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ACKNOWLEDGMENTS AND ADDRESSES

Received February 26, 1971, from the * *Control Analytical Research and Development and* † *Mechanical Engineering Departments, The Upjohn Co., Kalamazoo, MI 49001*

Accepted for publication June 8, 1971.

Presented in part to the 1970 Technicon International Congress, Advances in Automated Analyses, New York, N. Y.

Data for Fig. 4 were supplied by M. L. Knuth, Control Division, The Upjohn Co.

Dry Powder Aerosols I: A New Powder Inhalation Device

J. H. BELL, P. S. HARTLEY, and J. S. G. COX

Abstract □ A new portable device is described for administration of powdered drugs by inhalation. Powder contained in a standard hard gelatin capsule is induced to flow from the capsule into the air stream by a vibratory feed mechanism arising from a rotor driven by the inhaled air. The relationship between air flow rate, vibratory cycle, and powder emission was investigated, and the results indicate a good degree of coordination of dose administration with inhalation into the inspired air stream. The ability of the device to dispense size-graded fractions of lactose, in the range of 4–400 μ, was investigated. Poor flow of the finest powders was demonstrated and can be overcome by use of a coarse flow aid.

Keyphrases □ Aerosol powder drugs—portable inhaler □ Inhaler, portable—aerosol powder drugs

Aerosol therapy constitutes a major part of the therapeutic program of many patients with airways disease. It is not generally realized that, with the pressurized aerosol or other portable inhalers, the administration of medication requires coordination of activation with the inspiratory cycle of respiration if variation in the quantity and site of drug deposition in the airways is to be minimized. The introduction of medication into the inhaled air near the end of inspiration confines drug entry and deposition to the upper respiratory tract. Many of the finer drug particles in the inhaled air would have insufficient time to deposit by sedimentation in the large diameter airways of this region before being swept out by the exhaled air flow. In contrast, drug introduced at the beginning of deep inspiration could be carried far into the lungs by the inhaled air, increasing the opportunity for fine-particle deposition in the narrow airways of the deep lung and markedly altering the pattern of drug distribution. An ideal inhalation device would ensure administration of inhalant reproducibly and conveniently with minimal patient effort, cooperation, or need for coordination.

The depth and degree of penetration of particulate matter into the respiratory tract and its subsequent deposition are an integrated effect of independent variables concerned with the characteristics of the aerosol cloud and the respiratory cycle (1). In the laboratory, experimental aerosols varying in such properties as particle size and degree of polydispersion can be prepared by selection of a suitable aerosol generator, and the quantity administered to a patient can be accurately controlled by timing the period of inhalation. To achieve reproducible particle deposition, control must be achieved over the physiological events of rate and volume of inspiration, since these play a role in determining the sizes and areas of deposition of particles within the airways. These factors are significant for particles larger than 8–10 μ, which can gain entry to the upper airways during oral inhalation when the protection afforded by the nasal cavities is bypassed. These particles can represent a major fraction of the weight of drug administered in a pharmaceutical inhalant.

Control of the respiratory cycle in man is readily attained in the laboratory by use of a spirometer and metronome, which provide the subject with an immediate indication of breathing depth and rate (2). In clinical practice, however, it is difficult if not impossible to train many patients to inhale to a specific pattern and simultaneously to coordinate dose administration at a particular point in the inhalation cycle. Consequently, the amount and site of drug deposition in in the airways and lungs may be variable, notwithstanding high precision of dose metering by the adminis-

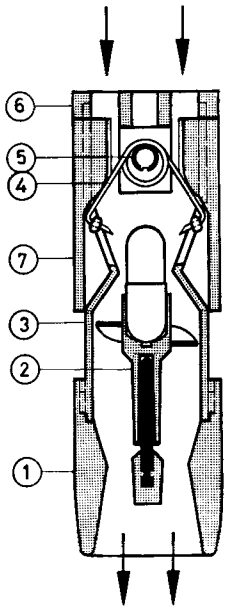

Figure 1—*The inhaler. The arrows indicate the direction of air flow during inhalation. Key: 1, mouthpiece; 2, tapered bearing; 3, casing; 4, piercing needle; 5, support and pivot for piercing needle; and 6, end cap. Scale: 1:1 approximately.*

tration device. This problem was recently studied by McIlreath *et al.* (3), using a new type of breath-actuated pressurized aerosol in which bronchodilator response in asthmatic children was used elegantly as an index of the depth of aerosol penetration. The results clearly showed the necessity for proper use of pressurized aerosols to achieve optimal response.

