Powder Inhalation Aerosol Studies I: Selection of a Suitable Drug Entity for Bronchial Delivery of New Drugs

Z. T. CHOWHAN [x] and A. A. AMARO

Abstract □ Micronized powders of 7-methylsulfinyl-2-xanthone carboxylic acid and its sodium salt with similar particle-size distributions were used in formulating powder inhalation aerosol dosage forms. Large differences between the two micronized powders were observed in the distribution on plates of the air sampler. The micronized powders were highly cohesive, the sodium salt being slightly more cohesive than the carboxylic acid. The absorption and desorption isotherms obtained at 23 and 37° indicated considerable moisture uptake following equilibration under different relative humidities and the occurrence of hysteresis of moisture content for the sodium salt–lactose blend and the empty gelatin capsules. The carboxylic acid–lactose blend gained only a small amount of moisture. The drug distribution to the lower plates of the air sampler from the sodium salt blend was reduced to a negligible amount after equilibration at high relative humidities during the moisture absorption experiment. There was no significant change in the drug distribution to the lower plates of the air sampler for the carboxylic acid–lactose blend equilibrated up to 93% relative humidity at 23° and up to 100% relative humidity at 37° during the moisture absorption experiment. During the moisture desorption experiment, essentially no change in the drug distribution to the lower plates of the air sampler was observed for the sodium salt blend at 23 and 37° and the carboxylic acid blend at 23°. At 37°, the drug delivery from the carboxylic acid blend appeared to improve during the desorption experiment. These data suggest that studies of this nature may be useful in the selection of appropriate drug species for designing powder aerosol dosage forms during early phases of the drug development program.

Keyphrases □ Aerosols, powder inhalation—micronized powders of substituted 2-xanthonecarboxylic acid and sodium salt, effect of lactose concentration, humidity, and temperature □ 2-Xanthonecarboxylic acid, substituted—and sodium salt, micronized powders used in formulating powder inhalation aerosols, effect of lactose concentration, humidity, and temperature □ Dosage forms—powder inhalation aerosols, micronized powders of substituted 2-xanthonecarboxylic acid and sodium salt, effect of lactose concentration, humidity, and temperature □ Powders, micronized—substituted 2-xanthonecarboxylic acid and sodium salt used in formulating powder inhalation aerosols, effect of lactose concentration, humidity, and temperature

Inhalation aerosols offer a unique drug delivery system for the administration of pharmacologically active substances in the treatment of bronchial obstructive disorders. By delivering drugs directly to the affected organs, relatively small amounts of very potent medicinal compounds may be employed with minimal side effects. The most popular dosage forms in this category are pressurized inhalation aerosol solutions and suspensions, inhalation aerosol solutions, and powder inhalation aerosols.

BACKGROUND

The use of fluorocarbon propellants in the preparation of pressurized inhalation aerosols has suffered adverse publicity. The major limitation of this delivery system, however, lies in the amount of drug that can be delivered per actuation. The total drug concentration in solution- and suspension-type pressurized systems is limited by the drug solubility in the fluorocarbon propellants and by the physical stability of the suspension. Most fluorocarbon-propelled canisters intended for bronchial drug delivery require synchronization of the inhalation and the generation of the aerosol cloud during the breathing cycle. In a recent clinical study (1), in spite of careful instructions, 14% of the patients used the pressurized device inefficiently. When patients who were unable to inhale correctly from a pressurized canister used a breath-actuated powder inhalation device, 95.5% had no difficulty (1).

Continuous liquid aerosol therapy is used widely in the treatment and control of obstructive respiratory diseases, particularly cystic fibrosis. The output of the liquid aerosol from inhalation aerosol solutions is limited by the physicochemical characteristics of drug solubility and solution viscosity (2). The evaporation of solvent continually increases the concentration of solute in the liquid remaining in the nebulizer. This increase, in turn, increases the concentration of airborne solute in the useful aerosol and shifts the size distribution of the residual aerosol to a larger volume.

One important factor that determines the site and extent of drug delivery to the respiratory tract is the particle-size distribution of the aerosol cloud. For formulating an aerosol suspension in pressurized canisters and for designing a powder aerosol dosage form, the drug particles should be in a finely divided state. Micronization is generally used to ensure that the drug particles are in the desirable particle-size range. The formulation of the powder inhalation aerosols of new drug substances requires some knowledge of the solid-state properties of the drug. Micronized powders of complex organic medicinals are generally cohesive and adhesive.

