A STUDY OF THE SPRAY DRYING PROCESS APPLIED TO PHARMACEUTICALS

By

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INTRODUCTION

This project was undertaken to find suitable method or methods for the preparation of spray dried colloidal substances, in an effort to improve their physical and pharmacological properties. Spray drying has been found useful in producing pharmaceutical substances in a dried form which is free flowing, more easily wetted, and upon dispersion yield a stable monodispersion. Since spray drying yields powders of smaller particle size and hence of larger surface area, we might expect an increased pharmacological activity. Solubility of a substance also depends upon the surface area exposed to the solvent and it will be quite legitimate to expect that spray dried substances would go into solution much quicker than the same substance before spray dried.

The wetting and dispersing characteristics of the spray dried powders can be improved by adding some surface active agents to the slurry before being spray dried. Use of protective colloids would stabilize the suspension upon redispersion of powders. The redispersion can be made without much difficulty. The spray dried powder will be coated with an extremely small, but significant amount which would prevent or slow down the settling of the original material.

Spray drying is an useful means to obtain powder free from aggregates. Such a type of powder is very useful from a pharmaceutical point of view.

Rate of sedimentation varies directly with the particle size. According to the Stoke's law the sedimentation rate is directly proportional to the square of the particle's radius considering the particle to be spherical in size. An aggregate of particles acts as if it were a single particle of large radius and hence the rate of sedimentation is greatly enhanced over that of a single particle. The common tools available to a pharmacist, e.g., the mortar and pestle, the spatula, and the muller are not quite effective to break up aggregation even with the use of dispersing agents.

It has been established that the surface area is an important physical characteristic of a drug, especially as an index of the rate of solubility and therapeutic activity.

Thus the problems encountered were:

(1) to find suitable manufacturing methods to prepare colloidal Sulfur;

(2) to find optimum percentage of Tragacanth and Methyl cellulose as protective colloids and dispersing agents;

(3) quantitative determinations of the substances in presence of protective colloids in the spray dried products;

(4) to correlate the particle size of spray dried Sulfathiazole with the concentration of it in solution when spray dried;

(5) to compare the rate of solution of spray dried Sulfathiazole with that of the U.S.P. sample.

COLLOIDAL SULFUR

It has been already established that the spray drying process is useful in improving physical characteristics of drugs. Increase in the rate of solution of the powders is one of the properties improved by spray drying. It is also possible to obtain spray dried colloidal sulfur which would form a monodispersed suspension.*

The first part of the work was mainly concerned with duplicating the previous work done by Mr. Riegelman in this department. The spray dried colloidal sulfur obtained before developed an odor of hydrogen sulfide on keeping. It was, therefore, necessary to find the cause of this odor and rectify it.

One of the probable reasons was thought that the odor of hydrogen sulfide was produced due to the action of certain sulfur bacteria, e.g., Thiobacteriales. The spray dried material always contains considerable amount of moisture unless kept in a vacuum desiccator after spray drying. This assumption proved correct.

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* For details regarding previous work reference may be made to the Ph.D. thesis of Sidney Riegelman at this University.

Method A - Batches of colloidal sulfur were prepared according to the method worked out by the previous worker, employing sodium thiosulfate and hydrochloric acid, tragacanth being used as suspending agent.

Test for chloride ions - The usual silver nitrate test for chloride ions in presence of colloidal sulfur was found particularly difficult - almost an impossible proposition. The following different methods were tried with some success:

(1) 15 cc. of colloidal suspension of sulfur was taken in an evaporating dish and carefully heated over a dull flame to oxidize the sulfur to sulfur dioxide. The heating was done inside the hood and took about half an hour. The residue was digested with water and filtered. The solution was acidified with nitric acid and tested for chloride ion with silver nitrate solution. The test sometimes gave brownish black precipitate on addition of silver nitrate, which was supposed to be silver sulfide.

(2) About 10 cc. of the colloidal suspension were taken and centrifuged for half an hour in a Sorvell type centrifuge. The clear liquid from the top was taken out carefully, acidified with nitric acid, and then tested for chloride with silver nitrate solution. This test was found unsuitable since it always gave a brownish black precipitate of silver sulfide.

(3) The sulfur present in the suspension was tried to be oxidized to sulfur dioxide by making the solution alkaline, adding sodium peroxide and heating to dryness in a low flame. The results were not quite satisfactory.

Four batches of colloidal sulfur prepared in the above procedure were combined together and spray dried. The inlet temperature was kept at 400° F (= 205°C). The temperature inside the chamber stayed between 65°-68°C. The slurry was pumped up to the feed of the atomizer. In order to obtain a steady flow, an empty 200 cc. round-bottom flask attached to an inverted T-tube was interposed in the feed line. This device took care of the back pressure and the feed was continuous. The feed rate could be varied by closing or opening the needle valve. The feed rate of the slurry was kept at about 10-15 cc. per minute. The feed rate was so controlled that no liquid slurry would collect on the wall of the spray dryer. However, it was found quite difficult to keep the wall dry at all times.

As soon as the spray drying was over, the collecting vessel was removed and the spray dried product taken out and kept in a vacuum desiccator for several days to get rid of the last traces of moisture. After a week the powders were taken out of the desiccator and kept in bottles. Even after several months no odor could be detected.

A method was devised to dialyse large quantities of solutions. Four wire screens, 1½' in diameter, were taken, each with two holes 1" in diameter. The screens were arranged one on top of the other and were fixed to a ring stand. About 10' of dialysing sac was arranged spirally on the screens thus permitting a greater volume of liquid to be dialysed. The whole set-up, screens, ring stand, and the sac was placed inside a 10 gallon crock. The dialysing sac was filled with the suspension of colloidal sulfur to be dialysed and the dialysation was carried out against distilled water. The set-up was not found to be too useful since the sac used was not strong enough to hold so much of the liquid, the wire screens formed rust in water, and the ferric ions diffused into the sac giving a brownish color to the suspension.

