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Technical Note

Preformulation Salt Selection. Physical Property Comparisons of the Tris(hydroxymethyl)aminomethane (THAM) Salts of Four Analgesic/Antiinflammatory Agents with the Sodium Salts and the Free Acids

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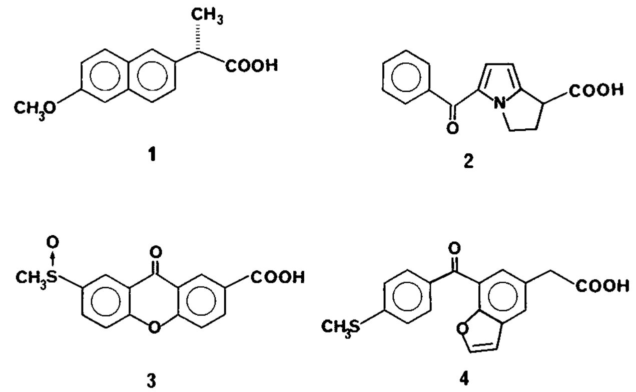
INTRODUCTION

The use of THAM, tris(hydroxymethyl)aminomethane, salt in pharmaceutical practices has received recent attention (1). Oral administration of THAM citrate was shown to improve the dissolution of uric acid calculi *in vitro* and *in vivo* (2). THAM and THAM aspartate were found to increase the aqueous solubility of zomepirac (3) and aspirin (4), respectively. The THAM salt of fosfomycin was reported to be more bioavailable than the calcium salt (5), and the THAM salt of prostaglandin $F_{2\alpha}$ was selected as the raw material for its better crystallinity and purity (6). The latter also marked the first THAM salt approved by the Food and Drug Administration (7). This paper compares the various physical properties of the THAM salt to those of the most commonly used sodium salt (8) and free acid for four analgesic/antiinflammatory compounds: naproxen (1), ketorolac (2), RS-7337 (3), and RS-82917 (4).



Scheme I

MATERIALS AND METHODS

Naproxen, ketorolac, RS-7337 (7′-oxo-7-thiomethoxyxanthone-2-carboxylic acid), RS-82917 [7-4(methylthiobenzoyl)benzofuran-5-yl-acetic acid], and their sodium and THAM salts were obtained from the Institute of Organic Chemistry, Syntex Research. Melting points were determined by differential scanning calorimetry (DSC) on a Perkin–Elmer DSC-2 calorimeter. For hygroscopicity measurements, drug samples were first dried under vacuum at 80°C overnight in the presence of P_2O_5. The dried samples were then stored at room temperature in desiccators maintained at constant relative humidities (RH) with various saturated salt solutions. After equilibration for 7 days, samples were weighed and compared with the day weight.

Solubility of the drug was determined by tumbling the suspension of the drug in the appropriate solution at 25°C for 3 days. The suspension was then filtered through a 0.45-μm Millipore filter and the pH of the filtrate was measured. The concentration of the drug in the filtrate was determined by UV (HP8450A spectrophotometer). The UV absorbance was determined at 230 nm for **1**, at 314 nm for **2**, at 253 nm for **3**, and at 320 nm for **4**.

For intrinsic dissolution rate measurements, ~100 mg of the drug was compressed at 2000 psi into a flat disk (surface area, 0.49 cm^2) which was mounted onto a dissolution apparatus (Hansen, Model 72R115). The rotating disk (100 rpm) was then lowered into the dissolution medium (500 ml), equilibrated at 37 ± 0.5°C. The drug concentrations at various time intervals were determined by UV.

RESULTS AND DISCUSSION

The various physical properties pertinent to preformulation development were examined for the THAM salt, sodium salt, and free acid of compounds **1–4**, and the results are summarized in Table I. The melting points of the different forms of the drug were found to vary significantly and showed no apparent trend among the drugs studied. Both the free acid and the THAM salt of compounds **1**, **2**, and **4** are virtually nonhygroscopic up to 81% RH at room temper-

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Table I. Physical Properties of the THAM Salt, Sodium Salt, and Free Acid of Compounds[1–4]

Compound	Melting point (°C)[a]	% weight gain[b]				Solubility (mg/ml)	Dissolution rate, k (mg/min/cm^2)		
		25% RH[c]	47% RH	67% RH	81% RH		pK_a[d]	pH 3.0[e]	pH 7.4[f]
Naproxen, 1									
Acid	160	0	0	0	0	0.016[g]	4.40	≤0.005	0.16
Sodium salt	267	0	0	13	21	178 (8.8)[h]		21	21
THAM salt	191	0	0	0	0	11 (7.1)[h]		1.0	1.2
Ketorolac, 2									
Acid	149	0	0.4	0.8	0.8	0.037[g]	3.46	0.014	0.28
Sodium salt	338	0	0	31	38	>500		29	30
THAM salt	165	0	0	0	0	>500		15	14
RS-7337, 3									
Acid	304	0	0	0	0	0.003[g]	3.76	0.0096	0.29
Sodium salt	350	6.4	19	24	29	35 (7.4)[h]		9.3	14
THAM salt	216	0.6	4.5	6.4	9.0	107 (6.6)[h]		5.3	9.3
RS-82917, 4									
Acid	159	0	0	0	0	0.001[g]	3.96	≤0.005	0.28
Sodium salt	125	8.6	8.6	21	23	10.4 (7.8)[h]		2.7	7.3
THAM salt	161	0	0	0	0	10.5 (7.6)[h]		2.7	7.6

[a] Determined by DSC.
[b] Samples were first dried under vacuum.
[c] Relative humidity.
[d] Calculated from pH–solubility relationship [Eq. (1)].
[e] 0.001 N HCl; $\mu = 0.1\ M$ with KCl.
[f] 0.02 M phosphate buffer; $\mu = 0.1\ M$ with KCl.
[g] Intrinsic solubility.
[h] Values in parentheses represent the final pH of the salt solution.

ature. The THAM salt of 3 adsorbed up to 9.0% of water at ≥81% RH. The sodium salts, on the other hand, were significantly more hygroscopic than both the THAM salt and the free acid at ≥25% RH for compounds 3 and 4 and at ≥67% RH for 1 and 2 (Table I). DSC thermograms of the samples after equilibration at 25% RH indicated that most of the water absorbed (6.4 wt%) onto the sodium salt of compound 3 was surface water, while the sodium salt of compound 4 converted to its hydrate form.

