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Nicotine Aerosol Generation from Thermally Reversible Zinc Halide Complexes Using the *Staccato*® System

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Application of the *Staccato* system to liquid drugs presents unique technological challenges. Liquids, such as nicotine, do not form physically stable films on vaporization substrates. We identified two thermally reversible zinc halides ($ZnCl_2$ and $ZnBr_2$) that complex with nicotine in a 1:2 mol ratio (zinc halide: nicotine) that can be coated as a solid film. Feasibility studies indicated that the chloride complex liberates a higher fraction of nicotine upon heating whereas the nicotine aerosol purity for both complexes was approximately 99%. Using a multidose *Staccato* device previously used in a Phase I clinical trial, we demonstrated that highly pure nicotine aerosol can be reliably generated from the chloride complex with the following qualities: aerosol purity approximately 99%, single emitted dose approximately 117 μg, particle fraction approximately 57%, and mean particle size approximately 0.8 μm. These results were supported by thermogravimetric analysis and differential scanning calorimetry.

Keywords nicotine; zinc halide; *Staccato*; condensation aerosol; thermally reversible

INTRODUCTION

The *Staccato* system is a breath-actuated inhaler that typically incorporates an unformulated solid thin film of drug on an inert metal substrate. The film is rapidly vaporized to generate a highly pure condensation aerosol (Myers et al., 2007; Rabinowitz et al., 2004, 2006). Thermal decomposition products are minimized by optimizing the film thickness and vaporization kinetics (Myers et al., 2007). We have previously demonstrated that the *Staccato* system can generate a highly pure drug aerosol with the appropriate physicochemistry for deep-lung deposition and intravenous (IV)-like pharmacokinetics (Rabinowitz et al., 2004, 2006).

Application of the *Staccato* system to drugs that are liquids or solids with low melting temperatures is highly desirable yet poses a significant technological challenge as liquids do not form physically stable thin films on a vaporization substrate. In addition, the increased ability to flow renders liquids more susceptible to the degradation mechanisms that can reduce shelf-life stability. Despite the obvious development challenges, there are many liquid drugs, for example, nicotine, with high therapeutic potentials when delivered to systemic circulation via inhalation into the deep lung.

Nicotine is a potent chemical that maintains a tobacco addiction (Benowitz, 1996). It is liquid at room temperature (MP = 194 K) and exhibits high vapor pressure in its free-base form (2.7 Pa at 298 K). It is currently used for the acute symptomatic treatment of smoking withdrawal in a smoking cessation program with marginal efficacy, but its therapeutic potential is also being assessed in the treatment of neurodegenerative disorders (notably Parkinson's [Fagerström, 1994] and Alzheimer's diseases [Jones, 1992; Villafane et al., 2007]). Nicotine is formulated into various smoking cessation products that are available by prescription, such as the Nicotrol® inhaler (nicotine inhalation system), and over-the-counter, such as Nicoderm CQ® (nicotine replacement patch). However, low smoking cessation rates undercut the therapeutic value of these products (11–13% after 12 months compared with placebo of 5–10% per Nicotrol® inhaler physicians insert).

The Nicotrol® inhaler physicians insert states that most of the nicotine released from the Nicotrol inhaler is deposited in the mouth whereas less than 5% reaches the lower respiratory tract. Buccal absorption is slow and peak plasma levels are

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reached within 15 min whereas bioavailability is approximately 50%. This pharmacokinetic profile is in sharp contrast to cigarette smoking that is characterized by high and rapid rise followed by rapid decline in nicotine arterial plasma levels (Schneider, Olmstead, Franzon, & Lunell, 2001).

It has been suggested that the inability of conventional nicotine replacement devices to achieve a single dose and pharmacokinetic profile comparable to a puff on a cigarette at least partially accounts for low smoking withdrawal rates (Schneider et al., 2001). The *Staccato* system may provide a platform for nicotine replacement therapy that would achieve a higher smoking cessation rate as we have previously demonstrated IV-like pharmacokinetics (Rabinowitz et al., 2004, 2006). For reasons mentioned above, nicotine must be physically stabilized before it can be incorporated into the *Staccato* system.

