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COMMUNICATION

Hydrotropic Properties of Sodium Salt of Ibuprofen

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INTRODUCTION

Hydrotropic agents have been used to increase the solubility of a number of drugs (1). Sodium salicylate is the most studied hydrotrope from the drug solubilization point of view as the other hydrotropes, such as aromatic sulfonates, are not suitable for this purpose. From the definition given by Saleh et al. (2) and the aggregation behavior of conventional hydrotropes (3), it is concluded that an amphiphile with a short hydrophobic part may function as a hydrotrope. We thought it worthwhile to investigate whether a drug with an amphiphilic structure can also exhibit hydrotropic properties. This phenomenon has a practical relevance as use of hydrotropes in drug formulation is well documented; also, as reported by Higuchi and Drubulis (4), a complex formation between the hydrotrope and the drug may influence the thermodynamic properties of the drug. In this study we sought to establish sodium ibuprofen as an effective hydrotrope and to characterize it using different techniques.

MATERIALS AND METHODS

Ibuprofen was obtained as a free sample from M/s.Sekhseria Chemicals, Bombay. It was purified by repeated crystallization before use and was found to be 99.9% pure. The sodium salt of ibuprofen (Na-Ip) was prepared by neutralizing ibuprofen with sodium hydroxide. The measurements of the solubility of ibuprofen in the aqueous solutions of its sodium salt were done at 303, 313, and 323 K. The solubility measurements at room temperature of 303 K were also done by maintaining the pH at 7 with phosphate buffer (0.1 mol/liter). The suspension of ibuprofen in its sodium salt solution was stirred in a glass reactor, in a constant temperature, bath for 2 hr to attain equilibrium. The concentration of the dissolved ibuprofen was determined by titration against a standard NaOH solution using a phenolphthalein as the indicator. All the measurements were done in duplicate.

The Na-Ip solutions were characterized using surface tension, conductivity, and fluorimetric studies. The surface tension of the solution of Na-Ip was measured using a Fischer tensiometer by the Du–Nuoy ring method. The conductivity of Na-Ip solution was measured using a Chemito digital conductivity meter. The fluorescence intensity of a dissolved probe, pyrene, was measured using a Sequia–Turner spectrofluorimeter. The excitation wavelength chosen for pyrene was 360 nm and the emission was measured at 540 nm. The fluorescence quenching of pyrene emission was done using Cu^{2+} as the fluorescence quencher.

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RESULTS AND DISCUSSION

The most important feature of a hydrotrope is its ability to increase the solubility of organic substances in the aqueous solutions. We selected ibuprofen itself in the acidic form as the solute because of its very low physical solubility (<0.1 g/liter) in water. Figures 1(a) and 1(b) show the solubility of ibuprofen in aqueous solutions of Na-Ip at three different temperatures and the corresponding variation in the pH of the solutions, respectively. The enhancement in solubility follows a characteristic sigmoidal pattern with the concentration of Na-Ip, which indicates solubilization to be a collective molecular phenomenon. The solubility rises only beyond a minimum hydrotrope concentration (MHC) of Na-Ip, which is about 0.15 mol/liter at 303 K. At a concentration of 1 mol/liter of Na-Ip, the solubility of ibuprofen is 48 g/liter which shows an increase of 480-fold. With increase in the temperature, the solubility rises further. At 313 K the increase in solubility of ibuprofen is 750-fold, while at 323 K it is 1000 times the solubility of ibuprofen in water. The pH of these saturated solutions also changes but only in the narrow range of 6.2–7.0; particularly at the higher temperature, the pH variation is between 6.8 and 7.0. This range of pH is also acceptable from the point of view of drug formulations. Considering the pK_a of Ibuprofen at 4.4 it seems that it is mostly solubilized in the molecular form; otherwise its dissociation would have decreased the pH of the solution. At higher concentration of the hydrotrope, the dissociation of the acid form is suppressed considerably, as shown by the pH of the solution.

