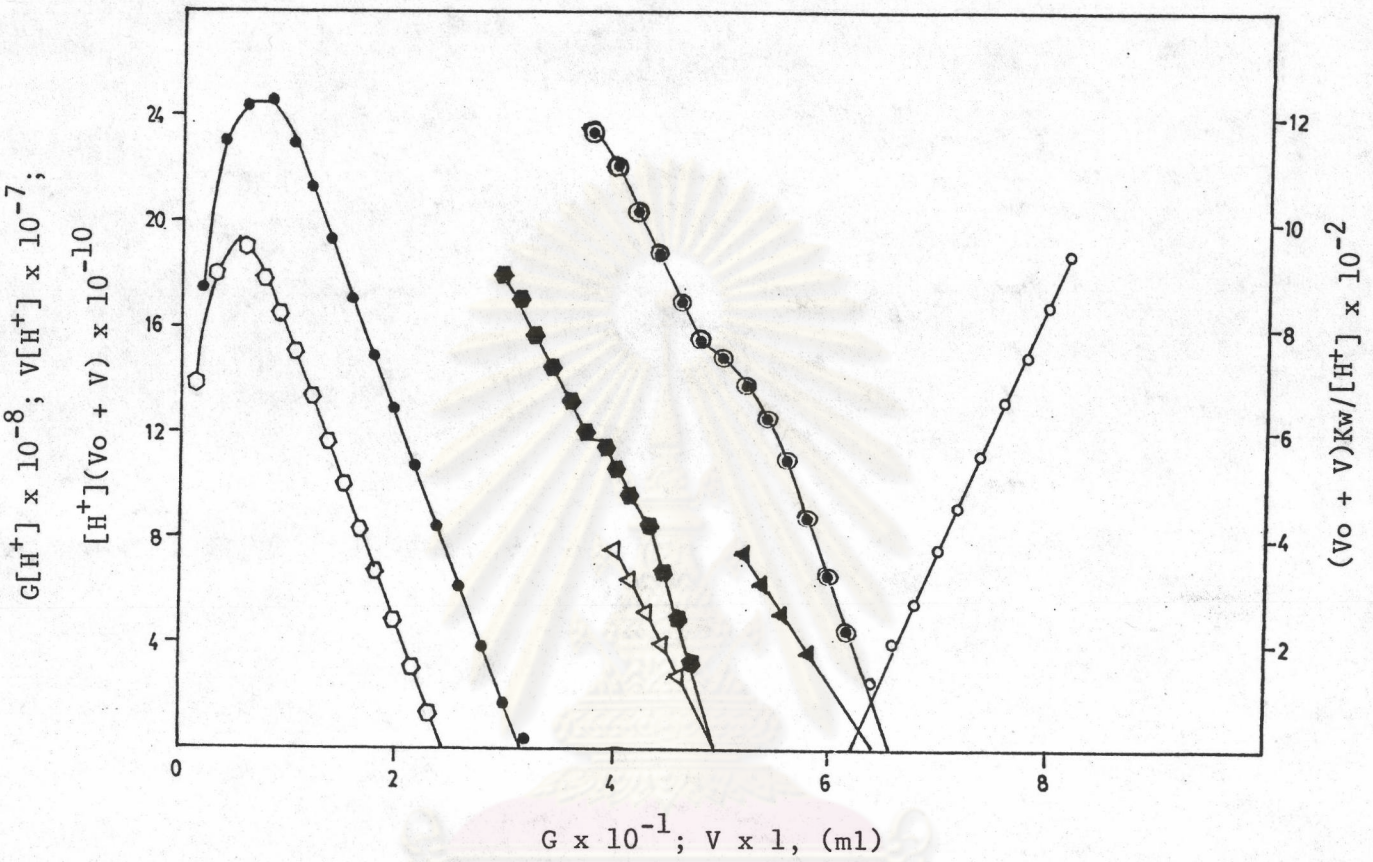

Figure 17 Gran plot for the titration of Chlorpheniramine maleate in 0.1M KCl with sodium hydroxide; G plot (⬡ , ⬢ , △), V plot (● , ◉ , ▲) and Va plot (○)

⬡ : G plot of $[H^+]$ vs.G

⬢ : G plot of $[H^+](G - Ve_1)$ vs.G

△ : G plot of $[H^+](Vo + V)$ vs.G

● : V plot of $V[H^+]$ vs.V

◉ : V plot of $[H^+](V - Ve_1)$ vs.V

▲ : V plot of $[H^+](Vo + V)$ vs.V

Table 10 Average End Point Volumes by Gran's Method for the Titration of Chorpheniramine maleate in 0.1M KCl with 0.07751N NaOH

(First neutralization)

Experiment	Wt. of sample (mg)	End point volumes (ml) Method 1	Method 2
A	96.10	3.16 ± 0.01	3.16 ± 0.01
B	96.04	3.15 ± 0.00	3.15 ± 0.00
C	96.18	3.16 ± 0.01	3.16 ± 0.01
D	96.16	3.16 ± 0.01	3.16 ± 0.01

Note: (a) average from three parallel titrations

(b) method 1 obtained from the plot of G[H+] versus G

method 2 " " V[H+] " V

(continued)

Table 11 Average End Point Volumes by Gran's Method for the Titration of Chorpheniramine maleate in 0.1M KCl with 0.07751N NaOH

(Second neutralization)

Experiment	Wt. of sample (mg)	End point volumes (ml) Method 4	Method 5	Method 3
A	96.10	6.32 ± 0.01	6.40 ± 0.01	6.31 ± 0.00
B	96.04	6.33 ± 0.00	6.41 ± 0.00	6.30 ± 0.00
C	96.18	6.35 ± 0.01	6.43 ± 0.01	6.31 ± 0.01
D	96.16	6.34 ± 0.00	6.42 ± 0.00	6.30 ± 0.02

Note: (a) average from three parallel titrations

(b) method 4 obtained from the plot of [H+](Vo+V) versus G

method 5 " " [H+](Vo+V) " V

method 3 " " (Vo+V)Kw/[H+] " V

end point determinations by G plot would yield results which were statistically identical to non-aqueous method and the plot of titration data after equivalence point.

Summary

Curvature occurred at the beginning of the plot would not affect the extrapolation value as seen with V plot of potassium hydrogenphthalate while the curvature near equivalence point would result in an overestimation of end point volume as observed with phenylpropanolamine HCl, pseudoephedrine HCl, triprolidine HCl and the second end point volume of chlorpheniramine maleate. The curvature was due to invalid assumption for $\frac{VN}{Vo+V} >> [H+] - [OH-]$

Although G plot needs more calculation than V plot for end point determination, this plot could give less curvature both at the beginning of the plot and near equivalence point. This should resulted in higher degree of accuracy and reproducibility.

Gran's method was employed satisfactorily in end point determination for the titration of weak acid with strong base that showed precipitation during the course of titration such as the titration of triprolidine HCl and diphenhydramine HCl with sodium hydroxide. However, it has limitation from precipitate redissolution during titration process as seen with the titration of dextromethorphan HBr. In addition precipitates may coat the electrodes and thus interfered with the pH measurement

during the course of titration. In this case Gran plot method would yield erroneous results eventhough a good linear line was obtained such as the titration of quinine sulfate.

Gran plot of titration data after equivalence point would be more convenient and easily calculated than the plot of titration data prior to equivalence point. It could give accurate and reproducible end point volume whether there was precipitation during the course of titration such as triprolidine HCl, diphenhydramine HCl and dextromethorphan HBr as long as precipitates did not interfere with pH measurement. Moreover, for determining end point volume of dibasic weak acid as with chorpheniramine maleate, it yielded exellent results. However, it also has limitation as in the alkaline region pH values would be affected by alkaline error of glass electrode.

Titration in Mixed Solvent

Gran's method had been employed successfully in determining end point volumes of weak acids and strong base titration in aqueous solvent even when there was precipitation during the course of titration. However, if precipitates could redissolve or interfere pH measurement, Gran's method would yield erroneous end point volumes. Thus, we should prevent the precipitation in order to avoid those problems by using mixed solvent of organic solvent and water which could give homogeneous solution throughout the course of titration.

Ethanol, one of the organic solvents,was mostly recommended for solvent in determining dissociation constant (potentiometric titrimetry) of weak acids which unionized form had low solubility and precipitated during the course of titration (42, 43).

Ethanol is capable of proton donor and/or proton acceptor same as water. It had a lower dielectric constant and a lower autoprotolysis constant than water. Ethanol would favor reactions in which unionized form was generated (44). Hence, it could be advantageous to carry out weak acids and strong base titrations in this solvent, especially weak acids that produced unionized species.

In this study, 40%v/v ethanol/water was exploited in order to get homogeneous solution throughout the

titrations. According to the properties of ethanol, the dielectric constant and autoprotolysis constant of this mixed solvent would be decreased. However, during the titration lyonium ion of this mixed solvent was still hydronium ion (H_3O^+) because ethyloxonium ion ($EtOH_2^+$) would occur only when percentage of ethanol approached near 100% (44, 45).

G plot was not employed for 40%v/v ethanol/water solvent system because the autoprotolysis constant for this solvent system is not known and thus only V plot was employed for the end point determination of the titration data prior to equivalence point.

Titrations of eight weak acidic compounds in 40%v/v ethanol/water could be divided into three groups as followded :

1. Monoprotic acid whose conjugate base has higher charge than its acid.

In this group, there was only one compound that was potassium hydrogenphthalate. The titration curve of this compound in 40%v/v ethanol/water also exhibited a well-defined inflection point in the region of equivalence point (Figure 18). However, the change in pH with respect to the change in volume of titrant was not quite as sharp as in aqueous solvent. This result was due to lower dielectric constant of 40%v/v ethanol/water (as compared to water) which would not favor the reaction of potassium

hydrogenphthalate and sodium hydroxide since they generated more highly charge products.

Table 12 showed average end point volumes obtained from Gran plots (V plot and the plot of titration data after equivalence point). Percentage purities based on these values were 100.3 ± 0.2% and 99.59 ± 0.3%, respectively. These results were statistically equivalent to the percentage purity of the titration in aqueous solvent which determined end point volumes by conventional method (100.1 ± 0.3%). Moreover, they were also identical to the percentage purities obtained from those three Gran plots of the titrations in aqueous solvent (Table 20).

