THE MEASUREMENT OF CAKING TENDENCIES IN SULFA DRUG SUSPENSIONS

A Thesis

Presented to

the Faculty of the College of Pharmacy

The University of Houston

In Partial Fulfillment

of the Requirements for the Degree

Master of Science in Pharmacy

by

Robert Denman Sartin

June 1968

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ABSTRACT

The resuspension of sedimented solids is recognized as a problem in certain types of pharmaceutical suspension systems. The particles of a uniform suspension will slowly settle to the bottom of a container. If the product is an oral or injectable pharmaceutical suspension, the sedimented particles must be evenly resuspended before the preparation can be put to its intended use.

When it becomes difficult to resuspend a sediment by simple shaking, the sedimented material is said to have "caked". The underlying factors in caking have been studied for only a few simple systems, and the existance of caking is usually determined empirically by noting the ease or difficulty of resuspension of the sedimented solid material. This thesis presents a method that can be used to demonstrate the existance of a caked sediment, and which measures the caking in terms of the force it takes to break the sediment. The method employs the recently available Fisher "Tensiomat", and the special "H" shaped test devices which were developed for this purpose in the course of the thesis work. The "H" shaped test devices were lifted through the caked sediments formed from a number of deflocculated sulfa drug suspensions, and the "Tensiomat" readings were taken as a measure of the relative hardnesses of the cakes formed.

Under the conditions of the experiment, it was found that there was a statistically significant difference in the degree of caking in the various sulfa drug suspensions. Caking tendencies proved to be inversely proportional to the particle sizes of the sulfa powders. The settling times of the suspended sulfa particles were directly proportional to the particle sizes, as would be expected.

TABLE OF CONTENTS

CHAPTER		PAGE
I	HISTORY AND INTRODUCTION	1
II	SURVEY OF THE LITERATURE	4
III	MATERIALS AND METHODS	7
	A. Test for the Presence of Wetting Agents in the Sulfa Drugs	7
	B. Materials	7
	C. Equipment	9
	D. Development of the "H" Shaped Test Devices	10
	E. The Suspension System	18
	F. Photomicrographs of Dry, Powdered Sulfa Particles	19
IV	RESULTS	20
V	DISCUSSION OF RESULTS	38
VI	SUMMARY	54
	BIBLIOGRAPHY	55

LIST OF TABLES

TABLE PAGE

1. Relative hardness of caked sediment formed in a three per cent aqueous suspension of Sulfathiazole, N.F. XI, containing fifteen-hundredths per cent wetting agent (Dioctyl Sodium Sulfosuccinate). 22
2. Relative hardness of caked sediment formed in a three per cent aqueous suspension of Sulfathiazole, N.F. XI, containing fifteen-hundredths per cent wetting agent (Dioctyl Sodium Sulfosuccinate). 23
3. Relative hardness of caked sediment formed in a three per cent aqueous suspension of Sulfathiazole, N.F. XI, containing fifteen-hundredths per cent wetting agent (Dioctyl Sodium Sulfosuccinate). 24
4. Relative hardness of caked sediment formed in a three per cent aqueous suspension of Sulfathiazole, N.F. XI, containing fifteen-hundredths per cent wetting agent (Dioctyl Sodium Sulfosuccinate). 25
5. Relative hardness of caked sediment formed in a three per cent aqueous suspension of Sulfathiazole, N.F. XI, containing fifteen-hundredths per cent wetting agent (Dioctyl Sodium Sulfosuccinate). 26
6. Correlation coefficients (Pearson "R" values) between five separate sets of data (Tables 1-5) representing "caking" properties of Sulfathiazole, N.F. XI. 27

LIST OF TABLES (continued)

TABLE PAGE

7. Relative hardness of caked sediment formed in a three per cent aqueous suspension of Sulfadiazine, U.S.P. containing fifteen-hundredths per cent wetting agent (Dioctyl Sodium Sulfosuccinate). 28

8. Relative hardness of caked sediment formed in a three per cent aqueous suspension of Sulfadiazine, U.S.P. containing fifteen-hundredths per cent wetting agent (Dioctyl Sodium Sulfosuccinate). 29

9. Relative hardness of caked sediment formed in a three per cent aqueous suspension of Sulfamerazine, U.S.P. containing fifteen-hundredths per cent wetting agent (Dioctyl Sodium Sulfosuccinate). 30

10. Relative hardness of caked sediment formed in a three per cent aqueous suspension of Sulfamerazine, U.S.P. containing fifteen-hundredths per cent wetting agent (Dioctyl Sodium Sulfosuccinate). 31

11. Relative hardness of caked sediment formed in a three per cent aqueous suspension of Sulfamethazine, U.S.P. containing fifteen-hundredths per cent wetting agent (Dioctyl Sodium Sulfosuccinate). 32

12. Relative hardness of caked sediment formed in a three per cent aqueous suspension of Sulfamethazine, U.S.P. containing fifteen-hundredths per cent wetting agent (Dioctyl Sodium Sulfosuccinate). 33

LIST OF TABLES (continued)

TABLE PAGE

13. Relative hardness of caked sediment formed in a three per cent aqueous suspension of Sulfanilamide, N.F. XI, containing fifteen-hundredths per cent wetting agent (Dioctyl Sodium Sulfosuccinate). 34

14. Relative hardness of caked sediment formed in a three per cent aqueous suspension of Sulfanilamide, N.F. XI, containing fifteen-hundredths per cent wetting agent (Dioctyl Sodium Sulfosuccinate). 35

15. Relative hardness of caked sediment formed in a three per cent aqueous suspension of Succinylsulfathiazole, U.S.P. containing fifteen-hundredths per cent wetting agent (Dioctyl Sodium Sulfosuccinate). 36

16. Text of significance (T-test) demonstrating differences in "caking" tendencies between various sulfa preparations. 37

LIST OF FIGURES

FIGURE		PAGE
1.	du Nouy Tensiometer Surface Tension Ring	12
2.	"O-ring" Test Device	14
3.	"Flat-plate" Test Device	16
4.	"H" Shaped Test Device	17
5.	Photomicrograph of Mallinckrodt Brand of Sulfathiazole, N.F. XI Particles (200X).	41
6.	Photomicrograph of Penick Brand of Sulfanilamide, N.F. XI Particles (200X).	42
7.	Photomicrograph of Merck Brand of Sulfanilamide, N.F. XI Particles (200X).	43
8.	Photomicrograph of Merck Sharp & Dohme Brand of Succinylsulfathiazole, U.S.P. Particles (200X)	44
9A.	Photomicrograph of City Chemical Corporation Brand of Sulfamerazine, U.S.P. Particles (200X).	45
9B.	Photomicrograph of City Chemical Corporation Brand of Sulfamerazine, U.S.P. Particles (640X).	46
10A.	Photomicrograph of Robinson Laboratory Inc. Brand of Sulfamerazine, U.S.P. Particles (200X).	47
10B.	Photomicrograph of Robinson Laboratory Inc. Brand of Sulfamerazine, U.S.P. Particles (640X).	48
11.	Photomicrograph of Robinson Laboratory Inc. Brand of Sulfamethazine, U.S.P. Particles (200X).	49

LIST OF FIGURES (continued)

FIGURE PAGE

12. Photomicrograph of City Chemical Corporation Brand of Sulfamethazine, U.S.P. Particles (200X). 50

13A. Photomicrograph of Robinson Laboratory Inc. Brand of Sulfadiazine, U.S.P. Particles (200X). 51

13B. Photomicrograph of Robinson Laboratory Inc. Brand of Sulfadiazine, U.S.P. Particles (640X). 52

14. Photomicrograph of Lederle Laboratories Brand of Sulfadiazine, U.S.P. Particles (200X). 53

CHAPTER I

HISTORY AND INTRODUCTION

The United States Pharmacopeia (1) defines suspensions as "preparations of finely divided, undissolved drugs dispersed in liquid vehicles". In addition, the term "powders for suspension", is used in connection with those preparations of finely powdered drugs which are intended for suspension in liquid vehicles prior to their use.

It can be seen that Pharmacy has chosen to use the word "suspension" in a more limited sense than it has been used in other fields of science. Colloid chemists and physical chemists consider a suspension to be any two-phase system in which a finely divided solid is dispersed in another solid, in a liquid, or in a gas. This more all-inclusive definition has served a number of purposes in colloidal or physical chemical work. However, it proved to be too general in context for the purposes of Pharmacy, and its pharmaceutical usage has been restricted to cases in which the solid is dispersed in a liquid medium.

Martin (2) has said that a pharmaceutical suspension is a coarse dispersion in which insoluble solid particles are dispersed in a liquid medium. He described the solid particles as being over 0.1 micron in diameter and capable of exhibiting Brownian movement if the dispersion medium was of a low viscosity. Schwarz (3) on the other hand, maintains that the particles dispersed in the usual pharmaceutical suspension are not small enough to exhibit Brownian movement. This question of particle size has led the pharmaceutical scientist to subdivide the area of suspensions into the more limited categories of suspensions, mixtures, magmas, gels, and colloidal suspensions. The principal distinction

between these different types of suspensions resides in the size of the suspended particle. In this system of classification, suspensions lie at one end of a size spectrum and colloidal suspensions lie at the other. The particles in a suspension are so large that they settle rapidly from the suspended state. In the colloidal suspension, the particles are so small that they remain permanently suspended due to the Brownian movement and the normal thermal currents which arise in such systems.

