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Physical Testing

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A great deal of space has been devoted to the subject of chemical testing. However, even if a product, chemically, is sufficiently stable to sustain e.g. a 3-year expiration date, physical changes may have occurred. In a solid dosage form, the dissolution may have slowed down to such an extent that the product is no longer as bioavailable

as it was at the time of manufacture, and more importantly, it may not meet the minimum required for efficacy. For a solution, a precipitate may have occurred. This may not affect the chemical content, but for a parenteral product it would, obviously, be quite unacceptable, and for an oral solution it would also be unsatisfactory, because the dispensing pharmacist would rightfully question the integrity of the product. The caking of a suspension impairs the dispensing of a known amount of drug in a teaspoon, and a separated or broken emulsion or cream obviously will not have the same emollient properties as would a proper product.

Physical stability will be treated by product category in the same order as in the case of chemical stability.

1. PHYSICAL STABILITY OF SOLUTIONS

Solutions are broadly divided into two categories: oral and parenteral solutions. Appearance, in both cases, is an important factor. In the case of oral solutions, organoleptic properties are also of great importance. Organoleptic evaluation is usually done subjectively, i.e., a tester (operator, technician), will judge the product and score it, either numerically or descriptively or both. In the case of appearance of solutions, there should always be a subjective statement (quantitative or subjective description) even if more quantitative instrumental parameters are recorded. A few words are therefore in order regarding organoleptic and appearance testing.

1.1. Organoleptic Testing

For organoleptic testing it is important to establish a test panel early in the stability program. (Or if a stability program is in place, but no such testing is carried out, a test panel should be selected at the first opportunity when a product with important taste or odor properties is placed on stability.) Many companies utilize just one tester for the task of organoleptic testing, but this can be shortsighted, because the tester may leave, go on vacation, or become ill, and in that case the logical solution is to assign someone else to the task. There may be an evaluational bias between the two testers, and this should be established at the onset.

First of all, the depth of organoleptic capacity should be tested. This can be done by asking the tester to taste serial dilutions of a bitter substance (e.g., quinine). Hence a sensitivity level can be established. A control of e.g. water or high dilutions should always be part of the protocol.

It should be noted that the technicians are not taste testers in the ordinary sense. That is, it is not necessary to match their "likings" to that of the general public. Rather, it is important that they can (a) duplicate their results and (b) remember them, since they will be asked to taste a preparation that they originally tested 3 or 6 months earlier. In so doing they would have to score the degree of flavoring, e.g., is it less than originally present, i.e., is the flavor being lost? They would also have to be able to describe the flavor well originally. For example, if the chemical is slightly anesthetizing, the duration of the anesthesia would be important. If there is interaction with a plastic bottle, are off flavors appearing in the product? Finally it is important to screen several testers to ascertain that they give the "same result."

In describing the flavor, several categories can be used (degree of sourness, degree of saltiness, level of flavor, type of flavor). Each of these may be assigned

to a level of e.g. 1–5. A flavor profile may hence be established, and this can then be reestablished at several time points in the room-temperature storage. It is not recommended to evaluate results from higher temperatures (although they may be carried out).

1.2 Subjective Appearance Testing

Solutions, particularly parenteral solutions, may have a tendency to discolor slightly. Often it is not possible, within analytical sensitivity, to establish either the source of the color or the level of the substance causing it. In this case it is a good practice to use a color standard to describe the "intensity" of the discoloration. Roche, for instance, uses the so-called Roche Color Standard (RCS), which uses a compound (the identity of which is a secret) that can be reliably reproduced and has exceptional color stability. Making up serial dilutions of this compound then gives solutions of different "slight" discolorations; they are denoted RSC#1, #2, etc., so that a solution can always be compared in this fashion. It is a bit like the old-fashioned Dubosque colorimeter (which can be used with advantage in this type of situation). The principle of the Dubosque colorimeter is to have a view of two test tubes from the top. One is the control, and the other is the solution being matched. It is possible to adjust the length of the light path in the second tube, and this is done until the intensity matches that of the standard. The length of the path is then an indication of the "concentration."

The RCS (and similar types of numbers) are difficult to analyze, but a Dubosque colorimeter gives numbers that follow Beer's law and are logarithmically proportional to concentration (although the proportionality factor cannot be known). In this fashion the "decomposition" could be represented simply as a first-order reaction, where the concentration, X, of the decomposition product would be given by

$$X = X_\infty[1 - \exp(-qt)] \tag{10.1}$$

or

$$\ln\left[1 - \frac{X}{X_\infty}\right] = -qt \tag{10.2}$$

where q is a constant, t is time, and X_∞ is found by iteration. This allows (from accelerated studies) a visual estimate of the worst appearance that a product could take on. The appearance of tablets can be treated differently and will be discussed later.

2. PARENTERAL SOLUTIONS

In parenteral solutions, physical stability includes interaction with a container and changes in chemical composition that give rise to physical changes. The latter will be discussed first.

One manifestation is slight discoloration. Thiamine hydrochloride solutions, for instance, may discolor slightly without showing detectable changes in content of parent compound. Such discolorations can be followed as described immediately

Table 1 Usual Concentrations of Antioxidants and Chelating Agents

Antioxidant	Usual concentration
Acetylcysteine	0.5%
Ascorbic acid	0.02–1%
BHT, BHA, and propyl gallate	0.005–0.02%
Citric acid (chelator)	Variable*
Sodium edetate (chelator)	0.01–0.075
Sulfites	0.1–0.15%
Thioglycerol	0.1–1.0%
Thiourea	0.5–1.0
Tochopherols	0.05–0.075

* Citric acid can be present in large amounts if it is present as a buffer (as well as present as a chelator).
Source: Table constructed from data published by Mendenhall (1984).

above, and at times they are detectable analytically. They are often oxidative in nature and metal ion catalyzed. Such a case in captopril (Lee and Notari, 1977).

Mendenhall (1984) has reviewed the stability aspects of parenteral products and has shown that discoloration is often either photochemical or oxidative. He has summarized the usually used antioxidants and chelating agents. These are shown in Table 1.

2.1. Swirly Precipitates

Often a parenteral solution will develop a swirly precipitate upon storage. This is most prevalent in vials and is usually an interaction with either the glass or the stopper. It may be difficult for the uninitiated to detect such slight changes, and the best person to use for this type of evaluation is a parenteral inspector. It is difficult to estimate the extent of the precipitate; it can be done by mechanical counting (e.g., with a Coulter counter), but the results are difficult to interpret. Often the count does not correspond to the "severity of the swirl." More to the point is how many swirls exist. If a box of e.g. 144 vials is placed on this type of stability, then the vials can be examined from time to time, and one may establish how many vials have become swirly. This number can then be treated in proper fashion to evaluate the severity of the problem, i.e., the stability parameter would be the number of swirly vials per box of 144.

Preferably there should be no swirls at all in the preparation, and if reformulation can be undertaken (which is wise), then an improved product would be the result. Otherwise, the stability program will establish the percentage probability of finding a vial with a swirl at the end of the expiration period. At times it is necessary to lyophilize products that are chemically stable, simply because the problem of swirls cannot be solved.

As mentioned, the occurrence of swirls is usually a container interaction, and a change in the stopper or the glass may often eliminate the problem. Vials should always be stored (a) upright, (b) on the side, and (c) upside down to check the interaction with the stopper. In this way primary evidence can be established as to the culpability of the closure.

2.2 Whiskers

McVean et al. (1972) reported on the case of a parenteral solution (morphine) where "whiskers" occurred at the tip of the ampul in a large percentage of ampuls upon room-temperature storage.

This is a defect that will occasionally occur in a product. It is due to pinholes in the glass. The solution wicks out, and the liquid evaporates on the outside. The solid that is formed serves to wick out more solution, and long crystals or "whiskers" may occur. One might ask why the pinholes have not been detected in the dye test used for autoclaved ampuls. There are two reasons. One is that the hole may be too small for detection (about 0.5 μm is the detection limit). The other is that the ampul was tight at the time of manufacture, but the heat sealing line was run too rapidly, or the flame temperature was incorrect, so that the glass did not have time to anneal properly, and the strain caused the crack during storage (not immediately after manufacture).

2.3 Cloud Times

Sometimes a cloud will appear in a product as the storage time progresses, and this is most often due to chemical changes in the system. If for instance an ester (e.g., polysorbate, which is a fatty acid ester) hydrolyzes, then the produced acid may be poorly soluble. If the solubility is denoted S, then the following holds: If the reaction in general is written

$$A + H_2O \rightarrow B \tag{10.3}$$

where A is a drug of initial concentration A_0 and B is the decomposition product with solubility S (which is assumed to be limited). Assuming first order, the concentration of B is then given by

$$[B] = A_0[1 - \exp(-kt)] \tag{10.4}$$

At time t^* the solubility will be exceeded, and t^* is what is denoted the cloud time. t^* is given by

$$S = A_0[1 - \exp(-kt^*)] \tag{10.5}$$

or

$$\ln\left[1 - \frac{S}{A_0}\right] = -kt^* \tag{10.6}$$

If $A_0 \gg S$ then this simplifies to

$$t^* = \frac{S}{kA_0} \tag{10.7}$$

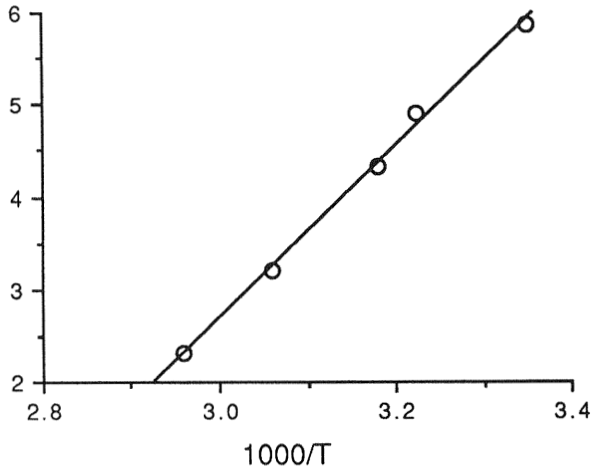


Fig. 1 Cloud times of a parenteral diluent containing polysorbate 80 and maleic acid. (Constructed from data published by Carstensen, 1972.)

Taking logarithms gives

$$\ln[t^*] = -\ln[A_0] + \ln\left[\frac{S}{k}\right]$$
$$= -\ln[A_0] + Q - \frac{\Delta H - E}{RT} = -\frac{\Delta H - E}{RT} + Q'' \tag{10.8}$$

where Q and Q'' are constants. This shows that the cloud times can be plotted by Arrhenius plotting. Such plotting is quite predictive, as is shown in Fig. 1.

The precipitation may also occur by the solubility product being exceeded, or from any situation leading to a product with limited solubility.

There are other causes for precipitation on storage, one being the original use of a metastable form, so that the solutions in question, in fact, are supersaturated solutions. It was the author's experience, at his tenure at Hoffmann–la Roche in 1965, that a product to be introduced (Taractan Injectable) was in this category. Several pilot batches had been successfully made, but the first production batches precipitated, a more stable polymorph crystallizing out. This necessitated reformulation to a lower strength (corresponding to the lower solubility of the stabler polymorph) and subsequent resubmission of data to the FDA. This points out the importance of careful preformulation studies of the solubility of compounds. Errors of the above type are costly, both in terms of resubmission and in lost market time. Even official products fall into this category.

Calcium gluceptate is used to treat calcium deficiency and (USP XX, 1980) is highly water soluble (up to 85%). Solutions, however, show a tendency to precipitate on standing at room temperature (Muller et al., 1979). The storage time required for precipitation is a function of the commercial source, as is pointed out by Suryanarayanan and Mitchell (1981). It was shown that the precipitate was a

sparingly soluble crystalline hydrate, and that the raw material was an amorphous (much more soluble) form of the drug. Seeds, and unfortuitous ratios of alpha and beta epimers of the calcium gluceptate, catalyzed the precipitation.

Precipitation is a nucleation and crystal growth phenomenon (Carstensen and Rodriguez, 1985, Rodriguez, Hornedo and Carstensen, 1985), and as such it can be impaired or prevented by inhibitors. These are often viscosity-impairing substances (carboxymethyl cellulose for instance), and hence the stability of the viscous component becomes important. The loss of this can be detected by following viscosity.

The viscosity of these agents is often Bingham bodies, i.e., they possess a yield value. The correct way of checking them is, therefore, with e.g. a cup-and-bob viscometer, so that a rheogram can be drawn. In this fashion it is possible to check both changes in yield value and slope of the rheogram (apparent viscosity). For very fluid solutions (dilute aqueous solutions) this is difficult, and most often it is best followed by the use of an Ostwald–Fenske pipette. Two pipettes (with different flow times) should be used in this case, because the difference in the measured viscosity is a measure of the yield value (although calculation of the yield value from the difference is a priori not possible). Both yield value and apparent viscosity are functions of concentration (Ben-Kerrour et al., 1980); in a multicomponent system there will usually be one main component responsible for viscosity, and it is the breakdown of this one compound that would be of importance. Often when drastic changes occur in viscosity, bacterial contamination can be suspected.

Precipitation is tied into solubility, as seen in the foregoing. Solubility can be augmented by various means. In the case of cloud times, the use of cosolvents (e.g., polyethylene glycol) will increase the value of S. Other methods are the use of a micellar approach and the use of complexation. A recent example of this latter is the work by Mehdizadeh and Grant (1984) on the complexation behavior of griseofulvin with fatty acids. Order of magnitude increases in solubility were reported.

2.4 Oral Solutions

The main types of changes in appearance of oral solutions (syrups, elixirs, etc.) are loss of dye, precipitation, and bacterial growth. Precipitation has already been dealt with to some degree, but some cases particular to oral solutions will be mentioned. Change in dye content will be treated below. Bacterial growth will be treated separately.

Scott et al. (1960) showed the loss of blue dye in a vitamin syrup, and showed that it could be treated exactly like a drug substance. Predictions by Arrhenius plotting are quite good in the case of degradation in solution, because the homogeneity is good. Figure 2 shows an example of this.

3. DISPERSE SYSTEMS

Disperse systems are suspensions and emulsions. The rationale for the physical tests carried out on these will be discussed below.

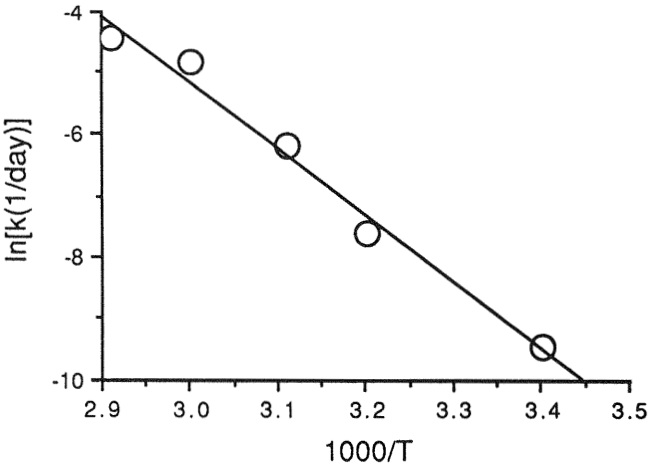


Fig. 2 Arrhenius plot of FDC Blue Dye #2 in a syrup. (Graph constructed from data by Scott et al., 1960.)

3.1 Suspensions

It would be desirable to have a suspension that did not settle (and there are such suspensions), but the general rule is that a suspension will settle, and therefore there are two parameters that are followed in this respect, namely sedimentation rate and sedimentation volume. When the sedimentation volumes are small, then there is a tendency for the suspension to cake, and hence various types of shaking tests are carried out.

Tests can be purely subjective, in that a tester notes that e.g. the suspension after three months' storage at 25°C was "difficult to resuspend, leaving some cake at the bottom." Such subjective tests should always be included in a program, but more quantitative means are desirable also. A typical quantitative test is to rotate the bottle under reproducible conditions. The type of setup used for solubility determinations is a good type apparatus for this purpose. The bottle is rotated x rotations, a sample of the supernatant is taken, and it is assayed. (This assay need not be stability indicating.) This is then repeated for twice the number of rotations, four times the number of rotations, and eight times the number of rotations. The time-relation of the assays is similar to that of a dissolution curve (although the phenomenon is redispersion), and it can often be represented by

$$Y = Y_\infty[1 - \exp(-kt)] \tag{10.9}$$

Y_∞, the asymptote value (found by iteration), should equal the dose, if caking has not occurred. The value of k is best found from the logarithmic presentation mode:

$$\ln\left[1 - \frac{Y}{Y_\infty}\right] = -kt \tag{10.10}$$

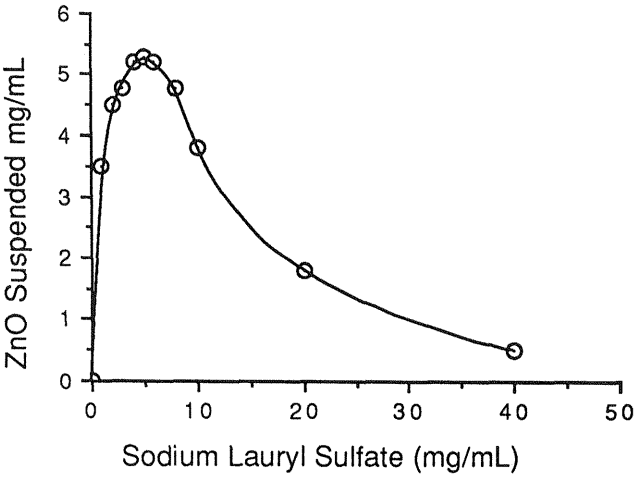


Fig. 3 Resuspension characteristics by controlled rotation. (Graph constructed from data published by Lemberger, 1967.)

k and Y_∞ can then be found by data treatment for extrapolated values or assessed in a room-temperature stability program to estimate the stability of the resuspendability parameter. Suspendability is also improved by the use of surfactants. Figure 3 shows a suspension isotherm (Moore and Lemberger, 1963) of the zinc oxide/sodium lauryl sulfate system. Such suspension isotherms should be carried out prior to the formulation of suspensions. They are in general not carried out in the preformulation effort, but rather by the formulator.

One way of accelerating the settling is to place the suspension product on a shaker at e.g. 37°C. This makes particle movement more rapid and allows the fine particles to slip into the interstices of the larger particles, hence promoting a close packing. This can then be used to judge qualitatively whether caking will take place.

It might be thought that centrifugation would be a good way in which to "accelerate" sedimentation, and the Stokes law indeed predicts this. However, it gives only an acceleration of the "initial settling rate," and the further settling, and the caking phenomena in which the formulator is interested, are not well predicted by this method.

Some caking is due to crystal growth, and this is accelerated by the use of freeze–thaw tests, i.e., alternating the temperature every 24 h from e.g. 25°C to −5°C (or some other low temperature above the freezing point of the product). The temperature cycle will promote crystal growth, and the effect of this on the product can be assessed. The freeze–thaw cycle has the advantage of emulating (and overstating) some real conditions to which the product could be exposed during shipping.

