Analysis of a Diffusion Dryer for the Respiratory Delivery of Poorly Water Soluble Drugs

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Purpose. The purpose of this study was to analyze a diffusion dryer as a means to remove organic solvents from aerosol particles of poorly water soluble drugs.

Methods. Aerosols of methanol, ethanol, and ethyl acetate were generated with an ultrasonic nebulizer, and inflow to outflow concentration ratio of vapor in a annular charcoal column was determined as a function of time by gas chromotography at two to four different airflow rates. In addition, the particle transmission efficiency was determined with an ethanol solution of the test compound, budesonide. The results were analyzed with equations originally developed for assessing the loss of drug from intravenous tubing along with independent measures of the adsorption isotherm of the vapors onto charcoal.

Results. Aerosol production was relatively constant with time, and the transmission of solid particles through the column occurred with efficiency nearing 100%. The inlet to outlet vapor concentration ratio was adequately described by a model of three resistances in series composed of the inner tube, the screen mesh, and the charcoal bed.

Conclusions. The diffusion dryer was found to be satisfactory for the removal of methanol, ethanol, and ethyl acetate and the efficiency may be assessed from the adsorption isotherms on charcoal and the geometry of the dryer.

KEY WORDS: respiratory drug delivery; aerosol; diffusion dryer; ultrasonic nebulizer; steroids.

INTRODUCTION

Our interest in respiratory drug delivery arises from the desire to find a suitable chemopreventive agent for lung cancer (1). Chemoprevention is the administration of a chemical agent to prevent the occurrence of cancer (1). While a relatively large number of compounds, such as vitamins, steroids, retinoids, and nonsteroidal antiinflammatory agents, have been identified as being effective in reducing the incidence of cancer, they all suffer from an unacceptable therapeutic index (TI) (2). This is not surprising since the TI of a chemopreventive agent must approach infinity. That is, side effects are minimally tolerated. As such, the search for a suitable chemopreventive agent can be viewed as a challenge to the development of a site-specific drug delivery system. In this case, methods are sought that will selectively deliver the drug to the site of action without distribution to sites that would lead to the undesirable side effects.

While site specific drug delivery is generally a daunting task, chemoprevention of lung cancer provides a number of inherent advantages. Most importantly, respiratory drug delivery has been developed to the extent that there is a remarkably good understanding of the factors that control drug deposition to the respiratory tract (3). Nevertheless, finding a suitable chemopreventive agent requires the screening of a number of compounds for evaluating the therapeutic index. Many methods are available for drug delivery to humans; however, these must be adapted and modified for use in laboratory animals. In particular, the ventilation of conscious animals can not be controlled as it can with humans. Thus, the site of deposition depends almost exclusively on the aerodynamic properties of the aerosol. While water-soluble compounds may be tested by nebulization from aqueous solutions, poorly water soluble compounds pose a special challenge because of their unique formulation requirements. Given this difficulty, the rapid screening of a large number of compounds poses a significant challenge.

Therefore, a new approach to respiratory drug delivery to laboratory animals was developed where drug is aerosolized from an organic solution by means of an ultrasonic nebulizer. The aerosol stream is then passed through a drying column containing an annular ring of charcoal. The solvent vapor is removed from the aerosol stream by adsorption onto the charcoal bed, leaving behind dry and inhalable particles. In this report, the performance and analysis of the aerosol generating system from experiments with methanol, ethanol, and ethyl acetate using the test compound, budesonide, are provided.

THEORY

The success of the method of proposed delivery of poorly water soluble compounds hinges primarily on the removal of the solvent from the aerosol cloud that initially consists of liquid droplets. The efficiency of the removal of the solvent by a cylindrical column containing an annular layer of adsorbent may be defined as:

$$E = 1 - C_s/C_o \qquad (1)$$

where C_s is the average outlet concentration and C_o is the inlet concentration of solvent.

For this transport problem, the aerosol cloud was assumed initially to be uniform in the radial direction, and convection was assumed to occur strictly in the axial direction. Solvent was assumed to be removed by instantaneous evaporation from the aerosol particles and radial diffusion of the vapor from the air/water interface of the particle to the surface of the screen. Diffusive transport then occurred through the screen, that separated the adsorbent charcoal from the inner open column containing the aerosol cloud, followed by diffusion to the solid/vapor interface of the charcoal particles, and finally, solvent adsorbed onto the charcoal particles.

