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Fast onset medications through thermally generated aerosols

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Abstract

Smoking involves heating a drug to form a mixture of drug vapor and gaseous degradation products. These gases subsequently cool and condense into aerosol particles that are inhaled. Here, we demonstrate rapid and reliable systemic delivery of pure pharmaceutical compounds without degradation products through a related process that also involves inhalation of thermally generated aerosol. Drug is coated as a thin film on a metallic substrate and vaporized by heating the metal. The thin nature of the drug coating minimizes the length of time during which the drug is exposed to elevated temperatures, thus preventing its thermal decomposition. The vaporized, gas-phase drug rapidly condenses and coagulates into micron-sized aerosol particles. For the commonly prescribed anti-migraine drug rizatriptan, inhalation of these particles results in nearly instantaneous systemic drug action.

Drug compounds can be delivered to the human body through a variety of routes, including injection, oral intake, and inhalation. For rapid delivery, deep lung inhalation has a number of key advantages, including the large absorptive surface area (~ 100 m^2) (West, 1990; Thurlbeck, 1967) of the deep lung (alveoli), the thinness and permeability of the barrier separating the alveolar airspace from the pulmonary capillary bed, and the direct passage of absorbed drug from the pulmonary circulation to the arterial circulation. These factors enable drug inhaled as aerosol particles to reach the body and brain in less than a minute—if the inhaled particles are of appropriate size to reach and deposit in alveoli (1 - 3 μm diameter) (Heyder, 1982), the particles dissolve rapidly, and the drug readily crosses from the alveoli to the bloodstream (Ehrhardt et al., 2002).

Although a variety of pulmonary delivery systems such as metered dose inhalers are used in current clinical practice, the efficiency of their delivery of particles to the deep lung is limited (Farr et al., 1995; Kim et al., 1985). These systems are therefore used mostly for local delivery of drugs to the pulmonary airways. Recently, substantial efforts have been devoted to developing technologies that generate smaller particles which reach alveoli and thus enable systemic drug delivery via inhalation. Such particles can be produced by either forcing liquid solutions of drugs through small holes (Schuster et al., 1997), or by dispersing dry powders (Johnson, 1997). The liquid aerosol approach has been shown in humans to result in reliable systemic absorption of drugs including insulin, morphine, and fentanyl (Henry et al., 2003; Thippawong et al., 2003; Mather et al., 1998). A relatively complex device is, however, required to eject the desired size particles of sterile drug solution. Because of limitations on the viscosity of the solution

for production of the desired aerosol particle size, this approach has focused on solutions consisting largely of water, with relatively small amounts of drug dissolved. The liquid aerosol approach is therefore limited to potent, water-soluble drugs. The dry powder approach, which to date has focused largely on delivery of insulin, has also been shown to result in reliable systemic delivery when the powder is appropriately formulated (Edwards et al., 1997; Newhouse and Corkery, 2001). The process of formulating and manufacturing dry powders, however, remains challenging, and generally requires substantial quantities of additives to facilitate dispersion of the powder into aerosol particles. Such dispersion becomes increasingly difficult as particle size decreases, due to increasing particle-particle aggregation (Hinds, 1999). Thus, while liquid aerosols and dry powders both have some desirable features, there remains a need for an alternative means of generating aerosols for systemic delivery via the deep lung that is low cost, convenient, and capable of producing small size particles, and that enables simple, additive-free formulation of both hydrophobic and hydrophilic medications.

Smokers of tobacco and illicit drugs have implicitly known for centuries that aerosols that are at least partially systemically absorbed upon inhalation can be readily produced by smoking (Friedlander, 1977; Porstendorfer and Schraub, 1972; Snyder et al., 1988). Smoking refers to the heating of drug substance to form vapor[1] that subsequently cools, condenses, and coagulates into aerosol particles that are inhaled. From a pharmaceutical perspective, however, smoking has never been considered a viable drug delivery process because of uncontrolled production of numerous thermal degradation products from the relevant drug and plant constituents (Stedman, 1968; Schmeltz and

Hoffmann, 1977; Martin et al., 1989; Lee et al., 1999; Freeman and Martin, 1981), and also because of lack of consistent or desirable aerosol particle size. Here we show that a thermal aerosol generation process analogous to smoking can be used to deliver pure drug substance reliably to the alveoli without thermal degradation products. The process involves heating a thin film of drug to form a pure vapor that then cools and condenses into 1 - 3 μm diameter particles that are inhaled. Inhalation of these particles results in systemic drug absorption and action in less than 60 seconds.