<u>Method B</u> - Since dialysing large quantities of solutions became a problem, other methods were sought to avoid it. One of these methods was to use methyl cellulose which could be coagulated by heating. This coagulum could be collected on a filter, washed with hot water, thereby removing impurities of the reaction. The coagulum would then redisperse in cold water and would once again

reproduce a mono-dispersed sulfur suspension. Working with this method, it was observed that much of the finer colloidal materials were lost while filtering the coagulated suspension.* The concentration of methyl cellulose 4000 c.p.s. was raised from 0.5% to 1%. Even then it was not found to hold all the colloidal particles. Further raise in the concentration of methyl cellulose was not attempted as it would decrease considerably the concentration of sulfur in the final product. Five 1 liter batches were made by this method and spray dried. The spray dried product was found to be quite fluffy in nature and when redispersed in water gave mostly monodispersed particles.

<u>Method C</u> - Attempts were made to utilize some other methods in which dialysation would not be necessary and also the colloidal sulfur could be obtained without much difficulty. Special attention was given to the method which could be used for manufacturing purposes. Thus, it was found that the method utilizing sulfur dioxide and hydrogen sulfide to prepare colloidal sulfur could be used without much difficulty.[1]

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* This method of purifying colloidal suspensions has been reported in literature and a U.S. patent no. 1,444,257 (February, 1923) issued to L. Lillienfeld, Poland.

This method has been worked out before. According to H. Vogel, the two gases, sulfur dioxide and hydrogen sulfide, are passed simultaneously into water containing a protective colloid. The hydrogen sulfide is kept in excess in order to increase the yield of colloidal sulfur and to reduce the formation of polythionic acids. The size of the particles depends on the temperature of the liquid, and is less than 25 $\mu\mu$ when the temperature is kept between -3° and 4°C. However, Harry S. Young, to whom a patent was issued (U.S. 1,917,351, July 11), prefers to use sulfur dioxide in such a manner that a slight excess is maintained in the reaction mixture.

Chemistry of the reaction - The final products of the reaction between hydrogen sulfide and sulfur dioxide are sulfur and water. The reaction can be represented:

$$2H_2S + SO_2 = 3S + 2H_2O$$

The polythionic acids are the intermediate products.

Methyl cellulose 4000 c.p.s. was used as protective colloid. Different concentrations of methyl cellulose were tried. The object was to find the lowest concentration of methyl cellulose which would give adequate amount of protection. It was observed that a suspension containing as low as 0.5% methyl cellulose would give sufficient protection. Batches were made in which hydrogen sulfide was kept in excess and in others sulfur dioxide was kept in excess, and the colloidality of the sulfur obtained was compared. There was no appreciable difference in the colloidal suspension. However, after the suspensions were spray dried, the one containing excess hydrogen sulfide gave out less odor than the other. It was assumed that the odor was due to the adsorbed sulfur dioxide on the spray dried powder.

The solubility of hydrogen sulfide in water is 0.7063 gram and that of sulfur dioxide is 22.83 grams per 100 grams of water at 0°C. Batches were prepared containing enough of hydrogen sulfide in solution and equivalent amount of sulfur dioxide according to the equation:

$$2H_2S + SO_2 = 2H_2O + 3S$$

Quantitative estimations were made on samples to find the total solid content since, for effective spray drying of sulfur slurrys, at least 1.5 - 2.0% of total solid content is necessary. The total solid content was found to come out as low as 0.75 - 0.8%. Thus, it was necessary to use hydrogen sulfide in excess of the amount that goes into solution.

11,750 cc. of distilled water were taken in a five gallon crock equipped with a stirrer (Waco, 1/16 h.p.). The crock was put inside a bigger vessel and the space in between was filled up with ice. After about half an hour when the temperature of the water came down to 8°C, hydrogen sulfide was passed in through two gas dispersion tubes for an hour. It was assumed that the water became saturated with hydrogen sulfide by that time. 1,250 cc. of methyl cellulose solution containing 75 grams of methyl cellulose, 4000 c.p.s. were added to the mixture and the stirring continued for another fifteen minutes. Hydrogen sulfide was passed continuously. 2000 cc. of sulfur dioxide saturated water at 3°C were added to the mixture, 200 cc. were added in each addition at intervals of half an hour. After all the solution was used up, the mixture was stirred for one hour more and then let stand till the next day. Adding 200 cc. of sulfur dioxide saturated water each time, there always remained excess of hydrogen sulfide in the mixture. The whole operation was carried out inside the hood.

Next day the mixture was filtered through cheese cloth so that ~~any of~~ the larger particles of sulfur were separated from the mixture. The suspension was now almost white and smelled of the excess hydrogen sulfide. Before the suspension was spray dried, air was bubbled through it for two hours to get rid of some excess hydrogen sulfide. However, this was not found to be ~~a~~ too satisfactory a method.

The spray drying was accomplished in the usual way. The inlet temperature was kept at 350°F. The spray dried product was of light yellowish color and gave a little odor of burnt sulfur. The powder was kept inside a vacuum desiccator for several days. The powder was then taken out and spread thinnly over a glass plate and kept outside. In a few days most of the odor seemed to have gone.

The spray dried powder, when taken up in water and a little glycerine, stayed in suspension for several weeks. ~~together~~. Even after that just a little shaking was necessary to get back the suspension.

Several batches were made following the above process and the product came out quite uniform in its color, particle size, and in sulfur content. However, several factors determine the colloidality of the suspension. It was observed that if the addition of sulfur dioxide saturated water is made drop by drop, the color of the solution turns yellow showing the prepondrance of larger particles. Temperature is another vital factor. The lower the temperature, the higher the colloidality of the particles was observed. However, the lowest temperature that could be obtained with the set-up worked with was 8°C.

Tragacanth was tried instead of methyl cellulose since it was found to be more viscous on per cent weight basis. A 13 liter aqueous solution of tragacanth (0.5%) was made up and cooled over night in a refrigerator.