The generation of an aerosol cloud comprised of singly dispersed solid particles from micronized powders is impossible. In some cases, the powder aerosol efficiency is improved by adding diluents. Unfortunately, only lactose has been studied and has gained general acceptance. Thus, the solid-state properties of the micronized drug substance generally control the characteristics of the generated aerosol. If the drug is hygroscopic, it may present additional problems of moisture transfer from the atmosphere to the hard gelatin capsule and to the drug in the capsule, acting as a sink (3). Unless careful controls are maintained during manufacturing, packaging, and storage, the net result may be a serious loss in the aerosolization efficiency.

Because of the nature of the powder inhalation aerosol dosage form, solid-state properties of the potential drugs may be important in determining the site and extent of drug delivery to the tracheobronchial tree. A proper choice between an organic acid and a salt, for example, may significantly affect the drug delivery characteristics. This investigation compared the aerosolization efficiency of 7-methylsulfinyl-2-xanthone carboxylic acid (I) and its sodium salt (II) from powder aerosol blends containing different ratios of lactose. Relative changes in the aerosolization efficiency of drug–lactose blends were monitored following equilibration of the powders under various humidity conditions at 23 and 37°. Comparative information on the aerosolization efficiency and changes in the aerosol characteristics as a function of the storage conditions was obtained. These data, in addition to the comparative absorption rates from the alveolar–capillary membranes (4), can be employed to select the most appropriate drug entity for designing a powder inhalation aerosol dosage form early in the drug development program.

EXPERIMENTAL

Materials—Phosphorus pentoxide[1] (solid), lithium chloride[1], potassium acetate[1], hydrated magnesium chloride[2], hydrated potassium carbonate[1], hydrated magnesium nitrate[2], sodium nitrite[1], sodium chloride[1], potassium chloride[1], monobasic ammonium phosphate[1], lead nitrate[2], and hydrochloric acid[1] were all analytical reagent grade. Potassium hydroxide[3] and hydrous lactose[4] were USP grade. The hard gelatin capsules[5] were size 2, with a brown cap and opaque brown body. The purity of I and II[6], as determined by high-pressure liquid chromatography, was 98.4 and 98.8%, respectively. The loss on drying at 60° under vacuum at equilibrium was 0.07% for I and 2.2% for II.

Methods—Similar conditions were used to micronize[7] I and II. The

[1] Mallinckrodt Chemical Works, St. Louis, MO 63160.
[2] J. T. Baker Chemical Co., Phillipsburg, NJ 08865.
[3] Matheson, Coleman & Bell, Norwood, OH 45212.
[4] Foremost Food Co., Foremost-McKesson, San Francisco, CA 94140.
[5] Elanco Products Co., Indianapolis, IN 46206.
[6] Institute of Organic Chemistry, Syntex Research, Palo Alto, Calif.
[7] Production micronizer, 10.1 cm (4 in.), Jet Pulverizer Co., Palmyra, N.J.

grind and feed pressures were 30–35 and 35–40 psi, respectively, throughout the micronization procedure. Regular grade lactose was screened[8] through a 200-mesh screen to remove particles smaller than 75-μm diameter. Samples of the drug–lactose blends were prepared by mixing the micronized drug and sieved lactose with a spatula. For the air sampler[9] particle-size distribution studies, blends of drug and lactose at different ratios were prepared. Hard gelatin capsules containing 10 mg of the active compound were made and used in the Andersen impactor studies.

Powder blends containing one part of micronized drug and two parts of sieved lactose were used in the relative humidity studies. The powder blends were evenly spread and accurately weighed (approximately 1.5 g) in 6-cm diameter glass petri dishes (bottoms only). Approximately 1.5 g of empty hard gelatin capsules, separated into caps and bodies, also was weighed accurately in 10-cm diameter petri dishes. The accurately weighed powder blend samples and empty capsule samples were used to monitor the weight changes as a function of the relative humidity. Additional samples of the powder blends also were prepared (approximately 3 g) in 10-cm diameter petri dishes. Approximately 200 mg of the powder blends was sampled following equilibration at each specific humidity condition, and capsules containing 10 mg of active compounds were immediately prepared and used in the air sampler test.

For maintaining constant relative humidity conditions at room temperature and 37°, desiccators containing saturated salt solutions were employed. The salt solution selections were similar to those used by Bell *et al.* (3) (Table I). For the water absorption curve, the samples were prepared by drying in desiccators containing phosphorus pentoxide at 45° until there was no weight loss. The samples were transferred to higher humidity conditions after each equilibration. The samples for the water desorption curves were prepared by equilibration above water or a salt solution at 23 or 37°. These samples were then transferred to lower humidity conditions after each equilibration.