The factors determining the efficiency and its time dependence are related to the total observed resistance, R'_{obs}, which in turn is related to a series of resistances:

$$R'_{obs} = R'_{GK} + R'_{sc} + R'_b \qquad (2)$$

where R'_{GK} is the resistance of the inner tube, R'_{sc} is the resistance of the screen, and R'_b is the resistance of the charcoal bed.

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Each resistance was treated separately and assumed to be additive to yield the observed total resistance. In addition, corresponding dimensionless resistances, R, were defined as

$$R = R'D/r \qquad (2')$$

where D is the diffusion coefficient of the vapor, and r is the radius of the inner tube.

The resistance for diffusion to the screen or equivalently the inner tube resistance has been solved with the assumption of instantaneous adsorption at the surface of the tube. The resulting resistance of the inner tube, R_{GK}, may be obtained from the Gormley-Kennedy equation (4):

$$R_{GK} = -4Gz/(-7.314Gz)^{0.819} \qquad (3)$$

where Gz is the Graezt number given by

$$Gz = \pi DL/2Q \qquad (3')$$

where D is the vapor diffusivity, L is the length of the column, and Q is the flow rate of air through the column. The time independent inner tube resistance is thus determined by the diffusivity of the vapor, the column length and air flow rate.

The resistance of the screen to the transport of vapor may be estimated based on the exposed surface area, thickness, and diffusion coefficient of the vapor. That is,

$$R_{sc} = H/rA_f \qquad (4)$$

where A_f is the fractional area available for transport of the vapor, and H is the screen thickness which lies between the thickness of one and two diameters of the screen wire. This approach for the resistance of the screen was necessarily an approximation because of the theoretical difficulty in adequately accounting for the complicated geometry of the screen.

The resistances from the inner tube and screen were assumed to represent time independent parameters whereas the resistance of the charcoal bed was assumed to be time dependent. Therefore, the observed resistance at zero time was equated to the sum of the resistances of the inner tube and the screen. Mathematically, the total observed resistance, R_{obs}, is given by

$$R_{obs} = R_{GK} + R_{sc} + R_b = -4Gz/[\ln(C_s/C_o)_{expt}] \qquad (5)$$

where R_{GK} is the resistance of the inner tube, R_{sc} is the resistance of the screen, R_b is the resistance of the charcoal bed, and $(C_s/C_o)_{expt}$ is the experimentally observed ratio of the concentrations. By calculating the inner tube resistance from the Gormley-Kennedy equation, the resistance of the screen may also be obtained from the difference between the total resistance at zero time, R_{obs},(t = 0), and the G-K resistance, that is:

$$R_{sc} = R_{obs}, (t = 0) - R_{GK} \qquad (6)$$

This can then be compared with the values calculated using equation (4).

For the simultaneous diffusion and adsorption of the vapor in the charcoal bed, the time dependent resistance of the charcoal bed was analyzed with equations originally derived by Roberts (5). The gas phase is assumed to be well mixed within the inner tube and diffusion is assumed to occur along the z-axis perpendicular to the direction of flow along the x-axis. Diffusion occurs within the semi-infinite charcoal bed of slab geometry, and the change in the total concentration of solute in the charcoal bed, C, with respect to time satisfies Fick's second law:

$$\partial C/\partial t = D_{eff}\, \partial^2 C/\partial z^2 \qquad (7)$$

where D_{eff} is the effective diffusion coefficient of the vapor in the porous charcoal bed.

For consideration of the simultaneous diffusion with adsorption, it was assumed there is equilibrium across the screen yielding one boundary condition:

$$K = C/C_s \qquad (8)$$

where K is the charcoal/inner tube equilibrium constant, C_s is the uniform concentration within the inner tube, and C is the total concentration of the vapor in the charcoal bed. The other boundary condition is

$$D_{eff}\partial C/\partial z = V/A[\partial C_s/\partial t + v\partial C_s/\partial x] \qquad (9)$$

where V is the volume of the inner tube, A is the cross sectional area of the interface between the inner tube and the charcoal bed, and v is the linear velocity of the vapor in the inner tube.

The solution obtained with Laplace transforms provided by Roberts (5) is

$$F_s' = C_s'/C_o = (1/s)\exp\{-(sx/v) - (KAD_{eff}qx)/(vV)\} \qquad (10)$$

where F_s' and C_s' are Laplace transforms of the outflow concentration fraction and outflow concentration of solute, respectively, C_o is the inflow concentration, s is the Laplace operator and q = v(s/D). The solution for an initially empty tube is (5):

$$C_s/C_o = \text{erfc}\{(KA\sqrt{D_{eff}})/[2Q(t - V/Q)^{1/2}]\} \qquad (11)$$

where erfc is the complementary error function.

