CHAPTER IV

RESULTS AND DISCUSSION

In titration of five weak acidic drugs whose dissociation constants are between 10^{-7} - 10^{-10}, such as: triprolidine hydrochloride, dextromethorphan hydrobromide, diphenhydramine hydrochloride, quinine sulphate and chlorpheniramine maleate in aqueous solvent, precipitations were observed during the course of titration because of low aqueous solubilities of their conjugated bases. Thus, in order to avoid problems of precipitation, the systems of mixed solvents should be employed in the titration which could give homogeneous solution throughout the course of titration. Mixed solvent systems, used in this investigation were ethanol-water, methanol-water and propylene glycol-water.

The end point volumes, which were obtained from Gran's method were used to determine the percentage purities of these weak acidic drugs. These results were then compared with that obtained from standard titration method as described in USP XX. To determine whether there was a statistically difference between these results, the t-test was employed at 99% confidence level.

For the titration of triprolidine HCl, quinine sulfate, dextromethorphan HBr and diphenhydramine HCl in those mixed solvent systems, the results indicated that all mixed solvent systems remained as homogeneous solution throughout the course of titration and the resulting titration curves showed more cleary defined inflection point than those obtained from aqueous solvent. Among those solvent systems, the inflection point was more cleary observed in system of ethanol-water than in methanol-water and propylene glycol-water. The higher the percentage of organic solvents, the more cleary defined inflection point were observed as shown in Figure 1, 9, 17, 25, 32, 39, 47, 53, 60, 66, 74, and 82. These results were due to the reaction of these weak acid and sodium hydroxide in mixed solvents, which generated unionized products and hence were favored by solvents with lower dielectric constant (more nonpolar solvents).

But for the titration of chlorpheniramine maleate with sodium hydroxide in mixed solvent systems, the titration curves had shown different manner from triprolidine HCl, quinine sulfate, dextromethorphan HBr and diphenhydramine HCl as shown in Figure 90-96, 104-110 and 118-122. These results were due to the overlapping of two dissociation constants of chlorpheniramine maleate.

1. Triprolidine Hydrochloride

This compound has the dissociation constant of 3×10^{-7} (pKa = 6.5). In titration of this compound in mixed solvents, the results can be shown as followed:

1.1 Methanol-Water System

In this mixed solvent system, the lowest percentage volume by volume (v/v) of methanol/water which would give single homogeneous phase throughout the course of titration was 30% methanol/water and the highest limit was 90% methanol/water. With high composition of organic solvent in solution, the responsiveness of the glass electrode to apparent pH decreased since hydronium ion concentration decreased. Dehydration of glass electrode would likely occurred as the composition of methanol in the mixed solvent system approached 100% .

Figure 1 showed the titration curves of triprolidine HCl with sodium hydroxide in 30-90% methanol/water. Table 3 illustrated average percentage purities which were calculated from end point volumes obtained from V plot, E plot (the plot from Gran's equation which used data before and after equivalence point respectively) and G plot (a plot from modified V plot equation taken into account the autoprotolysis of solvent which assumed to be the same value as autoprotolysis of water) in different composition of

Table 3 Average Percentage Purities by Gran's Method for Titration of Triprolidine Hydrochloride in Methanol-Water Solvent Systems with 0.08624 N NaOH

Solvent (Methanol in water)	Average Percentage Purity (%)			
	G plot	V plot	E plot	USP method **
30%	99.20 * (0.22)	99.06 * (0.16)	98.92 * (0.35)	
40%	99.30 * (0.29)	99.28 * (0.29)	98.90 * (0.33)	
50%	98.91 * (0.34)	99.08 * (0.53)	99.06 * (0.33)	
60%	99.24 * (0.27)	98.99 * (0.26)	98.77 * (0.25)	99.25 * (0.20)
70%	98.94 * (0.41)	99.10 * (0.40)	98.76 * (0.19)	
80%	98.10 (0.24)	97.60 (0.41)	98.43 (0.30)	
90%	98.04 (0.33)	98.16 (0.44)	97.45 (0.34)	

* Statistically indifference from reference non-aqueous titration at 99% confidence level

** Titrated in glacial acetic acid mercuric acetate TS with 0.1 N perchloric acid and determining the end point potentiometrically

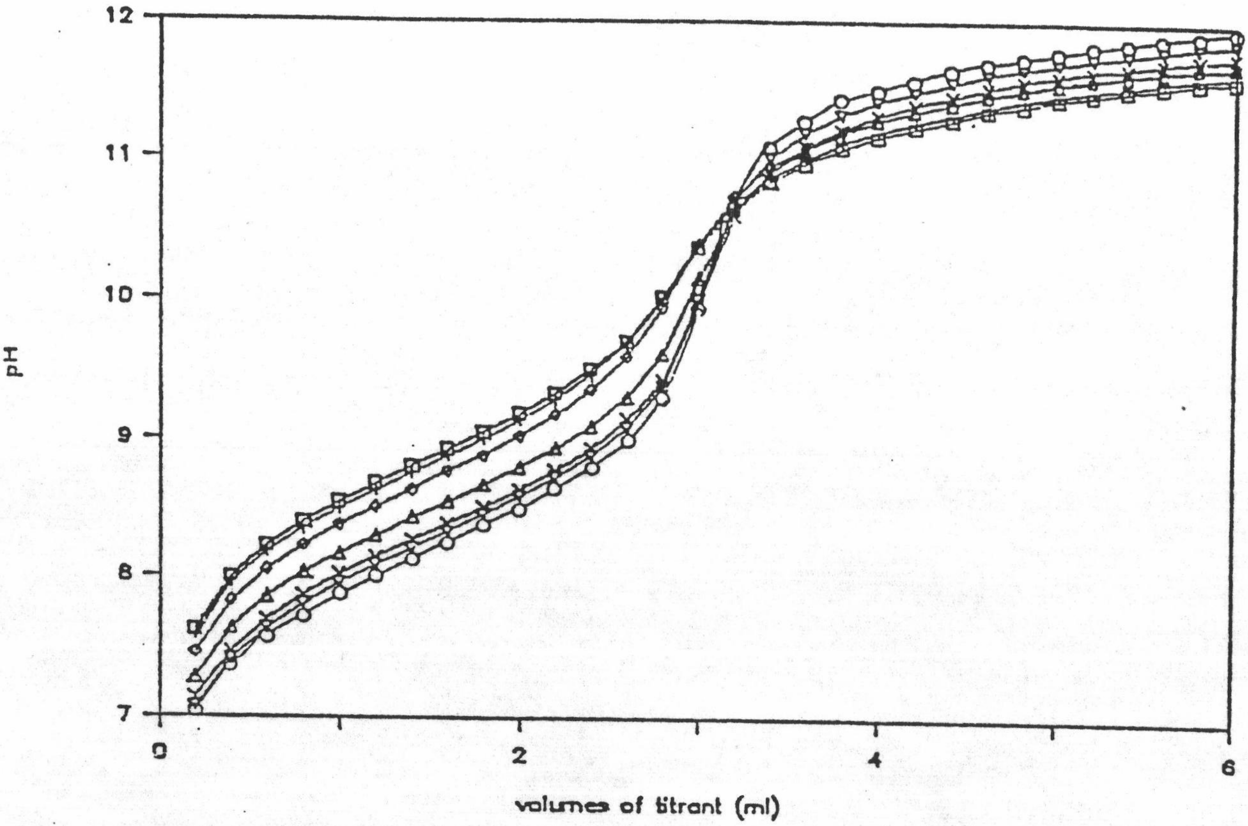

Figure 1 Titration Curves of triprolidine hydrochloride with sodium hydroxide in 30-90% v/v methanol/water
30% (□) 40% (+) 50% (◇) 60% (△)
70% (×) 80% (▽) 90% (o).

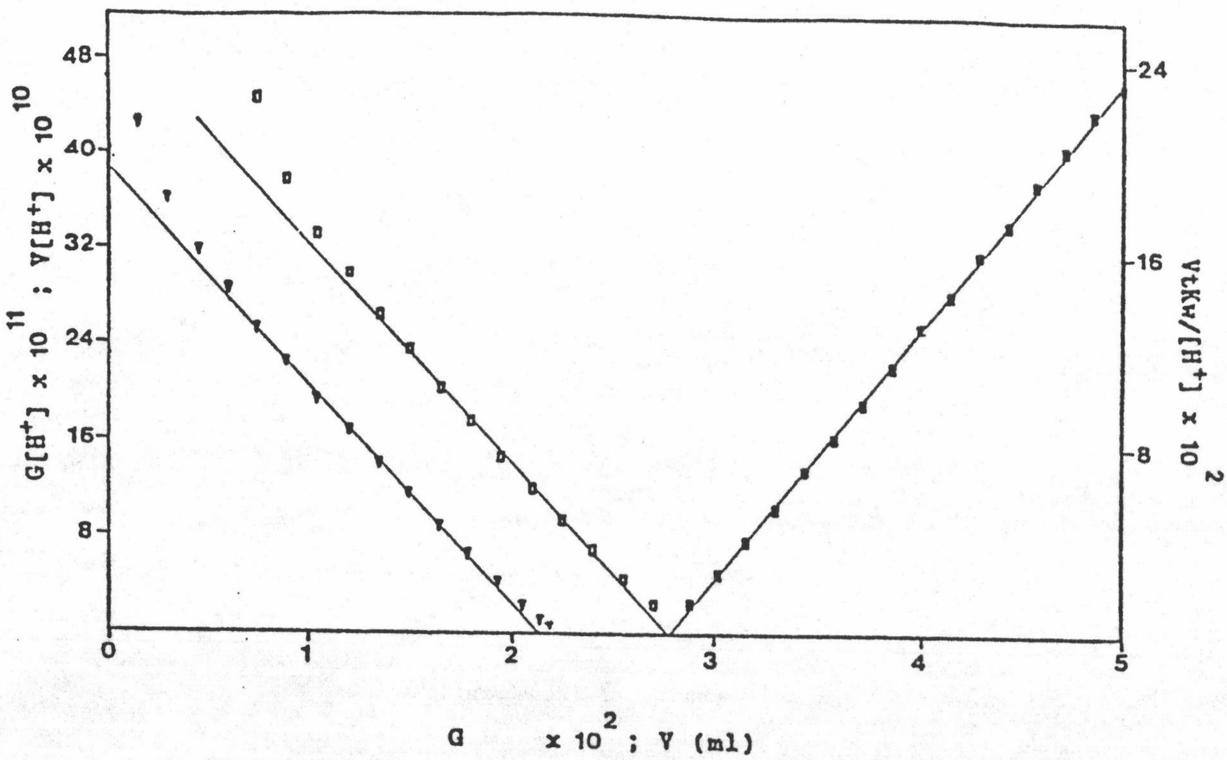

Figure 2 Gran's plot for the titration of triprolidine HCl with sodium hydroxide in 30% v/v methanol/water G plot (▼) V plot (□) E plot (■).

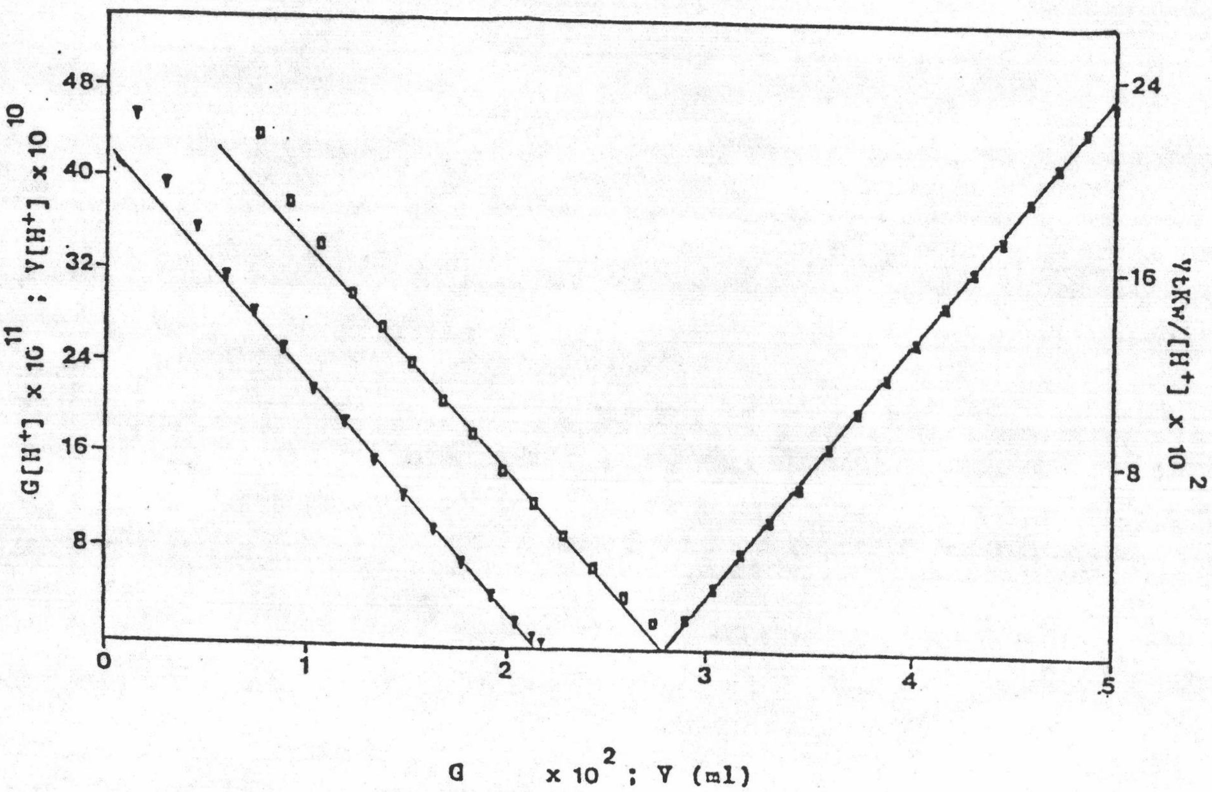

Figure 3 Gran's plot for the titration of triprolidine HCl with sodium hydroxide in 40% v/v methanol/water G plot (▼) V plot (□) E plot (■).

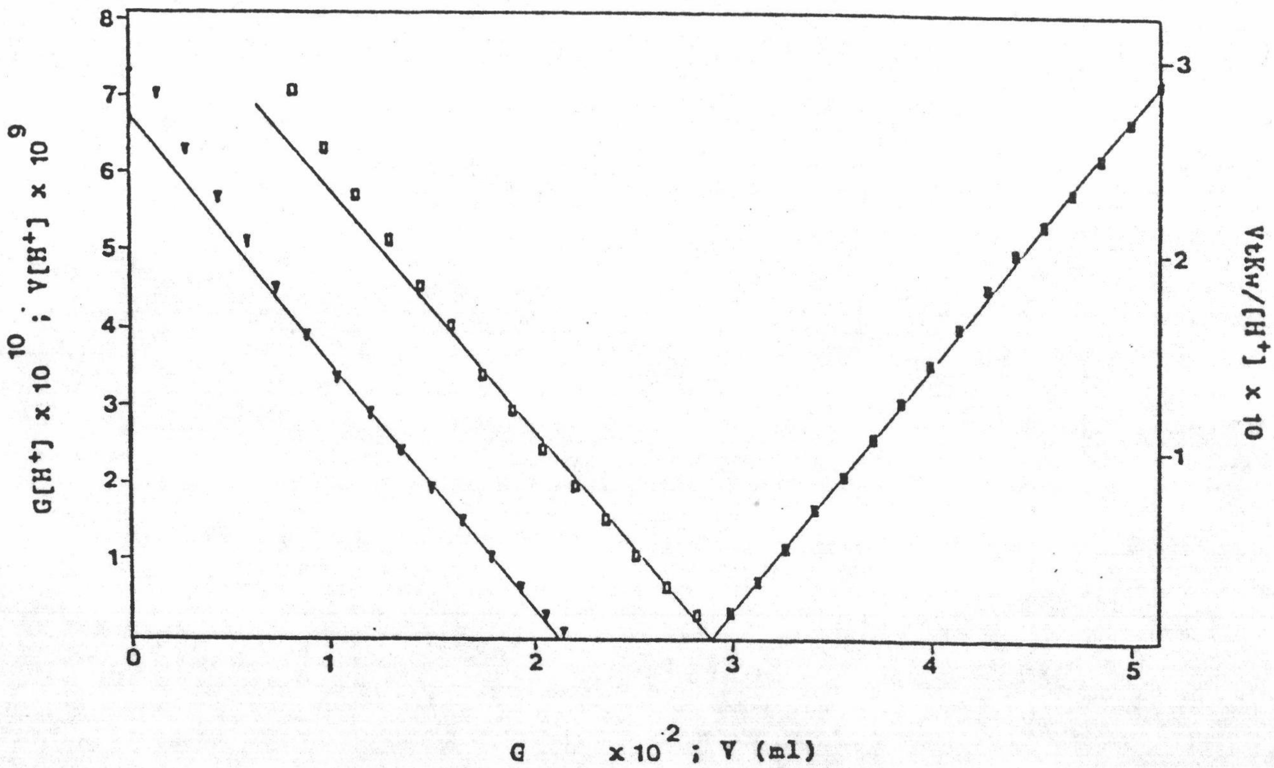

Figure 4 Gran's plot for the titration of triprolidine HCl with sodium hydroxide in 50% v/v methanol/water G plot (▼) V plot (□) E plot (■).

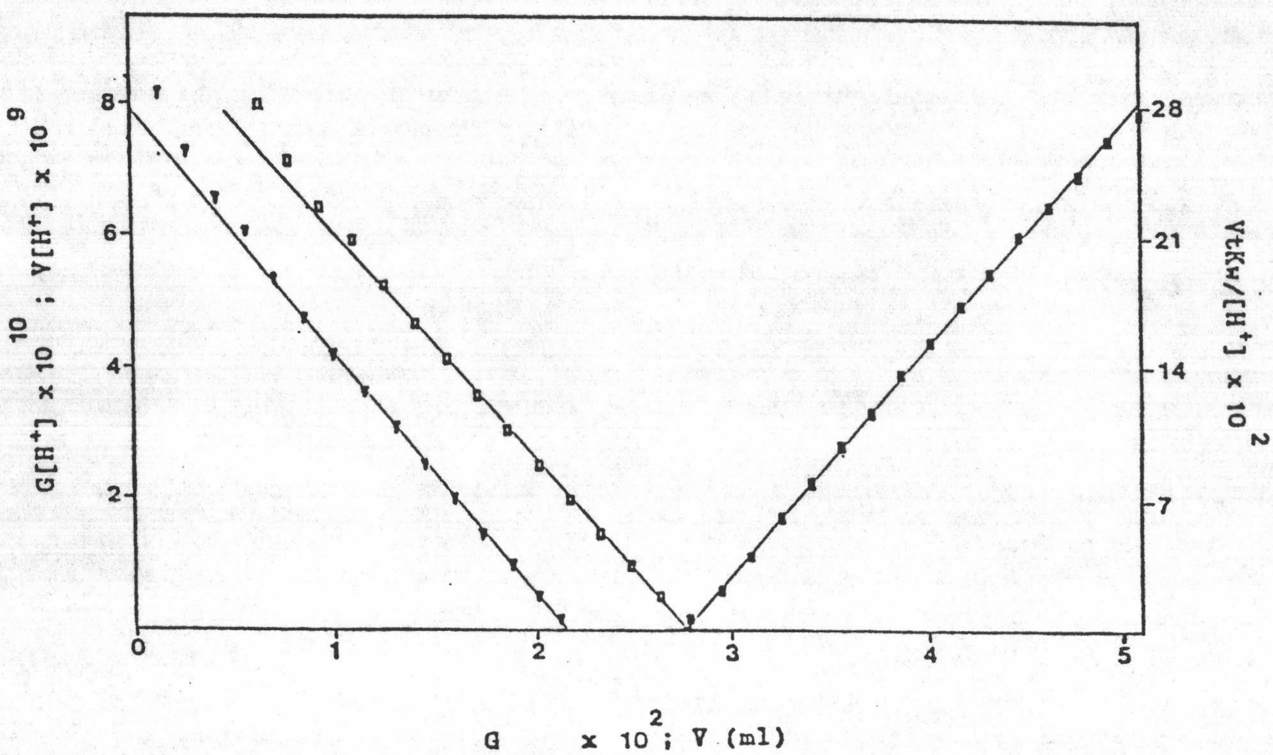

Figure 5 Gran's plot for the titration of triprolidine HCl with sodium hydroxide in 60% v/v methanol/water G plot (▼) V plot (□) E plot (■).

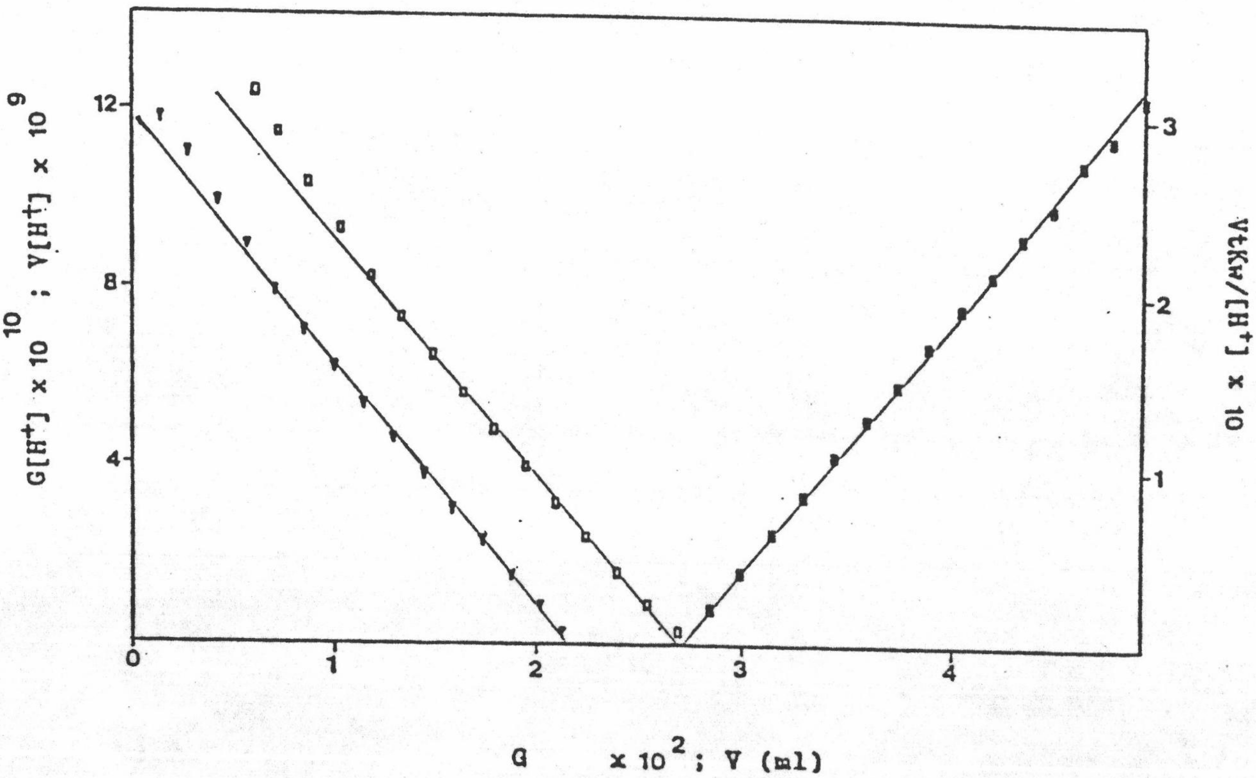

Figure 6 Gran's plot for the titration of triprolidine HCl with sodium hydroxide in 70% v/v methanol/water G plot (▼) V plot (□) E plot (■).

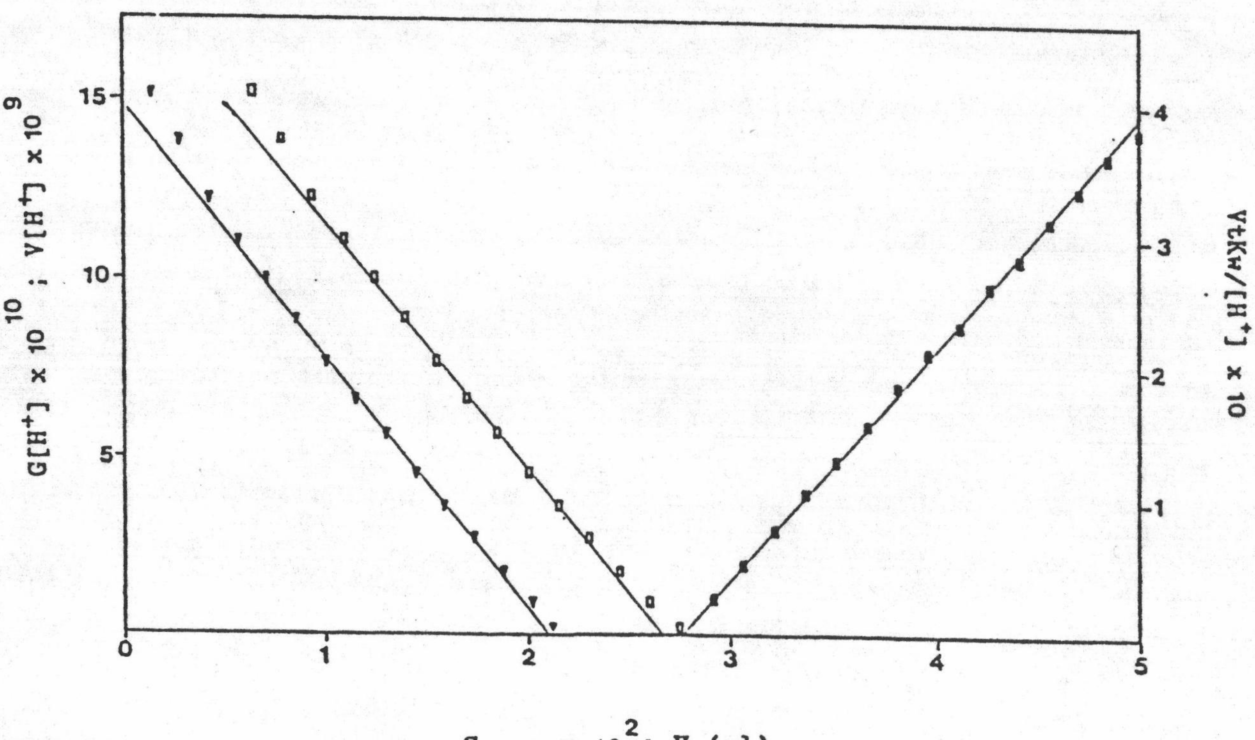

Figure 7 Gran's plot for the titration of triprolidine HCl with sodium hydroxide in 80% v/v methanol/water G plot (▼) V plot (□) E plot (■).

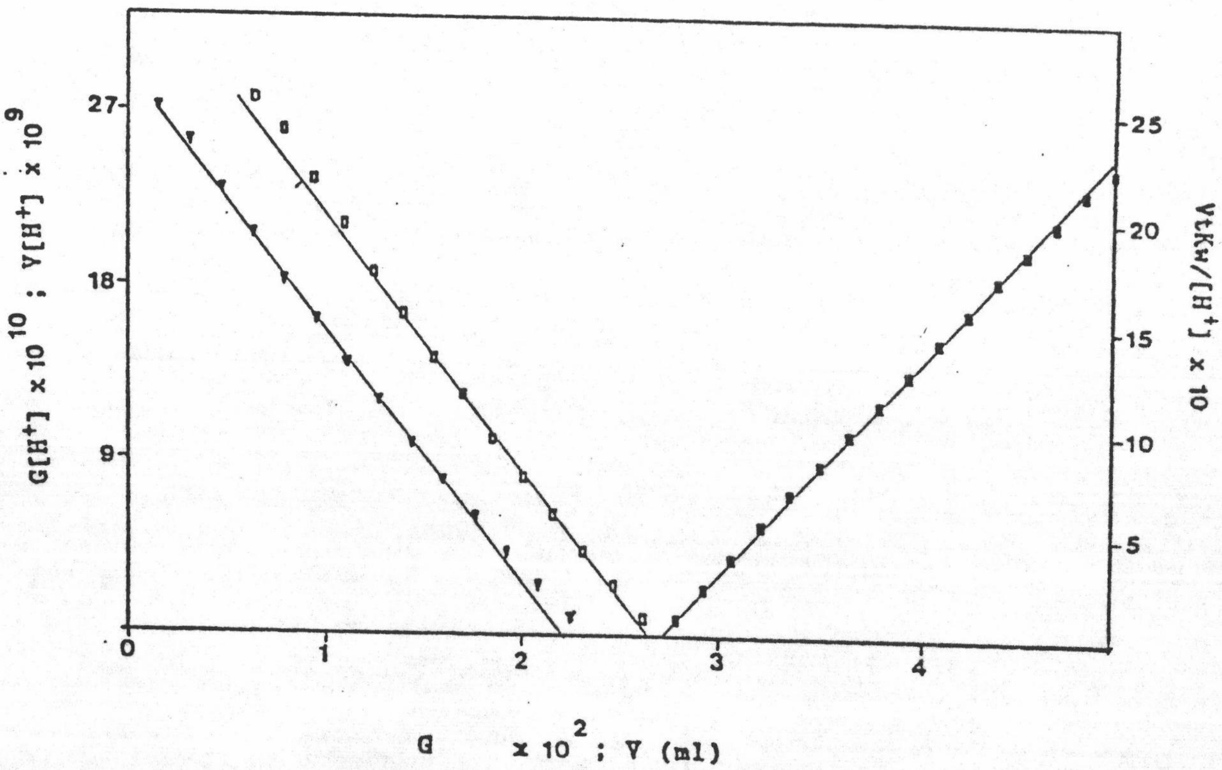

Figure 8 Gran's plot for the titration of triprolidine HCl with sodium hydroxide in 90% v/v methanol/water G plot (▼) V plot (□) E plot (■).

methanol-water mixed solvents. The V- shape Gran plots in different compositions of methanol-water solvents were shown in Figure 2-8.

The resulting G , V and E plots for the titration of triprolidine HCl in 30-70% v/v methanol/water, (Figure 2-6) were linear and when extrapolated to x-axis yielded accurate and reproducible end point volumes. The calculated percentage purities of triprolidine HCl were statistically indifferent from the values obtained by non-aqueous method (Table 3). In this study the selected pH range for V plot was between 5-9, hence, hydronium concentration and hydroxide concentration were much smaller than VN/(Vo+V) as assumed for the V plot. The results for the titration of triprolidine HCl in 30-70% v/v methanol/water, the value for autoprotolysis of water could be used as the autoprotolysis of mixed solvent for the titration in 30-70% v/v methanol/water.

The average percentage purities calculated from G , V and E plots for the titration in 80-90% v/v methanol/water (Table 3) were statistically different from that obtained from non-aqueous titration. Although, G , V and E plots were linear enough to be extrapolated to x-axis, but the resulting equivalence points were statistically different from value obtained from non-aqueous method. This might be due to the effect of neglecting the δ, correction factor in calculating the concentration of hydrogen ion from the pH values (22).

This assumption was based on Ong's study (22), in which he had determined the value of constant δ , correction for liquid junction potential and medium effect. For methanol-water mixtures, Ong concluded that δ values were small up to about 80% by weight methanol in water. Thus the true pH value of solution for the titration in about 30-70% v/v methanol/water systems were essentially same as pH value reading from pH meter . On the other hand, for the titration in 80-90% v/v methanol/water constant δ was too large to neglect, more than 0.1 pH unit. Since in high concentration of methanol, the liquid junction potential was rather large, it must be corrected for constant in the calculation of equivalence volume for the titration in 80-90% v/v methanol/water.

1.2 Ethanol-Water System

The titrations of triprolidine HCl were performed in 30-90% v/v ethanol/water which gave homogeneous solution throughout the titration. The titration curves of triprolidine HCl with sodium hydroxide in 30-90% v/v ethanol/water were shown in Figure 9. Table 4 illustrated average percentage purities which calculated from an end point volumes obtained from G, V and E plots in different composition

Table 4 Average Percentage Purities by Gran's Method for Titration of Triprolidine Hydrochloride in Ethanol-Water Solvent Systems with 0.08624 N NaOH

Solvent (Ethanol in water)	Average Percentage Purity (%)			
	G plot	V plot	E plot	USP method **
30%	98.88 * (0.18)	99.00 * (0.30)	99.16 * (0.19)	
40%	99.01 * (0.26)	99.03 * (0.33)	99.33 * (0.27)	
50%	97.61 (0.26)	97.88 (0.22)	97.71 (0.22)	
60%	97.64 (0.34)	97.76 (0.27)	-	99.25 * (0.20)
70%	97.79 (0.52)	97.66 (0.52)	-	
80%	97.91 (0.46)	97.84 (0.44)	-	
90%	97.50 (0.31)	97.71 (0.16)	-	

* Statistically indifference from reference non-aqueous titration at 99% confidence level

** Titrated in glacial acetic acid mercuric acetate TS with 0.1 N perchloric acid and determining the end point potentiometrically

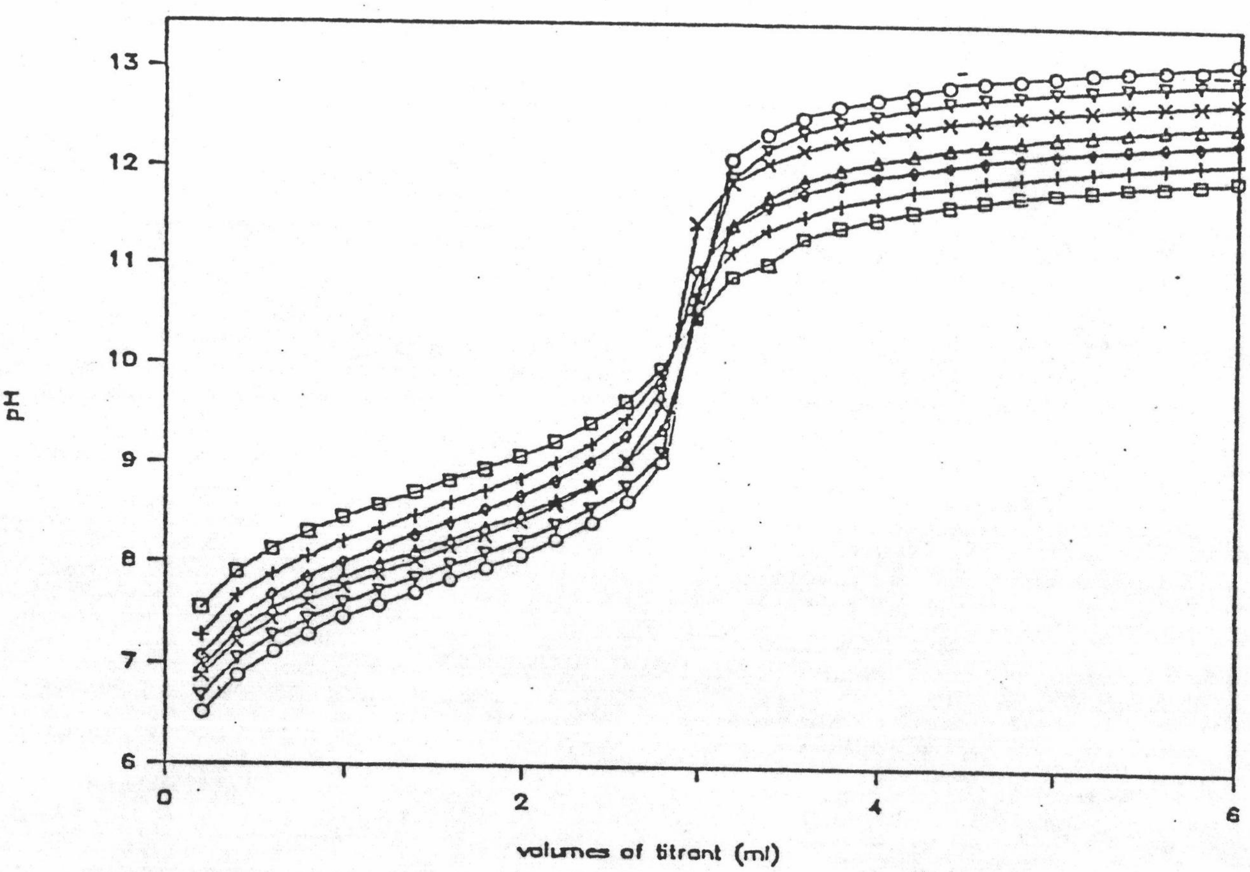

Figure 9 Titration curves of triprolidine hydrochloride with sodium hydroxide in 30-90% v/v ethanol/water
30% (□) 40% (+) 50% (◊) 60% (Δ)
70% (×) 80% (▽) 90% (○).

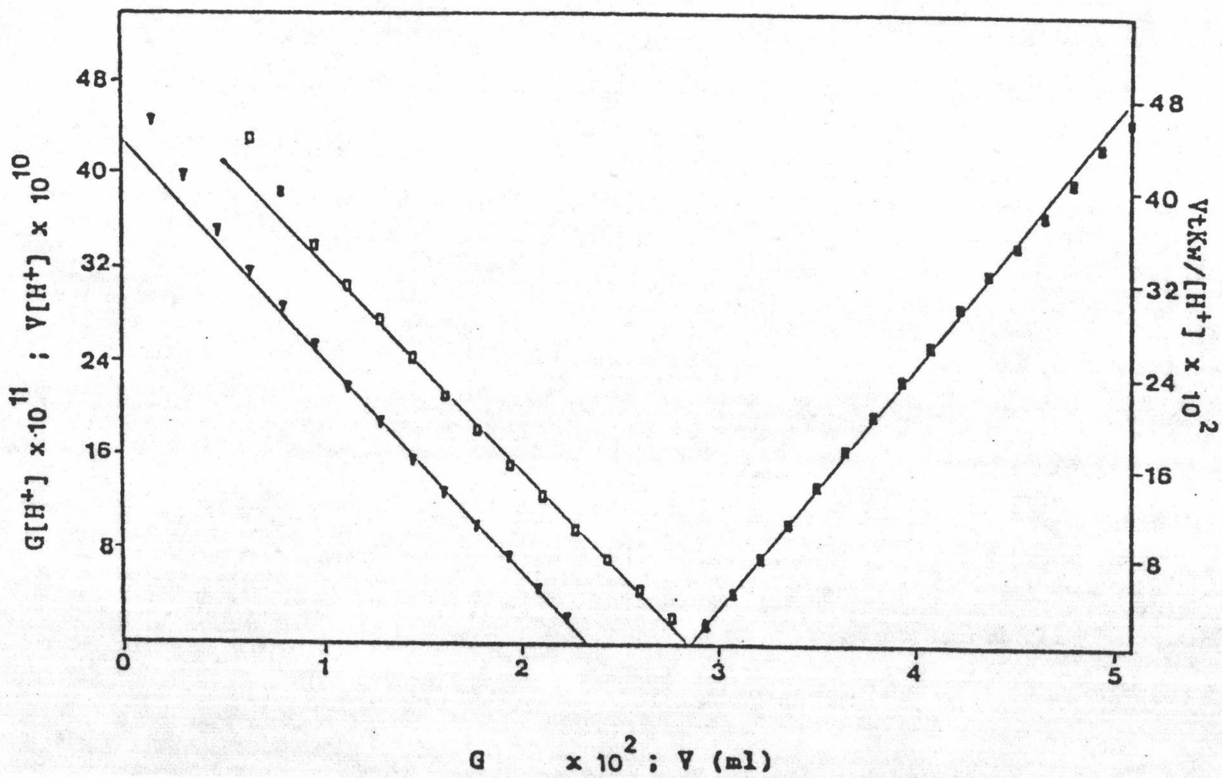

Figure 10 Gran's plot for the titration of triprolidine HCl with sodium hydroxide in 30% v/v ethanol/water G plot (▼) V plot (□) E plot (■).

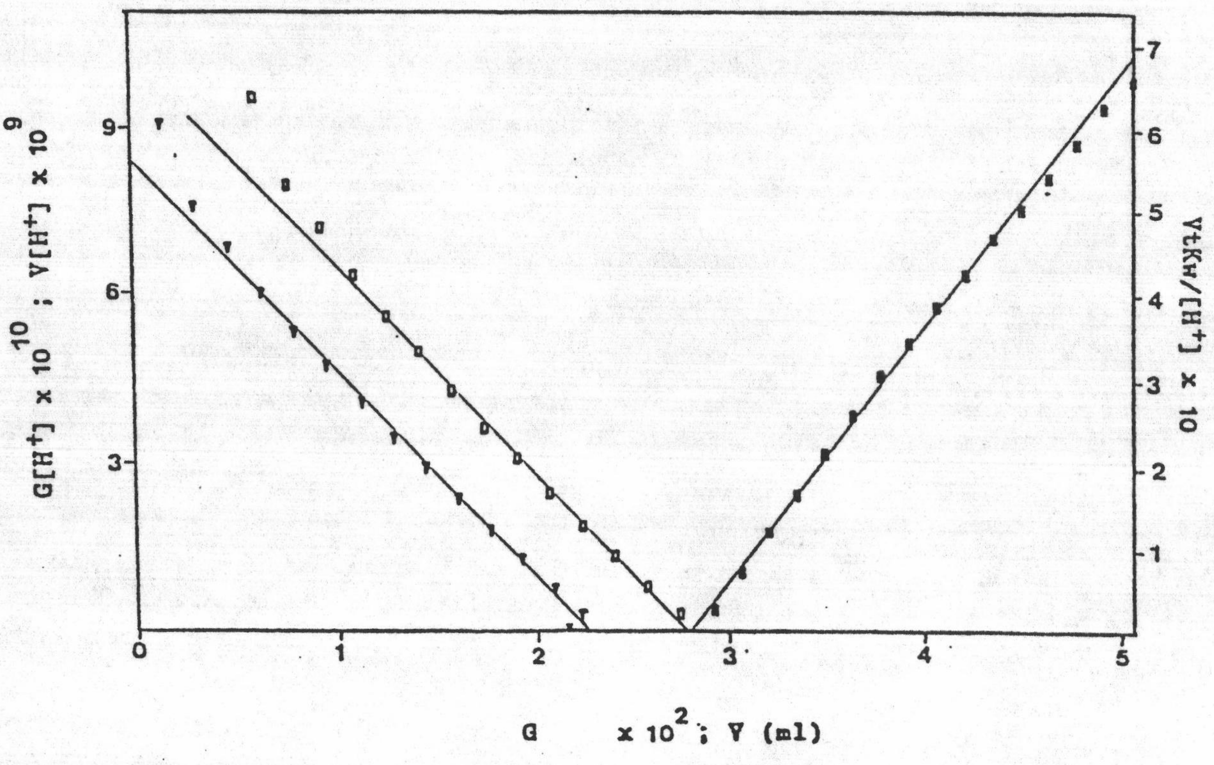

Figure 11 Gran's plot for the titration of triprolidine HCl with sodium hydroxide in 40% v/v ethanol/water G plot (▼) V plot (□) E plot (■).

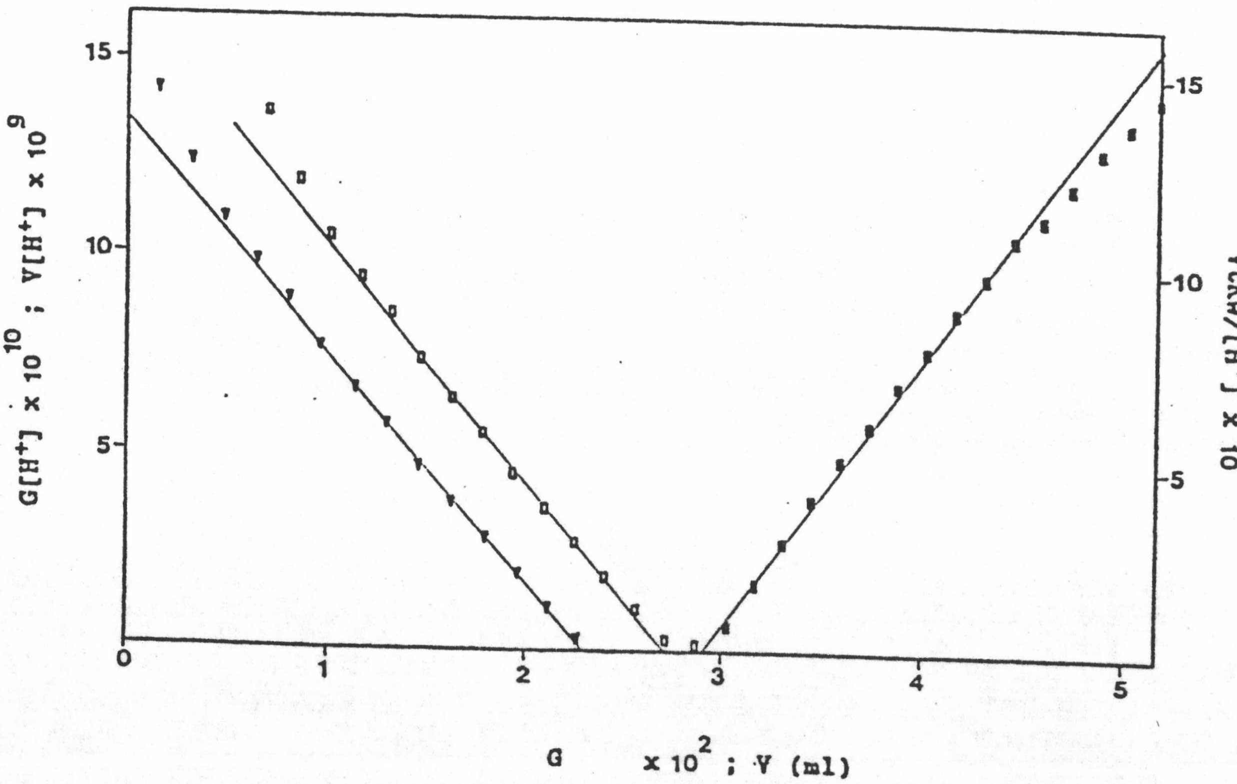

Figure 12 Gran's plot for the titration of triprolidine HCl with sodium hydroxide in 50% v/v ethanol/water G plot (▼) V plot (□) E plot (■).

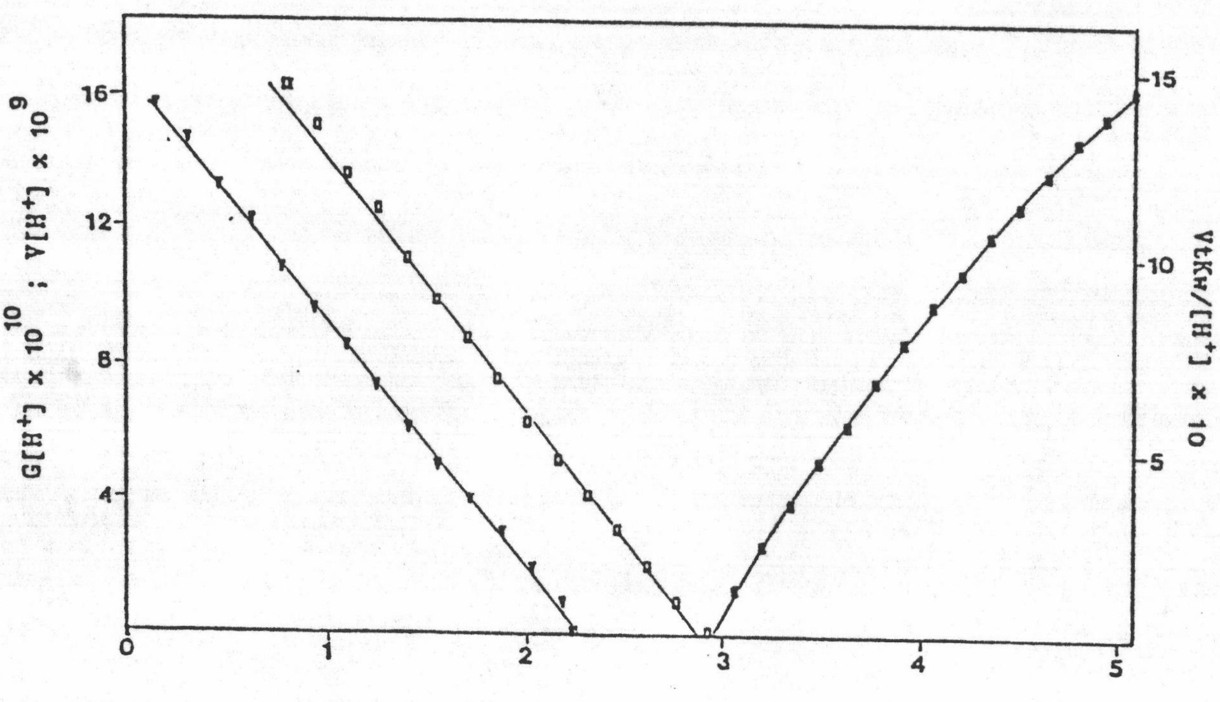

Figure 13 Gran's plot for the titration of triprolidine HCl with sodium hydroxide in 60% v/v ethanol/water G plot (▼) V plot (□) E plot (■).

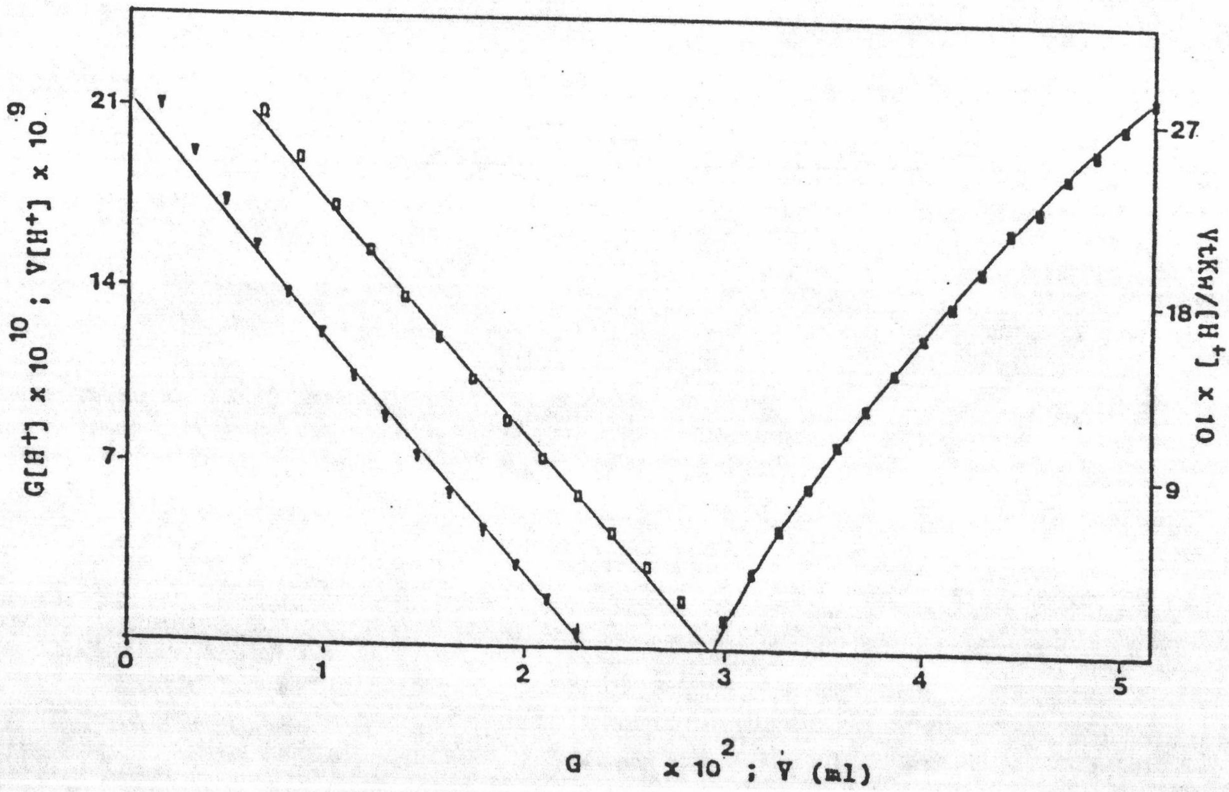

Figure 14 Gran's plot for the titration of triprolidine HCl with sodium hydroxide in 70% v/v ethanol/water G plot (▼) V plot (□) E plot (■).

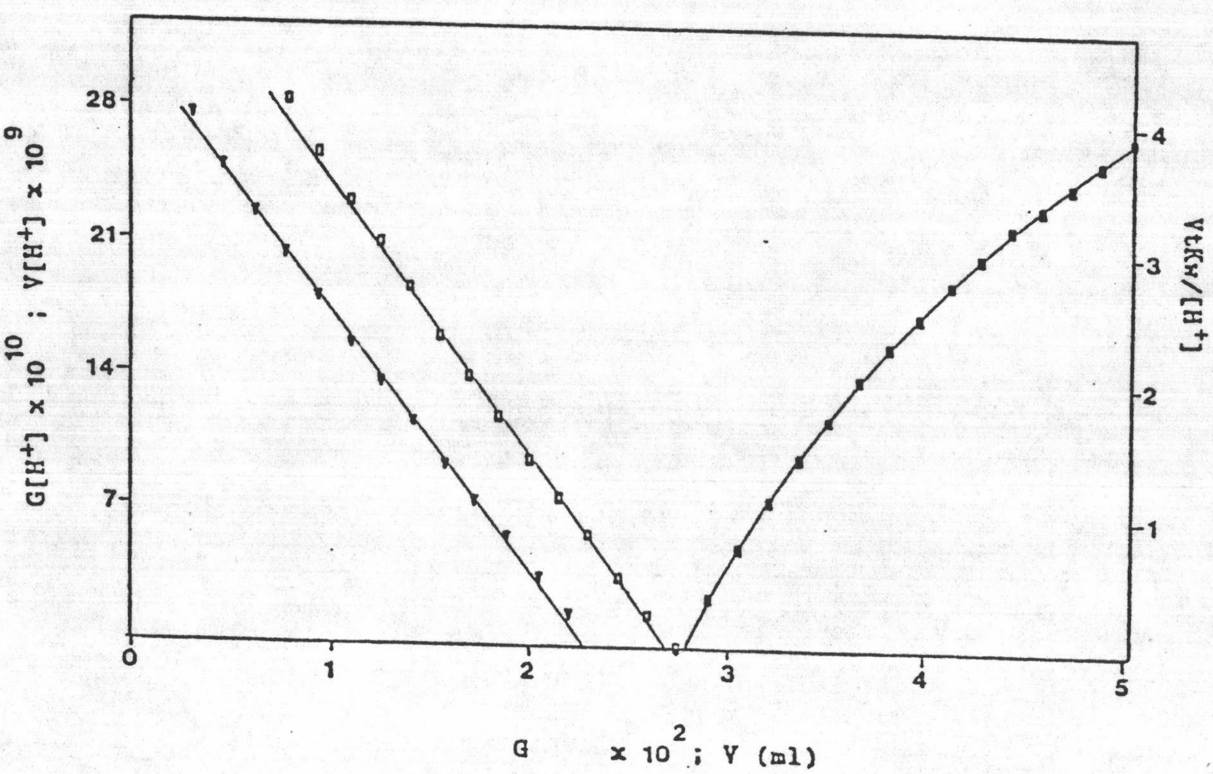

Figure 15 Gran's plot for the titration of triprolidine HCl with sodium hydroxide in 80% v/v ethanol/water G plot (▼) V plot (□) E plot (■).