The particle-size distribution of the micronized I and II was determined[10]. The electrolyte for the acid was 0.6% HCl, which was equilibrated with the micronized powder at room temperature. 2-Propanol containing 5% ammonium thiocyanate equilibrated with the micronized powder at room temperature was used as an electrolyte for the sodium salt. The electrolytes were filtered using a 0.45-μm average pore size filter[11]. Approximately 2 mg of the micronized powder was suspended in 50 ml of electrolyte solution using an ultrasonic bath[12], and the suspension was suitably diluted and used in the particle-size determination. A 50-μm aperture tube and a sample volume of 50-μl were used. The instrument was calibrated using 2.02-μm diameter latex particles[10], and the mean of three counts was taken.

Cohesiveness of the micronized powders was measured by a modification of the method introduced by Carr (5). A sonic sifter[13] was used in the determination of cohesiveness of micronized powders. For the test, 2 g of the micronized powder was placed on top of a nest of 60-, 120-, and 200-mesh screens. The sieve assembly was vibrated for 29 sec at a pulse and sift setting of 6. The amount of powder left on each sieve was weighed, and the results are expressed by scoring on a scale that allocated cohesiveness points for each 0.1 g as follows: on 60 mesh, 5 points; on 120 mesh, 2 points; and on 200 mesh, 1 point.

Figure 1 shows a diagram of the apparatus used for determining the particle-size distribution using an air sampling technique. It consisted of an air sampler[9], a throat assembly[14], an air pump[15], and a developmental inhalation device. The air pump was adjusted to draw 29 ± 1 liters/min of air through the air sampler using a flowmeter[16].

The cap of the hard gelatin capsule containing the powder blend was removed, and the body was inserted into the inhalation device. The inhalation device was then attached to the throat adaptor. The whole system was inspected for a tight fit. The pump was operated for 3 sec. Then the capsule body was removed and set aside, along with the top, for rinsing. Five capsules were emptied in the air sampler one after the other using the described procedure.

The inhalation device, the adaptor, and the capsules were washed with 0.1% potassium hydroxide solution into a 140-mm glass petri dish bottom. The throat and the first two aluminum pieces of the air sampler were rinsed into the next petri dish. Each of the seven glass plates was rinsed with 0.1% potassium hydroxide into separate glass petri dish bottoms. The aluminum piece below each plate was tapped to collect any adhering powder into the corresponding petri dish. The contents of each petri dish were transferred to volumetric flasks of appropriate sizes and diluted to volume with water. The absorbance of each sample was determined at 342 μm. The total amount of active compound recovered from each stage was calculated and used to determine the fraction of the total on each stage.

Table I—Saturated Salt Solutions Used for the Maintenance of a Constant Relative Humidity

Salt	Relative Humidity, % 23°	37°
Lithium chloride	13	11
Potassium acetate	20	20
Magnesium chloride hexahydrate	33	32
Potassium carbonate·1.5H_2O	44	40
Magnesium nitrate hexahydrate	54	50
Sodium nitrite	65	62
Sodium chloride	76	75
Potassium chloride	85	82
Monobasic ammonium phosphate	93	91
Lead nitrate	97	96
Water	100	100

RESULTS AND DISCUSSION

The results of the particle-size distribution of I and II micronized powders are given as log–probability plots in Fig. 2. Although the particle-size distributions were similar, 89% of the mass of the sodium salt was smaller than 5-μm diameter compared to the 82% of the mass of the carboxylic acid. These differences were also reflected in the mass median diameter, 2.5 μm for II compared to the 2.9 μm for I.

The cohesiveness of micronized I equilibrated at 23° with 0, 28, and 93% relative humidities was 75.9, 79.6, and 77.9, respectively. The cohesiveness of II equilibrated at 23° with 0, 28, and 93% relative humidities was 83.2, 84.1, and 86.7, respectively. The cohesiveness of these powders was measured by sifting the powders through the specified screens and allocating points on a scale of zero to 100. If all material remained on the 60-mesh screen, the score would have been 100; it would have been zero

