CHAPTER I

INTRODUCTION

In quantitative determinations of weak acidic drugs in pharmaceutical field, most of them are in the form of acid salts. Because of the low values of dissociation constants ($Ka < 10^{-7}$) for these acid salts (consequently reactions are not sufficiently complete to yield satisfactory end points in aqueous solvent systems), we generally must employ non-aqueous titration. However, there are some extra precautions that should be considered for non-aqueous titration:

First, moisture is generally to be avoided in using non-aqueous procedure, since water, being a weak acid, can compete with the weak acidic drugs for basic titrant and the sharpness of the end point could be obscured. Experimentally, it has been found that the moisture content in non-aqueous titrimetry should be held to less than 0.05% so as not to have any appreciable effect on end point determination (1).

Second, temperature must be fairly constant throughout the titration because of the high coefficient of expansion of organic solvents (2).

Third, utilization of indicators for determination of end points may not be totally satisfactory. The color change may not be as obvious as might be desired. Thus, the potentiometric end point determination should be employed in the quantitative analysis of some weak acidic drugs and determined the equivalence point by grapical method from titration curve or from first and second derivatives, such as triprolidine HCl (3). However, it is not generally practical.

Fourth, according to USP XX (4), in quantitative determination of some weak acidic drugs, such as quinine sulfate or other alkaloid salts, acetic anhydride which is employed as solvent is a special controlled chemical. Thus, it is not widely available.

Fifth, many non-aqueous solvents such as glacial acetic acid and perchloric acid are volatile irritants. Consequently, it is not safe for the routine analysis.

Finally, we should also considered the cost of solvent which is usually high.

Potentiometric titrations are useful in a wide variety of situations and can be used in those cases where a satisfactory visual indicator is unavailable or where substances are present in the titrated solution that would interfere with indicator action (5,6). There are various methods for determination of end point

volumes in potentiometric titrations: method based on the sigmoid form of titration curve, differential method and method based on mass balance and equilibrium equation. The optimal method for evaluating the end point of a particular potentiometric titration with respect to systemic error, precision and time required is the method based on mass balance, charge balance and equilibrium equation (7).

Seksiri (8) had employed Gran's method, the graphical method for end point determination in potentiometry, in quantitative determination of weak acidic drugs by titrating in aqueous solvent. The results of Seksiri's study suggested that Gran's method would yield results which were statistically indifferent from that of non-aqueous titration, except in the titration of acidic drugs whose non-ionic conjugate base posses low aqueous solubility and hence precipitations were observed during the course of titrations. In Seksiri's investigation, mixed solvent systems consisting of ethanol and water was employed in order to avoid the problem of precipitation and using Gran's method in determination of equivalence volumes.

GRAN'S METHOD

Gran's method (9) is the graphical method for end point determination in potentiometry which carried out by the technique of addition titration. Based on

mass balance, charge balance and equilibrium expression (9,10), it would allow us to plot and compute the end point of titrations. Experimental-wise, it is just a routine acid-base titration in which a known volume of titrant is tranfered to the titrated solution and measuring the pH values when equilibrium has reached (10,11,12).

Calculation of Equivalence Volume

Gran's method is based on original idea of Sorensen (13) who plotted the concentration of hydronium ion as a function of the volume of titrant added, disregarding the effect of the changing volume. Gran (9) had introduced a correction for the volume change during the course of the titration. However, the limit beyond which the simple Gran's equation do not yield satisfactory results can be considered as Ka $< 10^{-7}$, because Gran had not accounted for autoprotolysis of water. In 1966, Ingman and Still (9) modified by correcting the autoprotolysis of water in Gran's equation, for cases which are normally encountered in practice when very weak acids ($10^{-7} > Ka > 10^{-10}$) are titrated.

The derivation for some weak acids, acid salt drugs, and strong base titration based on Gran's method and also modified from Ingman and Still's idea are shown as followed:

1. Tirtration of Monoprotic Acid (8,9,10,13,14)

1.1 Derivations for titration data prior to equivalence point. (V < Ve)

When a weak acid, HB^+X^- , is titrated with a strong base, NaOH.

