Ultra-Fast Absorption of Amorphous Pure Drug Aerosols Via Deep Lung Inhalation

JOSHUA D. RABINOWITZ,1 PETER M. LLOYD,2 PATRIK MUNZAR,2 DANIEL J. MYERS,2 STEVE CROSS,2 RAMESH DAMANI,2 REYNALDO QUINTANA,2 DANIEL A. SPYKER,2 PRAVIN SONI,2 JAMES V. CASSELLA2

1Department of Chemistry and Lewis-Sigler Institute for Integrative Genomics, Princeton University, Princeton, New Jersey
2Alexza Pharmaceuticals, Inc., Palo Alto, California

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ABSTRACT: A deficiency of most current drug products for treatment of acute conditions is slow onset of action. A promising means of accelerating drug action is through rapid systemic drug administration via deep lung inhalation. The speed of pulmonary drug absorption depends on the site of aerosol deposition within the lung and the dissolution rate and drug content of the deposited particles. Alveolar delivery of fast-dissolving, pure drug particles should in theory enable very rapid absorption. We have previously shown that heating of thin drug films generates vapor-phase drug that subsequently cools and condenses into pure drug particles of optimal size for alveolar delivery. Here we present a hand held, disposable, breath-actuated device incorporating this thermal aerosol technology, and its application to the delivery of alprazolam, an anti-panic agent, and prochlorperazine, an anti-emetic with recently discovered anti-migraine properties. Thermal aerosol particles of these drugs exist in an amorphous state, which results in remarkably rapid drug absorption from the lung into the systemic circulation, with peak left ventricular concentrations achieved within 20 s, even quicker than following rapid (5 s) intravenous infusion. Absorption of the thermal aerosol is nearly complete, with >80% absolute bioavailability found in both dogs and human normal volunteers. © 2006 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 95:2438–2451, 2006

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INTRODUCTION

Numerous clinical conditions involve acute and intermittent symptoms. These include, for example, asthma, migraine, panic disorder, and paroxysmal supraventricular tachycardia. One approach to treating such conditions is to reduce the frequency and severity of the intermittent symptoms with chronic pharmacological therapy. Chronic drug administration, however, often results in significant side effects. Moreover, it frequently fails to eliminate fully the symptom episodes. Therefore, acute, symptomatic treatment is also a key element of therapy.

For treating acute symptoms, fast drug delivery and disposition is often beneficial. Metered dose inhalers for asthma provide a prototype for rapid delivery of drug to its site of action, as they produce beta agonist aerosols that deposit directly onto the target tissue of the pulmonary airways. The target tissues involved in treating other acute conditions, for example, migraine or panic attacks, are not similarly accessible to local therapy, however. Instead, they must be accessed through the systemic circulation. Thus, a rapid means of delivering drugs into the arterial circulation is required.
Rapid intravenous infusion is the fastest means of drug delivery used in common clinical practice. By introducing drug into the bloodstream very quickly, it produces a transient peak in arterial drug levels as the drug passes for the first time through the body, before its dilution into the full circulatory volume and distribution into tissues.\textsuperscript{1-3} For certain medications, this transient peak can be critical to efficacy: for example, adenosine will restore normal heart rhythm in patients with supraventricular tachycardia only if delivered very rapidly.\textsuperscript{4} Similarly, the efficacy of certain anti-migraine agents depends primarily on rate of delivery, not the total dose.\textsuperscript{5}

Because intravenous administration of drugs to outpatients is impractical, a comparably fast, non-invasive means of drug delivery has long been desired. One promising route involves inhalation of aerosol particles into the alveoli of the deep lung, as the alveolar blood supply passes directly to the pulmonary vein, left heart, and arterial circulation.

Common means of generating drug aerosols include nebulizers, pressurized metered dose inhalers, and dry powder inhalers. In general, these approaches generate particles that are too large and/or rapidly moving to reach the alveoli reliably, and thus are used primarily for delivering drugs to the pulmonary airways.\textsuperscript{6,7} Recent modifications of these technologies, including porous dry powders\textsuperscript{8} and liquid aerosols produced by pushing drug solutions through micron-sized holes,\textsuperscript{9} generate slower moving aerosols of smaller aerodynamic diameter, thereby enabling alveolar drug deposition and systemic absorption.\textsuperscript{10}

In general, the small-particle liquid aerosols may result in faster absorption than the porous dry powders, from which absorption may be retarded by specific excipients and/or slow particle dissolution.\textsuperscript{5} Nevertheless, available data suggest that even the liquid aerosol approach fails to mimic fully the speed of intravenous administration. For example, inhalation of liquid aerosol morphine results in a fast $T_{\text{max}}$ (~3 min), but peak plasma levels ~50% lower than for a bioequivalent intravenous dose given as a 3-min infusion. Although drug-specific issues of regional disposition and/or metabolism may play a role in this observation, the data show that aerosol entry into the central circulation is incomplete or takes at least 5 min.\textsuperscript{11}

Another means of generating small-particle aerosols of pharmacologically active substances is smoking: burning of organic matter in the presence of drug to generate a mixture of drug vapor, drug decomposition products, and combustion products, which condense together into particles that are inhaled.\textsuperscript{12-14} Although smoking produces aerosols of ill-defined dose amount contaminated with copious impurities, for nicotine and certain drugs of abuse, it results in rapid systemic absorption.\textsuperscript{15,16}

Recently, a new approach to generating aerosols for systemic drug delivery via inhalation has been introduced, thermal aerosol generation.\textsuperscript{17} It involves rapidly heating a thin film of pure drug, with the thin nature of the drug (typically ~5 µm) enabling its flash vaporization with minimal decomposition. Substantially (>95%) pure aerosols of over 175 different medications have been generated using this technology (U.S. Patent Application 20040099269).