The procedure followed has already been described. One advantage of using tragacanth is that it does not foam as much as methyl cellulose solution when gas is passed into the solution. It is for this reason that one can start with a tragacanth solution instead of pure water where methyl cellulose is used.

The yield of the powder after spray drying was about 100 grams for every 15 liter batch. Much of the sulfur was lost as it formed scales on the wall of the spray dryer.

Assay for sulfur in the spray dried sample - The method of assay prescribed by the U.S.P. XIII for Precipitated Sulfur with some modifications was used. After addition of alcoholic potassium hydroxide it was necessary to heat the mixture for about an hour and let stand ~~for~~ overnight to dissolve out all the sulfur. The clear solution was decanted off and the residue in the flask washed with more water. The washings were added to the earlier solution. Two to three washings were necessary. Again, after acidification and before diluting with water, the solution was filtered to get rid of some of the white precipitate formed due to the presence of methyl cellulose. The filter paper was washed a couple of times to be sure no sulfate was lost. The filtrate was diluted with 200 cc. of water and the assay followed according to the directions. The sulfur content of the spray dried material came uniformly as much as 74 - 75% in contrast to 66 - 69% in samples obtained by following Methods A and B.

AMMONIATED MURCURY

It was observed that the spray dried Ammoniated Mercury prepared by the previous worker gave conflicting results when the substance was subjected to bacteriological tests. However, the paste obtained from centrifuging the slurry of ammoniated mercury before spray drying was bacteriologically superior to the ammoniated mercury U.S.P.

It was first thought that the method of preparation may have something to do with it. Different methods of preparation with different concentrations of methyl cellulose 4000 c.p.s. ranging from 0.25 - 1% were used. Small batches were prepared and the particle sizes and the amount of aggregation were compared by observing through the microscope. It was found that 0.5% of methyl cellulose 4000 c.p.s. was suitable to reduce aggregation.

The reaction essentially is:

$$HgCl_2 + 2\,NH_4OH = NH_4Cl + HgNH_2Cl + 2H_2O$$

However, in consulting the literature it was felt that the reaction is not as simple as it seems to be. It has been reported that[2,3,4] $HgNH_2Cl$ is not the only mercury compound formed by the interaction of $HgCl_2$ and NH_4OH. Other compounds like $HgCl_2.2NH_3$, $HgCl_2.NH_2HgCl$, $(Hg_2NCl)_2.HgCl_2$, are also formed.

Method of Preparation

Eight grams of methyl cellulose 4000 c.p.s. were dissolved in 400 cc. of water and then 9.2 cc. of ammonium hydroxide (28% w/v) were added to it. The solution was then made up to 600 cc. and stirred by an electric stirrer. At the same time it was cooled by keeping in an ice-bath.

Ten grams of Mercuric Chloride (Merck) were dissolved in 400 cc. of water. This solution was also cooled in the ice-bath.

This solution of mercuric chloride was added to the former one, 5 cc. in each addition at an interval of 5 minutes. The resultant solution was white and quite viscous. A drop of the suspension when observed under the high power lens of the microscope showed the presence of very minute particles with brownian movement. There was no aggregation of particles.

Efforts were made to increase the concentration of ammoniated mercury by starting with larger quantities of mercuric chloride and ammonium hydroxide. It was possible to start with 20 grams of mercuric chloride and equivalent amount of ammonium hydroxide for 800 cc. of final solution. The method followed was the same except that the mercuric chloride solution had to be heated in order to get all the solid into solution and was then rapidly cooled.

The order of addition was also reversed to find out whether there was any advantage in adding ammonium hydroxide to mercuric chloride solution in methyl cellulose. The resultant mixture was the same white, semi-viscous suspension, and the particles under the microscope looked the same as before. Thus, there is no special advantage in reversing the order of addition.

The slurry as obtained after the reaction was centrifuged in a Sharples super-centrifuge. The solid phase was obtained as a paste form and weighed 8 grams for an 800 cc. batch. The wash was slightly whitish at first showing that it was not possible to separate completely all the suspended ammoniated mercury particles. These particles were evidently smaller than 15 mμ in diameter as the machine is intended to retain all particles up to 15 mμ when operated at 50,000 revolutions per minute.

The paste obtained was dried in a vacuum desiccator for several days and then assayed for ammoniated mercury by the process given in B.P. (1932) and found to contain 98.46% which compares favorably with the Ammoniated Mercury U.S.P.

A 4 liter batch of the ammoniated mercury slurry was spray dried at 400°F. The spray dried product was very fluffy.

Since we started with 75 grams of mercuric chloride, in the reaction mixture we should have about 73 grams of ammoniated mercury, 20 grams of methyl cellulose, and 15 grams of ammonium chloride. Thus, in the spray dried powder the concentration of ammoniated mercury should have been 70%. The assay was run on the spray dried powder and it was found to contain 52.3% of ammoniated mercury.

The loss in the $HgNH_2Cl$ content was explained by assuming that as heating was continued during the operation of drying the concentration of NH_4Cl increased. The increased concentration of NH_4Cl in presence of $HgNH_2Cl$ reversed the equation:

$$HgCl_2 + 2\,NH_4OH \rightleftharpoons HgNH_2Cl + NH_4Cl + 2\,H_2O$$

Thus, the product, after drying, contained a mixture of $HgCl_2$, $HgNH_2Cl$, and NH_4Cl; ammonium hydroxide apparently lost by heat. There is some possibility of formation of complexes like $(NH_4)_2HgCl_4$.

Same loss of $HgNH_2Cl$ content also occurred when 25 cc. of the slurry formed by the reaction was dried in the oven.

The explanation of the loss of $HgNH_2Cl$ was proved true by the fact that when a concentrated solution of ammonium chloride was added to a suspension of ammoniated mercury with heating, the ammoniated mercury went into solution immediately with evolution of ammonia. Thus, it was experimentally proved that ammoniated mercury can not be spray dried in presence of ammonium chloride.

