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In situ monitoring of pH titration by Raman spectroscopy

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ABSTRACT

Molecular speciation of organic compounds in solution is essential for the understanding of ionic complexation. The Raman technique was chosen because it allows the identification of compounds in different states, and it can give information about the molecular geometry from the analysis of the vibrational spectra. The effect of pH on organic compounds can give information about the ionisation of molecule species. In this study the ionisation steps of salicylic acid and paracetamol have been studied by means of potentiometry coupled with Raman spectroscopy at 30.0 °C in a solution of ionic strength 0.96 mol dm^{-3} (KNO_3) and 0.04 mol dm^{-3} (HNO_3). The protonation and deprotonation behaviour of the molecules were studied in different pH regions. The abundance of the three different species in the Raman spectra of aqueous salicylic acid have been identified satisfactorily, characterised, and determined by numeric treatment of the data using a multiwavelength curve-fitting program and confirmed with the observed spectral information.

1. Introduction

Technological improvements in Raman spectrometry have made this technique applicable for the quantitative and qualitative analysis of pharmaceuticals [1,2], especially for the on-line process monitoring and analysis of materials in the pharmaceutical industry. Considerable advantages result from the fact that Raman spectroscopy is a fast and non-destructive technique and that spectra can be recorded directly from specimens inside containers and packaging without interference for powders and solutions. Water is a very weak Raman scatterer, facilitating Raman measurements in an aqueous environment [3]. The intensity of a Raman line is directly proportional to the concentration of the scattering component of a sample in a laser beam,

$$I = \acute{\alpha} C$$

where I is the intensity of the Raman scattering, C is the concentration of the active ingredient and $\acute{\alpha}$ is a coefficient representing the features of the sample analysed and the spectrometer conditions [4,5].

Stability constants are key parameters for the investigation of equilibria in solution and are very important in many fields such as industrial chemistry [6], environmental studies [7], as well as medicinal [8] and analytical chemistry.

The determination of the dissociation constant of an acid in a binary mixed solvent provides useful data for the theoretical understanding of the ionisation process in systems where two dipolar entities, ethanol and water in our case, as well as the anions, can compete for the proton. The ionisation constants of acids are influenced by the nature of the solvent and in alcohol–water mixtures vary with solvent composition in a manner which is not completely understood [9–11].

Salicylic acid (H_2Sal) and its derivatives are also biologically important ligands, a well known and widely used derivative, aspirin, reduces the risk of many diseases associated with ageing and is used in the treatment of rheumatic fever, pain, and the prevention of thrombosis in the vascular system.

Salicylic acid comprises three organic functionalities; an aromatic ring, a carboxylic group and a phenolic hydroxyl group. Salicylic acid has a low pK_{a1} (2.8) which correspond to the ionisation of the proton of the carboxyl group and a high pK_{a2} (*ca.* 13.4) due to ionisation of the hydroxyl group [12].

The relatively high value of pK_{a2} is generally ascribed to the stabilisation of the ($HSal^-$) by intermolecular hydrogen bonds between the phenolic (OH) groups and the carboxylate groups [13,14].

4-Hydroxyacetanilide was first prepared by Morse in 1878. Under the names paracetamol, acetaminophen and panadol; it is now used as an analgesic and antipyretic drug [15,16]. Paracetamol, a weak acid having pK_a *ca.* 9.5, rapidly becomes absorbed and distributed after oral administration and is easily excreted in urine [17].

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Hydrogen bonding is a primary feature in the crystal structure of acetaminophen. There are two proton donors (NH, OH) within the molecule, and two proton acceptors (C=O, OH). The biological activity and pharmaceutical properties of drugs are strongly dependent on their structure. A continuous flow-based spectroscopic method for the determination of paracetamol in pharmaceuticals has been reported by Criado et al. [18].

Spectroscopic methods for determination of stability constants have the advantages of sensitivity and reliability and are suitable for determination of stability constants in solution under different experimental conditions. Overlapping of spectra of different chemical species involved in the equilibria is an important problem because it makes the determination of stability constants by classical methods difficult or even impossible and can cause uncertainties in the results. For this purpose, recently, most systems in the literature involved the use of both model-based and model-free chemometrics methods to estimate the number of species simultaneously present at equilibrium, their stoichiometries and their stability constants. Multiwavelength (multivariate) nonlinear least squares methods have been applied to spectroscopic data successfully. For this purpose, the postulation of chemical model and information about the number and nature of species is required.

Although the ionisation steps of salicylic acid have been studied by potentiometry, there is no previous report of this being investigated in different ionic media and Raman spectroscopy has not hitherto been applied to the system.