2. Monoprotic acid whose conjugate base has lower charge than its acid.

This group was composed of phenylpropanolamine HCl, pseudoephedrine HCl, triprolidine HCl, diphenhydramine HCl, dextromethorphan HBr and quinine sulfate. The titration curves of all these compounds in 40%v/v ethanol/water (Figure 19 - 24) showed more cleary defined inflection point than those in aqueous solvent. This result was due to the reactions of all these weak acids and sodium hydroxide in 40%v/v ethanol/water which generated unionized products and hence were favored by low dielectric solvent.

Table 13 showed average end point volumes obtained from V plot and the plot of titration data after

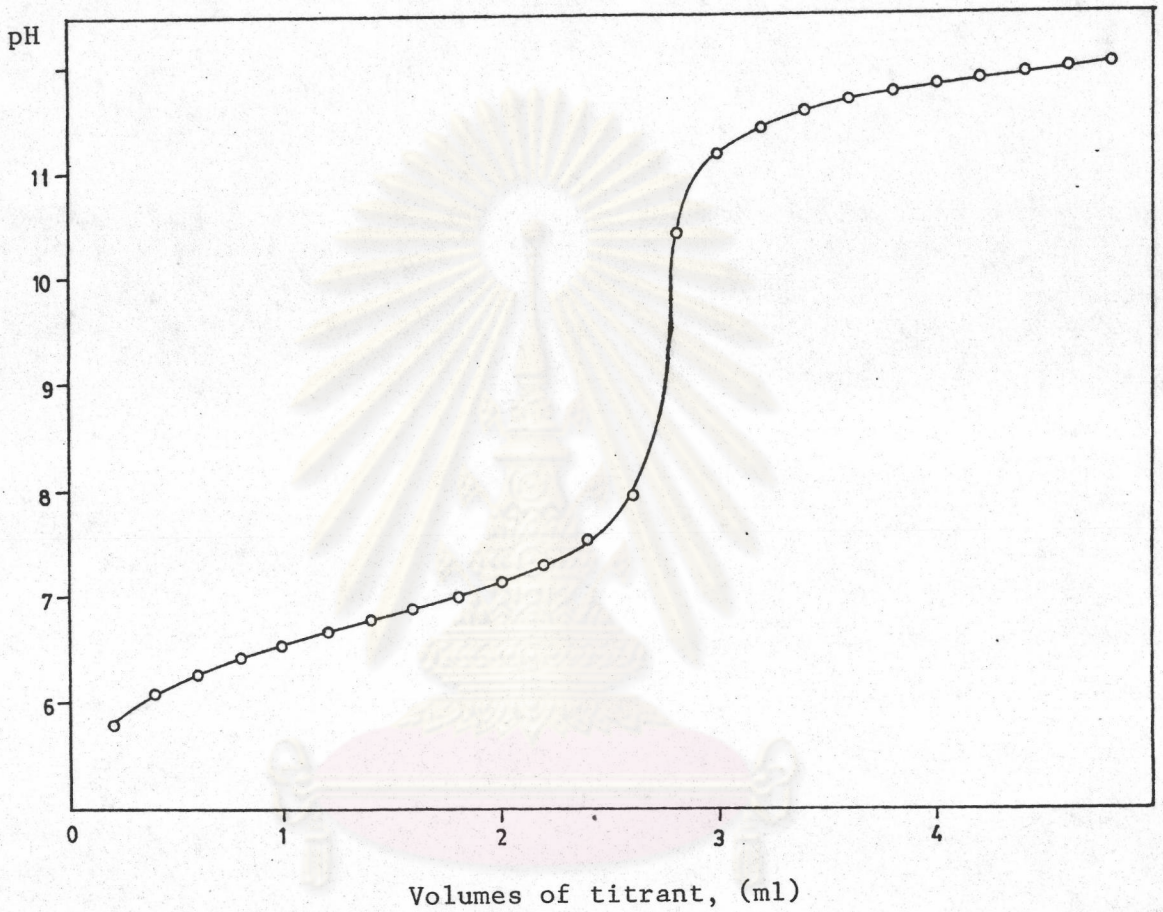

Figure 18 Titration curve of Potassium hydrogenphthalate in 40% v/v ethanol/water

during the course of titration. In this case Gran plot method would yield erroneous results eventhough a good linear line was obtained such as the titration of quinine sulfate.

Gran plot of titration data after equivalence point would be more convenient and easily calculated than the plot of titration data prior to equivalence point. It could give accurate and reproducible end point volume whether there was precipitation during the course of titration such as triprolidine HCl, diphenhydramine HCl and dextromethorphan HBr as long as precipitates did not interfere with pH measurement. Moreover, for determining end point volume of dibasic weak acid as with chorpheniramine maleate, it yielded exellent results. However, it also has limitation as in the alkaline region pH values would be affected by alkaline error of glass electrode.

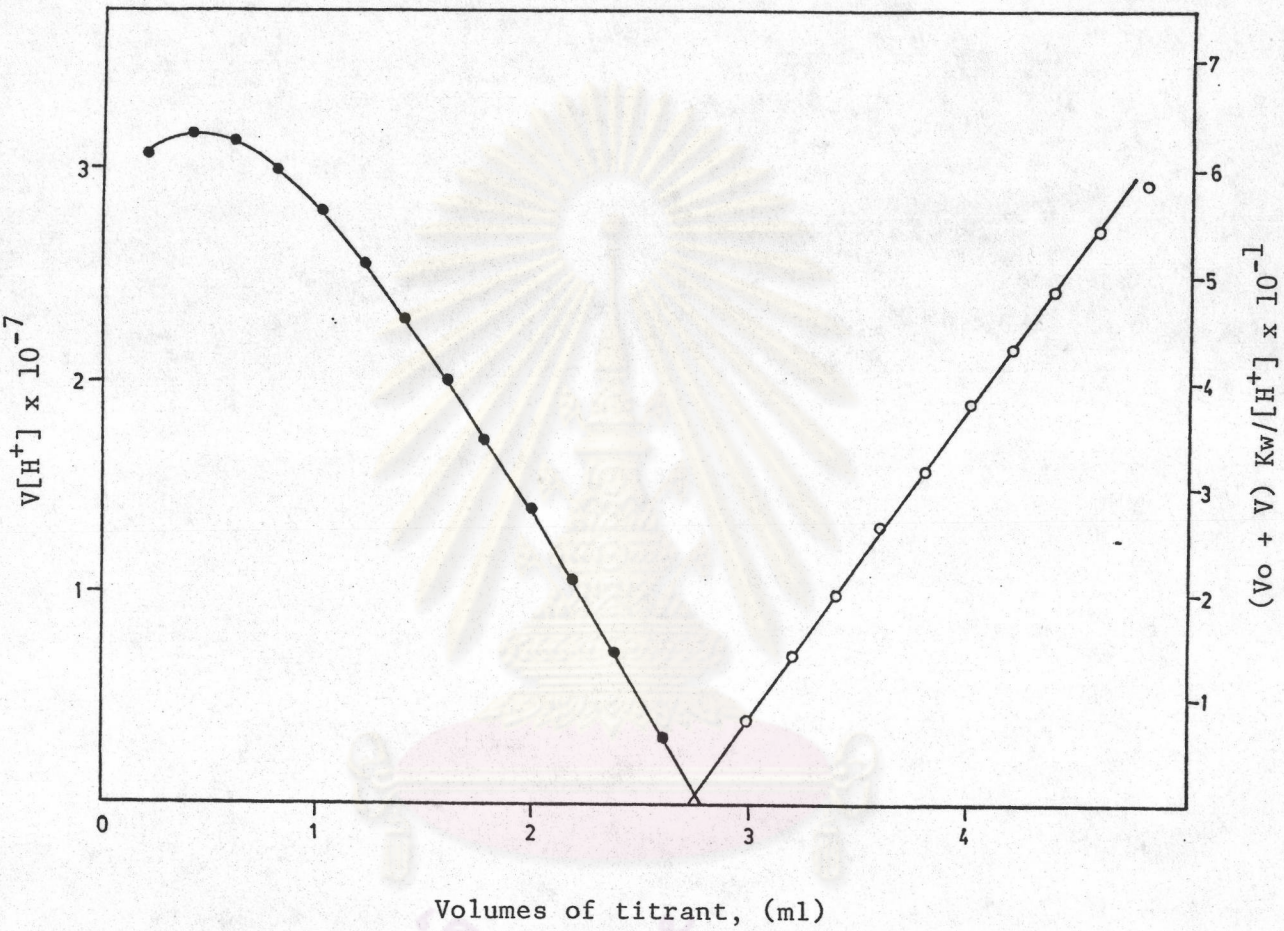

Figure 19 Gran plot for the titration of Potassium hydrogen-phthalate in 40% v/v ethanol/water with sodium hydroxide; V plot (●) and Va plot (o)

Table 12 Average End Point Volumes by Gran's Method for the Titration of Potassium hydrogenphthalate in 40%v/v ethanol/water with 0.08883N NaOH

Experiment	Wt. of sample (mg)	End point volumes (ml) Method 2	Method 3
A	50.46	2.79 ± 0.01	2.77 ± 0.01
B	50.58	2.79 ± 0.01	2.77 ± 0.01
C	50.70	2.81 ± 0.00	2.78 ± 0.00
D	50.96	2.82 ± 0.00	2.81 ± 0.03

Note: (a) average from three parallel titrations

(b) method 2 obtained from the plot of $V[H^+]$ versus V

method 3 " " $(Vo+V)Kw/[H^+]$ " V

equivalence of phenylpropanolamine HCl in 40%v/v ethanol/water. The V plot shape of Gran plots, as shown in Figure 25, exhibited less curvature than those in aqueous solvent because more complete reaction between phenylpropanolamine HCl and sodium hydroxide was achieved. Thus, V plot yielded the exellent end point volumes which when calculated in term of average percentage purity was 100.3 ± 0.2%. For the titration data after equivalence point, Gran plot also gave satisfied end point volumes and hence average percentage purity was 99.45 + 0.2%. Both results were statiatically indifferent from standard non-aqueous method (100.3 ± 0.1%).