Administration of certain drugs by inhalation may be impractical using available portable devices such as nebulizers or pressurized aerosols. The output of solution nebulizers is limited by the physicochemical characteristics of drug solubility and solution viscosity; the pressurized aerosol has limitations in the quantity of inhalant that can be dispensed before problems such as mechanical obstruction of valve orifices occur. The preparation of stable inhalant solutions or suspensions is complicated by the lack of adequate toxicity data for the usual range of formulation aids such as surfactants and suspending agents. The direct use of dry powders in inhalation devices offers an alternative approach to drug administration but involves problems of powder fluidization, flow, and dispersion, many of which require further research (4, 5).

The recent introduction of the drug cromolyn sodium[1] (6, 7), which is administered by inhalation using a novel device, provided an opportunity to study some of these problems. In this study, attention was concentrated on the degree of coordination of dose administration with inhalation into the inspired air stream, together with the general characteristics of this particular device.

EXPERIMENTAL

The Inhaler—The arrangement is shown in Fig. 1. Essentially, a small open tube contains a plastic rotor, which revolves at high speed when air is drawn through it. Powdered drug, contained in a standard hard gelatin capsule, is inserted in a holder on the rotor. The rotor is mounted in the inhaler body by means of a loose-fitting, plastic, tapered bearing on a stainless steel shaft, the latter being inserted axially at the mouthpiece end. When air is inhaled *via* the mouthpiece, the turbovibratory action of the rotor causes the powdered drug to be dispensed into the inspired air through two diametrically opposed perforations in the capsule wall. The perforations are made immediately before inhalation by the operation of the simple piercing mechanism shown in the diagram.

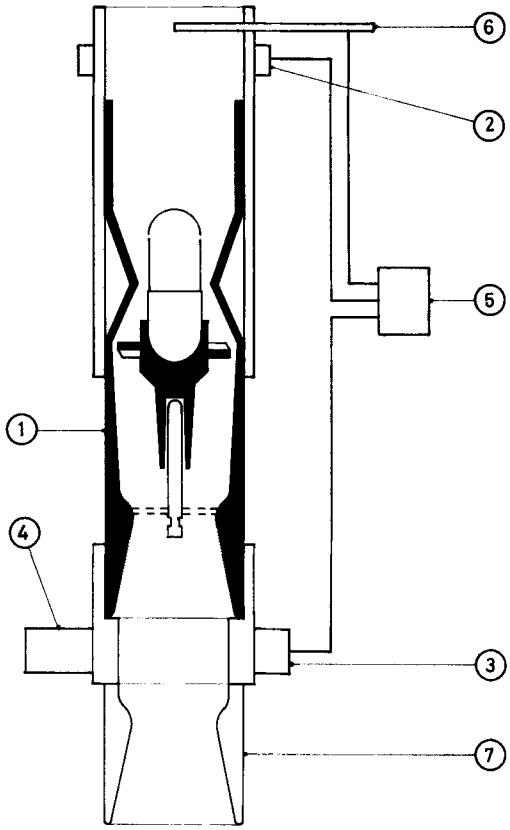

Figure 2—*Instrumentation of inhaler. Key: 1, inhaler; 2, strain gauge attached to close-fitting sleeve; 3, photoelectric cell; 4, light source; 5, multichannel recorder; 6, hot wire anemometer; and 7, mouthpiece.*

The powder is fluidized within the capsule by vibrations induced by the characteristic motion of the rotor bearing during rotation. In a normal lubricated bearing, a sliding contact would be established; in the inhaler, the relative dimensions of the rotor and shaft, together with the absence of lubricant, produce a rolling contact. This induces a whirling motion in the rotor, which is translated into a high frequency vibration of the capsule walls. The onset of this whirling causes powder to be conveyed along the capsule walls to the exit holes, irrespective of the orientation of the inhaler.