Zapata et al. (1984) have described the effect of freeze–thaw cycles on aluminium hydroxycarbonate and magnesium hydroxide gels. Coagulation after freeze–thaw cycles led to the formation of aggregates that were visible. These aggregates were particles in a primary minimum, and these were only reseparable by ultrasonic treatment. The freeze–thaw cycle affected content uniformity of both the gels, but the treatment did not alter the surface characteristics or the morphology

(as judged by x-ray powder diffraction). It did cause a reduction in the acid neutralization rate, and the rate of sedimentation increased. The effect was pronounced after the first cycle (and indeed most of the effect occurred at this point). The duration of freezing was not important, but the aggregate size grew inversely with the rate of freezing. The use of polymers in the suspensions reduced the effects of the freeze–thaw cycle.

Freeze–thaw cycles (aside from being a stability monitoring tool) can be used to screen products as well, the best of a series of suspensions or emulsions being the one that stands up best to the test. This on the surface may be logical, but without a theoretical basis it is difficult to judge the generality of such a statement.

3.2 Sedimentation Volumes

If a suspension is particulate, then the particles will (approximately) settle by a Stokes law relation, i.e., the terminal velocity, v, is given by

$$v = d^2 \cdot g \frac{\Delta\rho}{18\eta} \tag{10.11}$$

where the constant g is gravitational acceleration, $\Delta\rho$ is the difference in density between solid and liquid, η is the viscosity of the liquid, and d is the diameter of the particle. The final apparent volume of the sediment, provided it is monodisperse, would be given by the fact that in cubical loose packing a sphere of diameter d will occupy the space of its confining cube, i.e., the sedimentation volume will be

$$V = n \cdot d^3 \tag{10.12}$$

where n is the number of particles per cm^3 of suspension. Since their density is ρ g/cm^3, then (denoting the dosage level Q g/cm^3) the following holds:

$$Q = \frac{\rho \cdot n \cdot \pi d^3}{6} \tag{10.13}$$

so that, solving for n,

$$n = \frac{Q \cdot 6}{\rho \pi d^3} \tag{10.14}$$

which inserted in Eq. (10.12) gives

$$V = \frac{6Q}{\rho\pi} \tag{10.15}$$

In this view, each particle touches its neighbors. The potential diagram from two particles is as shown in Fig. 4.

When the particles touch, the potential energy becomes exceedingly large ($x = 0$), and from an equilibrium point of view they will be trapped in the primary minimum, which is the deep minimum at short distance in Fig. 4. Hence it becomes difficult to separate them, and the precipitate becomes a cake. This would prevent redispersion by shaking and would make proper dispensing impossible. It is a formulation goal to prevent this from happening, and this is done by adjusting the

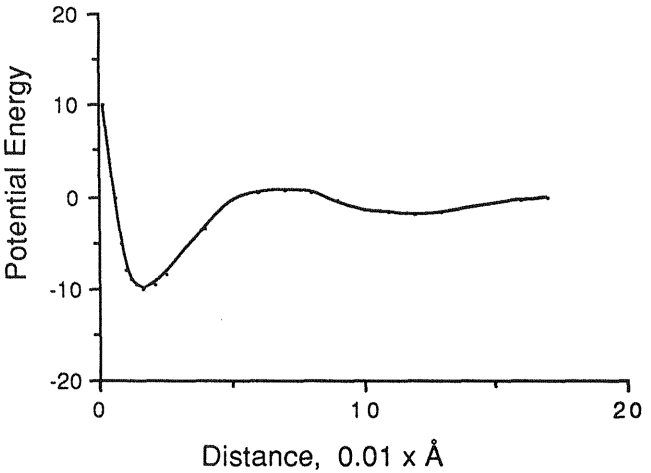


Fig. 4 Potential energy diagram for two particles.

zeta potential, as will be discussed shortly. From a formulation point of view, it is better to have the particles at larger distances, e.g., in the secondary minimum occurring at longer distances (Fig. 4).

A discussion of the connection between caking tendency and the so-called zeta potential is beyond the scope of this book. Suffice it to state the following: When particles are suspended in a liquid, they acquire a charge (and the liquid acquires a similar opposite charge, to maintain electroneutrality). The zeta potential is related to this charge, and caking is prone to happen if the charge potential is outside a range of −10 mV to +10 mV. If the zeta potential is high it can be lowered by the addition of negatively charged ions. Highly valent ions (e.g., citrate) are preferable. On the other hand, if the zeta potential is low, then it can be increased by the addition of positively charged ions (e.g., aluminium ions).

The zeta potential is measured with a zetameter. In this the particles are placed in an electrical field (between two electrodes, the voltage of which can be adjusted), they are tracked under a microscope, and their velocity is determined. The relation of velocity to voltage allows determination of the zeta potential.

It is worthwhile occasionally to check the zeta potential in a stability check of suspension (and emulsion) products. Counterions could be adsorbed and hence lose their capability of keeping the zeta potential close to zero, and this, in turn, could be the reason for subsequent caking.

When the zeta potential is close to zero, the suspension will be flocculated, i.e., the particles are positioned in the secondary minimum. The floccules are large and hence settle more slowly, but on the other hand the sedimentation volume is large. Since the particles are in the shallow minimum (small potential, i.e., easy to disrupt), they are easy to resuspend.

There are suspensions that do not settle. Here the yield value of the suspension is so large that the gravitational force does not exceed it. In this case it is very important to carry out complete rheological profiles at different time points in the stability program, to insure that the yield value is not changing. In such a system the yield value (Carstensen, 1973) is a function of the solids content and the viscosity of

the medium. If the viscosity imparting substance deteriorates, or if the flocculation characteristic (the "diameter" of the particles) changes, then the yield value may change, and what originally was not prone to cake might at a later time have such a propensity.

It has been stated elsewhere that for Bingham bodies, a yield diameter of the bottle can be calculated and below this bottle diameter there will be no settling.

3.3. Sedimentation Rates

The rational treatment of sedimentation rates has been described by Carstensen and Su (1970). Since the suspension, when placed on stability, has just been well agitated, the floccule size is not the same as it will be at equilibrium (it will be smaller). The first part of a settling curve is, therefore, governed by the reforming of the equilibrium floccule, and the latter part is governed by settling towards the equilibrium sedimentation volume. A typical plot of the final settling phase of kaolin suspensions is shown in Fig. 5. The intercept does not correspond to full height, because the settling is the final phase. The first phase, as mentioned, consists of reflocculation of the equilibrium floccule (which does not exist at time zero, because the suspension has been thoroughly shaken at that point).

The sedimentation curve is, therefore, two-phasic, and the equation for the settling curve is

$$Y - Y_\infty = A_0 \exp(-k_0 t) + A_1 \exp(-k_1 t) \tag{10.16}$$

and the curve can be deconvoluted by feathering, or by programmed four-parameter techniques.

3.4. Preservation Stability

Methyl, ethyl, propyl, and butyl esters of 4-hydroxybenzoic acid are used in various combinations in antacid suspension (and other pharmaceutical) products. The

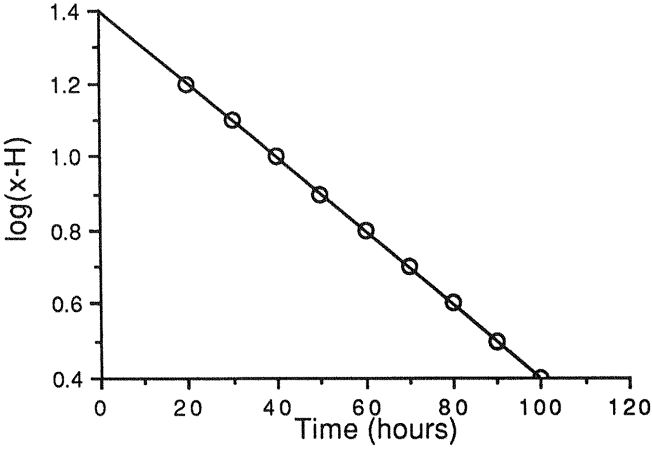


Fig. 5 Settling of kaolin suspensions. (Constructed from data published by Carstensen and Su, 1969.)

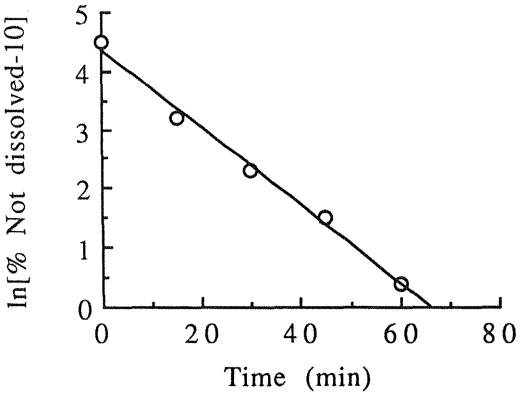


Fig. 6 The least squares fit equation is $y = 4.69 - 0.066x$ with $R^2 = 0.99$. (Graph constructed from data published by Cárdenas et al., 1994.)

antacids have high pH values, and hence hydrolysis of the esters occurs. The rationale for using several in combination is, exactly, to allow a certain amount to remain to retain preservative qualities of the suspension. An assay of the four esters and the parent acid (one of the decomposition products) in products where all occur has been described by Schieffer et al. (1984).

3.5. Dissolution of Suspensions

The 1987 Guidelines require testing of suspensions for dissolution. Cárdenas et al. (1994) have described the dissolution profiles from suspensions of benzoyl metronidazole, and a graph constructed from their published data is shown in Fig. 6. The curves should, by all rights, follow a cube root law without lag time, but they do not do so. If adjusted for amount not dissolved at the end (in the figure, 10%) they will adhere to a sigma minus plot.

3.6. Temperature Testing of Disperse Systems

A suspension is, as the name implies, a two-component system consisting of a solid and a liquid phase. (Gas phases are considered nonessential in this connection). Obviously, the solubility of the compound is a function of the temperature, and at a given temperature above 25°C this solubility will be reached. Testing about this temperature obviously has no meaning as far as suspension stability (neither physical nor chemical) is concerned. Prior to starting a program, this temperature should be established, so that unnecessary sampling stations can be avoided.

3.7. Semisolid Suspension Systems (Ointments, Suppositories)

Some semisolid systems (ointments and suppositories) are suspensions. Their testing is not different, in general philosophy, from what is described above, except that the rheology is checked differently. Davis (1987) has reviewed sophisticated means of checking the stability of such systems.

The factors checked for in stability programs of such products are the following:

1. Consistency, fell to the touch
2. Viscosity
3. Polymorphism

It is mentioned elsewhere that migration of a "disperse" phase within a semisolid product is quite possible when another phase is present. This situation may occur in the case of the use of benzocaine in, for instance, a suppository wrapped in aluminum foil coated with polyethylene. Polyethylene lining of aluminum wraps of suppositories is used to prevent contact between the metal and the suppository, and in most cases this has a positive effect.

However, a partitioning of drug or additive between the two phases may be possible if the drug or additive is suspended in the suppository. Denoting its solubility in the polyethylene S_p and the solubility in the suppository base S_s, the compound would disappear from solution in the suppository at a rate proportional to $S_p - S_s$, and "disappeared" compound would be replenished by dissolution from the solid phase.

The rate of disappearance would be governed in that the value of S_p would increase by a sigma minus relation (i.e., in the same manner as the appearance of decomposition product in a first-order reaction), and this then would be the overall "loss" of compound as a function of time. Since this is a first-order overall relationship, the "decomposition" would, initially, appear to be first order.

3.8. Ointments and Transdermals

Polymorphism can be followed by x-ray analysis and in some cases by thermal methods. There is, in fat systems, the possibility of trans esterification, and this can be tested for chemically.

The problem of morphology changes is often of particular importance and of particular frequency in the case of suppositories. In this type of product, it is also important to check for migration of suspended/dissolved substances. Often a substance is added to a suppository as a suspended particle, which is soluble in the suppository base to some extent. The phenomenon of dissolution will, of course, become evident by checking the particle size as a function of time. If a substance is soluble in the base, then it is preferable (if possible) to saturate the base with it at the onset. For this reason it is necessary to determine the solubility (S gm/gm) of the drug (or other) substance in the base. A Van't Hoff plot [solubility as a function of temperature (T°K), i.e., plotting $\ln[S]$ versus $1/T$] will allow extrapolation to room temperature. In manufacturing it is advisable to dissolve the drug (or other substance) to the extent of its solubility during the intermediate temperature phase of manufacturing (where the preparation is still quite fluid) and then suspend the rest at a lower temperature. An example is ascorbic acid, which is a good antioxidant in Carbowax bases. To exert its antioxidant action it must, however, be dissolved (and it is quite soluble in polyethylene glycols).

Dissolved drug (or other substance, e.g., benzocaine) will diffuse in the suppository base, and can, for instance, partition into polyethylene linings of the suppository wrap.

Release rates are important in many topical preparations, in particular in transdermal preparations. Here there are several investigational methods available. In-vitro methods involve placing the ointment on a membrane and measuring the appearance of drug in a receptor compartment on the sink side of the membrane. Hoelgaard and Møllgaard (1983) have, for instance, described the in-vitro release of linoleic acid through an in-vitro membrane. They mounted abdominal human skin in one case and skin from hairless rats in another to open diffusion cells. The dermal side was bathed with a receptor medium stirred at 37°C. The medium was 75 mL of 0.05 N phosphate buffer (pH = 7.4) which contained 0.05% Pluronic F68 and 0.01% butylhdroxytoluene, the latter two ingredients added in order to increase the lipid solubility. Linear, Ficksian diffusion curves were obtained. In a stability program, such tests are obviously useful and should be repeated periodically, but an "internal standard" or "calibrator" should be used, i.e., a stable test substance, the diffusion of which is known (e.g., salicylic acid). Other pseudo-in-vivo methods involve shaved or hairless rabbits, or cadaver skin. The interaction between ointment and container (patch) should also be part of the stability program.

Some of the testing applicable to semisolid emulsion systems is also applicable to ointment systems and will be discussed at a later point.

4. EMULSIONS

An emulsion should be thought of as a metastable system. In most cases the emulsion system (Fig. 7) is thermodynamically more energetic than the ground state system, which would simply be the totality of the two phases, separated. There will, therefore, always be the potential for oil droplets re-merging in an attempt to create the thermodynamically stable system.

Emulsion systems are taken orally (LipoGantracin™, Roche), parentally (as parenteral fat emulsions), and topically (creams).

4.1 The Emulsion Interface

The factors that stabilize the emulsion system are a layer of surfactant and protective colloid on the exterior of the droplet. The amount of these two must be such that they

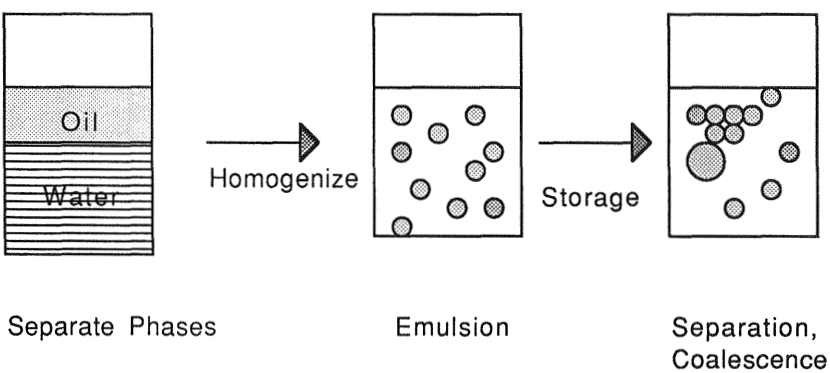


Fig. 7 Emulsion system.

cover the entire area of the droplets, otherwise coalescence will occur to the extent that the area, A, of the droplets will be reduced to such a point that it now will be completely covered by surfactant and protective colloid.

If, for instance, 1 g of emulsion contained W g of droplets of a size d μm and the oil had a density of ρ g/cm^3, then there would be n droplets per cm^3, where n is given by Eq. (10.14). Each particle has a surface area of πd^2, so that the total area is

$$A = n\pi d^2 = \frac{6Q}{\rho d} \tag{10.17}$$

Example 10.1.

If the density of the oil is 0.9 g/cm^3, the amount of oil phase per cm^3, is 0.75 g, and the diameter of the oil globules is 10 μm (10^{-3} cm) what is the surface area of the oil phase?

Answer.

$$A = \frac{0.75}{10^{-3}}\frac{6}{0.9} = 5 \cdot 103\,\text{cm}^2 \tag{10.18}$$

Example 10.2.

If a surface active agent of molecular weight 800 and cross-sectional molecular area of 30 Å is present in a concentration of 0.2% will that suffice to cover the surface in Example 10.1?

Answer

2 mg/cm^3 = 2/800 = $2.5 \cdot 10^{-3}$ millimoles = $2.5 \cdot 10^{-6}$ moles, which in turn equals $2.5 \cdot 10^{-6} \cdot 6 \cdot 10^{23} = 1.5 \cdot 10^{18}$ molecules = $30 \cdot 1.5 \cdot 10^{18}$ Å^2 = 4500 cm^2, this is the surface the surfactant could cover. This is slightly less than the 5000 cm^2 surface area of the oil, so that the entire surface of the oil globules cannot be covered by the surfactant.

The above calculations are oversimplified. They assume, for instance, that all the surfactant is adsorbed onto the oil, which is not the case. It is important, however, to check, originally, whether enough surface coverage of the oil is provided for. If not, there will be an initial shrinkage of surface area (increase in droplet size) attributable to this. Hence, if the coverage of the droplets with surfactants and/or protective colloid is incomplete at the time of manufacture, then the droplets will grow in size as time progresses. Rowe (1965) for instance demonstrated that the globule size decreases with increasing surfactant concentration, as shown in Fig. 8.

4.2. Globule Size and Viscosity

The breakage of suspensions will be dealt with shortly, but (Fig. 7) it might be suspected that breakage would be a function of Stoksian motion [Eq. (10.11)], i.e., the globules move and collide and hence coalesce. This is true in a sense, but

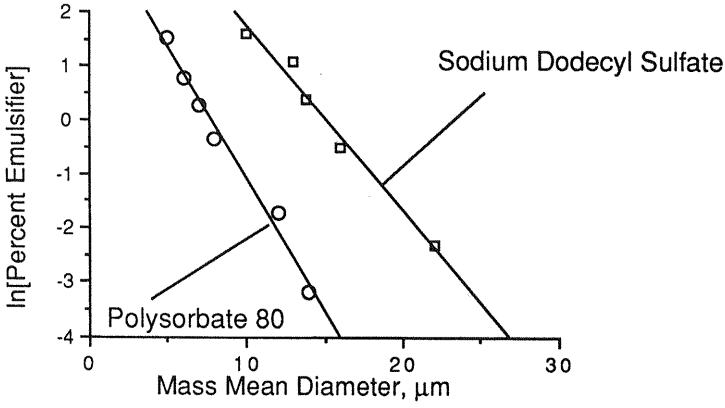


Fig. 8 Effect of emulsifier concentration of globule size. (Graph constructed from data by Rowe, 1965.)

the conclusion that might be drawn would then be that to increase viscosity [Eq. (10.11)] would reduce the severity of such impacts. However, Siragusa (1995) has demonstrated that although increased viscosity to some extent makes an emulsion more stable, the more important factor is the stability of the surfactant/protective colloid system at the interface. From a stability point of view, there is a correlation between the overall emulsion viscosity and the globule size. Figure 9 shows a typical example of viscosity as a function of droplet size and phase ratio (Sherman, 1964).