The equilibrium constant, K, may be related to the vapor adsorption isotherm as follows. Assuming adsorption of vapor onto charcoal follows a Langmuir's isotherm, the percent weight change of the charcoal, $\%W = 100(W_f - W_i)/W_i$, is related to the percent relative vapor pressure, %RVP = 100(partial pressure/saturation vapor pressure, P_{sat}), as follows

$$\%W = [ad(\%RVP)]/[1 + a(\%RVP)] \qquad (12)$$

where a and d are the affinity and capacity constants, respectively. Using the ideal gas law, the %RVP may be related to the molar concentration of vapor in the gas phase, C_g, as

$$\%RVP = 100C_gRT/P_{sat} \qquad (13)$$

and the difference between the final and initial weight of charcoal, $W_f - W_i$, is equal to the product of the moles of vapor adsorbed, n_v, and the molecular weight of vapor, M. The initial weight of the charcoal is given by the product of the total bed volume, V_b, and the apparent density, ρ_{app}. Making these substitutions into the original equation for Langmuir's isotherm yields

$$100n_vM/\rho_{app}V_b = [100adC_gRT/P_{sat}]$$
$$[1 + a(100C_gRT/P_{sat})] \qquad (14)$$

In the linear region of the isotherm, $1 >> a(100C_gRT/P_{sat})$, and the equation is reduced to

$$100n_vM/\rho_{app}V_b = [100adC_gRT/P_{sat}] \qquad (15)$$

The total concentration of vapor in the bed, C, as defined in the equation for Fick's second law is given by the sum of the moles of vapor adsorbed, n_v, and the moles in the gas phase, n_g, divided by the total bed volume, V_b, as

$$C = (n_v + n_g)/V_b \tag{16}$$

but $n_g/V_b = C_g V_g/V_b = C_g(1 - ø_c)$ where C_g is the concentration of vapor in the gas phase, V_g is the volume of the gas in the charcoal bed, and $(1 - ø_c)$ is the volume fraction of gas phase in the charcoal bed of volume fraction of charcoal, $ø_c$. The concentration of adsorbed vapor, n_g/V_b, is related to the gas phase vapor concentration by the equation derived from Langmuir's isotherm. Therefore,

$$C = [(adRT\rho_{app}/MP_{sat}) + (1 - ø_c)]C_g \tag{17}$$

It is noted that

$$K = C/C_s = (n_g/V_b + C_g)/C_g = [(adRT\rho_{app}/MP_{sat}) + (1 - ø_c)] \tag{18}$$

This may be substituted into the solution to Fick's second law. However, before doing so, it is important to address the effective diffusion coefficient. The effective diffusion coefficient is assumed to follow the two state model as

$$D_{eff} = D_g f_g + D_c f_c \tag{19}$$

where D_g is the ideal diffusion coefficient of the vapor in the gas phase, and f is the fraction of solute in the 'g' gas phase and 'c' adsorbed to the charcoal. Assuming the vapor is immobilized on the charcoal, $D_c = 0$, and the fraction of solute in the vapor phase is given by

$$D_{eff} = D_g[C_g(1 - ø_c)/C] \tag{20}$$

As above, the total vapor concentration may be related to the gas phase concentration as follows

$$D_{eff} = D_g\{C_g(1 - ø_c)/[adRT\rho_{app}C_g/MP_{sat} + C_g(1 - ø_c)]\} \tag{21}$$

Cancelling common terms and noting the form of the equation, it is recognized that

$$D_{eff} = D_s(1 - ø_c)/K \tag{22}$$

The effective diffusion coefficient must also be corrected for the excluded volume effects or more often porosity and tortuosity. Exact theoretical descriptions are lacking for the diffusion through the geometrically complicated charcoal bed (6). However, these correction factors should nearly be the same among low molecular weight vapors, and therefore, the self-consistency can be determined from the fitted data. Returning to the solution to the differential equation, and substituting for the effective diffusion coefficient and distribution coefficient,

$$\begin{aligned} C_s/C_o = \mathrm{erfc}\{(D_g^{1/2}\,(1 - ø)^{1/2}\,A/V)[adRT\rho_{app}/MP_{sat} \\ + (1 - ø_c)]^{1/2}[1/2(t - V/Q)^{1/2}]\} \end{aligned} \tag{23}$$

Therefore, a plot of the inverse complementary error function of C_s/C_o as a function of $1/2Q(t - V/Q)^{1/2}$ should yield a straight line passing through the origin with a slope related to the gas diffusion coefficient, Langmuir's constants, area, volumetric flow rate and the volume fraction and apparent density of charcoal. Each of these may be independently determined, after which the effect of porosity and tortuosity on the diffusion coefficients may be estimated from a comparison of several vapors.