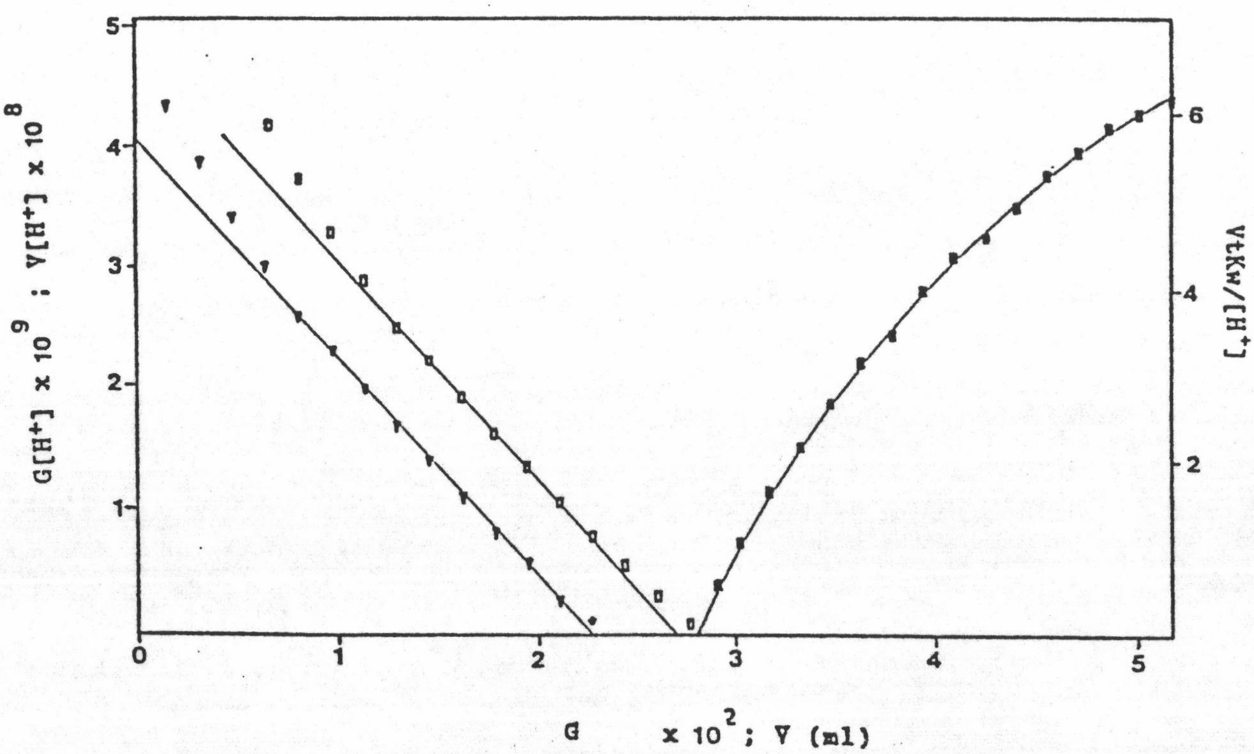

Figure 16 Gran's plot for the titration of triprolidine HCl with sodium hydroxide in 90% v/v ethanol/water G plot (▼) V plot (□) E plot (■).

of ethanol in mixed solvents. V-shape Gran's plots in different percentages of ethanol in mixed solvent system were shown in Figures 10-16.

For the titrations of triprolidine HCl in 30-40% v/v ethanol/water, the G, V and E plots showed linear portions which we could extrapolate to x-axis to obtain accurate and reproducible end point volume (Figure 10-11). The percentage purities for the titration in 30-40% v/v ethanol/water calculated from G, V and E plot were not significantly different from that obtained by non-aqueous method, as shown in Table 4. These indicated that the assumption for V and G plot was true for the titration of triprolidine HCl in low percentage of ethanol in water, 30-40% v/v ethanol/water.

For the titrations in 50-90% v/v ethanol/water, the percentage purities of triprolidine HCl calculated from G , V and E plots were statistically different fron non-aqueous titration. This result might be partly dued to the instability of glass electrode for measuring pH values in ethanol-water media which should be considered. Bate had concluded (39) that in 40% ethanol in water, glass electrode could be used in measuring pH value from pH 3 to 9.5, but in 50% ethanol in water deviation appeared at pH 7 and in 70% ethanol in water deviation appeared at pH 8 (39). Also according to Bate's studied (23), the value of δ constant in high compositions (80-90% v/v ethanol/water) which was rather large. Therefore calculation of hydrogen ion concentrations from pH value, not correcting for δ constant could give false results. The results of this study agree well with our expectation that the titration of triprolidine HCl in ethanol-water would yield accurate results for G, V and E plots only in low compositions of ethanol in water 30-40% v/v ethanol/water. In the higher compositions (50-90% v/v ethanol/water) there were some precautions which should be considered as discussed above.

Figure 12-16, the titrations of triprolidine HCl in 50-90% v/v ethanol/water the E plots showed significantly curvatures. Thus there were some ploblems on selecting the data points used in analysis. The percentage purities of triprolidine HCl calculated from E plots for the titration in 50-90% v/v ethanol/water were significantly different from non-aqueous titration and could not be determined for the titration in 60-90% v/v ethanol/water.

The reason of the curvature of E plots might be due to glass electrode falsely measured some of Na^+ ion in the solution for hydronium ion because in high alkaline region, concentration of Na^+ from addition of titrant, sodium hydroxide, would be significant. Therefore, actual pH should be higher than what was measured, resulting in false end point volumes.

1.3 Propylene Glycol-Water System

The titrations of triprolidine HCl were performed in 40-70% v/v propylene glycol/water which gave homogeneous solution throughout the titration. The limit of highest composition of propylene glycol in water for the titration was about 70% v/v propylene glycol/water. When the percentage of propylene glycol exceeded 70% v/v, the solution became very viscous and the equilibrium established slowly. The titration process became too time consuming and would not be practical for the routine analysis. The titration curves in 40-70% v/v propylene glycol/water were shown in Figure 17.

V-shape Gran's plots in different percentages v/v of propylene glycol in water were shown in Figure 18-21. G, V and E plots for the titration in 40-50% v/v propylene glycol/water were linear. Although the beginning of titration, the G and V plots showed some curvature but it did not affect end point determination and could be neglected.

For the titrations in 60-70% v/v propylene glycol/water, linear plots were obtained from G, V and E plots (Figure 20-21). However, the calculation of percentage purities from these plots were statistically lower than that obtained from non-aqueous titration as shown in Table 5. The calculated

Table 5 Average Percentage Purities by Gran's Method for Titration of Triprolidine Hydrochloride in Propylene Glycol - Water Solvent Systems with 0.08328 N NaOH

Solvent (Propylene glycol in water)	Average Percentage Purity (%)			
	G plot	V plot	E plot	USP method **
40%	99.34 * (0.17)	99.14 * (0.28)	98.98 * (0.22)	
50%	98.94 * (0.25)	98.88 * (0.23)	98.82 * (0.13)	
60%	98.29 (0.46)	98.35 (0.31)	98.28 (0.32)	99.25 * (0.20)
70%	97.92 (0.22)	97.91 (0.56)	98.14 (0.31)	

* Statistically indifference from reference non-aqueous titration at 99% confidence level

** Titrated in glacial acetic acid mercuric acetate TS with 0.1 N perchloric acid and determining the end point potentiometrically

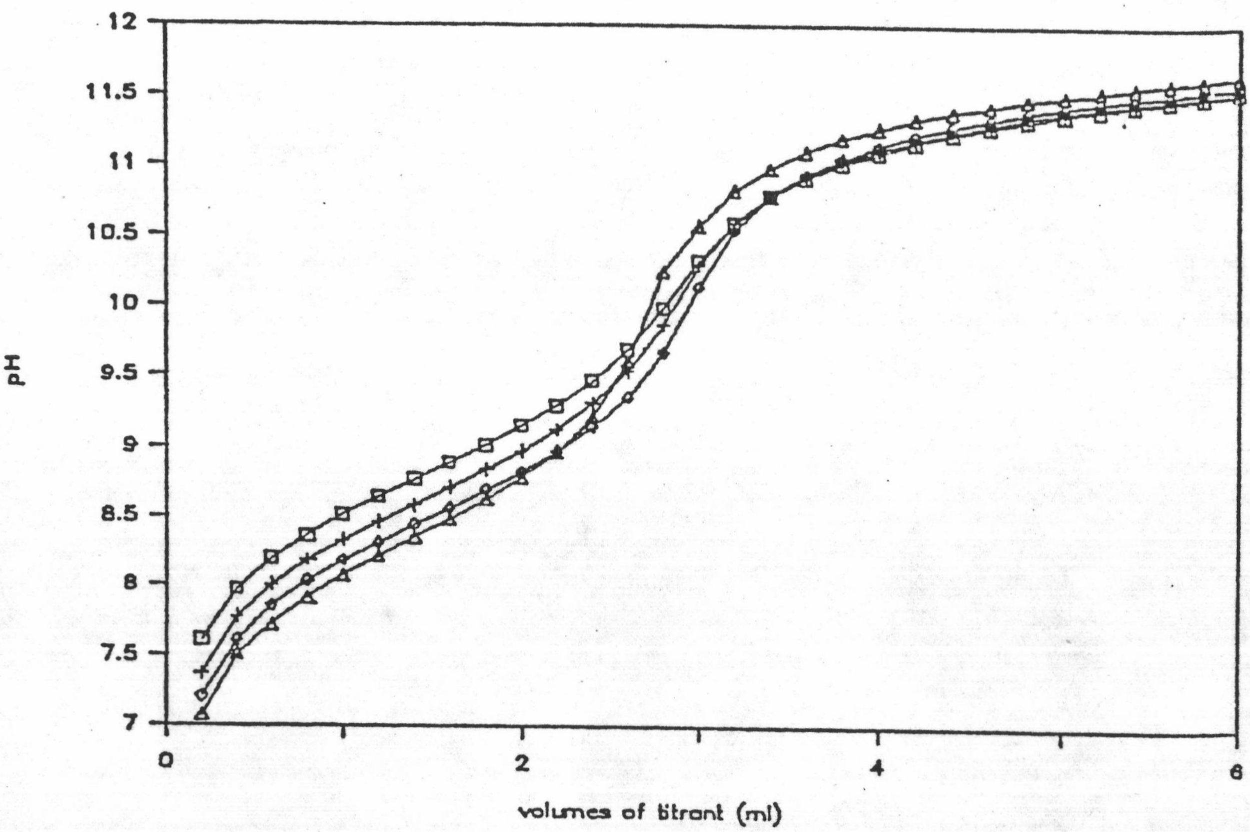

Figure 17 Titration Curves of triprolidine HCl with sodium hydroxide in 40-70% v/v propylene glycol/water
40% (□) 50% (+) 60% (◇) 70% (△).

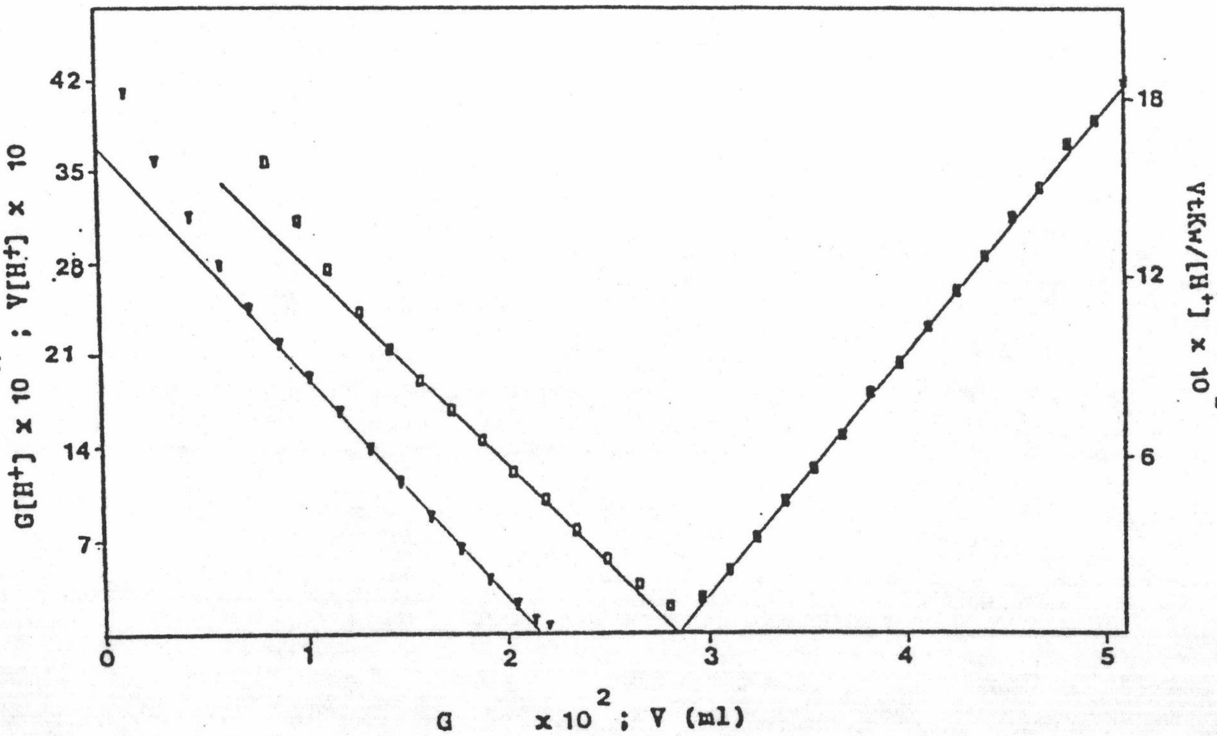

Figure 18 Gran's plot for the titration of triprolidine HCl with sodium hydroxide in 40% v/v propylene glycol/water G plot (▼) V plot (□) E plot (■).

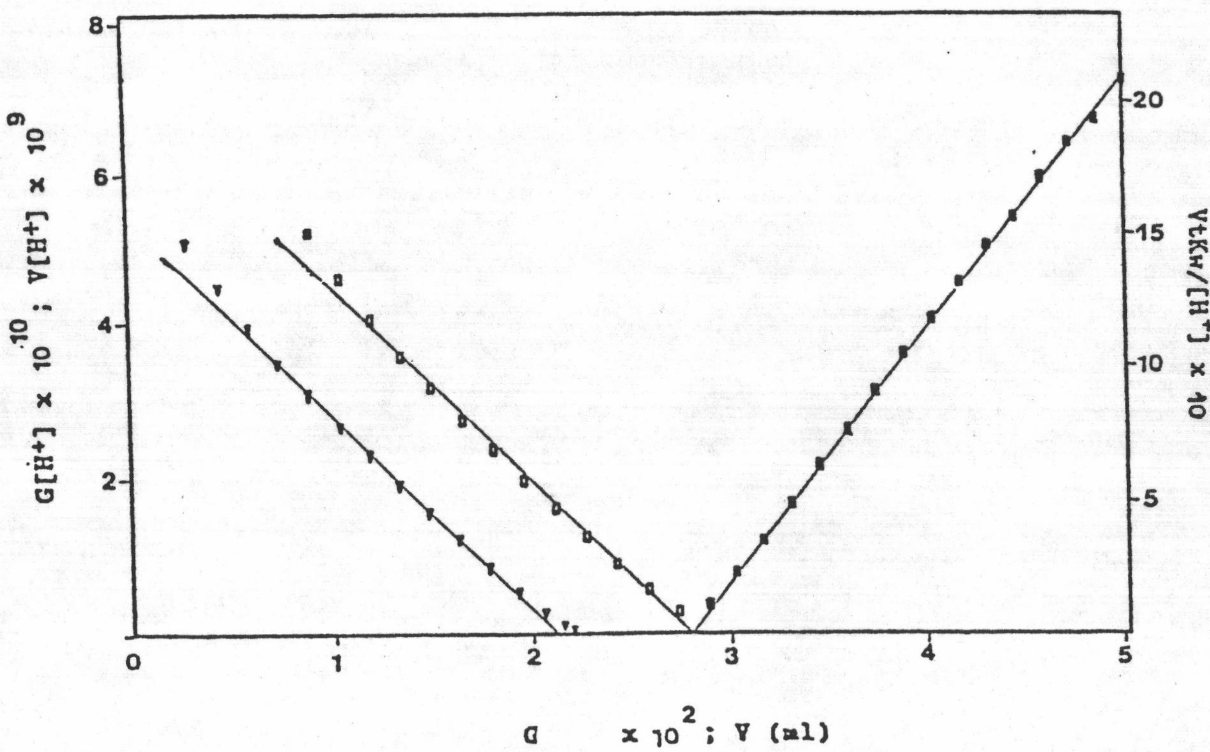

Figure 19 Gran's plot for the titration of triprolidine HCl with sodium hydroxide in 50% v/v propylene glycol/water G plot (▼) V plot (□) E plot (■).

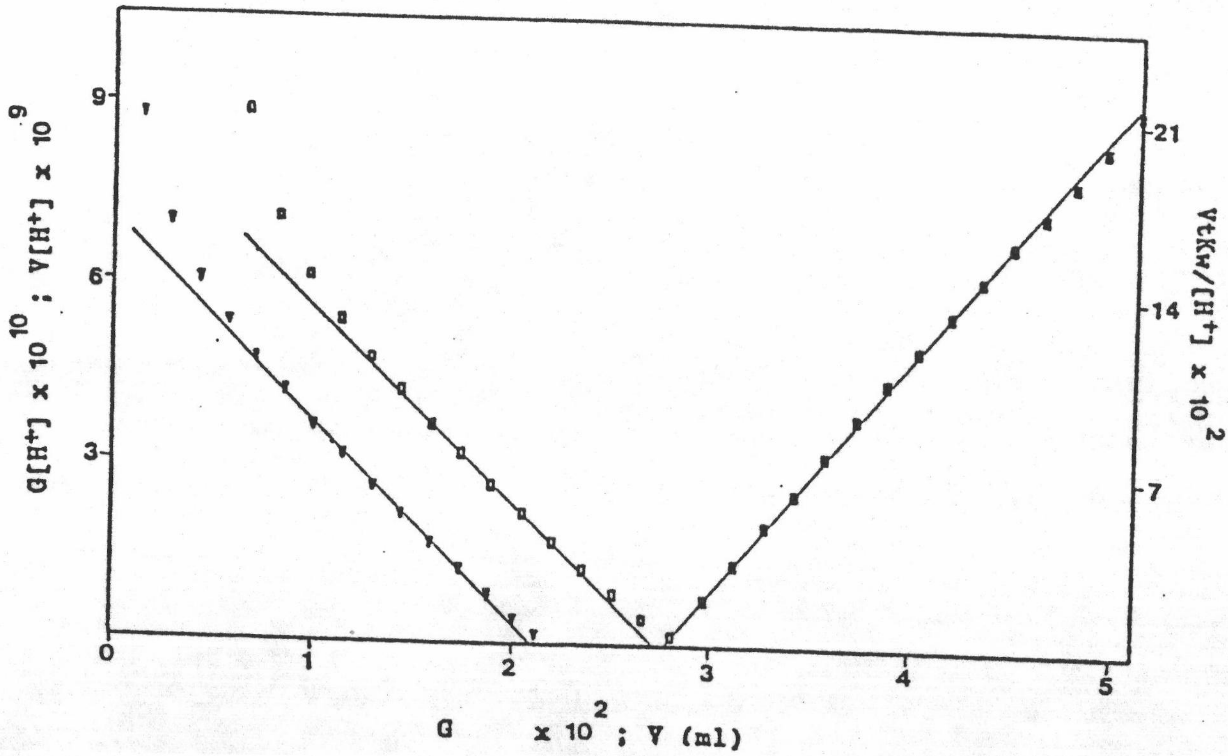

Figure 20 Gran's plot for the titration of triprolidine HCl with sodium hydroxide in 60% v/v propylene glycol/water G plot (▼) V plot (□) E plot (■).

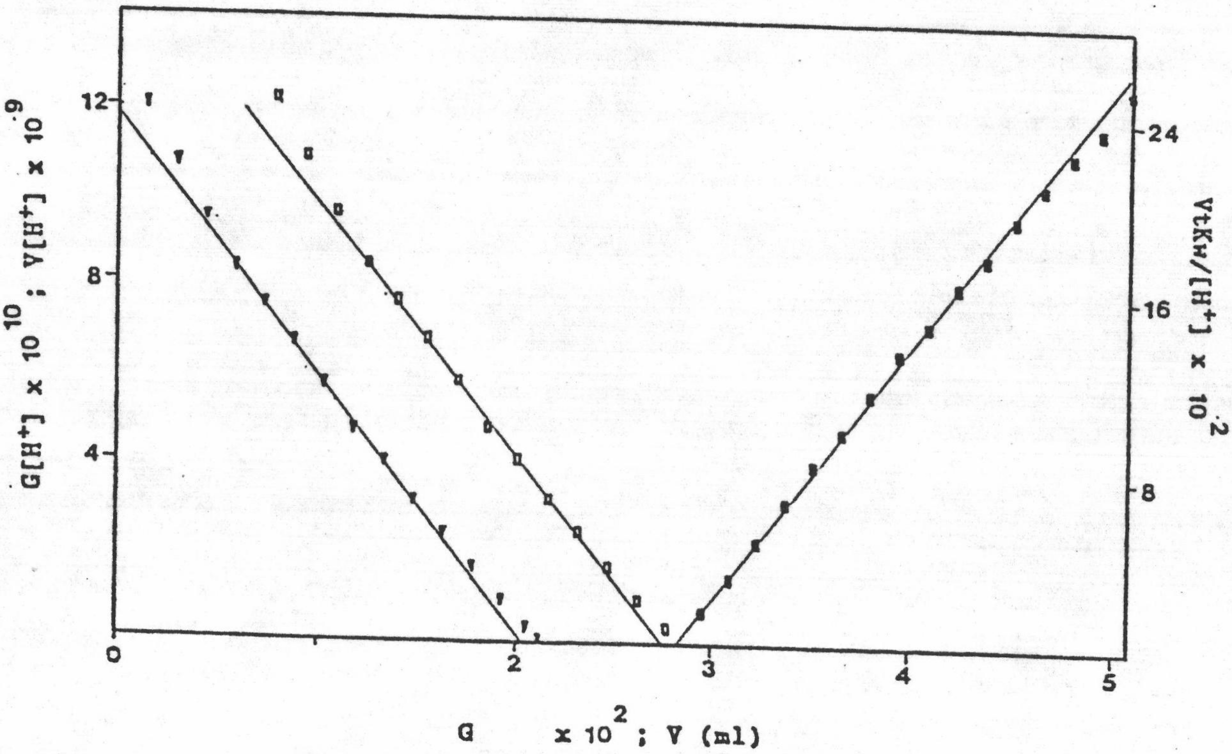

Figure 21 Gran's plot for the titration of triprolidine HCl with sodium hydroxide in 70% v/v propylene glycol/water G plot (▼) V plot (□) E plot (■).

percentage purities from G, V and E plots decreased with an incresaed in percentages of propylene glycol in the mixed solvent. This is probably resulting from the effects of viscosity or density of solution. The higher the density of the solution , the more viscous the solution would be. The relationship between density of solution and the activity coefficient of ionic species in the solution is given by Debye-Huckel equation (40):

$$-\log s\gamma i = \frac{(1.825 \times 10^{6}) Zi^{2}\sqrt{Id^{o}}}{(\varepsilon T)^{1/4} [1 + 50.29 (\varepsilon T)^{-1/2} a^{o}\sqrt{Id^{o}}}$$

where $s\gamma i$ is activity coefficient of ionic species (i)

- I is the ionic strength
- a^{o} is the ion-size parameter in A
- d^{o} is the density of the solvent
- T is the thermodynamic temperature
- ε is dielectric constant
- Zi is the valence of the species

Those results could be summarized in term of relative purity, the value that showed the relationship of percentage purity calculated from Gran's method and that calculated from non-aqueous titration as followed:

$$\text{Relative Purity} = \frac{\text{Av.\% Purity from Gran's Method}}{\text{Av.\% Purity from Non-aqueous Method}}$$

If relative purity = 1, it meaned that percentage purity calculated from Gran's method was equal to/or the same as that obtained from non-aqueous method. But if relative purity was lower or higher than 1, it meaned that there were the difference between those results. The ideal relative purity should be equal to 1.

For the titrations of triprolidine HCl in methanol-water, ethanol-water and propylene glycol-water systems, relative purity could be illustrated in Figures 22-24, respectively. Accurate results could be obtained from G , V and E plots for the titration in 30-70% v/v methanol/water and in 30-40% v/v ethanol/water. In the case of using propylene glycol-water system, accurate results could be obtained by titrating in 40-70% v/v propylene glycol/water.

2. Quinine Sulfate

This compound has the dissociation constant of 2×10^{-9} (pKa = 8.8).

2.1 Methanol-Water System

The titrations of quinine sulfate were performed in 40-90% v/v methanol/water and the titration curves in those mixed solvents were shown in Figure 25. Table 6 illustrated average percentage purities calculated from an end point volumes obtained from G , V and E plots.

V-shape Gran's plots in different

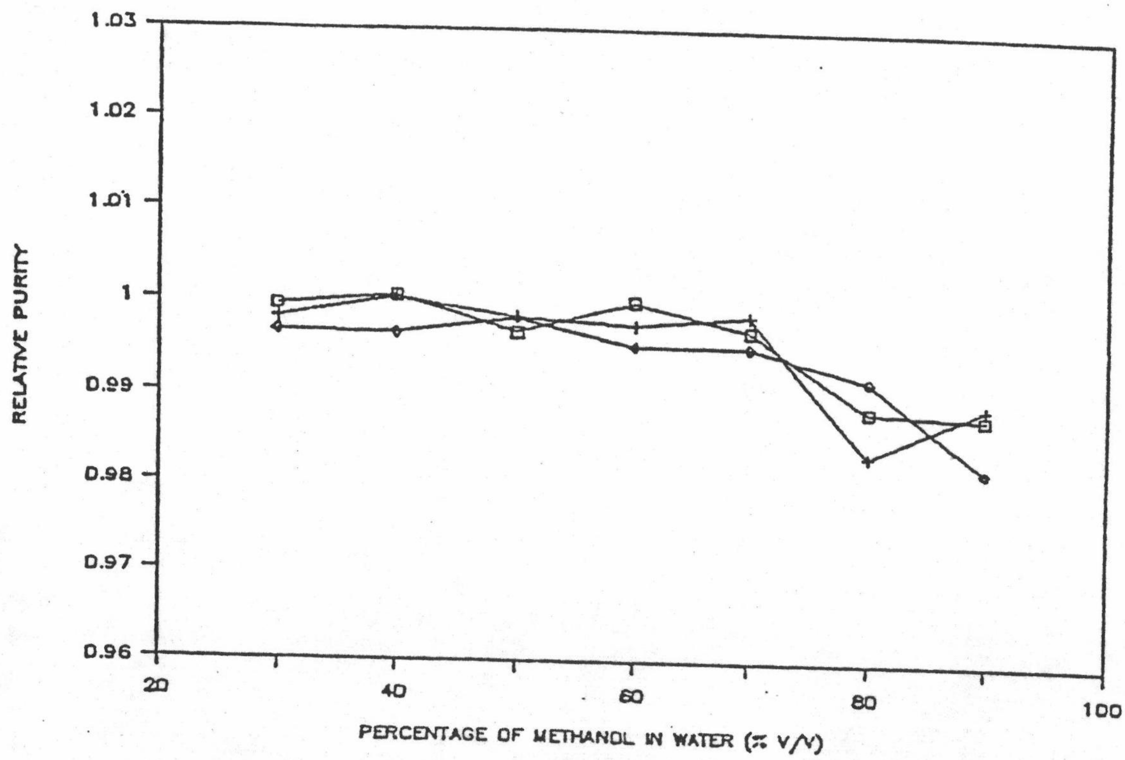

Figure 22   Relative purities of triprolidine hydrochloride in methanol-water solvents by using G plot (□) V plot (+) E plot (◇).

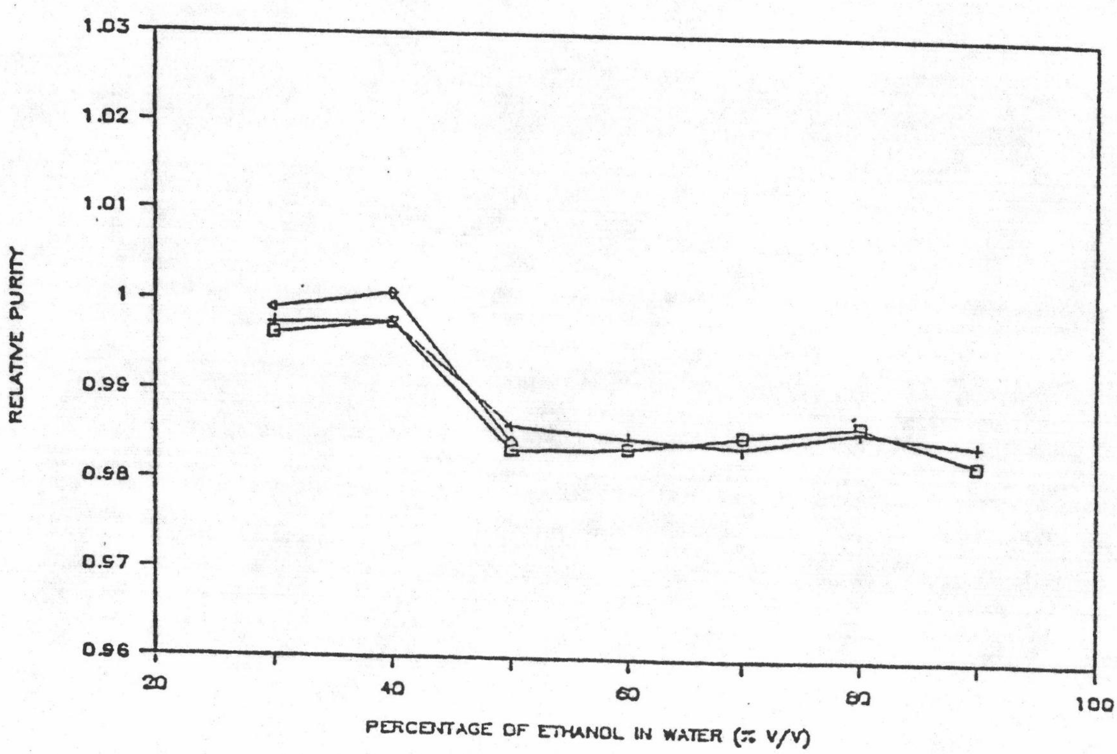

Figure 23   Relative purities of triprolidine hydrochloride in ethanol-water solvents by using G plot (□) V plot (+) E plot (◇).

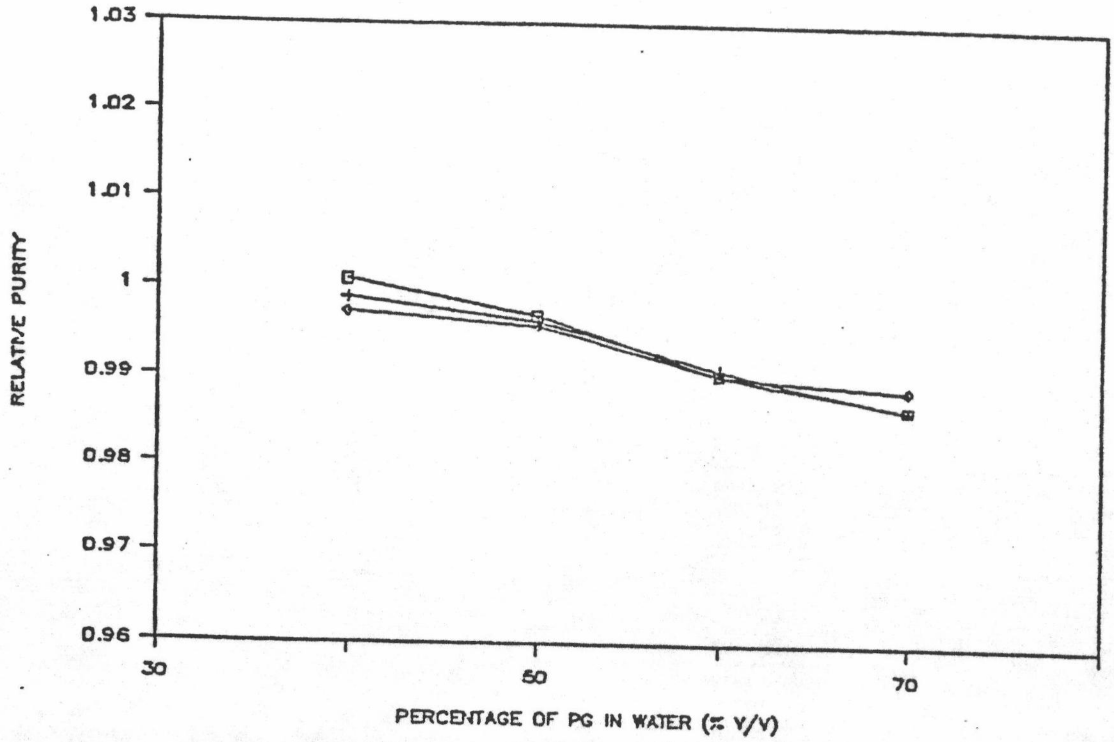

Figure 24 Relative purities of triprolidine hydrochloride in propylene glycol-water solvents by using G plot (□) V plot (+) E plot (◇).

Table 6 Average Percentage Purities by Gran's Method for Titration of Quinine Sulfate in Methanol-Water Solvent Systems with 0.08234 N NaOH

Solvent (Methanol in water)	Average percentage purity (%)			
	G plot	V plot	E plot	USP method **
40%	99.13 * (0.27)	98.81 * (0.42)	99.00 * (0.24)	
50%	98.91 * (0.26)	99.22 * (0.19)	98.92 * (0.25)	
60%	99.07 * (0.29)	98.91 * (0.23)	99.19 * (0.26)	
70%	99.13 * (0.32)	99.19 * (0.25)	98.86 * (0.53)	99.11 * (0.22)
80%	97.08 (0.48)	97.05 (0.53)	98.58 (0.27)	
90%	97.74 (0.32)	97.74 (0.13)	97.10 (0.38)	

* Statistically indifference from reference non-aqueous titration at 99% confidence level

** Titrated in glacial acetic acid and acetic anhydride with 0.1 N perchloric acid using p-naphtholbenzein TS as indicator

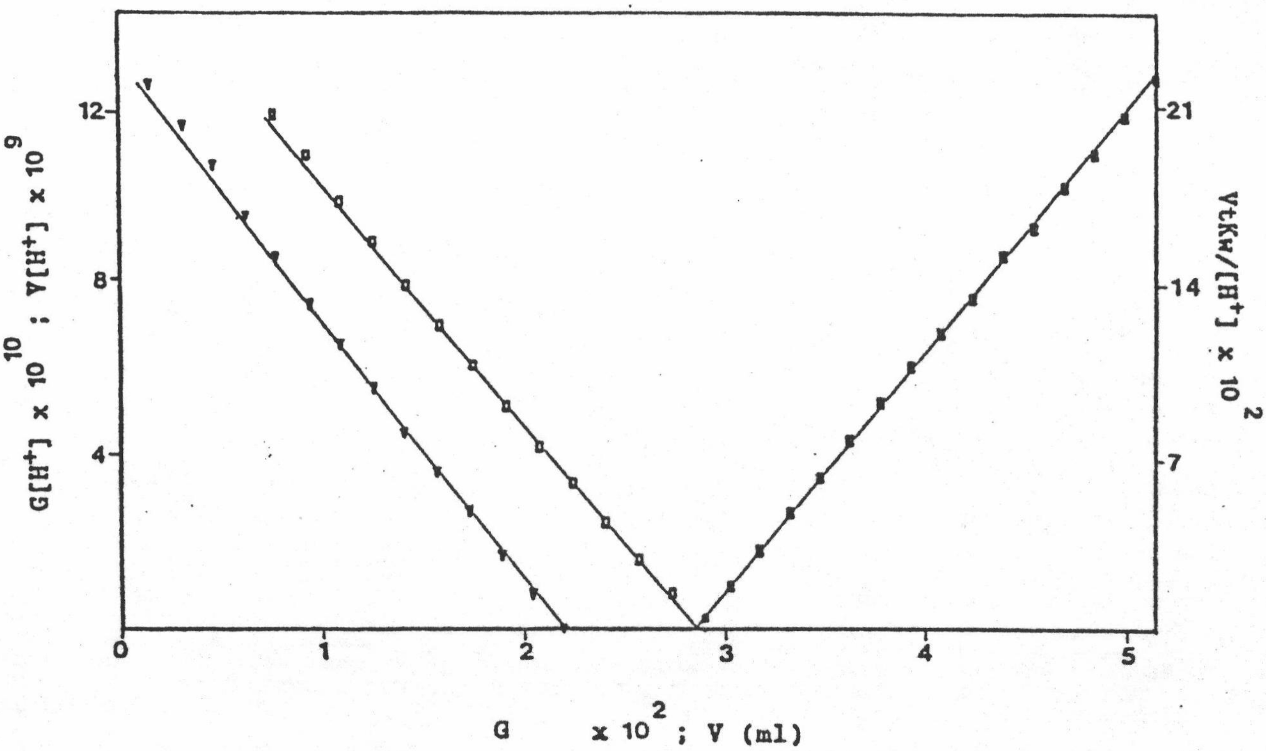

Figure 26 Gran's plot for the titration of quinine sulfate with sodium hydroxide in 40% v/v methanol/water G plot (▼) V plot (□) E plot. (■)

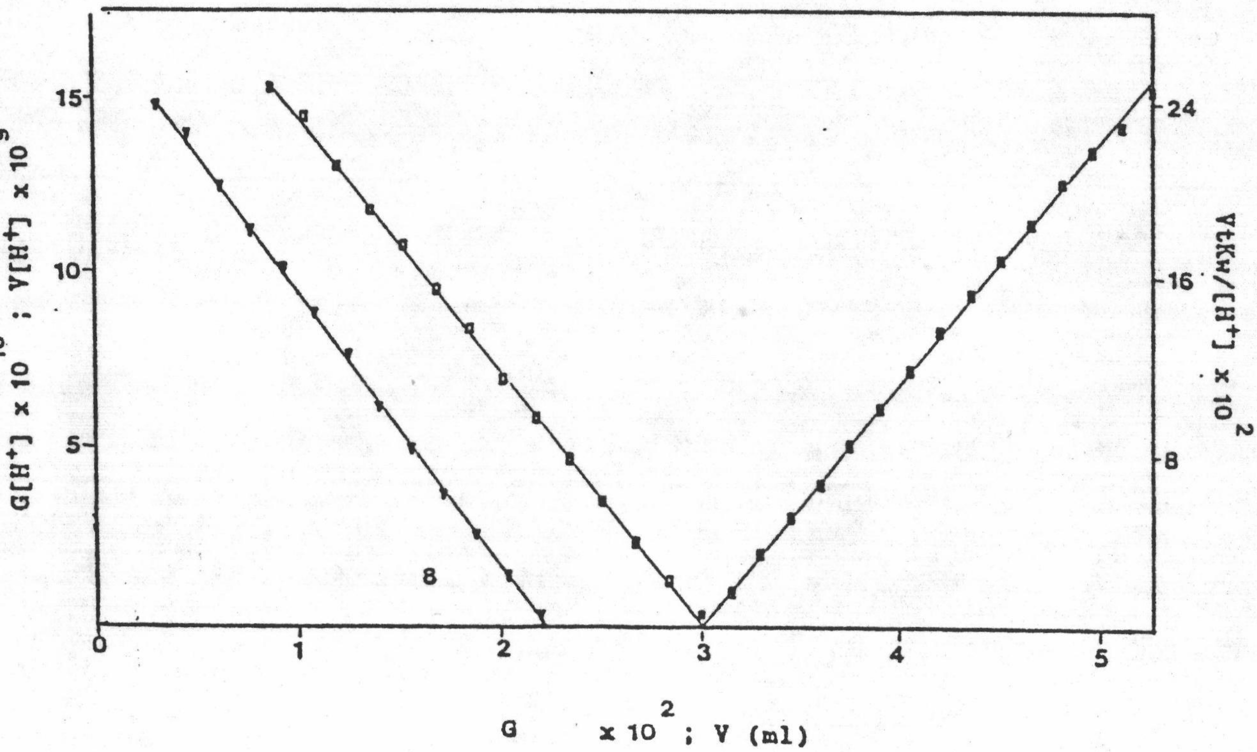

Figure 27 Gran's plot for the titration of quinine sulfate with sodium hydroxide in 50% v/v methanol/water G plot (▼) V plot (□) E plot. (■)

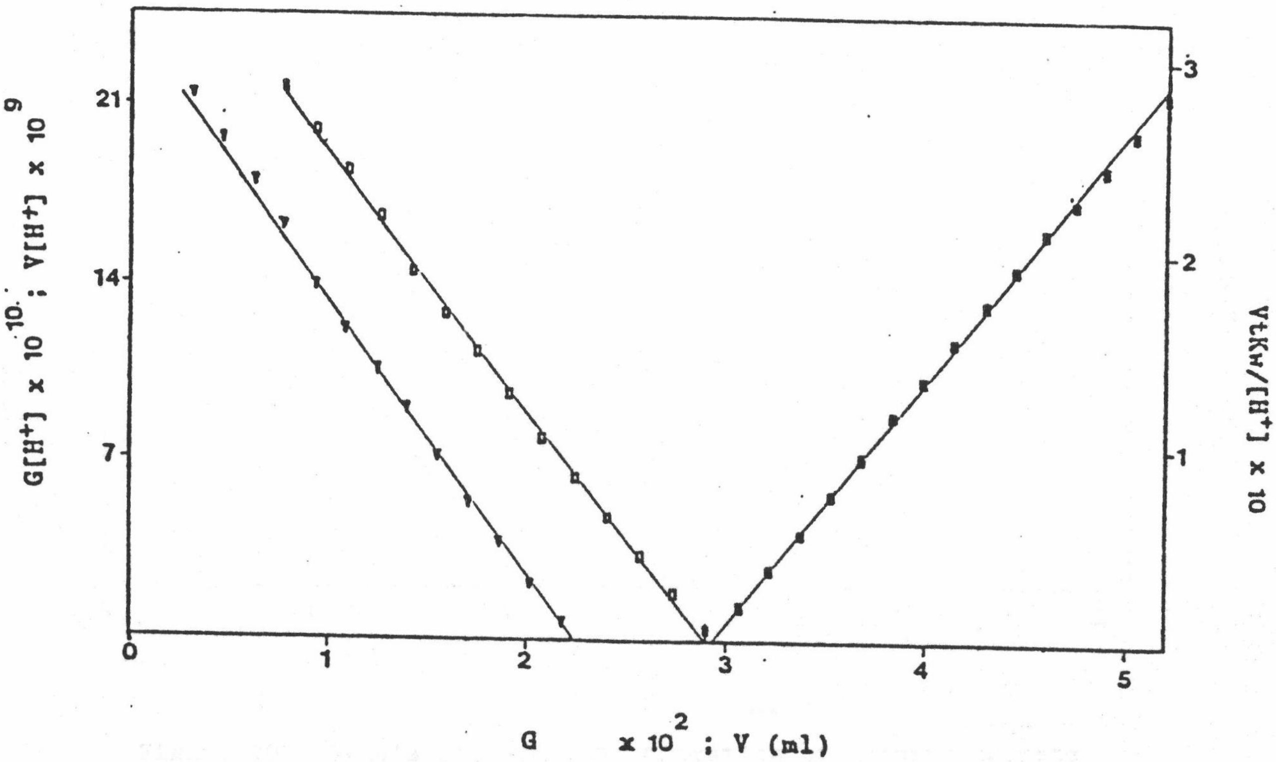

Figure 28 Gran's plot for the titration of quinine sulfate with sodium hydroxide in 60% v/v methanol/water G plot (▼) V plot (□) E plot. (■).

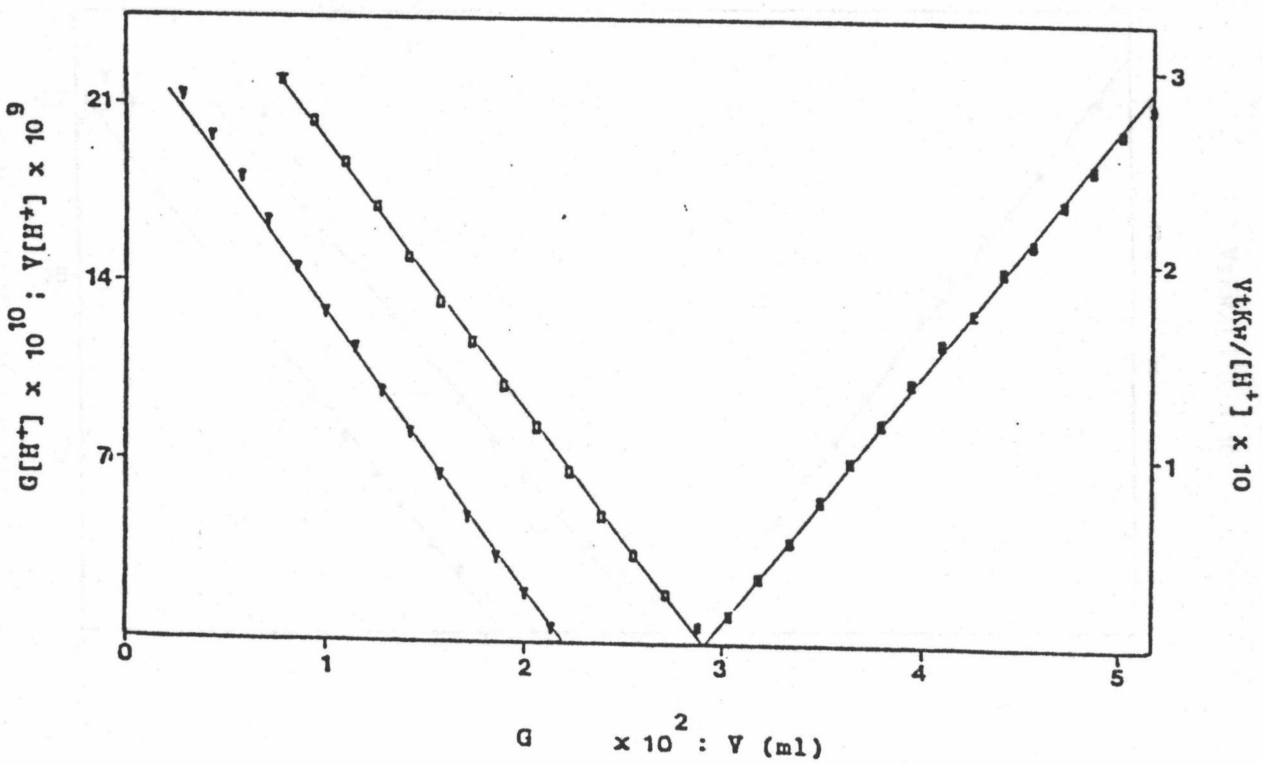

Figure 29 Gran's plot for the titration of quinine sulfate with sodium hydroxide in 70% v/v methanol/water G plot (▼) V plot (□) E plot. (■)

compositions of methanol in water solvents were shown in Figure 26-31. They showed that for the titrations of quinine sulfate with sodium hydroxide in 40-70% methanol/water, G , V and E plots were linear which when extrapolated to x-axis yielded accurate and reproducible end point volumes. The resulting percentage purities were statistically indifferent from the value obtained from reference non-aqueous method.

For the titrations in 80-90% v/v methanol/water, the average percentage purities of quinine sulfate calculated from G , V and E plots were statistically different from that obtained by non-aqueous titration. These results were same as the titration of triprolidine HCl in methanol-water systems. The maximum percentage of methanol in mixed solvent which could be employed for the titration of triprolidine HCl and quinine sulfate was 70% v/v.

2.2 Ethanol-Water System

The titrations of quinine sulfate were performed in 40-90% v/v ethanol/water which gave homogeneous solutions throughout the titration. The titration curves of quinine sulfate with sodium hydroxide in 40-90% v/v ethanol/water were shown in Figure 32. Table 7 illustrated average percentage purities which calculated from an end point volumes obtained from G, V and E plots in different compositions

Table 7 Average Percentage Purities by Gran's Method for Titration of Quinine Sulfate in Ethanol-Water Solvent Systems with 0.08234 N NaOH

Solvent (Ethanol in water)	Average percentage purity (%)			
	G plot	V plot	E plot	USP method **
40%	98.90 * (0.37)	98.85 * (0.38)	98.92 * (0.16)	
50%	98.17 (0.25)	98.43 (0.31)	98.40 (0.25)	
60%	98.28 (0.43)	98.45 (0.45)	98.27 (0.34)	99.11 * (0.22)
70%	98.14 (0.25)	98.28 (0.26)	98.25 (0.11)	
80%	96.86 (0.64)	97.50 (0.32)	-	
90%	96.51 (0.40)	96.42 (0.40)	-	

* Statistically indifference from reference non-aqueous titration at 99% confidence level

** Titrated in glacial acetic acid and acetic anhydride with 0.1 N perchloric acid using p-naphtholbenzein TS as indicator

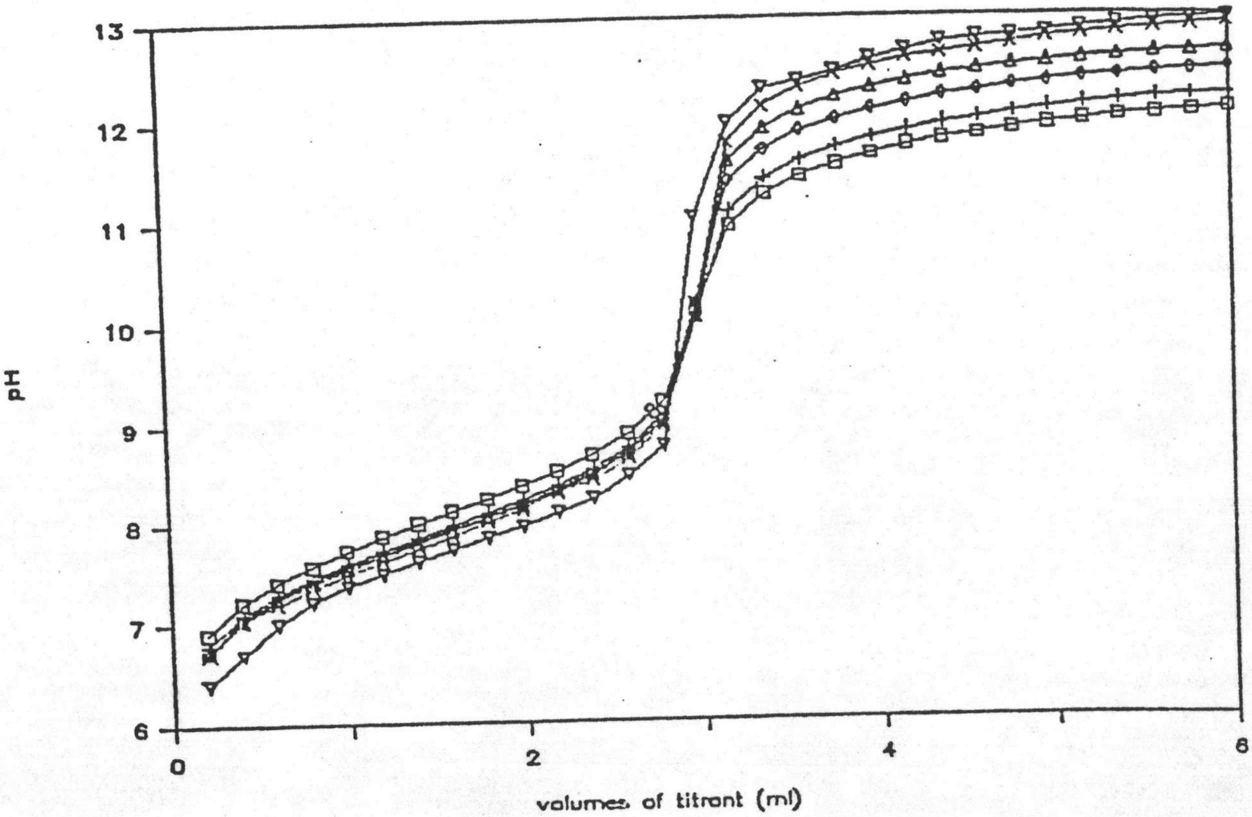

Figure 32 Titration Curves of quinine sulfate with sodium hydroxide in 40-90% v/v ethanol/water
40% (□) 50% (+) 60% (◇) 70% (△)
80% (×) 90% (▽).

