tions, the times and temperatures suggested in Tables II and III may be changed at will by choosing different points on the lines of the graph; *e.g.*, taking 70° as a storage temperature, the maximum and minimum times would be, respectively, 2.6 months and 9 days.

As implied, overages make no difference in the use of this method of evaluating stability characteristics. Overages are merely one means of assuring that potency will not be less than 90% of label claim after two years when greater stability cannot be built into the formulation in other ways. When using data from assays on formulas which contain overages, it is the per cent of *label claim* that should be used just as in the case of formulas in which there are no overages.

## NOTE ON POSSIBLE MISUSE OF THE GRAPH

As stated previously, this method is not intended to help in the determination of exact kinetic paths. Thus if, *e.g.*, the following two points were obtained: 80°, 1 month, and 45°, 4 months (to drop to 90%, etc.), it would appear that a line drawn through these points would cross the 25° line at about 10 months to indicate an unsuitable product. *This is not a true picture.* No line *should* be drawn through these points because the only aim in using this method is to see if the two points are above the 20 Kcal./mole line, which they are. Incidentally, in this example, two such points (if valid) would indicate an activation energy of about 8.8 Kcal./mole—something which is ruled out for reasons previously discussed as being an unreasonable possibility. The seeming paradox would have to be considered as due to experimental errors either in assay, timing, or temperature or due to the presence of additional degradative reactions. Naturally, two or more points which form a line with a *greater* slope than either of the two lines shown on the graph would tend to indicate a higher activation energy and longer than two-year shelf-life and would cause no concern.

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# Dioctyl Sodium Sulfosuccinate Tablet Coating

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**A tablet film coating process using dioctyl sodium sulfosuccinate was easily performed on tablets in a relatively short period of time using conventional coating equipment. The coating showed exceptional resistance to heat, light, and trauma. An inherent weakness to environmental moisture could be prevented. The coating has the advantage of being noncaloric in composition and does not hinder disintegration of the tablets.**

THE PHARMACEUTICAL industry has long been interested in tablet coating for the protection it affords the tablet ingredients which are adversely affected by environmental conditions, for the concealment of an unpleasant odor or taste, and for the elegant appearance it provides through a confectionary finish.

The numerous disadvantages of the usual sugar coating have lead to recent investigations for newer materials and methods of coating. In

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the search for a substitute for the sucrose in tablet coating formulas, many natural and synthetic materials have been studied, and a number of them have been found to be satisfactory as film coating agents—polyethylene glycol 6000 in ethanol (1), polyethylene glycol 6000 and carboxymethylcellulose in hydroisopropanol (2), sodium carboxymethylcellulose and hydroxyethylcellulose applied over a shellac prime coat (3), zein in isopropanol (4), polyvinylpyrrolidone and acetylated monoglycerides (5), and polyethylene oxide water soluble resins (6).

## EXPERIMENTAL

This investigation was concerned with the evaluation of dioctyl sodium sulfosuccinate (DSS)[1] as a film coating for sugar coated and noncoated compressed tablets with regard to methods of film application and the testing of several environmental effects. The tablets which were used in the experimental work are listed in Table I.

**Coating.**—The method of application of DSS coating solutions was similar to that for conventional sugar coating solutions; a model 29 Stokes polishing and coating machine equipped with a 10-in. copper coating pan was used.

Solutions containing between 15 and 25% DSS in alcohol produced relatively satisfactory results, although the film coat was somewhat soft and slightly tacky regardless of the thickness applied, drying time, or drying temperature. The surface tackiness became more pronounced with time, probably due to the slight hygroscopic nature of DSS.

This condition of coating softness was remedied by the addition of sodium benzoate to produce a comparatively hard surface. Propylene glycol was included in the formula to improve the glossy appearance and enhance the plasticity of the film coat.

A typical coating formula had the following percentage composition: DSS, 20; sodium benzoate, 2–15; propylene glycol, 0.5; alcohol 70% w/w, to make 100.

The best results were obtained by applying three to five coats at 15-minute intervals with sufficient of the coating solution to moisten the tablets completely. Cooled air for drying gave more desirable results than hot air since the tablet coating had a tendency to become uneven and flake off if dried too rapidly. Uneven coatings could be easily smoothed by the application of 70% w/w alcohol.

