(*b*) Evaluate the rheological characteristics of the standard material utilizing the hysteresis loop and procedures *C* and *E*.

(*c*) Relate the semisolid formulation under study to the standard material using the hysteresis loop and procedures *C* and *E*. It would be wise to make the comparison at several points in the temperature range 20 to 35° to simulate most temperatures of use.

SUMMARY

1. Some of the advantages and limitations of the Ferranti-Shirley cone and plate viscometer for the evaluation of pharmaceutical semisolids in the shearing region between 0 and 270 sec.$^{-1}$ are discussed.

2. Rheological procedures by which the spreading properties of pharmaceutical semisolids can be reproducibly measured are presented.

3. The usefulness of the data in the cases of white petrolatum U.S.P., white ointment U.S.P., and anhydrous lanolin U.S.P. is discussed.

4. The problem of slippage between the revolving cone and the sample is discussed.

5. Structural breakdown at constant shear, structural breakdown during repetitive cycling, and the structural theory possibly involved in some of the observed rheological changes are discussed.

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Color Stability of Ascorbic Acid Tablets Measured by Light Reflectance

By ROBERT B. WORTZ

The effect of eight commonly used lubricants and glidants on the color stability of ascorbic acid tablets was studied. Light reflectance measurements were used to measure color change after an accelerated aging test. Lubricants low in metallic ion content, such as stearic acid and hydrogenated vegetable oil, conferred maximum color stability to ascorbic acid tablets. The alkaline lubricants such as magnesium and calcium stearate and minerals such as talc and hydrated sodium silico-aluminate were shown to cause excessive color reversion. The importance of humidity control when accelerated test conditions are used to measure the stability of pharmaceutical tablets is shown. Color stability was found to be closely related to chemical stability.

IT IS WELL known that ascorbic acid tablets discolor during storage under normal conditions of temperature and humidity. In fact, tablets stored in closed amber bottles at room temperature will gradually age from a white to a yellowish-brown color. The color stability of ascorbic acid in tablet form is not only affected by conditions of humidity and temperature, but can be influenced by the fillers, lubricants, and binders which are usually found in tablet formulations (1, 2).

Pharmaceutical tablets are often subjected to accelerated aging tests at elevated temperatures and humidities so that color stability may be ascertained rapidly. The end point of most such studies has been visual examination of tablets for color change. However, this type of evaluation is dependent on the judgment of the individual making the observation. No physical measurement is recorded and further deterioration or destruction of sample tablets makes it impossible to compare new samples prepared at a later date.

Light reflectance measurements are widely used by the pulp and paper industry to measure discoloration. The standard brightness test used for evaluating the discoloration of paper measures reflectance in the blue range at 458 mμ (3, 4). This wavelength is considered to give the best measure of yellow color. Such a light reflectance test should be useful in evaluating discoloration of ascorbic acid tablets. Gunsel and Lachman have used light reflectance measurements in comparing formulations containing conventionally processed and spray-dried lactose (5).

The purpose of this study was to determine the effects of lubricants and glidants commonly used in pharmacy on the color stability of ascorbic acid

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tablets. The filler used in most cases was microcrystalline cellulose.

EXPERIMENTAL

Materials—Ascorbic acid used in this study was either the coated, fine crystal, or fine powder grade.[1] The diluents used included microcrystalline cellulose,[2] cornstarch,[3] and spray-dried lactose.[4] Lubricants included in the study were hydrogenated vegetable oil,[5] stearic acid,[6] magnesium stearate,[6] and calcium stearate.[6] The glidants used were submicroscopic pyrogenic silicas,[7] hydrated sodium silico aluminates,[8] and talc.[9]

Sample Preparation—Mixtures of microcrystalline cellulose and ascorbic acid were dry blended with the various lubricants and glidants. Formulations containing starch and lactose were granulated with a 10% starch paste, air dried, and ground through a 30-mesh screen on a Wiley mill. Fifteen grams of each formulation was pressed into 2.25-in. disks using a Carver[10] test cylinder at a pressure of 20,000 p.s.i. The disks were pressed on a Drake hydraulic press.[11] The 2.25-in. disks were used rather than tablets to obtain the necessary surface area for reflectance measurements.