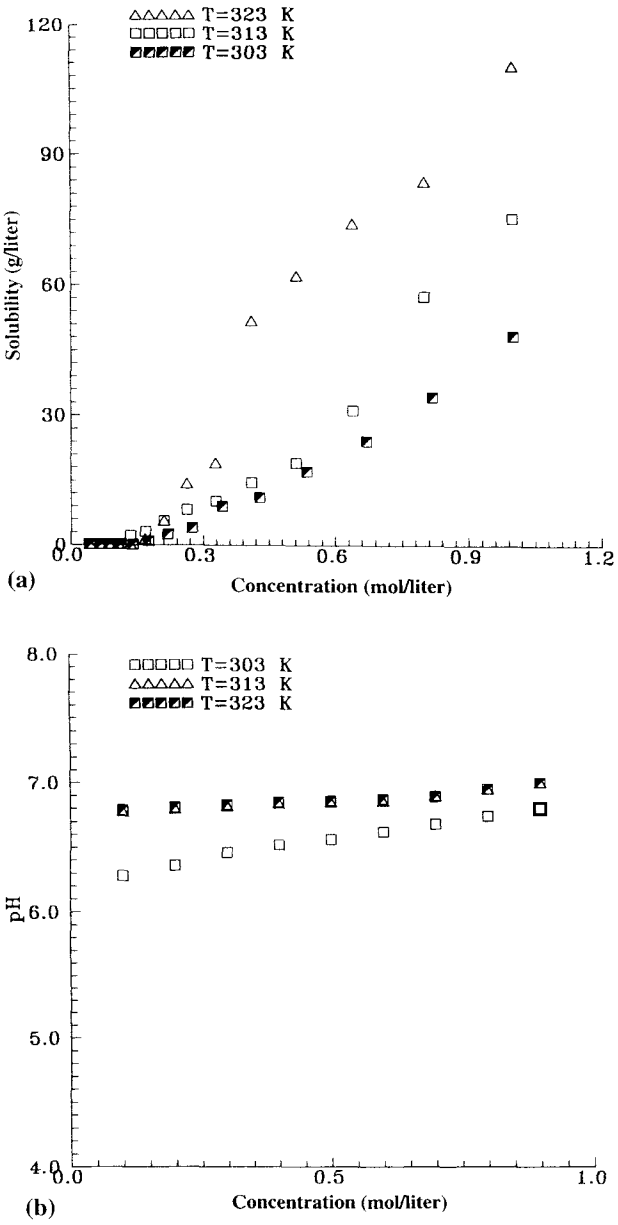

Figure 1. (a) Solubility of ibuprofen in Na-Ip solutions. (b) Variation in the pH on solubilization of ibuprofen in Na-Ip solutions.

The solubility of ibuprofen was also measured at a constant pH of 7.05, maintained with phosphate buffer, at a temperature of 303 K. The solubility obtained at the constant pH is slightly higher than that obtained without the buffer (Fig. 2).

The amphiphilicity of a molecule is considered to be a prerequisite for the molecule to function as a hydrotrope (5). Apparently, the aggregation of the hydrotrope is responsible for the hydrotropic solubilization(3). The amphiphilic nature of Na-Ip is evident from its molecular structure and thus it is expected to be surface active. The surface tension of aqueous solutions of Na-Ip shows that it is indeed surface active, with a minimum surface tension value (45 dyn/cm) being obtained at 0.2 mol/liter, which is close to the MHC obtained from the solubilization studies. Figure 3 also compares the surface tension of Na-Ip with sodium isobutyl benzene sulfonate (Na-IBB), which is a structurally similar aromatic sulfonate hydrotrope. The MHC of Na-Ip is lower than that of Na-IBB, the value for the latter being 0.3 mol/liter, probably because of the strongly ionic sulfonate head group. The MHC of Na-Ip is, however, much lower than the MHC of sodium salicylate (0.6–0.7 mol/liter); that is, a lower concentration of Na-Ip would be required, compared to Na-salicylate, for drug solubilization.

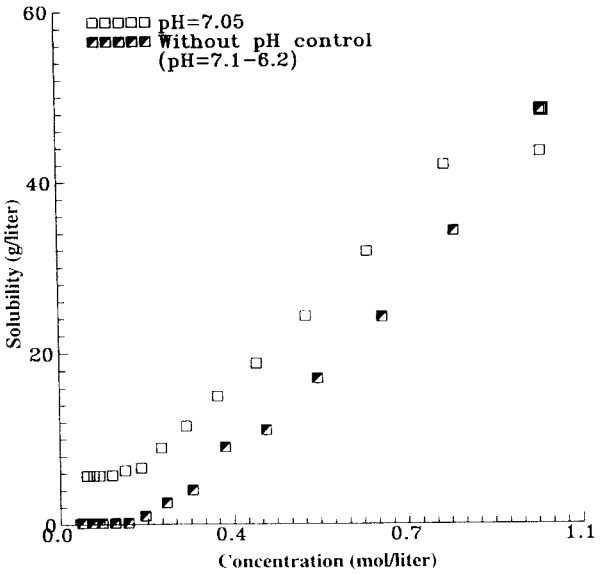

Figure 2. Solubilization of ibuprofen in Na-Ip in the presence and absence of buffer.

