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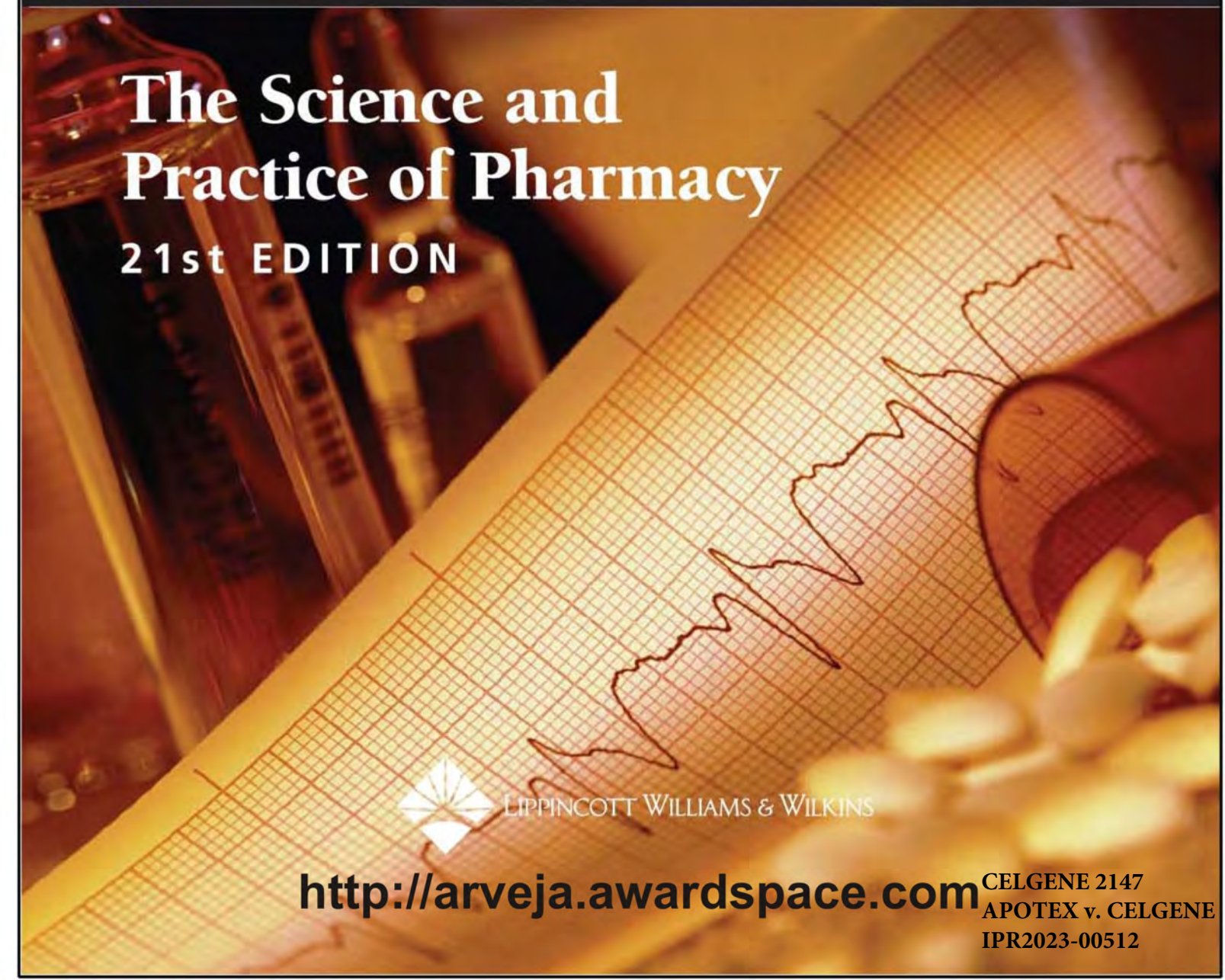
The Science and Practice of Pharmacy

21st EDITION



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21ST EDITION

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The Science and Practice of Pharmacy

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The Science and Practice of Pharmacy

LIPPINCOTT WILLIAMS & WILKINS
A **Wolters Kluwer** Company
Philadelphia • Baltimore • New York • London
Buenos Aires • Hong Kong • Sydney • Tokyo

Editor: David Troy
Managing Editor: Matthew J. Hauber

Lippincott Williams & Wilkins

351 West Camden Street
Baltimore, Maryland 21201-2436 USA

227 East Washington Square
Philadelphia, PA 19106

Printed in the United States of America

Entered according to Act of Congress, in the year 1885 by Joseph P Remington, in the Office of the Librarian of Congress, at Washington DC

Library of Congress Catalog Card Information is available
ISBN 0-683-306472

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Craig K Svensson, PharmD, PhD / Lyle & Sharon Bighley Professor in Pharmaceutical Sciences, College of Pharmacy, The University of Iowa. Chapter 58, *Basic Pharmacokinetics and Pharmacodynamics*

James Swarbrick, DSc, PhD / President, PharmaceuTech. Chapter 22, *Coarse Dispersions*

Timothy W Synold, PharmD / Assistant Professor, Department of Medical Oncology, City of Hope Comprehensive Cancer Center. Chapter 62, *Pharmacogenomics*

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Preface to the Twenty-First Edition

For over 100 years and throughout 20 previous editions, *Remington: The Science and Practice of Pharmacy* has stood as the definitive text and reference source of all aspects of the science and practice of pharmacy. In this new edition, you will find a text that is practice-oriented while maintaining its traditionally reliable coverage of scientific aspects. The 21st edition keeps pace with the changes in pharmacy curriculum and professional pharmacy practice in general.

In the years since the first publication of *Remington's Pharmaceutical Sciences*, there have been many changes in the field of pharmacy and pharmacy practice. Although this edition of *Remington* maintains the general philosophy of previous editions, several changes have been made to present fresh and new information and to take advantage of the advances made in recent years. Each section of the book has been critically reviewed and revised to reflect the emerging trends in the field. The overall organization of the book is the same as the previous editions.

The biggest change in the 21st edition is in the *Pharmacy Practice* section. This section has been reorganized and expanded to reflect the changing realities of comtemporary practice. The integration of new scientific information into clinical practice is often difficult, and one of the key purposes of this section is to help clinicians translate these scientific advances into clinical practice and care of patients. This section brings the reader up to date on the latest trends and approaches. New chapters have been added that cover the areas of:

- The application of ethical principles to practice dilemmas
- Statistics applied to pharmacy practice
- Technology and automation
- Professional communication
- Medication errors
- Re-engineering pharmacy practice
- Management of special risk medicines
- Specialization of pharmacy practice
- Disease state management
- Emergency patient care
- Wound care

The *Pharmaceutical and Medicinal Agents* section is the most very useful part of the book in terms of core drug information. For this edition, we've added more than 100 new drug monographs, and the previously existing material has been updated. We realize that this is a section that is nearly impossible to keep current, and we've tried to include as many new drugs as possible. Because of space constraints, we were limited to the most important or most widely used drugs.

