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ACKNOWLEDGMENTS AND ADDRESSES

Received August 17, 1972, from the *Squibb Institute for Medical Research, New Brunswick, NJ 08903*

Accepted for publication December 14, 1972.

The authors express their appreciation to Dr. G. Brewer and Dr. K. Florey for their encouragement and suggestions during this study, and to Dr. D. Frost for his helpful discussions during the preparation of this manuscript.

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PHARMACEUTICAL TECHNOLOGY

Evaluation of Inhalation Aerosols Using a Simulated Lung Apparatus

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Abstract □ A model lung chamber was designed for the evaluation of oral inhalation aerosols. The lung chamber was a compartmentalized unit based on certain parameters of the human respiratory tract. A vacuum system was used to regulate the flow rate through the chamber. Based on studies of air flow rate and evaluations with medicinal aerosol units, a vacuum of 30.4 cm. (12 in.) of mercury was chosen as the most suitable pressure for analysis of the aerosol samples within the chamber. Sampling of the chamber was by gravity, deposition of the nebula in sample collection vials attached to the base of each compartment, or full rinsing of each compartment. Samples were analyzed spectrophotometrically. The particle-size distributions of aerosolized talc samples from each chamber compartment were determined to evaluate the separation characteristics of the model lung chamber. Solutions of varying strengths of isoproterenol hydrochloride and phenylephrine hydrochloride aerosolized using several common aerosol devices demonstrated the model lung chamber to be a suitable device for evaluating medicinal and pharmaceutical aerosol units.

Keyphrases □ Inhalation aerosols—evaluated using simulated lung chamber □ Aerosols, inhalation—evaluated using simulated lung chamber □ Simulated lung chamber—design used to evaluate inhalation aerosols □ Lung chamber, simulated—design used to evaluate inhalation aerosols

Until recently, aerosol inhalation therapy has received comparatively little attention when compared with the more conventional dosage routes for drugs. However, with the development of pressurized aerosol technology and portable aerosol-generating equipment and an increasing appreciation of inhalation as a route for the administration of medicinals, considerable interest has developed in this area.

Inhalation therapy may be used to administer drugs for local and/or systemic response. By effecting depth of penetration and retention of inhaled medicinals, it is possible to obtain a purely local action without systemic effects or a combination of local and systemic action (1–3). Several parameters influence the penetration and deposition of inhaled materials in the lung.

Extensive research (4–12) has been conducted on the relationship of particle size to distribution and retention in the lungs. The conflict of theories and experimental results from these investigators has been attributed to such variable factors as species of animal used, nonuniform breathing rates, methods of measurement of particle-size distribution, methods of administering the agents used, and effects of lung moisture content on the size of inhaled particles (3, 6, 7, 13, 14). All authors agree, however, that depth of penetration increases with decreasing particle size while whole lung retention increases with increasing particle size (1, 6, 15, 16). The optimum particle-size range for inhalation of medicinals into the lungs is currently accepted as 0.5–5.0 μ (17, 18).

While the importance of particle size in inhalation therapy has been well documented, the other parameters effecting deposition and retention of inhaled matter have received less attention. In addition, pharmaceuticals are available in pressurized form for administration as either liquid droplets or fine solid particles. However, no evidence in the literature documents the superiority of solution systems of inhalation aerosols over suspension systems or vice versa.

Since *in vivo* evaluation of inhaled materials can lead to a disparity of results due to variable factors, there is a need for a good *in vitro* method of evaluating inhaled materials. This study describes the development of a collection chamber for *in vitro* analysis of materials from pressurized pharmaceutical aerosols or other aerosol-generating equipment.

