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XILOBAM: EFFECT OF SALT FORM ON PHARMACEUTICAL PROPERTIES

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ABSTRACT

In an effort to protect xilobam from the effects of high temperatures and high humidities without adversely affecting its dissolution from tablets, three arylsulfonic acid salts and the saccharin salt were prepared. All of the salts were determined to be more stable at 74% relative humidity and 70° than the free base.

In spite of the large differences between the effect of high humidity at a high temperature on the salts versus the free base, the dissolution of the most stable salt (1-napsylate) was essentially equivalent to

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the dissolution of the free base when both were prepared as formulated tablets.

INTRODUCTION

The importance of the salt form of a drug has been well documented in a review (1) which lists 294 references relating to the use of salt formation to modify the dissolution, solubility, organoleptic properties, stability, absorption, pharmacokinetics, pharmacology and toxicity of drugs.

Arylsulfonic acids are uniquely suited as salt forming acids for certain pharmaceutical applications. Sulfonic acids are strong acids, being ionized completely and soluble in aqueous media regardless of pH. However, the hydrophobic aryl group presents a barrier to dissolution which must be overcome for solution to be affected. In practical terms, arylsulfonic acids should protect their cationic salt forming partners from small quantities of water, e.g., moisture, or any small quantity of water which is quickly saturated to form a non-sink condition, but should permit dissolution and bioavailability under sink conditions. For example, the 2-naphthalenesulfonic acid salt of propoxyphene is less soluble than its hydrochloride counterpart, and, consequently, has superior organoleptic properties, less adverse effects on aspirin stability and reduced acute toxicity, but without alterations in bioavailability or clinical utility (2-6).

Xilobam, 1-(2,6-dimethylphenyl)-3-(1-(methyl-2-pyrrolidinylidene)urea, is a sparingly soluble base with a spectrophotometrically determined pKa of 6.1. The analysis of xilobam, the determination of its decomposition products, and an assessment of its stability has been described (7).

Originally, xilobam was prepared as the hydrochloride salt, the sulfate salt and the free base. As a result of their greater solubility, the xilobam portion of both salts hydrolyzed extensively upon two weeks storage at 40° and 80% relative humidity. Although the free base is more stable under these exaggerated environmental conditions, a potential stability problem was recognized. It was thought advisable to prepare less soluble salts which would provide greater chemical stability at high humidity and high temperature, but would not sacrifice bioavailability. This report describes the preparation, stability, and dissolution characteristics of three xilobam salts of arylsulfonic acids, plus the xilobam salt of saccharin, another strong acid containing an aryl group.

MATERIALS AND METHODS

Xilobam: Xilobam was used as received. Its preparation and characterization have been described (8).

Salt Preparation

Tosylate - A solution of xilobam (9.80 g, 0.04 mole) in acetone was combined with a solution of p-

toluene sulfonic acid (7.6 g, 0.04 mole) in acetone. The mixture was kept overnight at 40°. A white solid was separated by filtration and recrystallized from ethanol:ether (1:1). The resulting solid was dried under vacuum for six hours at 50°. The yield of the desired product was 15.1 g (90.4%), mp 167°-169°. Analysis calculated for $C_{14}H_{19}N_3O \cdot C_7H_8O_3S$: C, 60.41; H, 6.52. Found: C, 60.57; H, 6.60.

1-Napsylate - A solution of xilobam (9.80 g, 0.04 mole) in acetone was combined with a solution of 1-naphthalenesulfonic acid (9.76 g, 0.04 mole) in acetone. The solution was treated with charcoal, filtered through a diatomaceous earth pad and crystallized at 4°. The resulting off-white solid was recrystallized from ethanol:ether (1:1). After drying, the yield of the desired product was 10.1 g (55.7%), mp 176°-178°. Analysis calculated for $C_{14}H_{19}N_3O \cdot C_{10}H_8O_3S$: C, 63.55; H, 6.00. Found: C, 63.48; H, 6.05.