Hence, checking viscosity in the stability program, in a manner of speaking checks the globule size, which is the prime indicator of potential for progressing creaming and breaking. The viscosity is usually checked by a cup and bob method. The limitations of this will be discussed in the section dealing with semisolid emulsion systems.

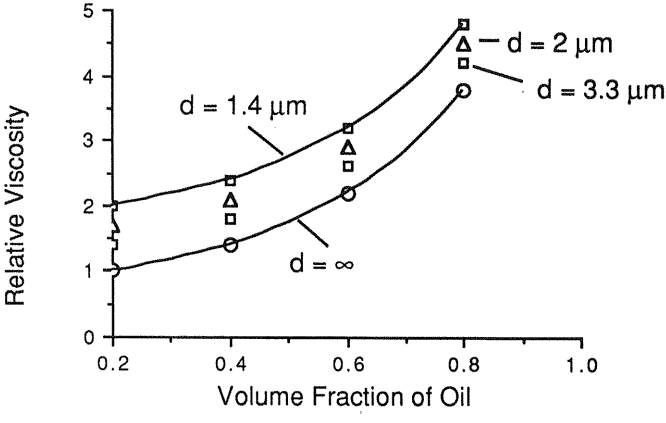


Fig. 9 Viscosity as a function of droplet size and phase ratio. (Constructed after data published by Davis, Sherman, 1964.)

Direct measurement of the droplet size can be accomplished in several ways: microscopy, electronic (Coulter) counters, photon correlation spectroscopy (for particles that are very small, Davis, 1967), diffuse reflectance spectroscopy (Akers and Lach, 1976) and the measurement of ultrasound (Rassing and Atwood, 1983). Davis (1987) points to the importance of choosing the proper techniques. He cites an example where a fat emulsion was tested for stability (as regards droplet size and distribution). The accelerated test used was a shaking test. The tests used were (a) microscopy (large globules), (b) electronic counting (medium size globule count) and (c) photon correlation spectroscopy (small particle count). Figure 10 shows the results.

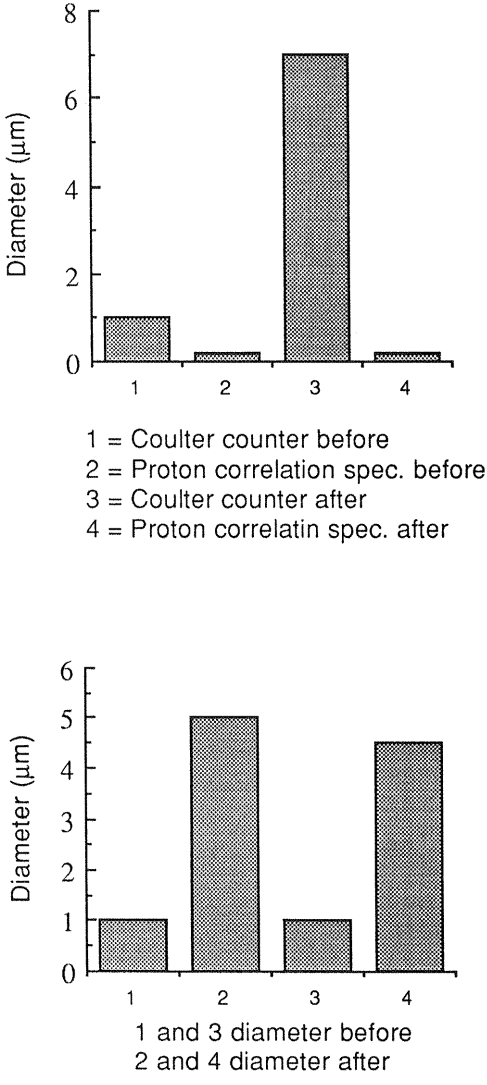


Fig. 10 Particle size analysis of accelerated test of emulsion system. (Constructed from data published by Davis, 1987.)

It is obvious that the small globule count does not change much, but that the intermediate count changes a lot. (The large globule count would then change in complement fashion to the intermediate count, and this was confirmed by the microscopy results.) What is important in this particular case (the system tested was a parenteral fat emulsion) is that there was formation of large oil droplets (not visible to the naked eye), and that these could have had a bearing on the toxicity of the product. This demonstrates that one method in itself is not enough, and that not one but several methods should be considered.

Reng (1984) has advocated electrical conductivity as an overall, common means of determining the state of dispersion of an emulsion system, and he shows that this parameter changes significantly over short periods of time, if the emulsion system is not satisfactory.

4.3. Stability of the Emulsifier/Protective Colloid System

The other phenomenon that may happen, which affects droplet size, is chemical breakdown in the surfactant. Nonionic surfactants are frequently used, and they are esters that may hydrolyze or interact with other components of the emulsion. Part of the formulator's job is, in independent experiments, to determine the pH profile and interaction potential of the surfactant (in a system simply consisting of the aqueous phase) with the other additives of the emulsion system. This can be done simply by cloud times (at accelerated temperatures) if the acid or alcohol from the hydrolysis or the interaction product is poorly soluble (as it is in the case of polysorbates and arlacels).

The problem with nonionic surfactant hydrolysis is exactly that it produces a fatty acid, which may become part of the oil phase and hence (aside from providing less coverage of the oil droplet) change the emulsion characteristics of the system.

In general the formulator also determines the HLB (hydrophilic/lyophilic balance) of the system he works with and matches it to the surfactant used [Atlas Chemical Company (now ICI Americas), 1963]. The HLB of the emulsifier can be adjusted by mixing two emulsifiers, e.g., arlacel 85 has an HLB value of 2.0 and polysorbate 80 one of 16.5. If an emulsion system required an HLB of 10 for instance, then the ratio of polysorbate (x) to arlacel ($1-x$) would be given by

$$2(1-x)+16.5x=10 \tag{10.19}$$

or

$$x=\frac{8}{14.5}=0.55 \tag{10.20}$$

4.4. Emulsion Type

In emulsion formulation, the type of emulsion is of concern. If it is desired to make an oil-in-water emulsion (o/w, i.e., oil is the discontinuous phase), then it is important that phase inversion not occur. Investigating this possibility must be a task in the stability program (and is usually carried out by the formulator, not the preformulator). Most often phase inversion is associated with creaming and separ-

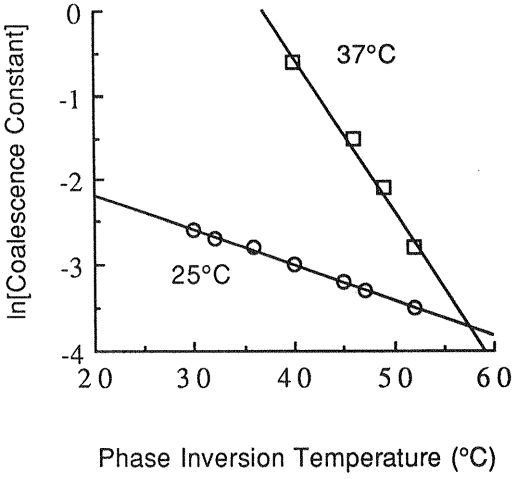


Fig. 11 Coalescence rate versus inversion temperature. (Graph constructed from data published by Enever, 1976.)

ation and will be noticed in the appearance testing of the emulsion. Such phenomena lead to graininess of feel. In some cases part of an emulsion will invert, another not, and then there is a distinct difference in appearances in various regions of the emulsion (creaming).

But the possibility for inversion should always be considered. It is the more likely the closer the system is to a close-packed system of spheres. In this connection, another of the formulator's tasks should be to determine the inversion temperature. (This is at times used to advantage in the manufacturing step, in that, in producing the emulsion, the inverse emulsion is produced at high temperature; this is then cooled, and at the inversion temperature, the "correct" type will result. Conversion in this manner gives rise to very small globules, and homogenization is then often not necessary.) If an inversion temperature exists, then accelerated testing above this temperature is meaningless. So preliminary testing is always advocated, if accelerated testing is contemplated, the philosophy being that there is no sense in testing a system above a temperature where it converts to a physical state that differs from that at room temperature (or recommended storage temperature). Enever (1976) has shown that there is a correlation between phase inversion temperature and the rate of coalescence (Fig. 11). It is possible to use a combination of sedimentation field flow fractionation and photon correlation spectroscopy to record droplet sizes in fat emulsions, and this would appear to be an excellent technique for studying the coalescence of finer spheres, and hence to obtain an extrapolatory tool early on in the storage of an emulsion system.

4.5. Rheological Properties

It has been mentioned that there is a gross correlation between viscosity and globule size. However, the rheological characteristics of an emulsion system in general depends on other factors as well (Sherman, 1955):

1. The viscosity of the internal phase

2. The viscosity of the external phase
3. The phase volume ratio
4. What emulsifiers are used and in what amount
5. The electroviscous effect
6. Distribution of particle sizes

4.6. Appearance of Emulsion Systems

The appearance of the emulsion will be a function of globule size, and Table 2 gives a gross correlation of these two factors. When an emulsion breaks, the hyponatant, rather than being a solution, will have one of the two first appearances in the table, i.e., will also be an emulsion, but with very fine droplets.

4.7. Breaking and Coalescence

It can be concluded from what has been mentioned that the reasons for breaking would include

1. Chemical incompatibility between the emulsifier and another ingredient in the emulsion system (Borax and gum acacia is a case in point)
2. Improper choice of surfactant pair (e.g., wrong HLB)
3. High electrolyte concentration
4. Instability of an emulsifier
5. Too low a viscosity
6. Temperature

As shown in the foregoing, breaking and creaming of emulsions are the typical defective criteria to be looked for in stability programs. Breaking implies that the emulsion separates into two distinct phases (Fig. 7). If this is a slow process, it often manifests itself in the appearance of small amounts of oil particles on the surface, and it then is referred to as *oiling*. When separation into two emulsions occurs (as described above), then the phenomenon is called *creaming*. A rapid test for this is to dip a finger into the preparation and notice if there are different "colors" present (Brown, 1953). Also, a creamed o/w emulsion will not drain off the skin with ease, and the converse holds for a creamed w/o emulsion.

A few words regarding the effect of ionic substances and the actual process of flocculation and coalescence are in order. Van den Tempel (1953) demonstrated that flocculation and coalescence are two different processes. Flocculation depends on electrostatic repulsion (and is akin to the zeta-potential considerations discussed previously). Coalescence depends on the properties of the interfacial film.

Table 2 Correlation Between Globule Size and Appearance of Emulsions

Globule size (μm)	Appearance
>0.005	Translucent (transparent)
0.005–0.1	Semitransparent, gray
0.1–1	Bluish-white emulsion
>1	Milky-white emulsion

Cations, as a whole, are less soluble in the oil phase than anions, and this gives rise to negatively charged droplets (akin to the creation of a zeta-potential in suspensions). The potential drop over the film depends on the nature of the electrolyte (and it should be noticed that there is a diffuse double layer in both liquids as opposed to the case of suspensions, where there is only one diffuse double layer).

Electrolytes may either improve or worsen the stability: If they eliminate the protection offered by the surfactant/protective colloid system then coalescence occurs. Most often electrolytes have the effect of reducing the emulsifying powers of surfactants and causing salting out or actually precipitating the surfactant. However, in some cases, electrolytes will favorably affect the potential drop over the two double layers, and in this case they may stabilize the suspension system.

4.8. Semisolid Dosage Forms

Semisolid emulsions (cold creams, vanishing creams) are not different, in general philosophy, from the above, except that the rheology is checked differently. Davis (1984) has reviewed sophisticated means of checking the stability of these types of systems. He lists the following properties as being important in stability programs for semisolid emulsions:

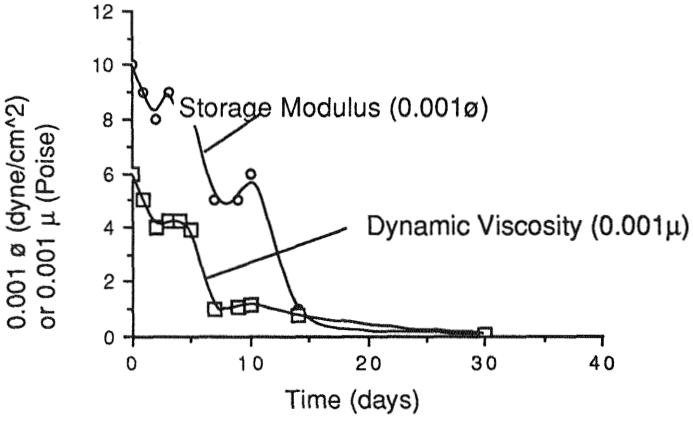
1. Particle size
2. Polymorphic/hydration/solvation states
3. Sedimentation/creaming
4. Caking/coalescence
5. Consistency
6. Drug release

Of these, particle size, sedimentation/creaming, caking-coalescence, and consistency have been discussed earlier.

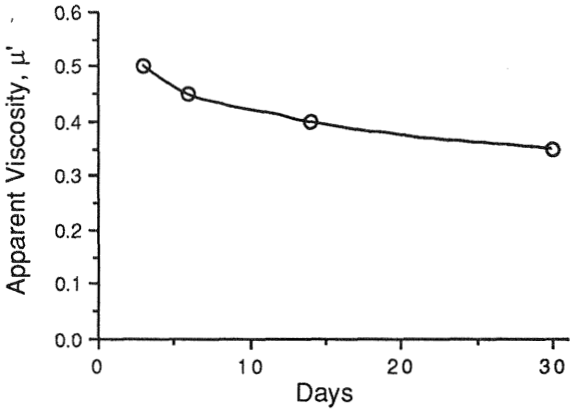
Following viscosity as a function of time is here of particular interest. The problem is how to measure the viscosity, and what viscosity in essence means. Davis (1987) points out that changes in viscoelastic properties are much more sensitive than simple continuous shear measurements (Barry, 1974). He demonstrates this via data published by Eccleston (1976). Here (Fig. 12) the variation of the dynamic viscosity (η) and the storage modulus (ϕ) are shown and compared with the same type of graph for apparent viscosity (μ') from continuous shear experiments. It is obvious that the two former measurements are much more sensitive.

4.9. Transdermals

The most important concern about transdermals is the release of drug substance from them and the stability of this property. Other properties (stickiness, appearance, etc.) are of importance as well, but the release characteristic is paramount. Kokobo et al. (1991) have described a means of checking this in vivo by using a single diffusion cell. The volume could be, for instance, 2.5 mL, and the diffusion area could be of the order of 1 cm^2. The matrix is placed, e.g., in contact with a 40% polyethylene glycol solution, which can be, e.g., removed in 500 μL quantities.



(a)



(b)

Fig. 12 (a) Dynamic viscosity (v) and storage modulus (ϕ) and (b) apparent viscosity (μ') as a function of storage time for cosmetic creams made from stearyl alcohol. (Graph constructed from data published by Eccleston, 1976.)

Kokobo et al. (1994) have reported on the interaction between pressure-sensitive adhesives and drug combinations used in transdermals. Their data are shown in Fig. 13. The data fit neither a diffusion equation (ln of retained versus time) nor a square root equation directly. It would appear that if one allows for either an initial dumping in the diffusion equation (or includes more than one term in the Barrer equation) or a lag time in a square root equation, then the data will

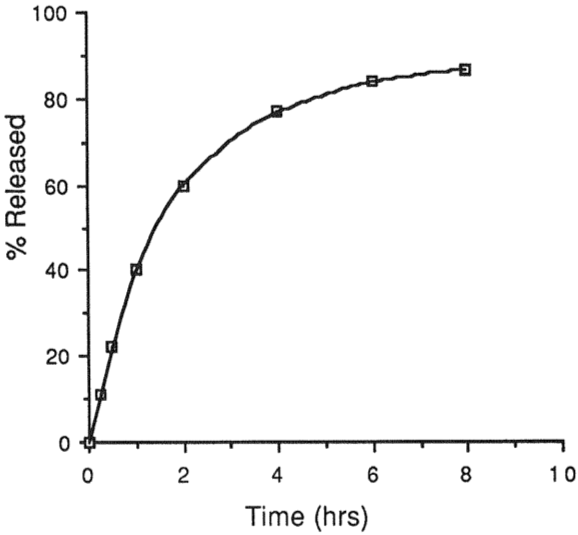


Fig. 13 Release of dipropylphthalate from 2-ethylhexylacrylate acrylic acid copolymer (2EHA/AA). (Graph constructed from data reported by Kokobo et al., 1994.)

fit either. A modified diffusion equation is probably the most likely. The authors suggest the use of the Williams–Landel–Ferry equation for fitting:

$$\{\log D\} - A = \frac{-896}{51.6 + (T - T_g)} \tag{10.21}$$

where D is the diffusion coefficient, A is a constant, and T_g is the glass transition temperature of the polymer.

5. ACCELERATED TESTING AND PREDICTION

Accelerated testing of physical properties of disperse systems is not as clear-cut as for instance chemical kinetics prediction. For instance, the stability of properties of semisolid materials is very difficult, for instance, for creams and ointments that give rise to bleeding there does not seem to be any reliable predictive test. Yet a series of stress tests are used for disperse systems. They include

Shaking tests
Centrifugal tests
Freeze–thaw tests
Elevated temperature tests

It should be cautioned that although these types of tests can be performed on a comparative basis (Is formula A better in one respect than formula B?), their interpretation, other than saying that A is better (or worse) than B, is uncertain, and predictive aspects are somewhat lacking, because the phenomena tested in the accelerated tests do not necessarily mimic what will happen in room temperature storage a/o shipping (Davis, 1987; Rhodes, 1979a and b).

For the freeze–thaw test, the question is what the minimum temperature should be, temperatures from −5° to +5°C being the most common. −5°C frequently gives rise to phase separation and irreversible changes that would not be seen in usual temperature ranges (Nakamura and Okada, 1976), but again, such tests may be used to select a "presumably best" formula from a series of preparations in product development. Results of a typical freeze–thaw cycle are shown in Fig. 10.

Centrifugation has been used by some investigators (Tingstad, 1964; Hahn and Mittal, 1979; and Ondracek et al., 1985). The general idea is that g can be increased in the terminal velocity predicted by Stokes's law (Eq. 11), but often the stresses caused by centrifugation may cause coalescence, which would not occur during normal collision stress.

Some investigators claim fair success in predictions by this means, but as Davis (1987) cautiously states, "as a general rule it can be stated that systems that withstand accelerated stress conditions should be stable under normal storage conditions. However the corollary is not necessarily true." That is, if the preparation fails the test it *may* still be all right, but if it passes the test it should be all right. Although this may be true overall, one can visualize that if a preparation is centrifuged right after manufacture, then the stress does not include the chemical changes (surfactant decomposition for instance) that occur on storage, and in this respect it may give too optimistic a prediction.

Buscall et al. (1979) have measured phase separation at several different centrifugal gs and have established from these data a so-called coalescence pressure. This (again recalling that the test does not account for chemical changes on storage) may be an appropriate parameter.

One predictive method in formulation is the correlation afforded by coalescence rates (Fig. 11), and this is rational in selecting the "best" of many formulations; in general the system with the highest phase inversion temperature is the best. The (nonchemical stability dictated) coalescence rate could theoretically be calculated prior to storage, and the difference between observed and calculated then attributed to chemical stability causes.

For emulsions, it should again be pointed out that rapid creaming and flocculation does not necessarily mean rapid coalescence. For emulsions there have been reports (Rhamblhau et al., 1977) that attempted to tie zeta-potentials to emulsion behavior on storage, but the generality of such an approach has been questioned (Davis, 1987).