Table I—Model Lung Chamber Flow Rates

Vacuum Setting, cm. (in.) of Mercury	Air Flow Rate through Lung Chamber, ft./sec.
7.6 (3)	2.5
15.2 (6)	3.0
22.8 (9)	3.5
30.4 (12)	3.5
38.1 (15)	4.0
50.8 (20)	5.0

EXPERIMENTAL

Construction of Model Lung Chamber—In the design of the lung chamber, it was desired to create a device that would relate to the pathway followed by an inhaled aerosol in the respiratory tract of man. The superstructure of the lung chamber was fabricated from an acrylic plastic tube 15.2 cm. (6.0 in.) in diameter [13.9-cm. (5.5-in.) i.d.] and 92.1 cm. (36.25 in.) in length.

The tube was partitioned into six compartments by cementing in place plastic plates at specified intervals. Each compartment was designed to represent a given segment of the human respiratory tract. The basic parameters used in design of the lung chamber were based on the measurements of Findeisen (4) and Landahl (8). Compartment 1 represented the trachea, Compartment 2 the primary bronchi, Compartment 3 the secondary bronchi, Compartment 4 the tertiary bronchi, Compartment 5 the quatenary bronchi, and Compartment 6 the remainder of the bronchial tree. The pathlength from the entrance into a compartment to the exit from that compartment was four times the length of the corresponding lung segment represented by the compartment. For example, the pathlength from the entrance orifice of Compartment 1 to the opening into Compartment 2 represented approximately four times the length of man's trachea.

The diameters of the openings into each lung compartment were five times the diameter of the corresponding component of the human lung. The sole exception was the tracheal opening (opening into Compartment 1) which was approximately actual size for more effective screening of large aerosol particles normally too large to penetrate into the lungs. Openings were located in a staggered up and down and off-center arrangement. The pathway from one orifice to the next was at varying angles. This arrangement was chosen to give a rough approximation of the tortuous path followed by inhaled aerosol particles in the lungs.

Entrance to the tracheal compartment of the lung chamber was *via* a segment constructed to represent the approximate actual size of the human mouth. The mouth segment was constructed by cementing a 7.6-cm. (3-in.) diameter [6.3-cm. (2.5-in.) i.d.] tube, 5.9 cm. (2.36 in.) in length, to the front portion of the chamber. The opening into the mouth compartment was designed to fit the mouthpiece of commercial aerosol units. The opposite end of the lung chamber was sealed with a plastic plate through which a center vacuum spout was affixed.

Threaded sample collection ports were centrally located at the base of Compartments 1–5. These threaded ports were fitted with 20-ml. glass vials for collection of aerosol samples from each compartment for spectrophotometric or particle-size analysis. For cleaning purposes the lung unit could be disassembled into four parts or sections. Flat rubber gaskets were used as seals between the lung sections. The sections were held together by two large plastic plates fitted on each end of the lung and pulled together by three threaded rods having wing nuts on each end.

Sample Collection Procedures—Two sample collection procedures were employed in the study of liquid aerosols. In the first method, a 3.0-ml. portion of distilled water was placed in each of the five collection vials. Samples of the nebula were collected by gravity deposition of the mist during aerosol delivery. Following the sampling sequence, the collection vials were removed and an additional 7.0-ml. portion of distilled water was added to each vial. After thorough mixing, the samples were analyzed spectrophotometrically.

The second method of sample collection employed rinsing of each chamber compartment and analysis of the resultant solution. The aerosol was delivered to the chamber, with dry collection vials attached to each collection port. Following aerosol delivery, the chamber was inverted, the collection vials were removed, and 20.0-ml. portions of distilled water were added to each compartment using a hypodermic syringe. In Compartments 1 and 2, the 20.0 ml. of distilled water was added directly into the compartment proper. In Compartments 3–5, the 20.0 ml. of distilled water was first directed around the orifice of the compartment endplate by means of a plastic tubing extension on the syringe to remove the impacted sample. The chamber was slowly rotated to wash thoroughly all sample from the sides. The collection vials were then attached, and the sample solutions were drained into the vials. Spectrophotometric analysis of the samples was then conducted.