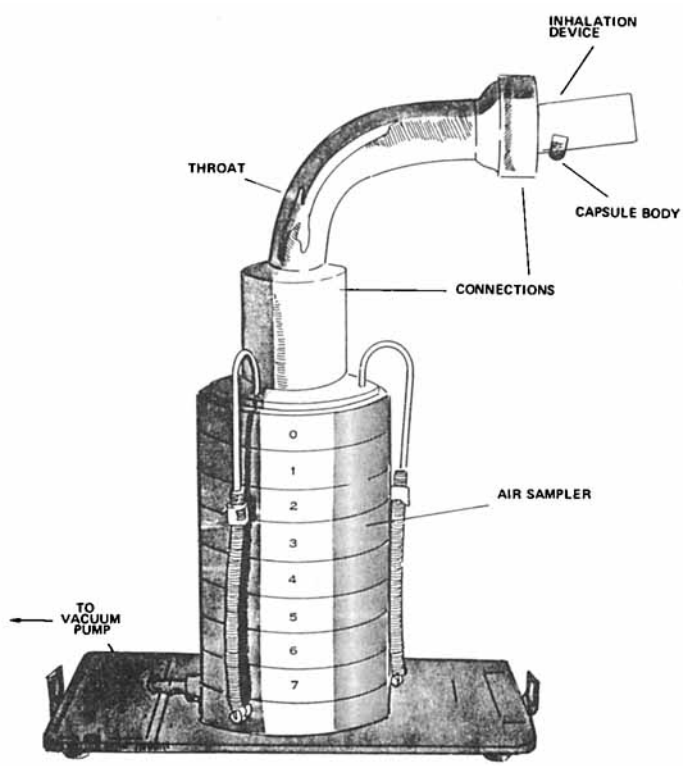

Figure 1—*Schematic representation of the apparatus used in testing the delivery of drugs to various stages of the air sampler.*

[8] Ro-Tap testing sieve shaker, W. S. Tyler Co., Cleveland, Ohio.
[9] Model 21-000, Andersen 2000, Salt Lake City, UT 84107.
[10] Coulter counter model TA, Coulter Electronics, Hialeah, FL 33010.
[11] Metricel GA-6, Gelman Instrument Co., Ann Arbor, Mich.
[12] Model 8845-6, Cole-Parmer Instrument Co., Chicago, IL 60648.
[13] Model L3P, Allen Bradley Co., Milwaukee, Wis.
[14] Syntex Research Shop, Palo Alto, Calif.
[15] Model 1531-109-G288, Gast Manufacturing Corp., Benton Harbor, Mich.
[16] Size 5, Roger Gilmont Instruments, Great Neck, NY 11021.

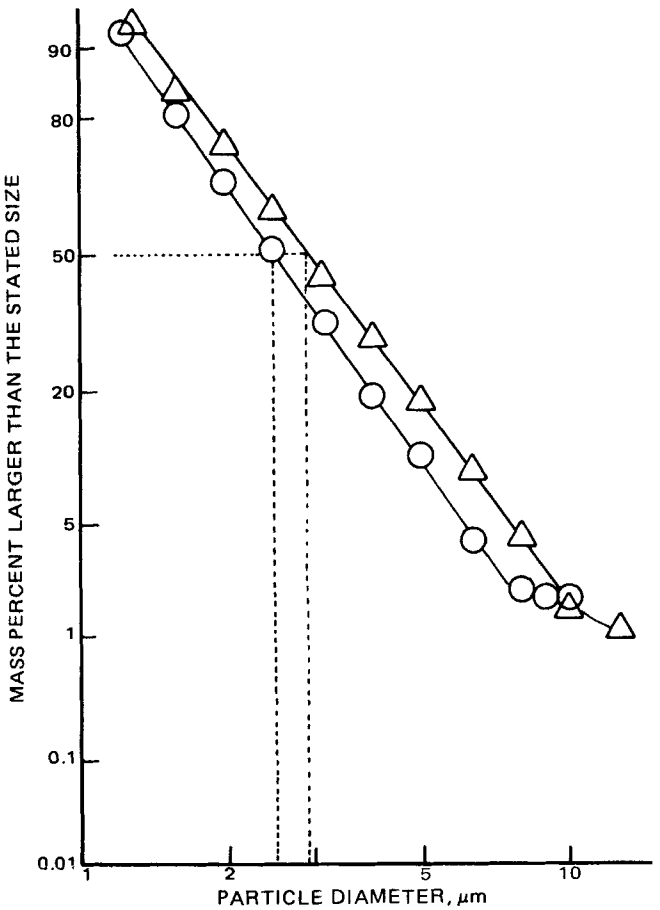

Figure 2—*Particle-size distributions of the micronized powders. Key: △, I; and ○, II.*

