J. Soc. Cosmetic Chemists, **17,** 313–327(1966)

Product Stability: Prognostication, Placement, Parameters—Part II*

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Synopsis—Chemical kinetics provides the basic principles which can help study of the deterioration of pharmaceutical and cosmetic products. Principles of kinetics, which could be used to predict long-term stability of finished formulations, are reviewed, and techniques are described which can be used in programming stability studies. Finally, those properties of emulsions, suspensions, and solids are discussed which are amenable to measurement and can be used as parameters for establishing and predicting deterioration of finished consumer products.

PARAMETERS

The purpose of this section will be to present a discussion of parameters, that is, physical properties of a formulation which can be measured and to which numerical values can be given. Furthermore, we will wish to examine parameters which change with the stress of time alone or after other challenging stresses (either with or without elapsed time) are applied to the formulations under study. Therefore, we will not be interested in all of the general stresses which are used to generate product development laboratory reports but rather in those which will cause changes in *parameters which can be plotted kinetically* so that we may try to predict stability by noting how the parameters are changed by the stresses. These are not always easy to find as some stresses, temperature and time included, will destroy the products, and we will be up against a limitation not unlike the Heisenberg Uncertainty Principle. Also, we want stresses and parameters which can be used on products *per*

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* Part I of this paper was published previously: *J. Soc. Cosmetic Chemists,* **17,** 135 (1966).

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se and not just on components, because the latter usually act differently when separated from their system.

This section will then be a partial and eclectic guide to the literature; it will be designed to suggest that what has been done in certain areas of the all-encompassing fields of pharmacy and chemistry may also be applicable to cosmetic product development work. It appears that not a great deal of work has been done on physical stability testing techniques; this observation was also noted by Lachman (17) in an article in which he discussed various aspects of physical and chemical stability testing. Some of the work cited here will illustrate the measurement of parameters the usefulness of which may be of a low order. However, it is hoped that these items will be of sufficient general interest so that the reader will consider them as pertinent as the author does because they touch upon this discussion. The references will be divided into categories based on general formulation type. Besides this categorization, no particular order will be followed; some references will describe theory, some suggest stresses or techniques, and others will illustrate kinetic plots.

Emulsions

Becher (18) pointed out in a discussion of spreading, HLB, and emulsion stability that a correlation exists between these factors. To effect correlation he used the concept of spreading coefficient, i.e., a parameter obtained by measurement of the surface (cohesion) and interfacial (adhesion) tensions involved. These are related to the mutual spreading properties of the two phases. When the work of adhesion is greater than the work of cohesion, spreading takes place (positive spreading coefficient); this is generally bad for stability. However, the author points out that too negative a spreading coefficient is not necessarily ideal because a balance between this coefficient and a low interfacial tension is needed.

An early discussion of the theoretical considerations concerning the electric double layer and its influence on emulsion stability is that of Cheesman and King (19). They especially noted the influence of electrolyte content on stability. Experimentally they followed stability by observing the separation represented by the rate of movement of the separation meniscus in a tube.

Higuchi and Misra (20) raised some very interesting points concerning emulsion stability. Usually we think of physical emulsion degradation as taking place only through coalescence. These investigators studied the physical degradation of emulsions *via* molecular diffusion, i.e., not contact-caused coalescence but a no-contact process in which one droplet grows while another dissolves. The process which predominates could be determined by whether forces exist which hold the droplets apart (latter) or by whether there is a very low degree of solubility of internal phase in the external phase (former).

Although no quantitative predictive technique was realized, Tober and Autian (21) pointed out that a straight-line relationship existed when time to reach 10% v/v sedimentation was plotted against the relative centrifugal force applied to an emulsion. This force is a function of the square of the revolutions per minute and the rotating radius. Stress of the formulation followed by such measurements might lead to predictive techniques.

Singleton and co-workers (22) were interested in making emulsions which would be stable to the heat of the sterilizing autoclave. They did not plot their data kinetically but did describe two of the stresses they used. One was steam autoclaving for 20 minutes at 121 °C; if the particle size became greater than 7μ, the formula was considered unstable. The other was a mechanical shock treatment in which 50 ml. of emulsion in a 100 ml. bottle was shaken horizontally 250 times per minute. Similarly, the emulsion was considered unstable if the particle sizes were greater than 7μ in less than one hour of shaking.

