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FENOCTIMINE SULFATE HYDRATION

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ABSTRACT

Fenoctimine sulfate was demonstrated to exist in two distinct crystalline forms, i.e., form A (low melting, 0.5 mole water of hydration), and form B (high melting, anhydrous). These forms can exist separately, in crystalline mixtures with each other, and with varying amounts of surface moisture. Each form can be converted into the other under appropriate wetting or drying conditions. In an aqueous environment, e.g., the gastro-intestinal tract, the surface of solid fenoctimine sulfate exists as form A.

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INTRODUCTION

The inclusion of water and other solvents in the crystal structure of medicinal compounds has led to complex problems in the characterization of those compounds, particularly under conditions of changing temperatures and vapor pressures (1-5). Early in the development of fenoctimine sulfate, 4-(diphenylmethyl)-1-[(octylimino) methyl]piperidine sulfate (1:1), an anti-secretory agent, samples were prepared which were low melting (ca. 128°-130°), high melting (ca. 155°-157°) and mixed melting (ca. 128°-130°, 155°-157°) and which contained small, variable amounts (0.35%-2.40%) of water. This report describes the characterization of fenoctimine sulfate samples according to melting range, water content and crystal form; the relationships which exist between the melting ranges, the water contents and the crystal forms, and the role which the environment plays in permitting one form to predominate over the other.

MATERIALS AND METHODS

Fenoctimine Sulfate: fenoctimine sulfate samples were used as received. The synthesis of fenoctimine sulfate has been described (6). A variety of crystallization methods were employed in an effort to improve yields, reduce impurities, reduce costs or prepare fenoctimine sulfate to specified water contents. As is often the case with a continually evolving industrial development program, some samples were not prepared in sufficient quantities or were not prepared at a time when all characterization methods were operational so as to permit their complete thermal, water content and crystal form characterizations.

Hot Stage Microscopy: Samples were tested on a microscope hot stage[1] mounted under 125X magnification. The samples were heated from 40° to 120° at 10° per minute, 120° to 125° at 2° per minute and from 125° to completion of the melting process at 1° per minute.

Karl Fischer Water Analysis Method: Samples (70 mg) were weighed onto weighing papers and added directly to the titration vessel of the Karl Fischer apparatus[2]. A 0.4 minute time delay was used to allow each sample to dissolve completely before the titration was started.

X-Ray Diffraction (XRD): X-ray diffraction patterns were determined on powder samples.[3] The following conditions were employed:

radiation:	copper K alpha
voltage:	40 kilovolts
amperage:	20 milliamps
entrance aperature:	0.6
receiving slit:	0.4
full scale:	$5x10^4$ to $1x10^5$ counts per second
time constant:	0.38 to 1.4 seconds
monochromator:	double beam, graphite crystal (Union Carbide)

Intrinsic Dissolution: Discs of fenoctimine sulfate weighing 700 mg and having a diameter of 13 mm were compressed at 3000 psi. Intrinsic dissolution rates were determined in 1800 ml of a pH 2, 0.1 M citrate buffer containing 10 percent alcohol maintained at 37°. The discs were rotated at 50 rpm in a horizontal plane with the upper side exposed to the medium. Three discs per lot were tested.

Six ml filtered (0.45 µm) samples were shaken with 10 ml of chloro-

form and 2 ml of 1 N sodium hydroxide. After centrifugation, the aqueous layers were aspirated and discarded. Seven ml of the chloroform layers were shaken with 7 ml of a saturated solution of methyl orange in pH 5, 0.2 M dibasic sodium phosphate buffer. After centrifugation, the aqueous layers were aspirated and discarded. Five ml of the chloroform layers were shaken with 5 ml of 1 N hydrochloric acid. After centrifugation, the aqueous layers were decanted and assayed spectrophotometrically at 505 mm versus 1 N hydrochloric acid. Calculations were based on the analysis of a standard solution prepared by dissolving 25 mg of each lot under test in 100 ml of methanol and diluting that solution 2/50 with the dissolution medium.

Equilibrium Solubility: Approximately 120 mg of fenoctimine sulfate were combined with 40 ml of pH 2, 0.2 M citrate buffer; simulated intestinal fluid, TS, USP, without pancreatin, and purified water, USP. The mixtures were shaken for 24 hours at 25°.