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

$$HB^+ \rightleftharpoons H^+ + B$$

Where B is the unionized form of weak acid, acid salt, HB^+X^-. The derivation is based on the following three conditions:

a) The law of mass balance is hold:

$$C_{HB^+} = [X^-] = [HB^+] + [B]. \qquad (1)$$

b) The law of charge balance, The solution must be electrically neutral, meaning that

$$[HB^+] + [H^+] + [Na^+] = [OH^-] + [X^-]. \qquad (2)$$

The concentration of sodium ion at any volumes of titrant is

$$[Na^+] = \frac{VN}{Vo + V} \qquad (3)$$

and at the equivalence point

$$C_{HB^+} (Vo + V) = VeN$$

also $$C_{HB^+} = \frac{VeN}{Vo + V} = [X^-]. \quad (4)$$

Substitution of Eq. (4) into (1) yields

$$[HB^+] + [B] = \frac{VeN}{Vo + V} . \quad (5)$$

When combined Eqs. (2) and (3), gives

$$[HB^+] + [H^+] + \frac{VN}{Vo + V} = [OH^-] + [X^-] . \quad (6)$$

Substitution Eq. (4) into (6), yields

$$[HB^+] = \frac{VeN}{Vo + V} - \frac{VN}{Vo + V} - [H^+] + [OH^-] . \quad (7)$$

Eq. (5) is substrated by Eq. (7), yields

$$[B] = \frac{VN}{Vo + V} + [H^+] - [OH^-] . \quad (8)$$

c) Equilibrium balance, the dissociation constant of HB^+ can be expressed by

$$Ka = \frac{[H^+][B]}{[HB^+]} . \quad (9)$$

Substitution Eqs. (7), (8) into (9)

$$Ka = \frac{[H^-]\left[\frac{VN}{Vo + V} + [H^+] - [OH^-]\right]}{\frac{VeN}{Vo + V} - \left[\frac{VN}{Vo + V} + [H^+] - [OH^-]\right]} \quad (10)$$

and rearrangement gives

$$G[H^+] = KaVeN - KaG \quad (11)$$

where $G = VN + [Vo + V]\{[H^+] - [OH^-]\}$. (12)

From Eq. (11), plot of $G[H^+]$ vs G will give linear relationship of which Ka is slope and from intercept, Ve can be obtained.

If $\frac{VN}{Vo + V} >> [H^+] - [OH^-]$ (13)

Eq. (12) can be reduced to

$$V[H^+] = KaVe - KaV \; . \qquad (14)$$

This is indeed a reasonable approximation, except when V is small (10). And also plot of $V[H^+]$ vs V will give a linear relationship of which Ka is slope and from intercept, Ve can be obtained.

1.2 Derivation for titration data after equivalence point. (V > Ve)

When an acid salt (HB^+X^-) is titrated, charge balance of the solution after the equivalence point is

$$[X^-] + [OH^-] = [Na^+] + [H^+] \qquad (15)$$

and the mass balance of the weak acid is

$$[X^-] = C_{HB^+} = \frac{VeN}{Vo + V} \; . \qquad (16)$$

Substitution Eq. (16) in (15), and subsequent rearrangement of the terms yields

$$[OH^-] - [H^+] = [Na^+] - \frac{VeN}{Vo + V} . \qquad (17)$$

In the alkaline region, generally $[OH^-] >> [H^+]$, Eq. (17) can be reduced to

$$[OH^-] = [Na^+] - \frac{VeN}{Vo + V} . \qquad (18)$$

Substituting Eq. (3) in (18) and from dissociation constant of water, $Kw = [H^+][OH^-]$, gives

$$\frac{Kw}{[H^+]} = \frac{VN}{Vo + V} - \frac{VeN}{Vo + V} \qquad (19)$$

which can be rearrange to

$$\frac{KwVt}{[H^+]} = (V - Ve)N \qquad (20)$$

where $Vt = Vo + V$.

In this case, plot of $KwVt/[H^+]$ vs V will give a linear relationship of which N is slope and from intercept, Ve can be obtained.

From the derivation above, we have three equations which would give linear plot, Eqs. (11) and (14) for the data before equivalence plot. Eq.(14) is the Gran's equation and Eq.(11) is the modified of Gran's equation which accounted the autoprotolysis of water. Eq. (20) is derived for the data after equivalence point.

2. Titration of Diprotic Acid Salt (8,9,10.13)

2.1 Derivation for titration data prior to equivalence point

When salt of weak base, $H_2B^{2+}X^{2-}$ is titrated.

