Journal of Thermal Analysis, Vol. 49 (1997) 897-905

SUBLIMATION MEASUREMENTS OF PHARMACEUTICAL COMPOUNDS BY ISOTHERMAL THERMOGRAVIMETRY

J. P. Elder

Merck and Co. Inc., P.O. Box 4, WP102-78 Sumneytown Pike, West Point, PA 19486, USA

Abstract

Procedures for measuring sublimation rates of pharmaceutical compounds by isothermal thermogravimetry are discussed. Experimental data was obtained using the Mettler TA4000 thermogravimetric system. The sublimation rate is measured directly from the mean weight loss per unit time in the linear region of the monitored TG profile at a set isothermal temperature. This data when fitted to the Arrhenius equation yields the sublimation enthalpy. For the benzoic acid reference, the enthalpy so calculated is 99% of the value obtained from direct vacuum TG measurements. Thermal degradation in the solid state or pre-melting can effect a departure from the characteristic linear mass loss–time sublimative profile. Data pertaining to several established Merck drugs is discussed. Examples where loss of residual solvent, onset of thermal degradation and pre-melting phenomena affect the measurement, are presented.

Keywords: ambient pressure, isothermal thermogravimetry, pharmaceuticals, sublimation, vapor pressure

Introduction

Estimates of vapor pressure are recommended as part of the supportive documentation for the environmental assessment submitted in an application for governmental approval of a new drug [1]. If it can be demonstrated that the compound's vapor pressure does not exceed the low-level criterion set by the US Food and Drug Administration (FDA), then its fate and effects in the atmosphere need not be considered further. Five general measurement methods have been proposed which can be applied in different vapor pressure range [2]. It is assumed that in all these methods, over a limited temperature range, the measured vapor pressure data obeys the linear logarithmic form of the Clapeyron equation [3].

There are essentially two procedures applicable to low vapor pressure solids, (10^{-3}–1 Pa), (a) the gas saturation method and (b) the vapor pressure balance method. The gas saturation technique [4] measures the uptake of the vapor freely subliming into a flowing, ambient pressure atmosphere and trapped in plugs of a suitable absorbent. It has been used to measure the vapor pressure and sublimation rate of pesticides spray-deposited on to glass plates [5]. Total experimental run times are of the order of one day. The entrapped vapors, removed by soxhlet extrac-

0368–4466/97/ $ 5.00

John Wiley & Sons Limited
Chichester

tion are assayed by gas chromatography. There are two vapor pressure balance techniques; the Langmuir free evaporation procedure and the Knudsen effusion methods [6]. The simplicity of the direct mass loss measurement inherent to both these methods is offset by the fact that they operate under high vacuum.

One may combine the simplistic features of the gas saturation and vapor pressure balance methods to measure sublimation rates by ambient pressure, isothermal thermogravimetry. Such an approach has been used to measure the volatility of automotive lubricating oils [7], and the development of a general method is currently being pursued by an ASTM task group [8]. It should be stressed that accurate vapor pressure data cannot result from such TG measurements. For liquids, the data may be too imprecise. The Institute of Petroleum has since abandoned its procedure [7] since inter-laboratory repeatability was considered unacceptable. However, for low vapor pressure solids, the method shows promise for purposes of estimating such data.

During the last two decades Gückel *et al.* [9–12] have made extensive contributions in the application of isothermal thermogravimetry to the measurement of sublimation rates, and the estimation of vapor pressures from such data. In a number of exacting studies, they investigated a variety of compounds [9] and formulated pesticide products [10], all of known vapor pressure. Detailed statistical analysis verified the precision of their measurements when performed under well controlled conditions [11]. Initially, experimental data obtained with a Cahn balance system at one temperature showed, for a variety of organic compounds, the linear logarithmic functional relationship between sublimation rates and vapor pressures [9]. They also confirmed the Arrhenius functionality between sublimation rates and temperature [9, 11]. More recently, this group has employed the Mettler TA50 thermobalance system for their measurements [12]. Not only did they confirm their previous data correlations, but extended the lower limits of vapor pressure determinations by three orders of magnitude. In all their work, the Gückel group employed sample preparation similar to that employed in the gas saturation method [5], namely, application of the material to the roughened surface of a small (~3.3 cm^2) rectangular plate, which was suspended into the furnace of the TG instrument.