Harrison and James (23) in a study of O/W emulsions showed the existence of relationships between the electrical resistance and the concentration of the dispersed phase. Although they did not use their data kinetically in a stability study, it is obvious that this might be done.

King and Mukherjee (24, 25), in an attempt to create a quantitative criterion of emulsion stability, defined the stability coefficient of an emulsion as the reciprocal of the rate of change of the interfacial area per unit area of existing emulsion interface. They also obtained curves of interest by plotting either the per cent of total number of droplets or the per cent of total oil volume against droplet diameter. They observed that, although the maximum number of droplets are of a certain size, the greatest volume of oil is in drops of a different diameter. These investigators also plotted specific interfacial area *vs.* time. The slopes, although they observed changes such that they used the early and steeper slopes, were equated to rates of decrease of area per unit area of interface. The latter quantity is known, and the rate of decrease could then be used to compare emulsions. Incidentally, one other parameter they suggested was a half-break time, or the time it takes to reach half of the initial specific area. The change in slopes mentioned, due to two rates of coalescence, an early fast one and a later slower one, indicated the existence of an exponential relationship. Levius and Drommond (26) also illustrated the heat stressing of emulsions after which the usual methods of size frequency analyses and calculations of interfacial areas were applied.

In our discussion of size and interfacial area relationships, it aids perspective and is interesting to note that Ross (27), in a discussion of emulsions, pointed out that 2-μ droplets have a surface area of about 30,000 cm.^{2}/cc. whereas 3-μ droplets have an area of 20,000 cm.^{2}/cc.

Higuchi, Okada, and Lemberger (28) studied O/W emulsions in which the droplets were about 1μ and the system relatively monodispersed. They use a Coulter counter to determine the distribution of the various sizes of droplet aggregates. Thus, they were able both to count and size the aggregates as a function of time. They developed a method which quantitatively studied aggregation directly so that the aggregation would not have to be deduced from creaming or sedimentation rates. Hence, emulsions could be stored and the size distribution after various times be determined; the distribution could indicate if larger aggregates are being formed. This would be a warning as larger aggregates would indicate an increased chance of coalescence in emulsions or caking in suspensions.

Of interest is the early paper of Berkman (29) who studied emulsion stability by a size distribution method utilizing a projection microscope to measure globule size; 1500 to 2000 measurements were made per curve. She found that changes in distribution were related to time and that the pattern of progression was followed and agreed with data taken on emulsions five years old.

Lotzkar and Maclay (30) obtained interfacial areas by a size frequency analysis employing photomicrographs. They were able to plot the log of the specific surface area of the dispersed phase *vs.* time and obtained straight line plots. They noted that the degree of dispersion and the initial viscosity (although viscosity will hinder creaming) did not always increase stability.

Mullins and Becker (31, 32) investigated factors influencing the stability of O/W emulsions using high pressure homogenization. They also studied the feasibility of adjusting the density of the phases by the addition of brominated oils and the possibility of making the internal phase thixotropic by adding wax. They used a size-frequency method of analysis and showed that specific interfacial area increases with increased homogenization pressure. The presence of internal wax did not help, although the density adjustment did in some cases. The emulsions were stored at room temperature and 45°C to hasten deterioration, after which a microscope was used to measure the diameters of 900 to 1000 globules to obtain the size frequency classification. The globules were divided into size groups, and the midpoints of these groups were considered to be the average diameters. Considering the globules to be spheres, the volume and area were calculated, and these were then used to obtain the area per unit volume or the specific interfacial area. When plotted against time this parameter, of course, showed a decrease.