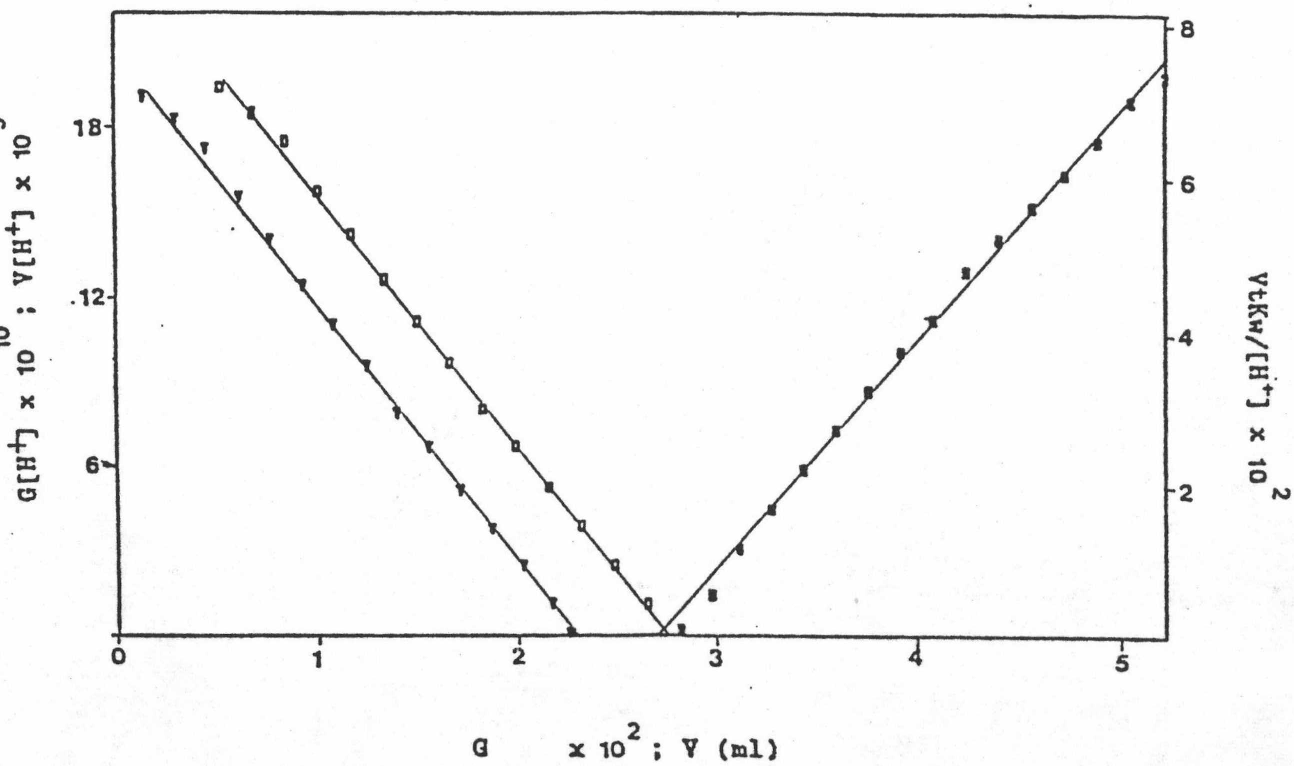

Figure 33 Gran's plot for the titration of quinine sulfate with sodium hydroxide in 40% v/v ethanol/water G plot (▼) V plot (□) E plot (■).

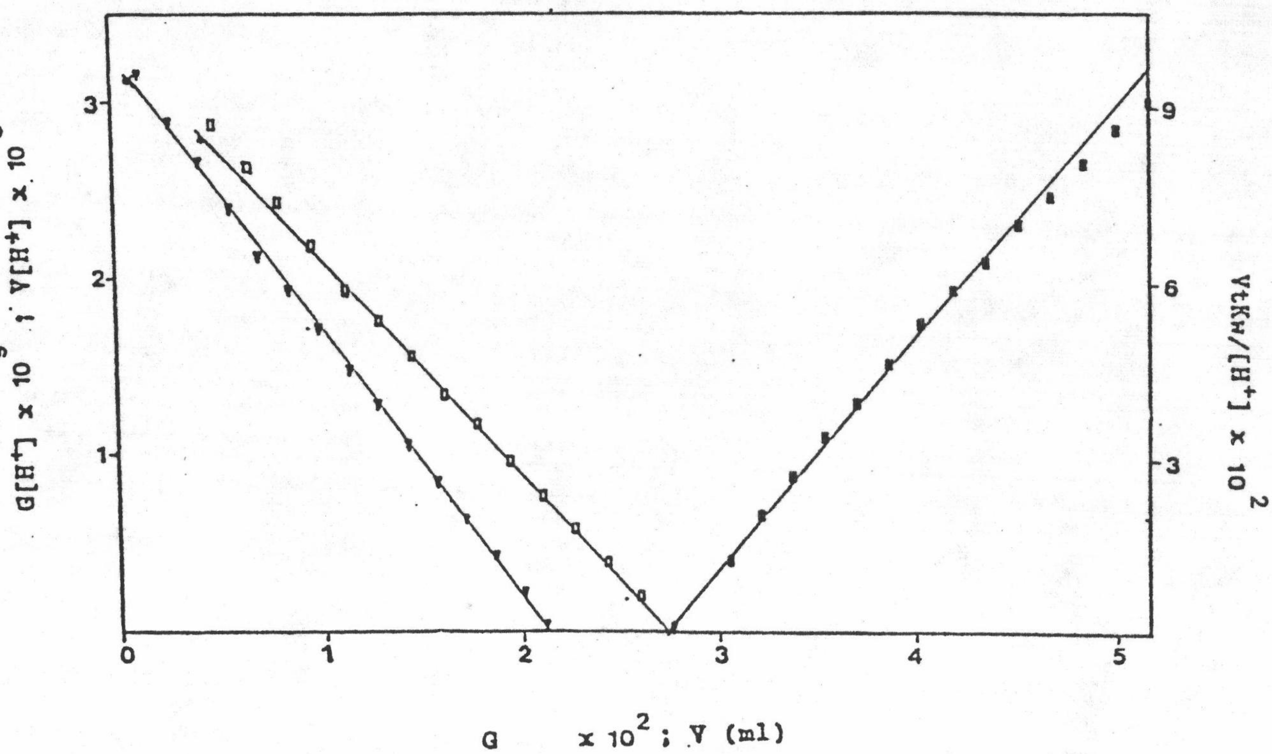

Figure 34 Gran's plot for the titration of quinine sulfate with sodium hydroxide in 50% v/v ethanol/water G plot (▼) V plot (□) E plot (■).

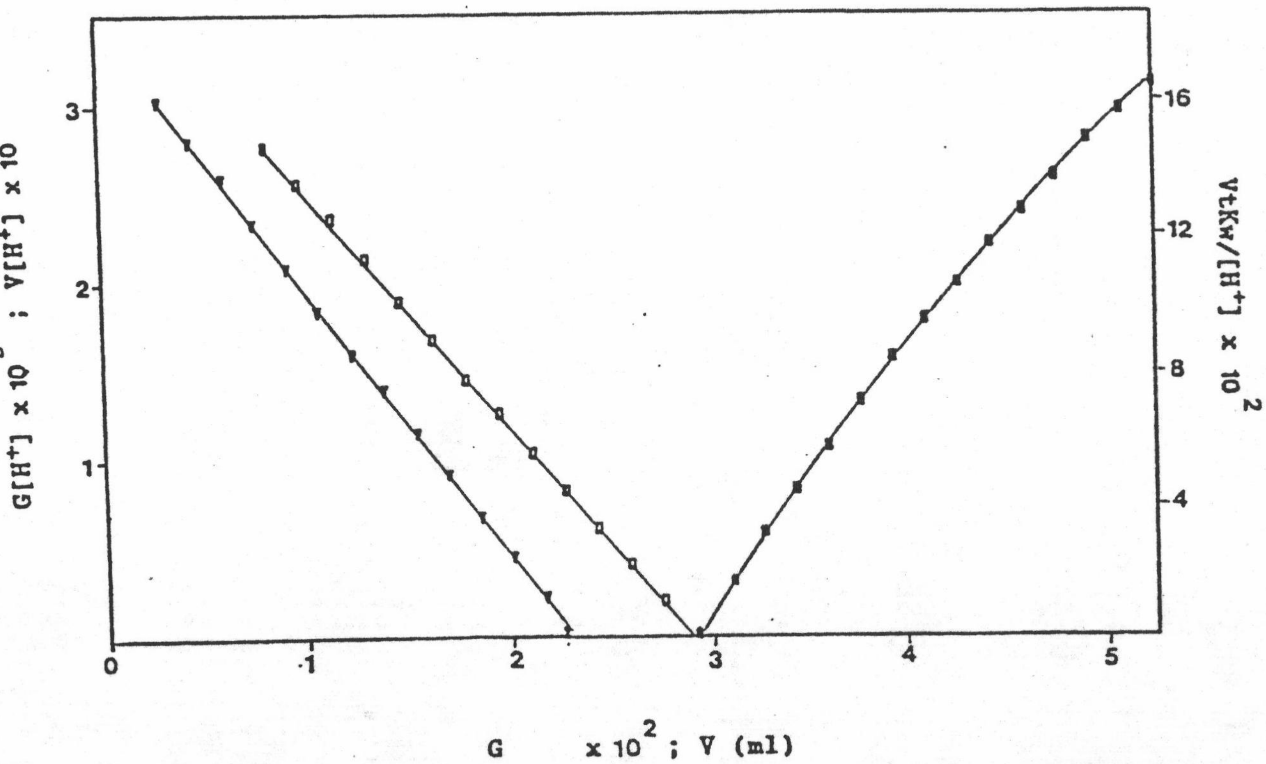

Figure 35   Gran's plot for the titration of quinine sulfate with sodium hydroxide in 60% v/v ethanol/water G plot (▼) V plot (□) E plot (■).

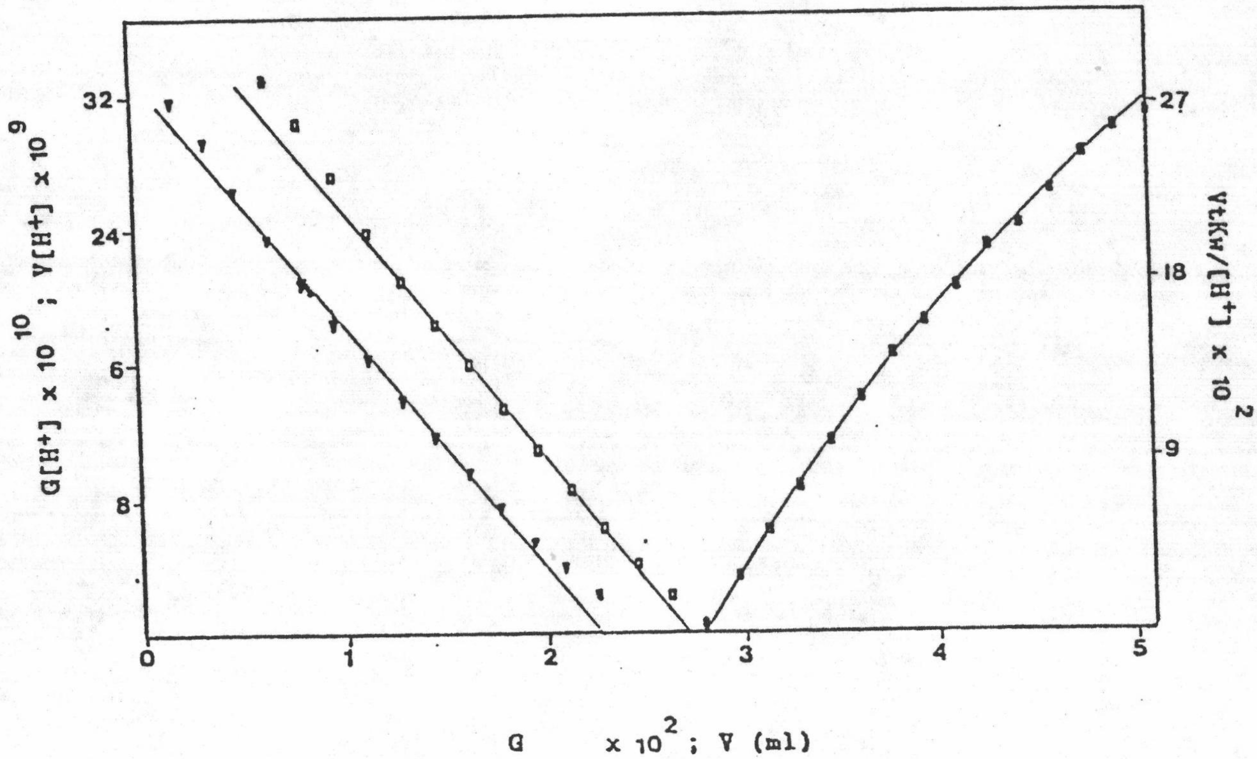

Figure 36   Gran's plot for the titration of quinine sulfate with sodium hydroxide in 70% v/v ethanol/water G plot (▼) V plot (□) E plot (■).

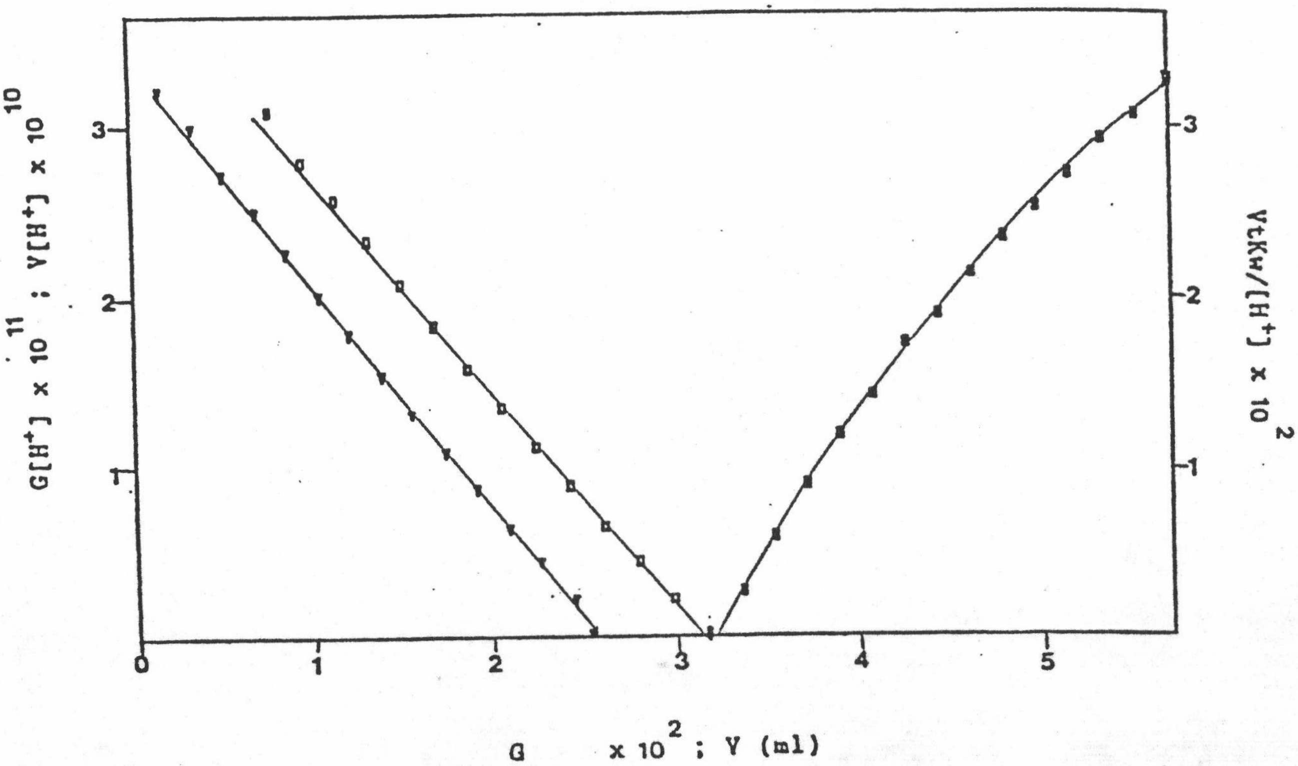

Figure 37 Gran's plot for the titration of quinine sulfate with sodium hydroxide in 80% v/v ethanol/water G plot (▼) V plot (□) E plot (■).

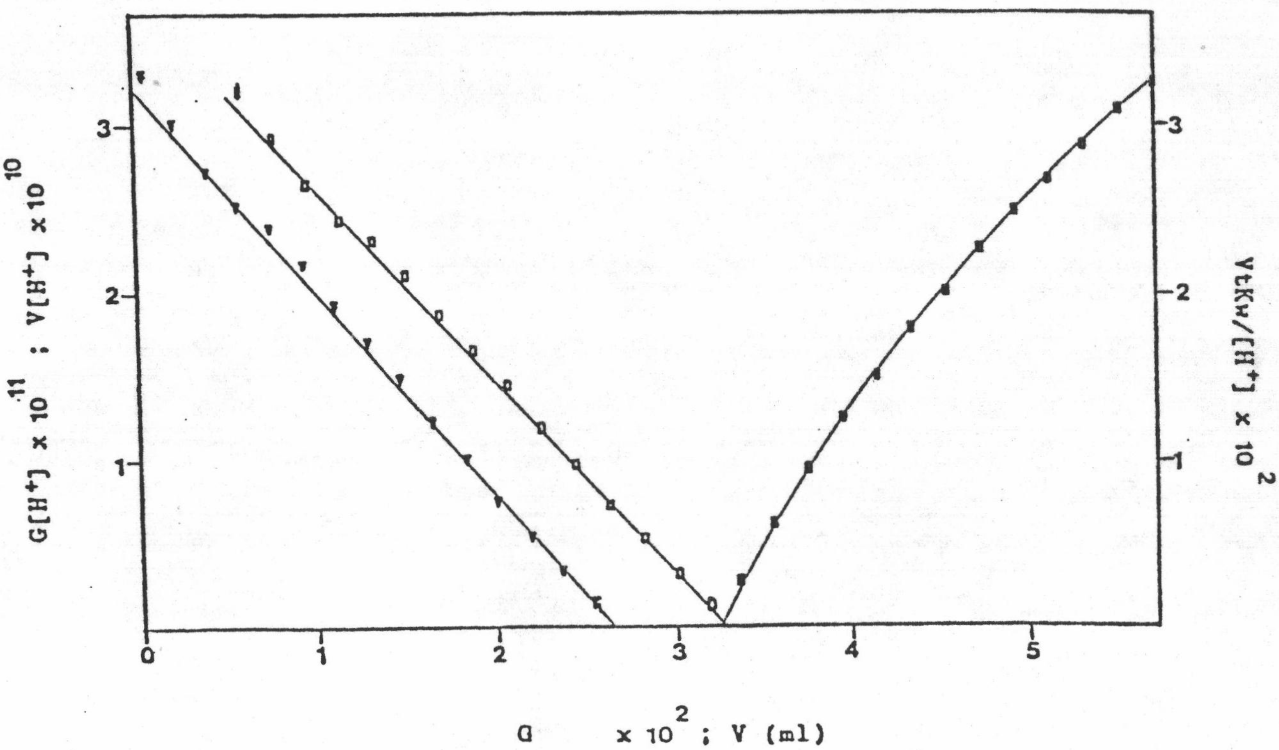

Figure 38 Gran's plot for the titration of quinine sulfate with sodium hydroxide in 90% v/v ethanol/water G plot (▼) V plot (□) E plot (■).

titration curves were shown in Figure 39. V-shape Gran's plot in different percentages of propylene glycol in mixed solvent were shown in Figures 40-43. G, V and E plots for the titration in 40-50% v/v propylene glycol/water were linear and gave enough titration data to extrapolate to x-axis eventhough the beginning of titration was curved. The calculated percentage purities of quinine sulfate from G, V and E plots for the titration in 40-50% v/v propylene glycol/water were statistically indifferent from that obtained from non-aqueous method, as shown in Table 8.

For the titrations in 60-70% v/v propylene glycol in water, low values of percentage purity of quinine sulfate were obtained. This might be partly due to the effect of density of solvent as described in the titration of triprolidine HCl in propylene glycol-water system.

Titration of quinine sulfate can be summarized in term of relative purity as shown in Figure 44-46. Accurate results for the titration of quinine sulfate in methanol-water system could be obtained in 40-70% v/v methanol/water (Figure 44). In ethanol-water system accurate results could be obtained by G, V and E plots for the titration in 40% v/v ethanol/water. For propylene glycol-water system, the accurate results could be obtained from G plot, V plot and E plot for the titrations in 40-50% v/v propylene glycol/water.

Table 8 Average Percentage Purities by Gran's Method for Titration of Quinine Sulfate in Propylene Glycol-Water Solvent Systems with 0.08340 N NaOH

Solvent (Propylene glycol in water)	Average percentage purity (%)			
	G plot	V plot	E plot	USP method **
40%	98.98 * (0.37)	99.16 * (0.32)	99.07 * (0.37)	
50%	98.88 * (0.30)	99.02 * (0.44)	99.32 * (0.39)	99.11 * (0.22)
60%	98.31 (0.35)	98.42 (0.42)	97.72 (0.35)	
70%	98.43 (0.39)	98.14 (0.43)	97.52 (0.15)	

* Statistically indifference from reference non-aqueous titration at 99% confidence level

** Titrated in glacial acetic acid and acetic anhydride with 0.1 N perchloric acid using p-naphtholbenzein TS as indicator

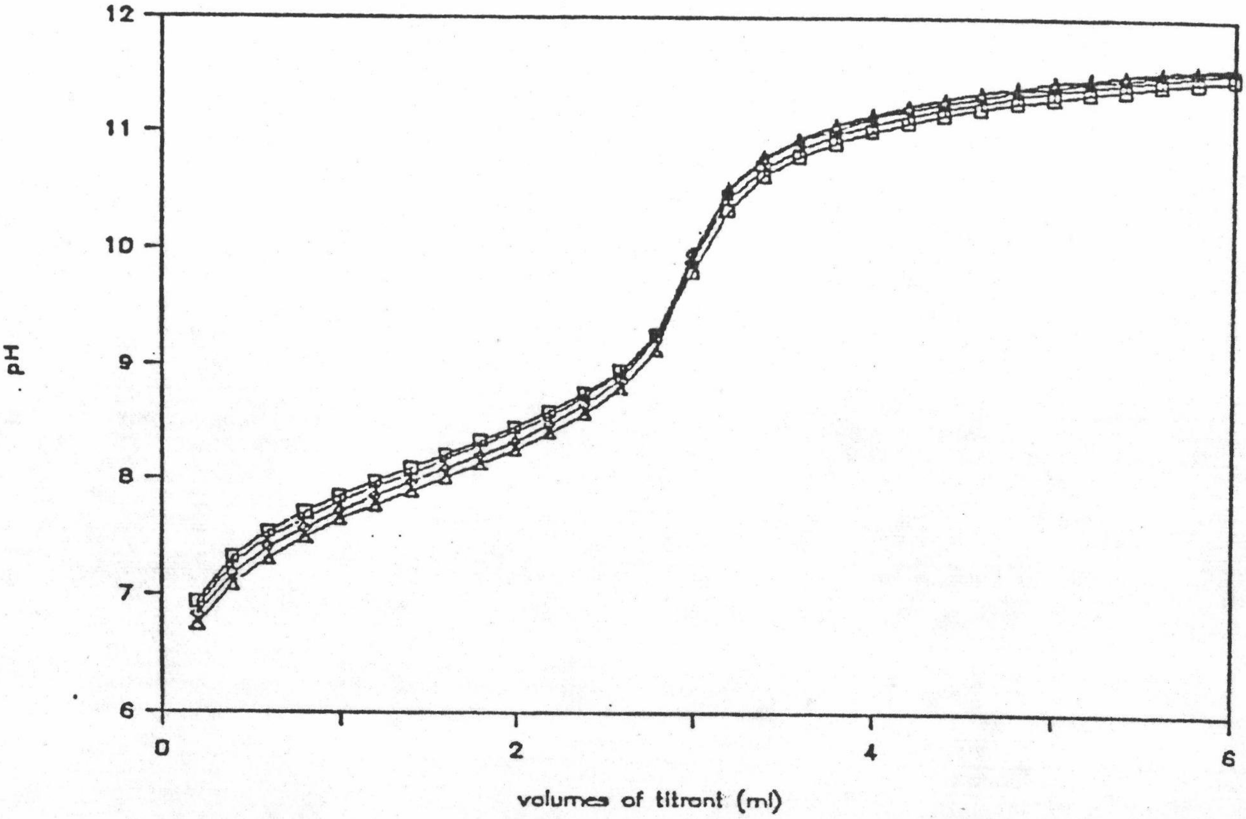

Figure 39 Titration Curves of quinine sulfate with sodium hydroxide in 40-70% v/v propylene glycol/water
40% (□) 50% (+) 60% (◇) 70% (Δ)

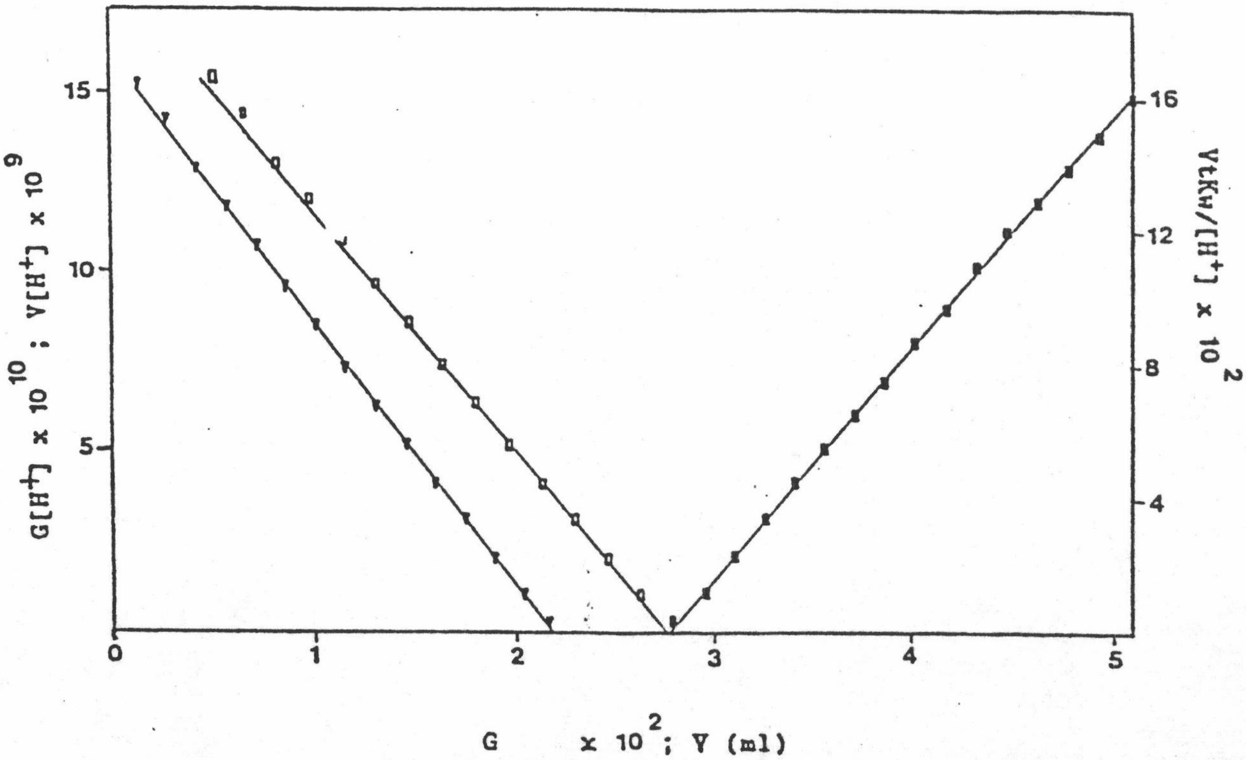

Figure 40 Gran's plot for the titration of quinine sulfate with sodium hydroxide in 40% v/v propylene glycol/water G plot (▼) V plot (□) E plot (■).

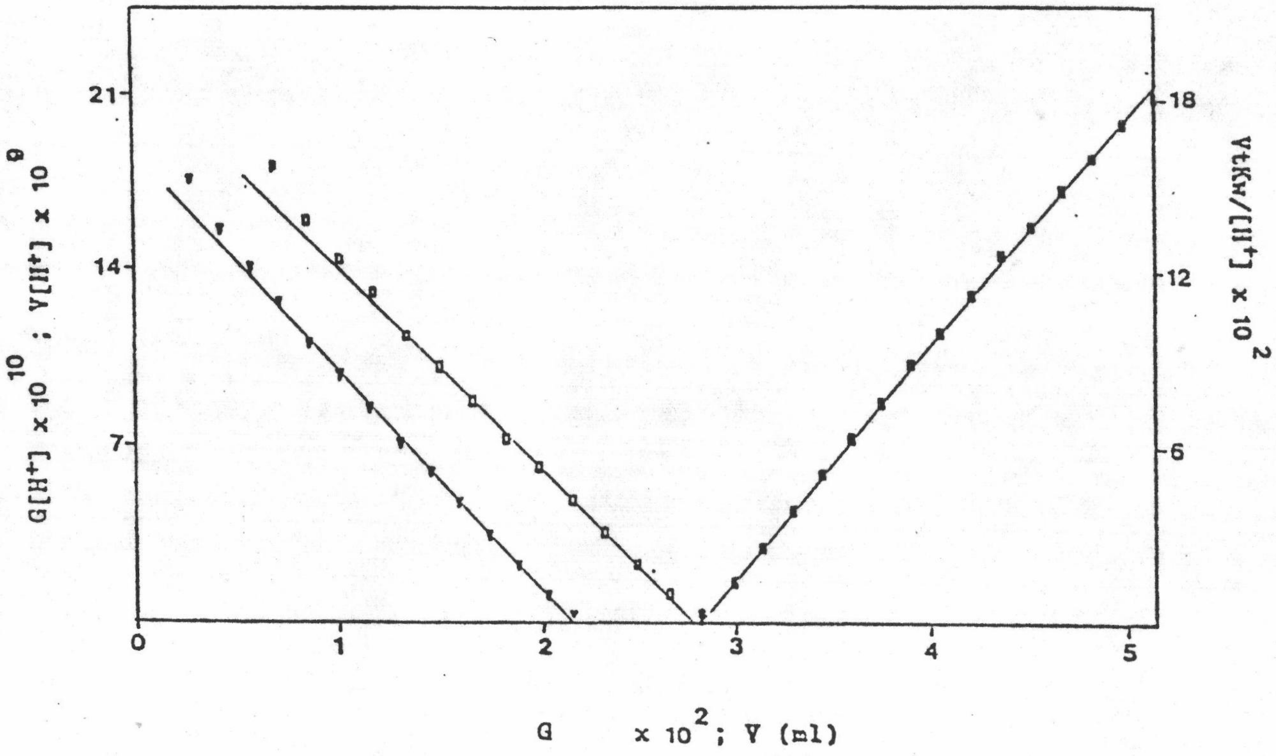

Figure 41 Gran's plot for the titration of quinine sulfate with sodium hydroxide in 50% v/v propylene glycol/water G plot (▼) V plot (□) E plot (■).

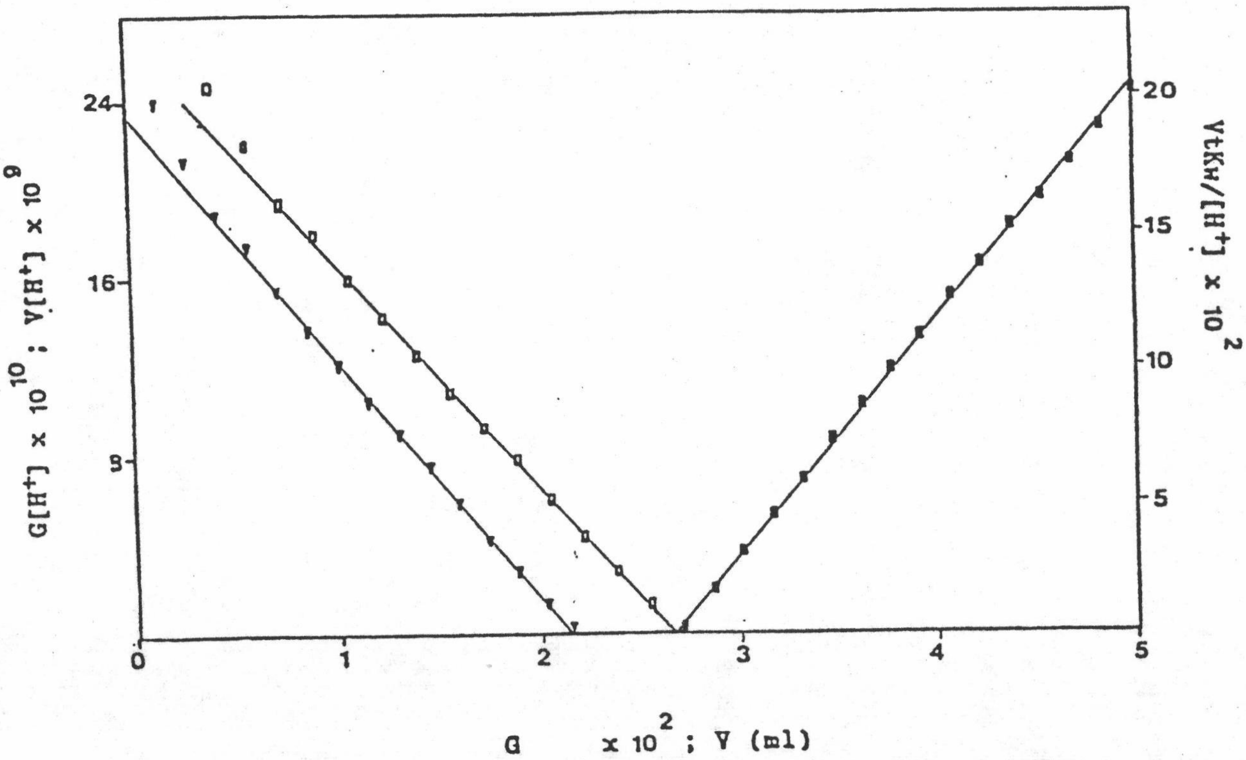

Figure 42 Gran's plot for the titration of quinine sulfate with sodium hydroxide in 60% v/v propylene glycol/water G plot (▼) V plot (□) E plot (■).

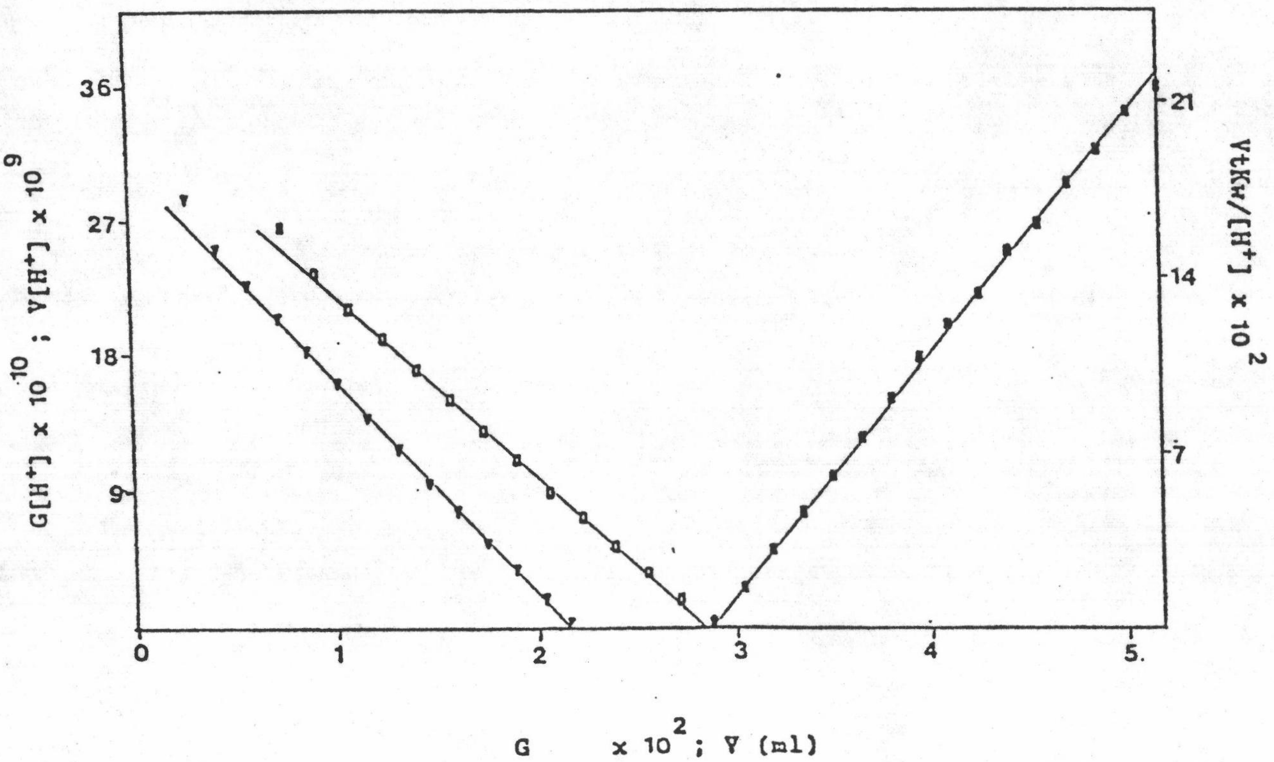

Figure 43 Gran's plot for the titration of quinine sulfate with sodium hydroxide in 70% v/v propylene glycol/water G plot (▼) V plot (□) E plot (■).

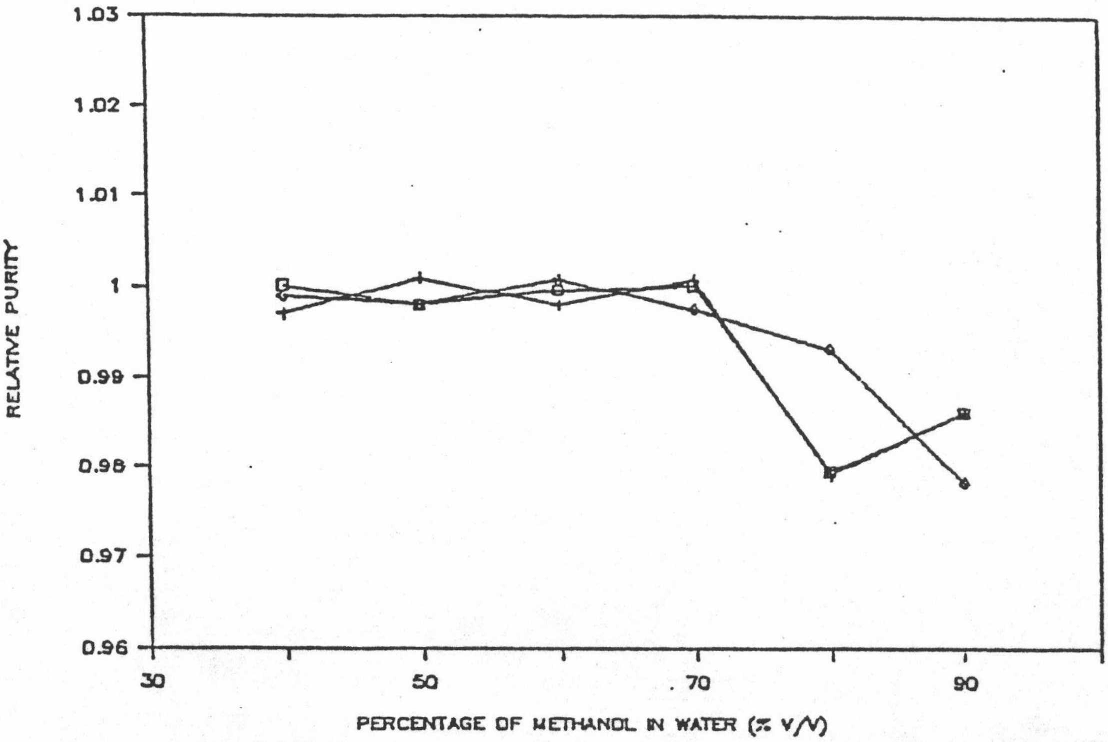

Figure 44 Relative purities of quinine sulfate in methanol-water solvents by using G plot (□) V plot (+) E plot (◊).

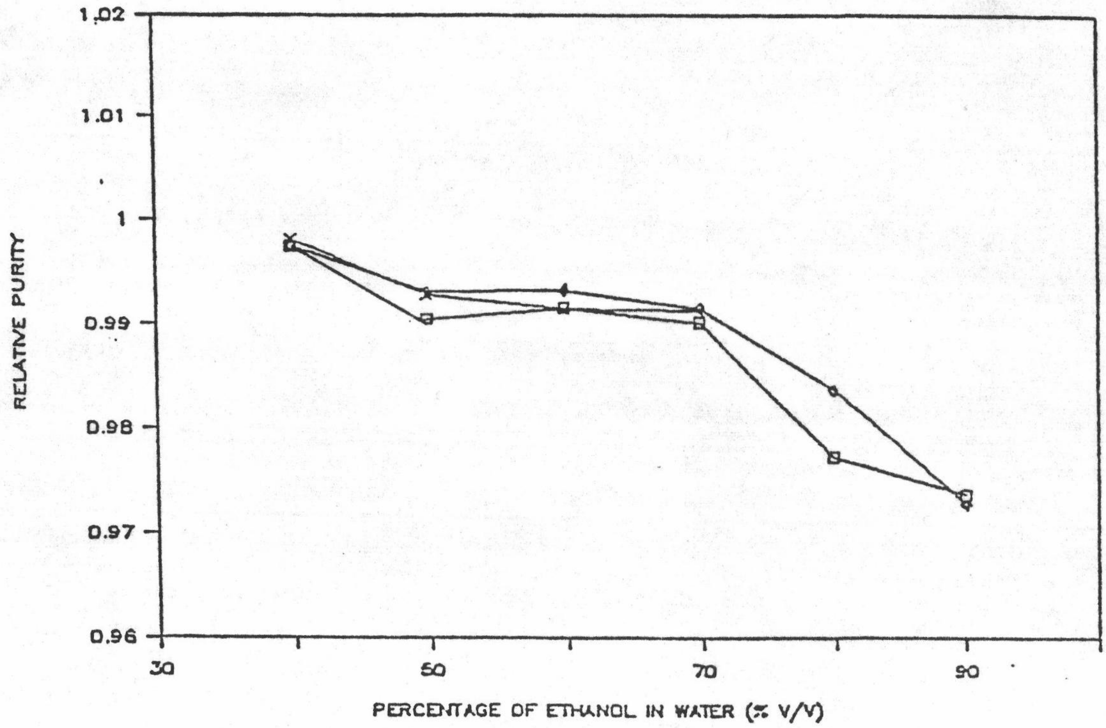

Figure 45 Relative purities of quinine sulfate in ethanol-water solvents by using G plot (□) V plot (+) E plot (◊).

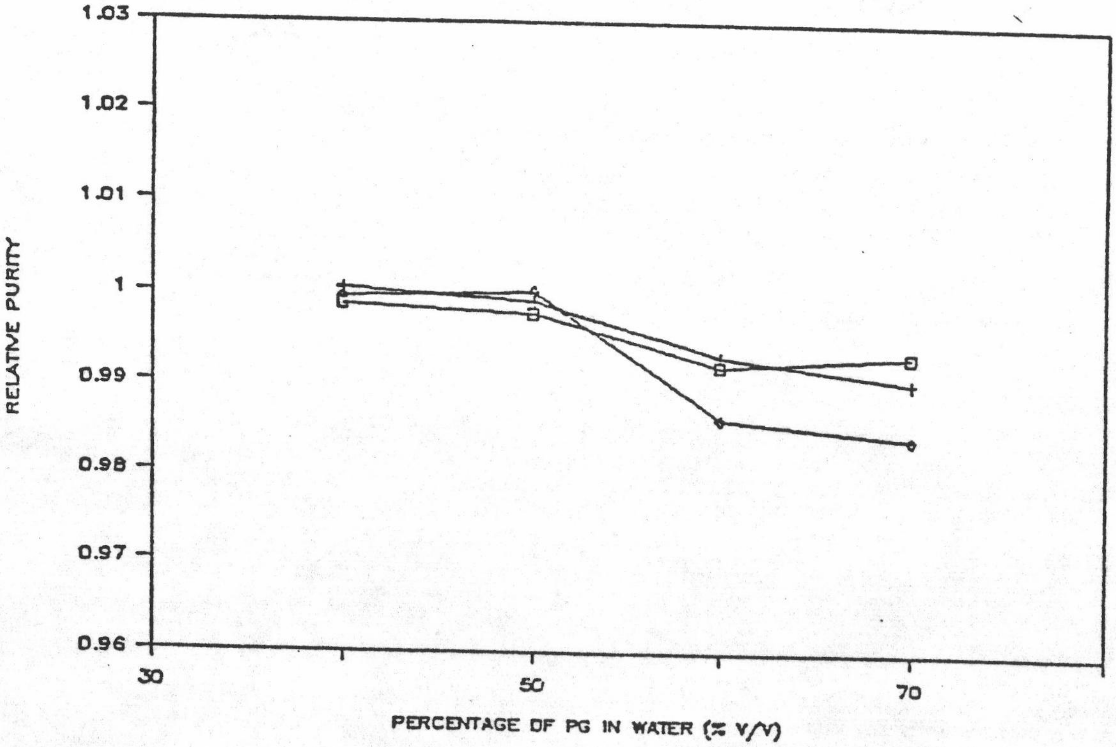

Figure 46 Relative purities of quinine sulfate in propylene glycol-water solvents by using G plot (□) V plot (+) E plot (◊).

3. Dextromethorphan Hydrobromide

This compound has the dissociation constant of 5×10^{-9} , pKa = 8.3.

3.1 Methanol-Water System

The titrations were performed in 50-90% v/v methanol/water. The titration curves in those mixed solvent were shown in Figure 47. V-shape Gran's plots for dextromethorphan HBr were illustrated in Figures 48-52.

The titration data prior to equivalence point, both G and V plots, gave satisfactory results in calculating the percentage purities of dextromethoephan HBr in 50-70% v/v methanol/water as shown in Table 9 . The limit for the titration was in the range of 80-90% v/v methanol/water, this was as previously discussed in the titration of triprolidine HCl and quinine sulfate.

The titration data after equivalence point, the percentage purity calculated from E plot was statistically lower than that calculated from non-aqueous method. The reason might be partly due to the effect of alkaline error because the apparent pH after equivalence point for the titration of dextromethorphan HBr with sodium hydroxide concentrations in 50-90% v/v methanol/water were rather high (pH range from 11.5-12).

Table 9 Average Percentage Purities by Gran's Method for Titration of Dextromethorphan Hydrobromide in Methanol-Water Solvent Systems with 0.08624 N NaOH

Solvent (Methanol in water)	Average Percentage Purity (%)			
	G plot	V plot	E plot	USP method **
50%	95.34 * (0.13)	95.08 * (0.28)	93.41 (0.18)	
60%	94.83 * (0.36)	94.85 * (0.52)	94.26 (0.22)	
70%	94.80 * (0.24)	94.85 * (0.62)	94.44 (0.17)	95.00 * (0.16)
80%	94.36 (0.32)	94.31 (0.09)	94.15 (0.45)	
90%	93.89 (0.32)	93.44 (0.18)	94.18 (0.14)	

* Statistically indifference from reference non-aqueous titration at 99% confidence level

** Titrated in glacial acetic acid and mercuric acetate TS with 0.1 N perchloric acid using crystal violet as indicator

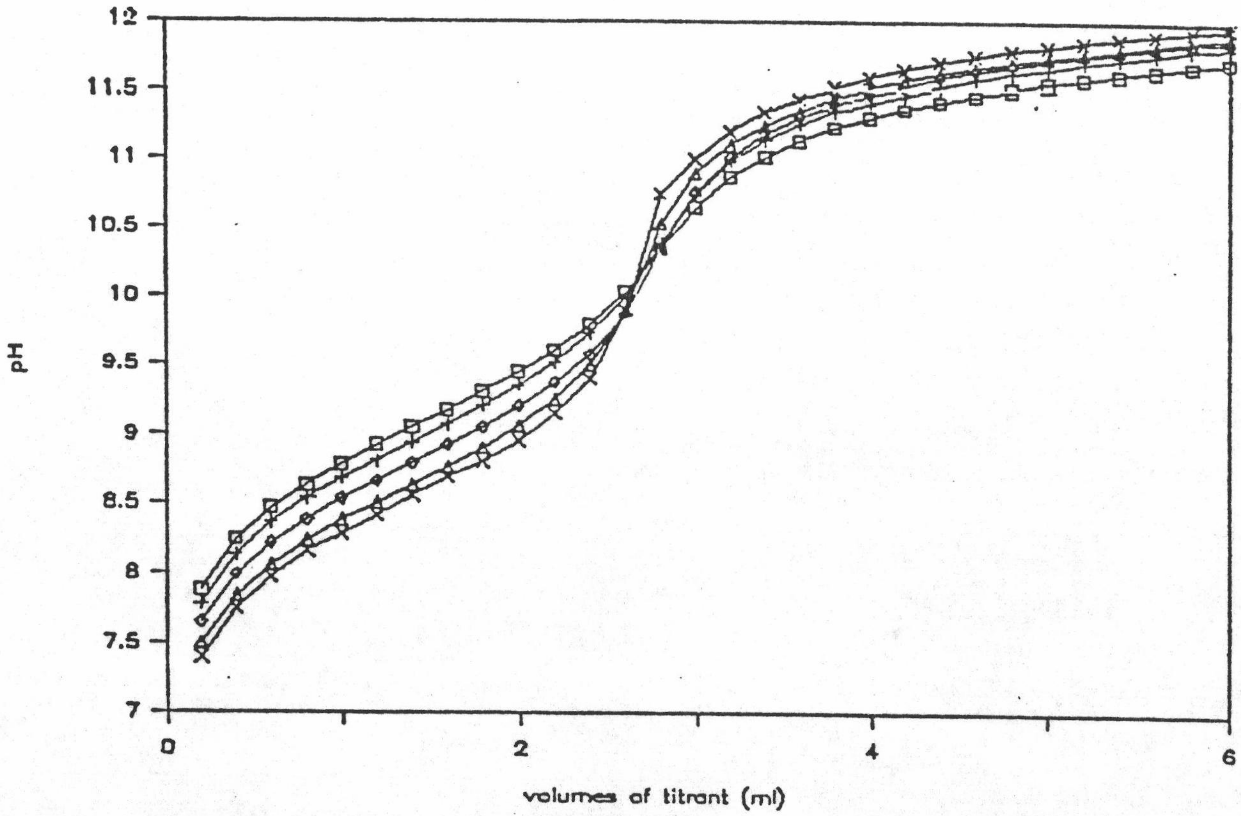

Figure 47 Titration Curves of dextromethorphan hydrobromide with sodium hydroxide in 50-90% v/v methanol/water
50% (□) 60% (+) 70% (◇) 80% (△) 90% (×).

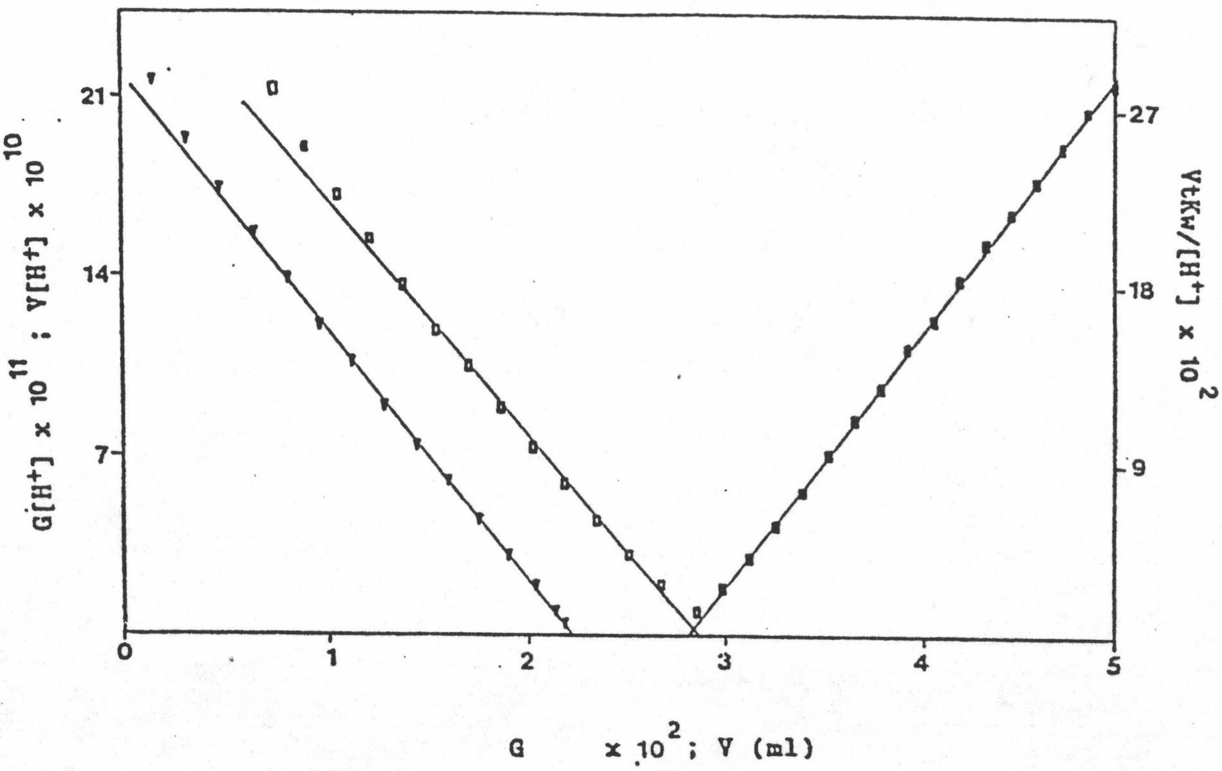

Figure 48 Gran's plot for the titration of dextromethorphan HBr with sodium hydroxide in 50% v/v methanol/water G plot (▼) V plot (□) E plot (■).