2-Napsylate - A solution of xilobam (6.20 g, 0.025 mole) in hot 2-propanol was combined with a solution of 2-naphthalene-sulfonic acid (5.65 g, 0.027 mole) in hot 2-propanol. The solution was treated with charcoal, filtered through a diatomaceous earth pad and crystallized under ambient conditions. An off-white solid was separated, washed with ether and recrystallized from ethanol:ether (1:1) to yield 8.83 g (77.8%) of the desired product, mp 171°-172°. Analysis calculated for $C_{14}H_{19}N_3O \cdot C_{10}H_8O_3S$: C, 63.55; H, 6.00. Found: C, 63.55; H, 6.02.

Saccarinate - A solution of xilobam (9.80 g, 0.04 mole) in 2-propanol was combined with a solution of saccharin (7.32 g, 0.04 mole) in 2-propanol. The solution crystallized at 4°. The solid was separated by filtration and recrystallized from ethanol: ether (1:1) to yield 13.5 g (78.7%) of the desired product, mp 149°-151°. Analysis calculated for $C_{14}H_{19}N_3O \cdot C_7H_5O_3S$: C, 58.86; H, 5.64. Found: C, 59.01; H, 5.69.

Specific Surface: The drug substances were used after being passed through an 80 mesh screen. The specific surface of each sample was determined by a 3 point nitrogen adsorption method on a commercial surface area analyzer.[1]

Solid State Stability: About 100 ml of a saturated sodium chloride solution were placed in a 500 ml, wide mouth jar with a tight, glass lid and a rubber seal to provide 74% relative humidity at 70° (9). A support stand was constructed from stainless steel screen and placed in the jar. Samples equivalent to 100 mg of the base which had been passed through an 80 mesh screen were weighed into a petri dish, placed on the supoprt stand and covered with an aluminum foil umbrella. The jar was sealed and placed in a 70° oven. At the prescribed time (120 or 168 hours), the sample was removed and transferred to a 120 ml screw cap bottle.

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[1] Quantasorb, Model No. QS7, Quantachrome Corp., Syosset NY 11791

Exactly 50 ml of chloroform and 25 ml of 0.1 N sodium hydroxide were added. The bottle was shaken for 20 minutes then centrifuged. The aqueous layer was aspirated and discarded. Fifteen ml of the chloroform layer was transferred to a 100 ml volumetric flask and the solution brought to volume with chloroform.

Five ml of the chloroform solution were added to 8 ml of cyclohexane and extracted for 30 minutes with 50 ml of 0.1 N hydrochloric acid. The sample was centrifuged and the aqueous layer decanted and retained.

Five ml of the aqueous layer were diluted with 15 ml of 0.1 N sodium hydroxide. The absorbance of the solution was determined on a recording spectrophotometer from 360 to 220 nm (maximum:245 nm) versus a solvent blank of 5 ml of 0.1 N hydrochloric acid mixed with 15 ml of 0.1 N sodium hydroxide. The results were compared to the absorbance of the reference standard assayed by the same procedure. Each form was tested in triplicate.

Dissolution: Compressed tablets containing the free base or the 1-napsylate salt as 200 mg equivalents of xilobam with dibasic calcium phosphate, 120 mg; starch, 80 mg; starch solids from starch paste, 27 mg; and magnesium stearate, 3 mg, were prepared. Dissolution tests were performed in 1000 ml dissolution vessels, USP, containing 750 ml of simulated gastric fluid, TS, USP, without pepsin, maintained at 37.5° ± 0.5°. A dissolution apparatus 2, USP, paddle was positioned 2.5

cm above the bottom of the vessels and rotated at 50 rpm. Five ml filtered[2] samples were removed at 5, 15, 30 and 60 minutes. Samples were diluted 2/42 with 0.1 N sodium hydroxide. The absorbance of the solution was determined on a recording spectrophotometer from 360 to 220 nm (maximum:245 nm) versus a solvent blank of 0.1 N sodium hydroxide. The results were compared to the absorbance of a 0.84 mg/ml solution of the base in simulated gastric fluid, TS, USP, without pepsin, diluted 4/24 and 2/22 with 0.1 sodium hydroxide.

Four tablets of the free base and the 1-napsylate were tested.

RESULTS AND DISCUSSION

Specific Surface: The specific surface determinations are reported in Table 1. Though the specific surfaces were not identical, they were of the same magnitude and were not expected to cause significant surface related differences in the pharmaceutical properties of the forms.