The ammonium chloride formed in the reaction mixture must be removed completely before the latter could be spray dried.

Assay

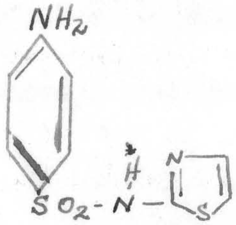
It was reported by the previous worker that difficulty was observed in applying the method of assay for ammoniated mercury given in U.S.P. XIII. However, method of assay given in B.P. 1932 was found to give good results. The assay requires addition of 3 grams of KI to 0.25 grams of sample in 50 cc. water and shaken until clear solution results. After that the solution is to be titrated against N/10 hydrochloric acid using solution of methyl orange as indicator.

The ammoniated mercury does not go into solution in KI in the presence of methyl cellulose. However, on keeping overnight, the ammoniated mercury goes into solution leaving methyl cellulose behind. The rate of solution could be made faster if the solution is kept in an ice-bath as methyl cellulose is more soluble in cold water.

SULFANILAMIDES

Sulfathiazole was chosen as representative of this class of drugs. The object was to find ways and means to obtain these drugs in smaller particle size and also in a form which can be easily wetted.

Sulfathiazole -



having an acidic $\overset{*}{H}$ is quite soluble at pH 9. It was reasoned that a solution of Sulfathiazole in ammonia water when spray dried would yield pure Sulfathiazole with ammonia escaping in the exhaust gas.

The solubility of Sulfathiazole can be determined theoretically at different pH knowing the ionization constant, K_a, and apparent solubility, K_s, of Sulfathiazole. The calculations may be made in the following way.

S (total solubility) $= K_s + S'$

where S' is the amount of Sulfathiazole ionized

$$\frac{[H^+]\ [S']}{HS} = K_a = 5.0 \times 10^{-8}$$

$K_s = 0.500$ gm/lt at 25°C.

at pH 9

$$1.0 \times 10^{-9} = \frac{[HS]}{[S']} \times 5.0 \times 10^{-8}$$

$$[S'] = \frac{[HS] \times 5.0 \times 10^{-8}}{1.0 \times 10^{-9}}$$

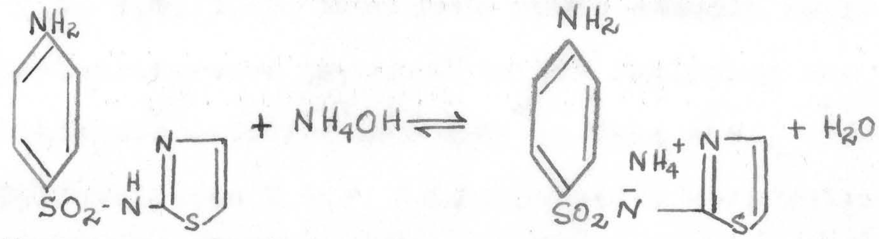
$[HS] = K_s$ since very little is ionized

$= 0.500$

$$[S'] = \frac{0.500 \times 5.0 \times 10^{-8}}{10^{-9}} = 25.0$$

Total Solubility $= 25.0 + 0.500 = 25.5$ gm/lt

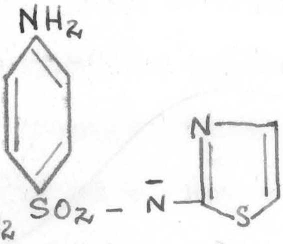
The reaction between ammonia and Sulfathiazole may be written,



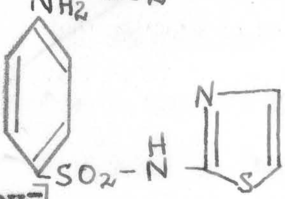
The equilibrium constant for the reaction can be written in the following way,

$$\frac{[A^-]\;[NH_4^+]}{[HA]\;[NH_4OH]} = K$$

where A^- represents



and HA represents



$$\text{or} \quad \frac{[H^+]\;[A^-]\;[NH_4^+]\;[OH^-]}{[HA]\;[NH_4OH]} = K \cdot K_w$$

or $K_a \times K_b = K \cdot K_w$

$$K = \frac{K_a \cdot K_b}{K_w}$$

$$= \frac{5.0 \times 10^{-8} \times 1.8 \times 10^{-5}}{1 \times 10^{-14}}$$

$$= 9.0 \times 10^{-13} \times 10^{14}$$

$$= 9.0 \times 10 = 90$$

Experimental Procedure

Different concentrations of Sulfathiazole solutions, 0.5, 1.0, 2.0, 3.0, 5.0%, were made up in ammonia water.

The solutions were prepared in the following way. A 3% Sulfathiazole solution was made in this case. 150 grams of Sulfathiazole U.S.P. (Mallinckrodt) were weighed and suspended in 3,500 cc. of water. Enough ammonium hydroxide (about 95 cc.) was added so that all the Sulfathiazole ~~goes~~ went into solution. More ~~of~~ Sulfathiazole was added to the solution to neutralize excess ammonia. The solution was then filtered through cheese cloth and spray dried immediately. The pH of the solution was determined using a Beckman pH meter and was found to be 9.0. The spray dried product was very fluffy in nature. It was kept in a vacuum desiccator for several days to get rid of the last traces of moisture.

Two batches were made up and kept overnight before being spray dried. The spray dried product contained the same amount of Sulfathiazole and the melting point as determined was found to be the same as Sulfathiazole U.S.P. Hence, the stability of Sulfathiazole is not altered easily in ammonia water.

The spray dried Sulfathiazole obtained did not wet quite readily and incorporation of some surface active agents was necessary. Agar, sodium arabate as prepared by the ion exchange method in this department, and ammonium stearate were used as surface active agents. They were added to the 2% solution of Sulfathiazole in ammonia water before spray drying. From the preliminary studies, the wetting action of sodium arabate seemed to be better than the other two. Different concentrations, 2, 5, 10 parts of sodium arabate per 100 parts of Sulfathiazole were used. Increase in the concentration of sodium arabate increased the wetting characteristics of the powder.