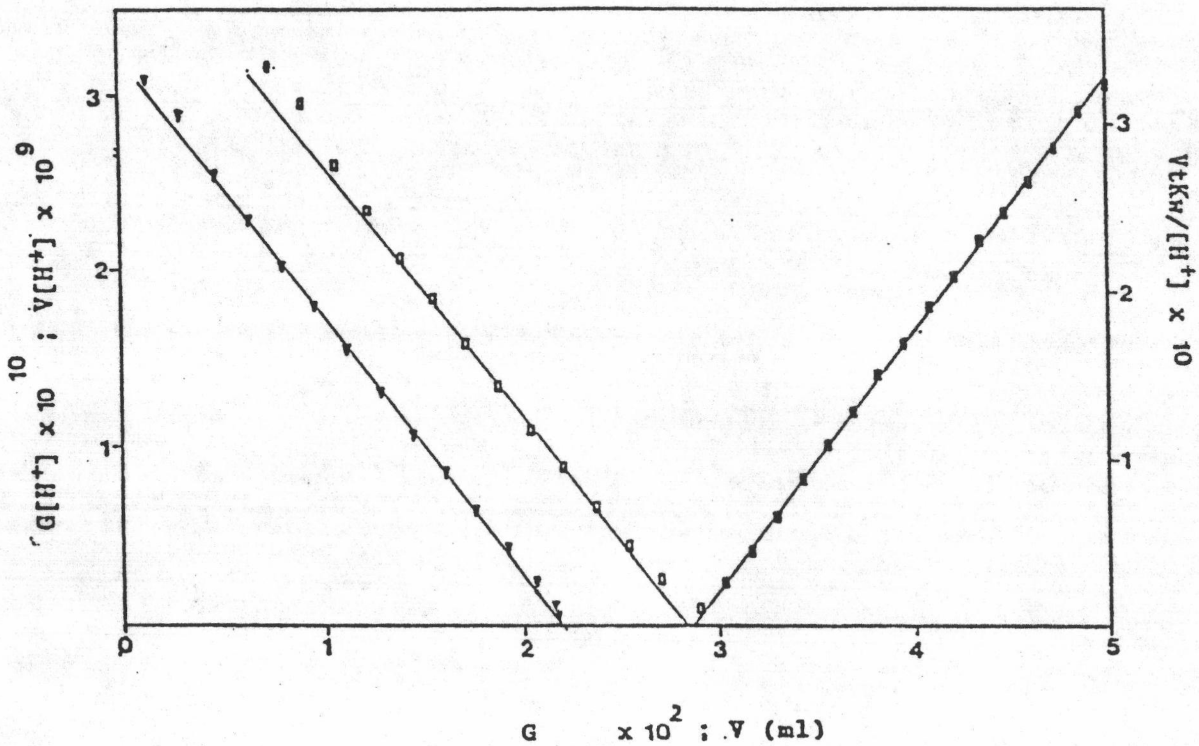

Figure 49 Gran's plot for the titration of dextromethorphan HBr with sodium hydroxide in 60% v/v methanol/water G plot (▼) V plot (□) E plot (■).

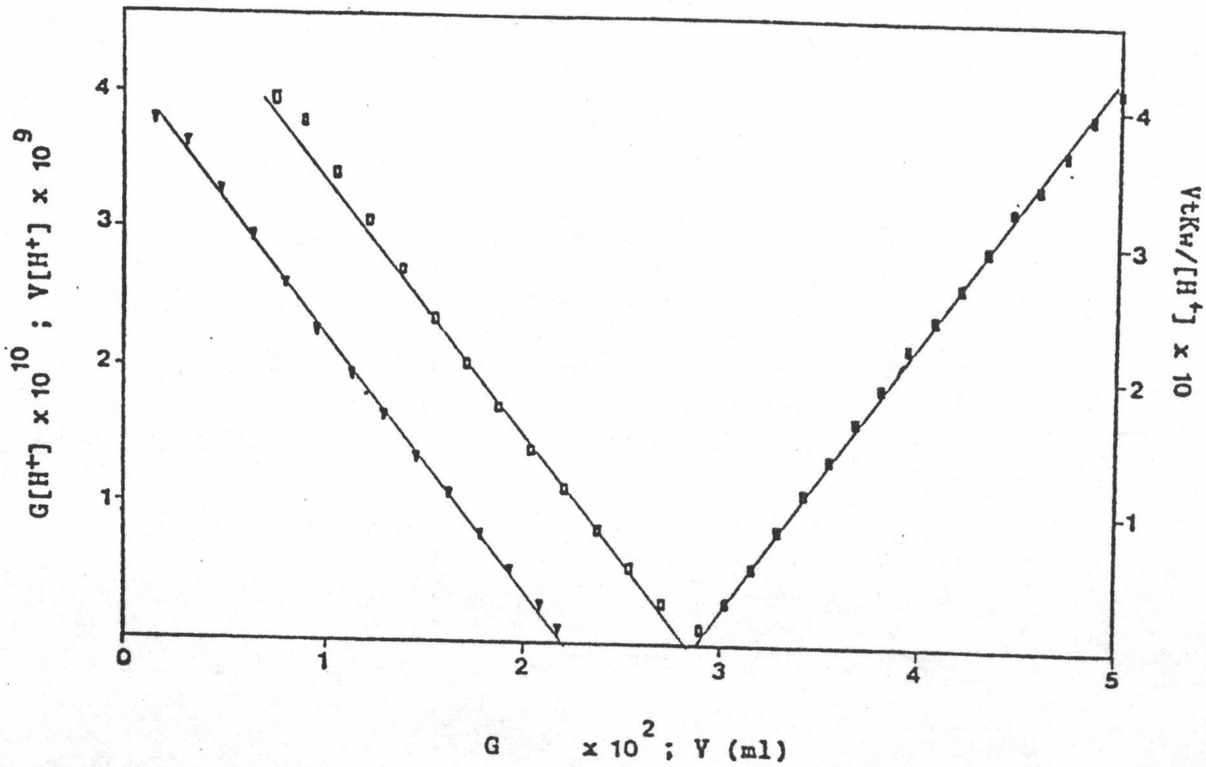

Figure 50 Gran's plot for the titration of dextromethorphan HBr with sodium hydroxide in 70% v/v methanol/water G plot (▼) V plot (□) E plot (■).

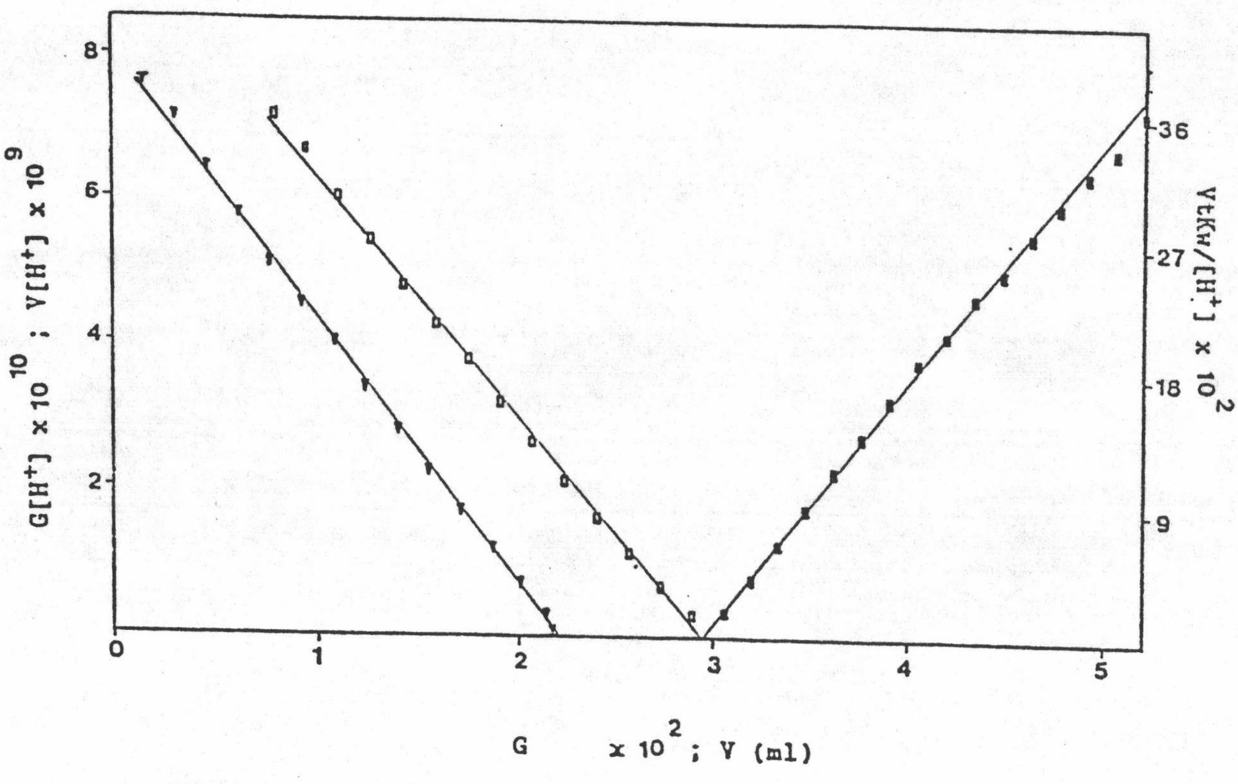

Figure 51 Gran's plot for the titration of dextromethorphan HBr with sodium hydroxide in 80% v/v methanol/water G plot (▼) V plot (□) E plot (■).

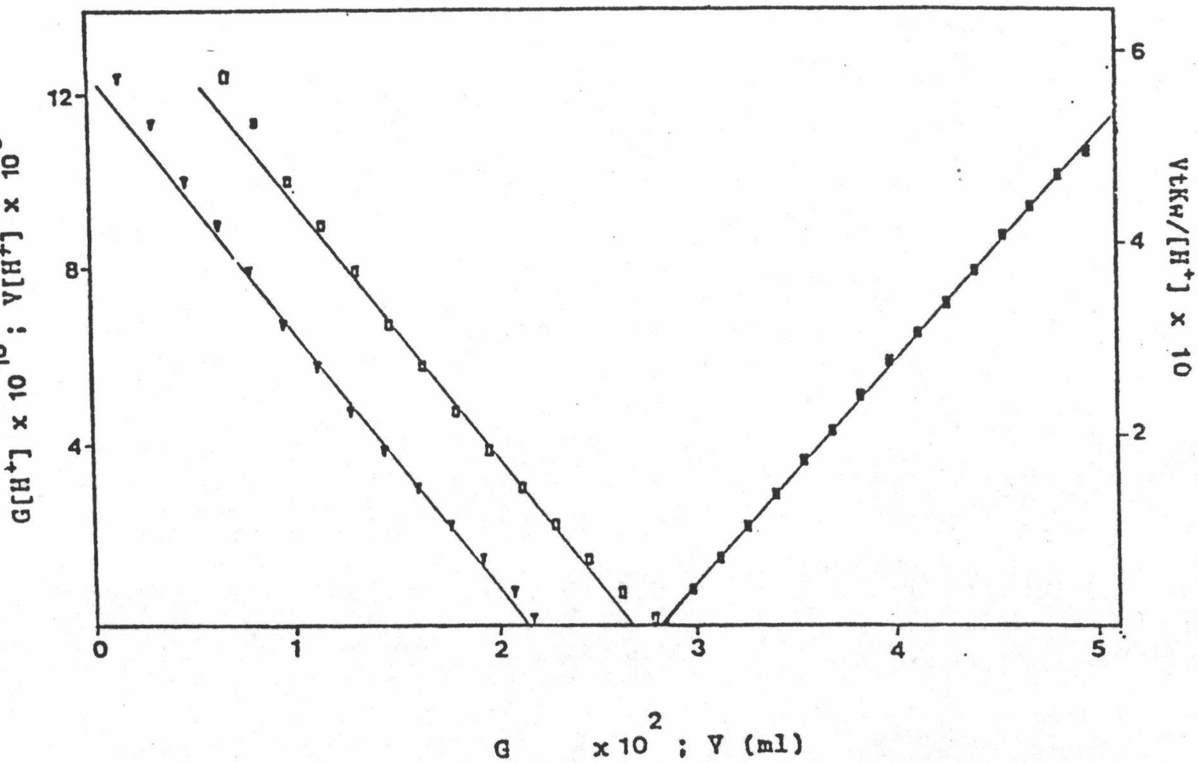

Figure 52 Gran's plot for the titration of dextromethorphan HBr with sodium hydroxide in 90% v/v methanol/water G plot (▼) V plot (◻) E plot (▮).

3.2 Ethanol-Water System

The titrations of dextromethorphan HBr were performed in 40-90% v/v ethanol/water. The titration curves in those mixed solvents were shown in Figure 53. The percentage purities of dextromethorphan HBr for the titration in 40% v/v ethanol/water, calculated from G and V plots comparing to non-aqueous titration were statistically indifferent, as shown in Table 10.

In higher composition of ethanol in water, 50-90% v/v ethanol/water, G and V plots could not be used accurately to determine the equivalence volumes because of high pH value for the titration of dextromethorphan HBr in ethanol-water systems and instability of glass electrode for measuring pH value in ethanol-water media.

The titrations after equivalence point for all ethanol-water systems, 40-90% v/v ethanol/water, the pH-volume of titrant plots significant curvature as shown in Figures 54-59 which resulted in low values of percentage purity of dextromethorphan HBr for the titrations in 40-90% v/v ethanol/water. The curvature of the plot was probably due to alkaline error since pH values in alkaline region for the titration of dextromethorphan HBr in ethanol-water were very high (higher than 12).

Table 10 Average Percentage Purities by Gran's Method for Titration of Dextromethorphan Hydrobromide in Ethanol-Water Solvent Systems with 0.08624 N NaOH

Solvent (Ethanol in water)	Average percentage purity (%)			
	G plot	V plot	E plot	USP method **
40%	94.90 * (0.31)	94.86 * (0.30)	93.94 (0.28)	
50%	92.60 (0.33)	94.03 (0.35)	93.26 (0.43)	
60%	93.09 (0.24)	93.89 (0.31)	94.23 (0.45)	
70%	93.39 (0.19)	93.97 (0.35)	94.33 (0.16)	95.00 * (0.16)
80%	92.70 (0.24)	92.74 (0.37)	-	
90%	92.58 (0.29)	92.78 (0.28)	-	

* Statistically indifference from reference non-aqueous titration at 99% confidence level

** Titrated in glacial acetic acid and mercuric acetate TS with 0.1 N perchloric acid using crystal violet as indicator

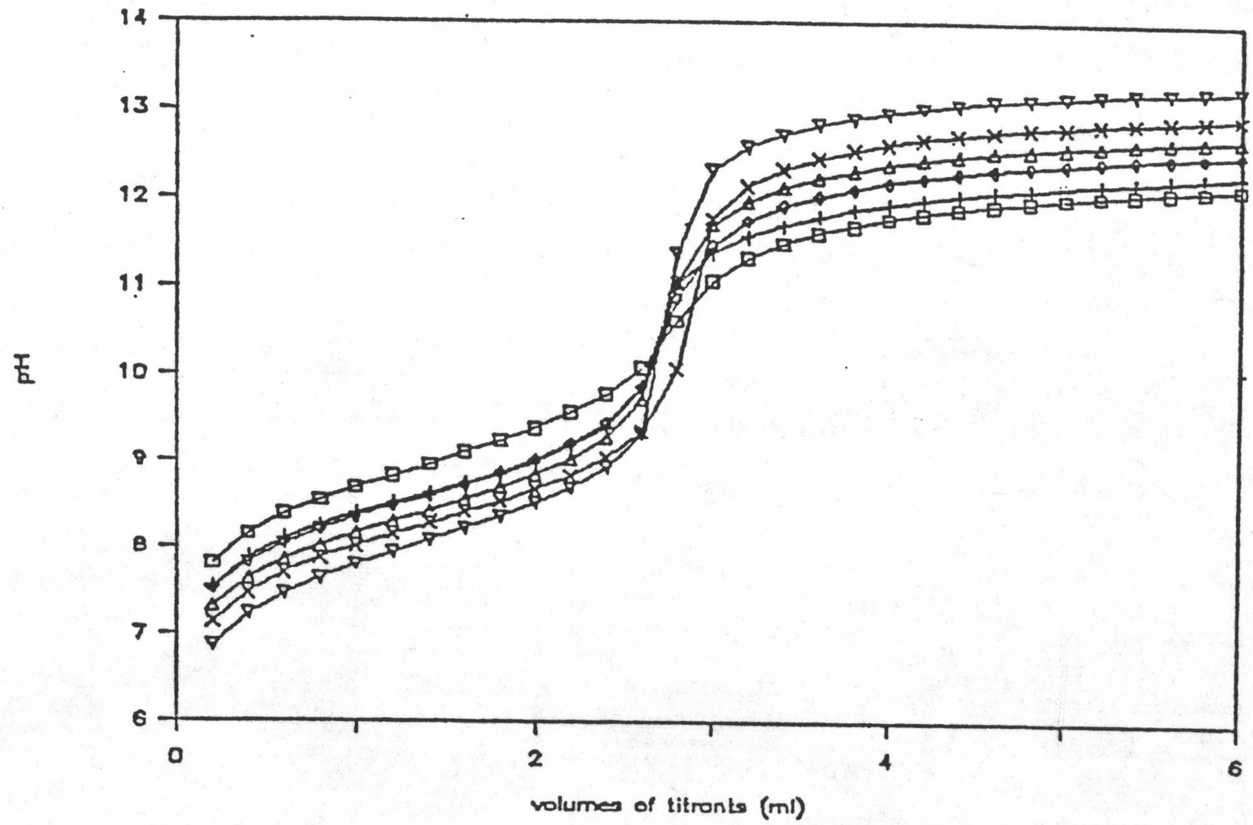

Figure 53 Titration Curves of dextromethorphan hydrobromide with sodium hydroxide in 40-90% v/v ethanol/water
40% (□) 50% (+) 60% (◇) 70% (△)
80% (×) 90% (▽).

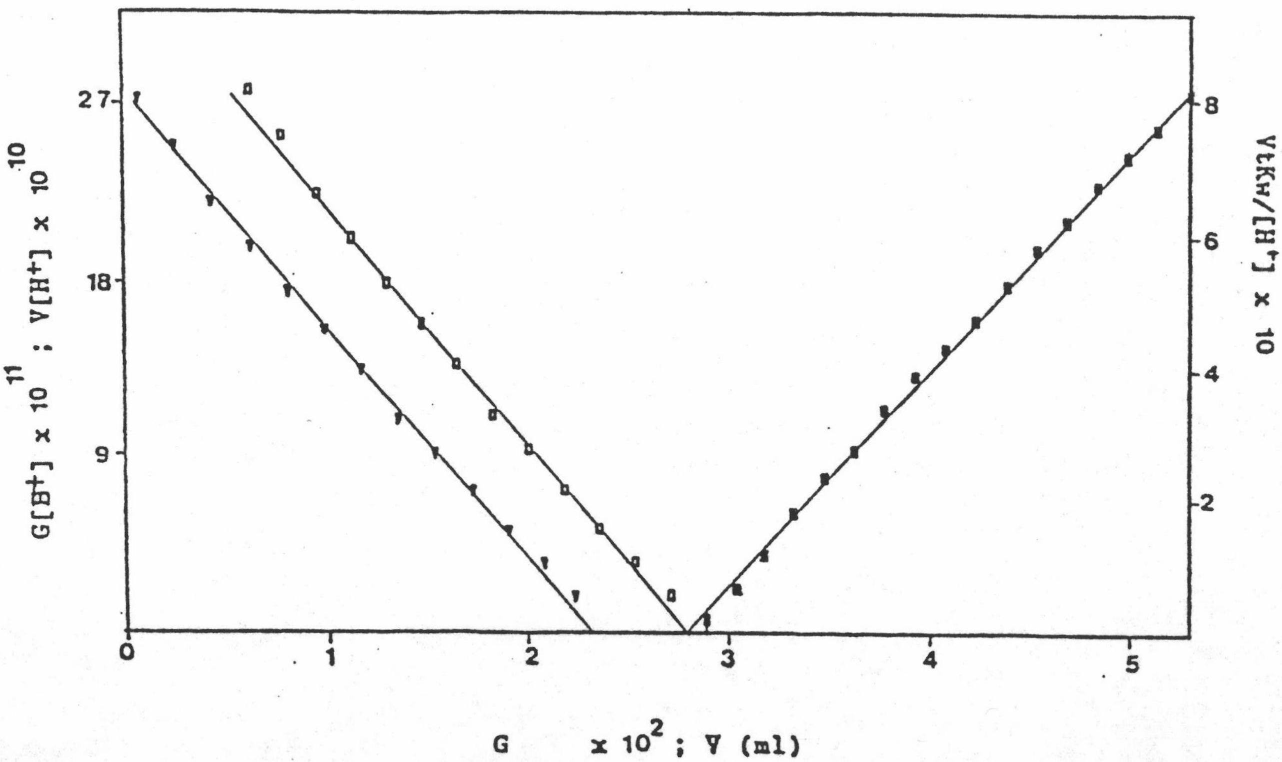

Figure 54 Gran's plot for the titration of dextromethorphan HBr with sodium hydroxide in 40% v/v ethanol/water G plot (▼) V plot (□) E plot (▮).

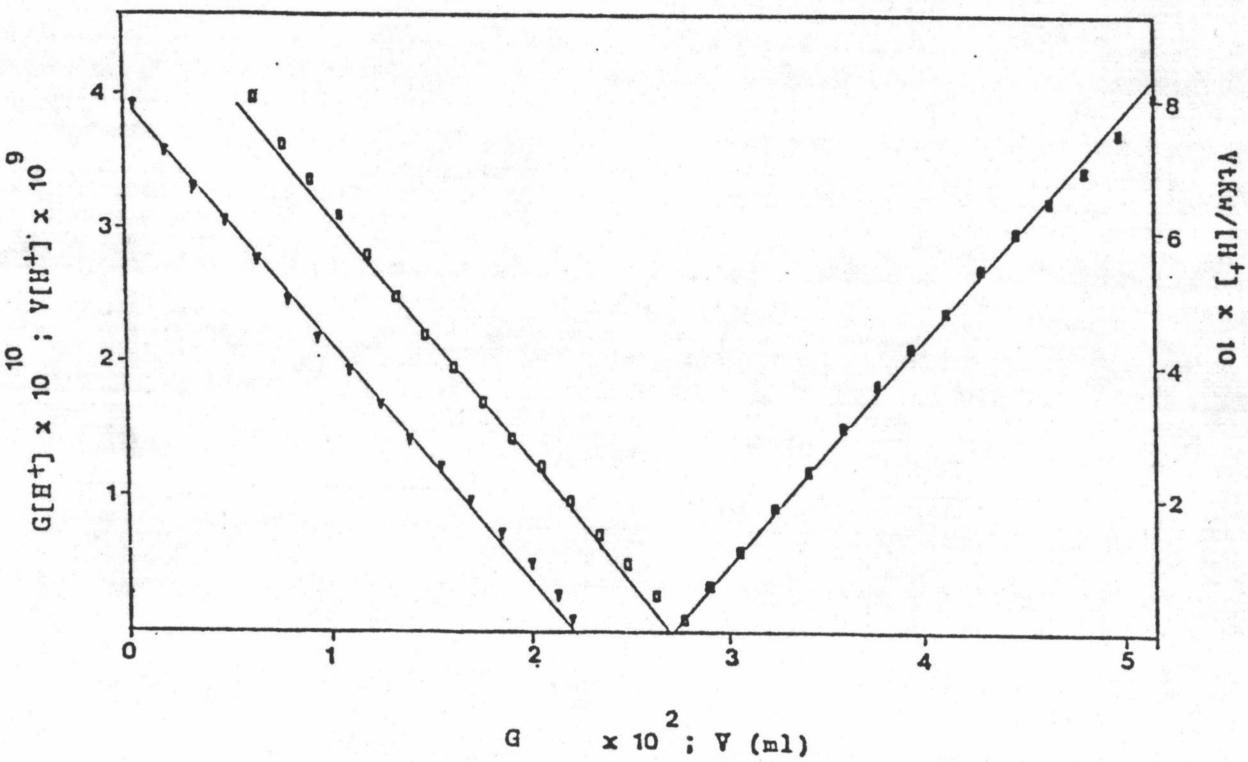

Figure 55 Gran's plot for the titration of dextromethorphan HBr with sodium hydroxide in 50% v/v ethanol/water G plot (▼) V plot (□) E plot (▮).

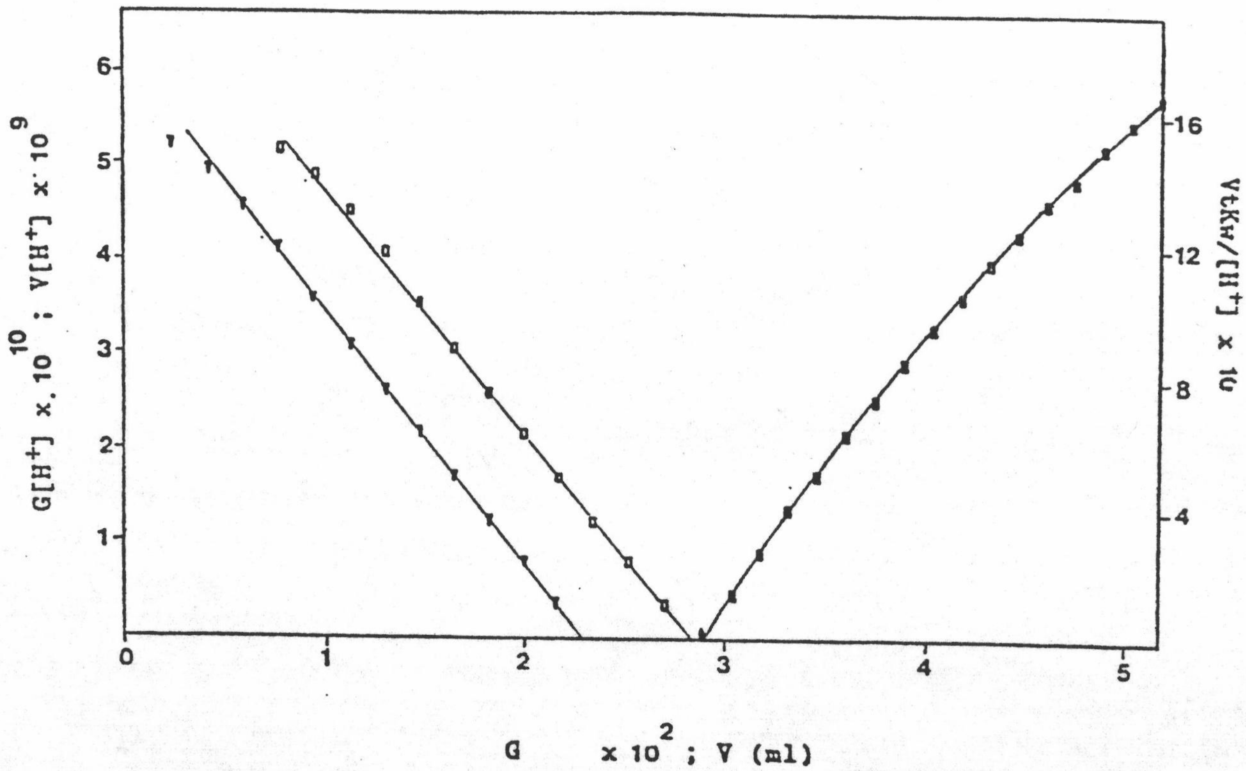

Figure 56 Gran's plot for the titration of dextromethorphan HBr with sodium hydroxide in 60% v/v ethanol/water
G plot (▼) V plot (□) E plot (■).

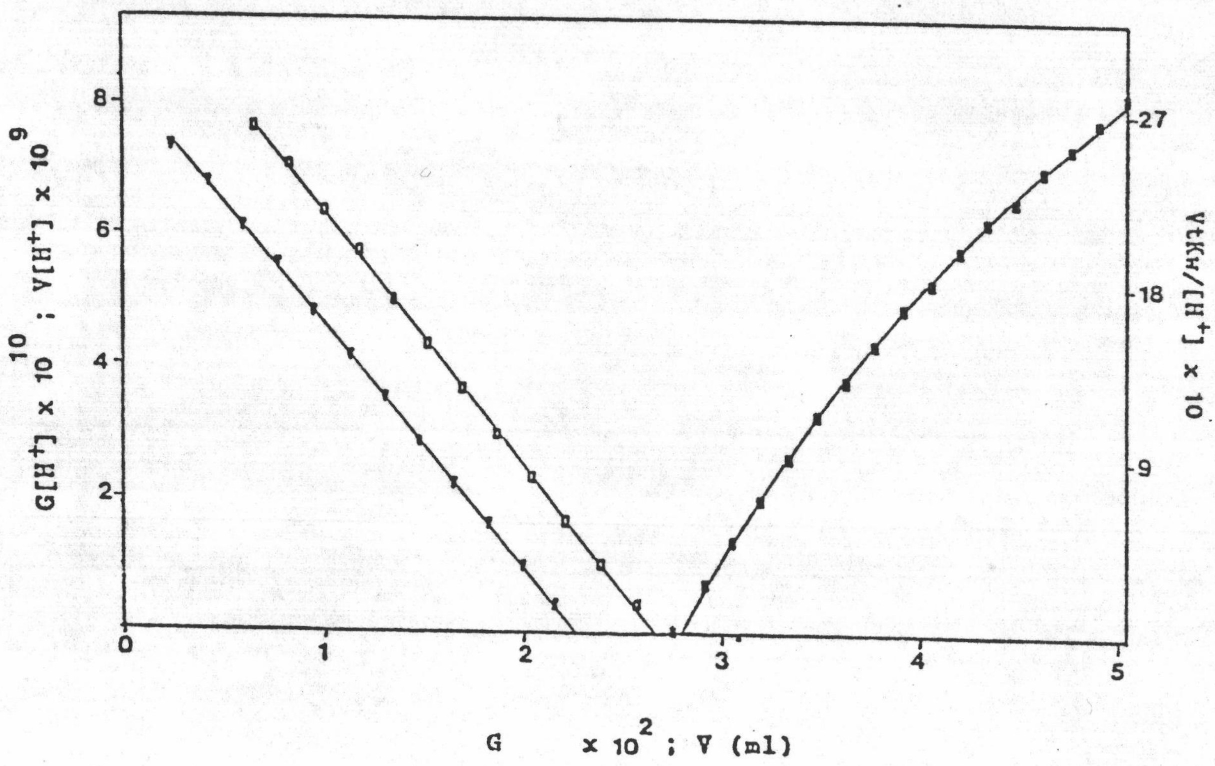

Figure 57 Gran's plot for the titration of dextromethorphan HBr with sodium hydroxide in 70% v/v ethanol/water
G plot (▼) V plot (□) E plot (■).

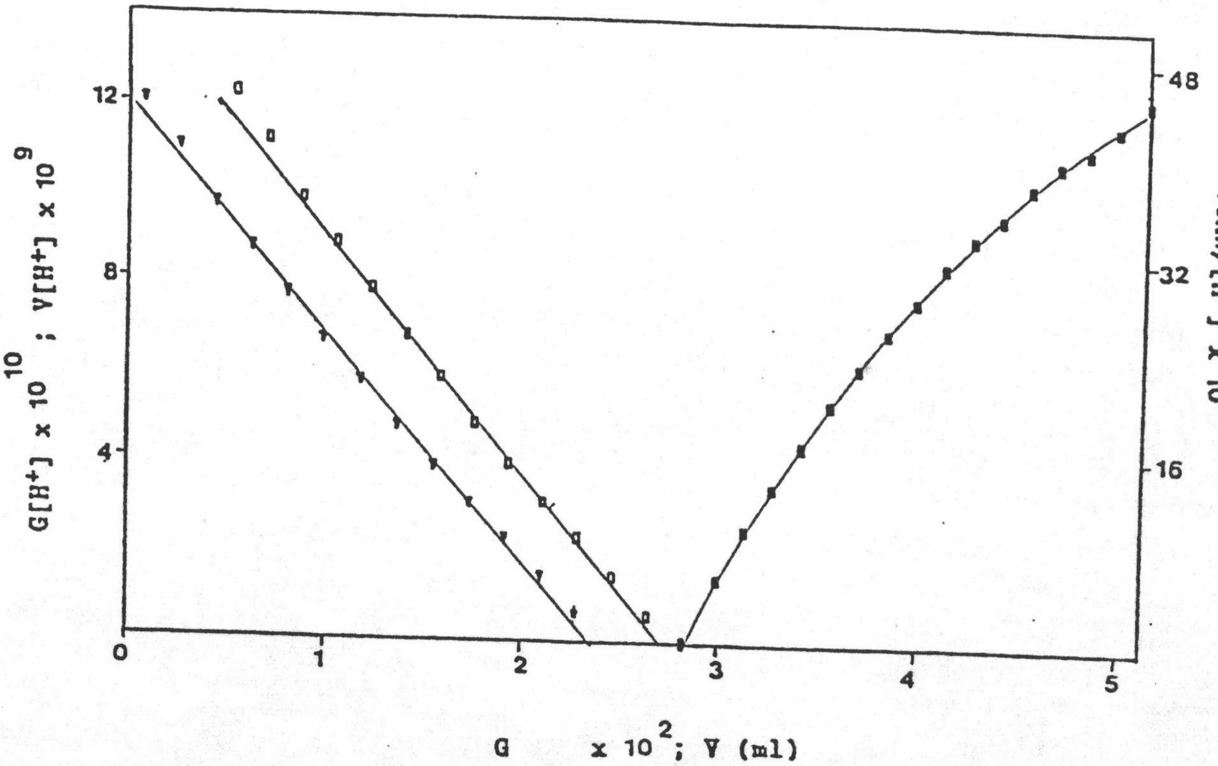

Figure 58 Gran's plot for the titration of dextromethorphan HBr with sodium hydroxide in 80% v/v ethanol/water G plot (▼) V plot (□) E plot (■).

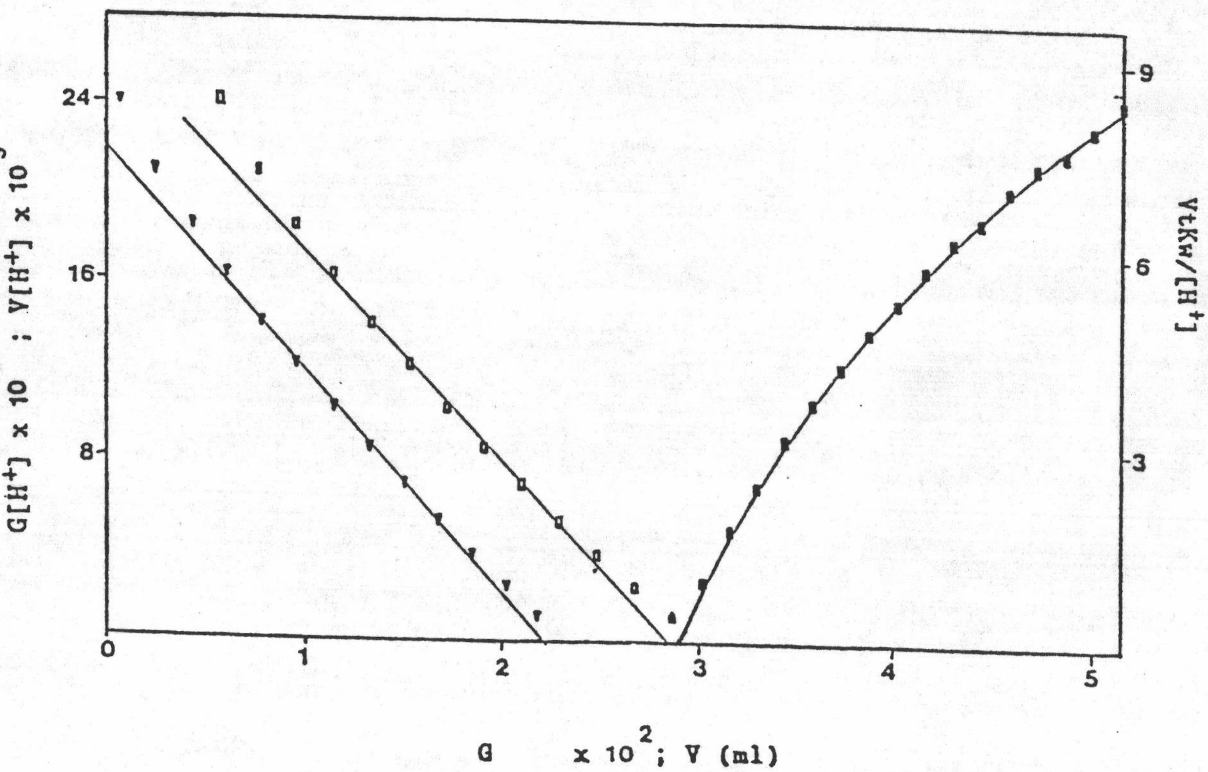

Figure 59 Gran's plot for the titration of dextromethorphan HBr with sodium hydroxide in 90% v/v ethanol/water G plot (▼) V plot (□) E plot (■).

3.3 Propylene Glycol-Water System

Dextromethorphan HBr could be dissolved moderately in propylene glycol. Thus, the titration in this solvent system could be performed only in 60-70% v/v propylene glycol/water which the composition of propylene glycol was rather high. The percentage purities of dextromethorphan HBr for the titrations in 60-70% v/v propylene glycol/water calculated from G V and E plots were statistically lower than obtained from non-aqueous titration, as shown in Table 11. The reason was the same as discussed in the titration of triprolidine HCl and quinine sulfate. V-shape Gran's plot were illustrated in Figures 61-62. The titration curves in propylene glycol/water system were shown in Figure 60.

The results could be summarized by using relative purity as shown in Figures 63-65. For the titration of dextromethorphan HBr, G and V plots would give satisfactory results for the titrations in 50-70% v/v methanol/water (Figure 63) and in 40% v/v ethanol/water (Figure 64). In the case of propylene glycol-water system, G , V and E plots could not be accurately used in quantitative determination of dextromethorphan HBr, Figure 65.

Table 11 Average Percentage Purities by Gran's Method for Titration of Dextromethorphan Hydrobromide in Propylene Glycol-Water Solvent Systems with 0.08340 N NaOH

Solvent (Propylene glycol in water)	Average Percentage Purity (%)			
	G plot	V plot	E plot	USP method **
60%	92.41 (0.46)	93.40 (0.73)	92.32 (0.55)	95.00 (0.16)
70%	92.44 (0.70)	92.95 (0.84)	91.35 (0.73)	

** Titrated in glacial acetic acid and mercuric acetate TS with 0.1 N perchloric acid using crystal violet as indicator

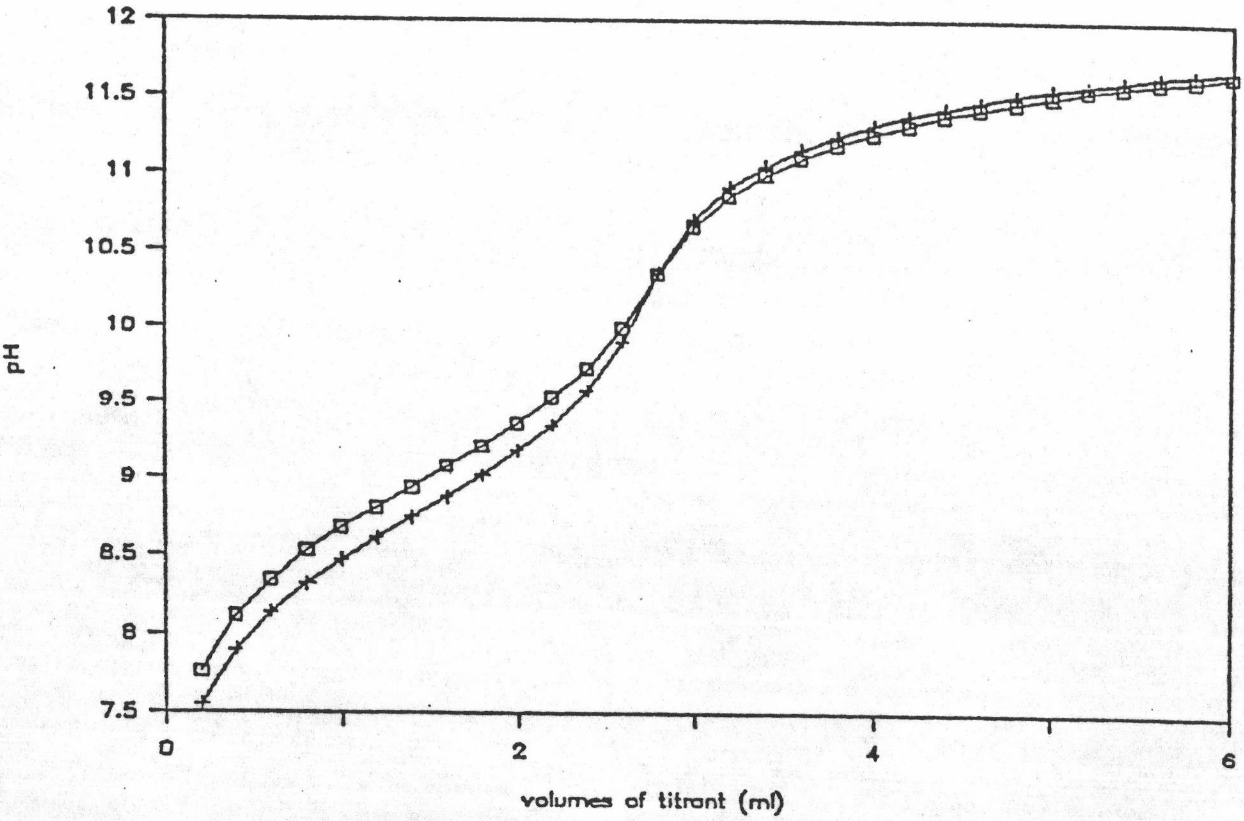

Figure 60 Titration Curves of dextromethorphan hydrobromide with sodium hydroxide in 60-70% v/v propylene glycol/water
60% (□) 70% (+).

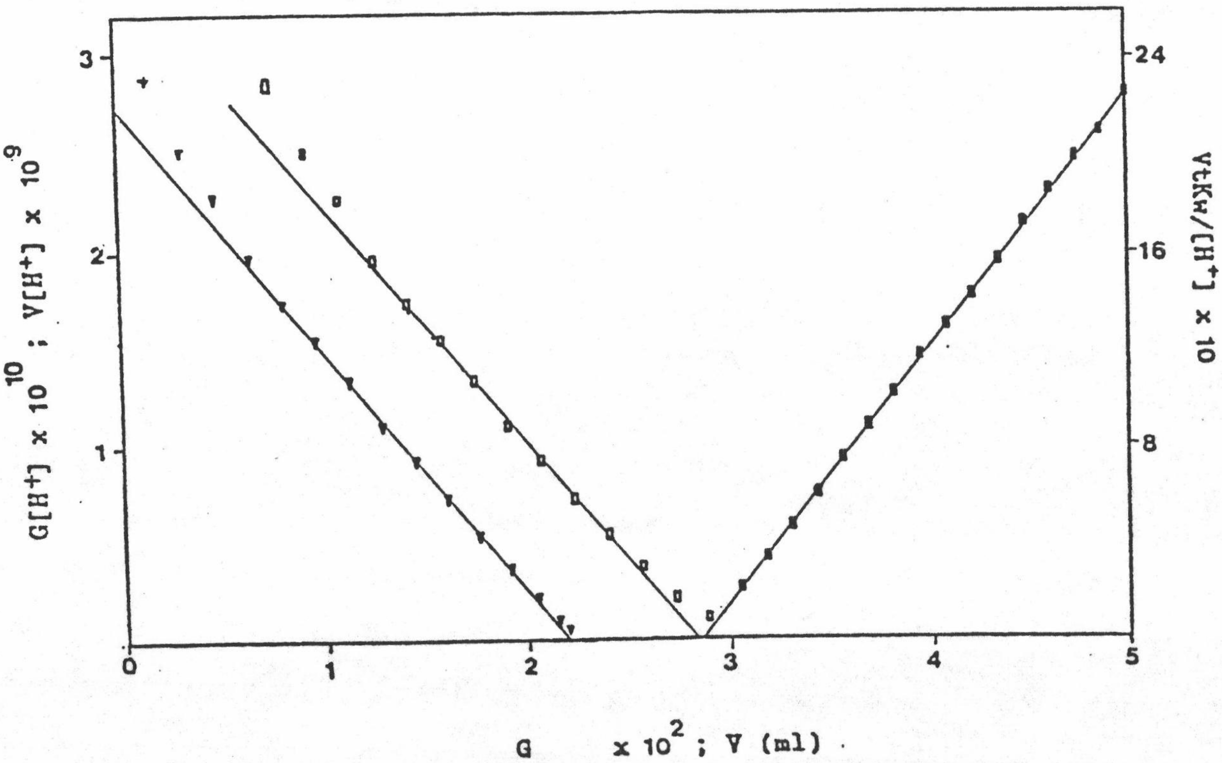

Figure 61 Gran's plot for the titration of dextromethorphan Hbr with sodium hydroxide in 60% v/v propylene glycol/water G plot (▼) V plot (□) E plot (■).

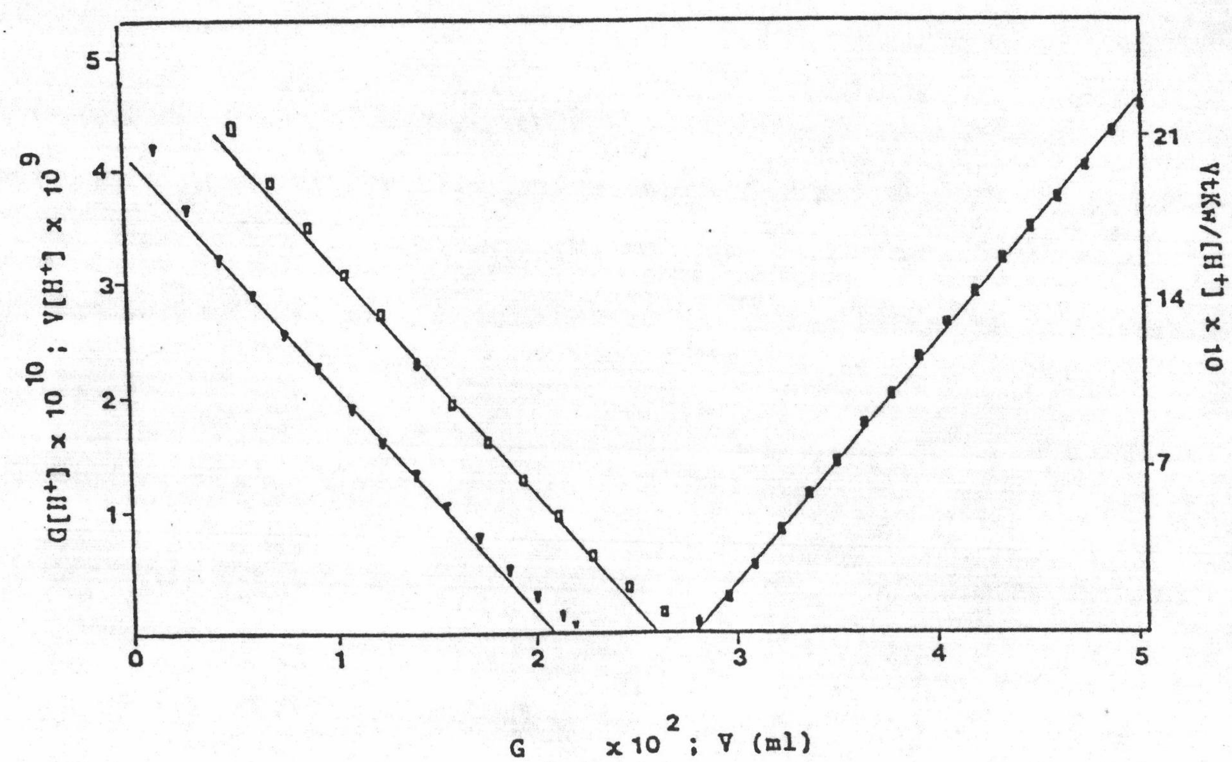

Figure 62 Gran's plot for the titration of dextromethorphan Hbr with sodium hydroxide in 70% v/v propylene glycol/water G plot (▼) V plot (□) E plot (■).

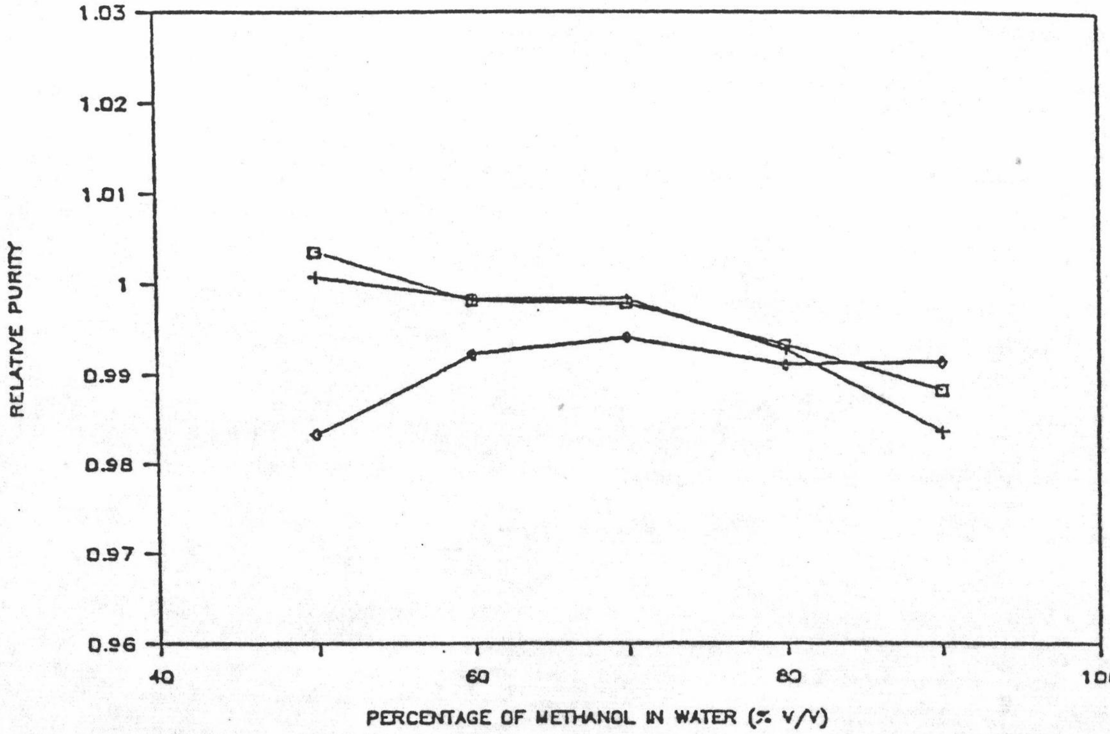

Figure 63 Relative purities of dextromethorphan hydrobromide in methanol-water solvents by using G plot (□) V plot (+) E plot (◊).

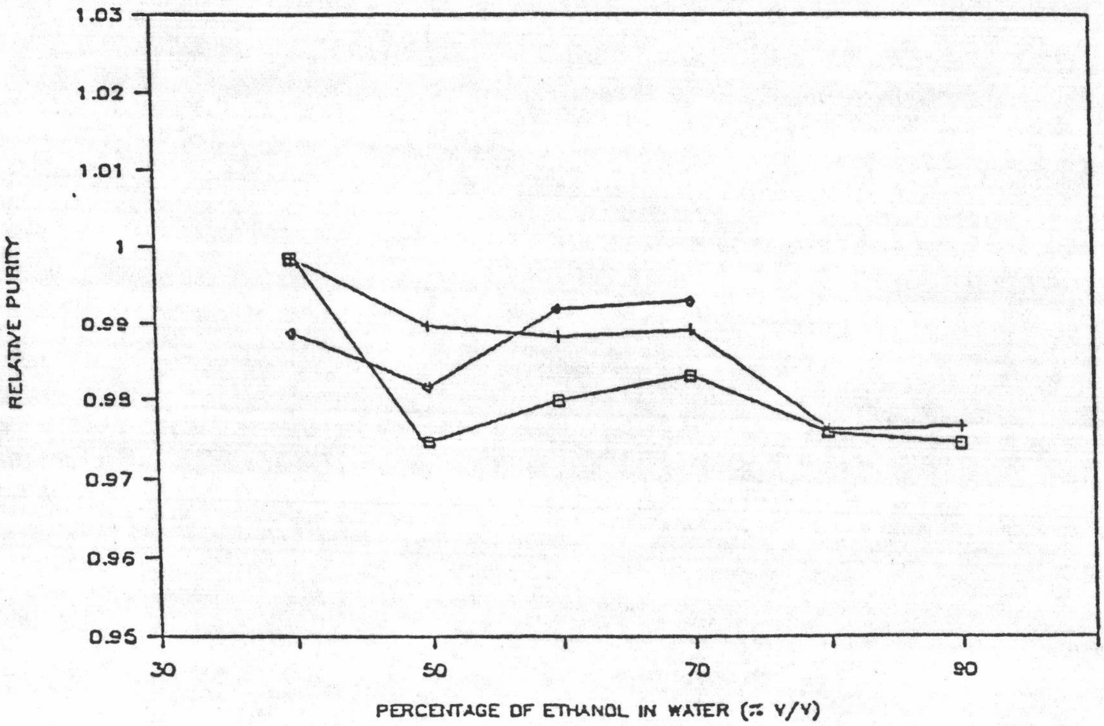

Figure 64 Relative purities of dextromethorphan hydrobromide in ethanol-water solvents by using G plot (□) V plot (+) E plot (◊).