Previously, thermal aerosol delivery of the anti-migraine agent rizatriptan was shown to enable rapid rizatriptan absorption and onset of pharmacodynamic action in a dog model.\textsuperscript{17} These early studies, however, utilized a bench-top apparatus rather than a handheld delivery unit and included only limited pharmacokinetic data. Here, we describe the performance of a handheld device incorporating thermal aerosol technology and the detailed pharmacokinetics of this mode of delivery. Remarkably, we find that thermal aerosol inhalation is unique among all modes of non-invasive pharmaceutical delivery, in that it not only matches, but slightly exceeds, the speed of intravenous delivery with respect to drug absorption into the left ventricle of the heart.

\section*{METHODS}

\subsection*{Materials and Supplies}

The single dose thermal aerosol generation devices utilized in the present study were manufactured by Alexza Pharmaceuticals (Palo Alto, CA) as described in U.S. Patent Application 20050079166 and comply with the current Good Manufacturing Practice guidelines of the U.S. Food and Drug Administration. Prochlorperazine base USP was obtained from Industria Chimica Milanese (Milan, Italy) (purity on receipt ~99.2%) and alprazolam USP was obtained from Fermion (Hanko, Finland) (purity on receipt >99.9%).

\subsection*{Chromatographic Methods for Aerosol Analysis}

Different high performance liquid chromatography (HPLC) methods were used for analysis...
of drug quantity versus purity, and for prochlorperazine versus alprazolam. All methods involved reverse phase HPLC with 10 μL injection volume and photodiode array (PDA) detection. Comprehensive information regarding the columns, buffers, and gradients employed in these methods is provided in Table 1. Purity is reported as follows:

\[
\text{Purity} = \frac{\text{peak area of the drug}}{\text{peak area of the drug} + \text{sum of the areas of all impurity peaks}}
\]

For practicality, impurity peaks present at <0.015% of the drug area have been omitted from purity calculations. In control experiments, both purity methods were shown to be able to detect a broad spectrum of species generated upon forced degradation of drug substance.

**Loaded Dose and Emitted Dose Characterization**

The loaded (i.e., coated) dose of the handheld thermal aerosol delivery units was determined by extraction of the drug-coated heat package with acetonitrile (for prochlorperazine) or methanol (for alprazolam) and analyzing the resulting extract by HPLC. The HPLC signal obtained upon analyzing the extract was compared to a standard curve comprised of drug solutions of known concentration. The volume of solvent used for extraction was selected to generate extracts of ~100 μg/mL drug, within the linear range of the assay standard curve.

The emitted dose was determined by connecting the mouthpiece of a handheld thermal aerosol device to a unit dose sampling apparatus (Copley Scientific, Nottingham, UK), which contained glass fiber filters (part number GF50 from Schleicher and Schuell, www.schleicher-schuell.com) to collect the emitted aerosol. Devices were actuated by applying vacuum sufficient to draw air through their airway at a flow rate of 28 L/min. The filters were extracted with acetonitrile (for

<table>
<thead>
<tr>
<th>Drug</th>
<th>Prochlorperazine</th>
<th>Alprazolam</th>
</tr>
</thead>
<tbody>
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<td>Quantitation</td>
<td>Purity Determination</td>
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<td>Waters Xterra C18, 4.6 × 150 mm, 3 μm Particle Size</td>
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<tr>
<td></td>
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<td>Isocratic (A:B)</td>
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<td>Gradient (Time-A:B) 0–100:0</td>
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<tr>
<td>Flow Rate</td>
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<td>1.0 mL/min</td>
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<tr>
<td>Detection</td>
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<td>Temperature</td>
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prochlorperazine) or methanol (for alprazolam) and the resulting extracts analyzed by HPLC.

A subset of devices employed in the emitted dose studies were further evaluated to determine the fate of any drug not emitted from the device, by extracting individual device components and assaying them for the presence of drug. This analysis revealed that, among the small fraction of drug not emitted from the device as aerosol, most (generally >90% of the non-emitted drug) deposits onto a poorly heated region of the heat package surface at the mouthpiece edge of the heat package. This region is visible as the dark stripe at the far right of the heat package thermal image shown in Figure 1C.

