CORRELATION OF WATER ABSORPTION WITH TABLET DISINTEGRATION TIME

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NORMAN FREDRICK BILLUPS

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APPROVED:

Redacted for privacy

Associate Professor of Pharmacy

In Charge of Major

Redacted for privacy

Dean of School of Pharmacy

Redacted for privacy

Chairman of School Graduate Committee

Redacted for privacy

Dean of Graduate School

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CORRELATION OF WATER ABSORPTION WITH TABLET DISINTEGRATION TIME

INTRODUCTION

Historical

The making of drugs into tablet-like forms dates back to the days of the Roman Empire, when drugs were molded into small compressed shapes (43, p. 9). Lozenges, troches, and pastilles were referred to by Hippocrates, Celsus, Cordi and other early writers (20, p. 821). Urdang states that the term "tablet" was probably first used by Jean de Renon in 1608, when the Latin word tabella (a board plank, writing tablet) was applied to a special type of troche used in medicine at that time (26, p. 366). The chief disadvantage with these early dosage forms was that they contained gummy adhesives which made them slow to dissolve. Because of the poor solubility of these dosage forms the compressed tablets were developed.

Although dosage forms resembling tablets have been in existance many years, compressed tablets are relatively new, coming into existance on December 8, 1843. It was then that Professor William Brockedon, a watchmaker, mechanic and painter of Devonshire Street, Queen Square, in the county of Middlesex, East London was granted a British patent (No. 9977) on a machine for "Shaping Pills, Lozenges and the Black Lead by Pressure in Dies" (20, p. 822). Brockedon secured the patent in order to compress graphite for use in lead pencils but he claimed priority in applying pressure to small steel

molds for tableting medicinal powders (20, p. 823). Brockedon's invention created great interest with manufacturers of pharmaceuticals and in a matter of a few years large numbers of tablets "of questionable value" appeared on the market. These tablets were not favorably received by the medical authorities because of their poor solubility, but this did not stop their widespread distribution by patent-medicine men. These irresponsible "hawkers" created a "tablet fad", a factor that ultimately led to the enactment of effective food and drug legislation in the United States (27, p. 56).

The term "compressed tablets" was originated by John Wyeth and his brother when they received the United States Registered Trade Marks Numbers 1001 and 1002 on March 13, 1877 to protect and restrict the term they had coined (20, p. 844). The term "compressed tablets" soon came to have widespread usage, however, and was declared to be public property as no other suitable descriptive phrases existed.

Since Brockedon's hammerblow type tablet compressing machine, there has been a gradual evolution of new machines. Various types of hand pressure machines came next only to be replaced by the present automatic electrically driven machines. According to Kebler the manufacture of "compressed pills" in the United States was begun by Jacob Dunton (20, p. 826). Other notable American pioneers in the development of these machines were Joseph Remington, Jabez H. Gill, John Lusby, Dr. Joseph Mc Ferran, Henry Bower and John and Maxwell Wyeth (43, p. 11).

With the development of faster machines, tablets became an increasingly popular dosage form. By the early 1890's tablets were advocated for all diseases. This period has been referred to by many writers as the time of the "tablet fad". The physician found that tablets provided an easy means of dispensing his own medication and manufacturers offered him long lists of tablets with an index specifying their use in the treatment of various ailments (26, p. 367).

From the preceeding discussion it can be seen that compressed tablets used for medicinal purposes are a relatively new dosage form. It is of interest to note that the first official tablet appeared in USP IX in 1916 (27, p. 56). Both USP IX (1916) and USP X (1926) recognized only one tablet. The first tablets were official in the NF V (1926) with the inclusion of eight tablets. In NF VI (1936), 48 tablets were official in the monographs. It was not until 1942 that the first really impressive entry of tablets into the USP occurred, when 51 tablets were given official recognition. It has thus been only in the last 20 years that tablets have enjoyed official recognition in the compendia (26, p. 367).

The main disadvantage of early tablets and a primary reason why they were not accepted as official in the monographs of the NF and USP, was their failure to dissolve (20, p. 846). Instead they would pass through the body and be excreted in the fecal material unchanged (4, p. 501). For this reason many of the early tablets were termed "brick bats" (21, p. 937). Sales for these "brick bats"

declined to an awakening public and manufacturers were forced to compress only soluble drugs.

Then in 1887 a discovery was made which revolutionized the tablet industry. It was in this year that Charles Kilgore discovered that starch, when compressed into the tablet with the other ingredients, would act to break the tablet apart (20, p. 846). He termed this phenomenon disintegration. Insoluble drugs could be compressed into tablets and with the aid of starch, would break apart as rapidly as soluble drugs. Since Kilgore's discovery many substances have been tested for their disintegrating properties, and though many new disintegrating agents have been tested, starch still remains as one of the best general purpose disintegrating agents to date.

Importance of Tablets

Since the tablet compressing machine of Brockedon, Dunton, Mc Ferran and others, tablets as a dosage form have been subjected to many refinements and today are by far the most frequently prescribed dosage form called for on prescriptions (34, p. 1). A survey taken in November 1957 of 3,074 prescriptions collected from 29 different pharmacies representing all of the geographical areas in Oregon, indicates that 46.9% were written for tablets as the dosage form to be dispensed, while liquids were second with 24.3% followed by capsules at 17.0% and ointments at 5.4% (33, p. 14). These results are in general agreement with other regional and national surveys.

Tablets have achieved their present popularity and importance due to economy of manufacture, ease of administration, convenience in

portability, stability, accuracy of dosage, and favorable pharmaceutical appearance (34, p. 1) (20, p. 820).

Classification of Ingredients Found in Tablet Formulas

De Kay has made a careful study of many tablets and their available formulas. From this study he has classified the ingredients that constitute a tablet into "medicaments" and "excipients" (26, p. 374). Kebler, in an earlier article, has classified the ingredients of tablets similar to that of De Kay (20, p. 847-848) (21, p. 937-939). The medicament is defined as that portion of the tablet containing the therapeutic value for which the tablet is prescribed. The excipient is defined as any ingredient or combination of ingredients in the tablet comprising the bulk of the tablet in excess of the medication (20, p. 847). The excipients are classified into liquids, adhesives, diluents, disintegrators, absorbents and lubricants. A typical tablet thus contains in addition to the medicament, various combinations and quantities of excipients. To better understand the various excipients, a detailed discussion of each of the above mentioned groups will be considered.

Liquids, the first of the excipients to be considered, are included in tablet formulations as the granulating agent. The liquids thus comprise a group of agents used to form the moist mass prior to granulation. Some liquids frequently employed for granulating purposes are water, alcohol, hydroalcoholic mixtures, and organic solvents (26, p. 374) (20, p. 848).

Some materials when granulated with water or alcohol revert to powder again when the water or alcohol is removed by drying. In order to prevent this, small amounts of adhesives are added to hold the powder together in a granular form which when compressed will make a tablet. A few of the more common adhesives are cane sugar, acacia, dextrin, liquid glucose, gelatin, pectin, starch paste, and some of the modern gum-like substances as sodium alginate, methycellulose and various Kelgins^{R}. Keltose^{R}, a seaweed derivative, has been found to be a very good adhesive when added dry or as a 1% solution. Keltose^{R} and the other Kelgin^{R} products in granules retain properties that make them good disintegrating agents as well as very effective binding agents (26, p. 375).

Frequently the liquid and the adhesive are mixed together for the dual purpose of functioning as both the granulating agent and adhesive. Such a combination of ingredients is frequently called a binding agent (34, p. 6). Some authors make no distinction between adhesives and binders (19, p. 94) (34, p. 6). Scoville summarizes well the purpose of the binder in a tablet formulation, stating that "the binder or adhesive is a substance added for two purposes: to hold the powders together as granules and to hold the granules together as tablets" (19, p. 94). Silver and Clarkson have listed the most widely used binding agents (in decreasing order according to their strength and binding qualities) as glucose, gum acacia, gelatin, sucrose, hydrolyzed starch, water and alcohol (34, p. 6).

Another of the excipients frequently incorporated into the tablet formulation is the disintegrating agent. Remington defines a disintegrating agent as "a substance or a mixture of substances added to the tablet to cause it to break apart or disintegrate in water or to hasten solution after administration" (28, p. 376). If tablets are expected to provide effective medication it is essential that the tablet dissolve or disintegrate with reasonable rapidity. Some substances which have been employed as disintegrating agents are bentonite, agar, alginic acid, Kelacid^{R} and Kelcosol^{R}, dried powdered citrus pulp, pectin, dried sponge, gelatin, methylcellulose, Veegum HV^{R}, the various gums as guar and karays gum, the starches of potato, rice, corn and wheat, and various combinations of two or more agents. Of all the substances used to date, most authors agree that starch is far the best agent in use as a tablet disintegrating agent (34, p. 23) (21, p. 937) (28, p. 376) (27, p. 68). Gross and Becker have made a comparative study of 22 tablet disintegrating agents and have found that dried powdered citrus pulp and dried powdered sponge compared favorably as tablet disintegrators with the best agents in use by pharmaceutical companies (13, p. 161).

The diluents, generally an inert group of drugs, are used to increase the final volume of the tablet. Some substances that have been used as diluents are, cane sugar, lactose, ammonium chloride, sodium carbonate, sodium citrate, dextrine, starch, talcum, kaolin and magnesium hydroxide (28, p. 377). Diluents, sometimes referred to as fillers, are frequently employed with potent drugs that require

only a small quantity of the active ingredient in each tablet.

The absorbents are still another class of excipients that may be incorporated into a tablet formulation. The absorbents function in tablets to aid in taking up liquid medications as fluid extracts, pilular extracts and tinctures. Frequently diluents are used as absorbents. The agents commonly used as absorbents are lactose, starch and magnesium carbonate (21, p. 938). Powdered glycyrrhiza has been used to some extent, but it has the disadvantage of producing a speckled tablet because of the brown color of the powdered licorice root (26, p. 375).