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Methods

Drug compounds. Phenytoin (Dilantin®), atropine, and zolpidem (Ambien®) were purchased from Sigma Chemical Co., St. Louis, MO. Fentanyl free base was purchased from Mallinckrodt, St. Louis, MO. A sample of midazolam (Versed®) was kindly provided by Gyma Laboratories of America, Inc., Westbury, NY. Sildenafil was extracted from Viagra® tablets (Pfizer, Inc.) by grinding the tablets to a fine powder which was then suspended in saturated aqueous sodium bicarbonate. The mixture was extracted with dichloromethane to give 98% yield of sildenafil, mp 185-185.5^{o}C (lit. 187-189^{o}C). Rizatriptan was extracted from Maxalt® tablets (Merck and Co., Inc.) by dissolving the tablets in 10mL of water. The resulting solution was adjusted to pH 11-12 by addition of aqueous 1N sodium hydroxide and extracted with diethyl ether to give 98% yield of rizatriptan free base, mp 120-121^{o}C (lit 120-121°C).

Metal cylinder vaporization apparatus. The metal cylinder vaporization apparatus (Fig. 1B) consists of a hollow stainless steel cylinder with electrical connections at both ends to capacitors, enabling the cylinder to be resistively heated when the capacitors are discharged through the cylinder. To heat selectively the walls of the cylinder (dimensions: diameter 12 mm, length 35 mm, wall thickness 0.12 mm), it was necessary for the walls to be the most electrically resistive portion of the electrical circuit. This was achieved by making the walls of relatively thin (high resistance) stainless steel and linking them to low resistance electrical connections consisting of (i) a split-ring clamp

placed directly around one end of the cylinder (right side of cylinder in diagram) and (ii) a split-ring clamp placed (at far left side of diagram) around a thick (3 mm diameter) copper rod (black in diagram) run through the center of the hollow cylinder and screwing into solid stainless steel at the cylinder's other end (far right side of diagram). This particular layout of electrical connections has the benefit of enabling all physical connections between the heating element and the capacitors (two 1 Farad capacitors in parallel) to be made geometrically at one end of the heating element (via a low impedance 12 volt relay), allowing airflow to carry the generated aerosol away from all of the electronics. For drug vaporization, the metal cylinder heating element is placed in a cylindrical glass airway (inside diameter 15 mm) through which air flows at a controlled rate (15 L/minute unless otherwise indicated), charging the capacitors to 20.5 V, and then closing the relay causing resistive heating of the stainless steel element to a temperature of ~ 350^{o}C in ~ 50 ms (measured with the infrared camera as described below).

Stainless steel foil vaporization apparatus. The stainless steel foil vaporization apparatus consists of a 0.005" thick stainless steel foil (302/304, Thin Metal Sales) connected to a 1 Farad capacitor, enabling the foil to be resistively heated when the capacitor is discharged. To perform a vaporization experiment, the foil is initially cleaned and then dip-coated in a drug solution (see below). One coated end of the foil is wiped clean of drug to ensure good electrical contact and then the foil is clamped between two electrodes, spaced 1" apart. The electrodes are held in a Delrin® block, which defines the airway (cross sectional area 3.2 cm^2). For drug vaporization, the capacitor is charged to

13.0 Volts and then discharged through the foil by closing a low impedance 12 V relay, which results in a temperature of 350°C in ~ 200 milliseconds (measured with the infrared camera as described below).

Drug coating. The above metal cylinder or stainless steel foil heating element was dip-coated (generally 5 cm/s withdrawal rate for the stainless steel foils and 15 cm/s withdrawal rate for the metal cylinder) using a computerized dip-coating machine with the coating solution containing the drug (free base form, ~ 100 mg/mL) in a suitable solvent or solvent combination: atropine and fentanyl, ethanol; midazolam and zolpidem, dichlormethane; rizatriptan, dichloromethane/methanol 33%/67%; sildenafil, chloroform/methanol 75%/25%. The dip-coating machine was built using a linear slide driven by turning of a screw by stepper motor. The motor and thus slide is controlled by a computer using the LabVIEW software package (National Instruments Corporation). The slide has a clamping mechanism that clasps objects to be coated, so that the object can be lowered and subsequently withdrawn from a solution of the compound at a controlled rate.

Following dip-coating, the heating elements were allowed to dry to remove solvent for at least 30 minutes inside a fume hood prior to vaporization experiments, followed generally by additional drying under vacuum. Thirty minutes was deemed to be an adequate drying time for the thin drug films based on weighing of elements, which revealed that all detectable loss of weight after coating due to solvent evaporation occurred in the first 5 minutes of drying. In addition, residual solvent analyses by

headspace gas chromatography were conducted on selected test films and revealed less than 0.01% solvent content in the films following 30 minutes of drying. Average coating thickness was calculated based on the quantity of drug deposited per unit surface area (SA), assuming a drug density of 1 g/cm^3 using the following equation:

$$\text{Coating Thickness} = \text{Mass Coated} / [\text{Density} \times \text{SA Coated}] \qquad \text{(Eqn. 1)}$$

Quantity of drug deposited was determined either by the difference in the weight of the drug dose form before coating from that after coating, or by coating a batch of dose forms and extracting selected dose forms with organic solvent followed by quantifying the amount of extracted drug by HPLC as described below. Comparison of coated drug amounts measured by gravimetric versus HPLC analysis technique revealed no significant differences, further confirming that the films contain essentially pure, solvent-free drug.