The goal of the pharmaceutical chemist is to produce a pharmaceutically elegant suspension product, as well as one which meets the rudimentary requirements of the dosage form. Appearance factors are important. So, too, is the fact that the insoluble solid must remain evenly dispersed during the period of time required for the removal of the dose. When the suspension has been set aside long enough for the particles to settle to the bottom of the container it must be possible for the Pharmacist or the patient to resuspend the solids in a uniform dispersion by simple agitation. If the sedimented material can not be shaken easily from the bottom of the bottle, the patient might not obtain the prescribed dose of a suspension medication. This thesis concerns itself with this problem of the ease of resuspension of sedimented solids.

Haines and Martin (4) state that when dispersed particles settle to form a compact mass at the bottom of a container, the suspension is said to have caked. Caking has been observed in several different types of pharmaceutical suspension systems. For example, it was one of the more common problems in the early formulation work on sulfonamide suspensions. Nash (5) notes that many companies experienced failures with oral sulfa

suspensions containing a number of common suspending agents. Smooth looking, viscid suspensions were obtained, but when these stood on the Pharmacist's shelf it was found that the particles settled to form a tight cake from which it was almost impossible to resuspend the solids by vigorous shaking. A more recent example of caking is found in parenteral suspensions of procaine penicillin G. Several batches of procaine penicillin G have been recalled by the manufacturer (6) in recent months due to the formation of hard sediments or cakes from which the solids could not be resuspended readily to provide a uniform injectable dose.

There have been several recent studies on caking (4,7,8), but in each case the authors were forced to rely upon empirical observations for the interpretation of their results. This is because no test method has been available for the measurement of caking. This thesis suggests a method which can be used to demonstrate the existence of caking in a sediment, and which will measure the degree of caking in terms of a force required to break the cake. It is hoped that it will provide a tool for the measurement and comparison of caking tendencies in pharmaceutical suspension, and be valuable in the study of such formulation variables as particle size, inter-particle bonding forces, and the addition of adjuvants to suspension systems.

CHAPTER II

SURVEY OF THE LITERATURE

A number of authors have discussed suspensions and touched briefly upon the subject of caking. However, once a cake, as defined by Haines and Martin (4), had formed most investigators were satisfied to report the phenomenon and to move on to more promising areas of research. Relatively few investigators have been interested in the caking phenomenon itself.

Rehbinder and Segalova (9) have defined two very general types of network structures that may form in sedimented solids, and which can then become responsible for the production of a caked sediment. The physical-chemical properties of the surfaces of the particles were said to have a controlling influence over the nature of the cake that is formed. They called the first type of network structure the condensation or strongly-bonded type. This is a structure which increases greatly in strength as it dries or cures, and which is typically found in thick suspensions or slurries such as those formed from clay or gypsum. These were the structures in which Rehbinder and Segalova were interested. The network forms at reactive sites through a cross-binding reaction followed by the elimination of a molecule of water. The condensation type appears in certain suspensions of magnesium oxide which are of pharmaceutical interest (10). Strongly bonded structures are usually thought of as being irreversible in their nature.

Rehbinder and Segalova (9) called the second type of network the coagulation or weakly-bonded type. This is a much more common type of structure than is the condensation type, and one which forms reversibly.

This structure can be formed, can then be broken by mechanical agitation, and will then subsequently reform as the particles again settle and come into close proximity with one another. Inter-particle attractions are established through the thin films of residual solvent which separate the particles, or at the points where they come into physical contact. The authors also observed that the strength of coagulation networks increases as the size of the particles is decreased. It is inferred that the increase in strength is a direct result of the increased number of points of contact which appear as the suspended particles are made smaller. The maximum strength of a weakly-bonded structure develops as the liquid suspension medium is gradually squeezed out and the particles settle closer to one another.

Another phenomenon, one not mentioned by Rehbinder and Segalova (9) but which may be important to the caking process, is Ostwald "ripening" (11). This occurs through the dissolution of substance from certain surfaces of sedimented particles followed by its deposition on other surfaces of the same or of other particles. The process is generally associated with a coarsening of the sediment. Kolthoff and Noponen (11) felt that Ostwald "ripening" might be responsible for caking in those cases where the dissolved material tended to deposit at points of contact between the particles. Crystalline inter-particle bridges were formed and these bonded the particles together as a single crystalline mass. This is, of course, an irreversible type of caking phenomenon.

No other specific references to caking are found in the literature. Wilson and Ecanow (8) have reported on certain aspects of the caking

process, but this was to compare the sediments formed from flocculated suspension systems against those formed from deflocculated suspensions of the same materials. They worked with powdered sulfamerazine suspended in dilute dioctyl sodium sulfosuccinate solutions and found that the deflocculated sulfamerazine particles settled to a dense sediment which had all the characteristics of a weakly-bonded sediment or cake. This offered an ideal system for further studies on the coagulation type of network structure, and one which has been utilized in this research work.

CHAPTER III

MATERIALS AND METHODS

A. TEST FOR THE PRESENCE OF WETTING AGENTS IN THE SULFA DRUGS: A test method developed by Wallin (12), based on the work of Jones (13), was used to detect the possible presence of small amounts of sulfonated surface active agents in the different sulfa powders used in this investigation. The test was thought to be necessary, inasmuch as any wetting agents originally present on the particle surfaces would be expected to have some influence upon the settling and caking characteristics of the suspended sulfa solids.

Wallin's method for the detection and determination of such surfactants depends upon the reaction between wetting agent anions and a suitable dyestuff cation, giving a highly colored chloroform-soluble salt. In this study, basic fuchsin was used as the dyestuff and the chloroform extracts were examined for the appearance of a characteristic color. The procedure is as follows:

> Place a 2 gm. sample of sulfa powder in a 125 ml. separatory funnel, and mix with 20 ml. of distilled water. Add approximately 5 drops of concentrated hydrochloric acid until a pH of 1.2 is obtained as determined by a pH meter. Add 2 ml. of 0.1% basic fuschin, mix, extract with 20 ml. of chloroform and allow to separate. Draw the chloroform layer off into a 100 ml. volumetric flask and observe for the appearance of a characteristic fluorescent, magenta-colored complex.

B. MATERIALS: The commercial grades of sulfa products which were studied during the investigation are listed in the table on the following page.

The wetting agent used throughout the study was Dioctyl Sodium Sulfosuccinate (which will often be referred to as DSS in the balance

Drug Material	Supplier	Batch Number
Succinylsulfathiazole, U.S.P.	Merck Sharp & Dohme West Point, Pennsylvania	D0318
Sulfadiazine, U.S.P.	Lederle Laboratories, Div. American Cyanamid Co. Pearl River, New York	3917-343
Sulfadiazine, U.S.P.	Robinson Laboratory Inc. San Francisco, California	502103
Sulfamerazine, U.S.P.	City Chemical Corporation New York, New York	VC805
Sulfamerazine, U.S.P.	Robinson Laboratory Inc. San Francisco, California	707593
Sulfamethazine, U.S.P.	City Chemical Corporation New York, New York	UB548
Sulfamethazine, U.S.P.	Robinson Laboratory Inc. San Francisco, California	707670
Sulfanilamide, N.F. XI	Merck & Co., Inc. Rahway, New Jersey	62622
Sulfanilamide, N.F. XI	S. B. Penick & Co. New York, New York	NHT-2286
Sulfathiazole, N. F. XI	Mallinckrodt Chemical Works St. Louis, Missouri	WSBG

of this report), as supplied by American Cyanamid Laboratories[1] under the brand name "Aerosol-OT" (Batch No. 762844).

The needles used in making the "H" shaped test devices (to be described later in the report), were 22G, 1½ inch stainless steel disposable needles as supplied by Becton, Dickinson and Company.[2] The needles were soldered together using the special stainless steel solder and flux supplied by the Eutectic Welding Alloys Corporation.[3]

C. EQUIPMENT: A du Nouy tensiometer[4] was used to measure the pulling force required to lift the "H" shaped test devices upwards through the caked sulfa sediments. A "Tensiomat" tensiometer[5] was chosen for this purpose because it is more precise than the simpler hand-operated du Nouy tensiometers. Through a constant speed motor connection, the "Tensiomat" gradually increases the pulling force at a rate which is constant from one measurement to the next. As a result, the tensiometer readings are not affected by those operator variables associated with the rate at which the upwards force is applied, as is the case with the manually operated machines. The "Tensiomat" also has the advantage that it automatically shuts itself off when the lifting arm rises; i.e., when a sufficient torsional force has been applied to lift the "H" shaped test device upwards through the sediment. The force required to break through the caked sediment was read directly from the instrument dial in dynes per centimeter. Although not an absolute figure, the lifting force thus obtained is a measure of the resistance the cake affords to the movement of the test device, and is therefore an indication of the relative hardness or cohesiveness of the cake.

Clear plastic trays were obtained from the Geigy Pharmaceutical Products Company.[6] They were rectangular in shape, having the surface dimensions of seven by twenty-two centimeters, and a depth of six centimeters.

The "H" shaped test devices were developed during the investigation. They were hand-made by the author to meet the particular requirements of the sulfa drug problem. They are described in detail in the following section.

D. DEVELOPMENT OF THE "H" SHAPED TEST DEVICES: When a sulfa powder is "wetted" with a Dioctyl Sodium Sulfosuccinate solution of the proper strength, it can be suspended in an aqueous medium as a typical deflocculated suspension system. If this suspension is allowed to sit, undisturbed, the sulfa particles will slowly settle to the bottom of the container to form a compact sediment. In some cases this sediment will be loosely formed, but more often it is a "caked" sediment, which varies in its hardness and in its resistance to attempts to resuspend the powder by shaking or other types of agitation. There is noticeable difference between the strengths of the sediments of "cakes" formed from different types of sulfa drugs, and between samples of the same sulfa as obtained from different manufacturers.