Another significant addition to this edition is the expansion of the *Pharmacodynamics and Pharmacokinetics* section to include the new, growing area of Pharmacogenomics. This chapter highlights many of the important advances including: practical applications and technological considerations, molecular diagnostics for optimizing drug therapy, and pharmacogenomics and drug development.

Many people were involved in creating this edition. I am grateful to all the Section Editors and authors for their skillful review of the literature and for incorporating their own unique perspectives and experience into their chapters. With this edition, we welcome five new Section Editors. They represent a wide geographic diversity and spectrum of experience. We also have approximately 100 new authors who represent over 32 universities as well as positions in governmental agencies and private industry.

I also gratefully acknowledge the extensive contributions of the authors and Section Editors of previous editions of *Remington* for laying the foundation for the current volume. I recognize that we all stand upon the shoulders of giants and are supported by those leaders who taught and inspired many previous generations.

I especially thank Alfonso R Gennaro, PhD for his continued support. Dr. Gennaro was *Remington* editor for the past four editions. No one is more familiar with *Remington* than he is. Dr. Gennaro has been instrumental in the creation and review of the drug monographs. Ensuring scientific accuracy is critical in a book such as *Remington*, and he has been very generous with his time and expertise in this area.

A heartfelt thanks also goes to Mr. John Hoover, author and indexer, who has been involved with *Remington* since the 1960s and has provided editorial guidance at every step of the process.

It is a pleasure and honor to work on a book with such a long and rich tradition.

Randy Hendrickson
Editor

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Preface to 1st Edition

The rapid and substantial progress made in Pharmacy within the last decade has created a necessity for a work treating of the improved apparatus, the revised processes, and the recently introduced preparations of the age.

The vast advances made in theoretical and applied chemistry and physics have much to do with the development of pharmaceutical science, and these have been reflected in all the revised editions of the Pharmacopoeias which have been recently published. When the author was elected in 1874 to the chair of Theory and Practice of Pharmacy in the Philadelphia College of Pharmacy, the outlines of study which had been so carefully prepared for the classes by his eminent predecessors, Professor William Proctor, Jr, and Professor Edward Parrish, were found to be not strictly in accord, either in their arrangement of the subjects or in their method of treatment. Desiring to preserve the distinctive characteristics of each, an effort was at once made to frame a system which should embody their valuable features, embrace new subjects, and still retain that harmony of plan and proper sequence which are absolutely essential to the success of any system.

The strictly alphabetical classification of subjects which is now universally adopted by pharmacopoeias and dispensatories, although admirable in works of reference, presents an effectual stumbling block to the acquisition of pharmaceutical knowledge through systematic study; the vast accumulation of facts collected under each head arranged lexically, they necessarily have no connection with one another, and thus the saving of labor effected by considering similar groups together, and the value of the association of kindred subjects, are lost to the student. In the method of grouping the subjects which is herein adopted, the constant aim has been to arrange the latter in such a manner that the reader shall be gradually led from the consideration of elementary subjects to those which involve more advanced knowledge, whilst the groups themselves are so placed as to follow one another in a natural sequence.

The work is divided into six parts. Part I is devoted to detailed descriptions of apparatus and definitions and comments on general pharmaceutical processes.

The Official Preparations alone are considered in Part II. Due weight and prominence are thus given to the Pharmacopoiea, the National authority, which is now so thoroughly recognized.

In order to suit the convenience of pharmacists who prefer to *weigh solids* and *measure liquids,* the official formulas are expressed, in addition to parts by weight, in *avoirdupois weight* and *apothecaries' measure.* These equivalents are printed in *bold type* near the margin, and arranged so as to fit them for quick and accurate reference.

Part III treats of Inorganic Chemical Substances. Precedence is of course given to official preparation in these. The descriptions, solubilities, and tests for identity and impurities of each substance are systematically tabulated under its proper title. It is confidently believed that by this method of arrangement the valuable descriptive features of the Pharmacopoeia will be more prominently developed, read reference facilitated, and close study of the details rendered easy. Each chemical operation is accompanied by equations, whilst the reaction is, in addition, explained in words.

The Carbon Compounds, or Organic Chemical Substances, are considered in Part IV. These are naturally grouped according to the physical and medical properties of their principal constituents, beginning with simple bodies like cellulin, gum, etc, and progressing to the most highly organized alkaloids, etc.

Part V is devoted to Extemporaneous Pharmacy. Care has been taken to treat of the practice which would be best adapted for the needs of the many pharmacists who conduct operations upon a moderate scale, rather than for those of the few who manage very large establishments. In this, as well as in other parts of the work, operations are illustrated which are conducted by manufacturing pharmacists.

Part VI contains a formulary of Pharmaceutical Preparations which have not been recognized by the Pharmacopoeia. The recipes selected are chiefly those which have been heretofore rather difficult of access to most pharmacists, yet such as are likely to be in request. Many private formulas are embraced in the collection; and such of the preparations of the old Pharmacopoeias as have not been included in the new edition, but are still in use, have been inserted.

In conclusion, the author ventures to express the hope that the work will prove an efficient help to the pharmaceutical student as well as to the pharmacist and the physician. Although the labor has been mainly performed amidst the harassing cares of active professional duties, and perfection is known to be unattainable, no pains have been spared to discover and correct errors and omissions in the text. The author's warmest acknowledgments, are tendered to Mr A B Taylor, Mr Joseph McCreery, and Mr George M Smith for their valuable assistance in revising the proof sheets, and to the latter especially for his work on the index. The outline illustrations, by Mr John Collins, were drawn either from the actual objects or from photographs taken by the author.

Philadelphia, October, 1885 JPR

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Contents

Index

CHAPTER 22

Coarse Dispersions

James Swarbrick, DSc, PhD
Joseph T Rubino, PhD
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This chapter includes the formation of suspensions and emulsions and the factors that influence their stability and performance as dosage forms. For the purpose of the present discussion, a dispersed system, or dispersion, will be regarded as a two-phase system in which one phase is distributed as particles or droplets in the second, or continuous, phase. In these systems, the dispersed phase frequently is referred to as the discontinuous or internal phase, and the continuous phase is called the external phase or dispersion medium. Discussion will be restricted to those solid–liquid and liquid–liquid dispersions that are of pharmaceutical significance, namely, suspensions and emulsions. However, more complicated phase systems (eg, a combination of liquid and liquid crystalline phases) can exist in emulsions. This situation will be discussed in the section dealing with emulsions.

