Title: **Determination of the acidity constant of drugs in simulated intestinal fluids.**

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The drug discovery process involves synthesizing a high number of compounds, although only a few of them will have success as drug candidates. In the early stages of the drug discovery process, different physical-chemical properties are determined, such as the acidity constant, solubility, permeability, etc. which serve to perform a first screening and select only those compounds that have suitable properties.

Almost all drugs are acids or bases. This means that the ionization degree has an important influence on its properties, and to understand the drug bioavailability it is useful to know the acidity constant of the drugs.

Drug administration in the human body has different routes: oral, parenteral, buccal, sublingal, pulmonary, etc. During the last decades, the oral route has been enhanced and has become the most common, convenient and economic route. To understand the in vivo behaviour that drugs have when administered orally, is necessary to use a simulated intestinal medium because it have similar characteristics to biological fluids. Exemples of these simulated fluids are Fasted-State Simulated Fluid (FaSSIF) and Fed-State Simulated Fluid (FeSSIF), which represent the gastrointestinal medium before and after food intake, respectively. Studying the behavior of the drug in water is often not representative because the composition differs greatty from the one of the gastrointestinal tract.

In this work, it has been determined the acidity constant of drugs in water and in simulated intestinal fluids by spectrophotometry and potentiometry. Then, the values obtained in water and in the simulated biological media were compared. The results obtained with the two different pK_a determination methods have been also compared.

It has observed that, for the acidic compounds, the acidity constant in biorelevant media differs from the value obtained in water. Due to a high concentration of surfactants, the variation in FeSSIF is greater than in FaSSIF. This difference can be explained by the interaction between the neutral form of the drugs and the micelles which are present in gastrointestinal

medium. Regarding basic compounds, they do not show variation in its pK_a values, probably due to the interaction that the positively charged species have with the surfactants, mainly anionic.

Comparing the results obtained with the different methodologies for determining the acidity constants, it has been observed that they do not differ significantly.

Keywords: acidity constant, pK_a, simulated gastrointestinal media, FaSSIF, FeSSIF, potentiometry, spectrometry.