Beiträge zur Tabakforschung International · *Contributions to Tobacco Research* Volume 19 · No. 6 · July 2001

DOI: 10.2478/cttr-2013-0715

# Thermochemical Properties of Nicotine Salts*

*by*

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SUMMARY

The thermal gravimetric analysis (TGA) and differential scanning calorimetry (DSC) results presented in this report clearly show that the thermal stability and the endothermic peak nicotine release temperatures are different for different nicotine salts and these temperatures appear to be linked to the general microstructural details of the salt itself. In addition, the peak nicotine release temperatures are highly dependent upon the sample size used. The heat of vaporization for neat (non-protonated) nicotine is also sample-size dependent. The TGA data showed that the least stable of the salts tested at elevated temperatures was the liquid salt nicotine triacetate followed by the crystalline materials (e.g., nicotine gallate) and finally, the amorphous salts (e.g., nicotine alginate). The DSC results revealed that the liquid and crystalline salts exhibit nicotine release endotherms that are strongly related to the sample weight being tested. The amorphous salts show nicotine endotherm peak temperatures that are nearly independent of the sample weight. The range of peak nicotine release temperatures varied depending upon the specific salt and the sample size from 83 °C to well over 200 °C. Based on these results, the evolution of nicotine from the nicotine salt should be expected to vary based on the composition of the salt, the details of its microstructure, and the amount of nicotine salt tested. [Beitr. Tabakforsch. Int. 19 (2001) 289–95]

ZUSAMMENFASSUNG

Die durch thermogravimetrische Analyse (TGA) und Differential Scanning Calorimetrie (DSC) erhaltenen Ergebnisse zeigen deutlich, dass sich die thermische Stabilität und die Temperaturen der endothermen Peak-Nikotinfreisetzung der verschiedenen Nikotinsalze voneinander unterscheiden. Diese Temperaturen stehen allem Anschein nach im Zusammenhang mit der spezifischen Mikrostruktur der Salze. Darüber hinaus sind die Temperaturen bei der Peak-Nikotinfreisetzung in hohem Maße von der untersuchten Probengröße abhängig. Die Verdampfungswärme von reinem (unprotoniertem) Nikotin ist ebenfalls von der Größe der Probe abhängig. Die Ergebnisse der TGA haben gezeigt, dass unter den bei erhöhten Temperaturen untersuchten Salzen das am wenigsten stabile Salz das flüssige Nikotintriacetat war, danach folgten die kristallinen Substanzen (z.B. Nikotingallat) und schließlich die amorphen Salze (z.B. Nikotinalginat). Die Ergebnisse der DSC haben gezeigt, dass bei den flüssigen und kristallinen Salzen eine endotherme Nikotinfreisetzung stattfindet, die in hohem Maße vom Gewicht der untersuchten Probe abhängt. Bei der endothermen Peak-Nikotinfreisetzung der amorphen Salze sind die Temperaturen nahezu unabhängig von der Größe der untersuchten Probe. Die Temperaturen der endothermen Peak-Nikotinfreisetzung variierten in Abhängigkeit vom spezifischen Salz und der Probengröße zwischen 83 °C und über 200 °C. Auf der Basis dieser Ergebnisse kann man erwarten, dass die Freisetzung von Nikotin aus Nikotinsalz von der Zusammensetzung des Salzes, den Feinheiten seiner Mikrostruktur und der Menge des untersuchten Nikotinsalzes abhängt. [Beitr. Tabakforsch. Int. 19 (2001) 289–95]

RESUME

Les résultats obtenus par thermogravimétrie (TGA) et analyse thermique différentielle (DSC) montrent clairement que la stabilité thermique et les températures du dégagement du pic endothermique de la nicotine sont