Four ml samples were filtered (0.45 µm) and diluted 2/100 with water. Ten ml of diluted samples were shaken with 30 ml of chloroform and 2 ml of 1 N sodium hydroxide. After centrifugation, the aqueous layers were aspirated and discarded. Seven ml of the chloroform layers were shaken with 7 ml of a saturated solution of methyl orange in pH 5, 0.2 M dibasic sodium phosphate buffer. After centrifugation, the aqueous layers were aspirated and discarded. Aliquots* of the chloroform layers

* medium	chloroform layer, ml	1 N hydrochloric acid, ml
standard	8	4
gastric fluid	8	4
intestinal fluid	5	5
water	5	10

were shaken with aliquots* of 1 N hydrochloric acid.
After centrifugation, the aqueous layers were decanted and assayed spectrophotometrically at 505 nm versus 1 N hydrochloric acid. Calculations were based on the analysis of a standard solution prepared by dissolving 23.9 mg of each lot under test in 100 ml of methanol and diluting that solution 2/100 with the pH 2 buffer.

RESULTS AND DISCUSSION

Hot Stage Microscopy

Forty-one samples of fenoctimine sulfate were analyzed. The results are reported in Table 1. Nineteen samples (46.3%) were classified as low melting, 11 samples (26.8%) were classified as mixed melting, and 11 samples (26.87%) were classified as high melting. Table 2 reports the means and standard deviations for the low melting samples and the low melting component of the mixed melting samples plus the same for the high melting samples and the high melting component of the mixed melting samples.

Karl Fischer Method

Table 3 reports the results from 23 samples analyzed for water by the Karl Fischer method. Table 4 arranges the results according to low, mixed and high melting categories. Unlike hot stage microscopy which would clearly classify all samples into three melting range categories, water analysis produced data which were wide ranging. All samples contained some water; samples containing a low melting component usually contained more water than high melting samples. Another view of the relationship of water content to thermal properties may be obtained from

TABLE 1

Melting Ranges (°C) of Fenoctimine Sulfate Samples

Sample No.	Melting Range, °C
2432:269E	126–127
2432:272B	125–128
2432:278B	129–130
2449:52	128–130
2449:65	127–129
2449:78	124–128
2449:79	128–132; 152–157
2449:95	129–130
2449:102	130–131; 155–157
2449:102A	130–132
2449:103	129–130
2449:104	155–157
2449:105	130–131
2449:107	130–132
2473:196A	129–139; 153–155
2473:196B	129–130; 153–156
2473:206A	130–132; 154–157
2473:226A	154–157
2473:238A	128–130; 156–156
2473:238B	156–157
2473:239A	156–158
2473:239B	155–157
2473:239C	128–129; 155–156
2473:253A	156–158
2473:254A	127–128; 157–157
2473:260A	128–130
2473:266A	130–131; 154–156
2473:275A	127–129
2473:275B	129–130
2473:275C	128–129
2473:277A	128–128
2473:277B	128–130
2473:278A	128–130
2902:30A	155–157
2902:19C	155–157
2902:20B	128; 154–157
2902:22A	154–156
2902:23A	154–156
2902:30A	155–157
2916:2A	123–127; 154–157
2916:3A	128–129

TABLE 2

Summary of Melting Ranges of Fenoctimine Sulfate Samples

Melting Range Category	Mean (Standard Deviation), °C
Low	128 (1.73) to 130 (1.39)
High	155 (1.17) to 157 (0.70)

TABLE 3

Water Contents of Fenoctimine Sulfate Samples

Sample No.	Melting Range[a]	Percent Water (Moles Water/ Moles Fenoctimine Sulfate[b])
2449:65	low	2.04 (0.564)
2449:95	low	1.73 (0.478)[c]
2449:102A	low	1.75 (0.483)[d]
2449:103	low	1.78 (0.492)
2449:104	high	1.54 (0.425)
2449:105	low	1.86 (0.514)
2449:107	low	1.80 (0.497)[e]
2473:196A	mixed	2.40 (0.663)
2473:196B	mixed	3.40 (0.939)
2473:206A	mixed	1.99 (0.550)
2473:226A	high	0.35 (0.097)[d]
2473:238A	mixed	1.64 (0.453)
2473:238B	high	0.72 (0.199)
2473:239C	mixed	1.71 (0.472)[e]
2473:253A	high	0.70 (0.193)
2473:254A	mixed	1.71 (0.472)
2473:260A	low	1.74 (0.481)
2473:277A	low	1.89 (0.522)
2473:277B	low	1.85 (0.511)
2473:278A	high	1.80 (0.497)[g]
2902:23A	high	1.70 (0.470)
2902:30A	mixed	1.51 (0.417)
2916:3A	low	1.91 (0.528)[f]

[a] See Table 1.