There are numerous instances in literature regarding the formation of solid nicotine complexes and salts from liquid free-base forms (Muralidharan, Udupa, & Nagaraja, 1988; Perfetti, 1983). Nicotine even exists in tobacco in the form of various organic (e.g., fumarate, malic, tartrate) salts (Perfetti et al., 2000; Riggs & Perfetti, 2001; Seeman, Fournier, Paine III, & Waymack, 1999). Early reports suggest that nicotine metal halide complexes are thermally reversible; upon heating, the metal halide is left behind whereas nicotine vaporizes away (Muralidharan et al., 1988). A thermally reversible solid drug complex in which the ligand is released upon heating would allow a liquid drug to be delivered using the *Staccato* system.

Complexation of metal halides with liquid pyridine-containing ligands (such as nicotine) is well characterized (Airoldi, Silva, & Chagas, 1986; Lot, Airoldi, & Chagas, 1994; Muralidharan et al., 1988; Steffen & Palenik, 1974) although we have not found reference of the application of these complexes for liquid drug stabilization or aerosol drug delivery. Here we present the technical feasibility of generating an excipient-free nicotine aerosol from zinc halide complexes using the *Staccato* system. We demonstrate that a therapeutically relevant dose of pure nicotine aerosol can be reliably generated from a multidose device that has successfully been used in a Phase I clinical trial.

MATERIALS AND METHODS

Nicotine is a hazardous material and should be handled with appropriate personal protective equipment and under adequate ventilation (see the Material Safety Data Sheet). Methods used to characterize aerosol have been previously introduced (Myers et al., 2007; Rabinowitz et al., 2004, 2006).

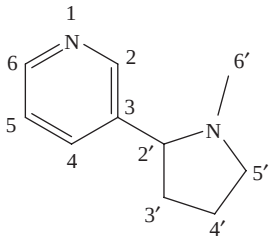
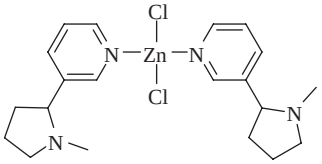
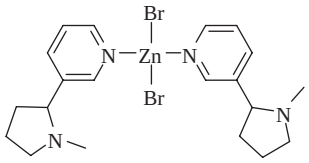
Synthesis of Metal Complexes

All chemicals were purchased from Sigma-Aldrich (USA) or VWR (West Chester, PA) and were used as received. Metal complexes were prepared using a method adapted from the work of Muralidharan et al. (1988). Solutions of $ZnBr_2$ (MW = 225.18, MP = 394°C) and $ZnCl_2$ (MW = 136.3, MP = 290°C) salts in methanol were mixed with (S)-(–)-nicotine ("nic," Table 1, reproduced with permission [Timmons et al., 2008]) in methanol at room temperature in a 1:2 (zinc halide: nic) molar ratio. The precipitated metal complexes were filtered, washed with ethanol, and recrystallized from dichloromethane, acetone, and hexane. The assigned structure (Table 1) of the coordination complexes was confirmed using proton NMR (400 MHz, $CDCl_3$). These complexes are generically referred to as $ZnX_2(nic)_2$ in this article.

Thermal Analysis

Thermal analysis was performed using differential scanning calorimetry (DSC, TA Instruments Q100; New Castle, DE, USA) and thermogravimetric analysis (TGA, TA Instruments Q500, USA). Weight loss profiles of $ZnX_2(nic)_2$ were studied using a TGA equilibrated at 25°C then ramped to 800°C at

TABLE 1
Nicotine (Left), Nicotine Zinc Halide (Right). (Copyright 2008 Virginia Commonwealth University. All rights reserved.)