EXPERIMENTAL

Materials

Budesonide was purchased from Sigma Chemical Co. (St. Louis, MO) and used as received. Charcoal (6–14 mesh), ethanol, ethyl acetate, and methanol was purchased from Aldrich Chemical Co. (Milwaukee, WI). The charcoal was activated prior to use by baking at 120 °C in a convection oven overnight. Charcoal was also activated after packing within the column by heating the outside with heating tape while passing an inert gas through the center of the column.

Methods

A Holmes ultrasonic nebulizer (frequency nominally at 2 MHz, Holmes Visible Mist, Holmes Product Corp., Milford, MA) was modified for the production of the initial aerosol particles (Fig. 1). An aluminum flange was constructed and attached to the screw mounts of the piezoelectric crystal to support an aluminum cylinder. The cylinder was 3.25 cm (id) and contained the organic solution of drug. A brass connector (0.5 cm) was attached to the cylinder to allow entrance of air. At the top of the aluminum cylinder, an 125 ml erlenmeyer flask was attached by a side arm (2.5 cm id) which extended from the lower portion of the flask. The upper conical portion of the flask was connected to the column containing charcoal. The outer column was brass (5 cm in diameter) and contained an annular stainless steel wire tube (16 mesh, wire diameter 0.018″) with an internal diameter of 1 cm. The projected area open for transport was 50 % of the total area. The central core was hollow and charcoal was placed within the annular space between the wire and the outer brass column. The ends were closed with rubber stoppers through which glass tubes were passed to connect with the wire tube. The total length of charcoal exposed to the aerosol was 60 cm.

The concentration of the organic solvent in the vapor phase was determined by gas chromatography (GC) as follows. Standards of the organic vapor or samples were collected and injected onto the GC by a 250 μl gas tight syringe (Hamilton). The GC was a 5830A Hewlett Packard with a 1885A terminal. The carrier gas was nitrogen at a flow rate of 10 ml/min, and a flame ionization detector was run with an air/oxygen mix at pressures of 25 and 20 psig. A solid support of 3% carbowax 20M on 80–100 WAW DMCS was packed into a 3′ x 1/8″ id glass column (Supelco). The injector temperature, column temperature, and FID temperature were 225, 100, and 250°C, respectively. Standards were prepared either by injecting the known volumes of the organic solvent into 125 ml flat bottom flasks and sealing the top with a serum sleeve rubber stopper for 24/40 joints or by mixing with water at appropriate compositions to yield the desired vapor pressure over the solution. Standard curves were linear typically with correlation coefficients of >0.999.

The total nebulization output rate was determined by measuring the total solvent concentration prior to entry into the charcoal column, that is the inlet concentration. The efficiency of the column in removing the organic solvents was determined

Table I. Total Volume Output Rate for Methanol, Ethanol, and Ethyl Acetate as a Function of Air Flow Rate

Solvent	Nebulization rate (μl/min) as a function air flow rate (lpm)[a]		Visocity,[b] cP	Density[b](g/ml)	Vapor pressure[b] (ppm)
	0.5 lpm	2.0 lpm			
Methanol	143 ± 23	599 ± 16	0.597	0.7914	96
Ethanol	97 ± 24	303 ± 28	1.200	0.7893	44
Ethyl acetate	184 ± 28	576 ± 16	0.455	0.9003	72.8

[a] Mean ± SD (n = 3).

[b] Determined at 20°C from (11).

by nebulizing the pure solvent and determining the outlet vapor concentrations as a function of time. The inlet vapor concentration was constant after an initial equilibration period of 5 minutes. The cumulative amount adsorbed of solvent adsorbed by the column was also determined from a plot of the outlet vapor concentration as a function of time by the trapezoidal rule with the assumption that the inlet vapor concentration was constant. The total observed resistance of the column, R_{obs}, in removing vapor was calculated from the ratio of the inlet, C_s, and outlet, C_o, vapor concentrations by equation (5).

