to the page in case the adhesive becomes weak in later years. The articles are filed consecutively by number. Each year's articles are placed in a separate hanging file in a conventional file drawer. The cards are coded after reading the article and are then filed. Retrieval of the articles via the card index has been found to be very rapid and efficient.

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Cellulose Acetate Succinate as an Enteric Coating for Some Compressed Tablets

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The preparation and testing of compressed tablets of barium sulfate and sodium chloride coated with cellulose acetate succinate (CAS) are described, and the statistical evaluation of the data obtained is presented. The most satisfactory coatings were obtained when the test material, in an acetone-ethyl acetate solution, was applied by a modified "pan" method using talc as a dusting powder. Generally, CAS coatings which were stable for 3 1/2 hours in Simulated Gastric Fluid USP XVI dissolved sooner than control coatings of CAP applied and treated in the same manner. Disintegration times were slightly lower for most tablets placed directly into Simulated Intestinal Fluid, USP XVI than they were for tablets first treated with Simulated Gastric Fluid USP XVI for 3 1/2 hours and then tested in the former solution. None of the tablet coatings showed signs of cracks as a result of storage at −2 ± 2° for 21 days or 45 ± 2° for 10 days; however, some of these showed statistically significant differences in average disintegration time when compared with samples stored at room temperature. When test and control tablets were stored at 40 ± 2° and approximately 81% humidity, the majority of coatings were unsatisfactory. Tablets lost less than 3.56% tablet weight as a result of the simulated gastric fluid treatment. Preliminary *in vivo* tests with human subjects indicate that CAS has merit as an enteric coating. Pancreatin appears to have little effect on the disintegration times of the test coating.

THE IMPORTANCE of a good enteric coating for compressed tablets has been long recognized (1–3). Recently, the interest in this area has been stimulated by reports (4–6) of new enteric coatings and improved methods of evaluating enteric coatings. While considerable studies have been reported on the use of cellulose acetate phthalate (CAP) (4, 7–9) as an enteric coating, little experimental work has been published on the use of cellulose acetate succinate (CAS) for this purpose. Malm, *et al.* (10), prepared some cellulose succinate compounds as early as 1940; however, the authors did not fully study the enteric coating properties of the compounds.

Since CAS and CAP appear to possess similar solubility properties, and since there still exists a need for more efficient and inexpensive enteric coating material, as well as more data on the substances presently employed for this purpose, this study was undertaken. Also, it was felt that CAS might be less toxic than corresponding phthalate products, if the former proved to be a satisfactory enteric coating material, since succinic acid is normally found in the body.

EXPERIMENTAL

Material.—The cellulose acetate phthalate and cellulose acetate succinate used were obtained from Eastman Kodak Co., Rochester, N. Y. CAS has the following composition (11): combined acetyl, 20.6%; combined succinyl, 33.6%; No. of acetyls per anhydroglucose unit, 1.65%; No. of succinyls per anhydroglucose unit, 1.15%; No. of hydroxyls per anhydroglucose unit, 0.20%; free succinic acid, 0.21%; free carboxyl (corrected for free succinic acid), 15.0%.

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TABLE I.—PROPERTIES OF SOME PLAIN AND ENTERIC COATED TABLETS

Type of Tablet	Coats	Average Weight, Gm. ± S.D.	Punch Size and Shape, cm.	Av. Disintegration,[a] min. ± S.D.[b]	Average Thickness, cm. ± S.D.[b] Edges	Side
Plain Compressed Tablets						
NaCl 1	..	0.36 ± 0.01	0.949 (3/8 in.) deep concave	3 ± 0.6	0.954 ± 0.001	0.368 ± 0.006
NaCl 2n	..	0.37 ± 0.00	0.949 (3/8 in.) deep concave	3 ± 0.6	0.954 ± 0.002	0.373 ± 0.003
$BaSO_4$	..	0.46 ± 0.01	0.949 (3/8 in.) deep concave	5 ± 0.5	0.955 ± 0.001	0.386 ± 0.005
Enteric Coated Tablets (No Subcoats)						
CAS Talc NaCl 1	15	0.42 ± 0.01	...	12 ± 0.8	0.993 ± 0.003	0.389 ± 0.005
CAS Talc NaCl 2	15	0.44 ± 0.01	...	10 ± 0.5	1.000 ± 0.004	0.398 ± 0.007
CAP Talc NaCl 1	15	0.41 ± 0.01	...	25 ± 2.5	0.985 ± 0.003	0.386 ± 0.003
CAP Talc NaCl 2n	15	0.45 ± 0.01	...	28 ± 5.2	0.998 ± 0.006	0.410 ± 0.009
CAS Talc $BaSO_4$ 1	20	0.57 ± 0.01	...	19 ± 1.3	1.018 ± 0.004	0.440 ± 0.008
CAS Talc $BaSO_4$ 2	20	0.60 ± 0.01	...	24 ± 1.7	1.032 ± 0.005	0.461 ± 0.010
CAP Talc $BaSO_4$	20	0.58 ± 0.01	...	51 ± 0.9	1.022 ± 0.004	0.432 ± 0.007