High speed photography of vaporization process. High speed digital video images of the vaporization process (1000 frames per second) were captured using a Phantom IV high speed digital video camera with a 105 mm focal length Nikon 35 mm camera lens with a Nikon c-mount adaptor. Images (512 x 512 pixels) were captured using software designed for the camera by Vision Research, Wayne, New Jersey. Lighting was provided by a Techniquip 250W fiber optic illuminator.

Infrared temperature measurement. A Thermacam SC 3000 infrared camera (FLIR Systems) was used to measure and record false color temperature images of the metal cylinder vaporization apparatus. The camera uses quantum well infrared photodetector technology for high sensitivity and accuracy and captures images at 180 Hz. Temperature is calculated based on the amount of emitted infrared light. The camera was calibrated by heating the metal cylinders (resistive heating with a constant current DC power supply) to various steady state temperatures between 200°C and 400°C and measuring the actual temperature with calibrated thermocouples (Omega). The emissivity factor of the heating substrate was found to be 0.19.

HPLC analysis of the purity and emitted dose of thermally generated aerosols. Aerosols were collected by passing the air stream containing the aerosol through a Teflon filter (Zefluor, 47 mm diameter, 2 µm pore size, Pall Corporation, Ann Arbor, MI) mounted in a Teflon holder (Savillex Corp., Minnetonka, MN). The filter was extracted with acetonitrile (HPLC grade, Fisher, Pittsburgh, PA.). In certain cases, in order to confirm that reliability of filter collection, experiments were also conducted with multiple filters and -70°C cold solvent traps in series. Extraction of these filters and traps revealed no detectable drug or decomposition products passing through the first Teflon filter. Extraction of the Teflon filter with additional solvents, including dichloromethane and water, revealed no additional decomposition products not extracted with acetonitrile.

The filter extracts were analyzed by high performance liquid chromatography (HPLC) using a C-18 reverse phase column (4.6 mm ID x 150 mm length, 5 µm packing,

"Capcell Pak UG120," Shiseido Fine Chemicals, Tokyo, Japan) eluted with acetonitrile/water (both containing 0.1% trifluoroacetic acid), 5%/95% to 98%/2% gradient with a flow rate of 1 mL/min and detection from 200 nm – 400 nm using a photodiode array detector. Purity was calculated by measuring peak areas from the chromatogram obtained at 225 nm. Confirmatory purity evaluations were additionally performed by inspection of the full 200 nm – 400 nm wavelength range. This qualitative analysis did not reveal major impurities other than those resolved at 225 nm. In addition, a portion of the filter extracts were analyzed by gas chromatography with mass spectrometric detection (GC/MS) and/or HPLC with mass spectrometric detection. Analyses by these alternate methods yielded similar purity results to the primary HPLC analysis.

The concentration of drug collected in the filter extract was determined by HPLC by comparing the area under the drug peak after injection of the filter extract to the area under the drug peak after injection of a standard containing a known concentration of drug. The concentration of drug in the extract was multiplied by the extract volume to determine the quantity of drug extracted from the filter, which is termed the absolute emitted dose. The percent emitted dose is determined by dividing the absolute emitted dose by the quantity of drug coated.

In certain experiments, the heating apparatus was also extracted to capture any drug not vaporized off of the heating substrate or re-deposited elsewhere in the apparatus, and the amount of unmodified drug in the extract determined by HPLC. Absolute total drug

recovery is the sum of the absolute emitted dose and the mass of drug remaining in the apparatus after vaporization, and percent total drug recovery is the absolute drug recovery divided by the quantity of drug coated. The difference between 100% and percent total drug recovery provides an upper bound on percent drug decomposed during the heating process. In addition to encompassing drug decomposition, incomplete total drug recovery may also encompass incomplete collection of the vaporized drug by the filters, incomplete filter extraction, or incomplete extraction of the heating apparatus.