*Received: 16th October 2000 – accepted: 8th May 2001

différentes pour les différents sels de nicotine et ces températures semblent être liées à la microstructure générale du sel lui-même. De plus, les températures du dégagement du pic de la nicotine sont fortement liées au poids de l'échantillon utilisé. La chaleur de vaporisation de la nicotine pure (non protonée) dépend également du poids de l'échantillon examiné. Les données TGA ont montré que parmi les sels testés aux températures élevées le sel le moins stable était le sel liquide de triacétate de nicotine, suivi par les matériaux cristallins (i.e. gallate de nicotine) et finalement les sels amorphes (i.e. alginate de nicotine). Les résultats DSC ont révélé que les sels liquides et cristallins présentent des dégagement endothermiques de la nicotine fortement liés au poids de l'échantillon testé. Les sels amorphes démontrent des températures de dégagement du pic endothermique de la nicotine presque indépendantes du poids de l'échantillon. Les températures de dégagement pic endothermique de la nicotine ont varié en fonction du sel spécifique et du poids de l'échantillon de 83 °C à plus de 200 °C. Ces résultats suggèrent que l'évolution de la nicotine à partir du sel de nicotine varie en fonction de la composition du sel, sa microstructure et le poids du sel de nicotine testé.
[Beitr. Tabakforsch. Int. 19 (2001) 289–95]

## INTRODUCTION

Nicotine exists in tobacco in the form of nicotine salts (2,5). Several studies involving the characterization and stability of nicotine salts have been reported in the literature (1,2,3). These reports describe the structural characteristics of various salts (1,2) as well as the dissociation and decomposition reactions that occur at elevated temperatures (3). Information on the physiochemical and thermochemical properties of nicotine salts is important to our understanding of the mechanisms involved in the processing of tobacco and the transfer of nicotine into the various smoke streams of cigarettes (2,4,5,8,9).

In an effort to obtain additional thermochemical information on nicotine and a variety of nicotine salts, a series of thermal studies were conducted using thermal gravimetric analysis (TGA) and differential scanning calorimetry (DSC). The "thermal stability" of a compound is a thermophysical property of the material and its exact definition can vary depending upon the technique used to measure it. Thermal stability can be evaluated by a number of techniques that give very different results depending on the end point of each technique and what the investigator believes to be the most important property associated with the decomposition of the compound being tested. For example, TGA information gives one picture of the thermal stability of a compound as measured either by the weight loss of the material as a function of temperature or as a function of time at temperature. Weight loss relates to evaporation as well as thermal stability/decomposition chemistry. DSC, on the other hand, can be used to measure thermal stability in terms of phase transitions, heats of vaporization and fusion, specific heats, oxidation reactions, etc. Essentially, an "energy signature" in the form of endothermic and exothermic events can be obtained for a given material as a function of temperature, time at temperature, heating rate, sample size, etc. For the experiments of this study, where all the samples were nicotine or nicotine salts, a DSC energy signature in the form of an endothermic event for neat (non-protonated) nicotine vaporization was identified. The DSC scans for the different nicotine salts that were tested in general contained two or more endothermic thermal events and occasionally, depending upon the particular salt, an exothermic event associated with oxidation.

The objectives of this study were threefold:

1) Characterization of the thermal stability of a variety of different nicotine salts using TGA and DSC
2) Ranking of the thermal stability of the salts in order of decreasing temperature for nicotine release
3) Determination of the thermal stabilities of the salts as related to their microstructural characteristics.

*Note:* The term "microstructure" as used herein refers to the degree of long-range order within the salt. "Crystalline" salts possess a high degree of long-range order with definitive melting points while "amorphous" salts exhibit very limited short-range order and a broad glass transition region. Prior work (1) has substantiated that the salts defined as "crystalline" and "amorphous" exhibit the behavior as defined above.

