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Research Article

PK_a CONSTANT OF MUPIROCIN

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ABSTRACT

pK_a constant of mupirocin and distribution of species of the drug molecule at various pH values were determined potentiometrically, using Irving-Rossotti method, where PEG ratio in pharmaceutical dosage forms was imitated to provide first experimental data on its pKa, to be used in commenting on its penetration through bio-membranes, and in its analysis.

Keywords: pK_a, protonation constant, dissociation constant, mupirocin, potentiometry.

INTRODUCTION

The antibacterial agent mupirocin (Fig 1) is used as a topical agent in the treatment of superficial infections by gram-positive bacteria, particularly Staphylococcus aureus[1]. It is also demonstrated that the compound inhibits the growth of a number of pathogenic fungi in vitro. It inhibits protein, RNA and DNA synthesis in bacteria[1,2]. Inside the topical mupirocin formulations, polyethylene glycol (PEG) 400 and 4000 exist at various ratios, both as solvent and skin penetration enhancer[3]. In a one of the most cited pharmaceutical formulation patent; mupirocin is used in ratios changing from 0.01% to 50% 0.01% to 50% and most preferably 2%, PEG 400 and PEG 4000 were used in ratios of 59% and 39%, respectively[3,4]. This formulation can be diluted with water in ratios of 1:1 to 1:20 before use. In another formulation, PEG 400 and 4000 were used in ratios of 74% and 24%, respectively[4,5]. PEG 400 was also used in a recent patented formulation[6]. Regarding these informations, since the calcium salt of mupirocin couldn't directly dissolve in water, and in order to imitate the media that it was applied in therapy, it was dissolved in 40% PEG solution before pK_a determination.

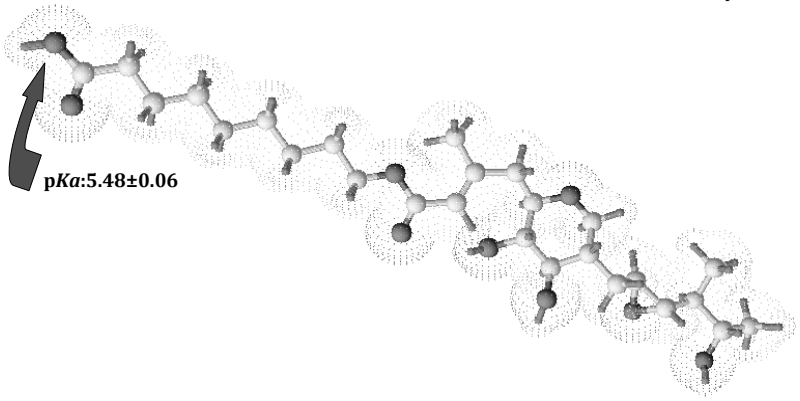


Fig. 1: Molecular structure of nonionized form of mupirocin (Dark balls are oxygen atoms)

The pK_a of a drug influences lipophilicity, solubility and permeability in biological systems[7]. pK_a is also important in choosing the optimum conditions in development of analysis methods for the drug molecules. To provide a data for such studies, the pK_a constant of mupirocin and its ionized and nonionized species in various pH values were determined potentiometrically, using Irving-Rossotti method[8].