The shaking test is usually carried out at 2–3 hertz (Davis, 1987), and the philosophy here is to intensify the collision frequency between globules (and to some degree also the intensity). This is therefore considered an accelerated test, but it actually is part of the product life (transportation). In any event, it should be included in protocols and simply reported.

6. AEROSOLS

Sciarra has reviewed pharmaceutical and cosmetic aerosols (1974). Aerosols are solutions, primary emulsions, or suspensions (i.e., suspensions in a suitable solvent such as ethanol) of active principle in chlorinated hydrocarbons, contained in a pressure can. Either a dip tube or a metering device connects the pressurized liquid contents to the valve. Upon activation of this, the internal pressure will force

the liquid through the valve orifice and atomize the suspension. The chlorinated hydrocarbon and the primary emulsion or suspension vehicle will evaporate, and the drug, in finely divided form, will be administered to the location of treatment (lung, skin).

In general the physical instability of aerosols can lead to changes in (a) total drug delivered per dose or (b) total number of doses that may be obtained from the container. It is intuitively obvious that the particle size range must be fine (i.e., the particles will have to pass through the valve).

In general the primary disperse system is filled into a seamless aerosol can, the valve assembly is attached, and the halogenated hydrocarbon is filled by pressure through the valve. The under-the-cap filling method has been described by Boegli et al. (1969). The halogenated hydrocarbon can, alternatively, be "liquid filled" at low temperature. For products that are moisture sensitive, this presents the problem of condensed ice and water in the product.

As far as "cleanliness of operation," aerosol lines are usually kept separate from conventional filling lines (Sciarra, 1974) (or the product is contract filled). Some attempts have been made to use ethylene oxide sterilization of the can (Joyner, 1969a, 1969b), and aseptic fillings (Harris, 1968; Sciarra, 1967) can be carried out.

6.1. Aerosol Testing

Some testing methods are official in the USP (XXI). The Chemical Testing Manufacturers Association has developed a series of tests described in the ASCM Handbook (Aerosol Guide, 1981).

Several test methods are used to detect physical aerosol instability, viz., (1) unit spray content, (2) color and odor, (3) rate of leakage, (4) moisture and trace catalytical substances, (5) particle size distribution, (6) spray characteristics, (7) moisture and trace catalytical substances, (8) pH, (9) delivery rate, (10) microbial limit tests, and (11) container compatibility.

Of the above, leak testing is official in the USP (XXI). This consists of obtaining the weight loss after at least 3 days of storage and converting it to loss per year. If plastic-coated glass containers are used, the test should be done at constant humidity. A faster method is to use an eudiometer tube described in the CSMA aerosol guide. This has the advantage of speed and also is advantageous in that it distinguishes between leakage from crimp versus leakage from valve gaskets.

For spray characteristics a qualitative measurement is to spray onto paper that is treated with a mixture of dye and talc, as described in the CSMA Aerosol Guide. There are also radiotracer techniques (Smith et al., 1984) and TLC graphic techniques (Benjamin et al. 1983). The Aerosol Guide, p. 77 also describes a method whereby the spray is sprayed through a pie shaped wedge onto a rotator.

Particle size analysis is the most important characteristic and hence the most important aerosol stability test. Sciarra states that particle sizes are between 1 and 10 μm and mostly between 3 and 5 μm. Particle size affects stability of delivery rate, effective dose, mass of drug delivered and of course the stability of the suspension itself. The methods used are microscopy, sedimentation methods, light scattering, cascade impactors, and liquid impingers. If the particle size distributions are determined by electronic methods (e.g., Coulter counter, Malvern), then allowance for solubility should be made.

Polli et al. (1969) have shown that the spray particle size is reduced by decreased drug particle size, by concentration of drug, and by the valve orifice size. Higher propellant temperature, vapor pressure, and using a surfactant in the formula also made the spray particle size smaller.

Particle sizes are important for reasons other than physical stability. For inhalation aerosols, for example, it should be recalled that particles larger than 20 μm do not go past the terminal bronchioles, and particles at 6 μm do not reach the lower alveolar ducts. Particles 0.5 to 5 μm reach the alveolar walls and are intermixed with alveolar fluid (Idson, 1970). The chance for a 1 μm particle depositing is less than 50%. There is therefore, particularly for inhalation aerosols, a very narrow particle size range of effectiveness.

Moisture testing is of importance, and except for foams, pharmaceutical aerosols are nonaqueous suspensions. Devices exist that will allow the transfer of the content of the can directly into a Karl Fisher apparatus. This is preferable over transfer by cutting the can open, since this method would allow for condensation of water into the product (which is chilled at the time of the opening of the can). A description of the can device for piercing the can is to be found in the CSMA Aerosol Guide; it allows direct sampling from the content of the aerosol. The moisture is measured by Karl Fisher titration, and there are a number of commercially available instruments that can accomplish this.

Pressure testing is also an official USP XXI method. A prepressurized gauge is placed on the valve stem, and the valve is actuated so that it is all the way open. In the CSMA Aerosol Guide, pressure testing is described. One method employs piercing the can; the other tests directly through the valve.

Microbial limits are described in the USP, e.g., betamethasone valerate topical aerosol. The microbial limits must meet the requirements of the tests for the absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa* under the Microbial Limit Tests.

Delivery rate is official in the USP XXI. The aerosol is allowed to temperature-equilibrate at 25°C. The weight is determined, the can is then actuated for 5 seconds, the weight is determined again, and the delivery rate is then calculated by difference. Delivery rates usually change on storage because of changes in elastomer hardness and gasket swelling. An apparatus is available from Peterson/Puritan Inc. that is accurate to four significant figures. In this assembly a solenoid can hold and actuate, and measure to 0.001 seconds by stop clock (Johnson, 1972).

Poiseuille's law applies to aerosol spray delivery rates: Fisher and Sheth (1973) have shown that delivery rate is linearly related to the container pressure and that it is inversely proportional to viscosity of the can content. Also for a satisfactory system, the delivery rate will not to any great extent be a function of how much of the can has been emptied out. Of course if a can is emptied in one fell swoop, then the cooling effect of expansion may slow down the rate. Also, fractionation of propellant mix occurs and may lead to increased variation of delivery rate.

Valve testing and evaluation should always be done on the final formula (i.e., not on selected solvent systems). A pure solvent will not fractionate, and hence the variation of spray rate may be smaller than with the final formula.

Finally there is the question whether there is an interaction between the can and the product. Can interaction and moisture content are closely related, since under

adverse conditions, the halogenated hydrocarbon will react with water and form a halogen acid that may corrode the can. Coating of cans can slow down the rate of this corrosion but not necessarily eliminate it. The control of moisture is therefore important not only for this reason but often also for the reason of chemical stability of the drug.

6.2 Sprays

These are mentioned here in distinction from aerosols; they are mostly nasal sprays. In testing these, the droplet size is important in metered-dose sprays, since small droplets can reach bronchi and alveoli, which would be undesirable, e.g., for delivery of corticosteroid treatment of rhinal disease. Yu et al. (1984) have described a simple experimental setup used for determining the droplet size of flunisolid nasal spray. It is a glass chamber with an air inlet and a plastic stopper that has a hole matching that of the spray unit. This is connected via a conical cavity to a cascade impactor and an appropriate flow meter. This can be done (more expensively) by laser holography (Yu et al., 1983). Such instrumentation may be used to follow possible changes in droplet size distribution as a function of time.

VanOort et al. (1994) and Byron (1990) emphasize that the size of the particles is one of the most important factors in the efficiency of deposition of solids from inhalation aerosols. The FDA has called for a sampling chamber size of 500 mL (Adams, 1989). VanOort et al. (1994) have modified the Anderson Impactor as shown in Fig. 14 and have shown that the chamber volume greatly affects the percentage respirable dose.

VanOort et al. (1994) also tested the effect of the chamber volume, as shown in Fig. 15. In an Andersen Sampler (Andersen Sampler Inc., Mark II 1 ACFM Nonviable Ambient Sampler), the manufacturer recommends that, at a flow rate of 28.3 L/min, the effective cutoff diameters (ECD) are 9, 5.8, 4.7, 3.3, 2.1, 1.1, 0.7, and 0.4 μm for stages 0 to 7.

7. POWDERS

Pharmaceutical powders are for reconstitution into either suspensions or solutions. A prescription example of the former is chloramphenicol palmitate, where the reconstitution is carried out by the pharmacist prior to dispensing. An example of the latter is Metamucil, where the customer reconstitutes the product (e.g., in orange juice). Examples of solutions are Achromycin IM (which is a parenteral powder, i.e., not a lyophylizate). Over-the-counter examples of oral solutions of this type are older products such as Vi Magna Granules (Lederle^{TM}). Analogies in the food area are fruit drink powders, which are sold in packets and reconstituted by the consumer to a certain volume.

The main physical concerns in this type of product are appearance, organoleptic properties, and ease of reconstitution. Only the latter will be treated here.

There are several reasons a powder may change dissolution time as a function of storage time. The most common reasons are (a) cohesion, (b) crystal growth, and (c) moisture sorption, which causes a *lumping up* of powders. The latter is simply due to the dissolution and bridge-forming that occurs and is akin to what happens in wet granulation.

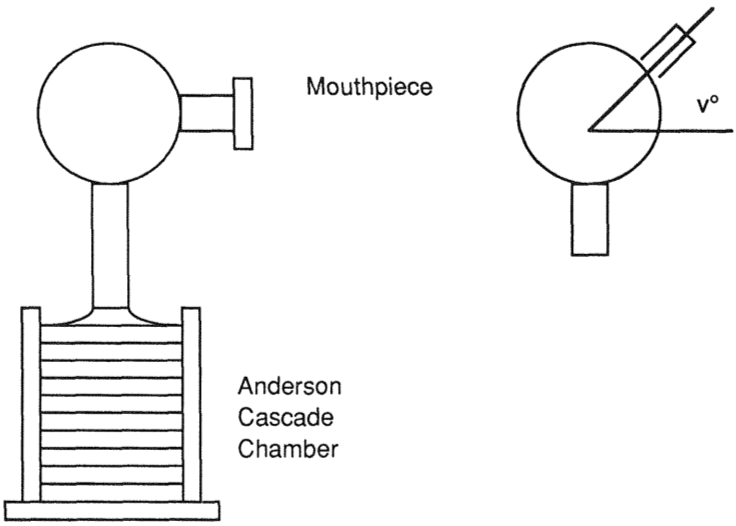


Fig. 14 Figure drawn from schematic published by VanOort et al. (1994).

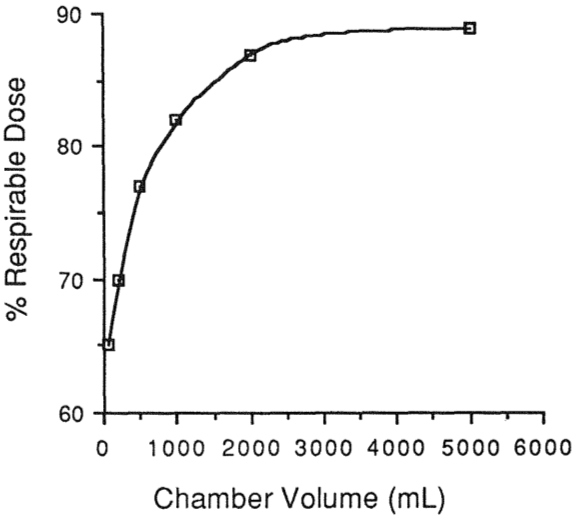


Fig. 15 Chamber volume vs. respirable dose. (Graph constructed from data published by VanOort et al., 1994.)

Cohesional force is the force between two particles, and *cohesion* in general is the stress (force per cm^2 of surface) that a particle experiences due to the surrounding particles. Problems due to cohesion are particularly predominant when a powder is fine, and great fineness of a powder is often required for dissolution reasons. Cohesional forces are inversely proportional to the square of the distance between the particles, so that in storage, where vibration, for instance, may consolidate the powder bed, these forces become large, and the powder "cakes up." This may give rise to problems in reconstitution.

There are two situations in *crystal growth*. One is due to the polymorphism. If the original product is either a metastable polymorph or amorphous, the conversion may occur in storage. For this to happen, some stress, e.g., the presence of moisture, must occur. The stress need not necessarily be moisture, conversion of a small amount of powder might occur in the filling head of the filling machine and then propagate in time.

If the content of the drug substance is such that there are no neighboring drug particles, then this conversion is limited. Particularly, contact points allow for propagation of conversions in situations where the spontaneous nucleation probability is low. The presence of moisture will accelerate conversions of this type, once a seed of the stable polymorph (or in the amorphate situation, once a crystal) has formed.

Crystal growth is, per se, not to be expected. It is true that, by the Ostwald–Freundlich equation, a larger crystal is thermodynamically favored over a smaller one; but the energy differences in the usual particle ranges is small and the activation energy high, so that the likelihood is rather low. If sufficient moisture is present so that the vapor pressure in the container exceeds that of a saturated solution, then some of the drug will dissolve in sorbed moisture. Fluctuations in temperature are never absent and would cause dissolution followed by precipitation, and this can lead to crystal growth. In cases where a drug substance is capable of forming a hydrate, and where an anhydrate is used, growth by way of hydrate formation is possible.

Ease of reconstitution is usually carried out subjectively, in that a tester carries out the reconstitution in the prescribed manner and records the length of time required to finish the operation. For this purpose it is important to have detailed directions on how the reconstitution is to be carried out, and to be sure that there is no operator-to-operator performance bias.

To insure the latter, a set of operators is usually selected for the operation at a point in the stability history. These operators will then be the test instruments for all testing of reconstitutability of oral powders.

The manner of screening operators could be as follows. A random sample is taken of a batch of a product. Random sets of four are taken from this random sample, and e.g. three operators tested. They are each given four samples to reconstitute on the first day, four on the second day, and four on the third day. It is a good policy to have two batches and mix them by day and operator, so as to carry out the test in a blind fashion. The results of such a screening could be as shown in Table 3.

Table 3 Screening of Operators for Reconstitution Testing. Reconstitution Time (min)

	Operator		
	1	2	3
Day 1	1.3±0.3	1.5±0.2	1.4±0.5
Day 2	1.7±0.5	1.4±0.4	1.5±0.3
Day 3	1.5±0.6	1.3±0.5	1.7±0.4

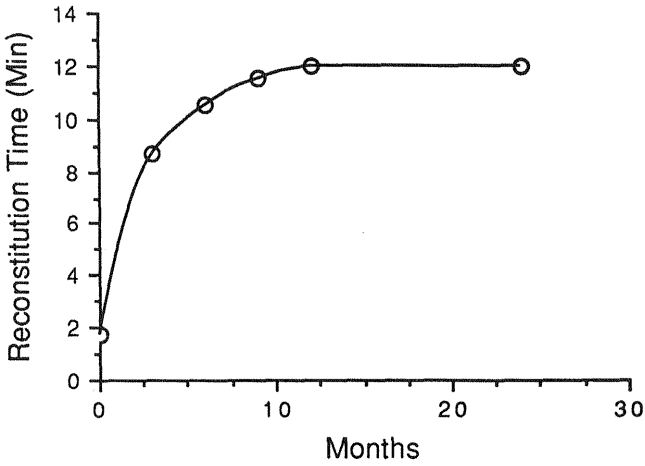


Fig. 16 Change of reconstitution time of a powder on storage.

The ranges shown denote standard errors of the mean. An F-test (Anova) will now fail to show a significant difference between operators. On storage, the reconstitution time could change as shown in Fig. 16.

As mentioned, the most common reason for increases in reconstitution time upon product storage is that the powder becomes more "lumpy" through cohesion developing over time or because it becomes coarser due to crystal growth. Both phenomena are associated with moisture content, and just as it is important to test the effect of the level of moisture content in the case of stability of a solid dosage form, so is it important to test it in the case of a powder.

If m is the number of mL of water adsorbed on one gram of powder, and if S is the solubility (in mg/mL) of all the soluble substances in the preparation, then, since the moisture layer is stagnant, the concentration of solubles at time t will be given by

$$C = S[1 - \exp(-qt)] \tag{10.22}$$

where q is the dissolution constant (kA/V).

The layer will have a higher viscosity (η), the more solid is dissolved, presumably by a power function:

$$\eta = \beta \cdot C^n \tag{10.23}$$

In analogy with the definition of viscosity, the force (F) needed to move two planes separated by a liquid is proportional to the viscosity. It would also be proportional to the amount of liquid, m, in the powder situation stated, so that combining this concept with Eqs. (10.22) and (10.23) gives

$$F = m \cdot \beta \cdot S^n \cdot [1 - \exp(-qt)]^n \tag{10.24}$$

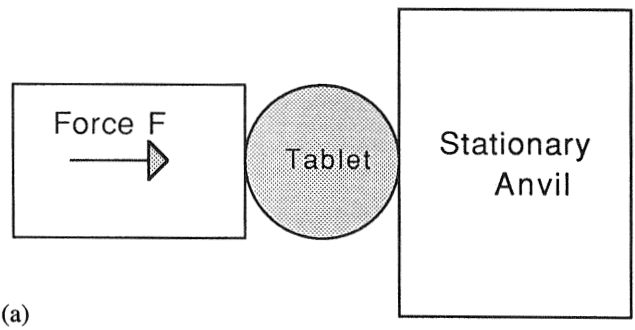
so the reconstitution time would be proportional to this. The data in Fig. 16 follow this pattern.

8. TABLETS

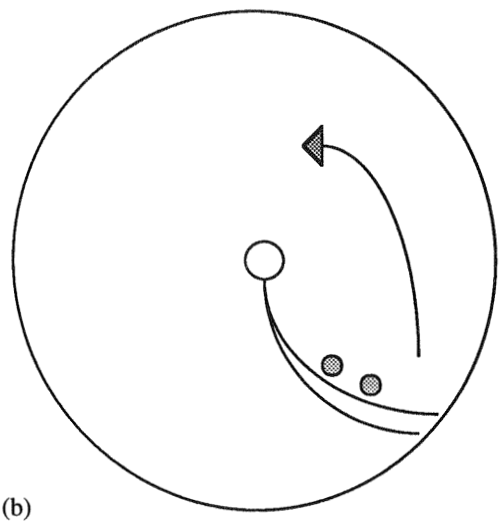
The physical properties associated with tablets are disintegration, dissolution, hardness, appearance, and associated properties (including slurry pH). For special tablet products (e.g., chewable tablets) organoleptic properties become important. These have been described earlier, but in the case of tablets, the chewability and mouth feel also become of importance. The properties will be discussed individually below.

8.1. Tablet Hardness

The "hardness" properties of a tablet are usually assessed by subjecting the tablets to a diametral failure test. The tablet is placed (Fig. 17) between two anvils, one of which is stationary. The other anvil is moved at constant speed against the tablet, and the force (as a function of time) is recorded. The force, at which the tablet breaks is denoted the "hardness" and is usually measured in kp (kilopond = kilogram



(a)



(b)

Fig. 17 (a) Hardness tester and (b) friabilator.

force). Other older units (Strong Cobb Units, SCU, or pound force) are used, usually when older instrumentation is used. Until recently, one limitation was that forces over 20 kp would simply register as F > 20 kp. Newer instrumentation allows for quantitation of higher forces. From a stability point of view this is important, since the better a parameter can be quantitated, the clearer the picture that emerges will be.