All the batches of Sulfathiazole obtained after spray drying were slightly tinged yellowish. However, the melting points of the powders were between 198 - 200°C which proves that there was no appreciable amount of decomposition.

A batch was prepared containing:

Sulfathiazole	60 gms.
Amm. hydroxide (28 w/v)	32 cc.
l-ascorbic acid	0.5 gm
water to make	2 lt

The above batch was spray dried at 350°F and the spray dried product had no trace of any coloration. Thus, the color which was produced before may be due to the oxidation of Sulfathiazole while being spray dried and was stopped by adding an antioxidant like l-ascorbic acid.

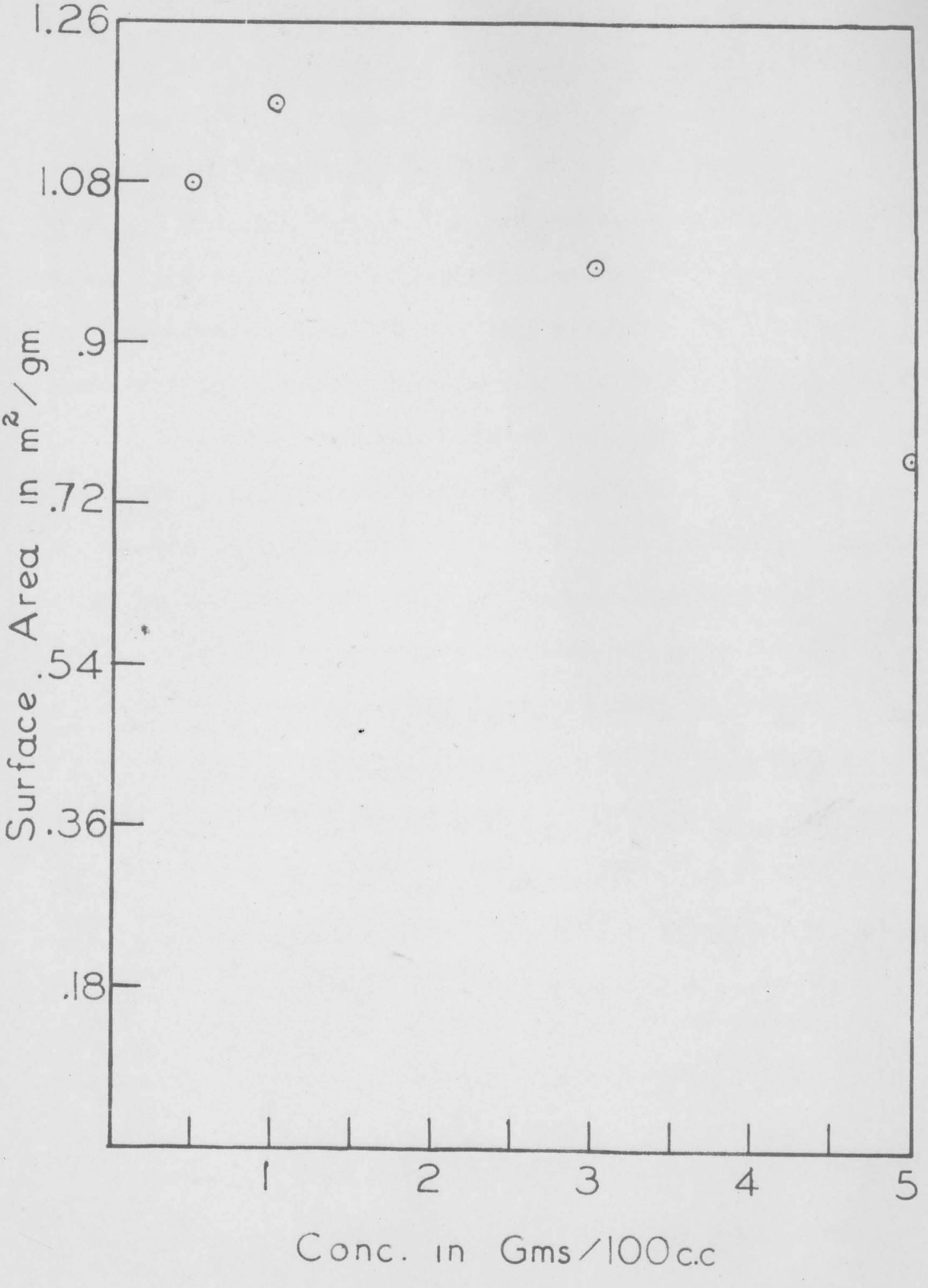
Free ammonia in the spray dried product - The amount of free ammonia present in the spray dried Sulfathiazole was determined. A weighed amount of sample was taken in a Kjedahl flask and 100 cc. of NaOH (8% w/v) was added. A few granules of zinc were added and the mixture distilled. 125 cc. of distillate were collected in an erlenmeyer containing 25 cc. of N/10 hydrochloric acid, with a few drops of methyl red added to it as indicator. The excess acid was titrated back with standard sodium hydroxide. The samples were found to contain 0.08% w/v of free ammonia.

Surface area determinations - Surface areas of 0.5%, 1%, 3%, 5% batches of spray dried Sulfathiazole were determined by low temperature nitrogen adsorption method.[*] Following are the results obtained:

% Soln Spray Dried	Surface Area in m^2/ gram	Average
0.5	1.06 1.11	1.08
1.0	1.16 1.18 1.16	1.17
3.0	0.973 1.00	0.99
5.0	0.756 0.802	0.78

The surface area of commercially available Sulfathiazole (Merck, Lot No. 42099) was found to be 0.486 m^2/ gm.

The values of the surface area of the particles were plotted against the concentration of solution spray dried. From the graph it is evident that as the concentration of the solutions are increased the surface area becomes smaller.