[a] End point for all sodium chloride tablets was taken when 100% of tablet passed through screen of disintegration apparatus. End point for plain barium sulfate tablets was taken when the tablet edges showed definite erosion. [b] For disintegration times, standard deviation of a single observation of six tablets; for tablet dimensions, standard deviation of a single observation of 20 tablets.

TABLE II.—DISINTEGRATION TIMES OF TEST TABLETS

Enteric Coating	No. of Coats	Plain (P) Subcoated (SC)	Tablet Substance	Batch No.	Time, min. Exposed to Simulated Gastric Fluid U.S.P. XVI	Disintegration Time,[a] min. ± S. D. in Simulated Intestinal Fluid U.S.P. XVI, after Gastric Fluid Treatment	Disintegration Time,[a] min. ± S. D. in Simulated Intestinal Fluid U.S.P. XVI Only	Weight, Gm. ± S. D. of Tablet plus Enteric Coat	Weight, Gm. ± S. D. of Tablet or Weight, Gm. ± S. D. of Subcoated Tablet
CAS Talc	15	P	NaCl	1	210	12 ± 0.8	12 ± 0.7	0.42 ± 0.01	0.36 ± 0.01
CAS Talc	15	P	NaCl	2	210	10 ± 0.5	11 ± 0.9	0.44 ± 0.01	0.36 ± 0.00
CAP Talc	15	P	NaCl	1	210	25 ± 2.5	21 ± 0.6	0.41 ± 0.01	0.36 ± 0.01
CAP Talc	15	P	NaCl	2n	210	28 ± 5.2	28 ± 1.2	0.45 ± 0.01	0.37 ± 0.00
CAS Talc	20	SC	NaCl	1	210	28 ± 0.9	24 ± 1.2	0.95 ± 0.04	0.70 ± 0.01[b]
CAS Talc	20	SC	NaCl	2	210	27 ± 2.6	21 ± 1.1	0.92 ± 0.03	0.70 ± 0.01[b]
CAP Talc	20	SC	NaCl	..	210	49 ± 3.9	39 ± 1.9	0.96 ± 0.03	0.70 ± 0.01[b]
CAS Talc[c]	20	P	$BaSO_4$	1	210	19 ± 1.3	15 ± 0.8	0.57 ± 0.01	0.46 ± 0.01
CAS Talc	20	P	$BaSO_4$	2	210	24 ± 1.7	17 ± 1.1	0.60 ± 0.01	0.46 ± 0.01
CAP Talc	20	P	$BaSO_4$	..	210	51 ± 0.9	42 ± 2.3 (44 ± 4.6)	0.58 ± 0.01	0.46 ± 0.01
CAP Talc[c]	15	P	$BaSO_4$	..	210	29 ± 2.5	28 ± 0.9	0.53 ± 0.01	0.46 ± 0.01
CAS Talc	15	SC	$BaSO_4$	2	210	20 ± 1.2	17 ± 0.9	1.02 ± 0.06	0.85 ± 0.04
CAS Talc	20	SC	$BaSO_4$	1	210	23 ± 1.4	20 ± 1.0	1.02 ± 0.06	0.85 ± 0.04
CAS Talc[c]	15	SC	$BaSO_4$	1	210	16 ± 2.0	15 ± 0.8	Insufficient sample	0.85 ± 0.04
CAP Talc	20	SC	$BaSO_4$	..	210	32 ± 2.3 (35 ± 2.7)	27 ± 2.0 (33 ± 1.3)	1.03 ± 0.07	0.85 ± 0.04
CAP Talc[c]	15	SC	$BaSO_4$	..	210	29 ± 1.5	28 ± 2.4	Insufficient sample	0.85 ± 0.04

[a] End point for all sodium chloride tablets was taken when 100% of tablet passed through screen of disintegration apparatus. End point for subcoated barium sulfate tablets was taken at the first appearance of core tablet. End point for plain barium sulfate tablets was taken when the tablet edges showed definite erosion. [b] Weight and standard deviations of the average weights of 20 samples consisting of 10 tablets each. [c] Slight cracks observed in a few coatings after simulated gastric fluid treatment.