Lubricants are substances added to the granulation to promote uniform feeding into the dies and to keep the granulation from adhering to the punches and the dies during compression. The lubricants which have been reported in the literature as having been used for various tablet granulations are arrowroot starch, boric acid (powder), calcium stearate, Carbowaxes^{R}, carnuba wax (powder), coca butter, ethereal solution of petrolatum (2%), french chalk, Lanette Wax^{R}, lycopodium, magnesium stearate, odorless hydrocarbon oil, paraffin waxes, paraffin oil, potassium oleate, powdered neutral white soap, spermaceti, starch, stearic acid, Sterotex^{R}, syrup and egg albumin mixtures (patented), and talcum (26, p. 375). Of the lubricants listed, Scoville lists liquid petrolatum, talc, magnesium stearate, and stearic acid as the most common. Strickland and Busse, in studying the mechanism of action of tablet lubricants, evaluated several classes of compounds and found that metallic salts of fatty acids were generally

the best lubricants (35, p. 35). A study of lubricants by Wolff and Jenkins has shown that there is no universal lubricant (42, p. 407). Another study has shown that the lubricants act best when added to the dried granules in the form of a fine powder or spray. This places the lubricant on the outside of the granules where it is in the position to act most efficently (42, p. 410). Hammerness and Thompson have found that a combination of lubricant and fines appear to have a synergistic action upon the rate of flow (14, p. 61). A maximum point is reached, however, which was the optimum ratio of fines to lubricant. The maximum was between 50-60% fines regardless of the concentration of the lubricant. Salisbury and Higuchi have shown that the extrusion forces for a series of tablet lubricants are in the approximate order of their efficiencies as tablet lubricants (31, p. 288). Many materials have a granular or crystalline structure and may be directly compressed without the aid of lubricants. Some of these substances are methenamine, sodium chloride, sodium bromide, chloral hydrate, potassium iodide, ammonium chloride, potassium chlorate, potassium permangenate, camphor, naphthalene and Formin (26, p. 375) (34, p. 20) (21, p. 939).

In addition to lubricants, other factors also influence the flow of the granulation into the dies. Hygroscopic substances are very difficult to compress for they offer resistance to uniform flow through the machine and stick to the punches and dies. Another factor which influences the flow of the granulation is the dryness of the particular granulation. The humidity during compression is still

another factor which affects the feeding of the granulation into the machine (28, p. 374).

An important group of tablet constituents not mentioned by De Kay, but one which should be included with the excipients, are the colors and flavors. Although this group of substances displays no physiological action on the patient and is not necessary to facilitate the manufacture of tablets, these ingredients are, however, important for the psychological value they promote. Flavors are especially valuable when incorporated into tablets which are to be dissolved in the mouth. In addition to their psychological benefit to the patient, flavors are frequently employed to mask the objectional taste of an ingredient, to distinguish a tablet from that of a competitor, or to mask an objectionable odor. Volatile oils are the most common flavors used in the tableting industry.

Role of Disintegrating Agents In Tablets

The importance of proper tablet disintegration can not be overly stressed. To be effective it is necessary for the tablet to break apart within a desirable period of time so that the medication may be absorbed. To accomplish this a substance is added to the tablet formulation that will react when brought into contact with fluids and, in turn, cause the tablet to break apart. Such a substance is termed a disintegrating agent.

Disintegrating agents have been reported to act in three ways: those which react with moisture to liberate a gas, those which react

with moisture to reconstitute a foam and those which "absorb water and swell" (7, p. 520). Those of the "absorb water and swell" type are by far the most commonly employed in industry today, and the group to which this study has been confined. Curlin has suggested that the theory of action behind disintegrating agents of the "absorb water and swell" type is capillary action (9, p. 16).

A study of the literature reveals that much empirical information is available on the relative efficacies of different tablet disintegrating agents. Cooper and Brecht have reported that surfactants in tablets improve disintegration (7, p. 520). Crisafi and Becker have studied natural sponge as a disintegrator in compressed tablets (8, p. 363). Gross and Becker have compared 22 tablet disintegrating agents (13, p. 157). Van Abbe and Rees have studied amberlite resin as a tablet disintegrator (38, p. 487). Gerding and De Kay studied alginic acid for its binding and disintegrating properties (11, p. 132). Berry and Ridout tried various combinations of potato starch and alginic acid for effectiveness as tablet disintegrators (5, p. 619). In such studies, however, no serious attempt has been made to correlate such physical factors as porosity, density, crystalline structure, compressibility, ability to swell, or moisture absorption with tablet disintegration time (15, p. 93).

Statement of Problem

The purpose of this paper is to study the mechanism of action of tablet disintegrating agents. The investigation of this problem was

carried out by studying the rate of water absorption and tablet disintegration time of nine selected disintegrating agents of the "absorb water and swell" type. From these two independent studies, statistical correlations can be made to reveal the relationships between water absorption and efficiency as disintegrating agents. A discussion of the results and the conclusions from these studies will appear at the end of this thesis.

EXPERIMENTAL PROCEEDURE AND RESULTS

Selection of Disintegrating Agents

The first consideration was the determination of a rational basis for the selection of the disintegrating agents to be tested. Of the three general types of disintegrating agents previously mentioned, this study employed only those agents which belong to the class which "absorb water and swell". The selection of the various disintegrating agents that were used and the reasons for their selection are given below.

Corn starch was chosen since it is the classical and still one of the best disintegrating agents known to date. Scoville states that "starch is the best and most-used disintegrator". (19, p. 95). Remington states that "the most popular disintegrator is either well dried potato or corn starch" (28, p. 376). Burlinson and Pickering have compared potato starch with 5 other types of starch and found no significant difference in any of the 6 varieties, despite considerable variation in the size of the starch grains (6, p. 632). A possible reason for the excellent disintegrating properties of starch is its ability to absorb water. Scoville states that starch is a very hygroscopic substance which absorbs about 1/5 of its weight of water in a moist atmosphere without appearing wet (19, p. 95). If starch is well dried it will swell when immersed in cold water. A domestic grade of cooking corn starch meeting USP specifications was employed in this study (37, p. 695).

Bentonite was chosen as a representative from the inorganic group of drugs reported to swell when placed in contact with water (26, p. 383). "In contact with water each flake of bentonite attempts to surround itself with a layer or shell of water". "Swelling of the mass results and bentonite can be expected to absorb up to 5 times its weight of water and increase from 12 to 15 times its bulk" (30, p. 532). Although bentonite possesses tremendous swelling powers when wet, experimentally bentonite has not been shown to be a very satisfactory tablet disintegrating agent (9, p. 16). A USP grade of bentonite was used (37, p. 81).

Lactose, a substance with no inherent tablet disintegrating properties, was used as the diluent. Gross and Becker found that lactose worked satisfactorily as the diluent in their tests (13, p. 158). In this study an omission of the disintegrating agent from one batch of tablets left only lactose, the lubricant and the binder. In this instance lactose was employed as the control as well as the diluent. A USP grade of lactose was used in all of the tests as the diluent (37, p. 375).

Gelatin, a brittle, nearly transparent organic substance, was selected because of its tremendous capacity to absorb water and swell. Gelatin is reported by Wilson and Gisvold to be "insoluble in cold water but swells and softens when immersed and gradually absorbs five to ten times its own weight of water" (41, p. 731). Gelatin is defined in the USP as "a product obtained by the partial hydrolysis of collagen derived from the skin, white connective tissue, and bones

of animals" (37, p. 307). Scoville states that "gelatin and agar are used as disintegrators, particularly in Europe, although their efficiency is less than that of starch and the appearance of the tablets is less attractive" (19, p. 95). Gelatin has also been evaluated as a tablet disintegrator by Gross and Becker (13, p. 159). In this study a USP granular grade of "Gelatin" was selected. The granule size was adjusted so that the largest particle would pass through a #60 sieve, thus constituting a "fine" particle.

The seaweed derivative sodium alginate, frequently called algin, has been successfully used as a disintegrating agent in many tablet formulations and was included in the study (26, p. 375) (5, p. 219) (11, p. 132). "Sodium Alginate" is official in the NF as "the purified carbohydrate product extracted from brown seaweeds by the use of dilute alkali and consists chiefly of the sodium salt of alginic acid" (1, p. 329). The use of a number of algin derivatives as binders and disintegrators has been studied by Gerding and De Kay (11, p. 132). Berry and Ridout found alginic acid to be a better disintegrator than potato starch (5, p. 137). Gross and Becker included algin as one of the 22 tablet disintegrating agents in their study (13, p. 159). Kelacid^{R} and Kelcosol^{R} have been shown to have definite and valuable properties as disintegrating agents (26, p. 375). A "Standard" grade of sodium alginate was obtained from Hathway Allied Products of California for this study.

Pectin, another successfully reported disintegrating agent, was included in the study (13, p. 159). Pectin is official in the

NF as "a purified carbohydrate product obtained from the dilute acid extract of the inner portion of the rind of citrus fruits or apple pomace" (1, p. 263). Gross and Becker found that powdered citrus pulp, a substance high in pectin content, compared favorably with starch as a disintegrating agent (13, p. 161). Pectin has been used as an emulsifying agent and as a stabilizing agent in ointments due to its ability to absorb moisture. Remington states that pectins are "water-soluble colloids which form a gel capable of absorbing large quantities of water" (28, p. 343). A USP grade of "Pectin" was used in this study.

Considerable attention has been given to the group of drugs classified as gums, for their disintegrating properties (11, p. 132). Among the various gums reported in the literature are Veegum^{R}, locust bean gum, karaya gum, guar gum and acacia gum. Karaya gum, official in the NF as "Sterculia Gum", was selected as the representative from this group of drugs. "Sterculia Gum" is official as the dried gummy exudation from various species of Sterculia (Fam. Sterculiaceae) or Coclospermum (Fam. Bixaceae) (1, p. 344). A grade of sterculia gum for "internal consumption" obtained from Albert Albek, Inc. of California was employed in this study.