The drug output rate and change in drug concentration with time were determined by nebulizing 25 ml of a 10 mg/ml budesonide solution. For the change in concentration in the nebulizer, aliquots were periodically drawn, diluted with ethanol and the absorbance measured. The concentration was interpolated from appropriate standard calibration curves. For the drug output rate, aerosols were collected at the outlet of the nebulizer and at the outlet of the charcoal column by means of a 47 mm microfiber glass filter contained within a filter holder unit (Millipore). The filter was extracted twice with 10 ml ethanol, and the dispersion was centrifuged in a table top centrifuge at high speed for 10 minutes. The UV absorbance of the supernatant was measured at 244 nm. The mass was calculated from the measured absorbance, appropriate standard calibration curves and dilution volumes. The particle transmission efficiency is defined as the percent of the inlet mass relative to the outlet mass of budesonide.

The adsorption isotherms of the vapor on the charcoal were measured at VTI Corporation, Hialeah, FL. The system included a completely integrated and automated instrument that combined a microbalance vacuum head with a vapor delivery manifold, a vacuum system, a pressure transducer and a refrigerated constant temperature bath (Model MB-300 G Microbalance System). The temperature was fixed at 25°C, and samples were held under vacuum until a constant weight was obtained prior to the start of the run. Both the adsorption and desorption isotherms were determined.

RESULTS

In Table I, the total output rates in μl/min of solvent nebulized is given as a function of airflow rate. At the higher airflow rate, the total output was also greater. Comparing the output rates among the three solvents indicates that ethanol had a significantly lower output in comparison to methanol and ethyl acetate. It appears that there is a relation between the observed output and viscosity, which are 0.597, 1.200, 0.455 cP for methanol, ethanol, and ethyl acetate, respectively.

Table II. Particle Transmission Efficiency (Mean ± SD, n = 3) for Budesonide in Ethanol at Two Solution Concentrations and Two Air Flow Rates

Drug concentration (mg/ml)	Efficiency at 0.5 lpm (%)	Efficiency at 2.0 lpm (%)
1.0	96 ± 2	94 ± 3
10.0	98 ± 1	98 ± 2

The solute output rate was 0.4 mg/min for the first 10 min and rose steadily to 0.49 mg/min for the time interval between 25 and 30 min. The low solute output rate in comparison to the total output rate is a consequence of solvent evaporation. In addition, the rise in solute output reflects the evaporation of solvent during the nebulization process, which in turn caused an increase in the concentration of the drug in the nebulizer. That is, of the 97 μl/min of total solvent output of ethanol, about 40 μl/min arose from aerosol droplets containing drug and the remaining 57 μl/min consisted of evaporated solvent. From the output rates at the inlet and outlet of the column, the particle transmission efficiency was calculated. The efficiencies were between 94 and 98% (Table II).

In Fig. 2, the percent solvent removal efficiency is given as a function of time at the different airflow rates for ethanol. The removal efficiency at the 0.5 lpm airflow rate was near 100% at early times. With an increase in the airflow rate, there was a decrease in the initial efficiency as well as greater rate of decline with time. The data obtained with methanol was very similar to that obtained with ethanol. For ethyl acetate, the inital efficiency at 0.5 lpm was again similar to that obtained

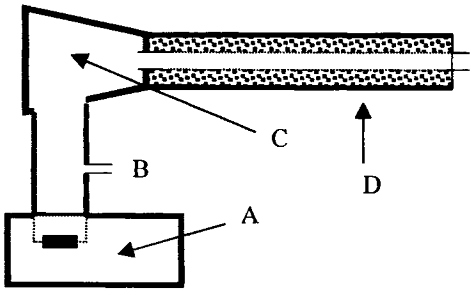

Fig. 1. Schematic diagram of the apparatus (A) ultrasonic nebulizer, (B) air inlet, (C) Erlenmeyer flask with side arm, (D) brass column with annular ring of charcoal.

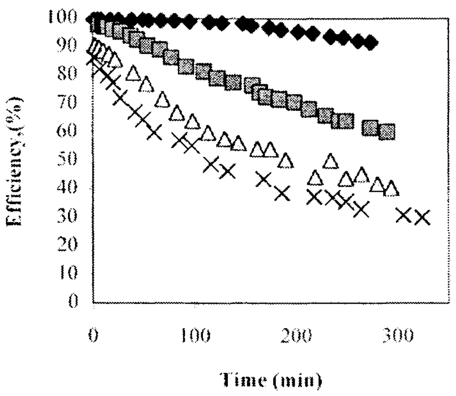

Fig. 2. Ratio of the outlet and inlet concentration of ethanol at air flow rates of (◆) 0.5 lpm (■) 1.0 lpm (▲) 1.5 lpm and (×) 2.0 lpm.

with ethanol, although the efficiency fell more rapidly with time than that observed with methanol and ethanol. At the higher air flow rate of 2.0 lpm, the initial efficiency was lower being only 74%, and it rapidly declined with time.