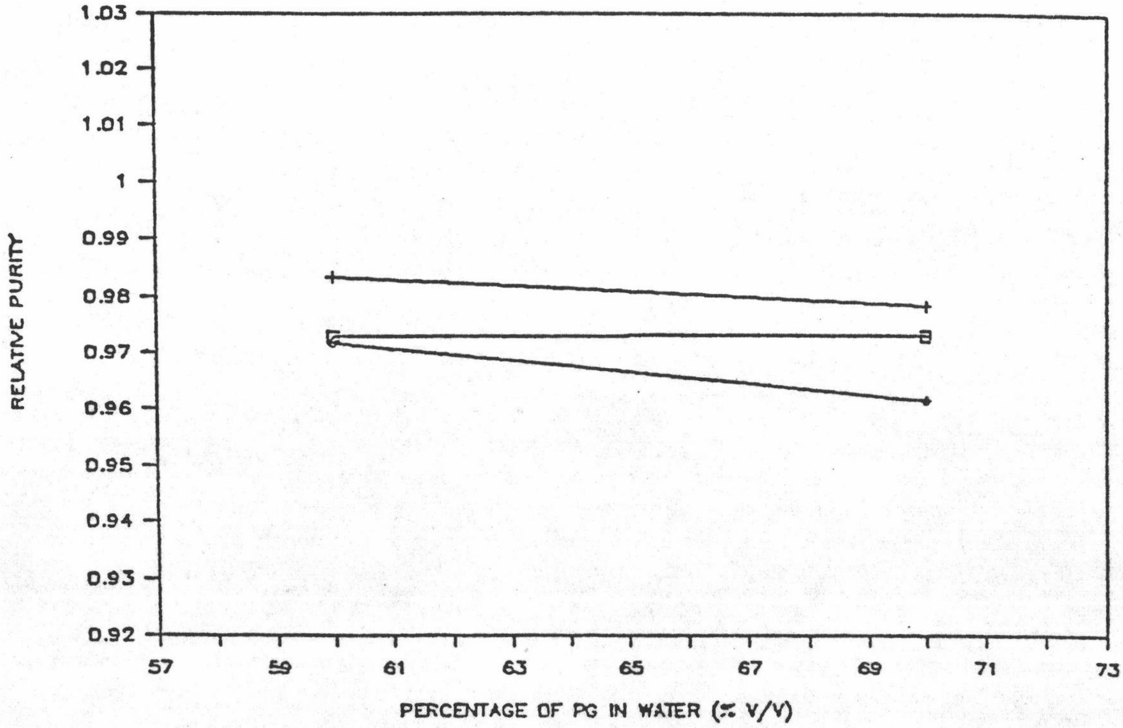

Figure 65 Relative purities of dextromethorphan hydrobromide in propylene glycol-water solvents by using G plot (□) V plot (+) E plot (◇).

4. Diphenhydramine Hydrochloride

This compound has the dissociation constant of 1×10^{-9} (pKa = 9). The result was obtained as followed.

4.1 Methanol-Water System

The titrations were performed in 30-90% v/v methanol/water and the resulting titration curves were shown in Figure 66. V-shape Gran's plots were illustrated in Figures 67-73.

For the titration in 30% v/v methanol/water, the percentage purities of diphenhydramine HCl calculated from G, V and E plots were equivalence to non-aqueous titration (Table 12). In 40-70% methanol/water, only G and V plots gave satisfactory results comparing to non-aqueous method whereas E plot gave significantly lower value. These might be partly resulted from error of using titration data at high alkalinity after equivalence point.

In the similar manner as triprolidine HCl, quinine sulfate and dextromethorphen HBr, G, V and E plots for the titrations of diphenhydramine HCl in 80-90% v/v methanol/water also gave the percentage purities statistically different from non-aqueous method.

Table 12 Average Percentage Purities by Gran's Method for Titration of Diphenhydramine Hydrochloride in Methanol-Water Solvent Systems with 0.08328 N NaOH

Solvent (Methanol in water)	Average Percentage Purity (%)			
	G plot	V plot	E plot	USP method **
30%	100.2 * (0.46)	100.3 * (0.53)	100.2 * (0.41)	
40%	99.88 * (0.18)	99.99 * (0.25)	99.23 (0.12)	
50%	99.82 * (0.23)	100.0 * (0.25)	99.00 (0.34)	
60%	99.77 * (0.35)	100.1 * (0.36)	98.79 (0.22)	100.2 * (0.11)
70%	100.2 * (0.39)	99.88 * (0.63)	97.92 (0.32)	
80%	98.78 (0.43)	98.92 (0.27)	99.09 (0.07)	
90%	97.21 (0.31)	97.31 (0.31)	97.10 (0.38)	

* Statistically indifference from reference non-aqueous titration at 99% confidence level

** Titrated in glacial acetic acid and mercuric acetate TS with 0.1 N perchloric acid using crystal violet as indicator

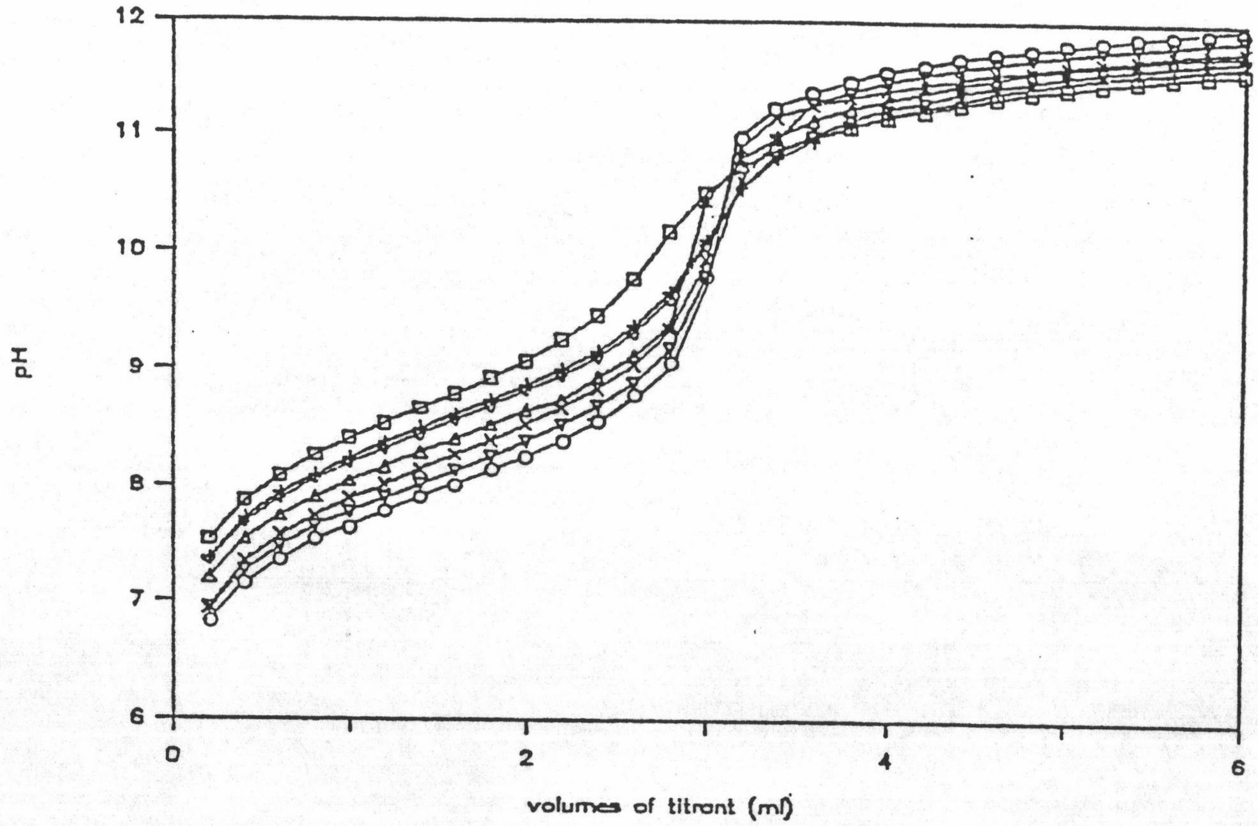

Figure 66 Titration curves of diphenhydramine hydrochloride with sodium hydroxide in 30-90% v/v methanol/water
30% (□) 40% (+) 50% (◊) 60% (△)
70% (×) 80% (▽) 90% (○).

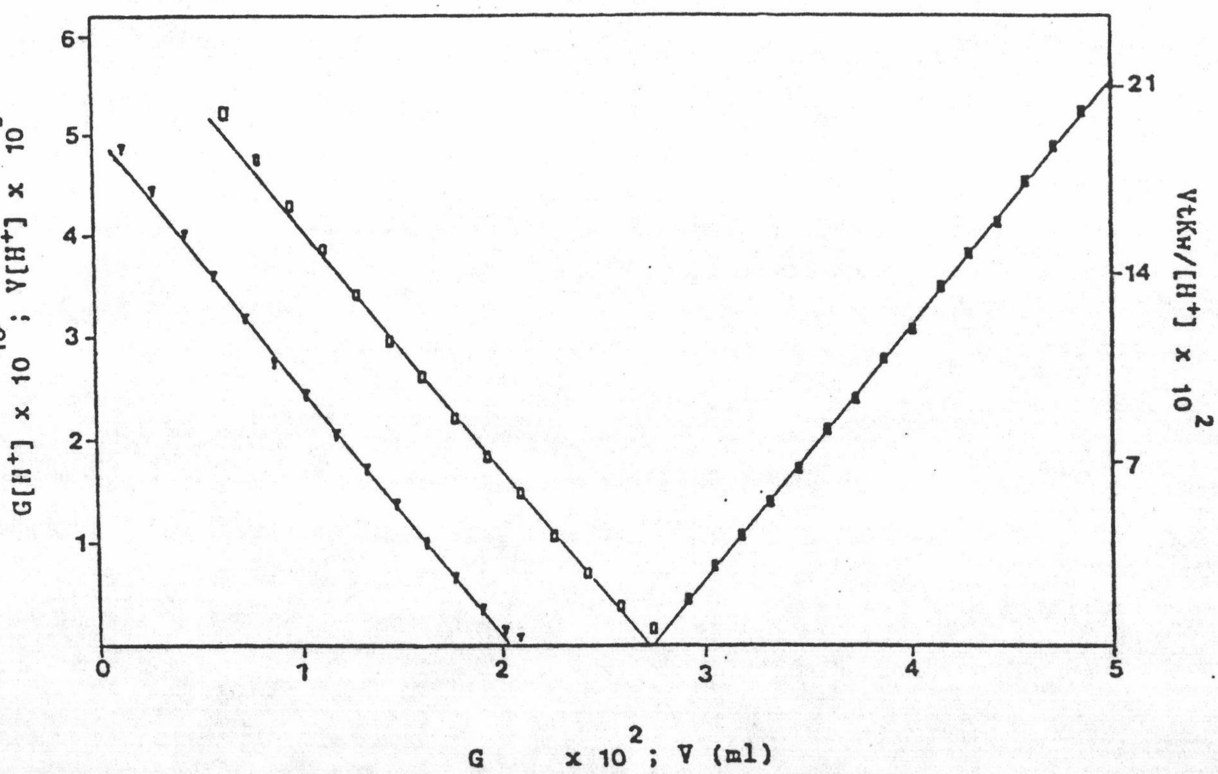

Figure 67 Gran's plot for the titration of diphenhydramine HCl with sodium hydroxide in 30% v/v methanol/water G plot (▼) V plot (□) E plot (■).

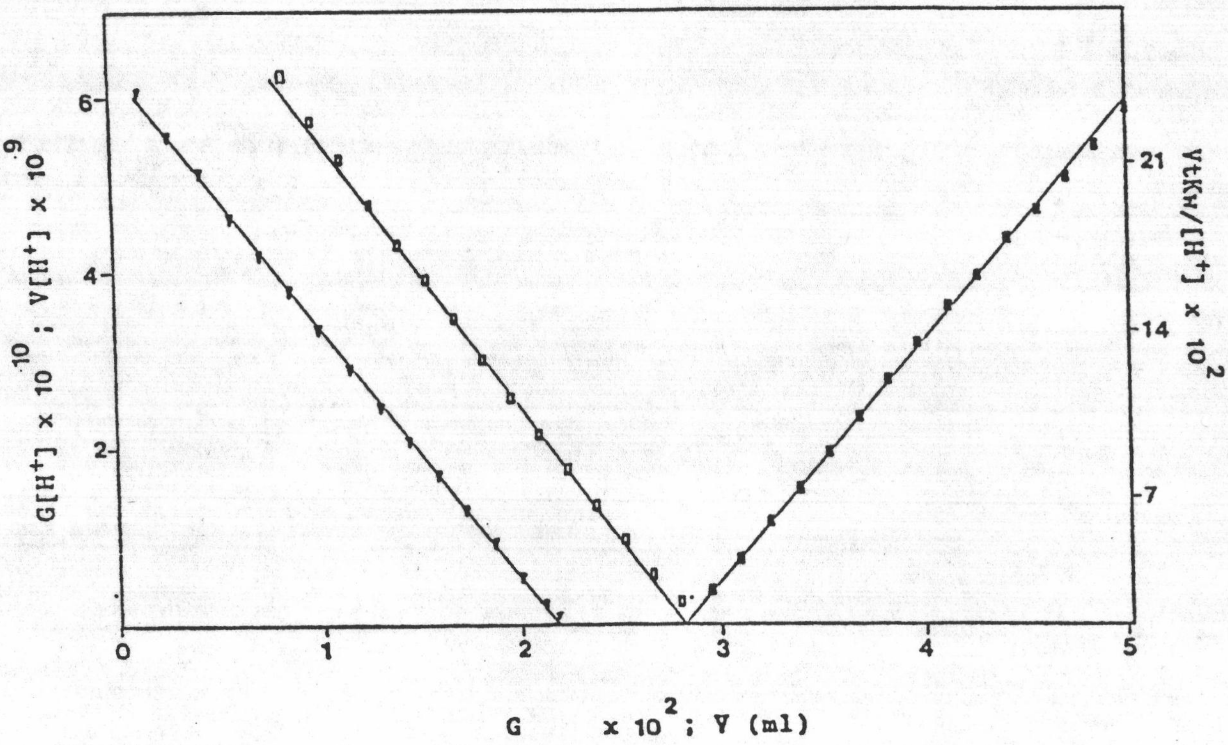

Figure 68 Gran's plot for the titration of diphenhydramine HCl with sodium hydroxide in 40% v/v methanol/water G plot (▼) V plot (□) E plot (■).

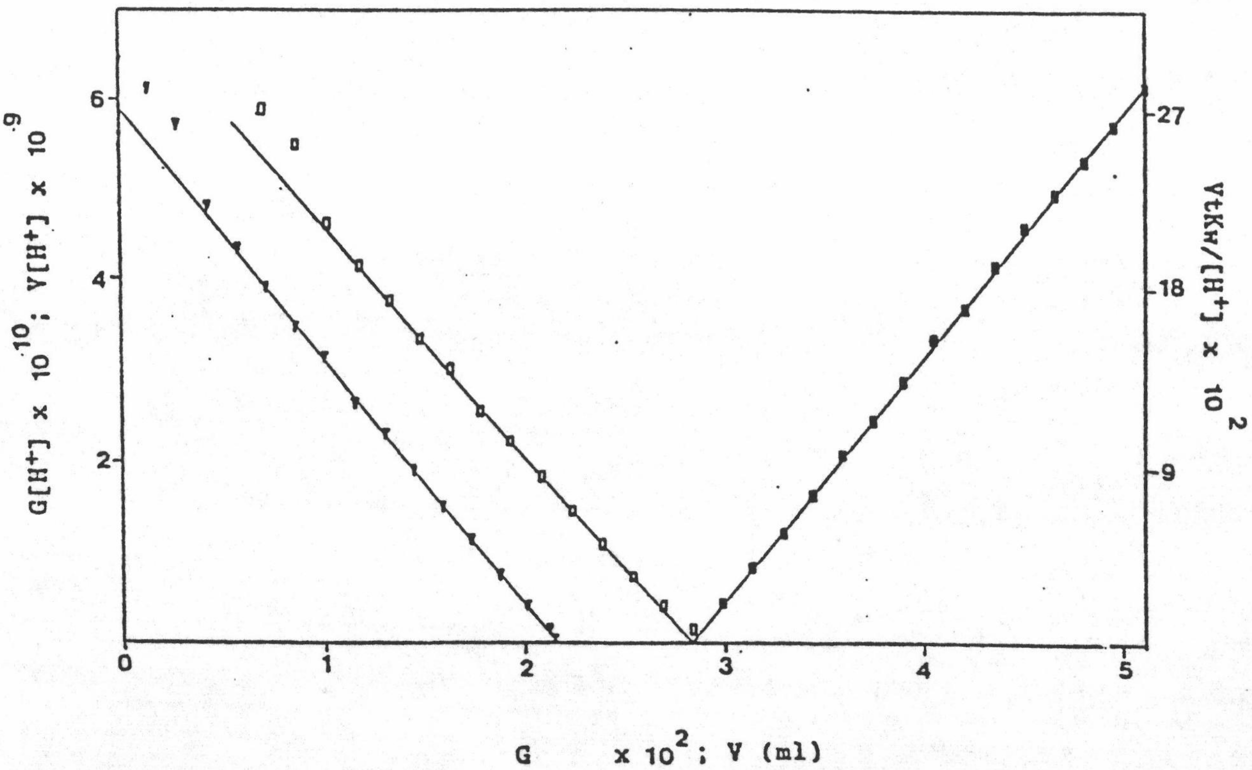

Figure 69 Gran's plot for the titration of diphenhydramine HCl with sodium hydroxide in 50% v/v methanol/water G plot (▼) V plot (□) E plot (■).

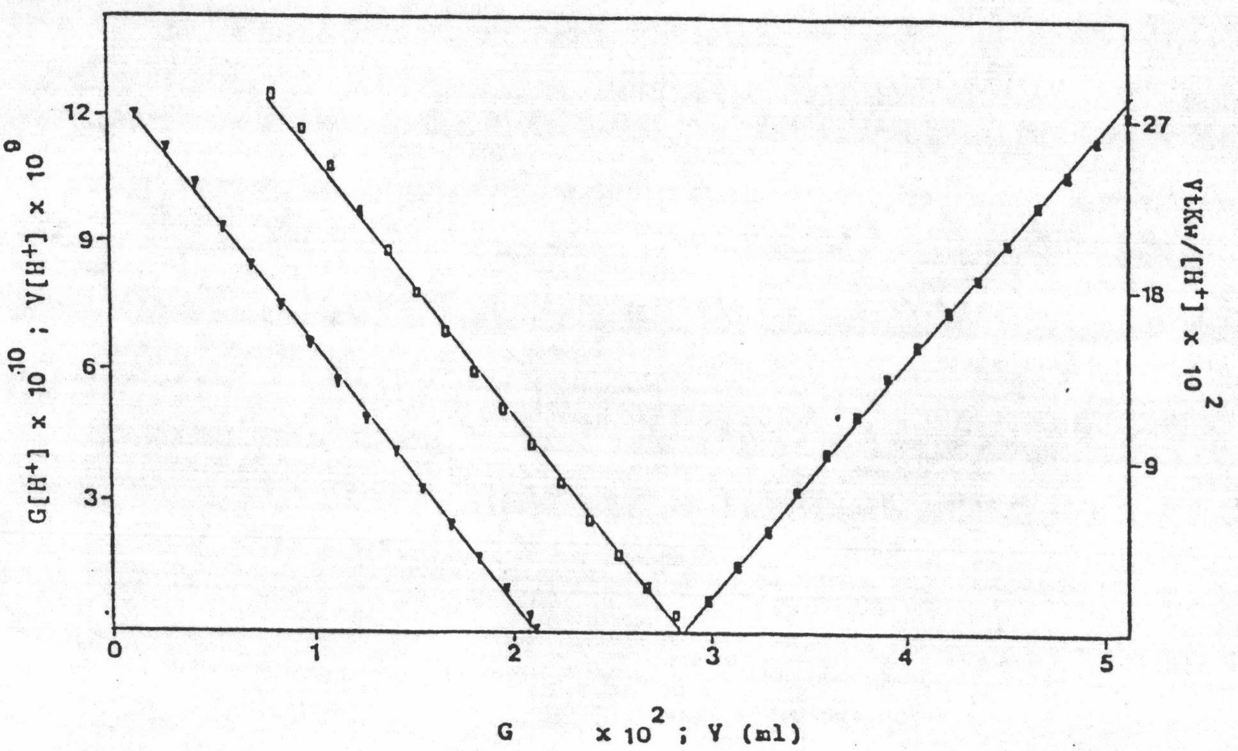

Figure 70 Gran's plot for the titration of diphenhydramine HCl with sodium hydroxide in 60% v/v methanol/water G plot (▼) V plot (□) E plot (■).

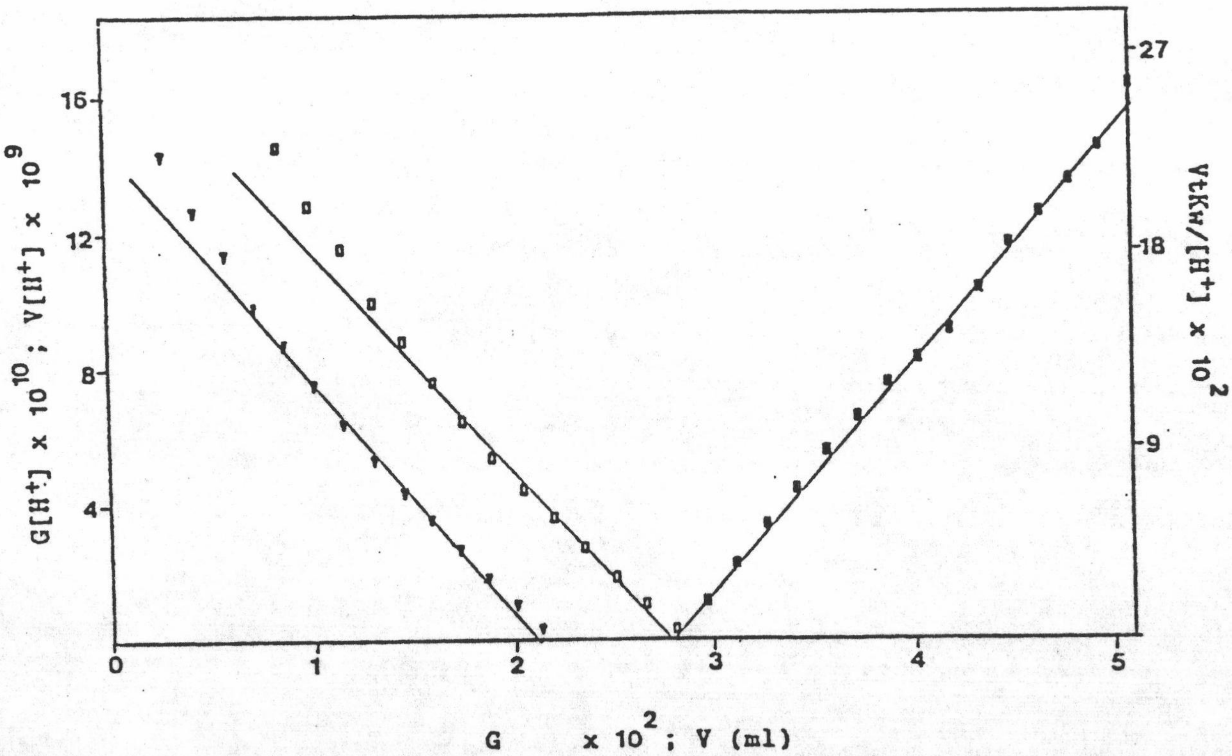

Figure 71 Gran's plot for the titration of diphenhydramine HCl with sodium hydroxide in 70% v/v methanol/water G plot (▼) V plot (□) E plot (■).

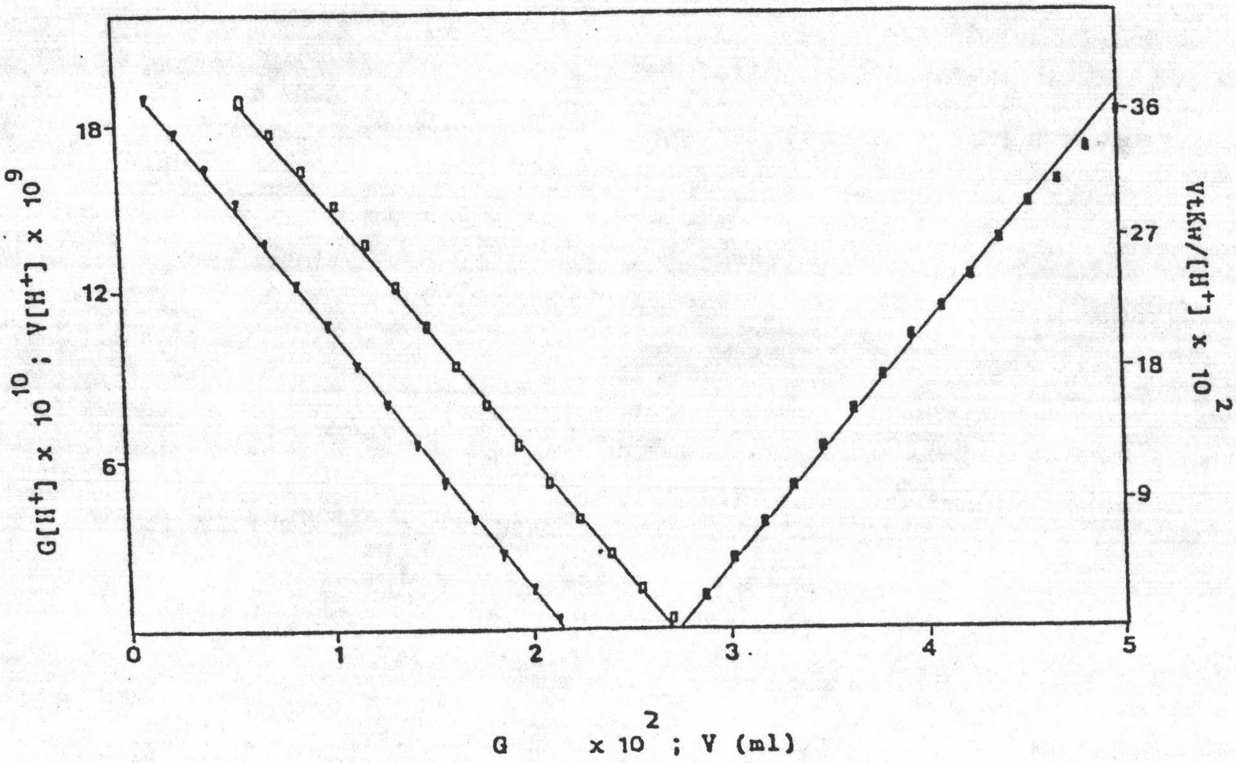

Figure 72 Gran's plot for the titration of diphenhydramine HCl with sodium hydroxide in 80% v/v methanol/water G plot (▼) V plot (□) E plot (■).

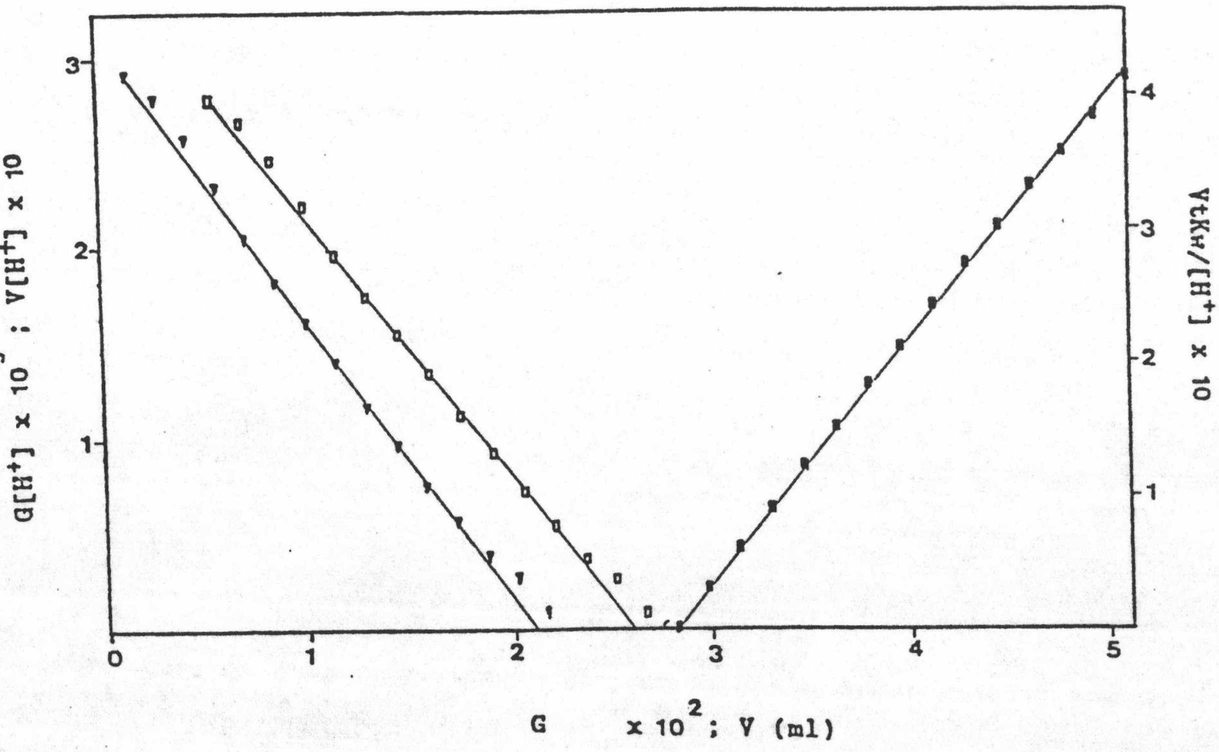

Figure 73 Gran's plot for the titration of diphenhydramine HCl with sodium hydroxide in 90% v/v methanol/water
G plot (▼) V plot (□) E plot (▮).

4.2 Ethanol-Water System

The titration curves in 30-90% v/v ethanol/water were shown in Figure 74. G , V and E plots were illustrated in Figure 75-81. Average percentage purities from these plots were shown in Table 13. Accurate results for the titration of diphenhydramine HCl in ethanol-water systems were obtained from G plot, V plot and E plot only for the titration in 30% v/v ethanol/water. In 40-90% v/v ethanol/water the percentage purities of diphenhydramine HCl calculated from G, V and E plots were statistically different from non-aqueous titration, espectially E plot whoch could not be employed for the titration in high composition of ethanol-water solvent (70-90% v/v ethanol/water). The reason was the same as previously discussed in triprolidine HCl, quinine sulfate and dextromethorphan HBr.

4.3 Propylene Glycol-Water System

The titrations were performed in 40-70% v/v propylene glycol/water. The titration curves in propylene glycol-water systems were shown in Figure 82 and the resulting Gran's plots were shown in Figures 83-86.

The titration data prior to and after equivalence point could be accurately used for the titration in 40% v/v propylene glycol/water. In higher

Table 13 Average Percentage Purities by Gran's Method for Titration of Diphenhydramine Hydrochloride in Ethanol-Water Solvent Systems with 0.08328 N NaOH

Solvent (Ethanol ia water)	Average Percentage Purity (%)			
	G plot	V plot	E plot	USP method **
30%	99.89 * (0.15)	100.0 * (0.30)	99.94 * (0.28)	
40%	98.06 (0.22)	99.16 (0.33)	98.11 (0.29)	
50%	97.45 (0.27)	98.16 (0.15)	98.25 (0.48)	
60%	97.95 (0.39)	97.20 (0.49)	98.02 (0.28)	100.2 * (0.11)
70%	97.23 (0.26)	97.42 (0.26)	-	
80%	96.60 (0.43)	97.28 (0.18)	-	
90%	97.40 (0.15)	98.41 (0.47)	-	

* Statistically indifference from reference non-aqueous titration at 99% confidence level

** Titrated in glacial acetic acid and mercuric acetate TS with 0.1 N perchloric acid using crystal violet as indicator

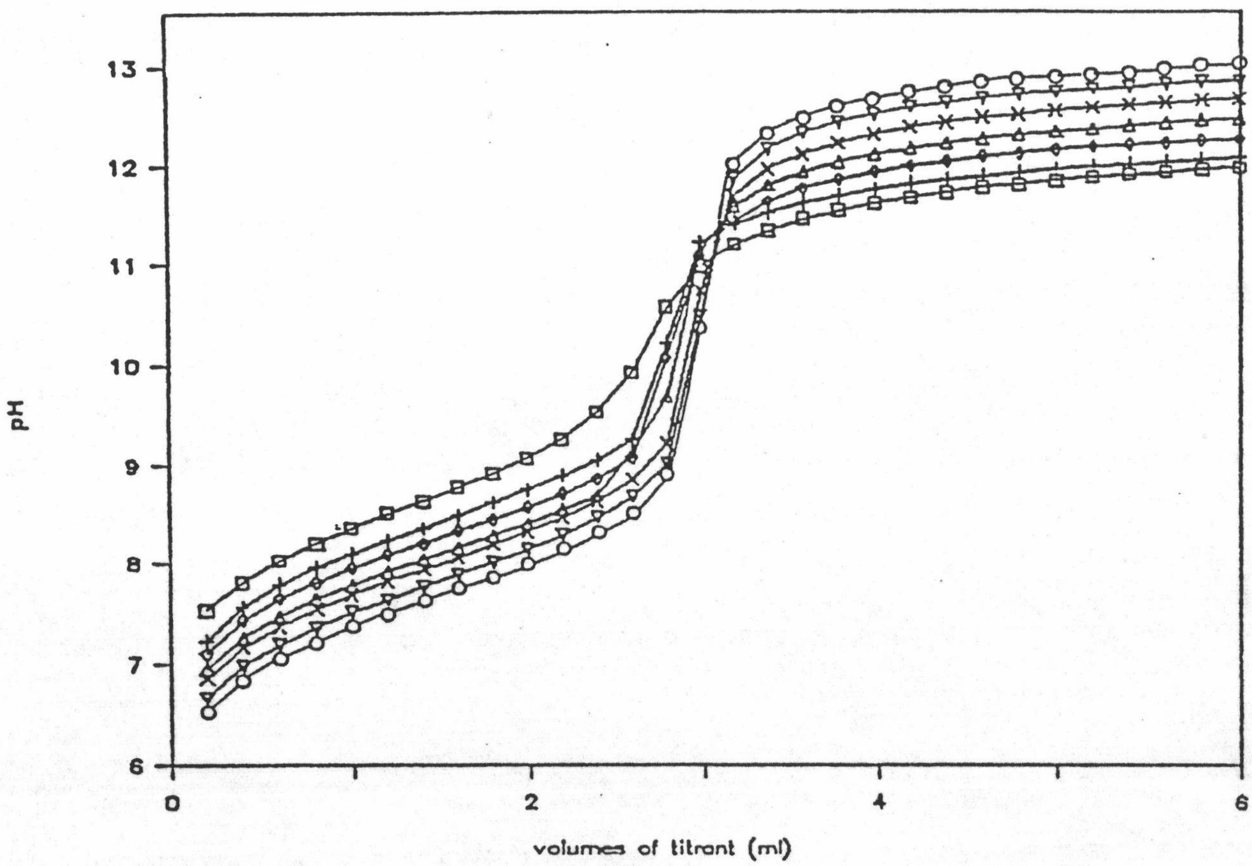

Figure 74 Titration curves of diphenhydramine hydrochloride with sodium hydroxide in 30-90% v/v ethanol/water
30% (□) 40% (+) 50% (◇) 60% (Δ)
70% (×) 80% (▽) 90% (o).

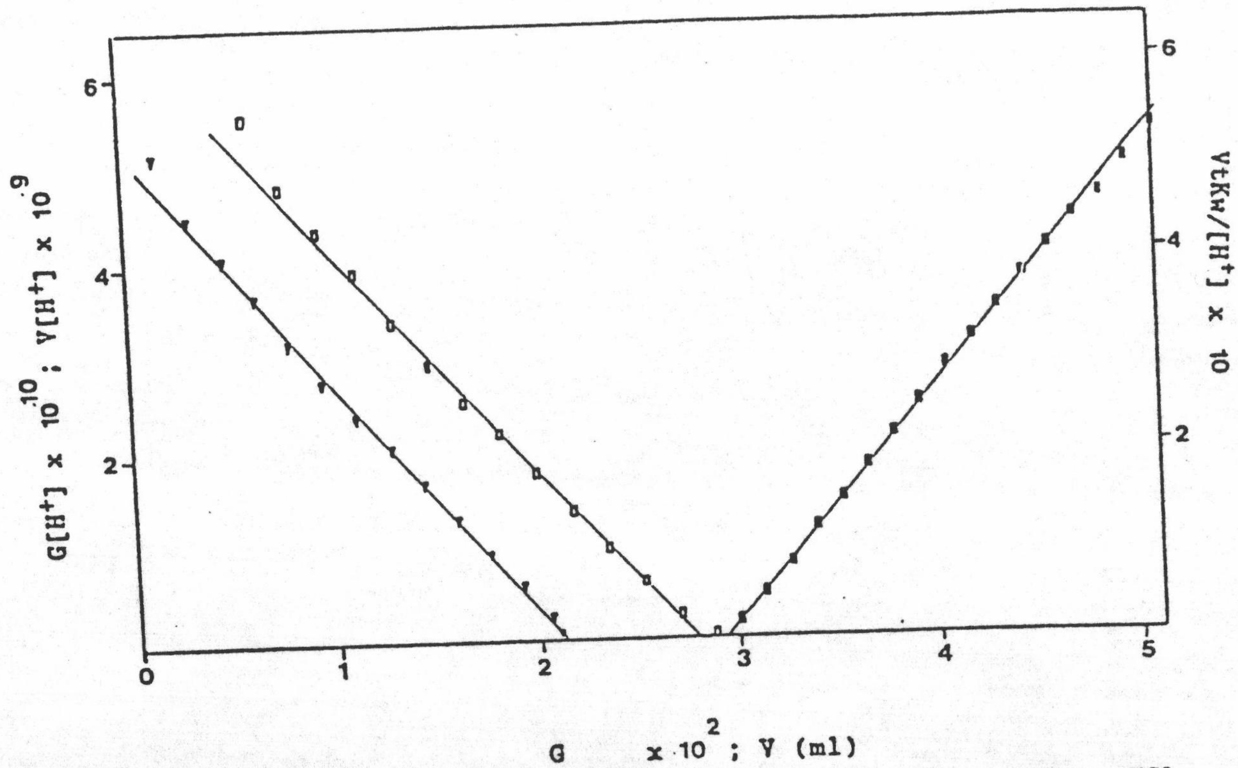

Figure 75 Gran's plot for the titration of diphenhydramine HCl with sodium hydroxide in 30% v/v ethanol/water
G plot (▼) V plot (□) E plot (■).

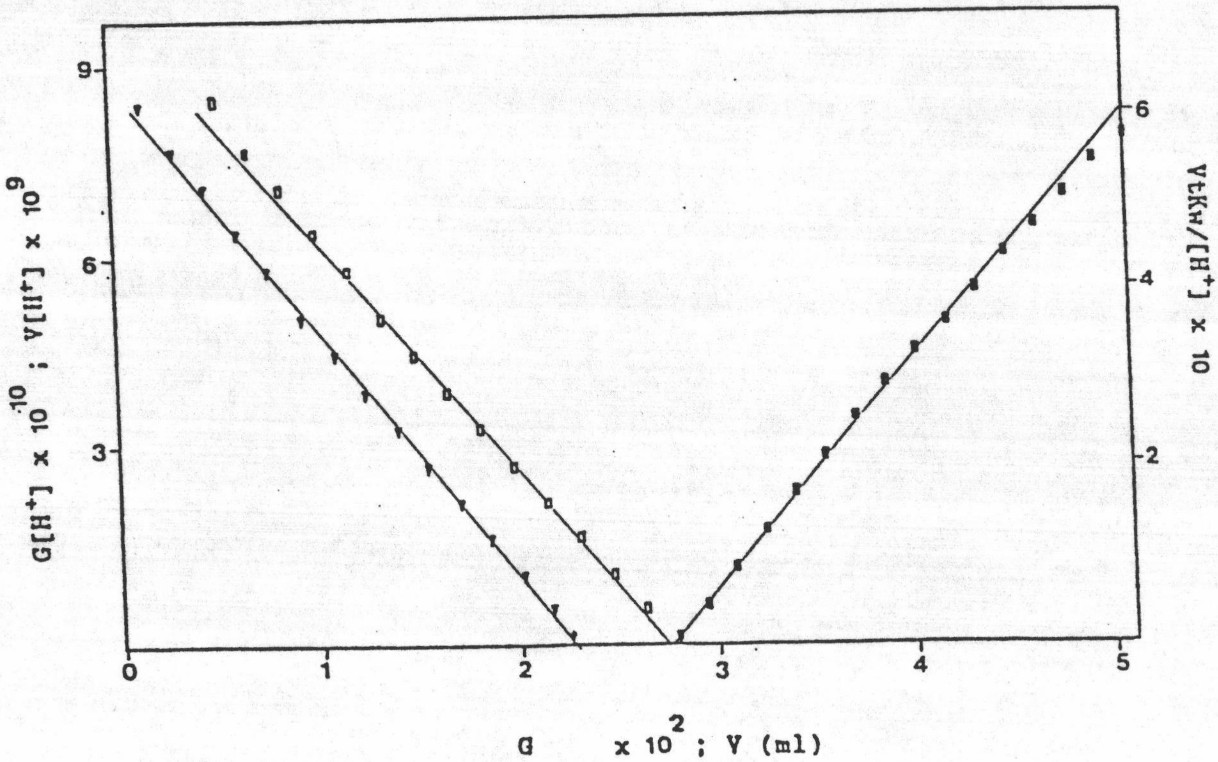

Figure 76 Gran's plot for the titration of diphenhydramine HCl with sodium hydroxide in 40% v/v ethanol/water
G plot (▼) V plot (□) E plot (■).

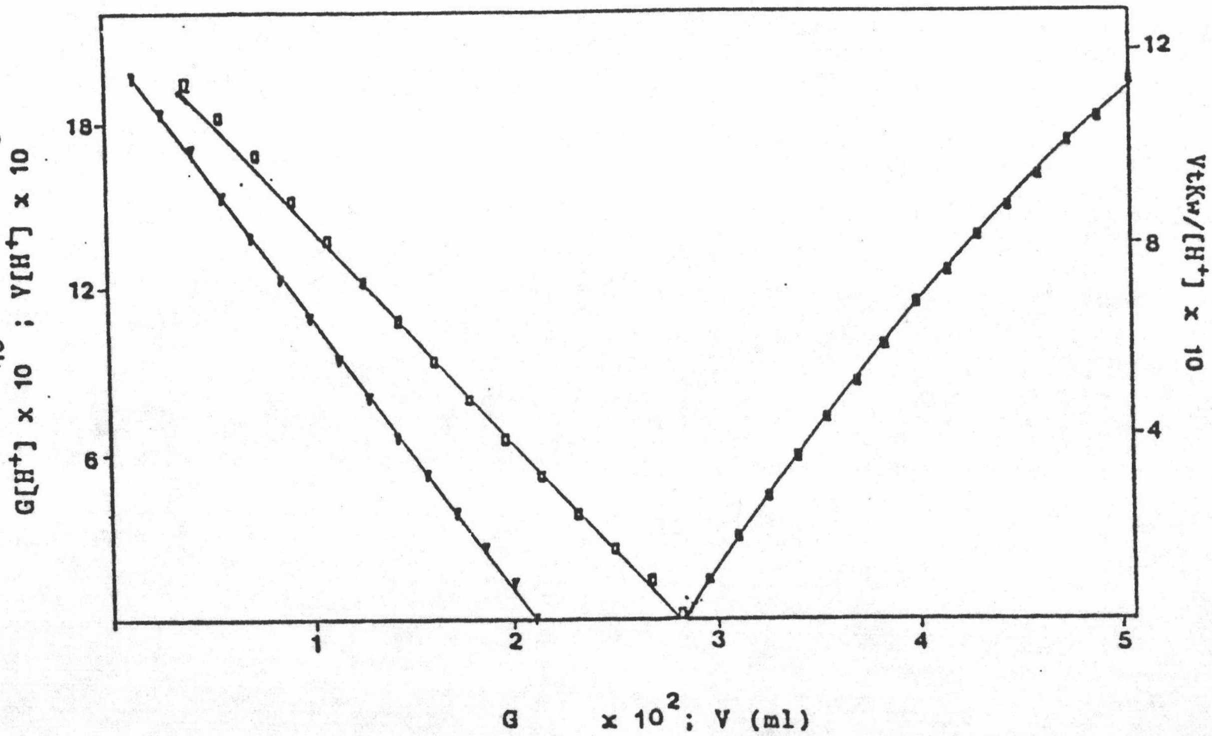

Figure 77 Gran's plot for the titration of diphenhydramine HCl with sodium hydroxide in 50% v/v ethanol/water G plot (▼) V plot (□) E plot (■).

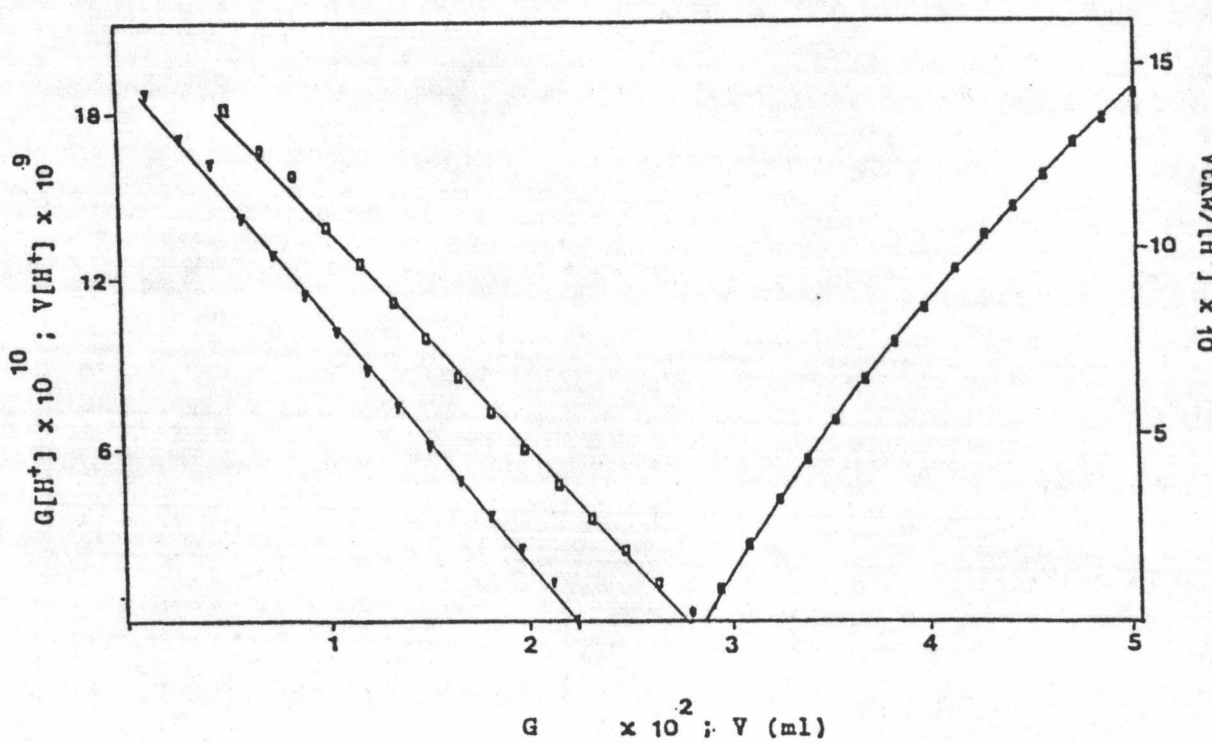

Figure 78 Gran's plot for the titration of diphenhydramine HCl with sodium hydroxide in 60% v/v ethanol/water G plot (▼) V plot (□) E plot (■).

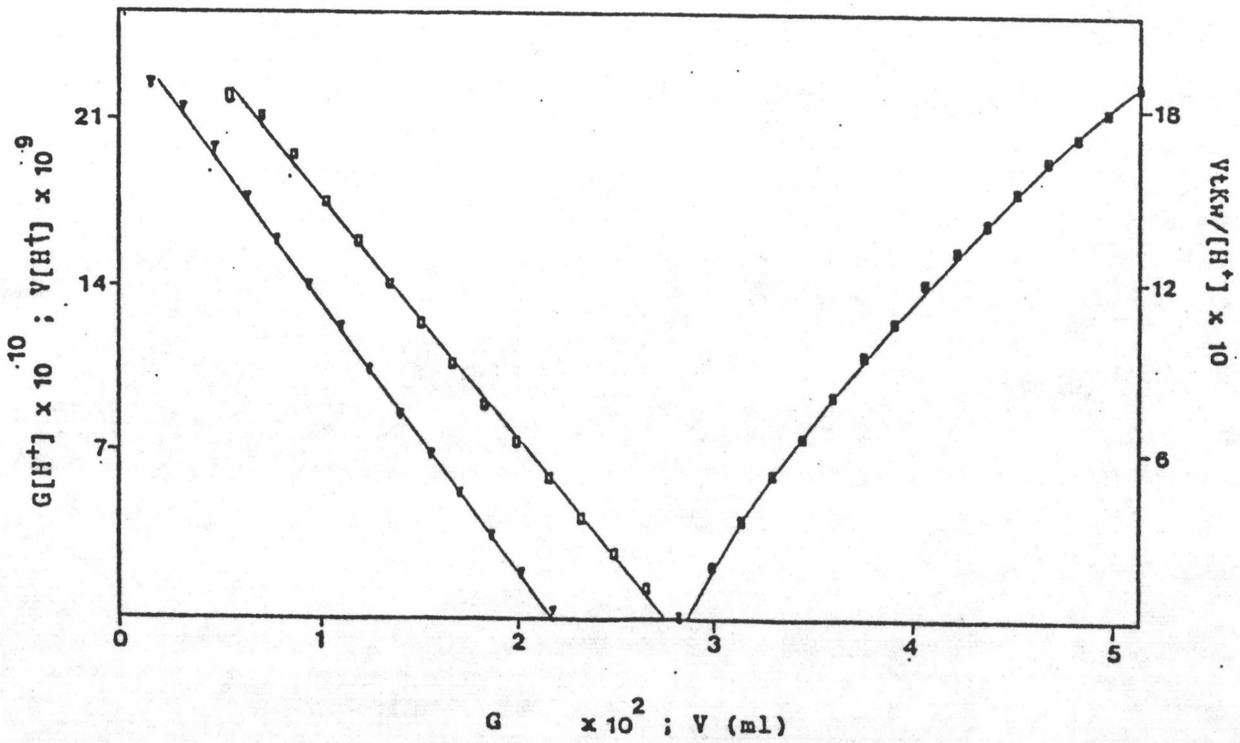

Figure 79 Gran's plot for the titration of diphenhydramine HCl with sodium hydroxide in 70% v/v ethanol/water G plot (▼) V plot (□) E plot (■).

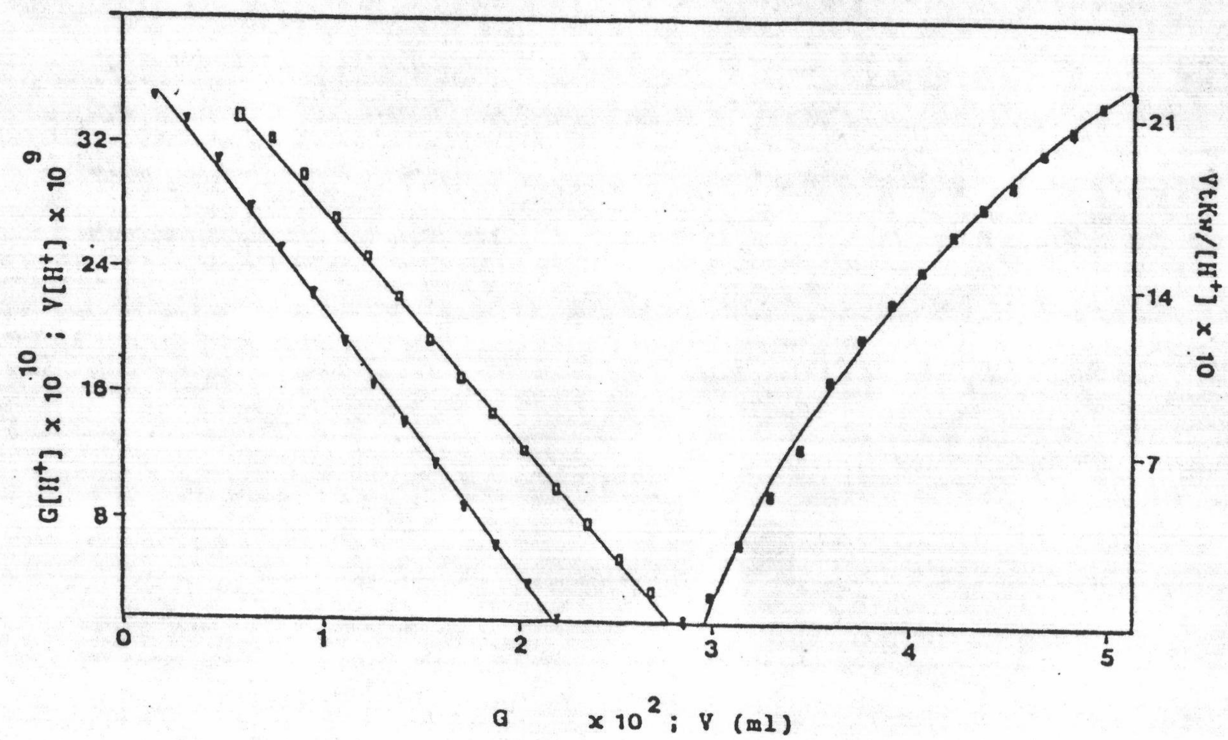

Figure 80 Gran's plot for the titration of diphenhydramine HCl with sodium hydroxide in 80% v/v ethanol/water G plot (▼) V plot (□) E plot (■).