Aerosol Purity and Particle Size Characterization

Extracts for determination of emitted aerosol purity were collected in the same manner as described for emitted dose, with the exception that a smaller volume of solvent was used, resulting in an extract concentration of ~500 μg/mL. This high concentration facilitated resolution of small impurity peaks. Aerosol particle size was measured according to USP (601) by connecting the handheld device mouthpiece to a calibrated eight-stage Andersen cascade impactor (www.thermoandersen.com) configured with a mock throat but no pre-separator, at an air flow rate of 28 L/min. For alprazolam, the stages of the impactor were sprayed with silicone oil to prevent particle re-entrainment ("bounce"). Silicon oil treatment was not necessary for prochlorperazine aerosols, as control experiments revealed that identical particle size data were obtained with either oil-coated or uncoated stages, consistent with the liquid nature of the prochlorperazine aerosol (Fig. 2). After device actuation and aerosol generation, the cascade impactor’s throat, stages, and filter were all extracted with methanol and analyzed by HPLC for total drug content. The mass median aerodynamic diameter (MMAD) and the geometric standard deviation (GSD) of the aerosol were then calculated using the resulting data as per the manufacturer’s instructions.

High Speed Thermal Imaging

Infrared temperature measurements were performed using a Thermacam SC 3000 infrared camera (FLIR Systems, Portland, OR) at 180 images per second. The emissivity factor of the steel surface was measured by spot-welding a calibrated thermocouple to a sample stainless steel foil (of the exact same type and lot used for making the heat packages), attaching the foil to a heating block, and raising the temperature of the foil to various temperatures ranging from 300 to 500°C. The emissivity in the infrared camera’s software was varied until the camera reading matched the corresponding thermocouple steady-state value. An emissivity value of 0.18 was found to give the best agreement.

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) was performed on a TA Instruments Model Q100 (www.tainstruments.com), pre-calibrated with indium and purged with nitrogen, with a 10°C/min temperature rise. Aerosols were captured immediately after their generation by impaction onto an aluminum DSC pan, which was fit into a modified filter housing. The collection efficiency of this approach was ~90%. The pan was then sealed and analyzed very shortly after collection. Typical sample masses were ~2 mg. Because of the relatively low sample masses, adequate temperature uniformity was obtained throughout the sample despite the relatively fast temperature gradient employed.

X-ray Powder Diffraction

X-ray powder diffraction analysis was performed at SSCI (West Lafayette, IN). An Inel XRG-3000 diffractometer equipped with a curved position sensitive detector collected diffraction data using copper Kα radiation at a resolution of 0.03°2θ. For aerosol collection for X-ray power diffraction analysis, a cascade impactor was modified by taping all of the holes on the top stage shut except for one, under which was placed a small aluminum pan. Aerosols were captured immediately after their generation by impaction onto this pan. The collected aerosol (5–10 mg) was then transferred by tapping out of the pan into a vial for transport to SSCI.

Scanning Electron Microscopy

Scanning electron microscopy was performed at Accurel Systems (Santa Clara, CA). Aerosols were captured shortly after their generation by gravitational sedimentation onto a silicon wafer. The samples were then coated with a thin (~5–10 nm) layer of gold/palladium, and the resulting metal-coated particles imaged using a Phillips XL30
FEG field emission instrument with an accelerating voltage of 2.5 kV. Similar particle shapes are also observed for thermal aerosol samples collected by impaction; however, sedimentation allows for more facile collection of individual aerosol particles, which is beneficial for imaging.

Canine Anesthesia and Surgical Procedure

All canine experimentation was conducted at Charles River Laboratories (Worcester, MA) and followed protocols approved by their Institutional Animal Care and Use Committee. For all dosing events, each animal was premedicated with atropine sulfate (0.02 mg/kg, intramuscularly) and acepromazine (3 mg, intramuscularly) and then anesthetized with propofol (4–8 mg/kg, intravenously), intubated, and maintained in anesthesia with isoflurane inhalant anesthetic delivered through a volume-regulated ventilator. Although this is a standard anesthesia regimen, it is possible that it impacted observed pharmacokinetic data (e.g., by altering cardiac output or pulmonary secretions). To enable collection of left ventricular samples, a midline incision was made in the neck and one of the carotid arteries was exposed. The artery was mobilized a distance of about 5 cm and two vessel loops (www.aspensurgical.com) were placed around it, proximally and distally. The loops were both tightened to temporarily occlude blood flow, and a small arteriotomy was made to allow the introduction of a 7 Fr Carmeda BioActive Surface catheter (Carmeda AB, Stockholm, Sweden) with a volume of 1.0 mL throughout its length. The distal tip of this catheter was introduced into the left ventricle via fluoroscopic guidance. The proximal end of the catheter was capped with a three-way stopcock and the catheter was filled with an isotonic solution. The jugular vein was also exposed and isolated in a similar manner, and an appropriately sized catheter was passed just into the vessel to facilitate venous blood collection. When the necessary arterial blood collection was completed, the catheters were removed, the vessel loops tightened, and the incisions repaired.