Other Materials Used.—Dimethyl phthalate (Eastman); ethyl acetate, N.F. and reagent; acetone, N.F. and technical; talc, U.S.P.; simulated gastric fluid U.S.P. XVI; simulated intestinal fluid U.S.P. XVI; sucrose U.S.P.; starch U.S.P.; calcium carbonate U.S.P.; amaranth U.S.P.; barium sulfate U.S.P., and sodium chloride, technical.

Preparation of Tablets.—Tablets of sodium chloride and barium sulfate-sucrose (5:2) were compressed on a power-driven Stokes model F single-punch machine using 3/8 in. deep concave punches. The weights of 10 tablets of sodium chloride and barium sulfate were maintained at approximately 3.60 and 4.60 Gm., respectively. The total weight of each granulation compressed was about 20 lb. Each batch was divided into two groups and designated as: (*a*) tablets to be enteric coated without a subcoat and (*b*) tablets to be subcoated prior to enteric coating. Simple syrup, subcoating powder (consisting of varying amounts of calcium carbonate, starch, and sucrose) and the conventional coating pan were used to apply the subcoats. For the barium sulfate tablets a small amount of amaranth, as an indicator, was added to some of

the subcoating powder and this mixture applied as the first two or three subcoats.

Tablets of each of the above two groups were then divided as follows: (*a*) tablets to be enteric coated without a dusting powder and (*b*) tablets to be enteric coated using talc as a dusting powder.

At a later date, another batch of sodium chloride (2n) was compressed as before, coated with CAP and talc, and used as a second control.

Enteric Coating.—The enteric coating solution used had the following composition: cellulose acetate succinate, 9.0 Gm.; dimethyl phthalate (plasticizer), 3.4 Gm.; ethyl acetate, 84.4 Gm.; acetone, 84.4 Gm. A solution containing the same concentration of commercially available CAP was used as the control.

The compressed tablets were enteric coated with the CAS or CAP solution using a modified "pan" coating technique. In place of the copper pan, a small porcelain container was used because the conventional pan was not suitable for small experimental lots of approximately 700 to 1500 tablets.

Twelve to fifteen milliliters of enteric coating solution were employed for each coat. The total number of coats applied per batch was 15 or 20. When a dusting powder was employed, approximately 12 to 15 Gm. of talc were used for each application. Controls were coated in a similar manner. It is estimated that the weight ratio of polymer to talc for tablets coated by this technique ranged from 1:10 to 1:15. Some properties of plain and enteric coated tablets are given in Tables I and II.

Enteric Coated Tablets.—*In vitro* tests were carried out by using the disintegration apparatus, simulated gastric fluid, and simulated intestinal fluid of the U.S.P. XVI.

Tablets coated only with 20 coats CAS or CAP did not resist the action of simulated gastric fluid U.S.P. XVI for $3^1/_2$ hours; therefore, they were rejected and not studied further.

All other enteric coated tablets were tested for disintegration in simulated intestinal fluid by two procedures: (*a*) by placing tablets directly into this fluid and (*b*) by placing the tablets in the simulated gastric fluid U.S.P. XVI for $3^1/_2$ hours prior to transferring them to the simulated intestinal fluid U.S.P. XVI. All disintegration times were recorded to the nearest minute.

The behavior of the tablets in the simulated gastric fluid, their disintegration times in simulated intestinal fluid, their end points for disintegration, and some of their physical properties are shown in Table II.

Effect of Storage.—Since it was observed by investigators that some enteric coatings may crack when subjected to various storage conditions, it was of interest to investigate the effect of cold, heat, and high humidity upon the test coatings. Eighteen to twenty-two tablets from each group of enteric coated tablets were exposed in open containers to: (*a*) refrigerator temperature of $-2 \pm 2°$ for 21 days, (*b*) oven temperature of $45 \pm 2°$ for 10 days, and (*c*) oven temperature of $40 \pm 2°$ and approximate humidity of 81%[1] for 10 days. At the end of the storage periods, tablets were allowed to return to room temperature, examined for cracks, weighed (except those rejected due to the action of high humidity chamber), and tested for disintegration as soon as possible. The condition in the humidity chamber was purposely made much more extreme than any which might be ordinarily found. With all sodium chloride test and control samples, a considerable amount of water was found in the storage containers and many of the coatings were broken. Most of the CAS and CAP coats on barium sulfate tablets containing no subcoats showed cracks; however, with the corresponding subcoated tablets, no breaks in the coatings were observed. These latter tablets increased in weight, but no further work was done with them. Test and control coatings stored in the heat and cold showed no cracks. The disintegration times for the samples are found in Table III.

