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Note

pK_a determination of nimesulide in methanol—water mixtures by potentiometric titrations

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Abstract

The pK_a of nimesulide was determined by potentiometric titrations of a series of semisqueous nimesulide solutions of known concentration and 34.47–60 Wt% of methanol in water, with a glass electrode, using a pH meter calibrated by means of standard aqueous buffer solutions. The estimated pK_a corresponding to a zero value of methanol was obtained from Yasuda–Shedlovisky plots and the pK_a value was 6.46. © 1997 Elsevier Science B.V.

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1. Introduction

An important factor governing the absorption of a drug, following oral administration, is its lipophilicity (Clarke and Cahoon, 1987; Henczi et al., 1995) and this lipophilicity may be one of the factors regulating bioavailability for several compounds.

The dissociation constants might show whether the drug is in the ionic or nonionic form, if it will be sufficiently soluble in the gastrointestinal fluid, or how the gastric fluid might affect the rate of dissolution of the drug (Benet and Goyan, 1967).

Nimesulide (4-nitro-2-phenoxymethanesulfonanilide) is a non-steroidal drug with anti-inflammatory activity and differs from most currently acidic antiinflammatory drugs in that its functional acidic group is not carboxyl. Although the synthesis of nimesulide dates back to 1976 and was carried out by Riker Laboratories, there is scant information about the dissociation constants of this pharmaco-compound. Magni (1991) described that the influence of methane sulfonanilides on the synthesis of prostaglandin (PG)

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was found to be closely correlated with the acidity of the former compounds. Agents having a pK_a of around 7 do not influence the synthesis of PG whereas those with a pK_a of ≥ 7 enhance the conversion of arachidonic acid to PGs.

Nimesulide is a methane sulfonanilide and its aqueous pK_a was expected to be around 7. This author referred to a pK_a value of 6.50 but nowhere in his work it is stated where such information comes from, and which method was employed employed for such determination.

Fallavena (1995) reported an analytical method for determining the concentration of nimesulide which uses potentiometric titrations with sodium hydroxide in a acetone medium, that would lead one to infer that the pK_a of the drug under examination could be lower than that quoted by Magni (1991). This fact could give rise to doubts as to the real capacity of the drug for inhibiting prostaglandin synthesis.

The present work thus originated from said doubts and has as its main objective the obtention of a method for determining the pK_a of nimesulide. Nimesulide is insoluble in water, but it is soluble in organic solvents, like methanol, ethanol, acetone and dimethylformamide (Fallavena, 1995). If a substance is virtually insoluble in water the determination of its pK_a in an aqueous solution can be difficult and problematic (Benet and Goyan, 1967; Hasegawa et al., 1984; Avdeef et al., 1993). Many methods for such determination of pK_a were offered: determination by liquid-liquid partition (Hasegawa et al., 1984), by high-pressure liquid chromatography (HPLC) (Henczi et al., 1995; Unger and Cook, 1978; Slater et al., 1994; Bona et al., 1995), and methods that involve potentiometric titrations in mixtures of solvents when the pK_a is determined by extrapolation in mixtures of methanol (Bacarella et al., 1955; Shedlovisky and Kay, 1956; Ong et al., 1964; Avdeef et al., 1993), ethanol, dimethyiformamide, acetone and dioxane (Avdeef et al., 1993). As the HPLC methods are very expensive and slow, it becomes desirable to use the potentiometric titrations with solvent mixtures. Potentiometric pH titration is by far the most convenient method for the determination of dissociation constants in water and if due care is taken, this method can give to the experimenter good reproducible results (Benet and Goyan, 1967).

The semiaqueous titration should be carried out in a methanol system, if possible, because its general effect on pK_a has been studied so extensively (Benet and Goyan, 1967; Avdeef et al., 1993). In numerous examples the pK_a is deduced by the extrapolation of the p_sK (the apparent pK_a) values corresponding to a zero value of methanol (Bacarella et al., 1955; Shedlovisky and Kay, 1956; Avdeef et al., 1993). Plots of p_sK versus weight percent of organic solvent rarely produce a straight line and this procedure is not suitable for extrapolations to a zero value of methanol (Avdeef et al., 1993). Yasuda–Shedlovisky proposed a plot of $p_sK + \log [H_2O]$ versus $100/D$ (D = dielectric constant) that is fairly linear below a value of $100/D = 2.00$ (Benet and Goyan, 1967).