Tablets are made either by wet processing (wet granulation) or by dry processing (direct compression or slugging/roller compaction). In the former case a binder in solution is added to the powder mixture (or is contained in the powder mixture, and wetting then carried out). The binder forms soft bridges between particles, and when the granulation is dried then these bridges become hard. They form the bonds during the compression, and this is one of the reasons for the addition of the binder. The hardness of the tablet is tied in with the strength of the bond. The nature of the actual bond formation will be discussed presently.

In order for a bond to form, the particles or binder bridges must first be exposed to stresses (pressures) that exceed the elastic limit of the material. On failure, the material will either deform plastically or experience brittle fracture. A material that flows well and has a low elastic limit is, therefore, easy to transform into a tablet, and several such materials, known as direct compression ingredients, are used in the manufacture of pharmaceutical tablets. In these cases drug is simply mixed with the direct compression excipient (and other excipients), lubricated, and compressed. If the drug content is less than (approximately) 20% then the tablet will (generally) have the properties of the direct compression ingredient. At higher percentages, direct compression is usually only feasible if the drug substance itself is fairly compressible (i.e., has a low elastic limit).

The hardness of a tablet will be a function of the strength of the bond and the number of bonds. However, this is statistically oversimplified. If there are, for instance, many bonds in the bottom of a tablet and only a few in the top, then the tablet will break easily. Hence it is the average bond density and the standard deviation of the bonds that are really of importance. The same is true about the strength of the bond. Train (1957) has shown that the particle density in a tablet varies from spot to spot, and hence there is a variation in the density of the bonds (and probably in their strength as well).

If the hardness of a tablet is plotted versus the applied pressure, then a plot such as shown in Fig. 18 results. It is seen that the curve goes through a maximum. For good formulations, this maximum does not occur until very high pressures (outside the range of pressures used in pharmaceutical tableting). The maximum occurs because above the critical pressure, P^*, the tablet will laminate or cap, and a laminated tablet (Fig. 19) will contain strata of air and hence be thicker and weaker. Tablet thicknesses will respond in a manner opposite to the hardness, i.e., show a minimum (e.g., at 500 MPa in Fig. 18).

The reason for this phenomenon is the following: As applied pressure increases, the number of bonds, N, increases as well. But assuming that there is a maximum number of bonds, N^*, that can be formed, then the strength, H, of the tablet will asymptote as well. In a simplified manner the relations would be

$$N = N \cdot [1 - \exp(-qP)] \tag{10.25}$$

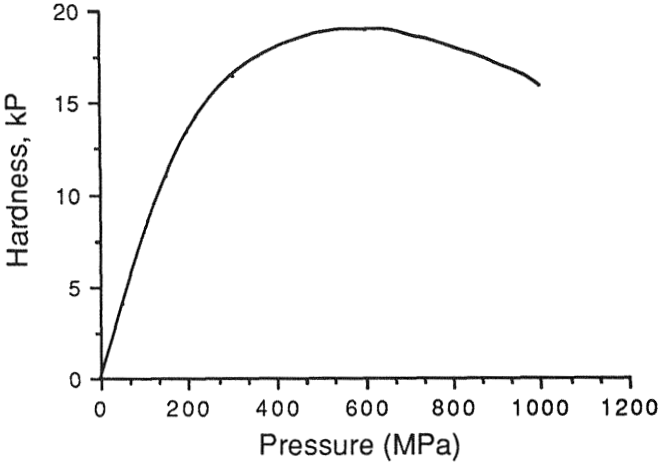


Fig. 18 Tablet hardness versus applied tableting pressure. (Graph constructed from data by Carstensen et al., 1986.)

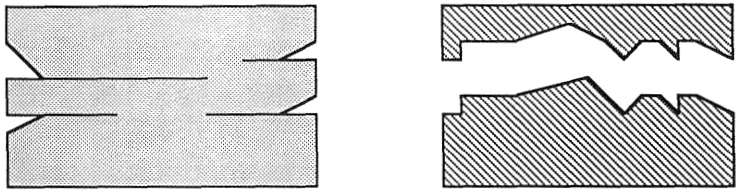


Fig. 19 Laminated and capped tablets.

If the hardness is assumed proportional to the number of bonds, then

$$H = \beta N = H \cdot [1 - \exp(-qP)] \tag{10.26}$$

where H is the capability of the tablet to withstand stress and β is a proportionality constant (Fig. 20).

During the tableting process, when the upper punch is released, a stress is exerted on the tablet, and this stress (S) is the larger, the larger the applied pressure, i.e.,

$$S = f(P) \tag{10.27}$$

At a given point, S becomes larger than H, and then fracture (lamination) occurs within the die, before the tablet is ejected.

There is a second type of stress that occurs during compression, and this happens upon ejection from the die. Here, many tablets expand, and this expansion is a stress that may also exceed H, i.e., laminated or capped tablets are formed.

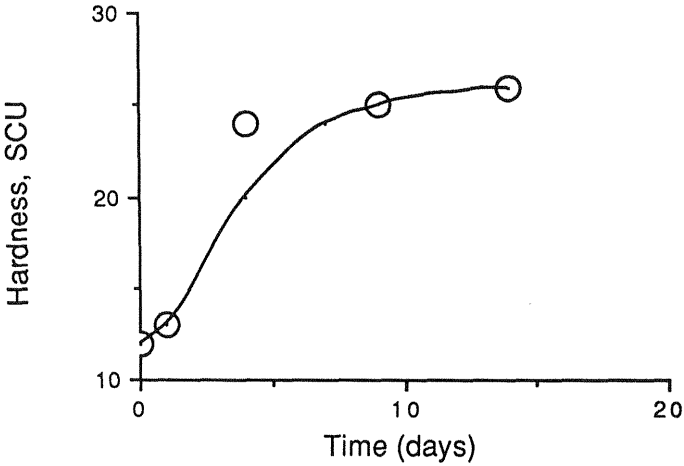


Fig. 20 Hardness as a function of time in pharmaceutical tablets. (Figure constructed from data published by Chowhan, 1979.)

On storage, this expansion can continue (Gucluyildiz et al., 1977), i.e., a tablet may become softer on standing for simple expansion reasons. Expansion is rarely checked as part of a stability program, and the cited article is one of the few published attempts to measure porosity as a function of time.

Frequently tablets will become either softer or harder within short periods of time after manufacture. Figure 20 shows hardness as a function of time for a series of tablets reported by Chowhan (1979).

Aside from the quoted instance of porosity changes and expansion, there are cases where crystallization of a soluble compound has occurred via the sorbed amounts of moisture in the tablet. This happens most often with very soluble compounds, and in such cases it is important to ascertain storage in a dry environment. A test that is now a requirement in the ICH Guidelines is storage in the final container at 40°C, 75% RH. During this test moisture is usually adsorbed by the tablets, and this can then cause softening of the binder bridge because of moisture uptake. At times, redrying will reinstitute the original hardness. Sometimes hardening occurs when the sorbed moisture causes recrystallization of a compound or excipient.

8.2. Softening

Softening can be associated with chemical interaction. Several furoic acids (Carstensen and Kothari, 1983), when tableted with microcrystalline cellulose, will cause a specific interaction leading to the formation of carbon monoxide (rather than decarboxylation of the acid). This interaction is not slow at 55°C, and it causes the tablets to crumble. At room temperature the effect is less pronounced yet significant.

Since a tablet, when produced, is not in equilibrium, there will be a redistribution of moisture. This could make the bonds of a lower or a higher moisture content, and there may for this reason be a change in hardness during a fairly short period of time after manufacture.

Table 4 Moisture Content of Selected Excipients

	Water content		
Excipient	TGA	Calcium carbide	Karl Fischer
Sta-RX 1500	10.8	9.7	10.4
Solca-Floc	5.8	4.6	6.4
CMC	9.2	3.7	14.9
Celutab	8.6	0	9.0
Microcryst. Cellulose	3.4	2.9	4.7
Polyvinyl-pyrollidone	5.4	2.9	6.4

Source: Table constructed from data published by Schepky (1974).

The moisture content of granules, when they are made initially, is a function of their particle size. Pitkin and Carstensen (1973) have shown that when granules are dried, each is associated with one given drying time, t^*. Since the drying (if it is countercurrent, or fluid bed) is a diffusional process, conventional diffusion theory predicts that the amount of moisture left in a granule, m, in relation to the initial amount, m_0, is given to a first approximation by

$$\frac{m}{m_0} = \exp\left[-\frac{D}{a^2}t\right] \tag{10.28}$$

where D is the diffusion coefficient of water in the granule and a is its diameter. The larger granules will hence, have a higher moisture content at the beginning, but the moisture will equilibrate, in most cases, on storage. However, Zoglio et al. (1975) have shown that in some cases (spray dried sucrose granules) there will be no redistribution of moisture between larger and smaller granules.

The moisture contents of various excipients have been reported by Schepky (1974) and are listed in Table 4.

In stability situations it is often the change in moisture as a function of storage time that is of importance. In such cases (Shepky, 1974), the thermogravimetric method may be of advantage.

It is of interest, in cases where moisture equilibrates and causes change in hardness on storage, to be able to assess the extent of moisture transfer within the tablet. As mentioned at an earlier point, the situation is that (in a simple case of a two-component tablet) the two components (I and II) have different moisture isotherms. These are approximated in linear fashion in Fig. 21. This is best illustrated by example.

Example 10.3.

A tablet is made of two components, I and II. It has a given moisture content, 10 mg of water per g of dry tablet weight. The moisture isotherms are as shown in Fig. 21. Calculate the final moisture contents of the two components after the moisture has equilibrated.

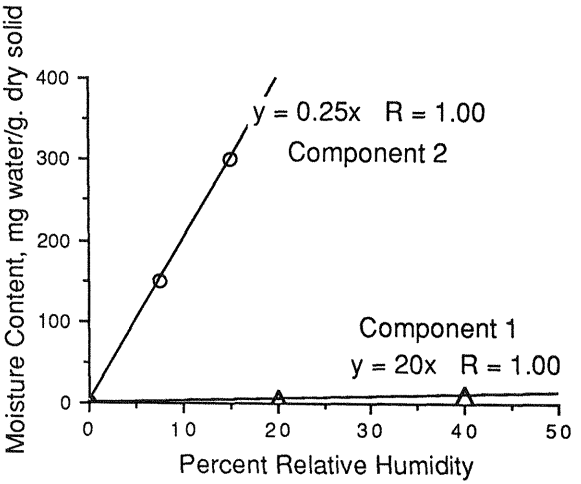


Fig. 21 Moisture exchange between ingredients.

Answer.

For component II, 10 mg of moisture per g of dry solid corresponds to a relative humidity of 40%, i.e., the equation for the isotherm for II is given by

$$y_2 = \frac{10}{40} x_2 = 0.25 x_2 \tag{10.29}$$

since it passes through the point (10, 40). The moisture isotherm for I has the equation

$$y_1 = \frac{300}{15} x_1 = 20 x_1 \tag{10.30}$$

since it passes through the point (15, 300). At the tablet moisture content (10 mg/g dry solid) it is in equilibrium with a gas phase of relative humidity

$$x_1 = \frac{10}{20} = 0.5\% \text{ RH} \tag{10.31}$$

Hence the situation is not an equilibrium situation, because there is no common vapor pressure over the solids. Component I will, therefore, give up (q grams of) water, and II will pick up (q grams of) water until a common vapor pressure (X^*) in the porous and external vapor space has been achieved.

The equilibrium relative humidity is given by

$$X^* = 0.25(10 - q) \tag{10.32}$$

and

$$X^* = 20(0.5 + q) \tag{10.33}$$

and equating the two right hand sides then gives

$$2.5 - 0.25q = 10 + 20q \tag{10.34}$$

or

$$20.25q = 12.5 \tag{10.35}$$

or

$$q = \frac{12.5}{20.25} = 0.6\,\text{mg} \tag{10.36}$$

It simplifies the computation that the moisture content is given in mg of moisture per g of dry solid (i.e., not in percent, which would be related to mg of moisture per g of total weight). It should be noted that this situation is simplified by assuming the isotherm to be linear.

8.3. Disintegration

Tablets (whether coated or not) are usually subjected to a disintegration test. The disintegration was the first in-vitro test used by the U.S.P. It is now not obligatory compendially (but is recommended); in an obligatory sense it has been replaced by the dissolution test. This latter, hence, is the more important test, but it will be seen that there often is a correlation between the two, and since the disintegration test is much more easily carried out, a stability program will check disintegration frequently, and dissolution less frequently, primarily due to labor intensity.

The apparatus used (U.S.P. XX, p. 958) is shown schematically in Fig. 22. It is an apparatus where six tubes are placed in holders on a circular screen, which is then raised and lowered between 29 and 32 times per minute through a distance of 5.3–5.7 cm in a 1000 mL beaker containing the disintegration medium (either water or N/10 hydrochloric acid). The wire mesh oscillates so that it is 2.5 cm (or more) below the surface at the upstroke and 2.5 cm (or more) from the bottom of the

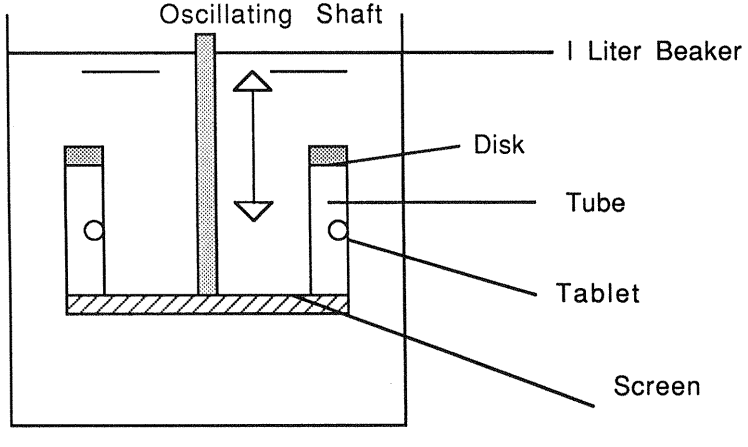


Fig. 22 Disintegration apparatus.

1000 mL beaker at the downstroke. The open-ended glass tubes are 17.75±0.25 cm long and have an inside diameter of 21.5 cm. The glass thickness is 0.2 cm.

Each tube is provided with a disk 95 mm thick and 20.7 mm in diameter, made of plastic of a specific gravity between 1.18 and 1.20 g/cm^3. There are five 2 mm holes in the cylinder (one of them in the axis). The disk also has notches in it and serves to keep the tablet within the tube and submerged during the stroke of the assembly.

To operate the apparatus, one tablet is placed in each of the six tubes, disks are added, and the apparatus is operated at 37°C in the immersion fluid. For quality control release purposes as well as for investigational purposes the time is noted when all tablets have disintegrated completely, and if not all tablets have disintegrated at the end of the specification limit, then the basket is removed and the tablets observed. If one or two tablets have failed, then 12 more tablets are tested, and these must all disintegrate within the limit. However, in stability testing it is important to note the time that each individual tablet disintegrates.

It should be pointed out that complete disintegration is defined as "that state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus is a soft mass having no palpably firm core." There are apparatuses on the market that have a sensor attached to the disk and can determine this state automatically and record the time at which it occurred. Such an attachment is strongly recommended for stability studies, since it provides an easy means of recording the time of disintegration of each tablet.

There are relatively few articles in the pharmaceutical literature that deal with the subject of the change in disintegration and dissolution upon storage, yet these qualities are as important as the retention of potency of the active compound. If a product falls short of specifications during its shelf life, it becomes unsatisfactory, regardless of the particular parameter that is shortfalling.

One fairly systematic study of this is the work by Chowhan (1979). Here disintegration and dissolution times of e.g. dicalcium phosphate based tablets were studied for prolonged times at 25 and 37°C. The pattern is a sigma minus type of pattern as shown in Fig. 23.

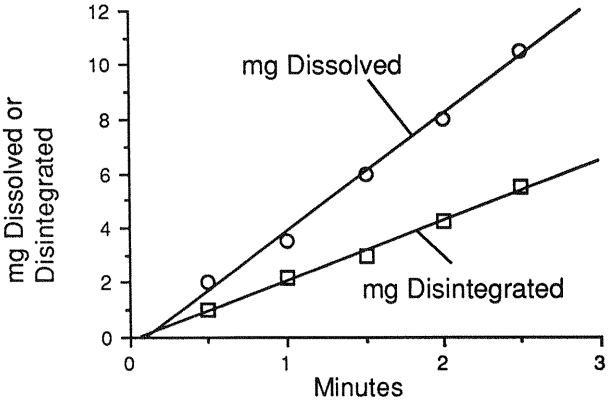
Carstensen et al. (1980a, 1980b) have shown that there often is a correlation between dissolution and disintegration, and Carstensen et al. (1978a, 1978b) have shown the theoretical basis for this. Figure 24 shows such a correlation of dissolution and disintegration times in a U.S.P. apparatus.

Couvreur (1975) has shown that the disintegration of a tablet is a function of several factors. If the tablet disintegrates by virtue of a disintegrant which expands, once it is wetted, then the most important attribute is the rate at which the disintegrating liquid penetrates the tablet, and hence the contact angle between the solid and the liquid is of importance.

8.4. Porosity of Tablets

Cruaud et al (1980) showed that there was a direct correlation between dissolution and porosity in a case where the correlation between disintegration and dissolution was not apparent.

There is one well documented case (Gucluyildiz et al., 1977) where the porosity was shown to change in a tablet as a function of time. What this indicates is that if



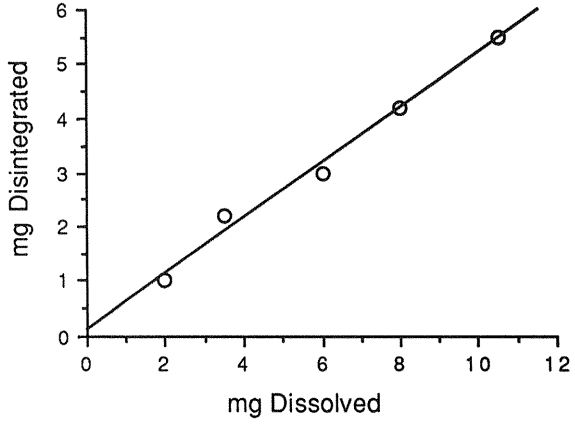


Fig. 23 Top figure: Correlation between dissolution and disintegration upon storage. (Graph constructed from data published by Carstensen et al., 1980a.) Bottom figure: Direct correlation between dissolution and disintegration.

dissolution and disintegration change on storage, then they may be functions of the change in porosity, if indeed porosity changes as a function of storage time.

A rational way of studying this would be to study mercury intrusion as a function of time in tablets of a drug, and to study simultaneously the disintegration and dissolution profiles.

There is a distinct effect of moisture uptake or equilibration on disintegration (and hence, indirectly, on dissolution). If the liquid penetrates an "average" pore, then it encounters, on its way, disintegrant particles. It is assumed that there are q disintegrant particles per linear length of pore. It is also assumed that N particles (per pore) must have been wetted before the tablet can break up (disintegrate).

