weighed quantities of the powder were placed in 10.0 ml. of 75% 3A alcohol and allowed to stand approximately 1 hr. Hydrocortisone standards approximating the steroid content of powder samples were also prepared and analyzed. When absorbances of hydrocortisone standard and powdered tablets are plotted, a single line (Fig. 5) can be drawn through absorbance values for both standard and tablets. Covariance analyses of the data were performed, and no significant differences in results were found.

Studies were performed to determine the efficiency of the automated procedure by adding varying amounts of powdered tablets to a particular standard. Table II shows that recoveries were good.

Assays of steroid tablets were carried out for 5 lots of each particular steroid by the automated procedure and compared to the method essentially as directed by U.S.P. XVII. The data in Table III show good agreement. The automated procedure is suggested for single-tablet assays and should be of value when complying with content-uniformity tests of U.S.P. XVII and N.F. XII.

After completion of this report, several modifications in the automated procedure were made that are considered worthy of reporting. Tetrabutylammonium hydroxide is substituted for tetramethylammonium hydroxide, and filtration of this reagent is no longer a requirement. A small glass wool in-line filter is placed in the flowing stream just prior to the cell debubbler, eliminating the possibility of eroded tubing and other particles entering into the cell.

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Design and Operation of a Laboratory Glass Spray Drier

By JOHN D. TOPHAM

A spray drier made from borosilicate glass is described, which has been used to dry streptomycin without loss of activity and also other pharmaceuticals. Its advantages over other spray driers are: low cost, complete vision of the drying process, and its ease of adaptation to produce sterile powders.

MANY PAPERS have been published on the spray drying of pharmaceuticals (1–5) since the erection of a spray drier at Manchester University in 1939 (6). So far, to the author's knowledge, no work has been published on the spray drying of antibiotics, although one manufacturer has installed a spray drier for this purpose. All the spray driers which are used in industry are made of metal, which is not a satisfactory material when solutions of substances, which are very sensitive to oxidation, are to be dried. Since glass is used to replace metal in the apparatus described, oxidative discoloration does not take place when streptomycin is dried in the apparatus. Also, it is difficult to observe the drying process if metal apparatus is used. These 2 considerations, plus cheapness, persuaded the author to design a spray drier made of borosilicate glass.[1]

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[1] An application has been made to patent the apparatus.

Temperature.—Borosilicate glass softens at 700° and will crack as a result of thermal shock, if sudden temperature fluctuations take place. Consequently, at no time during the operation of the drier should a temperature of 500° be exceeded. In fact, 320° is the maximum temperature to which the apparatus, described in this article, has been subjected. The temperature range within which the spray drier has been used is 140–220°. The normal operating temperature was 160°.

Wetting.—The contact angle between glass and water is zero. Consequently, any drops of solution which come into contact with the walls of the apparatus will adhere. This difficulty has been overcome by silicone coating the apparatus, using a 2% solution of dimethyldichloro-silane in carbon tetrachloride.

Sealing of Joints.—A film of silicone grease was applied to most joints which were then clipped together using simple metal clips.

Spray.—After considerable experimentation it was found that the best spray was produced using an atomizer device constructed from standard laboratory glassware (Fig. 1). This was con-

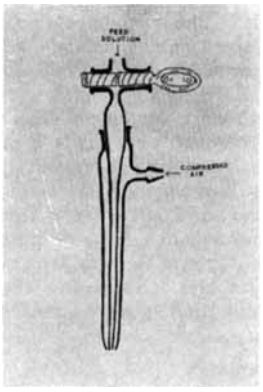

Fig. 1.—Atomizer unit.

nected to an Edwards compression and vacuum pump model RB4, which gave a maximum pressure of 18 lb./sq. in.

Sterilization.—When sterile powders were required, all connecting tubing was sterilized in an autoclave. Sterile filters of nonabsorbent cotton wool 4 cm. thick, supported in calico, were placed at each of the air inlets. The atomizer device and receiver were sterilized by heating in a hot air oven at 160° for 1 hr. The rest of the apparatus was sterilized by passing filtered hot air through the apparatus for 1 hr. at 180–200°.

Method of Operation.—A domestic suction cleaner is used to produce a stream of air at a displacement of approximately 240 L./min. This flows through 4 parallel tubes, each containing a firelighter element of 1.8-kw. capacity. The hot air then enters the drying chamber from above through a fused alumina pipe (Fig. 2). The spray enters the drying chamber alongside the hot air inlet and is dried as it passes through the chamber in the air stream.

The drying temperature can be controlled by switching on and off the heating elements, but greater temperature control is brought about by regulating the rate of flow of the solution through the atomizer.

On leaving the chamber, the dried product and steam pass into a cyclone separator, where the product falls into a previously warmed receiver, and the excess hot air and steam pass out through a dust bag. The receiver must be warmed initially; otherwise water vapor will condense on its inner surfaces, causing the product to become damp.

A positive pressure is required above the surface of the solution to be dried, otherwise air from the atomizer section will blow up the capillary when the feed vessel is almost empty. The rate of drying is 1 L./hr. for concentrated solutions.

Design Considerations.—Ideally, the apparatus should operate from a compressor capable of supplying sterile, oil-free air. This would make possible the continuous production of sterile products.

Originally the hot air inlet tube was made of copper, but it was found that, when streptomycin was spray dried, oxidative discoloration took place, which was due presumably to the catalytic effect of the metal. Hence, the copper tube was replaced by one of fused alumina, although other tubes, constructed of materials which do not contain heavy metals, could be used.

