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# SOLUBILITY PROPERTIES OF THE SEROTONERGIC AGONIST 2,3,4,5-TETRAHYDRO-8-(METHYLSULFONYL)-1H-3-BENZAZEPIN-7-OL

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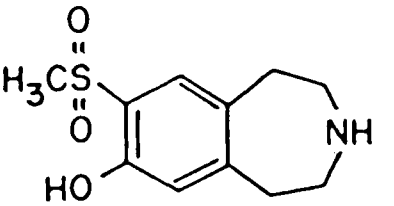
## ABSTRACT

The apparent solubility of SK&F 103829 (2,3,4,5-Tetrahydro-8-(methylsulfonyl)-1H-3-benzazepin-7-ol) as a function of pH was determined in the presence of methane sulfonic, acetic and hydrochloric acids. The mesylate salt of SK&F 103829 was observed to be highly soluble in water (solubility - 441.3 mg/mL). However, the addition of NaCl to solutions of the mesylate salt was observed to cause a dramatic decrease in solubility which was determined to be due to the formation of the poorly soluble hydrochloride salt (saturated solubility in water 1.0 mg/mL). An unique solubility profile was observed when acetic acid was used in the studies. A plausible explanation for this unique solubility profile and the implication of the solubility data generated on development of a parenteral formulation is discussed.

## INTRODUCTION

2,3,4,5-Tetrahydro-8-(methylsulfonyl)-1H-3-benzazepin-7-ol (1, SK&F 103829) is a serotonergic agonist that is currently undergoing development as a novel treatment for gastroesophageal reflux disease (GERD) since it is selective for the smooth muscle of the lower esophageal sphincter (LES)[1]. It is believed that by increasing the tone of the LES, SK&F 103829 can prevent reflux into the esophagus and allow for symptomatic relief and, possibly, healing of GERD.

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As part of the pharmaceutical development of SK&F 103829 for parenteral use in Pathology/Toxicology and early clinical studies, the aqueous solubility of various salts of the compound such as hydrochloride, mesylate and acetate was evaluated. The preliminary solubility data in water indicated some interesting differences in the solubility characteristics of the various salts by themselves and in the presence of added buffer and salt such as sodium chloride. This observation led us to more thoroughly investigate the pH solubility profile of SK&F 103829 free base in various acids and is the topic of this publication.

## MATERIALS AND METHODS

The mesylate (SK&F 103829-J), hydrochloride (SK&F 103829-A) and acetate salts of SK&F 103829 were prepared from the free

base using standard procedures. The crystalline salts were characterized using IR, NMR and elemental analysis. The purity of the salts was determined to be greater than 99% by HPLC methodology. The $pK_a$ determinations were accomplished by potentiometric titration. All other chemicals employed were reagent grade. Water was obtained from a Milli-Q system (Millipore) and was filtered and degassed prior to use.

Solubility determinations were carried out by adjusting the pH of a saturated solution of SK&F 103829 free base with excess solid in water to the desired value with an appropriate acid. The samples were shaken for 24 h at ambient temperature. Preliminary experiments established that this time period was sufficient for equilibration. The suspensions at equilibrium were centrifuged and the clear supernatant was removed using a cotton-tipped pipet. The pH of the supernatant was determined at ambient temperature using an Orion Research Analyzer (Model 501) pH meter. The samples were diluted in 50 mM phosphate buffer (pH 8.0) and assayed for SK&F 103829 content spectrophotometrically at 320 nm using a Beckman DU-7 spectrophotometer. The solutions followed Beer's law under these conditions.

## RESULTS AND DISCUSSION

The solubility behavior of SK&F 103829 free base was investigated in the presence of three acids - hydrochloric, methane sulfonic and acetic. The reasons for utilizing these particular acids were two-fold. Firstly, in water, the equilibrium solubility for the hydrochloride salt (SK&F 103829-A) was approximately 1 mg/mL while the mesylate salt had an equilibrium solubility of over 400 mg/mL. The origin of this drastic difference needed to be elucidated. Secondly, the effect of the $pK_a$ of the acid was of interest and, therefore, acetic acid was a logical choice since its $pK_a$ (4.75) is over five units higher than that of methane sulfonic acid.

The pH of the SK&F 103829 free base in water was 8.3 for a saturated solution (concentration: 11.1 mg/mL). As shown in Figure 1, the addition of increments of HCl to this solution caused an initial increase in the saturation solubility until it reached a maximum of 23.6 mg/mL at a pH of 7.2. Below this pH, the solubility of SK&F 103829 steadily decreased with increasing amounts of HCl. The minimum detected solubility in this study was 1.7 mg/mL at a pH of 1.0. This value is similar to the saturation solubility of the hydrochloride salt of SK&F 103829.

When aliquots of methane sulfonic acid were added to the saturated aqueous solution of SK&F 103829 free base, the solubility of SK&F 103829 continued to increase as evidenced in Figure 1. Unlike the profile for the solubility of SK&F 103829 free base in HCl, the profile obtained with methane sulfonic acid showed a marked increase in the saturation solubility of SK&F 103829 as the pH became more acidic. In fact, at a pH of 4.5 the equilibrium solubility was greater than 400 mg/mL. This pH solubility profile is what one would expect since the $pK_a$ values for the two ionizable groups in SK&F 103829 are 7.3 and 9.7 for the phenolic and secondary amine functionalities, respectively.