In the similar manner as phenylpropanolamine HCl, Gran plots of the titration in 40%v/v ethanol/water of pseudoephedrine HCl, triprolidine HCl, diphenhydramine HCl, dextromethorphan HBr and quinine sulfate also gave the V plot shape with less curvature than the titration in aqueous solvent (Figure 26 - 31). In addition, accurate and reproducible end point volumes of each compounds were obtained from V plot and the plot of titration data after equivalence point. The percentage purities of each compounds which calculated from those end point volumes showed statistically same values as the percentage purities obtained from non-aqueous method (Table 20). There was only one limitation for the plot of titration data after equivalence point of pseudoephedrine HCl which yielded an underestimation values. This may be partly

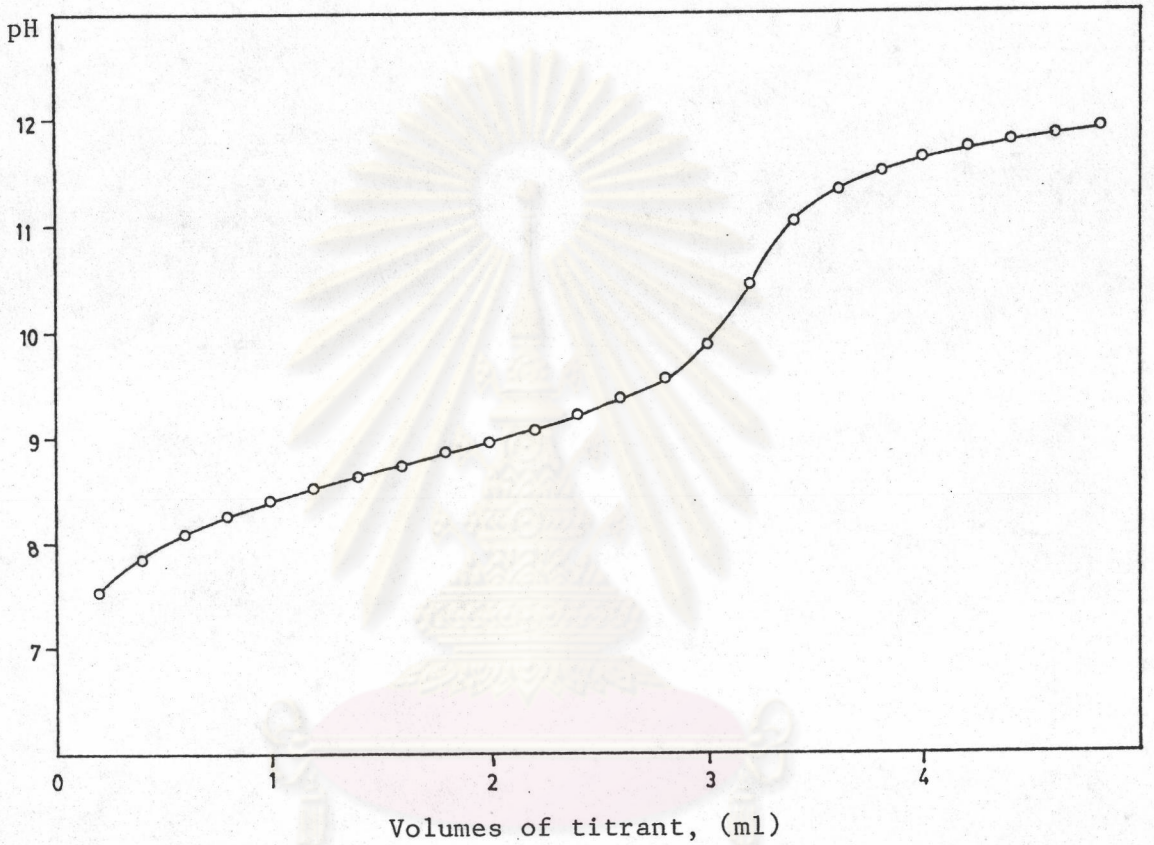

Figure 20 Titration curve of Phenylpropanolamine HCl in 40% v/v ethanol/water

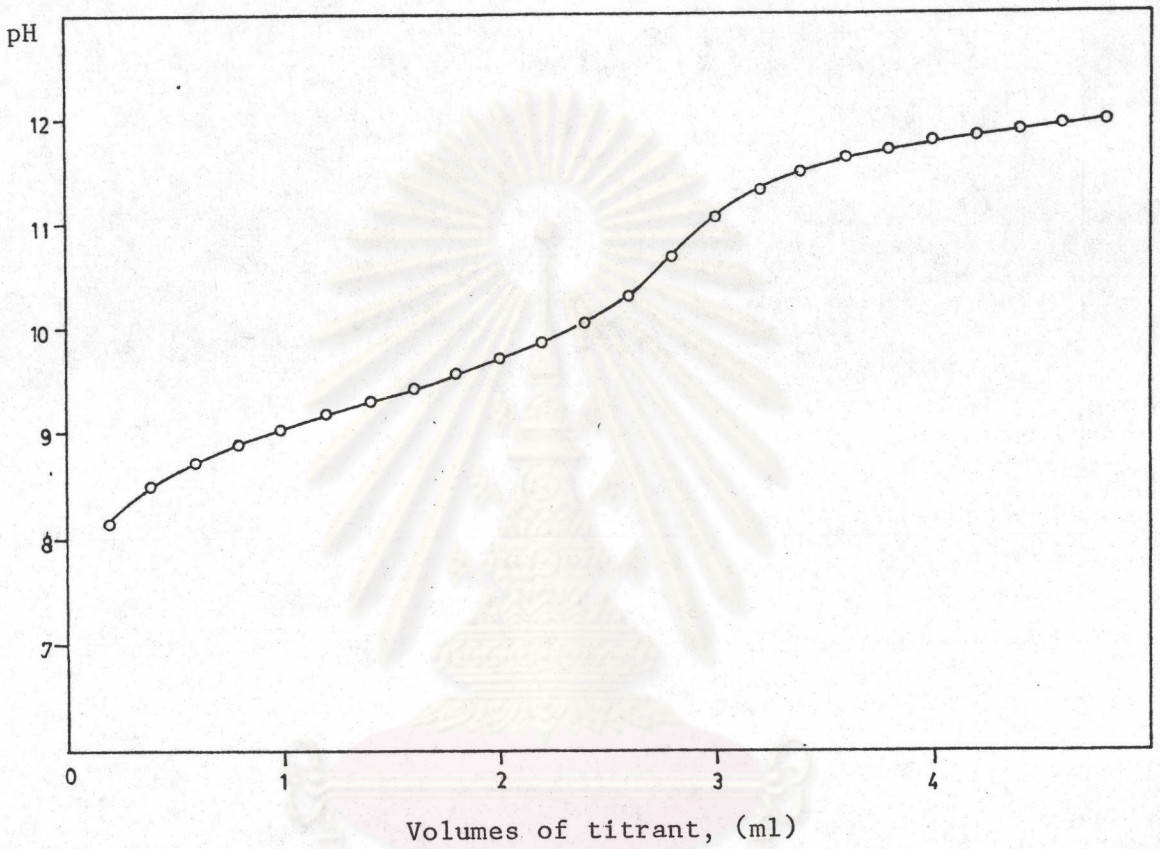

Figure 21 Titration curve of Psuedoephedrine HCl in 40% v/v ethanol/water

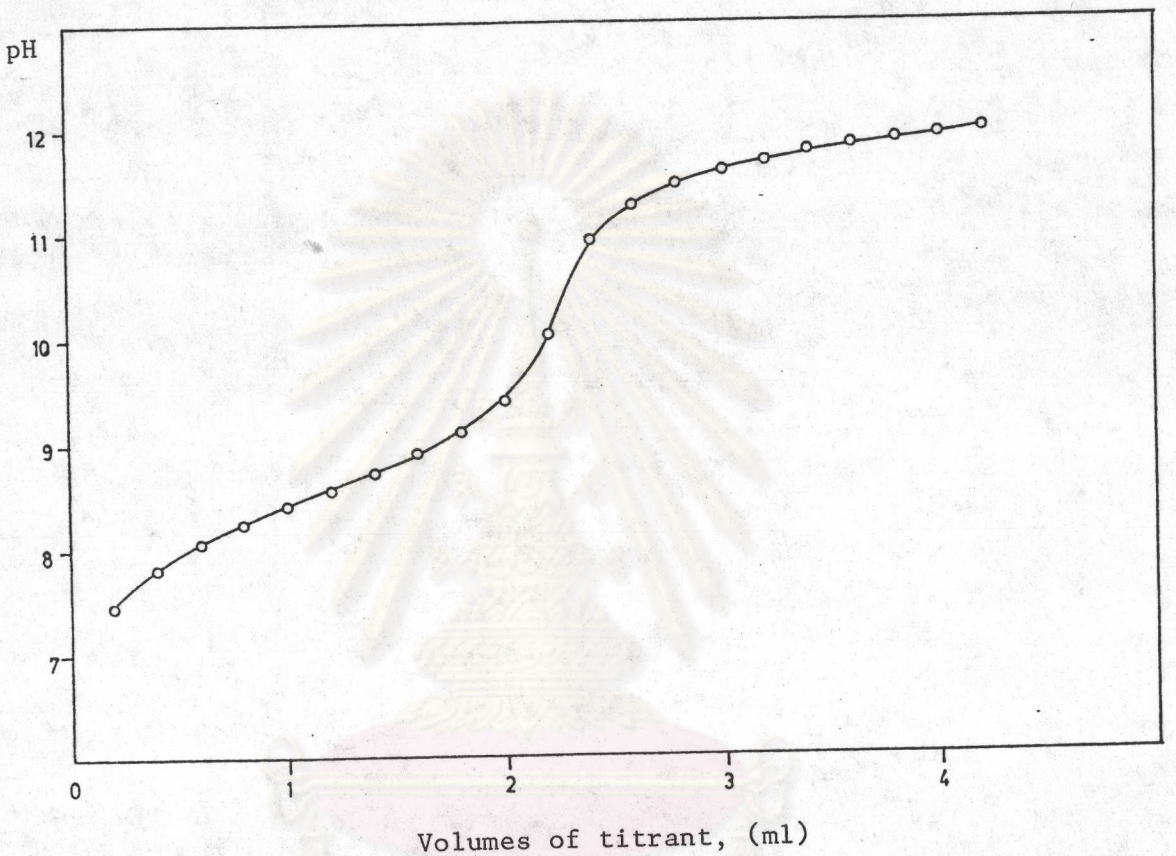

Figure 22 Titration curve of Triprolidine HCl in 40% v/v ethanol/water

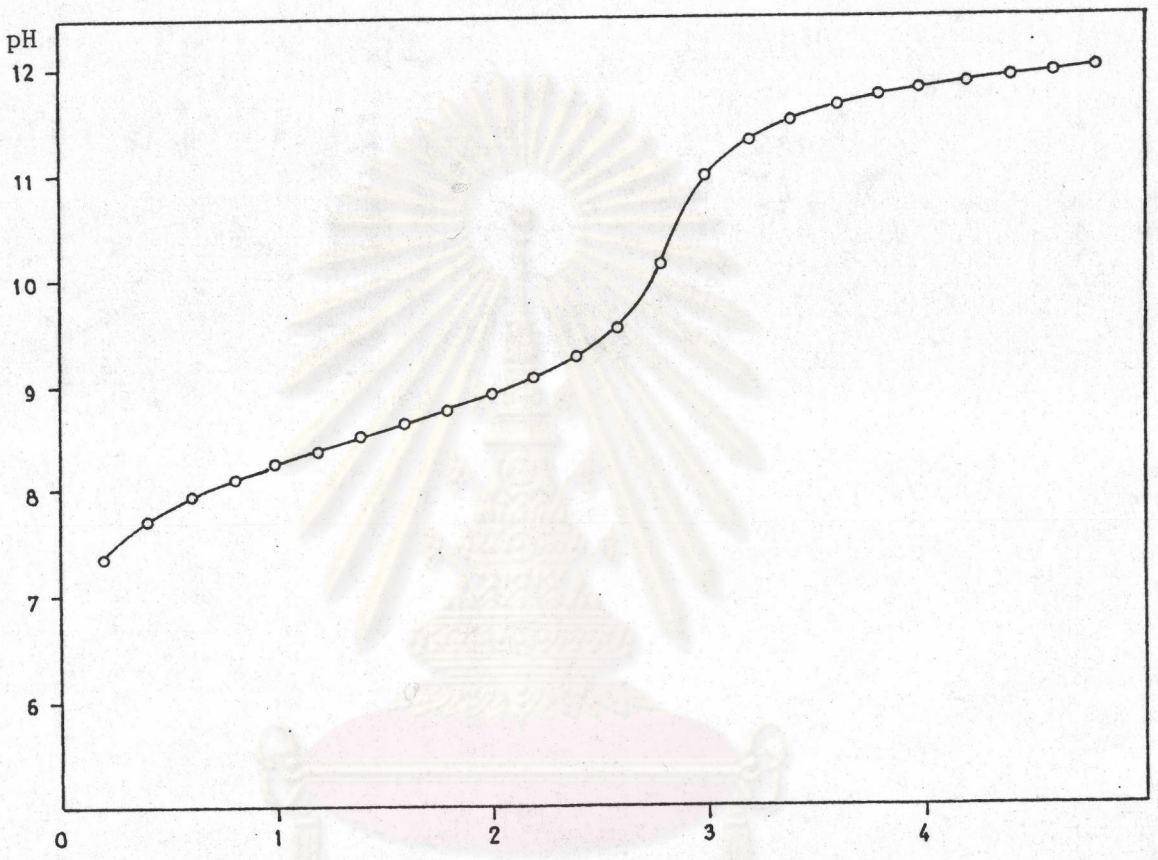

Figure 23 Titration curve of Diphenhydramine HCl in 40% v/v ethanol/water