The du Nouy tensiometer surface tension rings,[7] (Figure 1) which are made of a platinum-iridium alloy, were selected for the initial measurement of the cohesive forces within a caked sediment. The procedure and results of one of these initial trials are summarized on the following page.

A suspension of Sulfamerazine was prepared in a one per cent concentration in the presence of the wetting agent DSS in a one-tenth per cent concentration. The suspension was then placed in a flat-bottomed container holding the platinum-iridium rings, and the system was allowed to sit undisturbed for seventy-two hours. The rings were then pulled using the du Nouy tensiometer. The experiment was repeated two more times so that the results could be analyzed statistically.

	Test I	Test II	Test III
Ring 1.	79.00*	83.71	80.56
Ring 2.	78.00	79.08	79.81
Ring 3.	82.00	80.31	79.59
Sums	239.00	243.10	239.96
N	3	3	3
Means	79.67	81.03	79.99
(G)	722.06		
(N)	9		

$$CF = \frac{G^2}{N} = \frac{521370.64}{9} = 57930.07$$

(SS) = 19049.00 + 19710.71 + 19194.12
= 57953.83 - 57930.07
= 23.76

SS* = 19042.72 + 19701.63 + 19196.00
= 57940.35 - 57930.07
= 10.28

SS = 23.76 - 10.28
= 13.48

Source of Variation (VS)	Degrees of Freedom (DF)	Sums of Squares (SS)	Mean Squares (MS)	Variance Ratio (F)
Between groups SS*	2	10.28	5.14	2.28
Within groups SS	6	13.48	2.25	
TOTAL	8	23.76		

It can be concluded from the results of the above analysis of variance that there is no significant difference in values either between groups or within groups.

*Empirical dial readings from tensiomat.

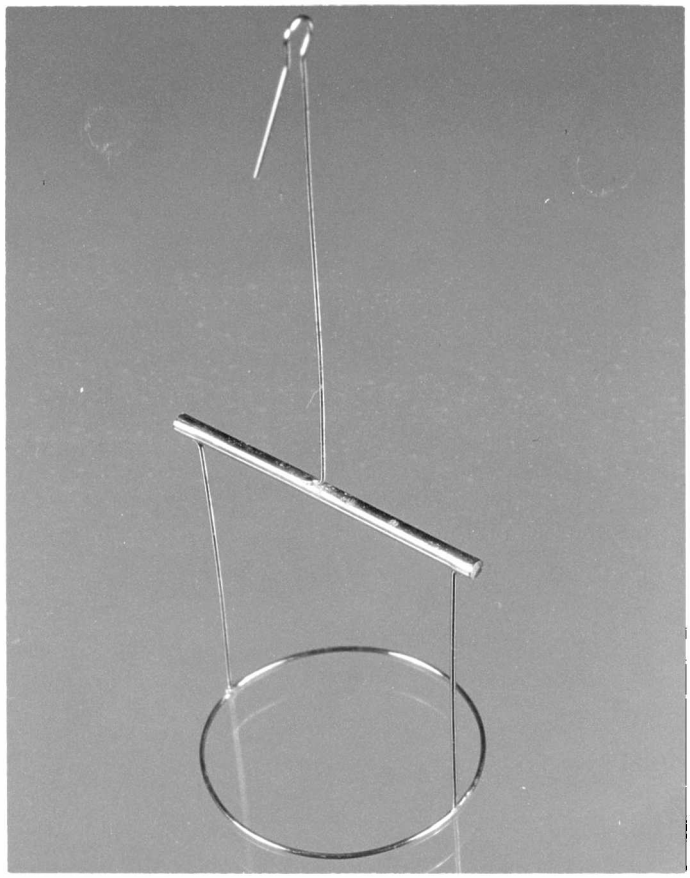

Figure 1. du Nouy Tensiometer Surface Tension Ring

The du Nouy tensiometer rings were thus found to give usable results, but the cost of the rings prohibited their further use. A large number of experiments were planned and since only three rings were available in the laboratory too much time was required to obtain sufficient data. It was also found that the du Nouy tensiometer rings were easily bent out of the flat plane of the ring and that once bent, they would no longer sit flat on the bottom of the plastic tray and give dependable results. Some portions of the bent rings pulled up through lesser thicknesses of sediment and gave lower readings. The end result was that the statistical deviation in the data became excessive.

An effort was made to develop test rings using flat "O-ring" washers of brass or copper, because these would not be as easily bent out of shape as were the tensiometer rings. Treble fish hooks were straightened and affixed to the washers with epoxy cement to make an "O-ring" test device (Figure 2). These devices proved to be of little value in measuring the cohesive forces within sediments because they lifted a portion of the cake on the flat surface of the washer, while shearing upwards through the cake. The weight of the caked material being lifted was variable in its amount and tended to obscure the value of the force required for the shearing action. It was also observed that the "O-ring" devices sometimes tended to lift at one side and slice through the cake, rather than pulling straight upwards through it. This added to the variations observed in the results.

An attempt was then made to develop a suitable test device from the metal type-spacers which are used in the printing business. These

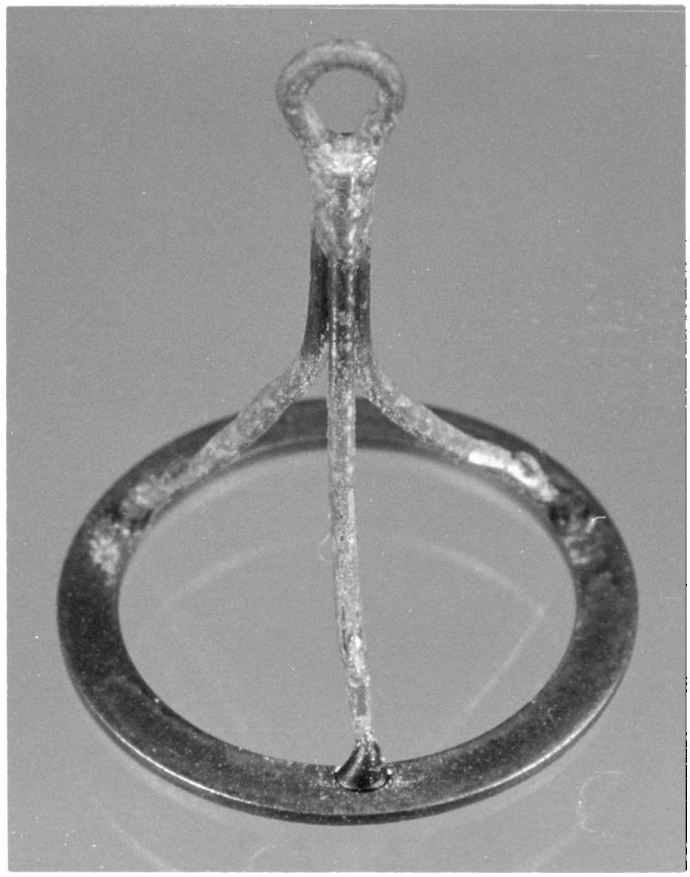

Figure 2. "O-ring" Test Device

spacers are flat rectangular pieces of brass, having the dimensions of one by three centimeters and a thickness of one-tenth millimeter. Pieces of small silver wire, three centimeters long, were bent and the ends affixed to the brass plates with epoxy cement. The resultant "Flat-plate" test devices (Figure 3) could be pulled up through the cake that was formed over them. It was found that the lifting at the edge and the slicing effect were even more evident with this shape than they were with the "O-ring" device. There was even a type of plate-to-plate adhesion between the flat metal strip and the bottom of the plastic tray. These phenomena contributed to false or inaccurate readings, and further work with flat-surfaced test devices was abandoned.

It was concluded that some type of wire-like structure was needed, and that an "H" shape might be the most ideal for the base of the device which was to be pulled up through the caked sediment (Figure 4). The wire used to make this "H" shaped structure had to be light, rigid, uniform in diameter, and rust resistant. A number of materials were considered, but stainless steel hypodermic needles were chosen because they were readily available and their tubular construction promised to add to their rigidity. The needles were carefully cut to one and four-tenths centimeters in length and stainless steel flux and solder were used to join them into an H-shape. A four centimeter length of needle was then soldered to the center of the middle bar and perpendicular to the plane of the "H". The tip of this needle was heated in a flame to remove the temper and it was then easily bent at the free end to form a small loop. This loop provided the hook to which the Tensiomat could