Sherman (33) pointed out the influence of the kinetics of globular coagulation or aggregation (precursors to coalescence) on the rheological properties of aging emulsions. His goal was to predict viscosity changes over long aging periods. Since the changes depend on globule size, he made emulsions of various sizes to get a picture of what would happen in the future. He noted that this technique may be better than centrifugation or high temperature storage, even though such stresses may produce an increase in average globule size. He interrelated many measurements and developed a parameter, called the inhomogeneity factor, which increases with time. The factor essentially converted data obtained by measuring 2000 globules to a distribution parameter which accounts for globule number, size, and area. Also as a further and more detailed comparison, Sherman calculated the average distance between globules which is also related to the average diameter. Finally, this average distance of separation was related to viscosity data, which means that globule diameter is related to viscosity. Thus, if globule diameter increases and has an effect on viscosity, both old and fresh emulsions of the same globule size should have the same viscosity. Sherman found that when relative viscosity was plotted against the distance separating the globules, or against time, the data from both new and old emulsions could be superimposed; thus viscosity changes over long aging periods could be predicted.

This discussion of finished emulsions and coalescence is somewhat reminiscent of the coalescence time test of Cockbain and McRoberts (34). In essence, their test requires that the emulsion be put together in two parts: the oil phase is layered over the water phase after which an oil drop is introduced from the bottom underneath the water. After the drop rises to the interface, one checks to see how long it takes for it to coalesce. Of course, the longer this time, the more stable the completed emulsion is considered to be.

Lloyd (35) related the per cent reflectance of color and the surface average diameter obtained microscopically in a study of the change in distribution pattern of the globule sizes of O/W emulsions. A straight line plot resulted when the log per cent reflectance was plotted against the log surface average diameter. The latter quantity, which of course is inversely related to interfacial area, is then also capable of relating stability to reflectance. We note also that interfacial area simulates a concentration factor as it can be expressed as interfacial area per unit volume of oil. Lloyd found that a plot of log diameter *vs.* time gave a curve which rose steeply in first order fashion and then reached a plateau which indicated limiting of the coalescence.

Menczel, Rabinovitz, and Madjor (36) used a selectively soluble dye (soluble in only one of the phases as used for the differentiation of emulsion types) to color their test emulsions with an exact amount of such a dye. They then developed a colorimetric method to determine volumes of separated internal phase at various times. The rate of this separation is then equated to the rate of de-emulsification. They employed a dye soluble in the internal phase and used a separatory funnel to collect the separated portion from the emulsion bulk. The internal phase was thus collected at various times from a series of preparations; its volume was determined colorimetrically by measuring the dye concentration with a photoelectric colorimeter. The volumes were converted to per cent separation. A straight line log-log relationship was found by plotting the log of the per cent separation *vs.* log time. A family of lines resulted; the position of any particular line of the family then is an indication of the stability rank of the particular emulsion.

Vold and Groot (37) developed an ultracentrifugal method to determine emulsion stability. They investigated the utility of an ultracentrifuge which permitted observation of the emulsion while it was being rotated. When the per cent of oil separated was plotted *vs.* the time of centrifugation, a plateau curve was obtained. It was noted that the separation rate was very rapid at first, then slower and more-or-less constant while 20 to 60% of the oil separated, and finally, the rate was slow. Naturally, increased speeds caused higher rates of oil separation. Centrifugation speeds up to 56,100 r.p.m. were employed. Garrett (38) also studied the use of the ultracentrifuge in predicting pharmaceutical emulsion stability, especially as it pertains to oil flotation or creaming. A linear graph resulted when flotation rate was plotted *vs.* the square of the centrifuge revolutions per minute. The flotation rate is represented by the slope of the line which results when the log distance of emulsion-water boundary from the rotor center is plotted *vs.* time for each revolutions per minute.

An earlier example of the use of centrifuge studies is the work of Merrill (39). This investigator studied the mechanical stability of O/W and W/O emulsions by measuring the rate of separation of internal phases when the emulsions were subjected to a constant centrifugal force. The quantitative index of stability used was the reciprocal of the initial rate of separation at a certain centrifugal speed. Plots of per cent oil separated *vs.* time of centrifuging were linear.

Suspensions and Selected Solutions

Martin (40) discussed the physical-chemical principles involved in suspensions. Such parameters as sedimentation height were noted; here one determines the ratio of the ultimate height of the sediment to the initial height of the suspended material. Naturally, the larger this fraction is the better is suspendability. He also noted the applicability of electrophoresis which employed a microelectrophoresis apparatus. Such instrumentation could measure migration velocity with respect to the surface electric charge or the familiar zeta potential, which has units of viscosity times electrophoretic mobility, or, more familiarly, voltage.

