Rheological Estimation of the Spreading Characteristics of Pharmaceutical Semisolids

By JAMES C. BOYLAN

A Ferranti-Shirley cone and plate viscometer was utilized to characterize the spreading properties of white petrolatum U.S.P., white ointment U.S.P., and anhydrous lanolin U.S.P. Data were obtained for structural breakdown during repetitive cycling and for structural breakdown at constant shear. The problem of slippage at the revolving cone/sample interface is discussed. An attempt is made to relate rheological differences and molecular structure.

THE EASE of application of a pharmaceutical semisolid to the skin is an important factor in consumer product acceptance. Realizing that each individual applies ointment-like materials to the skin with a slightly different motion, stroke, and rate, any rheological estimation of this process, however good, involves some degree of error. However, good approximations of the shearing rates involved in spreading can still be made. Kostenbauder et al. (1, 2) estimated the shearing rates for a pharmacist compounding an ointment with a spatula and for a consumer spreading ointment on a surface (such as skin) as 200 sec.$^{-1}$ and 120 sec.$^{-1}$, respectively. Interestingly, it was recently shown that for ointments comprised mainly of white petrolatum or white ointment, 120 sec.$^{-1}$ represented the point of greatest resistance to flow at low rates of shear (3). In addition, it was clear from this study that the shearing region of 0 to 250 sec.$^{-1}$ would be important when characterizing the spreading properties of the 13 pharmaceutical semisolids studied.

In recent years significant progress has been made in the area of rheologically defining the spreading and extrusion properties of pharmaceutical ointments and lotions. In particular, Kostenbauder and co-workers (1, 2) and Wood and associates (4–6) have published useful information in this area.

Kostenbauder and Martin (1) after consultation with several dermatologists, grouped pharmaceutical ointments into 3 classes. Ophthalmic ointments, the softest products, constituted class

I. The common medicated ointments, such as ammoniated mercury ointment and boric acid ointment, comprised class II. These products are soft, but stiff enough to remain at the point of application. Class III consisted of protective ointments, such as zinc oxide paste, which are hard and stiff enough to remain at the site of moist, ulcerated areas. Rheological evaluation of various bases selected by dermatologists for these classes indicated that the values in Table I were acceptable guideposts.

Wood and co-workers (4–6) used several techniques to measure a variety of properties concerned with the rheology of pharmaceutical semisolids and lotions. They were able to measure the force required to extrude products from a plastic bottle as a function of bottle design, wall thickness, type of orifice, and rheological character of the contents (4). In another study (5), they used a modified Castor-Severs extrusion rheometer to extrude samples from collapsible tubes and to measure the shear rates involved in simulated high speed tube filling. Wood and his associates (6) also evaluated the increase in tackiness that occurs in some lotions and ointments as they dry. An empirical test was devised that directly measured the cohesive-adhesive capability of skin surface during absorption after rub-in.

The Ferranti-Shirley cone and plate viscometer has instrumental advantages that make it worthwhile to evaluate its usefulness in studying the spreading properties of semisolid materials. These advantages are: the direct recording of a continuous, rather than a multipoint-rheogram, the ease of maintaining a constant shearing rate for an indefinite period of time, and a shearing geometry that (a) closely duplicates that of ap-

TABLE I—AVERAGE CONSISTENCIES OF OINTMENTS AS SELECTED BY PHYSICIANS[a]

| | 125 sec.$^{-1}$ | | 210 sec.$^{-1}$ | |
	Class I	Class II	Class I	Class II
dynes/cm.^{2}	800–900	4000–10000	2000–2500	5000–12000
poises	23–31	30–38	14–18	20–26

[a] Adapted from Kostenbauder and Martin (1). Data were not presented for class III ointments.

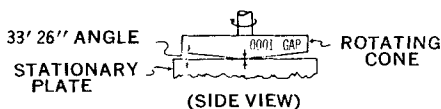33′ 26″ ANGLE   .0001 GAP   ROTATING CONE
STATIONARY PLATE
(SIDE VIEW)

Fig. 1—Schematic representation of the Ferranti-Shirley cone and plate.

plying materials with a circular motion and (b) subjects all portions of the sample to uniform shearing stress (see Fig. 1).

It is the purpose of this paper to illustrate 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.$^{-1}$ and, also, to present rheological procedures for estimating the spreading properties of semisolid materials using this instrument.

