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Quantitative Determination of Weak Acidic Drugs by Gran's Method(การหาปริมาณตัวยาที่เป็นกรดอ่อนโดยวิธีของแกรน)

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ORIGINAL ARTICLE

Quantitative Determination of Weak Acidic Drugs by Gran's Method

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ABSTRACT

End point volume determinations by Gran's method were shown to be as accurate and reproducible as that of the reference nonaqueous titration methods which are described in the USP XXI. Gran's method gave satisfactory results even in cases which the unionized drugs precipitated out of solutions during the course of titrations. Mixed solvent of 40% v/v ethanol/water was utilized in order to increase the solubilities of the precipitates and in this case, Gran's method was still employed advantageously for the end point determinations. (Th. J. Pharm. Sci., Vol. 15 No. 1, 19-31 (1990))

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INTRODUCTION

Volumetric titrations are widely used for routine analysis because of their rapidness, convenience and accuracy. However, most weak acidic drugs are usually not titrated in aqueous solvent because their dissociation constants are generally too low and that their reactions are not sufficiently complete to yield satisfactory end points. Another reason is their poor aqueous solubilites. Thus, neutralization titrations of these weak acidic salts are generrally conducted in non-aqueous system. However, extra precautions must be considered for the non-aqueous titration. Moisture content of the solution must be strictly controlled. Room temperature ahould be nearly constant from the time which the titrant was standardized to the time which it was used to titrate the sample. Any significant change in temperature would lead to the change in normality of the standardized titrant. Change in color of the indicator may not be as obvious as might be desired and in this case, potentiometric end point determination should be employed. Sharpness of end point datermination by potentiometric titration may be interfered by precipitation of the titrated specie. Mixed solvent system of water with organic solvent had been found to be useful in reducing precipitation and potentiometry can be employed when a suitable indicator is not available. This, however, cannot circumvent the problem of identifying the equivalence point.

Gran's method is based on idea of Sorensen (1), who plotted the antilogarithm of the pH as a function of the titrant volume which gave a straight line instead of sigmoid form of titration curve. Gran (2) introduced a correction for the volume change during the course of titration which resulted in a better straight line than Sorensen's method. However, Ingman and Still (3) found that Gran's method could not evaluate end point of weak acid with pKa <7 as Gran did not accounted for autoprotolysis of water.

Although Gran's method have been applied to determination of acids and bases by various researchers (2, 4), its accuracy and reprocibility in determination of equivalence point for very weak acids have not yet been fully established. The scope of the present study was to determine whether Gran's method would yield end point volumes in aqueous titration with the same degree of accuracy and reproducibility as that of the standard titration methods as described for each specific drug in the United States Pharmacopeia XXI (generally involved utilization of indicators to detect end point volumes in non -aqueous titrations). An additional purpose of this study was to study whether Gran's plot would yield accurate end point volumes for acid-base titrations for drugs which have limited solubilities and precipitated out during the course of titration and in these cases, we also looked at application of Gran's method to the solvent system consisting of 40% v/v ethanol/water (to reduce the problem of precipitations).

Basically, the derivation of Gran's equation is modified from Ingm and Still (3). This equation has been used by various workers. Here, we will present only the derivation for the titration of monoprotic weak acid whose unionized conjugate base precipitate out of solution during the course of titration.

$$HB^+X^- + NaOH \longrightarrow B + NaX + H_2O$$

Where B is the unionized conjugate base of the weak acid HB^+.

Prior to the equivalence point, the solution still contains significant concentration of HB^+ and the addition of the titrant will result in neutralization reaction with the acid. The aquesus dissociation constant of HB^+ is

$$Ka = \frac{[H^+][B]}{[HB^+]} \qquad \text{Eq. 1}$$

The net positive charges in the solution must equal the net negative charges, thus the charge balance equation of the solution is

$$[HB^+] + [Na^+] + [H^+] = [OH^-] + [X^-] \qquad \text{Eq. 2}$$

and the mass balance equation is

$$Ca = [X^-] = \frac{VeN}{Vo + V} = [HB^+] + [B] \qquad \text{Eq. 3}$$

Where Ca is the total concentration of the weak acid being titrated. The concentration of Na+ at any time can be calculated with

$$[Na+] = \frac{VN}{Vo + V} \qquad \text{Eq. 4}$$

Substituting Eqs. 3 and 4 into Eq. 2 gives

$$[HB+] = \frac{VeN}{Vo + V} \left(\frac{VN}{Vo + V} + [H^+] - [OH^-] \right) \qquad \text{Eq. 5}$$

Where V, Ve, Vo and N are volume of titrant, volume at equivalence point, initial volume of titrated sample and normality of the titrant, respectively.

