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Acidity of several polyprotic acids, amiodarone and quetiapine hemifumarate in pure methanol

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Abstract

Methanol is the organic solvent closest to water and able to dissolve a huge amount of organic compounds. Therefore, it is a good candidate for pK_a determination of drugs sparingly soluble in water or a basic drug presented as a salt which pK_a is close to that of its counter-acid. In this work, the acidic dissociation constants in pure methanol of the most common acids used in pharmaceutical preparations (lactic, tartaric, fumaric, maleic and citric) were determined. In addition, the pK_a values of the antipsychotic quetiapine presented as hemifumarate (Seroquel) and the very insoluble antiarrhythmic amiodarone were also determined by potentiometry. From these values, the aqueous pK_a of these drugs were estimated by means of previously established equations. Estimated values are consistent with those from literature and show the interest of methanol for drug discovery pK_a measurements.

Keywords: pK_a in methanol; pK_a in water; Drugs; Potentiometry; Polycarboxylic acids; Amiodarone; Quetiapine hemifumarate; Seroquel

1. Introduction

Despite the fact that many drugs are sparingly soluble in water, the evaluation of the aqueous dissociation constants is an unavoidable requirement in drug discovery [1]. In these instances, experimental pK_a determination requires the use of an organic or hydroorganic solvent [2]. The first approach was the method proposed by Hall that relates the half neutralization potential in an organic solvent and aqueous pK_a values [3,4]. Nowadays, potentiometry is the preferred technique because of the excellent response of the glass electrode in many pure and binary solvents and the easy automation of the experimental measurements [5]. For aqueous pK_a ($^{w}_{w}$pK_a) determination purposes two main potentiometric approaches were developed. Both methods employ hydroorganic mixtures as sample solvents and require a suitable extrapolation equation to estimate the $^{w}_{w}$p$K_a$value, from the experimental constants in the binary solvent ($^{s}_{s}$pK_a). The first method involves the determination of $^{s}_{s}$pK_a in several hydroorganic mixtures and further extrapolation by means of the Yasuda–Shedlovsky equation [6–10]. The most employed solvent in these hydroorganic mixtures is methanol but, very recently, a mixture of equal volumes of methanol, dioxane and acetonitrile (MDM) has successfully proposed [6]. Good results are achieved using this method, particularly when mixtures with low organic content can be employed. The main limitation is again the solubility of the drug since the linearity of the Yasuda–Shedlovsky equation is kept until about 60% (w/w) of methanol or 50% (w/w) of MDM and it is not possible to use it at higher percentages. Therefore, this method hardly attains for the proper estimation of the $^{w}_{w}$pK_a values of very insoluble drugs. The second approach, developed for methanol/water mixtures, involves linear relationships to estimate the $^{w}_{w}$pK_a from a unique $^{s}_{s}$pK_a value determined in a suitable mixture. The slope and intercept of these linear equations can be easily calculated according to the methanol fraction of the binary solvent and the nature of the acid-base group of the drug. In this instance, it is possible to use a solvent with high methanol content although the precision of the extrapolated $^{w}_{w}$pK_a value is slightly lower than that achieved from poor methanol binary solvents [10–12].

Both approaches show a limitation in the determination of $^{w}_{w}$p$K_a$of drugs when they are presented as a salt formulation, which is very common. Thus, when the pK_a values in the working solvent of a basic drug and its counter-acid are close, the resolution of the concomitant equilibria involves a lost in the

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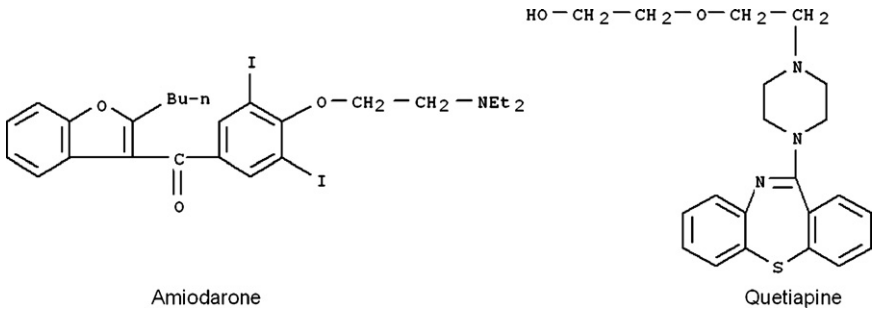

Fig. 1. The studied drugs.