Particle size control and measurement. To determine the effect of air flow rate on aerosol particle size, 3 mg of rizatriptan was coated at ~ 3 μm thickness on the outside surface of the metal cylinder heating element which was then heated as described above to vaporize the rizatriptan which then rapidly condensed into an aerosol. The particle size distribution of the aerosol was measured using an Andersen 8-stage cascade impactor (www.thermoandersen.com) per the manufacturer's instructions. Additional airflow (make up air) was added downstream of aerosol formation and before entry into the cascade impactor to insure the correct flow into the impactor. Flow rates were varied by using flow restrictors (needle valves) placed after the impactor and at the entrance of the make up air. The quantity of rizatriptan aerosol deposited on each stage of the impactor was determined by extracting each metal stage with acetonitrile spiked with internal standard and determining the amount of rizatriptan relative to internal standard in the extract by HPLC. Analogous methods involving Andersen 8-stage cascade impaction were used to determine the particle size of the aerosols of the drugs shown in Table 1, except that external rather than internal standards were used in the HPLC analysis.

Administration of thermally generated aerosols to dogs. Beagle dogs weighing 7 – 10 kg were intubated, anesthetized with isoflurane, and mechanically ventilated. For aerosol dosing, the dogs were manually forced to exhale to residual volume by lightly squeezing their thorax, after which ~ 0.5 L of air containing aerosol was administrated by positive pressure inhalation over ~ 3 s at a flow rate of 10 L/min. After a breath hold of 5 s, the dogs were allowed to exhale with any exhaled aerosol directed into a filter for measurement (exhaled fraction < 20% in all experiments). Aerosol generation was achieved by vaporizing drug that had previously been dip-coated onto a stainless steel wire (0.6 mm diameter, 25 cm length; coating thickness ~ 2 µm for the 1.2 mg dose level and ~ 6 µm for the 3.9 mg dose level). The wire was heated by applying 27 volts AC to the wire for 0.2 s starting 0.2 s into the 3 s positive pressure inhalation. Geometrically, the 25 cm-long wire was arranged in a helical coil of 15.5 turns with an outside diameter of 4.5 mm and a length of 3 cm and placed in a cylindrical glass airway 15 mm in diameter and 5 cm long. Percent emitted was > 90% in all experiments. The aerosol particle size distribution as measured by mass median aerodynamic diameter (MMAD) ± geometric standard deviation was 1.7 µm ± 3.1 and 2.1 µm ± 1.9 at the 1.2 mg and 3.9 mg dose levels, respectively. Aerosol doses are for the canine experiments are expressed as absolute emitted doses.

Measurement of rizatriptan plasma concentration. Rizatriptan concentrations in the range of 2 ng/mL to 2000 ng/mL were determined in heparinized beagle dog plasma samples by HPLC with MS/MS detection by PHARMout Laboratories, Inc., Sunnyvale, CA using a

protocol validated in their laboratory. Briefly, blood was drawn from a femoral vein into heparinized tubes, stored at room temperature for ⩽ 2 hours, centrifuged to obtain plasma, and the plasma stored in 0.2 mL aliquots at -70°C until analysis. After thawing, each 0.20 mL plasma sample aliquot was prepared by addition of 100 µL methanolic internal standard solution, followed by addition of 500 µL acetonitrile/methanol (80/20, v/v). The sample was then mixed and centrifuged. An aliquot of the supernatant was injected into an LC/MS/MS instrument (Micromass Inc., Beverly, MA). Concentrations of the detected rizatriptan were calculated by comparison to a standard curve using the associated automated data acquisition system (MassLynx, Micromass Inc., Beverly, MA).

Measurement of vascular response to rizatriptan. Changes in cerebral vascular resistance in response to rizatriptan were calculated by dividing mean arterial pressure by mean carotid arterial flow. Arterial pressure was measured from a cannulated femoral artery. A Millar® 5 French catheter (www.millarinstruments.com) was introduced through the arterial sheath into the artery a distance of about 5 cm. This catheter was then attached to a Millar® MPC-500 Mikro-Tip catheter pressure transducer to allow for the continuous recording of the direct arterial blood pressure on the BioPac® MP100 electronic recording system (www.biopac.com). The blood flow in the common carotid artery was measured by a flow probe (Transonics volume flowmeter #T208, 2.5 – 3.0 mm, Transonic System, Inc., Ithaca, NY) surgically placed around the artery between 45 and 90 minutes prior to exposure of the dog to rizatriptan and connected to the BioPac system in order to continuously monitor and record blood flow through the artery.

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Results

To investigate the potential to vaporize a drug without causing thermal decomposition, we examined the case of a film of drug deposited on a heated surface, with the film thin enough (e.g. < 50 μm) for the temperature throughout the drug's thickness to be approximately uniform. With ambient air flowing over the drug film, vaporization of the drug—escape from the hot liquid or solid state into the gas phase where cooling occurs in microseconds—kinetically competes with drug degradation. Thus, vaporizing a drug without substantial degradation might potentially be achieved by sufficiently increasing the vaporization rate. The vaporization rate of any bulk substance (liquid or solid) is in theory directly proportional to the substance's vapor pressure multiplied by the surface area of the air-substance interface (Atkins, 1990). Hence, a rapid vaporization rate might potentially be achieved at relatively low temperatures by providing a high surface area for vaporization. Therefore, we hypothesized that a high vaporization surface area could enable complete vaporization of selected drugs in a brief enough time to minimize drug degradation.