[b] 1.81 percent equals 0.5 mole of water per mole of fenoctimine sulfate.

[c] Mean of seven determinations.

[d] Mean of four determinations.

[e] Mean of two determinations.

[f] Mean of five determinations.

[g] Mean of six determinations.

TABLE 4
Water Content as a Function of Melting Range Category

	Mole Water/Mole Fenoctimine Sulfate		
	Low Melt	Mixed Melt	High Melt
Mean	0.506	0.592	0.300
Range	0.478–0.564	0.453–0.939	0.097–0.470
Std. Dev.	0.025	0.187	0.156
No.	11	6	6

TABLE 5

Water Content as a Function of Melting Range Category

Water Content (Mole Water/Mole Fenoctimine)	Low Melting	Mixed Melting	High Melting
0.051–0.100			1
0.101–0.150			
0.151–0.200			2
0.201–0.250			
0.251–0.300			
0.301–0.350			
0.351–0.400			
0.401–0.451		1	2
0.451–0.500	6	2	1
0.501–0.550	4	1	
0.551–0.600	1		
0.601–0.650			
0.651–0.700		1	
0.701–0.750			
0.751–0.800			
0.801–0.850			
0.851–0.900			
0.901–0.950		1	

Table 5. Water contents for the low melting samples were mostly in the 0.451 to 0.550 mole per mole of fenoctimine sulfate range with mean water content of ca. 0.5 mole per mole of fenoctimine sulfate. Water contents for the mixed and high melting samples ranged widely with respective standard deviations of six to seven times that of the low melting samples. For example, mixed melting samples generally tended to contain ca. 0.5 mole of water per mole of fenoctimne sulfate with the exception of one sample which contained ca. 1.0 mole of water per mole of fenoctimine sulfate, and high melting samples contained water from a nearly anhydrous level up to ca. 0.5 mole of water per mole of fenoctimine sulfate.

X-Ray Diffraction (XRD)

Two characteristic XRD patterns were observed for fenoctimine sulfate. These patterns are illustrated in Figure 1. The XRD patterns were sufficiently different so that by the measurement of the ratio of the peak height at $2\theta = 19.3^{\circ}$ for form A (lot 2916:3A) to the peak height at $2\theta = 20.0^{\circ}$ for form B (lot 2473:226A) of known ratios of the two lots, the standard curve illustrated in Figure 2 was generated. Its correlation coefficient was 0.995.

In another set of experiments also with known ratios of samples 2916:3A and 2473:226A, the ratios of form composition were compared to the water contents as determined by the Karl Fischer method. This relationship is illustrated in Figure 3. The resulting correlation coefficient was 0.999. Thus, a strong relationship between water content and crystal form as determined by XRD was demonstrated. Form A was associated with "hydrated" fenoctimine sulfate (ca. 0.5 mole of water per mole of fenoctimine sulfate) and form B was associated with "anhydrous"