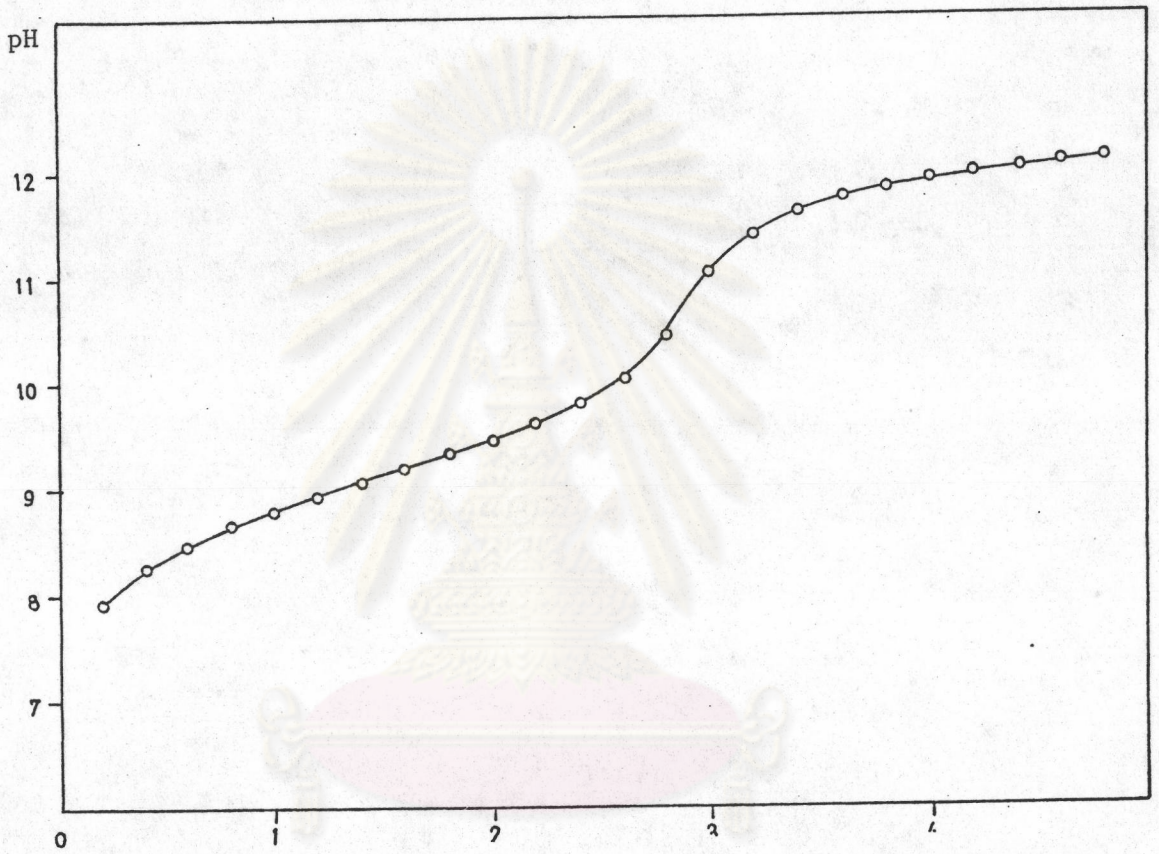

Figure 24 Titration curve of Dextromethorphan HBr in 40% v/v ethanol/water

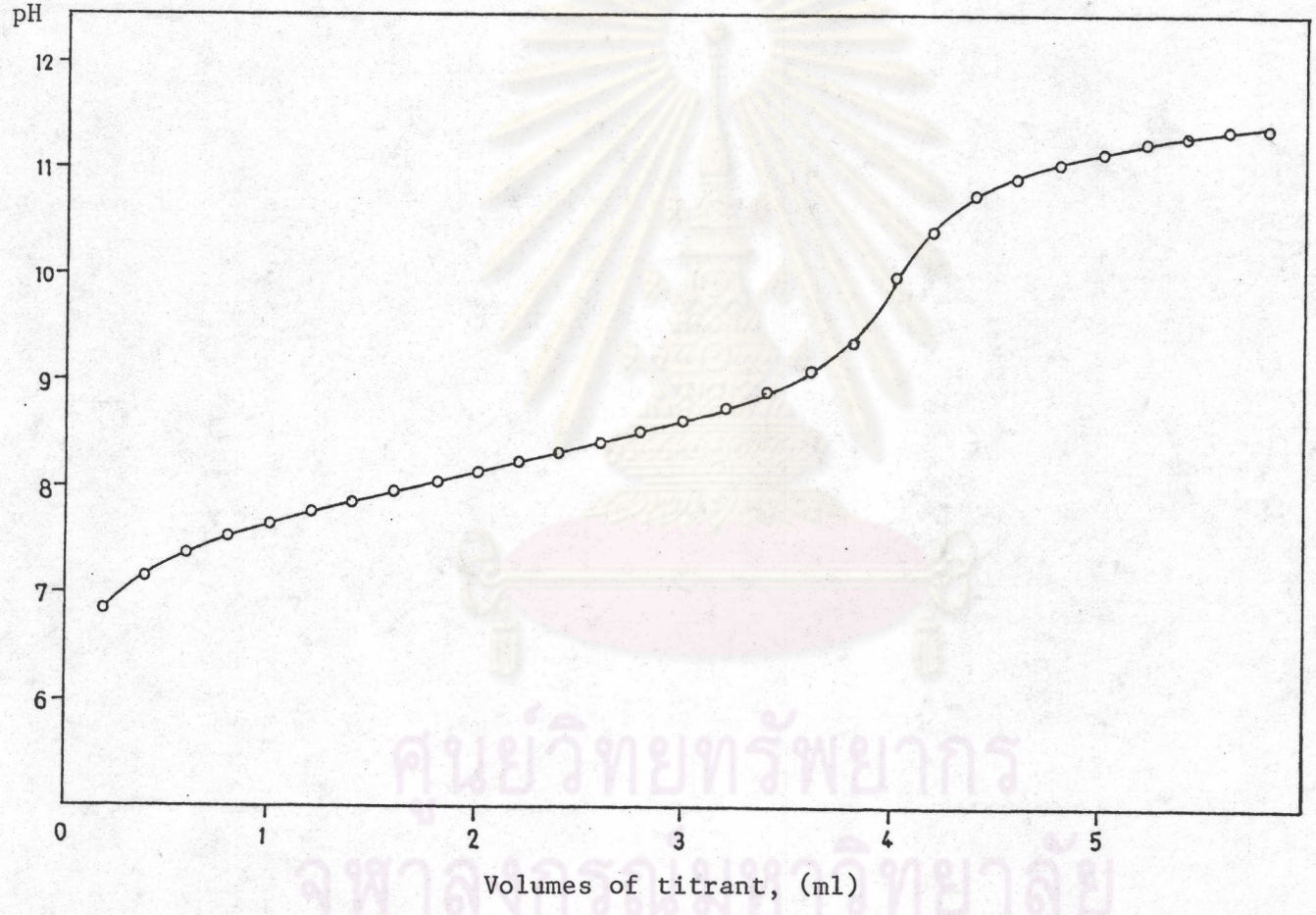

Figure 25 Titration curve of Quinine sulfate in 40% v/v ethanol/water

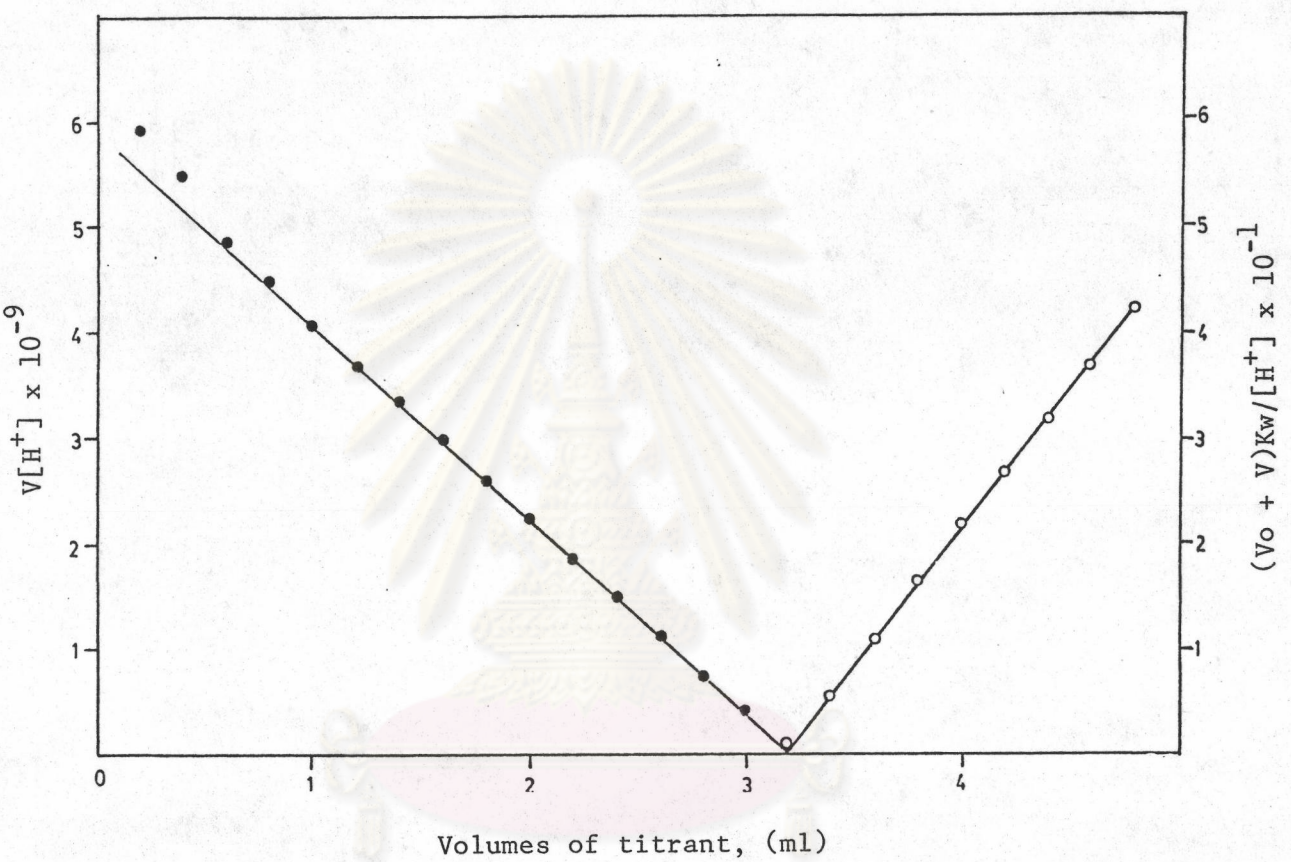

Figure 26 Gran plot for the titration of Phenylpropanolamine HCl in 40% v/v ethanol/water with sodium hydroxide; V plot (●) and Va plot (O)

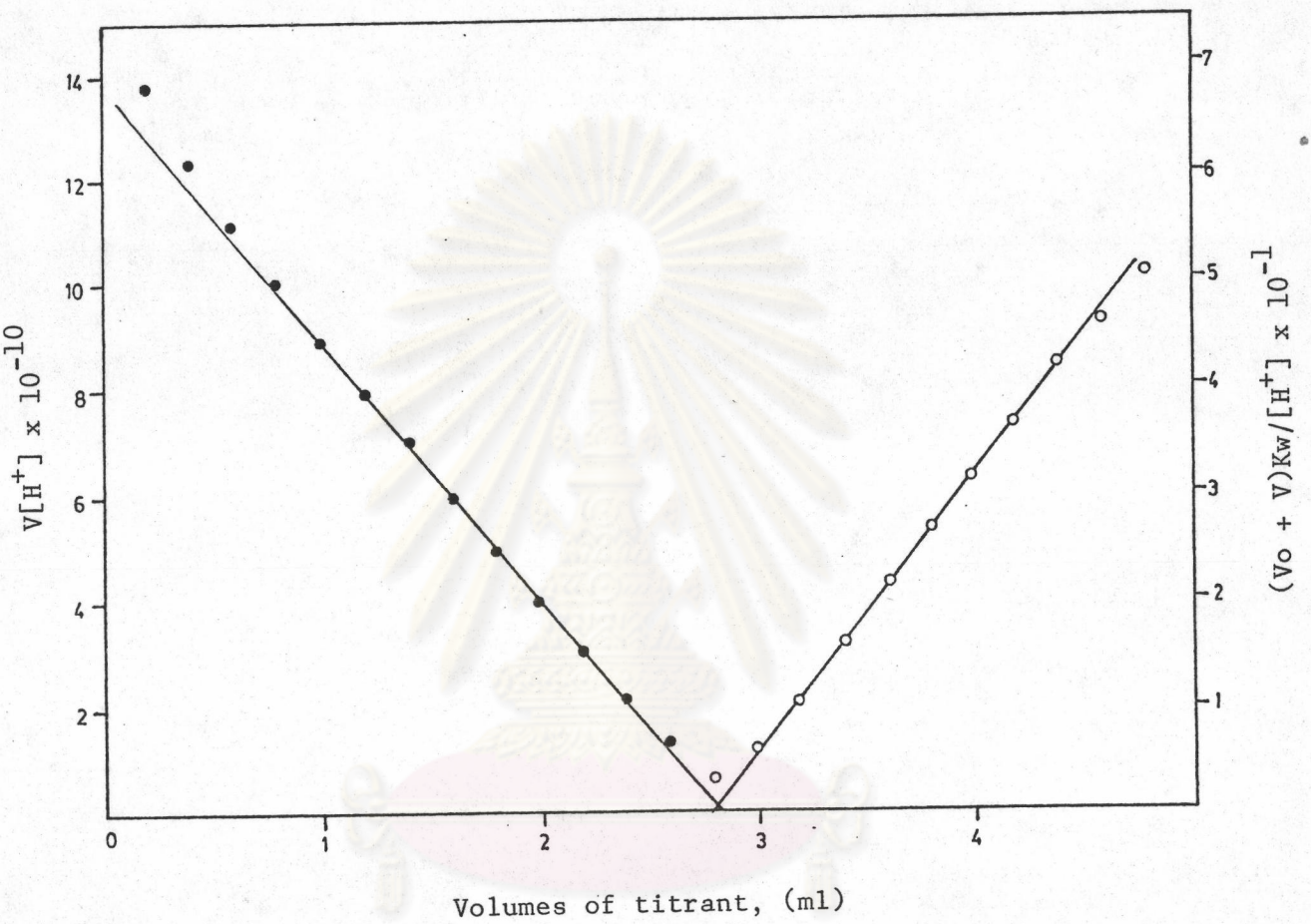

Figure 27 Gran plot for the titration of Pseudoephedrine HCl in 40% v/v ethanol/water with sodium hydroxide; V plot (●) and Va plot (O)