All dispersions may be classified into three groups based on the size of the dispersed particles. Chapter 21 deals with one such group—colloidal dispersions—in which the size of the dispersed particles is in the range of approximately 1 nm to 0.5 μm. Molecular dispersions, the second group in this classification, are discussed in Chapter 20. The third group, consisting of *coarse dispersions* in which the particle size exceeds 0.5 μm, is the subject of this chapter. Knowledge of coarse dispersions is essential for the preparation of both pharmaceutical suspensions (solid–liquid dispersions) and emulsions (liquid–liquid dispersions).

THE DISPERSION STEP

The pharmaceutical formulator is concerned primarily with producing a smooth, uniform, easily flowing (pouring or spreading) suspension or emulsion in which dispersion of particles can be effected with minimum expenditure of energy.

In preparing suspensions, particle–particle attractive forces need to be overcome by the high shearing action of such devices as the colloid mill, or by use of surface-active agents. The latter greatly facilitate wetting of lyophobic powders and assist in the removal of surface air that shearing alone may not remove; thus, the clumping tendency of the particles is reduced. Moreover, lowering of the surface free energy by the adsorption of these agents directly reduces the thermodynamic driving force opposing dispersion of the particles.

In emulsification, shear rates are frequently necessary for dispersion of the internal phase into fine droplets. The shear forces are opposed by forces operating to resist distortion and subsequent breakup of the droplets. Again surface-active agents help greatly by lowering interfacial tension, which is the primary reversible component resisting droplet distortion. Surface-active agents also may play an important role in determining whether an oil-in-water (O/W) or a water-in-oil (W/O) emulsion preferentially survives the shearing action.

Once the process of dispersion begins there develops simultaneously a tendency for the system to revert to an energetically more stable state, manifested by flocculation, coalescence, sedimentation, crystal growth, and caking phenomena. If these physical changes are not inhibited or controlled, successful dispersions will not be achieved or will be lost during shelf-life.

INTERFACIAL PROPERTIES

Because suspensions and emulsions are dispersions of one phase within another, the process of dispersion creates a tremendous increase in interfacial area between the dispersed particles or droplets and the dispersion medium. When considering the interfacial properties of dispersed particles, two factors must be taken into account, regardless of whether the dispersed phase is solid or liquid. The first relates to an increase in the free energy of the surface as the particle size is reduced and the specific surface increased. The second deals with the presence of an electrical charge on the surface of the dispersed particles.

SURFACE FREE ENERGY—When solid and liquid materials are reduced in size, they tend to agglomerate or stick together. This clumping, which can occur either in an air or liquid medium, is an attempt by the particles to reduce the excess free energy of the system. The increase in surface free energy is related to the increase in surface area produced when the mean particle size is reduced. It may be expressed as

$$\Delta F = \gamma \Delta A \qquad (1)$$

where ΔF is the increase in surface free energy in ergs, ΔA is the increase in surface area in cm^2, and γ is the interfacial tension in dyne/cm, between the dispersed particle or droplet and the dispersion medium. The smaller ΔF is, the more thermodynamically stable is the suspension of particles. A reduction in ΔF is effected often by the addition of a wetting agent (discussed in Chapter 20), which is adsorbed at the interface between the particle and the vehicle, thereby reducing the interfacial tension. This causes the particles to remain dispersed and settle relatively slowly. Unfortunately, in solid–liquid suspensions, the particles can form a hard cake at the bottom of the container when they eventually settle. Such a sediment, which can be extremely difficult to redisperse, can lead to dosing errors when the product is administered to the patient.

SURFACE POTENTIAL—As discussed in Chapter 20, both attractive and repulsive forces exist between particles in a liquid medium. The balance between these opposing forces determines whether two particles approaching each other actually make contact or are repulsed at a certain distance of separation. Although much of the theoretical work on electrical surface potentials has been carried out on lyophobic colloids, the theories developed in this area have been applied to suspensions and emulsions.

SUSPENSIONS

A *pharmaceutical suspension* may be defined as a coarse dispersion containing finely divided insoluble material suspended in a liquid medium. Because some products occasionally are prepared in a dry form to be placed in suspension at the time of dispensing by the addition of an appropriate liquid vehicle, this definition is extended to include these products.

Suspension dosage forms are given by the oral route, injected intramuscularly or subcutaneously, instilled intranasally, inhaled into the lungs, applied to the skin as topical preparations, or used for ophthalmic purposes in the eye. They are an important class of dosage form that can offer several advantages. Suspensions offer an alternative oral dosage form for patients who cannot swallow a tablet or capsule such as pediatric and geriatric patients. Oral antibiotics, analgesic and antipyretic drugs are commonly administered as suspensions to these groups of patients. Suspensions are often used to deliver pooly water-soluble drugs that cannot be formulated as a solution. In addition, drugs that have an unpleasant taste may preferably be formulated as a suspension to reduce interaction of drug with taste receptors in the mouth. Because suspended drug must undergo a dissolution step prior to crossing biological membranes, suspensions offer a way to provide sustained release of drug by parenteral, topical, and oral routes of administration

There are certain criteria that a well-formulated suspension should meet. The dispersed particles should be of such a size that they do not settle rapidly in the container. However, in the event that sedimentation does occur, the sediment must not form a hard cake. Rather, it should be capable of redispersion with a minimum of effort on the part of the patient. Finally, the product should be easy to pour, have a pleasant taste, and be resistant to microbial attack.

The three major concerns associated with suspensions are

1. Ensuring adequate dispersion of the particles in the vehicle.
2. Minimizing settling of the dispersed particles.
3. Preventing caking of these particles when a sediment forms.

Much of the following discussion will deal with the factors that influence these processes and the ways in which settling and caking can be minimized.

FLOCCULATION AND DEFLOCCULATION—Zeta potential, φ_z, is a measurable indication of the potential existing at the surface of a particle. When φ_z is relatively high (25 mV or more), the repulsive forces between two particles exceed the attractive London forces. Accordingly, the particles are dispersed and are said to be *deflocculated*. Even when brought close together by random motion or agitation, deflocculated particles resist collision due to their high surface potential.

The addition of a preferentially adsorbed ion whose charge is opposite in sign to that on the particle leads to a progressive lowering of φ_z. At some concentration of the added ion, the electrical forces of repulsion are lowered sufficiently and the forces of attraction predominate. Under these conditions the particles may approach each other more closely and form loose aggregates, termed *flocs*. Such a system is said to be *flocculated*.

Some workers restrict the term "flocculation" to the aggregation brought about by chemical bridging; aggregation involving a reduction of repulsive potential at the double layer is referred to as *coagulation*. Other workers regard flocculation as aggregation in the secondary minimum of the potential energy curve of two interacting particles and coagulation as aggregation in the primary minimum. In the present chapter, the term *flocculation* is used for all aggregation processes, irrespective of mechanism.