Loss of Tablet Weight.—It was observed that many of the tablets gained weight during the simulated gastric fluid treatment and during the humidity storage period. This indicated that some liquid had entered into the tablets. Also, it was shown from the results of the humidity storage experiment that considerable sodium chloride was present in the water which had accumulated in the storage containers holding the nonsubcoated enteric coated sodium chloride tablets. These observations appear to substantiate Gakenheimer's (13) conclusion that CAP coatings may act as a semipermeable membrane. Therefore, it was of interest to determine whether the simulated gastric fluid caused any loss of tablet material during the testing procedure. Representative samples stored at room temperature, $-2 \pm 2°$ and $45 \pm 2°$ were weighed, placed in the simulated gastric fluid for $3^1/_2$ hours, and then dried to constant weight at $105 \pm 5°$. Corresponding samples not treated with the above solution but dried to constant weight at $105 \pm 5°$ served as controls. Considerable variation in tablet weight loss of both treated and control samples was observed. Results indicate, however, that not more than 3.56% tablet weight is lost as a result of the simulated gastric fluid treatment. Findings expressed as per cent weight loss of tablet material appear in Tables IV, V, and VI.

Effect of Different Solutions on Disintegration Times.—Bauer and Masucci (14) found that the disintegration of CAP coatings in the intestinal contents, which is on the acid side, is the result of the hydrolytic action of intestinal esterases and not upon the alkalinity of the solution. *In vitro* tests carried out in this study indicated that the per cent of pancreatin in the simulated intestinal fluid U.S.P. XVI had little effect upon the disintegration times of CAS or CAP coatings.

Findings suggest that if the pancreatic enzymes of the simulated intestinal fluid solubilize the coats by cleaving the ester linkages, the process is slow and overshadowed by the alkalinity of the solution. Results are given in Table VII.

In Vivo Test.[2]—Wagner (4) has pointed out that an adequate evaluation of an enteric coating necessitates both *in vitro* and *in vivo* tests. While a com-

[1] The proper humidity was maintained by placing in the bottom of a desiccator a saturated solution of ammonium sulfate containing an excess of the salt (12).

[2] We are indebted to Dr. J. H. Lawson, Consulting Radiologist, Health Center, University of Texas, for his help in evaluating the X-ray films.

TABLE III.—DISINTEGRATION TIMES OF TEST TABLETS FOLLOWING STORAGE

Enteric Coating	No. of Coats	Plain (P) Subcoated (SB)	Tablet Substance	Batch No.	Time, min. Exposed to Simulated Gastric Fluid U.S.P. XVI	Disintegration Time,[b] min. ± S.D.[c] in Simulated Intestinal Fluid U.S.P. XVI after Gastric Fluid Treatment and after Varied Storage Conditions: 45 ± 2° for 10 days	−2 ± 2° for 21 days
CAS Talc	15	P	NaCl	1	210	12 ± 1.1	12 ± 1.5
CAS Talc	15	P	NaCl	2	210	11 ± 0.2	10 ± 1.1
CAP Talc	15	P	NaCl	1	210	25 ± 2.8	24 ± 2.6
CAP Talc	15	P	NaCl	2n	210	30 ± 2.5	30 ± 1.5
CAS Talc	20	SC	NaCl	1	210	28 ± 2.1	24 ± 1.8
CAS Talc	20	SC	NaCl	2	210	27 ± 1.9	24 ± 1.4
CAP Talc	20	SC	NaCl	..	210	55 ± 4.2	45 ± 3.2
CAS Talc[a]	20	P	$BaSO_4$	1	210	13 ± 1.3	17 ± 0.6
CAS Talc	20	P	$BaSO_4$	2	210	22 ± 1.4	Not tested
CAP Talc	20	P	$BaSO_4$	..	210	53 ± 3.6	Not tested
CAP Talc[a]	15	P	$BaSO_4$	..	210	32 ± 1.3	31 ± 1.7
CAS Talc	15	SC	$BaSO_4$	2	210	18 ± 0.9	17 ± 1.3
CAS Talc	20	SC	$BaSO_4$	1	210	22 ± 1.5	20 ± 0.9
CAP Talc	20	SC	$BaSO_4$	..	210	33 ± 3.6	32 ± 2.0 34 ± 2.1
CAP Talc[a]	15	SC	$BaSO_4$	..	210	28 ± 1.5	24 ± 1.4

[a] Slight cracks observed in a few coatings after simulated gastric fluid treatment. [b] End point for all sodium chloride tablets was taken when 100% of tablet passed through screen of disintegration apparatus. End point for subcoated barium sulfate tablets was taken at the first appearance of core tablet. End point for plain barium sulfate tablets was taken when the tablet edges showed definite erosion. [c] Standard deviation of a single observation of disintegration times of six tablets.