a) The dissociation of this acid is

$$H_2B^{2+} \rightleftharpoons HB^+ + H^+$$

$$Ka_1 = \frac{[HB^+][H^+]}{[H_2B^{2+}]} \qquad (21)$$

and

$$HB^+ \rightleftharpoons B + H^+$$

$$Ka_2 = \frac{[B][H^+]}{[HB^+]} \quad . \qquad (22)$$

If $Ka_1 >> Ka_2$, such that neutralization of the first acidic function is complete prior to neutralization of the second acidic function, the reaction before first equivalence point is

$$H_2B^{2+} + NaOH \longrightarrow HB^+ + H_2O + Na^+ \; . \qquad (23)$$

b) The charge balance equation for the solution is

$$[H^+] + [HB^+] + 2[H_2B^{2+}] + [Na^+] = [OH^-] + 2[X^{2-}]. \qquad (24)$$

c) The mass balance of weak acid gives

$$C_{H_2B^{2+}} = [X^{2-}] = [HB^+] + [H_2B^{2+}] \; . \qquad (25)$$

Substracting Eq. (24) with (25) yields

$$[H^+] + [H_2B^{2+}] + [Na^+] = [OH^-] + [X^{2-}] . \quad (26)$$

If, $$[X^{2-}] = C_{H_2B^{2+}} = \frac{Ve_1N}{Vo + V} \quad (27)$$

substitution Eqs. (3) and (27) into (26), yields

$$[H_2B^{2+}] = \frac{Ve_1N}{Vo + V} - \frac{VN}{Vo + V} + [H^+] - [OH^-] . \quad (28)$$

Substitution Eq. (28) into (25) and combining with (27) which may be rearranged to

$$[HB^+] = \frac{VN}{Vo + V} + [H^+] - [OH^-] . \quad (29)$$

Substitution Eqs. (28) and (29) into (21), gives

$$Ka_1 = \frac{[H^+]\left[\frac{VN}{Vo + V} + [H^+] - [OH^-]\right]}{\frac{Ve_1N}{Vo + V} - \left[\frac{VN}{Vo + V} + [H^+] - [OH^-]\right]} . \quad (30)$$

Substitution G in Eq. (30) and rearrangement yields

$$[H^+]G = Ka_1Ve_1N - Ka_1G . \quad (31)$$

Before second equivalence point, it is assumed that $[H_2B^{2+}]$ is approximately zero. The reaction is

$$HB^+ + NaOH \longrightarrow H_2O + B + Na^+ \quad (32)$$

and charge balance

$$[H^+] + [HB^+] + [Na^+] = [OH^-] + 2[X^{2-}] . \quad (33)$$

The mass balance of weak acid is

$$C_{HB^+} = 2[X^{2-}] = [HB^+] + [B] \quad (34)$$

where $$C_{HB^+} = 2[X^{2-}] = \frac{Ve_2N}{Vo + V} \quad (35)$$

and $$[HB^+]t = \frac{Ve_1N}{Vo + V} + [HB^+] \quad . \quad (36)$$

Substitution Eqs. (35) and (3) into (33), gives

$$[HB^+] = \frac{Ve_2N}{Vo + V} - \frac{VN}{Vo + V} + [H^+] - [OH^-] \quad . \quad (37)$$

Eqs. (34), (36) and (37) gives

$$[B] = \frac{VN}{Vo + V} + [H^+] - [OH^-] - \frac{Ve_1N}{Vo + V} \quad . \quad (38)$$

Substitution Eqs. (37) and (38) in (22)

$$Ka_2 = \frac{[H^+]\left[\frac{VN}{Vo + V} + [H^+] - [OH^-] - \frac{Ve_1N}{Vo + V}\right]}{\frac{Ve_2N}{Vo + V} - \left[\frac{VN}{Vo + V} + [H^+] - [OH^-]\right]} \quad (39)$$

Substitution G in Eq. (39) and rearrangement gives

$$[H^+](G - Ve_1N) = Ka_2Ve_2N - Ka_2G \quad . \quad (40)$$

If it is assumed that $\frac{VN}{Vo + V} >> [H^+] - [OH^-]$

Eqs. (31) and (40) are reduced to, respectively

$$V[H^+] = Ka_1Ve_1 - Ka_1V \quad (41)$$

$$[H^+](V - Ve_1) = Ka_2Ve_2 - Ka_2V \quad . \quad (42)$$

For the titration of diprotic acid salt, Eqs. (31), (41) are linear equations. Eq. (31) involves the autoprotolysis of water and the change of volumes during the course of titration whereas Eq. (41) corrects only the change of titration volumes. Both Eqs. (31) and (41) are employed for first end point determination. Eqs. (40) and (42) can be reduced to simple linear equations once Ve is known and the second end point determination can be obtained from extrapolation of the linear lines.