For each solvent, the column efficiency was estimated from the diffusion coefficients, tube geometry, and air flow rates using the Gormley-Kennedy equation. These are 99.9% at an air flow rate of 0.5 lpm but range from 86 to 96% at 2 lpm. Thus, initially the efficiencies were in reasonable agreement with the calculated values but fell off at later times. In contrast, at the high air flow rates of 2.0 lpm, the observed efficiencies were well below the calculated values even at early times and the discrepancy rapidly increased with time.

The total observed resistance less the inner tube resistance, calculated from the G-K equation, is plotted as a function of the cumulative amount of solvent adsorbed by the charcoal (Fig. 3). It should be noted that the calculated inner tube resistances fall within a narrow range of 0.492 to 0.538 despite the varied airflow rates and different solvents. At early times, the data largely converge to a common point. In addition, the data for ethanol and ethyl acetate largely overlapped, although the data obtained with methanol at later times was lower and appeared to rise with a smaller slope. From the linear region of these curves, the data was extrapolated to zero amount adsorbed to estimate the resistance of the screen. The estimates of the screen resistance are given in Table III. In addition, the resistances of the screen calculated by equation 4 are also provided. It can be seen that significant differences exist between the calculated resistances and the experimental quantities.

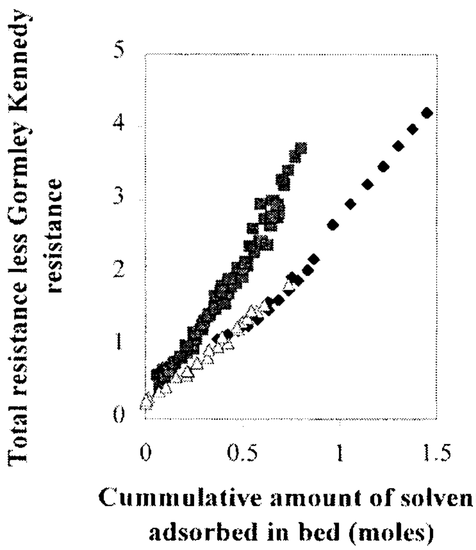

Fig. 3. Total resistance less the inner tube resistance given as a function of the cumulative amount of solvent adsorbed for (◆) methanol, (■) ethanol, and (▲) ethyl acetate.

The inverse error function of the ratio of the inlet to outlet concentration was analyzed by plotting it as a function of $t_{min}/\sqrt{(t\text{-}t_{min})}$ according to equation (23) where t_{min} is calculated as the ratio of the inner tube volume and the air flow rate, V/Q. The results are given in Fig. 4 and are seen to represent linear relationships. The best-fit slopes were found to be 471, 416, and 251 $min^{-1/2}$ for methanol, ethanol, and ethyl acetate, respectively.

For the adsorption isotherms for the solvents and charcoal there was a rapid rise in the mass adsorbed at, low relatively

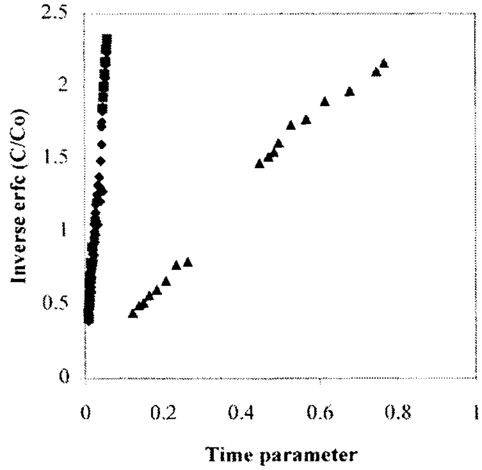

Fig. 4. Inverse error function of the ratio of the outlet and inlet concentration as a function of the time parameter for (◆) methanol, (■) ethanol, and (▲) ethyl acetate (see text for details).

Table III. Extrapolated Resistance (Mean ± SD, n = 3) and Calculated Screen Resistance

Solvent	Extrapolated resistance as a function air flow rate				Calculated resistance
	0.5 lpm	1.0 lpm	1.5 lpm	2.0 lpm	
Methanol	0.084 ± 0.044			0.326 ± 0.048	0.183
Ethanol	0.552 ± 0.012	0.261 ± 0.016	0.361 ± 0.053	0.379 ± 0.039	0.183
Ethyl acetate	0.203 ± 0.019			0.242 ± 0.017	0.183

vapor pressures with a gradual increase at higher vapor pressures.