TABLE IV.—LOSS OF WEIGHT DURING GASTRIC FLUID TREATMENT OF TABLETS STORED AT ROOM TEMPERATURE (CONTROLS)

Enteric Coating	No. of Coats	Plain (P) Subcoated (SC)	Tablet Substance	Batch No.	Weight Loss of Tablets Subjected to Gastric Fluid Treatment and 100 ± 5° Drying, %	Weight Loss of Tablets Subjected Only to 100 ± 5° Drying, %
CAS Talc	15	P	NaCl	1	3.57	0.397
CAS Talc	15	P	NaCl	2	3.08	0.579
CAP Talc	15	P	NaCl	1	1.62	0.605
CAS Talc	20	SC	NaCl	1	2.44	2.10
CAP Talc	20	SC	NaCl	..	3.15	2.71
CAS Talc	20	P	$BaSO_4$	2	2.38	1.27
CAP Talc	20	P	$BaSO_4$	..	1.15	1.01
CAS Talc	15	SC	$BaSO_4$	2	3.09	1.85
CAS Talc	20	SC	$BaSO_4$	1	2.26	2.09
CAS Talc	15	SC	$BaSO_4$	1	3.09	2.21
CAP Talc	20	SC	$BaSO_4$	..	2.80	1.73

TABLE V.—LOSS OF WEIGHT DURING GASTRIC FLUID TREATMENT OF TABLETS STORED AT 45 ± 2° FOR 10 DAYS

Enteric Coating	No. of Coats	Plain (P) Subcoated (SC)	Tablet Substance	Batch No.	Weight Loss of Tablets Subjected to Gastric Fluid Treatment and 100 ± 5° Drying, %	Weight Loss of Tablets Subjected Only to 100 ± 5° Drying, %	Weight Loss of Tablets During Storage at 45° for 10 Days, %
CAS Talc	15	P	NaCl	1	3.95	0.40	0.26
CAS Talc	15	P	NaCl	2	3.68	0.37	0.26
CAP Talc	15	P	NaCl	1	2.52	0.41	0.27
CAS Talc	20	SC	NaCl	1	1.13	1.06	1.16
CAS Talc	20	SC	NaCl	2	1.48	0.73	1.16
CAP Talc	20	SC	NaCl	..	0.94	1.15	1.16
CAS Talc	20	P	$BaSO_4$	1	1.46	0.90	0.79
CAS Talc	20	P	$BaSO_4$	2	0.97	0.67	0.59
CAP Talc	20	P	$BaSO_4$	..	0.88	0.87	0.39
CAS Talc	20	SC	$BaSO_4$	1	0.76	0.88	1.03
CAP Talc	20	SC	$BaSO_4$	..	0.93	1.07	0.88

plete *in vivo* study on CAS as an enteric coating was beyond the scope of this work, it was felt that a preliminary *in vivo* study on humans would be of interest to those working in the field of enteric coatings.

Two subjects were given CAS talc sc barium sulfate (20 coats) No. 1 tablets in the following manner: subject 1 fasted 6 hours before and during the experiment except for a cup of coffee at 10:00 a.m. A tablet was taken at 7:30 a.m. and again at 11:00 p.m. X-rays were taken at 11:05 a.m. and at 2:05 p.m. The radiologist's report states, "the 11:05 a.m. film shows an opacity resembling a medicinal coated tablet in the right lower quadrant which is probably in the ileum. On the 2:04 p.m. film fragmented density in the right lower quadrant indicates dissolution of the enteric coating with the material still in the ileum. A new tablet is observed in the right upper quadrant which is either in the distal end of the stomach or in the descending duodenum."

Subject 2 took food at 7:30 a.m. and at 12:15

TABLE VI.—LOSS OF WEIGHT DURING GASTRIC FLUID TREATMENT OF TABLETS STORED AT −2 ± 2° FOR 21 DAYS

Enteric Coating	No. of Coats	Plain (P) Subcoated (SC)	Tablet Substance	Batch No.	Weight Loss of Tablets Subjected to Gastric Fluid Treatment and 100 ± 5° Drying, %	Weight Loss of Tablets Subjected Only to 100 ± 5° Drying, %
CAS Talc	15	P	NaCl	2	2.30	0.579
CAP Talc	15	P	NaCl	1	2.35	0.605
CAP Talc	15	P	NaCl	2n	1.29	1.75
CAS Talc	20	SC	NaCl	2	2.60	2.19
CAP Talc	20	SC	NaCl	..	2.55	2.71
CAS Talc	20	P	$BaSO_4$	2	2.46	1.27
CAS Talc	15	SC	$BaSO_4$	2	2.90	1.85
CAS Talc	20	SC	$BaSO_4$	1	2.32	2.09
CAP Talc	20	SC	$BaSO_4$	..	1.88	1.73
CAP Talc	15	SC	$BaSO_4$	..	2.94	1.86