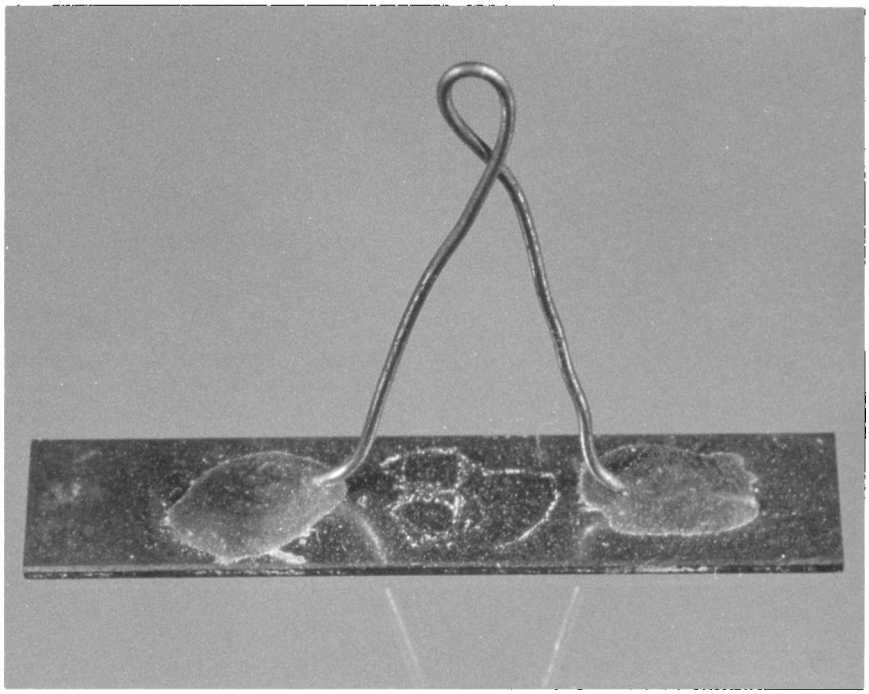

Figure 3. "Flat-plate" Test Device

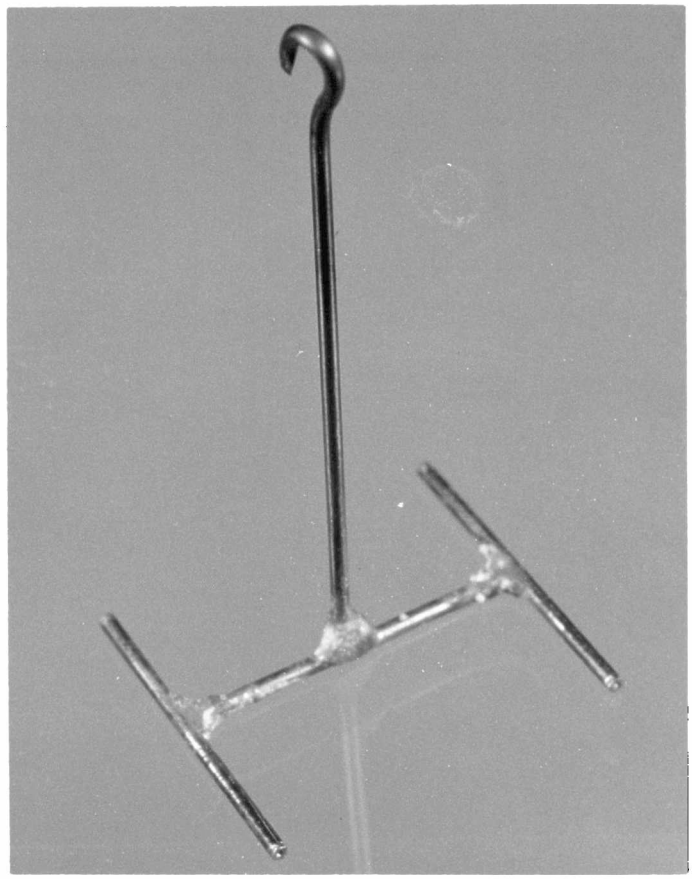

Figure 4. "H" Shaped Test Device

be attached to pull the devices up through the cake. The initial trials with the "H" shaped test devices were promising, and thirty of them were made for use in the further experimental work. Since they were soldered and formed by hand, it was difficult to make them all exactly alike. The variation in their construction brought about a relatively large statistical deviation in the results obtained in the testing of any one of the sedimented systems, but fortunately, the difference between the strengths of the caked sediments formed from the different sulfa drug materials was so great that it was possible to easily distinguish between them using the "Tensiomat" and the "H" shaped test devices. The precision of the test method could presumably have been improved if the "H" shaped devices could be made more uniform.

E. THE SUSPENSION SYSTEM: Deflocculated aqueous suspensions were prepared from the various sulfa drugs. In each case, the concentration of the suspended sulfa was three per cent weight to volume, and the concentration of the wetting agent, Dioctyl Sodium Sulfosuccinate, was held at fifteen-hundredths of one per cent. In preparing the suspensions, the dry sulfa powder was weighed on a torsion balance, transferred to a six ounce glass mortar, and triturated with fifteen milliliters of a concentrated DSS solution, until a smooth slurry was obtained. The concentrated wetting agent solution that was used was prepared by placing five grams of the surfactant in five milliliters of alcohol in a one hundred milliliter volumetric flask. After the DSS had dissolved in the alcohol, distilled water was added to bring the volume up to one hundred milliliters. A fresh wetting agent concentrate was used for each

suspension system. The slurry of sulfa drug was transferred, with rinsing of the mortar, to a five hundred milliliter volumetric flask and this was brought to its final volume. The suspension of the sulfa drug was shaken prior to use, in order to insure an evenly mixed suspension of the deflocculated particles.

F. PHOTOMICROGRAPHS OF DRY, POWDERED SULFA PARTICLES: Photomicrographs were made of each sulfa drug used in the experiment to see if there was any apparent correlation between the size and shape of the particles and the caking tendencies of the different sulfa powders. A magnification of 200X was used in most of the photomicrographs, but in the case of those sulfa powders of very fine particle size, a larger magnification was needed to demonstrate the exact particle shape. A magnification of 640X was used in these instances.

---

[1]American Cyanamid Company, 30 Rockefeller Plaza, New York, New York, 10020.

[2]Becton, Dickinson & Company, Rutherford, New Jersey, 07070.

[3]Eutectic Welding Alloys Corporation, 5917 Armour, Houston, Texas, 77023.

[4]Fisher Scientific Company, 101 Fisher Building, 717 Forbes Avenue, Pittsburgh, Pennsylvania, 15219.

[5]Fisher Scientific Company, 101 Fisher Building, 717 Forbes Avenue, Pittsburgh, Pennsylvania, 15219.

[6]Geigy Pharmaceuticals, P. O. Box 430, Yonkers, New York, 10702.

[7]Fisher Scientific Company, 101 Fisher Building, 717 Forbes Avenue, Pittsburgh, Pennsylvania, 15219.

CHAPTER IV

RESULTS

The tabular data which follow present the "Tensiomat" dial readings obtained with the "H" shaped test devices, as used to measure the caking tendencies in the sediments of the various sulfa drug preparations. Since the method used for these measurements is unique in design, it should be recognized that the individual "Tensiomat" values are simply indices which can be used to compare the relative hardnesses of the caked sediments. They are not absolute values for the hardnesses of the cakes.

Tables 1 through 5 present values for identical preparations of Sulfathiazole, N.F. XI. These five tests were completed in order to establish the validity and precision of the method and of the equipment used for test purposes.

The values shown in Table 6 demonstrate the inherent precision of the readings obtained with each of the individual "H" shaped testing devices. The values obtained with a specific "H" shaped test device over five identical tests were compared to confirm the fact that consistant readings were being obtained.

Tables 7 through 15 present values for the other nine experiments that were run. Table 7 shows the values obtained using Sulfathiazole, N.F. XI from different manufacturers. Tables 8 through 13 contain the data on three other sulfa drugs. Since each of these three sulfas was obtained from two different manufacturers, there was a total of six individual caking tests. The data are presented in pairs to facilitate a comparison of the results. The final tables, namely Tables 14 and 15, show the

results of caking tests on other sulfas. The drugs in these cases were sulfas not previously tested, and which were manufactured by different companies.

It should be noted that the data in Tables 1 through 5, and 7 through 13, represent the results of individual tests. Beneath each of these tables are the results of the analyses of variance, or "F" tests, which were performed on the data.

Table 16 summarizes the results of a statistical analysis which compares the hardness of the cakes formed by each of the sulfa drugs.

Table 1. Relative hardness of caked sediment formed in a three per cent aqueous suspension of Sulfathiazole, N.F.XI* containing fifteen-hundredths per cent wetting agent (Dioctyl Sodium Sulfosuccinate).

Device No.	Tray I	Tray II	Tray III
1.	26.89	26.03	33.68
2.	26.31	29.99	33.73
3.	25.95	29.68	33.61
4.	28.07	32.53	34.06
5.	29.81	29.00	26.39
6.	34.67	31.59	34.41
7.	31.57	31.98	27.73
8.	30.63	33.09	29.31
9.	28.79	29.19	28.07
10.	29.96	28.29	34.31
Mean			30.31
Standard deviation			± 2.75
Standard error of mean			± 0.50

Source of variation (VS)	Degrees of freedom (DF)	Sums of squares (SS)	Mean squares (MS)	Variance ratio (F)
Between groups	2	26.10	13.05	1.75
Within groups (Error)	27	200.81	7.44	
TOTAL	29	226.91		

*Sulfathiazole, N.F.XI, Batch No. WSBG, as supplied by Mallinckrodt, St. Louis, Missouri.

Table 2. Relative hardness of caked sediment formed in a three per cent aqueous suspension of Sulfathiazole, N.F.XI* containing fifteen-hundredths per cent wetting agent (Dioctyl Sodium Sulfosuccinate).

Device No.	Tray I	Tray II	Tray III
1.	26.99	24.39	36.07
2.	25.78	28.45	35.58
3.	24.86	34.56	36.39
4.	28.36	28.72	31.24
5.	31.18	28.50	28.78
6.	33.61	31.62	33.21
7.	28.38	34.31	28.00
8.	29.89	29.84	25.76
9.	27.75	28.39	27.99
10.	28.59	26.95	30.57

Source of variation (VS)	Degrees of freedom (DF)	Sums of squares (SS)	Mean squares (MS)	Variance ratio (F)
Between groups	2	40.71	20.36	2.12
Within groups (Error)	27	259.34	9.61	
TOTAL	29	300.05		

*Sulfathiazole, N.F.XI, Batch No. WSBG, as supplied by Mallinckrodt, St. Louis, Missouri.