Stanko and DeKay (41) evaluated suspensions by electrokinetic methods. Since pH, sedimentation rate, and viscosity would not necessarily indicate everything that is happening in the system, it was felt that the electrokinetic properties, that is, the zeta potential and critical potential (zeta potential at which flocculation occurs) would be illuminating. The zeta potential was obtained in a microelectrophoresis apparatus from which the rate of movement of particles could be obtained. These workers plotted the weight of sediment *vs.* time and obtained gently curving lines. Although no kinetic plots were made, it was shown that the zeta potential changes upon the addition of additives and that it is related to stability.

Haines and Martin (42, 43) studied some formulation factors which influence the stability of suspensions. They correlated zeta potential to the measure of visually observed caking. The zeta potential was determined by microscopic electrophoresis, and it was found that certain zeta potentials produced more stable suspensions because flocculation was controlled.

Foernzler, Martin, and Banker (44) studied the effect of thixotropy on suspension stability. They obtained straight line graphs by plotting the sedimentation velocity in a centrifuge at a particular RPM in ml./

min. against the reciprocal of the thixotropic area. The sedimentation velocity was obtained by plotting the sedimentation volume *vs.* time. The thixotropic area is the area of the hysteresis loop formed when the viscosity of a non-Newtonian liquid is taken continuously over a range of stress-strains and back; the area was measured with a planimeter on the plots of rate of shear *vs.* shearing stress. The authors thus attempted to predict physical stability by the rheologic evaluation of thixotropy. Incidentally, Wood (45) used these workers' data to show that a similar or better correlation exists if the reciprocal of the yield value is plotted against the sedimentation velocity.

Wood, Catacalos, and Lieberman (46) studied aging magnesium aluminum silicate suspensions. They found new, interesting, logarithmic, atypical kinetic relationships involving the time and temperature of storage and shear rate and shear stress. Plots of log shear stress *vs.* log shear rate produced a family of straight lines for a particular storage temperature in which the slopes decreased with sample age, although the older samples' lines "started higher," i.e., required more stress to get the same shear rate as the younger. Thus plots of log apparent viscosity *vs.* log age were linear for each particular shear rate. These workers also pointed out that plots of log apparent viscosity at a single shear rate *vs.* either log age at a particular temperature or $1/T$ at a particular age were linear; the latter indicates that viscosity build-up follows an Arrhenius type of relationship. Thus plots of log age to attain a given viscosity at a particular shear rate *vs.* $1/T$ were also linear. For practical purposes it is noted that work such as this illustrates that clay and gum hydration is not attained instantaneously—it is part of the aging process and is not necessarily completed even by the stress a formulation undergoes in a manufacturing procedure.

Garrett and Carper (47) studied the color stability of a multisulfa suspension after it was exposed to accelerated temperature storage conditions. They followed the UV absorbance of the supernatant liquid after the suspension was centrifuged. They observed that the absorbance *vs.* time at the different temperatures provided straight lines from which they could calculate first order rate constants. Their data also fit an Arrhenius plot from which they could predict after a four-week study the rate of deterioration of the color after one year at room temperature.

Levy (48) studied the stability of the viscosity of various molecular weight sodium carboxymethylcelluloses and sodium alginates in aqueous solutions stored at an elevated temperature. When the log per cent of the initial viscosity was plotted aginst time, a linear first order plot resulted from which a viscosity half-life could be calculated. This half-life decreased with increasing molecular weight.

In a study of the viscosity of suspending agents, Joslin and Sperandio (49) noted straight line (and some curved) relationships obtained by plotting viscosity *vs.* time. Not surprisingly, some experiments resulted in a family of lines with respect to different storage temperatures and also, some samples became thicker with time, some thinner. Storage at elevated temperatures accelerated the particular changes.

Zacek (50) illustrated the use of ductility as a response variable of pharmaceutical suspensions. In essence, he suggests placing the suspension between two plates which are then pulled apart vertically. A thread between the plates forms, and the distance at which it breaks is measured.