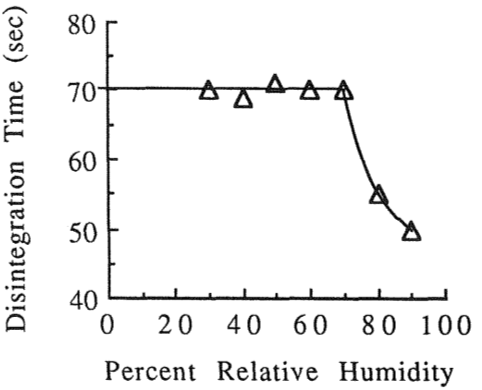


Fig. 24 Effect of storage at various relative humidities on disintegration time of an antidiabetic tablet. (Graph constructed from data published by Grimm and Schepky, 1980a.)

According to the Washburn equation (Washburn, 1921; Nogami et al., 1966; Carstensen, 1980), the length, L, of penetration of liquid at time t is given by

$$L^2 = \left(\frac{r \cdot f \cdot \cos \phi}{2\eta}\right) t = \beta \cdot dt \tag{10.37}$$

where

$$\beta = \frac{f \cdot \cos \phi \cdot r}{4\eta} \tag{10.38}$$

and where f is the interfacial tension, d is the average pore diameter, r is the pore radius, ϕ is the contact angle, and η is the viscosity.

The number of particles wetted n, is related to L by

$$q = \frac{n}{L} \tag{10.39}$$

or

$$L = \frac{n}{q} \tag{10.40}$$

where q is a proportionality constant. The disintegration time, t_N, occurs where $n = N$, so

$$LN = \frac{N}{q} \tag{10.41}$$

and

$$LN^2 = \beta \cdot t_N \cdot d \tag{10.42}$$

Combining these two equations gives

$$t_N = \frac{(N/q)^2}{\beta \cdot d} \tag{10.43}$$

Hence, the following hold for the disintegration time, t_N:

1. It is the larger the more disintegrating particles must swell to make the tablet disintegrate.
2. It is the longer the finer the pore (the smaller d is).
3. It is the smaller the larger the disintegrant concentration, q.
4. It is the smaller the larger the value of β (the smaller the contact angle and interfacial tension).

Of these, N may change, e.g., if the disintegrant becomes wetter, and partly expanded as a result of moisture uptake, this will affect the disintegration adversely. For instance, the Joel Davis test (40°C, 75% RH for three months) has an adverse effect on disintegration for this reason, although it is only true if the relative humidity of the testing station is above a certain critical moisture content (Grimm and Shepky, 1980a). This is demonstrated in Fig. 24.

8.5. Dissolution

The dissolution apparatuses used are usually USP Method I (basket apparatus) or USP Method II (paddle apparatus). Carstensen et al. (1976a,b) have pointed out that the hydrodynamics of the basket method is poor and results in highly different liquid velocities in different parts of the apparatus, and also causes a phenomenon known as coning: powder accumulates at the bottom of the dissolution vessel, where it is fairly stagnant and hence dissolves slowly. Most tests nowadays are therefore carried out with the paddle apparatus.

The assembly is described in USP XX p. 959 and is basically as shown in Fig. 25. The original apparatus could be operated at 50, 100, or 150 RPM, but the more up-to-date apparatus has a variable speed rheostat. In almost all instances the

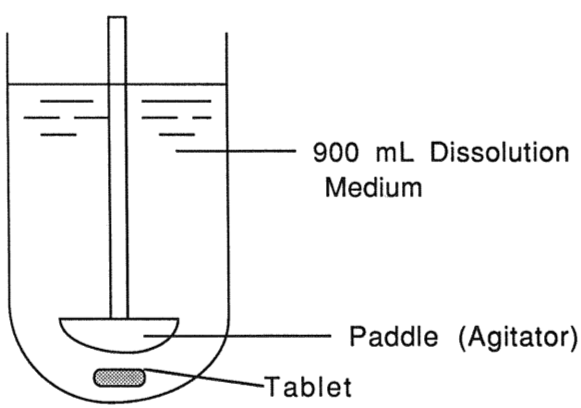


Fig. 25 USP dissolution apparatus.

FDA asks for 50 RPM (sometimes 100 RPM), but only rarely does it accept 150 RPM and insist on the test being "discriminating".

The apparatus should be subjected to a suitability test (USP XX, p. 959), using one tablet of the USP dissolution calibrator, disintegrating type, and one tablet of the USP dissolution calibrator, nondisintegrating type. The apparatus is satisfactory if the data are within the stated range of acceptability for each calibrator.

The dissolution medium is water, hydrochloric acid, or pH 7 buffer. These should be deaerated, since dissolved air may interfere with the dissolution rates.

The procedure used is to transfer usually 900 mL of the dissolution medium to the dissolution vessel and bring it to 37°C. After temperature is equilibrated, the thermometer is removed and one dosage unit is placed in the apparatus. Care is taken to exclude air bubbles from the surface of the tablet and to operate the apparatus right away. After given times, samples are removed from the supernatant and assayed, and the concentration is plotted as function of time. The results may be expressed as percentage of the highest possible concentration (D/V, where D is the dose and V is the volume of the liquid). Monographs specify, usually, a given time at which a certain percentage of label claim, Q, must be dissolved, and the term Q_{30} for instance is frequently used; it indicates the percent of label claim dissolved after 30 minutes. This is known as a one-point assay. For quality control purposes, this is acceptable, but for stability purposes, if rational graphing is contemplated, a dissolution curve rather than a one-point determination should be determined. This will allow determination of the dissolution constants, which will be discussed shortly.

It is often (particularly with slowly dissolving or sustained release products) of importance to have the value "at infinite time." This is usually imitated by increasing the rotational speed (e.g., to 150 RPM) and running the dissolution for an extra two hours. It is, in this scheme, assumed that all the drug will dissolve under such circumstances.

Shortcomings of the apparatus are still (a) that tablets made with excipients of high density will have a tendency to "cone," i.e., after disintegration accumulate in the dead spot just below the agitator; this gives false lows in dissolution rates, and (b) that capsules (and some tablet formula) may float. To avoid floating, a coil is usually placed about the capsule. It is interesting that some tablet formula with relatively small changes in composition (or compression pressure) will change their density, so that they float in one composition (or pressure) and sink in another (only slightly different) composition (or pressure). Expansion of tablets during storage may also change the density so that a table can change from a sinking to a floating composition which will give rise to an apparent slowing down of the dissolution rate.

It should be pointed out that dissolution testing of pharmaceutical products is carried out for several different reasons. In the early stages, the intent of dissolution testing is to get a feel for the comparative estimated bioavailability (on a rank order scale) of different formulations.

In preformulation, intrinsic dissolution rate constants are usually estimated. Although it is not possible, in a direct manner, to tie this in with an estimated bioavailability, it gives a feel for whether the drug substance will be exceedingly problematic, very problematic, problematic, or (in rare cases) not problematic. This feel is comparative with the intrinsic dissolution properties (obtained in a similar fashion) for other drug substances previously developed.

Table 5 Relative Rankings of Furosemide In-Vivo Versus In-Vitro (Random Cross-Over, 12 Patients)

	Rank dissolution	AUC (h-μg/mL)	C_{max} (mg/mL)	T_{max} (h)*
1	B	D	D	D
2	D	A	A=B=E	A=B=C=D
3	A=C	B=E	A=B=E	A=B=C=D
4	A=C	B=E	A=B=E	A=B=C=D
5	E	C	C	A=B=C=D

* Smallest T gets best rank, highest AUC and C gets best rank (i.e., lowest number in column 1).
Source: Table constructed from data published by McNamara et al. (1987).

In formulation, it is generally assumed that if e.g. three formulae, A, B, and C (Table 5) are developed, then the one that has the fastest dissolution rate should be the best. Whether this general statement is correct is debatable (Table 5), but lacking other criteria it is an accepted yardstick.

In postformulation, i.e. at the point where the new product is manufactured, and when the new product has become an established or old product, dissolution is in the domain of quality assurance. Here it is part of a specification, and the intent of conducting the test is to declare to the public (given the criterion that in-vitro dissolution within certain limits corresponds to in-vivo performance) that the product made on day X, year Y, is comparable to (and should perform in a manner similar to) the batches made year previously on day Z, year Q, when it was tested in the clinic.

If this premise were generally correct, then an in-vitro dissolution test would be universal for all formulae, and it will be seen below that that is an unwarranted extension. The question whether batches of the same formula fall under such a rank order rule is probably acceptable. In the history of a product, however, small changes are often made, and the question whether these small changes shift the in-vitro to in-vivo interrelation is, of course, not known a priori. What constitutes smallness is not clear (and actually is not determinable). Minor changes are defined, now, as changes that tighten specifications and do not involve change in procedure, equipment, or raw material.

If a "substantial" (major) formula change is made, then the bioequivalence between the clinical formula and the new formula must be established.

If subsequent formula changes are made (e.g., a bioequivalence study is carried out in year Y, then another in year Y + 1, etc.), then comparisons should be made with the original clinical formula, not with the previous formula. If the formulae are denoted A (clinical), B, C, etc., then if successive comparisons were made and performance were denoted P, then PB could be 0.8 times PA (and deemed equivalent), PC could be 0.8 times PB (and deemed equivalent), but PC would be $0.8^2 = 0.64$ times PA and hence no longer equivalent. Hence, equivalence testing should always test back to the formula used in the original clinical batches that were part of the medical scheme (and the results of which were approved by the Food and Drug Administration).

8.6. Percolation Thresholds

When a solid is compressed, then one might imagine that at "full" compression, the tablet would be similar to a perfect crystal, in that there would be no void space left in it. This is never achieved, however, and the fraction of void is called the porosity. This may be visualized as isolated pockets of void space or, as the porosity increases, strings of void, eventually terminating at the surface. The porosity at which this latter situation is achieved is denoted the threshold value.

Threshold values for a drug and its excipients in combination are important because they govern such properties as dissolution, hardness, and disintegration. For this purpose, percolation studies are often employed in pharmaceutical research.

Leuenberger and Leu (1992) and Leu and Leuenberger (1993) introduced the concept of drug percolation to the pharmaceutical sciences. By this, a pharmaceutical system is described as a bond/site system. In this concept, a cluster is defined as a group of nearest neighbor sites where all positions consist of the same component. There is a concentration where there is maximum probability that the clusters will start to percolate, and this is the percolation threshold. If the measured porosity of the tablet is denoted ε_m and (after dissolution) the porosity created by loss of dissolved matter is denoted ε^*, then the so-called β property is

$$\beta = -c\varepsilon_c + c\varepsilon \tag{10.44}$$

where $\varepsilon = \varepsilon_m + \varepsilon^*$ is the initial + developed (matrix) porosity, c is a constant, and ε_c is the critical porosity threshold for percolation. This ties in with the Higuchi type plot, the slope of which is b, and β is defined as

$$\beta = \frac{b}{[2A - \varepsilon S]^{1/2}} \tag{10.45}$$

where A is the drug load (g/cm^3 of total tablet) and S is solubility. When porosity is plotted versus β value, then a straight line ensues that cuts the x-axis at the percolation porosity.

The threshold for drug percolation may be obtained when more drug is available than that described in Chapter 9. Soriano et al. (1998) have described percolation methods that are done primarily by conducting dissolution studies with drug substance at various concentrations. They employ the method of Bonny and Leuenberger (1993) and Leuenberger and Leu (1992) for this purpose.

8.7. Multipoint Determinations

In post NDA testing, there is some reason for not carrying out dissolution at more than one time point, because of both human resources and equipment. In pre-NDA situations, however, as described e.g. by Prandit et al. (1994), the importance of carrying out multiple time points in dissolution cannot be stressed enough. Conclusions are difficult to reach if this is not done.

For instance Prandit et al. (1994) reported that aging affected the dissolution of nalidixic acid tablets and concluded that the effect was not attributable to an increase in disintegration time (as measured in a dissolution apparatus). Published data often

suffer from being *one point data*, so dissolution/disintegration correlations cannot be deduced from the reported figures.

8.8. Dissolution Media

There is always the problem of what dissolution medium to use. For poorly soluble drugs there are several approaches: cosolvents, micellar systems, and/or large dissolution volumes. Naylor et al. (1993) studied the mechanism of dissolution of hydrocortisone in simple and mixed micelle systems by using a rotating disk and found the Levich equation to hold.

8.9. In-Vivo to In-Vitro Correlation

The problem of whether an in-vitro dissolution test generally measures in-vivo performance on a rank scale basis is still open to debate, when the problem is considered in general, i.e., if product A from manufacturer A has a dissolution rate curve "above" that of manufacturer B, will his product also have a better in-vivo performance as far as large magnitude (C_{max}) and short peak time (T_{max}) for the maximum of the blood level curve and high value for the area under the blood level curve (AUC)? The general premise is that the answer is yes, but as shall be seen below, this is not necessarily so. The correct general statement is that if two batches of the same product and formula are tested, then such a comparison is correct, i.e., that a "higher" dissolution curve implies at least one of the following: lower T_{max}, higher C_{max}, or higher AUC. An example of noncorrelation, when the formula is not the same, is the work by McNamara et al. (1987), in which furosemide from five manufacturers was tested against a solution. The relative rankings are shown in Table 5.

It is seen, then, that the best performer in vivo (D) is by no means the best performer in vitro, and that the worst performer in vitro (E) is not the worst performer in vivo.

The best and simplest method for correlation of in-vitro to in-vivo data would appear to be the mean residence time (MRT), and such comparisons have recently been described by Block and Banakar (1988). MRT is defined by many authors as shown in Fig. 26. The MRT factual definition is a measure of the "average" length of time a drug molecule is in the body (Fig. 26).

Mean residence time via statistical moment has also been described by Yamaoka et al. (1978). Podzeck (1993) has compared in-vitro dissolution profiles by calculating mean dissolution time and mean residence time.

Of late, deconvolution has been often reported and may form part of the 1995 USP. This method consists of comparing a blood level curve after solid dosage form administration with one after either solution or IV administration. The amount dissolved in the GI tract is then obtained by deconvolution. Sugawara et al. (1994) tested a series of controlled release preparations of prednisolone in alginate gel beads, all in a drug-to-alginate ratio of 1:4. As seen in Fig. 27, they were able to obtain in-vitro methods that "matched" the amount released in-vivo.

It is seen in the figure that for the fast releasing formulation (a), the in-vitro test, whether at pH 1.2 or at pH 6.8, follows the deconvoluted in-vivo results fairly well, but for the slow formula, it is only the pH 1.2 in-vitro test that correlates with the deconvoluted in-vivo dissolution test.

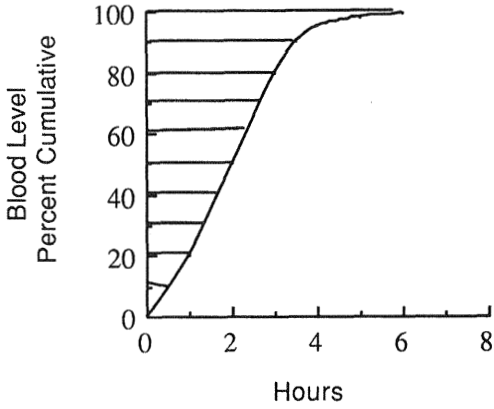


Fig. 26 Cumulative blood level curve (or urinary excretion curve, or dissolution curve).

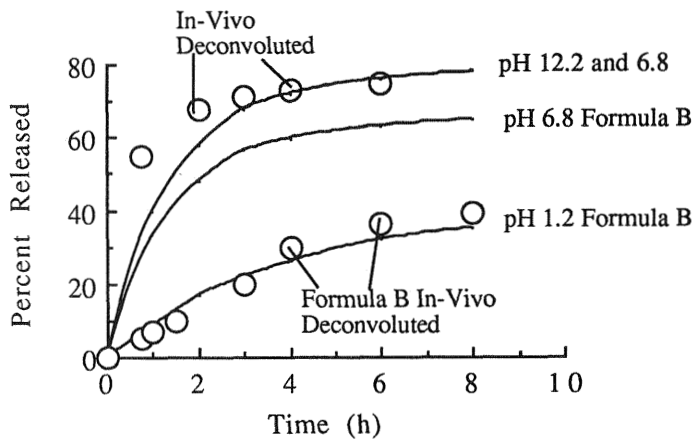


Fig. 27 Time vs. percent released. (Graph constructed from data published by Sugawara et al., 1994.)

The deconvolution method used was the one that has been described by Katori et al. (1991). Other, more recently developed methods are those of Gillespie and Cheng (1993). They first created a hypothetical clean curve with convolution. Then the absorption rates and cumulative amounts absorbed of the drug and metabolite were estimated by the proposed deconvolution method. For this purpose, polyexponential functions were fitted to the simulated data. The resulting parameters were compared by a multidimensional deconvolution program NDCREV (user-friendly IBM compatible).

8.10. Stability of Dissolution Curves

The problem from a stability point of view is that at times the dissolution curve will change as a function of storage time [as e.g. shown by Chafetz (1984) for hard shell capsules], but the bioavailability "stays the same." In such a case the in-vitro

MRT (or dissolution curve) would change but the in-vivo (either MRT or deconvolution curve) would not, so how can there be a correlation between the two?

The accelerated test in the ICH Guideline (40°C, 75% RH) is too severe a test for hard- and soft-shell capsules. Upon dissolution, a skin (a pellicule, or as some authors call it, a pellicle) will form around the capsule in the dissolution apparatus, and this will prevent dissolution. For instance, Dey et al. (1993) exposed etodolac capsules to the accelerated test so that they formed pellicules and showed that the dissolution was not affected when tested with enzymes, but that pellicules formed and dissolution decreased drastically on storage when nonenzymatic fluids were used. They showed that there was no difference in blood level curves of fresh, stored, and failed batches.

In the case of hard- and soft-shell capsules, gelatin can interact with substances in the fill. Gautum and Schott (1994) demonstrated an interaction of anionic compounds (substituted benzoic and sulfonic acid dyes) with gelatin. Capsule fills that contain, or on storage produce, keto groups will always show this phenomenon (Carstensen and Rhodes, 1993).

It should be pointed out that when disintegration of a dosage form changes on storage, it usually happens quite rapidly (usually within 12 weeks) at room temperature. Often, however, the tablet is not checked until 6 months after manufacture. There are then instances where it would seem to be logical to attempt an accelerated test at higher temperature. There has, to date, not been any convincing correlation between disintegration (and dissolution) profiles at higher temperature, vis-à-vis those at lower temperatures. Judging from the factors that affect these two properties, this is not surprising. But what is more to the point is that changes can usually be determined rapidly at room temperature. It is therefore more rational to determine disintegration at 4, 8, and 12 weeks at room temperature in stability programs, and to dispense with testing at higher temperatures.

Gordon et al. (1993) have reported on the effect of aging on the dissolution of wet granulated tablets containing superdisintegrants. Often the decay in dissolution efficiency is due to the lengthening of the disintegration time.

There is, obviously, a correlation between particle size and dissolution, and if the particle size changes as a function of storage time, there may be a correlation between accelerated temperature storage and dissolution. But in such a case the correlation should be established on the neat drug, as was done e.g. by Grimm and Shepky (1980b). Their data for oxytetracycline are shown in Fig. 28.