Substituting Eq. 5 into Eq. 3 gives

$$[B] = \frac{VN}{Vo + V} + [H^+] - [OH^-] \qquad \text{Eq. 6}$$

Combining Eqs. 5 and 6 with Eq. 1 leads to

$$Ka = \frac{[H^+] \left(\frac{VN}{Vo + V} + [H^+] - [OH^-] \right)}{\frac{VeN}{Vo + V} - \left(\frac{VN}{Vo + V} + [H^+] - [OH^-] \right)} \qquad \text{Eq. 7}$$

or

$$G [H^+] = KaVeN - KaG \qquad \text{Eq. 8}$$

Where

$$G = VN + (Vo + V) ([H^+] - [OH^-] \qquad \text{Eq. 9}$$

If $VN >> (Vo + V) ([H^+] - [OH^-])$, then Eq. 7 reduces to

$$V [H^+] = KaVe - KaV \qquad \text{Eq. 10}$$

Thus the plot of G $[H^+]$ against G (Eq. 8) or V $[H^+]$ against V (Eq. 10) would yield straight lines and the equivalence point volume can be easily obtained from these two plots. For the G plot (Eq. 8), this value can be calculated from :

$$Ve = \frac{\text{intercept}}{N \cdot \text{slope}} \qquad \text{Eq. 11}$$

Similarly, the equivalence point may be calculated from Eq. 10 :

$$Ve = \frac{\text{intercept}}{\text{slope}} \qquad \text{Eq. 12}$$

After the equivalence point, the concentration of HB^+ is negligible, the solution will have predominantly only the specie B. Charge balance of the solution is

$$[X^-] + [OH^-] = [Na^+] + [H^+] \qquad \text{Eq. 13}$$

Substituting Eqs. 3 and 4 into Eq. 13 yields

$$[OH^-] - [H^+] = \frac{VN - VeN}{Vo + V} \qquad \text{Eq. 14}$$

or

$$\left(\frac{Kw}{[H^+]} - [H^+]\right) = \frac{VN - VeN}{Vt} \qquad \text{Eq. 15}$$

Where $Vt = (Vo + V)$ and Kw is the aqueous dissociation constant of water. In the alkaline solution, normally, $[OH^-]$ is much larger than $[H^+]$ and Eq. 15 reduces to

$$\frac{Kw}{[H^+]} = \frac{VN - VeN}{Vt} \qquad \text{Eq. 16}$$

Rearranging Eq. 16 gives

$$\frac{Vt \cdot Kw}{[H^+]} = VN - VeN \qquad \text{Eq. 17}$$

In this case, plot of $Vt \cdot Kw/[H^+]$ against V will be linear with slope of N and intercept of VeN. The equivalence point may be calculated with Eq. 12.

Derivation of Gran's equation for other acidic or basic compounds are similar to the derivation above with the exception of the charge balance equation. For the titration of monoprotic salt whose unionized conjugate base precipitated during the course of solution, Eq. 1 was modified to

$$Ka = \frac{[H^+]\,[B]s}{[HB^+]} \qquad \text{Eq. 18}$$

Where [B]s is the saturated concentration of the conjugate base, B. Thus, Eq. 7 becomes

$$Ka = \frac{[H^+]\,[B]s}{\frac{VeN}{Vo + V} - \left(\frac{VN}{Vo + V}\right)([H^+] - [OH^-])} \qquad \text{Eq. 19}$$

and

$$[H^+]]\,(Vo + V) = \frac{KaVeN - KaG}{[B]s \qquad [B]s} \qquad \text{Eq. 20}$$

In this case, plot of $[H^+]\,(Vo + V)$ against G will result in straight line and the equivalence point can be calculated from Eq. 11 again, if $VN >> (Vo + V)\,([H^+] - [OH^-])$, Eq. 20 reduces to

$$[H^+]]\,(Vo + V) = \frac{KaVeN}{[B]s} - \frac{KaVN}{[B]s} \qquad \text{Eq. 21}$$

where [B] is the saturated concentration of the conjugate base. In this case, Eq. 12 can again be used to evaluate the value of the end point.

Once the end point volume was obtained, the percentage purity is then calculated with the following equation :

$$\%\ \text{purity} = \frac{Ve \times N \times Eq.Wt \times 100}{Wt} \qquad \text{Eq. 22}$$

Where Eq.Wt and Wt are the equivalence weight and sample weight of the weak acid, respectively.

EXPERIMENTAL SECTION

Materials :

1. Test Drugs : tripolidine hydrochloride, dextromethorphan hydrobromide, quinine sulfate, diphenhydramine hydrochloride, phenylpropanolamine hydrochloride, chlorpheniramine maleate, pseudoephedrine hydrochloride.

2. Other Reagents: potassium hydrogen phthalate AR (E-Merck), sodium hydroxide AR (E-Merck), potassium chloride AR (J.T. Baker Chemical, absolute ethanol AR (E-Merck), glacial acetic acid AR (E-Merck), perchloric acid AR (E-Merck), mercuric acetate AR (E-Merck).

Methods:

Preparation of Weak Acid in 0,1 M Potassium Chloride:

All weak acids were accurately weighted to give about 5×10^{-3} M. The acids were dissolved in the solution of 0.100 M KCl in distilled deionized water or 40% v/v ethanol/water and adjust to volume with respective solvent. Fifty milliliter aliquots of the resulting solution were transfered to a 100-ml beaker for titration. 0.10 N HaOH (using deionized-distilled water as solvent) was employed as titrant for both the aqueous and 40% v/v ethanol/water samples.