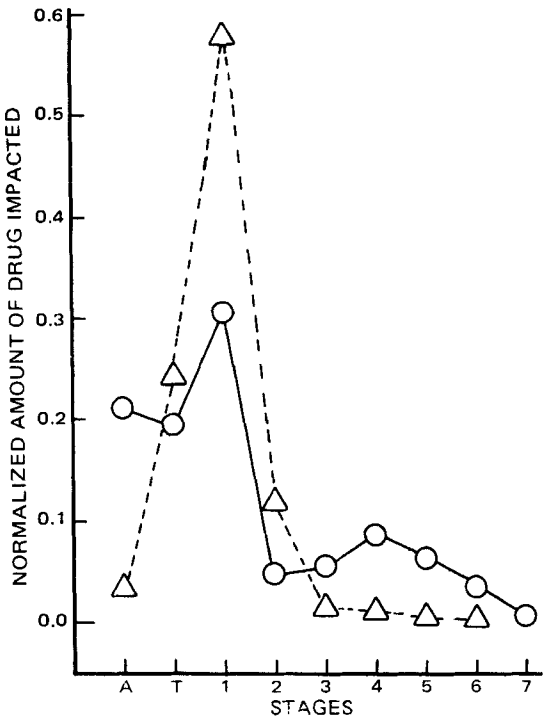

Figure 3—*Distribution of drug to stages of the air sampler under ambient conditions. Stage A represents the amount remaining in the capsule plus the amount impacted in the inhalation device. Stage T represents the amount impacted on the throat plus the amount impacted on stage zero. Key: △, II; and ○, I.*

if all powder passed through a 200-mesh screen. The intermediate results provide a suitable measure of the cohesiveness by relating it to the amount of energy spent in pulling apart the aggregates in a specified time.

These results are means of three experiments and indicate that both powders are highly cohesive, II being more cohesive than I at all relative humidities. The cohesiveness of the powders did not increase significantly as a function of the relative humidity, perhaps because both powders gave a relatively high score for cohesiveness after equilibration at 0% relative humidity.

Lactose was added to the micronized drugs to improve aerosolization properties by breaking up the cohesive bonds of the drug particles. Preliminary studies suggested that the lactose particles retained on a 200-mesh screen resulted in optimized aerosol properties. Microscopic examination of the lactose particles retained on a 200-mesh screen indicated no cohesion of lactose particles. It was not possible to test the cohesiveness of the mixture of micronized drug and coarse lactose particles. For testing cohesiveness by the described method, the particles of the powder mixtures must be smaller than the smallest screen size (200 mesh) used.

Figure 3 shows the delivery of I and II to the inhalation device, throat, and stages 1–7 of the air sampler from a mixture of 10 mg of drug and 20 mg of lactose. Indirect means of particle-size measurements such as impaction should be used for simulating powder inhalation aerosols, because the deposition of aerosol particles in the respiratory tract involves mechanisms such as inertial impaction, gravitational sedimentation, and Brownian diffusion. Impaction devices provide one simple method of determining activity distribution in terms of the aerodynamic diameter. The aerodynamic diameter is the diameter of a sphere of unit density having the same settling velocity as the particles in question, regardless of their shape and density. Thus, a small particle of high density has the same aerodynamic diameter as a large particle of lower density.

The impaction devices[9], like other similar devices, provide an *in vitro* model for the human lungs and have obvious similarities in its ability to separate particles of different sizes. At each stage of the impactor, air impinges upon a glass-collecting surface and is deflected through 90°. Particles with sufficient inertia are thrown out of the air stream onto a collecting surface. By decreasing the jet width, the air velocity through the jet becomes progressively larger so that each stage collects smaller particles than the preceding stage. The calibration of the instrument was carried out using spherical particles of carnauba wax.

The particles retained on each stage corresponded to a narrow size distribution. Stages 4–7 corresponded to particles smaller than 5.5-μm aerodynamic diameter. According to the air sampler model[9], these particles are deposited in the trachea, bronchi, and alveoli, depending upon the size. In the treatment of bronchial obstructive disorders, the powder aerosol should deliver particles to the tracheobronchial tree. The efficiency of delivering drug particles to stages 4–7 of the air sampler would be expected to serve as a good index of what is expected *in vivo*.

The data in Fig. 3 indicate that the delivery of the drug to stages 4–7 from the II–lactose blend was considerably lower than from the I–lactose blend (1.4% from II compared to 18.8% from I). This result could not be predicted based on the particle-size distribution data (Fig. 2), but it is not surprising since the particle-size distribution represents the size distribution of singly dispersed particles. The micronized powders of organic medicinals, however, do not generate aerosol clouds of singly dispersed particles because of the cohesive nature of the powders. The test used for measuring cohesiveness did not distinctly separate the large differences between the two powders seen in the air sampler study. Although micronized II appeared to be more cohesive than micronized I, the differences were small.

The results of the effect of various drug to lactose ratios on the percent drug impacted on stages 4–7 are given in Fig. 4. The drug delivery from the II blend was only improved when the powder mixture contained 10 mg of drug and 40 mg of lactose. A considerable increase in the percent drug delivery from the I blend was produced by adding lactose to the formulation. Although some differences in the cohesiveness of the I and II powders were observed, the test measuring cohesiveness was not sensitive enough to explain fully the large differences in the particle-size distribution.

