

granules to a maximum, following which a decrease was obtained upon addition of more finer particles. The maximum flow rate was specific for each binary component system and varied with the concentration and size of the added particles.

(b) Flow rates of granulations were found to vary considerably, depending upon the degree of wetness and upon the granulating agent used. Granulating agents in order of increasing effectiveness were: 10% starch, 2% methylcellulose, 10% PVP, 10% gelatin, and 10% methylcellulose.

(c) Faster flow rates of granulations and blended systems of various particle size distributions were associated with an increase in proportion of 10/60 mesh granules and a decrease in proportion of <100 mesh granules.

(d) Effectiveness of glidants was found to be dependent upon particle size of the granules to which they were added. Cornstarch and <100 mesh particles of the same material were found to be more effective for coarse particles; whereas, fumed silicon dioxide, talc, and magnesium stearate were more effective with finer particles.

#### REFERENCES

- (1) Augsburg, L. L., and Shangraw, R. F., *J. Pharm. Sci.*, **55**, 418(1966).
- (2) Knoechel, E. L., Sperry, C. C., and Lintner, C. J., *ibid.*, **56**, 116(1967).
- (3) Tucker, S. J., and Hays, H. M., *J. Am. Pharm. Assoc., Sci. Ed.*, **48**, 362(1959).
- (4) Hammerness, F. C., and Thompson, H. O., *ibid.*, **47**, 58(1958).

- (5) Crosby, E. J., *Am. Perfumer Aromat.*, **43**, 75(1960).
- (6) Nelson, E. J., *J. Am. Pharm. Assoc., Sci. Ed.*, **44**, 435(1955).
- (7) Neumann, B. S., "Flow Properties of Disperse Systems," Interscience Publishers, Inc., New York, N. Y., 1953, Chap. 10.
- (8) Craik, D. J., *J. Pharm. Pharmacol.*, **10**, 73(1958).
- (9) Craik, D. J., and Miller, B. F., *ibid.*, **10**, 136T(1958).
- (10) Pilpel, N., *ibid.*, **16**, 705(1964).
- (11) Gold, G., Duvall, R. N., Palermo, B. T., and Slater, J. G., *J. Pharm. Sci.*, **55**, 1291(1966).
- (12) *Ibid.*, **55**, 1133(1966).
- (13) Snedecor, G. W., "Statistical Methods," 5th ed., The Iowa State University Press, Ames, Iowa, 1956, p. 413.
- (14) Jones, T. M., and Pilpel, N., *J. Pharm. Pharmacol.*, **18**, 429(1966).
- (15) Dixon, W. J., and Massey, F. J., Jr., "Introduction to Statistical Analysis," 2nd ed., McGraw-Hill Book Co., Inc., New York, N. Y. 1957, p. 139.
- (16) Huntsberger, D. V., "Elements of Statistical Inference," Allyn and Bacon, Inc., Boston, Mass., 1961, p. 203.
- (17) Goedicke, V., "Introduction to the Theory of Statistics," Harper and Brothers, New York, N. Y., 1953, p. 155.
- (18) Munzel, K., "The Influence of Glidants on the Flow Properties of Granules," First Industrial Pharmaceutical Conference, Land O'Lakes, Wis., June 1959.
- (19) Burak, N., *Chem. Ind.* 1966, 844.



#### Keyphrases

Granule flow—factors affecting  
Lactose granules—wet granulation  
Flow rate—granulating process effect  
Particle size—flow rate effect  
Glidant—flow rate, granules

## Rheologic Studies on Dermatologic Lotions

By IVO SETNIKAR, GIUSEPPE GÁL, and SERGIO FANTELLI

The rheologic properties of some dermatologic lotions were studied. The changes in the viscosity, thixotropy, and yield value of the lotions during storage and following various degrees of agitation were recorded. The relevance of these phenomena to production processes and to therapeutic use are discussed. The range of optimum viscosity values of dermatologic lotions is indicated.

**D**ERMATOLOGIC LOTIONS are milky, fluid pharmaceutical preparations consisting of a disperse phase of liquid or solid particles in a predominantly aqueous phase.

The rheologic properties of lotions are generally of non-Newtonian type. Indeed, their viscosity often depends upon the shear rate and may be of the dilatant, pseudoplastic, plastic, or Bingham type. They may even exhibit an isothermic reversible decrease in viscosity after an imposed shear rate (thixotropy) or an increase in viscosity (rheopexy).