The solubilities of the acids of 1–4 were studied in aqueous solution as a function of pH and were found to follow the pH–solubility relationship (9)

$$S = S_i[1 + 10^{(pH-pK_a)}] \qquad (1)$$

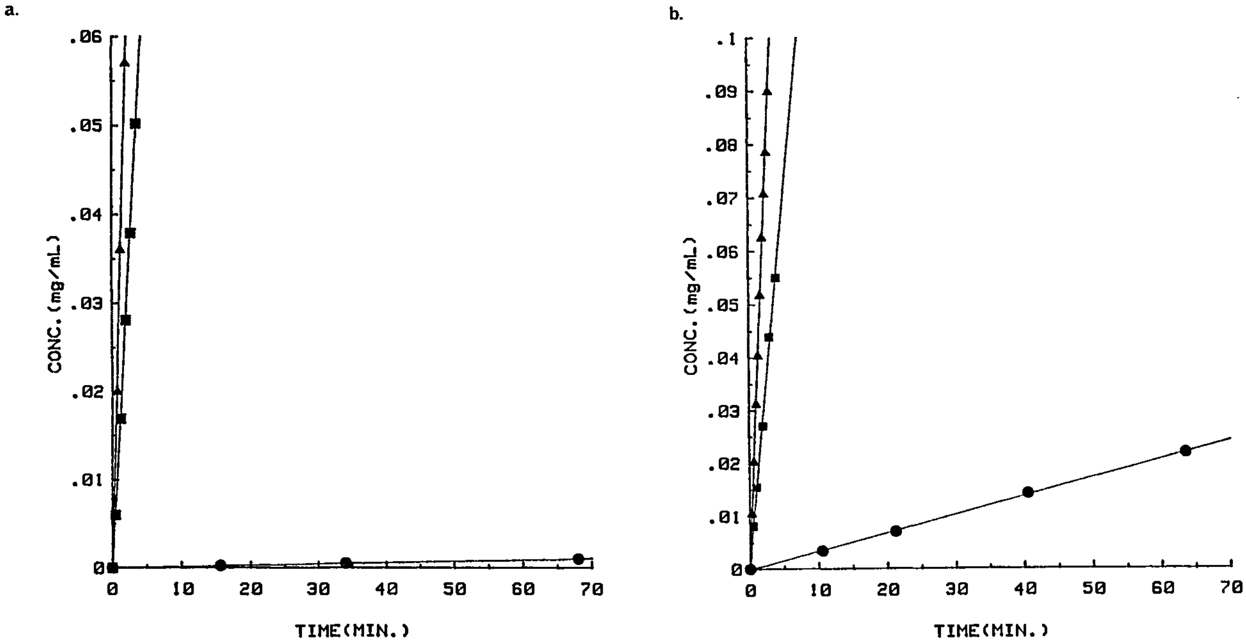

Fig. 1. Intrinsic dissolution rate of the free acid (●), sodium salt (▲), and THAM salt (■) of ketorolac (2) from a surface area of 0.49 cm^2 at 37°C and (a) pH 3.0 and (b) pH 7.4. Data are expressed as free-acid equivalents.

Values of the observed intrinsic solubility (S_i) and the pK_a's derived are summarized in Table I. The solubilities of the various sodium and THAM salts in water were also determined. In most cases, the pH values of the final salt solutions were within ±0.3 unit of those expected from Eq. (1) (Table I). The final pH (=6.6) of the THAM salt of **3**, however, was much lower than that calculated (=8.4), indicating a possible complex formation between the drug and the salt moiety (10). The sodium salt of **1** was approximately 12 times more soluble than the THAM salt of **1** in water, whereas the sodium salt of **3** was four times less soluble than the THAM salt of **3**. For compounds **2** and **4**, the sodium salt and the THAM salt showed similar solubilities. Comparing these solubility data with the melting points, it is clear that no simple solubility–melting point relationship can be established for the salts (11).

The intrinsic dissolution rate of the various compounds was studied at 37°C and at two different pH's. Typical dissolution plots for compound **2** are given in Fig. 1, and the values of dissolution rate constants (slope/surface area) for compounds **1–4** are summarized in Table I. At pH 7.4, both salts had much better dissolution rates than the free acid, reflecting the strong buffering effect of the salts on the diffusion-layer pH (12). This phenomenon is more evident in pH 3.0 solutions because the dissolution rate of the salts changed little from that found at pH 7.4, while the dissolution rate of the free acids at pH 3.0 was at least 20 times slower than that at pH 7.4.

CONCLUSIONS

Using analgesic/antiinflammatory agents **1–4** as examples, it is demonstrated that the THAM salt has a superior hygroscopicity property to the sodium salt for each drug and does not suffer loss in aqueous solubility and intrinsic dissolution rate, except for **1**. Considering the many advantages of handling less hygroscopic drug raw material for storage and formulation purposes (13), more use of the THAM salts of drug materials in the future may be warranted.[3]

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[3] The THAM salt of ketorolac (**2**) is awaiting FDA approval for marketing in the United States.