Instrumented Inhaler—The passage of air through the inhaler (Spinhaler) initiates vibrations in the rotor, felt throughout the body of the device, together with discharge of powder from the capsule. These events were individually monitored, using an instrumented inhaler shown in Fig. 2. A constant-temperature hot wire anemometer[2] mounted at the air entry port was used to detect the rapid changes in air flow rate encountered during inhalation. Since the particular motions of the rotor prevented direct mounting of a vibration sensor, a semiconductor strain gauge[3] was bonded indirectly onto the inhaler casing and served to detect vibrations transmitted *via* the stainless steel shaft. A photoelectric cell[4], mounted across the mouthpiece, detected powder discharge by 90° light scattering. Output from the three sensors was recorded simultaneously on a three-track high speed UV recorder[5]. The instrumented inhaler was operated by inserting a capsule [with holes drilled pre

[1] Intal, Fisons, (di)sodium cromoglycate.

[2] C.T.A. type 55DO5, probe type 55A, Disa, Harrow, Middlesex, England.
[3] PIXI model 8101, Endevco Corp., Royston, Herts, England.
[4] Photo duo-diode, type BPY 69, Mullard, England.
[5] Type SE 2000, S. E. Laboratories, Feltham, Middlesex, England.

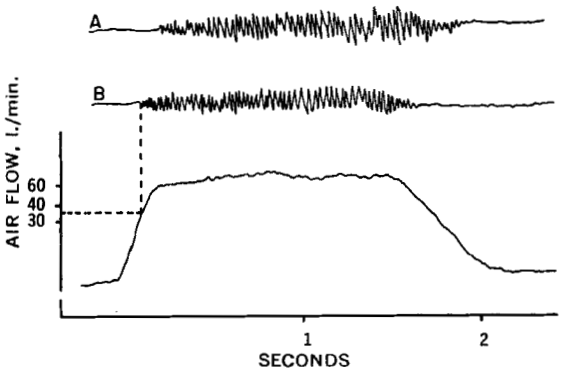

Figure 3—*Example of chart recording showing sequence of events occurring during inspiration through the inhaler. Key: A, powder discharge; and B, rotor vibration.*

viously at 0.07-cm. (0.028-in.) diameter] in the holder, starting the recorder, and then inhaling through the tube. A typical trace is shown in Fig. 3. Actual air flow rates were obtained by calibration of the hot wire anemometer against a flowmeter[6] in a separate experiment.

Effect of Powder Particle Size on Discharge of Powder from the Capsule—The flow of powders is affected by a number of factors such as particle size and size distribution, particle shape and density, surface roughness, hardness, moisture content, and bulk density (4). The influence of particle size is probably the most important; over a given size range, however, differences may be found between materials due to varying contributions from these other effects. It was of interest to examine the behavior of powders of varying properties in the inhaler. In the first instance, differing particle size was used to achieve this variation. The test powder used was lactose BP from which eight narrow size fractions were prepared using a centrifugal classifier[7], jet sieve[8], and test sieves[9] covering the range in steps from 4 to 400 μ. Capsules were partially filled at a standard volume, which gave mean fill weights ranging from 45 to 60 mg. for the

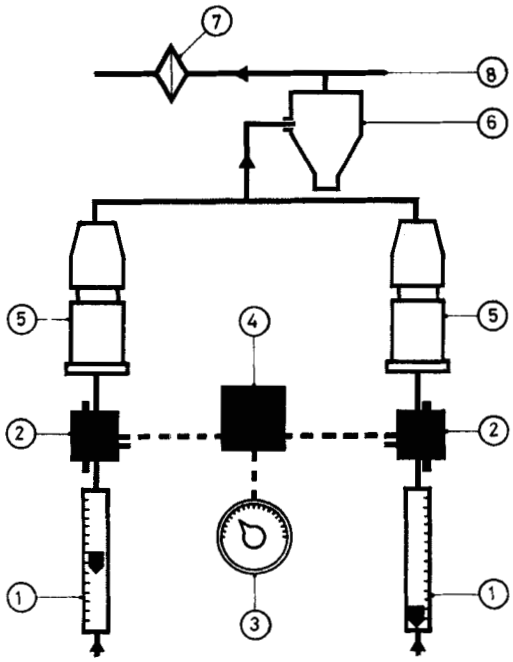

Figure 4—*Test rig used to evaluate powder flow from inhaler capsule. Key: 1, flowmeters; 2, solenoid valves; 3, timer; 4, changeover relay; 5, inhalers; 6, cyclone; 7, filter; and 8, air bleed.*

[6] G. A. Platon Ltd., Basingstoke, Hants, England.
[7] Bahco Ltd., Bahco House, London, E.C.1, England.
[8] Type 200, Alpine (Machinery) Ltd., Uxbridge, Middlesex, England.
[9] British Standard Institute, Specification No. 410.