It is important to know the rheologic properties of a lotion, and the changes they undergo during preparation and during storage in order to adapt

the manufacturing operations to these properties and ensure that the lotion possesses the most suitable rheologic properties when it is used therapeutically; few studies on these lines have been published. Woodman and Marsden (1) described the thixotropic properties of a lotion they had prepared. They used "Rheomat" and "Rotovisco" viscosimeters, which involve decanting the lotion into the viscosimeter vessel to measure the viscosity, an operation that alters the rheologic status of a sample with pronounced thixotropic or rheopexic properties.

The ideal instrument for defining the rheologic properties of lotions should (a) permit measurement at various shear rates, and (b) not require decanting, so that the viscosity of a lotion is not altered before measurement. The latter point is

Received June 13, 1967, from the Research Division, Recordati s.a.s., Milano, Italy.

Accepted for publication October 12, 1967.

especially important when checking after an interval of time, for the viscosity of a lotion is liable to undergo considerable change during storage. Not even the thixotropic effect can be determined correctly if the lotion has been subjected to shear, *e.g.*, as with decanting. Of the various types of instruments, reviewed by Bottoni (2), neither capillary viscosimeters (Ostwald, Ubbelohde) nor falling (Hoepler) or ascending sphere viscosimeters (Cochins) comply with either of the requisites specified above. Brebender, MacMichael, or Ferranti-Shirley viscosimeters permit the study of viscosity in very precisely defined geometric and dynamic conditions, but they require decanting of the liquid and so do not comply with requirement *b*. Brookfield's viscosimeter does not allow the strict definition of geometric and dynamic conditions and so yields conventional viscosity values; on the other hand, it does not require decanting of the liquid, and so it complies with condition *b*.

The authors used Brookfield's viscosimeter for their investigations, as it was felt that it was more important to define thixotropy or rheopexy and changes in viscosity after a long storage than it was to obtain viscosity values that are only formally more accurate using other viscosimeters.

## EXPERIMENTAL

**Rheologic Determinations**—The Brookfield RVF viscosimeter was used, calibrated with Brookfield L-3 standard fluid (10 poise at 25°).

The determinations were made at 24° on 600 ml. of lotion in containers with a diameter of 9 cm. To alter the physical status of the sample as little as possible, the spindle was introduced edgewise and very gently into the sample, thus ensuring the minimal shear and the absence of air bubbles on the undersurface of the spindle. The spindle was then screwed on to the apparatus and readings were taken, starting at the lowest speed (2 r.p.m.). The maximum shear stress value shown on the instrument was recorded and readings were taken in the same way at 4, 10, and 20 r. p. m. ("up" curve). Immediately after the sample was subjected in the same container, for 3 min., to the action of a stirrer with two blades (each of 45 × 25 mm.) spinning at 100 r.p.m. The viscosimeter readings were then taken again at decreasing spindle speeds, from 20 to 2 r.p.m. ("down" curve).

The "initial yield value," that is, the maximum stress value required before shear starts, was determined by extrapolating the rheograms up to the intersection with the abscissa (shear rate = 0).

**Composition and Method of Preparing the Lotions**—The compositions are specified in Table I. Lotions 1 and 2 were prepared by melting at 70° and mixing stearic acid, esters of saturated fatty acids, sorbitan monopalmitate, and polyoxyethylene sorbitan monolaurate and dissolving the propyl-*p*-oxybenzoate in this mixture. The deionized water was heated in another container to 70° and the

TABLE I—COMPOSITION OF LOTION BASES

Constituents	Gm./100 ml.		
	Lotion 1	Lotion 2	Lotion 3
Stearic acid	1.00	1.00	...
Esters of saturated fatty acids	6.00	6.00	...
Sorbitan monopalmitate	4.50	6.00	...
Polyoxyethylene sorbitan monolaurate	2.00	2.00	...
Cetostearyl alcohol	...	...	3.00
Cetylpolyglycol ether	...	...	0.60
Propylene glycol	5.00	5.00	5.00
Methyl- <i>p</i> -oxybenzoate	0.15	0.15	0.15
Propyl- <i>p</i> -oxybenzoate	0.03	0.03	0.03
Deionized water <i>q.s. to:</i>	100 ml.	100 ml.	100 ml.

methyl-*p*-oxybenzoate was dissolved therein. The oily phase was poured into the aqueous phase and this mixture was passed through an ALM-O homogenizer (Auguste and Moutis, Paris). The lotion was cooled while stirring and, at 30°, the propylene glycol was added.