Dukes (1984) and Murthy and Ghebre Sellassie, (1993) have discussed storage stability of dissolution profiles in general, and Rubino et al. (1985) have described the specific storage stability of the dissolution of phenytoin sodium capsules. Carstensen et al. (1992) have discussed the mathematical basis for change in dissolution curves of dosage forms as a function of storage time. They employ the sigma minus model for dissolution, i.e.,

$$\frac{M}{M_0} = 1 - \exp[-k(t - t_i)] \tag{10.46}$$

where t is dissolution time, t_i is dissolution lag time, M_0 is initial amount in the dosage form, M is the amount left undissolved at time t, and k is a dissolution constant (time^{-1}). t_i is primarily a function of disintegration time.

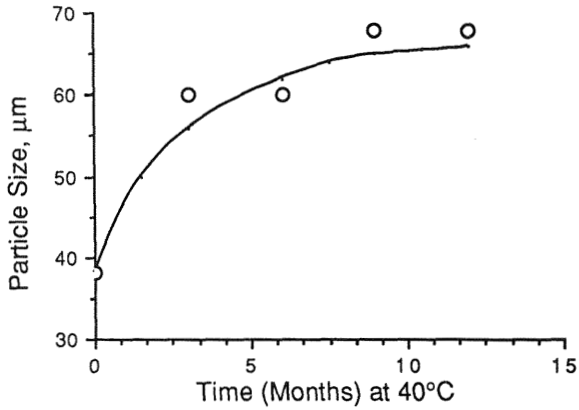


Fig. 28 Particle growth in accelerated storage of oxytetracycline. (Graph constructed from data published by Grimm and Schepky, 1980b.)

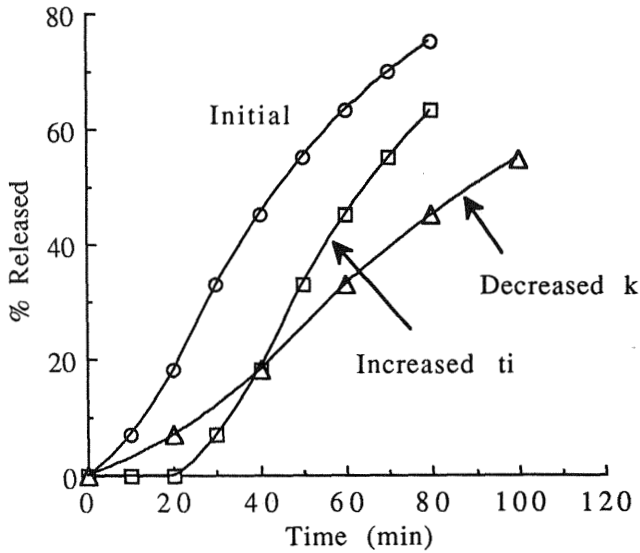


Fig. 29 Dissolution upon storage.

Frequently, upon storage, t_i may change, but k may not, in which case the dissolution curves simply move in parallel to higher and higher mean dissolution times. k, however, may change, and t_i may stay constant, in which case the curve becomes "flatter" (Fig. 29). Finally, both may change, giving rise to a flattening *and* a parallel displacement of the curves. If such parameters as t_{90} (the length of time for 90% to be dissolved) or Q_{45} (the amount dissolved at 45 minutes) are employed, then power function relationships result, and these are difficult to interpret. A better approach is to study and plot k and t_i as a function of storage time. If t_i on storage approaches 45, then the storage stability curve may have a shape as in Fig. 30.

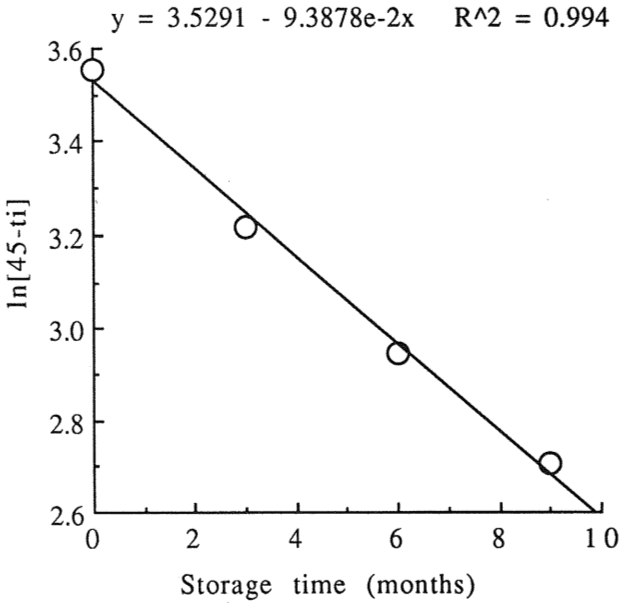


Fig. 30 Storage stability of lag time.

For instance, if a secondary parameter, such as the time needed for 50% dissolution, t_{50}, is followed, then

$$\ln 0.5 = -0.693 = -k(t_{50} - t_i) \tag{10.47}$$

or

$$t_{50} = \left(\frac{0.693}{k}\right) t_i \tag{10.48}$$

and if

$$t_i = t_i^{\infty}[1 - \exp(-q\phi)] + t_i^0 \tag{10.49}$$

where t_i^0 is initial lag time, t_i^{∞} is lag time at infinite storage time, ϕ is storage time, and q is the stability constant, then

$$t_{50} = \left(\frac{0.693}{k}\right)\{t_i^{\infty}[1 - \exp(-q\phi)] + t_i^0\} \tag{10.50}$$

If, now, the storage stability of k is of importance, the expression for t_{50} becomes even more complicated (but can obviously be deduced).

Jørgensen and Christensen (1996, 1997) have approached this problem by introducing a so-called Order Model. By this an order of reaction, n, is assigned to the dissolution curve, and the expression becomes

$$\frac{M}{M_0} = 1 - [1 - \{(1-n)k(t - f(t_0))\}]^{1/(1-n)} \tag{10.51}$$

where $f(t_0)$ is the lag time function given by

$$f(t_0) = t_0\left[1 - \exp\left(\frac{-t}{t_0}\right)\right] \tag{10.52}$$

t is, again, the dissolution time.

8.11 Appearance of Tablets and Capsules

A stability program should record the appearance of tablets as a function of storage time. This is most often done by subjective description, or by a rating index (0 for unchanged, 5 for vastly changed). Quantitative methods exist and are the following:

Comparison with color chips or charts (Rothgang, 1974)
Dissolving the dosage form and measuring the solution spectrophotometrically (Hammouda and Salakawy, (1971)
Photography (Armstrong and Marsh, 1974)
Reflection measurements (Matthews et al. (1974/75), Carstensen et al. (1964), Carstensen (1964), Goodhart et al. (1967), Turi et al. (1972), Wortz, R. B., (1967)

In the case of the second and fourth methods, a qualitative appearance description is always necessary, because the instrument will "average" the product. Comparison with chips can be used but is somewhat subjective. Such color charts have triangularly arranged chips, and the operator matches the object with a chip, which has a coordinate number. In fact the degree of whiteness (L), redness, (a) and yellowness (b) can be calculated from this, and it will be seen later on that this will allow for quantitative treatment of the change of the color of a pharmaceutical tablet or capsule.

Photography, of course, is relying on stringent adherence to conditions (exposure, aperture, and development) to insure that it is actually the tablets that are being compared, not the procedure for making the photograph.

Reflection measurements are often carried out in tristimulus meters and have been used quite extensively with varying degrees of success. If a tablet (or other surface) is placed in the meter, then reflectance values at three spectral regions are registered and recorded as x, y and z values. Rowe (1985) has reviewed these and points out that the whiteness index is $4(100Z/Z_0) - 3Y$, and the yellowness index is $100[1 - (100Z/\{Y \cdot Z_0\})$, where $Z_0 = 118.1$. In actuality, the degree of whiteness, L, the degree of redness, a, and the degree of yellowness, b, are given by the formula (for a Hunter tristimulus meter):

$$L = 100\left(\frac{Y}{100}\right)^{1/2}$$

$$a = 175\frac{(X/98.041) + (Y/100)}{(Y/100)^{1/2}}$$

$$b = 70\frac{(Y/100) - (Z/118.103)}{(Y/100)^{1/2}}$$

Table 6 Tristimulus Parameters for Some Colors

Color	x	y	z	L	a	b
White	82.3	84.3	101.1	91.8	−0.7	−1.0
Light yellow	65.0	69.9	7.0	83.5	−7.4	53.5
Yellow ochre	32.9	28.7	7.5	53.6	16.1	29.3
Scarlet	36.2	20.6	4.3	45.4	62.2	26.2
Magenta	23.9	13.0	23.9	36.0	55.2	−13.9
Turquoise	13.8	21.0	44.7	45.8	−26.5	−25.7
Emerald green	17.7	30.1	12.3	54.8	−38.3	25.1

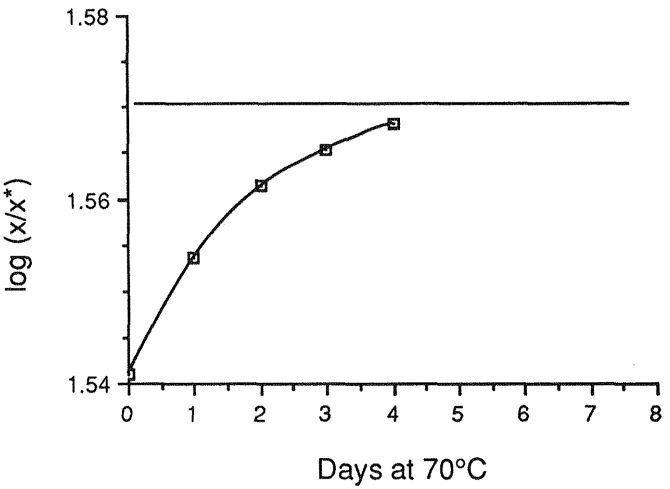


Fig. 31 Reflectance X values (with initially $X = X^*$) of vitamin C tablets as a function of storage time. (Graph constructed from data published by Carstensen et al., 1964.)

Komerup and Wanscher (1967) and Rowe (1983) give as an example the following values for some standard colors (Table 6).

The values calculated in the last three columns by Roe correspond quite well with those obtained from or listed in color charts (Komerup and Wanscher, 1967).

It should be pointed out first of all that reproducibility in reflectance meters is poor, and so results should always be obtained as averages of at least nine independent measurements. Since these are rapidly carried out, the labor is not all that intensive.

Changes in these values are difficult to interpret from a qualitative point of view, but the following procedure allows extrapolation, using x, y, or z (or composites).

Carstensen et al. (1964) have shown that the response values (Y) can be plotted as a function of storage time (t) to give graphs as shown in Fig. 31. This type of plot can be plotted as a sigma minus function:

$$Y = Y_\infty\{1 - \exp(-kt)\} \tag{10.53}$$

The k values can be plotted as an Arrhenius plot, i.e., one may, after short periods of time, at elevated temperature, calculate an extrapolated k value at room temperature. By sampling daily at 55°C, one can determine the Y value ($Y_{\text{lower limit}}$), which corresponds to the poorest appearance that is acceptable. Since k is known for room temperature (k_{25}), it is possible to calculate a "shelf life date" (t^*) based on appearance from inserting $Y_{\text{lower limit}}$ into Eq. (10.54):

$$\ln\left\{1 - \frac{Y_{\text{lower limit}}}{Y_\infty}\right\} = -kt^* \tag{10.54}$$

9. SUSTAINED RELEASE PRODUCTS

There are several types of sustained release principles used in pharmaceutical products, and a detailed description is beyond the scope of this book. What will be done here is simply to state the types of dissolution profiles that can be expected, and how the parameters could change with time.

9.1 Coated Beadlets and Granules

The coated nonpareil seed is the original sustained release form invented by SKF in the 1950s. Here a drug is applied (in the form of a sugar syrup) to monodisperse sugar crystals. Drying is carried out after each application step, so that the drug eventually is in a sugar matrix around the original seed. This beadlet is then coated with either a semipermeable film or an impermeable film with a soluble filler. The latter, upon exposure to dissolution medium, will allow the soluble filler to dissolve, so that pinholes are created in the film. Liquid then diffuses in through the film (or the holes in it), becomes saturated on the inside of the beadlet, and the dissolved drug then diffuses out. The diffusion takes place under an (approximately) constant concentration gradient (the solubility of the drug in the medium), as long as there is undissolved material inside the beadlet (and the concentration is low in the outside fluid creating sink conditions). Once the last drug has dissolved, the concentration inside the beadlet will decrease, and the diffusion slows down. It is, therefore, often, difficult to get the last 5–10% of material to release from this type (and other types of sustained release) dosage forms.

There are, obviously, three stages in the dissolution (Fig. 32):

$0 < t < t_i$: Penetration of liquid into the pellet. t_i is the time it takes for this to complete, and it is denoted the lag time.

$t_i < t < t_f$: t_f is the point in time where all the drug inside the pellet has dissolved.

$t > t_f$: This is the final period where dissolution is slower.

The general dissolution pattern in the period $t_i < t < t_f$ is

$$\ln\left[\frac{M}{M_0}\right] = -k(t - t_i) \tag{10.55}$$

M is the mass not dissolved (and M_0 is the dose) and is obtained by multiplying concentration with dissolution liquid volume and subtracting this (the amount dissolved) from M_0. k is the dissolution constant and will be the smaller (and t_i

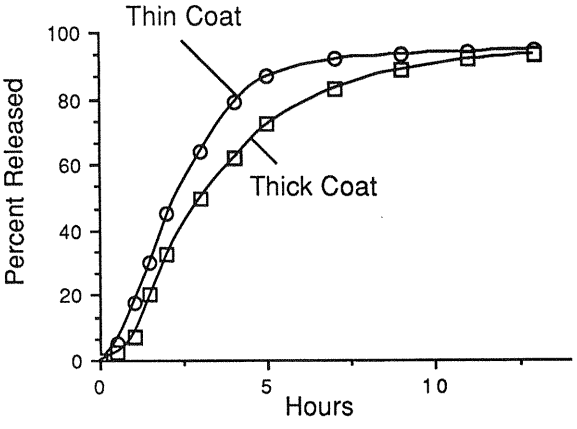


Fig. 32 Release patterns of thinly and thickly coated pellets.

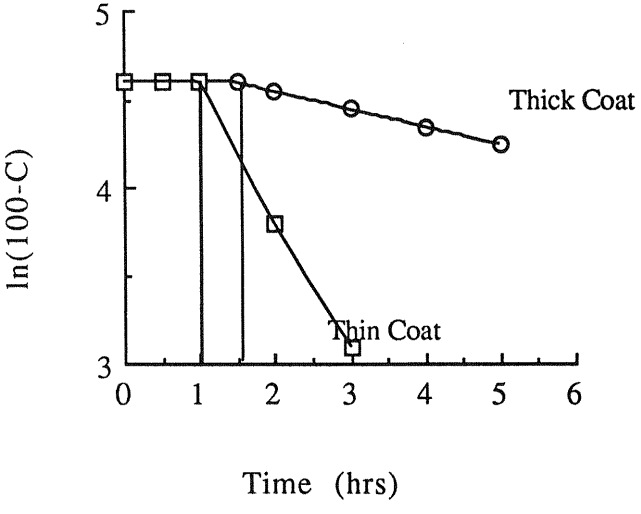


Fig. 33 Dissolution curve of sustained release beads. The thickness of the coat of II is 1.6 times that of I. The graph shows the decrease in slope and the increase in lag time with increased thickness. (Graph constructed from data published by Carstensen, 1973.)

the longer), the thicker the film and the lower the amount of soluble filler in the film. Figures 32 and 33 show this type curve (Carstensen, 1973). The first two points have been omitted, as have the last three points, i.e., t_i = about 1.5 hours and t_f = about 5 hours. The points omitted are such that the remaining points give the best linearity. It is seen from the graph that the least squares fit equations are

$$\text{I} \qquad \ln[M_1] = 5.09 - 5.04t \tag{10.56}$$

$$\text{II} \qquad \ln[M_2] = 4.8 - 0.29t \tag{10.57}$$

so that, as expected, the slopes are in a ratio of 5/3, i.e., the inverse of the ratio of thicknesses. The actual lag times are found by setting $\ln[M] = \ln[100]$, and they are $t_I = 0.67$ hours and $t_{II} = 0.96$ hours, i.e., again in the correct ratio. t_f is the point of inflection, i.e., occurs when all the drug inside the pellets will have dissolved (although not all will have diffused out).

In stability programs, t_i and k are the logical parameters to follow, i.e., complete dissolution curves should be determined. Again, it is wise to do this at room temperature storage at fairly short intervals at the onset (4, 8, and 12 weeks). Again, accelerated testing is not of much use.

9.2 Erosion Tablets

Tablets can be made of e.g. a waxy substance, which does not dissolve or disintegrate, but erodes away. The drug in the eroded portion will dissolve, and (in theory) the drug in the noneroded part will not have dissolved. There is, however, always some penetration of liquid into the waxy tablet, so that more than the eroded drug will often have dissolved. If pure erosion occurs, then the dissolution equation will be

$$M = M_0^{1/3} - K_e(t - t_i) \tag{10.58}$$

where K_e is an erosion constant (cube root dissolution rate constant) and t_i is the length of time of wetting. Both of these parameters can be calculated at different storage periods, and changes can be monitored in a logical fashion. Accelerated studies of this are not meaningful.

9.3 Insoluble Matrices

If a drug is enclosed in an insoluble matrix that is porous, then the release rate is given by the Higuchi square root law (Higuchi, 1963):

$$Q = K_i(t - t_i)^{1/2} \tag{10.59}$$

or

$$Q^2 = K_i^2 \cdot (t - t_i) \tag{10.60}$$

where

$$K_i^2 = a^2\left[2DS\varepsilon\left\{A - \frac{S\varepsilon}{2}\right\}\right] \tag{10.61}$$

a is here the surface area through which the diffusion takes place, ε is the porosity, and A is the loading, the amount of drug per cm^3 of dosage form. ε, the porosity, is the inherent porosity of the tablet plus the porosity created by the drug that has dissolved (i.e., A/ρ, where ρ is the density of the drug).

Eq. (10.61) applies to situations where the drug dosage, A, is larger than $S\varepsilon 2$. If this is not the case (Table 7), then the equation takes the form (Fessi et al., 1982)

$$Q^2 = a^2Dt \tag{10.62}$$

Table 7 Dissolution According to Eq. (10.62)

Time (min)	Amount released (mg)	Square root of time ($min^{1/2}$)	Amount released
0	0	0	0
8	12.3	2.87	151
15	19.8	3.87	392
45	43.4	6.71	1884
78	59.4	8.83	3528
96	67	9.80	4489
128	75.5	11.31	5700
164	80	12.8	6400
216	84.9	14.7	7209
276	87.7	16.6	7691

Source: Data from Fessi et al. (1982).

Certain products are not porous but depend on the dissolution of the drug to create the porosity. In such cases there is a minimum drug content necessary for creating a porous network, and some of the drug will be occluded, i.e., will never release. A practical minimum is about 20% drug is such cases.

The derivation of Eq. (10.59) is based on the assumption that the penetration of liquid is faster than the dissolution of the drug. If, e.g., the contact angle (wettability) changes with storage (e.g., due to moisture redistribution), then this assumption could be rendered false.

Equation (10.59) applies only as long as there is undissolved material in the matrix (and until liquid has penetrated into the center of the tablet) The parameters K_i and t_i may be monitored at various periods of room temperature storage time. In the case of insoluble matrices, accelerated studies might be possible in certain instances (i.e., when neither matrix nor drug changes physically at the higher temperatures). Table 8 gives an example of Eq. (10.62).