	Nicotine	$ZnCl_2(nic)_2$		$ZnBr_2(nic)_2$	
Structure					
Molecular weight (MW)	162.23	460.86		549.66	
Composition (% of total MW)		Nicotine	70.4	Nicotine	59.0
		$ZnCl_2$	29.6	$ZnBr_2$	41.0

10°C/min under a nitrogen purge. Sample sizes were approximately 10 mg. Complementary high-performance liquid chromatograph (HPLC) analyses were performed to quantify the amount of nicotine remaining at selected temperatures. A DSC calibrated with indium was used to evaluate phase transitions under nonhermetic conditions. Open aluminum pans containing 0.05–2.5 mg $ZnX_2(nic)_2$ were heated under a nitrogen purge using a thermal ramp of 10°C/min. TGA and DSC data were analyzed using Universal Analysis 2000 (v4.3A, TA Instruments). All thermal experiments were performed in triplicate or greater; the results section shows representative results.

Aerosol Characterization

Two stages of aerosol characterization were completed: a feasibility stage using a benchtop apparatus to evaluate the technical feasibility of generating nicotine aerosol from zinc halide complexes, and a development stage that evaluated the feasibility of generating nicotine aerosol from the most promising zinc halide complex using a multidose device similar to that used in a recent Phase I clinical trial (Macleod, Spyker, Habib, Ho, & Gan, 2007; Macleod, Spyker, Houghton, Ikeda, & Gan, 2007). Coating and vaporization methods were adapted from methods previously described (Myers et al., 2007; Rabinowitz et al., 2004). $ZnX_2(nic)_2$ was deposited as a thin film onto stainless-steel foil substrates in a range of film thicknesses. To generate aerosol, the substrates were rapidly heated (<200 ms to 300–400°C) under a constant airflow of 20 L/min for purity and emitted dose studies and 28.3 L/min for particle size distributions. Nicotine aerosol and vapor was captured using glass fiber filters (Whatman Inc. (Florham Park, NJ), treated with 2% oxalic acid) and a 12 in denuder coated with oxalic acid to facilitate vapor absorption (Ferm, 1979; Lewis, Colbeck, & Mariner, 1994). The nicotine from coated foils, glass fiber filters, and the denuder was recovered by redissolution and quantified and analyzed for purity using an HPLC method capable of separating nicotine from its degradants (e.g., cotinine).

The particle size distribution of vaporized nicotine was measured using a laser diffractometer fitted with an R1 (0.1/0.18, 35 μm) lens (Sympatec, Helos/BF, Clausthal-Zellerfeld, Germany) in series with the vaporization apparatus. Vapor fraction in vaporized nicotine was determined using an annular glass denuder coated with oxalic acid under airflow of 5 L/min. Nicotine aerosol particles were collected at the outlet using glass fiber filters treated with oxalic acid. The nicotine was extracted from the denuder and filters and evaluated using HPLC.

RESULTS AND DISCUSSION

Structural and Thermal Analysis

The assigned structures in Table 1 were consistent with NMR data (all similar except where noted [δ 1.65 (m, 1, C3′), 1.83 (m, 1, C4′), 1.94 (m, 1, C4′), 2.14 (s, 3, NCH_3), 2.23 (m, 1, C3′), 2.36 (q, 1, C5′), 3.22 (t, 1, C2′), 3.24 (t, 1, C5′ for Cl complex), 3.22 (t, 1, C5′ for Br complex), 7.51 (d o d, 1, C5), 8.03 (d, 1, C4), 8.67 (d, 1, C6 for Cl complex), 8.72 (d, 1, C6 for Br complex), 8.70 (s, 1, C2 for Cl complex), 8.74 (s, 1, C2 for Br complex)]).

TGA analysis revealed a three-stage weight loss profile (Figure 1) for both $ZnX_2(nic)_2$ complexes. The first weight loss in each sample occurred in the range of approximately 115–200°C and matched the weight of approximately half of