MATERIALS AND METHOD

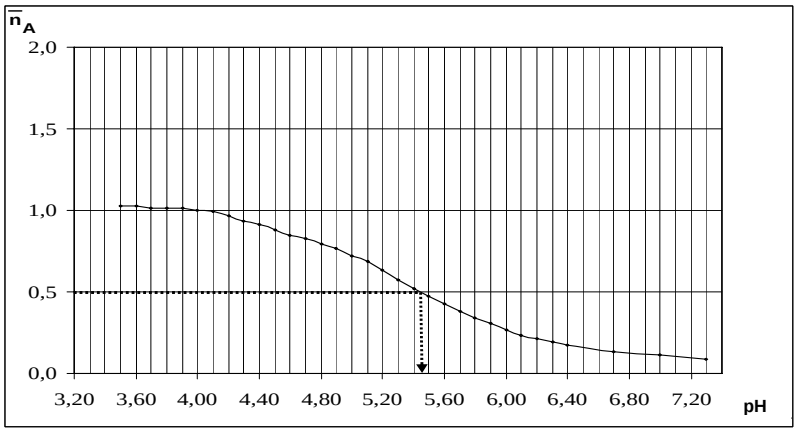
50.00 mL solutions each including; 0.154 mol L^{-1} NaCl (to provide an ionic strength equivalent to 0.9% isotonic NaCl solution), $4.00x10^{-3}$ mol L^{-1} HCl, 40.00 mL 40% PEG 400 solution and $1.00x10^{-3}$ mol L^{-1} mupirocin calcium salt (equivalent to $2.00x10^{-3}$ mol L^{-1} mupirocin, since 2 molecules of mupirocin exists in one molecule of mupirocin calcium salt) were titrated along with their blanks, under N_2 atmosphere, using 0.1000 mol L^{-1} titrisol NaOH. Titrations were performed at 25±1^{0}C, I=0.154 (NaCl). The titration curves were plotted versus mL values (Graph 1). Using the titration values, $\bar{n}_A$ values were calculated according to Irving-Rossotti method[8] and were plotted versus pH. The pKa constant was determined from the pH axis, corresponding to $\bar{n}_A$ =0.5 on $\bar{n}_A$ = f(pH) curve. Distributions of ionized and nonionized species of the drug were calculated, using the pKa value.

RESULTS AND DISCUSSION

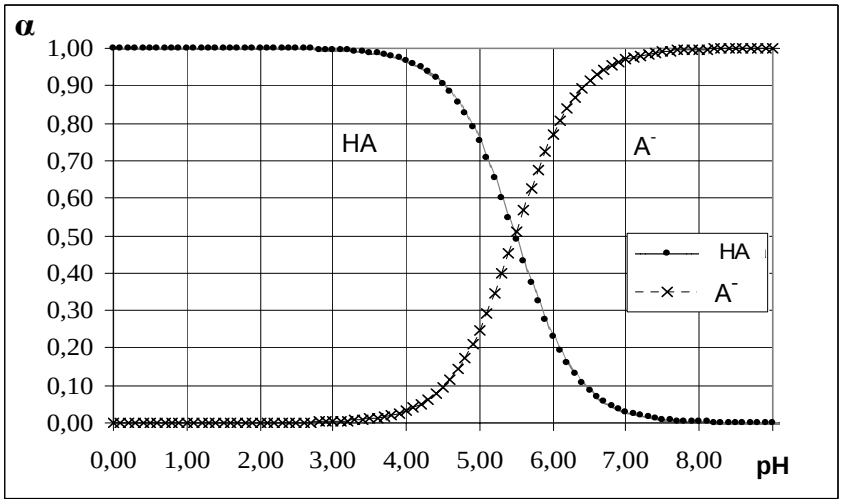
pK_a constant was determined as 5.48±0.06 (n=6) (Graph 1). This pK_a value is due to the ionization of the carboxylate group on the molecule. The obtained results were in accordance with the value of 4.88, which had been found theoretically using pK_a Pallas computer program[9]. This is the first experimental study on the pK_a constant of mupirocin.

Performing the experiments in 0.9% isotonic NaCl solution, using PEG 400 as a solubilization agent, aided the imitation of the biological conditions that it is delivered to the organism, to relate its pK_a with its transfer from the membranes. Mupirocin is mostly used on skin. As seen from Graph 2, half of mupirocin remains nonionized at pH of the skin (5.5) in the ratio of PEG where pharmaceutical dosage from is imitated and since nonionized forms of drug molecules penetrate easier through the biomembranes, penetration of mupirocin is expected to increase as the pH of the ointment decreases, because that means the increase of the ratio of the nonionized form. There are various pharmaceutical bases which started to take place of PEG's. It would also be useful to determine pK_a constants in these bases, to predict its membrane transfer

correctly. pK_a is more important in penetration in infectious wounds. pKa of mupirocin will also serve as a data in development of quantification and separation methods. To know which form of a drug molecule exists in which ratio in a definite solvent media is no doubt, of great use in choosing the right separation technique during the quantification procedures.



Graph 1: A sample pH- $\bar{n}_A$ graph of mupirocin. pK_a=5.48±0.06 (n=6)



Graph 2: Distribution of mupirocin species at various pH values

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