## EXPERIMENTAL

### *Reagents*

The (*S*)-(–)-isomer of nicotine (*l*-nicotine) and nicotine ditartrate dihydrate (nicotine tartrate) were purchased from Fisher Scientific (Pittsburgh, PA). Nicotine salicylate was purchased from Indofine Chemical (Somerville, NJ). Nicotine di-*p*-toluoyltartrate (nicotine ditoluoyltartrate) was purchased from ICN (Costa Mesa, CA). Nicotine quadraoxalate dihydrate (nicotine oxalate) and nicotine gallate were obtained from T.D.C. Research (Blacksburg, VA). The nicotine salts were used as received. Nicotine triacetate (nicotine acetate), nicotine alginate, nicotine tannate and nicotine galacturonate were prepared as described in the literature (1,4) and were used as prepared. The water of hydration for the nicotine salts are as noted by the suppliers. The water content (crystalline water) of the prepared salts were not measured prior to use.

### *Instrumentation*

Each nicotine salt was scanned with both a TA Instruments model 2920 differential scanning calorimeter and a TA Instruments model 2950 Hi Resolution thermogravimetric analyzer (TA Instruments, Inc., New Castle, DE). The heating rate used was 5 °C/min from 40 °C to 400 °C. The TGA experiments were conducted in

**Table 1.**
**Physical forms of nicotine salts; thermal gravimetric analysis (TGA) tests**

| Nicotine salt | Sample weight (mg) | Physical form |
|---|---|---|
| Neat nicotine | 28.776 | Liquid |
| Nic. acetate | 38.742 | Viscous liquid |
| Nic. galacturonate | 8.051 | Viscous gum |
| Nic. alginate | 14.460 | Amorphous solid |
| Nic. tannate | 19.570 | Amorphous solid |
| Nic. ditoluoyltartrate | 7.817 | Crystalline solid |
| Nic. gallate | 5.213 | Crystalline solid |
| Nic. ditartrate dihydrate | 6.591 | Crystalline solid |
| Nic. salicylate | 15.663 | Crystalline solid |
| Nic. oxalate | 3.341 | Crystalline solid |

flowing air at a rate of 90 mL/min and the DSC studies were conducted in open pans in still air. Each of the specific salts was scanned multiple times with different sample weights in the DSC. Data from each scan were then plotted and analyzed.

## RESULTS AND DISCUSSION

### *Experimental results – TGA*

Table 1 shows the specific salts used in the TGA tests, the weight of each sample that was scanned, and the physical form of the material tested. Figure 1 is a composite TGA plot for the sample of neat nicotine as well as the liquid nicotine acetate and the crystalline nicotine salts. Figure 1 shows that the liquid neat nicotine and the acetate salt are the least thermally stable of the samples plotted. Both neat nicotine and nicotine acetate volatilize/decompose completely when the temperature reaches 150 °C. The crystalline salts, on the other hand, exhibit varying thermal stabilities depending upon the particular salt. Nicotine ditoluoyltartrate begins to rapidly disappear when the temperature reaches 150 °C. Of the crystalline salts, however, the nicotine ditoluoyltartrate exhibits the largest ash content (as defined by the weight of residue remaining in the pan after completion of the TGA scan). The most stable of the crystalline salts appears to be nicotine oxalate. This salt appears to be relatively stable, in terms of weight loss, up to a temperature of about 180 °C. The nicotine salicylate salt, on the other hand, experiences a significant weight loss as the temperature rises over about 115 °C. Nicotine tartrate is a dihydrate and its thermogram clearly shows the loss of water prior to 100 °C. The tartrate and gallate salts of nicotine gradually lose weight up to about 160 °C and exhibit a major weight loss between 170–190 °C.

Shown in Figure 2 is a composite TGA plot for the amorphous nicotine solids (alginate and tannate salts) and gum (nicotine galacturonate) and for comparative purposes, the TGA plot obtained from the neat nicotine.