Storage Conditions—The accelerated test conditions used to store the samples were 2 weeks at 40° and 75% relative humidity. Selected samples were also stored for 16 to 32 weeks at 6 different conditions of humidity and temperature. The various humidity conditions were established by storing the samples in closed desiccators containing the saturated salt solutions listed in Table I (6). The

TABLE I—STORAGE CONDITIONS

Saturated Salt Soln.	Temp., °C.	% R.H.
$KC_2H_3O_2$	24	23
$Ca(NO_3)_2$	24	51
NaCl	24	75
KF	40	23
NaBr	40	52
NaCl	40	75

variations in temperature were ±1°. All disks were stored in the absence of light.

Assay of Ascorbic Acid—The ascorbic acid concentrations were determined by the U.S.P. XVI method (7).

Reflectance Measurements—The light reflectance of the disks was measured with a tristimulus reflectometer both before and after the 14-day stability test. A Gardner precision reflectometer exposure head[12] and a Gardner automatic photometric unit were used for the reflectance measurements. Measurements were made using blue, amber, and green light.

[1] Merck & Co., Inc., Rahway, N. J.
[2] Marketed as Avicel PH by FMC Corp., American Viscose Division, Marcus Hook, Pa.
[3] Corn Products Co., New York, N. Y.
[4] Foremost Dairies, Appleton, Wis.
[5] Sterotex, Capitol City Products Co., Columbus, Ohio.
[6] M. W. Parsons, Plymouth Division, New York, N. Y.
[7] Marketed as Cab-O-Sil by Cabot Corp., Boston, Mass.
[8] Zeolex, J. M. Huber Corp., New York, N. Y.
[9] Sierra Talc & Clay Co., Pasadena, Calif.
[10] Fred S. Carver, Inc., Summit, N. J.
[11] Drake Corp., Grand Haven, Mich.
[12] Gardner Laboratories, Bethesda, Md.

RESULTS AND DISCUSSION

The ascorbic acid formulations listed in Table II were pressed into disks and stored for 14 days at 40° and 75% relative humidity. Table III compares the initial and final reflectance values of the disks using green, amber, and blue light. The per cent change in reflectance or the per cent reversion was calculated by the formula:

$$\% \text{ reversion} = \frac{\text{initial reflectance} - \text{final reflectance}}{\text{initial reflectance}} \times 100$$

Calculation of the per cent color reversion enables direct comparison of data without having to compensate for differences in the initial reflectance of each sample.

The color of the disks after the accelerated stability test ranged from off-white to a yellowish-brown color. In all cases the greatest change in reflectance was detected with the blue light. The per cent reversion obtained with the green and amber light was less than one-half the magnitude of that obtained with the blue light. The blue light was also much more sensitive to small color changes. For example, formulation *5* showed a reversion of 8.9% with blue light while reversions of only 2.4 and 1.4% were detected with the green and amber lights. Due to the increased sensitivity of the blue light to color change as the tablets aged, only blue light reflectance values are reported for the remainder of the paper.

The change in reflectance units that could be detected by visual observations was determined. Disks prepared from the same tableting formulation were removed from the oven at close intervals to obtain samples having similar reflectance values. Disks having blue light reflectance values of 89.7, 88.3, 85.9, 84.2, and 82.5 were examined. Five observers arranged the samples in order of decreasing reflectance values. The data demonstrate that a change in reflectance as small as 1.4 units could be detected by visual examination. When this is expressed in terms of per cent color reversion, a change as small as 1.6% could be detected by visual examination. Several observers were able to distinguish between the samples having a reflectance difference as small as 0.8 units. The reproducibility limit of the reflectance measurements was approximately ±0.3 reflectance units.

The data listed in Table III demonstrate a definite relationship between tablet color stability and the lubricants and glidants present in the tablet. Formulations *1*, *2*, *3*, and *4* which contained either magnesium stearate, hydrated sodium silico aluminates, or talc displayed excessive color reversion. However, formulations *5* and *6*, with either stearic acid or hydrogenated vegetable oil as lubricants and pyrogenic silica as a glidant, displayed the same discoloration as the control (formulation *8*).

The formulations described in Table II were assayed for ascorbic acid before and after storage for 2 weeks at 40° and 75% R.H. In Table IV, the assay and the per cent color reversion obtained with blue light are listed. Color stability is shown to be closely related to chemical stability.