Reference Procedure :

The sodium hydroxide solution was standardized with potassium hydrogen phthalate and end point volume was determined by potentiometry (parallel tangents method). Weak acidic drugs were titrated in non-aqueous systems as described in the United States Pharmacopeia XXI (5).

Equipments:

Potentiograph E536 (Metrohm Herisau), Electrode AG9100 (Metrohm Herisau), automatic titrator 655 Multi-Dosimat (Metrohm Herisau) with exchange unit model 3005 (501), Magnetic Stirrer E649 (Metrohm Herisau).

RESULTS AND DISSCUSSION

Aqueous Titration:

The titration curves for the eight weak acidic compounds are shown in Figures 1 and 2. The summary for the purity determinations are listed in Table 1. Figure 5 showed Gran's plots (G, V and E plots) for pseudoephedrine HCl. Generally, G plot (Eq. 8) was found to give results which were statistically indifferent from that of the reference procedures at 95% confidence level. The modified G plot (Eq. 20) for cases where precipitates were observed gave accurate and reproducible results with the exceptions of the dextromethorphan HBr and quinine sulfate. The modified G and V (Eq. 21) plots for dextromethorphan HBr are shown in Figure 6, along with the E plot (Eq. 17). In the case of dextromethorphan, the precipitates possess very fine particle sizes which possibly were redissolved when the stirer was turned on to affect the mixing of the titrant and the sample solution. This could lead to temporary supersaturated solution which would invalidate Eq. 20. The titration of quinine sulfate yielded light and fluffy precipitates which physically deposited on the glass electrode and thus, interfered with the ion-exchange process at the membrane of electrode. Consequently, the pH measurement of the solution would be erroneous.

Titration of chlorpheniramine maleate was different from others in that the first equivalence point was actually titration of the maleic acid moiety ($Ka = 6 \times 10^{7}$) and the second neutralization was the titration of the protonated chlorpheniramine molecule. Titration of maleic acid was much like that of potassium hydrogen phthalate and the normal G plot (Eq. 8) was used for the determination of the equivalence point whereas the modified G plot (Eq. 20) for precipitation was used for the determination of the second equivalence point which involved precipitation of the chlorpheniramine free base. As expected, volume of the second equivalence point found by the modified G plot was exactly twice the volume of the first equivalence point determined from the G plot.

In general, the V plot (Eq. 10) gave unsatisfactory results as compared with the reference procedures. Only potassium hydrogen phthalate, diphenhydramine HCl and the titration of the second proton of maleic acid of chlorpheniramine maleate gave results which were statistically indifferent from that of the reference procedures. This clearly point to the problem with the assumption that $VN >> (Vo + V)([H^+] - [OH^-])$. For our system, if we let

N = 0.1 normal and Vo = 50 ml, we would find that this condition would hold only in the pH range of about 5-9. Examination of the pH-volume of titrant plot for all the compounds showed that only potassium hydrogen phthalate, dipphnhydramine HBr and chlorpheniramine maleate had significant data between this pH range. Thus we can conclude that for the V plot to give accurate results, the pH range which we can apply the V plot should be about 5-9. This, of course, apply to the modified V plot (Eq. 22) as well.

E plot (Eq. 17) gave equivalence points which were statistically indifferent from the reference procedures except in the cases of pseudoephedrine HCl and quinine sulfate. Pseudoephedrine HCl was the weakest acid in this study with pKa of 9.9. The pH of solution after equivalence point was higher than 11. At this high pH, the alkaline error of glass electorde will be significant, especially in the presence of high concentration of potassium chloride which was used to adjust the ionic strenght of the solution. Under this condition, the glass electrode would falsely measured some of the Na^+ ions in the solution for hydronium ion. In the case of quinine sulfate, the problem was as discussed previously.

Titration in 40% v/v Ethanol/Water :

To get around the problem of precipitation of unionized conjugate base which was formed during the course of the titration, 40% v/v ethanol/water solvent system was chosen as the media for the titration. Ethanol has been recommended as solvent in determination of dissociation constant (potentiometric titrimetry) of weak acids whose unionized from possesses low solubility and precipitated during the course of titration (6-8). Ethanol is capable of proton donor and /or proton acceptor. It possesses lower dielectric constant and lower autoprotolysis constant than water. Being less polar than water, ethanol should favor reactions in which unionized form was generated. However, using 95% ethanol would have the problems similar to the non-aqueous solvents. Therefore, we chose the lowest concentration of ethanol which will keep the solution homogenous throughout the course of the titration and this was found to be 40% v/v ethanol/water.