Aerosol Delivery System for Intubated Dogs

A computer-controlled automatic aerosol administration system (AAAS) was used to administer the drug aerosols to intubated dogs. Prior to aerosol administration, the dogs were mechanically ventilated using a standard respirator attached to the dog’s endotracheal tube by a control valve (model 2020 from Hans Rudolph, Inc., Kansas City, MO) that places the dog’s endotracheal tube in-line with either the ventilator or the AAAS. Immediately prior to aerosol administration, the system control valve was switched from having the ventilator to having the AAAS in-line with the endotracheal tube. With a second AAAS valve (the “exhalation valve”) open to the ambient atmosphere, the dogs were manually forced to exhale to residual volume by lightly squeezing their thorax. The AAAS system was then actuated, which simultaneously closed the exhalation valve and opened an inhalation valve starting an inspiratory flow driven by clean compressed air and regulated by a flowmeter set to 10 L/min. The initiation of flow through the AAAS triggered the activation of a single-dose thermal aerosol device contained within the AAAS and loaded with either prochlorperazine or alprazolam. After an inspiratory duration of ~5 s, corresponding to a total inspiratory volume of ~0.9 L, the inspiratory valve was closed for a 5-s breath hold, after which the exhalation valve was opened, the dogs allowed to exhale, and the system control valve returned to its original setting with the ventilator in-line with the dog’s endotracheal tube. The AAAS included a system for monitoring pressure during inspiration and terminating inspiratory flow when pressure exceeded 30 cm water. This safety system was triggered during a small number of dosing occasions, resulting in a few animals inspiring slightly less than the target 0.9 L.

Canine Dosing and Pharmacokinetic Sampling Protocol

Four young adult, female, mongrel dogs having body weights between 19.8 and 22.5 kg were treated with either prochlorperazine (7 mg) or alprazolam (0.7 mg) via thermally generated aerosol inhalation and 5-s intravenous infusion in two separate surgical/dosing sessions separated by ~48 h, with separate sets of animals used for the two different drugs. The intravenous infusions consisted of either 5 mg/mL prochlorperazine edisylate for injection USP solution or 0.2 mg/mL alprazolam in 50:50 sterile propylene glycol:water. Following treatment in each surgical/dosing session, blood samples were collected from the left ventricle and from a peripheral vein for bioanalysis. Left ventricular samples were obtained at start of treatment (t = 0; initiation of
inhalation or intravenous infusion), and then 5, 10, 15, 20, 25, 30, 40, 50, 60, 75, 90, 120, 150, and 180 s, and 5 and 10 min post \( t = 0 \). Venous samples were obtained prior to treatment and then 15, 30, 60, 120, and 180 s; 5, 10, 20, 30, 60, 120, and 240 min; and 8, 12, 16, and 24 h post \( t = 0 \). To enable left ventricular samples to be collected on the <30-s time scale, a special sample collection procedure was employed. In this procedure, sample collection involved aspirating 1 mL of blood into a surgically implanted left ventricular catheter having a 1 mL volume. This sample was then expelled into an appropriately labeled blood tube through a double acting check valve following aspiration of the next time point into the catheter.

**Verification of Performance of Devices Utilized in the Canine Pharmacokinetic Studies**

Aerosol samples were captured from the AAAS before and after dose administration and analyzed as described above. The results confirmed that the AAAS, when loaded with prochlorperazine (nominal emitted dose 7 mg), generated an emitted dose from the dog’s endotracheal tube of 6.71 ± 0.56 mg (\( N = 3 \) samples taken before and \( N = 3 \) samples taken after dosing) with an average MMAD of 2.1 \( \mu \)m, an average GSD of 1.8, and a purity \( \sim 97.5\% \). For alprazolam (nominal emitted dose 0.7 mg), the emitted dose from the dog’s endotracheal tube was 0.69 ± 0.05 mg (\( N = 3 \) samples taken before and \( N = 3 \) samples taken after dosing) with an average MMAD of 2.4 \( \mu \)m, an average GSD of 2.3, and a purity \( \sim 98\% \).

**Clinical Study Design**

Following acceptance of an Investigational New Drug Application by the U.S. Food and Drug Administration for the prochlorperazine thermal aerosol drug product and study approval by a governing Institutional Review Board, normal healthy volunteers were enrolled in a study of the safety, tolerability, and pharmacokinetics of prochlorperazine thermal aerosol versus intravenous administration conducted at PPD, Inc. (Austin, TX). Subject inclusion criteria included males or females of age between 18 and 45 years, free of tobacco and drug use, normal weight, non-pregnant, English proficient, and in good general health. The portion of the study described here involved eight volunteers, consisting of 6 men and 2 women of median body weight 72.5 kg (range 60.6–85.2 kg) and median age 29.5 years (range 21–45 years). Each volunteer received in a randomized, non-blinded, cross-over design 0.5 mg of prochlorperazine on two occasions separated by a minimum 5-day washout: once by thermal aerosol inhalation as a single deep breath (using the handheld delivery unit with a 0.625 mg coated prochlorperazine dose and mean emitted dose fraction determined in laboratory testing of 81%, as described in Tab. 2) and once by 5-s intravenous infusion via an indwelling venous forearm catheter. Venous blood samples for pharmacokinetic analysis were obtained from the opposite forearm via a second indwelling venous catheter or direct venipuncture just prior to treatment and then at 0.5, 1, 2, 3, 5, 10, 15, 20, 30, 45 min and 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h post dose. Safety was assessed via subject history, physical exam, clinical laboratory tests, frequent vital signs, pulse oximetry, pulmonary function tests, and ECG. There were no serious adverse events and no subjects dropped out after exposure to inhaled prochlorperazine.