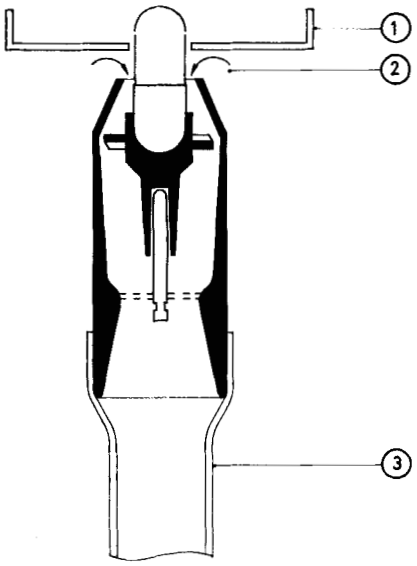

Figure 5—*Arrangement used to collect powder emerging directly from inhaler capsule. Key: 1, powder collection tray; 2, air flow lines; and 3, connection to vacuum line.*

various powder fractions using a Tevopharm Cap. III[10] semiautomatic filling machine.

A test rig was constructed to provide a reproducible air flow through the inhaler (Fig. 4). Air was drawn through an inhaler, at rates that could be varied by adjusting an air leak, and measured by means of a flowmeter. An exactly similar circuit was arranged parallel to the test circuit so that air flow rates could be accurately adjusted. The test circuit was brought into operation for a predetermined period by means of a timer[11] energizing solenoid valves[12]. Powder aerosol in the air from the test circuit was removed

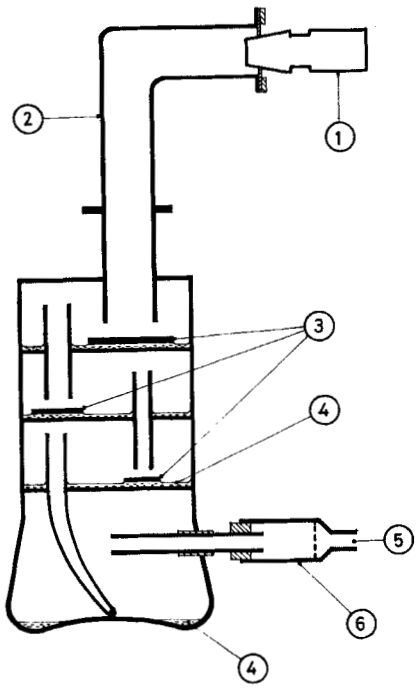

Figure 6—*Multistage liquid impinger. Key: 1, inhaler; 2, simulated "throat"; 3, impaction stages; 4, impingement liquid; 5, to vacuum; and 6, filter.*

[10] Tevopharm-Schiedam N.V., Holland.
[11] Type 144, Crouzet (England) Ltd., Thanet House, Brentford, Middlesex, England.
[12] Type 4801, Burkert Contromatic Ltd., South Ascot, Berks, England.

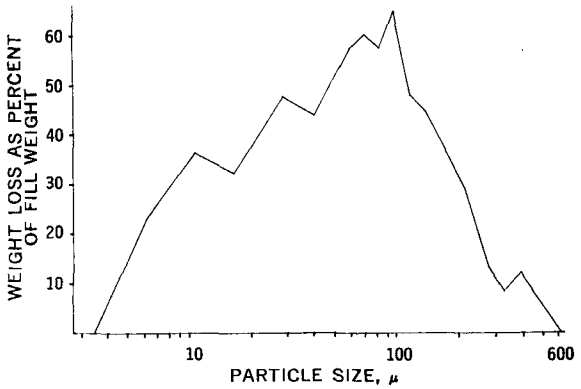

Figure 7—*Loss of powder from the inhaler capsule under standard air flow conditions as mean particle size of powder action was changed.*

by a cyclone, backed by a filter placed immediately before a vacuum pump. Holes were drilled at 0.07-cm. (0.028-in.) diameter in filled No. 2 hard gelatin capsules and "flash" removed with a scalpel blade. The weight of powder lost in each experiment was determined by weighing 100 filled capsules, representing each size fraction, before and after exposure to the air flow. An air flow rate of 60 l./min. and an air flow period of 2.0 sec. were used.