**"Farmomac" Metering-Bottling Machine**—Some samples of the lotions were put through the metering-bottling machine used in manufacturing, with a view of studying the effects of this machine on the rheologic properties of the lotions. The metering-bottling machine was the "Farmomac F 37," made by Messrs. Farmomac of Bologna. Basically it is a syringe by which a certain volume of lotion is sucked, and through an inlet-outlet valve is injected into the final containers. Suction and filling, advancement, and container closure is automatic and may be performed under sterile conditions. The measured volume can be regulated between 0 and 100 ml. and the advancement speed up to 4,500 bottles/hr. From the hydrodynamic point of view the maximum shear of the liquid is reached in the valve and in the bottling needle, with shear rates depending on the delivered volume and on the advancement speed. Under these working conditions the maximum shear rate was approximately 2000 sec.<sup>-1</sup> with a duration of 0.5 sec.

## RESULTS

**Influence of the Number of Revolutions of the Spindle on the Viscosity of the Sample**—When the viscosimeter is set in motion the pointer quickly marks the maximum value and then begins to fall back because of the thixotropy of the lotion (Fig. 1). The maximum viscosity value found is thus the closest value to the true viscosity of the sample before it is affected by thixotropy. The viscosity readings were therefore always compared to this maximum value obtained by noting the position of the pointer during the first revolutions of the spindle and stopping the viscosimeter when the pointer reached the highest position on the dial (usually at the third revolution).

**Rheologic Properties of the Lotions Being Tested**—The consistency curves before and after stirring

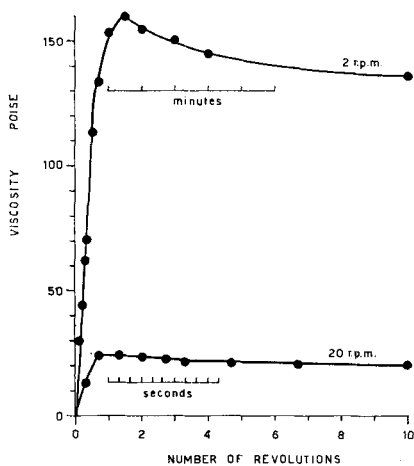


Fig. 1—Changes of viscosity during measurement. Spindle No. 2, 24°, at 2 r.p.m. (approx. 0.6 sec.<sup>-1</sup> shear rate) and at 20 r.p.m. (approx. 6 sec.<sup>-1</sup> shear rate). Viscosity appears related to the number of revolutions of the spindle.

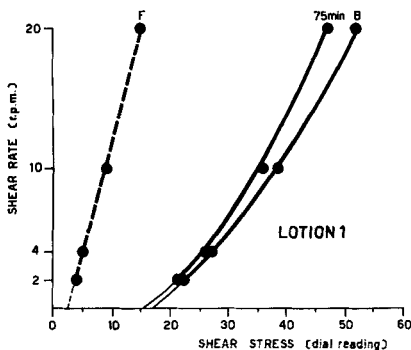


Fig. 2—Lotion 1, spindle No. 2, 24°. Rheogram before (B) and after 75 min. (75) stirring. The dash-line curve (F) is the rheogram after the run through the Farmomac. B is the up curve, the others are down curves.

are given in Figs. 2-4. The viscosity tends to decrease as the shear rate increases and the consistency curve extrapolates to a defined stress value (yield value). The behavior is characteristic of a Bingham-type non-Newtonian liquid.

Stirring diminishes the viscosity and the yield value. The lotions thus show evidence of thixotropy.

Certain types of agitation, such as occur in the Farmomac, may on occasion produce a viscosity which is higher than the lowest viscosity reached by "gentle" stirring.

**Dependence of Thixotropy Upon the Type and Duration of Agitation**—Figures 2-4 show that the degree of thixotropy depends upon the intensity (*cf.* the F curves) and upon the duration of shear. The two factors must therefore be distinguished and accurately defined when analyzing the thixotropic phenomena. This distinction was drawn by Green and Weltmann (3), who quantified the thixotropic breakdown "by time" and "by velocity."

With traditional methods the thixotropic breakdown measurement is based on the shear imposed by the viscosimeter itself (*cf.* 4) and evaluated by the difference between the "up" and the "down" curve.