Table II—Average (Three Trials) Deposition Patterns for Two Commercial Medicinal Aerosol Units at Several Vacuum Settings

Compartment	Mercury 7.6 cm. (3 in.)	15.2 cm. (6 in.)	22.8 cm. (9 in.)	30.4 cm. (12 in.)	38.1 cm. (15 in.)	50.8 cm. (20 in.)
Isoproterenol HCl[a], % Deposition per Compartment of Aerosol Depositing in Chamber Compartments 1–5						
1	55.9	58.1	46.7	45.0	42.8	35.5
2	17.5	12.9	11.7	10.7	12.5	12.4
3	6.4	5.5	6.4	6.1	7.2	9.0
4	5.3	6.0	10.9	11.8	12.6	17.0
5	14.9	17.5	24.3	26.4	24.9	26.1
Isoproternol Sulfate[b], % Deposition per Compartment of Aerosol Depositing in Chamber Compartments 1–5						
1	39.4	38.6	34.3	33.6	33.0	30.7
2	23.0	22.1	21.5	22.9	23.4	16.8
3	12.9	10.9	13.9	10.9	11.3	7.7
4	10.8	12.2	13.9	12.9	14.5	18.8
5	13.9	16.2	16.4	19.7	17.8	26.0

[a] Isuprel Mistometer, Winthrop Laboratories, New York, NY 10016. [b] Medihaler-Iso, Riker Laboratories, Northridge, CA 91324

For sample collection of powder aerosols, dry sample vials were attached to each collection port of the lung chamber. Following delivery of the powder aerosol, the powder collected in each compartment was shaken into the collection vials or pushed into the vials using a spatula. The samples were analyzed using a Coulter counter[1] to determine the solid particle distribution of the powder sample from each compartment of the lung chamber.

Aerosol Devices—Two metered commercial medicinal aerosol units and one commercial pharmaceutical aerosol unit were employed in evaluating the operating characteristics of the lung chamber. One of the commercial medicinal aerosol units was a fine-particle suspension of isoproterenol sulfate in an inert propellant of fluorochlorohydrocarbons. Each metered dose delivered 75 mcg. of isoproterenol sulfate. The second metered aerosol employed was a solution of isoproterenol hydrochloride, alcohol, and fluorochlorohydrocarbon propellants. Each measured dose of the unit delivered approximately 125 mcg. of isoproterenol hydrochloride. For delivery of aerosol to the chamber, the units were in the inverted operating position with the mouthpiece inserted into the mouth of the chamber by a clamp arrangement. The requisite number of actuations was then made. One commercial pharmaceutical aerosol unit, a pressurized perfumed talc spray, was used in the study. Delivery of powder to the lung chamber was by means of short bursts directed into the mouth of the lung.

Several nonpressurized aerosol devices were employed, including an air-displacement aerosol unit, a hand nebulizer for solutions and a powder nebulizer adapted for hand operation. The air-displacement aerosol unit consisted of two pieces, a compressor and a nebulizer. The compressor was connected to the nebulizer by means of a plastic air hose. The diaphragm-type compressor was designed to deliver oilless air to the nebulizer at approximately 12 p.s.i. pressure. The nebulizer unit was baffled and vented so that a reverse air flow produced an increased delivery of finer particles. For use with the lung chamber, the air-displacement aerosol unit was adapted for continuous flow, the rate of delivery being approximately 5 ml. of solution/min. Solutions of isoproterenol hydrochloride or phenylephrine hydrochloride were delivered on a timed basis. The nebulizer unit was positioned with its tip inserted into

[1] Model B, Coulter Electronics, Hialeah, Fla.