Wood flour and wood bark were included in the study as new products having not previously been tested and reported in the literature for their tablet disintegrating properties. The wood flour was obtained locally from the Forest Products Research Laboratory as a commercial sample and consisted of the powdered inner wood

from Douglas fir. The powdered wood bark was supplied by the Silvatek Products Division of the Weyerhaeuser Timber Company of Longview, Washington under the trademark of Silvacon^{R}. Appearing for the first time in the 1958 Annual Report of the Weyerhaeuser Timber Company, Silvacon^{R} is a relatively new product (40, p. 15). The three basic types of Silvacon^{R} are "pliable, spongy flakes, tough needle-like fibers and fine amorphous powders". Since the disintegrating agents were chosen on their ability to absorb water, the pliable spongy flake type of Silvacon^{R} was selected for use in this study. Silvacon^{R} type 383-G is a super refined form of corky, pliable, spongy flakes separated from the remainder of the bark by a patented fractionation method (39, p. 2). Being a natural plastic, Silvacon^{R} contains the plasticizers, cellulose and resins found in Douglas fir bark (39, p. 2). Preliminary tests made on wood flour and Silvacon^{R} indicated that both of these substances absorbed a considerable amount of moisture when placed in a 98% humidity chamber. On this basis both of the wood products were tested as "absorb moisture and swell" disintegrators.

Methylcellulose, a methyl ether of cellulose whose methoxy content varies between 26% and 33%, was included for comparison with the wood flour and powdered bark (37, p. 431). Methylcellulose has been used for years as a bulk producing laxative and as a thickening agent due to its ability to swell (28, p. 1026). Gross and Becker have taken advantage of this characteristic by using methylcellulose as a tablet disintegrator (13, p. 159). A USP

grade of "Methylcellulose" (Dow Methocel^{R}) having a viscosity of 4000 cps was employed in this study.

Water Absorption Study

With the disintegrating agents chosen, the research program was then divided into two distinct phases, the measurement of water absorption by the various selected disintegrating agents and the manufacture and subsequent testing of the disintegration time of tablets containing these same disintegrating agents.

The water absorption study was conducted in an atmosphere of 98% relative humidity maintained in three 8" dessicators made air tight with a grease seal. An agent was intentionally selected that produced a relative humidity slightly under 100% in order to remove the troublesome influence of condensing water. This was accomplished by placing a saturated solution of lead nitrate in the bottom of each of the dessicators, which when maintained at 20° C. produced an atmosphere of 98% relative moisture (23, p. 1454). Three disintegrating agents were placed in each of two dessicators, and three disintegrating agents plus lactose, the control substance was placed in the third dessicator.

An equivalent volume of 15 ml. of each of the 10 disintegrating agents (approximately 3 to 5 grams) were placed in 1 1/2" ceramic crucibles in a Colton Drying Oven (model 1030 E) at 46° C. until dry. This drying process was conducted for a period of 10 days in order to insure complete water removal. In working under similar conditions, Sanger states that "shrinkage curves under usual conditions

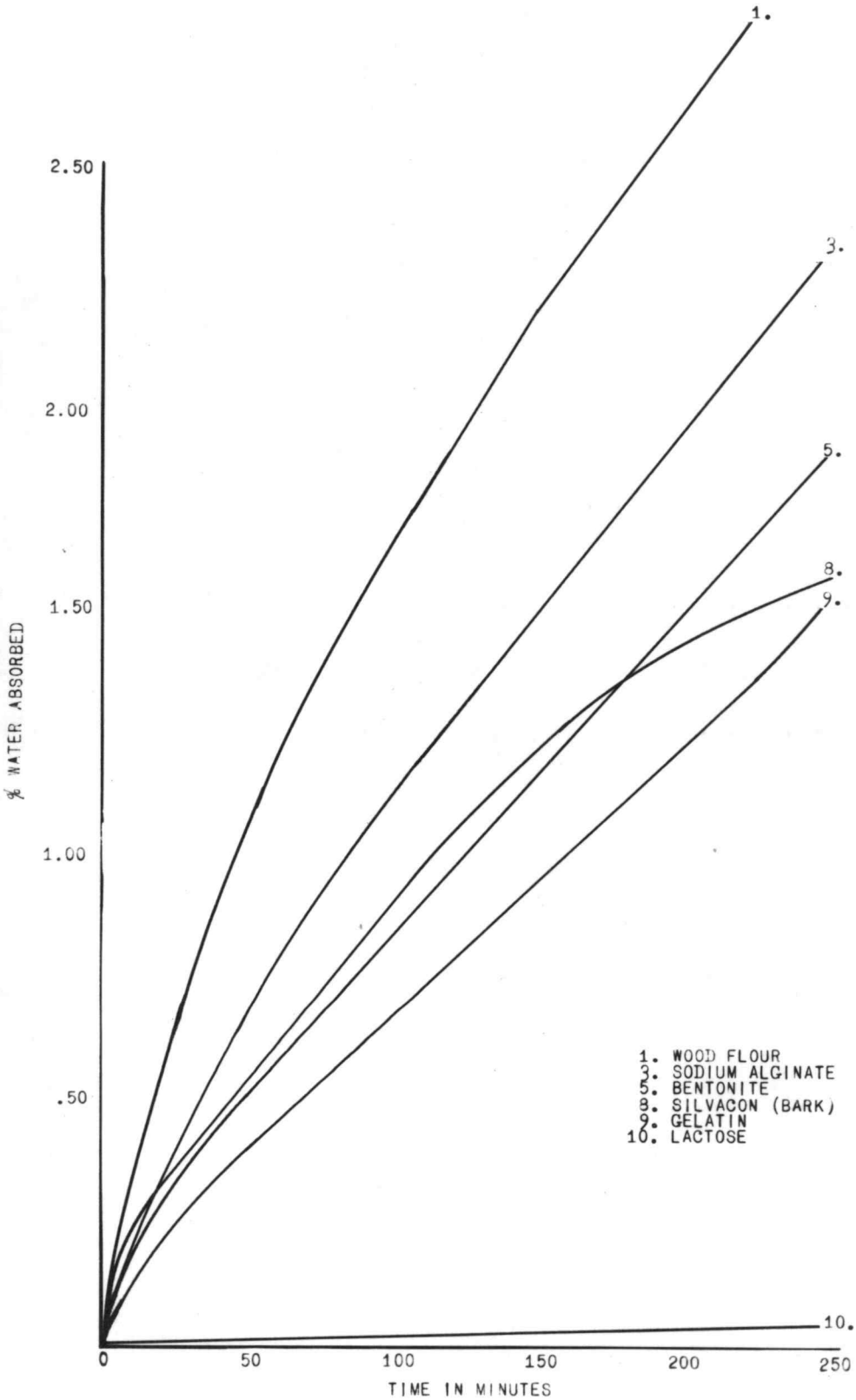
show that complete removal of water is drawn out not in hours but days" (32, p. 334). The disintegrating agents were considered dry when there was no further weight loss (0.5 mg) between daily weighings. For the moisture determination weighings a Mettler (type H5) Micro Gram-Atic balance was used. In order to avoid absorption of moisture from the atmosphere while cooling, the samples were placed in a dessicator over concentrated sulfuric acid until cool and then weighed. When dry the 10 disintegrating agents were placed in the humidity chamber and exact weighings (0.5 mg) were made every 10 minutes for 4 hours, then every 4 hours for 2 days then once daily for 9 days, and thereafter at 5 day intervals until 75 days had elapsed. From the weighings the percent moisture absorbed was computed, (TABLES I AND II) the results of which are plotted against time and shown in figures 1a, 1b and 2.

Since both the short term effect and long term effect of moisture absorption were to be correlated with tablet disintegration, two graphs were made, one plotting the percentage of moisture uptake against the time in minutes and the other plotting the percentage of moisture uptake against the time in days. Each of these moisture determination studies was then statistically correlated with the tablet disintegration times. The intent of using both the short term and long term approach was to enhance the possibility of finding a correlation between the rate of moisture absorption and tablet disintegration time.

TABLE 1

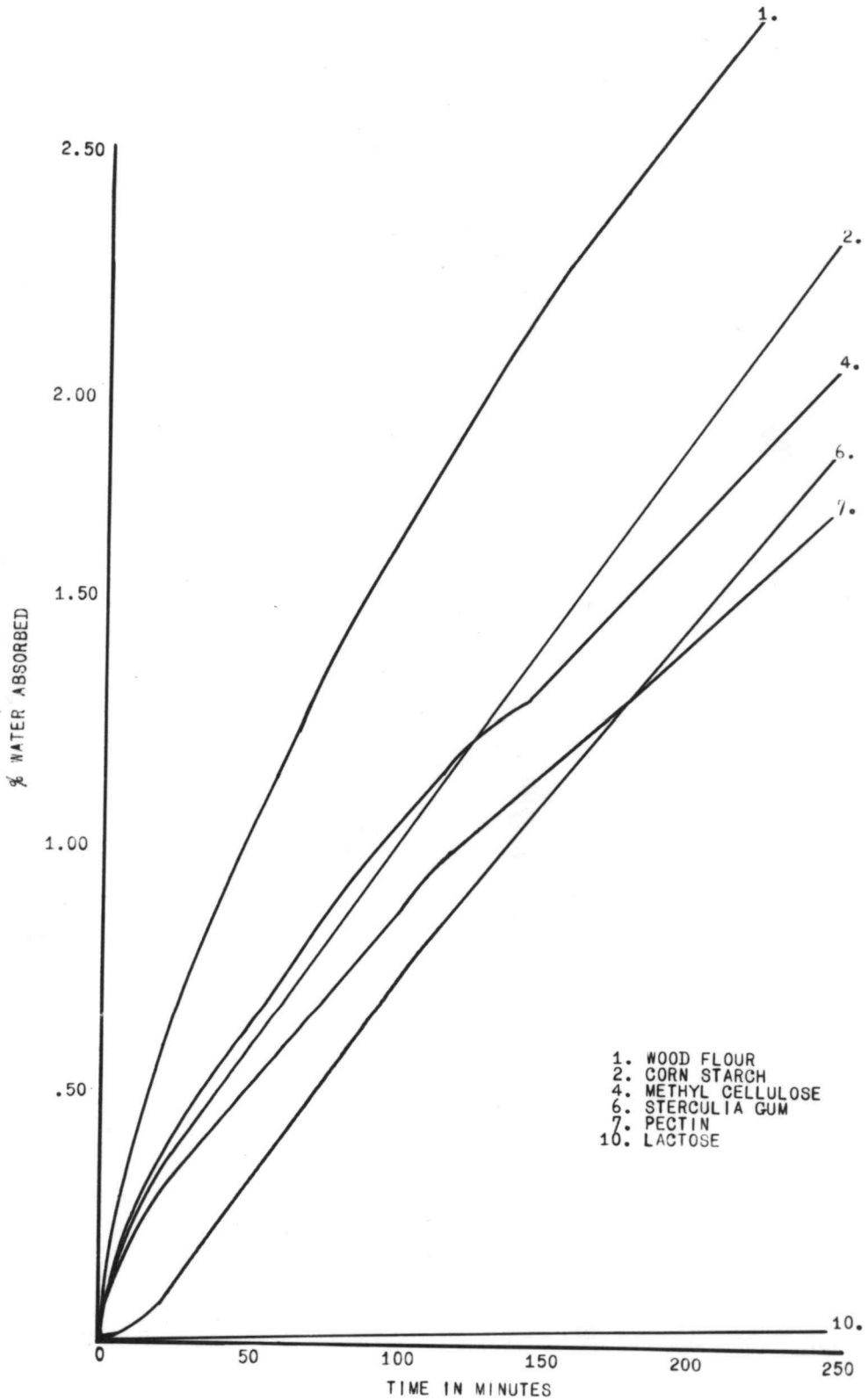
PERCENT WATER ABSORPTION BY SELECTED DISINTEGRATING AGENTS
(Short Term Effect)

