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QUANTITATIVE DETERMINATION OF WEAK ACIDIC DRUGS IN MIXED SOLVENTS USING GRAN'S METHOD(การหาปริมาณตัวยาที่เป็นกรดอ่อนด้วยวิธีของแกรน ในตัวทำละล...

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ปฐมนิพนธ์

ORIGINAL ARTICLE

QUANTITATIVE DETERMINATION OF WEAK ACIDIC DRUGS IN MIXED SOLVENTS USING GRAN'S METHOD

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ABSTRACT

Gran's method for determination of end point of potentiometric titration was extended to mixed organic/aqueous solvent systems. In general, the calculated percentage purities of the acidic drugs were statistically indifferent from that obtained with the USP XXI method when the organic solvents were present below 30-40% v/v. (Th. J. Pharm. Sci., Vol.15 No.1, 33-42 (1990))

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INTRODUCTION

Gran's method is a graphical method for end point determination in potentiometry (1). This method is based on charge balance, mass balance and equilibrium expression which would allow us to plot and compute the end point of titrations. Various workers (1-5) had studied the applications of Gran's method in the determination of end point of acid-base titrations in aqueous solution. For monoprotic acid, the Gran's equation for data prior to the equivalence point is:

$$G[H^+] = KaVeN - KaG \qquad \text{Eq.1}$$

where

$$G = VN + (Vo + V)([H^+] - [OH^-]) \qquad \text{Eq.2}$$

Ka, V, Ve, Vo, and N are the aqueous dissociation constant of the weak acid, volume of the titrant added to the titrated sample, volume at equivalence point of the titration, initial volume of the sample and normality of the titrant, respectively.

If $VN >> (Vo + V)([H^+] - [OH^-])$, then Eq. 1 reduces to

$$V[H^+] = KaVe - KaV \qquad \text{Eq. 3}$$

For the data after the equivalence point, the Gran's equation would be:

$$\frac{KwVt}{[H^+]} = (V - Ve)N \qquad \text{Eq.4}$$

where Kw is the aqueous dissociation constant for water. Once the end point volume is calculated, the percentage purity is then calculate from the following equation:

$$\% \text{ purity} = \frac{Ve \times N \times Eq.Wt \times 100}{Wt} \qquad \text{Eq. 5}$$

where Eq.Wt and Wt are the equivalence weight and weight of the weak acid, respectively. Seksiri (2) employed the Gran's method to determine the end point of various weak acids by titrating in aqueous solution and 40% v/v ethanol/water. The results showed that for aqueous solutions, Gran's method would yield end point volumes which were statistically indifferent (at p = 0.95) from the reference non-aqueous procedures as described for each specific weak acidic drug in the USP XXI. except in the cases which precipitations of the unionized conjugate bases occured. In attempt to avoid the problem of precipitations, mixed solvents system consisting of 40% v/v ethanol/water was employed and the results showed that Gran's method still gave and points which were statistically indifferent to that of the reference USP XXI procedures. Thus, it would be of interest to investigate different solvent systems which may be utilized to avoid the problem of precipitation so that the Gran's method may be utilized to its fullest capacity. Again, the non-aqueous USP XXI methods were chosen as the references to which the results from the Gran's method were compared. Methanol, ethanol and propylene glycol were chosen as the organic solvent in our study because of their reasonably low coefficiency of volume expansion and low cost. In Seksiri's study (2), the G plot (Eq. 1) was not extended to the mixed solvent system of 40% v/v ethanol/water because of uncertainly concerning the extent of the autoprotolysis of water in such solvent system. Ong *et al.* (6), Bates *et al.* (7) and Bacarella *et al.* (8) had shown that ordinary pH meter with glass electrode would display nearly the theoretical response to hydrogen ion, at least up to alcohol concentration near 80% w/w. Therefore in our current study, we applied G plot to all of the mixed solvent system with the assumption that the dissociation constant of H_2O would not increase excessively as we increased the percentage of organic solvent in the system. For Eq.1 (G plot) and Eq. 4 (E plot), the normal value of Kw (1.00×10^{-14}) would be employed.