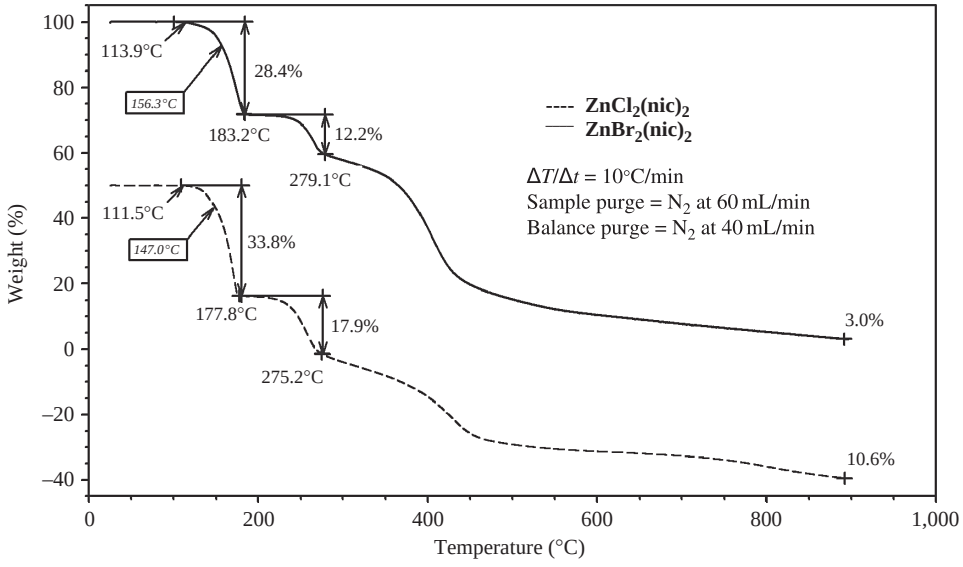


FIGURE 1. Representative TGA profiles (with y-axis offset) showing weight loss as a function of temperature for $ZnCl_2(nic)_2$ and $ZnBr_2(nic)_2$ complexes. Temperatures in boxes denote the peak of the DSC melting endotherm.

the starting nicotine in each sample (1 of 2 mol). Samples that were heated to 200°C using the TGA and analyzed for nicotine content using HPLC confirmed that approximately half of the nicotine remained. The second weight loss occurred in the range of 200–280°C and corresponded to approximately 12% of the original weight of the sample in both $ZnX_2(nic)_2$ complexes. The final stage of weight loss (T > 280°C) is most likely attributed to decomposition of any remaining organic material and sublimation of zinc halide (MP: $ZnCl_2$ ~ 290°C, $ZnBr_2$ ~ 394°C; bp: $ZnCl_2$ ~ 732°C, $ZnBr_2$ ~ 697°C). This is reasonable as the residue amounted to only approximately 11% in the case of $ZnCl_2(nic)_2$ and 3% in the case of $ZnBr_2(nic)_2$. Sublimation of zinc halides following the release of alkaloids from similar coordination complexes has been reported elsewhere (de Moura, de Oliveira, & de Farias, 2003).

DSC scans (Figure 2) show that the melt endotherm for both complexes (peak ~ 146°C for $ZnCl_2(nic)_2$ and ~156°C for $ZnBr_2(nic)_2$) is saddled by an endothermic baseline pertubation that is likely attributable to nicotine vaporization. Despite a higher melting point for the $ZnBr_2(nic)_2$ complex, the heat of fusion was lower.

Significant weight losses were observed in the TGA thermograms well before the DSC extrapolated melting onsets and peaks (Figure 2) of the complexes. The bromide complex exhibited a 5% weight loss prior to the extrapolated melting onset of approximately 155°C and the chloride complex exhibited a 4% weight loss prior to the extrapolated melting onset of approximately 145°C. Further analysis of the DSC scans of both complexes show endothermic DSC baseline perturbations before the sharp endothermic melting peak. TGA weight loss is most rapid during and following the sharp endothermic DSC peak attributed to melting (~146°C for the chloride complex and ~156°C for the bromide complex).

Using TGA under similar experimental conditions as used in this study, Muralidharan et al. (1988) reported two stages of thermal decomposition for the same $ZnX_2(nic)_2$ complexes. They postulated that the first step (240–300°C) corresponded to the complete loss of nicotine (observed 70% loss in the case of $ZnCl_2(nic)_2$ and 59% loss in the case of $ZnBr_2(nic)_2$) and the formation of metal halide and that the second step (440–600°C) corresponds to the formation of metal oxide. Despite repeated efforts, we were not able to duplicate these results.