1.26
1.08
.9
.72
.54
.36
.18
Surface Area in m² / gm
1
2
3
4
5
Conc. in Gms/100 c.c

The Preparation of Arabic Acid and Sodium Arabate Powder by the Spray Drying Process *

Since the commonly used methods of drying solutions of arabic acid produce an insoluble meta-arabic acid, the spray drying process, because of its extremely rapid drying, was applied to the preparation of the powdered form of arabic acid and sodium arabate. Physical constants were determined and indicate that no changes occurred in the compound during the spray drying process.

Up to the present time no successful attempts at the large scale production of arabic acid in the powdered state has been reported. To date, it has been obtainable only in the solution form which has been limited more or less to 20% or lower concentration which makes for the necessity of transporting large volumes of water. Therefore, it was considered desirable to investigate the use of the spray dryer to evaporate solutions of this acid and its salts in order to obtain them in the powdered form which, if possible, would make this useful substance much more readily available.

Preparation of arabic acid solution was accomplished by applying the ion-exchange method.

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* For details, refer to Mr. R. Schleif's work done in this department.

The arabic acid solution obtained was spray dried with the inlet temperature kept at 400°F and at the rate of 12 cc. per minute.

The spray drying of arabic acid was compared with other processes of drying in order to determine its usefulness. Samples were dried at 25° and 50°C under vacuum. The solid product obtained in each case was insoluble. Thus, spray drying of arabic acid solution has definite advantagesover other methods of drying.

The spray dried powder was white and of a fine consistency. It proved to be water soluble. Viscosity studies, pH titration curves, and equivalent weight determinations were made before and after spray drying as a check on possible changes which may have occurred in the compound. From the results it may be noted that no significant change occurred.

Sodium arabate was prepared by neutralizing solution of arabic acid with sodium hydroxide and then spray dried at 400°F. The powder form of sodium arabate as obtained by spray drying was white and fluffy in nature. None of the physical constants of sodium arabate seemed to have changed due to spray drying.

APPARATUS

The apparatus used for the spray drying was a table model Bowen Spray Dryer.

Spray dryers consist essentially of a drying chamber, a source of hot gases, a means of atomizing the liquid feed, and a method of separating the dry product from the exhaust gases.

The Bowen Laboratory Spray Dryer used in these experiments consisted of stainless steel drying chamber about three feet in diameter and approximately two and one-half feet in height. The heating source is a gas burner at the side of the main drying chamber and is connected to it by a conduit leading to the top of the chamber. The air temperature is controlled by a mercury thermal element working on a pressure control switch which automatically adjusts the flow of gas to the burner. The atomization is accomplished by the use of a centrifugal atomizer run at 50,000 revolutions per minute by compressed air at one hundred pounds pressure. The compressed air is furnished by a specially installed compressor. The separation is accomplished by a cyclone collector. The entire system is under a suction fan.

Hot gases enter around the centrifugal atomizer and are given a swirling motion by fixed vanes. This aids in the intimate mixing between the hot gases and the spray. Cold air inlets at the side of the drying chamber near the bottom allow for more rapid cooling of the dry product if it be desired. The gases convey the dry product to the cyclone collector. An air sweeper, driven by the reaction of high velocity air jets issuing from its trailing edge, keeps the chamber floor clean by blowing any product which accumulates on the floor into the exhaust gas. The atomizer disk is of the inverted saucer type with a two-inch diameter.

From the outset the apparatus was not intended to serve as an engineering tool. Instead, it was used to investigate the properties of the dry products resulting from the spray drying.

RESULTS AND DISCUSSION

From the results obtained in this work it is quite evident that spray drying process is a very efficient and handy tool to improve some of the physical characteristics of powders. However, it has been found that the substance must be in solution or in very small particles in the slurry before spray drying.

The addition of suspending agents or wetting agents further improves the spray dried powder. Among the suspending agents Methyl Cellulose and Tragacanth have been found to be quite suitable for our purposes while sodium arabate, dreft, and agar serve well as wetting agents.

In spray drying slurries of colloidal sulfur it has been found that the total solid content of the slurries must be above 1.5% to ensure effective spray drying. However, in case of spray drying of Sulfathiazole solution in ammonia water, the lower concentration yields powder with larger surface area. Thus, it has to be borne in mind the effective concentration of a substance before spray drying to ensure successful spray drying and at the same time powders with large surface area.

STUDY OF THE RATE OF SOLUTION OF SPRAY DRIED SULFATHIAZOLE

This study was undertaken to compare the rate of solution of spray dried Sulfathiazole with that of the U.S.P. material. It is already established that solubility of a substance is dependent on the particle size.[8]

In the present work investigation was carried out
(1) to compare the rate of solution of spray dried Sulfathiazole with that of U.S.P. material;
(2) to correlate the results obtained with the surface area of the particles.

Experimental Procedure

Material - A batch containing

Sulfathiazole	20	gm
Ammonium hydroxide	10.5	cc
Water to make	2	lt

was spray dried. The spray dried product was used for this investigation. (For further details please refer to page 22 of this thesis.)

For the purpose of the investigation, 50 mg of spray dried Sulfathiazole of the above batch were weighed into a 100 cc volumetric flask containing 75 cc of boiled distilled water. The flask was suspended in a constant temperature water bath, kept at 25°C and could be shaken at a constant rate by means of a mechanical device.

Samples were withdrawn by means of a pipette at definite intervals of time, filtered through fine sintered glass funnels (F 15, Corning Glass Co.). Concentrations of Sulfathiazole in the filtrate were determined by means of a Beckman Spectrophotometer.

All determinations were made at 285 mμ, a wavelength at which maximum adsorption of Sulfathiazole occurs with Corex cells. The extinction coefficient at this wave length was determined and was found to be 69.5.

It may be mentioned here that the extinction coefficient of spray dried Sulfathiazole at 285 mμ did not differ from the above value.