EXPERIMENTAL SECTION

Materials:

1. Test Drugs : dextromethorphan hydrobromide, quinine suflate, diphenhydramine hydrochloride, chlorpheniramine maleate, triprolidine hydrochloride.
2. Other Reagents: methanol AR (E-Merck), ethanol (E-Merck), propylene glycol (Vidhyasom), potassium hydrogen phthalate AR (E-Merck), sodium hydroxide AR (Vidhyasom), glacial acetic acid AR (E-Merck), perchloric acid AR (E-Merck), mercuric acetate AR. (E-Merck).

Methods:

Preparation of weak acidic drugs in organic solvent/water:-

All weak acidic drugs were accurately weighed to produce final concentrations of about 5×10^{-3} M. The acidic salts were dissolved with portioned of distilled water. Required volume of the organic solvent was added and then adjust to volume by distilled water. The solutions were then allowed to cool down to room temperature before making the final adjustment to volume with distilled water. Sample aliquotes of 50 ml were volumetrically transfered to a 100-ml beaker for titration with aqueous solution of 0.1 N NaOH. Choosing aqueous solvent for the titrant would allow us to use the same standardized titrant solution for two to three weeks without having to be concerned about the volume change due to change in room temperature.

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 (9).

Equipments:

Potentiograph E536 (Metrohm Herisau), electrode AG9100 (Metrohm Herisau), automatic titrator 655 Multi-Dosimat (Metrohm Heisau with exchange unit model 3005 (501), magnetic stirrer E649 (Metrohm Herisau).

RESULTS AND DISCUSSION

The percentage of the organic solvent in the mixed solvent system was determined by the solubility of each individual drug. We found that normally the lowest persentage of organic solvent needed to maintain a homogeneous solution throughout the titration was at least 30% v/v organic/water. The titration curves of triprolidine HCl in various concentration of methanol/water, ethanol/water and propylene glycol/water are shown in Figures 1-3, respectively. Titration curves for other compounds are similar to that of quinine sulfate. The calculated percentage purities of the weak acids are listed in Tables 1-5, along with the percentage purity of the individual drug as determined with the reference USP XXI non-aqueous titration method.

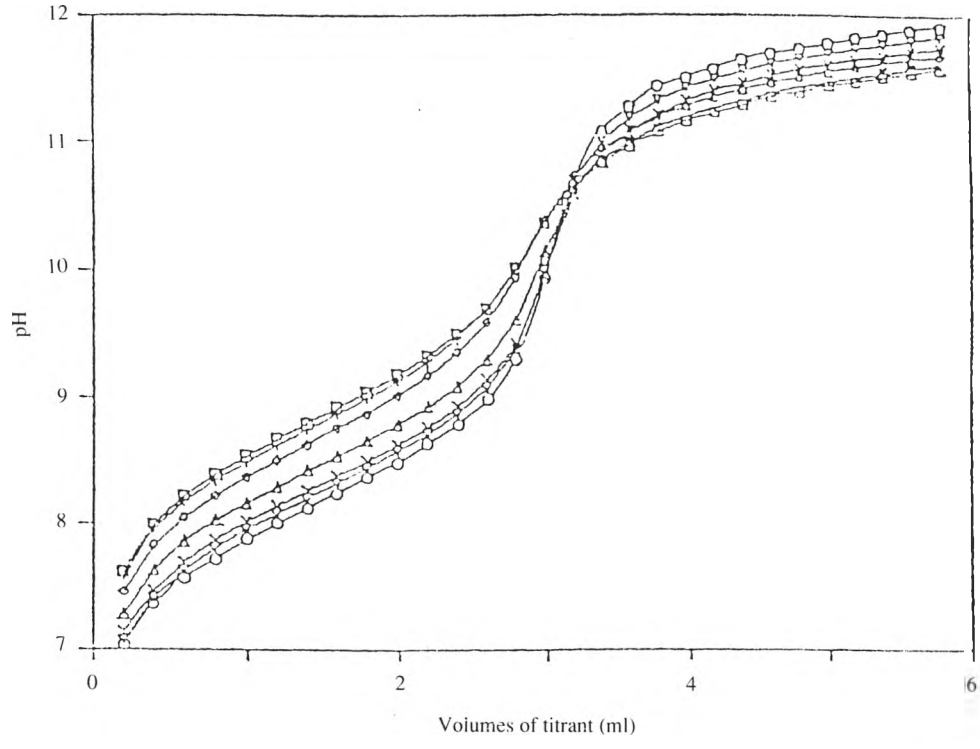

Figure 1 Titration curve of triprolidine HCl in 30-90% v/v methanol/water
Key : 30% (□), 40% (+), 50% (◇) 60% (Δ), 70% (X),
80% (∇), 90% (○)

