# *In Vitro* Method of Comparing Clouds Produced from Inhalation Aerosols for Efficiency in Penetration of Airways

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**Abstract** □ The efficiency of a pressurized inhalation aerosol depends, to a large extent, upon the particle-size distribution of the emitted aerosol cloud. Methods of determining the particle-size distribution of these clouds are difficult and time consuming. A method was evolved for determining comparatively the proportion of the emitted dose which succeeded in penetrating a system of wet-lined tubes and arriving at a filter. The amount of medicament attaining the filter was determined chemically. Clinical work with bronchodilators showed that the method enabled comparisons to be made between different formulations of the same dose of the same drug. These comparisons afforded some indication of the relative clinical efficacy of the formulations.

**Keyphrases** □ Aerosols, inhalation—*in vitro* penetration efficiency evaluation □ Bronchodilators, aerosol—*in vitro* penetration efficiency, *in vivo* comparison □ Inhalation aerosols—*in vitro* penetration efficiency evaluation

During the last decade, many potent drugs (especially bronchodilator drugs) have been formulated as aerosol inhalers using the propellant power of the chlorofluorohydrocarbon propellants. These inhalers are formulated in one of two ways. Either the active drug is dissolved in a cosolvent such as ethanol which is miscible with the liquefied propellant, or the active drug is premicronized and suspended in the liquefied propellant. The formulation is packed into 10- or 15-ml. vials provided with metering valves; at each actuation, the valve releases a single dose of from 25 to 100 μl. These doses are of very short duration, 25 μl. being emitted in about 70 msec.

It is considered, particularly in the case of bronchodilator drugs, that the onset of relief should be as rapid as possible. Immediate relief is obtained by the action of particles attaining the alveolar region; particles that impact in the upper part of the respiratory tract are absorbed into the general circulation, their bronchodilator effect is retarded, and they contribute to side effects. Thus, the particle size of the emitted aerosol should be the optimum for penetration of the particles into the alveolar region and for their retention there. There is some disagreement among investigators as to the optimum particle-size range for penetration and retention of particles in the alveolar region. However, it is generally accepted that particles larger than 7 μm. in diameter tend to impact in the upper airways and that particles less than 2 μm. in diameter tend to be exhaled before drug absorption can occur (1–3).

Many attempts have been made to determine the particle-size distribution of the aerosol cloud emitted from an inhalation aerosol. These methods fall into the three main types: (*a*) image-forming methods, (*b*) methods based upon the separation of the spray into fractions, and (*c*) light-scatter methods.

Among the image-forming methods, microscopy has the disadvantage that representative sampling is difficult; small particles tend to be carried past the slide in the air and vapor stream. Lefevbre *et al.* (4) attempted to overcome this disadvantage in the case of aerosols from continuous flow pressure packs by firing them down a cardboard tube, positioned vertically over a slide, and allowing a period for the smaller particles to settle. The disadvantage of this method, however, is that liquid droplets shrink by evaporation during the settling period. When an aerosol is discharged at a slide, nonvolatile liquid particles appear as flattened lenticular droplets. The diameters of the original droplets have been calculated *via* a determination of the focal lengths of these lenticular droplets. Attempts have been made to preserve the droplets in their original size and shape by allowing them to impact upon a slide coated with mag-