Technical Feasibility and Aerosol Characterization

The feasibility stage evaluated nicotine aerosol purity and emitted dose using a benchtop screening device. In this stage, aerosol purity of nicotine released from the zinc halide complexes was evaluated in two experiments: aerosol purity was first evaluated over a range of vaporization temperatures (300–400°C) using 0.6 mg/cm^2 films and then aerosol purity was evaluated over a range of film thicknesses (0.6–1 mg/cm^2) using the vaporization temperature that gave the highest purity in the first stage.

In this study, increasing film thickness did not substantially affect aerosol purity (Figure 3—right, reproduced with permission [Timmons et al., 2008]); in the thickness range tested, aerosol purity was stable at approximately 99%. However, higher vaporization temperatures directly correlated with lower values for aerosol purity (Figure 3—left, reproduced with permission [Timmons et al., 2008]). The $ZnCl_2(nic)_2$ complex exhibited a greater sensitivity to elevated temperatures than the $ZnBr_2(nic)_2$ complex, as evidenced by lower aerosol purity at 350 and 400°C. The purity optimized vaporization temperature for both complexes was 300°C. At this temperature, both complexes exhibited similar aerosol purity (~99%).

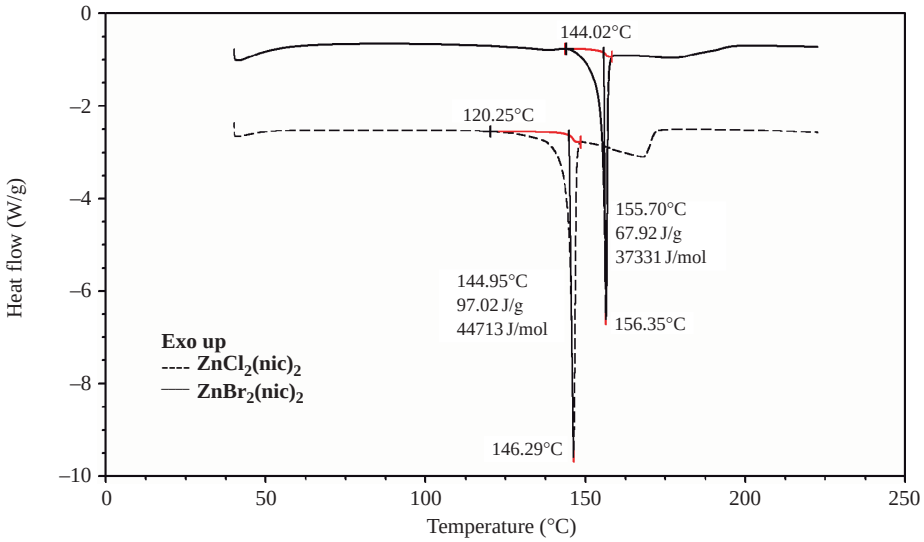


FIGURE 2. DSC thermograms (with y-axis offset) of the $ZnX_2(nic)_2$ complexes. Open pans were used with a linear temperature ramp of 10°C/min.