G plot was not employed for the 40% v/v ethanol/water solvent system since we could not determine the autoprotolysis constant for this solvent system and thus only V and E plots would be utilized. Of the eight weak acids studied, only the V plot of chlorpheniramine gave equivalence point which was statistically different from that of the reference procedure. The titration curves for the eight weak acids are shown in Figure 3 and 4, the resulting calculated purities are listed in Table 2. Unlike in the case of aqueous medium, the titration curve of chlorpheniramine maleate showed only single inflection point. In 40% v/v tehanol/water, protonated chlorpheniramine can dissociated much better than in aqueous media as the unionized product would be favored by the reduce in polarity of solvent. Thus this would result in higher dissociation constant for the protonated chlorpheniramine. This effect is clearly observed in the titration curve of potassium hydrogenphthalate. The overall effect is the overlapping dissociations of protonated chlorpheniramine and the second proton of mateic acid, leading to erroneous V plot.

As in the case of V plot, the E plots also gave equivalence points which are in good agreement with the reference procedures, with the exceptions of pseudoephdrine HCl and dextrometorphan HBr. In the case of pseudoephedrine HCl, the curvature of the E plot (Figure 7) lead to underestimation of the equivalence point. In the case of the dextromethorphan HBr (Figure 4), pH of the solution after equivalence point was excessively high (near 12). This condition would lead to the same errors as we had discussed earlier in the aqueous titration. It was interesting to note that while the alkaline error would become noticeable in aqueous solvent system at pH slightly higher than 11. In 40% ethanol/water, the apparent pH of the solution must reach about 11.5 before the alkaline error become noticeable. Previously, Ingman and Still (3) suggested from their study that the curvatures in the Gran's plot were due to the failure to take into account the auroprotolysis of water. However, we found that for some titrations, G and E plots in aqueous solution still showed some curvatures (both in the absent and present of precipitations. This would suggest that there are other factors involved which caused the nonlinearity besides the autoprotolysis of water. Since the value of the equivalence point depend upon the slope and intercept of the plots, it was essential that we found the linear portion of the G, V and E plots. This would be a minor problem if we have enough data points and computer program could be used to help us find the best linear portion of the curve.

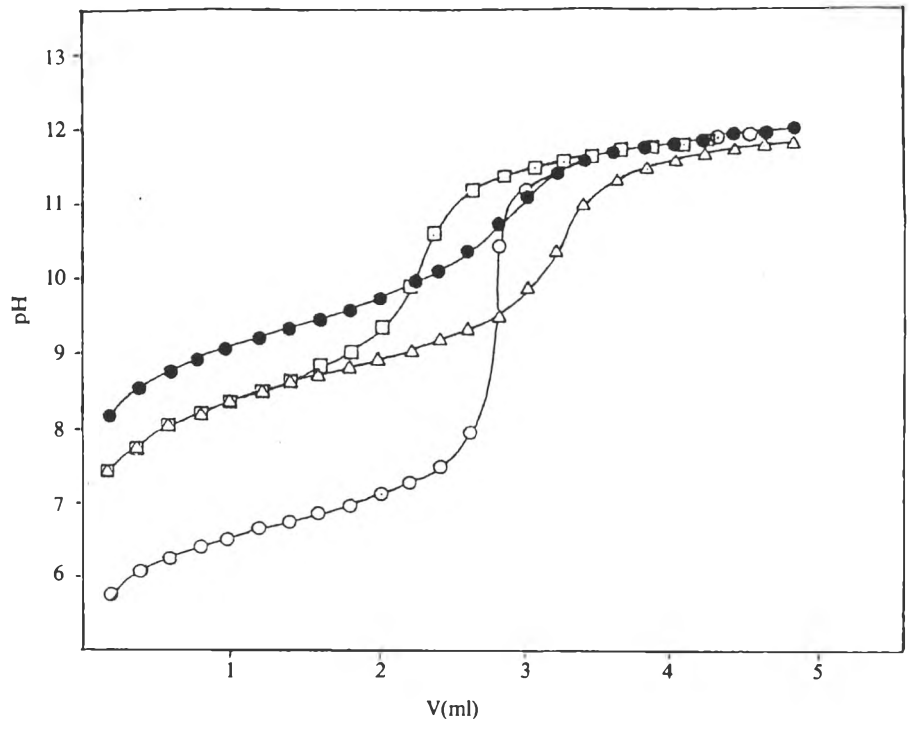

Figure 1 Titration of weak acids in aqueous solvent.
Key : (○) potassium hydrogen phthalate;
(□) phenylpropanolamine HCl;
(Δ) pseudoephedrine HCl.