As a result of these meticulous studies, Gückel and his co-workers are to be commended for demonstrating the precision capable of the TG method, and for laying the groundwork of parameter correlation, irrespective of the nature of the materials and temperatures used. Concurrently, a parallel development was undertaken at Merck in 1991. Ambient pressure, isothermal thermogravimetry was used to measure free evaporation from open crucibles of solid drug candidates. This paper describes the simple operating procedure and presents sublimation rate data and estimated vapor pressures for several Merck pharmaceutical compounds. The selected vehicles of this study demonstrate the necessity of considering their overall thermal behaviour for evidence of the occurrence of concomitant thermophysical transitions, such as premelting, and onset of thermochemical degradation, in employing mass loss data to estimate the vapor pressure of the drug.

Experimental

All mass loss determinations were carried out using the Mettler TA4000 system with the TG50 vertically-oriented thermobalance, and the TA72 software for data representation and evaluation. Both 70 μl (small) and 150 μl (large) alumina crucibles were employed with a 100 ml min^{-1} nitrogen purge. Uncompacted powdered drug reference and an organic standard were used for all measurements. Sample loading was carried out at 25°C. Following a ~20 min interval, sufficient to purge all air from the free furnace space surrounding the crucible, the experimental run was initiated. The sample was either heated rapidly or at a controlled rate to the programmed isothermal temperature. In either case, system control prevents overshoot of the actual sample temperature. The steady state mass loss was then monitored over a defined period of time, sufficient to enable an accurate measure of the mass loss.

Experimental caveats

It should be pointed out that, in the initial investigational stages with a new compound, it is not necessary to monitor data over an extended time interval. One should establish as quickly as possible, the optimum temperature range for linear mass losses, and the order of magnitude of the sublimation rate, which enables the selection of the time interval for the most accurate measurement. One should also establish at this stage the temperature at which (a) there is an indication of material degradation, (b) visible evidence of condensed sublimate on any part of the balance suspension mechanism. In the case of crystalline solids, if one intends to measure below but close to the fusion temperature, one should establish whether or not some pre-melting occurs during the isothermal hold period. In the case of the low vapor pressure pharmaceuticals investigated in this study, it was found advantageous to monitor data over a 15 hour period. This allowed for overnight runs, with, using the TA72 software, automatic storing of the data on diskettes, thereby allowing for other uses of the equipment during the normal working day.

Results and discussion

Figure 1 shows a set of experimental mass loss data, without smoothing, for a set of samples of benzoic acid. The sample material, Sigma B-3250, of DSC-determined 99.95 mol% purity and 122.8°C melting point, was loaded into the small crucible, and brought to the isothermally programmed temperature rapidly. Measurements of the mass loss were made at temperatures 40 to 70°C at 5°C increments. As can be seen, the linearity over the 15 h interval is excellent. Table 1 lists the rate of mass loss, dm/dt (μg min^{-1}). This data obeys the Arrhenius rate equation (1) with a 0.9987 correlation coefficient.

$$\ln(dm/dt) = A - \Delta H_s / RT \quad (1)$$

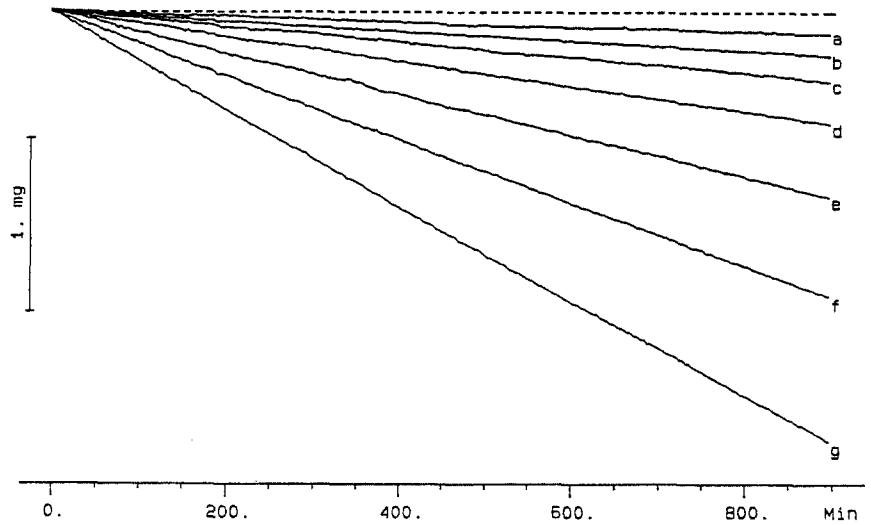

Fig. 1 15 hour isothermal TG sublimation record of Benzoic Acid at a) 40°C, b) 45°C, c) 50°C, d) 55°C, e) 60°C, f) 65°C and g) 70°C (unsmoothed experimental data)