Assessment of Powder Dispersion—The inhaler has two distinct actions: (*a*) the transfer of the powder from the capsule into the airstream, and (*b*) the breakup and dispersion of the powder cloud into fine particulate material suitable for inhalation. Examination of powder emerging from the capsule inside the inhaler was carried out using the arrangement shown in Fig. 5, the inhaler capsule being exposed by cutting away part of the casing. Suction applied at the mouthpiece caused the capsule to spin and transport powder to the punctured holes. The powder particles emerging directly from the capsule were collected on a tray coated with a thin film of polyethylene glycol 300 as an adhesive; size analysis was carried out by microscope counting[13].

Particle-size analysis of the whole cloud produced after the particles pass through the inhaler may be carried out using the cascade impaction technique described by May (8) and widely used in aerosol studies. Commercially available instruments based on this technique are usually designed for the analysis of dilute aerosols and are unsuitable for concentrated powder aerosols such as those generated by the inhaler. A more suitable instrument for analysis is the multistage liquid impinger (9) (Fig. 6), in which the impaction surfaces consist of sintered-glass disks immersed in liquid, backed up by a liquid swirl impinger to trap very fine particles. A 90° glass bend, 2.5 cm. in diameter, coated with polyethylene glycol 300 as adhesive, was fitted prior to the first stage to simulate impaction conditions in the throat, An additional impaction stage and filter separated the powder into six fractions. The air flow rate was set at 60 l./min. by adjustment of a vacuum pump. The inhaler with drilled capsule in place was inserted, the pump was switched on, and

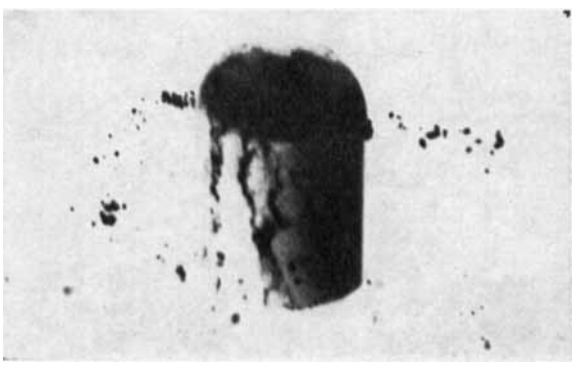

Figure 8—*Frames from high-speed film showing large agglomerates of drug and lactose emerging from inhaler capsule prior to dispersion.*

[13] British Standard Institute, Specification No. 3406: Part 4, 1963.

Table I—Analysis of Inhaler Cloud by Multistage Liquid Impinger

Percent by Weight of Drug Retained on					
"Throat"	1	2	3	4	Filter
68.9	7.2	4.2	7.0	11.3	1.4

the flow of air was maintained for 30 sec. Water was used as the impingement liquid. Each stage was carefully washed out and diluted appropriately with phosphate buffer at pH 7.4. The cromolyn sodium content was determined spectrophotometrically at 326 nm. using absorptivity (*a*) 16.3.

RESULTS AND DISCUSSION

Instrumented Inhaler—The traces obtained when air was inhaled through the inhaler were of the form illustrated in Fig. 3. The inhaler air flow rate rapidly built up to a maximum, which was maintained for most of the inhalation period, followed by a gradual decay. Vibrations in the rotor began at flow rates of 35–40 l./min. and ceased when the inhalation rate fell below this value. Powder emission followed almost exactly the occurrence of the vibrations. The short time interval between the detection of vibration and powder discharge was attributed to the time required for powder transport from the capsule to the location of the photoelectric cell across the mouthpiece of the inhaler. Powder was only discharged during inhalation through the device, which thus automatically coordinated dispensing of the drug with the inhalation of air.