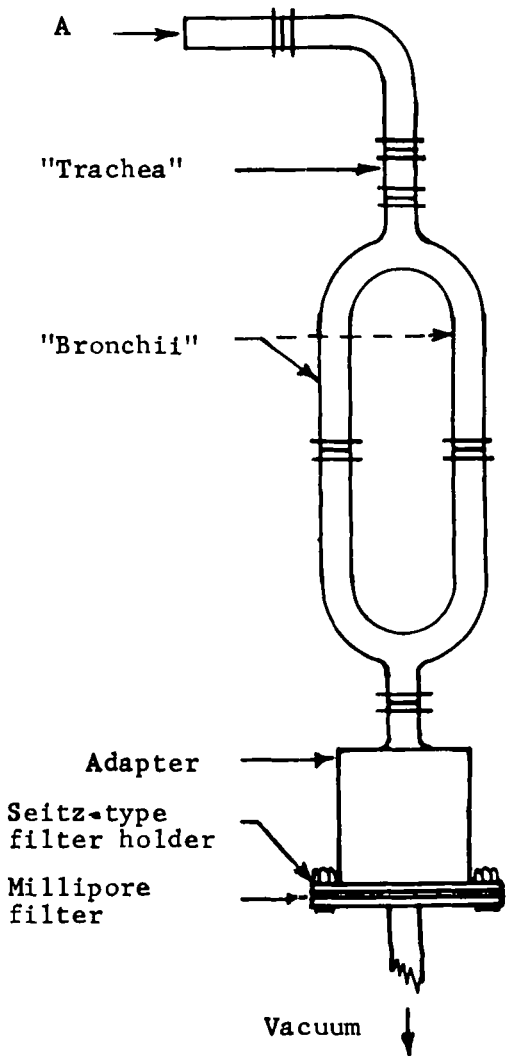


**Figure 1**—*Apparatus for the* in vitro *comparison of the efficiency of inhalation aerosols.*

**Table I**—Penetrative Efficiency from the Mouthpiece of Inhalation Aerosols (Isoprenaline Sulfate, 2 mg./ml.)

| | Mean Penetrative Efficiency, % | Standard Deviation, % |
|---|---|---|
| 10 units, same mouthpiece | 54.5 | 3.9 |
| 1 unit, 10 mouthpieces | 55.8 | 2.8 |

**Table II**—Effect of Isoprenaline Sulfate Concentration (Suspension) and Valve Dose Volume upon Penetrative Efficiency

| Formulation | Isoprenaline Sulfate, mg./ml. | Valve Dose Volume, µl. | Mean Penetrative Efficiency from Mouthpiece, % |
|---|---|---|---|
| A | 2 | 50 | 55.2 |
| B | 4 | 25 | 53.9 |
| C | 10 | 50 | 32.8 |
| D | 20 | 25 | 35.4 |

nesium oxide (4). Counting and measuring droplets are time-consuming processes unless a scanning-spot microscope is available. Above all, the sample represents only a fraction of the total aerosol (which may not be homogeneous), and only a very small fraction of the total number of particles is sized and counted.

High-speed flash photomicrography of the emerging aerosol cloud suffers from the disadvantage of the very short depth of focus (125 µm.) imposed by the wide apertures necessary and from the limit of resolution of 3–4 µm.

Attempts have been made to use laser holography to determine the particle-size distribution of the aerosols delivered by inhalation aerosols but, again, there is the limitation imposed by a resolution limit of 3–4 µm.

Among spray-fractionating methods that have been evaluated are the cascade impacter (5), the Timbrell aerosol spectrometer, the Goertz spectrometer (6), and the conifuge of Sawyer and Walton (7). All of these methods have the disadvantage of requiring a large sample of the aerosol, and the collection of a representative sample from an almost instantaneous dose is difficult.

**Table III**—Summary of Results of Clinical Comparison of Formulations C and D from Table II

| Formulation | Mean Increase in $FEV_1$, % | Standard Error |
|---|---|---|
| C | 25.4 | 2.9 |
| D | 20.9 | 4.6 |

**Table IV**—Penetrative Efficiencies of Aerosol Inhalations (Solution Type)

| Formulation | Valve Dose Volume, µl. | Mean Penetrative Efficiency from Mouthpiece, % |
|---|---|---|
| Isoprenaline sulfate, 2 mg./ml. | 50 | 9.3 |
| Isoprenaline sulfate, 10 mg./ml. | 50 | 5.3 |
| Isoprenaline sulfate, 0.225% w/w | 50 | 13.0 |

**Table V**—Effect of Mouthpiece Length upon Penetrative Efficiency of Inhalation Aerosols

| Mouthpiece Length, cm. | Percent of Dose from Valve Retained by Adapter | Penetrative Efficiency from Valve, % | Penetrative Efficiency from Mouthpiece, % |
|---|---|---|---|
| 8.00 | 41.0 | 47.4 | 80.4 |
| 3.75 | 5.4 | 49.1 | 51.8 |

**Table VI**—Penetrative Efficiency from the Valve of Experimental Formulations E and F

| Formulation | Penetrative Efficiency from Valve, % |
|---|---|
| E | 64.2 |
| F | 20.1 |

Light-scatter methods include that of light-scatter decay by Dimmick *et al.* (8) and stream-scanning methods such as the use of the Royco counter. Both of these methods suffer from the disadvantage that larger particles tend to settle too rapidly for inclusion in the final analysis. Bell (9) described the use of a settling box in conjunction with the Royco counter to overcome sampling difficulties.