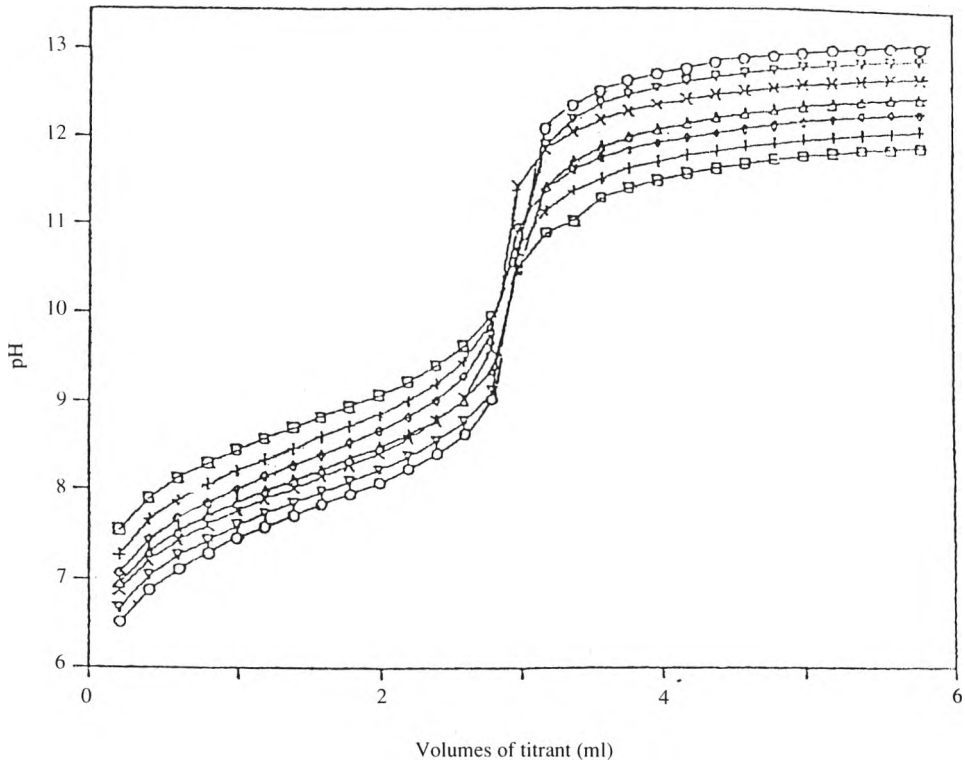

Figure 2 Titration curves of triprolidine HCl in 30-90% v/v ethanol/water.
Key : 30% (□), 40% (+), 50% (◇) 60% (Δ),70% (X),
80% (∇), 90% (○)