These results clearly suggest that II would deliver a small fraction of the dose to the tracheobronchial tree compared to I and thus would not provide a suitable drug entity for a powder inhalation aerosol drug delivery system. However, I would be an appropriate drug entity for such a system and should deliver around 10% of the dose to the tracheobronchial tree.

Another aspect that should be thoroughly investigated during the initial stages of the development of a powder inhalation aerosol dosage

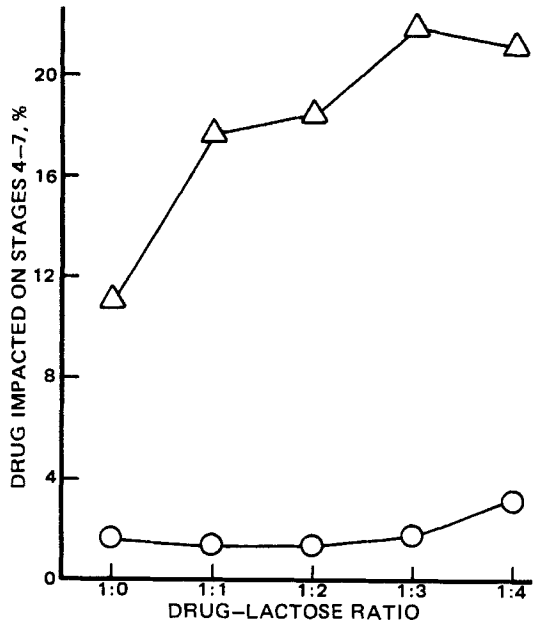

Figure 4—*Effect of drug–lactose ratio on the percent drug impacted on stages 4–7. Key: △, I; and ○, II.*

form relates to the physical stability of the powder with regard to the generation of an aerosol cloud. If the dosage form utilizes hard gelatin capsules, moisture exchange characteristics between the gelatin capsules and the powder should be evaluated carefully. Moisture could be gained or lost by pharmaceutical powders in contact with hard gelatin capsules (6). Bell *et al.* (3) reported that moisture transfer occurred from hard gelatin capsules to cromolyn sodium–lactose blends at elevated temperature during shelf tests, even if the materials were equilibrated previously at the same relative humidity.

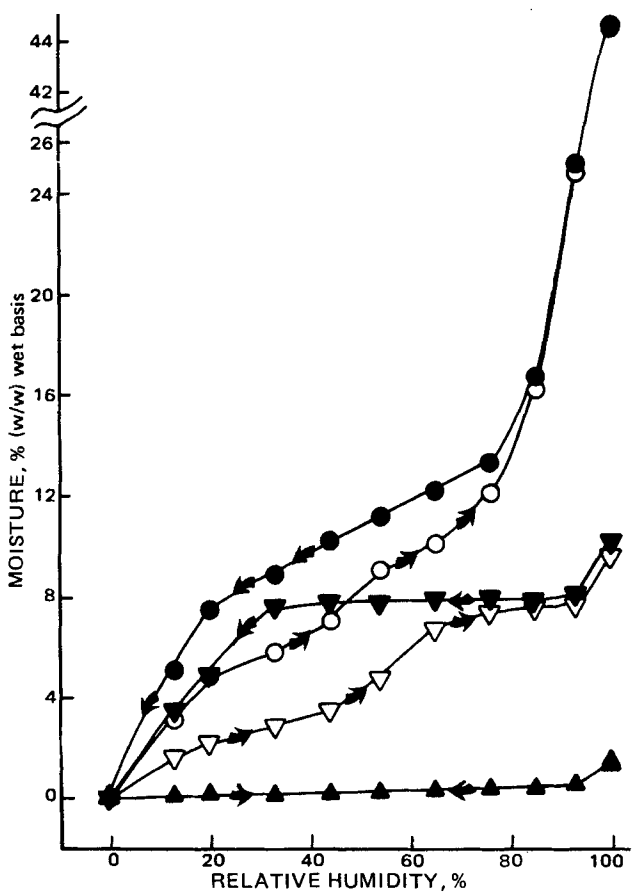

Figure 5—*Absorption and desorption isotherms at 23°. Key: ○ and ●, empty hard gelatin capsules; ▽ and ▼, II; and △ and ▲, I. Open symbols represent absorption isotherms; closed symbols represent desorption isotherms.*