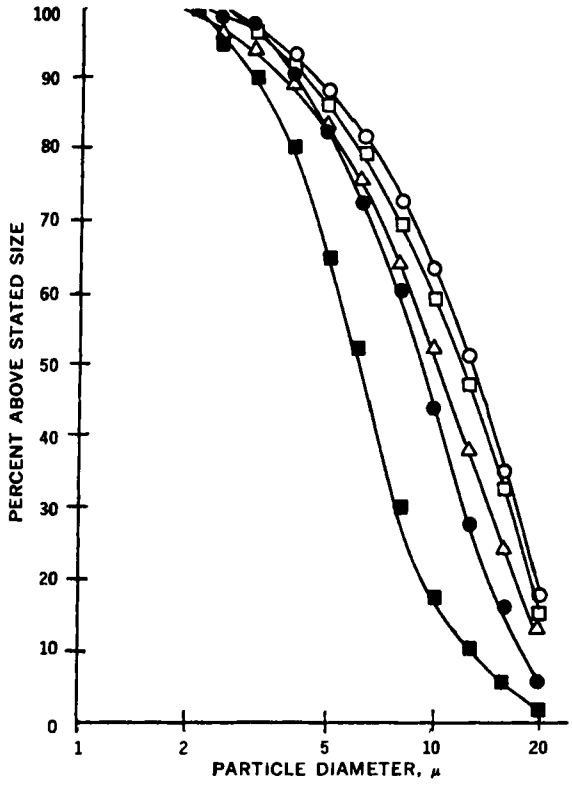

Figure 1—*Particle-size distributions for nebulized talc USP samples collected from lung chamber compartments. Key: ○, Compartment 1; □, Compartment 2; △, Compartment 3; ●, Compartment 4; and ■, Compartment 5.*

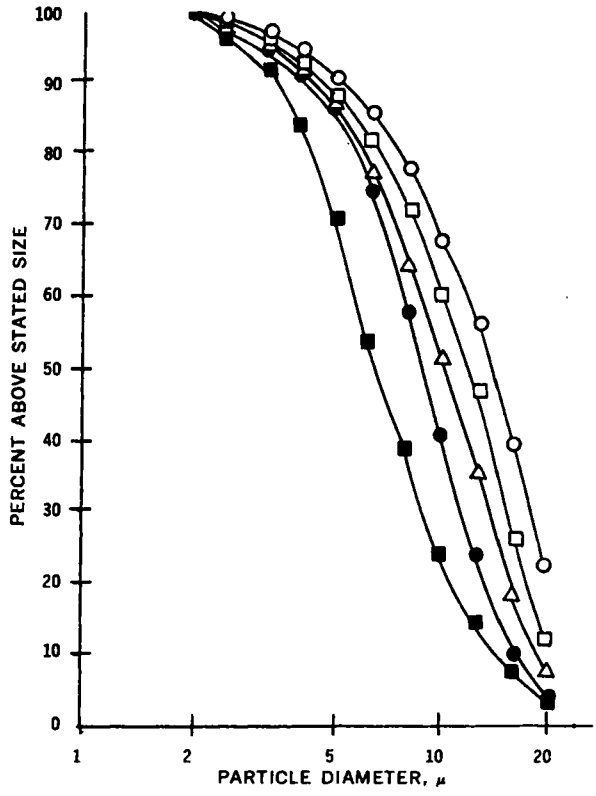

Figure 2—*Particle-size distributions for commercial talc spray samples collected from lung chamber compartments. Key: ○, Compartment 1; □, Compartment 2; △, Compartment 3; ●, Compartment 4; and ■, Compartment 5.*

the chamber mouth using the same arrangement employed for the pressurized medicinal aerosols.

Both the solution nebulizer and the powder nebulizer were operated by means of a rubber hand bulb. Solutions of isoproterenol hydrochloride were aerosolized by a given number of compressions of the hand bulb per trial. The powder blower was used to nebulize talc USP for delivery to the lung chamber.

Analytical Instrumentation—Solutions of phenylephrine hydrochloride and isoproterenol hydrochloride were analyzed using a spectrophotometer[2]. A slit width of 0.3 and a sensitivity setting of 0.4 were used for all solutions analyzed. Absorbances were determined in 1-cm. silica cells using distilled water as the blank. Absorbance determinations were made at 279 nm. for isoproterenol hydrochloride and 273 nm. for phenylephrine hydrochloride. A standard plot of absorbance *versus* concentration was prepared for each drug. Samples from the lung chamber were analyzed within 2 hr. after collection to minimize possible formation of degradation products and their possible influence on the results.