To test this hypothesis, we built a simple, magic marker-sized experimental apparatus consisting of a thin-walled stainless steel cylinder inside of a cylindrical airway through which ambient air can be readily drawn at a controlled rate (Fig. 1A). Discharge of a capacitor through the metal cylinder (Fig. 1B) heats the steel over ~ 50 ms to ~ 350°C (Fig. 1C). Drug coated onto the metal vaporizes when the steel is heated, yielding

gas-phase drug molecules that condense into aerosol particles over a period of < 1 s (Fig. 1C). When vaporized in this manner, a number of high clinical utility drugs, including some drugs which normally degrade upon heating (lower red traces, Fig. 2), yield high (e.g. > 95%) purity aerosols (middle blue traces, Fig. 2; Table 1).

Particle size in thermally generated aerosols is controlled by the physics of the condensation and coagulation process that generates the aerosols from the drug vapor. This process consists of repeated collisions of particles to form larger ones, with the number of particles per unit volume (N) decreasing over time according to the equation:

$$dN/dt = - k_0 N^2 \qquad \text{(Eqn. 2)}$$

where k_0 is the coagulation coefficient (Hinds, 1999). Given the magnitude of k_0, a saturated vapor will condense and coagulate into approximately 10^{10} particles per cm^3 within 0.1 s and 10^9 particles per cm^3 within 1 s. Particle size in the resulting aerosol is determined by the amount of drug contained in this relatively fixed number of particles. To a rough approximation, particle size is therefore described by the following equation[2]:

$$D = [(6Q)/(N\pi\varphi)]^{1/3} \qquad \text{(Eqn. 3)}$$

where D is the diameter of the typical aerosol particle, Q is the mass of vaporized drug per unit volume of aerosol (vapor concentration), and φ is the aerosol particle density. The parameter in Eqn. 3 most readily manipulated to change aerosol particle size is Q,

the vapor concentration. For a fixed drug dose, we hypothesized that a desired particle size could be most readily achieved by altering the amount of air into which that drug is mixed, by altering the air flow rate over the vaporizing drug. Figure 3 shows that increasing airflow through the test device, by diluting the drug vapor, decreases the size of the typical aerosol particle formed. Table 1 shows that 1 – 3 μm particle diameter aerosols can be formed for a variety of clinically important medications.

The clinical utility of thermal aerosol generation depends on the reliability of the aerosol dose delivered, as well as the speed and reliability of absorption of the drug from the lungs. Emitted dose reliability could in theory be achieved by dip-coating a metal surface with a fixed amount of drug as a thin film, and then applying adequate energy to the metal to vaporize almost all coated drug. To determine the reliability of dip-coating, 19 identical dose forms were dip-coated and the mass of coated drug (rizatriptan) determined by gravimetric analysis of the dose forms before and after coating. The mean coated amount was 1.3 mg, with a standard deviation of 0.08 mg (6%). To determine the emitted dose efficiency, dip-coated dose forms (flat stainless steel foils) were electrically resistively heated. This dose form geometry minimizes re-condensation of vaporized drug, resulting in an emitted dose for five tested drugs greater than 80%, exceeding 90% for four of the drugs (Table 1). Dose emitted from the flat foil geometry is also highly reproducible, with a relative standard deviation in emitted dose across N = 3 experiments less than 5% for each of the five drugs shown in Table 1.

To examine the speed and reliability of absorption of thermally generated aerosol of the migraine medication rizatriptan, we connected a thermal aerosol generation device to the pulmonary tract of an anesthetized and intubated dog. Pharmacokinetic data for delivery of rizatriptan thermal aerosol are provided in Fig. 4A. Rizatriptan is rapidly and almost completely absorbed with excellent reproducibility across multiple dogs and approximate dose proportionality across the two tested dose levels.

Rizatriptan is a serotonin 1B/D receptor agonist that treats migraine headache by constricting intracranial blood vessels that are thought to be pathologically dilated during migraine (Friberg et al., 1991). To determine the onset of pharmacological activity of inhaled rizatriptan, we measured cerebral vascular resistance in dogs receiving rizatriptan by the thermal aerosol versus the subcutaneous route (Feniuk et al., 1989). As shown in Fig. 4B, inhalation of rizatriptan thermal aerosol results in an almost immediate increase in cerebral vascular resistance.

Discussion

Smoking is the oldest and most common method of inhalation drug delivery. It provides rapid onset of drug action, and the resulting ability of the drug user to carefully titrate their drug intake to the minimum effective dose (Goldfarb et al., 1976). However, smoking is unsuitable for delivery of pharmaceutical products because it results in drug degradation, delivers drug contaminated with combustion products, and fails to deliver a reliable amount of drug.