With respect to stressing suspensions, the freeze-thaw cycle technique is very applicable. This treatment facilitates particle growth and may indicate the probable future state of affairs after long storage at room temperature.

Schwarz and Levy (51) studied the viscosity of sodium alginate solutions after freezing and thawing. They showed that the viscosity increased upon such treatment. They also demonstrated that excessively long shearing lowered the viscosity, although the freeze-thaw cycle caused all to have the same viscosity regardless of the initial. They also pointed out, however, that an increased rate of shearing may give a permanent loss of viscosity, as will higher temperatures, because of the degradation of polymer chains.

Head and Lauter (52) used an ultrasonic generator to study the depolymerization of natural polymers. It is known that such insonation will depolymerize, but it also can facilitate gum hydration. They showed through viscosity measurements that the molecular weight decreased and that a straight line plot resulted when the molecular weight was plotted against the duration of irradiation. Carrageenan, agar, locust bean gum, and methylcellulose all degraded first order; gum tragacanth degraded according to zero order kinetics; karaya and acacia were not degradable by their method.

Semi-solids and Solids

Urbanyi and co-workers (53) measured the changes in reflectance of colored tablets with a reflectometer attachment on a spectrophotometer, choosing the best wavelength for observation. Reflectance was compared to a standard. They used this technique to determine the influence of light of 45 and 550 foot-candles intensity. Absorbance was plotted against time, and some first order rate constants were obtained, although the plots were not ideal as the lines were segmented. Naturally, the constants increased at the higher light intensities. Lachman *et al.* (54) in additional work which was part of an extensive study of tablet dyes checked the fading of the corresponding lakes. From absorbance and time data, they obtained first order rate constants and showed that the lakes studied had poorer photostability than the dyes.

Carstensen and collaborators (55) employed photometric reflectance to observe the appearance of tablets and powders stored at elevated temperatures. Their data provided them with both zero order and first order rate constants which were amenable to Arrhenius plot treatment.

Everhard and Goodhart (56) studied the fading of dyes in tablets. Their aim was to quantitate the time-intensity relationships involved in the storage of a single tablet dye at various concentrations (0.015 to 0.060%). The tablets were stored under 655 foot-candles, fluorescent lights at 80 foot-candles, fluorescent light and amber glass at 11 foot-candles, and under incandescent light of 50 foot-candles. They pointed out that others had plotted log of log $1/R$ *vs.* time where R represented the fraction of light reflected at a specified wavelength. These workers pointed out that the previous work inferred that log $1/R$ was proportional to concentration but that this was not so because different rate constants were obtained for different dye concentrations. Thus, they noted the need for an equation to relate reflectance to concentration and also a need to bring light intensity into the kinetic picture. They showed that a parameter called ϑ_t was proportional to concentration where: $\vartheta_t = (1 - R_t)^2/2R_t$ and R_t = the measured reflectance at the minimum wavelength in a reflectance-wavelength curve. Then, considering fading to be proportional to time and intensity, a straight line resulted when ϑ_t was plotted *vs.* $I \times t$ in foot-candle hours.

McKeehan and Christian (57) studied the color stability of a bentonite base cream with an integrating sphere reflectometer, which is useful for the study of opaque solids and semisolids. When the creams were stored at various elevated temperatures, they were able to plot reflectance (relative to magnesium carbonate) *vs.* time and obtain straight lines. They were also able to construct Arrhenius plots to permit prediction of the time when the color would be unsatisfactory. They also proposed use of the technique for the study of coated tablets, powders, and granulations.