In the formulation of inhalation aerosols, one is concerned with the ability of the emitted aerosol cloud to penetrate the system of wet-lined tubes which constitute the upper part of the respiratory tract, and particle size is only important insofar as it affects this function. In view of this fact and of the difficulties in determining the particle-size distribution of an aerosol for inhalation, an empirical method was designed to compare the relative proportion of the doses, administered from various aerosol units, which would penetrate an artificial system designed to simulate the upper part of the respiratory tract.

## EXPERIMENTAL

The apparatus shown in Fig. 1 was constructed from 2.54-cm. (1-in.) Pyrex pipe line[1]. The upper part resembled, in shape and size, a stylized human "trachea" and "bronchi." The two bronchi joined and proceeded to an adapter holding a membrane filter capable of retaining particles with a diameter of 1 µm. or greater. To simulate the moist conditions of the respiratory tract, the whole of the glass tubing was lined with 3% agar gel, in which the small doses of water-soluble drugs dissolved on contact. Air was drawn through the apparatus at a rate of 16 l./min., controlled by a flowmeter.

The experimental method was as follows: The amount of active ingredient delivered from the device by a definite number of valve actuations was determined chemically. The mouthpiece of the inhaler was then inserted into the apparatus at A (Fig. 1) by means of a rubber filter cone or, better, a jig molded from plaster of paris. A definite number of doses was then fired into the apparatus, the filter was removed, and the medicament which had attained it was washed off and determined chemically.

It was then possible to express the relative efficiency of the inhaler as the percentage of the dose emitted from the valve that arrived at the filter. In this paper, the term "penetrative efficiency from the valve" is used to describe this percentage. Alternatively, by determining the percentage of the dose emitted from the valve that was retained in the mouthpiece, the amount of drug to arrive at the

[1] Q.V.F. Ltd.

Table VII—Percentage Improvements in FEV by Two Experimental Formulations, E and F

| Time after Administration, min. | Improvement in $FEV_1$ | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Leeds (15 Patients) | | | | York (10 Patients) | | | |
| | Formulation E | | Formulation F | | Formulation E | | Formulation F | |
| | Mean, % | *SE* | Mean, % | *SE* | Mean, % | *SE* | Mean, % | *SE* |
| 5 | 22 | 2.97 | 19 | 2.56 | 31 | 4.88 | 12 | 3.19 |
| 10 | 22 | 3.18 | 16 | 2.56 | 26 | 4.52 | 14 | 3.98 |
| 15 | 22 | 2.87 | 11 | 2.36 | 28 | 5.71 | 14 | 3.99 |
| 30 | 20 | 2.96 | 8 | 2.39 | 25 | 5.41 | 9 | 4.21 |

Table VIII—Comparison of Clinical Results with Those Obtained by Artificial Airway Experiment

| | |
|---|---|
| Mean FEV Improvement over First 15 Min. | |
| Leeds | |
| E | 22% |
| F | 16% |
| F/E × 100 | 72.7% |
| York | |
| E | 28% |
| F | 14% |
| F/E × 100 | 50.0% |
| Artificial Airway Results | |
| Log penetrative efficiency E | 1.8075 |
| Log penetrative efficiency F | 1.3032 |
| Log F/Log E × 100 | 72.1% |

filter could be expressed as a percentage of the dose leaving the mouthpiece. This is referred to as the "penetrative efficiency from the mouthpiece."

## RESULTS

A series of initial determinations was made using a single inhalation aerosol and mouthpiece, containing a suspension of 2 mg./ml. of isoprenaline sulfate suspended in a mixture of halogenated hydrocarbon propellants, with a pressure of 50 psig. at 25° and fitted with a metering valve delivering doses of 50 μl. The isoprenaline had been premicronized to a mass median diameter of not more than 4 μm., and not less than 85% of the particles had an equivalent sphere diameter of between 2 and 7 μm. The results of these determinations showed close agreement.