EXPERIMENTAL

Materials—The semisolids studied were white petrolatum U.S.P. and anhydrous lanolin U.S.P. These substances were chosen for this study because they are widely used in formulating pharmaceutical and cosmetic products and because they are dissimilar in their spreading characteristics. The white petrolatum was also used to prepare white ointment U.S.P. Storage of all samples was at room temperature.

Rheological Evaluation—The viscometer used in this study was a Ferranti-Shirley cone and plate viscometer[1] equipped with a 400 Gm.-cm. spring, an automatic gap setting device, an *x-y* recorder,[2] and a constant-temperature water bath.[3] The use of this viscometer has been described elsewhere (7). Calibration of the instrument was carried out using N.B.S. standard viscosity oils. The sample to be evaluated (about 1 ml.) was gently put on the plate of the viscometer with a spatula. The plate was immediately raised into position with the cone. The sample then remained undisturbed for 5 min. (to allow temperature equilibration at 30 ± 0.1°) before obtaining the rheogram. All rheograms were obtained using a truncated cone having an angle of 33 min. 26 sec. and a radius of 2 cm.

Procedure A—This procedure was designed to measure the amount of slippage at the cone/sample interface. The instrument was set to achieve a maximum of 100 r.p.m. (1074 sec.$^{-1}$). Using a fresh sample of white petrolatum each time, rheogram upsweep times (0–100 r.p.m.) were 10, 20, 40, 60, 120,

240, 480, and 600 sec. The downsweep time was identical to the upsweep time in each instance.

Procedures B, C, and D—These procedures were designed to measure the amount of structural breakdown at a constant rate of shear (see Table II).

Procedure E—This procedure was designed to measure structural breakdown as a result of repetitive cyclic shearing. The instrument was set to achieve a maximum of 11 r.p.m. (120 sec.$^{-1}$) in 13.3 sec. (instrument sweep time setting of 120 sec.). The downsweep time was identical. Immediately upon completion of the first cycle, the cycle was repeated on the same sample 4 additional times. Then a 6th cycle was immediately run utilizing a maximum r.p.m. of 100 (1074 sec.$^{-1}$).

Procedure F—This procedure was identical to procedure E in every respect except one—25 r.p.m. (270 sec.$^{-1}$) was the maximum r.p.m. for the first 5 cycles, instead of 11 r.p.m.

Tackiness—None of the procedures used was intended to measure tackiness. For this, special instrumentation, such as the modified tackmeter described by Wood and Lapham (6), is needed.

RESULTS AND DISCUSSION

Slippage—Evidence of slippage between the rotating member of the viscometer and the sample, resulting in reproducible artifacts, has been observed by several authors working with pharmaceutical substances. To minimize this problem, Kostenbauder and Martin (1) found it necessary to have a grooved bob prepared for the modified Stormer viscometer. Likewise, Wood and co-workers (4) "ribbed" the bobs for their Hercules Hi-Shear viscometer.[4] Wood attributes this artifact to the development of slippage planes at the wall-sample interface (artifact) and compares it with internal sample slippage planes (true yield value). Bruss (8) advocates the use of a star-shaped rotor. A star-shaped rotor is commercially available with the Haake Rotovisco viscometer.[5]

The Ferranti-Shirley viscometer used in this study offers another approach to the solution of this problem. The portions of rheograms shown in Figs. 2 and 3 illustrate the dramatic effect that the speed at which the shearing rate is increased can have on the rheogram. These data were obtained by procedure *A*. A comparison of Figs. 2 and 3 shows also that interpretation of the upcurve suffers more severely than does interpretation of the downcurve. The downcurve patterns show that shearing to 1074 sec.$^{-1}$ has destroyed most of the structure and also the rotating cone has been able to "catch up" and minimize any slippage effect.

It is felt that when using the Ferranti-Shirley cone and plate viscometer with semisolids, proper

TABLE II—RHEOLOGICAL PROCEDURES USED TO MEASURE STRUCTURAL BREAKDOWN AT A CONSTANT RATE OF SHEAR

Procedure	Max. r.p.m.	Shearing Time (0 to max. r.p.m.), sec.	Time Held at Max. r.p.m., sec.	Shearing Time (Max. r.p.m. to 0), sec.
B	11 (120 sec.$^{-1}$)	67[a]	40	67[a]
C	11 (120 sec.$^{-1}$)	1[b]	40	1[b]
D	25 (270 sec.$^{-1}$)	2.5[b]	40	2.5[b]

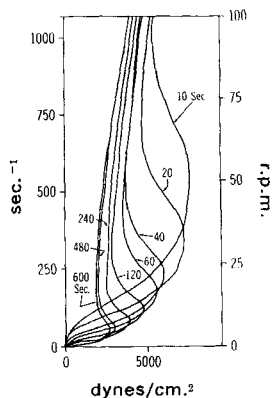[a] Sweep setting of 600 sec.   [b] Sweep setting of 10 sec.