**Application of Color.**—The addition of varying concentrations of certified dyes (FD&C Blue No. 1, FD&C Red No. 3, FD&C Yellow No. 5) to the DSS coating solution failed to give uniformity of color to the tablets. However, if a dye concentration of 0.5% in diluted alcohol was included in the tablet granulation and the tablets coated in the usual manner with 0.25% dye added to the coating solution, satisfactorily colored tablets resulted.

Uniform coloring of tablets was also accomplished by the addition of 0.25 to 0.5% dye solution in diluted alcohol to the uncoated tablets just prior to applying a shellac prime coat or DSS coat. The normal coating process would follow, using 0.25% dye in the coating solution.

[1] Marketed as Aerosol OT by the American Cyanamid Co., Pearl River, N. Y.

TABLE I.—TABLETS AND COATINGS USED IN THE TESTS

| Code | Tablet | Size and Type | Maker |
|---|---|---|---|
| 1 | Sodium chloride | 10 gr., standard punch 3/8 in. | A |
| 2 | Placebo | 250 mg., oval | B |
| 3 | Ferrous sulfate | 5 gr., coated | C |
| 4 | Ferrous sulfate | 5 gr., coated | D |
| 5 | Effervescent aspirin and sodium phosphate | 7 1/2 gr., standard punch 3/8 in. | A |
| 6 | Methenamine | 5 gr. | E |
| 7 | Lactose-starch | 4 gr., standard punch 11/16 in. | A |
| 8 | Lactose-starch | 7 gr., standard punch 3/8 in., colored | A |
| OT | ... | DSS coated | .. |
| OT-B | ... | DSS 15% sodium benzoate | .. |
| OT-W | ... | DSS coated and polished | .. |
| P-OT | ... | Shellac prime coated and coated with DSS | .. |

All prime coats were composed of freshly prepared solutions of 20 Gm. white arsenic-free shellac to 40 ml. alcohol (7).

**Taste.**—A bitter aftertaste was noted with the DSS coatings. The addition of 2% saccharin sodium to the coating solution would almost completely mask this taste, although some aftertaste was noted from the saccharin itself. Sodium cyclamate in a concentration of 5% proved more desirable, and a mixture of 2.5% sodium cyclamate and 0.25% saccharin was equally successful. A polish coat would also eliminate most of the bitter taste.

**Weight of Coating.**—The DSS coating increased the weight of commercial sugar coated tablets approximately 5 to 12 mg. per tablet and of noncoated compressed tablets about 20 to 45 mg. per tablet. The surface texture and the difference of tablet size were the main factors influencing the variance in weight.

**Polish Coat.**—The polishing procedure was accomplished in a 20-in. galvanized iron, canvas-lined polish pan. The tablets were sprayed with a warm solution of a 2% wax mixture (eight parts white beeswax, five parts carnauba wax) in chloroform (8). This polish coat slightly improved the glossy appearance of the film coat, lessened the effect of humidity, and partially masked the taste of DSS.

**Durability Test.**—This test was designed to compare the effect of physical trauma on coated and noncoated tablets. Samples of 100 tablets of each type were placed in clear 4-oz. dry prescription squares, filling the containers from one-half to one-third their capacity. The bottles were shaken lengthwise through a total distance of about 3 in. 200 times per minute in a size 2 bottle shaker (International Equipment Co., Boston, Mass.).

The tablets were inspected at 15-minute intervals during a 2-hour shaking period and were screened after each time interval to remove any powder that resulted from tablet deterioration. At each inspection there was a progressively greater wear on the