2.2 Derivation for titration data after equivalence point.

For ionized diprotic acid salt ($H_2B^{2+}X^{2-}$), the charge balance of the solution in alkaline region is

$$2[X^{2-}] + [OH^-] = [Na^+] + [H^+] \qquad (43)$$

and mass balance of this weak acid is

$$2[X^{2-}] = C_{H_2B^{2+}} = \frac{VeN}{Vo + V} . \qquad (44)$$

Substitution Eqs. (44) and (3) in (43) yields

$$\frac{VeN}{Vo + V} + [OH^-] = \frac{VN}{Vo + V} + [H^+] \qquad (45)$$

and in the similar way as derived previously

$$\frac{KwVt}{[H^+]} = (V - Ve)N . \qquad (46)$$

Eqs. (20) and (46) are identical equations which are employed in determination of end point volumes of weak acids for titration data after equivalence point.

In all derivations, we have neglected activity correction in calculating hydrogen ion concentration. This will be alter the gradient of the curves, but it will not affect the determination of the equivalence volumes (10).

The Advantage of Gran's Method

1. In Gran's plot (15), it is necessary to obtain only a few points for the linear plot. The end point can be easily determined by extrapolating the linear line to the horizontal axis. Points only need to be accurately determined a bit away from the equivalence point where the titrant is in sufficient excess to suppress dissociation of the titration product and where electrode response is rapid because one of the ions is at relatively high level compared to the level at the equivalence point. So, measurements need not be made close to the equivalence point ; therefore, problems associated with incompleteness of reaction or instability of measurements close to be end point can be avoided (16). In case of small inflection points, the end point is more readily defined by a Gran's plot.

2. Fewer titration points need to be taken than conventional method (16).

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

4. The end points obtained by a linear Gran extrapolation are much more precise than those obtained by the differential method, especially if the titration curve is not symmetrical (14).

5. Preliminaly estimation of equivalence point is not necessary for Gran plot method

6. Gran's method can be applied, particularly when analyte concentration is too low to give well defined end points. Frazer and coworkers (17) had presented end point determination for the titration which was run on low concentration sample near the detection limited of the electrode by Gran's method which yielded excellent results.

The Gran's method seem to be the most suitable method for utilizing in routine work because of its accuracy, precision, rapidness and simplicity in calculation (10,13,14).

Ambrocio Sanchez-perez and his friends (18) had determined cimetidine in tablet by an aqueous potentiometric titration and estimated the end point by Gran graphical method. They found that the results obtained demonstrate good precision, good accuracy and compared well with those obtained from polarographic method.

Seksiri (8) had studied quantitative determination of weak acidic drugs, such as diphenhydramine hydrochloride, dextromethorphan hydrobromide, phenylpropanolamine hydrochloride, psuedoephdrine hydrochloride, chlorphenilamine maleate, triprolidine hydrochloride and quinine sulfate, by titrating them in aqueous solvent and using Gran's method in determination of equivalence point. She found that the results from Gran's method for the analysis of phenylpropanolamine hydrochlride and psuedoephedrine hydrochloride were statistically indifferent when compared with the results obtained from non-aqueous titrations. However, as expected, Gran's plot would give erroneous results for drugs which precipitated from aqueous solution during the course of titrations. In order to overcome problems arised from precipitation, Seksiri had used solvent system consisted of 40% v/v ethanol in water (8).

Mixed solvents of organic solvents and water could be employed in the acid-base titrations to

increase the solubility of drugs and to give homogeneous solution throughout the course of titration, and it is possible that the resulting Gran's plot might still be useful in detection of equivalence point.

The method of using mixed solvents in potentiometric titration originated with Mizutani (19), which used in determination of dissociation constant of substances that could not dissolve in aqueous solvent. There are many mixed solvent systems that were used for determining dissociation constant of weak acids which unionized form had low solubility and precipitated during the course of titration.

Marshall (19) determined the dissociation constant of various antihistamines in ethanol-water mixture. A methanol-water solvent was used by Chatten and Harris (19) to study phenothiazine and sympathomimetic amines. Speakman (20) determined the dissociation constant of some acid in water-alcoholic mixtures. Rubino and Berryhill (21) had studied the effect of polarity of solvent on the acid dissociation constant of benzoic acid by potentiometric titrimetry in ethanol-water, propylene glycol-water.