Table 3. Relative hardness of caked sediment formed in a three per cent aqueous suspension of Sulfathiazole, N.F.XI* containing fifteen-hundredths per cent wetting agent (Dioctyl Sodium Sulfosuccinate).

Device No.	Tray I	Tray II	Tray III
1.	28.69	25.07	36.67
2.	25.79	36.73	33.87
3.	25.50	30.78	28.89
4.	26.19	28.56	30.73
5.	27.28	27.30	26.78
6.	34.31	31.96	33.09
7.	28.49	31.68	29.37
8.	34.71	32.07	28.76
9.	29.99	28.56	28.83
10.	28.64	30.49	33.41

Source of variation (VS)	Degrees of freedom (DF)	Sums of squares (SS)	Mean squares (MS)	Variance ratio (F)
Between groups	2	13.31	6.66	0.66
Within groups (Error)	27	272.72	10.10	
TOTAL	29	286.03		

*Sulfathiazole, N.F.XI, Batch No. WSBG, as supplied by Mallinckrodt, St. Louis, Missouri.

Table 4. Relative hardness of caked sediment formed in a three per cent aqueous suspension of Sulfathiazole, N.F.XI* containing fifteen-hundredths per cent wetting agent (Dioctyl Sodium Sulfosuccinate).

Device No.	Tray I	Tray II	Tray III
1.	27.80	24.16	35.29
2.	24.73	29.69	34.63
3.	26.19	34.07	36.55
4.	31.42	31.99	30.07
5.	29.97	29.39	28.36
6.	35.50	28.58	36.58
7.	28.09	33.51	29.04
8.	30.31	30.53	28.20
9.	26.89	25.86	26.97
10.	27.04	27.94	31.64

Source of variation (VS)	Degrees of freedom (DF)	Sums of squares (SS)	Mean squares (MS)	Variance ratio (F)
Between groups	2	45.77	22.89	2.05
Within groups (Error)	27	301.17	11.15	
TOTAL	29	346.94		

*Sulfathiazole, N.F.XI,Batch No. WSBG, as supplied by Mallinckrodt, St. Louis, Missouri.

Table 5. Relative hardness of caked sediment formed in a three per cent aqueous suspension of Sulfathiazole, N.F.XI* containing fifteen-hundredths per cent wetting agent (Dioctyl Sodium Sulfosuccinate).

Device No.	Tray I	Tray II	Tray III
1.	30.09	24.86	36.30
2.	27.73	36.33	32.72
3.	25.05	31.94	34.66
4.	26.28	27.31	28.42
5.	27.71	24.79	25.49
6.	34.20	32.49	36.65
7.	27.83	30.26	26.89
8.	31.31	34.06	26.31
9.	29.71	26.37	28.19
10.	27.00	29.39	35.46

Source of variation (VS)	Degrees of freedom (DF)	Sums of squares (SS)	Mean squares (MS)	Variance ratio (F)
Between groups	2	29.32	14.66	1.03
Within groups (Error)	27	385.16	14.27	
TOTAL	29	414.48		

*Sulfathiazole, N.F.XI, Batch No. WSBG, as supplied by Mallinckrodt, St. Louis, Missouri.

Table 6. Correlation coefficients (Pearson "R" values) between five separate sets of data (Tables 1-5) representing "caking" properties of Sulfathiazole, N.F XI.

Data Compared	Tables 1 & 2	Tables 1 & 3	Tables 1 & 4	Tables 1 & 5
Pearson "R" values	0.77	0.70	0.78	0.72
Pearson "R" Mean value				0.74

Table 7. Relative hardness of caked sediment formed in a three per cent aqueous suspension of Sulfadiazine, U.S.P.* containing fifteen-hundredths per cent wetting agent (Dioctyl Sodium Sulfosuccinate).

Device No.	Tray I	Tray II	Tray III
1.	118.39	112.18	119.96
2.	114.61	118.77	123.08
3.	115.98	116.31	127.91
4.	160.09	178.08	178.76
5.	113.89	128.37	167.81
6.	176.38	119.21	156.38
7.	160.51	164.89	112.87
8.	158.48	147.68	116.58
9.	119.71	116.77	119.73
10.	120.05	156.86	168.67
Mean			136.97
Standard deviation			± 23.52
Standard error of mean			± 4.29

Source of variation (VS)	Degrees of freedom (DF)	Sums of squares (SS)	Mean squares (MS)	Variance ratio (F)
Between groups	2	73.30	36.65	0.06
Within groups (Error)	27	16521.04	611.89	
TOTAL	29	16594.34		

*Sulfadiazine, U.S.P., Batch No. 3917-343, as supplied by Lederle Laboratories, Pearl River, New Jersey.

Table 8. Relative hardness of caked sediment formed in a three per cent aqueous suspension of Sulfadiazine, U.S.P.* containing fifteen-hundredths per cent wetting agent (Dioctyl Sodium Sulfosuccinate).

Device No.	Tray I	Tray II	Tray III
1.	89.31	110.65	94.68
2.	96.77	99.39	101.60
3.	96.06	104.11	96.21
4.	99.52	99.74	99.18
5.	95.87	117.87	98.06
6.	83.19	88.43	117.83
7.	109.38	87.00	85.20
8.	113.73	88.38	89.74
9.	89.10	81.09	103.39
10.	93.21	112.52	99.27
Mean			98.02
Standard deviation			± 9.78
Standard error of mean			± 1.79

Source of variation (VS)	Degrees of freedom (DF)	Sums of squares (SS)	Mean squares (MS)	Variance ratio (F)
Between groups	2	30.29	15.15	0.14
Within groups (Error)	27	2839.35	105.16	
TOTAL	29	2869.64		

*Sulfadiazine, U.S.P., Batch No. 502103, as supplied by Robinson Laboratory Inc., San Francisco, California.

Table 9. Relative hardness of caked sediment formed in a three per cent aqueous suspension of Sulfamerazine, U.S.P.* containing fifteen-hundredths per cent wetting agent (Dioctyl Sodium Sulfosuccinate).

Device No.	Tray I	Tray II	Tray III
1.	64.89	66.37	71.64
2.	59.51	69.80	67.78
3.	55.47	73.11	70.38
4.	74.29	59.93	74.91
5.	69.10	54.36	66.45
6.	65.36	67.08	76.04
7.	72.99	68.75	53.11
8.	70.48	64.83	56.76
9.	74.33	73.19	79.08
10.	67.71	78.27	69.69
Mean			67.85
Standard deviation			± 6.81
Standard error of mean			± 1.24

Source of variation (VS)	Degrees of freedom (DF)	Sums of squares (SS)	Mean squares (MS)	Variance ratio (F)
Between groups	2	7.94	3.97	0.08
Within groups (Error)	27	1383.25	51.23	
TOTAL	29	1391.19		

*Sulfamerazine, U.S.P., Batch No. VC805, as supplied by City Chemical Corporation, New York, New York.

Table 10. Relative hardness of caked sediment formed in a three per cent aqueous suspension of Sulfamerazine, U.S.P*, containing fifteen-hundredths per cent wetting agent (Dioctyl Sodium Sulfosuccinate).

Device No.	Tray I	Tray II	Tray III
1.	72.68	78.70	82.19
2.	73.47	70.12	76.50
3.	59.59	83.99	76.68
4.	68.41	69.96	84.01
5.	83.83	59.68	79.08
6.	62.98	74.89	86.73
7.	80.17	77.61	68.79
8.	78.49	68.77	69.21
9.	73.20	73.50	75.59
10.	67.62	83.32	70.09
Mean			74.33
Standard deviation			± 7.02
Standard error of mean			± 1.28

Source of variation (VS)	Degrees of freedom (DF)	Sums of squares (SS)	Mean squares (MS)	Variance ratio (F)
Between groups	2	118.41	59.21	1.18
Within groups (Error)	27	1360.09	50.37	
TOTAL	29	1478.50		

*Sulfamerazine, U.S.P., Batch No. 707593, as supplied by Robinson Laboratory Inc., San Francisco, California.

Table 11. Relative hardness of caked sediment formed in a three per cent aqueous suspension of Sulfamethazine, U.S.P.* containing fifteen-hundredths per cent wetting agent (Dioctyl Sodium Sulfosuccinate).

Device No.	Tray I	Tray II	Tray III
1.	83.89	81.69	91.27
2.	81.20	90.00	93.82
3.	84.41	91.34	93.79
4.	89.08	89.72	91.06
5.	87.53	87.51	90.85
6.	89.71	94.83	97.78
7.	92.68	86.38	88.36
8.	86.65	92.19	86.91
9.	89.06	88.99	92.53
10.	93.11	94.16	83.71
Mean			89.74
Standard deviation			± 3.92
Standard error of mean			± 0.72

Source of variation (VS)	Degrees of freedom (DF)	Sums of squares (SS)	Mean squares (MS)	Variance ratio (F)
Between groups	2	54.31	27.16	1.80
Within groups (Error)	27	407.23	15.08	
TOTAL	29	461.54		

*Sulfamethazine, U.S.P., Batch No. 707670, as supplied by Robinson Laboratory Inc., San Francisco, California.

Table 12. Relative hardness of caked sediment formed in a three per cent aqueous suspension of Sulfamethazine, U.S.P.* containing fifteen-hundredths per cent wetting agent (Dioctyl Sodium Sulfosuccinate).