The continued addition of the flocculating agent can reverse the above process, if the zeta potential increases sufficiently in the opposite direction. Thus, the adsorption of anions onto positively charged, deflocculated particles in suspension will lead to flocculation. The addition of more anions eventually can generate a net negative charge on the particles. When this has achieved the required magnitude, deflocculation may occur again. The only difference from the starting system is that the net charge on the particles in their deflocculated state is negative rather than positive. Some of the major differences between suspensions of flocculated and deflocculated particles are presented in Table 22-1.

FLOCCULATION KINETICS—The rate at which flocculation occurs is a consideration in the stability of suspended dispersions. Whether flocculation is judged to be rapid or slow depends on the presence of a repulsive barrier between adjacent particles. In the absence of such a barrier, and for a monodispersed system, rapid flocculation occurs at a rate given by the Smoluchowski equation

$$\delta N/\delta t = -4\pi DRN^2 \qquad (2)$$

where $\delta N/\delta t$ is the disappearance rate of particles/mL, R is the distance between the centers of the two particles in contact, N is the number of particles per mL, and D is the diffusion coefficient. Under these conditions the rate is proportional to the square of the particle concentration. The presence or absence of an energy barrier is influenced strongly by the type and concentration of any electrolyte present. When an energy barrier does exist between adjacent particles, the flocculation rate likely will be much smaller than predicted by Equation 2.

SETTLING AND ITS CONTROL

To control the settling of dispersed material in suspension, the pharmacist must be aware of those physical factors that will af-

Table 22-1. Relative Properties of Flocculated and Deflocculated Particles in Suspension

DEFLOCCULATED	FLOCCULATED
1. Particles exist in suspension as separate entities.	1. Particles form loose aggregates.
2. Rate of sedimentation is slow, as each particle settles separately and particle size is minimal.	2. Rate of sedimentation is high, as particles settle as a floc, which is a collection of particles.
3. A sediment is formed slowly.	3. A sediment is formed rapidly.
4. The sediment eventually becomes very closely packed, due to weight of upper layers of sedimenting material. Repulsive forces between particles are overcome and a hard cake is formed that is difficult, if not impossible, to redisperse.	4. The sediment is packed loosely and possesses a scaffold-like structure. Particles do not bond tightly to each other, and a hard, dense cake does not form. The sediment is easy to redisperse, so as to reform the original suspension.
5. The suspension has a pleasing appearance, as the suspended material remains suspended for a relatively long time. The supernate also remains cloudy, even when settling is apparent.	5. The suspension is somewhat unsightly, due to rapid sedimentation and the presence of an obvious, clear supernatant region. This can be minimized if the volume of sediment is made large. Ideally, volume of sediment should encompass the volume of the suspension.

fect the rate of sedimentation of particles under ideal and nonideal conditions. Also important are the various coefficients used to express the amount of flocculation in the system and the effect flocculation will have on the structure and volume of the sediment.

Sedimentation Rate

The rate at which particles in a suspension sediment is related to their size and density and the viscosity of the suspension medium. Brownian movement may exert a significant effect, as will the absence or presence of flocculation in the system.

STOKES' LAW—The velocity of sedimentation of a uniform collection of spherical particles is governed by *Stokes' law*, expressed as

$$v = \frac{2r^2(\rho_1 - \rho_2)g}{9\eta} \tag{3}$$

where v is the terminal velocity in cm/sec, r is the radius of the particles in cm, ρ_1 and ρ_2 are the densities (g/cm^3) of the dispersed phase and the dispersion medium, respectively, g is the acceleration due to gravity (980.7 cm/sec^2), and η is the Newtonian viscosity of the dispersion medium in poises (g/cm sec). Stokes' law holds only if the downward motion of the particles is not sufficiently rapid to cause turbulence. Micelles and small phospholipid vesicles do not settle unless they are subjected to centrifugation.

While conditions in a pharmaceutical suspension are not in strict accord with those laid down for Stokes' law, Equation 3 provides those factors that can be expected to influence the rate of settling. Thus, sedimentation velocity will be reduced by decreasing the particle size, provided that the particles are kept in a deflocculated state. The rate of sedimentation will be an inverse function of the viscosity of the dispersion medium.

However, too high a viscosity is undesirable, especially if the suspending medium is Newtonian rather than shear-thinning (see Chapter 23), because it then becomes difficult to redisperse material that has settled. It also may be inconvenient to remove a viscous suspension from its container. When the size of particles undergoing sedimentation is reduced to approximately 2 μm, random Brownian movement is observed and the rate of sedimentation departs markedly from the theoretical predictions of Stokes' law. The actual size at which Brownian movement becomes significant depends on the density of the particle as well as the viscosity of the dispersion medium.

EFFECT OF FLOCCULATION—In a deflocculated system containing a distribution of particle sizes, the larger particles naturally settle faster than the smaller particles. The very small particles remain suspended for a considerable length of time, with the result that no distinct boundary is formed between the supernatant and the sediment. Even when a sediment becomes discernible, the supernatant remains cloudy.

When the same system is flocculated (in a manner to be discussed later), two effects are immediately apparent. First, the flocs tend to fall together, so a distinct boundary between the sediment and the supernatant is readily observed; second, the supernatant is clear, showing that the very fine particles have been incorporated into the flocs. The initial rate of settling in flocculated systems is determined by the size of the flocs and the porosity of the aggregated mass. Under these circumstances it is perhaps better to use the term *subsidence*, rather than sedimentation.

Quantitative Expressions of Sedimentation and Flocculation

Frequently, the pharmacist needs to assess a formulation in terms of the amount of flocculation in the suspension and compare this with that found in other formulations. The two parameters commonly used for this purpose are outlined below.

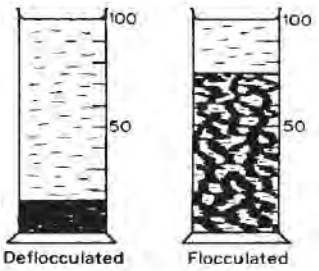


Figure 22-1. Sedimentation parameters of suspensions. Deflocculated suspension: $F_\infty = 0.15$. Flocculated suspension: $F = 0.75$; $\beta = 5.0$.

SEDIMENTATION VOLUME—The *sedimentation volume*, F, is the ratio of the equilibrium volume of the sediment, V_u, to the total volume of the suspension, V_0. Thus,

$$F = V_u/V_0 \tag{4}$$

As the volume of suspension that appears occupied by the sediment increases, the value of F, which normally ranges from nearly 0 to 1, increases. In the system where $F = 0.75$, for example, 75% of the total volume in the container is apparently occupied by the loose, porous flocs forming the sediment. This is illustrated in Figure 22-1. When $F = 1$, no sediment is apparent even though the system is flocculated. This is the ideal suspension for, under these conditions, no sedimentation will occur. Caking also will be absent. Furthermore, the suspension is esthetically pleasing, there being no visible, clear supernatant.