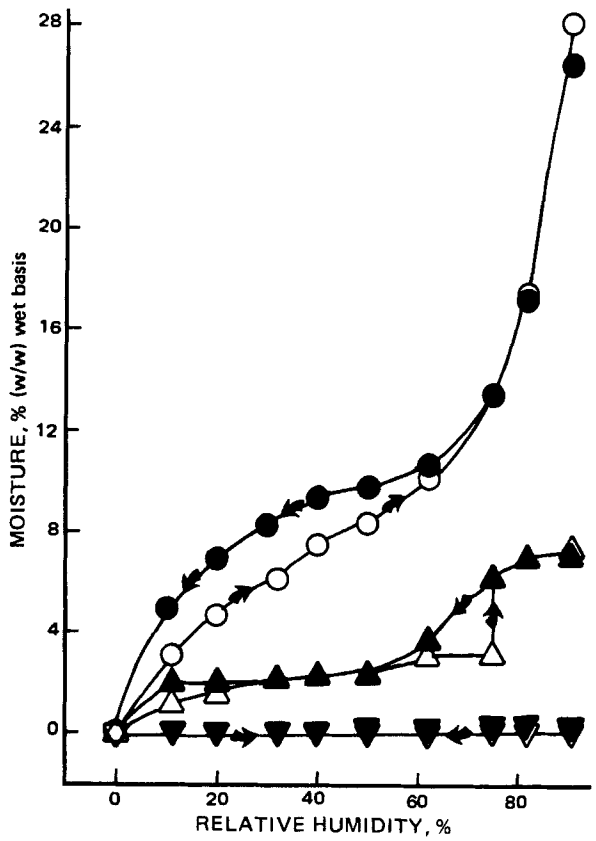

Figure 6—*Absorption and desorption isotherms at 37°. Key: ○ and ●, empty hard gelatin capsules; △ and ▲, II; and ▽ and ▼, I. Open symbols represent absorption isotherms; closed symbols represent desorption isotherms.*

Figure 5 gives the results of the absorption and desorption isotherms for hard gelatin capsules and for the blends of I and II (one part drug and two parts lactose) at 23°. These data indicate that the I blend absorbed only a small amount of moisture up to almost 93% relative humidity. At 100% relative humidity, the total amount of water absorbed was 1.5%. The absorption and desorption isotherms were essentially the same. However, the empty gelatin capsules absorbed a considerable amount of water, depending upon the relative humidity. Since the powder blend of I did not absorb significant moisture, the moisture transfer effects from the capsule wall to the powder blend would be minimal, even at high humidities. The II blend however, absorbed a considerable amount of water, depending on the relative humidity.

The absorption and desorption isotherms of the II blend and the empty gelatin capsules suggest the occurrence of hysteresis of the moisture content. The existence of a hysteresis loop for the capsules confirms earlier work (3). Hysteresis loops have been reported for other pharmaceuticals including cromolyn sodium (3), pentobarbital sodium, bacitracin, casein, corn starch, and aluminum magnesium silicate (7). Based on previous observations (3), one might predict that moisture transfer would occur from the hard gelatin capsule to the II blend even if the materials were equilibrated previously. These results suggest that the aerosolization efficiency of the II blend would decrease considerably as a result of the moisture transfer effects.

Figure 6 gives the results of the absorption and desorption isotherms for hard gelatin capsules and for the powder blends of I and II at 37°. No noticeable differences at 37° were seen in the absorption and desorption isotherms of the I blend. The percent moisture absorbed by the II blend was lower at 37°, and the absorption and desorption isotherms showed only a small hysteresis of moisture.

The results of the percent drug impacted on stages 4–7 of the air sampler as a function of the relative humidity during the moisture absorption experiment from the powder blends of I and II at 23 and 37° are given in Fig. 7. Drug delivery from the I powder blend equilibrated under various relative humidities at 23 and 37° remained essentially similar.

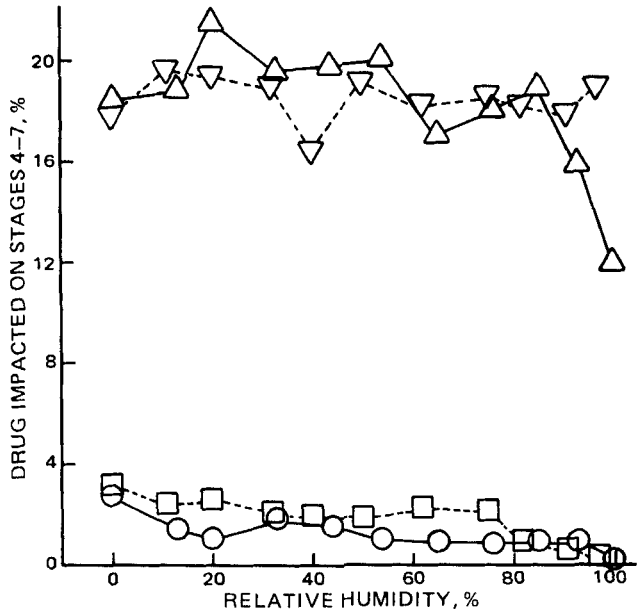

Figure 7—*Percent drug delivery to stages 4–7 as a function of the relative humidity during the moisture absorption experiment. Key: △, I at 23°; ▽, I at 37°; ○, II at 23°; and □, II at 37°.*