Fig. 2—The effect of sweep time on the ascending portion of the white petrolatum U.S.P. rheogram.
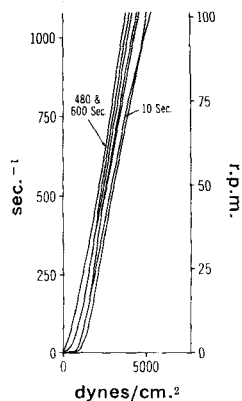

Fig. 3—The effect of sweep time on the descending portion of the white petrolatum U.S.P. rheogram.

into account when interpreting the rheograms. Typical results are shown in Figs. 4 and 5.

Procedure *B* was disappointing as a technique. It was readily apparent from Fig. 4 that when using procedure *B* much structural breakdown had occurred before reaching 120 sec.$^{-1}$.

The information gained from procedures *C* and *D* (Fig. 5) illustrates the importance of maintaining a constant maximum r.p.m. for reproducible and comparative results. Slippage is very evident in this figure. To follow structural breakdown from figures similar to Figs. 4 and 5, while at the same time eliminating slippage artifacts, the reduction in dynes/cm.^{2} was ignored for the constant shear interval 0–10 sec. The data obtained with procedures *C* and *D* are shown in Fig. 6. From Fig. 6 it can be seen that, as shearing continues (10–20 sec., 20–30 sec., 30–40 sec.) breakdown becomes proportionately less (*i.e.*, most structural breakdown occurs early).

When using the 400 Gm.-cm. torque spring, only white petrolatum and white ointment could be measured satisfactorily at 270 sec.$^{-1}$. In Fig. 6 it is interesting to compare the 270 sec.$^{-1}$ and the 120 sec.$^{-1}$ curves for these semisolids. The 270 sec.$^{-1}$ curves do not follow an apparent first-order
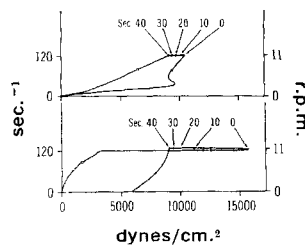

Fig. 4—Typical rheograms of anhydrous lanolin U.S.P. obtained using procedures B (top) and C (bottom).

sweep time selections can overcome serious slippage artifacts. Accordingly, it was not felt advisable to score the cone used for this study. However, the warning is clear. Each laboratory must recognize that this problem exists and determine how serious a problem it is for their particular instrument and samples, and deal with it accordingly.

Structural Breakdown at Constant Shear— Procedures *B*, *C*, and *D* were used to gather data on structural breakdown at constant shear. Two approaches were tried. Procedure *B* permitted a very slow increase in shearing rate in an attempt to minimize cone/sample slippage during measurement. Procedures *C* and *D* relied on a minimum of time being spent in the interval 0 to 120 sec.$^{-1}$ or 0 to 270 sec.$^{-1}$ to minimize prebreakdown of structure before the 120 sec.$^{-1}$ or 270 sec.$^{-1}$ constant shear rate. It was recognized that procedures *C* and *D* would be subject to cone/sample slippage artifacts, but it was felt that this could be taken
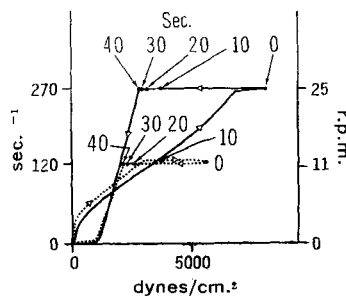

Fig. 5—Typical rheograms of white petrolatum U.S.P. obtained using procedures C (---) and D (——),
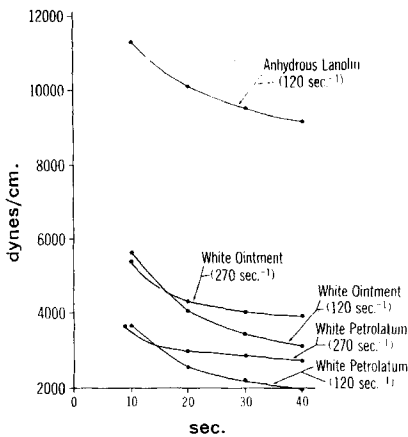
Fig. 6—*Structural breakdown at constant shear. Data obtained using procedure* C *(120 sec.⁻¹ max.) and procedure* D *(270 sec.⁻¹ max.)*
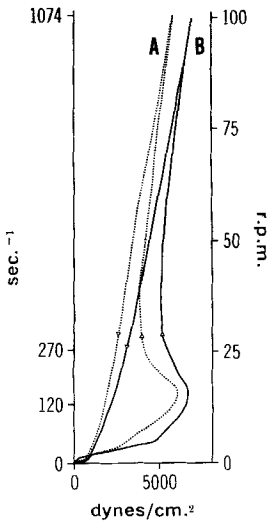