DEGREE OF FLOCCULATION—A better parameter for comparing flocculated systems is the *degree of flocculation*, β, which relates the sedimentation volume of the flocculated suspension, F, to the sedimentation volume of the suspension when deflocculated, F_∞. It is expressed as

$$\beta = F/F_\infty \tag{5}$$

The degree of flocculation is, therefore, an expression of the increased sediment volume resulting from flocculation. If, for example, β has a value of 5.0 (see Fig 22-1), this means that the volume of sediment in the flocculated system is five times that in the deflocculated state. If a second flocculated formulation results in a value for β of say 6.5, this latter suspension obviously is preferred, if the aim is to produce as flocculated a product as possible. As the degree of flocculation in the system decreases, β approaches unity, the theoretical minimum value.

FORMULATION OF SUSPENSIONS

The formulation of a suspension possessing optimal physical stability depends on whether the particles in suspension are to be flocculated or to remain deflocculated. One approach involves use of a structured vehicle to keep deflocculated particles in suspension; a second depends on controlled flocculation as a means of preventing cake formation. A third, a combination of the two previous methods, results in a product with optimum stability. The various schemes are illustrated in Figure 22-2.

DISPERSION OF PARTICLES—The dispersion step has been discussed earlier in this chapter. Surface-active agents commonly are used as wetting agents; maximum efficiency is obtained when the HLB value lies within the range of 7 to 9. A concentrated solution of the wetting agent in the vehicle may be used to prepare a slurry of the powder; this is diluted with the required amount of vehicle. Alcohol and glycerin may be used sometimes in the initial stages to disperse the particles, thereby allowing the vehicle to penetrate the powder mass.

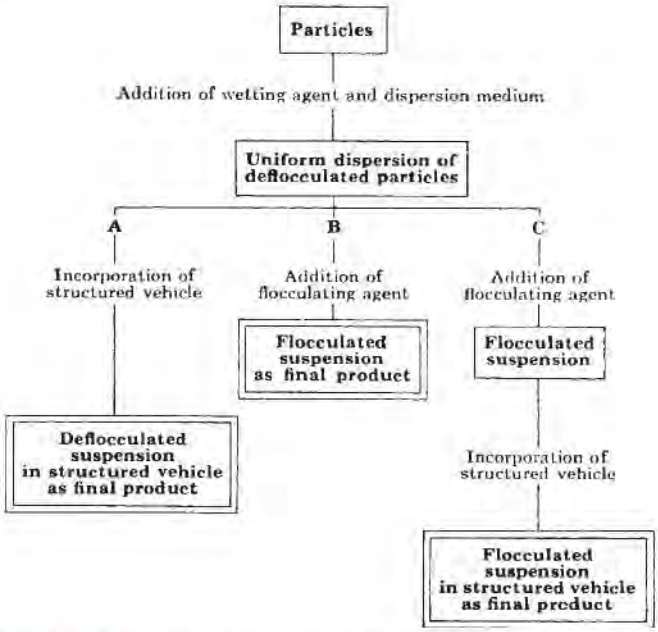


Figure 22-2. Alternative approaches to the formulation of suspensions.

Only the minimum amount of wetting agent should be used, compatible with producing an adequate dispersion of the particles. Excessive amounts may lead to foaming or impart an undesirable taste or odor to the product. Invariably, as a result of wetting, the dispersed particles in the vehicle are deflocculated.

STRUCTURED VEHICLES—*Structured vehicles* are generally aqueous solutions of polymeric materials, such as the hydrocolloids, that are usually negatively charged in aqueous solution. Typical examples are methylcellulose, carboxymethylcellulose, bentonite, and carbomer. The concentration employed will depend on the consistency desired for the suspension that, in turn, will relate to the size and density of the suspended particles. They function as viscosity-imparting suspending agents and, as such, reduce the rate of sedimentation of dispersed particles.

The rheological properties of suspending agents are considered elsewhere (Chapter 23). Ideally, these form pseudo-plastic or plastic systems that undergo shear-thinning. Some degree of thixotropy is also desirable. Non-Newtonian materials of this type are preferred over Newtonian systems because, if the particles eventually settle to the bottom of the container, their redispersion is facilitated by the vehicle thinning when shaken. When the shaking is discontinued, the vehicle regains its original consistency, and the redispersed particles are held suspended. This process of redispersion, facilitated by a shear-thinning vehicle, presupposes that the deflocculated particles have not yet formed a cake. If sedimentation and packing have proceeded to the point where considerable caking has occurred, redispersion is virtually impossible.

CONTROLLED FLOCCULATION—When using the controlled flocculation approach (see Fig 22-2*B* and *C*), the formulator takes the deflocculated, wetted dispersion of particles and attempts to bring about flocculation by the addition of a flocculating agent; most commonly, these are electrolytes, polymers, or surfactants. The aim is to *control* flocculation by adding that amount of flocculating agent that results in the maximum sedimentation volume.

FLOCCULATION USING ELECTROLYTES—*Electrolytes* are probably the most widely used flocculating agents. They act by reducing the electrical forces of repulsion between particles, thereby allowing the particles to form the loose flocs so characteristic of a flocculated suspension. As the ability of particles to come together and form a floc depends on their surface charge, zeta potential measurements on the suspension, as an electrolyte is added, provide valuable information as to the extent of flocculation in the system.

This principle is illustrated by reference to the following example, taken from the work of Haines and Martin.[2] Particles of sulfamerazine in water bear a negative charge. The serial addition of a suitable electrolyte, such as aluminum chloride, causes a progressive reduction in the zeta potential of the particles. This is due to the preferential adsorption of the trivalent aluminum cation. Eventually, the zeta potential will reach zero and then become positive as the addition of $AlCl_3$ is continued.

If sedimentation studies are run simultaneously on suspensions containing the same range of $AlCl_3$ concentrations, a relationship is observed (Fig 22-3) between the sedimentation volume F, the presence or absence of caking, and the zeta potential of the particles. To obtain a flocculated, noncaking suspension with the maximum sedimentation volume, the zeta potential must be controlled so as to lie within a certain range (generally less than 25 mV). This is achieved by the judicious use of an electrolyte. A comparable situation is observed when a negative ion such as PO_4^{3-} is added to a suspension of positively charged particles such as bismuth subnitrate.

Work by Matthews and Rhodes[3–5] involving both experimental and theoretical studies has confirmed the formulation principles proposed by Martin and Haines. The suspensions used by Matthews and Rhodes contained 2.5% *w/v* of griseofulvin as a fine powder together with the anionic surfactant sodium dioxyethylated dodecyl sulfate (10^{-3} mcolar) as a wetting agent. Increasing concentrations of aluminum chloride were added and the sedimentation height (equivalent to the sedimentation volume, see Chapter 21) and the zeta potential recorded. Flocculation occurred when a concentration of 10^{-3} molar aluminum chloride was reached. At this point the zeta potential had fallen from −46.4 to −17.0 mV. Further reduction of the zeta potential, to −4.5 mV by use of 10^{-2} molar aluminum chloride did not increase sedimentation height, in agreement with the principles shown in Figure 22-3.