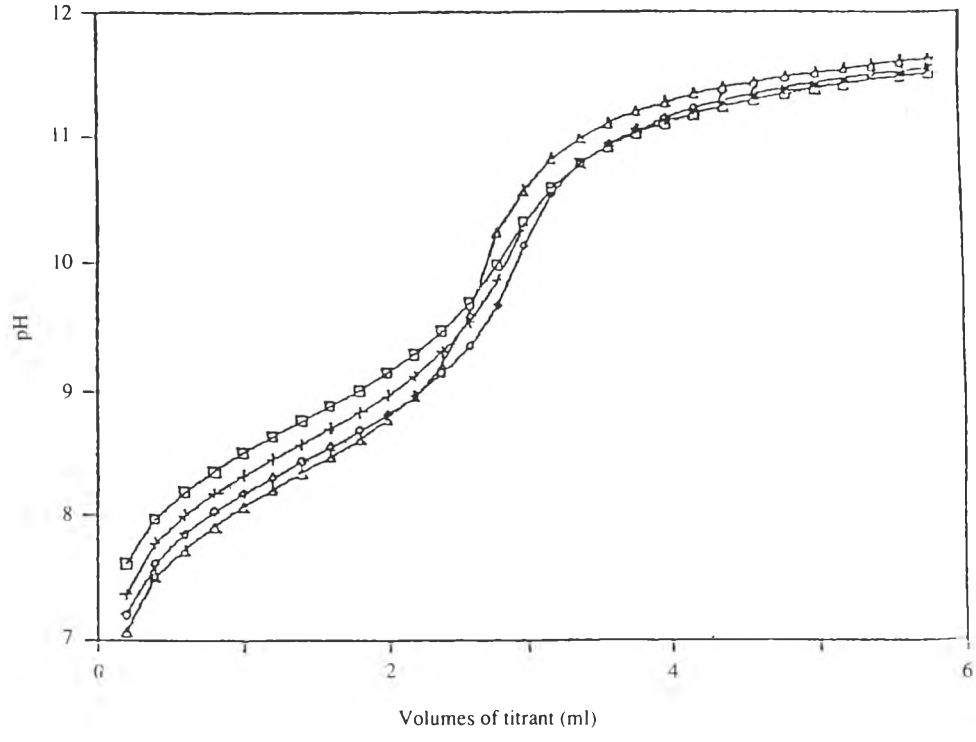

Figure 3 Titration curves of triprolidine HCl in 40%-70% v/v propylene glycol/water. Key : 40% (□), 50% (+), 60% (◇), 70% (Δ)

Table 1 Percentage Purities of Triprolidine HCl

Organic solvent % v/v	Percentage Purity G Plot	V Plot	E Plot	USP XXI
Methanol				
30%	99.20 ± 0.22	99.06 ± 0.16	98.92 ± 0.35	99.25 ± 0.20
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	
70%	98.9 ± 0.41	98.99 ± 0.40	98.76 ± 0.19	
80%	98.10 ± 0.24*	99.10 ± 0.41*	98.43 ± 0.30*	
90%	98.04 ± 0.33*	98.16 ± 0.44*	97.45 ± 0.34*	
Ethanol				
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*	-	
70%	97.79 ± 0.52*	97.76 ± 0.52*	-	
80%	97.91 ± 0.46*	97.84 ± 0.44 *	-	
90%	97.50 ± 0.31*	97.71 ± 0.16*	-	
Propylene Glycol				
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*	
70%	97.92 ± 0.22*	97.91 ± 0.56*	98.14 ± 0.31*	

* result is statistically different from that of the reference USP XXI method at p = 0.99.

Table 2 Percentage Purities of Quinine Sulfate

Organic solvent % v/v	Percentage Purity G plot	V Plot	E Plot	USP XXI
Methanol				
40%	99.13 ± 0.27	98.81 ± 0.42	99.00 ± 0.24	99.11 ± 0.22
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	
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*	
Ethanol				
40%	98.90 ± 0.37	98.85 ± 0.38	98.92 ± 0.16	
50%	98.17 ± 0.25*	98.45 ± 0.31*	98.40 ± 0.25	
60%	98.28 ± 0.43*	98.45 ± 0.45*	98.27 ± 0.34*	
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*	-	
Propylene Glycol				
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	
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*	

* result is statistically different from that of the reference USP XXI method at p = 0.99.

Table 3 Percentage Purities of Dextromethorphan HBr

Organic solvent % v/v	Percentage Purity G Plot	V Plot	E Plot	USP XXI
Methanol				
50%	95.34 ± 0.13	95.08 ± 0.28	93.41 ± 0.18*	95.00 ± 0.16
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*	
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*	
Ethanol				
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 ± 0.23*	
70%	93.39 ± 0.19*	93.97 ± 0.35*	94.33 ± 0.16*	
80%	92.70 ± 0.24*	92.74 ± 0.37*	-	
90%	92.58 ± 0.29*	92.78 ± 0.28*	-	
Propylene Glycol				
60%	92.41 ± 0.46*	93.40 ± 0.73*	92.32 ± 0.55*	
70%	92.44 ± 0.70*	92.95 ± 0.84*	91.35 ± 0.73*	

* results is statistically different from that of the reference USP XXI method at p = 0.99.