Cleaning.—Each section can be washed in a normal-size sink. The cyclone separator presents some difficulties, but if steel ball bearings are used, the dirt can be "rumbled" away.

EXPERIMENTAL

A 500-ml. quantity of double strength nutrient broth was spray dried in the previously sterilized apparatus. The dry product was collected in 8 sterile containers and sterile water was added to each. These were then incubated at 37° for 3 days, and observed daily for growth. The experiment was duplicated.

Of the 16 containers holding the reconstituted broth 15 were sterile. Growth in the sixteenth container presumably was due to accidental contamination during the transference of the sterile water to the spray-dried product.

After the 3-day incubation period, each sample

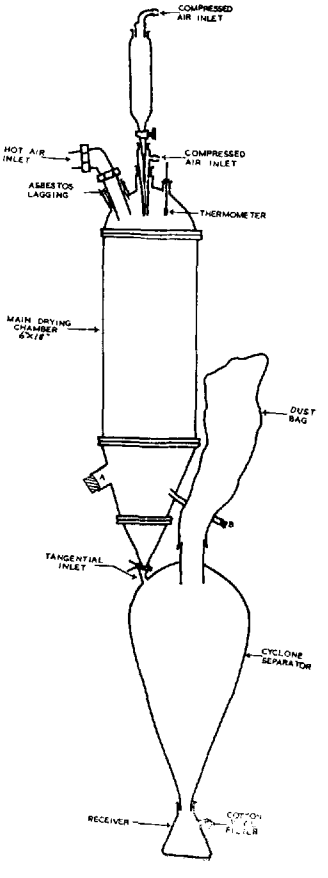

Fig. 2.—Appendages *A* and *B* were part of the original design but are no longer used.

TABLE I.—STREPTOMYCIN ASSAY RESULTS (ZONES OF INHIBITION MEASURED IN mm.)

Plate	Std. S_1	Std. S_2	Spray Dried T_1	Spray Dried T_2
1	16.5	19.5	16.5	20
2	17	20	16.5	20.5
3	17.5	19.5	17.5	19.5
4	17	19	17	19
Total	68.0	78.0	67.5	79.0
Av.	17.0	19.5	16.875	19.75

TABLE II.—PENICILLIN ASSAY RESULTS (ZONES OF INHIBITION MEASURED IN mm.)

Plate	Std. S_1	Std. S_2	Spray Dried T_1	Spray Dried T_2
1	26.5	28.5	26	29
2	26	28	26	28
3	25.5	28.5	25.5	27
4	26	28.5	26	29
Total	104	113.5	103.5	113
Av.	26	28.375	25.875	28.25

was inoculated with a loopful of a culture of *Micrococcus pyogenes*. Every sample became opalescent within 18 hr., indicating that the broth was capable of supporting growth of microorganisms.

Streptomycin sulfate has been spray dried without loss of activity as shown by the assay laid down in the "British Pharmacopoeia," 1958. Four Petri dishes containing seeded nutrient agar were used for each assay. In each dish 4 × 8 mm. holes were bored and the solutions T_1, T_2, S_1, and S_2 added to each plate. The strengths of the standard and test solutions were 5 and 10 units/ml. (Table I). After spray drying, the potency was 100.3% of the original (limits of results 86.7–115.3%).

A similar assay was carried out on sodium benzyl penicillin. The strengths of the test and standard solutions were 3 and 6 units/ml. (Table II). After spray drying, the potency was 96.6% of the original (limits of results 83.9 to 119.1%).

Seaweed extract, coffee, aluminum hydroxide gel, and an aluminum hydroxide complex have also been dried to produce free-flowing powders, which (except for the alumina) readily redissolved in water. Spores of *Bacillus subtilis* have also been dried with a 50% mortality. The powders, when viewed under the microscope, all showed the hollow spheres characteristic of spray-dried powders.

SUMMARY

1. The apparatus permits the drying process to be observed continuously; consequently, any obstruction to flow is readily noticed before damage to the product occurs.

2. It can be used to produce sterile powders more rapidly than freeze drying.

3. It is suitable for drying solutions and suspensions of materials which are prone to oxidation in the presence of metals.

4. The dried products are free flowing and lend themselves to aseptic transfer into sterile containers.

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Notes

Dissolution Rate–Solubility Behavior of 3-(1-Methyl-2-pyrrolidinyl)-indole as a Function of Hydrogen-Ion Concentration

By W. E. HAMLIN and W. I. HIGUCHI*

An investigation of the hydrogen-ion dependence of the dissolution rate of 3-(1-methyl-2-pyrrolidinyl)-indole (U-11028) is reported. Theoretical equations are developed which are in good agreement with the experimental data. This agreement shows clearly that it is the much greater diffusion coefficient of hydrochloric acid (D_H = 3.1 D_B) that is responsible for the deviation from the Noyes-Whitney theory.

CONSIDERABLE evidence has been presented to show that the initial rate of dissolution of a pellet is directly proportional to the solubility of the compound in a test fluid (1). This relationship, derived from the Noyes-Whitney law (2), states that

$$R = kC_s \qquad \text{(Eq. 1)}$$

where R is the initial dissolution rate per unit surface area of the pellet (mg./cm.²/hr.), k is a constant (2.24 for the given test conditions), and C_s is the solubility of the compound (mg./ml.). However, some data do not follow Eq. 1. One such compound which shows a significant positive deviation is 3-(1-methyl-2-pyrrolidinyl)-indole (U-11028). Since this deviation is observed in 0.05 N HCl but

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* Present address: College of Pharmacy, University of Michigan, Ann Arbor.