Matthews and Rhodes then went on to show, by computer analysis, that the DLVO theory (see Chapter 21) predicted the results obtained—namely, that the griseofulvin suspensions under investigation would remain deflocculated when the concentration of aluminum chloride was 10^{-4} molar or less. Only at concentrations in the range of 10^{-3} to 10^{-2} molar aluminum

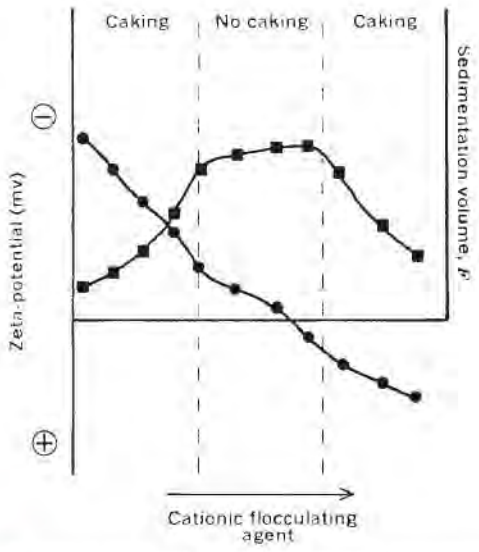


Figure 22-3. Typical relationship between caking, zeta potential, and sedimentation volume, as a positively charged flocculating agent is added to a suspension of negatively charged particles. ●: zeta potential. ■: sedimentation volume.

chloride did the theoretical plots show deep primary minima, indicative of flocculation. These occurred at a distance of separation between particles of approximately 50 Å, which led Matthews and Rhodes to conclude that coagulation had taken place in the primary minimum.

Schneider et al[6] have published details of a laboratory investigation (suitable for undergraduates) that combines calculations based on the DLVO theory carried out with an interactive computer program with actual sedimentation experiments performed on simple systems.

FLOCCULATION BY POLYMERS—*Polymers* can play an important role as flocculating agents in pharmaceutical suspensions. As such, polymers can have an advantage over ionic flocculating agents in that they are less sensitive to added electrolytes. This leads to a greater flexibility in the use of additives such as preservatives, flavoring, and coloring agents that might be needed for the formulation.

The effectiveness of a polymer as a stabilizing agent for suspensions primarily depends on the affinity of the polymer for the particle surface as well as the charge, size, and orientation of the polymer molecule in the continuous phase. Many pharmaceutically useful polymers contain polar functional groups that are separated by a hydrocarbon backbone. As a result of this structure, a polymer molecule may adsorb to particle surfaces while maintaining a degree of interaction with the solvent. As observed with ionic flocculating agents, polymers can produce both flocculated and deflocculated suspensions. It is believed that the primary mechanism by which polymers act as flocculants is due to the bridging of the polymer between the surfaces of different particles. The effect can be highly concentration dependent as illustrated in Figure 22-4. The effect has been interpreted as follows.

At very low concentrations of polymer, a large number of sites on the surface of the dispersed solid are available for adsorption of polymer. Bridging between particles occurs as a result of the simultaneous adsorption of a polymer molecule onto the surfaces of different particles. At very low polymer concentrations, the number of particle–particle bridges is relatively low. At somewhat higher concentrations of polymer, sufficient binding sites are still available on the particles, permitting additional interparticle attachments to form. It is these intermediate concentrations that result in optimum flocculation and sedimentation volume. At high concentrations of polymer, complete coverage of the particle surface with polymer occurs and insufficient binding sites remain on the particles to permit interparticle bridging. In this case, the degree of flocculation is low, but the close association of individual particles is inhibited by a phenomenon known as steric stabilization. In general, *steric stabilization* refers to the ability of adsorbed polymers to prevent close approach and cohesion of dispersed particles due to the fact that the mixing of polymers adsorbed at the particle surfaces is energetically unfavorable. Suspensions formulated with relatively high concentrations of polymer would be deflocculated and therefore tend to have small sedimentation volumes.

Flocculation using polymers may be influenced by the length of time and magnitude of mixing during the formulation process. In some cases, gentle mixing could result in a flocculated suspension; however, continued or more vigorous mixing could result in reorientation of the polymer at the particle surface with fewer interparticle bridges formed. The opposite phenomenon may also occur. Polymers are also frequently used to produce structured vehicles with relatively high viscosity. This effect may overshadow any effect on flocculation and is typically considered the most important use for pharmaceutical polymers in suspensions. Practical considerations in the formulation of suspensions using polymers have been presented by Scheer.[7]

The sedimentation volume achieved by addition of polymeric flocculating agents may or may not agree with DLVO theory. For example, Kellaway and Najib[8] found that sulfadimidine suspensions stabilized with the anionic polymer sodium carboxymethylcellulose obeyed the expected relationship between electrophoretic mobility, a measurement that is proportional to zeta potential, and to sedimentation volume in agreement with Figure 22-3. However, stabilization of the suspension with the nonionic polymer polyvinylpyrrolidone (PVP) did not obey the expected relationship between electrophoretic mobility and sedimentation volume. At high concentrations of PVP, particles had a low zeta potential, but contrary to the predictions of Figure 22-3 a low sedimentation volume was observed. Although adsorption of the polymer reduced the charge at the plane of shear, flocculation did not occur. This is believed to be due to steric stabilization of the particles at high concentrations of PVP with few interparticle bonds resulting in a low degree of flocculation.