DISCUSSION

The ultimate goal of this work was to develop a means to screen rapidly a large number of compounds for their use in cancer chemoprevention. To this end, a system was developed primarily to overcome the problems associated with the delivery of poorly water-soluble compounds. We have provided the analysis of a diffusion dryer composed of a cylindrical charcoal column to remove organic solvent that allows this method to be used for long term animal studies.

The solute and total output rates of the nebulizer are reasonable for an ultrasonic nebulizer. The piezoelectric transducer produced a liquid fountain from which a relatively dense aerosol cloud was formed. It appears that viscosity correlates with the number density of the aerosol cloud (7). Higher output rates could have been achieved through a baffle system that would have allowed more efficient entrainment of the aerosol particles in the air stream, but at the expense of added complexity. It should also be noted that the frequency of the nebulizer and the properties of the solvent (surface tension and density) determine the initial particle size, which taken with the initial solute concentration determines the final particle size. Thus, for solutes such as budesonide, this approach allows production of aerosol particles with aerodynamic diameters of 0.6 μm that is preferred for the delivery of drug to the peripheral alveoli of rodents (1). The final particle size is dependent on the cube root of the solute concentration, but the dose may be varied by alternative means such as exposure time and diluting air down stream from the column.

The particle transmission efficiency through the charcoal column was very high as theoretically expected. Specifically, the G-K equation was used to estimate the loss of particles by diffusional impaction with the screen. Due to the relatively small diffusion coefficient of the aerosol particles, this contribution is negligible. Sedimentation is also possible and perhaps provides a better explanation for the modest loss. Finally, the screen does not present an aerodynamically smooth surface and thus may have caused local turbulence that enhanced the loss of particles.

In analyzing the performance of the column for solvent removal, three contributions to the resistances were independently analyzed. While providing a reasonable approach, it is inherently flawed in that the resistances are quantitatively linked but treated separately. Moreover, the resistances are ascribed to specific regions of the column that may not be strictly valid.

For the inner tube resistance, the use of the G-K equation requires laminar flow conditions, uniform concentration at the inlet, and instantaneous adsorption at the surface. As alluded to above, laminar flow conditions may not have existed at the surface of the screen. In addition, upon entry of the aerosol cloud into the column, a certain length, ($L \sim 0.1*R*Re$) where R is the radius and Re is the Reynold's number, must be transversed for full development of laminar flow (8). Another concern is the presence of aerosol particles containing solvent. The GK equation requires an initial uniform concentration from which a specific concentration gradient will evolve with adsorption of the solvent onto the surface. With the presence of solvent in the aerosol particles, it would seem likely that with removal of the solvent due to diffusion into the bed, the concentration within the inner tube will remain near that dictated by the saturation vapor pressure until the aerosol particles have become dry. With this consideration, the G-K equation will likely overestimate the resistance of the inner tube. Finally, as the bed adsorbs solvent, the assumption of instantaneously adsorbing surface is no longer valid leading again to an inappropriate application of the G-K equation and the calculated resistance. An iterative approach has been used (9), but as was recognized, it only leads to a relatively minor effect on the calculated resistances

The next barrier for consideration is the screen. This has been estimated from the physical dimensions of the screen assuming it consists of a uniformly thick barrier with a well-defined available area for diffusion. It was also estimated as the difference between the resistance at time zero and the inner tube resistance obtained from the G-K. In the former approach, the weaknesses are self-evident, and for the latter approach, the weakness of the G-K applies here as well. Nevertheless, the similarity, within a factor of two or less, is suggestive that the resistance has been adequately treated. This is especially true given the fact that this represents a small contribution to the overall resistance.

The final resistance for consideration arises from the charcoal bed. Implicit in the present approach is that the bed resistance is equal to the time dependent resistance, and all time independent resistance to solvent removal arises from the inner tube and screen. In addition, an equilibrium distribution across the screen was assumed which appears to conflict with the above statements concerning the resistance of the screen. These two tenets are not strictly correct, but represent reasonable simplifying assumptions that become progressively better with time. To further substantiate the approach, the slope was calculated from independently determined parameters that included the geometry of the column, volume fraction of charcoal, adsorption isotherms of the solvent, and the diffusion coefficient of the vapors in air.