Thermal aerosol generation provides the fast onset of action, easy titration, and convenience of smoking while ensuring consistent delivery of pure drug substance without degradation products or other unwanted additives. The delivery of pure drug substance is enabled by heating a thin layer of the pure drug on coated onto a substrate, and vaporizing, cooling, and recondensing the drug sufficiently rapidly so as to avoid thermal decomposition.

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Reproducible delivery of a drug substance through the thermal aerosol route requires that a reproducible amount of drug is coated on the heating surface, that a high fraction of the coating is reliably vaporized, and that the resulting aerosol particles are of appropriate size to reach and deposit on the alveolar surfaces of the deep lung. Reproducible coating of drug was achieved here through dip-coating, with virtually all the coated drug emitted by heating the substrate with more than adequate energy to

vaporize the entire coating. Furthermore, aerosol particles in the size range of 1 µm to 3 µm were reliably produced, using a range of airflow rates. Particles between 1 µm and 3 µm in diameter are preferred for deep lung delivery, because such particles are small enough to traverse the mouth, larynx, and branching airways without inertial impaction while being large enough to settle onto alveolar surfaces due to gravity (Gonda, 1997).

The current study revealed a number of surprising findings. Most unexpected was the ability to vaporize several important therapeutic drugs, including one with molecular weight over 400 g/mol (sildenafil, Table 1), without thermal decomposition. Also unexpected was the ability to generate aerosols of 1 µm to 3 µm particle diameter with this process. It is well known that cigarette smoke contains primarily particles of mass median aerodynamic diameter near 0.6 µm (Porstendorfer and Schraub, 1972), outside of the desirable 1 µm to 3 µm size range. Previously, Hong *et al*. (2002) studied the relationship between condensation aerosol particle size and mixing of vapor into air, using a drug surrogate dissolved into solvent as the model system. They found a trend, consistent with the one shown in Fig. 3, in which increasing volumes of mixing air resulted in smaller aerosol particle size. Overall particle sizes, however, were smaller than in our study and the effect of different airflow rates on particle size was not determined.

The ability to vaporize a large number of medically important drug substances without thermal degradation and to condense these drug vapors into pure drug particles of optimal size for systemic delivery through inhalation opens the possibility of treating a

variety of acute and episodic conditions, including breakthrough pain (fentanyl, Fig. 2A), migraine headache (rizatriptan, Table 1 and Fig. 4), nerve gas poisoning (atropine, Table 1), erectile dysfunction (sildenafil, Table 1 and Fig. 2B), insomnia (zolpidem, Table 1) and seizures (phenytoin, Fig. 1, and midazolam, Table 1). Such treatments will be particularly clinically valuable in cases, such as pain, where patients have acute sensory awareness of their need for medication and can therefore control the timing and amount of their drug intake safely and reliably (Graves et al., 1983).

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Footnotes

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[1]The term vapor refers to the gaseous state of a substance that exists primarily as a solid or liquid at room temperature and pressure. Thus, for drugs other than inhalational anesthetics, gas and vapor have identical meaning and are used interchangeably.

[2]Eqn. 3 assumes a monodisperse aerosol, i.e. all particles having equivalent size. In a real (polydisperse) aerosol, the calculated mass median particle diameter is larger by a factor of $\exp(3/2(\ln \sigma)^2)$ where σ, the geometric standard deviation of the aerosol diameter, is a unit-less parameter reflecting the spread of particle sizes in the aerosol. Given a typical value for σ of 2, the resulting mass median particle diameter is approximately twice as large for a real aerosol as for a monodisperse aerosol.

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Legends for figures

Fig. 1. Heating of thin films of drug to form drug aerosol. (A) The core vaporization apparatus consisting of a heating substrate (metal cylinder) coated with drug in a cylindrical airway. (B) The metal cylinder heating element. Capacitive discharge through the circuit (black) results in heating of the highest resistance portion, the thin walls of the hollow cylinder, shown here covered with drug (red). An electrically insulating plastic piece (green) at one end of the hollow cylinder provides mechanical support. (C) Time-lapse photographs of the vaporization process (normal photographs; series of panels on left) versus the substrate heating process (infrared photographs shown in false color to reflect temperature; series of panels on the right). Shown on the left is the metal cylinder coated with the anti-epileptic drug phenytoin prior to heating and 50 ms, 100 ms, 200 ms, and 500 ms into the heating process, and on the right the temperature of the cylinder in color code. Near maximum temperature is achieved within 50 ms, and most aerosol generation occurs over the first 200 ms, with no drug left on the cylinder walls after 500 ms.