It is possible that dilatometry can serve to monitor changes such as hidden phase transitions (formation of solid solutions or immiscible phases) and polymorphic transformations in semisolids such as pastes and ointments. Such techniques were employed by Ravin and Higuchi (58) in part of a series of studies on the melting behaviors of some fats and waxes of pharmaceutical importance. The procedures are reproducible and entail determining the specific volume of a system as a function of temperature. Although it was not done by these investigators, it is possible that samples would be stressed in the usual accelerated storage tests, after which dilatometric studies would be performed. Possibly, a plot of specific volume at a certain temperature *vs.* time of storage would give data from which predictions could be made. The utility of a different type of dilatometry, constant temperature dilatometry, has been pointed out by Mahler (59). In this technique the aim is to avoid the effect of temperature on polymorphic changes. Thus, the material is kept at room temperature in something akin to a mercury densitometer. The volume change, either an increase or a decrease, is then followed by recording the displacement of mercury in a connected capillary tube as a function of time. When the per cent change in volume is plotted against time, the curves plateau out, either upward or downward depending on whether a volume increase or decrease takes place. From the early part of these curves, which are essentially hyperbolas, one can calculate the time required to complete the variations in volume which are due to polymorphic transformations. Thus, the time to make observations for surface defects which are caused by such transformations can be predicted for such products as lipsticks, eyebrow pencils, suppositories, etc.

Reese, Chong, and Swintosky (60) studied lipid raw materials *via* photomicrography. They were able to demonstrate that some changes (crystal transformations, growth, cracks) occurred during aging at room and accelerated temperatures. Certainly, the integrity of lipid materials affects the quality of creams and ointments, and it is possible that, even though it may be difficult to quantitate, this camera-microscope technique could be used to detect incipient graininess in ointments. Also, it may be possible to observe the solid phase of suspensions this way.

Maclay, Shepherd, and Lotzkar (61), in a study of pectin in medicated pastes and ointments, measured the viscosity and pH of such products stored at various temperatures. Although the pH gradually decreased, the viscosity was relatively stable. However, they could demonstrate by analytical techniques a slow demethoxylation of the pectin.

Szepesy (62) studied the consistency of ointment bases by obtaining penetrometer readings at 6°, 25°, 35°, and 45°C initially and after storage of the ointments.

An interesting property which permits evaluation of lotions, creams, and ointments is that of tack. Wood and Lapham (63) described an instrument, the tackmeter, which permits the evaluation of tack of such products, both after they are dried on plates or after application to the skin. The tackmeter described is essentially a balance assembly which permits determination of a withdrawal weight and time of break to separate a flat surface of the device from the skin. Wood, Giles, and Catacalos (64) also described a revised tackmeter in which forces were recorded by a strain gauge instead of by weights.

Borchardt and Daniels (65) studied the application of differential thermal analysis to reaction kinetics. Although they used solutions, one could visualize the application of the technique to semisolids such as pastes, ointments, and lipsticks. The method detects the net heat of reaction as the temperature of the system is raised. The difference in temperature of the reacting solution and a reference solution obtained while both are heated is plotted against time (temperature). The equations enable one to calculate the heat of reaction from the area under the curve and the reaction rate constant at any particular temperature from the slope and height of the curve at the particular temperature. The heat of activation and the order of reaction are then obtained from plots of log k *vs.* $1/T$.

Pohle, Gregory, and Taylor (66) described work on the comparison of analytical techniques for predicting the relative stability of fats and oils to oxidation. Most of these stability testing methods attempt to force the oxidation of the fat or oil, after which either oxygen absorption is measured or organoleptic or chemical methods are used to monitor the degradation of the product. As part of a series of studies on the oxidation of emulsified and solubilized oils, Carless and Nixon (67) studied the oxidation of methyl linoleate. They measured oxygen uptake manometrically in a Warburg apparatus, in addition to the more usual checking of peroxide values. Somewhat along this line, Ravin, Kennon, and Swintosky (68) studied an oxidative reaction by measuring oxygen uptake in a Warburg respirometer; the oxygen uptake was monitored while the system was stressed with a sun lamp. They showed that oxygen uptake was linear with time and that it stopped when the light was turned off. Briefly continuing these comments on oxidation, we note that Reese and Guth (69) irradiated calamine lotions with UV, sunlight, and both incandescent and fluorescent lamps and checked peroxide formation iodometrically; it is known that aqueous zinc oxide may produce hydrogen peroxide. They showed that the source of the zinc oxide and other ingredients influences the peroxide generation by the zinc oxide. They found that the increase in hydrogen peroxide concentration with time was not linear.