Device No.	Tray I	Tray II	Tray III
1.	93.31	92.79	99.78
2.	97.47	97.08	94.38
3.	95.91	96.91	102.04
4.	100.56	94.08	98.91
5.	94.73	98.89	96.17
6.	103.96	104.73	106.86
7.	96.49	97.35	98.58
8.	98.85	101.61	99.75
9.	95.08	94.77	93.13
10.	91.66	95.93	97.52
Mean			97.64
Standard deviation			± 3.60
Standard error of mean			± 0.66

Source of variation (VS)	Degrees of freedom (DF)	Sums of squares (SS)	Mean squares (MS)	Variance ratio (F)
Between groups	2	19.02	9.51	0.69
Within groups (Error)	27	369.71	13.69	
TOTAL	29	388.73		

*Sulfamethazine, U.S.P., Batch No. UB548, as supplied by City Chemical Corporation, New York, New York.

Table 13. Relative hardness of caked sediment formed in a three per cent aqueous suspension of Sulfanilamide, N.F.XI* containing fifteen-hundredths per cent wetting agent (Dioctyl Sodium Sulfosuccinate).

Device No.	Tray I	Tray II	Tray III
1.	56.71	56.34	68.53
2.	54.68	72.20	63.46
3.	50.93	62.86	60.39
4.	64.05	67.37	67.78
5.	61.32	61.09	58.30
6.	68.26	60.74	61.74
7.	60.15	50.89	60.20
8.	61.47	68.46	59.49
9.	58.53	57.51	55.82
10.	71.14	61.73	71.11
Mean			61.78
Standard deviation			± 5.55
Standard error of mean			± 1.01

Source of variation (VS)	Degrees of freedom (DF)	Sums of squares (SS)	Mean squares (MS)	Variance ratio (F)
Between groups	2	19.48	9.74	0.29
Within groups (Error)	27	904.97	33.52	
TOTAL	29	924.45		

*Sulfanilamide, N.F.XI,Batch No. 62622, as supplied by Merck & Co., Inc., Rahway, New Jersey.

Table 14. Relative hardness of caked sediment formed in a three per cent aqueous suspension of Sulfanilamide, N.F.XI* containing fifteen-hundredths per cent wetting agent (Dioctyl Sodium Sulfosuccinate).

Device No.	Tray I	Tray II	Tray III
1.	30.09	28.76	29.54
2.	30.43	30.19	32.31
3.	33.58	34.22	31.76
4.	34.96	33.93	35.23
5.	31.21	31.98	33.59
6.	36.20	36.46	34.61
7.	37.10	34.27	38.70
8.	35.89	37.05	35.04
9.	30.39	32.70	33.65
10.	31.74	37.28	33.18
Mean			33.53
Standard deviation			± 2.55
Standard error of mean			± 0.47

Source of variation (VS)	Degrees of freedom (DF)	Sums of squares (SS)	Mean squares (MS)	Variance ratio (F)
Between groups	2	2.15	1.08	0.15
Within groups (Error)	27	192.19	7.12	
TOTAL	29	194.34		

*Sulfanilamide, N.F.XI, Batch No. NHT-2286, as supplied by S. B. Penick & Co., New York, New York.

Table 15. Relative hardness of caked sediment formed in a three per cent aqueous suspension of Succinylsulfathiazole, U.S.P.* containing fifteen-hundredths per cent wetting agent (Dioctyl Sodium Sulfosuccinate).

Device No.	Tray I	Tray II	Tray III
1.	65.06	66.63	72.57
2.	67.49	59.68	67.63
3.	57.97	64.20	57.19
4.	58.15	70.45	58.56
5.	68.79	58.71	59.74
6.	59.22	72.25	66.00
7.	69.30	69.56	61.29
8.	60.81	56.71	58.73
9.	64.50	57.49	70.95
10.	57.98	58.03	67.86
Mean			63.45
Standard deviation			± 5.18
Standard error of mean			± 0.95

Source of variation (VS)	Degrees of freedom (DF)	Sums of squares (SS)	Mean squares (MS)	Variance ratio (F)
Between groups	2	17.85	8.94	0.30
Within groups (Error)	27	797.35	29.53	
TOTAL	29	815.20		

*Succinylsulfathiazole, U.S.P., Batch No. D0318, as supplied by Merck Sharp & Dohme, West Point, Pennsylvania.

Table 16. Test of significance (t-test) demonstrating differences in "caking" tendencies between various sulfa preparations.

Preparations Compared					
Drug	Company	Batch Number	Table Number	"t" Value	Probability of Error
Sulfamerazine, U. S. P.	Robinson Laboratory Inc.	707593	10	3.63	< 0.001
Sulfamerazine, U. S. P.	City Chemical Corporation	VC805	9		
Sulfamethazine, U.S.P.	Robinson Laboratory Inc.	707670	11	8.41	< 0.001
Sulfamethazine, U.S.P.	City Chemical Corporation	UB 548	12		
Sulfanilamide, N.F. XI	Merck & Co., Inc.	62622	13	25.36	< 0.001
Sulfanilamide, N.F. XI	S. B. Penick & Co.	NHT-2286	14		
Sulfadiazine, U.S.P.	Robinson Laboratory Inc.	502103	8	8.38	< 0.001
Sulfadiazine, U.S.P.	Lederle Laboratories	3917-343	7		
Sulfamerazine, U.S.P.	Robinson Laboratory Inc.	707593	10	10.32	< 0.001
Sulfamethazine, U.S.P.	Robinson Laboratory Inc.	707670	11		
Sulfamerazine, U.S.P.	Robinson Laboratory Inc.	707593	10	10.78	< 0.001
Sulfadiazine, U.S.P.	Robinson Laboratory Inc.	502103	8		
Sulfamethazine, U.S.P.	Robinson Laboratory Inc.	707670	11	4.45	< 0.001
Sulfadiazine, U.S.P.	Robinson Laboratory Inc.	502103	8		
Sulfathiazole, N.F. XI	Mallinckrodt	WSBG	1	30.97	< 0.001
Succinylsulfathiazole, U.S.P.	Merck Sharp & Dohme	D0318	15		

CHAPTER V

DISCUSSION OF RESULTS

Initially, tests were performed to determine the possible presence of wetting agents of the anionic type in the dry sulfa powders. Wetting agents of this type might have been added during the basic manufacturing processes. These tests confirmed the absence of wetting agents in the dry sulfa powders which had been selected for study. This eliminated the possibility of variable concentrations of the wetting agent between sulfa drug suspensions, since this could possibly have altered the caking tendencies.

An analysis of variance, using the F ratio, was applied to the data from each of the experimental runs. If was found that there was no statistically significant difference ($P > 0.05$) between the three individual "trays" of each test run.

To establish further validity for the test method, the correlation coefficient, or Pearson "R" test was used. (Table 6). This test was applied to the data for sulfathiazole, N.F.XI in Tables 1 through 5. The average "R" value obtained was ± 0.76. This indicates, in conjunction with the number of tests performed, that the correlation between the variables could occur by chance alone less than 0.1% of the time, in the absence of any real association. Comparisons were made to determine if the differences in caking tendencies of the various sulfa drugs were statistically significant. The comparisons made were of three types. The first was between three different sulfa drugs, all of which were manufactured by the same drug company. The second comparison was made between the same sulfa drug, as prepared and/or supplied by different

drug companies. The third comparison was made between two different sulfa drugs, which were sold by different companies. The difference in the caking tendencies between the sulfa drugs in each of these comparisons was statistically significant ($P < 0.001$ in every case).

A photomicrographic study was performed to see if there was any correlation between the particle sizes of the various sulfa powders and their caking tendencies. It was found that there is a probable correlation between particle size and shape, and the "hardness" of the cake that is formed. The settling times of the suspension were also observed to be very much dependent upon particle size. The sulfa particles of those suspensions prepared using Sulfathiazole, N. F. XI (Mallinckrodt) and Sulfanilamide, N.F.XI (Penick), settled very rapidly and formed loose sediments which had very little tendency to cake. This appeared to correlate with the particle size of these two sulfa powders, since these appeared as the largest in the photomicrographs. Sulfanilamide, N.F.XI (Merck) and Succinylsulfathiazole, U.S.P. (M S & D) were slightly smaller in particle size. They were observed to have slower settling rates in suspension, and to demonstrate a definite tendency toward the formation of hard "cakes".

Sulfamethazine, U.S.P., in particular, provided an example of the differences in the settling and caking characteristics that exist between manufacturers' products of the same sulfa drug in different particle sizes. The Robinson lot of Sulfamethazine, U.S.P. was clearly shown by the photomicrographs to contain particles of a larger size than those present in the City Chemical Company's Sulfamethazine, U.S.P.

The smaller sized particles of Sulfamethazine, U.S.P. settled much more slowly but having settled they formed a harder cake.

The two brands of Sulfamerazine, U.S.P. contained particles of about the same size, shape, and complexity, and as was to be expected, showed relatively little difference in the hardnesses of the cakes formed. Upon first glance, the photomicrographs of the particles make it appear that the Robinson product contains much larger particles. Upon closer observation at a higher magnification (640X), it can be seen that the Robinson brand seems larger in particle size only because the very fine particles of which it is composed have tended to aggregate. The individual particles are of approximately the same size as the particles present in the City Chemical Sulfamerazine, U.S.P. product.

Sulfadiazine, U.S.P. (Lederle) appeared to be the only drug tested in which the caking tendency was not inversely proportional to the particle size. However, it was seen on close observation of the photomicrographs that the Sulfadiazine, U.S.P. (Lederle) particles were in the form of crystalline needles, rather than having the irregular spherical or rod-shaped forms that were typical of the other powdered materials. It was also observed that the cake formed upon settling was of such a nature that it kept the "H" shaped device from cutting through the cake as it was pulled upwards by the "Tensiomat". Instead, the cake broke into clumps which hindered the rise of the test device. It is felt that this phenomenon was due to the monoclinic form of these particles.