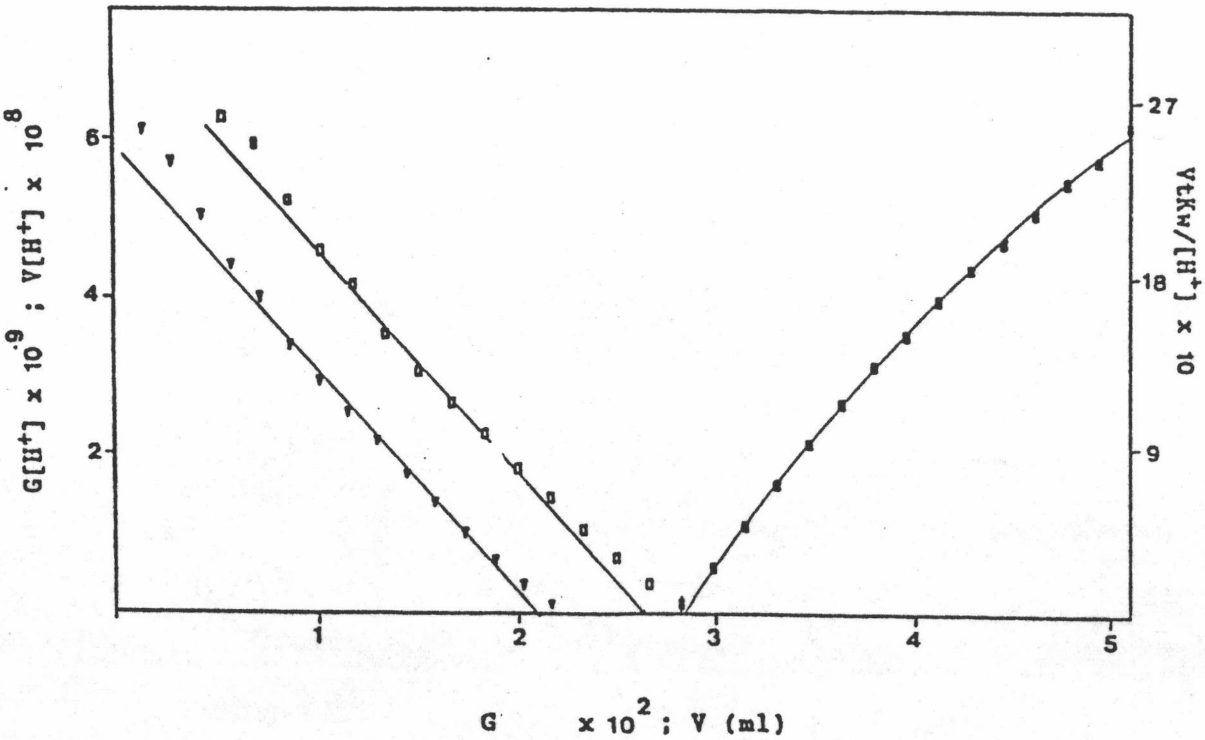

Figure 81 Gran's plot for the titration of diphenhydramine HCl with sodium hydroxide in 90% v/v ethanol/water G plot (▼) V plot (□) E plot (■).

composition of propylene glycol, 50-70% v/v propylene glycol/water, the percentage purities of diphenhydramine HCl were statistically different from that obtained by non-aqueous titration, as shown in Table 14. This was similar to the tiration of triproliodine HCl, quinine sulfate and dextromethorphan HBr in propylene glycol-water systems.

The results could be summarized in term of relative purity as shown in Figures 87-89. They indicated that for the titration of diphenhydramine HCl, G and V plots would give satisfactory results for the titrations in 30-70% v/v methanol/water and E plot for the titration in 30% v/v methanol/water (Figure 87). In ethanol-water system, G, V and E plots could be used for the titration only in 30% v/v ethanol/water (Figure 88). For the titration in propylene glycol-water system, G, V and E plots could be employed for the titration only in 40% v/v propylene glycol/water.

5. <u>Chlorpheniramine Maleate</u>

This compound has two dissociation constants, the first indicated the neutralization of the second proton of maleic acid , $Ka = 6 \times 10^{-7}$ (pKa = 6.23), and the second was the titration of protonated chlorpheniramine, $Ka = 6 \times 10^{-10}$ (pKa = 9.2). For the titration in aqueous solvent (11) the difference between pka and pka was high enough and thus would not

Table 14 Average Percentage Purities by Gran's Method for Titration of Diphenhydramine Hydrochloride in Propylene Glycol-Water solvent systems with 0.08340 N NaOH

Solvent (Propylene glycol in water)	Average percentage purity (%)			
	G plot	V plot	E plot	USP method **
40%	99.89 * (0.16)	100.2 * (0.26)	99.71 * (0.57)	
50%	98.74 (0.33)	99.16 (0.33)	97.40 (0.16)	100.2 * (0.11)
60%	97.66 (0.55)	97.84 (0.62)	97.10 (0.22)	
70%	97.67 (0.54)	97.38 (0.36)	97.22 (0.31)	

* Statistically indifference from reference non-aqueous titration at 99% confidence level

** Titrated in glacial acetic acid and mercuric acetate TS with 0.1 N perchloric acid using crystal violet as indicator

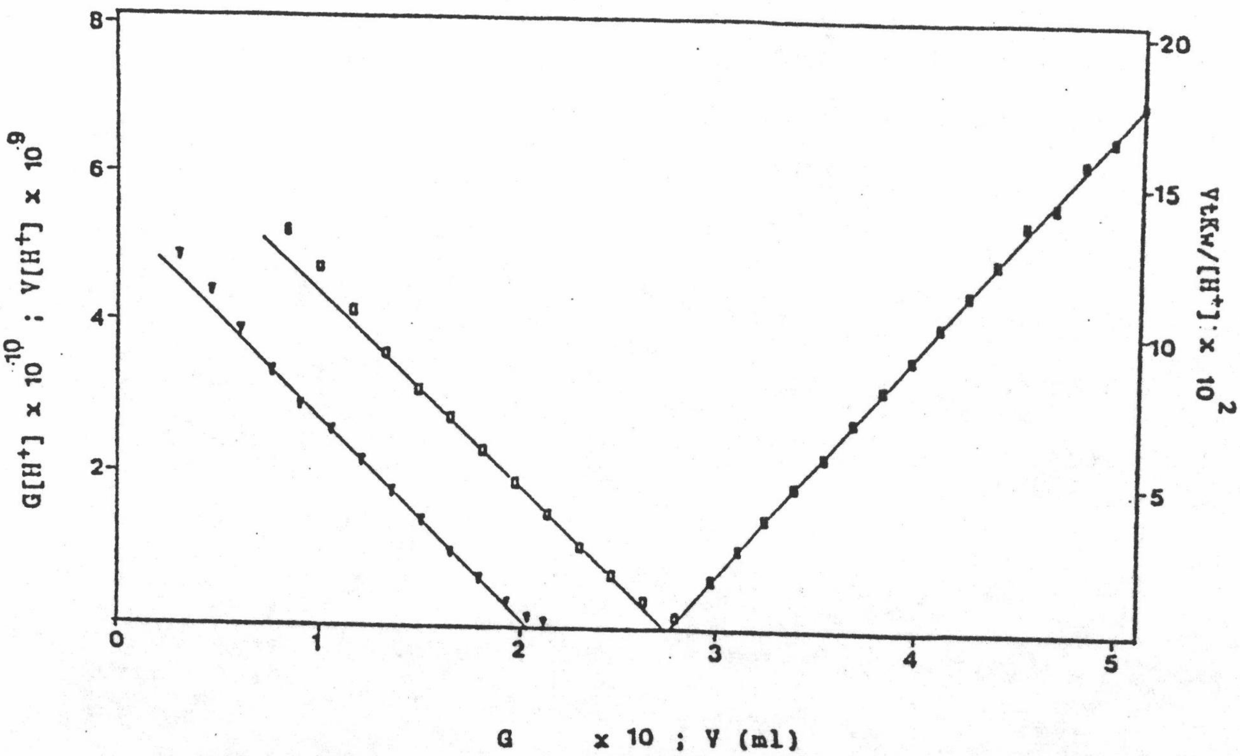

Figure 83 Gran's plot for the titration of diphenhydramine HCl with sodium hydroxide in 40% v/v propylene glycol/water G plot (▼) V plot (□) E plot (∎).

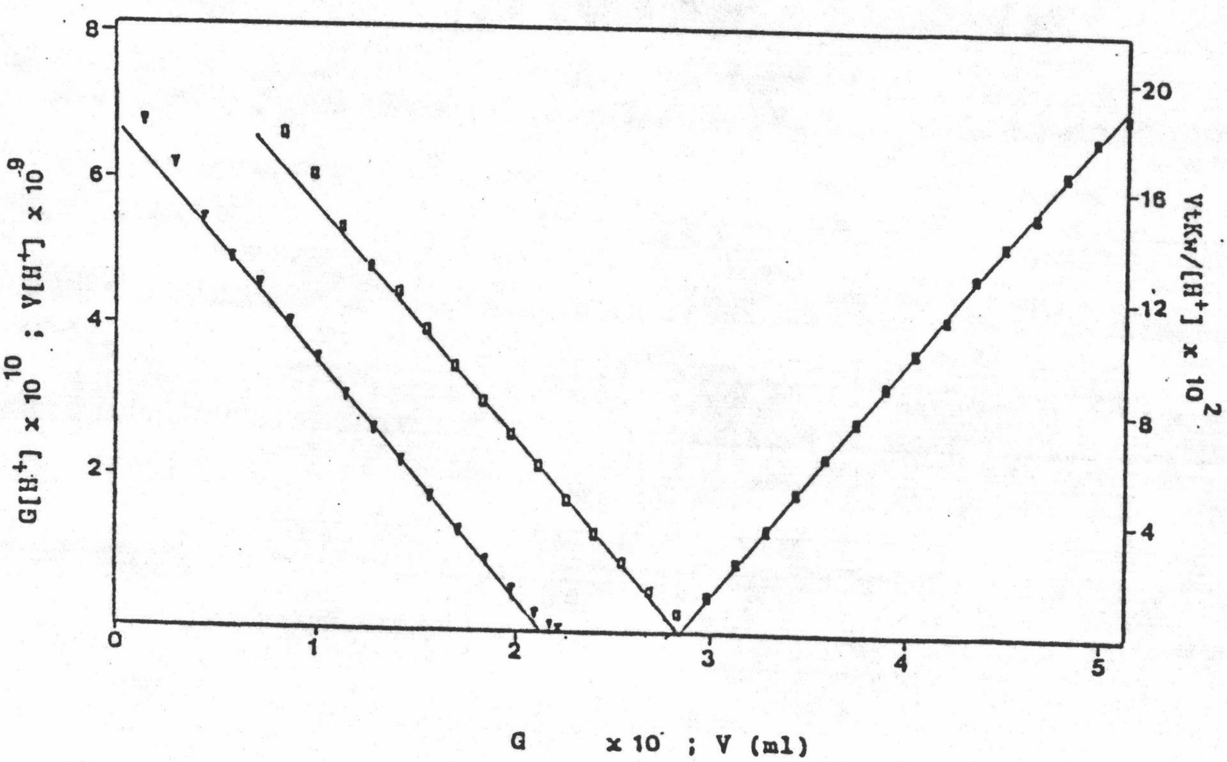

Figure 84 Gran's plot for the titration of diphenhydramine HCl with sodium hydroxide in 50% v/v propylene glycol/water G plot (▼) V plot (□) E plot (∎).

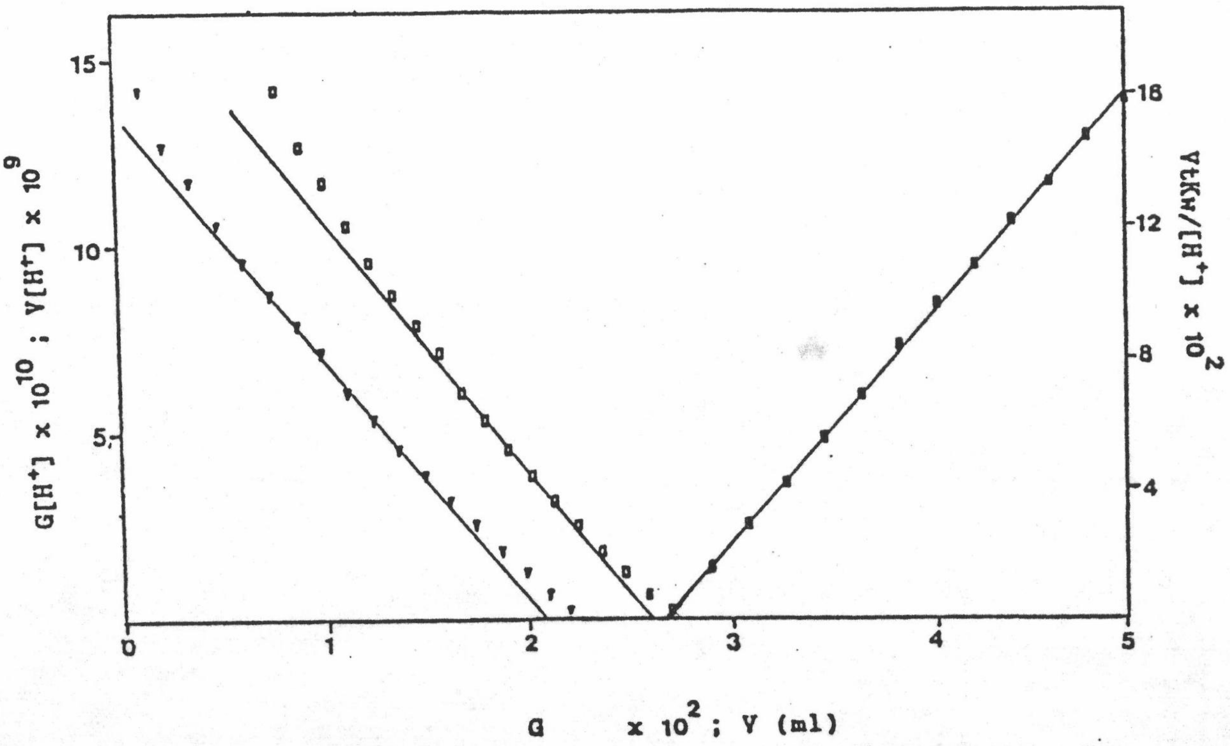

Figure 85 Gran's plot for the titration of diphenhydramine HCl with sodium hydroxide in 60% v/v propylene glycol/water G plot (▼) V plot (□) E plot (■).

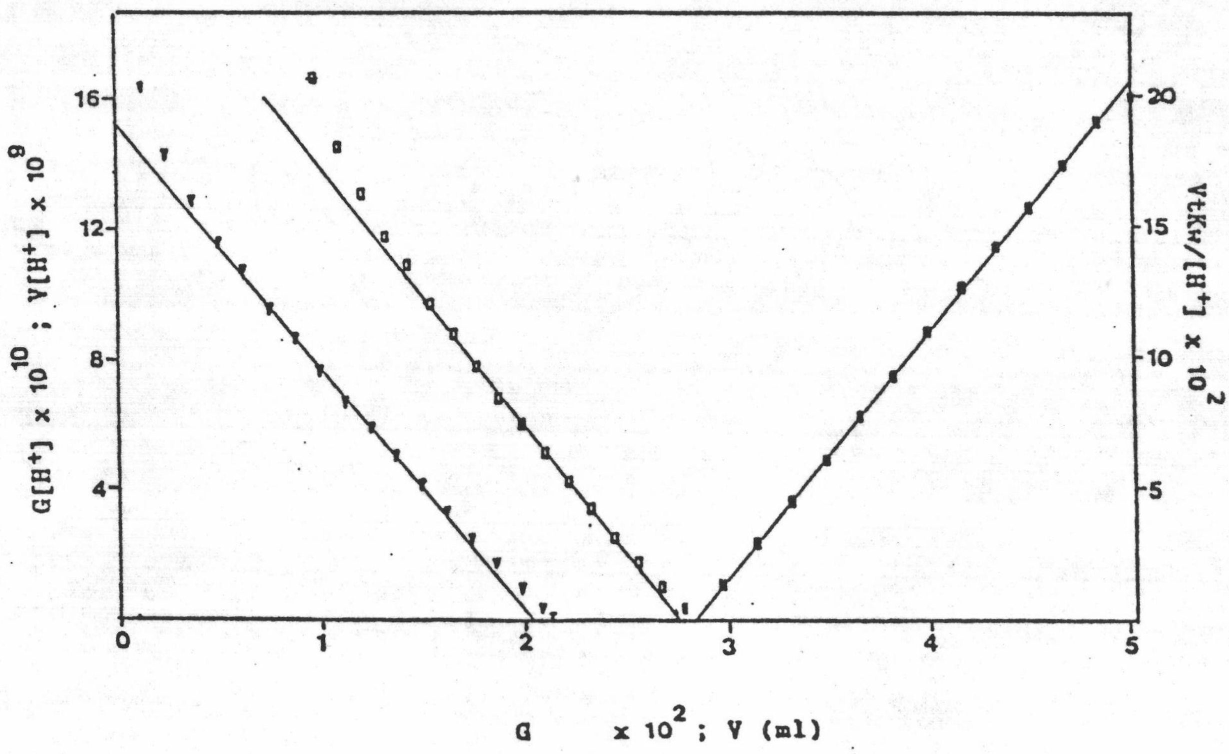

Figure 86 Gran's plot for the titration of diphenhydramine HCl with sodium hydroxide in 70% v/v propylene glycol/water G plot (▼) V plot (□) E plot (■).

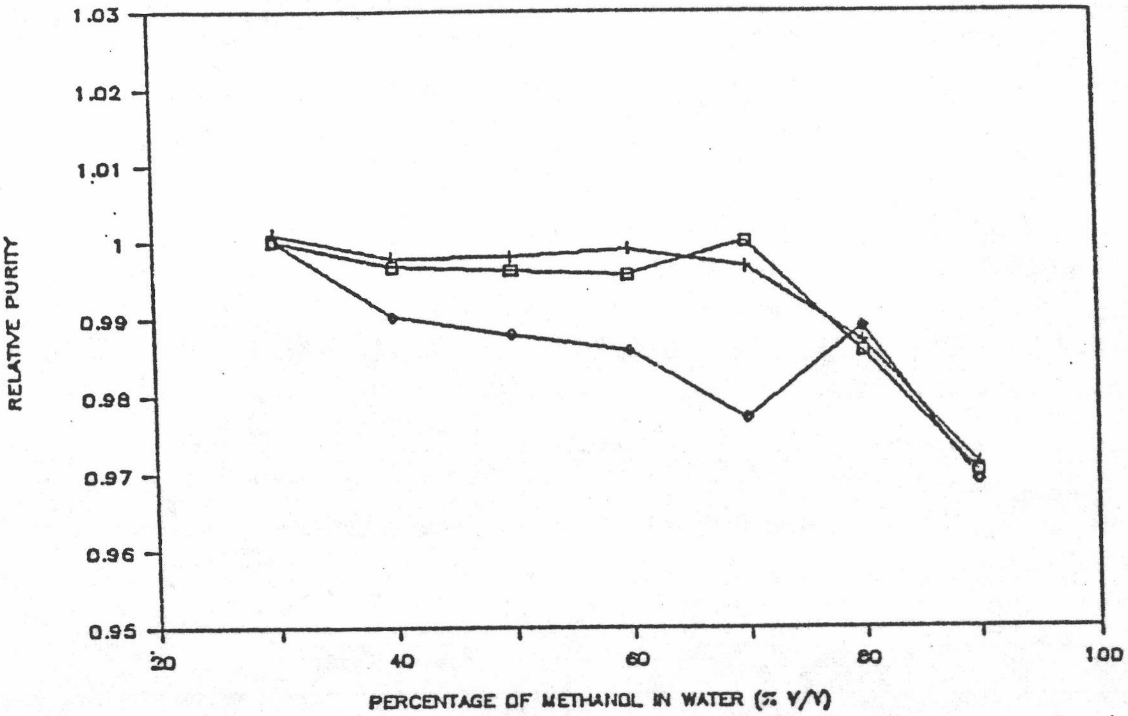

Figure 87 Relative purities of diphenhydramine hydrochloride in methanol-water solvents by using G plot (□) V plot (+) E plot (◇).

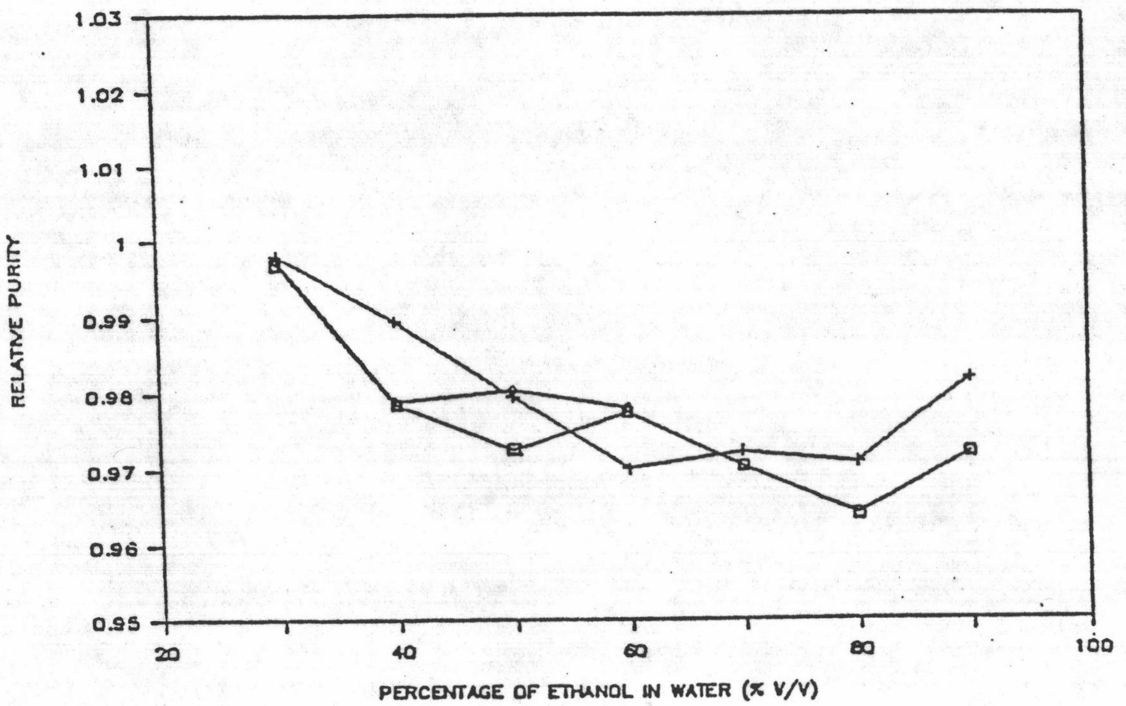

Figure 88 Relative purities of diphenhydramine hydrochloride in ethanol-water solvents by using G plot (□) V plot (+) E plot (◇).

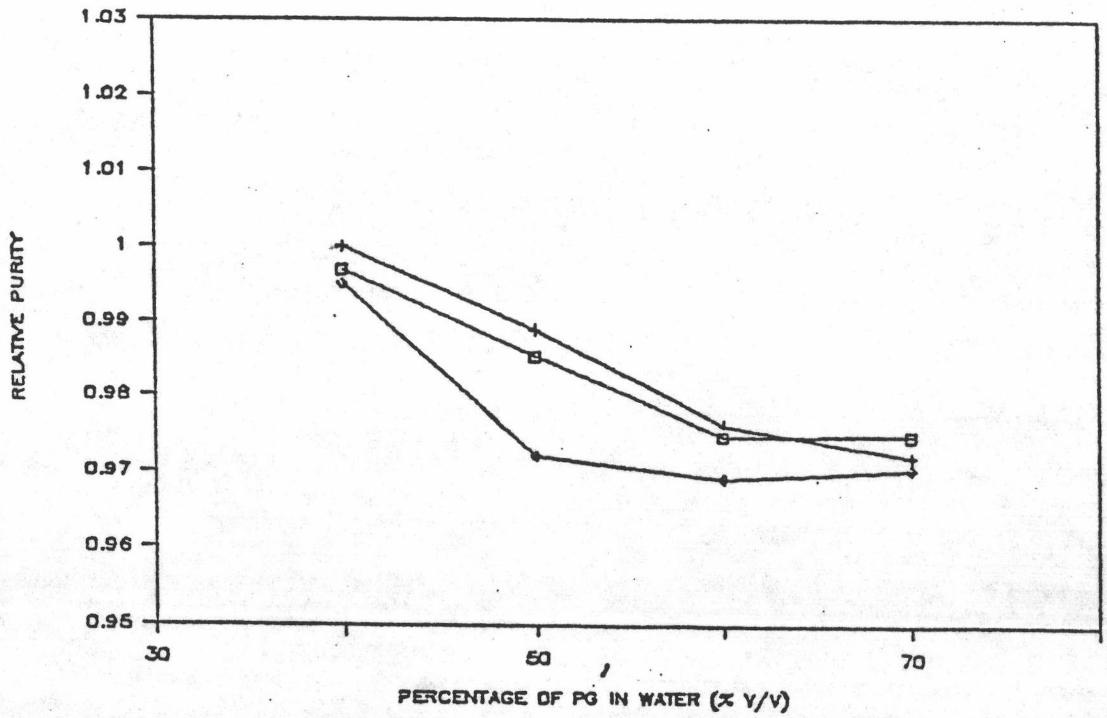

Figure 89 Relative purities of diphenhydramine hydrochloride in propylene glycol-water solvents by using G plot (□) V plot (+) E plot (◊).

interfere with each other, however, the precipitation of chlorpheniramine was observed during the course of titration. By titrating in mixed solvent systems, the problem of precipitation could be avoided but the overlapping of the dissociation constants would occur.

5.1 Methanol-Water System

The titrations were performed in 30-90% v/v methanol/water. Figures 90-96 showed the titration curves of chlorpheniramine maleate with sodium hydroxide in 30-90% v/v methanol/water. G and V plots of this compound showed significant curvatures (Figure 97-103), resulting from overlapping of dissociation constants of protonated chlorpheniramine and second proton from maleic acid. In methanol-water systems, protonated chlorpheniramine could dissociate much better since the formation of unionized product were favored by decreasing the polarity of 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 whose titration product had higher charge than reactants and therfore, the dissociation constant would be lowered when compared with the value in water ($Ka < 10^{-7}$). The resulting effect was that the two dissociation constants would approach each other such that the neutralization of protonated chlorpheniramine and sodium hydroxide would begin while the neutralization reaction of the second

Table 15 Average Percentage Purities by Gran's Method for Titration of Chlorpheniramine Maleate in Methanol-Water Solvent Systems with 0.08184 N NaOH

Solvent (Methanol in water)	Average Percentage Purity (%)			
	G plot	V plot	E plot	USP method **
30%	58.92 (0.31)	58.93 (0.31)	99.74 * (0.22)	
40%	69.46 (0.31)	69.73 (0.38)	100.1 * (0.23)	
50%	90.44 (0.45)	90.49 (0.45)	99.94 * (0.17)	
60%	100.2 * (0.29)	100.3 * (0.17)	99.84 * (0.17)	99.90 * (0.21)
70%	102.6 (0.47)	102.8 (0.22)	100.2 * (0.10)	
80%	97.14 (0.24)	97.72 (0.23)	96.61 (0.23)	
90%	84.48 (0.21)	96.97 (0.45)	96.04 (0.54)	

* Statistically indifference from reference non-aqueous titration at 99% confidence level

** Titrated in glacial acetic acid and mercuric acetate TS with 0.1 N perchloric acid using crystal violet TS as indicator

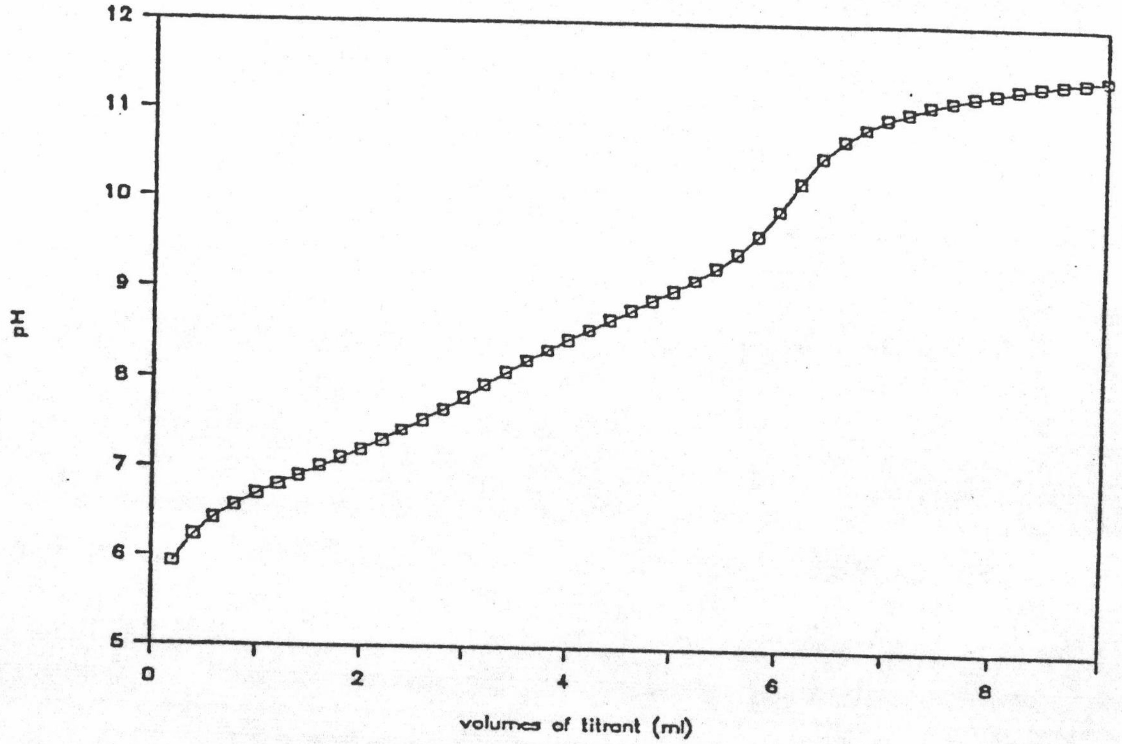

Figure 90 Titration curve of chlorpheniramine maleate with sodium hydroxide in 30% v/v methanol/water

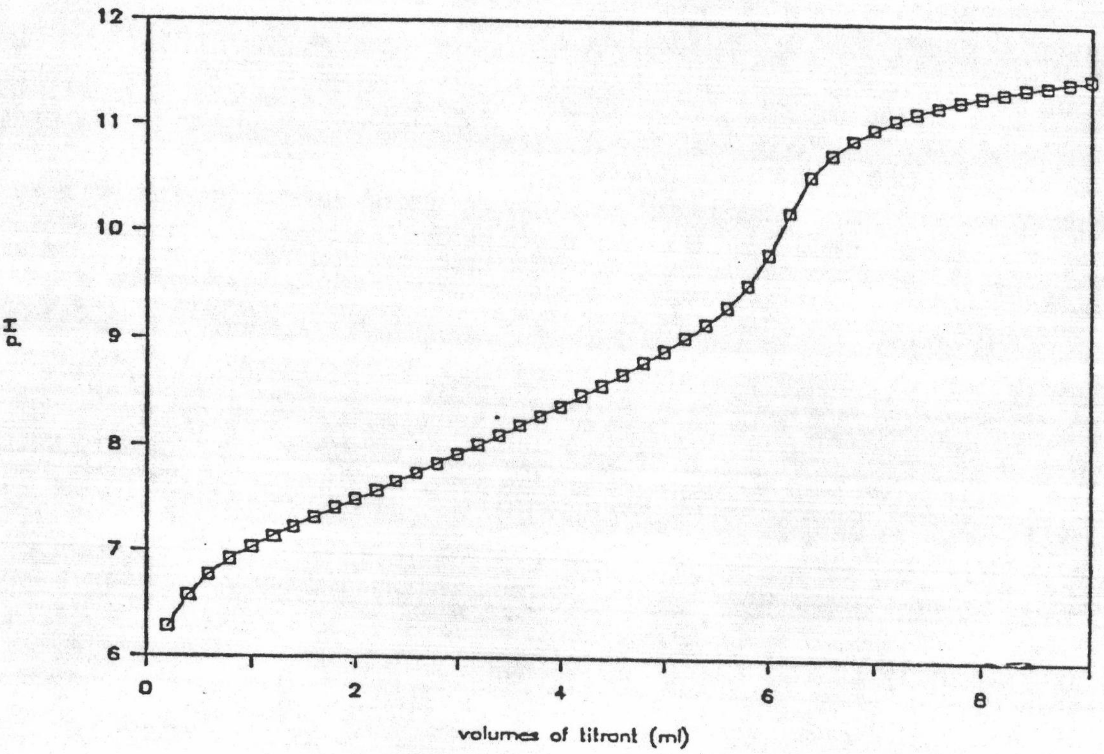

Figure 91 Titration curve of chlorpheniramine maleate with sodium hydroxide in 40% v/v methanol/water

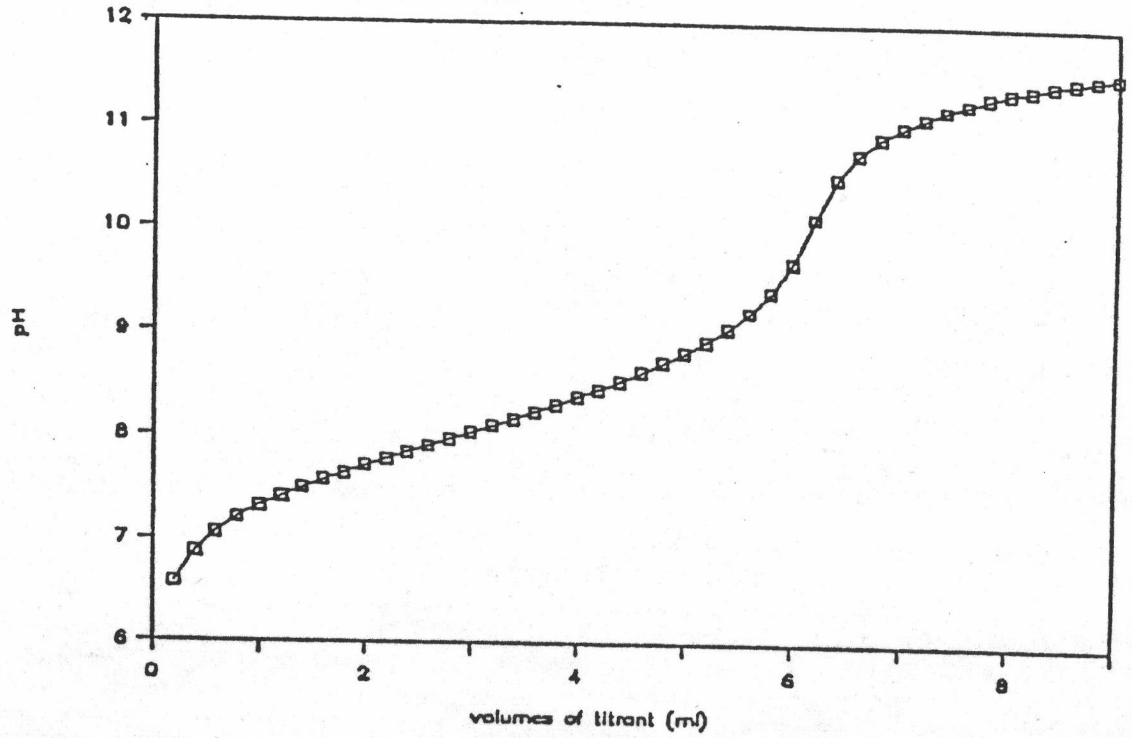

Figure 92 Titration curve of chlorpheniramine maleate with sodium hydroxide in 50% v/v methanol/water

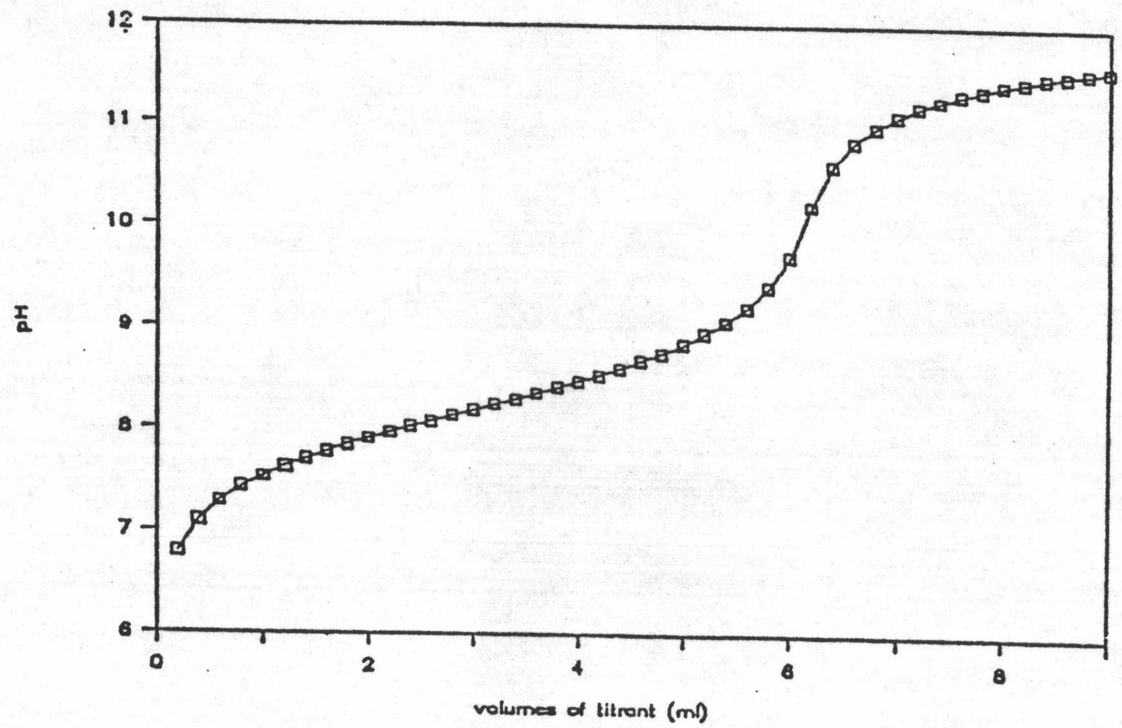

Figure 93 Titration curve of chlorpheniramine maleate with sodium hydroxide in 60% v/v methanol/water

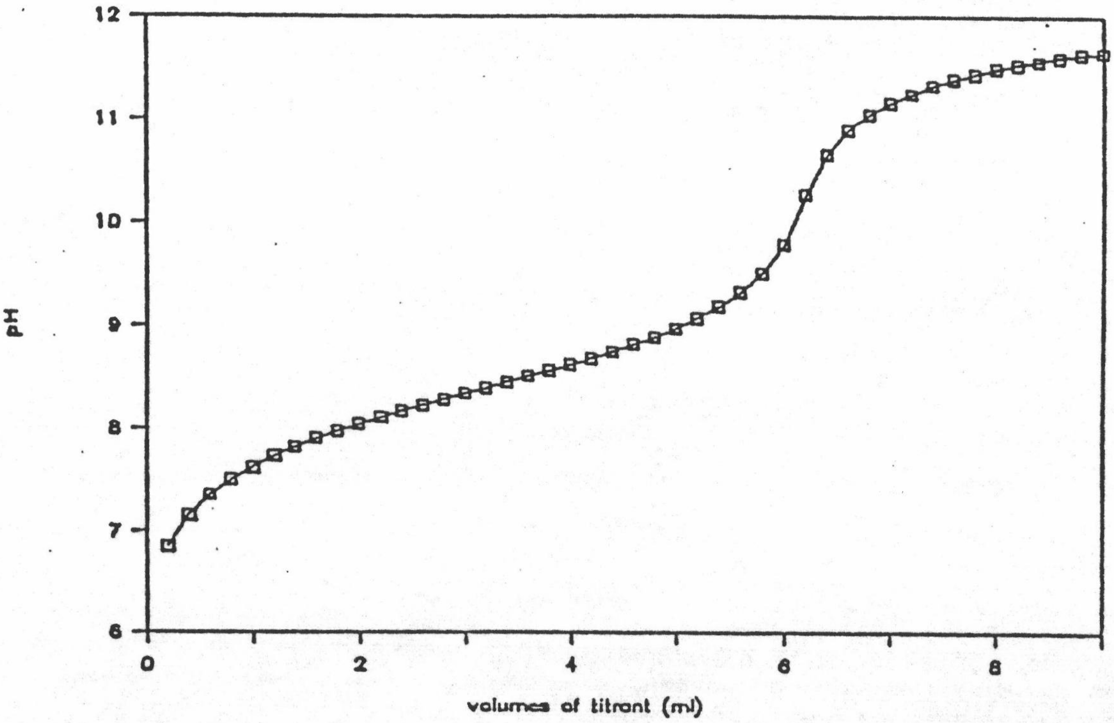

Figure 94 Titration curve of chlorpheniramine maleate with sodium hydroxide in 70% v/v methanol/water

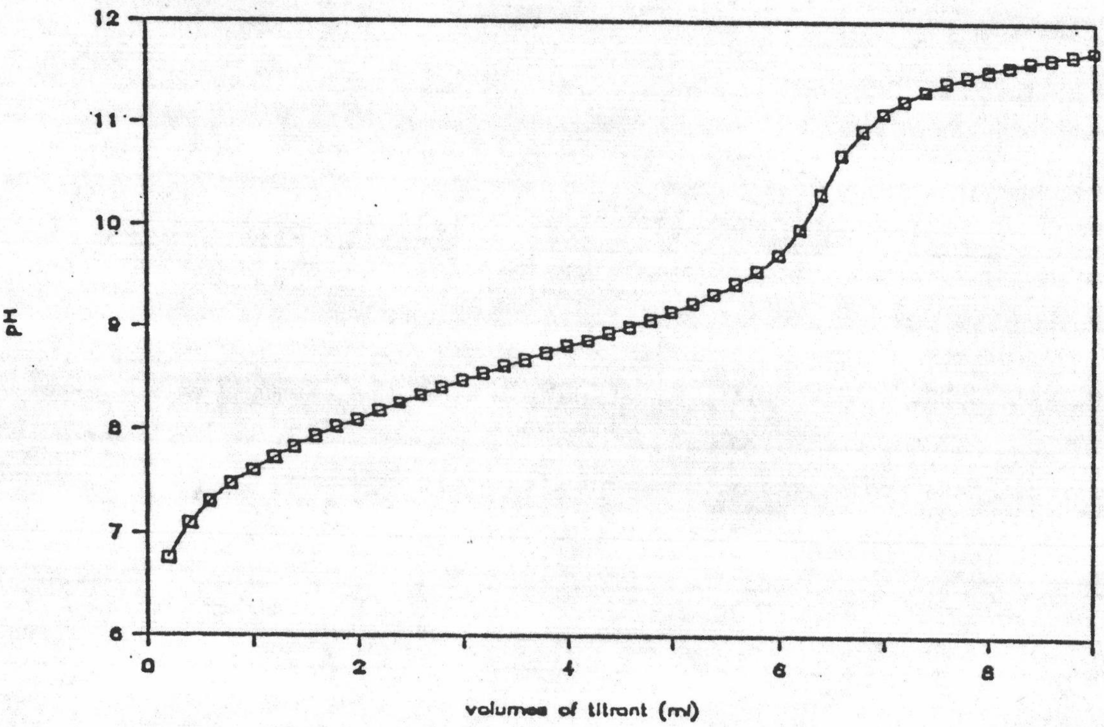

Figure 95 Titration curve of chlorpheniramine maleate with sodium hydroxide in 80% v/v methanol/water

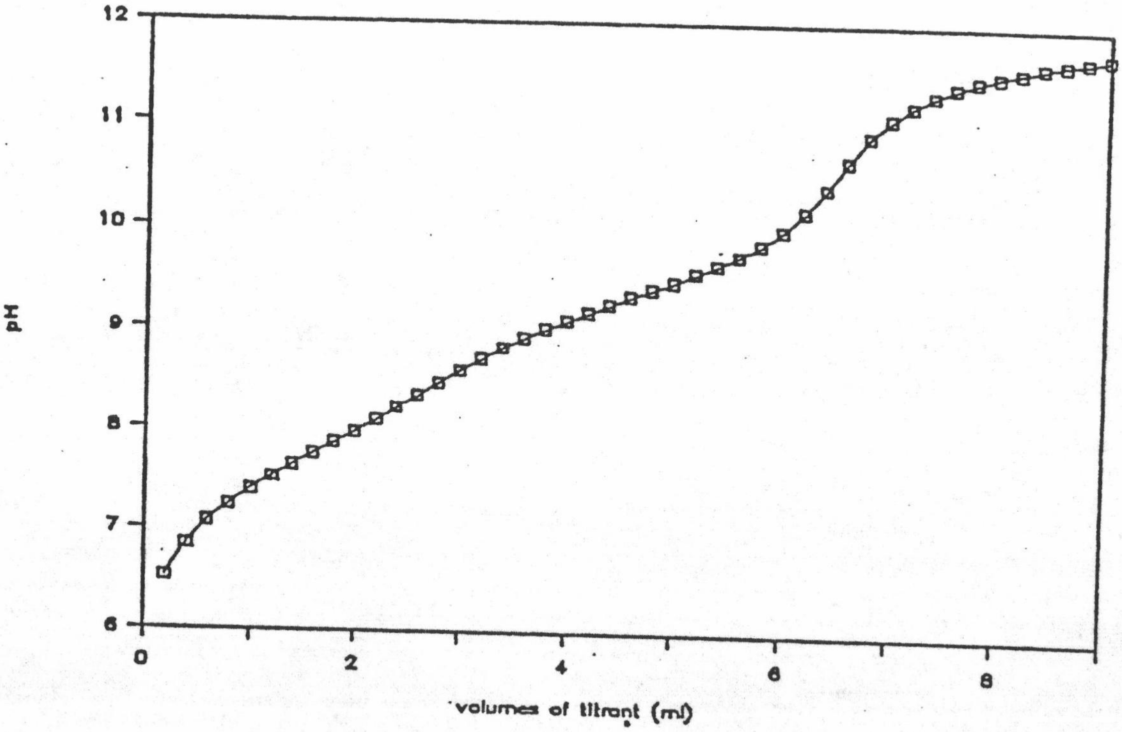

Figure 96 Titration curve of chlorpheniramine maleate with sodium hydroxide in 90% v/v methanol/water

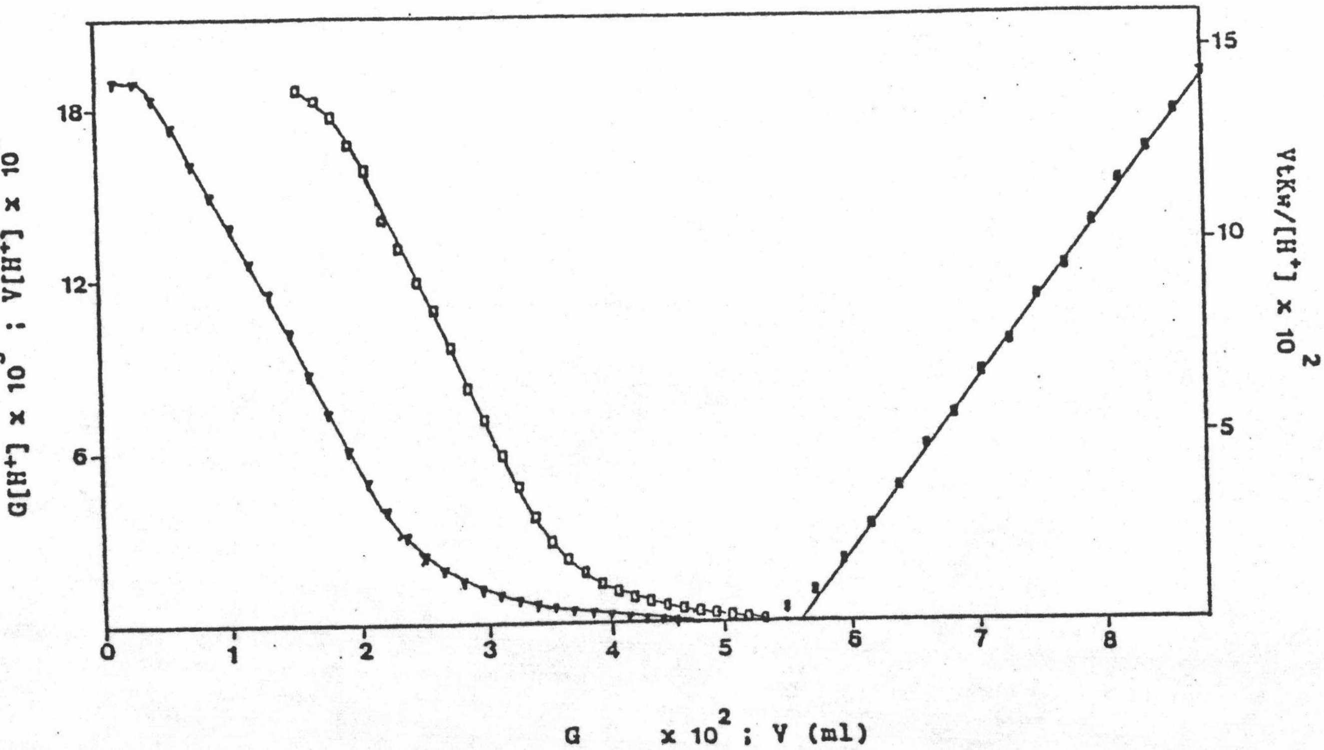

Figure 97 Gran's plot for the titration of chlorpheniramine maleate with sodium hydroxide in 30% v/v methanol/water G plot (▼) V plot (□) E plot (■).

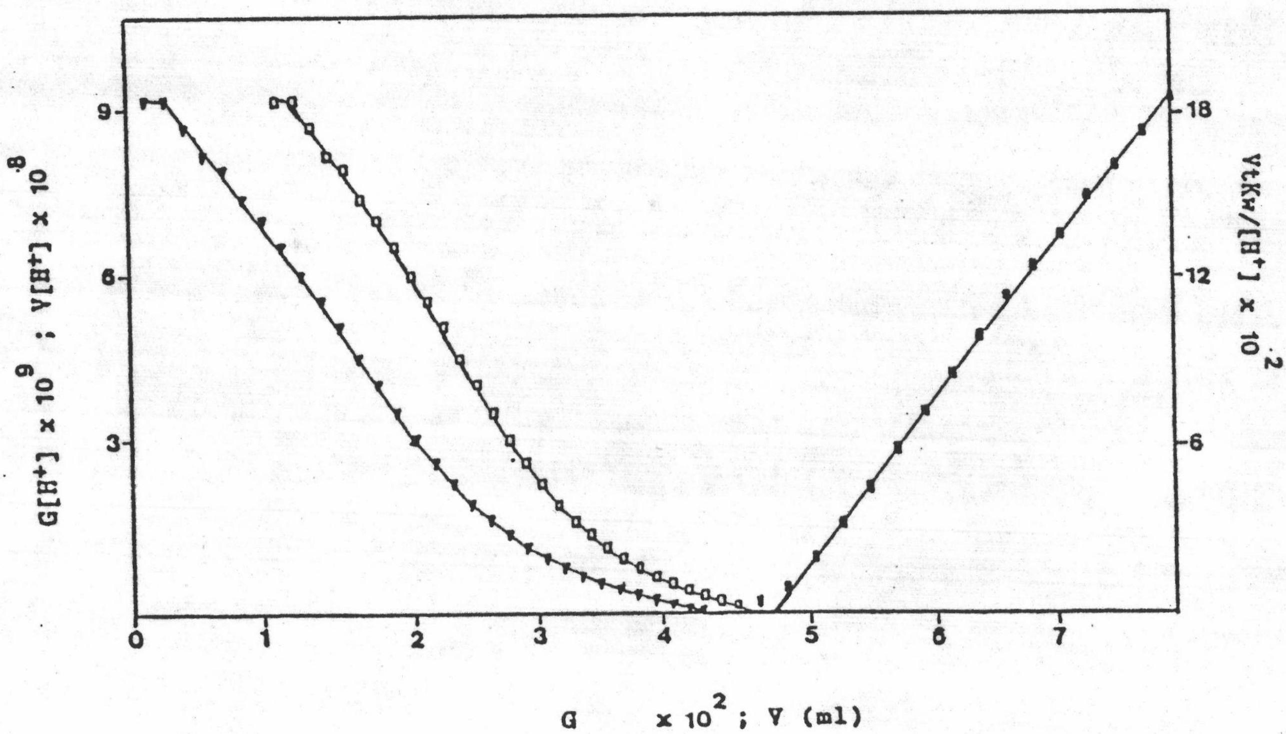

Figure 98 Gran's plot for the titration of chlorpheniramine maleate with sodium hydroxide in 40% v/v methanol/water G plot (▼) V plot (□) E plot (■).