**Bioanalysis of Canine and Human Samples**

Whole blood samples were centrifuged. The plasma was extracted and placed in a \(-70^\circ C\) refrigerator.
freezer (−20°C for prochlorperazine human samples) within 90 min from the time of collection. Samples were then shipped to the laboratory responsible for their analysis on dry ice: CTBR Bio-Research (Sennville, Quebec, Canada) for prochlorperazine canine samples and PHARMout laboratories (Sunnyvale, CA) for prochlorperazine human samples and alprazolam canine samples. Samples were stored at −70°C until analyzed. Concentrations of prochlorperazine in canine and human plasma samples were measured using distinct, validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods (limit of quantitation of 2.0 ng/mL for the canine plasma method and 0.1 ng/mL for the human plasma method); concentrations of alprazolam in canine plasma were measured using a validated LC-MS/MS method with a limit of quantitation of 1.0 ng/mL. In brief, plasma samples were mixed with internal standard (2H3-prochlorperazine or 2H5-alprazolam) and sodium bicarbonate, and then purified using solid phase extraction (Oasis HLB, Waters Corporation, Milford, MA). Extracts were separated by gradient HPLC on a Phenomenex (Torrance, CA) Synergi Hydro-RP, 4 μm particle size column and subjected to tandem mass spectrometry (MDS Sciex API 3000, Concord, Ontario, Canada) with electrospray ionization in positive ion mode and multiple reaction monitoring detection. Drug concentrations were calculated by comparing drug/internal standard ratios to a standard curve in dog or human plasma as appropriate.

Pharmacokinetic Analysis Procedures

Individual plasma concentration-time data were analyzed using non-compartmental pharmacokinetic methods. Areas were calculated using the linear trapezoidal rule. The maximum observed plasma concentration (Cmax) and the time at which Cmax occurred (Tmax) were determined by inspection. Venous plasma AUCinf was determined as follows: AUCinf = AUC0-last + (Clast*half-life)/ln2, where Clast was the last detectable plasma concentration and half-life was determined by fitting the terminal log-linear portion (at least three points) of the plasma concentration versus time curve using a nonlinear, least-squares minimization algorithm (RSTRIP, MicroMath, version 5.0). Other pharmacokinetic calculations were performed using Microsoft® Excel 2000, version 9.0. Bioavailability was determined as the ratio of AUCinf after aerosol administration to the AUCinf after intravenous administration, corrected for the observed mean emitted dose from the thermal aerosol device.

RESULTS

Thermal aerosol generation involves rapid heating of drug films to form vapor, followed by condensation of the vapor phase drug into aerosol particles that are inhaled.17 Accordingly, all thermal aerosol devices require an energy source for heating a substrate upon which drug is coated as a thin film. Figure 1 shows the aerosol generator used in the pharmacokinetic studies reported here: a single-dose, disposable, handheld thermal aerosol device that utilizes as its energy source an exothermic chemical redox reaction hermetically sealed within a stainless steel container (heat package). Triggering of a starter to initiate the redox reaction results in rapid and transient release of a fixed quantity of heat (~100 calories) inside the heat package. Because the redox reactants sealed inside the heat package are in physical contact with the stainless steel, heat quickly conducts to the exterior of the heat package and vaporizes the thin film of drug coated there. The dosage of aerosol produced is controlled by the quantity of drug coated on the stainless steel, with about 90% of the coated drug vaporized and emitted from the device as aerosol (Tab. 2). Drug aerosol generated by heating of the stainless steel is directed into the respiratory tract of an inhaling patient by a surrounding airflow made of medical grade polycarbonate plastic. The airway also serves to insulate the patient from the transiently hot vaporization surface.

The handheld thermal aerosol device includes a sensor which initiates aerosol generation in a breath-activated manner. Inspiration of air through the device is detected by the breath sensor, which generates an electrical signal to activate the starter. This leads to rapid heating of the exterior surface of the stainless steel to approximately 400 ± 50°C within 250 ms (Fig. 1C). Heat transfers into the drug film on the heat package exterior. Because the thin film has a high surface area to volume ratio, vaporization is very rapid, occurring in less than 1 s and before substantial thermal decomposition occurs (Tab. 2). Once vaporized, the drug cools in the airflow generated by patient inspiration and condenses...
to form aerosol particles. The resulting aerosol is characterized by a MMAD within the range generally considered optimal for alveolar drug delivery, 1–3 μm (Tab. 2). The GSD of the aerosol particle size distribution, a unitless parameter characterizing the width of the distribution, is generally /C24 2, indicating that the aerodynamic size of about 70% of the aerosol particles falls within a twofold range around the MMAD. The performance of the device is quite reproducible, as indicated by a relative standard deviation of the emitted dose of <5%.