Particle-size determinations of powder aerosol samples were made using the Coulter counter with a converter[3]. Each sample was analyzed using both the 70- and 140-μ aperture tubes. A 0.85% solution of sodium chloride was used as the dispersion medium. Samples were dispersed for counting by use of a suitable mechanical stirrer.

RESULTS

Establishment of Operating Vacuum—Measurements of the air flow rate through the chamber at several vacuum settings, as well as evaluations of the two commercial medicinal aerosol units at the same vacuum settings, were conducted to establish the operating vacuum of the lung chamber. Measurements of the flow rate were made at several different vacuum settings using a meter[4] (Table I). As expected, there was a gradual increase in flow rate through the chamber as the vacuum setting was increased. The measured flow rate at 22.86 and 30.4 cm. (9 and 12 in.) of mercury was identical.

Evaluations of aerosol samples delivered by the commercial medicinal aerosol units were undertaken at vacuum settings of 7.6, 15.2, 22.8, 30.4, 38.1, and 50.8 cm. (3, 6, 9, 12, 15, and 20 in.) of mercury. Three trials were conducted for each vacuum setting, with sample collection being by full chamber rinsing of each compartment. A total of 2250 mcg. of isoproterenol sulfate or isoproterenol hydrochloride was delivered to the chamber per trial. The average deposition patterns are presented in Table II for two commercial inhalation aerosol products.

The data in Table II reveal that at either end of the vacuum range there are marked changes in deposition pattern. The pattern of percent deposition per compartment at a setting of 7.6 cm. (3 in.) of mercury vacuum is markedly different from the pattern at 50.8 cm. (20 in.) of mercury. On the other hand, at vacuum settings in the middle of the range studied, deposition patterns do not reflect wide deviation. Deposition patterns at 22.8, 30.4, and 38.1 cm. (9, 12, and 15 in.) of mercury vacuum are similar. These results correlate well with the measurements of the flow rate through the chamber. Based on these findings, a vacuum setting of 30.4 cm. (12 in.) of mercury was chosen for operation of the lung chamber.

A check of the total sample delivered from the medicinal aerosol units revealed absorbance values twice as large as expected. The interfering substance in the isoproterenol hydrochloride solution was the ascorbic acid present in the formulation. Sorbitan trioleate[5] was determined to be the ingredient interfering with the analysis of the isoproterenol sulfate suspension aerosol. Solutions of varying concentrations of both the ascorbic acid and the sorbitan trioleate were analyzed spectrophotometrically at 279 nm. A linear absorbance *versus* concentration plot was obtained for each drug. All available evidence indicated approximately the same interference by each compound.

[2] Beckman DU-2, Beckman Instrument Co., Fullerton, Calif.
[3] Model M.
[4] Wallac-Thermex GGA2, Gelman Instrument Co., Chelsea, Mich.

[5] Span 85, ICI Atlas Chemical Industries, Wilmington, DE 19899

Table III—Average (Six Trials) Absorbance and Deposition Values for 30-min. Air-Displacement Aerosol Unit Delivery of Solutions of Isoproterenol Hydrochloride and Phenylephrine Hydrochloride

5.0% Isoproterenol Hydrochloride Solution

Compartment Number	A[a]	Drug, mcg.[b]	Percent Deposition per Vial of Total Aerosol Sample Collected
1	0.600	535	37.3
2	0.334	298	20.8
3	0.191	170	11.9
4	0.319	285	19.8
5	0.164	146	10.2
Total	1.608	1434	

5.0% Phenylephrine Hydrochloride Solution

Compartment Number	A	Drug, mcg.[c]	Percent Deposition per Vial of Total Aerosol Sample Collected
1	0.552	627	36.1
2	0.338	384	22.1
3	0.183	208	12.0
4	0.306	348	20.0
5	0.149	169	9.8
Total	1.528	1736	