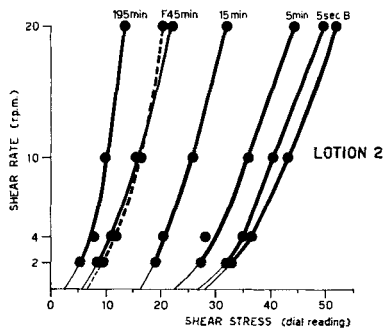


Fig. 3—Lotion 2, spindle No. 2, 24°. Rheogram before (B) and after different times of stirring. The total time of stirring to which the sample was subjected is shown. The dash-line curve (F) is the rheogram of the lotion after the run through the Farmomac. B is the up curve, the others are down curves.

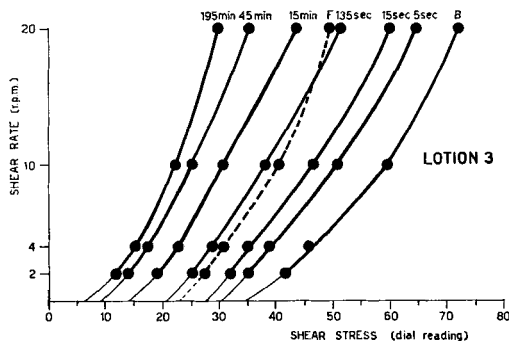


Fig. 4—Lotion 3, spindle No. 2, 24°. Rheogram before (B) and after different times of stirring. The total time of stirring to which the sample was subjected is shown. The dash-line curve (F) is the rheogram of the lotion after the run through the Farmomac. B is the up curve, the others are down curves.

The total shear thus gradually increases from beginning to end of the determination and is not constant in intensity. The result is a loop expressing a superposition of time and intensity of shear that is difficult to analyze.

If a defined quantity of shear is interposed between the consistency measurements, distinct and nearly parallel curves are obtained instead of loops (Figs. 2-4). The distance between the initial (up) curve and the curves after shears of different duration (down curves) expresses thixotropy by time.

The curves obtained differ from those worked out by Green and Weltmann (3) for other types of fluids, because there is also a decrease in yield value [thixotropic coefficient of Goodeve (5)]. Perhaps the difference is due partly to our method, which results in determinations that are less biased by initial thixotropic phenomena, since the operations preceding the determination are less destructive on the structure of the samples.

**Effects of the Composition of the Lotion**—An alteration of the quantities of the constituents obviously alters the rheologic properties of the lotion, including the thixotropic phenomena. This is illustrated by Figs. 2 and 3, referring to lotions with a different quantitative composition, and by Fig. 4, referring to a lotion with a different qualitative composition.

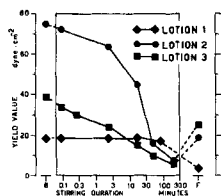


Fig. 5—Yield values at 24° observed for 3 lotions before (B) stirring, after stirring for various periods, and after passage through the Farmomac (F). The values were obtained by extrapolating on the abscissa the consistency curves of Figs. 2-4.

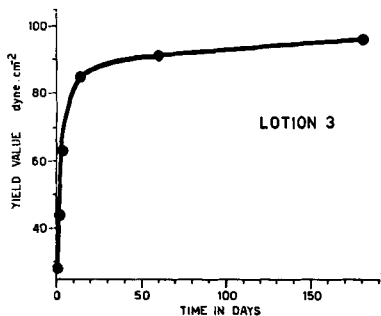


Fig. 6—Lotion 3. Yield values at 24° observed after storage for various periods. This batch of lotion 3 differs from that of Fig. 4.

In Fig. 2 the thixotropy, as a result of 75 min. stirring, is less evident than in the case of Fig. 3. Passage through the bottling machine considerably lowers the viscosity. In Figs. 3 and 4 the thixotropy is marked and the run through the bottling machine determines, in contrast to what happens in Fig. 2, a viscosity intermediate between the initial viscosity and the minimum obtainable with gentle stirring. This effect could be due to a change in particle size or shape or to rheopectic phenomena.

**Yield Value**—The yield value estimates obtained by means of the Brookfield viscosimeter are represented by a torque and must be referred to the spindle used. To obtain the yield value in dynes·cm.<sup>-2</sup>, the following formula may be used:

$$Y = \frac{m}{2\pi r^2 \cdot r \sqrt{1/2}} = \frac{m}{4,986 \cdot r^3} \quad (\text{Eq. 1})$$

where  $Y$  = yield value in dynes·cm.<sup>-2</sup>;  $m$  = torque measured in dynes·cm., referred to the intercept of the consistency curves with the shear stress axis; and  $r$  = radius of the spindle in centimeters.