TABLE VII.—EFFECT OF DIFFERENT SOLUTIONS ON TABLET DISINTEGRATION TIME

Tablet	Coats	Solution	Disintegration Times, min. ± S. D.[a]
CAS Talc subcoated $BaSO_4$	15	Simulated intestinal fluid U.S.P. XVI	17 ± 0.9
CAS Talc subcoated $BaSO_4$	15	Simulated intestinal fluid U.S.P. XVI less pancreatin	19 ± 0.6 14 ± 0.6
CAS Talc subcoated $BaSO_4$	15	Simulated intestinal fluid U.S.P. XVI less NaOH (pH 5.15)	No significant disintegration in 150 min.
CAP Talc subcoated $BaSO_4$	15	Simulated intestinal fluid U.S.P. XVI	28 ± 2.4
CAP Talc subcoated $BaSO_4$	15	Simulated intestinal fluid U.S.P. XVI less pancreatin	25 ± 3.8
CAP Talc subcoated $BaSO_4$	15	Simulated intestinal fluid U.S.P. XVI less NaOH	No significant disintegration in 150 min.

[a] Standard deviation of a single observation of disintegration times of six tablets.

p.m., only one tablet was taken at 8:00 a.m. X-rays were taken at 11:38 a.m. and at 2:10 p.m. The radiologist reported, "that both films show an undissolved medicinal coated tablet in the stomach."

A third subject also took food at breakfast and lunch. This subject received three CAS talc sc barium sulfate (15 coats) No. 2 tablets in the following way: one tablet was taken at 7:45 a.m., another at 10:00 a.m., and the third at 12:15 p.m. Only one X-ray was taken at 2:05 p.m. The results reported by the radiologist states, "A fairly homogeneous opaque material is noted in the caecum on the film. There is no indication of separation of the opaque material and this could be one or three tablets. There is one density at the top of the film overlying the spine which appears to be a tablet in the stomach, however, the stomach is not sufficiently included on the film for this determination to be definite."

Evaluation of Results.—Statistical evaluation of the results was performed using the *t*-test for determination of significant differences between two means. The *t* values that are greater than 95% probability *t* value at the appropriate degrees of freedom are considered significant. Results are given in Table VIII.

DISCUSSION

Generally, duplicate batches of each type of tablet were enteric coated and tested in an attempt to obtain reliable results.

Measurements of tablet thickness on the edge and side were made only for plain sodium chloride; plain barium sulfate; nonsubcoated, enteric coated sodium chloride; and nonsubcoated, enteric coated barium sulfate tablets because it was difficult to achieve satisfactory measurements with the subcoated, enteric coated tablets. Although the enteric coats of the latter tablets were quite evenly applied, the subcoats were not completely smooth. However, the weights of subcoats and enteric coats of these tablets were fairly uniform, and the tablets in general had an acceptable appearance. Overcoming the coating inconsistencies appeared to be a matter of developing a better coating technique.

While an attempt was made during the coating procedure to keep constant the volumes of enteric coating solution, the weight of dusting powder, the time between the addition of enteric coating solutions and the addition of talc, and the drying time between coats, it was noted that the movement of the tablets in the coating container had an effect upon the quantity of talc adhering to the tablets per application. When tablets were mixed frequently by hand while they were in the coating container, it appeared that less dusting powder adhered to the coatings. Two batches were rejected because it was felt they were not coated correctly. With one of these, the coatings contained some clear spots where little or no talc appeared to be present. The weight and instability of CAS talc plain barium sulfate No. 1 tablets in simulated gastric fluid appears to substantiate this observation. While this batch received the same number of coats as CAS talc plain barium sulfate No. 2, there was less enteric coating material on the tablets. A minimum amount of tablet stirring should be done during the coating procedure in order to prevent erosion of talc from the coatings. Wagner, *et al.* (4), has reported the importance of the talc concentration in three modern enteric