The adsorption of the vapors can be characterized as type I isotherms where there appears to be a monotonic approach to a limiting adsorption. Although not specifically relevant, it may be noted that only minor hysteresis was observed and then only with methanol. The data were well fit by the Langmuir equation with correlation coefficients of 0.998, 0.994, and 0.992 and chi squared values of the fit of 4.0, 15.9, and 8.61 for methanol, ethanol, and ethyl acetate, respectively. To provide a tractable solution, the adsorption was considered to be in the linear region of the isotherm. This can not be true for the initial region of the column if equilibrium is also established across the screen.

With regards to the diffusion coefficient, a correction was made to account for the relatively immobile vapor molecules on the surface of the charcoal using the two-state model. This represents the most important correction of the vapor diffusion coefficient in air relative to that expected in the charcoal bed. However, no corrections were applied for the tortuosity or porosity of the bed. Given that the charcoal represents a close packed system with a void space of less than 25%, there is a significant overestimate of the diffusivity in the column. Nevertheless, theoretical efforts in this arena have been limited and therefore the ratio of the observed to calculated ratio of

Table IV. Parameter Values Related to the Bed Resistance

	Methanol	Ethanol	Ethyl acetate
Saturation vapor pressure[a], torr	110.72	52.074	79.552
Diffusion coefficient[a], cm^2/s	0.158	0.135	0.087
Charcoal affinity constant[b]	0.203 ± 0.012	0.408 ± 0.033	1.39 ± 0.37
Charcoal capacity constant[b]	32.68 ± 0.30	39.64 ± 0.33	24.52 ± 0.22
Calculated slope, $sec^{-1/2}$	151	265	181
Slope[c], $sec^{-1/2}$	60.8	53.7	27.8
Observed/calculated slopes	0.36	0.203	0.153

[a] Determined at 20°C from (11).

[b] Values represent fitting parameters and associated error of the least squares nonlinear regression of the adsorption isotherm.

[c] Values represent fitting parameters of the least squares linear regression of the data in Figure 4.

the slope is provided with the recognition that this ratio should be circa 0.25.

Examining the ratio in the Table IV shows that the ratio of the observed to calculated slope decreases from 0.36 for methanol to 0.153 for ethyl acetate. As such, the agreement is very good. The source of the minor discrepancies is most likely related to the assumption that the transport occurs strictly within the linear region of the adsorption isotherm. This would account for the decrease in the slope ratio with an increase in the affinity constant of the isotherm. In spite of this relatively minor problem, it would appear that the column efficiency is related to the equilibrium adsorption isotherm of the vapor.

Summarizing the data analysis, it has been shown that the dryer efficiency can be explained in terms of a series of resistances where the overall effective resistance is given as a sum of the resistances to transport in the open tube, across the screen mesh and the adsorbent bed. Furthermore, the resistance attributed to the screen was independent of the solvent, air flow rate and accumulated solvent. Finally, the resistance attributed to the charcoal bed was dependent on the solvent and its degree of accumulation, but independent of the air flow rate. Moreover, the bed resistance can be related to the vapor isotherms of the solvents.

The column design presented here is useful in identifying the important aspects of the solvent removal that in turn can form the basis for designing smaller and more efficient columns. Clearly, the design of the inner tube length and radius can be developed within the context of the GK equation and considerations of the air flow rate needed for drug delivery. While other geometries are possible, the annular design has the advantage maximizing the exposure area of the adsorbent to the passing aerosol cloud. The resistance of the screen or other supporting material can not be neglected and may be approximated from the geometry using a relatively simple approach.

Charcoal is relatively inexpensive and its nonspecific nature allows adsorption of a wide range of organic molecules. For the results presented here, both diffusion and adsorption are important. In the present design, a fairly deep bed of charcoal was used; however, this is not needed for animal studies, since the resistance becomes substantial with small depths of vapor penetration. The optimal dimensions may be determined from the solvent isotherm, which is readily obtained with currently available automated instruments.

Finally for practical considerations, several drugs have been nebulized with an ultrasonic nebulizer in ethanol that has been subsequently removed by passing the aerosol cloud through a column containing an annular ring of charcoal (unpublished data). These include budesonide, beclomethasone dipropionate, indomethacin, and 9-cis retinoic acid. Since each of these compounds is soluble in ethanol and their presence did not significantly influence the removal of ethanol by a cylindrical charcoal column, it was a relatively simple procedure to identify the optimal solution concentration and airflow rate to achieve the required dose and particle sizes. Therefore, minimal time was required to formulate these compounds for testing of their chemopreventive activity in rodents.

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