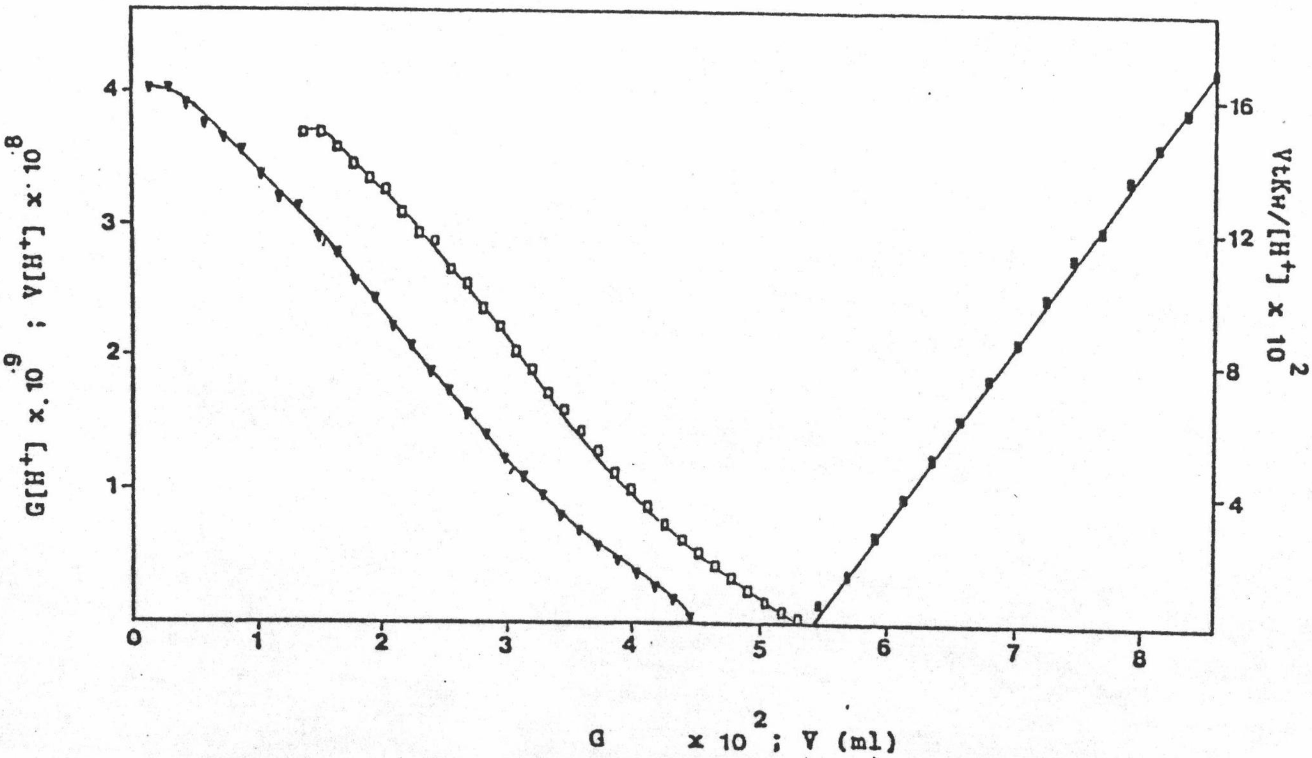

Figure 99 Gran's plot for the titration of chlorpheniramine maleate with sodium hydroxide in 50% v/v methanol/water G plot (▼) V plot (□) E plot (■).

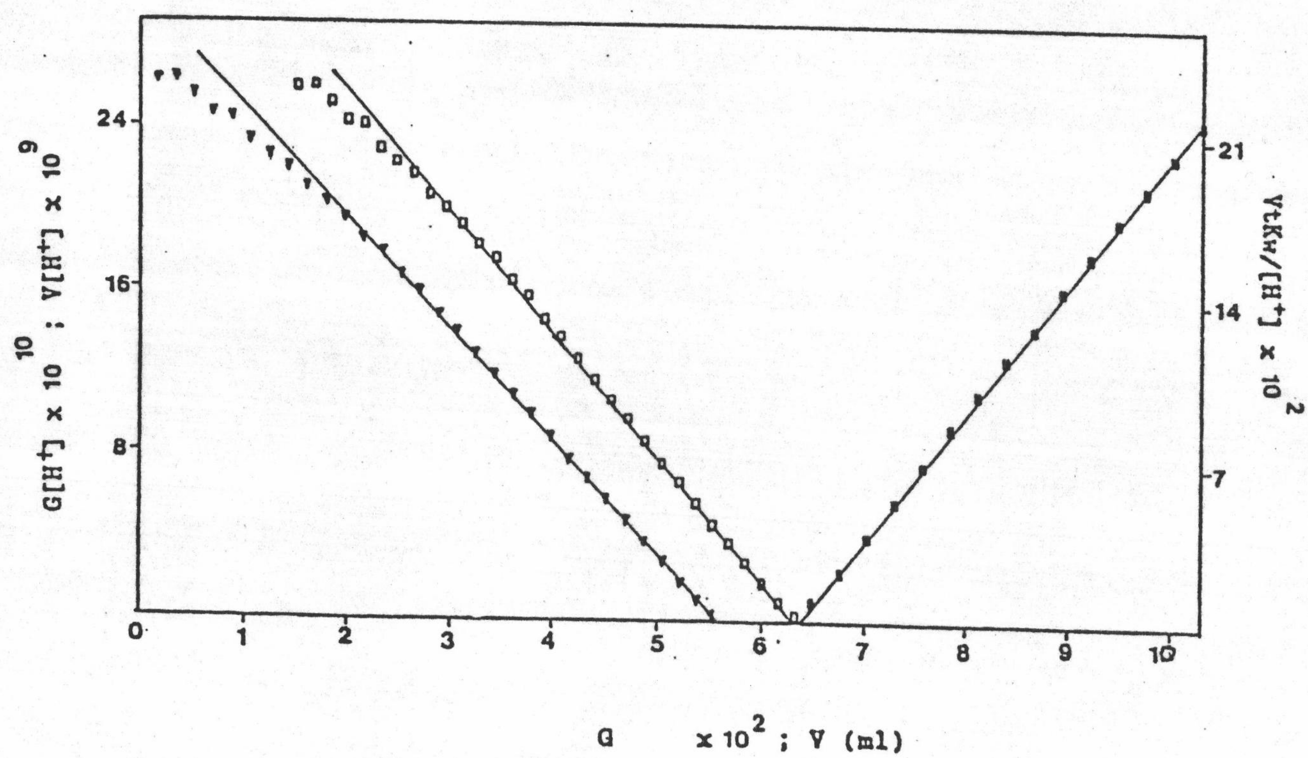

Figure 100 Gran's plot for the titration of chlorpheniramine maleate with sodium hydroxide in 60% v/v methanol/water G plot (▼) V plot (□) E plot (■).

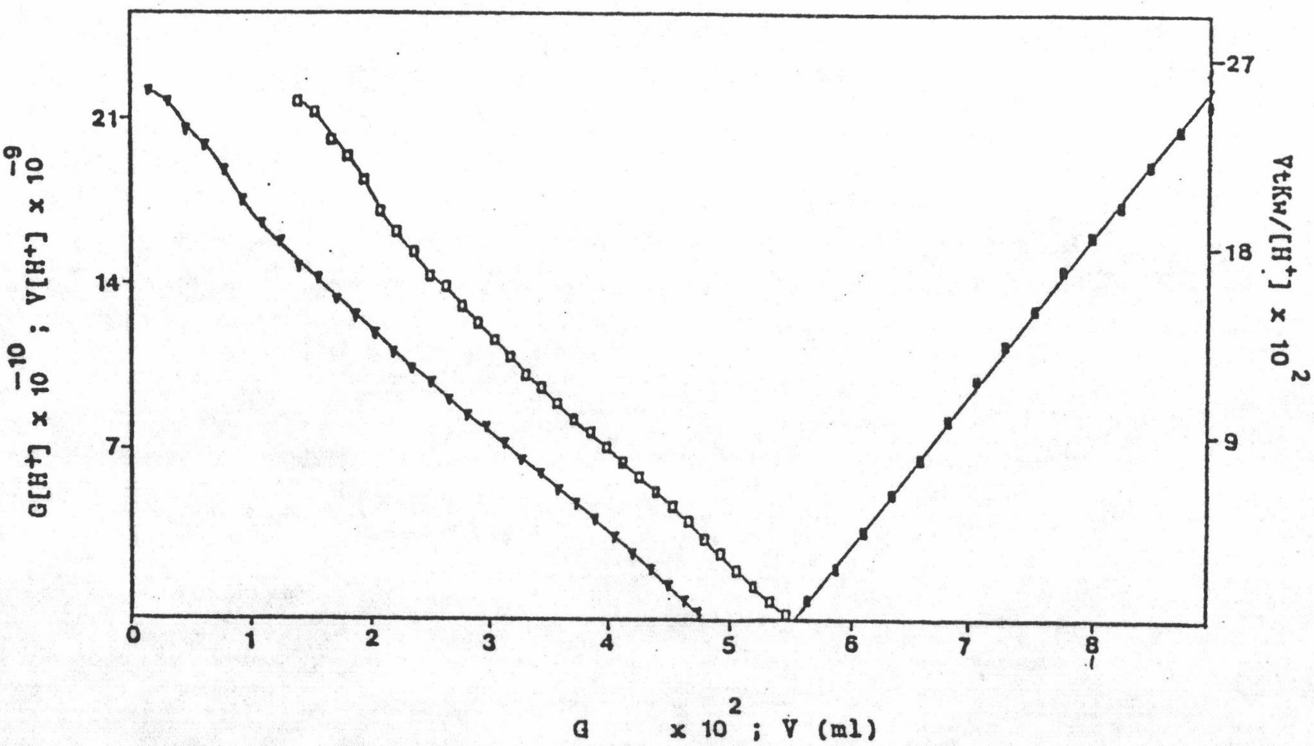

Figure 101 Gran's plot for the titration of chlorpheniramine maleate with sodium hydroxide in 70% v/v methanol/water G plot (▼) V plot (□) E plot (■).

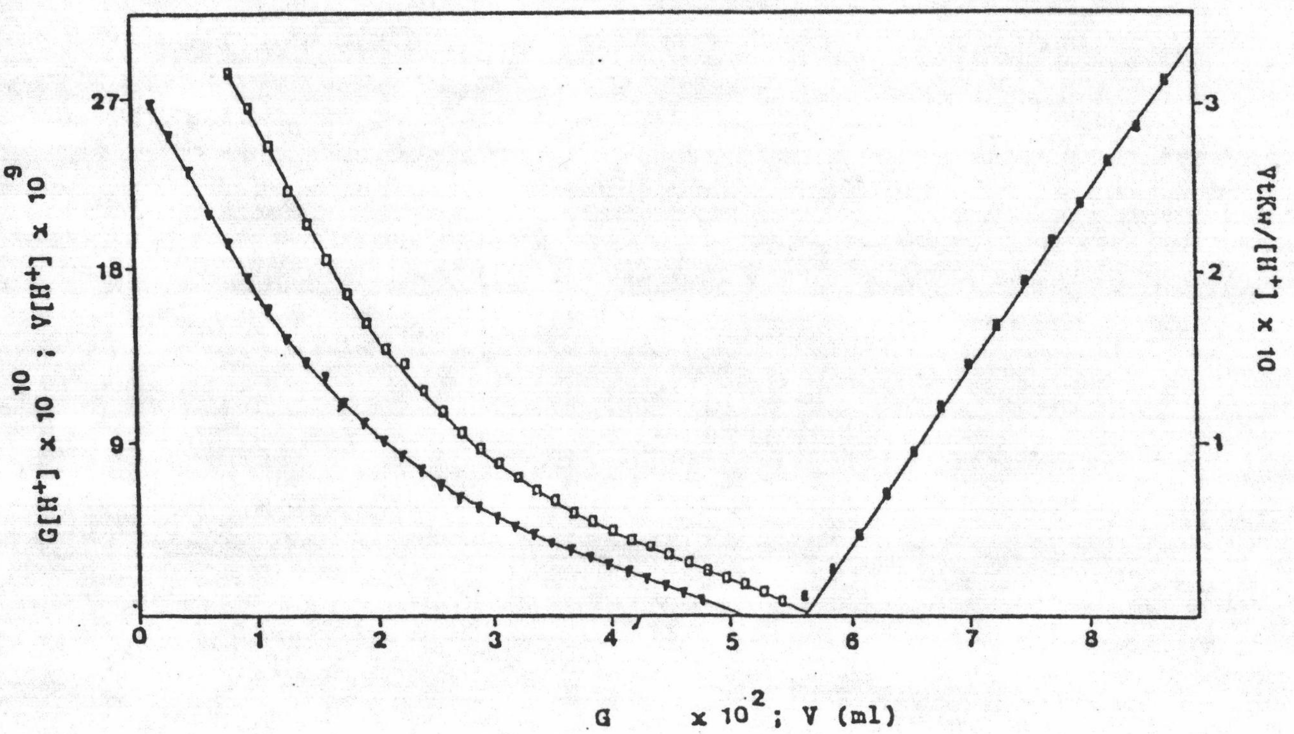

Figure 102 Gran's plot for the titration of chlorpheniramine maleate with sodium hydroxide in 80% v/v methanol/water G plot (▼) V plot (□) E plot (■).

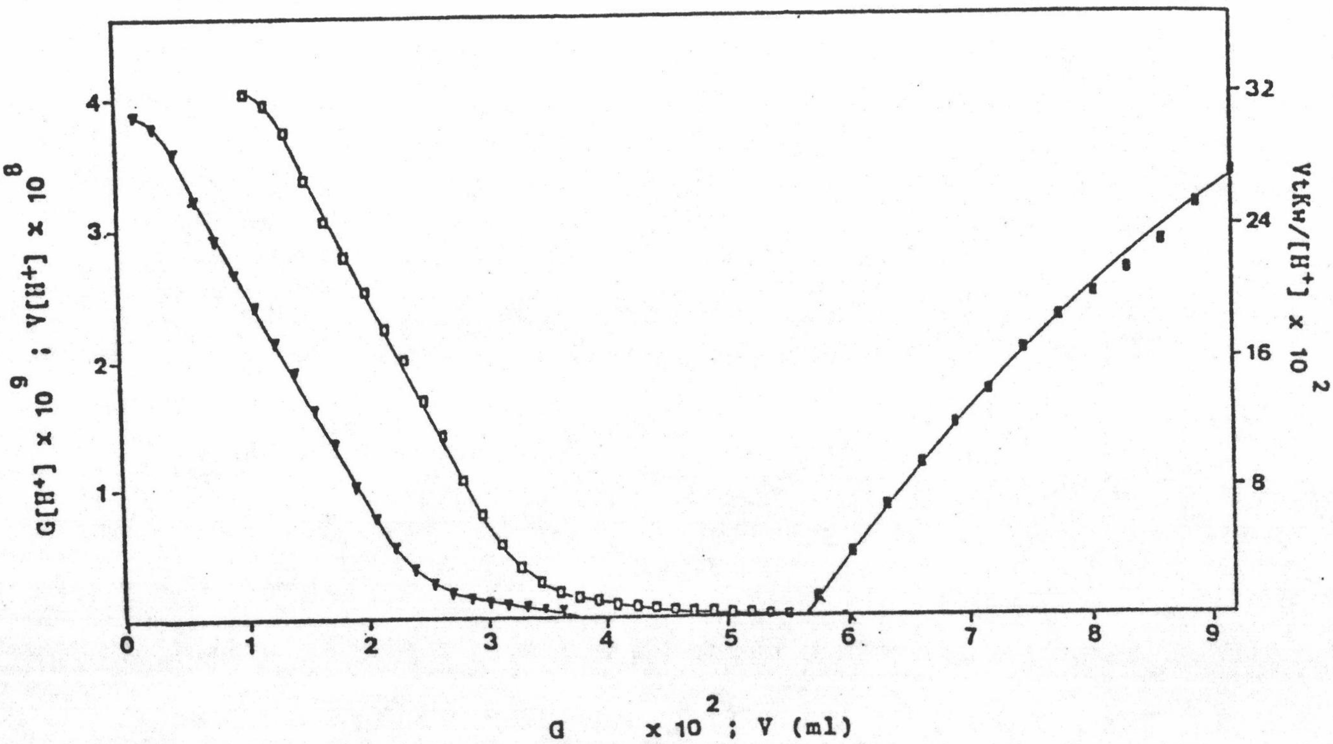

Figure 103 Gran's plot for the titration of chlorpheniramine maleate with sodium hydroxide in 90% v/v methanol/water G plot (▼) V plot (□) E plot (■).

proton of maleic acid and sodium hydroxide was occurring.

The titration curves of chlorpheniramine maleate showed only one inflection point for the titration in 30-90% v/v methanol/water (Figures 90-96). Hence, Eqs. (31), (40), (41), and (42) would be invalid. By using Eqs. (11) and (14), Figures 97-99 showed that G and V plots were curved for the titrations in 30-50% v/v methanol/water. This also due to the overlapping of two dissociation constants of chlorpheniramine maleate. However, for the titration in 60% v/v methanol/water, Figure 100, G and V plots were linear and the percentage purities of chlorpheniramine maleate could be calculated from the end point volumes which obtained from the extrapolation, as shown in Table 15. This might be resulting from the two dissociation constants of chlorpheniramine maleate were shifted to approximately the same value, which would suggest that the neutralization of protonated chlorpheniramine and the second proton of maleic acid were occurring simultaneously when methanol concentration reached approximately 60% v/v methanol/water. For the titrations in 70-90% v/v methanol/water, G and V plots were curved again, this probably resulting from the first dissociation of the second proton of maleic acid was shifted to be lower than that from the titrations in 30-60% v/v methanol/water and to be lower than the second dissociation constant of protonated chlorpheniramine which was shifted to higher value. However, the difference of these two dissociation constants was not large enough and therefore the neutralization of the second proton of maleic acid and of the protonated chlorpheniramine would still interfere with each other (Figures 101-103). The percentage purities of chlorpheniramine maleate for the titrations in 30-50% and 70-90% v/v methanol/water which calculated from G and V plots were significantly different from non-aqueous titration due to the overlapping of the two dissociation constants resulting on curvature of the plots.

By using E plot in the determination of equivalence volume (Table 15) for titrations of chlorpheniramine in 30-70% v/v methanol/water, the resulting percentage purities were statistically indifferent from that obtained by non-aqueous method. These results were same as the titration of triprolidine HCl and quinine sulfate in methanol-water systems which was as expected since E plot utilized only data obtained after equivalence points.

5.2 Ethanol-Water System

The titrations were performed in 30-90% v/v ethanol/water. Figures 104-110 showed the titration curves of chlorpneniramine maleate with sodium hydroxide in 30-90% v/v ethanol/water. In the same manner as the titration in methanol-water systems, the overlapping of two dissociation constants had occurred. Figures 111-117 showed G and V plots in 30-50% and 70-90% v/v ethanol/water. Significant curvatures were observed in these plots. As in methanol/water solvent system, the optimum solvent system was found to be 60% v/v ethanol/water. The percentage purity calculated from G and V plot was statistically same as that obtained by non-aqueous titration (Table 16).

By using E plot, the percentage purities of chlorpheniramine maleate for the titration in 30-70% v/v ethanol/water were significantly different from non-aqueous method. This was probably due to the alkaline error, since the pH for the titration in these regions was very high (more than 12).

5.3 Propylene Glycol-Water System

The titrations were conducted in 30-70% v/v propylene glycol/water. Figures 118-122 showed the titration curves of chlorpheniramine maleate with sodium hydroxide in 30-70% v/v propylene glycol/water. These looked similar to the titrations in methanol/water and ethanol/water systems. G and V plots were linear for the titration in 70% v/v propylene glycol/water as shown in figures 123-127. However, the accurate percentage purities of chlorpheniramine maleate for the titration

Table 16 Average Percentage Purities by Gran's Method for Titration of Chlorpheniramine Maleate in Ethanol-Water Solvent Systems with 0.08137 N NaOH

Solvent (Ethanol in water)	Average Percentage Purity (%)			
	G plot	V plot	E plot	USP method **
30%	62.35 (0.29)	62.56 (0.08)	98.64 (0.21)	
40%	84.38 (0.53)	84.18 (0.33)	98.41 (0.13)	
50%	98.67 (0.12)	99.00 (0.18)	98.84 (0.36)	
60%	99.99 * (0.15)	100.1 * (0.11)	98.60 (0.17)	99.90 * (0.21)
70%	98.00 (0.27)	99.22 (0.19)	98.90 (0.18)	
80%	96.75 (0.15)	98.16 (0.39)	-	
90%	92.64 (0.50)	96.58 (0.12)	-	

* Statistically indifference from reference non-aqueous titration at 99% confidence level

** Titrated in glacial acetic acid and mercuric acetate TS with 0.1 N perchloric acid using crystal violet TS as indicator

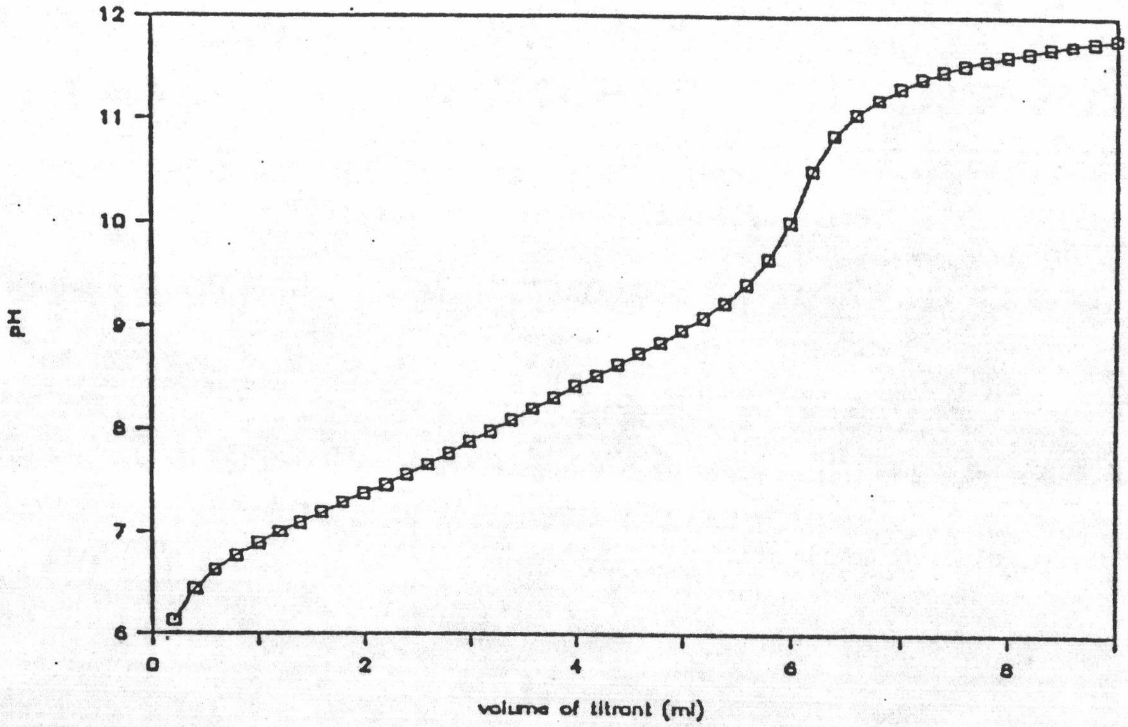

Figure 104 Titration curve of chlorpheniramine maleate with sodium hydroxide in 30% v/v ethanol/water

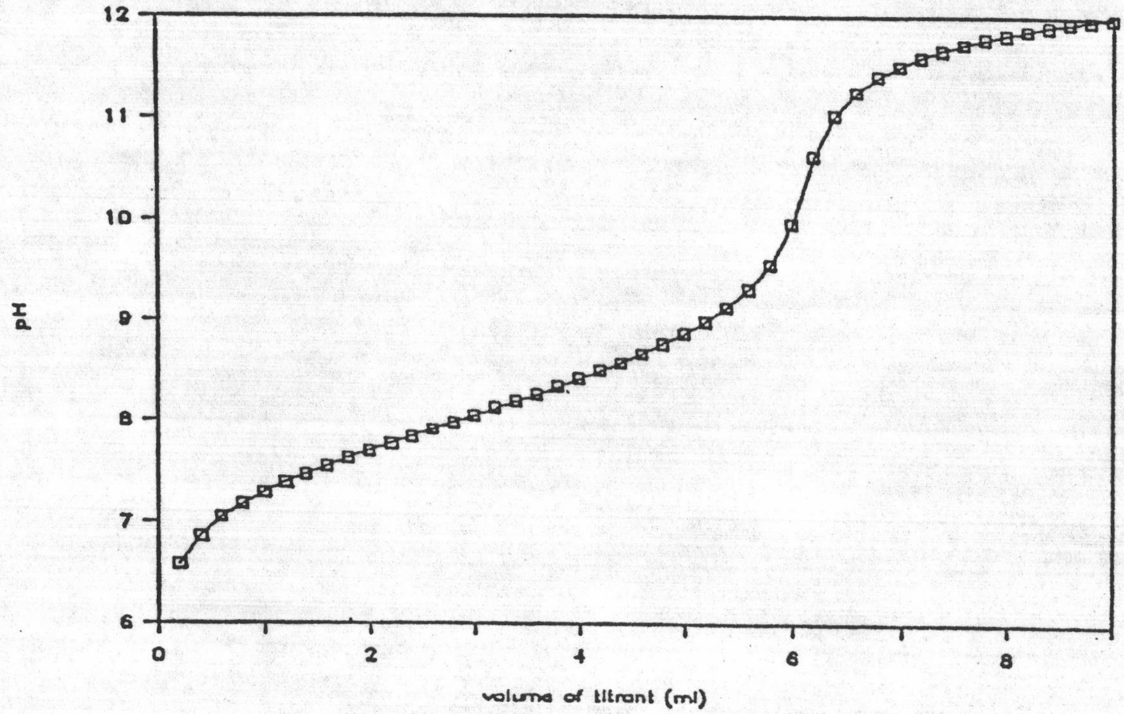

Figure 105 Titration curve of chlorpheniramine maleate with sodium hydroxide in 40% v/v ethanol/water

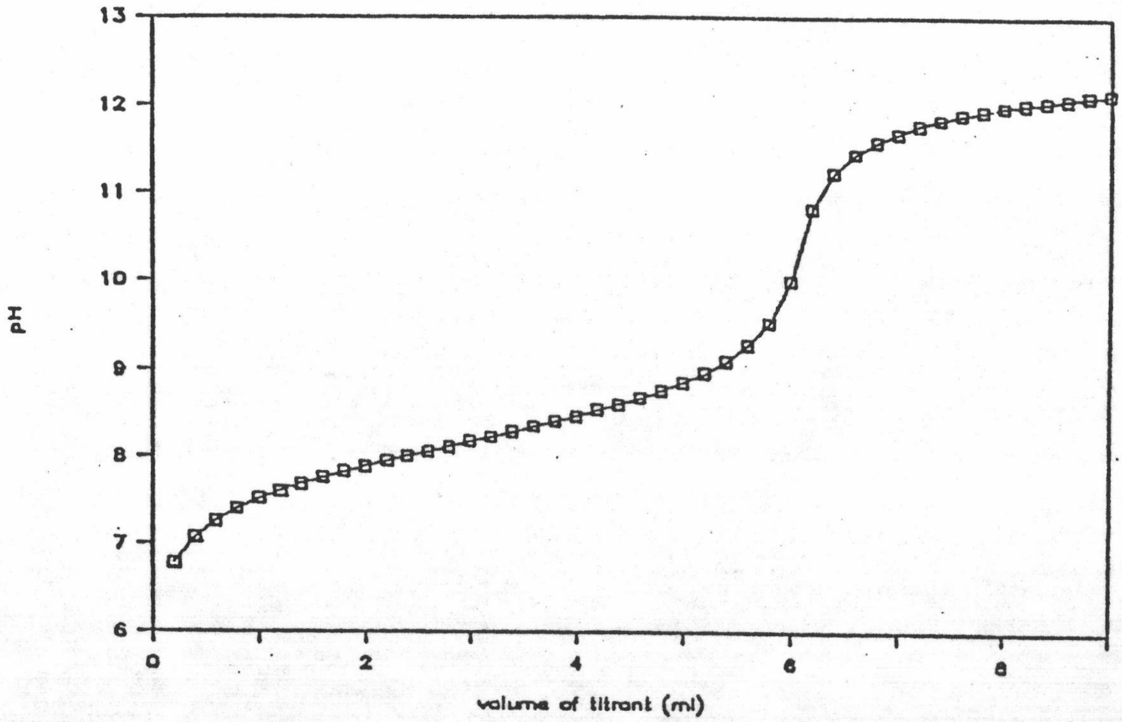

Figure 106 Titration curve of chlorpheniramine maleate with sodium hydroxide in 50% v/v ethanol/water

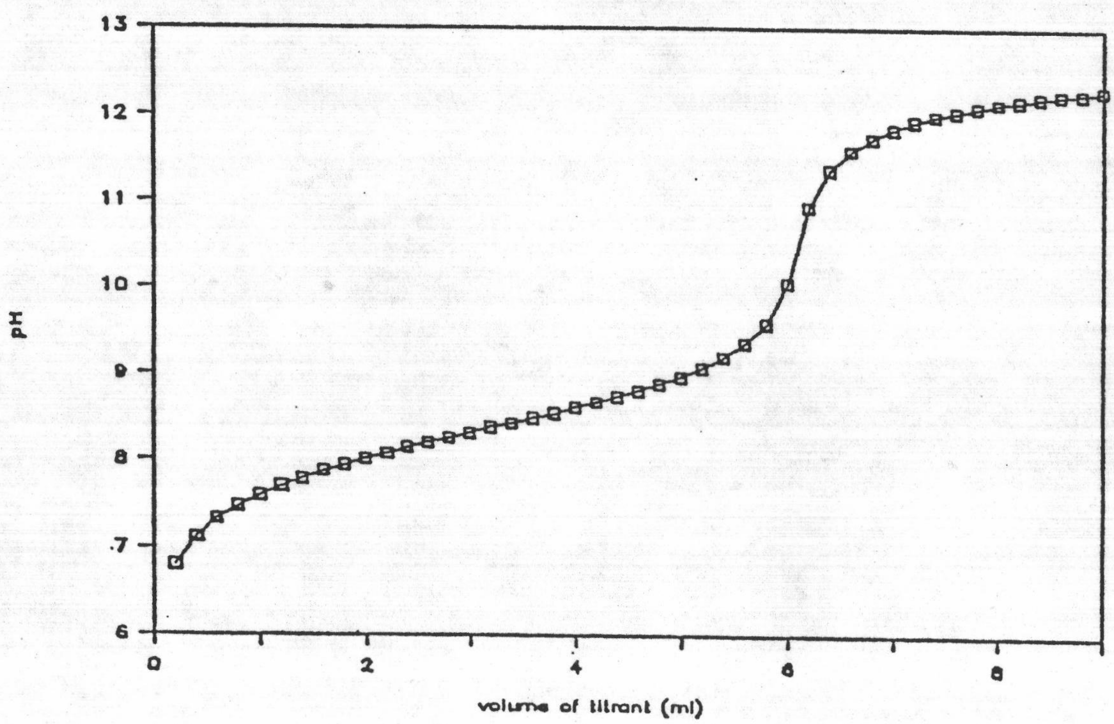

Figure 107 Titration curve of chlorpheniramine maleate with sodium hydroxide in 60% v/v ethanol/water

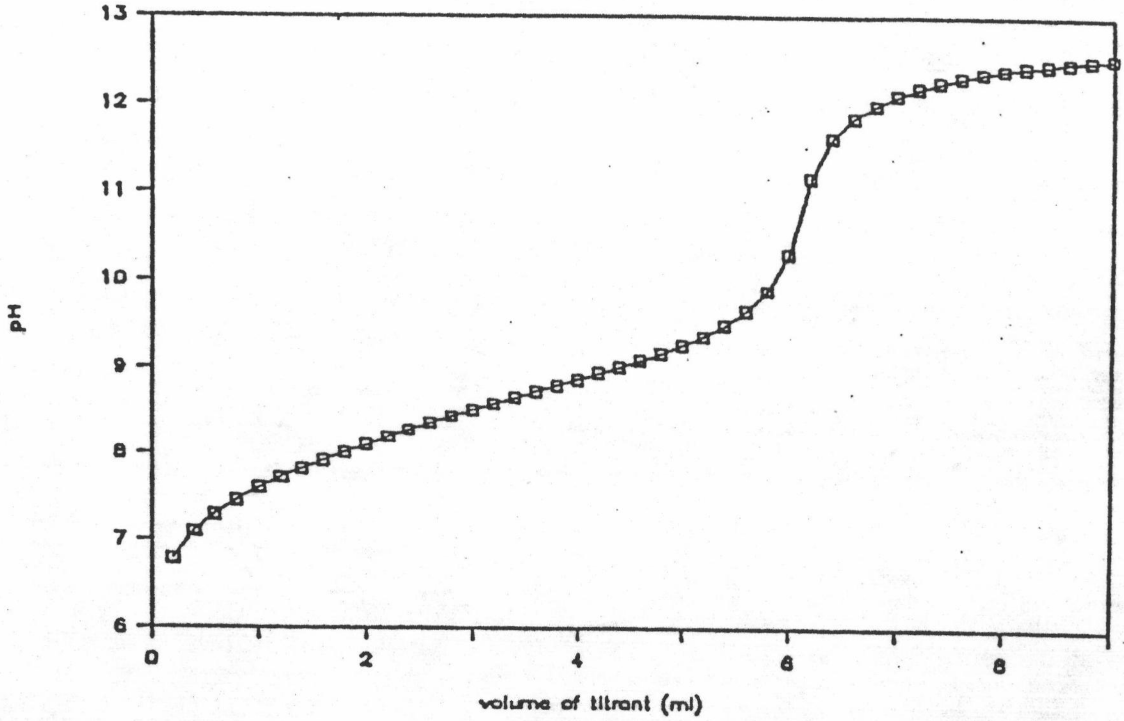

Figure 108 Titration curve of chlorpheniramine maleate with sodium hydroxide in 70% v/v ethanol/water

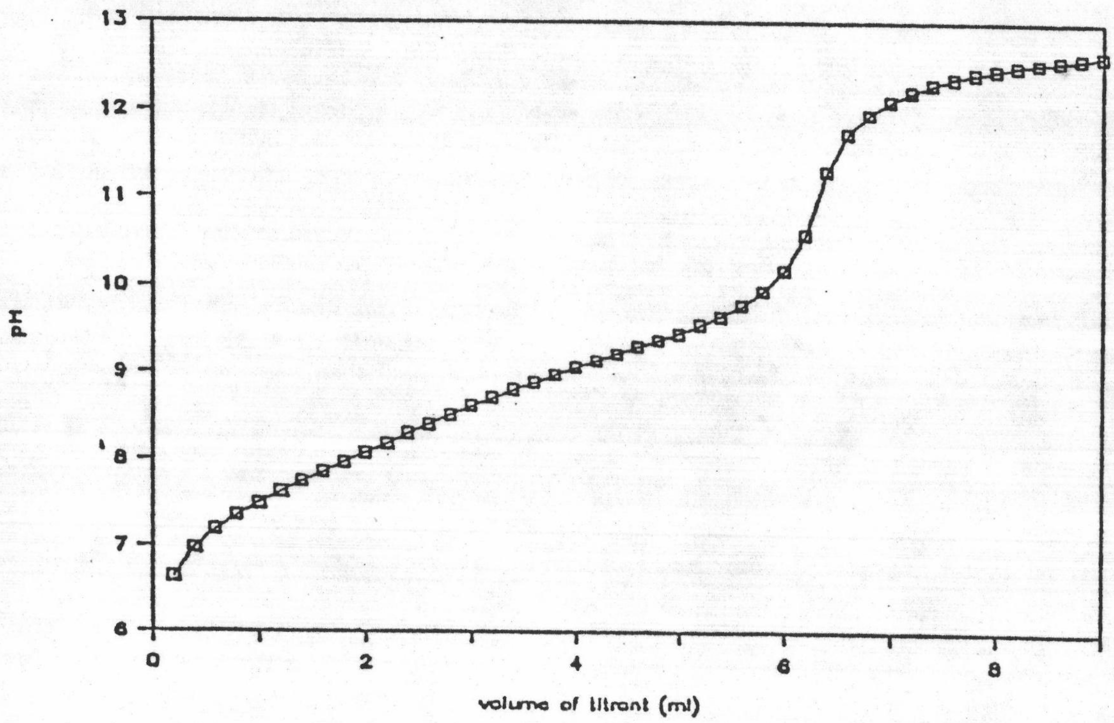

Figure 109 Titration curve of chlorpheniramine maleate with sodium hydroxide in 80% v/v ethanol/water

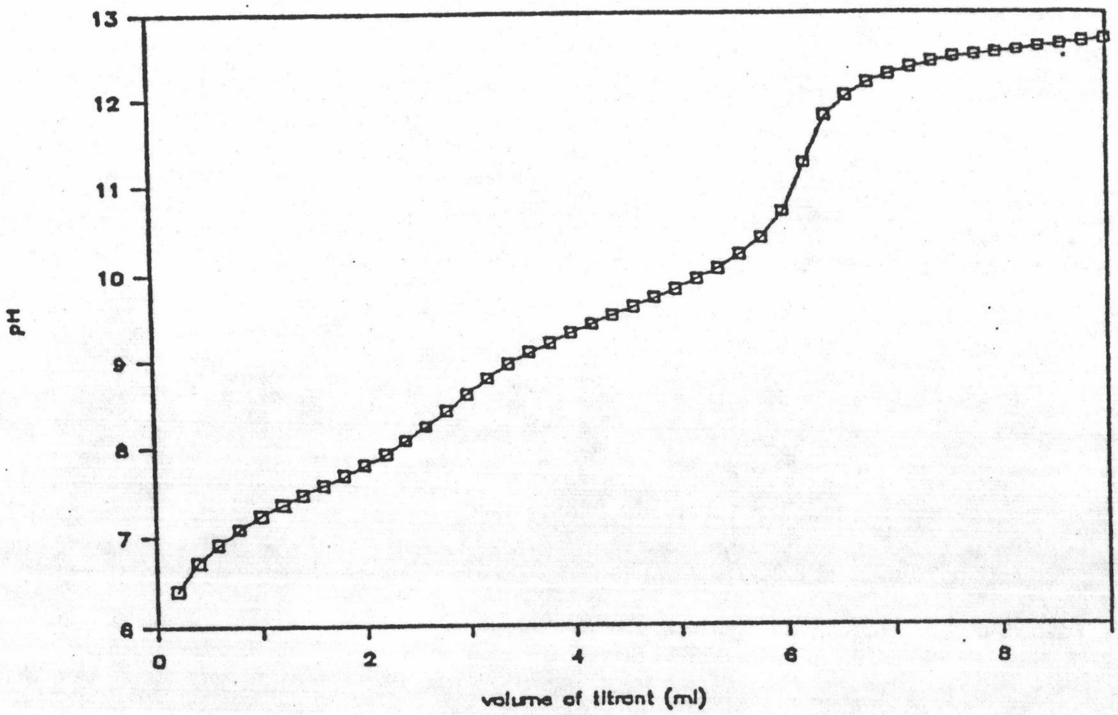

Figure 110 Titration curve of chlorpheniramine maleate with sodium hydroxide in 90% v/v ethanol/water

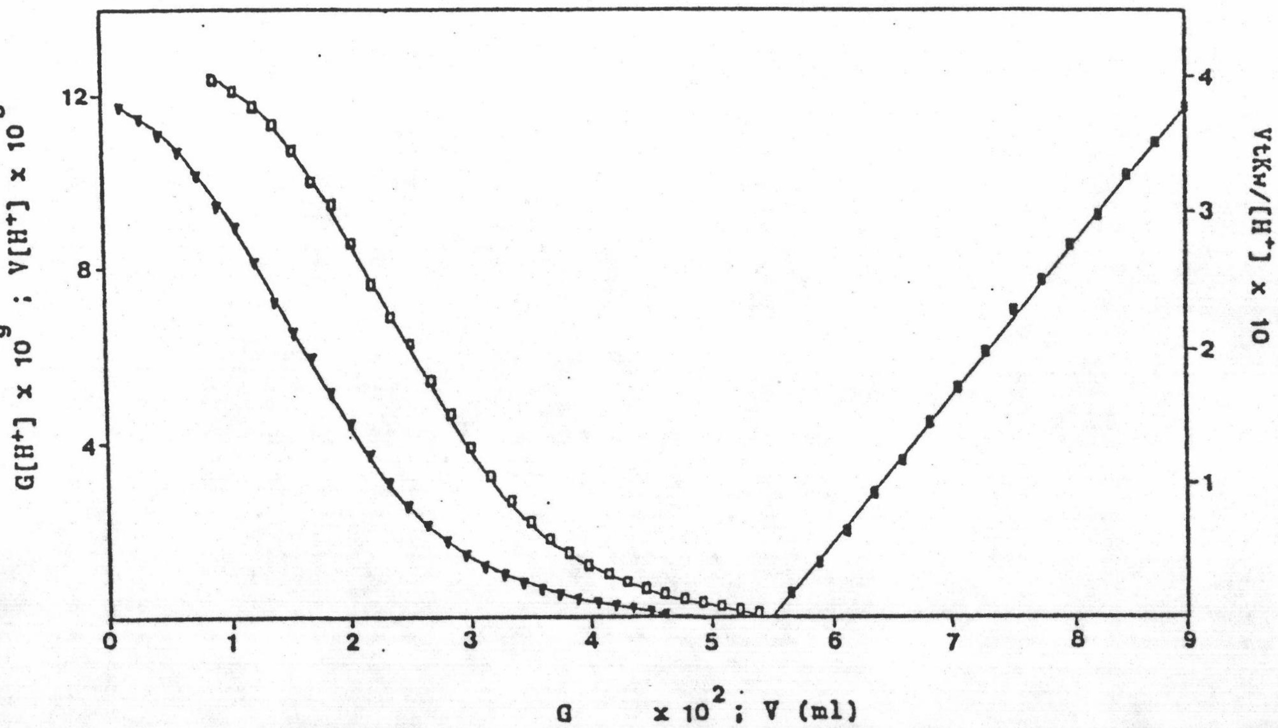

Figure 111 Gran's plot for the titration of chlorpheniramine maleate with sodium hydroxide in 30% v/v ethanol/water G plot (▼) V plot (□) E plot (▪).

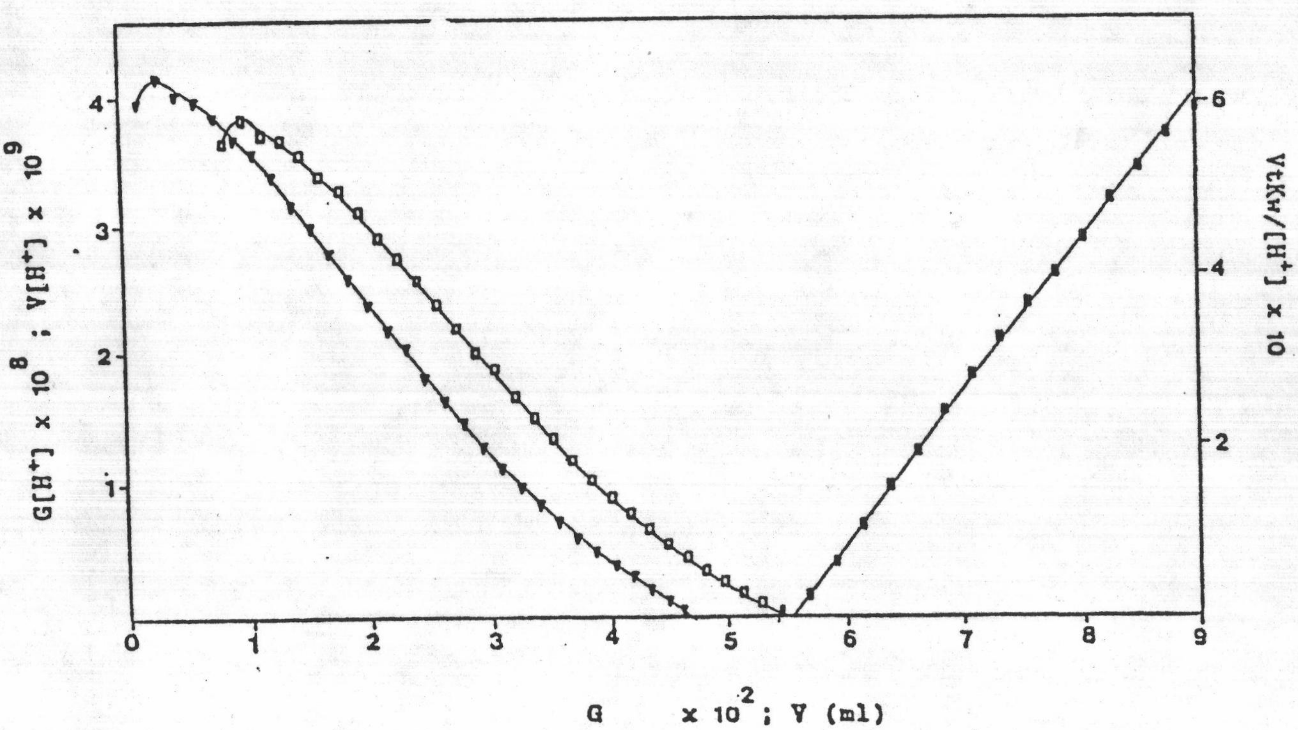

Figure 112 Gran's plot for the titration of chlorpheniramine maleate with sodium hydroxide in 40% v/v ethanol/water G plot (▼) V plot (□) E plot (▪).

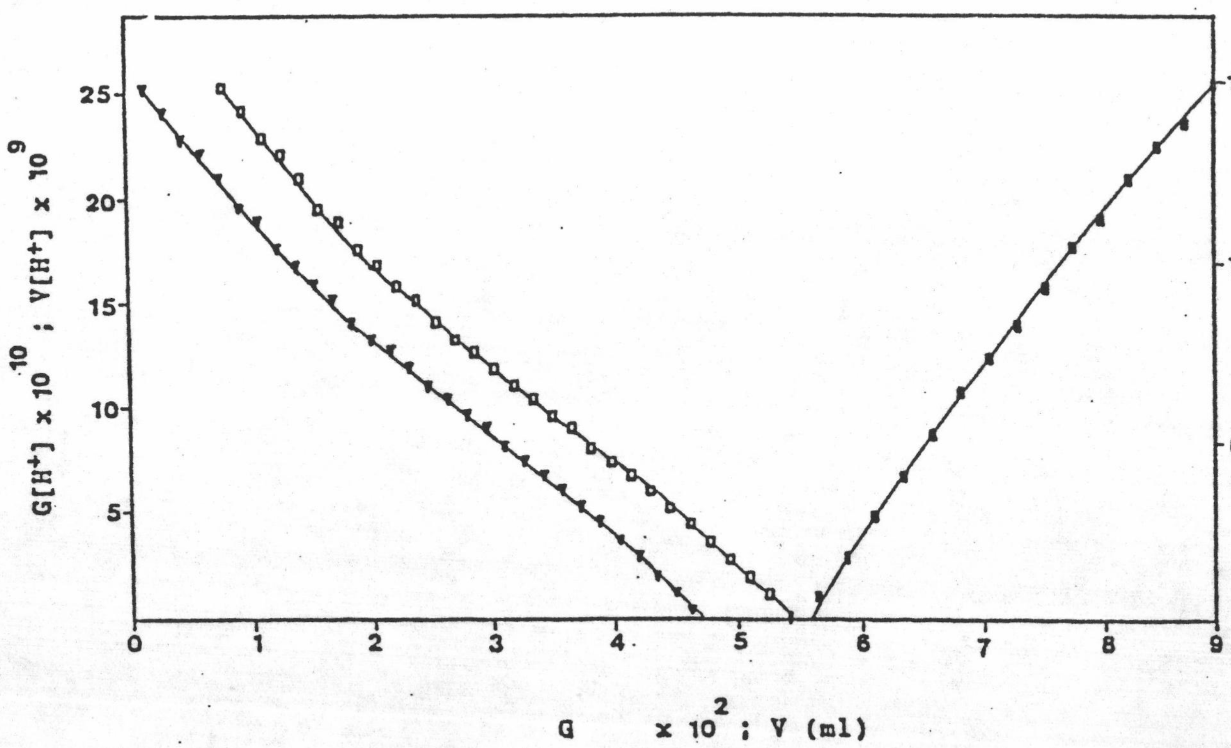

Figure 113 Gran's plot for the titration of chlorpheniramine maleate with sodium hydroxide in 50% v/v ethanol/water G plot (▼) V plot (□) E plot (■).

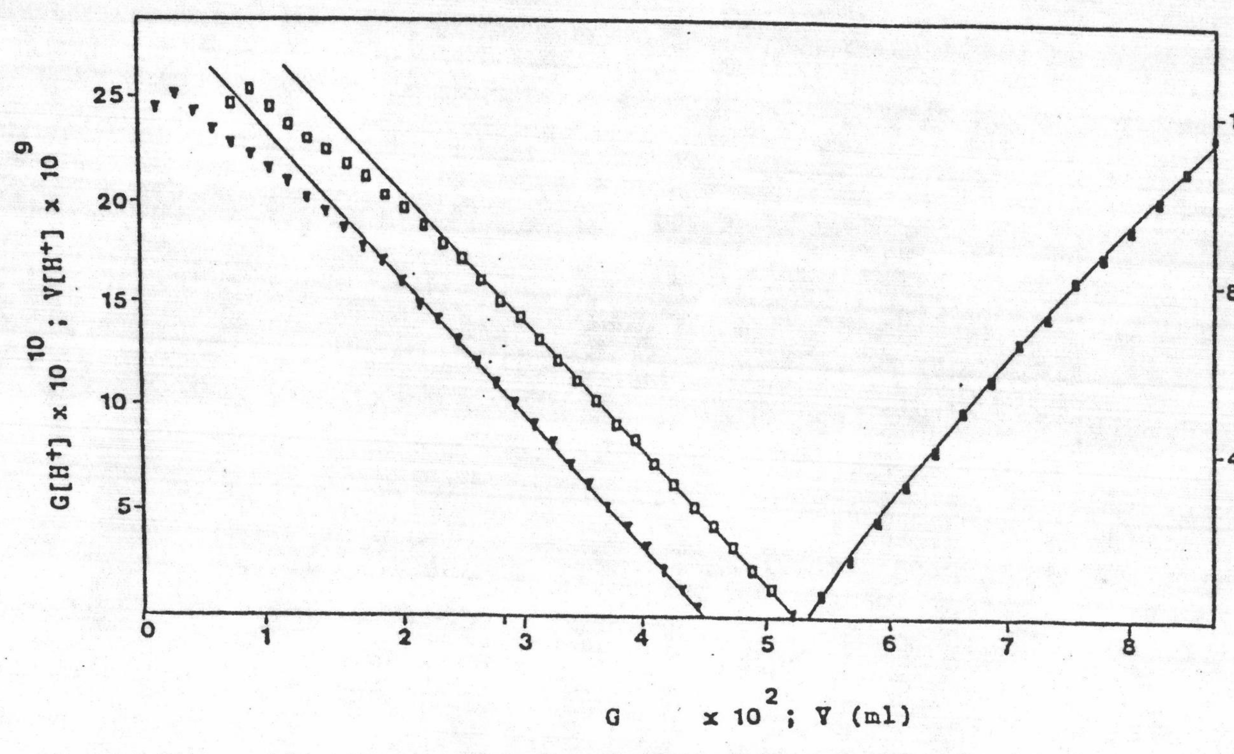

Figure 114 Gran's plot for the titration of chlorpheniramine maleate with sodium hydroxide in 60% v/v ethanol/water G plot (▼) V plot (□) E plot (■).

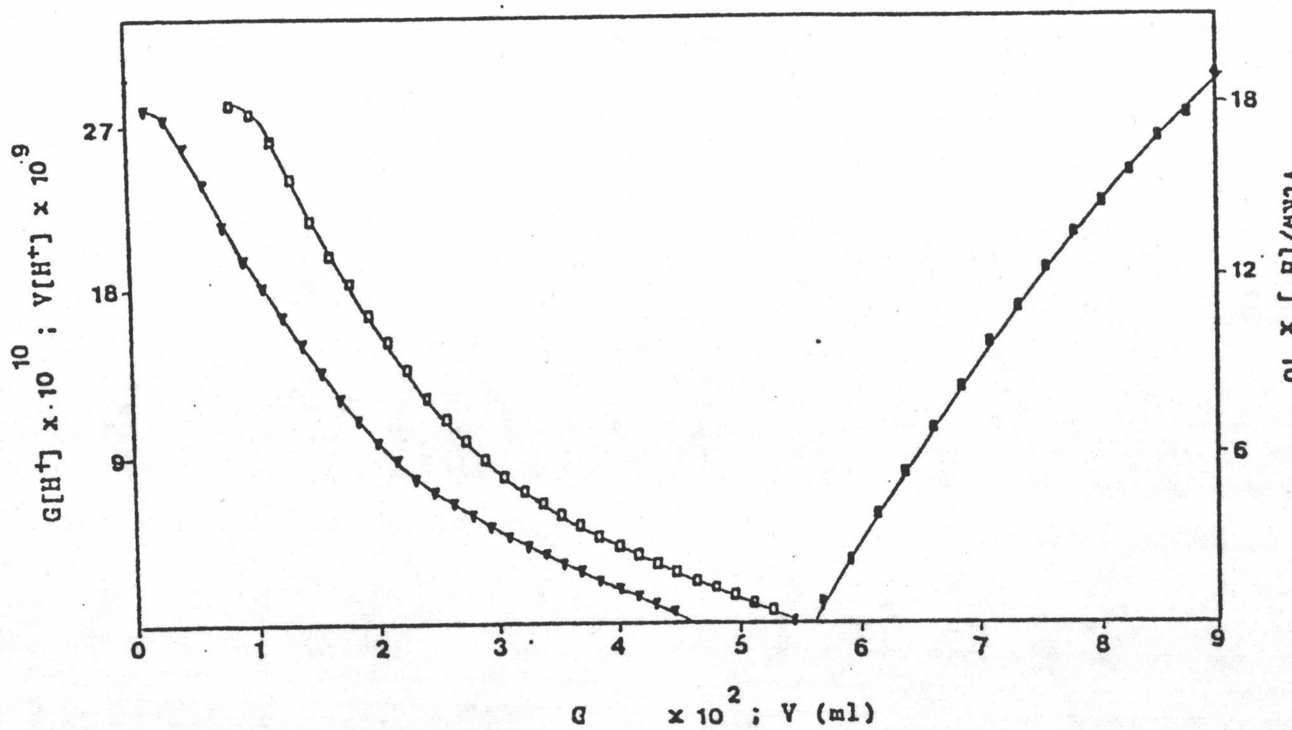

Figure 115 Gran's plot for the titration of chlorpheniramine maleate with sodium hydroxide in 70% v/v ethanol/water G plot (▼) V plot (□) E plot (■).