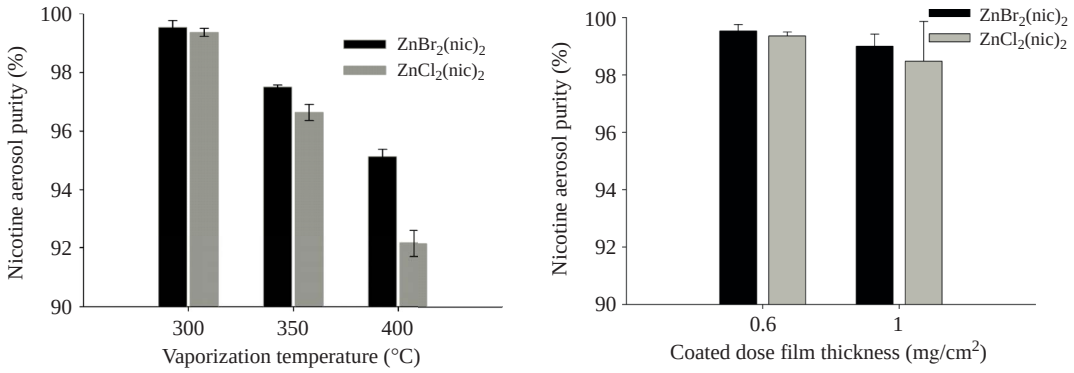


FIGURE 3. Nicotine aerosol purity as a function of vaporization temperature (generated from 0.6 mg/cm^2 films) (left) and Nicotine aerosol purity as a function of film thickness (generated at 300°C). Error bars show 1 SD from the mean for $N = 3$ (right).

Greater sensitivity to increased temperature may be explained by the differences in heat of fusion/ vaporization for the two complexes. Recalling from the DSC analysis above, the chloride complex has a higher heat of fusion/ vaporization than the bromide complex. Thus, more heat is required to melt and liberate the nicotine from the chloride complex. Associating lower aerosol purity with compounds that have higher heats of fusion is reasonable since vaporization and thermal degradation are kinetic events. Higher vaporization temperatures increase the temporal duration that the drug is exposed to degradation catalysis.

Using conditions optimized for aerosol purity (vaporization temperature = 300°C and coating thickness of ~1 mg/cm^2), nicotine aerosol emitted dose was 51.0% (±3.5%, $N = 12$) for the $ZnBr_2(nic)_2$ complex and 59.1% (±2.2%, $N = 12$) for the $ZnCl_2(nic)_2$ complex. These findings are supported by TGA and complementary HPLC analysis (above), where roughly 50% of the starting nicotine was liberated from the complex during the first stage of weight loss.

A primary objective of this study was to evaluate the performance of the *Staccato* system in aerosol generation from metal-complexed drugs that are liquids at room temperature and pressure. Having shown that we could generate nicotine aerosol using the metal halide complexes and a benchtop screening device, we next tested the metal complex on the *Staccato* multidose system that was recently used in a Phase I clinical trial. We used the device unmodified, simply coating nicotine complex in place of fentanyl. Unlike the screening device, the multidose *Staccato* system, which has 25 doses in a small cartridge (Figure 4, reproduced with permission [Timmons et al., 2008]), has a smaller surface area available for drug coating. Because the aerosol emitted dose was higher for the chloride complex and the aerosol purity was similar for both complexes, the chloride complex was selected for experiments in this stage.

The $ZnCl_2(nic)_2$ complex was physically stable at thicknesses above 2 mg/cm^2. However, as Figure 5 shows, nicotine aerosol yield dropped precipitously when generated from coatings above 1 mg/cm^2, thereby limiting the maximum achievable dose to approximately 120 µg. The $ZnCl_2(nic)_2$ complex exhibited lower emitted drug doses than typically seen with pure, excipient-free drugs; however, we were still able to achieve a therapeutically relevant dose of approximately 120 µg.