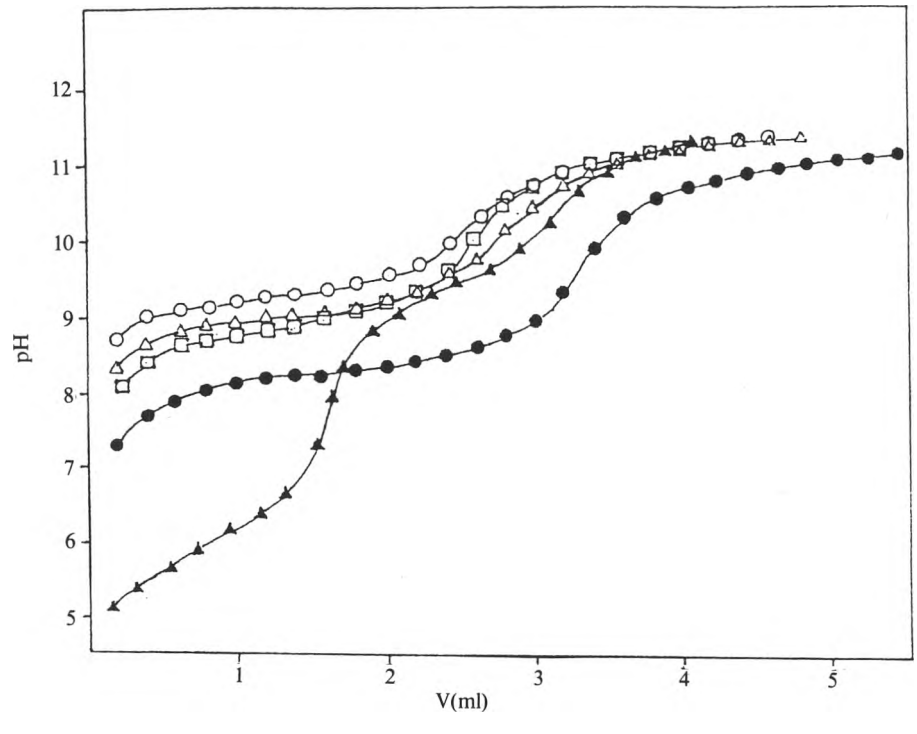

Figure 2 Titration of weak acids in aqueous solvent.
Key : (Δ) triprolidine HCl;
(□) diphenhydramine HCl;
(○) dextromethorphan HBr;
(●) quinine sulfate;
(▲) chlopheniramine maleate.

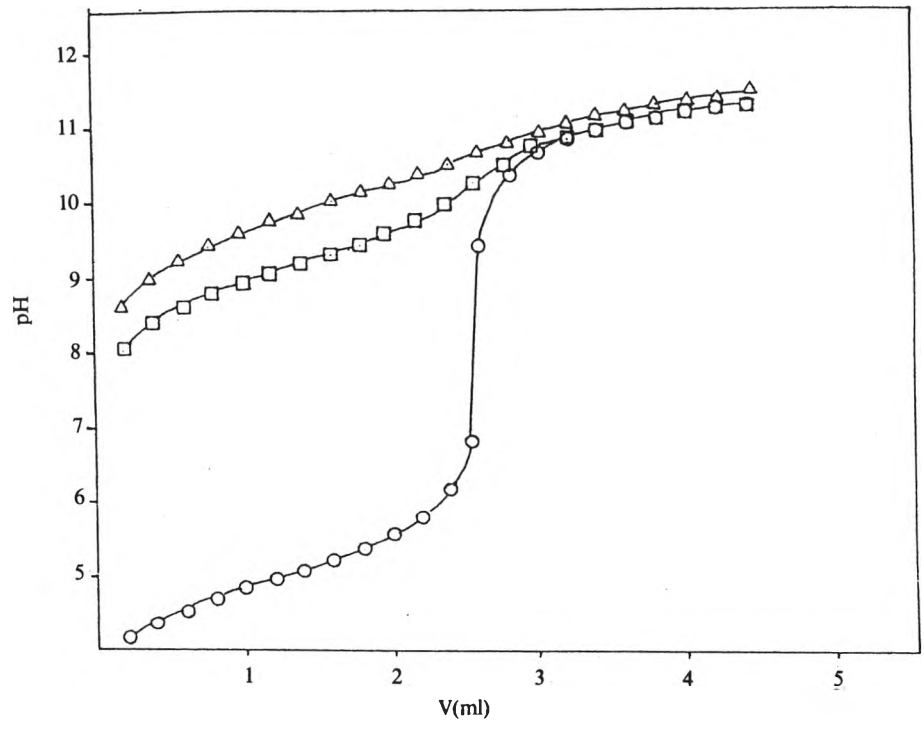

Figure 3 Titration of weak acids in 40% v/v ethanol/water.
Key : (○) potassium hydrogen phthalate;
(Δ) phenylpropanolamine HCl;
(●) pseudoephedrine HCl;
(□) tripolidine HCl.