The photomicrographs discussed above are shown as Figures 5 through 14, in the same order as the data on the various types or groups of sulfa drugs were presented in the previous tables.

Figure 5. Photomicrograph of Mallinckrodt Brand of Sulfathiazole, N.F.XI Particles (200X).

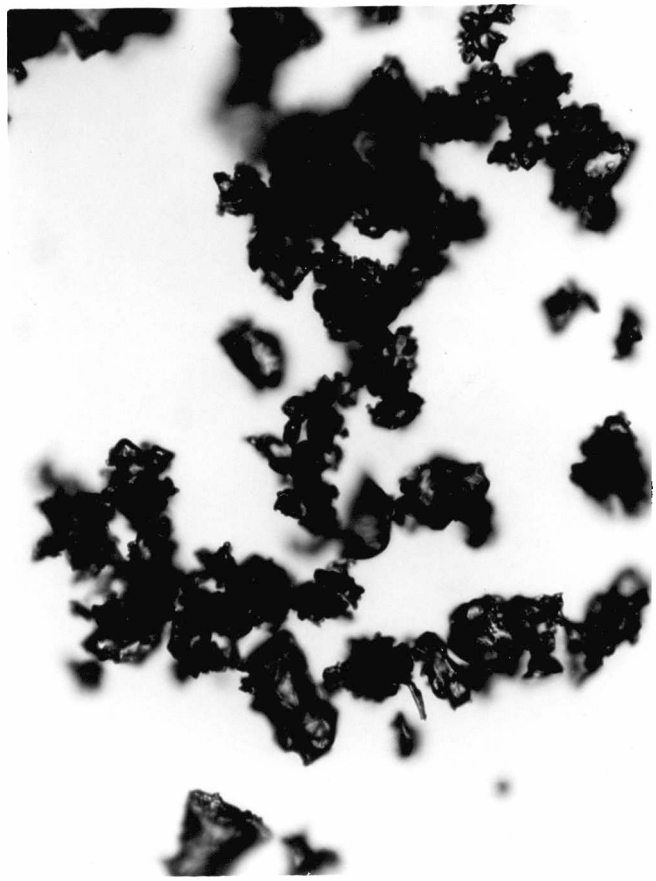

Figure 6. Photomicrograph of Penick Brand of Sulfanilamide, N.F.XI Particles (200X).

Figure 7. Photomicrograph of Merck Brand of Sulfanilamide, N.F.XI Particles (200X).

Figure 8. Photomicrograph of Merck Sharp & Dohme Brand of Succinylsulfathiazole, U.S.P. Particles (200X).

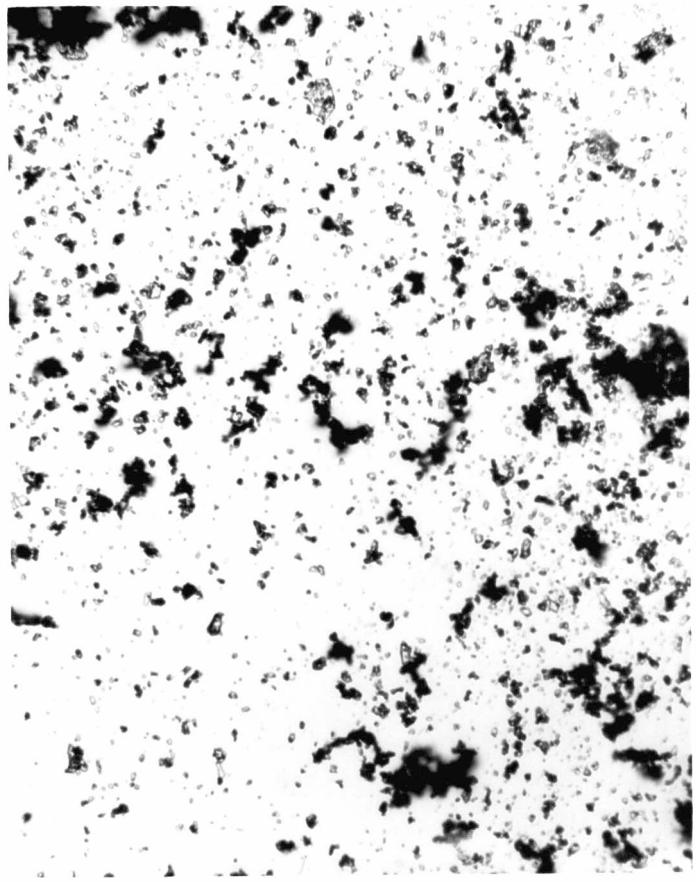

Figure 9A. Photomicrograph of City Chemical Corporation Brand of Sulfamerazine, U.S.P. Particles (200X).

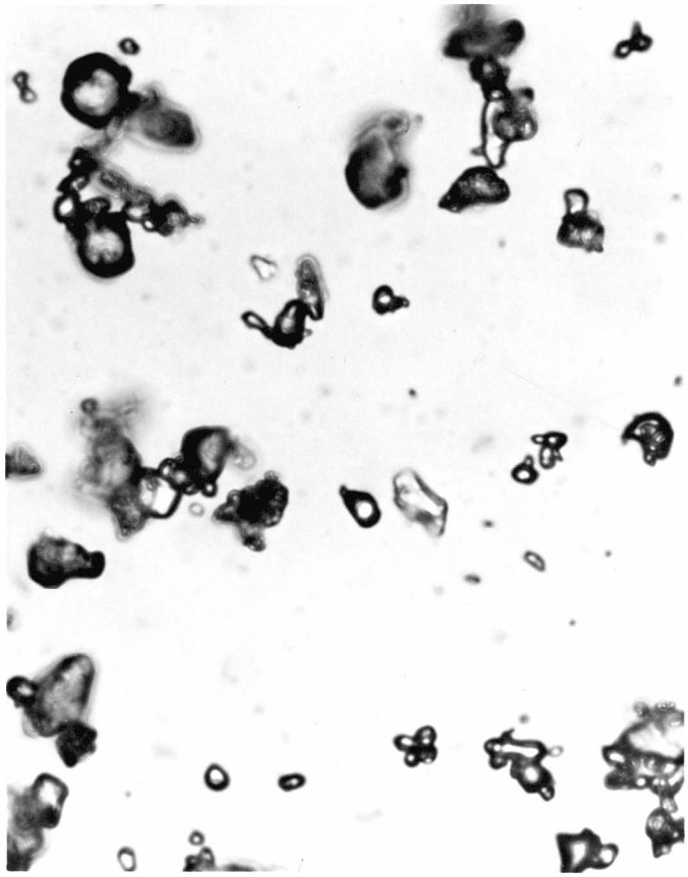

Figure 9B. Photomicrograph of City Chemical Corporation Brand of Sulfamerazine, U.S.P. Particles (640X).

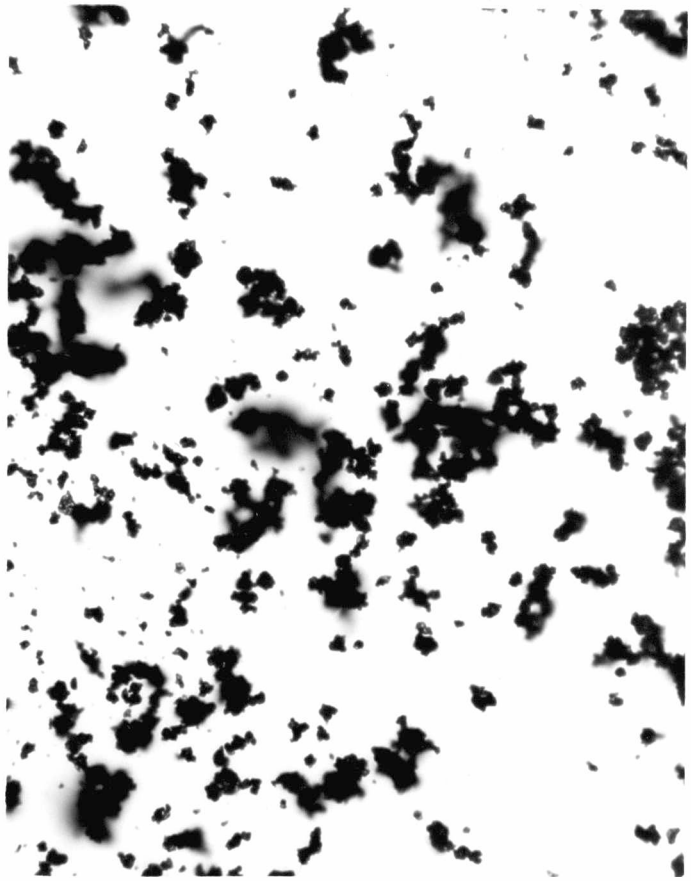

Figure 10A. Photomicrograph of Robinson Laboratory Inc. Brand of Sulfamerazine, U.S.P. Particles (200X).