accuracy and precision of the computed ${}^{s}_{s}pK_a$ values and, consequently, of the estimated ${}^{w}_{w}pK_a$. Stability considerations have led manufacturers to select counter-ions that show a minimum difference of three pK_a units between the ionizable groups of the drug and its counter-acid [13]. However, it is important to note that this difference can become much lower when the organic content of the solvent is high (>30%). This is a common feature since the pK_a values of neutral or anionic acids increase with the organic content in the solvent but the opposite behaviour should be expected for basic compounds (cationic acids) [6,10,11]. Calculations can be carried out using the ${}^{s}_{s}pK_a$values of the salt-forming acid as constant values, but very often these values are unknown. Recently, we have published ${}^{s}_{s}pK_a$ values of several common counter-acids in aqueous mixtures up to 60% (w/w) of methanol which can be used for these purposes [14]. As a working example, we determined the ${}^{s}_{s}pK_a$values of quetiapine formulated as hemifumarate using the suitable ${}^{s}_{s}pK_a$ of fumaric acid in various methanol/water mixtures. Further, the Yasuda–Shedlovsky model was used to estimate the ${}^{w}_{w}pK_a$values. The obtained ${}^{w}_{w}pK_{a1}(3.53 \pm 0.27)$ of quetiapine shows a high standard deviation due to the proximity between this pK_a and those of fumaric acid in the working binary solvents, whereas ${}^{w}_{w}pK_{a2}$ (6.92 ± 0.07), whose value is far from those of fumaric acid, shows a very good precision [14]. Alternatively, a look-up procedure can be used to iterate the experimental pH values and get all the involved equilibrium constants.

In this work, we propose pure methanol as a solvent to determine the ${}^{s}_{s}pK_a$ for very insoluble drugs because of all the organic solvents, methanol is the one closest to water and shows a high ability to dissolve organic compounds. We also propose methanol as suitable solvent to determine the ${}^{s}_{s}pK_a$ for drugs presented in salt form and whose aqueous pK_a is close to those of their salt-forming counterpart. This is because the ${}^{s}_{s}pK_a$ in methanol is well known to be about 5 pK units higher than ${}^{w}_{w}pK_a$for carboxylic acids, 4 units higher for phenols and only 1 unit or less for amines and pyridines, which are cationic acids (basic compounds) [15]. Since a salt is always composed by a base and an acidic compound, close pK_a values in water or water-rich binary mixtures become far away enough in methanol. Therefore, pure methanol could be a suitable option for this kind of salts.

Moreover, potentiometric measurements can be carried out with the glass electrode calibrated with standard aqueous buffers leading to ${}^{s}_{w}pH$ values, that is to say, to the pH values in the intersolvental pH scale. Since the δ quantity is well known (−2.34 in the molality scale and −2.24 in the molarity scale), easy change is allowed from the intersolvental pH scale (${}^{s}_{w}pH$) to the specific pH scale for pure methanol (${}^{s}_{s}pH$) [16–20], by means of

$$ {}^{s}_{s}pH = {}^{s}_{w}pH - \delta \quad (1) $$

and, therefore, experimental ${}^{s}_{w}pH$ measurements allow to get the ${}^{s}_{s}pH$ and also the ${}^{s}_{s}pK_a$ values. Since linear equations such as

$$ {}^{s}_{s}pK_a = a {}^{w}_{w}pK_a + b \quad (2) $$

were established for a variety of chemical families [11,15,21], these relationships can be used to estimate ${}^{w}_{w}pK_a$ from ${}^{s}_{s}pK_a$values obtained in pure methanol.

Two pattern drugs were selected for this study. The first one is an antianginal and antiarrhythmic drug used in treatments of heart diseases, amiodarone. This is a highly hydrophobic compound with a very small solubility in water (0.7 mg/mL) [22], which forms micelles with very low critical micelle concentration (0.5 mg/mL) [23]. Amiodarone requires, at least, 40% methanol/water [24] mixtures to prepare a solution of suitable concentration in a wide pH range. The other drug is the quetiapine hemifumarate, commercially named Seroquel, which belongs to the dibenzothiazepine derivatives. It is widely used to treat psychotic disorders and symptoms such as hallucinations, delusions and hostility [25]. Since ${}^{w}_{w}pK_{a1}(3.02)$ and ${}^{w}_{w}pK_{a2}(4.38)$ of fumaric acid [26] are very close to ${}^{w}_{w}pK_{a1}$ of quetiapine (3.30), three acid-base equilibria coexist in the moderately acidic pH range in aqueous solution [14]. Both drugs are shown in Fig. 1.

2. Experimental

2.1. Apparatus

- pH measurements were taken with a Ross combination electrode Orion 8102 (glass electrode and a reference electrode with a 3.0 M KCl solution in water as a salt bridge) in a Crison micropH 2002 potentiometer with a precision of ± 0.1 mV.
- Potentiometric titrations were carried out by means of a Methrom 665 Dosimat autoburet controled by the VALORA program specially designed for titrations in non-aqueous