RESEARCH ARTICLE

The Solution Properties of Mefenamic Acid and a Closely Related Analogue are Indistinguishable in Polar Solvents but Significantly Different in Nonpolar Environments

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ABSTRACT: This study investigates the cosolute effects of mefenamic acid (XA) and flufenamic acid (FA). These compounds serve as model of a drug discovery lead compound and a structural analogue. The activity coefficients of XA and FA in different solvents were obtained from solubility measurements at 25°C. The effect of varying concentrations of FA on the solubility of XA in four different solvents, including toluene, cyclohexane, ethanol, and an ethanol–water mixture (80:20, v/v), was investigated. The magnitude of change in the activity coefficient of XA in the presence of FA in different solvents was used to elucidate the thermodynamic effect of FA on the solubility of XA. Nuclear magnetic resonance and Fourier-transform infrared spectroscopy were used to obtain molecular level information about the interactions of the compounds in solution. The presence of FA increases XA solubility in toluene and in cyclohexane as much as seven-fold. Conversely, in ethanol and the ethanol–water mixture, similar levels of FA have essentially no effect on the solubility of XA. The solution properties investigated show that despite the close structural similarity between XA and FA, the two compounds are strongly distinguishable in nonpolar solvents. Conversely, the solution properties of the same two solutes are indistinguishable in polar solvents. A solubilization model based on solute-cosolute interactions is presented. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

Keywords: Mefenamic acid; Flufenamic acid; Solubility; Cosolute effect; Complexation; Solubilization; Activity coefficients; Thermodynamic activity; Chemical analogues; Solubilization model

INTRODUCTION

Medicinal chemists engaged in drug discovery often explore leads through the synthesis of series of structurally related compounds. The drug candidate series is then optimized with regard to two critical aspects. One is for potency and specificity toward the target. The other aspect pertains to physicochemical properties, and aims at improving the chances for a viable new drug molecule. With respect to the latter criterion, solubility and permeability are recognized as properties of critical importance.[1] Structure–activity relationship/structure–property relationship (SAR/SPR) have proven useful in systematically studying structurally related analogs, where the effect of different substituents on a common core moiety are ascertained in terms of biological activity and physicochemical properties. These studies are statistically based, so that larger numbers of compounds in a series, as well as wider variety in their chemical diversity, improve the robustness of the results. SAR/SPR studies are critical in reducing a large series to a handful of lead candidate compounds. As candidate selection is approached however, the need for discriminating information among the (small number of) best leads becomes increasingly important. At such stages, the information from SAR/SPR studies may be too general for the desired goal. Beyond studies on homologous series, there is little detailed information available on the that a small change in chemical structure can have on the solubility properties of drug-like molecules.

Additional Supporting Information may be found in the online version of this article. Supporting Information

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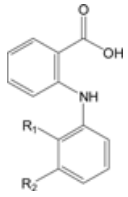
Table 1. Physical Properties of N-(2,3-Xylyl)Anthranilic Acid (XA) and N-(3-Trifluoromethylphenyl) Anthranilic Acid (FA)

Structure			
			
XA $R_1 = CH_3$ $R_2 = CH_3$		FA $R_1 = H$ $R_2 = CF_3$	
XA Form I	XA Form II	FA Form III	FA Form I
Low melting $\Delta H_t = 2.6$ kJ/mol[3] (5°C/min) $t_t = 160$°C	High melting $\Delta H_m = 38.24$ kJ/mol[4] m.p. = 231.5°C	Low melting $\Delta H_t = 1.7$ kJ/mol[3] (2°C/min) $t_t = 115°C$	High melting $\Delta H_m = 27.7$ kJ/mol[3] m.p. = 134°C

[a] ΔH_t is the enthalpy of the solid–solid (polymorphic) transformation.
[b] m.p. and t_t are the temperatures of melting and solid–solid phase transition, respectively, in degrees Celsius.

On a related subject, the synthesis of organic active pharmaceutical ingredients (API's) invariably entails the presence of small amounts of impurities in the final product. Low levels of impurities are often associated with variability in physical or chemical attributes among different batches of the same API, even if produced by the same synthetic path and crystallization method. Small amounts of impurities can have important effects on the quality attributes of the particular API lot. This is arguably due to the fact that many of the impurities in such situations posses some degree of structural similarity with the API. Structural similarity leads to particularly influential modes of interaction between the impurity and the main compound; structural resemblance can result in more "intimate" interactions between the API and the impurity, than when there is no structural commonality. For the same reason, structurally related impurities may be more difficult to control and separate, and can have stronger influence on the behavior of particular lots of the compound of interest. Increases in drug solubility induced by the presence of structurally related compounds have been reported, but the phenomenon has not been thoroughly investigated.[2]

In this report, we present a systematic study involving two structurally similar compounds. We investigate the manner in which two different substituents on a common main moiety impact the solubility behavior of the resulting compounds. We also explore the way in which one of the compounds, if viewed as an impurity, affects the solution properties of the other. We used the compounds N-(2,3-xylyl) anthranilic acid and N-(3-trifluoromethylphenyl) anthranilic acid. The former (mefenamic acid), with its xylyl substituent, is denoted as XA. The latter (flufenamic acid), with its trifluoromethylphenyl group, is denoted as FA. These compounds have nonsteroidal anti-inflammatory activity and their chemical structures are shown in Table 1. The difference between the two molecules resides on the substituents R_1 and R_2, linked to the N-phenyl moiety of anthranilic acid.

This study consists of three parts. The first section deals with solution phenomena, discussed from the standpoint of thermodynamic activity and solubility. The second part uses spectroscopic techniques to ascertain the structural basis for the observations of the first section. The third and last part combines the information from the first two parts of the report in the form of a quantitative model based on the solubility and spectroscopic observations of the study.

EXPERIMENTAL

Materials

N-(2,3-Xylyl) anthranilic acid (XA), N-(3-trifluoromethylphenyl) anthranilic acid (FA), tetramethylsilane (TMS), and cyclohexane were purchased from Sigma–Aldrich (St. Louis, Missouri). Ethanol was obtained from Pharmco (Brookfield, Connecticut). Aqueous trifluoroacetic acid 0.1% (v/v) was purchased from Aldrich Chemical Company, Inc. (Milwaukee, Wisconsin), and high-performance liquid chromatography (HPLC)-grade acetonitrile and toluene were obtained from Mallinckrodt Baker, Inc. (Phillipsburg, New Jersey). Water was double-distilled and filtered with a Milli-Q® ultrapure water purification system (Millipore, Billerica, Massachusetts).

Solubility Measurements (Activity Coefficient Determination)

Excess amounts of each FA and XA in solid form were dissolved in glass vials filled with the appropriate solvent [ethanol, an (80:20, v/v) ethanol–water mixture