	DISINTEGRATING AGENT									
Time In Minutes	Bentonite	Corn Starch	Gelatin	Lactose	Methyl Cellulose	Pectin	Silvacon^{R}	Sodium Alginate	Sterculia Gum	Wood Flour
10	.1935	.1727	.1326	.0100	.2165	.2028	.1182	.1744	.0303	.4235
20	.2923	.3394	.2010	.0100	.3566	.2935	.2390	.3154	.0708	.5948
30	.3931	.4358	.2914	.0220	.4966	.3675	.3126	.4154	.1820	.7435
40	.4676	.5221	.3677	.0220	.5781	.4606	.4465	.5334	.2527	.9213
50	.5100	.6105	.4099	.0220	.6494	.5250	.5385	.6385	.3356	1.0409
60	.6007	.7029	.4702	.0220	.7513	.5847	.6094	.7257	.4326	1.1346
70	.6833	.8033	.5305	.0220	.8455	.6801	.7118	.8539	.5256	1.3351
80	.7357	.8796	.6068	.0260	.9092	.7445	.7880	.9411	.5924	1.4191
90	.8022	.9680	.6269	.0260	.9805	.8352	.8905	1.0642	.6793	1.5581
100	.8627	1.0683	.7053	.0260	1.0697	.8853	.9404	1.1385	.7642	1.6454
110	.9211	1.1226	.7475	.0300	1.1079	.9641	1.0218	1.2411	.8208	1.7844
120	.9796	1.2169	.7836	.0300	1.1970	1.0237	1.0691	1.3078	.9017	1.8749
130	1.0542	1.2933	.8520	.0300	1.2556	1.0786	1.1348	1.3924	.9846	1.9751
140	1.1106	1.3756	.8921	.0300	1.2989	1.1216	1.1899	1.4383	1.0392	2.0527
150	1.1832	1.4419	.9444	.0340	1.3625	1.1812	1.2398	1.5335	1.1221	2.1529
160	1.2356	1.5262	.9846	.0340	1.4006	1.2242	1.2740	1.6053	1.2009	2.2402
170	1.2920	1.6066	1.0549	.0340	1.4713	1.3149	1.3633	1.7155	1.2818	2.3695
180	1.3706	1.6869	1.1111	.0380	1.5535	1.3722	1.4106	1.7873	1.3303	2.4147
190	1.4271	1.7732	1.1654	.0380	1.6223	1.4127	1.4395	1.8540	1.4112	2.5053
200	1.5097	1.8817	1.2357	.0380	1.7038	1.4485	1.4631	1.9001	1.5082	2.5408
210	1.5903	1.9579	1.2960	.0380	1.7395	1.4867	1.4920	1.9514	1.5688	2.6184
220	1.6871	2.0483	1.3663	.0420	1.8082	1.5774	1.5417	2.0181	1.6517	2.7251
230	1.7556	2.1487	1.4367	.0420	1.8719	1.6346	1.5522	2.1489	1.7326	2.8091
240	1.8241	2.2411	1.5231	.0420	1.9585	1.6943	1.5969	2.2309	1.8195	2.8932



RATE OF WATER ABSORPTION BY SELECTED DISINTEGRATING AGENTS
(SHORT TERM EFFECT)

fig. 1a



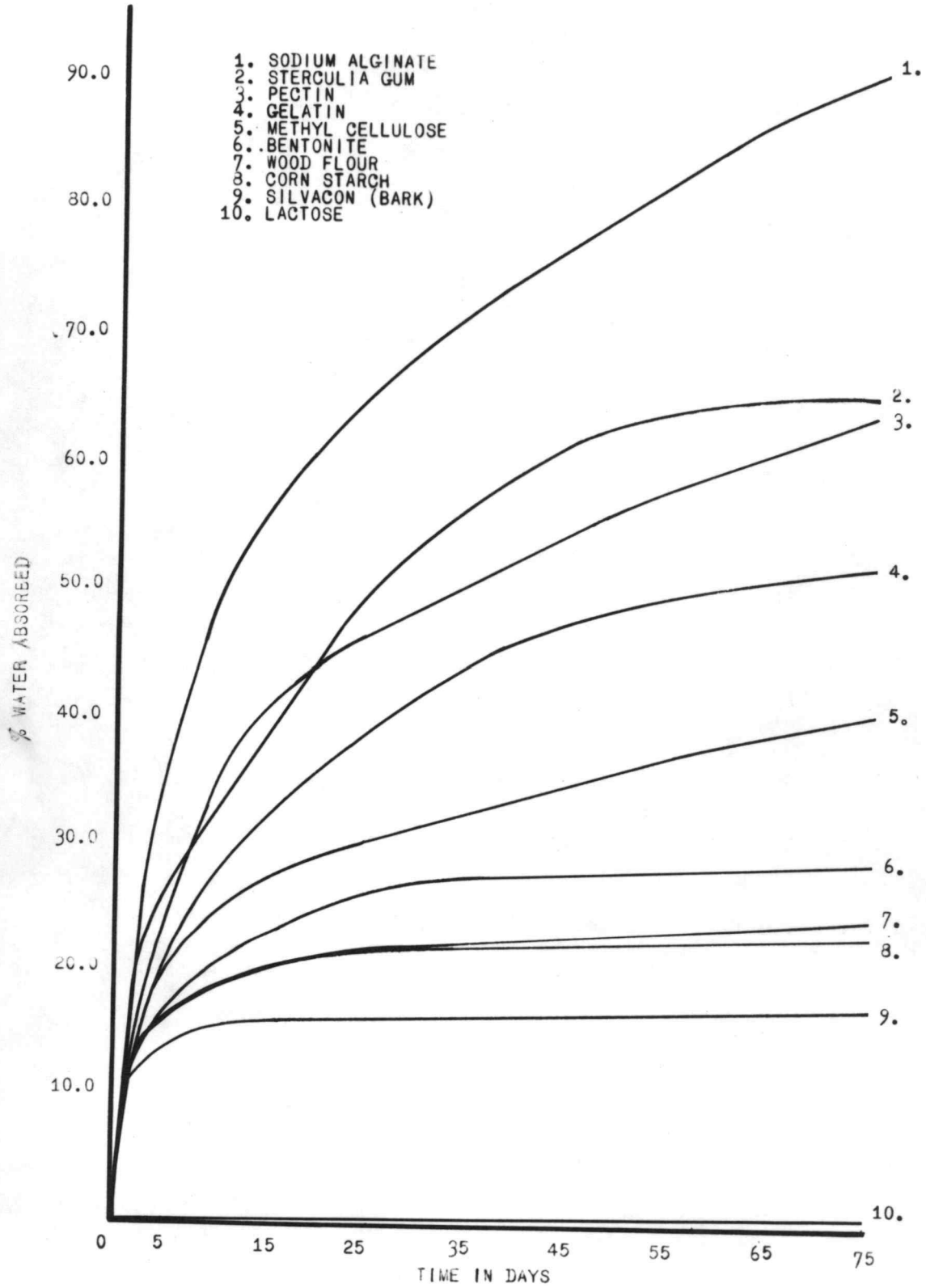
RATE OF WATER ABSORPTION BY SELECTED DISINTEGRATING AGENTS
(SHORT TERM EFFECT)

fig. 1b

TABLE 11

PERCENT WATER ABSORPTION BY SELECTED DISINTEGRATING AGENTS
(Long Term Effect)