As the absorption rate of a drug formulation often depends on the formulation’s dissolution characteristics, which in turn often depend on a drug’s physical state (amorphous vs. crystalline), we explored the crystallinity of thermal aerosols of two important pharmaceuticals that are useful in treating acute and intermittent conditions: the dopamine antagonist prochlorperazine and the benzodiazepine alprazolam. In the case of prochlorperazine, which is a viscous liquid in its native amorphous state, visual and microscopic inspection of collected thermal aerosol particles revealed that they were viscous liquid: although they did not flow freely, they coalesced upon touching each other to form a bulk liquid. These observations were confirmed by the absence of a melting endotherm in DSC of prochlorperazine thermal aerosol particles (Fig. 2A). In the case of alprazolam, which arrives from commercial sources as a crystalline powder, collected thermal aerosol particles formed a solid. Scanning electron microscopy of the particles revealed solid spheres with a smooth appearance suggestive of a glassy (amorphous) material (Fig. 2B). DSC of these particles revealed a crystallization exotherm during heating, indicative of amorphous alprazolam (Fig. 2C). The amorphous nature of the alprazolam was further confirmed by X-ray power diffraction (Fig. 2D). Thus, both the prochlorperazine and alprazolam thermal aerosol particles consist of >97% pure, additive-free drug in amorphous form, with the prochlorperazine particles viscous liquid and the alprazolam particles solid but non-crystalline.

Having characterized the physical nature of the prochlorperazine and alprazolam thermal aerosols, we proceeded to determine their detailed absorption pharmacokinetics following delivery over a single deep breath to anesthetized, intubated, mechanically ventilated dogs. We were particularly interested in the initial absorption of drug from the alveoli into the pulmonary vein and...
left heart, and accordingly placed a catheter in the left heart, from which we sampled every 5 s during the first 30 s following initiation of inhalation delivery, and also frequently thereafter. We also collected peripheral venous samples to evaluate arterial-venous differences. For comparison purposes, identical samples were also collected following rapid (5 s) intravenous infusion into the saphenous vein.

The observed inhalation pharmacokinetics for both drugs (Fig. 3) are strikingly similar to each other, and also, on the timescale of a few minutes or more, strikingly similar to rapid intravenous infusion of the same dose of the same agent. In both cases, a substantial drug gradient exists between the left ventricle and venous circulation over the first ~100 s, but dissipates within 5 min of drug administration, with peak left ventricular concentrations exceeding peak venous concentrations by approximately threefold for prochlorperazine and sixfold for alprazolam (Tab. 3). Notably, within 5–10 s of initiation of inhalation, substantial drug concentrations are achieved within the left ventricle of the heart. The time to peak plasma levels in the left ventricle is somewhat quicker for thermal aerosol inhalation than for 5 s intravenous infusion delivery, with the difference in left ventricular $T_{\text{max}}$ values for the two delivery routes statistically significant when the prochlorperazine and alprazolam data are analyzed together ($p = 0.006$ by two-tailed, paired $T$-test with $N = 8$ pairs of observations corresponding to eight different animals, four for each drug). No other statistically significant differences between aerosol and intravenous administration were observed. Overall bioavailability of thermal aerosol delivery was high for both prochlorperazine and alprazolam (>80%) (Tab. 3).

To assess whether similar pharmacokinetics would be achieved in the absence of intubation in
human subjects taking a single deep inhalation, venous pharmacokinetic samples were collected during a Phase I human trial assessing the safety of prochlorperazine thermal aerosol in eight normal volunteers. As shown in Figure 4, thermal aerosol inhalation of prochlorperazine by humans resulted in similar pharmacokinetic data to those observed from the venous plasma of dogs, with peak drug concentrations obtained in 1–3 min in all individuals (Tab. 4). The pharmacokinetics of thermal aerosol inhalation of prochlorperazine by humans were very similar to those of 5-s intravenous infusion in humans, with no statistically significant differences found among the data in Table 4. Substantial variability in plasma drug concentrations following both intravenous and aerosol administration was observed; however, inter-patient variability by the inhalation route did not exceed that following the rapid intravenous infusion. The absolute bioavailability of prochlorperazine following inhalation was 81% based on AUC_{inf} normalized to coated dose, and 100% based on the emitted dose, which was 81% of coated dose (Tabs. 2 and 4).

**DISCUSSION**

Aerosol inhalation is unique among all non-invasive routes of drug administration in providing the anatomical possibility of delivering drug almost directly into the left heart. To achieve such delivery, it is necessary for the inhaled drug to deposit and dissolve in the alveoli. Alveolar drug can then be absorbed into the pulmonary capillary circulation, with the absorption rate expected to be directly proportional to the permeability coefficient of the drug, the total drug-exposed

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**Figure 3.** Pharmacokinetics of prochlorperazine (7 mg/dog, panels A and B) and alprazolam (0.7 mg/dog, panels C and D) following thermal aerosol inhalation (open symbols) versus rapid (5 s) intravenous infusion (closed symbols) to anesthetized and intubated mongrel dogs (N = 4 per condition). Circles represent left ventricular drug concentrations and squares represent venous drug concentrations. Panels A and C show both left ventricular and venous data over the first 5 min following drug delivery, whereas Panels B and D focus specifically on left ventricular concentrations over the first minute. Error bars in Panels B and D indicate + one standard error of the mean.
alveolar surface area, and the concentration gradient across the membrane.²⁰