Paired determinations were then performed upon 10 of these aerosol units, using the same mouthpiece throughout, and then upon one of the units, using 10 individual mouthpieces of the same type. The results, shown in Table I, gave a combined mean of 55.2% with a standard deviation of ±4.8. Thus, for an inhalation aerosol having this formulation and type of valve and mouthpiece, the penetrative efficiency from the adapter would be expected to fall between the 95% confidence limits of 45.6–64.8%.

Other suspension formulations, which contained different concentrations of isoprenaline sulfate and which had valves delivering different dose volumes, were studied (Table II). Propellant pressure was the same in each case. It is seen that in the case of Formulations A and C, doubling the isoprenaline sulfate content and halving the valve dose volume have no effect upon penetrative efficiency.

The relative efficiency of Formulations C and D was studied in 28 patients[2] by readings of forced expiratory volume during 1 sec. ($FEV_1$) taken before administration of the medicament and at 3, 5, and 15 min. after inhalation (Table III). The increase in $FEV_1$ effected by each formulation was statistically significant, and there was no statistically significant difference between the two results. Thus, the results of the clinical and of the *in vitro* experiments are in agreement that the performance of these two formulations is substantially the same.

Investigations, using the artificial airway method, were made into the performance of commercially available inhalation aerosols formulated to contain isoprenaline sulfate in solution in mixtures of halogenated propellants and ethanol. The results (Table IV) obtained for solution formulations by this method are much lower than those obtained for corresponding suspension preparations.

The effect of the length of the mouthpiece upon penetrative efficiency was then studied. Determinations were performed using an aerosol containing a suspension of 2 mg. isoprenaline sulfate/ml. propellant and a mouthpiece with a length of 8 cm. The mouthpiece was then cut down to the more normal length of 3.75 cm., and further determinations were carried out using the same inhaler. The results are shown in Table V.

The proportion of the dose from the valve to reach the filter was practically unaffected by the length of the mouthpiece. On shortening the mouthpiece, the proportion of medicament retained by the adapter decreased greatly. However, a much lower proportion of the material passing out from the mouthpiece reached the filter. It is apparent that with the longer mouthpiece the larger particles are baffled out; with the shorter, they remain in the upper part of the artificial airway system.

Two experimental formulations, each containing 4 mg./ml. of isoprenaline sulfate and fitted with 25-μl. valves but having different propellant systems, were then compared using the artificial airway. The results are shown in Table VI. The two experimental formulations were then compared for their effect upon the $FEV_1$ of patients in two trials[3].

In each trial, $FEV_1$ readings were taken initially and at 5, 10, and 15 min. after inhalation. In addition, in the Leeds trial, further readings were taken at 30, 60, 120, and 180 min. after inhalation. In both trials, all patients received inhalations from each formulation with a suitable time interval between them. Percentage improvements in $FEV_1$ were then calculated. The mean results are shown in Table VII.

Since the penetrative efficiency from the mouthpiece represents the dose of the drug delivered, the ratio of the logarithms of these values for the two formulations was compared with the ratio of the FEV results (Table VIII). The ratio of the results from the artificial experiment shows correlation with the ratio of the mean $FEV_1$ improvements obtained at the Leeds Chest Clinic. It does not show agreement with the ratio of the results from the Clinic at York, where, however, difficulty was experienced with the functioning of the inhalers of Formulation F.

## SUMMARY AND CONCLUSIONS

Consistent results for "penetrative efficiency" can be obtained for an aerosol of a given formulation using the method described. Clinical results show that "penetrative efficiency" gives some indication of the likely therapeutic efficacy of different inhaler formulations of the same active ingredient. The method offers a relatively rapid and convenient means of estimating the possible effect upon efficacy in the patient of differences between the formulations and mechanisms of pressurized inhalers.

