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Solubility and pK_a determination of six structurally related phenothiazines

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ABSTRACT

Solubilities of six structurally related phenothiazines, namely chlorpromazine hydrochloride, fluphenazine dihydrochloride, promazine hydrochloride, thioridazine hydrochloride, trifluoperazine dihydrochloride, and triflupromazine hydrochloride at constant pH were measured in the temperature range from 290 K to 350 K in three important drugs solvents: water, ethanol and 1-octanol using the dynamic method and UV–vis method. Dissociation constants and corresponding pK_a values of drugs were obtained with Bates–Schwarzenbach method at temperature 298.15 K in the buffer solutions. Our experimental pK_a values for chlorpromazine hydrochloride, fluphenazine dihydrochloride, promazine hydrochloride, thioridazine hydrochloride, trifluoperazine dihydrochloride, and triflupromazine hydrochloride are 9.15, 10.01, 9.37, 8.89, 8.97, and 9.03, respectively. The basic thermal properties of pure drugs i.e. melting and solid–solid phase transition as well as glass-transition temperatures, the enthalpy of melting and phase transitions and the molar heat capacity at glass transition (at constant pressure) were measured with differential scanning microcalorimetry (DSC) technique. Molar volumes were calculated with Barton group contribution method. The experimental solubility data were correlated by means of three commonly known G^E equations: the Wilson, NRTL and UNIQUAC with the assumption that the systems studied here have revealed simple eutectic mixtures. The root-mean-square deviations of temperature were used for the precision of the correlation. The activity coefficients of drugs at saturated solutions in each correlated binary mixture were calculated from the experimental data. These new data will help in all prediction-methods and their precision.

1. Introduction

The main objective of the present study was to examine the temperature dependent solubility of six drugs: chlorpromazine hydrochloride (CHLPRO), fluphenazine dihydrochloride (FLPHE), promazine hydrochloride (PRO), thioridazine hydrochloride (THRID), trifluoperazine dihydrochloride (TFLPER), triflupromazine hydrochloride (TFLPRO) at constant, natural pH in water, ethanol and 1-octanol. Another objective is the study of thermophysical properties of chosen drugs, namely the temperature of melting and phase transitions, the enthalpy of melting and phase transitions, which are necessary for the thermodynamic description of solubility. Approaches for modelling the data measured with different correlation G^E models are usually evaluated. The parameters of the correlation models are capable to describe the drug solubility at temperatures other than measured and in ternary systems, for example in the binary solvent mixture. As a result of the correlation, the activity coefficients of drugs in aqueous and alcoholic solutions were achieved. One more objective was the study of the pK_a values, which are useful for physico-chemical measurements, describing the extent of ionization of functional groups with respect to pH. In this work the Bates–Schwarzenbach method is proposed for all compounds (Bates and Gary, 1961) as the continuation of our previous work with many drugs (Domańska et al., 2009, 2010, 2011a, 2011b). In our opinion this method is more exact; it is the spectrophotometric method not using the high dissolution and extrapolation to the pure substance data.

The solubility of drugs is usually measured with different methods: for very low solubility the classical static-saturation shake-flask method at one temperature is commonly used (Baka et al., 2008; Bergström et al., 2004) and for higher solubility the visual, dynamic method, where the solubility as a function of temperature is obtained (Domańska et al., 2009). The positive of the static-saturation shake-flask method is that the pH-dependent sigmoidal solubility profile can be obtained at constant temperature (Bergström et al., 2004; Avdeef et al., 2000).

All drugs studied have a phenothiazine structure with different functional groups. Phenothiazine derivatives (PHTHs) are the constituents of neuroleptics revealing antipsychotic properties (Szydłowska-Czerniak et al., 2001; Madej and Kościelniak, 2008). PHTHs belong to a big group of tricyclic aromatic compounds. They easily react with halide and organic complexes with metals and form well-defined ion-associated complexes (Monzón and Yudi, 2008). PHTHs, due to their pharmacological properties

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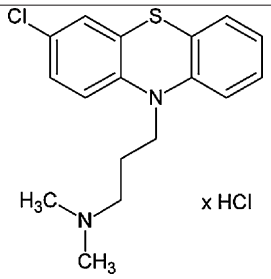
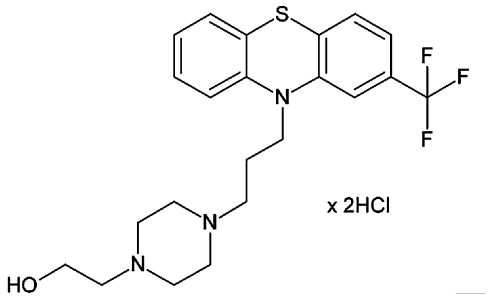
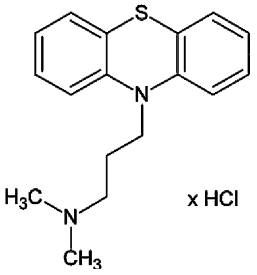
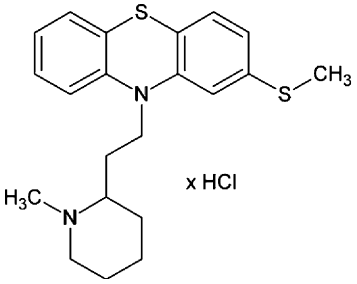
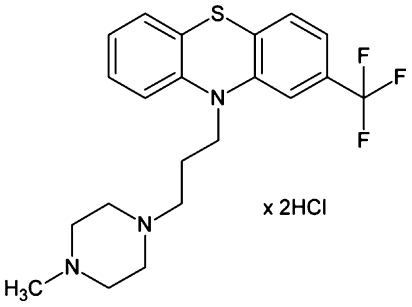
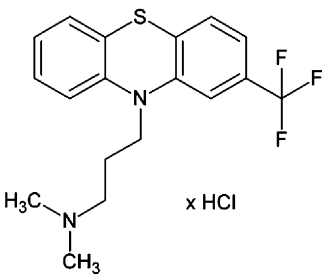
Table 1
Investigated compounds: name, abbreviation, structure, and molar mass.

Name of compound	Structural formula	M (g mol^{-1})
Chlorpromazine hydrochloride (CHLPRO)		355.33
Fluphenazine dihydrochloride (FLPHE)		510.50
Promazine hydrochloride (PRO)		320.90
Thioridazine hydrochloride (THRID)		407.40
Trifluoperazine dihydrochloride (TFLPER)		480.43
Triflupromazine hydrochloride (TFLPRO)		388.80