Effect of Particle Size on Powder Flow from the Capsule—The graph of Fig. 7 shows the variation in lactose powder loss from the inhaler capsule under standard air flow conditions as the mean particle size of the powder fraction was changed. Maximum powder flow was obtained with powder particles in the size range of 70–100 μ, with marked reductions occurring with the finer and coarser samples. Examination of capsules containing the lactose powder less than 10 μ in size revealed extensive coating of the internal wall of the hard gelatin capsule. Poor flow of fine powder particles is a well-documented occurrence (10); the vibratory motion of the capsule probably was inadequate to overcome the interparticulate and adhesive forces between the finer particles and the gelatin. In the case of very coarse particles, such forces would be unlikely to play any part. A possible explanation for the low rates of flow found is that intermittent blocking occurred during passage of the particles through the drilled holes.

The poor flow exhibited by the finest powders is of significance in formulation since these particle sizes are important in inhalation

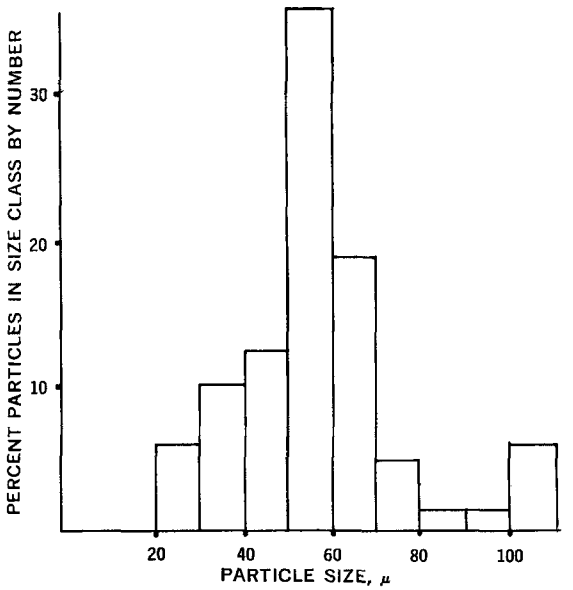

Figure 9—*Particle-size distribution of agglomerates emerging directly from inhaler capsule.*

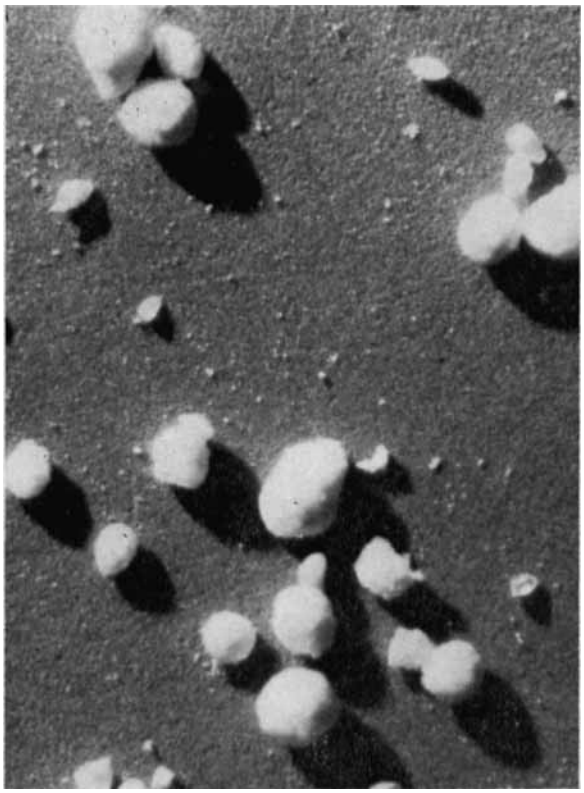

Figure 10—*Photomicrograph of larger agglomerates of drug and lactose which emerge directly from the inhaler capsule prior to dispersion. The rounded shape is characteristic.*

therapy. Means were sought to overcome this problem, the simplest being to mix the very fine particles with a suitable flow aid. The use of a proportion of particles in a coarser size range has been found to be effective. When powder mixtures of this type are prepared, any degree of flow can be produced according to the proportion of free-flowing diluent selected. For example, cromolyn sodium, after grinding in a micronizer, typically has a mass median diameter of 2.6 μ with a geometric standard deviation of 1.4 measured by the Coulter counter. The material is cohesive, exhibits the poor flow properties characteristic of powders in this particle-size range, and will not empty alone from an inhaler capsule. When mixed with coarse lactose, containing 70% by weight of particles between 30 and 60 μ in size, the flow properties improve significantly; preparations can then be formulated which are acceptable in routine management of patients with airways disease.