TABLE II.—TABLET DURABILITY TEST

| Tablet Formula | Time, Min. 15 | 30 | 45 | 60 | 75 | 90 | 105 | 120 |
|---|---|---|---|---|---|---|---|---|
| *1* S[g] | CB[d] | CB | D | D | D | D | D | D |
| OT | A[b] | BB[c] | BB | CB | CB | CB | CB | CB |
| P-OT | A | BB | BB | BB | CB | CB | CB | CB |
| OT-W | A | A | BB | BB | BB | BB | CB | CB |
| *2* H[h] | O[a] | A | A | BB | BB | CB | CB | CB |
| OT | O | O | O | O | A | A | A | A |
| P-OT | O | O | O | O | O | O | A | A |
| OT-W | O | O | O | O | O | O | A | A |
| *3* M[f] | A | BW | BW | BW | BW | CW | CW | CW |
| OT | O | O | A | A | A | A | A | BW |
| OT-W | O | O | A | A | A | A | A | A |
| *4* M | A | A | BW | BW | CW | CW | CW | CW |
| OT | O | O | A | A | A | A | A | A |
| OT-W | O | O | O | O | O | O | A | A |
| *5* S | CB | CB | D | D | D | D | D | D |
| OT | O | A | A | A | BW | CW | CW | D |
| P-OT | O | O | A | A | A | BW | BW | CW |
| OT-W | O | O | A | A | A | BW | CW | CW |
| *6* S | CB | D[e] | D | D | D | D | D | D |
| OT | BW[c] | BW | CB | CB | CB | CB | CB | D |
| P-OT | BW | BW | BW | BW | BW | BW | CW | CB |
| OT-W | A | BW | CW | CW | CB | CB | CB | CB |
| *7* H | BW | BW | CW[d] | CW | D | D | D | D |
| OT | O | A | A | A | A | A | A | BW |
| P-OT | O | O | A | A | A | A | A | A |
| OT-W | O | O | A | A | A | A | A | A |

[a] O, No effect. [b] A, Very slight powdering or chipping of coat. [c] BW, BB, Wearing of edges or breaking of tablet. [d] CW, CB, Coating completely worn off or tablets in small chips and powdering. [e] D, Tablet completely disintegrated. [f] M, Manufacturer's coating. [g] S, Soft punched, as indicated by Monsanto hardness tester. [h] H, Hard punched, as indicated by Monsanto hardness tester.

nontreated tablets compared to that of the DSS coated tablets. The coated soft punched tablets were particularly susceptible to disintegration, which might be attributed to the fact that the coating did not provide enough protection against the prolonged shaking period.

Table II gives the complete results of these tests.

**Shelf-Life Studies.**—Samples of film coated tablets were stored in clear tightly stoppered 2-ounce dry prescription squares for 6 months at temperatures fluctuating between 15 and 37°. The tablets were exposed to indirect sunlight over this period, and the bottles were handled at intervals that would simulate drugstore treatment. Upon examination there were no visual changes to the tablet coatings. There was some apparent, though slight, adhesion of the tablets due to moisture entering the bottles at times of relatively high humidity. This condition was

TABLE III.—TABLET HUMIDITY TEST

| Tablet Formula | Time, Hr. 1 | 3 | 6 | 9 | 24 | 36 | 48 | 60 |
|---|---|---|---|---|---|---|---|---|
| *1* S[g] | A[b] | A | A | A | B | B | C | C |
| OT | A | A | A | B | B | B | C | C |
| P-OT | A | A | A | B | B | B | B | B |
| OT-W | O[a] | A | A | A | B | B | B | B |
| *2* H | O | A | A | A | B | B | B | B |
| OT | A | A | A | A | B | B | B | B |
| P-OT | A | A | A | A | A | B | B | B |
| OT-W | O | O | A | A | B | A | A | A |
| *3* M[f] | O | A | A | B | B | B | C | D |
| OT | A | A | A | B | B | B | C | D |
| OT-W | O | A | A | A | B | B | B | C |
| *4* M | A | A | A | B | B | B | C | D |
| OT | A | A | A | B | B | B | C | D |
| OT-W | O | A | A | A | B | B | C | C |
| *5* S | A | B[c] | B | B | C[d] | C | D[e] | D |
| OT | O | A | B | B | C | C | D | D |
| P-OT | O | A | A | A | B | C | C | D |
| OT-W | O | O | A | A | A | B | C | C |
| *6* S | A | A | A | B | B | C | D | D |
| OT | A | A | A | B | B | C | D | D |
| P-OT | A | A | A | B | B | C | C | D |
| OT-W | O | A | A | A | B | B | C | C |
| *8* H[h] | O | O | A | A | A | A | B | B |
| OT | O | A | A | A | A | A | B | B |
| P-OT | O | A | A | A | A | A | B | B |
| OT-W | O | O | A | A | A | A | B | B |

[a] O, No effect. [b] A, Slight softening of tablet surface. [c] B, Surface coat or surface deteriorated. [d] C, Tablet breaking. [e] D, Complete deterioration of tablet. [f] M, Manufacturer's coating. [g] S, Soft punched. [h] H, Hard punched.