Table 1 Benzoic acid sublimation rates and vapor pressures

T/°C	dm/dt/μg min^{-1}	p/Pa*
40	0.143	0.910
45	0.281	1.546
50	0.456	2.582
55	0.733	4.245
60	1.195	6.878
65	1.818	10.985
70	2.742	17.306

*Calculated using the data of Wiedemann [13]

The sublimation enthalpy, $\Delta H_s = 86.7$ kJ mol^{-1}, is 98.9% of the value computed from the integral form of the Clausius-Clapeyron equation [3] correlating Wiedemann's effusion data [13], namely, 87.7 kJ mol^{-1}. This agreement indicates that, at least for purposes of estimation, one can extrapolate the vapor pressure data to the temperature range employed in this study. Such extrapolated values are also shown in Table 1. Linearly regressing the vapor pressure and the sublimation rate data, one obtains

$$\ln(p) = 1.0096 \cdot \ln(dm/dt) + 1.781 \quad (2)$$

A similar correlation has recently been presented by Gückel *at al.* [12] from a series of measurements on twelve different materials at several temperatures. These

workers obtained a degree of precision of 96.5%, indicating validity over a wide temperature range. Based upon this observation with the TG50 thermobalance, even with a different means of supporting the sample material, it is assumed that the Eq. (2) correlation is also applicable with other samples and at other temperatures.

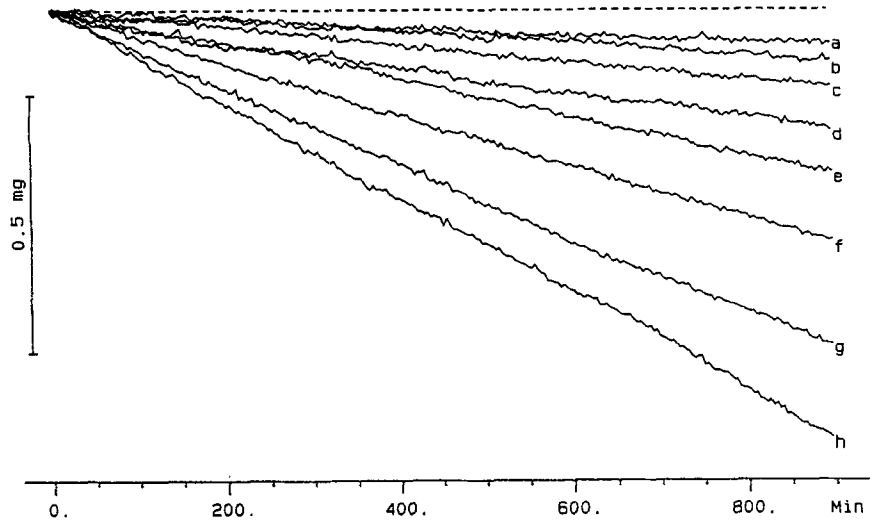

Fig. 2 15 hour isothermal TG sublimation record of Finasteride(II) at a) 180°C, b) 190°C, c) 195°C, d) 200°C, e) 205°C, f) 210°C, g) 215°C and h) 220°C (unsmoothed experimental data)

Figure 2 shows a set of experimental mass loss data, without smoothing, for one sample of the high temperature form(II) of Finasteride [14] (melting point 258.7°C) [15] at various temperatures in the range 180–220°C. Again, the uncompacted sample, contained in the 70 µl crucible, was rapidly heated to the set isothermal temperature. Following each run, the sample holder hang-down assembly was examined for evidence of condensed sublimate. A very small amount of the crystalline condensate was observed after a scan at 220°C, but not at any of the lower temperatures. Although the 220°C TG signal appeared to be linear throughout the scan, this data was not used in linearly regressing the rate data for the esti-

Table 2 Finasteride(II) sublimation rates and estimated vapor pressures

T/°C	dm/dt/µg min^{-1}	"Estimated" p/Pa
190	0.1067	0.62
195	0.1622	0.95
200	0.2556	1.50
205	0.3545	2.08
210	0.4989	2.94
215	0.7200	4.26