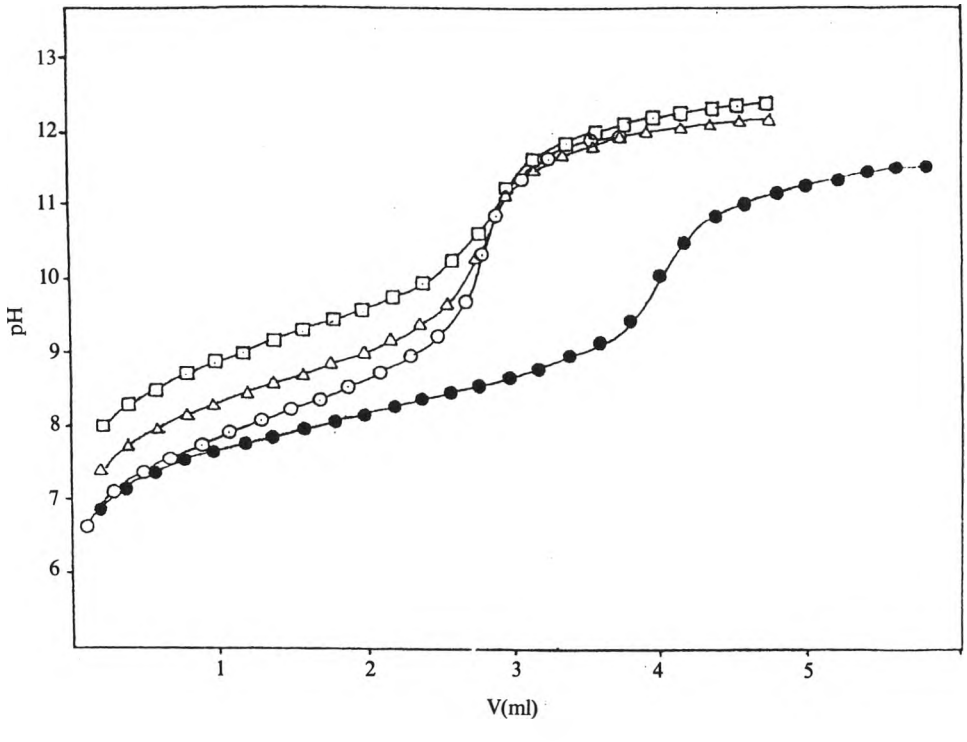

Figure 4 Titration of weak acids in 40% v/v ethanol/water.
Key : (Δ) diphenhydramine HCl;
(□) dextromethorphan HBr;
(●) quinine sulfate;
(○) chlopheniramine maleate.

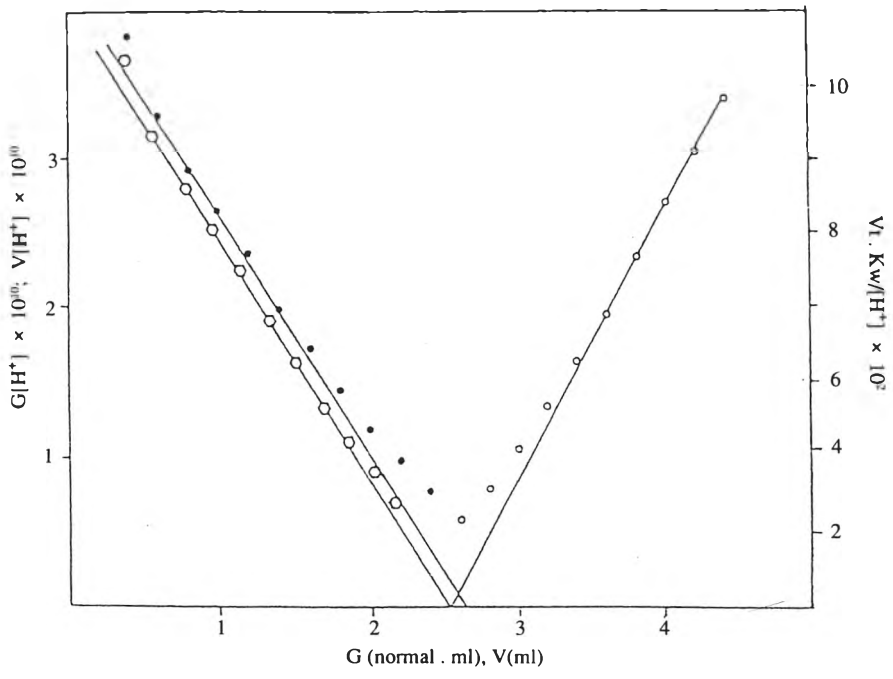

Figure 5 Gran's plot for the titration of pseudoephedrine HCl in aqueous solution.
Key : G plot (○), V plot (●), E plot (○)