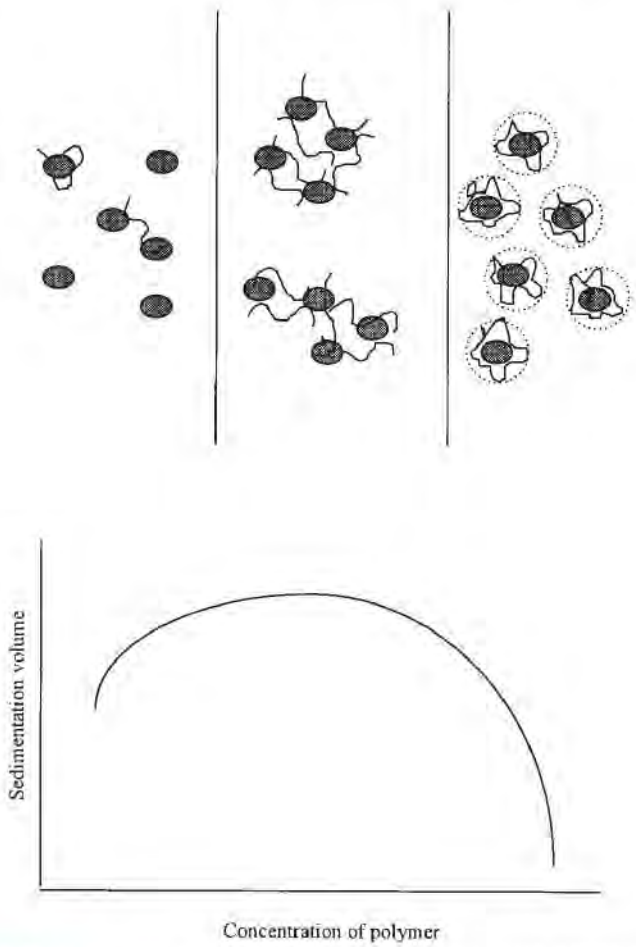


Figure 22-4. Flocculation by hydrophilic polymers. Optimal degree of flocculation and sedimentation volume occurs when a large number of interparticle bridges are formed. High concentrations of polymer result in a deflocculated suspension via steric repulsion.

The conformation of the polymers in the continuous phase may also have an effect on the degree of flocculation. At concentrations where flocculation occurs, polymers that have a linear conformation in the continuous phase will generally be more effective flocculants than polymers that are coiled in the continuous phase.

In some situations, a combination of polymeric and ionic flocculating agents have been used. In general, the sensitivity of the dispersed solid to flocculation by added electrolyte is enhanced by the presence of the polymer.

Table 22-2 contains a list of suspending agents that have been used in the formulation of pharmaceutical suspensions. Many of these can serve dual functions as flocculating/stabilizing and viscosity enhancing agents.

FLOCCULATION USING DETERGENTS—Both ionic and nonionic *detergents* can be used to produce flocculation in suspensions. Ionic detergents can produce flocculation in a

Table 22-2. Suspending Agents Used in the Formulation of Pharmaceutical Suspensions

TYPE OF POLYMER	EXAMPLES	STRUCTURE	COMMERCIAL NAMES
Cellulose derivatives			
Anionic	Carboxymethylcellulose (CMC)	Cellulose ether	
	Microcrystalline cellulose blends	Crystalline cellulose + cellulose ether	Avicel
Nonionic	Methylcellulose (MC)	Cellulose ether	Methocel, Metocel, Tylopur, Culminol, Celocol, Walsroder
	Ethylcellulose (EC)		EC - Ethocel
	Hydroxyethylcellulose (HEC)		HEC - Natrasol, Cellocize, Bermocol, Tylose, Blanose
	Hydroxypropylcellulose (HPC)		HPC - Klucel, Lacrisert
	Hydroxypropylmethylcellulose (HPMC)		HPMC - Methocel, Methlose, Pharmacoat, Culminol, Tylose, Celocol
Natural polymers			
Anionic	Alginates, carageenan, xanthan gum, acacia, tragacanth	Polysaccharide	
Nonionic	Locust bean gum, guar gum	Polysaccharide	
Synthetic polymers			
Anionic	Carbomers	Crosslinked polyacrylate	Carbopol
Nonionic	Polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA) poloxamer		Plasdone, Povidone, Kollidon
Clays	Magnesium aluminum silicate (Veegum), bentonite	Hydrated aluminum silicate	
	Hectorite	Magnesium hectorite	

manner that is similar to other electrolytes; they can reduce the zeta potential of the dispersed particles. Nonionic detergents have also been observed to reduce the zeta potential of dispersed particles. Both flocculation and deflocculation can occur. Relatively high concentrations of nonionic detergents can form a hydrated layer around particles that can lead to deflocculation via a mechanism that is similar to steric stabilization described for polymers. Alternatively, some liquid detergents can induce flocculation through the formation of liquid bridges between particles. High-molecular-weight detergents would be expected to behave similarly to polymers with regard to their action as a flocculant or stabilizer of suspensions.

FLOCCULATION IN STRUCTURED VEHICLES—The ideal formulation for a suspension would seem to be when flocculated particles are supported in a structured vehicle. As shown in Figure 22-2 (under *C*), the process involves dispersion of the particles and their subsequent flocculation. Finally, a lyophilic polymer is added to form the structured vehicle. In developing the formulation, care must be taken to ensure the absence of any incompatibility between the flocculating agent and the polymer used for the structured vehicle. A limitation is that virtually all the structured vehicles in common use are hydrophilic colloids and carry a negative charge. This means that an incompatibility arises if the charge on the particles is originally negative. Flocculation in this instance requires the addition of a positively charged flocculating agent or ion; in the presence of such a material, the negatively charged suspending agent may coagulate and lose its suspendability. This situation does not arise with particles that bear a positive charge, as the negative flocculating agent that the formulator must employ is compatible with the similarly charged suspending agent.

A method that can be used to circumvent incompatibilities between an anionic suspending agent and a cationic flocculating agent is to reverse the charge on the particle through the use of a positively charged surface active material such as gelatin. Adsorption of gelatin to the surface of a negatively charged particle can reverse the particle charge when the continuous phase is adjusted to a relatively low pH. This may permit flocculation to be achieved with an anionic flocculating agent such as citrate ion or phosphate ion. Addition of these flocculating agents would be compatible with polymeric suspending agents that largely consist of molecules of anionic charge. Martin *et al*[9] have suggested that this effect can also be achieved using surface active amines, provided their toxicity does not prevent their use.

PARTICLE SIZE AND DISTRIBUTION—Particle size is an important consideration for the physical stability of a suspension. As predicted by Stokes' law, particles of small diameter tend to settle more slowly compared to larger particles; however, small particles will have an increased tendency to cake upon settling if they are not flocculated. In addition, particle–particle interactions can also have a significant effect on suspension stability. For suspensions with a relatively high percentage of solids, interparticle interactions may produce more viscous or thixotropic dispersions. Smaller particles will have a high surface area/weight ratio that favors interactions between the particles and may produce desirable rheological characteristics.

In addition to the effects on the physical properties of a suspension, particle size has important implications on the biopharmaceutical performance of the drug. Aqueous suspensions can effectively serve as a means to deliver poorly water-soluble drugs by the enteral, parenteral, and topical routes. For drugs whose solubility in water is low, the dissolution rate of the drug particles may be a primary factor that limits absorption of the drug. In these cases, the rate and extent of absorption of the drug may be enhanced through the use of small particles. Small particles dissolve faster than larger particles due to the increased surface area per unit weight of drug of the former. Lastly, the uniformity of dosing over the life of the product will be enhanced by ensuring that a relatively small particle size is achieved. This is especially true for suspensions whose individual doses are withdrawn from a larger container, such as suspensions for oral use. Additional information on the bioavailability of drug from suspensions is presented at the end of this chapter.