Fig. 7—*Rheograms obtained using an upsweep time of 120 sec. Key: A, white petrolatum U. S. P.; B, white ointment U. S. P.*
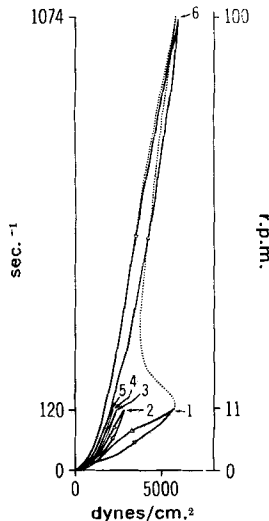

Fig. 8—*The effect of repetitive cyclic shearing (procedure E, 6 cycles) on white petrolatum U. S. P. The dotted line is from Fig. 7.*

pattern, whereas the 120 sec.⁻¹ curves do. In both instances the white ointment has a greater resistance to flow and in both instances an approximately equal difference is maintained between the white ointment and white petrolatum for the interval 10–40 sec. This can be explained by the fact that while the white wax in the ointment is dispersed throughout the petrolatum it does not contribute to chemical structure, only to stiffness. Furthermore, microscopic examination shows the white wax particles to be unaffected as a result of shearing.

One feature of the curves in Fig. 6 for white ointment and white petrolatum that at first glance appears unusual is that apparently less structural breakdown occurs at 270 sec.⁻¹ than at 120 sec.⁻¹. Intuitively it would be expected that the higher constant shearing rate would cause a greater breakdown of structure. This is not so and can best be explained by referring to Fig. 7. Here it can be seen that for white petrolatum and white ointment much structural breakdown has already occurred by the time 270 sec.⁻¹ has been reached.

Also from Fig. 6 it is readily seen that even after 40 sec. of shearing at 120 sec.⁻¹ anhydrous lanolin is still over twice as stiff as white ointment or white petrolatum were after only 10 sec. of shearing.

This type of information regarding structural breakdown is among the most useful data obtainable from a rheological study.

Structural Breakdown by Repetitive Cyclic Shearing—Procedures *E* and *F* were used to gather data on structural breakdown by repetitive cyclic shearing. It was quickly evident that the 25 r.p.m. used in procedure *F* was sufficient to destroy most of the structure on the first cycle. Consequently, the data were collected using procedure *E* (11 r.p.m. maximum). Typical results obtained for white petrolatum are shown in Fig. 8. For all 3 ointment bases studied the trend is similar; namely, the major structural change occurs during the first cycle. Breakdown continues linearly, but very slowly, as cycling continues (Fig. 9). Finally, when the 6th cycle (0–100 r.p.m.) is run, it nearly coincides with portions of the 1 cycle 0–100 r.p.m. rheogram for white petrolatum (Fig. 8, dotted line). Figure 8 is an excellent example of the effect previous sample shearing can have on results and why it is
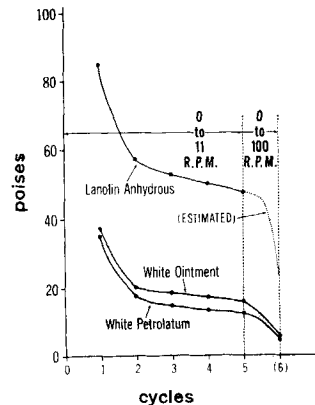

Fig. 9—*Structural breakdown during repetitive cyclic shearing. Data obtained using procedure* E.

TABLE III—FATTY ACIDS OF LANOLIN ISOLATED BY WEITKAMP (12)

Series	Structural Formula	n
Normal	CH_3—$(CH_2)_{2n}$—$COOH$	4 to 12 incl.
2-Hydroxyl	CH_3—$(CH_2)_{2n-1}$—CH—$COOH$ $\mid$ OH	6, 7
iso	CH_3—CH—$(CH_2)_{2n}$—$COOH$ $\mid$ CH_3	3 to 11 incl.
Anteiso	C_2H_5—CH—$(CH_2)_{2n}$—$COOH$ $\mid$ CH_3	2 to 13 incl.

essential to run samples that have been equilibrated with respect to structure as well as temperature.