Time In Days	DISINTEGRATING AGENT									
	Bentonite	Corn Starch	Gelatin	Lactose	Methyl Cellulose	Pectin	Silvacon[R]	Sodium Alginate	Sterculia Gum	Wood Flour
.17	2.3705	3.4813	2.3829	.1264	3.8927	3.9482	4.2078	5.3604	3.3613	4.9630
.33	4.4026	5.4036	4.4173	.1383	5.9039	5.6276	5.9715	8.3501	5.4774	7.1802
.50	5.2555	6.8103	5.5627	.1600	7.1463	6.9893	6.9997	9.0095	6.9633	8.3172
.83	6.8571	9.0413	7.7593	.1600	9.5445	9.3888	8.6132	14.5586	9.7162	10.1864
1.00	7.7641	9.8654	8.7064	.1600	10.5425	10.4045	9.2908	16.3252	10.8672	10.9135
1.77	8.2886	10.6002	9.5615	.1600	11.2630	11.3679	9.7706	17.7496	12.0489	11.5606
1.33	8.7511	11.0144	10.1662	.1600	11.9148	12.0839	9.9815	19.0784	12.8805	11.7385
1.50	9.4538	11.5888	10.9932	.1600	12.6327	12.9166	10.3111	20.5758	13.9375	12.6511
2.00	11.2517	12.8656	12.8434	.1600	14.4708	14.9520	11.1627	23.9078	16.6160	13.9583
3.00	14.0867	14.7941	15.4185	.1936	16.9022	17.8926	12.0327	28.8429	20.2530	15.4768
4.00	16.3670	16.3815	18.2519	.2074	19.1237	21.4123	13.3377	33.3098	23.5770	16.8948
5.00	17.9487	17.4309	20.4886	.2272	20.7159	24.5319	14.3106	36.8633	26.1527	17.7327
6.00	19.0078	18.0520	22.8274	.2568	21.8743	27.2351	14.6085	40.5954	28.7021	18.6892
7.00	19.8446	18.5880	24.2631	.2864	22.5158	29.9282	15.2281	43.2807	30.2449	19.0502
8.00	20.5733	18.9432	25.4806	.3062	23.2058	32.2854	15.6842	45.6790	31.6695	19.3828
9.00	21.1220	19.2335	26.4878	.3259	23.8906	34.4074	16.0269	47.8433	32.9146	19.5246
15.00	23.3643	20.7864	32.8514	.3891	27.0984	41.1131	16.3960	56.9660	40.2236	20.8884
20.00	24.8800	21.6065	36.2315	.4049	28.9442	46.3404	16.7282	61.7148	44.4910	21.4788
25.00	26.2372	22.0652	38.8666	.4188	30.5685	47.5553	16.7414	65.2456	48.3336	21.6258
30.00	27.6287	22.4184	42.0044	.4405	31.7345	49.9728	16.7677	69.1212	52.2311	22.1311
35.00	27.8990	22.5382	44.7337	.5136	33.2468	51.5417	16.8205	71.6630	56.8211	22.5411
45.00	29.0702	22.9462	48.1778	.5333	36.8161	55.6246	17.3715	77.2977	61.8881	23.3274
55.00	29.6909	23.4557	50.6308	.5333	37.4729	60.0012	17.3847	84.0321	65.2909	23.5079
75.00	29.6909	23.5471	52.5431	.5333	40.6680	64.5950	17.7933	92.6767	66.3851	24.7454



RATE OF WATER ABSORPTION BY SELECTED DISINTEGRATING AGENTS
(LONG TERM EFFECT)

fig. 2

Preparation of Granulations

The second phase of the research program concerned the manufacture and testing of tablets, each containing one of the 10 disintegrating agents used in the moisture determination. Two 20 lb. lactose granulations were made by different methods so that the results obtained from this phase of the study would more nearly duplicate the differences commonly encountered by various methods of manufacture. In this way the statistical analysis could be performed on two completely separate observations and the conclusions made independent of any individual idiosyncrasies which may have appeared in either method.

In preparing the first granulation, 20 lbs. of lactose were placed in a Hobart mixer adjusted to run at slow speed and USP Syrup was added until the mass had attained the proper consistency (37, p. 732). The tablet granulation is considered to have reached this consistency when a handful of the mass can be readily compressed by hand into a spherical form that breaks apart into several fragments when the thumb is inserted into it. This is frequently referred to in drug manufacturing as the "thumb test". After reaching this consistency the granulation was passed through a #12 mesh sieve and spread out on pans which were placed in the oven to dry at 46° C. for 24 hours. The material was taken from the oven and regranulated through a #14 mesh sieve and divided into fines and granules. The fines were particles sufficiently small in size as to

pass through a #60 mesh sieve, and the granules of such size as to pass through a #14 mesh sieve but large enough to be retained by the #60 mesh sieve. The fines and granules were later made into tablets. All of the sieves employed in this study complied with the standards specified in the USP (37, p. 932).

The second granulation was prepared in a manner similar to the first except that an excess of syrup was added which caused it to become excessively wet and mass together. The gummy mass was broken up with the fingers into "slugs" 1 cm. in diameter and placed in the oven to dry. The dry hardened pieces of lactose-syrup offered resistance to regranulation with a sieve so they were passed through a Wiley Mill, reducing them in size and enabling them to be more easily sieved into granules and fines. The dry granulations are generally ground in a Fitzpatrick comminuting machine or a mikropulverizer but since neither of these machines was available the Wiley Mill was adapted to work quite satisfactorily. Work on granulations by Forlano and Chavkin indicates that a 16-40 mesh range will produce the best lactose tablets while a 16-60 mesh range will produce the least capping and best disintegration time in sodium bicarbonate tablets (10, p. 69).

A search of the literature showed references made to lactose granulations with the most common binding agent being a 2% solution of liquid glucose, but no specific references were found concerning the granulation of syrup and lactose (14, p. 58). This combination

undoubtedly been tried by drug manufacturers. For the most part however, the drug manufacturers shroud their research techniques in secrecy and are hesitant to publish their methods of manufacture in the literature (13, p. 157).

Manufacture of Tablets

The fines and granules previously sieved, were next ready to be incorporated into the final granulations which would be made into tablets. Past experience from other tablet formulations and trial runs on these granulations showed that the most uniform tablets in hardness and weight were produced when 20% fine particles of #60 mesh and smaller were combined with 80% granules of #14 mesh to #60 mesh. This is in direct agreement with Tucker and Hayes statement that the number of fines used in a granulation is relative and depends upon the particular tablet formulation under consideration (36, p. 362). Silver and Clarkson state that 10%-20% "fines" are the amount generally used to fill the spaces between the granules and produce a tablet of smooth appearance (34, p.4). Arambulo and Deardorff found that tablets were produced which were more uniform in weight and better in appearance when definite amounts of small granules were used. (2, p. 694).

The size of the tablet is generally determined by the amount of active ingredient that is necessary to give the desired therapeutic effect and a physical size convenient for compression. Preliminary tests indicated that a 500 mg. tablet would be the most satisfactory size with which to work.

Once the tablet size has been determined, the punch size is then selected. Although the densities of various drugs differ, Little and Mitchell have compiled a table for the "average tablet" suggesting various punch sizes to use with various tablet weights (25, p. 53). On this basis 3/8" punches were chosen and found satisfactory.

A minimum amount of lubricant was added to the granulation, since larger amounts tend to waterproof the tablet thus rendering it insoluble. For this particular formulation 1% magnesium sterate was determined to be the least amount of lubricant that could be added and still maintain optimum efficiency in lubrication.

With the tablet size and weight determined, and having decided upon the percent of lubricant that was to be used, the granulations were than prepared. Each of the 10 disintegrating agents were incorporated into a tablet formulation in both 5% and 10% concentrations for each of the two granulations. The disintegrating agents and magnesium sterate were passed through a #60 mesh sieve and, when incorporated into the tablet mixtures, replaced their weight of lactose fines. Each of the 20 lb. lactose granulations were divided into 20 smaller 12 oz. granulations which yielded 40 batches of granulation. Individually the 40 batches were then compressed into tablets on a Stokes Model B2 rotary tablet machine.

To obtain the ease and accuracy of adjustment of a rotary type tablet machine and still have the economy of materials afforded

during the adjustment of a single punch type machine, blank dies* were fitted into 14 of the 16 stations on the Stokes B2 tablet machine. This left only 2 of the 16 stations operating which were placed 180 degrees out of phase to insure uniformity in filling of the dies. By devising such a techinque it was found that only 20% of the normal quantity of granulation was required to prepare the same amount of tablet batches.

The weight and hardness were carefully regulated during the manufacture of the tablets. Using an Exact Weight shadow-graph the combined weight of 10 tablets was taken to determine the average weight of each tablet, further reducing the experimental error. The variation in tablet weight was maintained well within the 5% limit of error specified by the USP XVI (37, p. 942). A Strong Cobb tablet hardness tester was employed to determine the average hardness for each batch of tablets, the hardness arbitrarily regulated for this tablet formulation to 11±1 Strong Cobb units. Ten tablets were tested to arrive at the average hardness for each batch.

USP XVI Tablet Disintegration Test

The disintegrating apparatus specified in the USP XVI consists of a basket-rack assembly, a suitable vessel for the immersion fluid (preferably a 1-liter beaker), a thermostatic arrangement for heating the fluid between 35° and 39°, and a device for raising and lowering the basket in the immersion fluid at a constant frequency rate

*Prepared to our specification on the Oregon State College campus by the Physics Department Shop.

between 28 and 32 cycles per minute through a distance of not less than 5 and not more than 6 cm. The volume of the fluid in the vessel is such that at the highest point of the upward stroke the wire mesh remains at least 2.5 cm. from the bottom of the vessel on the downward stroke. The basket-rack assembly consists of 6 open-ended glass tubes each 7.75 ± .25 cm. long and having an inside diameter of approximately 21.5 mm. The tubes are held in a vertical position by 2 plastic plates, each about 9 cm. in diameter with 6 holes, equidistant from the center of the plate and equally spaced from one another. Attached by screws to the undersurface of the lower plate is a 10 mesh wire screen. The design of the basket-rack assembly may be varied somewhat provided the specifications from the glass tubes and the screen mesh size are maintained.

The maximum length of time for uncoated tablets to dissolve in such an apparatus is 60 minutes unless otherwise specified in the particular monograph. The majority of manufacturers today, however, have set standards for their particular tablets within the range of thirty seconds to ten minutes, well within the range of the USP tests (26, p. 374).

Other types of tablet disintegrating apparatus have been tried by Hoyle (18, p. 279), Prance, Stephenson and Taylor (29, p. 286) and Berry (4, p. 501).

Tablet Disintegration Study

The tablets were tested immediately after manufacture for disintegration time with a gershberg-Stoll type disintegration

apparatus (12, p. 284). Simulated gastric juice was compared with distilled water, and since the two gave identical disintegration times, distilled water was used as the disintegration solution for all of the tablets tested. The 40 batches of compressed tablets were tested according to the official tablet disintegration tests in USP XVI (37, p. 934). Results of the tests are given in TABLE III. The data from TABLE III has been condensed into a bar graph (fig. 3) comparing the time required for the tablets to disintegrate containing the nine selected disintegrating agents.