Powder Dispersion—Examination of the material emerging directly from the capsule showed decreasing amounts of aggregation of the particles as the mean size of the fractions increased. This finding was not unexpected considering the known properties of powders (4, 10). When mixtures of fine and coarse particles were used, examination of the material emerging from the capsule revealed that the fine particles were formed into large agglomerates, either alone or around the coarser flow aid. High speed photography confirmed this effect (Fig. 8). A particle-size distribution for the agglomerates from one batch of a 1:1 mixture of coarse lactose and micronized cromolyn sodium is shown in Fig. 9, which reveals an absence of fine particles less than 20 μ. The turbulent airstream created in the inhaler by a patient's deep inspiration causes many of these agglomerates of drug and lactose to break up, producing fine particles which pass with the inhaled air into the respiratory tract (Figs. 10 and 11). A typical analysis, by the multistage impinger, of the cloud generated by the inhaler is given in Table I. The stages of the impinger represent increasing fineness of particles and have increasing possibility of penetration into the respiratory tract, the 50% effective cut-off sizes (11) being approximately 20 μ for the "throat" and 9.8, 5.5, 3.1, and 0.46 μ for successive stages. About 25% by weight of the cromolyn sodium particles are less than 6 μ in size and, hence, likely to penetrate into the deeper airways (9).

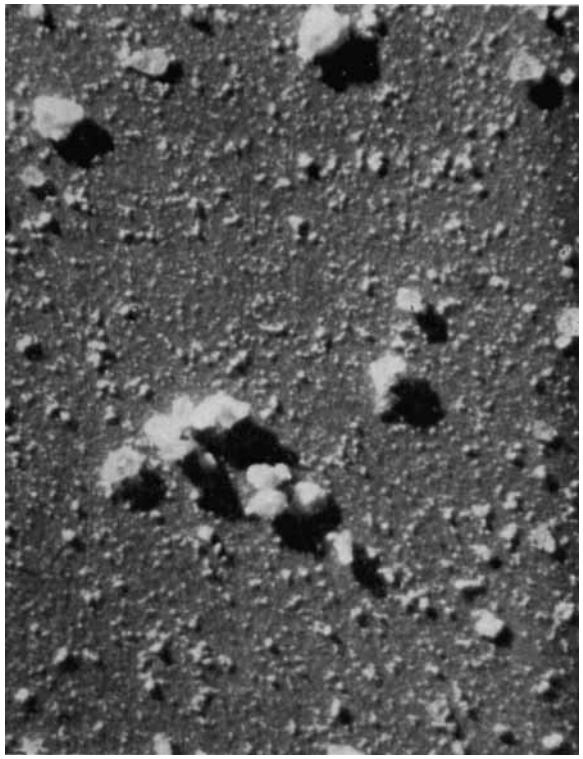

Figure 11—*Photomicrograph of powder after dispersion by the inhaler. The large particles are lactose with some adherent fine drug particles.*

The ability of the inhaler to disperse very fine powders is limited ultimately by the energy available from the patient's inhalation effort. Further work in the design of inhalers of this type and in the properties of powders for inhalation should lead to increased knowledge of the mechanisms of powder dispersion in turbulent airstreams and improvement in the efficiency of such devices.

CONCLUSION

The new inhaler achieves coordination of inspiratory effort and inhalant administration by a mechanism involving a rotor, driven by the inhaled air, avoiding the use of propellants such as liquified fluoroalkane gases. The drug is presented in convenient unit dosage form, and the total dose administered can be controlled by the capsule fill weight. Release of medicament occurs early in the inhalation period and continues while adequate air flow into the lungs is maintained, providing distribution of inhalant over the surface of the airways. The preparation of powders with the requisite flow and dispersion properties suitable for use in devices of this type represents a challenge in pharmaceutical technology. The characteristics of the inhaler will prove of interest in the administration of other drugs *via* the inhalation route.

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ACKNOWLEDGMENTS AND ADDRESSES

Received February 16, 1971, from the *Research and Development Laboratories, Fisons, Pharmaceutical Division, Loughborough, Leicestershire, England.*

Accepted for publication June 2, 1971.

Presented in part to the Industrial Pharmaceutical Technology Section, APhA Academy of Pharmaceutical Sciences, Washington, D. C. meeting, April 1970.