The results when acetic acid was used were very similar to those obtained with methane sulfonic acid (see Figure 1). As increasing amounts of acetic acid were added to an aqueous solution of SK&F 103829 free base, the solubility increased and reached a maximum of 322 mg/mL at the lowest pH investigated of 3.8. However, when employing acetic acid, the solubility of SK&F 103829 tends to level off in the pH region of 4.9-6.8 (limiting solubility in this area is approximately 140 mg/mL), yielding a very unique solubility profile. This plateau was confirmed by repeated solubility measurements. The acetate salt of SK&F 103829 was prepared and its equilibrium solubility in

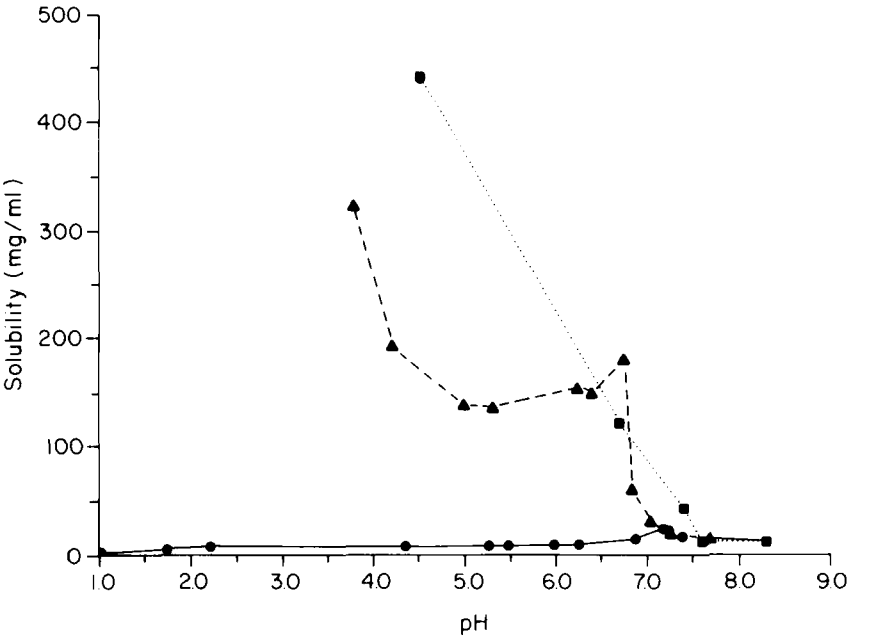


Figure 1: Comparison of the pH solubility profiles for SK&F 103829 free base in hydrochloric acid (●), methane sulfonic acid (■) and acetic acid (▲).

water was found to be 141.0 mg/mL. This value is nearly identical to the solubility value obtained in the plateau region in Figure 1. Thus, this plateau is a result of the limiting solubility of the acetate salt of SK&F 103829.

The subsequent solubility increase of SK&F 103829 that occurs at pH values below the plateau region was unexpected (see Figure 1). Since the solubility of SK&F 103829 increased with increasing amounts of acetic acid (beyond the plateau region where the acetate salt has been formed), the role of acetic acid in this observed solubility enhancement was investigated. As evidenced in Figure 2, the solubility of the acetate salt of SK&F 103829 increased as a function of acetic acid concentration. This result implies that there is some

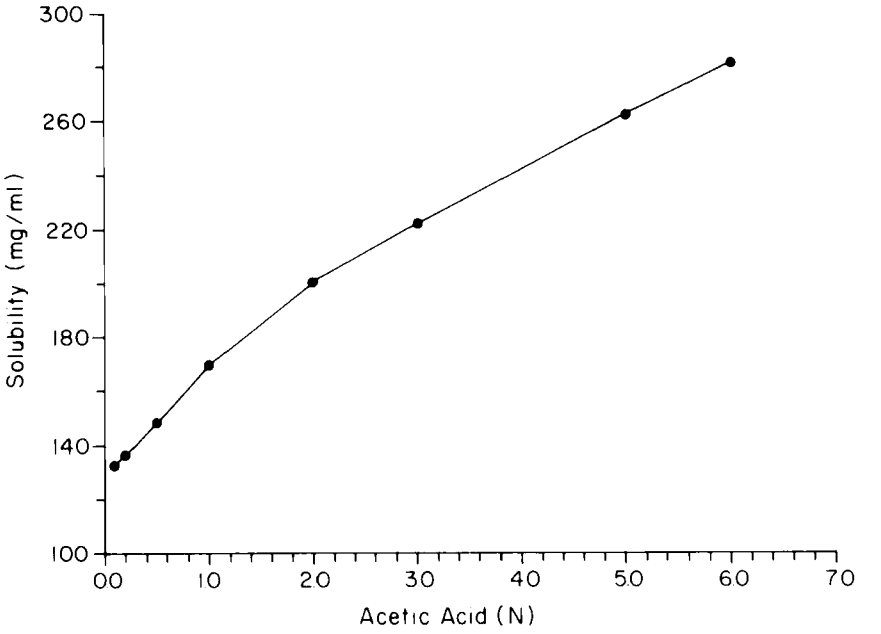


Figure 2: Effect of acetic acid concentration on the solubility of the acetate salt of SK&F 103829.



type of interaction occurring between the acetate salt of SK&F 103829 and acetic acid that leads to a substantial solubility enhancement. The mechanism of this interaction is not currently understood.