The data obtained using procedure E are shown in Fig. 9. This figure clearly shows that although structural breakdown during repeated cycling with anhydrous lanolin occurs at a faster rate than with either white petrolatum or white ointment, it still possesses more than twice the viscosity of either other vehicle. This agrees well with data obtained under constant shear conditions (Fig. 6).

Structural Changes with Shear—*White Petrolatum*—Despite the widespread use of white petrolatum, much remains unknown regarding its composition. Franks (9) attributes this lack of knowledge to the formidable problems of analysis and the general familiarity and satisfaction with the material.

Variation from lot to lot of white petrolatum may be due to several factors. These include (9): (*a*) the type of crude oil started with, (*b*) the extent to which the volatile oils are removed during distillation, (*c*) whether any refining is done before dewaxing, (*d*) the type of process used for separating waxy constituents, (*e*) the viscosity and other characteristics of the oil used to soften the crude petrolatum before refining to U.S.P. specifications by filtration.

Schulte and Kassem (10) separated petrolatum into *n*-, iso-, and cyclic paraffin fractions. Their experiments showed that the rheological properties of petrolatum are determined by the ratio of these constituents to each other, the best pharmaceutical petrolatums containing a low content of *n*-paraffins. During mechanical strain, structural collapse of isoparaffins is less than *n*-paraffins. Schulte and Kassem feel a principal reason for this is because isoparaffins form a finer crystallite gel structure. A fine crystallite structure is less susceptible to mechanical strain than is a large crystallite structure. Also, as the crystallite size decreases, the viscosity of the petrolatum increases.

An explanation for the "bulge" in the upcurve of the rheograms of white petrolatum and white ointment and also the breakdown at constant shear rates for these products may be as follows. At rest, the petrolatum structure is probably a three-dimensional gel comprised of *n*-, iso-, and cyclic paraffins attached through random entanglement and chemical bonding. As the shear rate increases the *n*-paraffins tend to align in the direction of shear, whereas the iso and cyclic paraffins cannot align as readily and serve to retain some of the three-dimensional character of the system. As the shear rate further increases, the paraffins become further

aligned concurrent with rupture of some of the entangled paraffin chains. At this point, the difference between the upcurve and downcurve becomes minimal.

Anhydrous Lanolin—Since lanolin is a product of animal synthesis, it shows a great deal of variation due to differences in heredity, environment, and age of the animal, time of shearing, age and storage conditions of the greasy wool, and variations in lanolin processing (11).

Purified anhydrous lanolin contains approximately 96% esters, 2% free alcohols, 1% free fatty acids, and 1% hydrocarbons (11). The alcohols that result from saponification of the esters of lanolin, and the free alcohols, can be classified as aliphatic, triterpene, or sterol. The aliphatics comprise about 23% of the total alcohols. Most of these are normal (C_{18}–C_{26}) or branched (C_{17}–C_{25}) chain alcohols. Triterpene alcohols, principally lanosterol and dihydrolanosterol, constitute about another 25%. Sterols (mostly cholesterol) comprise about 30% of the alcohols in lanolin. At present about 20% of the lanolin alcohols remain unclassified (11).

Weitkamp (12) formed the methyl esters of lanolin fatty acids, fractionated them by vacuum distillation, and identified 32 acids. Table III summarizes his results.

As was the case with white petrolatum, it is difficult to visualize what is occurring when anhydrous lanolin is mechanically sheared. There is undoubtedly some alignment of long-chain molecules in the direction of shear and some rupturing of weak chemical bonds at higher shear rates. Any additional speculation is hindered by the unknown constitution and complexity of lanolin.

Recommended Plan of Approach for Evaluating Spreading Properties—On the basis of the findings discussed above, it is apparent that when a user applies white petrolatum or anhydrous lanolin to the epidermis, or a pharmacist levigates these materials, the first few seconds of shearing stress serve to destroy much of the structural integrity, making the use of these materials much easier. This is desirable from a user's acceptance viewpoint. In addition, differences among the common ointment bases studied are great enough to allow a ranking of formulas. The following procedure would appear to be useful when using the Ferranti-Shirley cone and plate viscometer to evaluate the spreading properties of pharmaceutical semisolids.

(*a*) Establish a semisolid material as a standard of acceptable spreadability. This should involve the judgment of several experienced people.

(*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