Figures 2-4 show that the lotions considered always exhibit a yield value greater than zero.

The yield value changes as a result of stirring. Figure 5 shows the decreases in yield value for the

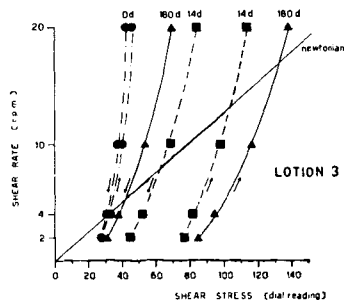


Fig. 7—Lotion 3 (different batch from that of Fig. 4). Consistency curves at 24°. The initial (0 d) up and down curves and the up and down curves after 14 days (14 d) and after 180 days (180 d) are shown. The straight line represents the consistency curve of a Newtonian liquid. As a rule, spindle No. 2 was used. For the 14-day and 180-day samples, spindle No. 3 was used as well. The values were then referred to spindle No. 2 by extending the scale of the abscissas beyond the value 100.

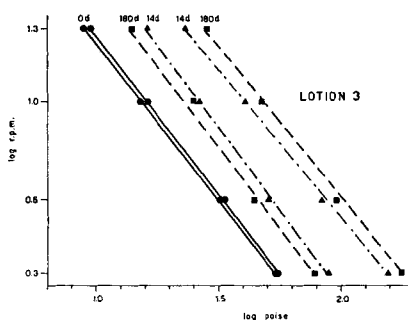


Fig. 8—Results of Fig. 7 plotted on a diagram in which the ordinate is log r.p.m.; the abscissa log poise. By this means the experimental points are on a straight line.

three lotions after different periods of stirring and after passing through the Farmomac.

The yield value of a lotion may increase during storage. An example of this is shown in Fig. 6 which refers to lotion 3.

**Changes in Viscosity and Thixotropy During Storage**—Five samples of lotion 3 were stored in sealed containers at 24° and not moved until viscosimetry. The viscosity and thixotropy values are given in Table II and in Fig. 7.

The viscosity increases considerably with time, i.e., about threefold after 6 months' storage. The thixotropy increases also: evaluated as average percentile decrease of viscosity after standardized stirring it is about 6% in the freshly prepared lotion and rises to 55% after 6 months' storage.

The Fig. 7 viscosity data are drawn in Fig. 8 on a diagram with poise and r.p.m. values in logarithmic

TABLE II—VISCOSITY OF LOTION 3 AFTER MOTIONLESS STORAGE AT 24° FOR VARIOUS INTERVALS OF TIME

r.p.m. of Spindle	Initial		Viscosity in Poise									
	B <sup>a</sup>	A <sup>b</sup>	After 1 day		After 3 days		After 14 days		After 60 days		After 180 days	
			B	A	B	A	B	A	B	A	B	A
2	55	55	83	65	118	76	155	88	165	90	176	78
4	33	31.5	47	37.5	66	44	82.5	50	90	52.5	92.5	44
10	16	15	22.8	18.2	30.8	22	40	26	45	28	47	22
20	9.4	8.8	13.2	11	18	13.6	23	16	27.6	17.5	28	14

<sup>a</sup> Columns B show the values before stirring. <sup>b</sup> Columns A show the values recorded after stirring at 100 r.p.m. for 3 min.

TABLE III—VISCOSITY IN POISE DETERMINED AT 2 r.p.m. AND AT 24° ON FOUR BATCHES OF LOTION 1 OBSERVED AFTER SEVERAL STORAGE PERIODS

No. Days After Preparation	Batch 1		Batch 2		Batch 3		Batch 4	
	N <sup>a</sup>	F <sup>b</sup>	N	F	N	F	N	F
0	23	2.5	19	3.3	15.8	3.8	20.3	2.8
7	39	1.8	32	3				
17	45	1.8	37	3				
35	45	1.8	39	2.5	30.5	5	42	2
56	47	1.7	52	3.5				
75	50	2.8	53	4.3				

<sup>a</sup> Columns N give the values observed on samples not run through the Farmomac. <sup>b</sup> Columns F give the values for the samples run through the Farmomac on the day of preparation.