Here we show that one convenient way of generating 1–3 μm diameter particles appropriate for alveolar delivery is via a handheld, single dose, disposable thermal aerosol device (Fig. 1). This breath-actuated delivery unit, which has been designed to be cost competitive with other single use pharmaceutical products when manufactured in large scale, produces a high emitted dose fraction (>80%) and consistent total emitted dose (Tab. 2). A key factor favoring effective alveolar delivery from the device, beyond the aerosol particle size, is the quick generation of particles with low velocity (momentum). The low momentum of the particles is expected to minimize drug deposition in the oropharynx,²¹ while the high fraction of particles delivered in the first half of a patient breath is expected to increase the amount of drug reaching the alveoli.²²

A distinguishing feature of thermal aerosol particles is that they consist of the pure active pharmaceutical without excipients, solvents or other additives. In addition, the pure active drug generally exists in amorphous form, as shown here for prochlorperazine and alprazolam (Fig. 2). The amorphous nature of the drug pure particles results from their being formed by rapid cooling of concentrated drug vapor without sufficient time to organize into crystals. The vaporization process renders the drug amorphous at the time of patient inhalation. Accordingly, although physical state changes during product storage could potentially impact product stability, the act of vaporization eliminates concerns about physical state changes during storage affecting aerosol morphology or absorption.

The combination of the small size, high purity, and amorphous nature of the thermal aerosol particles results in rapid drug absorption, with peak plasma levels in the left ventricle achieved in 20 s, slightly faster even than following 5 s intravenous bolus infusion. Several aspects of the delivery process likely contribute to this fast rate, including alveolar deposition of most of the inhaled drug due to the small aerosol particle

### Table 3. Pharmacokinetic Parameter Estimates for Thermal Aerosol Inhalation Versus Rapid Intravenous Delivery of Prochlorperazine (7 mg/dog) and Alprazolam (0.7 mg/dog) in N = 4 Dogs per Drug

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prochlorperazine</th>
<th>Alprazolam</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aerosol</td>
<td>5 s IV Infusion</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD (%)</td>
<td>Mean ± SD (%)</td>
</tr>
<tr>
<td>Left ventricular C&lt;sub&gt;max&lt;/sub&gt; ng/mL</td>
<td>3260 ± 980 (30%)</td>
<td>3480 ± 770 (22%)</td>
</tr>
<tr>
<td>Left ventricular T&lt;sub&gt;max&lt;/sub&gt; min</td>
<td>0.33 ± 0.07 (20%)</td>
<td>0.50 ± 0.14 (27%)</td>
</tr>
<tr>
<td>Venous C&lt;sub&gt;max&lt;/sub&gt; ng/mL</td>
<td>887 ± 268 (30%)</td>
<td>1300 ± 1270 (97%)</td>
</tr>
<tr>
<td>Venous T&lt;sub&gt;max&lt;/sub&gt; min</td>
<td>1.00 ± 0.71 (71%)</td>
<td>1.06 ± 0.72 (68%)</td>
</tr>
<tr>
<td>Venous half-life hrs</td>
<td>1.27 ± 0.29 (23%)</td>
<td>1.37 ± 0.10 (7%)</td>
</tr>
<tr>
<td>Venous AUC&lt;sub&gt;inf&lt;/sub&gt; ng hr/mL</td>
<td>250 ± 58 (23%)</td>
<td>305 ± 59 (19%)</td>
</tr>
<tr>
<td>Venous F&lt;sub&gt;a&lt;/sub&gt; %</td>
<td>85.9 ± 13.6 (16%)</td>
<td>—</td>
</tr>
</tbody>
</table>

²⁰SD, standard deviation; CV, coefficient of variation.
²¹Fa based on the experimentally observed aerosol emitted dose of 6.7 mg for prochlorperazine and 0.69 for alprazolam; Fa based on the nominal aerosol dose of 7.0 mg for prochlorperazine is 82.2% and on the nominal aerosol dose of 0.7 mg for alprazolam is 95.5%.
size, rapid drug dissolution due to the amorphous nature of the particles, formation of a large drug concentration gradient across the alveolar-capillary membrane as the pure drug particles quickly dissolve, and involvement of a large surface area of alveolar-capillary contact in drug absorption. Also likely contributing is substantial membrane permeability of prochlorperazine and alprazolam, both compounds with limited water solubility (log $P$ of 4.8 and 2.1, respectively). As rapid delivery—albeit without adequate sampling to prove equivalent speed to that observed here for prochlorperazine and alprazolam—has also been demonstrated for thermal aerosol rizatriptan, a more water soluble agent (log $P$ of $-0.7$), these initial examples of the thermal aerosol approach suggest that it results in fast absorption of both water soluble and insoluble compounds. Because water insoluble agents are frequently difficult to administer via other delivery routes, the ability to administer such drugs as thermal aerosols may prove particularly valuable in the long run.

The left ventricular absorption data reported here are, to our knowledge, unique in the literature in capturing with precision the rate of passage of drug from the lungs to the left heart, and accordingly the first to document substantial systemic drug absorption through a non-invasive delivery route in less than 30 s. They are consistent with the prior observation of Henningfield et al. that cigarette smoking results in substantially higher arterial than venous nicotine concentrations. However, the physical properties of nicotine, including its size and vapor pressure, are quite different from typical pharmaceuticals, and accordingly, until the present work, it was not known whether pulmonary delivery could produce such gradients of normal pharmaceutical compounds. In addition, unlike the work of Henningfield et al., the present report clearly captures the upstroke in drug concentration in the heart, demonstrating a smooth rise over $\sim 15$ s to peak concentrations very similar to those achieved by rapid intravenous infusion.