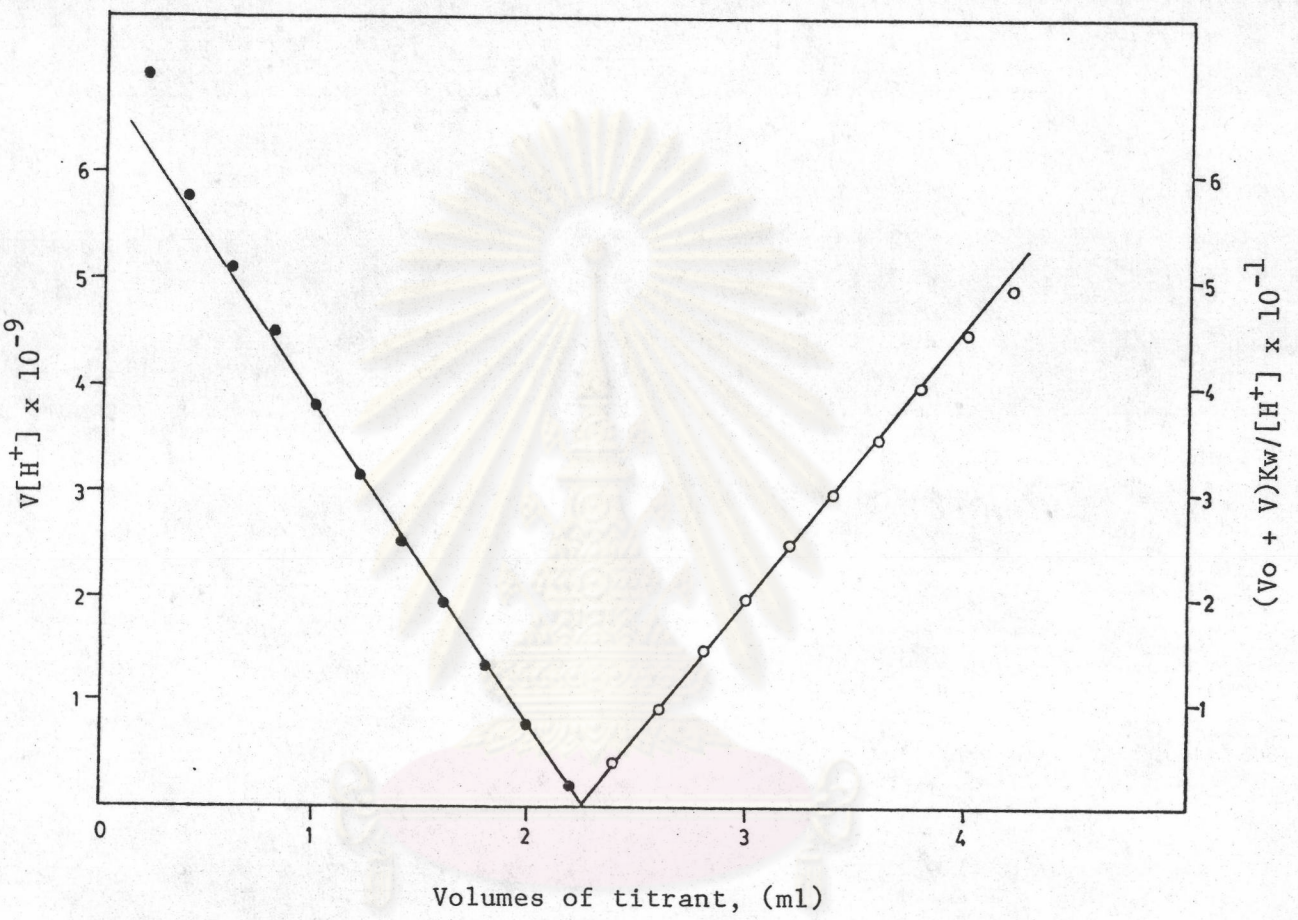

Figure 28 Gran plot for the titration of Triprolidine HCl in 40% v/v ethanol/water with sodium hydroxide; V plot (●) and Va plot (○)

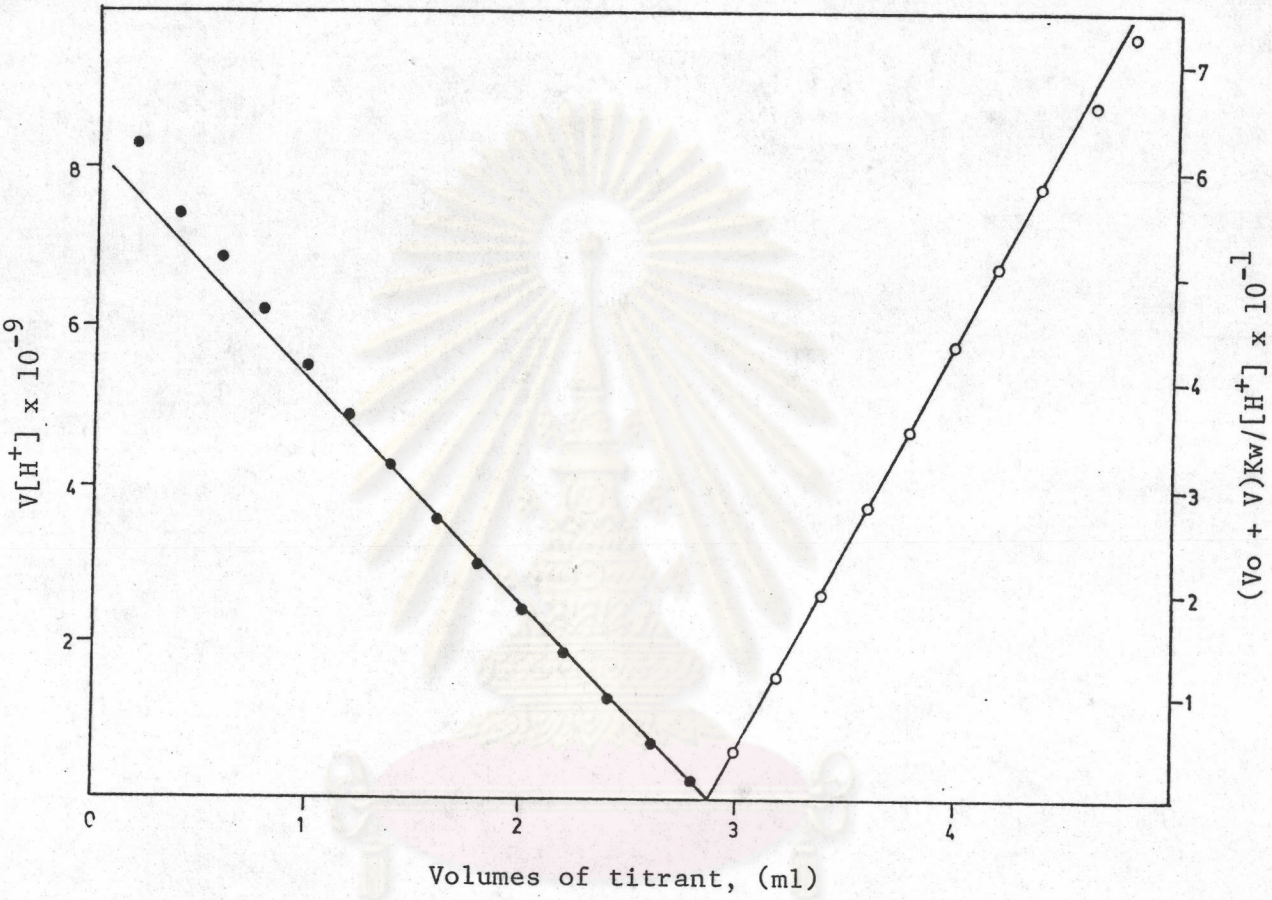

Figure 29 Gran plot for the titration of Diphenhydramine HCl in 40% v/v ethanol/water with sodium hydroxide; V plot (●) and Va plot (○)

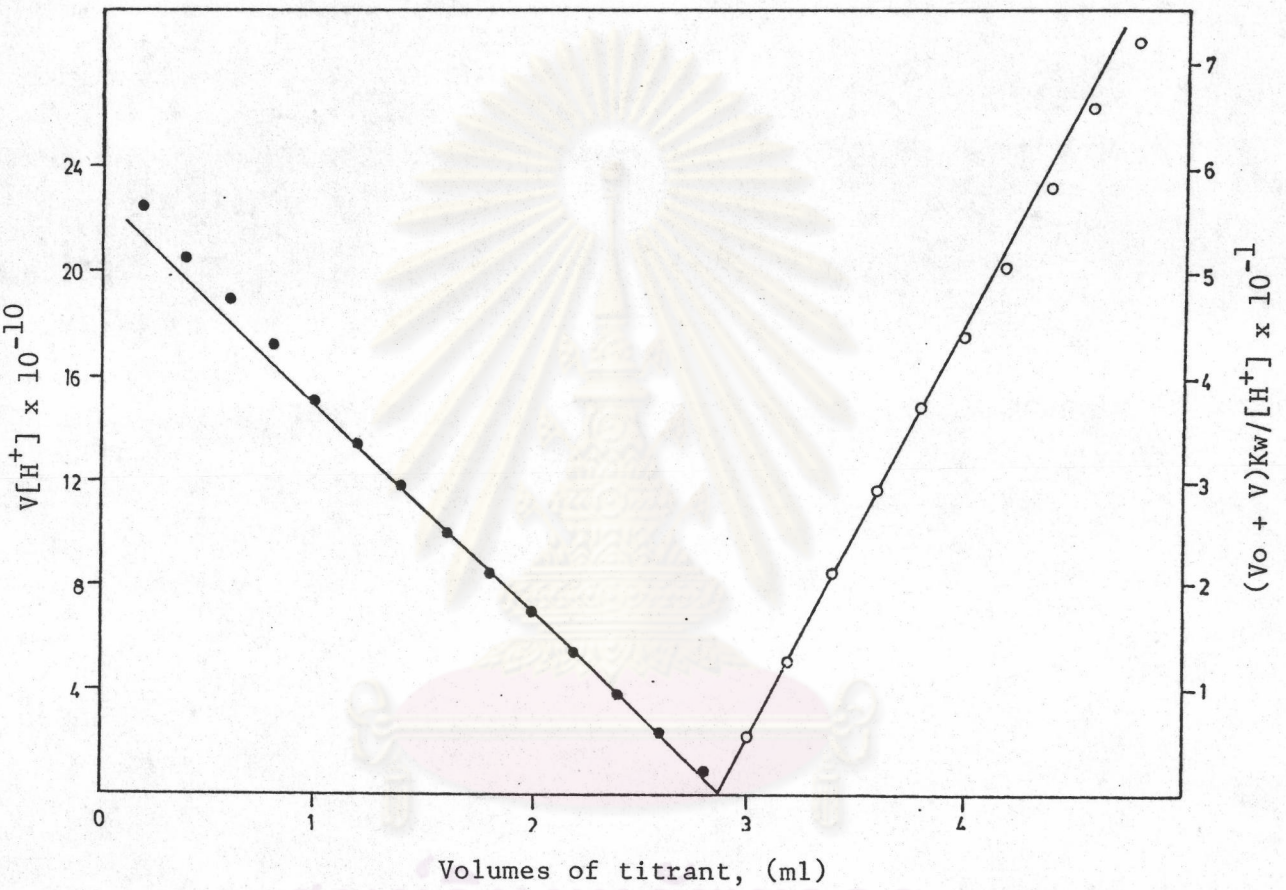

Figure 30 Gran plot for the titration of Dextromethorphan HBr in 40% v/v ethanol/water with sodium hydroxide; V plot (●) and Va plot (O)