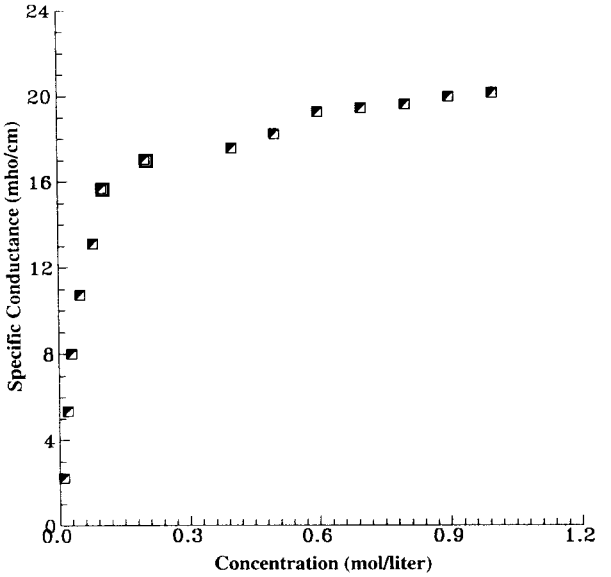

Figure 4. Variation in the specific conductance of Na-Ip with concentration.

The aggregation behavior of Na-Ip is also manifested in the conductivity of Na-Ip solutions, which shows a sharp break at 0.2 mol/liter, in a manner analogous to the micelle-forming surfactants (Fig. 4). Further insight into the hydrophobic character of Na-Ip comes from the fluorescence probe experiments. We chose to solubilize pyrene in Na-Ip solutions because of its extremely low solubility in water. A fluorophore is expected to be protected from the quencher if it is embedded within the aggregates of the surface-active materials. We monitored the ability of the hydrotrope to protect the probe from fluorescence quenching by Cu^{2+}. The paramagnetic

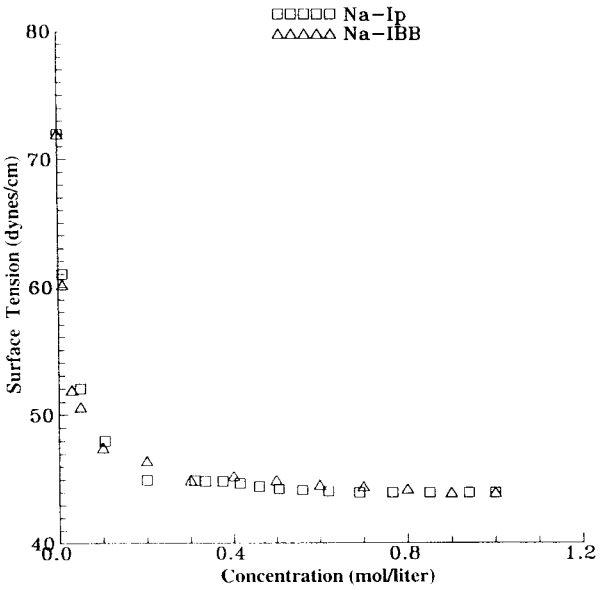

Figure 3. Surface tension plots of Na-Ip and Na-IBB solutions.

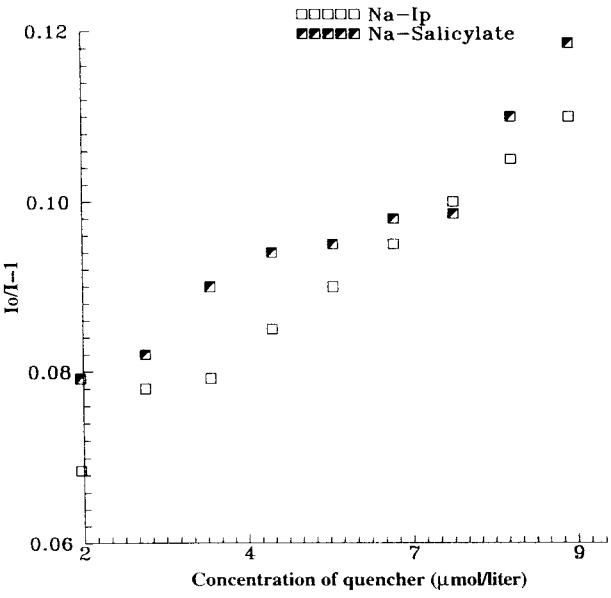

Figure 5. Stern–Volhmer plots for Na-Ip and Na-salicylate solutions.

quenching of the aromatic fluorescence depends on the access of the quencher to the aromatic probe. Figure 5 shows the Stern–Volmer quenching plots for pyrene in Na-Ip (1 mol/liter) and Na-salicylate (1 mol/liter) solutions, their concentrations being well above their respective MHCs. It is seen that Na-salicylate and Na-Ip protect or shield the probe almost to the same extent.

CONCLUSIONS

Na-ibuprofen is an effective hydrotrope and can increase the solubility of ibuprofen by 3 orders of magnitude, particularly at higher temperature or at higher concentration. The MHC value of Na-Ip is much lower than that of sodium salicylate, which is conventionally used for drug solubilization. It would, however, be necessary to consider the efficacy of Na-Ip when used as a drug solubilizer for other water-insoluble drugs.

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