RESULTS AND DISCUSSION

Table A

Time in min.	Sulfathiazole(Merck Lot No.42099)			Sulfathiazole Spray Dried	
	U.S.P.		Recrystallized from water		
5	0.388 0.354	0.371	0.181	0.451 0.417 0.447	0.438
10	0.489 0.429	0.459	0.298	0.452 0.476 0.486 0.471	0.471
20	0.475 0.449	0.462	0.442	0.471 0.468 0.491 0.491	0.480
40	0.468 0.472	0.470	0.462	0.498 0.489 0.492	0.493
60	0.491 0.460	0.476	0.486	0.501 0.508 0.515 0.484	0.501

All the above solubilities are expressed in gms per liter.

The solubility of Sulfathiazole at equilibrium was determined. 50 mg of Sulfathiazole, recrystallized from water, was put in a volumetric flask containing 75 cc. of boiled distilled water. The flask was suspended in a constant temp. water bath, kept at 25°C and shaken. After four days, allowing the contents of the flask to come to an equilibrium point, the solution was filtered through a "Fine" sintered glass funnel. Quantitative determinations were made on the filtrate and was found to be 0.502 gms per lt. at 25°C.

Assuming that,

(1) rate of solution follows Fick's Law, and

(2) the area of the solid phase does not change,

we can show that,

$$\log \frac{Ceq - Ct}{Ceq} = \frac{kt}{2.303}$$

where,

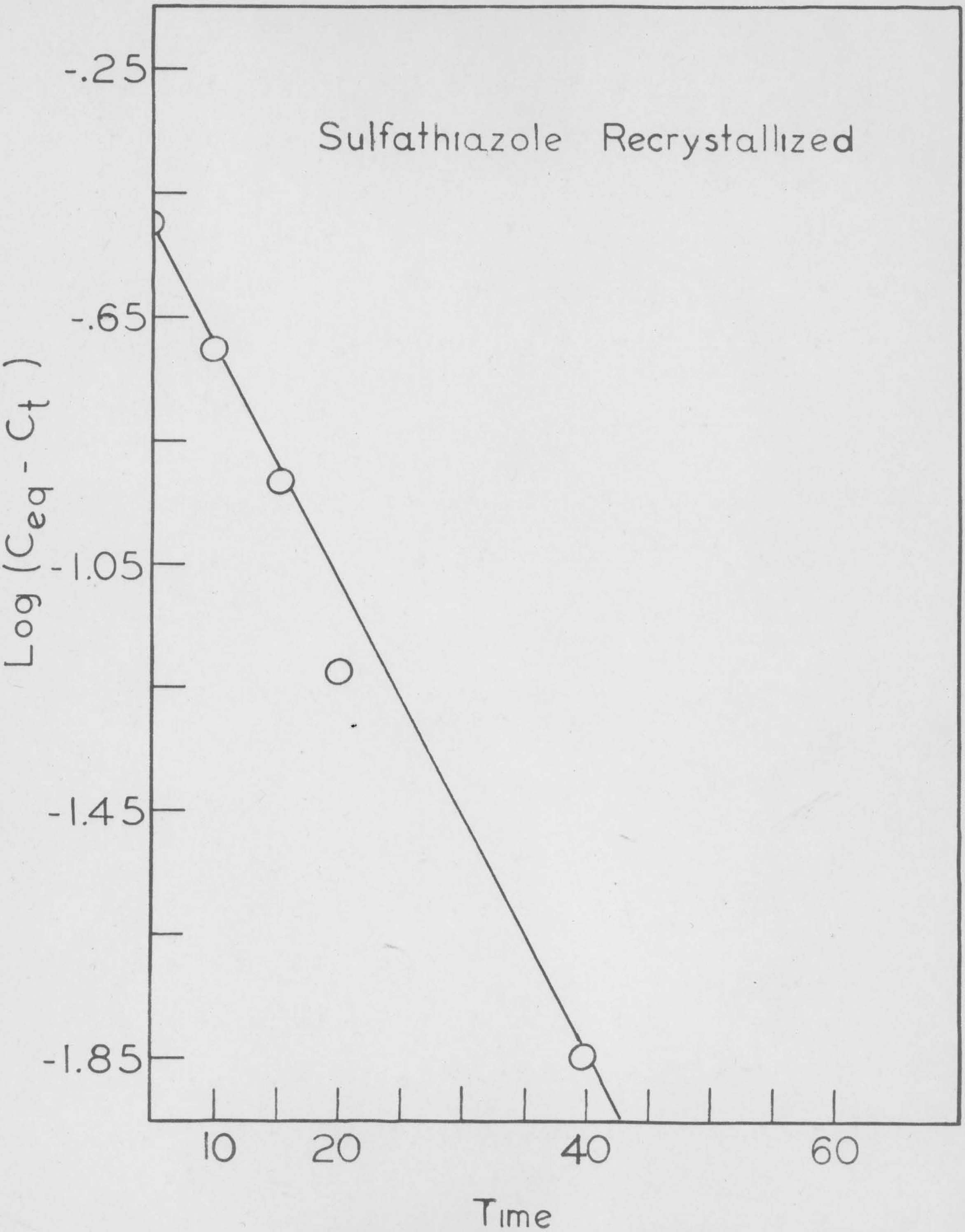
Ceq = conc. at equilibrium point.

Ct = conc. at time t minutes after start.

t = time in minutes

k = constant.