To study the separate effect of various lubricants and glidants, blends were made up to contain 69% fine powder ascorbic acid, 30% microcrystalline

TABLE II—ASCORBIC ACID TABLETING FORMULATIONS IN WEIGHT PER CENT

	Formulation							
	1	2	3	4	5	6	7	8
Ascorbic acid fine crystal	60	60	60	60	60	60	60	60
Microcrystalline cellulose	36	37	37	37	37.5	37.5	38.5	40
Stearic acid	..	..	..	..	...	2	...	..
Hydrogenated vegetable oil	..	..	..	2	2	...	...	..
Magnesium stearate	1	2	2	..	...	...	...	..
Hydrated sodium silico aluminates	..	1	..	1	...	...	...	..
Pyrogenic silica	..	..	1	..	0.5	0.5	0.5	..
Talc	3	..	..	..	...	...	...	..
Calcium stearate	..	..	..	..	...	...	1	..

TABLE III—REFLECTANCE VALUES OF ASCORBIC ACID TABLETING FORMULATIONS BEFORE AND AFTER 2 WEEKS' STORAGE AT 40° AND 75% R.H.

Formulation	Green Light			Amber Light			Blue Light		
	Reflectance		%	Reflectance		%	Reflectance		%
	Initial	Final	Reversion	Initial	Final	Reversion	Initial	Final	Reversion
1	94.8	82.5	13.0	96.5	86.8	10.1	89.2	65.5	26.6
2	96.6	70.8	26.7	98.3	76.5	22.2	91.0	50.4	44.6
3	96.1	80.8	15.9	98.0	85.9	12.4	90.7	60.4	33.4
4	95.1	75.5	20.6	97.5	81.3	16.6	89.6	54.2	39.5
5	96.4	94.1	2.4	98.3	96.9	1.4	90.8	82.7	8.9
6	96.6	93.6	3.1	98.4	96.5	1.9	90.9	81.4	10.5
7	96.3	90.7	5.8	98.0	92.2	5.9	91.0	76.4	16.0
8	95.7	92.2	3.7	97.4	94.7	2.8	90.2	81.7	9.4

TABLE IV—CHEMICAL AND COLOR STABILITY OF ASCORBIC ACID FORMULATIONS STORED FOR 2 WEEKS AT 40° AND 75% R.H.

Formulation	Initial Activity, mg./Gm.	Activity After 2 Wk. mg./Gm.	%	% Color Reversion with Blue Light After 2 Wk.
1	270	253	93.7	26.6
2	270	249	92.2	44.6
3	269	255	94.8	33.4
4	270	255	94.4	39.5
5	273	271	99.3	8.9
6	268	266	99.3	10.5
7	269	268	99.6	16.0
8	272	271	99.6	9.4

TABLE V—SEPARATE EFFECTS OF LUBRICANTS AND GLIDANTS ON COLOR REVERSION OF ASCORBIC ACID TABLETS[a]

Sample	Initial Reflectance	Final Reflectance	% Reversion (Blue Light)
Control	94.1	87.5	7.0
Magnesium stearate	94.2	76.0	19.3
Calcium stearate	93.6	81.2	13.2
Stearic acid	92.9	88.8	4.4
Hydrogenated vegetable oil	95.1	88.9	6.5
Hydrated sodium silico aluminates	93.3	57.2	38.7
Talc	94.2	82.4	12.5
Pyrogenic silica	95.1	87.9	7.6

[a] Tablets contained 69% fine powder ascorbic acid, 30% microcrystalline cellulose, and 1% lubricant or glidant. Stored 2 weeks at 40° and 75% R.H.

cellulose, and 1% of the tested material. Data listed in Table V indicate that formulations containing stearic acid, hydrogenated vegetable oil, or pyrogenic silica displayed approximately the same discoloration as the ascorbic acid–microcrystalline cellulose control sample. Discoloration increased markedly over the control when magnesium stearate, calcium stearate, talc, or hydrated sodium silico aluminates were used.

The effect of lubricant concentration on color stability is shown in Table VI. Color reversion increased with lubricant concentration when magnesium stearate and talc were used. However, with stearic acid and hydrogenated vegetable oil, the degree of discoloration was independent of lubricant concentration.

Blaugh, Chakravarty, and Lach (1) have indicated that precoating ascorbic acid with ethylcellulose and granulating with ethylcellulose helped protect against decomposition due to metallic contamination. Coated ascorbic acid is prepared by granulating ascorbic acid with an alcoholic solution of ethylcellulose. To determine if the use of coated ascorbic acid improved color stability in tablets prepared by direct compression, formulations were prepared both with the coated and uncoated ascorbic acid. Various lubricants and glidants were added separately to formulations containing 75 parts ascorbic acid and 33 parts microcrystalline cellulose. Data listed in Table VII demonstrate that, in most cases, no improvement in color stability is gained by using coated ascorbic acid. In fact, formulations with stearic acid or hydrogenated vegetable oil showed greater stability with the regular ascorbic acid. The only significant improvement in color stability with the coated ascorbic acid was in the formulation containing hydrated sodium silico aluminates. There is no apparent explanation for the increased discoloration in the formulations containing coated ascorbic acid.