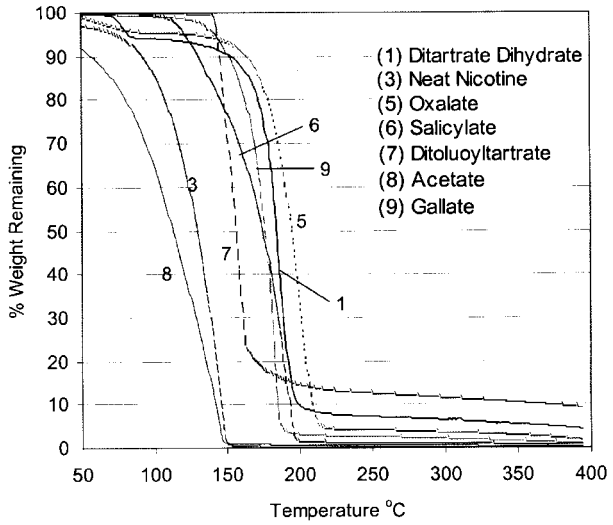


**Figure 1.**
**TGA: liquid and crystalline nicotine salts**

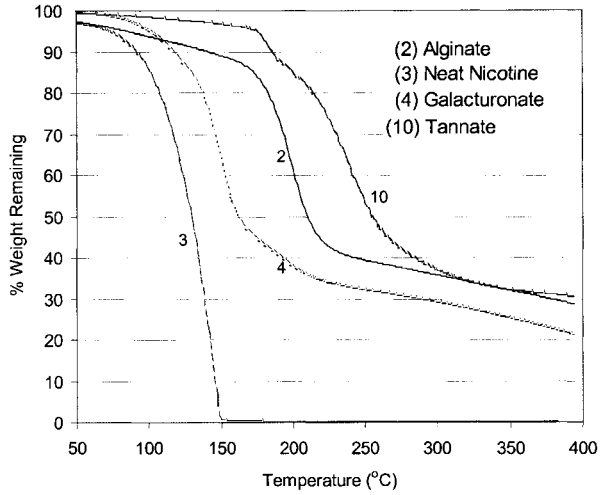


**Figure 2.**
**TGA: amorphous nicotine salts and gums**

Figure 2 reveals that the amorphous solid and gum salts of nicotine, in general, appear to have higher ash contents than the crystalline salts and liquids. The primary weight loss regions associated with the nicotine alginate and nicotine tannate salts are found at significantly higher temperatures than the liquid and crystalline salts shown in Figure 1. The general shape of the weight loss curves for all of the amorphous salts is also quite different from that of the crystalline salts and liquids shown in Figure 1.

The most stable of all the salts tested, in terms of weight loss, would appear to be the nicotine tannate. This material is fairly stable up to a temperature of about 190 °C. Volatilization and decomposition reactions then appear to result in weight losses that progress at a somewhat moderate, less severe, rate than those exhibited by all the other salts. It is interesting to note that nicotine tannate experiences a "foaming" reaction as it is heated. As the decomposition of this material progresses, the volatiles that are generated form gas bubbles in the body