TABLE VIII.—EVALUATION OF TABLET DISINTEGRATION TIMES DATA AFTER VARIED STORAGE CONDITIONS

Enteric Coating	No. of Coats	Plain (P) Subcoated (SC)	Tablet Substance	Batch No.	RT 45°/10 days (H) −2°/21 days (C)	Standard Error	Degrees of Freedom	t Calcd.[a]	t at 95% Level
CAS Talc	15	P	NaCl	1	RT	0.33			
CAP Talc	15	P	NaCl	1	RT	1.0	10	12.1	2.228
CAS Talc	20	SC	NaCl	1	RT	0.37			
CAP Talc	20	SC	NaCl	1	RT	1.6	10	12.8	2.228
CAS Talc	20	SC	$BaSO_4$	1	RT	0.57			
CAP Talc	20	SC	$BaSO_4$	..	RT	0.92	9	8.33	2.262
CAS Talc	15	P	NaCl	1	C	0.61			
CAP Talc	15	P	NaCl	1	C	1.2	9	8.93	2.262
CAS Talc	20	SC	NaCl	1	C	0.74			
CAP Talc	20	SC	NaCl	1	C	1.4	10	13.3	2.228
CAS Talc	20	SC	$BaSO_4$	1	C	0.37			
CAP Talc	20	SC	$BaSO_4$	..	C	0.82	10	15.6	2.228
CAS Talc	15	P	NaCl	1	H	0.45			
CAP Talc	15	P	NaCl	1	H	1.1	10	10.8	2.228
CAS Talc	20	SC	NaCl	1	H	0.86			
CAP Talc	20	SC	NaCl	1	H	1.7	10	14.1	2.228
CAS Talc	20	SC	$BaSO_4$	1	H	0.61			
CAP Talc	20	SC	$BaSO_4$	1	H	1.0	10	9.4	2.228
CAS Talc	15	P	NaCl	1	RT	0.33			
CAS Talc	15	P	NaCl	1	C	0.61	10	0.0	2.228
CAS Talc	15	P	NaCl	1	RT	0.33			
CAS Talc	15	P	NaCl	1	H	0.45	10	00.0	2.228
CAS Talc	20	SC	NaCl	1	RT	0.37			
CAS Talc	20	SC	NaCl	1	C	0.74	10	4.84	2.228
CAS Talc	20	SC	NaCl	1	RT	0.37			
CAS Talc	20	SC	NaCl	1	H	0.86	10	0.0	2.228
CAP Talc	15	P	NaCl	1	RT	1.0			
CAP Talc	15	P	NaCl	1	C	1.2	9	0.64	2.262
CAP Talc	15	P	NaCl	1	RT	1.0			
CAP Talc	15	P	NaCl	1	H	1.1	10	0.0	2.228
CAP Talc	20	SC	NaCl	1	RT	1.6			
CAP Talc	20	SC	NaCl	1	C	1.4	10	1.89	2.228
CAP Talc	20	SC	NaCl	1	RT	1.6			
CAP Talc	20	SC	NaCl	1	H	1.7	10	2.02	2.228
CAS Talc	20	P	$BaSO_4$	1	RT	0.53			
CAS Talc	20	P	$BaSO_4$	1	C	0.25	10	3.42	2.228
CAS Talc	20	P	$BaSO_4$	1	RT	0.53			
CAS Talc	20	P	$BaSO_4$	1	H	0.53	10	8.0	2.228
CAP Talc	15	P	$BaSO_4$	..	RT	0.37			
CAP Talc	15	P	$BaSO_4$	..	C	0.69	10	2.55	2.228
CAP Talc	15	P	$BaSO_4$	..	RT	0.37			
CAP Talc	15	P	$BaSO_4$	..	H	0.53	10	4.62	2.228
CAP Talc	20	P	$BaSO_4$	..	RT	0.69			
CAP Talc	20	P	$BaSO_4$	..	H	1.0	10	1.64	2.228
CAP Talc	20	SC	$BaSO_4$	..	RT	0.92			
CAP Talc	20	SC	$BaSO_4$	..	C	0.82	10	0.81	2.228
CAP Talc	20	SC	$BaSO_4$	..	RT	0.92			
CAP Talc	20	SC	$BaSO_4$	..	H	1.0	10	0.74	2.228
CAS Talc	20	SC	$BaSO_4$	1	RT	0.57			
CAS Talc	20	SC	$BaSO_4$	1	C	0.37	10	4.42	2.228
CAS Talc	20	SC	$BaSO_4$	1	RT	0.57			
CAS Talc	20	SC	$BaSO_4$	1	H	0.61	10	1.2	2.228

[a] t was calculated by $t = \frac{|X_1 - X_2|}{\sqrt{(S\bar{x}_1)^2 + (S\bar{x}_2)^2}}$ as found in Martin, E. W., and Cook, E. F., "Remington's Practice of Pharmacy," 12th ed., Mack Publishing Company, Easton, Pa., 1961, pp. 109–110.

coatings. Sheffield, *et al.* (15), also, found some differences between tablets enteric coated in small lots and those enteric coated in pilot-size batches. These differences might be reflected in the amount of extra rubbing caused by the increase in number of tablets used.