The authors acknowledge the technical assistance of Mr. K. Brown, Mr. S. Gregory, and Mr. J. E. Taylor.

Automated *In Vitro* Dissolution-Rate Technique for Acidic and Basic Drugs

ASHOK C. SHAH

Abstract □ A continuous, automated, potentiometric titration technique for studying *in vitro* dissolution rates of acidic and basic type drugs from their compressed tablet formulations is described. The application of this technique was demonstrated by evaluating dissolution rates of sulfa- and sulfonylurea tablets, representing acidic drugs, and an antibiotic drug tablet formulation, representing a basic drug. The results obtained by the titration assay were confirmed by other analytical methods. Tablet excipients (lactose, sucrose, starch, magnesium stearate, polyvinylpyrrolidone, calcium phosphate, fumed silica, talc, and microcrystalline cellulose) present in these formulations did not interfere with the titration assay. The titration technique was utilized also in measuring release rates from drug pellets having constant surface area.

Keyphrases □ Tablets, *in vitro* dissolution rates—determination, automated potentiometric titration method □ Potentiometric titration, automated—determination, *in vitro* tablet dissolution rates

An automated method for determining *in vitro* dissolution rates of solid dosage forms was developed by Schroeter and his coworkers (1, 2). The essential features of this method were the circulation of the dissolution fluid through a spectrophotometer flowcell and the automatic recording of the change in absorbance as a function of time. Dissolution-rate determinations using this principle were reported in several studies (3–6), and this technique is still probably widely employed throughout the pharmaceutical field. The automated spectrophotometric method, however, cannot be applied to many solid dosage forms for a number of reasons, including the lack of characteristic absorbance by the drug molecule, interference by other tablet ingredients in the spectral assay, and the use of dissolution fluid containing pepsin and pancreatin enzymes. In such instances, these studies have to be conducted by withdrawal of dissolution fluid samples at several time intervals and their subsequent individual sample analysis to determine the drug concentration.

The present study was initiated to develop a convenient *in vitro* dissolution-rate procedure for the enteric coated tablet formulations of a weak basic drug. The spectrophotometric method proved to be unapplicable in this case because of the reasons mentioned earlier. Hence, a continuous titration technique was developed for the automated dissolution-rate evaluation of this product. According to this technique, the drug, as it dissolves in solution, is rapidly titrated by the addition of the required amount of titrant liquid to maintain a set constant pH of the dissolution media. This is monitored by a pH-stat titrator instrument. From the amount of titrant added as a function of time, which is recorded on a chart, the dissolution rate of the drug is estimated. A similar technique was previously employed in evaluating dissolution and reaction rates of antacid compounds (7, 8). In the present report, the general application of the titration technique as an automated dissolution method for the tablet formulation of acidic or basic drugs is evaluated. Also, the use of this technique in studying dissolution rates from a constant-surface pellet of a drug was investigated.

EXPERIMENTAL

Test Samples and Reagents—Two different 250-mg. compressed tablet formulations of an antibiotic drug and their corresponding enteric coated tablets, 500-mg. compressed tablets of a sulfa drug, and 500-mg. compressed tablets of sulfonylurea were used as samples. The excipients present in these formulations were lactose, starch, sucrose, polyvinylpyrrolidone, calcium phosphate, fumed silica, talc, magnesium stearate, and microcrystalline cellulose. The quantity of excipients present in these formulations constituted approximately 10–50% of the total tablet weight.

Hydrochloric acid and sodium hydroxide titrant solutions of known normality were prepared in carbonate-free distilled water. Pancreatin NF, polysorbate 80 USP, and other chemicals (all analytical grade) were used.

Instrumentation—The instrumental setup shown in Fig. 1 was employed in most of the experiments. It consisted of a pH-stat automatic recording titrator[1] (A), titration buret (B), dissolution test apparatus (C), a pulsating-type pump[2] (D), and a Beckman model DBG recording spectrophotometer (E). With this setup, the dissolution rates could be determined simultaneously by the automated titration technique as well as by the automated spectrophotometric analysis. Both these techniques were employed in the

[1] Radiometer, Copenhagan Type TTTI titrator and Type SBR2 Titrigraph.
[2] New Brunswick Corp. model PA-60 pump.