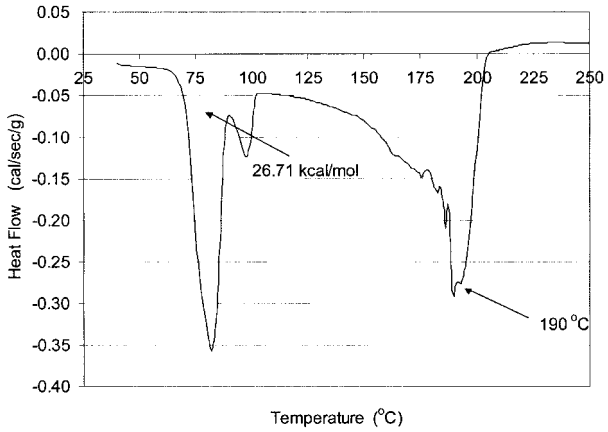


**Figure 3.**
**DSC: nicotine ditartrate dihydrate**

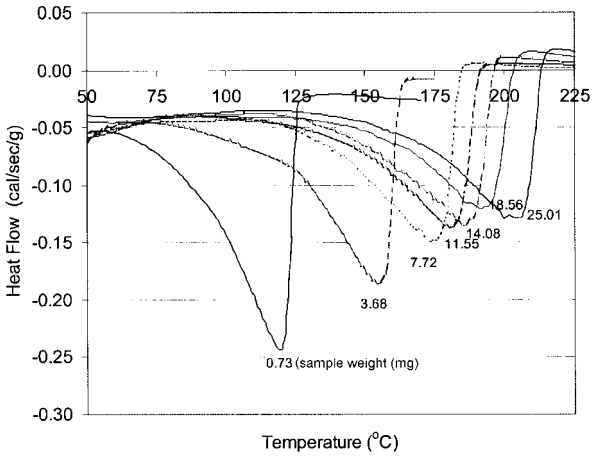


**Figure 4.**
**Free base nicotine DSC results**

of the sample. The gas cannot escape fast enough relative to the rate of change in the material's viscosity, and this results in severe foaming of the sample. This was evident when the heat-treated samples were examined and it can be seen, though not shown here, on the TGA weight loss derivative curves.

The TGA results on the nicotine salts indicate that the weight loss curves seem to be fairly dependent upon the form of the salt. In general, the liquid salt (nicotine acetate) is the least thermally stable, followed in order by the crystalline salts and finally, the amorphous salts.

*Experimental results – DSC*

While the TGA is a useful instrument for acquiring a general picture of the thermal stability of the various nicotine salts tested, it gives little or no information about the actual release of nicotine from the salt itself unless the purge gas is coupled to a secondary analytical device such as a gas chromatograph or mass spectrometer (2). The DSC, however, while not the ideal instrument for measuring nicotine release, does provide information that can be used to estimate nicotine release temperatures. The energy signature of the neat nicotine sample can be compared against those of all the other salts. Since neat nicotine is a pure sample, the evaporation of nicotine, as the temperature is increased, results in an endotherm on the DSC scan. The position of this endotherm can then be compared against endothermic events that appear on the scans for the other nicotine salt samples. In this manner, the effect of the salt structure on the release of the nicotine can be estimated.

The validity of the DSC method for analyzing nicotine release temperatures can be verified by comparing results obtained from the DSC studies with those obtained by SEEMAN *et al.* (2) using thermal gravimetric analysis (TGA) and differential thermal analysis (DTA). On studies using nicotine ditartrate dihydrate salt, SEEMAN *et al.* (2) determined using TGA and the Ozawa kinetic method (6) that the "activation energy" for the melting of the nicotine ditartrate dihydrate was 27.5 kcal/mol and the peak temperature for the nicotine release endotherm using DTA was 200 ± 5 °C. When a nicotine ditartrate dihydrate sample weighing 1.53 mg is scanned on the DSC, the energy signature shown in Figure 3 is obtained. Analysis of this scan reveals that the endotherm associated with the melting of the salt absorbs 26.7 kcal/mol and the peak of the nicotine release endotherm is found at 190 °C. Both of these results agree fairly well with those reported by SEEMAN *et al.* (2). The position of the nicotine release peak will vary depending on the weight of the sample as will be shown below.

While evaluating the standard deviation in the DSC energy signature of neat nicotine samples, it was noted that the position of the evaporative endotherm (in terms of peak temperature) was shifting rather significantly from one sample to another. This shift in position was unexpected until the endotherm peak temperature was plotted as a function of the sample weight. Shown in Figure 4 are the DSC energy signatures obtained from several samples of neat nicotine of varying weight. The numbers next to each scan represent the sample weight in milligrams. It is clearly evident from Figure 4 that the position of the evaporative endotherm shifts significantly as the weight of the sample increases. The correlation between the peak position and the sample weight is almost a perfect logarithmic relation as can be seen in Figure 5. These results are significant because if one is to evaluate the release of nicotine from a salt compared to that of neat nicotine via DSC then the sample size of the neat nicotine sample must be noted. SEEMAN *et al.* (2) reported the peak release temperature for neat nicotine to be 115 ± 5 °C but did not report a specific sample weight. Sample weights reported by SEEMAN *et al.* (2) were between 3–10 mg for nicotine and the nicotine salts examined. Based on the experimental procedure of SEEMAN *et al.* (2), the sample weights would have been low as mass spectrometry of the off-gases were analyzed. The peak release temperature for neat nicotine in this study was 128 °C for a 1 mg size sample. Figure 4 also