TABLE VI—EFFECT OF LUBRICANT OR GLIDANT CONCENTRATION ON COLOR STABILITY[a]

Wt. % of Lubricant	% Color Reversion (Blue Light) Magnesium Stearate	Talc	Stearic Acid	Hydrogenated Vegetable Oil
0.0	7.0	7.0	7.0	7.0
0.1	11.0	...	5.4	...
0.3	13.3	...	4.5	...
0.5	17.4	11.4	6.6	6.5
1.0	19.3	12.5	4.4	6.5
1.5	...	...	4.6	...
2.0	...	16.9	...	...

[a] Tablets contained 75 parts fine powder ascorbic acid and 33 parts of microcrystalline cellulose. Stored 2 weeks at 40° and 75% R.H.

TABLE VII—COMPARISON OF COLOR STABILITY OF COATED AND REGULAR ASCORBIC ACID[a]

	% Color Reversion Fine Powder Ascorbic Acid	Coated Ascorbic Acid
Control	7.0	9.0
Magnesium stearate	19.3	21.7
Calcium stearate	13.2	12.3
Stearic acid	4.4	8.9
Hydrogenated vegetable oils	6.5	9.9
Hydrated sodium silico aluminates	38.7	26.3
Talc	21.9	18.0

[a] All blends contained 75 parts of ascorbic acid and 33 parts microcrystalline cellulose. All materials added at a 1% concentration except talc which was present at 3%. Stored 2 weeks at 40° and 75% R.H.

TABLE VIII—COLOR STABILITY OF FORMULATIONS WITH LACTOSE AND STARCH AS FILLERS[a]

	Formulations *9*	*10*	*11*
Ascorbic acid, fine crystal	63.6	82.8	60.0
Microcrystalline cellulose	...	...	37.5
Lactose	17.6	6.4	...
Starch	15.8	6.9	...
Talc	2.9	3.0	...
Magnesium stearate	1.0	1.0	...
Hydrogenated vegetable oil	...	...	2.0
Pyrogenic silica			0.5
	Color Stability		
Initial reflectance	92.3	92.8	92.5
Final reflectance	56.3	58.4	85.8
% reversion	38.3	37.2	7.2

[a] Amount of each ingredient listed as the weight per cent. Stored 2 weeks at 40° and 75% R.H.

Table VIII compares the color stability of tablets containing starch and lactose fillers with those containing microcrystalline cellulose. Since microcrystalline cellulose by itself requires no lubrication in direct compression it is possible to use the less efficient lubricants such as hydrogenated vegetable oil or stearic acid. Formulations *9* and *10* in Table VIII resemble those found in commercial ascorbic acid tablets. The tableting formulation with microcrystalline cellulose as the filler was markedly more stable to color reversion than those containing lactose and starch.

The relationship between the color reversion

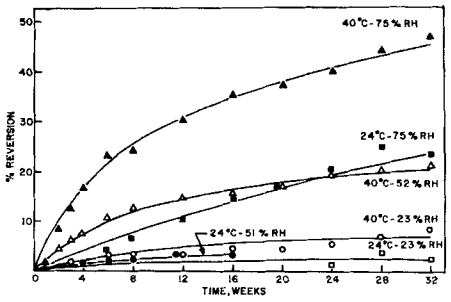

Fig. 1—Per cent color reversion plotted versus *storage time for formulation containing 60% ascorbic acid, 38.5% microcrystalline cellulose, 2% stearic acid, and 0.5% pyrogenic silica.*

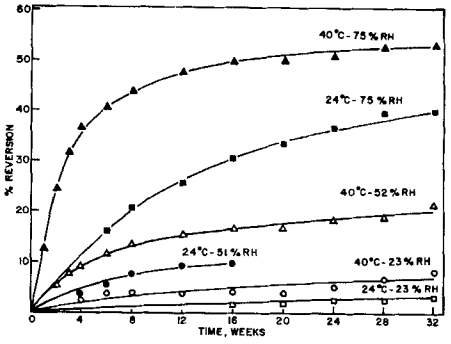

Fig. 2—Per cent color reversion plotted versus *storage time for formulation containing 60% ascorbic acid, 38.5% microcrystalline cellulose, 1% magnesium stearate, 0.5% pyrogenic silica.*