While high humidity affected most of the coatings, this problem does not appear to be a serious one. Water-proof coatings can be applied to either the plain or finished tablet without too much difficulty. A desiccant can also be packaged with the finished product.

Some test and control tablets stored in the cold and heat showed significant changes in disintegration times when compared statistically with those kept at room temperature; however, it is felt that the differences were not too serious from a practical aspect. It should be noted that some water could have come in contact with the tablets stored at $-2 \pm 2°$ for 21 days inasmuch as they were stored in open containers directly under the freezing unit of the refrigerator.

Significant differences in disintegration times in simulated intestinal fluid were observed between CAS and CAP coated tablets. These results might be due to the differences in the chemical structure

of the two coating materials. Hiatt (16) stated that those cellulose acetate phthalates having a free carboxyl content between 9 and 15% by weight are most preferable for enteric coating. The CAS used in this report had a free carboxyl content of 15% by weight.

Wagner, *et al.* (17), also reported that the minimum pH at which starch acetate phthalates dissolve depends upon the percentage of free carboxyl groups on the polymer molecule.

Our findings on the disintegration times for tablets in simulated intestinal fluid following treatment in simulated gastric fluid, as compared with disintegration times for tablets placed directly into the former solution, generally agree with data reported by Wagner, *et al.* (4). Further work on this phase of the problem will be considered at a later date.

Pancreatic enzymes may cleave the ester linkages of CAS; however, this was not demonstrated in this study chiefly because of the relatively high pH of the solutions used. Further work using buffer solutions at pH values from 1.2 to 6.9 might indicate the pH dependency and stability of CAS.

Wagner and Long (4) point out that an adequate *in vitro* comparison of two or more enteric coatings as done here with CAP and CAS requires testing the tablets coated with the enteric material at several levels. The slopes and positions of lines obtained by plotting disintegration times against mean weight of coating per tablet or mean weight of enteric substance per tablet should then be compared. These investigators also state that the amounts of enteric material and dusting powder employed are equally as important as the nature of the enteric substance when comparisons are made.

In this study the two different coatings were compared only at two levels of enteric substance; however, an attempt was made to control the amount of talc applied so that test and control tablets would receive the same amount of dusting powder per tablet. Our results, at the levels tested, showed that CAS coatings dissolved faster than CAP coatings in simulated intestinal fluid; however, it is possible in light of the work of Wagner, *et al.* (4), at higher or lower levels of coating, the reverse might take place.

Preliminary *in vivo* tests show that CAS has merit as an enteric coating. While considerable *in vivo* testing is still required before definite conclusions can be drawn, it is of interest to note that with one test subject a CAS coated tablet remained in the stomach for a period of more than 6 hours. X-ray films of two other test subjects indicated that the CAS coated tablets dissolved shortly after entering the intestines.

SUMMARY AND CONCLUSIONS

1. The preparation and testing of cellulose acetate succinate coated tablets of sodium chloride and barium sulfate are described and the statistical evaluation of the data obtained is presented.

2. Satisfactory enteric coated tablets were obtained, in most instances, when CAS, in an acetone-ethyl acetate solution, was applied by a modified "pan" method using talc as a dusting powder.

3. None of the test coatings showed signs of cracks as a result of storage at $-2 \pm 2°$ for 21 days or at $45 \pm 2°$ for 10 days; however, some test and control coatings showed differences in disintegration times in simulated intestinal fluid U.S.P. XVI when compared statistically with samples kept at room temperature.

4. CAS coatings which were stable for $3^1/_2$ hours in simulated gastric fluid dissolved sooner than control coatings of CAP applied and treated in the same manner.

5. Disintegration times are slightly lower for most tablets placed directly into simulated intestinal fluid than for tablets first treated with simulated gastric fluid for $3^1/_2$ hours and then tested in the former solution.

6. Of the tablets tested, none lost more than 3.56% tablet weight as a result of the $3^1/_2$ hours treatment in simulated gastric fluid.

7. The presence of pancreatin in the simulated intestinal fluid appeared to have little effect upon the rate at which the coatings dissolved.

8. Preliminary *in vivo* tests with human subjects indicate that CAS has merit as an enteric coating.

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