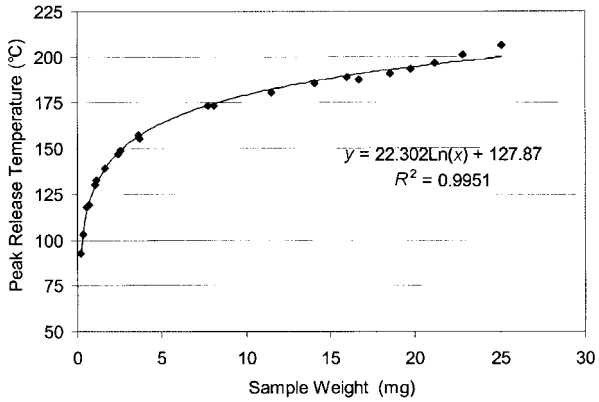


**Figure 5.**
**Correlation between the peak position and the sample weight of neat nicotine**

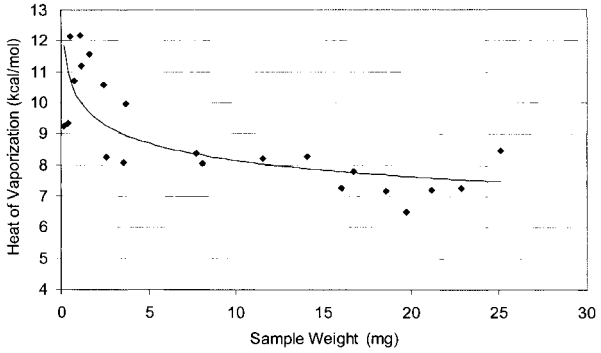


**Figure 6.**
**DSC heat of vaporization: neat niotine**

shows that the total area associated with the evaporative endotherm varies with the sample size. The heat of vaporization of the neat nicotine is thus dependent upon the size of the sample tested. Shown in Figure 6 is a plot of the heat of vaporization of the neat nicotine as a function of the sample size. DSC samples of very low weight exhibit heats of vaporization of the order of 12.2 kcal/mol while higher weight samples exhibit heats of vaporization of approximately 6–8 kcal/mol. SEEMAN *et al.* (2) have reported the heat of vaporization of nicotine to be between 13.2–14.4 kcal/mol. The CRC Handbook reports the heat of vaporization of nicotine as 12.3 kcal/mol (7).

Since the evaporative endotherm associated with neat nicotine is sample size dependent, it was reasoned that the endotherms associated with the release of nicotine in the various salts tested might also be sample size dependent. As such, each salt tested in the DSC was run multiple times at differing sample weights. It was found that temperature position of the nicotine endotherm for almost every salt was dependent upon the weight of the sample tested. Once again, the relationship between the endotherm peak temperature and the sample weight was found to be logarithmic. As the DSC sample weight changed, only the endotherm associated with the nicotine vaporization moved. The peak temperatures for the other thermal events for each nicotine salt, such as that associated with the melting of the crystalline salts, remained the same. By determining the intercept of the logarithmic relationship between sample weight and peak release temperature, i.e. the peak release temperature for a 1 mg size sample, an index of the thermal stability of the nicotine salts can be obtained. At a 1 mg sample size, a nicotine salt that exhibits a lower peak nicotine release temperature can be considered to be less thermally stable than another salt exhibiting a higher nicotine peak release temperature for the same 1 mg sample size.