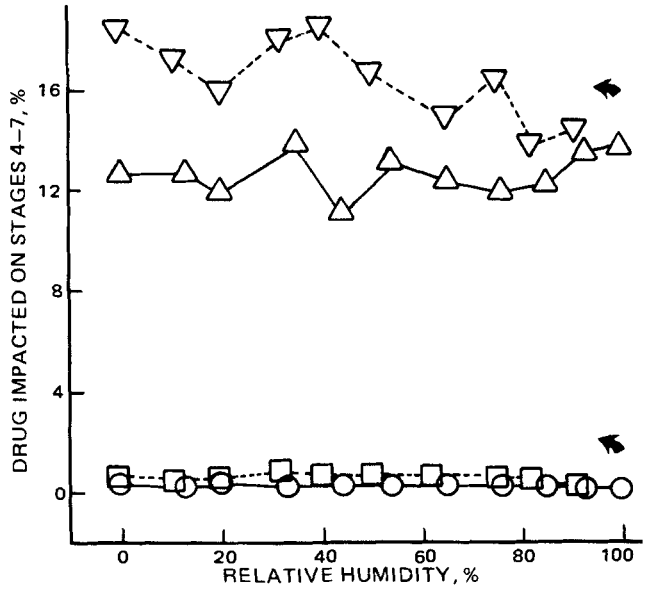

Figure 8—*Percent drug delivery to stages 4–7 as a function of the relative humidity during the moisture desorption experiment. Key: △, I at 23°; ▽, I at 37°; ○, II at 23°; and □, II at 37°.*

Some decrease in drug delivery was observed from the powder blends equilibrated at 23° under 100% relative humidity. The already low delivery of the II blend showed a considerable decrease after equilibration at higher humidities.

Similar data were obtained during the moisture desorption experiment for I and II blends (Fig. 8). Drug delivery remained essentially zero when the II blends, which were equilibrated under 100 or 91% relative humidity at 23 and 37°, were gradually equilibrated at lower humidities. At 23°, the drug delivery from the I blend initially equilibrated at 100% relative humidity did not improve during the moisture desorption experiment. Samples of the I blend initially equilibrated under 91% relative humidity at 37° showed some improvement in the air sampler delivery at lower humidities during the moisture desorption experiment. These results suggest that the reduction of the drug delivery from the I blend caused by moisture uptake at 91% relative humidity can be reversed by storing the powder blend at slightly elevated temperature.

Each data point in Figs. 3, 4, 7, and 8 represents the mean of five capsules emptied one after the other in the air sampler. The variability from test to test was small due to our interest in the sum of the drug impacted on stages 4–7 of the air sampler. The data in Figs. 7 and 8 showing the effect of two temperatures and various relative humidities on aerosol properties of the drug–lactose mixtures illustrate the good reproducibility of the test method.

In summary, the results demonstrate the importance of the selection of the proper drug entity in designing powder inhalation aerosol dosage forms. The usefulness of such studies at an early stage of the drug development program cannot be overemphasized.

REFERENCES

(1) I. C. Paterson and G. K. Crompton, *Br. Med. J.*, **1**, 76 (1976).

(2) J. H. Bell, P. S. Hartley, and J. S. G. Cox, *J. Pharm. Sci.*, **60**, 1559 (1971).

(3) J. H. Bell, N. A. Stevenson, and J. E. Taylor, *J. Pharm. Pharmacol. Suppl.*, **25**, 96P (1973).

(4) Z. T. Chowhan and A. A. Amaro, *J. Pharm. Sci.*, **65**, 1669 (1976).

(5) R. L. Carr, Jr., *Chem. Eng.*, **Jan. 8, 1965**, 163.

(6) W. A. Strickland, Jr., and M. Moss, *J. Pharm. Sci.*, **51**, 1002 (1962).

(7) W. A. Strickland, Jr., *ibid.*, **51**, 310 (1962).

ACKNOWLEDGMENTS AND ADDRESSES

Received August 16, 1976, from *Syntex Research, Palo Alto, CA 94304.*

Accepted for publication November 17, 1976.

[x] To whom inquiries should be directed.