There are some considerations in choosing organic solvents to be employed as cosolvent with water :

1. They should be miscible with water and give homogeneous solutions.

2. They should have lower dielectric constant and lower autoprotolysis constant than water.

3. They should not have toxicity for the routine analysis.

4. And also they should have the low prices.

There are many solvents for mixing with water that are used as mixed solvents which would satisfied the above criteria, such as ethanol, methanol and propylene glycol.

pH Scale for Organic Solvent-Water as Mixed Solvents

The quantity of pH, measured by the pH meter, can be written

$$pH = \bar{E}j - \log a_H \quad (47)$$

$$a_H = {}_w\gamma_H m_H \quad (48)$$

where $\bar{E}j$ is the unknown liquid junction potential (in pH units)

a_H is the activity of hydrogen ion in the standard state in water

${}_w\gamma_H$ is the activity coefficient of hydrogen ion in the standard state in water

m_H is the concentration of hydrogen ion

From Eqs.(47) and (48)

$$pH = \bar{E}j - \log {}_w\gamma_H m_H \quad (49)$$

Measurement of pH in a mixed solvent when the electrode is standardized with an aqueous solution has little significant in terms of possible hydrogen ion activity, because of the unknown liquid junction potential , which can be rather large, depending on the solvent. Measurement made in this way are usually referred to as apparent pH ; pa_H^* , where a_H^* may be defined as the hydrogen activity in mixed solvent

$$pa_H^* = -\log(m_H)({}_s\gamma_H) \qquad (50)$$

where ${}_s\gamma_H$ is the activity coefficient of hydrogen ion in mixed solvent

Now, combining Eqs. (49) and (50), would yield

$$pa_H^* = pH - \bar{E}j + \log {}_w\gamma_H - \log {}_s\gamma_H$$

$$= pH - \bar{E}j + \log \frac{{}_w\gamma_H}{{}_s\gamma_H} \qquad (51)$$

The ratio between activity coefficient of ion in water and activity coefficient of ion in mixed solvent was ${}_m\gamma_H$, the medium effect when hydrogen ion is tranferred from the saturated state in water to the standard state in the mixed solvent. This medium effect in depended on the solvent composition but independent of the solute composition (22).

From Eq. (51) $pa_H^* = pH - \bar{E}j + \log {}_m\gamma_H$

$$pa_H^* = pH - \delta \qquad (52)$$

where $\delta = \bar{E}j - \log m\gamma_H$ and is a constant for a medium of a given composition (19,22).

Ong (22) and Bate (23) had determined the value of the constant δ for methanol-water mixtures and for ethanol-water mixtures, it had be seen that δ is small up to 80% w/w alcohol in water in both solvent series. This is apparently because $\bar{E}j$ and $\log m\gamma_H$ compensate to a considerable extent in this region of solvent composition.

It appear from those findings that measurements of relative hydrogen ion activity in aqueous alcoholic solvents are possible. The usual pH meter with glass electrode is suitable for many measurements of this sort, as many glass electrode display nearly the theoretical response to hydrogen ion, at least up to alcohol concentration near 80% w/w. These observations were in good agreement with workdone by Bacarella, Grunwald and Purlee (24).

Seksiri (8) had titrated weak acidic drugs which precipitated in aqueous solvent, in mixed solvent (40% v/v ethanol-water) and used Gran's method for determining the equivalence point in quantitative analysis. By employing 40% v/v ethanol-water, an improvement in determination end point volumes by Gran's plot was achieved and yielded satisfactory results. However, the limitation of using the data in high pH

region should still be considered especially for the plot employing titration data after equivalence point.

Moreover, there are some considerations when employing titration data prior to equivalence point. It would yield errorneous results in the titration of diprotic acid, if there was overlapping between the two dissociation constants , such as the titration of chlorpheniramine maleate in 40% v/v ethanol-water (8).

Chlorpheniramine maleate had two dissociation constants; the first is the dissociation of the second proton of maleic acid ($Ka = 6 \times 10^{-7}$) and the second was the dissociation of protonated chlorpheniramine ($Ka = 6 \times 10^{-10}$). In aqueous titration of chlorpheniramine maleate, nonionized free base precipitated out during the course of titration. Thus, the titration in mixed solvent (40% ethanol/water) was performed.

In 40% ethanol/water solvent, protonated chlorpheniramine can dissociate much better since the formation of unionized producted was favored by the solvent. This resulting in higher dissociation constant in ethanol-water system when compared with value in water ($Ka \approx 10^{-10}$). On the other hand, the second proton of maleic acid which titrated product had higher charge than reactants would decrease the dissociation. Therefore, the second dissociation constant for maleic acid would be lowered when compared with the value in

water (Ka ≈ 10^{-7}). The two dissociations would approach to each other such that the neutralization of protonated chlorpheniramine and sodium hydroxide would occur while the neutralization reaction of the second proton of maleic acid and sodium hydroxide was happening. Hence, Eqs. (40) and (42) which used in determination of equivalence volume for diprotic acid drugs would be invalid and then end point volumes obtained from Gran's plot would be erroneous when calculated in term of percentage purity.