In the present paper, the objective is to measure the p_sK of nimesulide using a potentiometric titration method proposed by Ong et al. (1964) and to extrapolate p_sK values of an aqueous pK_a, the plotting $p_sK + \log [H_20]$ versus 100/D is as defined by Yasuda–Shedlovisky (Benet and Goyan, 1967; Avdeef et al., 1993).

2. Materials and methods

Methanol (Labsynth Itda, Analytical reagent, ACS, $< 0{,}05\%$ water) was used without further purification. Nimesulide, as raw material, was provide by Sintofarma S.A. and the solutions of the drug were made using methanol–water solvents. The glass electrode was standardized with aqueous Buffer solutions (Merck S.A.), phosphate (pH 7.0), boric acid/potassium chloride (pH 10) and citrate/hydrochloric acid (pH 4.0). The sodium hydroxide (Reagen s.a.) solution was 0.01 M.

Potentiometric titrations were made at 25°C with a Hanna glass electrode -Hl1131 (Refillable glass combination pH electrode). The apparatuses used were a pH meter from MANNA instruments 8417 ($pH \pm 0.01$) and a magnetic stirrer. The aqueous pK_a was determined by the equation (Ong et al., 1964):

$$pK_a = pH - \log \alpha/1 - \alpha - \log_{s\gamma A/s\gamma HA} \quad (1)$$

Where pH is the meter reading, α is the fraction of nimesulide converted into a base, $s\gamma A$ is the activity coefficient of nimesulide ion and $s\gamma HA$ is the activity coefficient of neutral molecules of nimesulide. The activity coefficients of neutral molecules were taken as unity and those of the ionic species were calculate by means of the equation:

$$-\log_{s\gamma A} = AI^{1/2}/(1 + I^{1/2}) \quad (2)$$

Values of A, the Debye-Huckel constant, were calculated using dielectric constant data reported by Bacarella et al. (1955). The ionic strength was determined by means of the following equation:

$$I = \tfrac{1}{2}\sum(c_i z_i^2) \quad (3)$$

The value of aqueous pK_a was determined by the Yasuda–Shedlovisky plots that use p_sK (apparent pK_a) + log [H_2O] versus $100/D$, wherein D is the dielectric constant.

For pK_a determination, solutions of nimesulide equivalent of 3.2×10^{-4} M were titrated with 0.01 M aqueous sodium hydroxide, with parallel addition of methanol to maintain the methanol–water composition constant. The composition of methanol in the methanol–water mixtures was 34.47–60.00 Wt%. Nimesulide could only be dissolved in solutions with > 34 Wt % methanol. In the titration, the stirrer was turned on as titrant was added and vigorous stirring continued for 5 s after addition. Then the stirrer was turned off. The temperature was 25°C. About 8 pH measurements were made during the course of each titration, from 20 to 80% of neutralization. The values of p_sK (obtained by Eq. (1) and $p_sK + \log [H_2O]$ are presented in Table 1. Fig. 1 contains plots of $p_sK + \log [H_2O]$ versus $100/D$ for nimesulide.

3. Results

Having in mind the primary objective of the present work, it has been possible to obtain a method for determining the pK_a of nimesulide based on Ong et al., 1964 and Avdeef et al. (1993). Ong et al., 1964 point out that Eq. (1) gives good apparent p_sK values. Avdeef et al. (1993) report that plots of p_sK versus wt.% organic solvent, $R = 0$–60 Wt%, rarely produce a straight line, and values of $R > 60\%$ are not suitable for extrapolation. Avdeef et al. (1993) propose the utilization of Yasuda–Shedlovisky plot wherein $p_sK + \log [H_2O]$ versus $100/D$, produce a straight line. In this work, for the reasons set forth above, the author preferred to use the method proposed by Ong et al., 1964 and to employ the Yasuda–Shedlovisky plots quoted by Avdeef et al. (1993).

Table 1
Values of p_sK and $p_sK + \log [H_2O]$ for nimesulide in methanol water mixtures

Methanol Wt%	p_sK[a]	$p_sK + \log[H_2O]$
34.47	6.83	8.65
44.10	6.96	8.69
50.00	7.06	8.76
54.20	7.12	8.78
60.00	7.24	8.84

[a] Mean of three determinations.