From the bar graph (fig. 3) it may be seen that considerable variation exists among the nine disintegrating agents. Berry lists the following factors as causes in the variations which occur in the rate of disintegration of tablets:

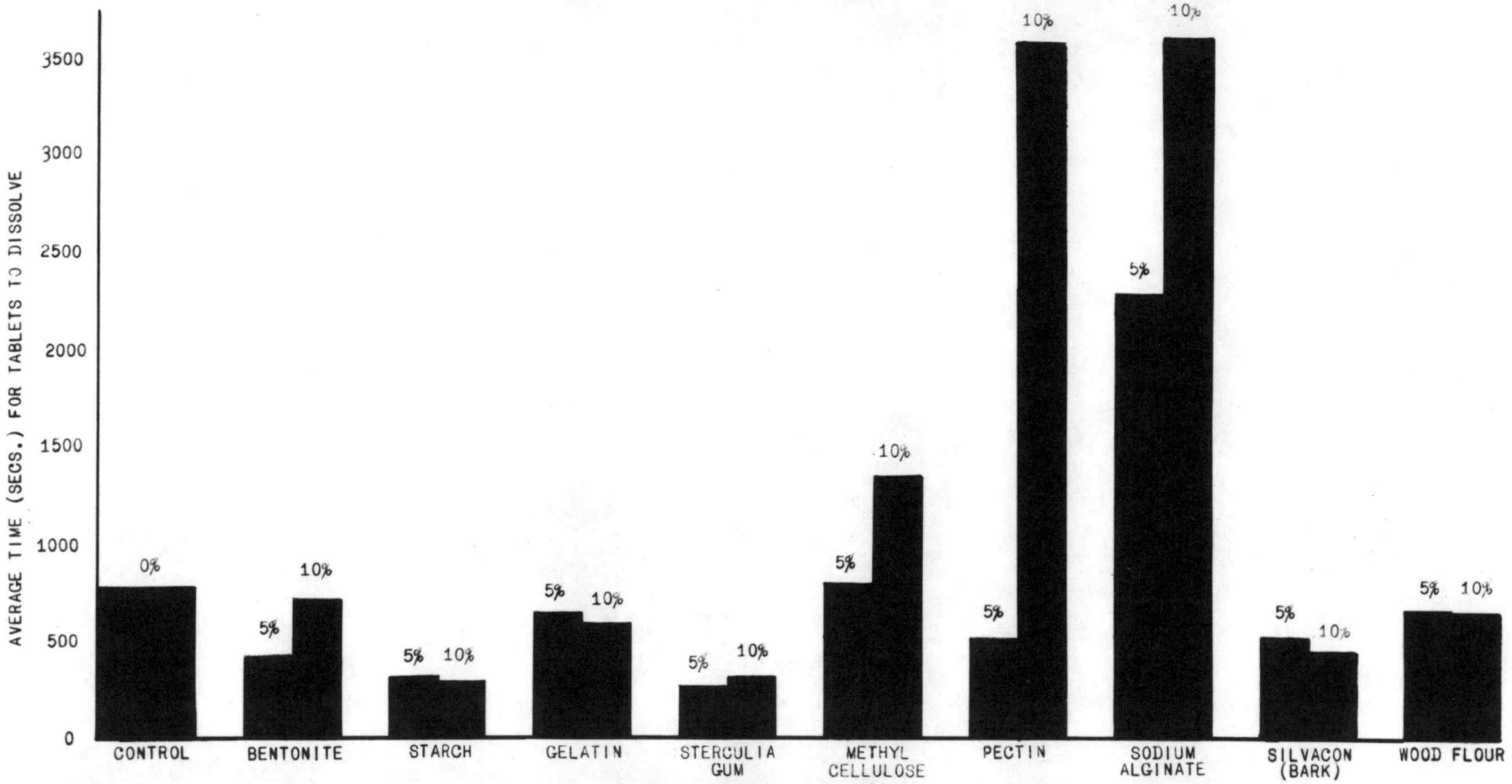
1. The formula used in the preparation of the granules (particularly the binding agent, disintegrating agent, and lubricant used)
2. The degree of compression
3. The speed of compression
4. The size of the particles of the medicament
5. The type of hopper feed in the machine
6. The age of the tablets.

Of the 6 items listed Berry indicates that factors 1 and 6 are the most important (4, p. 505).

TABLE III

TABLET DISINTEGRATION TIME USING VARIOUS DISINTEGRATING AGENTS

Disintegrant Used	Time Required To Disintegrate (ave. in secs. for 12 tabs.)		
	Lot 1	Lot 2	Total
Bentonite 5%	486	388	874
Bentonite 10%	791	642	1433
Corn Starch 5%	352	285	637
Corn Starch 10%	336	246	582
Gelatin 5%	710	583	1293
Gelatin 10%	665	551	1216
Methyl Cellulose 5%	873	718	1591
Methyl Cellulose 10%	1484	1247	2731
Pectin 5%	566	469	1035
Pectin 10%	3600	3600	7200
Silvacon® 5%	585	477	1062
Silvacon® 10%	486	403	889
Sodium Alginate 5%	2274	2306	4580
Sodium Alginate 10%	3600	3600	7200
Sterculia Gum 5%	300	240	540
Sterculia Gum 10%	357	281	638
Wood Flour 5%	713	601	1314
Wood Flour 10%	692	597	1289
CONTROL	868	707	1575



TABLET DISINTEGRATION STUDY

fig. 3

In this study the type of disintegrating agent and the concentration employed were regulated as the variable. All of the other factors listed by Berry were critically maintained constant.

It was observed during the tablet disintegration tests that after approximately 10 to 15 minutes the sodium alginate tablets floated to the top of the basket rack assembly. The tablets remained there failing to dissolve within 60 minutes. When plastic plungers were used to keep the tablets from floating, the tablets still failed to dissolve within 60 minutes. Upon examination of the tablets a slimy, water-impervious layer of gum had formed on the exterior of the tablet. Thus any disintegration was impossible.

Gross and Becker found that the tablets which did not appear to disintegrate within 10 minutes contained disintegrating agents incapable of absorbing large quantities of water. "On close examination it was found that a slimy, water-impervious layer of gum had formed on the exterior of the tablet" (13, p. 160).

STATISTICAL ANALYSIS AND DISCUSSION

Introduction

The research program was divided into two distinct phases, the measurement of water absorption by the various disintegrating agents and the manufacture and subsequent testing of the disintegration time of tablets containing these same disintegrating agents. The test for F, a statistic which follows the F distribution, was used as the method of statistical analysis for the water absorption and tablet disintegration studies. From these two independent studies, correlations were made of water absorption with tablet disintegration time.

It is important to note that significant results from the water absorption study and the tablet disintegration study were necessary if valid correlations between the two studies were to be made.

The reference tables used in the statistical analysis were from the text, "Introduction to Statistical Inference" by Jerome C. R. Li (24, p. 487-533).

Water Absorption

The various time intervals recorded during the water absorption study for the nine selected disintegrating agents (TABLES I and II) were subjected to statistical analysis. The results of the statistical analysis have been condensed into two analysis of variance tables, the first table showing the short term water absorption (TABLE IV) and the second table showing the long term water absorption (TABLE V) of the various selected tablet disintegrating agents.

TABLE IV

SHORT TERM WATER ABSORPTION STUDY

Analysis of Variance

Source of Variation	Sum of Squares	Degrees of Freedom	Mean Square	F*
Disintegrators	43.652 765 743	9	4.850 307 305	
Due to $\bar{b}$	52.284 847 826	1	52.284 847 826	20221.82
Among b's	7.627 579 880	9	0.847 508 876	327.79
Error	0.568 824 597	220	0.002 585 566	
Total	104.134 018 040	239		

TABLE V

LONG TERM WATER ABSORPTION STUDY

Analysis of Variance

Source of Variation	Sum of Squares	Degrees of Freedom	Mean Square	F*
Disintegrators	26691	9	2966	
Due to $\bar{b}$	23733	1	23733	553.00
Among b's	12347	9	137	3.19
Error	9478	220	43	
Total	72249	239	302	

*Significance at 5% level

The "F test" was employed as the method of analysis to determine if the nine selected disintegrating agents absorbed significantly different amounts of water. In the statistical analysis of the short term and long term water absorption studies the computed values of F (F=20221.82 with 1 and 220 d.f. and F=553 with 1 and 220 d.f. respectively) were larger than the values for F=3.85 obtained from the F TABLE using the 5% significance level with 1 and 220 d.f. This indicated that the nine selected disintegrating agents employed in this study absorbed significantly different total amounts of water in both the short term and long term water absorption studies.

The "F test" was then used to determine if the rate of water absorption for each of the nine selected disintegrating agents varied significantly when compared with one another. From TABLES IV and V the computed values of F for the short term and long term water absorption studies (F=327.79 with 9 and 220 d.f. and F=3.186 with 9 and 220 d.f. respectively) were larger in both instances than the value for F=1.88 obtained from the F TABLE using the 5% significance level with 9 and 220 d.f. The conclusion drawn from this analysis was that the rate of water absorption for each of the nine disintegrating agents varied significantly when compared with one another in both the short term and long term water absorption studies.

Tablet Disintegration Time

The length of time required for the disintegration of tablets containing the nine selected disintegrating agents was subjected to statistical analysis. The final tabulations of the statistical analysis

have been condensed into an analysis of variance table (TABLE VI).

TABLE VI

TABLET DISINTEGRATION STUDY

Analysis of Variance

Source of Variation	Sum of Squares	Degrees of Freedom	Mean Square	F *
Replication	84 981	1	84 981	
Control vs disintegrator	87 902	1	87 902	45.47
Concentration	2 919 542	1	2 919 542	1510.37
Disintegrator	26 375 773	8	3 926 971	1705.62
Concentration x disintegrator	8 713 663	8	1 089 208	563.48
Error	34 802	18	1 933	
Total	38 216 663	37	1 032 883	

*Significance at 5% level

The test for F with 1 and 18 d.f. (TABLE VI) was used to determine if the nine selected disintegrating agents as a group varied significantly from the control in their ability to cause tablet disintegration. The calculated value of F=45.47 with 1 and 18 d.f. (TABLE VI) was larger than the value for F=4.4139 obtained from the F TABLE using the 5% significance level with 1 and 18 d.f. This indicated that the nine selected disintegrating agents as a group varied significantly from the control in their ability to cause tablet disintegration.