TABLE IV.—TABLET DISINTEGRATION TEST

| Tablet Formula | Control Min.:Sec. | Time Variation for Coated Tablets: OT Min.:Sec. | P-OT Min.:Sec. | OT-W Min.:Sec. |
|---|---|---|---|---|
| 1 | 5:51 | −0:18 | +2:16 | +1:18 |
| 2 | 83:20 | −25:06 | −2:40 | −23:05 |
| 3 | 81:45 | −21:08 | ... | −18:31 |
| 4 | 96:56 | −20:09 | ... | −15:48 |
| 5 | 3:30 | −0:04 | +1:00 | +0:17 |
| 6 | 2:59 | −0:05 | +1:03 | +0:47 |
| 7 | 18:40 | −1:07 | −0:56 | −1:05 |

corrected by the addition of a desiccant packet to each container.

**Humidity Test.**—A glass desiccator equipped with a porcelain crucible holder and crucibles and filled with approximately 2 in. of water acted as a humidity control chamber. The sealed desiccator was allowed to stand 48 hours at 25° before it was used. One tablet was placed in each of the seven crucibles and examined frequently over a period of 60 hours. Duplicate series were performed with each tablet variety.

Table III shows these humidity effects. The tablets coated with DSS and wax polish proved to be most durable in this respect, with the prime coated-DSS coated tablets and the DSS-coated tablets following in that order.

**U.S.P. Disintegration Tests.**—These tests were performed using procedures and equipment prescribed in the U.S.P. XV (9). The temperature of the inner bath of the disintegration unit (Scientific Glass Apparatus Co., Bloomfield, N. J.) was maintained at 37 ± 2°. Distilled water was used as the tablet solvent in the inner bath and was changed with each batch of tablets.

Table IV gives the average results obtained from duplicate tests on six tablets of each type. This table shows that the disintegration rates were not impeded by the DSS coatings. The shortened disintegration time was particularly noticeable with tablets coated only with DSS. This was to be expected as a result of Cooper and Brecht's (10) work with 21 surface-active agents which indicated that DSS was an effective additive to tablet granulations to reduce disintegration time.

## SUMMARY AND CONCLUSIONS

Upon examination of the shortcomings of sugar coatings and the many tests required of these coatings, it can quickly be surmised what constitutes the desirable features of an ideal tablet coating. Once a list of these factors is relatively complete, it can be used as a means of measuring the coating results. An ideal coating must be physically stable, therapeutically compatible, chemically inert, economically feasible and, finally, have a patient product acceptability.

The DSS coating has shown exceptional resistance to heat, light, and trauma; on the other hand, an inherent weakness toward environmental moisture is prevalent. This hygroscopic nature of the compound is a condition that can be counteracted, but still remains a disadvantage as far as this coating is concerned. DSS can serve as a final protective coating for either sugar or uncoated tablets.

The materials in the basic coating formula are quite safe in regard to toxicity. DSS exhibits a very low order of toxicity. The acute oral $LD_{50}$ for mice has been determined to be approximately 1 Gm./Kg. of body weight (11).

The coating is almost completely noncaloric in composition, even when sweetened and flavored. The coating will not hinder disintegration of the tablets; thus, it will not slow therapeutic absorption of the coated drugs.

No incompatibility has been encountered while applying the coating to the various tablets. DSS is compatible with all medications normally dispensed in tablet form.

The chief advantage of film coating is the reduction of operational costs. DSS coatings are easily applied to tablets using conventional coating equipment; therefore, no conversion of equipment now in use is necessary. There is a drastic reduction in the application time of this film coating, with about 1 to 3 hours required to coat a batch of tablets completely. This is far less time than is necessary for the sugar coating operation and, in turn, results in a lowered labor cost. The thinner film coating and resultant small change in tablet weight or size provide a substantial reduction in bottle size, shipping, and storage space needed. Less skill and experience are necessary to employ this coating procedure successfully compared to those required for the sugar coating process.

Probably the most important single factor in the use of medicinal agents today is patient acceptance. The thin coating provides tablets of smaller size so that swallowing is facilitated. Although the DSS coating is odorless, it produces an undesirable bitter aftertaste which can be masked with flavoring agents or limited by a wax polish coating. Since the DSS basic coating is colorless, a wide variety of colors may be employed. This formula gives a uniform, elegant, glossy appearance necessary for favorable acceptance.

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