TABLE IV—VISCOSITY IN POISE RECORDED AT 2 r.p.m. AND AT 24° ON TWO BATCHES OF LOTION 1 IMMEDIATELY AFTER PREPARATION AND AFTER 75 DAYS STORAGE

Batch	Initial			After 75 Days Storage					
	B <sup>a</sup>	A <sup>a</sup>	Δ <sup>b</sup>	Not Run Through Farmomac			Run Through Farmomac		
	B	A	Δ	B	A	Δ	B	A	Δ
1	23	22	1	50	34	16	2.8	3.3	-0.5
2	19	17	2	53	33	20	4.8	4.5	-0.3

<sup>a</sup> Columns B and A show the values before (B) and after (A) agitation at 100 r.p.m. for 3 min. <sup>b</sup> Columns Δ give the difference between A and B, an index of thixotropy.

scales. By this means the experimental points can be aligned in straight lines and described empirically by

$$\ln v = -A \ln s + B \quad (\text{Eq. 2})$$

where  $v$  = viscosity;  $s$  = shear rate; and  $A$  and  $B$  = two constants.

By imposing a defined quantity of shear a different line is obtained, in which constant  $A$  of Eq. 2 does not change and in which constant  $B$  decreases. In these conditions the decrease of  $B$  quantizes empirically the thixotropy.

These conclusions do not agree formally with the measurement of thixotropy by coefficient  $M$  of Schulte and Kassem (4). It should be noted, however, that in coefficient  $M$  thixotropic breakdown by time is superposed on thixotropic breakdown by shear, whereas our method permits a separate measurement of thixotropic breakdown by shear.

**Effects of Initial Agitation on Changes in Viscosity and Thixotropy Occurring Through Time: Role of the Metering-Bottling Machine**—A given quantity of lotion was passed through the Farmomac, an operation equivalent to violent agitation. The changes in viscosity during storage of the lotions thus treated were measured and compared with the changes in viscosity of samples of the same lotion not passed through the Farmomac.

Table III shows the results observed on 4 batches of lotion 1. The run through the Farmomac resulted in a considerable decrease of viscosity. Further, during storage, in the samples not passed through the Farmomac viscosity increased greatly (up to 2.5-fold in 75 days) along with thixotropy (up to 8-fold in 75 days, *cf.* Table IV). Both phenomena did not occur in the samples run through the Farmomac. Thus, as a result of the run through this machine an irreversible change in the rheologic properties of the lotion occurred.

Since the implications of these phenomena for lotion manufacture are important, the authors studied one of them. Observations on the performance of the Farmomac showed that the maximum shear rate occurs at the level of the bottling needles, where it may be estimated as high as 2000 sec.<sup>-1</sup>. Viscosity changes due to the bottling process

TABLE V—VISCOSITY IN POISE MEASURED AT 2 r.p.m. AND AT 24° ON TWO BATCHES OF LOTION 1 BEFORE AND AFTER THE RUN THROUGH THE FARMOMAC FITTED WITH BOTTLING NEEDLES OF DIFFERENT BORE

Batch	Initial	6-mm. Needles	3-mm. Needles
1	23	4	2.5
2	19	4.8	3.3

on some lotions using bottling needles with bores of 6 and 3 mm. were therefore studied. The former yielded shear rates of up to 120 sec.<sup>-1</sup> and the latter up to 2000 sec.<sup>-1</sup>. Table V shows the viscosity values observed for two lotions before and after passage through the Farmomac in these conditions. As suspected, the decrease under viscosity was greater in the samples run through the smaller bore.

## DISCUSSION

We have already discussed the ways in which thixotropy recorded by the method used in this study differs from that recorded by traditional methods, such as those used by several authors (6-9). Briefly, the thixotropic breakdown obtained by traditional methods depends on the relatively small shear imposed by the measuring instrument itself and is represented by a loop, formed by the up and down curves, in which thixotropy by time and thixotropy by velocity are mingled. The dimensions and shape of the loop depend upon instrumental factors and on the speeds at which the measurements are taken. The very shape of a loop is solely due to the fact that the apical closing point of the loop is the only one to be unaffected, at a given shear rate level by differences in shearing quantity and duration.

Instead of determining immediately the down curve, the authors interposed a set quantity of shear between the initial (up) and the final (down) consistency measurement, and imposed this shear by means that are independent of the measuring instrument. In these conditions the consistency curves before and after shear are almost parallel and may be expressed by Eq. 2.

"Thixotropic hysteresis loop" is an unhappy misnomer, too, as it implies some resemblance to elastic or magnetic hysteresis. The latter have defined physical dimension and meaning and are independent of measuring instruments. The thixotropic loop has neither, and the magnitude of its area supplies no more information than the average decrease in thixotropy between the two consistency curves.