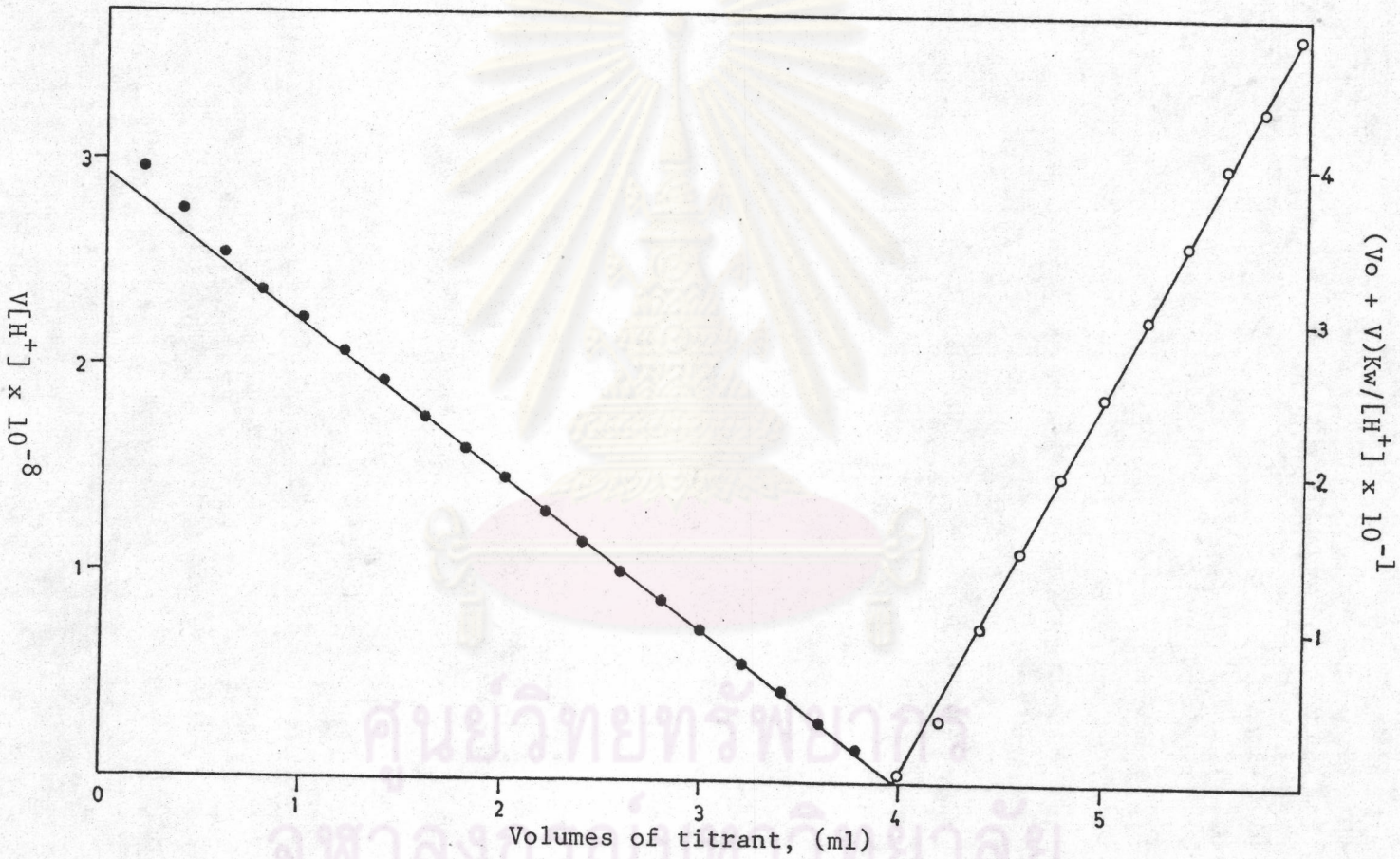

Figure 31 Gran plot for the titration of Quinine sulfate in 40% v/v ethanol/ water with sodium hydroxide; V plot (●) and Va plot (○)

Table 13 Average End Point Volumes by Gran's Method for the Titration of Phenylpropanolamine HCl in 40%v/v ethanol/water with 0.07835N NaOH

Experiment	Wt. of sample (mg)	End point volumes (ml) Method 2	Method 3
A	47.12	3.21 ± 0.01	3.18 ± 0.01
B	46.62	3.18 ± 0.01	3.15 ± 0.01
C	46.50	3.18 ± 0.01	3.15 ± 0.01
D	46.80	3.19 ± 0.00	3.17 ± 0.02

Note: (a) average from three parallel titrations

(b) method 2 obtained from the plot of $V[H^+]$ versus V

method 3 " " $(Vo+V)Kw/[H^+]$ " V

Table 14 Average End Point Volumes by Gran's Method for the Titration of Pseudoephedrine HCl in 40%v/v ethanol/water with 0.08883N NaOH

Experiment	Wt. of sample (mg)	End point volumes (ml) Method 2	Method 3
A	50.22	2.82 ± 0.00	2.78 ± 0.01
B	50.42	2.82 ± 0.00	2.78 ± 0.00
C	50.40	2.82 ± 0.01	2.77 ± 0.01
D	50.56	2.82 ± 0.02	2.79 ± 0.01

Note: (a) average from three parallel titrations

(b) method 2 obtained from the plot of $V[H^+]$ versus V

method 3 " " $(Vo+V)Kw/[H^+]$ " V

Table 15 Average End Point Volumes by Gran's Method for the Titration of Triprolidine HCl in 40%v/v ethanol/water with 0.08883N NaOH

Experiment	Wt. of sample (mg)	End point volumes (ml) Method 2	Method 3
A	66.78	2.24 ± 0.01	2.24 ± 0.01
B	66.98	2.25 ± 0.01	2.25 ± 0.01
C	66.86	2.25 ± 0.00	2.24 ± 0.01
D	66.90	2.24 ± 0.01	2.25 ± 0.01

Note: (a) average from three parallel titrations

(b) method 2 obtained from the plot of V[H+] versus V

method 3 " " (Vo+V)Kw/[H+] " V

Table 16 Average End Point Volumes by Gran's Method for the Titration of Quinine sulfate in 40%v/v ethanol/water with 0.07751N NaOH

Experiment	Wt. of sample (mg)	End point volumes (ml) Method 2	Method 3
A	118.24	4.01 ± 0.01	4.01 ± 0.01
B	119.08	4.03 ± 0.01	4.02 ± 0.01
C	143.40	4.84 ± 0.01	4.84 ± 0.01
D	158.36	5.34 ± 0.01	5.32 ± 0.01

Note: (a) average from three parallel titrations

(b) method 2 obtained from the plot of $V[H^+]$ versus V

method 3 " " $(Vo+V)Kw/[H^+]$ " V

Table 17 Average End Point Volumes by Gran's Method for the Titration of Dextrometorphan HBr in 40%v/v ethanol/water with 0.08883N NaOH

Experiment	Wt. of sample (mg)	End point volumes (ml) Method 2	Method 3
A	70.06	2.13 ± 0.00	2.10 ± 0.00
B	95.66	2.90 ± 0.01	2.86 ± 0.00
C	91.74	2.78 ± 0.01	2.74 ± 0.00
D	90.16	2.73 ± 0.00	2.69 ± 0.01

Note: (a) average from three parallel titrations

(b) method 2 obtained from the plot of $V[H^+]$ versus V

method 3 " " $(Vo+V)Kw/[H^+]$ " V

Table 18 Average End Point Volumes by Gran's Method for the Titration of Diphenhydramine HCl in 40%v/v ethanol/water with 0.08883 N NaOH

Experiment	Wt. of sample (mg)	End point volumes (ml) Method 2	Method 3
A	73.72	2.84 ± 0.00	2.83 ± 0.01
B	72.94	2.81 ± 0.01	2.80 ± 0.00
C	72.84	2.81 ± 0.00	2.80 ± 0.00
D	72.42	2.79 ± 0.00	2.78 ± 0.00

Note: (a) average from three parallel titrations

(b) method 2 obtained from the plot of $V[H^+]$ versus V

method 3 " " $(Vo+V)Kw/[H^+]$ " V

resulted from using titration data in the high pH region which had effect of alkaline error.

3. Mixture of monoprotic acids

The compound in this group was chlorpheniramine maleate of which the titration curve (Figure 32) showed only one inflection point eventhough it had two different dissociation constants.

V plot of this compound yielded a curve line (Figure 33) resulting to two overlapping dissociation of protonated chlorpheniramine and second proton from maleic acid (29). In 40%v/v ethanol/water, protonated chlorpheniramine can dissociate much better since the formation of unioized productd were favored by the solvent. This resulted in higher dissociation constant when compared with this value in water ($Ka > 10^{-10}$). On the other hand, the second proton of maleic acid which titration product had higher charge than reactants would decrease the dissociation. Therefore, the dissociation constant would be lowered when compared with the value in water ($Ka < 10^{-7}$). The two dissociations would approach to each other such that the neutralization of protonated chlorpheniramine and sodium hydroxide would occur while the neutralization reaction of the second proton of maleic acid and sodium hydroxide was carrying out. Hence, equations 51 and 53 would be invalid and then end point volumes obtained from V plot were erroneous (Table 20) which when calculated in