In conclusion, we may note the fact that Bartels (70) has pointed out the possible utility of various types of quantitative microscopy in solving problems connected with cosmetic R&D work. In fact, speaking of parameters, he suggests that parameters which indicate a good correlation to the effect we wish to observe be created, regardless of whether they are common to the present scientific literature or not.

CONCLUSION

Early theoreticians and experimentalists have given us a heritage, part of which we recognize as the principles of what today is known as physical chemistry. The seemingly necessary—or at least ever-present—pace of today has stimulated workers in the pharmaceutical industry to use some of this inheritance, namely that portion specifically pertinent to the present discussion, i.e., basic chemical kinetic concepts. The promise of tomorrow seems to be that even more of these techniques will be found to be applicable to product development efforts in the cosmetic industry. The thoughts expressed here concerning further progress in this direction have taken the form of suggestions based on a discussion of possible quantitative ways which monitor the changes formulations go through upon storage. Of course, more data are required before firm conclusions can be reached, but if work along this line is implemented, many exciting areas may be opened up for study. Certainly, our aim must be to do everything we can to enhance our knowledge of the "systems" we call "products."

ACKNOWLEDGMENTS

The author gratefully acknowledges the fact that Dr. R. F. Doerge, Professor of Pharmaceutical Chemistry at the College of Pharmacy of Oregon State University, brought to his attention references 6 and 7 describing the Japanese work on vitamin B_1. The author also expresses his appreciation to Miss Lillian Capro for the secretarial work involved in the preparation of the drafts and of the final manuscript.

(Received October 27, 1965)