For the different nicotine salts tested, it was found that the slope of the logarithmic relationship was highly dependent upon the nature of the particular salt. The intercept values (sample weight = 1 mg) were also very different depending upon the particular salt tested. These results are summarized in Table 2.

An examination of Table 2 reveals that the peak release temperature for the nicotine endotherm for a salt sample size of 1 mg (the intercept value shown in Table 2) varies between 83.8 °C and 203.4 °C depending upon the salt. The liquid and viscous gum salts exhibit the lowest

**Table 2.**
**DSC nicotine release temperatures and sample weight relationships**

| Nicotine salt | Physical form | Nicotine release temperature/ weight relationship slope (°C/mg) | Nicotine release temperature intercept (°C)[a] |
|---|---|---|---|
| Nicotine acetate | Viscous liquid | 15.7 | 83.8 |
| Neat nicotine | Liquid | 22.6 | 127.9 |
| Nicotine galacturonate | Viscous gum | -1.3 | 148.7 |
| Nicotine gallate | Crystalline | 2.5 | 163.3 |
| Nicotine ditoluoyltartrate | Crystalline | 15.8 | 165.7 |
| Nicotine alginate | Amorphous | 0.4 | 172.0 |
| Nicotine salicylate | Crystalline | 17.5 | 177.4 |
| Nicotine ditartrate dihydrate | Crystalline | 5.1 | 187.9 |
| Nicotine tannate | Amorphous | 2.1 | 192.1 |
| Nicotine oxalate | Crystalline | 3.6 | 203.4 |

[a]Release temperature for a 1 mg size sample.

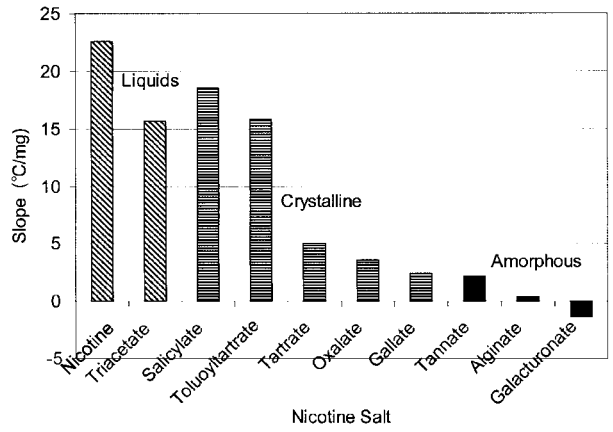


**Figure 7.**
**Slope of nicotine endotherm peak position as related to sample weight**

nicotine release temperatures while the crystalline and amorphous nicotine salts release their nicotine at significantly higher temperatures.

The relationship between the sample size, the nicotine release temperature of the salt, and the microstructural characteristics of the salt can also be seen in Table 2. If one examines the slope of the sample weight/peak temperature relationship, it is found that the nicotine release temperature of the liquid samples is very sensitive to the weight of the sample being tested. These samples exhibit relatively large slope values, which means that a small change in weight produces a large change in the position of the peak temperature. For example, high weight samples show a displacement of the peak towards relatively high temperatures. The crystalline salts on the other hand, exhibit slopes that range from fairly high values to relatively low values. The amorphous salts and the gum sample have very low sensitivity to the sample weight and show nicotine release temperatures that are almost independent of sample weight. These results are summarized in Figure 7. A comparative representation of all the salts is also shown in Figure 8.

## CONCLUSIONS

TGA and DSC were used to characterize the thermal stability of a variety of different nicotine salts. The general order of thermal stability based on TGA weight loss of the nicotine salts tested in this study is as follows: the liquid salt is the least thermally stable, followed in order by the crystalline salts and finally, the amorphous salts.