Since thixotropy depends on the type, degree, and duration of shear, no absolute definition of it is possible, and the study of the phenomenon must be approached keeping in mind the actual conditions which may provoke thixotropic phenomena, and the reasons for which thixotropy may be relevant.

Thixotropy also alters the shape of the consistency curve, since any measurement is affected by the shear imposed by the measurement instruments and by the history of the sample (3). This drawback may to some extent be overcome by using Brookfield's "helipath," by which the spindle shifts vertically in the course of measurement so that it keeps changing its position in the sample. For the lotions considered, the helipath did not prove to have advantages over the method adopted, partly because the bars of this instrument are not designed to register the relatively low viscosities of the authors' lotions and partly because, by the authors' method, thixotropy can be prevented from interfering seriously with viscosity measurement.

For the physical stability of a lotion, an important property is that shear does not begin until a stress of some magnitude is applied (Bingham's yield value). Before the stress applied attains this value, the sample behaves as a solid, "imprisoning" the suspended particles, which thus can neither come to the top nor sediment (11). It is even possible to calculate a critical yield value below which the particles separate out into layers. For example, for the lotions studied, it may be assumed that the particles in suspension are spherical, have a diameter of  $4 \mu$ , and a density of 0.9, and that the density of the continuous phase is 1.0. In these conditions every particle receives an upthrust of  $3.4 \cdot 10^{-9}$  dynes and, as every particle has a surface of  $5 \cdot 10^{-7}$  cm.<sup>2</sup>, the fluid must possess a yield value of at least  $6.9 \cdot 10^{-3}$  dynes. cm.<sup>-2</sup> to prevent the particles from coming to the top. This value is much lower than the actual yield values of our lotions, which are 100-1000 times greater and which thus ensure good stability during storage. It should be noted, however, that the rheologic properties of a lotion are the properties of the fluid as a whole, that is of the continuous phase together with the particles in suspension, and so the foregoing calculations can not be considered very rigidly.

The yield value increases during storage and this improves the physical stability of a lotion. It decreases if the lotion is stirred. If the agitation is very violent the yield value may be abolished altogether and so the stability of the lotion may be affected.

The passage of the lotion through the metering-bottling machine, which is usually the final step in the pharmaceutical process, imposes on the lotion a heavy shear of short duration. This is not comparable to a more gentle stirring of longer duration, since viscosity and yield values may be influenced differently in the two conditions. In fact the violent

shear may modify some qualities of the emulsion such as increase of surface area of the internal phase, size and shape of the particles, *etc.*, which may decrease or increase viscosity or yield value, and therefore also the physical stability of the lotion.

Storage increases also the viscosity of the lotions under consideration, thereby slowing down the rate at which the particles come to the top or sediment. An undue increase in viscosity has its snags, however. First, it cancels out the advantages of lotions over creams as regards therapeutic use, second, the lotion becomes more difficult to get out of its container, and third, lotions of different ages exhibit different rheologic properties, a fact that is likely to worry the consumer.

**Optimum Viscosity for a Dermatologic Lotion**—Although the rheologic definition is an essential technologic datum for dermatologic lotions, the pharmacopeias make no reference to it. The USP XVII, the NF XII, and the BP 1963 simply carry a few examples of lotions without describing their physicochemical properties or specifying methods for determining them.

It is highly desirable for the rheologic properties of lotions to be stated and studied, as knowledge of these properties is indispensable: (a) for checking that the formula adopted yields the degree of viscosity suited to the therapeutic use for which the lotion is intended; (b) for adjusting the production and bottling equipment to the rheologic properties of the product in the various stages of production, and (c) for checking and ensuring the physical stability of the lotion over a period of time.

With regard to point a, lotions are usually preferred to creams when the area to be treated is painful or the skin very delicate, in which case the process of rubbing to spread the cream would be painful. Lotions are also preferable when the areas to be treated are large or there are skinfolds or hairy areas or when the lesions are scabbed or chapped, that is when the lotion reaches the target more easily than a cream. For all these reasons viscosity should be kept as low as possible. On the other hand, a liquid with low viscosity tends to run off easily from skin surface, which is never perfectly horizontal. Hence, one has to seek a compromise between these opposite requirements.