The second test for F with 1 and 18 d.f. (TABLE VI) was used to determine if the concentration of the disintegrating agents had an

effect on the time required for tablets to disintegrate. The calculated value of F=1510.37 with 1 and 18 d.f. (TABLE VI) was larger than the value for F=4.4139 obtained for the F TABLE using the 5% significance level with 1 and 18 d.f. The conclusion drawn from this analysis was that the concentration of the disintegrating agents caused significant variations in the ability of disintegrating agents to disintegrate tablets.

The test for F with 8 and 18 d.f. (TABLE VI) was employed to determine if the nine disintegrating agents varied when compared with each other in their ability to cause tablet disintegration. The calculated value of F=1705.62 was larger than the value of F=2.5102 obtained from the F TABLE using the 5% significance level with 8 and 18 d.f. This analysis indicated that the nine disintegrating agents varied significantly when compared with each other in their ability to cause tablet disintegration.

The second test for F with 8 and 18 d.f. (TABLE VI) was used to determine if the concentration of the nine selected disintegrating agents would effect the ability of these disintegrating agents to cause tablet disintegration. The effect of the concentration X disintegrator is defined by Li as the interaction, the tabulation which may be seen in TABLE VII. The calculated value of F 563.48 with 8 and 18 d.f. (TABLE VI) was larger than the value for F=2.5102 obtained from the F TABLE using the 5% significance level with 8 and 18 d.f., and the interaction is thus significant. From this analysis it was concluded that the time required for tablets to disintegrate, containing

TABLE VII

TABLET DISINTEGRATING TIME USING VARIOUS DISINTEGRATING AGENTS

Disintegrating Agent	Concentration of Disintegrating Agent 5%	10%
Bentonite	874	1433
Corn Starch	637	582
Gelatin	1293	1216
Methylcellulose	1591	2731
Pectin	1035	7200
Silvacon^{R}	1062	889
Sodium Alginate	4580	7200
Sterculia Gum	540	638
Wood Flour	1314	1289

5% and 10% concentrations of disintegrating agent, was significantly different for each of the nine selected disintegrating agents.

Although the disintegrating agents as a group were found to vary significantly from the control (F=45.47 from TABLE VI), it was considered necessary to compare the individual disintegrating agents with the control. This was accomplished by use of the least significant

difference (LSD) method of analysis. When the difference between any two treatment means exceeds a certain quantity it si considered significant. This quantity is called the least significant difference (LSD) between two treatment means (24, p. 233). Employing the LSD method of analysis, the results of the study are tabulated in TABLE VIII.

TABLE VIII

LSD METHOD FOR COMPARING TABLET DISINTEGRATION TIME OF SELECTED DISINTEGRATING AGENTS

Disintegrating Agent	Concentration	Difference between control and d. a. treatment totals
Bentonite	5%	701
	10%	142*
Corn Starch	5%	938
	10%	993
Gelatin	5%	282
	10%	359
Methylcellulose	5%	16*
	10%	1140
Pectin	5%	540
	10%	5625
Silvacon®	5%	513
	10%	686
Sodium Alginate	5%	3005
	10%	5625
Sterculia Gum	5%	1035
	10%	937
Wood Flour	5%	261
	10%	286
LSD		185

*non-significant

The value of the LSD at the 5% significance level was computed as 184.7445. In referring to TABLE VIII the LSD method concerns only the magnitude of variation between the control and the disintegrators and does not consider whether the variation is positive or negative. Thus the tablet batches varied significantly with the control if they disintegrated 185 seconds faster then the control or, if they required 185 seconds longer than the control to disintegrate. The values for LSD in TABLE VIII indicated that each of the nine selected disintegrating agents varied significantly from the control (except for 10% bentonite and 5% Methylcellulose) in their ability to cause tablet disintegration.

Correlation of Water Absorption With Tablet Disintegration Time

Since the findings from the water absorption and the tablet disintegration studies were found to be significant, correlations between the two studies could be made with validity. The statistical method used in this study employed the use of correlation coefficients (r). Li states that the "Correlation coefficients (r) may be used as an index measuring the closeness of fit of the n observed points to the estimated line of regression" (24, p. 265). Li further points out "the larger the absolute value of r, the closer the points will fit the line of regression". Thus if r is exactly equal to ± 1, the residual SS will be equal to zero and every point will be exactly on the line (24, p. 265). The computed correlation coefficients for water absorption with tablet disintegration time are listed in TABLE IX.

TABLE IX

SHORT TERM WATER ABSORPTION STUDY VS. TABLET DISINTEGRATION TIME

r=0.0936	(computed)
r=0.6319	for 8 d.f. at 5% sig. level from table

LONG TERM WATER ABSORPTION STUDY VS. TABLET DISINTEGRATION TIME

r=0.6518	(computed)
r=0.6319	for 8 d.f. at 5% sig. level from table

In the short term water absorption study (TABLE IX) the computed value of r=0.0936 is less than the value for r=0.6319 obtained by using the value from the F TABLE of F=5.3177 with 1 and 8 d.f. in the equation $F=\frac{r^2(n-2)}{1-r^2}$ (24, p. 266). This equation was solved in terms of r as $r=\sqrt{\frac{F}{F+n-2}}$. The conclusion drawn is that no significant correlation existed between short term water absorption and tablet disintegration time.

The long term water absorption study (TABLE IX) showed a slight positive correlation with tablet disintegration time, since the calculated value of r=0.6518 was slightly larger than the value r=0.6319 from the F TABLE for 8 d.f. at the 5% significance level. The conclusion is that the disintegrating agents which absorbed the most water in the long term water absorption study were the disintegrating agents which, when incorporated into tablets, required the longest time for tablet disintegration.

TABLE X and TABLE XI were prepared from the correlation studies of short term and long term water absorption with tablet disintegration time. The graphical relations of the values in TABLES X and XI are presented in figures 4 and 5 respectively. In figure four, 9 out of

TABLE X

CORRELATION OF MOISTURE ABSORPTION (SHORT TERM) WITH TABLET DISINTEGRATION TIME

Disintegrating Agent	Average Time (Secs.) For Tablets To Disintegrate	% Moisture Absorbed Per Minute
Sterculia Gum	294.50	.007734
Gelatin	627.25	.005660
Methylcellulose	1080.50	.007025
Bentonite	576.75	.006760
Corn Starch	304.75	.008542
Wood Flour	650.75	.010381
Silvacon^{R}	487.75	.006304
Control	787.50	.000124
Pectin	2058.75	.006304
Sodium Alginate	2945.00	.008593

TABLE XI

CORRELATION OF MOISTURE ABSORPTION (LONG TERM) WITH TABLET DISINTEGRATION TIME

Disintegrating Agent	Average Time (Secs.) For Tablets To Disintegrate	% Moisture Absorbed Per Minute
Sterculia Gum	294.50	.911894
Gelatin	627.25	.717394
Methylcellulose	1080.50	.468401
Bentonite	576.75	.362379
Corn Starch	304.75	.227256
Wood Flour	650.75	.216211
Silvacon^{R}	487.75	.140116
Control	787.50	.006527
Pectin	2058.75	.854412
Sodium Alginate	2945.00	1.170979