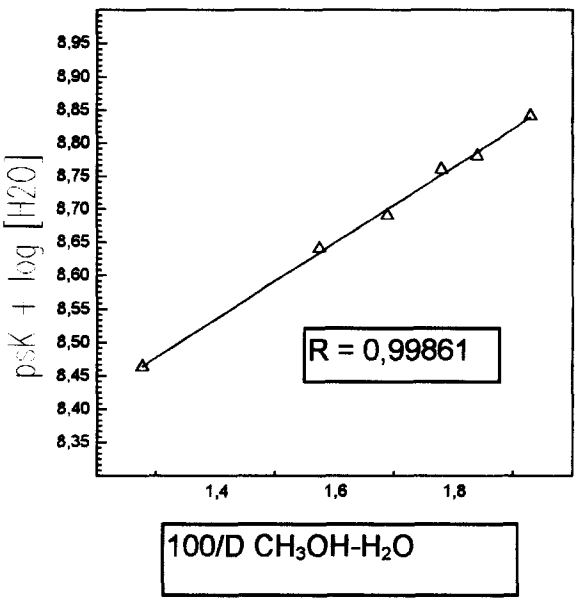

Fig. 1. Yasuda–Shedlovisky plots for the nimesulide in methanol–water mixtures.

The pK_a value obtained by this method was 6.46, and the data of literature report pK_a values for anti-inflammatory activity of nimesulide as being 6.5. These are very close values. The present work shows that by using Ong et al., 1964 method and Yasuda–Shedlovisky plots it becomes possible measure the aqueous pK_a of nimesulide at a low cost and fast.

References

Avdeef, A., Comer, J.E.A., Thomson, J.S., 1993. pH-Metric log P.3. Glass electrode calibration in methanol–water, applied to pK_a determination of water-insoluble substances. Anal. Chem. 65, 42–49.

Bacarella, A.L., Grunwald, E., Marshall, H.P., Purlee, E.L., 1955. The potentiometric measurement of acid dissociation constants and pH in the system methanol–water. J. Org. Chem. 20, 747–762.

Benet, L.Z., Goyan, J.E., 1967. Potentiometric determination of dissociation constants. J. Pharm. Sci. 56, 663–680.

Bona, M., Boudeville, P., Zekri, O., Christen, M.O., Burgot, J.L., 1995. Water/*n*-octanol partition coefficients of 1,2-dithiole-3-thiones. J. Pharm. Sci. 84, 1107–1112.

Clarke, F.H., Cahoon, N.M., 1987. Ionization constants by curve fitting. J. Pharm. Sci. 76, 611–619.

Fallavena, P.R.B., 1995. Estudo de Metodos Fisico-Qulmicos pare Analise de nimessulida. Disserta çáo de mestrado. Curso de Pós-Graduaçáo, cao em Ciencias Farmaceuticas, Faculdade de Farmacia, UFRGS—Rio Grande do Sul, Brasil.

Hasegawa, J., Fujita, T., Hayashi, Y., Iwamoto, K., Watanabe, J., 1984. pK_a determination of verapamil by liquid—liquid partition. J. Pharm. Sci. 73, 442–445.

Henczi, M., Nagy, J., Weaver, D.F., 1995. Determination of octanol–water partition coefficients by an HPLC method for anticonvulsant structure–activity Studies. J. Pharm. Pharmacol. 47, 345–347.

Magni, E., 1991. Drugs 3, 1–3.

Ong, K.C., Robinson, R.A., Bates, R.G., 1964. Interpretation of potentiometric titrations of weak acids in methanol–water solvents. Anal. Chem. 36, 1971–1972.

Shedlovisky, T., Kay, L.R., 1956. The lonization constant of acetic acid in water–methanol mixtures at 25° from conductance measurement. J. Phys. Chem. 60, 151–156.

Slater, B., McCormick, A., Avdeef, A., Comer, J.E., 1994. pH-Metric log P.4. Comparison partition coefficients determined by HPLC and potentiometric methods to literature values. J. Pharm. Sci. 83, 1280–1283.

Unger, S.H., Cook, J.R., Hollenberg, J.S., 1978. Simple procedure for determining octanol–aqueous partition, distribution, and lonization coefficients by reversed-phase high-pressure liquid chromatography. J. Pharm. Sci. 67, 1364–1366.