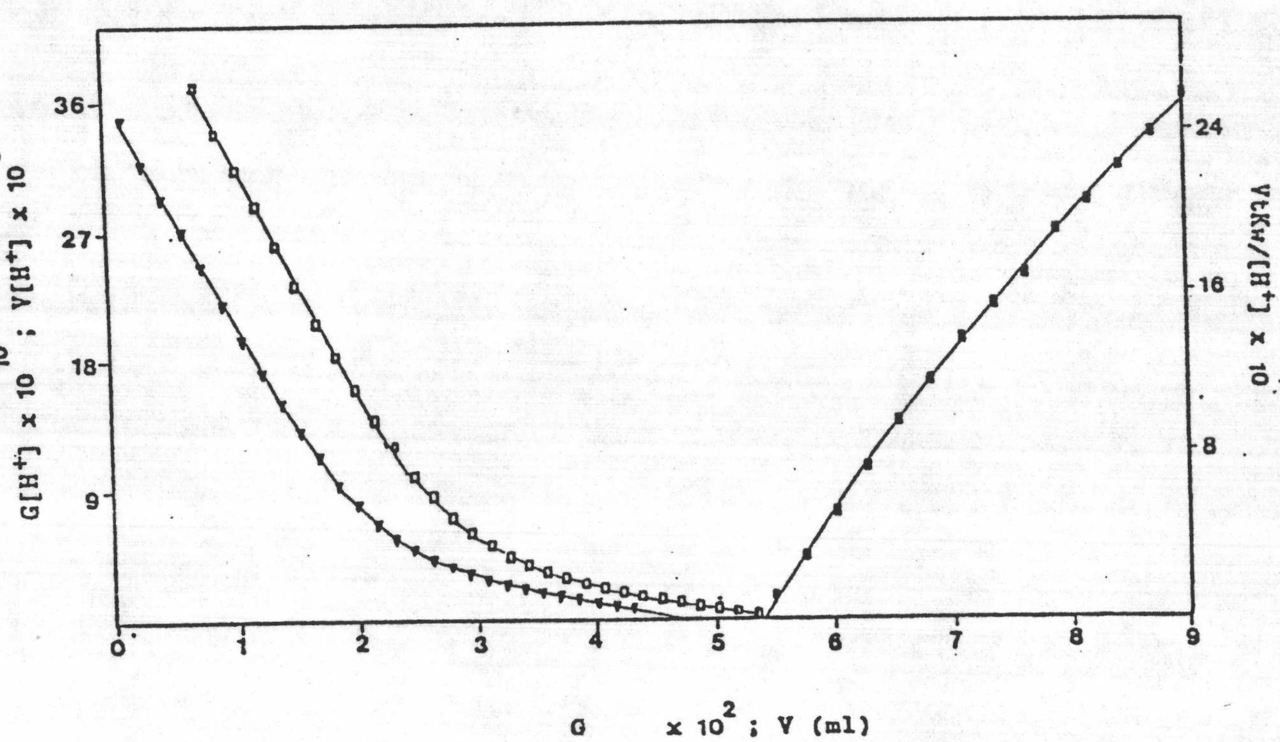

Figure 116 Gran's plot for the titration of chlorpheniramine maleate with sodium hydroxide in 80% v/v ethanol/water G plot (▼) V plot (□) E plot (■).

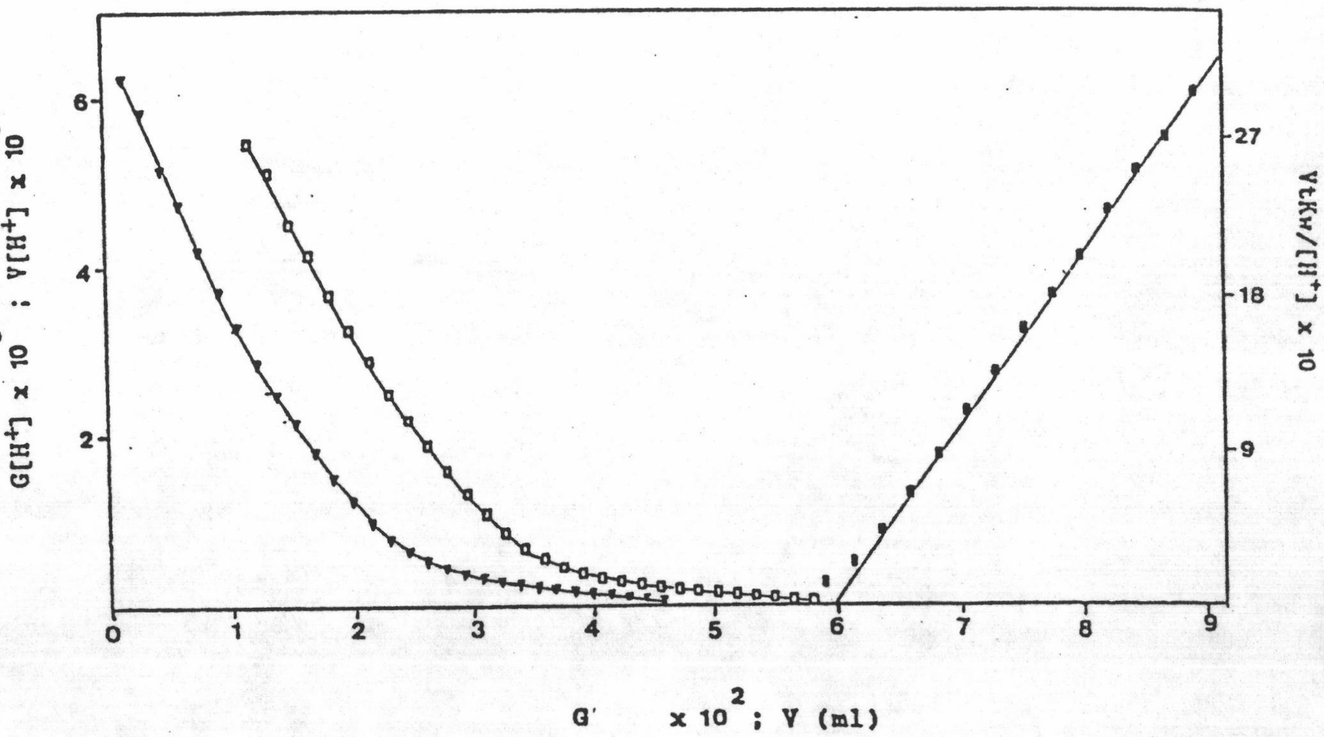

Figure 117 Gran's plot for the titration of chlorpheniramine maleate with sodium hydroxide in 90% v/v ethanol/water G plot (▼) V plot (□) E plot (■).

in 70% v/v ethanol/water could not be obtained as expected (Table 17), resulting from the density of solution effect.

E plot could be accurately used for the titration of chlorpheniramine maleate in low composition of propylene glycol in mixed solvent, 30-50% v/v propylene glycol/water. As the propylene glycol in solution increased over 50%, the effect of density of solution became more pronounced.

For the titration of chlorpheniramine maleate in mixed solvent systems, the problem of the overlapping of dissociation constants could affect on the determination of eqivalence volumes. In methanol/water systems the optimum condition was the titration in 60% v/v methanol/water and ethanol/water by using G and V plots, as shown by relative purity plot in Figures 128 and 129. E plot could be satisfactory employed only for the titrations in 30-70% v/v methanol/water, but not in ethanol/water. In propylene glycol/water systems, only E plot would yield accurate result for the titrations in 30-50% v/v propylene glycol/water (Figure 130).

From those results we could summarized them into group according to the solvent systems

Table 17 Average Percentage Purities by Gran's Method for Titration of Chlorpheniramine Maleate in Propylene Glycol-Water Solvent Systems with 0.08184 N NaOH

Solvent (Propylene glycol in water)	Average Percentage Purity (%)			
	G plot	V plot	E plot	USP method **
30%	55.63 (0.35)	55.57 (0.34)	99.44 * (0.49)	
40%	62.53 (0.10)	62.55 (0.10)	99.66 * (0.20)	
50%	76.60 (0.39)	76.62 (0.39)	99.60 * (0.25)	99.90 * (0.21)
60%	94.93 (0.27)	96.34 (0.13)	99.18 (0.24)	
70%	98.31 (0.16)	98.98 (0.40)	97.13 (0.16)	

* Statistically indifference from reference non-aqueous titration at 99% confidence level

** Titrated in glacial acetic acid and mercuric acetate TS with 0.1 N perchloric acid using crystal violet TS as indicator

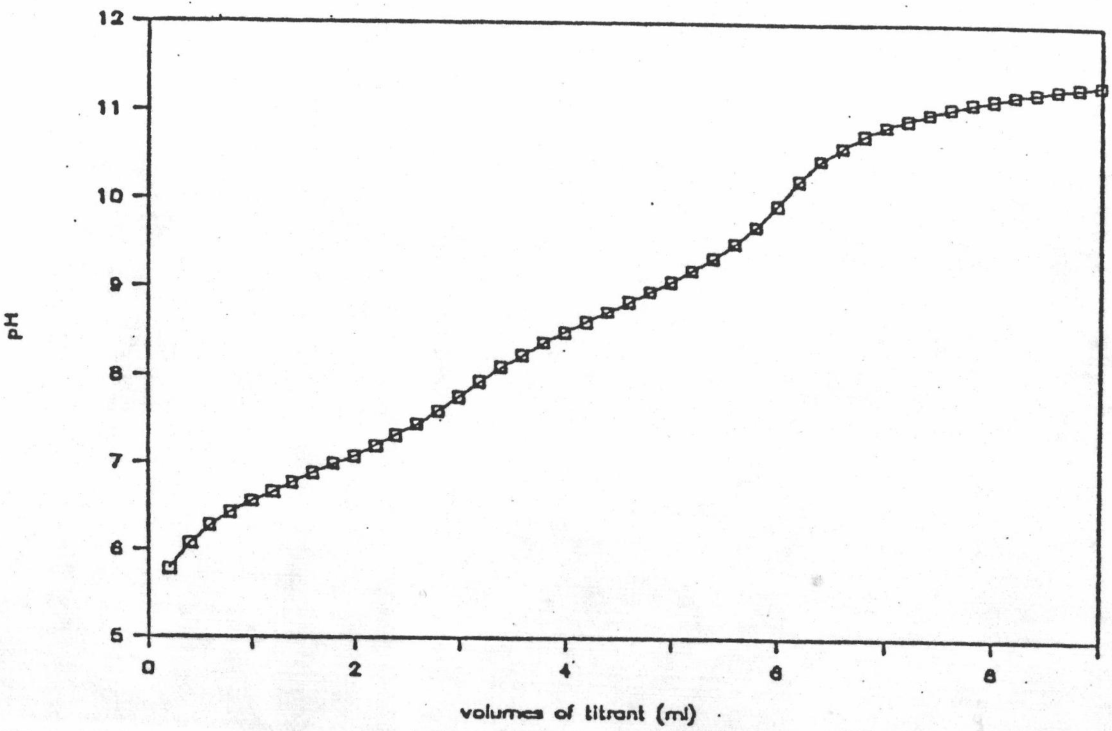

Figure 118 Titration curve of chlorpheniramine maleate with sodium hydroxide in 30% v/v propylene glycol/water

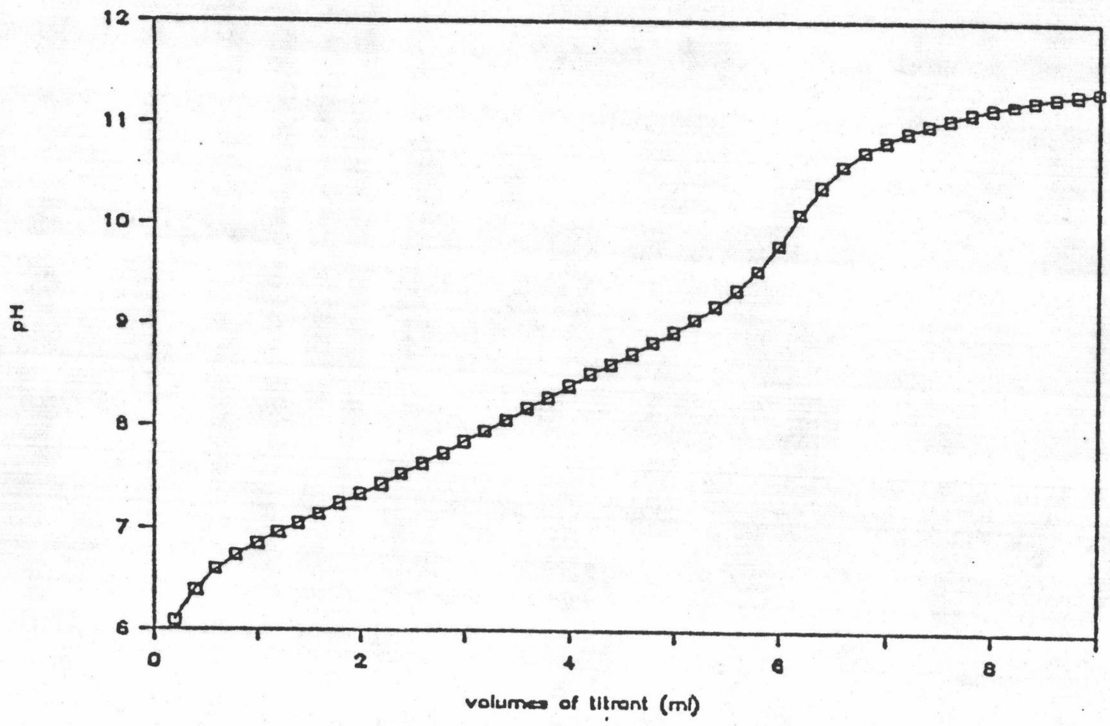

Figure 119 Titration curve of chlorpheniramine maleate with sodium hydroxide in 40% v/v propylene glycol/water

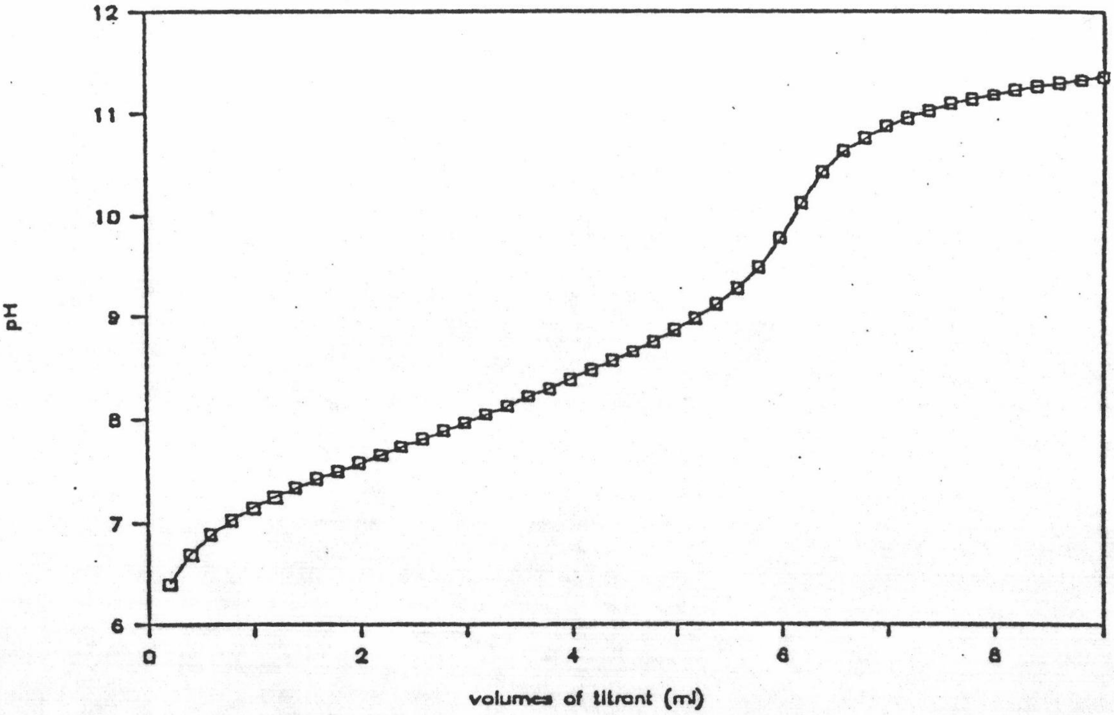

Figure 120 Titration curve of chlorpheniramine maleate with sodium hydroxide in 50% v/v propylene glycol/water

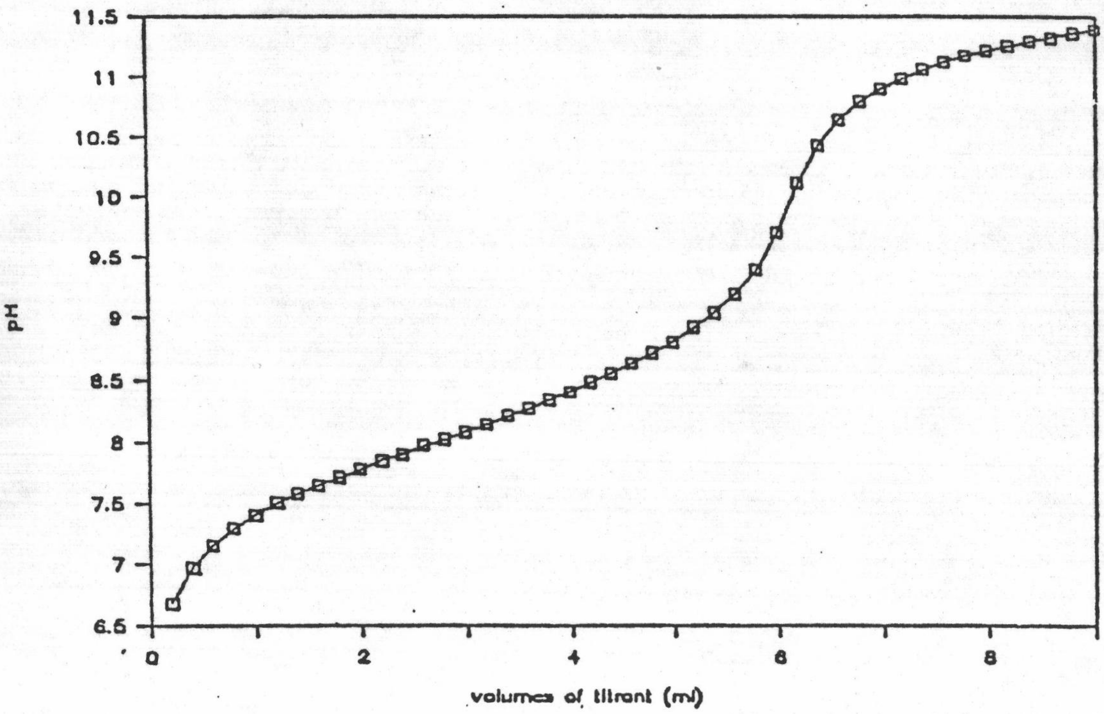

Figure 121 Titration curve of chlorpheniramine maleate with sodium hydroxide in 60% v/v propylene glycol/water

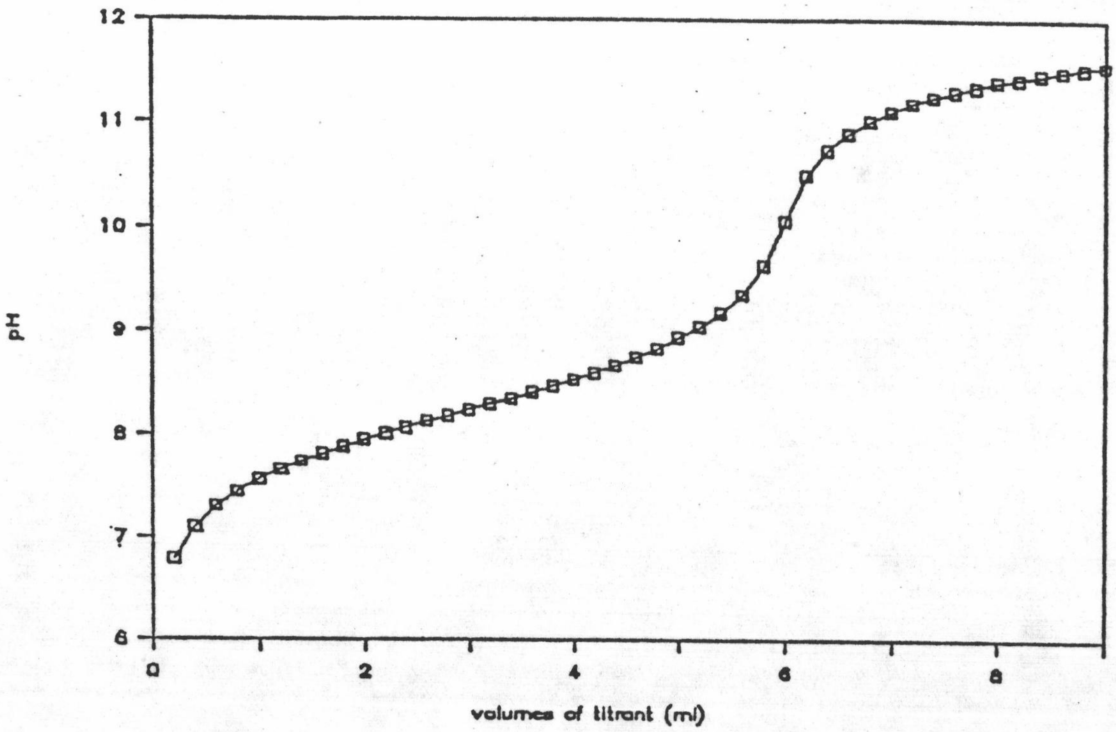

Figure 122 Titration curve of chlorpheniramine maleate with sodium hydroxide in 70% v/v propylene glycol/water

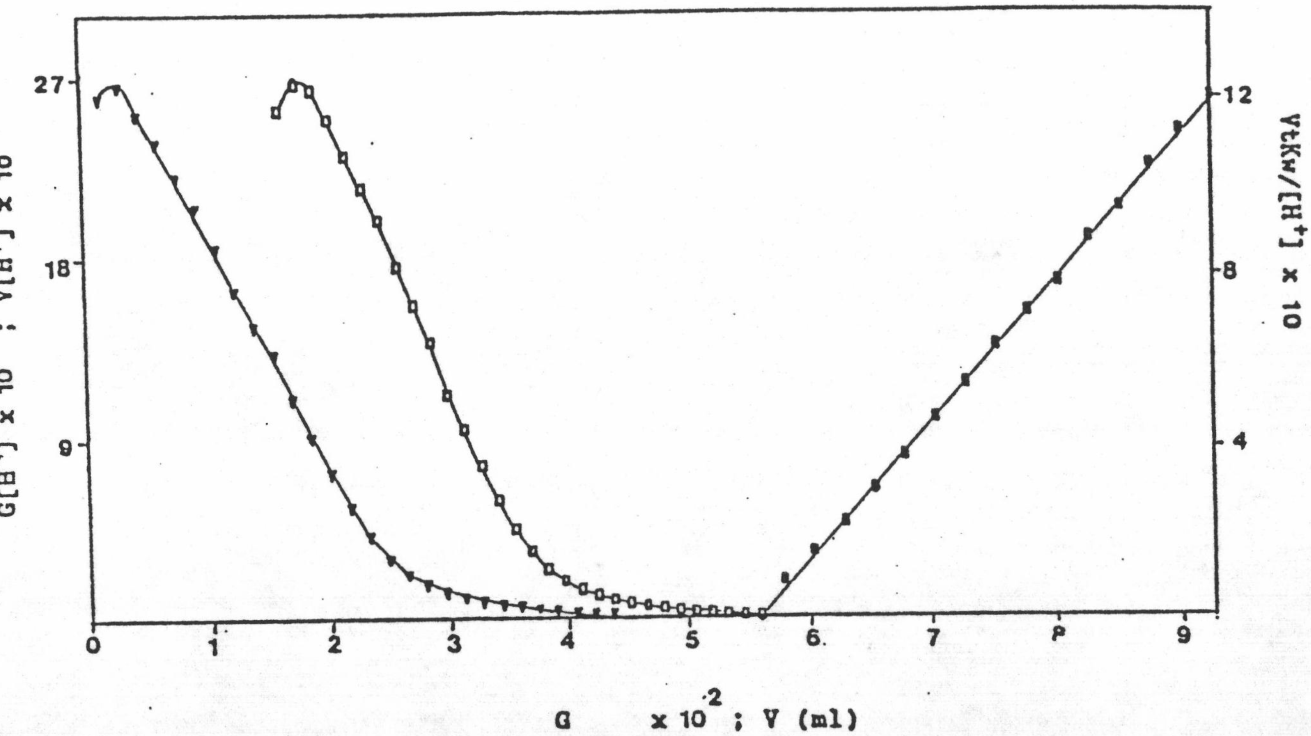

Figure 123 Gran's plot for the titration of chlorpheniramine maleate with sodium hydroxide in 30% v/v propylene glycol/water
G plot (▼) V plot (□) E plot (■).

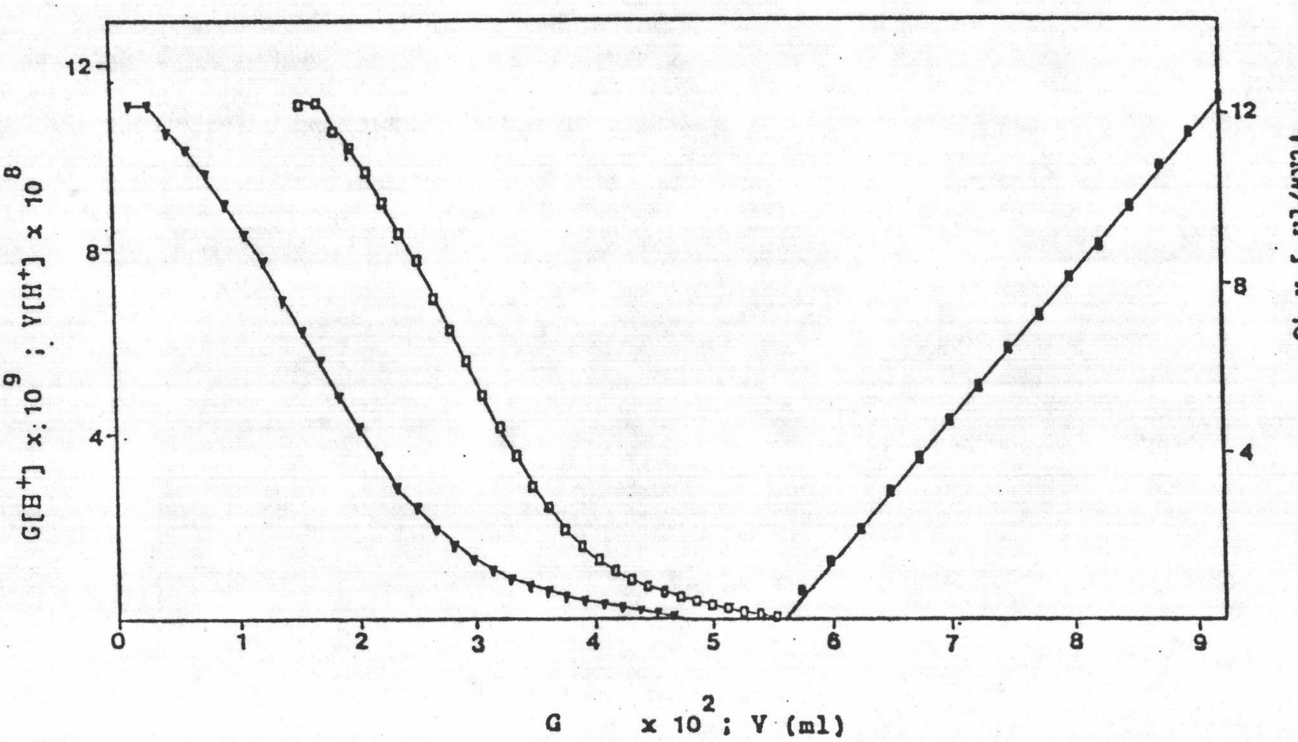

Figure 124 Gran's plot for the titration of chlorpheniramine maleate with sodium hydroxide in 40% v/v propylene glycol/water
G plot (▼) V plot (□) E plot (■).

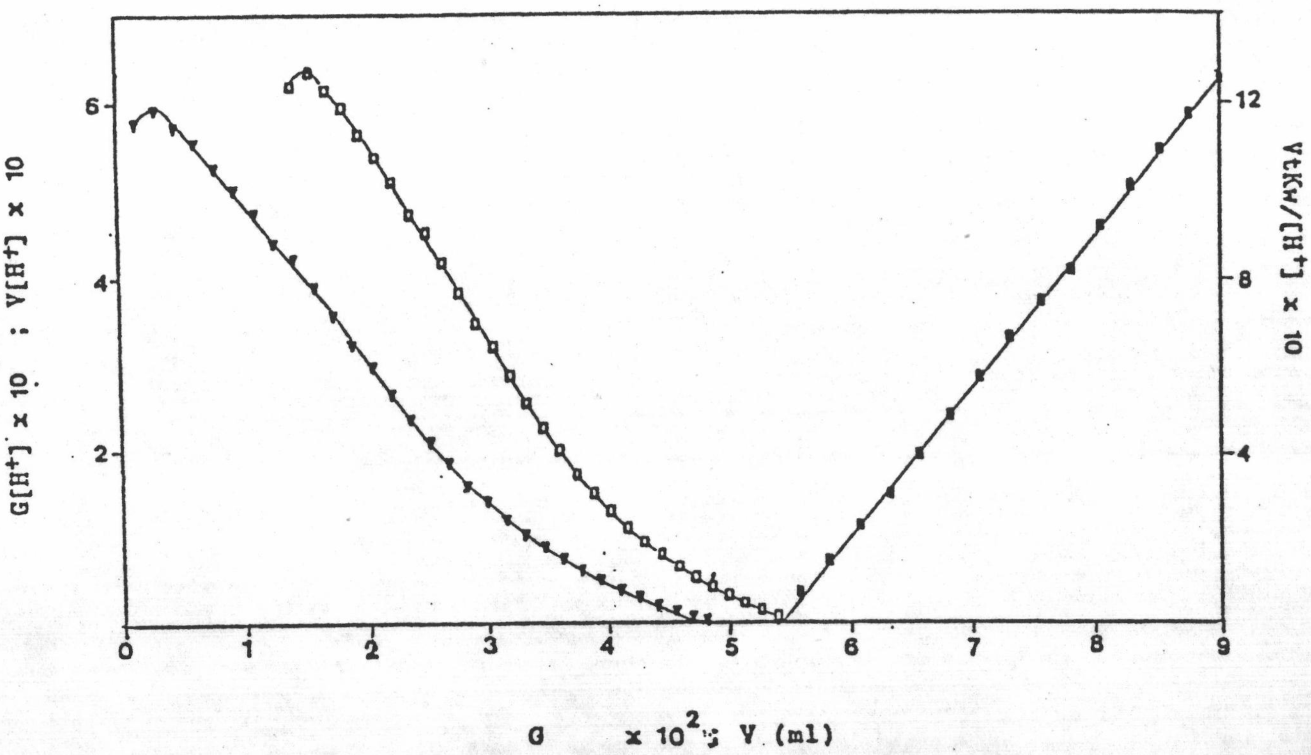

Figure 125 Gran's plot for the titration of chlorpheniramine maleate with sodium hydroxide in 50% v/v propylene glycol/water
G plot (▼) V plot (□) E plot (■).

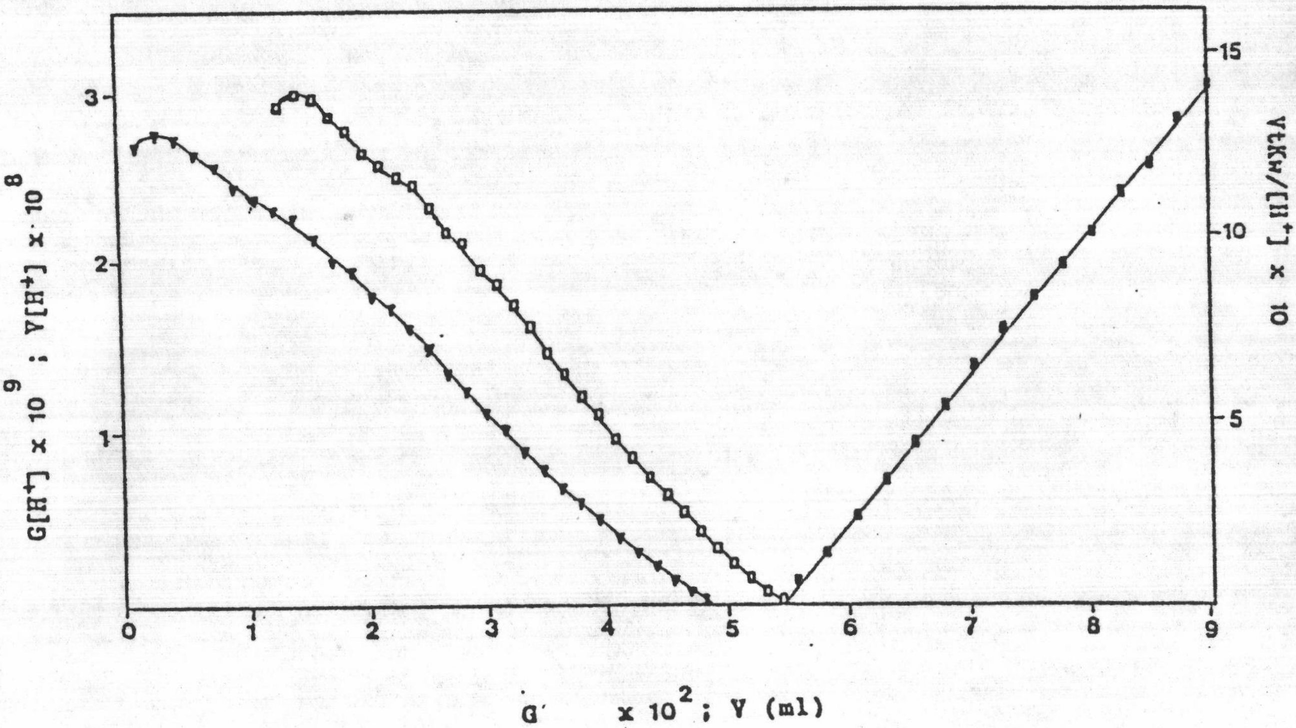

Figure 126 Gran's plot for the titration of chlorpheniramine maleate with sodium hydroxide in 60% v/v propylene glycol/water
G plot (▼) V plot (□) E plot (■).

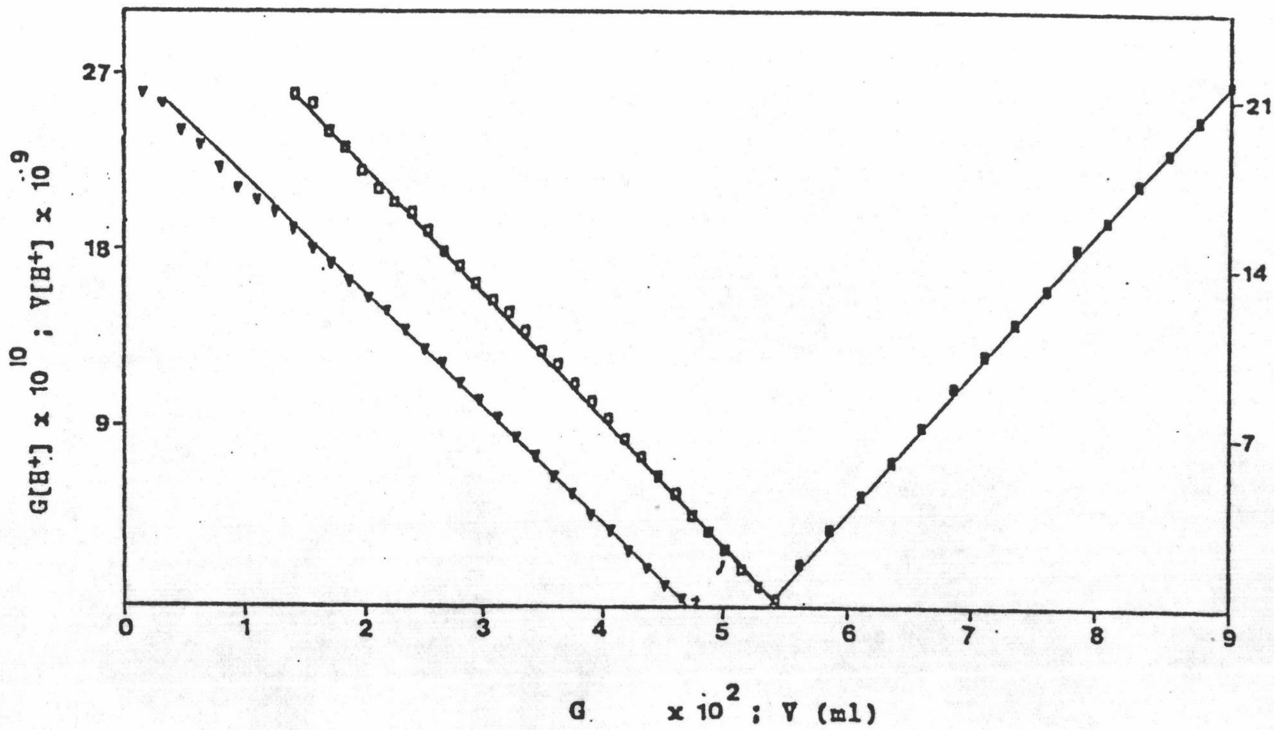

Figure 127 Gran's plot for the titration of chlorpheniramine maleate with sodium hydroxide in 70% v/v propylene glycol/water
G plot (▼) V plot (□) E plot (■).

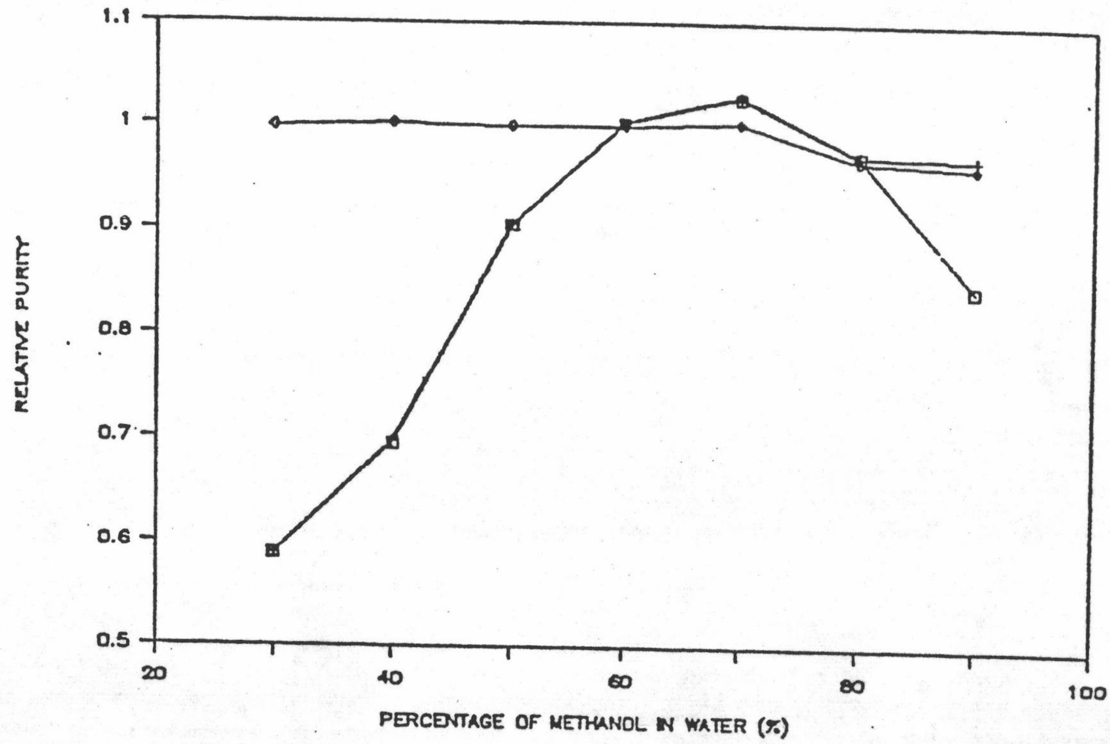

Figure 128 Relative purities of chlorpheniramine maleate in metahnol-water solvents by using G plot (□) V plot (+) E plot (◊).

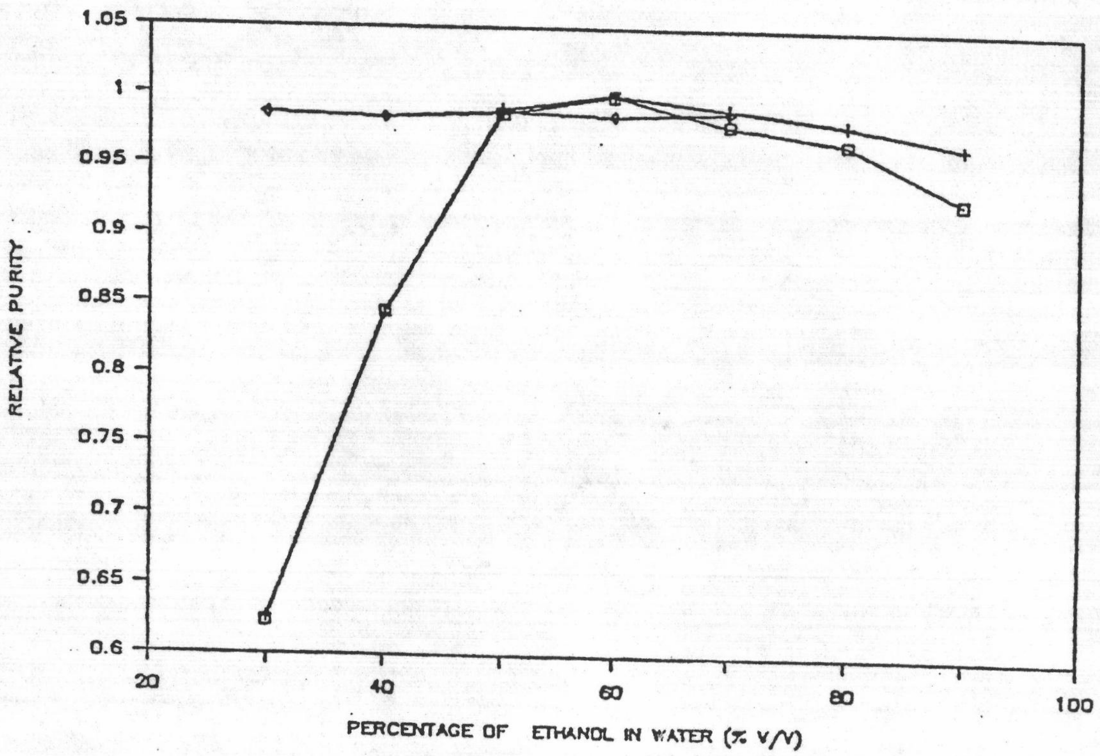

Figure 129 Relative purities of chlorpheniramine maleate in etahnol-water solvents by using G plot (□) V plot (+) E plot (◊).

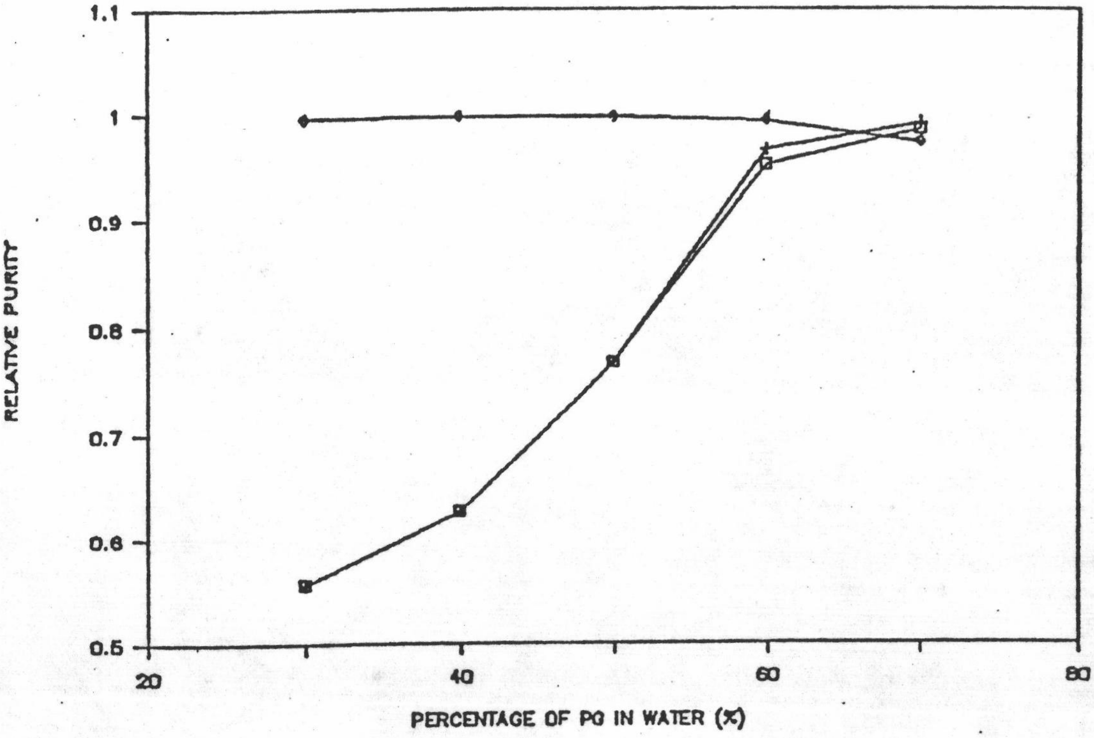

Figure 130 Relative purities of chlorpheniramine maleate in propylene glycol-water solvents by using G plot (□) V plot (+) E plot (◊).

A. Methanol-Water System

Results shown in Table 3, 6, 9 and 12 indicated that Gran's method (V and E plots) and modified Gran's method (G plot) could be accurately used for the quantitative determination of weak acidic drugs, such as triprolidine HCl, quinine sulfate, dextromethorphan HBr and diphenhydramine HCl, by titrating in low percentage of methanol in mixed solvent system, not exceeding 70% v/v methanol/water. However, for the titration of dextromethorphan HBr and diphenhydramine HCl, E plot could not be employed, because pH of solution were quite high (pH exceed 12).

In higher compositions of methanol in water (80-90% v/v) G , V and E plots could not be used for an end point volume determinations because in those systems, the effect of liquid junction potential and medium effect were too large to neglect.

For this solvent system, the optimum condition which G and V plots could be accurately employed for determination of triprolidine HCl, quinine sulfate, dextromethorphan HBr and diphenhydramine HCl was to keep methanol lower than 70% v/v in water.

For the titration of chlorpheniramine maleate in methanol/water system, we had the problem of overlapping of ionization of the acid salt of chlorpheniramine and maleic acid which affected the determination of equivalence volume. The optimum condition was the titration in 60% v/v methanol/water (Table 15). At this particular concentration of methanol in water, the two dissociation constants of chlorpheniramine maleate to be shift to approximately the same value and gave the linear G and V plots. And similar to triprolidine HCl and quinine sulfate, chlorpheniramine maleate could be accurately used E plot for the titrations in 30-70% v/v methanol/water.

B. Ethanol-Water System

Data shown in Table 4, 7, 10 and 13 indicated that the limits of using G, V and E plots for the quantitative determination of weak acidic drugs such as triprolidine HCl, quinine sulfate, dextromethorphan HBr and diphenhydramine HCl in ethanol-water solvent system were lower than that of methanol-water solvent system. They could be employed for the titration in low percentage of ethanol in mixed solvent system, not exceeding 30-40% ethanol/water. The results were due to the unstability of glass electrode for measuring pH values in solvent of high composition the deviation could be occured in high composition of ethanol (39). Bate (23) had reported that for the titration in high composition of ethanol (80-90% v/v ethanol/water) there were the effect of liquid junction potential and medium effect which was rather large and the calculation of hydrogen ion concentration calculated from pH value, not correcting δ constant could give the false results. These were the limits for using high composition of ethanol in water as the solvent for the titration.

Moreover, the titration data after equivalence point for the titration of triprolidine HCl, quinine sulfate, dextromethorphan HBr and diphenhydramine HCl in ethanol-water systems, the E plots showed significant curvatures which is more exagerated at higher concentration of ethanol. This due to error of high alkalinity since those systems were titrated in the pH values of more than 12. For the titration in 30-90% v/v ethanol/water, E plot would give unsatisfactory results.

The optimum condition for the quantitative determination of all four drugs was the titrations in 30-40% v/v ethanol/water by using G or V plot which would give accurate results for the determination of equivalence point.

In similar manner as the titration in methanol-water, the percentage purities of chlorpheniramine maleate could be accurately obtained only for the titration in percentage of ethanol in water which yielded linear G and V plots. This referred to the titration in 60% v/v ethanol/water.

C. Propylene Glycol-Water System

The titration in propylene glycol-water solvent could be employed only in narrow range of propylene glycol concentration. The upper limit was 70% v/v propylene glycol/water. Beyond 70% v/v, equilibrium established slowly due to high viscosity of solution which lead to difficulty in determination of pH value. The lower limit would depend upon the solubility of the acidic drugs.

At the beginning of the titration, the solutions (concentration of propylene glycol between 40-70%) were dense and viscous. With the addition of titrant, sodium hydroxide solution, density of solution would continously changed. The variation of solution's density could affect the activity coefficient of ionic species in the solution, espectially hydrogen ion. This could lead to error in calculating $[H^+]$ in Gran's equation.

Table 5, 8, 11 and 14 showed that the accurate percentage purity could be obtained by G, V and E plots for the titration of triprolidine HCl, quinine sulfate, dextromethorphan HBr and diphenhydramine HCl for the titration in 40-50% v/v propylene glycol/water. However, the optimum condition which could be accurately used in quantitative determination of all four drugs was the titration in 40% v/v propylene glycol/water, by using G , V and E plots.

As shown in Table 17, the percentage purity of chlorpheniramine maleate could not be accurately obtained by using G and V plots for the titration in propylene glycol/water solvent eventhough the G and V plots were linear for the titration in 70% v/v propylene glycol/water. This was due to the effect of density of solution which would affect the activity of hydrogen ion as discussed previously. However, by using data after equivalence point, E plot could be accurately used in quantitative determination of chlorpheniramine maleate for the titrations in 30-50% v/v propylene glycol/water.

In another perspective, we could summarize the results according to different type of Gran's plot.

1. <u>V plot</u>

V plot is Gran plot using data prior to equivalence point. From the present data it indicated that V plot could be accurately used for the titration of triprolidine HCl, quinine sulfate, dextromethorphan HBr and diphenhydramine HCl in 30-70% v/v methanol/water. For chlorpheniramine maleate, V plot could be accurately used for the titration in 60% v/v methanol/water . The limit for methanol is 70% v/v. In ethanol-water systems, V plot could be employed and gave satisfactory results for the titrations of triprolidine HCl, quinine sulfate, dextromethorphan HBr and diphenhydramine HCl in low percentage of ethanol in water. These indicated that the limit for using V plot for the titration of those four drugs in high concentration of ethanol in water was 40% v/v ethanol/water. However, for the titration of chlorpheniramine maleate, V plot could be accurately used for the titration in 60% v/v ethanol/water.

For propylene glycol-water systems, V plot could not be widely employed. Satisfactory result was gained for the titration in low percentage of propylene glycol in water, 40-50% v/v propylene glycol/water, as in the titration of triprolidine HCl, quinine sulfate and diphenhydramine HCl.

2. G plot

G plot is modified fron V plot which correcting for the autoprotolysis of water. G plot could be accurately used when comparing with non-aqueous titration and gave similar results as V plot for the titration of triprolidine HCl, quinine sulfate, dextromethorphan HBr, diphenhydramine HCl and chlorpheniramine maleate in methanol-water, ethanol/water and propylene glycol-water systems. Thus, the limit of using G plot was same as V plot.

3. E plot

E plot is Gran's plot using data after equivalence point. The limit of E plot depended upon pH value after equivalence point. E plot could be accurately used for the wide range of percentage methanol in water up to 70% v/v except for the titration of diphenhydramine HCl and dextromethorphan HBr which the pH value after equivalence point were rather high (about 12) .

For ethanol/water systems the pH value after equivalence point were very high (more than 12). These resulted in curvature of the plot and consequently error in the quantitative determination of purity of drugs. E plot should be used for the titration of less than 50% v/v of ethanol in water, and lower than 50% v/v of propylene glycol in water. Due to the effect of density of solution, higher than 60% v/v of propylene glycol should not be used as solvent for the titration.

Our study suggested that there were many factors which would affect the determination of purities of acid drugs in mixed solvent systems. The important part is due to the character of solvent systems which could affect:

- pH Value of the solution as shown in ethanol-water systems. When the pH value after equivalence point in ethanol/water systems was very high (approaching 12), E plot would show significant curvature.

- Density of solution, as shown in propylene glycol-water systems. The density of solution could have an effect on activity coefficient of hydronium ion.

- Amount of organic solvent was also important. In high composition of organic solvent, it could generate high liquid junction potential and medium effect which should be correcting for δ constant in determination the true value for calculating hydronium ion concentration using in Gran's equation.