CORRELATION OF MOISTURE ABSORPTION (SHORT TERM) WITH TABLET DISINTEGRATION TIME

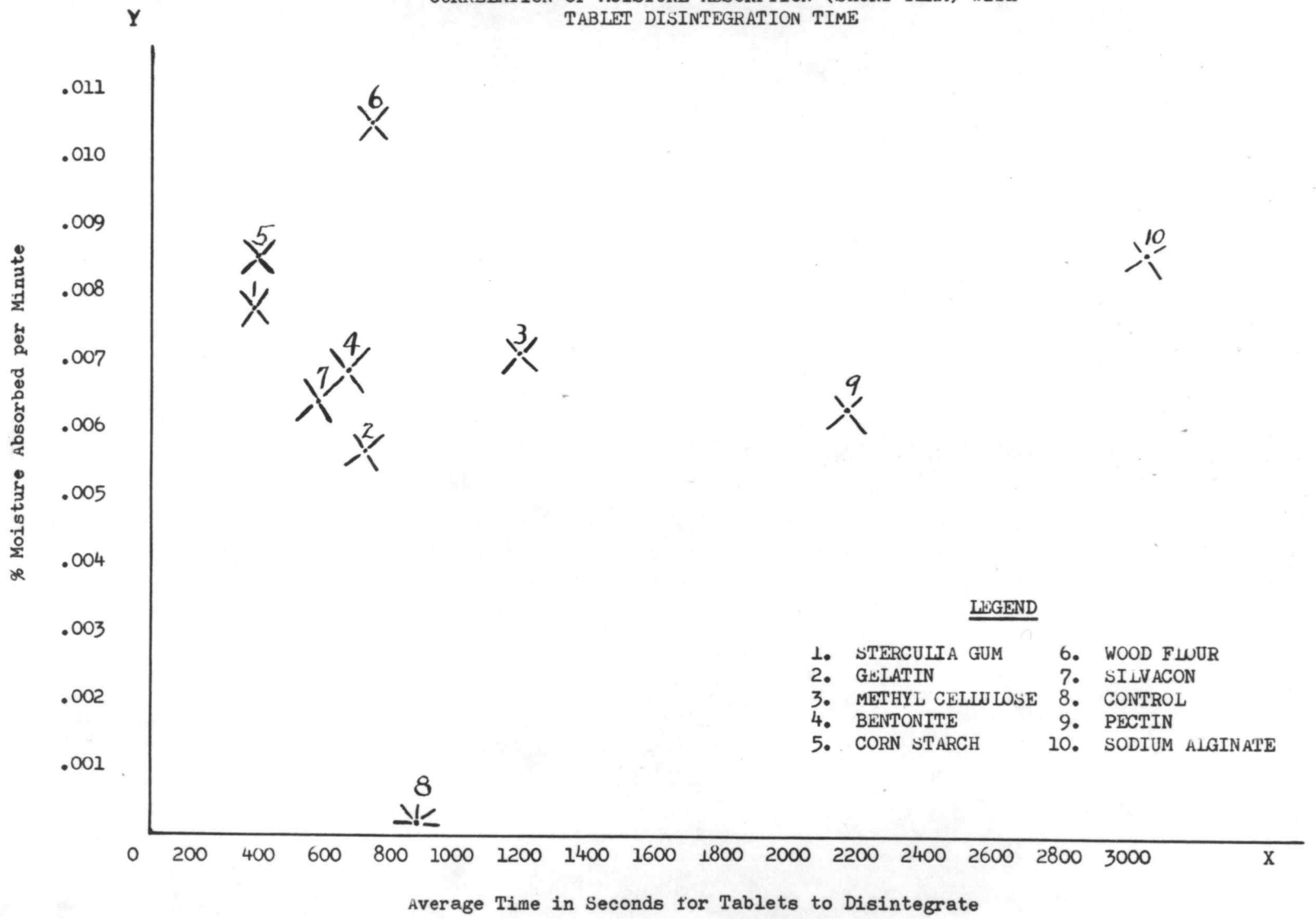


fig. 4

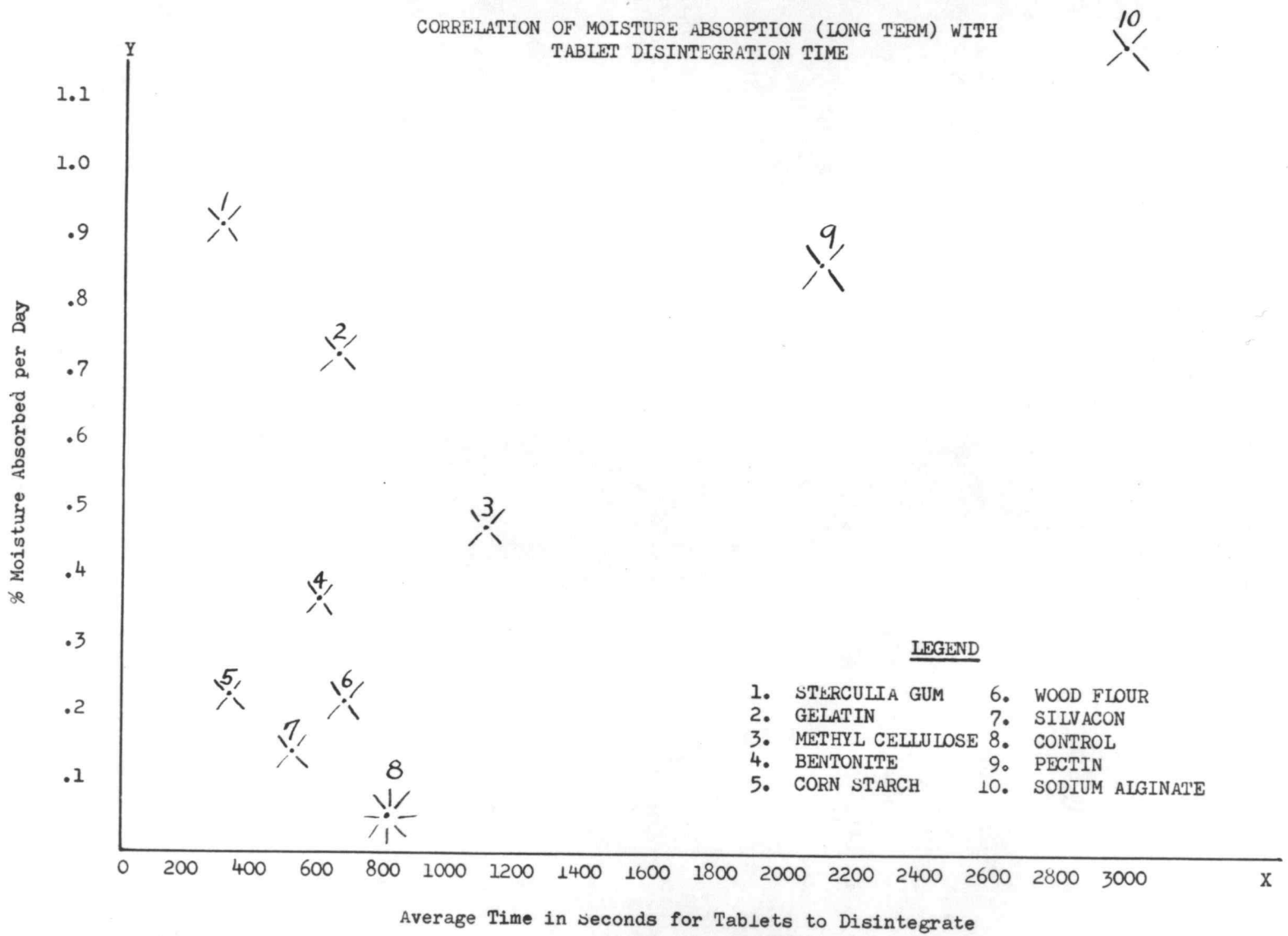

CORRELATION OF MOISTURE ABSORPTION (LONG TERM) WITH TABLET DISINTEGRATION TIME
Y
1.1
1.0
.9
.8
.7
.6
.5
.4
.3
.2
.1
% Moisture Absorbed per Day
0 200 400 600 800 1000 1200 1400 1600 1800 2000 2200 2400 2600 2800 3000
X
Average Time in Seconds for Tablets to Disintegrate
LEGEND
1. STERCULIA GUM
2. GELATIN
3. METHYL CELLULOSE
4. BENTONITE
5. CORN STARCH
6. WOOD FLOUR
7. SILVACON
8. CONTROL
9. PECTIN
10. SODIUM ALGINATE

fig. 5

10 points tend to follow the time axis in the upper portion of the graph. This indicated that all of the disintegrating agents (except the control) absorbed a high percentage of water but took various lengths of time to cause tablet disintegration. This observation is substantuated by the earlier conclusion that no correlation existed between short term water absorption and tablet disintegration time.

Figure 5 shows that 8 of the 10 points are on the left hand edge of the graph with a clustering of 6 points in the lower left hand corner. This indicated that the disintegrating agents which absorbed the least amount of water in the long term study proved to be better tablet disintegrating agents. This observation is substantuated by the earlier conclusion that a slight positive correlation existed between long term water absorption and tablet disintegration time.

SUMMARY AND CONCLUSIONS

The purpose of this thesis is to study the mechanism of action of tablet disintegrating agents. The investigation of this problem was carried out by studying the rate of water absorption and tablet disintegration time of nine selected disintegrating agents of the "absorb water and swell" type.

The research program was divided into two distinct phases, the measurement of water absorption by the nine selected disintegrating agents and the manufacture and subsequent testing of the disintegration time of tablets containing these same disintegrating agents. A new method of preparing tablet granulations was devised, employing the Wiley Mill to break apart the large hardened pieces of lactose-syrup into homogeneous finely divided granules.

Statistical analyses were performed on the data obtained from the water absorption and tablet disintegration time studies. The conclusions from the statistical analyses of these studies are:

1. The nine selected tablet disintegrating agents employed in this study absorbed significantly different total amounts of water in both the short term and long term water absorption studies. Wood flour, corn starch and sodium alginate absorbed high percentages of water in the short term moisture absorption study. The remainder of the disintegrating agents absorbed significantly but comparatively less moisture. Lactose, the control, was the only disintegrating agent which failed to absorb a significant amount of water. Sodium alginate, Sterculia Gum, and pectin were the disintegrating agents

which absorbed the highest percentage of water in the long term water absorption study, followed by gelatin, methyl cellulose, bentonite, wood flour, cornstarch, and Silvacon^{R}. Lactose again failed to absorb a significant amount of water.

2. The rate of water absorption for each of the nine disintegrating agents varied significantly when compared with one another in both the short term and long term water absorption studies.

3. The nine selected tablet disintegrating agents employed in this study as a group varied significantly from the control in their ability to cause tablet disintegration.

4. The 5% and 10% concentrations of disintegrating agents as separate groups caused significant variations in the time required for tablets to disintegrate. Unusually long tablet disintegration times were obtained with 5% and 10% sodium alginate and with 10% pectin. It was noted that tablets containing 5% and 10% sodium alginate and 10% pectin formed an insoluble mass during the tablet disintegration study. Thus an incompatability between sodium alginate and lactose and between pectin in higher concentrations and lactose appeared to be the chief factor in retarding the disintegration rates of these tablets. The nature of this incompatability was not investigated.

5. The nine selected disintegrating agents varied significantly when compared with each other, in their ability to cause tablet disintegration.

6. Each of the nine selected tablet disintegrating agents varied significantly between the 5% and 10% concentrations in their ability

to cause tablet disintegration. The optimum percentage varied with the individual disintegrating agents.

7. The LSD method of statistical analysis was used to compare the individual disintegrating agents, in both 5% and 10% concentrations, with the control. The values for LSD in TABLE VIII indicated that each of the nine selected disintegrating agents varied significantly from the control (except for 10% Bentonite and 5% Methyl cellulose) in their ability to cause tablet disintegration.

8. No significant correlation existed between short term water absorption and tablet disintegration time.

9. A slight positive correlation existed between long term water absorption and tablet disintegration time. Thus, the disintegrating agents which absorbed the most water in the long term water absorption study were the disintegrating agents which, when incorporated into tablets, required the longest time for tablet disintegration.

From this study it is concluded that water absorption may be a qualitative but not a quantitative characteristic in determining the effectiveness of tablet disintegrating agents. This study has shown that water absorption is not directly proportional to disintegration time. The evidence that water absorption is inversely proportional to tablet disintegration time is considered inconclusive.

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