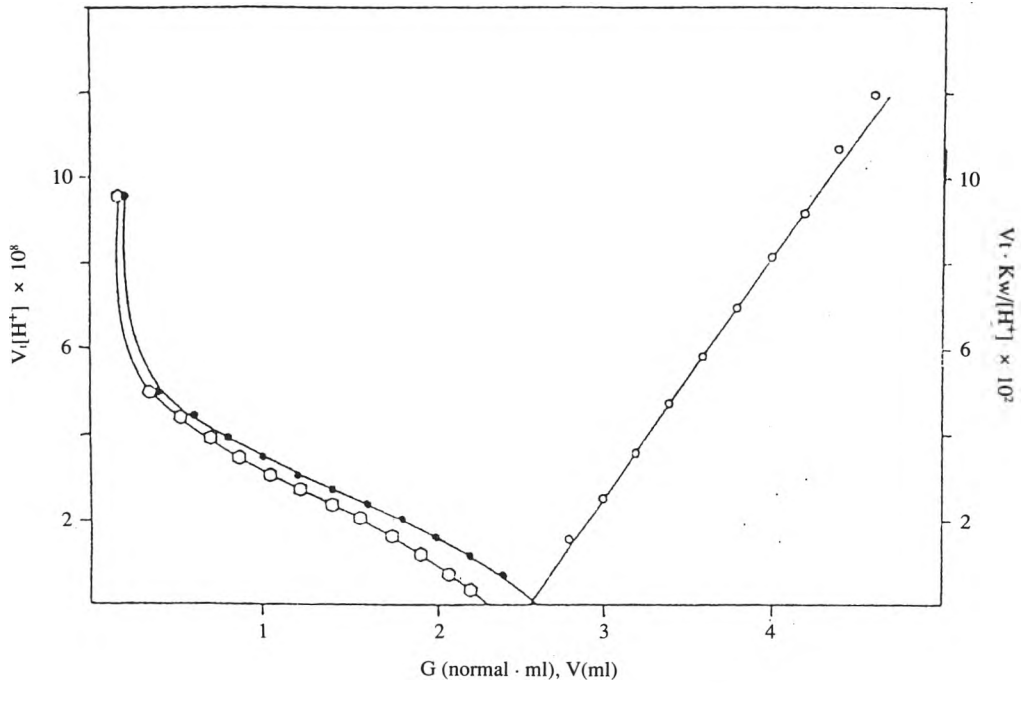

Figure 6 Gran's plot for the titration of dextromethorphan HBr in aqueous solution.
Key : G plot (○), V plot (●), E plot (○)

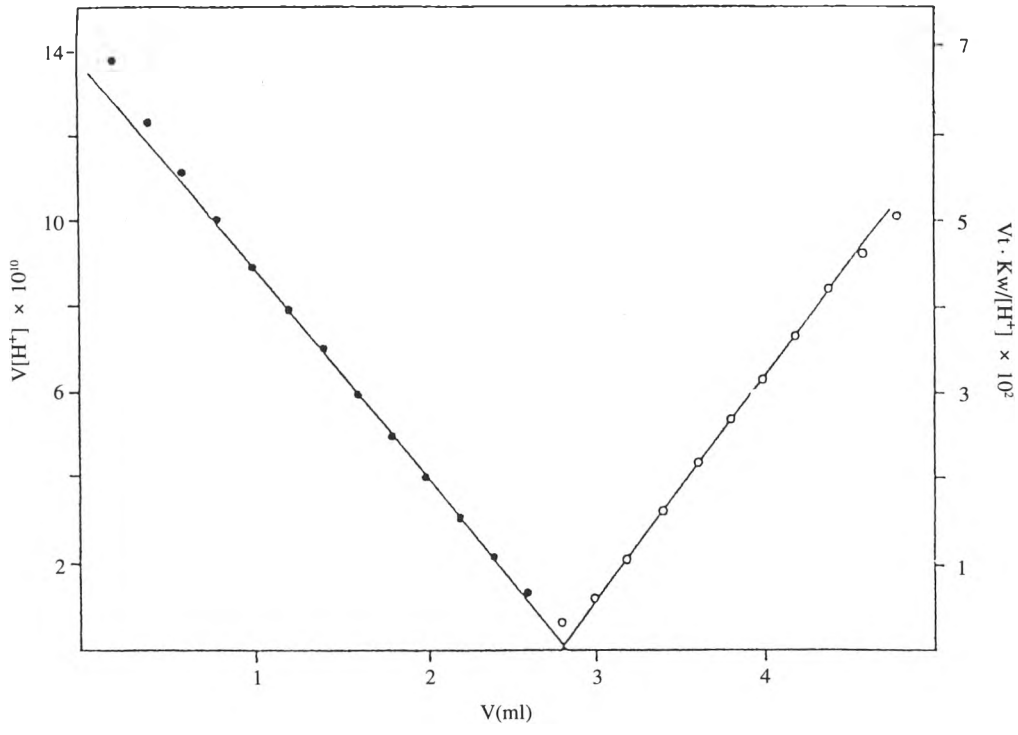

Figure 7 Gran's plot for the titration of pseudoephedrine HCl in 40% v/v ethanol/water.
Key : V plot (●), E plot (○)