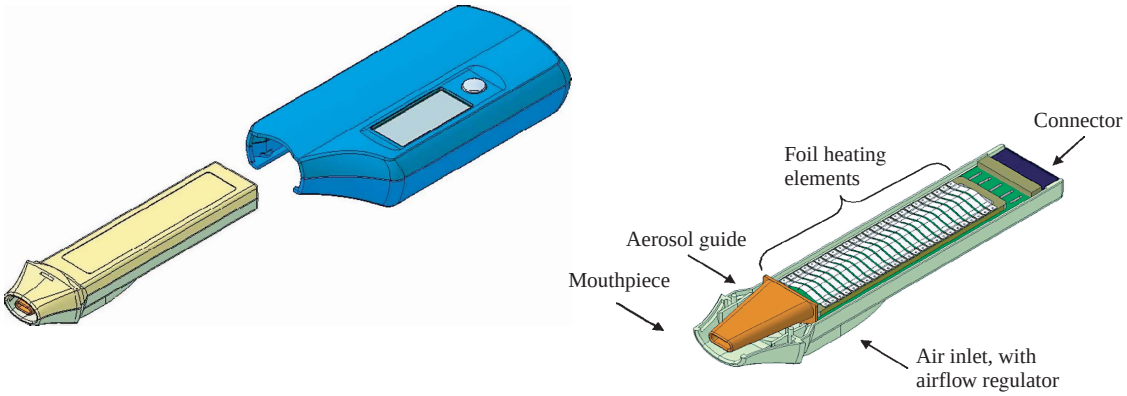


FIGURE 4. The hand-held *Staccato* device showing the controller and dose cartridge (left) and the 25-dose array within the dose cartridge (right). (Copyright 2008 Virginia Commonwealth University. All Rights reserved.)

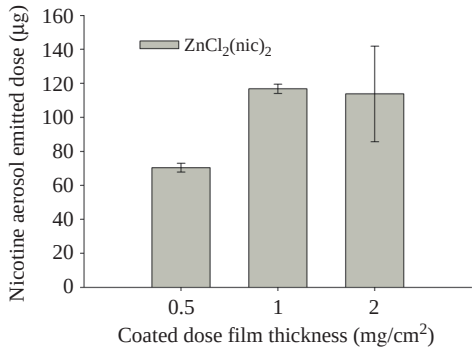


FIGURE 5. Nicotine aerosol emitted dose as a function of coated dose film thickness (generated at 300°C). Aerosol was generated from the multidose *Staccato* device from $ZnCl_2(nic)_2$ films coated on 0.18 cm^2 surface area. Error bars show 1 *SD* from the mean for $N = 3$.

TABLE 2
Properties of Nicotine Aerosol Emitted from the Multidose *Staccato* Clinical Device. (Copyright 2008 Virginia Commonwealth University. All Rights Reserved.)

Property	Value ± *SD*, $N \geq 3$
Aerosol purity	98.5 ± 0.19%
Aerosol emitted dose	116.8 ± 2.7 µg
Particle fraction	57 ± 6.5%
Particle size, volume mean diameter (VMD)	0.8 ± 0.05 µm

We used the lowest coating thickness that corresponded to the maximum emitted dose to verify that the aerosol purity, particle size, and particle fraction were in an acceptable range using the unmodified multidose clinical device (Table 2, reproduced with permission [Timmons et al., 2008]). Aerosol purity was relatively high (>98%) and comparable with that obtained using the benchtop screening device. The particle fraction in this aerosol was 57% (43% vapor) where mean diameter was approximately 0.8 µm, which is within the respirable range (Hinds, 1999).

It is widely reported that cigarettes deliver 100–200 µg nicotine per puff (Benowitz & Jacob, 1984; Hammond et al., 2006) and we have shown that the *Staccato* system can reproducibly generate nicotine aerosol from the zinc halide complexes having nicotine doses within this range. In addition, the particle fraction (57%) and size (0.8 µm) suggests that most of nicotine would reach the lower respiratory tract. This is a significant improvement over the reported values for nicotine inhaled from other devices, where emitted doses were as low as 13 µg/puff and may be composed substantially of vapor (Prochazka, 2000; Schneider et al., 2001).

CONCLUSIONS

We have demonstrated that, using the *Staccato* system, therapeutically relevant doses of aerosol of a volatile liquid drug, nicotine, can be generated from a physically stabile and thermally reversible zinc halide complex film. Physical stabilization of nicotine using metal halide complexes allowed us to leverage Alexza's significant experience with solid, small-molecule drugs using our technology platform to deliver liquid drugs. The multidose *Staccato* system is an ideal platform for nicotine delivery as it can deliver an aerosol single dose similar to a single puff of a cigarette and without the undesirable tobacco by-products.

A therapeutically significant dose of nicotine may have profound implications in exploring the potential of nicotine in alleviating the symptoms of numerous diseases such as Alzheimer's and schizophrenia. Patients with these ailments appear to self-medicate with cigarette smoking (Kumari & Postma, 2005); unlike other nicotine delivery systems on the market (patch, gum, inhaler), our multidose device may be able to closely mimic both the pharmacokinetics and dose of cigarette smoking and could facilitate exploration of new treatment paradigms.

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