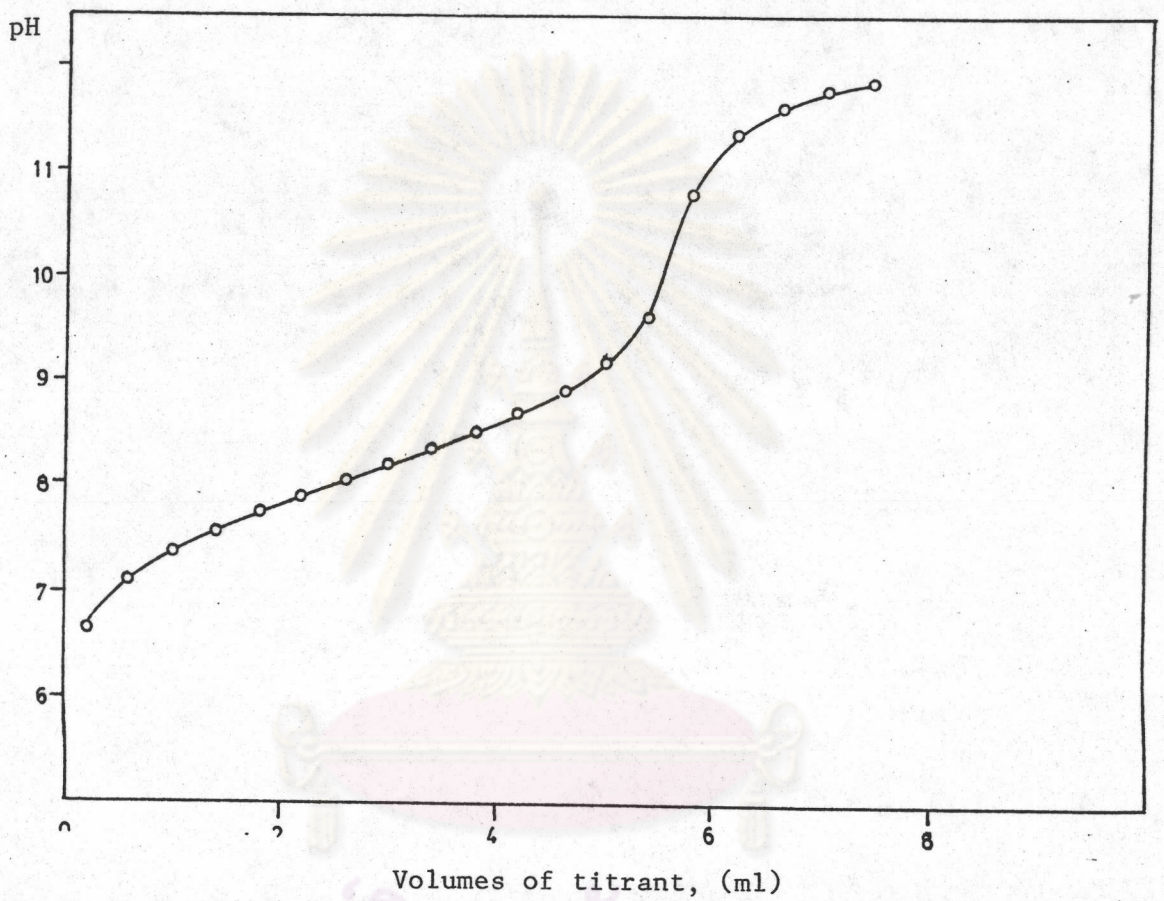

Figure 32 Titration curve of Chorpheniramine maleate in 40% v/v ethanol/water

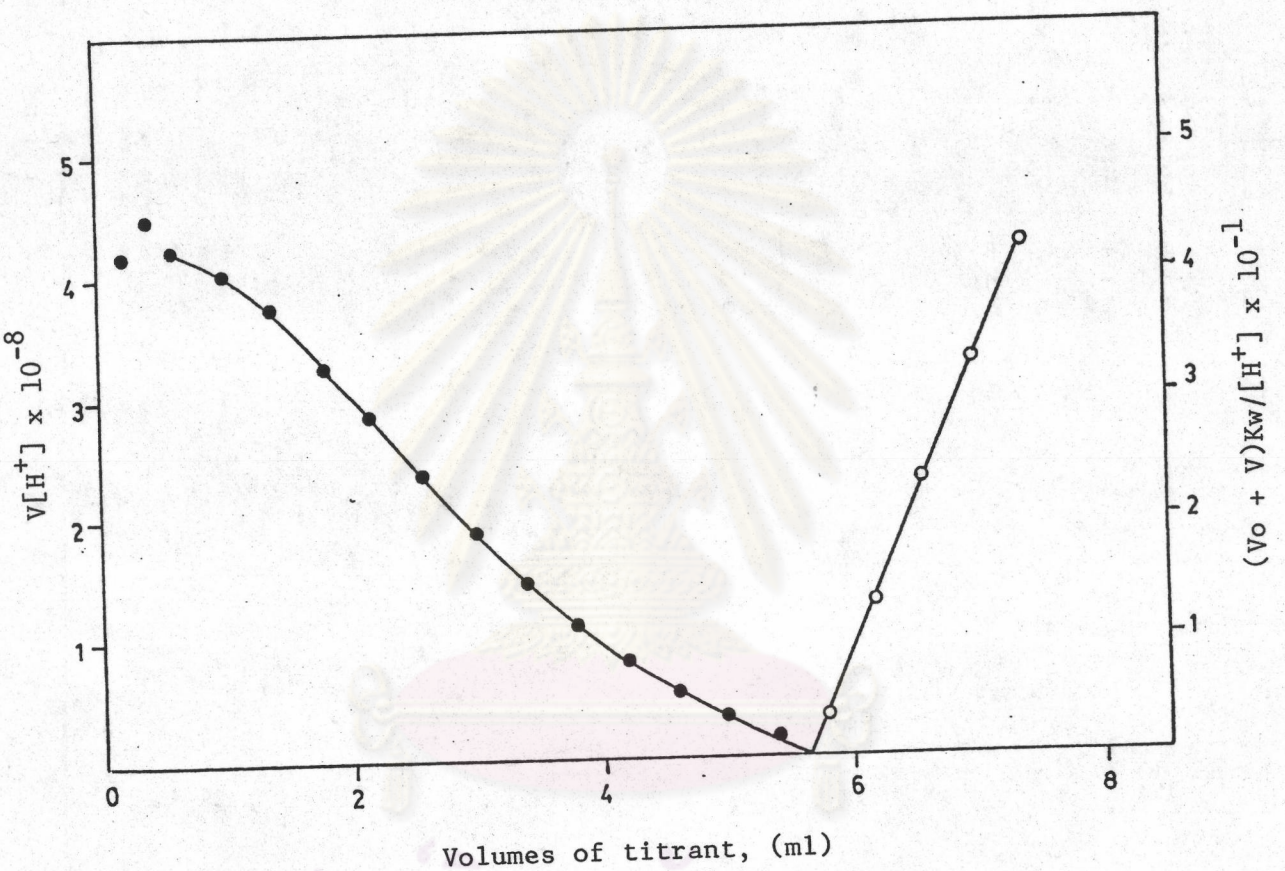

Figure 33 Gran plot for the titration of Chlorpheniramine maleate in 40% v/v ethanol/water with sodium hydroxide; V plot (●) and Va plot (O)

Table 19 Average End Point Volumes by Gran's Method for the Titration of Chorpheniramine maleate in 40%v/v ethanol/water with 0.08883N NaOH

Experiment	Wt. of sample (mg)	End point volumes (ml) Method 2	Method 3
A	98.66	5.66 ± 0.01	5.67 ± 0.01
B	97.04	5.53 ± 0.01	5.57 ± 0.02
C	98.26	5.59 ± 0.01	5.64 ± 0.01
D	100.3	5.72 ± 0.01	5.75 ± 0.01

Note: (a) average from three parallel titrations

(b) method 2 obtained from the plot of $V[H^+]$ versus V

method 3 " " $(Vo+V)Kw/[H^+]$ " V

Table 20 Average Percentage Purities of Weak Acidic Compounds Compared between Gran's Method and USP Method

Substance	Aqueous solvent			Mixed solvent		USP method
	G Plot	V Plot	Va Plot	V Plot	Va Plot	
Potassium hydrogenphthalate	99.86 (±0.35)	99.48 (±0.35)	100.4 (±0.24)	100.3 (±0.17)	99.59 (±0.29)	100.1 (±0.14)
Phenylopropanolamine HCl	100.2 (±0.29)	102.0 (±0.77)	99.83 (±0.39)	100.3 (±0.19)	99.45 (±0.19)	100.3 (±0.09)
Pseudoephedrine HCl	100.2 (±0.54)	106.7 (±0.96)	95.71 (±0.75)	100.2 (±0.28)	98.83 (±0.29)	99.98 (±0.32)
Triprolidine HCl	99.02 (±0.35)	99.63 (±0.20)	98.92 (±0.22)	99.25 (±0.22)	99.25 (±0.18)	98.49 (±0.58)
Diphenhydramine HCl	100.1 (±0.21)	100.2 (±0.17)	100.2 (±0.35)	99.90 (±0.07)	99.54 (±0.07)	99.73 (±0.09)

(continued)

Table 20 (continued)

Substance	Aqueous solvent G Plot	Aqueous solvent V Plot	Aqueous solvent Va Plot	Mixed solvent V Plot	Mixed solvent Va Plot	USP method
Dextrometorphan HCl	102.0 (±0.38)	104.8 (±0.88)	99.90 (±0.22)	99.76 (±0.17)	98.34 (±0.19)	99.97 (±0.10)
Quinine sulfate	100.6 (±0.39)	100.8 (±0.50)	100.7 (±0.46)	97.86 (±0.25)	97.71 (±0.38)	97.94 (±0.46)
Chorpheniramine maleate	99.52* (±0.11) 99.84** (±0.16)	99.52* (±0.11) 101.1** (±0.17)	99.36 (±0.09)	99.08 (±0.36)	99.65 (±0.10)	99.95 (±0.18)

Note : G Plot was Gran plot accounted for autoprotolysis constant

V Plot was Gran plot unaccounted for autoprotolysis constant

Va plot was Gran plot after equivalence point

* from first neutralization

** from second neutralization

term of percentage purity (99.08 ± 0.4%), it was significantly different from value obtained by non-aqueous method (99.95 ± 0.2%).

For the plot of titration data after equivalence point, accurate and reproducible end point volumes were obtained. Percentage purity based on these values was 99.65 ± 0.1% and statistically equivalent to the non-aqueous method.

Summary

By employing 40%v/v ethanol/water, an improvement in determination end point volumes by Gran plot (V plot and the plot of titration data after equivalence point) was achieved. V plot was very useful especially when autoprolysis constant of 40%v/v ethanol/water was not exactly known and G plot could not be employed. However, V plot employing titration data prior to equation point would yield erroneous results if there was overlapping between the two dissociation constant as seen in the titration of chlorpheniramine maleate in 40%v/v ethanol/water.

The plot of titration data after equivalence point would give same results as the standard non-aqueous method. However, high pH region after equivalence point could affect end point determination in the similar way as titration in aqueous solvent.