pKa Determinations for Montelukast Sodium and Levodropropizine

Ibrahim Narin · Salih Sarioglan · Beril Anilanmert · Hayati Sari

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Abstract The pK_a constants and relative abundances of unionized and ionized forms of Montelukast sodium {the sodium salt of 2-[1-[(1R)-1-[3-[2-(7-chloroquinolin-2-yl)ethenyl]phenyl]-3-[2-(2-hydroxypropan-2-yl)phenyl]propyl]sulfanylmethyl]cyclopropyl]acetic acid} and Levodropropizine {(2S)-3-(4-phenylpiperazin-1-yl)propane-1,2-diol} were determined potentiometrically from measurements at various pHs. These determinations were in order to relate their pK_a values with their bioavailability and to provide chemical data to be used in their analysis.

Keywords Potentiometric titration · Drug research · Acidity · Protonation · Dissociation constant · Ionization

1 Introduction

Because most drugs are weak acids or bases, information about their ionization at physiological pH values carry important information related to the behavior of drugs in penetrating different parts of the body. The pK_a of a drug influences its lipophilicity, solubility and...
permeability that, in turn, directly affect pharmacokinetic (PK) characteristics such as absorption, distribution, metabolism and excretion (ADME) [1]. The value of $pK_a$ is also an important parameter in choosing optimum conditions when developing analysis methods for the drug molecule.

Montelukast is a fast acting LTD$_4$ (CysLT$_1$) receptor antagonist [2] that is used orally in the treatment of asthma [3]. It reaches its maximum plasma concentration 3 hours after oral administration on an empty stomach. The bioavailability is 70% for oral administration [4] and 99% of the drug binds to plasma proteins [2]. Levodropropizine is used orally in the symptomatic treatment of cough [5]. It is rapidly absorbed (bioavailability $\geq 75\%$) and distributed throughout the body after oral administration. Binding to plasma proteins is low (11–14\%).

There is only one published (2007) study on the determination of $pK_a$ constants of Montelukast sodium, which was performed using spectrophotometric and fluorimetric methods in the ethanol + water solvent system (Table 1) [3], while no study exists on the determination of $pK_a$ constants of Levodropropizine. In our study, the $pK_a$ constants of Montelukast sodium were determined using a different method (potentiometry), a different solvent system, dioxane + water (40:60 v/v) and the results are compared with the previous values.

Acid dissociation constant determination studies have been performed for drugs like epirubicin-HCl and irinotecan-HCl [6], cefetamet [7] and many other drugs used as antiinflammatories, antibiotics, $\beta$-blockers, etc. Mixed solvents were used for some of these drug studies, because of solubility problems in water at the concentrations used in the experiments [8]. In this study, the $pK_a$ constants of Montelukast sodium and Levodropropizine were determined potentiometrically using the Irving–Rossotti method [9, 10]. Relative abundances of the ionized and unionized species were calculated at various pHs.

## 2 Experimental

Titrations were performed using an Isolab digital burette with 0.01 mL sensitivity, WTW 340I model pH meter with a WTW SenTix 41 combined glass electrode, and a temperature sensor. The pH meter was calibrated with certificated WTW pH buffers at pH = 4.01 and 7.00. NaClO$_4$·H$_2$O(s), HClO$_4$(aq), 0.1000 mol·L$^{-1}$ NaOH(aq), and 1,4-dioxane(l) were purchased from Merck (Darmstadt, Germany). All of the reagents were analytical grade. Montelukast sodium and Levodropropizine were standard gifts kindly provided by Abdi Ibrahim Ilac (Turkey). All solutions were prepared using water that was freshly distilled before analysis. Montelukast sodium solutions were prepared just prior to each titration. All titrations were performed at 25 ± 1 °C, under a N$_2$ atmosphere.

50.0 mL of dioxane + water (40:60 v/v) solutions (1) containing 0.010 mol·L$^{-1}$ HClO$_4$, 0.100 mol·L$^{-1}$ NaClO$_4$ and $4.00 \times 10^{-4}$ mol·L$^{-1}$ Montelukast sodium, and 50.0 mL of aqueous solutions (2) containing 0.010 mol·L$^{-1}$ HClO$_4$, 0.100 mol·L$^{-1}$ NaClO$_4$ and $4.00 \times 10^{-4}$ mol·L$^{-1}$ Levodropropizine, were prepared freshly just before the potentiometric pH titrations. Because the protonated form of Montelukast sodium does not dissolve significantly in water, a dioxane + water (40:60 v/v) solvent media was used (where the $4.00 \times 10^{-4}$ mol·L$^{-1}$ Montelukast sodium remains soluble throughout the titration). The same procedures were applied also for the blank solutions, which were prepared exactly as solution 1 and 2 but without the drug. Each mixture was titrated potentiometrically under a N$_2$ atmosphere with 0.1000 mol·L$^{-1}$ NaOH at 25 ± 1 °C at the ionic strength $I = 0.11$ mol·L$^{-1}$ (NaClO$_4$). Thus, two titrations were carried out for each repeat experiment: (1) titration of the acid (blank) and (2) titration of the ligand + acid solution.