This problem does not yet seem to have been approached. We have therefore carried out acceptance tests with lotions of varying viscosity on normal subjects and on patients suffering from skin diseases. The results showed that the extreme range of acceptable viscosity, determined at 20 r.p.m. with a No. 2 spindle at 24°, is between 1 and 20 poise and that the optimum range of viscosity is between 2 and 5 poise. To generalize this indication to other viscosimeters it may be added that the above shear rate corresponds to about 6 sec.<sup>-1</sup>. This shear rate is at the lower levels of those actually applied to lotions when rubbed on skin. In fact the layers of lotion may be estimated between 0.02 and 0.3 cm., the velocity of rubbing between 1 and 5 cm.·sec.<sup>-1</sup>. This is to say that shear rates between 3 and 250 sec.<sup>-1</sup> may be involved during therapeutic use.

## REFERENCES

- (1) Woodman, M., and Marsden, A., *J. Pharm. Pharmacol. Suppl.*, 18, 198 S(1966).

- (2) Bottoni, R., *Boll. Chim. Farm.*, **97**, 76(1958).  
 (3) Green, H., and Weltmann, R. N., *Ind. Eng. Chem. Anal. Ed.*, **15**, 201(1943).  
 (4) Schulte, K. E., and Kassem, M. A., *Pharm. Acta Helv.*, **38**, 34(1963).  
 (5) Goodeve, C. F., and Whitfield, G. W., *Trans. Faraday Soc.*, **34**, 511(1938).  
 (6) Kostenbauder, H. B., and Martin, A. N., *J. Am. Pharm. Assoc., Sci. Ed.*, **43**, 401(1954).

- (7) Bernstein, H. B., and Barr, M., *ibid.*, **44**, 375(1955).  
 (8) Foerzler, E. C., Martin, A. N., and Banker, G. S., *ibid.*, **49**, 249(1960).  
 (9) Hamill, R. D., and Petersen, R. V., *J. Pharm. Sci.*, **55**, 1268(1966).  
 (10) Boylan, J. C., *ibid.*, **55**, 710(1966).  
 (11) Meyer, R. J., and Cohen, L., *J. Soc. Cosmetic Chemists*, **10**, 143(1959).



## Keyphrases

Dermatological lotions—rheological properties  
 Rheology, lotion—changes during aging  
 Brookfield viscosimeter—shear stress values

Metered bottling machine—rheological effect  
 Viscosity—shear rate relation  
 Thixotropy—agitation type, duration

## Thermodynamic Effects in the Compression of Solids

By EDWARD J. HANUS\* and LOUIS D. KING

The temperature changes of solids undergoing compression were determined. Compounds of known heat capacity were compressed into tablets at varying speeds and pressure and collected into thermally insulated vessels containing a suitable liquid. The resulting increase in temperature of the liquid was measured after equilibrium was established, and it was found that the increases in temperature were directly related to speed of compression and to compression pressure. Extrapolation of the data provided a technique for predicting tablet temperatures at time of compression. Thermal energy was converted to its mechanical equivalent thus providing a means for estimating the energy expended in the tablet compression process. The use of thermochromic indicators qualitatively supported the validity of the conclusions and quantitative confirmation was obtained by direct heating of samples.

MEASUREMENT of thermal energy developed in a dynamic operation such as the compression of solids with a tablet machine is a difficult and challenging problem. The reasons are numerous: (a) the heat content of a compressed compact is very quickly dissipated to its environment, (b) the high pressures applied during compression would crush ordinary temperature measuring devices such as thermometers or thermistors, and (c) during compression, the granulation is virtually encased within a steel chamber consisting of the die and punches, and thus is not physically accessible at the moment when temperatures are at a maximum.

In the compaction of powders, the following processes contribute to the total energy of compression (1, 2).

(a) Packing—Initially within a bed of powder there is essentially only one point of contact between two neighboring particles. As pressure is applied, consolidation takes place by the particles sliding one over the other and heat is generated. The extent to which this occurs is influenced to a large degree by the frictional properties of the two sliding surfaces (3, 4).

(b) Elastic and plastic deformation—In this phase of compression, most of the energy is consumed in the deformation of particles and by die-wall friction.

(c) Cold working with or without fragmentation—When fragmentation occurs, the specific surface area of tablets increases directly with pressure to a maximum and then decreases (5).

(d) Removal of the upper punch from the die after compression.

(e) Tablet ejection.

Nelson *et al.* (2), using an instrumented single punch tablet machine, found it possible to estimate the energy expended in the tablet compression.

Received April 18, 1967, from Rutgers, The State University, College of Pharmacy, Newark, NJ 07104.

Accepted for publication December 20, 1967.

Portion of a dissertation submitted to the Graduate School, Rutgers, The State University, by Edward J. Hanus in partial fulfillment of the Doctor of Philosophy degree.

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