Solid State Stability: In developing this test, considerable time was spent finding the combination of temperature, humidity, time and storage container volume which would permit the degradation of the free

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2 MF-Millipore Filter, No. HAWP 02500, Millipore Corp., Bedford, MA, 01730.

TABLE 1

Specific Surfaces

form	m^2g^{-1}
free base	0.66
tosylate	0.26
saccharinate	0.28
2-napsylate	0.59
1-napsylate	0.50

base at a rate convenient for experimental purposes. Under the selected conditions, five days was the longest period of time at which the base was "stable". Any salt which decomposed to a significant extent by the fifth day was established as being less stable than the free base. Similarly, seven days was the time required for the base to decompose almost completely. Any salt which decomposed to a significantly lesser extent by the seventh day was established as being more stable than the free base.

The importance of temperature, humidity and time in any accelerated aging test is understood. In this study, storage container volume was also found to be important since the rate of decomposition also appeared to depend on the concentration of basic degradation products in the test atmosphere (7). For example, preliminary studies in larger containers required longer times for decomposition to become evident.

The results reported in Table 2 show that all of the salts tested were more stable than the free base--

TABLE 2

Solid State Stability at 70° and 74% Relative Humidity

Percent Intact Xilobam

Days	free base	tosylate	saccharinate	2-napsylate	1-napsylate
5	93.6	97.9	99.7	98.0	100.1
	93.0	98.1	99.0	98.7	99.7
	93.8	97.8	98.4	99.4	100.8
	$\bar{x}$=93.5	$\bar{x}$=97.9	$\bar{x}$=99.0	$\bar{x}$=98.7	$\bar{x}$=100.2
7	15.6	88.1	78.7	83.4	100.0
	24.6	79.7	82.5	72.9	99.4
	13.8	79.6	82.2	76.8	99.4
	$\bar{x}$=18.0	$\bar{x}$=82.5	$\bar{x}$=81.1	$\bar{x}$=77.4	$\bar{x}$=99.6

$\bar{x}$ = mean

especially after seven days. The 1-napsylate was the most stable form. There were no specific surface related differences in the stabilities.

Dissolution: Dissolution from compressed tablets of the same formulation in simulated gastric fluid, TS, USP, did not reflect the difference in the sensitivity to high humidity at a high temperature of the two forms (Figure 1). In fact, the tablet containing the 1-napsylate actually released xilobam at a faster rate. Thus, it has been demonstrated that a strong acid with an aryl group can protect an easily hydrolyzed base from the adverse effects of high humidity at a high temperature under non-sink conditions while at the same time dissoci-

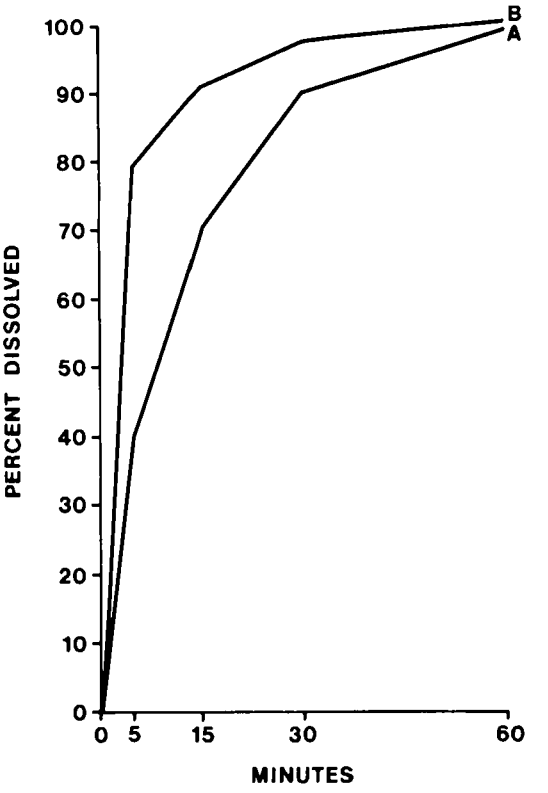

FIGURE 1

Dissolution of Xilobam From Tablets

Key: A, free base; B, 1-napsylate

ating from that base under appropriate sink conditions, as in a dissolution test, to permit rapid availability of the base.

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