For both fast intravenous infusion and thermal aerosol inhalation, it is likely that the rise time for left ventricular drug concentrations substantially reflects the transit time for blood from delivery location (infusion site or alveoli) to the left ventricle, with the peak cardiac drug levels in both cases reduced by spreading of the drug bolus over an increasing plasma volume as different molecules of the active agent take divergent paths through the pulmonary capillary bed. For drug administered intravenously, mixing and dilution may also occur in the venous circulation, right heart, and pulmonary artery. In contrast, drug entering via the alveoli, with their large absorptive surface area, passes directly into the pulmonary vein and left heart. Likely due to the short distance between the alveoli and the left heart, left ventricular drug concentrations over the first 10 s after thermal aerosol inhalation exceed those following rapid intravenous infusion.

While thermal aerosol inhalation produces substantial left ventricular drug concentrations in less than 10 s, onset of action of the drug requires its disposition via the arterial system to its target organ, a process that introduces an additional pharmacokinetic time lag, even before

### Table 4. Pharmacokinetic Parameter Estimates for Thermal Aerosol Inhalation Versus Rapid Intravenous Delivery of Prochlorperazine (0.5 mg) to $N=8$ Normal Human Volunteers

<table>
<thead>
<tr>
<th>Parameter (Venous)</th>
<th>Units</th>
<th>Aerosol Mean ± SD (% CV)</th>
<th>5 s IV Infusion Mean ± SD (% CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{max}$ $^a$</td>
<td>ng/mL</td>
<td>1.38 ± 0.561 (41%)</td>
<td>1.30 ± 0.823 (63%)</td>
</tr>
<tr>
<td>$T_{max}$ $^a$</td>
<td>Minutes</td>
<td>2.00 (1.00, 3.00)</td>
<td>2.50 (0.600, 360)</td>
</tr>
<tr>
<td>AUC$_{0-24}$ h</td>
<td>ng h/mL</td>
<td>5.09 ± 1.10 (22%)</td>
<td>4.28 ± 2.39 (56%)</td>
</tr>
<tr>
<td>AUC$_{inf}$ $^b$</td>
<td>ng h/mL</td>
<td>7.12 ± 2.23 (31%)</td>
<td>7.07 ± 2.40 (29%)</td>
</tr>
<tr>
<td>Fa$^c$</td>
<td>%</td>
<td>100 ± 68 (68%)</td>
<td>—</td>
</tr>
</tbody>
</table>

Note that the 0.625 mg coated dose strength of prochlorperazine for inhalation resulted in an emitted dose of 0.5 mg and is accordingly compared to 0.5 mg intravenous.

$^a$Median (range) reported instead of mean ± SD, as data do not approximate a normal distribution.

$^b$Adequate data to determine AUC$_{inf}$ were not available for one patient; according $N=7$ for AUC$_{inf}$ and Fa.

$^c$Calculated based on the geometric mean of the AUC$_{inf}$ ratios, using the observed aerosol emitted dose of 0.51 mg; Fa = 81% of the 0.625 mg loaded dose.
pharmacodynamic response time is considered. The time interval required to reach a target organ will depend directly upon the circulatory volume that must be traversed to reach the target, and inversely on the flow through the organ. For the coronary circulation, the distance from the left ventricle is minimal, and according the time lag would be as well. For other major organs, the lag is likely to be on the order of 10–20 s; thus, thermal aerosol administration can be expected typically to produce meaningful target tissue drug concentrations in <30 s.

In addition to its speed, absorption of the thermally generated aerosols described here is notable for its completeness (bioavailability >80% of the emitted dose), with the large plasma drug concentrations observed over the first few minutes after delivery suggesting that essentially all of the administered drug is quickly absorbed. These pharmacokinetic results imply that most of the inhaled drug is reaching the alveoli.

The speed and completeness of drug delivery by thermal aerosol inhalation demonstrates that the benefits of rapid intravenous infusion can now be captured non-invasively. Extracting clinical value from this technology will rely on identifying drugs that both effectively abort acute patient symptoms and are safe to deliver with intravenous-like pharmacokinetics. In this respect, prochlorperazine has a long track record of safe use via the intravenous route to treat episodes of nausea and vomiting. Alprazolam, in contrast, has been marketed only as an oral agent. Nevertheless, intravenous alprazolam delivery has proven safe in clinical trials, and there has been long-standing interest in a fast-acting benzodiazepine product for aborting panic attacks. Alprazolam, in contrast, has been marketed only as an oral agent. Nevertheless, intravenous alprazolam delivery has proven safe in clinical trials, and there has been long-standing interest in a fast-acting benzodiazepine product for aborting panic attacks. Therefore, prochlorperazine and alprazolam thermally generated aerosols are both poised to contribute to improved patient care. While the ultimate utility of thermally generated aerosols can only be proven through more extensive clinical trials, the ultrafast absorption of these aerosols suggests the potential of this novel technology to revolutionize treatment of acute and intermittent conditions.

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REFERENCES