Table 3 Summary of sublimation and estimated vapor pressure parameters

Sample	Sublimation rate parameters		$T/°C$ $V.P.\leq 1.33\cdot10^{-5}$/Pa	$V.P./Pa$ @25°C
	A	ΔH_s/kJ mol^{-1}		
benzoic acid	31.437	86.7		
finasteride	34.759	143.7	80	$7\cdot10^{-10}$
famotidine	59.534	207.0	72	$9.4\cdot10^{-11}$
timolol maleate	101.05	360.3	107	$2.3\cdot10^{-19}$
indinavir sulfate	6.50	28.9	–	$3.2\cdot10^{-2}$

mation of the vapor pressure. The 180°C data was considered too close in value to that measured at 190°C and similarly was not utilized in the regression analysis. The sublimation rates are listed in Table 2, together with the estimated vapor pressures obtained with the use of Eq. (2). The sublimation rate data obeys Eq. (1) with a 0.9989 correlation. As is seen from Table 3, at room temperature, Finasteride(II) exhibits an estimated vapor pressure of $7\cdot10^{-10}$ Pa, well below the FDA low-level criterion of $1.33\cdot10^{-5}$ Pa (i.e. 10^{-7} torr), which is exhibited at 80°C.

One does not always have the luxury of such a relatively wide temperature range over which to carry out such measurements. Famotidine [14] exhibits low level thermal degradation in the solid state when isothermally stressed for extended periods in an inert atmosphere in the 130 to 155°C region, prior to the onset of melting at 160.3°C [16]. Figure 3 shows the 15 h mass loss records of an uncompacted powdered sample of Famotidine in the 70 µl crucible at 115, 120, 125 and

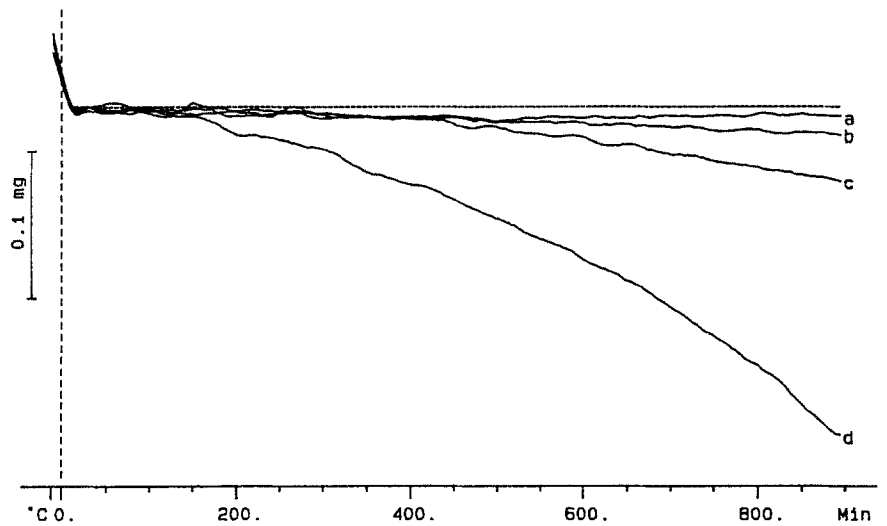

Fig. 3 15 hour isothermal TG sublimation record of Famotidine at a) 115°C, b) 120°C, c) 125°C and d) 131°C (smoothed experimental data)