Table 1 Percentage Purities of Weak Acid in Aqueous Solvent

Substance	pKa [a]	G Plot	V Plot	E Plot	Reference
Potassium hydrogenphthalate	5.4	99.86 (± 0.35)	99.48 (± 0.35)	100.4 (± 0.2)	100.1[b] (± 0.1)
Phenylpropanolamine HCl	9.4	100.2 (± 0.3)	102.0[d] (± 0.8)	99.83 (± 0.39)	100.3[c] (± 0.1)
Pseudoephedrine	9.9	100.2 (± 0.5)	106.7[d] (± 1.0)	95.71[d] (± 0.75)	99.98[c] (± 0.32)
Triprolidine HCl[e]	6.5	99.02 (± 0.35)	99.63[d] (± 0.20)	98.92 (± 0.22)	98.49[c] (± 0.58)
nhydramine HCl[e]	9.0	100.1 (± 0.2)	100.2 (± 0.2)	100.2 (± 0.4)	99.73c (± 0.09)
Dextrometorphan HBr[e]	8.3	102.0[d] (± 0.4)	104.8[d] (± 0.9)	99.90 (± 0.22)	99.79[c] (± 0.10)
Quinine sulfate[e]	8.8	100.6[d] (± 0.4)	100.8[d] (± 0.5)	100.7[d] (± 0.5)	97.94[c] (± 0.46)
Chlorpheniramine maleate[e]	6.2[f]	99.52[g] (± 0.11)	99.52[g] (± 0.11)	99.36[d] (± 0.09)	99.95[c] (± 0.18)
	9.2[h]	99.84 (± 0.16)	101.1d (± 0.2)		

[a] (9)
[b] determine end point volumes from potentiographs, using parallel tangent method.
[c] non-aqueous titration, USP XXI.
[d] statistically different from the reference method at p = 0,95.
[e] precipitation observed during the course of the titration. Modified G (Eg. 18) or V (Eq. 20) was employed for the calculation of the equivalence point.
[f] pKa for the second proton of maletic acid.
[g] from titration of the second proton of maleic acid.
[h] pKa for protonated form of chlopheniramine.

Table 2 Percentage Purities of Weak Acid in 40% v/v Ethanol/water

Substance	V Plot	E Plot	Reference
Potassium hydrogenphthalate	100.3 (± 0.2)	99.59 (± 0.3)	100.1[a] (± 0.1)
Phenylpropanolamine HCl	100.3 (± 0.2)	99.45 (± 0.19)	100.3[b] (± 0.1)
Pseudoephedrine HCl	100.2 (± 0.3)	98.83[c] (±0.29)	99.98[b] (± 0.32)
Triprolidine HCl	99.25 (± 0.22)	99.25 (± 0.18)	99.49[b] (± 0.28)
Diphenhydramine HCl	99.90 (± 0.07)	99.54 (± 0.07)	99.37[b] (± 0.09)
Dextrometorphan HBr	99.76 (± 0.17)	98.34[c] (± 0.19)	99.97[b] (± 0.10)
Quinine sulfate	97.86 (± 0.25)	97.71 (± 0.38)	97.94[b] (± 0.46)
Chlorpheniramine maleate	99.08[c] (± 0.36)	99.65 (± 0.10)	99.95[b] (± 0.18)

[a] determine end point volumes from potentiographs, using parallel tangent method.
[b] non-aqueous titration, USP XXI.
[c] statistically different from the reference method at p = 0,95.

CONCLUSION

In general, E plot appeared to give excellent results in both the aqueous and 40% v/v ethanol/water even in the cases which precipitation occured during the course of the titration, provided that the acid possesses dissociation constant of at least 4×10^{-10} and that the data used in constructing the E plot should not exceed pH of 11.5. Problem of precipitation which lead to erroneous equivalence point determination could be overcome by employing mixed solvent of 40% v/v ethanol/water. Other mixed solvent system probably could be employed to give satisfactory titration results.

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

1) Simplicity - The end point volume was obtained by extrapolation of linear regression line which was easier than employing some geometrical constructions in order to fix the end point volume of the sigmoid curve or drawing the first and second derivatives of titration curves and the linear regression would also involved less human error.

2) Rapidness - The end point determination by Gran's plot would be faster than the conventional methods since it needed fewer data for evaluation and measurements of titration data need not be made close to equivalence point and the over titration data (beyond the equivalence point) were still useful.

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

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การหาปริมาณตัวยาที่เป็นกรดอ่อน โดยวิธีของแกรน

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*อ. เสกสิริ อาตมางกูร**

บทคัดย่อ

ในการหาปริมาณของยาที่เป็นกรดอ่อนด้วยด่างแก่โดยเทคนิคทางโพเทนชิโอเมตริกไตเตรชั่น สามารถใช้วิธีของแกรนตรวจหาจุดยุติที่มีความถูกต้องและแม่นยำได้เช่นเดียวกับวิธีการไตเตรตในตัวทำละลายที่ไม่ใช่น้ำ ซึ่งมีปรากฏอยู่ในตำรายาแห่งชาติสหรัฐอเมริกา ฉบับที่ 21 นอกจากนี้วิธีของแกรนยังให้ผลที่น่าพอใจ แม้ว่าในขณะกำลังไตเตรตนั้นจะมีการตกตะกอนของตัวยาลงมา อย่างไรก็ตามเพื่อเป็นการหลีกเลี่ยงการตกตะกอนของตัวยา จึงใช้ทำตัวละลายผสมระหว่างอัลกอฮอล์ 40 เปอร์เซ็นต์ในน้ำ (โดยปริมาตร) และพบว่าวิธีของแกรนยังคงมีประโยชน์ในการตรวจหาจุดยุติได้เช่นกัน (ไทยเภสัชสาร ปีที่ 15(1) : หน้า 19-31 (2533))

* ภาควิชาเภสัชเคมี คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
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