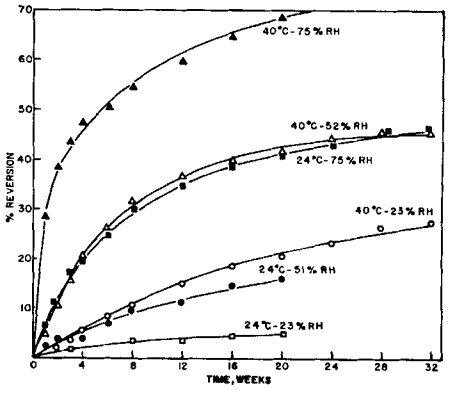

Fig. 3—Per cent color reversion plotted versus *storage time for formulation containing 63% ascorbic acid, 18% lactose, 16% starch, 1% magnesium stearate, 3% talc.*

obtained under accelerated test conditions with that obtained at room temperature was determined. Three formulations that displayed varying degrees of color stability were stored for 16 to 32 weeks under 6 different conditions of temperature and humidity. In Figs. 1, 2, and 3 the per cent color reversion is plotted against storage time. The storage times required for each sample to display a reversion of

TABLE IX—STORAGE TIMES REQUIRED FOR THE FORMULATIONS IN FIGS. 1–3 TO SHOW REVERSIONS OF 10%

Storage Conditions	Storage Time, Days Fig. 1	Fig. 2	Fig. 3
40°, 75% R.H.	5	2	14
40°, 50% R.H.	34	11	42
40°, 23% R.H.	...	50	..
24°, 75% R.H.	25	11	67
24°, 51% R.H.	112	64	..

TABLE X—STORAGE TIMES EQUIVALENT TO 2 WEEKS AT 40° AND 75% R.H.

Storage Conditions	Time, Wk.
40°, 50% R.H.	6–11
40°, 23% R.H.	50
24°, 75% R.H.	8–11
24°, 51% R.H.	45–64

10%, at each condition of temperature and humidity was extracted from the figures and listed in Table IX. These data were used to determine storage times that were equivalent to 2 weeks at 40° and 75% R.H. (See Table X.)

The importance of humidity control, when accelerated test conditions are used to measure color stability, is clearly shown. At a constant temperature, color reversion increased markedly with increasing relative humidity. For example, after 12 weeks' storage at 40°, the formulation listed in Fig. 2 had color reversions of 4, 15, and 47% at relative humidities of 23, 52, and 75%, respectively. The formulations shown in Figs. 1 and 3 displayed approximately the same color reversion when stored at 40° and 52% R.H. or at 24° and 75% R.H. Very little color change was detected in samples stored at 24° and 23% R.H. The accelerated test conditions used, 2 weeks at 40°, and 75% R.H., were shown to be equivalent to approximately 1 year of storage at 24° and 51% R.H.

SUMMARY AND CONCLUSIONS

The light reflectance values of ascorbic acid tablets were measured before and after aging with a tristimulus reflectometer using amber, green, and blue light. The blue light reflectance values were found to be most effective for detecting small color changes in ascorbic acid tablets as they degraded from a white to a yellowish-brown color. The blue light reflectance values correlated closely with color changes detected by visual examination. Color stability was found to be closely related to chemical stability.

The color stability of ascorbic acid tablets was shown to be affected by the lubricants and glidants present in the tablet. Of the seven lubricants and glidants studied, stearic acid, hydrogenated vegetable oil, and pyrogenic silica were found to confer maximum stability to formulations of ascorbic acid. Tablets containing alkaline stearates such as magnesium or calcium stearate and minerals such as talc or hydrated sodium silico aluminate all displayed excessive color reversion. Use of ethylcellulose coated ascorbic acid did not improve color stability of tablets prepared by direct compression.

The importance of humidity control when accelerated stability tests are used to determine tablet stability is clearly shown. At a constant temperature color reversion of ascorbic acid tablets increased dramatically with increasing relative humidities. Two weeks' storage at 40° and 75% R.H. was found to be equivalent to storage for approximately 1 year at 25° and 50% R.H.

The use of reflectance measurements to measure tablet color stability greatly improved the reliability and usefulness of data obtained from accelerated stability tests.

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