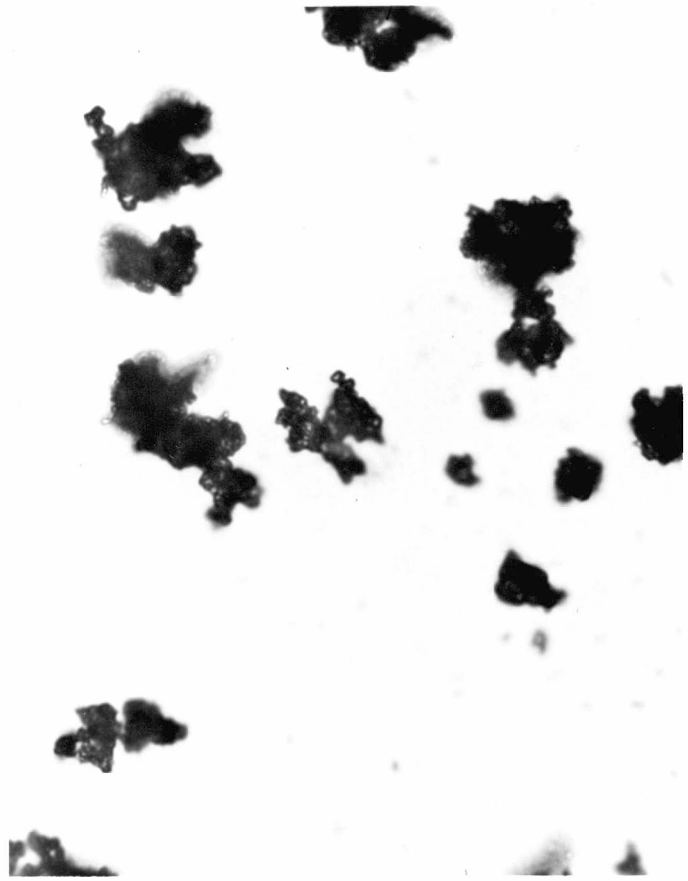

Figure 10B. Photomicrograph of Robinson Laboratory Inc. Brand of Sulfamerazine, U.S.P. Particles (640X).

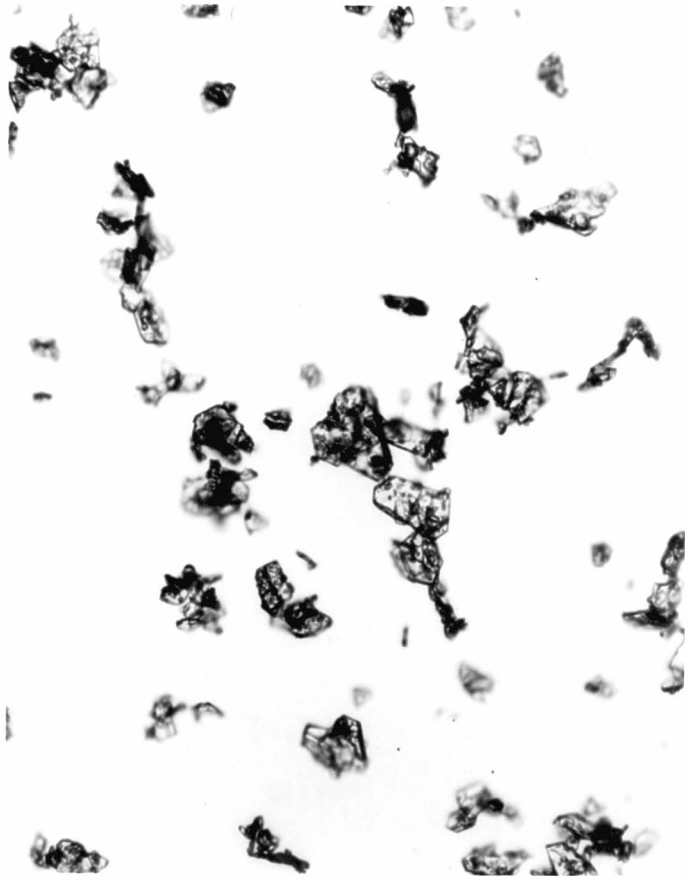

Figure 11. Photomicrograph of Robinson Laboratory Inc. Brand of Sulfamethazine, U.S.P. Particles (200X).

Figure 12. Photomicrograph of City Chemical Corporation Brand of Sulfamethazine, U.S.P. Particles (200X).

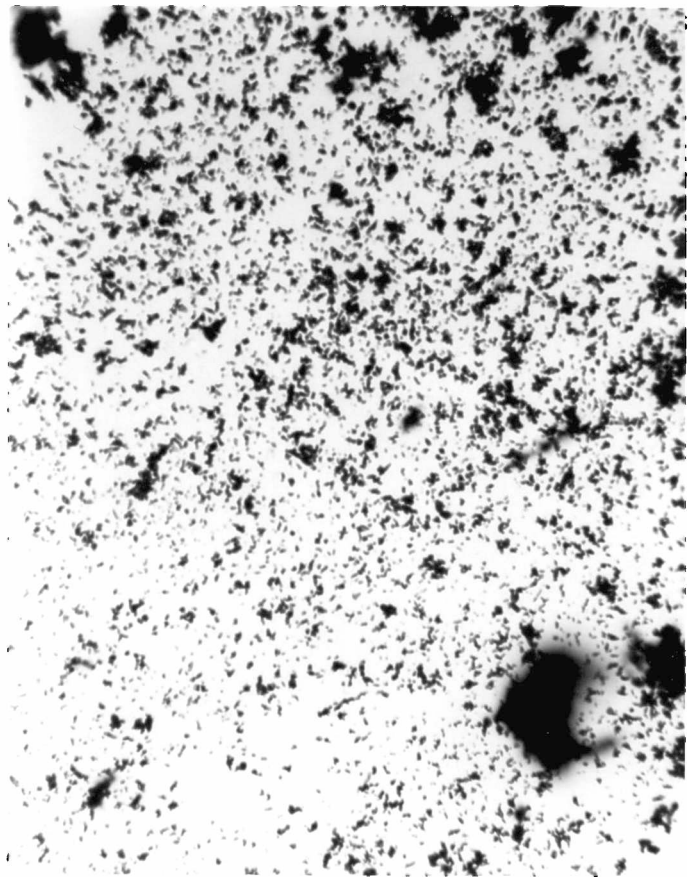

Figure 13A. Photomicrograph of Robinson Laboratory Inc. Brand of Sulfadiazine, U.S.P. Particles (200X).

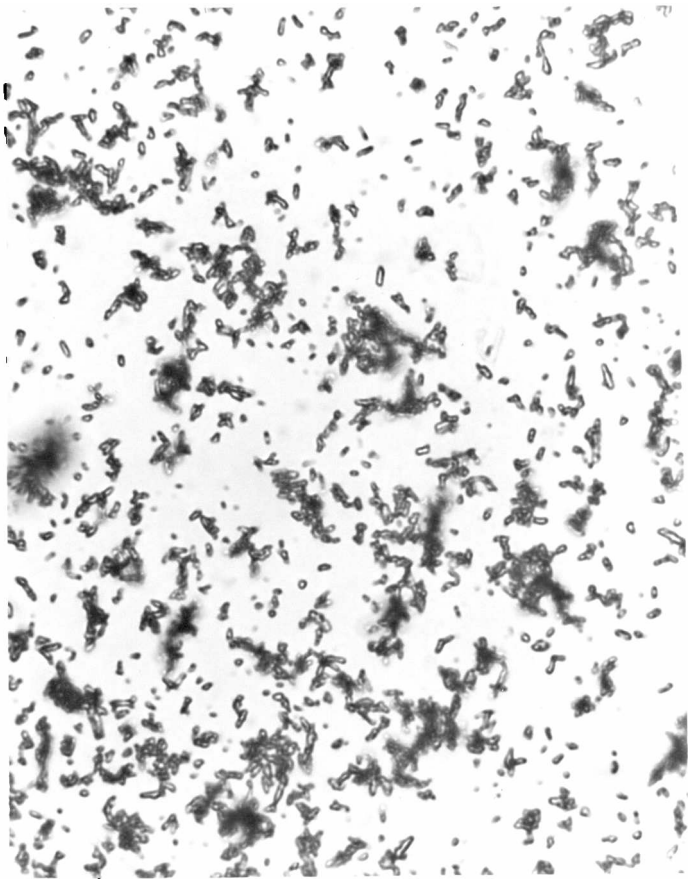

Figure 13B. Photomicrograph of Robinson Laboratory Inc. Brand of Sulfadiazine, U.S.P. Particles (640X).

Figure 14. Photomicrograph of Lederle Laboratories Brand of Sulfadiazine, U.S.P. Particles (200X).

CHAPTER VI

SUMMARY

Various deflocculated sulfa drug suspensions were prepared using three per cent weight to volume concentrations of a number of powdered sulfa drug materials. The concentration of the wetting agent, Dioctyl Sodium Sulfosuccinate, was fifteen-hundredths of one per cent weight to volume. Each suspension was prepared and placed in clear plastic trays containing the "H" shaped test devices, and the suspensions were allowed to settle undisturbed for seventy-two hours. A duNouy "Tensiomat" was then used to lift the "H" shaped test devices through the cake which had formed, and the "Tensiomat" reading was taken as a measure of the relative hardness of the cakes formed.

Under the conditions of the experiment, it was found that the degree of caking in sulfa suspensions was statistically different between the various sulfa drugs, and was generally inversely proportional to the gross particle sizes of the powders, as seen in the photomicrographs. An exception was noted in the case of Sulfadiazine, U.S.P. (Lederle), where the particles were in the form of needle-like crystals. The settling time of the suspended sulfa particles was directly proportional to the particle size, as would be expected from Stöke's Law.

It is concluded that particle size must be carefully considered in suspension formulation work, not only for its effect upon settling rates but also for its influence upon the "caking" tendency of the fully sedimented material. This fact has been substantiated through the development and application of a test method that measures and compares the relative hardness of caked sediments in similar suspension systems.

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