The DSC results clearly showed that the peak release temperatures for the neat nicotine endotherm are very strongly influenced by the actual weight of the sample tested. The measured heat of vaporization for neat nicotine is also affected by the sample weight. Sample weights of 2 mg or less, for example, result in heats of vaporization for the neat nicotine of about 12 kcal/mol. Higher weight samples yield heats of vaporization in the range of 6–8 kcal/mol. The exact reasons for this anoma-

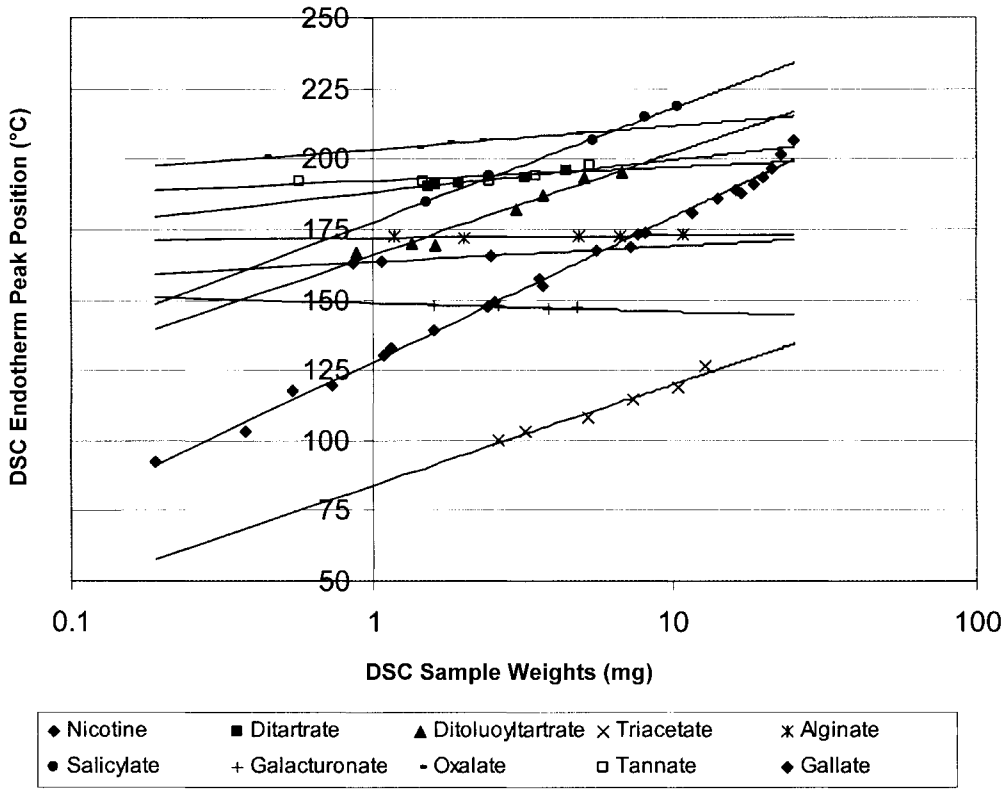


**Figure 8.**
**Nicotine salt endotherm peak temperatures**

lous behavior are not yet clearly understood but it is known that the heat of vaporization for neat nicotine is a slowly varying function of temperature. This behavior is usually attributable to the fact that nicotine is a highly associated liquid, i.e. there is a high degree of intermolecular forces associated with nicotine, similar to those of water and ammonia (8,9,10,11). These associative properties of the nicotine may be the basis for the behavior observed in this study but more research needs to be done to further explain these results.

When various nicotine salts were scanned in the DSC, it was found that the nicotine endotherm peak release temperature was also influenced to varying degrees, depending on the particular salt, by the size of the sample tested. In general, the liquid sample was most strongly affected by the sample weight followed by the crystalline salts. The amorphous salts had peak nicotine release temperatures that were nearly independent of the sample weight. These results show that it is very important to quote a sample size when reporting nicotine vaporization data.

*Acknowledgements*

The authors would like to acknowledge Dr. Jeffrey I. Seeman for his help and guidance in the final preparation of this manuscript.

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