1.25% Isoproterenol Hydrochloride Solution

Compartment Number	A	Drug, mcg.[b]	Percent Deposition per Vial of Total Aerosol Sample Collected	$\frac{A\ 1.25\%\ \text{Solution}}{A\ 5.0\%\ \text{Solution}} \times 100, \%$
1	0.156	139	39.0	26.0
2	0.092	82	23.0	27.5
3	0.046	41	11.5	24.1
4	0.069	62	17.3	21.6
5	0.037	33	9.2	22.9
Total	0.400	357		0.400/1.608 = 24.9

2.5% Phenylephrine Hydrochloride Solution

Compartment Number	A	Drug, mcg.[c]	Percent Deposition per Vial of Total Aerosol Sample Collected	$\frac{A\ 2.5\%\ \text{Solution}}{A\ 5.0\%\ \text{Solution}} \times 100, \%$
1	0.260	295	36.7	47.1
2	0.158	180	22.3	44.1
3	0.089	101	12.5	48.6
4	0.127	144	17.9	41.5
5	0.075	85	10.6	50.3
Total	0.709	805		0.709/1.528 × 100 = 46.4

1.0% Isoproterenol Hydrochloride Solution

Compartment Number	A	Drug, mcg.[b]	Percent Deposition per Vial of Total Aerosol Sample Collected	$\frac{A\ 1.0\%\ \text{Solution}}{A\ 5.0\%\ \text{Solution}} \times 100, \%$
1	0.113	100	36.6	18.8
2	0.070	62	22.6	20.9
3	0.037	33	12.0	19.4
4	0.059	53	19.1	18.5
5	0.030	29	9.7	18.3
Total	0.309	275		0.309/1.608 × 100 = 19.2

1.25% Phenylephrine Hydrochloride Solution

Compartment Number	A	Drug, mcg.[c]	Percent Deposition per Vial of Total Aerosol Sample Collected	$\frac{A\ 1.25\%\ \text{Solution}}{A\ 5.0\%\ \text{Solution}} \times 100, \%$
1	0.121	137	39.2	21.9
2	0.065	74	21.0	19.2
3	0.031	35	10.0	16.9
4	0.063	72	20.4	20.6
5	0.029	33	9.4	19.5
Total	0.309	351		0.309/1.528 × 100 = 20.2

[a] A = absorbance. [b] Drug = isoproterenol hydrochloride. [c] Drug = phenylephrine hydrochloride.

Calibration with Solid Particle Aerosols—To calibrate the particle separation of an aerosol sample by the model lung chamber, two trials employing talc were performed. In one experiment, talc USP was nebulized using a powder blower. The second experiment involved the delivery of talc to the chamber from a pressurized commercial perfumed talc spray. A setting of 30.4 cm. (12 in.) of mercury vacuum was used. Samples were analyzed using the Coulter counter, and analysis was conducted with both the 70- and 140-μ aperture tubes (Figs. 1 and 2).

Examination of the data reveals a similar type of selective particle deposition occurring in the lung chamber as occurs in the respiratory tract of man. The larger particles in a disperse system of particle sizes are filtered out by the trachea and upper regions of the respiratory tract, with the finer particles penetrating to greater depths before depositing. Thus, as the aerosol sample proceeds into the respiratory tract, the particle-size distribution changes from high percentages of larger particles to high percentages of fine particles. The same type of deposition pattern is shown by the results of the talc analysis presented in Figs. 1 and 2. Compartment 1 shows the highest percentage of the larger particles of the talc sample, while Compartment 5 shows the highest percentage of the smaller particles from the talc sample. As the sample proceeds from Compartment 1 through to Compartment 5, the percentage of large particles in the distribution gradually decreases while the percentage of fine particles in the distribution gradually increases.