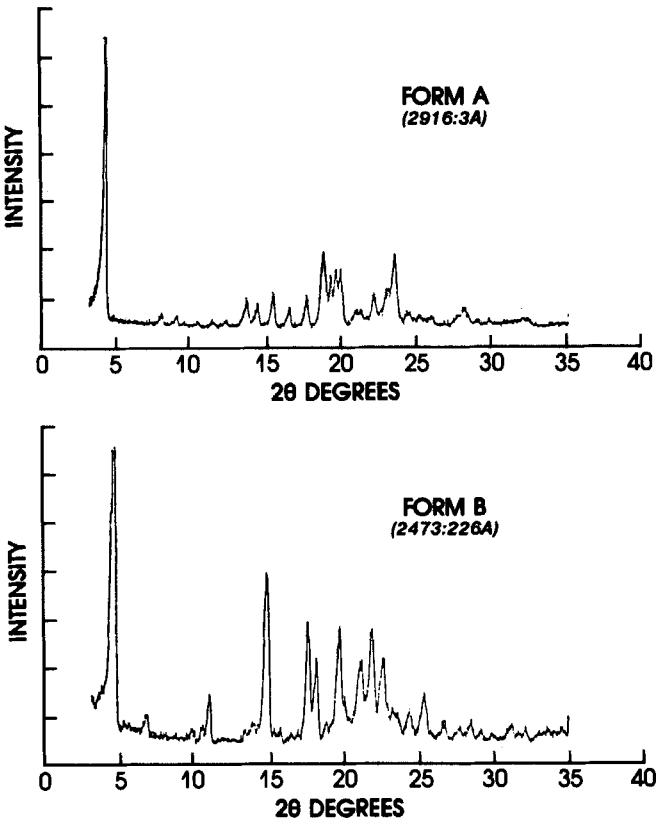

FIGURE 1: X-Ray Diffraction Patterns of Forms A and B

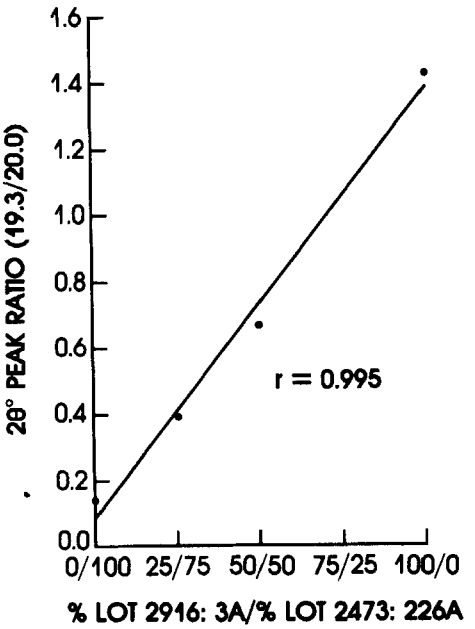

FIGURE 2: Fenoctimine Sulfate X-Ray Diffraction Standard Curve

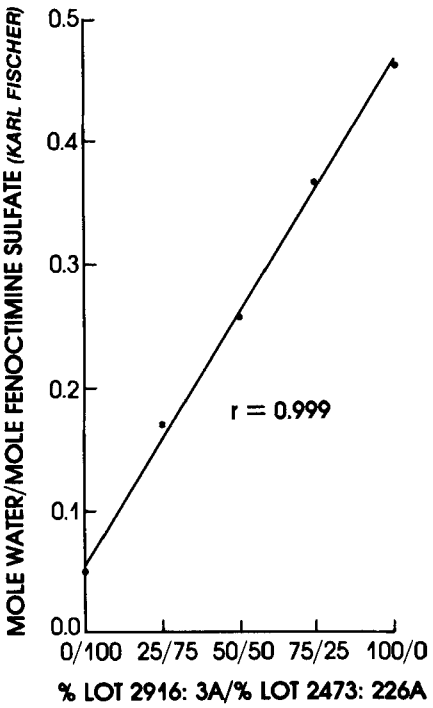

FIGURE 3: Fenoctimine Sulfate Water Content as Determined from Known from Known Mixtures of Two Lots

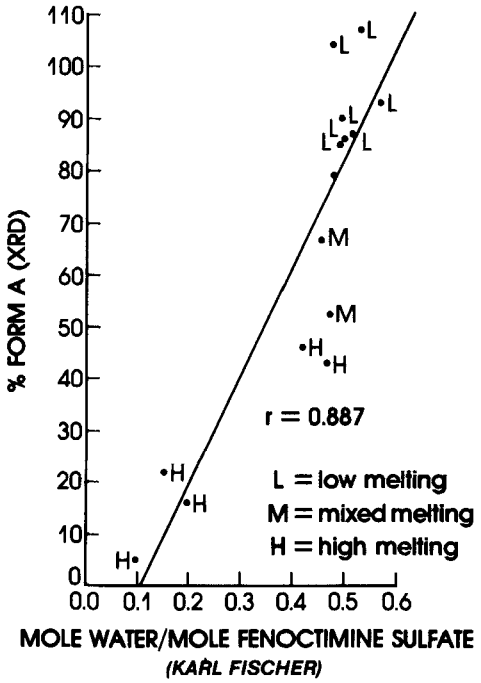

FIGURE 4: Fenoctimine Sulfate Form as a Function of Water Content for Low, Mixed and High Melting Samples

fenoctimine sulfate (ca. 0.05 mole of water per mole of fenoctimine sulfate).