Fig. 2. Vaporization of thin drug films in contrast to drug powder yields pure drug aerosol. (A) HPLC determination of purity of aerosol of the opioid analgesic fentanyl. The fentanyl starting material (trace 3, black) is > 99% pure, while aerosol generated by vaporization of an ~ 1 μm film of fentanyl using the approach shown in Fig. 1 (trace 2, blue) is ~ 99% pure, and aerosol generated by heating fentanyl powder on a 300°C hot plate (trace 1, red) is ~ 70% pure. (B) HPLC determination of purity of aerosol of the erectile dysfunction drug sildenafil. The sildenafil starting material (trace 3, black) is >

99% pure, while aerosol generated by vaporization of an ~ 1 μm film of sildenafil using the metal foil vaporization apparatus (trace 2, blue) is > 99% pure, and aerosol generated by heating sildenafil powder on a 350°C hot plate (trace 1, red) is ~ 75% pure.

Fig. 3. Particle size in rizatriptan thermally generated aerosols. Particle size is determined by the concentration of drug per volume of air as the vaporized drug condenses into particles. Increasing airflow over the vaporizing compound dilutes the vaporized drug into a greater volume of air, decreasing aerosol particle size. Geometric standard deviation of the approximately log-normal particle size distribution (a unit-less parameter describing the breadth of the distribution) was between 1.7 and 2.2 for each of the experiments.

Fig. 4. Absorption kinetics and pharmacological response to the anti-migraine drug rizatriptan inhaled as a thermally generated aerosol. (A) Absorption pharmacokinetics of the aerosol versus subcutaneous injection. Shown are mean ± SD of measured drug concentrations (N = 4 for each inhalation dose and N = 2 for subcutaneous injection; SD for subcutaneous injection is not shown for simplicity but is larger than for inhalation). (B) Pharmacological response to rizatriptan delivered by inhalation (N = 4), subcutaneous injection (N=2), or orally (N=3). The pharmacological action measured is the constriction of cerebral blood vessels that are pathologically dilated during migraine.

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Table 1. Emitted dose, purity, and particle size distribution of thermally generated aerosols. Each drug was dip-coated onto multiple stainless steel foil heating substrates. Selected substrates were extracted to allow HPLC determination of the amount of coated drug, and thus the average coating thickness. The other coated substrates were vaporized by heating the foil to ~ 350°C, and the resulting aerosol was either collected in a filter and analyzed for quantity and purity by HPLC, or collected in a cascade impactor for analysis of aerosol particle size. Values in the table reflect the mean ± standard deviation from N = 3 experiments.

Drug	MW	Melting Point (°C)	Coating Thickness (μm)	Emitted Dose[a] (%)	Total Drug Recovery[b] (%)	Aerosol Purity (%)	MMAD[c] (μm)	GSD[d]
Midazolam	326	160	2.2	99.6 ± 0.7	99.6 ± 0.7	99.9 ± 0.1	2.5 ± 0.1	1.8 ± 0.03
Zolpidem	307	196	2.4	92 ± 5	94 ± 5	99.4 ± 0.1	1.9 ± 0.1	2.0 ± 0.2
Rizatriptan	269	121	2.1	98 ± 2	99 ± 2	98 ± 0.1	1.8 ± 0.1	2.7 ± 0.1
Atropine	289	116	2.9	98 ± 4	98 ± 4	97 ± 0.2	2.6 ± 0.1	1.7 ± 0.03
Sildenafil	475	189	0.53	84 ± 3	96 ± 4	97 ± 0.3	1.1 ± 0.1	1.9 ± 0.2

[a]Emitted dose is the percentage of coated drug that is released from the heating apparatus as aerosol
[b]Total drug recovery is the sum of the percentage of coated drug emitted and the percentage found unmodified in the heating apparatus
[c]MMAD is the aerosol mass median aerodynamic diameter
[d]GSD is the geometric standard deviation (measure of breadth) of the aerosol particle size distribution; GSD is a unit-less parameter $\geqslant 1$