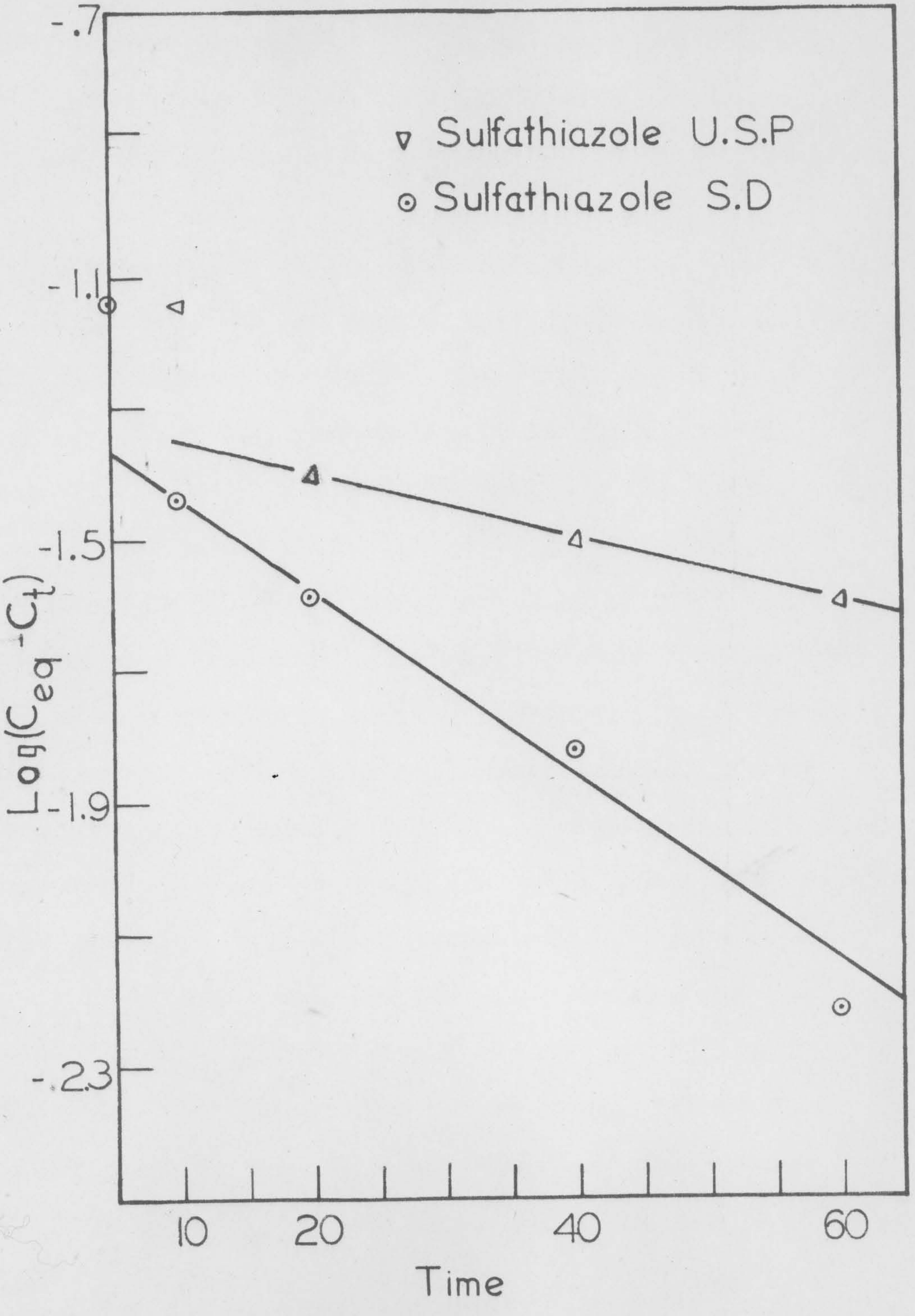
Graphs were drawn plotting log (Ceq-Ct) against t (min) for Sulfathiazole; U.S.P.; spray dried, and recrystallized.


Sulfathiazole Recrystallized
Log (C_{eq} - C_t)
-.25
-.65
-1.05
-1.45
-1.85
10
20
40
60
Time

The graph, in the case of recrystallized Sulfathiazole is a straight line, whereas in the case of U.S.P. and spray dried samples the graph seems to follow a curvature. This is probably due to the decrease in the area of solid phase with the time contrary to our assumption made before.

The results given in Table A seem to point to the fact that the rate of solution of spray dried Sulfathiazole in water may be faster than that showed by Sulfathiazole U.S.P. or Sulfathiazole recrystallized. The increased rate of solution is probably due to the existence of more smaller particles in spray dried powder than that in U.S.P. or recrystallized powders. These smaller particles may be assumed to have lower activation energy and thus, goes into solution much faster than bigger crystals. Thus, in the course of time, when most of the smaller particles have gone into solution leaving large particles in solid phase, the spray dried material probably behaves like U.S.P. powder.

It was necessary to find out whether the concentration of the filtrate would change if a finer filter was used. The filter ~~that was used~~ selected was 'Ultra Fine' filter (60 U,F, Corning Glass Company) which keeps back all particles bigger than 1μ in contrast to the 'Fine' filter used in the earlier part of the experiment which

▽ Sulfathiazole U.S.P
⊙ Sulfathiazole S.D
-.7
-1.1
-1.5
-1.9
-2.3
Log(C_eq - C_t)
10
20
40
60
Time

filters all particles smaller than 10μ. The procedure followed was the same as before. The following ~~is~~ are the average results obtained:

Table B

Time in min.	Sulfathiazole U.S.P. gms/lt	Sulfathiazole Spray Dried gms/lt
5	0.321	0.380
10	0.342	0.410
20	0.361	0.443
19 hrs.	0.538	0.546

Results obtained in Table B seem to point to the assumption previously made, that the smaller particles existing in the spray dried material are responsible for the increased rate of solution.

However, since the 'ultra fine' filter ~~filters~~ permits only particles smaller than 10μ to pass through, some of the particles which passed through the fine filter were kept back and thus showed a lower concentration in the filtrate. Comparing the results, it seems that the spray dried material has a definite increased rate of solution over U.S.P. or recrystallized materials.

BIBLIOGRAPHY

1. Z. Chem. Ind. Kolloide, 8, 186 - 93 (1911).

2. Am. Chem. Jour., 47, 368 (1912).

3. Zeitsch. Anorg. Chem., 57, 72 (1908).

4. Ibid., 59, 136 - 42.

5. Journ. Am. Pharm. Assoc. (Sc. Ed.), 38, 210 (1949).

6. Phil. Trans., 103, 57 (1813).