Table 6 lists 46 samples for which XRD patterns were obtained. Where available, thermal properties and water contents are also listed. A linear regression of the water content for Karl Fischer data versus XRD (15 samples) yielded a correlation coefficient of (0.887). The Karl Fischer to XRD relationship is presented in Figure 4.

The linear regression equation from the data in Figure 3 is $y=0.0041x + 0.057$. The transposed regression equation from the data in Figure 4 is $y=0.0048 x + 0.11$. The similarity in the slopes indicates that the water content to crystal form relationship is the same for both collections of data. The higher intercept and the lower correlation coefficient obtained from the data in Figure 4 indicate that the 15 laboratory samples had higher water contents and naturally had a more random relationship than the specially prepared samples described in Figure 3. The differences in the intercepts was possibly due to higher surface moisture in the 15 laboratory samples than in the two samples selected for the preparation of the standard ratios.

Table 7 summarizes the relationship between the thermal properties and the form of fenoctimine sulfate. There is a definite relationship between the percent form A, means and ranges, and the melting properties. Though there is considerable overlap between low melting and mixed melting, the mean percent form A is highest in the low melting samples, lowest in the high melting samples and intermediate in the mixed melting samples. It is also clear that the terms "low" and "high" melting do not necessarily imply that a sample is only or nearly all form A or form B. Note in Figure 4 that low, mixed and high melting samples definitely populate respective regions of the form A versus water content relationship, but that these regions are fairly large and loosely defined.

TABLE 6
Crystal Form Content

Lot No.	Treatment	Melting Range	Water Content[a]	% Form A
2449:52	initial	low	--	99
2449:65 (7903324)	initial	low	0.564	93
2449:78	initial	low	--	84
2449:79 (8000310)	initial	mixed	--	64
2449:79 (8000310)	triturated	high	--	11
2449:95 (8001237)	initial	low	0.478	104
2449:95 (8001237)	80° x 1 mo.	--	--	78
2449:102	initial	mixed	--	76
2449:103	initial	low	0.492	85
2449:104	initial	high	0.425	46
2449:105	initial	low	0.514	87
2449:107 (8002165)	initial	low	0.497	90
2473:196B (7800218)	initial	mixed	--	49
2473:196B (7800218)	RT x 9 mo.	--	--	56
2473:196B (7800218)	RT x 9 mo.	--	--	55
2473:206A (7802539)	initial	mixed	--	64
2473:206A (7802539)	compressed & trit.	--	--	60
2473:206A (7802539)	RT x 20 mo.	--	--	62
2473:226A	initial	high	0.097	5
2473:238A	initial	mixed	0.453	66
2473:238A	dried	--	--	63
2473:238B	initial	high	0.199	16
2473:239A	initial	high	--	2
2473:239B	initial	high	--	18
2473:239C	initial	mixed	0.472	52
2473:253A	initial	high	0.193	21
2473:260A	initial	low	0.481	79
2473:266A	initial	mixed	--	87
2473:278A	initial	low	0.497	86
2473:278B	initial	low	--	53
2473:278B	80 mesh	--	--	50
2473:278B	triturated	--	--	52
2902:20B	initial	--	--	44
2902:20B	RT x 20 mo.	--	--	51
2902:23A	initial	high	0.470	43
2902:23A	80 mesh	--	--	45
2902:23A	triturated	--	--	43
2916:2A	initial	low	--	92
2916:2A	compressed & 80 mesh	mixed	--	94
2916:3A (7900442)	initial	low	0.528	107
2916:3A (7900442)	3 hr. x 105°[b]	--	--	65
2916:3A (7900442)	3 hr. x 105° + RT x 18 hr[b]	--	--	69
2916:3A (7900442)	RT x 5 mo.	--	--	95
2916:3A (7900442)	60° x 5 mo.	--	--	83
2916:3A (7900442)	80° x 3 mo.	--	--	62
2916:3A (7900442)	80° x 3 mo.	--	--	81

[a] Moles of water per moles of fenoctimine sulfate

[b] Stored in open containers

TABLE 7

Crystal Form Content as a Function of Melting Range Category

	Percent Form A		
	Low Melting	Mixed Melting	High Melting
Mean	91	69	20
Range	79-107	49-94	2-46
Std. Dev.	8.7	15.8	16.3
No.	11	8	8

TABLE 8

Effect of Environment on the Form of Fenoctimine Sulfate as Determined by XRD

Month	Form A Lot 2916:3A at 80° %	Form B Lot 2473:226A at 40°/80% RH %
0	107	94
1	79	46
2	70	50
3	61	--
6	<9	0

Form Interconversion

Though it is useful to describe fenoctimine sulfate samples in terms of their thermal behaviors, water contents and crystal forms and more importantly, to relate these properties to each other, it is also necessary to determine if and how one form can be converted into the other and to determine whether or not one form is preferable over the other.