These data are depicted graphically in Fig. 34. It is seen that the least squares fit is given by

$$Q^2 = -2.55 + 0.477t \tag{10.63}$$

when the linear points are used. [These are, again, obtained by successively omitting terminal points (beginning and end) until the best linear fit is obtained.] It is noted that the first two and the last three points have been omitted, i.e., $t_i = 2.55/0.477 = 5$ minutes and t_f (from the best, high point omitted) is 128 minutes. Again, 75.5% are released at this point, and this is quite characteristic, and it calculates out well for most such dosage forms as the point dissolved at the time the tablet has filled up with dissolution medium.

Curing of the product is at times necessary. The work of Omelczuk and McGinnity (1993) has, for instance, shown that matrix tablets containing poly(DL-lactic acid) change release pattern if thermally cured. Drug release from

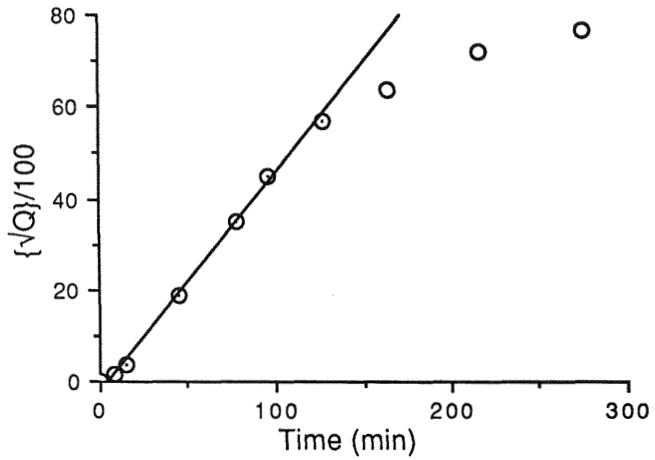


Fig. 34 Dissolution pattern in matrix dissolution. (Graph constructed from data published by Fessi et al., 1982.)

the tablets is neatly square root of time dependent as predicted by the Higuchi equation (Higuchi, 1962) shown in Eq. (10.58).

9.4. Osmotic Pump

The osmotic pump is a tablet coated with an impervious film, into which is (laser-)drilled a hole of exacting dimensions. Dissolution liquid will penetrate into the interior of the tablet, and a saturated solution will form. The excipients are chosen so that they have a given solubility and hence produce a given osmotic pressure. (The drug itself contributes to this as well.) This will be larger than the osmotic pressure in the outside liquid, and the difference between the osmotic pressure inside and outside will be the driving force by which liquid is being forced out through the hole. This gives rise to zero-order kinetics (which biopharmaceutically is an advantage), and the osmotic pump in many experimental situations, as well as in marketed situations, seems to be the dosage form that gives the most desirable release pattern, and also the one most likely to give in-vivo results that are predictable from in-vitro data. Dissolution data will therefore plot linearly, when amount released is plotted as a function of time. There may be a small nonzero (negative y-) intercept, i.e., a lag time. There will also be a point in time when there is no more solid drug inside the tablet, and deviations from linearity will occur from this point on.

There is no literature published on the stability pattern of this type of dosage form, but it is to be expected that it would be no more (and probably less) prone to change on storage than the other types mentioned.

9.5. Gel Forms

There are sustained release tablets that rely on gel-forming substances to accomplish the sustained release. In these cases the dissolution liquid will form a gel when it

encounters the surface of the tablet. Drug must dissolve and diffuse out through this gel layer. As time goes on, the gel layer gets thicker, and the diffusion path becomes longer. The data can be represented by Eq. (14.49) (Bamba et al., 1979). There is also the possibility of some "sloughing off" (i.e., erosion) of gel, and in this case the release becomes a hybrid between erosion and diffusion through increasing thickness of gel.

10. COATED TABLETS

Tablets are often film coated and, less frequently, they are sugar coated. Sugar coating, when properly applied, provides an excellent moisture and quite an adequate oxygen barrier. Film coating does the same, but not quite as effectively. For instance, vitamin A beadlets are more stable in a (properly made) coated tablet, less so (but yet quite stable) in a film coated tablet, of course provided there are no drastic incompatibilities in the core.

Film coating offers many advantages and often is the coat of preference, because (a) its application is much less labor intensive (cycle times being in hours for film coated tablets, in days for sugar coated tablets); (b) they also provide the advantage of allowing an engraving to "show through," i.e., identification requires no extra operation. On the contrary, sugar coated tablets, for identification, require a separate printing step; and (c) there is an inherent advantage in film coating in that it allows the appearance of a deep color without the use of much dye. If an uncoated tablet is colored, the dye is present throughout the tablet, whereas in a film coated tablet it is only present in the outer layer (the film itself).

Enteric coated tablets belong in the category of coated tablets and will be treated below as well.

10.1. Film Coated Tablets

Film coated tablets are produced either in a coating pan or by column coating (Wurster coating). Most coatings, nowadays, are aqueous film coats (hydroxymethyl cellulose, hydroxypropyl methylcellulose). There are several types of defects that can occur originally (orange peel effect for instance). All coatings, essentially, are such that each applied coat is not complete, so that there are overlaps, and in essence there is always an orange peel effect, except in a "good" tablet this cannot be seen. It is simply assumed in this writing, that the tablets placed on stability are not defective.

From a stability point of view there may be changes in appearance, mostly due to dislodging or rupture of the film. Sometimes these changes are first seen in the engraving. To properly record changes in appearance of the film, descriptive means can be used, but it is often a good idea to take a photomicrograph originally of all coated tablets (be they sugar or film coated). If defects show up in the coating as a function of time, then the question arises whether this is due to the formula (film and uncoated tablet) or to the way in which it was made (initial defective procedure, possibly not noticeable). Most often, these problems result in efforts in the formulation area, and recording (visually or photographically) at many intervals (3, 6, 9, 12 months) is therefore advisable. In this manner reformulation can be carried out as soon as the problem is identified.

One property that should be monitored, both for film and for sugar coated tablets, is their gloss. This is usually done subjectively. Rowe (1987) has described a glossmeter that assesses the gloss, but points out that there is still a great deal of subjectivity in the use of it.

As a problem-solving tool, scanning electron microscopy is advised, because of the augmented detail it offers, a detail that often pinpoints the individual problem.

In some formulation setups, it is possible (e.g., with an Instron tester) to measure the force necessary to strip a film from a substrate. If this substrate is the tablet surface, it is possible to evaluate films, moisture contents, effect of additives, etc., to ascertain which is the proper way in which to reformulate the film.

The actual appearance (i.e., the color) of the film coated tablet can be checked by means of a reflectance meter (or by diffuse reflectance), as described in the previous section.

Dissolution and disintegration are, of course, sensitive parameters, because any change in the film will be reflected in these properties.

10.2. Sugar Coated Tablets

Detailed descriptions of sugar coating procedures are beyond the scope of this writing. In brief, in sugar coated tablets there is applied (usually in a coating pan) first a barrier coat (frequently shellac or other polymer), then a subcoat (frequently terra alba/gelatin, with talc used as a conspergent), then a dye coat (consisting usually of sucrose syrup and lake dye), then a finishing coat (usually sugar syrup), and finally a polish coat (usually beeswax either dry or in solvent solution). The latter is carried out in a canvas coated coating pan.

The typical defects on storage are chipped tablets and tablets that split in the periphery. The former can be tested for by using a friabilator test. In such cases, a correlation with an actual shipping test should be attempted. In such a shipping test, tablets are sent by various routes (rail, truck, air) from the plant to several destinations and then back again. In so doing, it is possible to observe whether the artificial stress test is comparable to the actual transportation test.

When tablets split in the periphery it is usually due to trapped moisture (i.e., the tablet may not have been quite dry at the time one of the coats was applied). Very often it is due to an improperly applied barrier coat.

Again, photomicrography (and in problem cases, scanning electron microscopy) is advocated as a reference for changes in appearance. The actual appearance (i.e., the color) of the coat can be checked by means of a reflectance meter (or by diffuse reflectance), as described in the previous section.

Dissolution and disintegration are, of course, sensitive parameters, because any change in the film will reflect in these properties.

10.3. Enteric Coated Tablets

An enteric coat is an attempt "to administer two doses in one tablet." This is done by placing an acid resistant film (e.g., a polymer containing a carboxyl group with a pK of 4–6) on an uncoated tablet and then sugar coating it. The first dose is contained in the core, and the second dose is applied in the sugar coat, which should release the material immediately.

Enteric coating is a delicate operation, and often there is, in the production write-up, a statement that in-vitro dissolution must be carried out after e.g., the seventh coat. The e.g. eighth coat may then be applied or not depending on the outcome of the in-vitro test. This latter is usually the USP test that calls for placing one tablet in each of the six tubes of the basket in water at room temperature for 5 minutes. The apparatus is then operated without discs in simulated gastric fluid at 37°C. After one hour the basket is removed and the tablets are observed, and they should show no sign of disintegration, softening, or cracking.

Next a disk is added to each tube, and the apparatus is filled with simulated intestinal fluid TS at 37°C for 2 hours (or whatever the monograph or the in-vitro to in-vivo relation calls for). If all of the tablets have disintegrated at the prescribed endpoint time, then the batch is acceptable, but if one or two tablets fail, then it is retested sequentially by testing an additional 12 tablets, all of which must pass.

Enteric coats (e.g., cellulose acetate phthalate) have tendencies to polymerize. (Shellac is particularly vulnerable in this respect.) Hence disintegration on storage should be monitored at all intervals (3, 6, 9, 12, 18, 24, and 36 months).

It is noted that the initial dose (in the coat) should be available immediately, and a check should be made (one or two points) to assure that disintegration of the coat also results in dissolution of the drug (which it usually does).

The behavior at accelerated temperatures is not necessarily indicative of (nor extrapolable to) room-temperature characteristics.

11. HARD AND SOFT SHELL CAPSULES

Grimm and Schepky (1980a) have demonstrated how, depending on the sorption isotherms of the capsule fill, a capsule shell can lose moisture to the capsule fill and become brittle, or conversely under opposite sorption isotherm conditions can draw moisture out of the fill and become soft.

As mentioned earlier, dissolution rate of the gelatin decreases in water. HCl, and aqueous buffer solution on storage, but gastric juice containing enzymes might well eliminate such a problem. A thorough review of the problem with cross-linking of gelatin and the occurrence of pellicule formation has been discussed by Digenis et al. (1994).

Ofner and Schott (1987) have studied the swelling of gelatin (Fig. 35) and have applied Eq. (10.64) to their considerations. If W grams of aqueous buffer solution is absorbed by 1 gram of gelatin at time t, then

$$\frac{t}{W} = A + Bt \tag{10.64}$$

where A and B are constants. The effect of additives can then be studied.

Vastly different behavior of gelatin was experienced with different drugs. This, obviously, is a powerful preformulation tool (when combined with data regarding the hygroscopicity of the drug, as demonstrated e.g. in Example 10.3).

York (1981) has reported on the moisture isotherms of gelatins. Knowing the moisture isotherm of the powder mixture in the gelatin, it is possible (as shown in the previous section dealing with tablets) to calculate the shift in moisture from shell to powder mixture (or vice-versa).

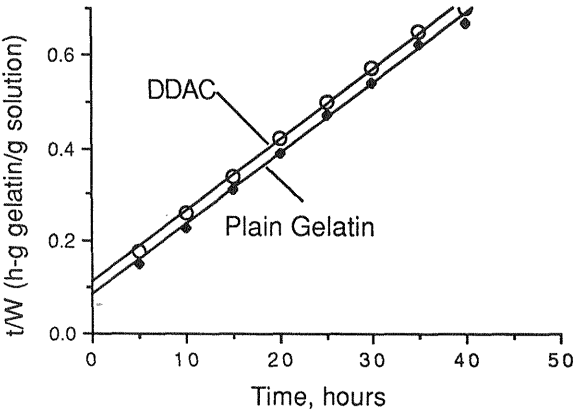


Fig. 35 Swelling isotherms of gelatin.

12. MICROCAPSULES

Microcapsules may decompose as a function of time. This has been reported by Makine et al. (1987) for the case of poly(L-lactide) microcapsules. Logical means of estimating the loss of intact polymer is (a) from the decrease in weight-averaged molecular weight, (b) by monitoring the loss in weight of polymer by gel permeation chromatography, and (c) by determining the amount of lactic acid formed. Figure 36 is an example of the decrease in weight-averaged molecular weight upon storage.

13. LIGHT SENSITIVITY TESTING

Both the ICH and the 1987 Guidelines advocate exposure of dosage forms to UV light, and although this might be instructive, it does not represent a test that simulates conditions in actual commerce (in general). There are exceptions: certain products are liable to be kept in handbags and kept out in the open, but these are the exception. In general products are considered to be kept in controlled plant environments, in warehouses or in controlled pharmacy conditions or in (short) transit.

To define a storage condition it is necessary to examine the actual conditions in the marketplace, and this has been done by Esselen and Barnby (1939), Lachman and Cooper (1959a, 1959b), and Lachman et al. (1960). They determined the spectral composition of light and light intensity in the typical American pharmacy, and in general it is assumed that the average foot-candles in a pharmacy is 5–15, and 10 is used as an average.

One could now proceed by checking a product for three years under such conditions, but rather than do that, it is desirable to accelerate the conditions so as to obtain an answer somewhat more rapidly. The guidelines' suggestion of using more energetic (UV) light is not good for such acceleratory attempts, because the more energetic light will (or may) give rise to reactions that would never take place in the light in a pharmacy (which is much more poor in ultraviolet light).

Lachman and Cooper determined that a #48 12 CWRS GE lamp 1.5″ in diameter and 48″ long produced a good average spectrum and produced 3250 lumens per

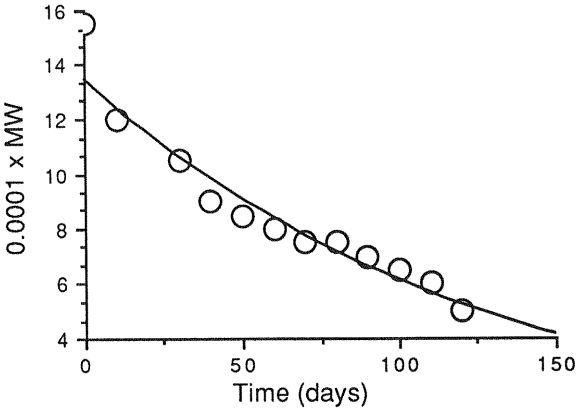


Fig. 36 Weight-averaged molecular weight of poly(L-lactide) microcapsules. (Figure constructed from data reported by Makine et al., 1987.)

Table 8 Appearance Change of a Tablet as a Function of Time in a Lachman–Cooper Light Cabinet

Storage (weeks)	Open dish	Amber bottle
0	0.302	0.302
4	0.212	0.315
8	0.188	0.312
12	0.190	0.309

60 watts. They suggested accelerating the test by increasing the lumen reached by the dosage form, and they increased this by placing it closer to the light source. The light quanta absorbed by the dosage form are inversely proportional to distance (d) of the dosage form from the light source squared, i.e., proportional to $1/d^2$. They describe a light cabinet, equipped with shelves close to the described light source, adequately ventilated so that the temperature does not rise substantially. Light meters on the shelves allow either movement of the shelf so that the light intensity is always the same, or simply serves as a device to control when the bulbs should be changed.

If used as described, 1 month in the light cabinet is equivalent to 24 months on the average pharmacist's average shelf. A typical set of data of the discoloration of a dyed tablet (as gauged by optical density) is shown in Table 8.

It is seen that the cabinet allows for evaluation of the means of preventing photoinduced changes or reactions to take place (use of the amber bottle). This could be accomplished by other means as well (coating of a tablet, using an opaque rather than a transparent capsule, using a capsule with a dye that screens out the part of the spectrum that causes the photoreaction).

In the case of uncoated tablets, most often the dye will discolor or fade in the upper layer only. If the tablet is broken, the color is still intact on the inside. If it fades all the way through, then this is indicative of photoinduced interaction. In the case of ethinyl estradiol and an FDC dye, Kaminski et al. (1979) showed

interaction, but this interaction was first noticed in a light test and was photocatalyzed.

The regulations on light testing suggest the use of xenon lamps. In these a very high intensity light is applied in a very short period of time (minutes), and the effect on the dosage form (and the drug and the drug product) is recorded. The correlation of this with "real time and exposure" is unknown, and a database will have to be established before it can be rationally analyzed.

14. DIAGNOSTIC PAPERS

There is very little in literature regarding the stability of diagnostic product. In the case of diagnostic papers, the reagent is adsorbed on filter paper. The adsorption is usually governed by a Langmuir isotherm; there will, however, be active sites on the paper, and these may bind part (often a large percentage) of the reagent. Hence there will be an initial "loss" of reagent, and this will have to be compensated for by excesses, since only the reagent that is not chemisorbed will be available for the reaction in the diagnosis.

Stability data are gauged on the basis of initial assay (not theoretical content). Usually the stability is evaluated in a semiquantitative manner by an in-use test, i.e., an operator will carry out the diagnosis initially. For example, if it is a test that monitors sugar content (e.g., in urine), the filter paper will be judged against sucrose solutions of various concentrations. The instructions may state that the reaction is "positive" if a certain color is achieved (i.e., the concentration of sucrose is above a level, L) and negative if the response level is below another concentration, L^*, where $L^* < L$. The area in between is then "doubtful," and this would call for a retest. Initially the test should evoke the correct response (since the batch is, presumably, quality control released). As time goes by there will be a certain decomposition, which will vary from strip to strip, so at time t, a fraction of all the strips, q, may give an incorrect response. The best parameter to follow, stability-wise, is this parameter q, which should be such that it could be said at the expiration date with 95% confidence that q is below 5%.

15. EXPIRATION PERIODS

It was shown in the chapter dealing with statistics and expirations periods that there are mathematical means of calculating expiration periods from chemical stability data. This is not directly possible with physical testing. The reason for this is often the difficulty that exists in quantitating the physical property. Davis et al. (1977) state broadly that "the physicochemical changes that can occur ... upon storage or after processing or other external influence, should not be such that they can alter the therapeutic efficacy of the product." This is a good guideline, but the only way to test it is somehow to transform the experimental data into some quantity that can be extrapolated.

For instance, a suspension may start caking, but there are degrees of caking, and if it still can be shaken up in a reasonable length of time, then it should be all right. Here, a criterion must be set by the investigator, the quality control group, and the regulatory group within an organization. Such a criterion can be set up much like a test panel. Several containers of different degrees of caking can be

evaluated, and the "worst acceptable" (akin to the lower acceptable quality limit in release philosophy) agreed to. The investigator now can do a rotation test on this in the fashion described by Moore and Lemberger (1963), and state e.g. that after 20 controlled rotations, an assay of the supernatant must not be less than L mg/mL. This type of test can then be carried out at various storage times at room temperature; L can be plotted versus time, and a usual statistical test performed on this number. In other words, for physical testing that has no number associated with it, it is important to attempt to find such a number.

In some cases this is not possible. A case in point is the particle size of an intravenous oil emulsion. Coalescence and formation of free oil will result in toxic manifestations, but it is next to impossible to determine an acceptable upper limit for droplet size (Davis, 1987).

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