Figure 1

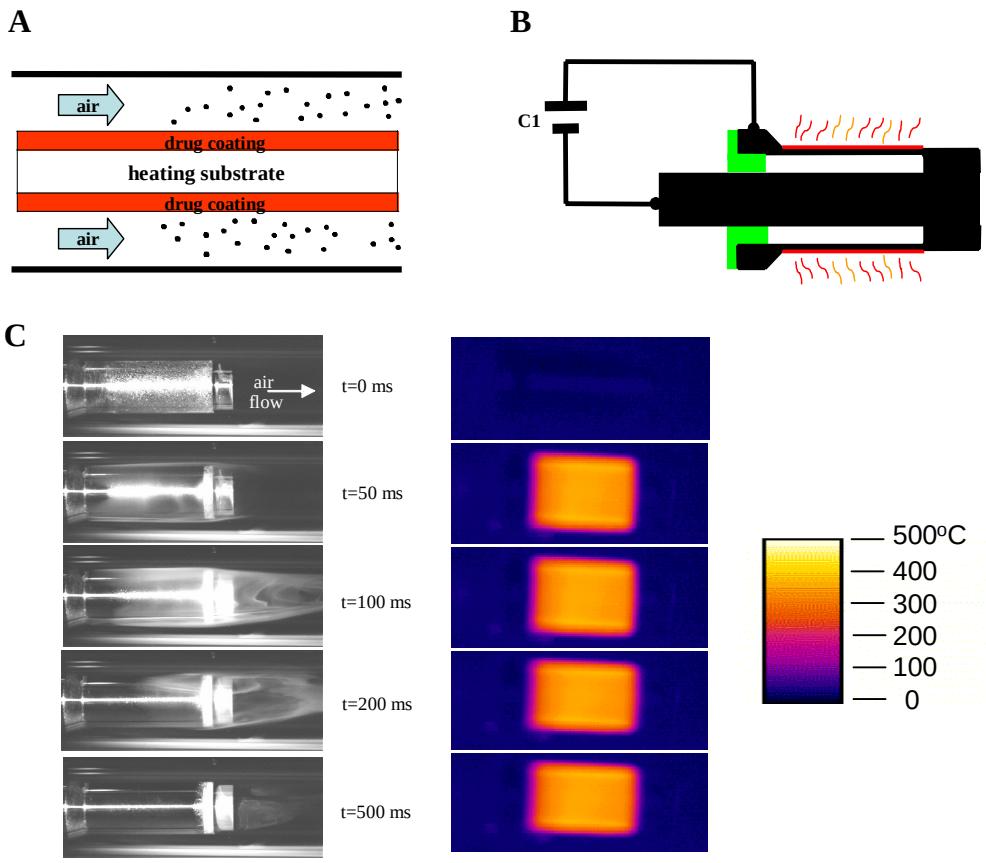

Figure 2

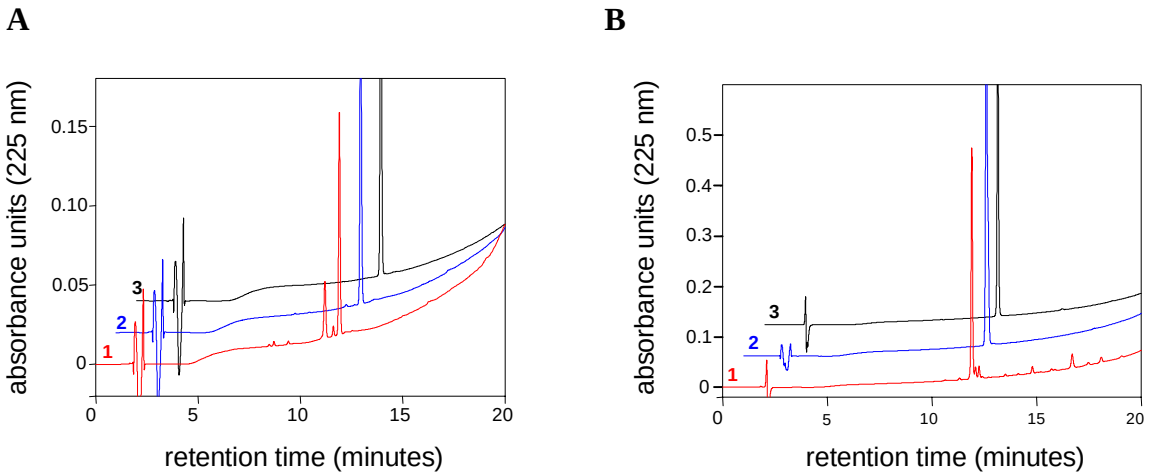

Figure 3

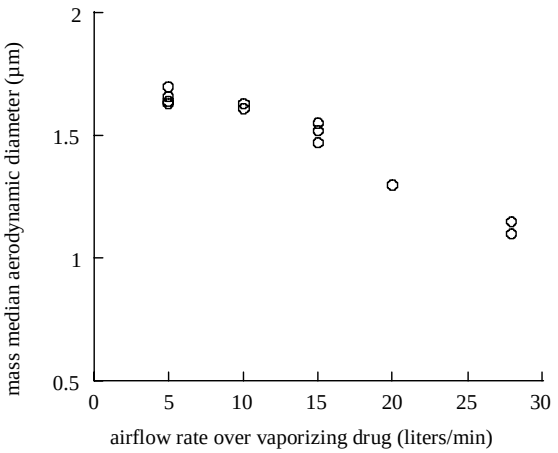

Figure 4