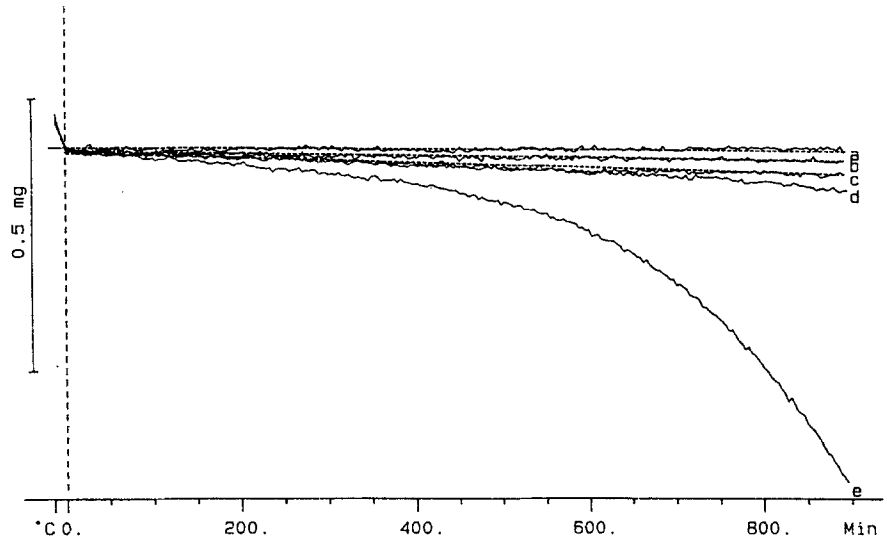

Fig. 4 15 hour isothermal TG sublimation record of Timolol Maleate at a) 135°C, b) 140°C, c) 145°C, d) 150°C and e) 155°C (unsmoothed experimental data)

131°C. At $T \leq 110$°C measurable mass losses were not observed over the 15 h period. For clarity of presentation, the data, which at the indicated sensitivity is quite noisy, has been smoothed, using the TA 72 software.The onset of low level degradation is apparent in the slight curvature of the 125°C trace, curve c, and significantly so at 131°C, curve d. The unsmoothed, measured data in the 115–122.5°C region results in the Arrhenius equation (1) with $r^2=0.999$. As is seen in Table 3, at $T \leq 72$°C, the vapor pressure is lower than the FDA limiting criterion of $1.33 \cdot 10^{-5}$ Pa and at room temperature, the estimated vapor pressure is $9.4 \cdot 10^{-11}$ Pa. For crystalline drug substances which thermally decompose rather than melt, exemplified by Timolol Maleate [17], similar behaviour is obtained. Figure 4 shows the 15 h mass loss record of an uncompacted reference standard sample of this compound contained in the small alumina crucible at five isothermal temperatures, in the range 135 to 155°C [18]. At 155°C, after ca. 8 hours stress, thermal degradation commences – the initially linear TG trace (curve e) starts to show curvature – after the completion of the run, the residue was light brown in color. At 150°C (curve d), although the mass loss trace does not exhibit significant curvature, end-of-run examination showed the residue to be slightly discolored and somewhat tacky to the touch.The sublimation rate data between 135 and 145°C fits the Arrhenius equation (1) with a 99% correlation. As shown in Table 3, the calculated enthalpy of sublimation, $\Delta H_s = 360.3$ kJ mol^{-1}. Again, estimated vapor pressures result by combining Eqs (1) and (2). At $T \leq 107$°C, the vapor pressure is estimated to be less than the FDA criterion of $1.33 \cdot 10^{-5}$ Pa, while at room temperature the estimated vapor pressure is $2.3 \cdot 10^{-19}$ Pa.

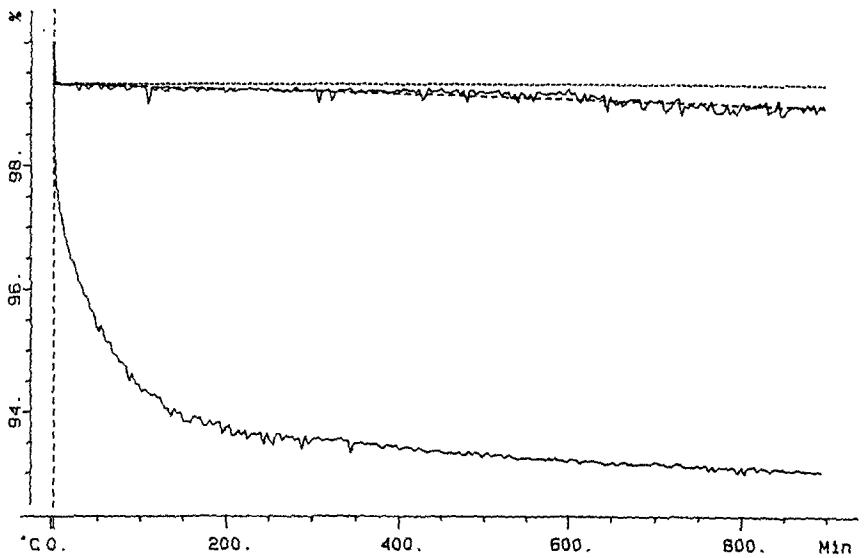

Fig. 5 15 hour isothermal TG record of the solvent drying of Indinavir Sulfate and its subsequent sublimation record, both at 100°C (unsmoothed experimental data)