Table 8 describes the effect of high temperature (80°) and ambient humidity from a constant temperature oven on the crystal form of sample 2619:3A (form A) and the effect of warm (40°) and humid (80% relative humidity) conditions from storage in a constant temperature/humidity oven on sample 2473:226A (form B). In both cases, given sufficient time, each form was converted to the other, i.e., form A was dried to form B and form B was hydrated to form A.

In Table 9, it is demonstrated that when prepared as a suspension suitable for administration to laboratory animals, form A remained form A, while form B was converted to form A with much of the conversion occurring within a few minutes after preparation of the suspension. This means that regardless of the form used in a suspension, the greater proportion of the fenoctimine sulfate will be present as form A within 24 hours and much of the conversion to form A will occur within minutes. Complete conversion to form A was not demonstrated to occur within three weeks probably because water was not able to completely penetrate the slightly soluble fenoctimine sulfate particles.

Intrinsic dissolution is a measure of the rate of dissolution of a solid independent of the surface area of that solid. It is evident from Table 10 that form A dissolves slightly more rapidly than form B though in practical terms, their intrinsic dissolution rates are equivalent and

TABLE 9

Form of Fenoctimine Sulfate Recovered from Suspension Stored at Room Temperature as Determined by XRD

Suspension	Composition	Form A Initial %	Form A Final %	Final Age of Suspension
B 1882-G	Lot 2449:102A, 30 mg/ml in 0.5 tragacanth	110	109	21 days
B 1882-H	Lot 2437:226A, 30 mg/ml in 0.5 tragacanth	0	75	21 days
3592:22C	Lot 2473:226A, 30 mg/ml in water	0	42	5 min.
		0	77	19 hrs.

TABLE 10

Effect of the Form of Fenoctimine Sulfate on the Intrinsic Dissolution of Fenoctimine in pH 2.0 Buffer Containing 10 Alcohol at 37°.

Lot	XRD Form A %	Intrinsic Dissolution mg*/cm^2/min
2916:3A	107	0.080
2449:107	90	0.067
2473:266A	87	0.067
2473:206A	64	0.066
2473:196B	49	0.068
2473:226A	5	0.061

* Fenoctimine

TABLE 11

Effect of Form of Fenoctimine Sulfate on the Equilibrium Solubility of Fenoctimine at Room Temperature

Medium	Solubility, mg*/ml	
	Lot 2916:3A Form A	Lot 2473:226A Form B
gastric fluid, TS, USP, without pepsin (pH 1.2)	0.067, 0.070	0.055, 0.065
intestinal fluid, TS, USP, without pancreatin (pH 7.3)	0.68, 0.64	0.67, 0.66
purified water, USP**	1.39, 1.31	1.26, 1.37

* Fenoctimine

** pH 2.4 after saturation

bear little relationship to the percent of form A or form B present. It was not unexpected that form A dissolved faster than form B as their thermal properties demonstrated that such a thermodynamic relationship existed. However, the lack of a major difference in dissolution rate, the failure to demonstrate a dependence of dissolution rate on the composition of the sample and the proven ease of conversion from form B to form A in water suggests that on the surface of the discs used in the intrinsic dissolution experiments form B converted to form A.

While Table 10 describes the weak effect of the fenoctimine sulfate form on intrinsic dissolution (the rate of dissolution), Table 11 describes the total lack of effect of fenoctimine sulfate form on equilibrium solubility (the extent of dissolution). In practical terms, regardless of the form of fenoctimine sulfate employed, it is form A which ultimately exists at the water/fenoctimine sulfate interface and, consequently, it is form A which is exposed to the aqueous environment of a biological system.

FOOTNOTES

1 FP2 hot stage, Mettler Instrument Corp., Hightstown, NJ 08520.

2 Aquatest IV, Photovolt Corp., New York, NY 10010.

3 ES Laboratories, Wrightstown, NJ 08562.

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