Table 4 Percentage Purities of Diphenhydramine HCl

Organic solvent % v/v	Percentage Purity G Plot	V Plot	E Plot	USP XXI
Methanol				
30%	100.2 ± 0.5	100.3 ± 0.5	100.2 ± 0.4	100.2 ± 0.1
40%	99.88 ± 0.18	99.99 ± 0.25	99.23 ± 0.12*	
50%	99.82 ± 0.23	100.0 ± 0.3	99.00 ± 0.34*	
60%	99.77 ± 0.35	100.1 ± 0.4	98.79 ± 0.22*	
70%	100.2 ± 0.4	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*	
Ethanol				
30%	99.89 ± 0.15	100.0 ± 0.3	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*	
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*	-	
Propylene Glycol				
40%	99.89 ± 0.16	100.2 ± 0.3	99.71 ± 0.57	
50%	98.74 ± 0.33*	99.16 ± 0.33*	97.40 ± 0.16*	
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*	

* result is statistically different from that of the reference USP XXI method at p = 0.99.

Table 5 Percentage Purities of Chlorpheniramine Maleate

Organic solvent % v/v	Percentage Purity G Plot	V Plot	E Plot	USP XXI
Methanol				
30%	58.92 ± 0.31*	58.93 ± 0.31*	99.74 ± 0.22	99.90 ± 0.21
40%	69.46 ± 0.31*	69.73 ± 0.38*	100.1 ± 0.2	
50%	90.44 ± 0.45*	90.49 ± 0.45	99.94 ± 0.17	
60%	100.2 ± 0.3	100.3 ± 0.2	99.84 ± 0.17	
70%	102.6 ± 0.5*	102.8 ± 0.2 *	100.2 ± 0.1	
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*	
Ethanol				
30%	62.35 ± 0.29*	62.58 ± 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 ± 0.1	98.60 ± 0.17*	
70%	98.99 ± 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*	-	
Propylene Glycol				
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	
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*	

* result is statistically different from that of the reference USP XXI method at p = 0.99.

Methanol/water system:

The results from both G. (Eq. 1) and V (Eq. 3) plots were statistically indifferent (t-test) from the reference procedure at p = 0.99 as long as the percentage of methanol does not exceed 70% v/v. Once the percentage of methanol is over 70%, the effect of liquid junction potential of the electrode and the medium effect became too large to neglect and none of the Gran's plots (G, V and E plots) would give satisfactory result. E plot (Eq. 4) did not do as well as the G and V plots in the determination of end point volumes in methanol/water. For all the titrations, we found that as the percentage of the methanol in the solvent increased, the pH of the solutions prior to the equivalence point decreased and the pH of the solution after the equivalence point increased as compare to the solution of lower percentage of methanol. This would indicate that the dissociation constant of H_2O decreased significantly as the polarity of the solvent system decreased. Thus by employing 1×10^{-14} as the value for the dissociation constant in mixed solvent system in Eq. 4, would lead to error in calculation of the hydroxide concentration and consequently, the E plot would yield erroneous results. Another reason for the failure of the E plot is that the apparent pH of the solution after equivalence point were in the region which glass electrode would falsely measure the Na^+ ions in the solution for hydronium ions. The E plot, in general, gave satisfactory results only for data under pH of 11.5.

Chlorpheniramine maleate is actually a mixture of monoprotic acids of monohydrogen maleate and protonated chlorpheniramine. In methanol/water solvent system, the dissociation constants of these two acids were close enough together such that the neutralization of protonated chlorpheniramine by sodium hydroxide would begin while neutralization of the second proton of maleic acid had not completed. Under this condition, both Eqs. 1 and 3 would not be valid and erroneous results were obtained. However, at 60% v/v methanol/water, the results from G and V plots were statistically indifferent from non-aqueous titration. It is possible that the two dissociation constants of chlorpheniramine maleate were shifted to approximately the same value and, thus, Eqs. 1 and 3 are, again, applicable. Since the E. plot (Eq. 4) did not depend upon the dissociation constant of the acid, in general, it would give satisfactory results as long as data were obtained from the region with pH less than 11.5 as we had discussed earlier.