If a sample of a material contains residual process solvent(s), the loss on drying can swamp any measure of a sublimative loss. As recently emphasized by Gückel *et al.* [11], all solvent must be removed prior to any attempt at measuring sublimation rates. As an example, Fig. 5 shows the mass loss curve for a sample of Indinavir Sulfate [19], the recently FDA-approved protease inhibitor HIV drug, containing ~6% ethanol, and for comparison, that of the dried material. The uncompacted drug was loosely loaded into the large, 150 µl alumina crucible, for a 15 h thermal stress at 100°C. As can be seen, drying is complete following this treatment. The dashed line through the sublimative mass loss trace attests to the overall linearity of the TG record, and the horizontal dotted line indicates that a loss did, in fact, occur. Indinavir Sulfate with a DSC-assessed melting point, T_f=134.6°C, does exhibit pre-melting and partial thermal degradation when isothermally stressed at 110°C for 15 hour [20]. The upper temperature limit for sublimative loss measurements is 105°C, and below 95°C one cannot measure a significant loss in this time interval. It is these measurement limitations, rather than the inherent behaviour of the dry drug, which result in the low value of the sublimation parameters and relatively high estimated vapor pressure at room temperature listed in Table 3. The observable fact, that at 95°C and below, mass losses were barely recordable confirms this interpretation.

Conclusions

It has been demonstrated that isothermal thermogravimetry is a useful means for measuring sublimation rates of uncompacted, as-received samples of bulk active

drugs. In agreement with information presented by other investigators, there is a linear logarithmic relationship between sublimation rates and vapor pressures of reference materials. Such relationships appear to be independent of the material used and the measurement temperature range. However, they must be developed for the speci fic instrumental system and sample containment procedure employed. The technique has proved useful for estimating room temperature vapor pressure values of a number of drug compounds in order to confirm that environmental assessment criteria established by regulatory agencies have been met.

References

1 USFDA Environmental Assessment Technical Guide No. 10.03, March 1987.
2 Official Journal of the European Communities L 251, 27 (1984) 25.
3 R. E. Dickerson, Molecular Thermodynamics, W. A. Benjamin Inc., Menlo Park, Cal. 1969, Chap. 5, pp. 229-232.
4 W. F. Spencer and M. M. Cliath, Environ. Sci. Technol., 3 (1969) 670.
5 W. F. Spencer, T. D. Shoup, M. M. Cliath, W. J. Farmer and R. Haque, J. Agric. Food Chem., 27 (1979) 273.
6 R. C. Paule and J. L. Margrave in The Characterization of High Temperature Vapors ed. J. L. Margrave, Wiley, N.Y. 1967, Chap. 6, pp. 130-151.
7 Institute of Petroleum Committee ST G-9, method IP 393/91.
8 ASTM E37 Committee on Thermal Measurements, task group E37.01.19.
9 W. Gückel, G. Synnatschke and R. Rittig, Pestic. Sci., 4 (1973) 137.
10 W. Gückel, R. Rittig and G. Synnatschke, Pestic. Sci., 5 (1974) 393.
11 W. Gückel, R. Kastel, J. Lewerenz and G. Synnatschke, Pestic. Sci., 13 (1982) 161.
12 W. Gückel, R. Kastel, T. Krohl and A. Parg, Pestic. Sci., 45 (1995) 27.
13 H. G. Wiedemann, Thermochim. Acta, 3 (1972) 355.
14 J. A. McCauley and H. G. Brittain, in Physical Characterization of Pharmaceutical Solids Ed. H. G. Brittain, Marcel Dekker Inc., N.Y. 1995, Chap. 8, pp. 241–243.
15 J. P. Elder, Internal Report (Merck and Co.) July 26, 1990.
16 J. P. Elder, Internal Report (Merck and Co.) September 24, 1992.
17 Merck Index, 11th edition, 1989, # 9374.
18 J. P. Elder, Internal Report (Merck and Co.) October 13, 1992.
19 Chemical and Engineering News (American Chemical Society) January 1, 1996, p. 6.
20 J. P. Elder, Internal Report (Merck and Co.) February 5, 1996.