Evaluations with an Air-Displacement Aerosol Generator—When using the air-displacement aerosol generator, experiments were conducted using both high volume and low volume aerosol delivery. In the high volume aerosol delivery experiments, solutions of 5.0, 1.25, and 1.0% isoproterenol hydrochloride and 5.0, 2.5, and 1.25% phenylephrine hydrochloride were delivered to the chamber for 30 min./trial. Six trials were conducted for each solution strength listed. Sample collection was by gravity deposition of the nebula in collection vials containing 3 ml. of distilled water. Table III lists the average absorbance values and patterns. Reference to the table shows that the deposition pattern is the same for all solutions tested. This demonstrates that the deposition at a particular vacuum flow setting is a function of this particular aerosol-generating device and not the drug or strength of drug in solution.

The deposition values of the 1.25 and 1.0% isoproterenol hydrochloride solution trials are approximately 25 and 20%, respectively, of the 5.0% isoproterenol hydrochloride solution values, as expected. This same type of relationship is also demonstrated by the results from the three different strength phenylephrine hydrochloride solutions (Table III). Although the relationship is not as close as for the isoproterenol hydrochloride solutions, the deposi-

Table IV—Average (Six Trials) Absorbance and Deposition Values for Hand-Operated Nebulizer Aerosols

Compartment Number	2% Isoproterenol Hydrochloride Solution: A[a]	Drug, mcg.[b]	Percent Deposition per Compartment of Aerosol Depositing in Compartments 1–5
1	0.247	442	32.1
2	0.160	286	20.8
3	0.113	202	14.7
4	0.108	193	14.1
5	0.141	252	18.3
Total	0.769	1375	

Compartment Number	1% Isoproterenol Hydrochloride Solution: A	Drug, mcg.	Percent Deposition per Compartment of Aerosol Depositing in Compartments 1–5	$\frac{A\ 1\%\ \text{Solution}}{A\ 2\%\ \text{Solution}} \times 100$, %
1	0.150	268	31.8	60.7
2	0.097	173	20.6	60.6
3	0.072	129	15.2	63.7
4	0.072	129	15.2	66.7
5	0.081	145	17.2	57.4
Total	0.472	844		0.472/0.769 × 100 = 61.4

[a] A = absorbance. [b] Drug = isoproterenol hydrochloride.

tion patterns are similar. The low volume aerosol delivery experiments did not show significantly different patterns.

Evaluations with a Hand-Operated Nebulizer—The aerosol produced by a hand-operated nebulizer (for solutions) was evaluated in the lung chamber. Solutions of 1.0 and 2.0% isoproterenol hydrochloride were nebulized using 50 actuations/trial. Six trials were conducted for each solution at a vacuum setting of 30.4 cm. (12 in.) of mercury. Sample collection was accomplished by rinsing each compartment with 20.0-ml. portions of distilled water.

The deposition patterns of the 1.0 and 2.0% solutions appear to be nearly identical (Table IV). The absorbance values from the 1.0% isoproterenol hydrochloride samples are about 61% of the 2.0% solution values. One primary disadvantage of the hand nebulizer is a lack of accurate dosage control, the amount of pressure applied to each squeeze of the rubber hand bulb varying the amount of aerosol produced (Table IV).

SUMMARY

The design of a model lung chamber was shown to be a suitable method for evaluating medicinal or pharmaceutical aerosols, free from the many variables of *in vivo* analysis. Construction of the unit was based on literature values for the size of the human respiratory tract. An operating vacuum of 30.4 cm. (12 in.) of mercury was established based on measurements of air flow and evaluations with commercial medicinal aerosol units. The solid particle segregation of solid particle aerosols by the lung chamber was used to evaluate the aerosols produced by different aerosol-generating devices. By using the lung chamber unit, it should be possible to compare liquid solution aerosols to solid suspension aerosols of a drug to determine if there is any difference in their deposition in the respiratory tract.

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ACKNOWLEDGMENTS AND ADDRESSES

Received April 17, 1972, from the *Industrial and Physical Pharmacy Department, School of Pharmacy and Pharmacal Sciences, Purdue University, Lafayette, IN 47907*

Accepted for publication November 13, 1972.

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