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# Effect of Adjuvants on Tackiness of Polyvinylpyrrolidone Film Coating

**ABU S. ALAM* and EUGENE L. PARROTT▲**

**Abstract** □ Two formulations were developed using polyvinylpyrrolidone for the film coating of tablets by the pan-coating method. The addition of ethylcellulose and shellac eliminated the tackiness sometimes associated with polyvinylpyrrolidone coating due to the hygroscopicity of the film former. The film coats increased the resistance of the tablet to mechanical stress, did not significantly increase the weight of the tablet, and were physically acceptable after storage at 2 and 45°. The film coats did not interfere with the disintegration and dissolution of the tablet since the film coats were rapidly removed from the tablet in water, simulated gastric fluid, and simulated intestinal fluid.

**Keyphrases** □ Polyvinylpyrrolidone film-coated tablets—addition of ethylcellulose and shellac to eliminate tackiness, dissolution □ Tablets, film coated—elimination of tackiness in polyvinylpyrrolidone coatings □ Pan-coating method—polyvinylpyrrolidone film-coating formulations

Since the first commercial film-coated tablet was marketed in 1954, the use of polymeric substances, such as polyvinylpyrrolidone, for the film coating of tablets has become widely accepted (1). Ellis *et al.* (2) adequately described the advantages and process of film coating. Banker (3) discussed the theory and recent developments in film-coating technology.

Although many polymeric substances have been investigated for use in film coating, the use of hydroxypropylmethylcellulose (4), hydroxyethylmethylcellulose (5), ethylcellulose (6), hydroxypropylcellulose (7), sodium carboxymethylcellulose (8), polyethylene glycols (9, 10), and polyvinylpyrrolidone has been most acceptable.

Polyvinylpyrrolidone possesses many of the desired characteristics of a polymer to be used in film coating; however, because polyvinylpyrrolidone is hygroscopic, in a humid atmosphere the film coat may be tacky and cause the tablets to adhere (11). Ahsan (12) reported that this disadvantage could be overcome by the addition of acetylated monoglycerides to the coating solution.

This study was conducted to determine the effect of various adjuvants on moisture uptake and tackiness of polyvinylpyrrolidone film-coated tablets.

## EXPERIMENTAL

**Tableting and Coating Procedure**— The tablets to be coated were prepared by the wet granulation method using a 20% by weight acacia solution. Each tablet contained 298.2 mg. of lactose, 8.1 mg. of acacia, and 3.7 mg. of magnesium stearate. The tablets were compressed to a hardness of 5.5 ± 0.5 kg. by means of 1.08-cm. ($^{13}/_{32}$-in.) standard concave punches and dies in a rotary tablet machine[1].

The pan-coating method was used to coat the tablets. One thousand tablets were placed in a 20.3-cm. (8-in.) coating pan. While the pan was rotating at 25 r.p.m., 10 ml. of the coating solution was applied to the tablets. The tablets were stirred by hand to ensure distribution of the coating solution. After 2 min., a stream of air at room temperature was directed into the pan for 2–3 min. The pan was stopped, and a stream of air at room temperature was allowed to flow onto the tablet bed for 10 min. Successive applications of 5, 3, 3, 3, and 3 ml. of coating solution were made. For the acceptable formulations, six applications provided a smooth and uniformly colored coating. Polishing was accomplished by placing 1000 coated tablets in a 15.24-cm. (6-in.) canvas-lined pan, which had been impregnated with a molten mixture of carnauba wax, white wax, and paraffin (8:1:1), and by rotating it at 20 r.p.m. for 2 hr.

**Coating Solutions**—In the initial design of the project, it was decided to use a coating solution containing 5% of polyvinylpyrrolidone as the film-forming agent and 0.1% FD&C Red No. 3 as a colorant, which would facilitate visual evaluation of the uniformity of the coating. Isopropanol, acetone–alcohol (1:1), and 70, 75, 80, 85, and 95% alcohol were tested as solvents. It was found that the coating was least tacky and most uniform if 75% alcohol was used as the solvent.

Polyvinylpyrrolidone K 29–32 and K 90 were used in combination in 75% alcoholic solutions containing 0.1% FD&C Red No. 3 in the following percentages: 3.75 and 1.25, 3.33 and 1.67, 2.50 and 2.50, 1.67 and 3.33, and 1.25 and 3.75, respectively. The coating solution containing 2.5% polyvinylpyrrolidone K 29–32 and 2.5% polyvinylpyrrolidone K 90 appeared to be least tacky and to warrant

[1] Stokes model B-2.