Ethanol/water system:

The results in ethanol/water were similar to that of the methanol/water . Originally, we had thought that Gran's method would actually work better in ethanol/water than methanol/water since ethanol is less polar than methanol and therefore acidic salt compound would have higher dissociation constant value in ethanol/water than methanol/water. The titration curves of the acidic -salt drugs did show that pH of the solutions, prior to the equivalence point actually lower than the corresponding methanol/water system. This means VN should be much larger than (Vo + V) ($[H^+]$ - $[OH]$) and hence, V plot should work well. However, the opposite were observed. Table 1-5 showed that G and V plots would give satisfactory results only if the ethanol concentration is 40% or below.

In their work with ethanol/water solvent system, Bates *et al.* (7) had concluded that glass electrode could be used to measure pH of 40% ethanol/water solution for the pH range of 3 to 9.5; in 50% ethanol/water, deviation of pH mea-surement became apparent at pH 9; and when percentage of ethanol increased to 70%, deviation appeared at pH 8. It would appear that the effect of liquid junction potential of the ethanol on the electrode was more significant than the effect of methanol on the electrode.

After the equivalence point, pH of the solution rose rapidly, pH of the solution was higher than that of the corresponding percentage of methanol. This was due to the effect of the decrease in polarity of the solvent on the dissociation constant of H_2O and as in the case of methanol/water solvent system, E plot did not work as well as the G or V plot.

Propylene glycol/water system:

The highest composition of propylene glycol employed in the titrations was 70% v/v beyond which the solution became very viscous and establishment of the equilibrium was too time consuming. In general, G,V and E plots gave satisfactory results for solvent systems containing 40% or less of propylene glycol. However, minimum of 30% to 40% of propylene glycol was normally needed to keep the unionized drug molecules in solution. As the percentage of propylene glycol in the solution increased, the viscosity of the solutions also increased. The effect of the viscosity on the activity coefficients and diffusion coefficients of the chemical species in the solution is probably the primary factor leading to the erroneous end point determination as the percentage of propylene glycol reachs 50% or more.

CONCLUSION

In general, G, V and E plots gave accurate and reproducible titration end points for solutions containing single acidic specie. While both G and V plots performed better than E plots, the V plot has the advantage in term of simplicity. If the value of the dissociation constant of H_2O in that particular solvent system were not known, E plot would yield erroneous end point volume eventhough the plot showed good linearity. Of the three solvent systems under this study, methanol appeared to give the best results. For mixture of monoprotic acid such as chlorpheniramine maleate, E plot gave the most accurate results as it would not be interfered by the overlapping neutralizations of the acidic species.

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การหาปริมาณตัวยาที่เป็นกรดอ่อนด้วยวิธีของแกรน ในตัวทำละลายผสม

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บทคัดย่อ

การตกตะกอนของยาที่เป็นกรดอ่อนบางตัว เมื่อทำการวิเคราะห์โดยการติเตรตกับด่างแก่ในตัวทำละลายที่เป็นน้ำ สามารถแก้ไขได้โดยทำการติเตรตในตัวทำละลายผสมระหว่างน้ำและตัวทำละลายอินทรีย์ (เอธิลอัลกอฮอล, เมธิลอัลกอฮอล และไพรพีลีนไกลคอล) การติเตรตระหว่างตัวยาที่เป็นกรดอ่อนและด่างแก่ในตัวทำละลายผสมดังกล่าวกระทำโดยอาศัยเทคนิคทางโพเทนทิโอเมตรี พบว่าสามารถใช้วิธีของแกรนในการตรวจหาจุดยุติเพื่อนำมาคำนวณหาปริมาณของตัวยาที่มีความถูกต้องและแม่นยำได้เช่นเดียวกับวิธีการติเตรตในตัวทำละลายที่ไม่ใช่น้ำ ซึ่งมีปรากฏอยู่ในตำรายาแห่งชาติของสหรัฐอเมริกาฉบับที่ 21 (ไทยเภสัชสาร ปีที่15 (1) : หน้า 33-42 (2533))

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**ภาควิชาเภสัชเคมี คณะเภสัชศาสตร์ มหาวิทยาลัยสงขลานครินทร์