REFERENCES

(17) Lachman, L., *Am. Perfumer*, **77** (9), 25 (1962).
(18) Becher, P., *J. Soc. Cosmetic Chemists*, **11,** 325 (1960).
(19) Cheesman, D. F., and King, A., *Trans. Faraday Soc.*, **35,** 241 (1940).
(20) Higuchi, W. I., and Misra, J., *J. Pharm. Sci.*, **51,** 459 (1962).
(21) Tober, T. W., and Autian, J., *J. Am. Pharm. Assoc., Pract. Ed.*, **19,** 422 (1958).
(22) Singleton, W. S., White, J. L., Benerito, R. R., and Talluto, K. F., *J. Am. Oil Chemists Soc.*, **35,** 265 (1958).
(23) Harrison, I. H., and James, K. C., *J. Pharm. Pharmacol.*, **14,** 503 (1962).
(24) King, A., and Mukherjee, L. N., *J. Soc. Chem. Ind.*, **58,** 243 (1939).
(25) King, A., and Mukherjee, L. N., *Ibid.*, **59,** 185 (1940).
(26) Levius, H. P., and Drommond, F. G., *J. Pharm. Pharmacol.*, **5,** 743 (1953).
(27) Ross, S., *J. Soc. Cosmetic Chemists*, **6,** 184 (1955).
(28) Higuchi, W. I., Okada, R., and Lemberger, A. P., *J. Pharm. Sci.*, **51,** 683 (1962).
(29) Berkman, S., *J. Phys. Chem.*, **39,** 527 (1935).
(30) Lotzkar, H., and Maclay, W. D., *Ind. Eng. Chem.*, **35,** 1294 (1943).
(31) Mullins, J. D., and Becker, C. H., *J. Am. Pharm. Assoc., Sci. Ed.*, **45,** 105 (1956).
(32) Mullins, J. D., and Becker, C. H., *Ibid.*, **45,** 110 (1956).
(33) Sherman, P., *J. Phys. Chem.*, **67,** 2531 (1963).
(34) Cockbain, E. G., and McRoberts, T. S., *J. Colloid Sci.*, **8,** 440 (1953).
(35) Lloyd, N. E., *Ibid.*, **14,** 441 (1959).
(36) Menczel, E., Rabinovitz, M., and Madjor, A., *Am. J. Pharm.*, **132,** 315 (1960).
(37) Vold, R. D., and Groot, R. C., *J. Phys. Chem.*, **66,** 1969 (1962).
(38) Garrett, E. R., *J. Pharm. Sci.*, **51,** 35 (1962).
(39) Merrill, R. C., Jr., *Ind. Eng. Chem., Anal. Ed.*, **15,** 743 (1943).
(40) Martin, A. N., *J. Pharm. Sci.*, **50,** 513 (1961).
(41) Stanko, G. L., and DeKay, H. G., *J. Am. Pharm. Assoc., Sci. Ed.*, **47,** 104 (1958).
(42) Haines, B. A., Jr., and Martin, A. N., *J. Pharm. Sci.*, **50,** 753 (1961).
(43) Haines, B. A., Jr., and Martin, A. N., *Ibid.*, **50,** 756 (1961).
(44) Foernzler, E. C., Martin, A. N., and Banker, G. S., *J. Am. Pharm. Assoc., Sci. Ed.*, **49,** 249 (1960).
(45) Wood, J. H., *Am. Perfumer*, **76** (10), 37 (1961).
(46) Wood, J. H., Catacalos, G., and Lieberman, S. V., *J. Pharm. Sci.*, **52,** 354 (1963).
(47) Garrett, E. R., and Carper, R. F., *J. Am. Pharm. Assoc., Sci. Ed.*, **44,** 515 (1955).
(48) Levy, G., *J. Pharm. Sci.*, **50,** 429 (1961).
(49) Joslin, R. S., and Sperandio, G. J., *Drug. Std.*, **25,** 72 (1957).
(50) Zacek, H., *Acta Fac. Pharm. Bohemoslov.*, **8,** 125 (1963) through *Intnl. Pharm. Abstr.*, **2,** 356d (1965).
(51) Schwarz, T. W., and Levy, G., *J. Am. Pharm. Assoc., Sci. Ed.*, **46,** 563 (1957).
(52) Head, W. F., Jr., and Lauter, W. M., *Ibid.*, **46,** 617 (1957).
(53) Urbanyi, T., Swartz, C. J., Lachman, L., and Cooper, J., *Ibid.*, **49,** 163, 165 (1960).
(54) Lachman, L., Weinstein, S., Swartz, C. J., Urbanyi, T., and Cooper, J., *J. Pharm. Sci.*, **50,** 141 (1961).
(55) Carstensen, J. T., Johnson, J. B., Valentine, W., and Vance, J. J., *Ibid.*, **53,** 1050 (1964).
(56) Everhard, M. E., and Goodhart, F. W., *Ibid.*, **52,** 281 (1963).
(57) McKeehan, C. W., and Christian, J. E., *J. Am. Pharm. Assoc., Sci. Ed.*, **46,** 631 (1957).
(58) Ravin, L. J., and Higuchi, T., *Ibid.*, **46,** 732 (1957).
(59) Mahler, E., *J. Soc. Cosmetic Chemists*, **15,** 727 (1964).
(60) Reese, D. R., Chong, C. W., and Swintosky, J. V., *J. Am. Pharm. Assoc., Sci. Ed.*, **49,** 85 (1960).
(61) Maclay, W. D., Shepherd, A. D., and Lotzkar, H., *Ibid.*, **33,** 113 (1944).

(62) Szepesy, A., *Acta Pharm. Hung.*, **34** (4), 164 (1964); through *Chem. Abstr.*, **61,** 15938g (1964).
(63) Wood, J. H., and Lapham, E. A., *J. Pharm. Sci.*, **53,** 825 (1964).
(64) Wood, J. H., Giles, W. H., and Catacalos, G., *J. Soc. Cosmetic Chemists*, **15,** 565 (1964).
(65) Borchardt, H. J., and Daniels, F., *J. Am. Chem. Soc.*, **79,** 41 (1957).
(66) Pohle, W. D., Gregory, R. L., and Taylor, J. R., *J. Am. Oil Chemists' Soc.*, **39,** 226 (1962).
(67) Carless, J. E., and Nixon, J. R., *J. Pharm. Pharmacol.*, **12,** 348 (1960).
(68) Ravin, L. J., Kennon, L., and Swintosky, J. V., *J. Am. Pharm. Assoc., Sci. Ed.*, **47,** 760 (1958).
(69) Reese, D. R., and Guth, E. P., *Ibid.*, **43,** 491 (1954).
(70) Bartels, P. H., *J. Soc. Cosmetic Chemists*, **15,** 485 (1964).