In this study, the effect of pH on salicylic acid and paracetamol were investigated by means of Raman spectroscopy. The vibrational spectra of salicylic acid and paracetamol were first measured in aqueous ethanol (50%, v/v) at 0.4 mol dm^{-3} and compared with the spectra of the crystalline forms. The pH-spectra and potentiometric data were treated by a model-based nonlinear least squares curve-fitting program using a Newton–Gauss–Levenberg–Marquardt algorithm. Protonation constants, distribution diagrams (concentration profiles) and spectral profiles of each component can be the extracted by using the mentioned method. Secondly, we will determine the limit of detection for salicylic acid and paracetamol using peak areas and intensities and compare these methods.

2. Experimental

2.1. Materials

Salicylic acid, 4-hydroxyacetanilide (paracetamol), potassium nitrate, potassium hydroxide and nitric acid were procured from Sigma–Aldrich, UK. Solutions of the pharmaceutical were prepared in deionised water and absolute ethanol (50:50, v/v) potassium nitrate and nitric acid were added to maintain the ionic strength of the solutions and as an internal standard for Raman measurements.

All titrations were performed using an automatic titrator (665 Dosimat) with magnetic stirrer stand and electrode holder (see Fig. 1). All titrations using standardized 1.0 mol dm^{-3} KOH were performed in solutions of 0.96 mol dm^{-3} (KNO_3) and 0.04 mol dm^{-3} (HNO_3), with the temperature maintained at 30.0 ± 0.1 °C.

The *in situ* monitoring through the vessel was achieved with Renishaw portable Raman analyser 'RIAS' (Wotton-under-Edge, UK).

The calibration of the pH meter was carried out in the usual way using two buffer solutions in aqueous media. The pH values in ethanol/water solvent mixtures were corrected using the equation of Douheret: $pH^* = pH(R) - \delta$, Where pH^* is the corrected reading and $pH(R)$ is the meter reading obtained in partially aqueous organic solvent mixtures. The values of δ for an aqueous solution containing varying proportions of each of the organic solvents were determined by Douheret. For ethanol/water mixed solvent, up to 60 wt% of ethanol, the value of δ is small (<0.20). Douheret reported (0.02–0.03) deviations in pK_a values as a result of using this method for pH correction [19,20].

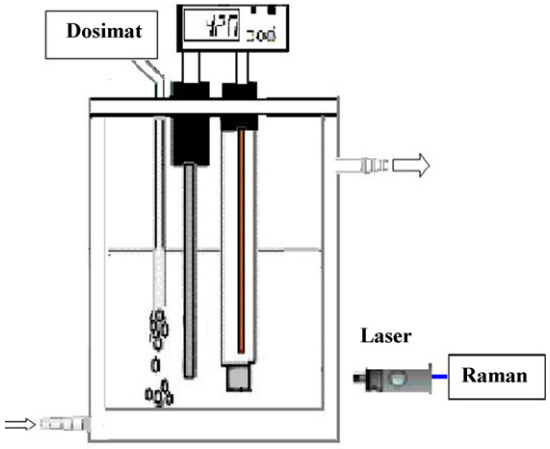

Fig. 1. Schematic diagram of experimental setup.

2.2. Spectroscopy

2.2.1. Renishaw portable Raman analyser RX210 'RIAS'

The RIAS is equipped with a diode laser emitting at 785 nm and a thermoelectrically cooled charged coupled device (CCD) detector. An attached fibre-optic probe was equipped with a 75 mm focal distance lens. The diffraction grating (1000 lines/mm) limits the spectral range to ~2100–100 cm^{-1} with a spectral resolution of 10 cm^{-1}. The maximal output power of the diode laser at the source is 500 mW and ~50 mW at the sample. Daily calibration of the wavenumber axis is required and is achieved by recording the Raman spectrum of silicon (1 accumulation, 10 s) for static modes. (If necessary, an offset correction is performed to ensure that the position of the silicon band is 520.50 ± 0.10 cm^{-1}.) Spectra were recorded with the accumulation of 2 scan, 10 s exposure and full laser power.

2.3. Computer hardware and software

All Raman spectra were digitised and transferred in ASCII format to a GRAMS/AI version 8 for analysis. Determination of acidity constants was performed by regression analysis of the Raman spectra using a written program in our laboratory running in the MATLAB 7.2 (The MathWork Co.) environment. Calculations were performed by an iterative procedure by using the Newton–Gauss–Levenberg/Marquardt (NGL/M) algorithm of non-linear least squares fitting [21,22].

All digitised spectra (Raman intensities) at different pHs for each titration were combined in a single file. The noise filtering was carried out based on singular value decomposition (SVD). For this purpose after decomposition of the data file matrix to two matrices (the loading and score matrices), the data matrix was reconstructed by considering the major principal component that is equal to the number of Raman active components involved in acid–base equilibria of the pharmaceuticals. Then the data were processed using the proposed chemical equilibria (model) and an initial estimate of the pK_a values. The program then minimizes the following equation based on the variation of pK_a in each titration and considers some restrictions such non-negativity in concentration and the spectral