Since the addition of aliquots of methane sulfonic acid and acetic acid increases the water solubility of SK&F 103829, the adverse effect seen with HCl must be classified as a common ion effect. Further evidence to support this claim has been obtained by the addition of increasing amounts of sodium chloride to a saturated solution of SK&F 103829-J (see Figure 3). The pH of the solutions in this study varied from 4.0 (no NaCl) to 7.3 (1.0 M NaCl). A dramatic decrease in the solubility occurs at concentrations of NaCl as low as 0.05 M, i.e. the solubility goes from 441.3 mg/mL to 62.0 mg/mL. At 1.0 M NaCl

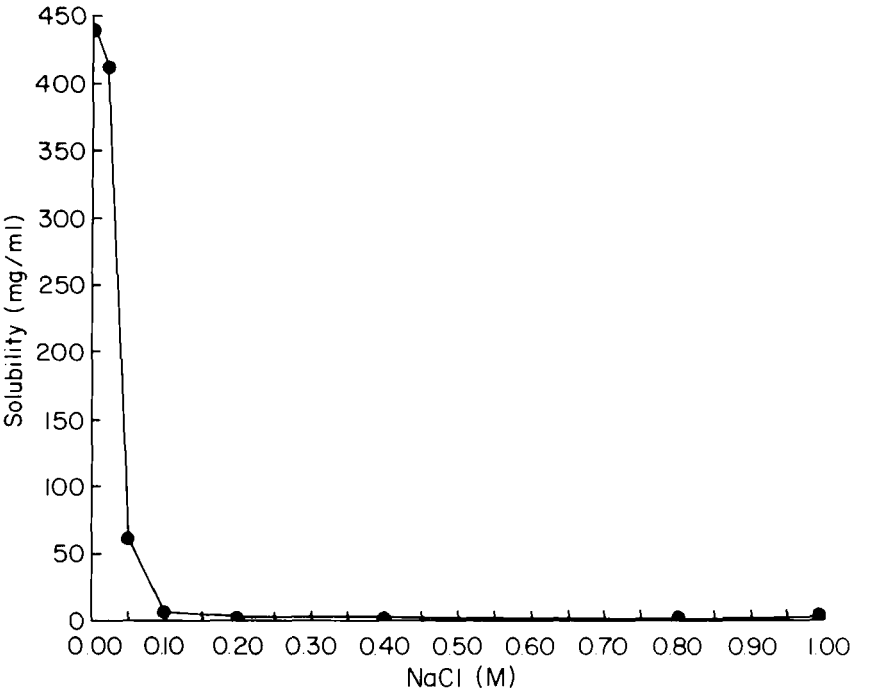


Figure 3: Effect of sodium chloride concentration on the water solubility of SK&F 103829-J.

the solubility of SK&F 103829 reaches a minimum of 1.0 mg/mL. Furthermore, the resulting precipitate in the NaCl solution was isolated, dried and subjected to DSC and elemental analysis. Its DSC was identical to the DSC for authentic SK&F 103829-A (mp: 367°C), the hydrochloride salt (the mesylate salt melts at 268°C under identical DSC conditions). The elemental analysis of the precipitate also matched the expected results for the hydrochloride salt of SK&F 103829 (Table 1).

The hypothesis for the conversion of SK&F 103829-J to SK&F 103829-A upon addition of NaCl is based on the dramatic solubility differences of the mesylate and hydrochloride salts. As a small amount of the hydrochloride salt is formed, precip-

TABLE 1: Elemental Analysis of the Precipitate Obtained by Addition of Sodium Chloride (0.15 M) to SK&F 103829-J in Water.

| ELEMENT | PRECIPITATE (found) | SK&F 103829-A (theory) |
|---|---|---|
| C | 47.69 | 47.56 |
| H | 5.65 | 5.81 |
| N | 4.99 | 5.04 |
| Cl | 12.92 | 12.76 |

itation of SK&F 103829-A begins to occur and this insolubility acts as a "sink" and causes more conversion of the mesylate salt until eventually the only species present is SK&F 103829-A, which in water has a maximum solubility of 1.0 mg/mL, the same value obtained when 1.0 M NaCl was added to an aqueous solution of SK&F 103829-J.

This observation of a common chloride ion effect precludes the use of sodium chloride as an isoosmotic agent in the formulation or the use of saline solutions as diluents in the clinical studies. Both of these problems have been overcome by employing mannitol as the isoosmotic agent and 5% dextrose as a diluent.

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