As most pharmaceutical powders are polydipserse rather than monodisperse, the distribution of particle sizes may also play an important role in the physical stability of a suspension. A relatively narrow distribution of particle sizes is desirable for good stability. A narrow particle size distribution provides a more uniform settling rate and allows for better predictability of suspension properties from batch to batch of finished suspension. In addition, the phenomenon of Ostwald ripening will be minimized when the distribution of particles is narrow. *Ostwald ripening* is the phenomenon in which larger particles grow in size due to the dissolution of smaller particles. This phenomenon could result in pharmaceutically unstable suspensions (caking) and alter the bioavailability of the product through an alteration in the dissolution rate. The use of an appropriate polymer with an affinity for the surface of the dispersed solid reduces or eliminates crystallization in suspensions that may occur due to Ostwald ripening or dissolution/crystallization phenomenon caused by temperature fluctuations. This effect occurs at concentrations of polymer that provide complete surface coverage of the particles. Thus, a hydrophilic colloid, such as a cellulose derivative, with high affinity for the particle surface is often added initially to the suspension formulation to provide a protective action.

In flocculated suspensions, a narrow distribution of particles also tends to result in floccules with a more opened structure. If a flocculated suspension is prepared using a powder with a wide distribution of particles, the floccules would consist of links between larger particles with small particles filling the voids created by the interparticle links between larger particles. This would create a floccule that is more dense compared to the more open structure that would be expected from a floccule composed of particles of more uniform size. The more opened floc structure is desirable, as it may exhibit thixotropic properties in addition to a large sedimentation volume.

NONAQUEOUS SUSPENSIONS—Although most pharmaceutical suspensions have a primarily aqueous continuous phase, formulation of a drug in a nonaqueous continuous phase is occasionally required. Suspension of a water-soluble drug in a nonaqueous vehicle may provide a means to prepare a liquid formulation of a drug that has poor long-term stability in aqueous solution. Dispersions of drugs in oleaginous vehicles can also provide a sustained release form of drug as observed with certain depot injections and topical products.

Aerosols represent another important class of nonaqueous suspensions. The physical stability of suspended drugs in nonaqueous propellents for aerosol products can have a significant impact on the uniformity of dose and operation of the aerosol system. Caking of the suspended particles can cause clogging of the various mechanical components of the aerosol system.

According to Coulomb's law, the force between two charges is inversely proportional to the dielectric constant of the medium between the charges:

$$f \propto \frac{q_1 q_2}{Dx} \tag{6}$$

where f is the force between the particles, q_1 and q_2 are the charges on the particles, D is the dielectric constant, and x is the distance between the charges.

In general, most nonaqueous pharmaceutical liquids have a dielectric constant that is lower than water. This would result in a greater attraction between ions or particles of opposite charge and greater repulsion between ions or particles of similar charge. The effect of a continuous phase of low dielectric constant can therefore affect a suspension formulation in different ways. The use of added electrolytes will be less useful due to their low degree of ionization and poor solubility in some nonaqueous media. In addition, the density of charges on the particle surfaces will be reduced, but repulsion between particles may be facilitated. The result is that controlled flocculation using electrolytes is difficult to achieve as with aqueous suspensions, and caking may occur upon settling. Thus, alternate means of producing pharmaceutically acceptable suspensions must be employed.

Nonionic surfactants of low HLB values can be used to improve the physical stability of the suspensions. Stearic and other aliphatic acids and stearate salts, particularly aluminum monostearate, have been used as suspending agents. These materials increase the viscosity of the oil and produce a structured medium that can hinder the settling of drug particles. Alternatively, thickening agents such as Avicel, colloidal silicon dioxide, and long-chain alcohols can be used to reduce the sedimentation rate in nonaqueous suspensions.

Few studies have been performed to predict formulation and physical stability of drugs in nonaqueous suspensions. Parsons *et al*[10] found that the suspension properties of a number of solids in a nonaqueous aerosol propellant depended on the surface properties of the solids. Solids that had relatively polar surfaces tended to aggregate to larger extents than solids with relatively nonpolar surfaces. The moisture content of the dispersed solid and continuous phase may also play an important role on the aggregation of the solid. Adsorbed moisture on the dispersed solid may help to create a liquid bridge between particles when dispersed in certain nonaqueous solvents. If carefully controlled, this could provide a means to obtain some degree of flocculation in certain nonaqueous vehicles. Examples are discussed by Hiestand.[1]

CHEMICAL STABILITY OF SUSPENSIONS—Particles that are completely insoluble in a liquid vehicle are unlikely to undergo most chemical reactions leading to degradation. However, most drugs in suspension have a finite solubility, even though this may be of the order of fractions of a microgram per milliliter. As a result, the material in solution may be susceptible to degradation. However, Tingstad *et al*[11] developed a simplified method for determining the stability of drugs in suspension. The approach is based on the assumptions that

1. Degradation takes place only in the solution and is first order.
2. The effect of temperature on drug solubility and reaction rate conforms with classical theory.
3. Dissolution is not rate-limiting on degradation.

PREPARATION OF SUSPENSIONS—The small-scale preparation of suspensions may be undertaken readily by the practicing pharmacist with the minimum of equipment. The initial dispersion of the particles is best carried out by trituration in a mortar, the wetting agent being added in small increments to the powder. Once the particles have been wetted adequately, the slurry may be transferred to the final container. The next step depends on whether the deflocculated particles are to be suspended in a structured vehicle, flocculated, or flocculated and then suspended. Regardless of which of the alternative procedures outlined in Figure 22-2 is employed, the various manipulations can be carried out easily in the bottle, especially if an aqueous solution of the suspending agent has been prepared beforehand.

For detailed discussion of the methods used in the large-scale production of suspensions, see the relevant section in Chapter 39.

EMULSIONS

An *emulsion* is a dispersed system containing at least two immiscible liquid phases. The majority of conventional emulsions in pharmaceutical use have dispersed particles ranging in diameter from 0.1 to 100 μm. As with suspensions, emulsions are thermodynamically unstable as a result of the excess free energy associated with the surface of the droplets. The dispersed droplets, therefore, strive to come together and reduce the surface area. In addition to this flocculation effect, also observed

with suspensions, the dispersed particles can coalesce, or fuse, and this can result in the eventual destruction of the emulsion. To minimize this effect, a third component, the *emulsifying agent*, is added to the system to improve its stability. The choice of emulsifying agent is critical to the preparation of an emulsion possessing optimum stability. The efficiency of present-day emulsifiers permits the preparation of emulsions that are stable for many months and even years, even though they are thermodynamically unstable.

In recent years, it has been recognized that complex multiple-phase combinations can exist in emulsions. Thus, liquid crystalline phases and gel structures can form from the combination of the basic three-component mixture of water, oil, and surfactant (emulsifying agent). Often, these structures confer significant stability to the emulsion and therefore are to be desired. Such multiple-phase emulsions and their stability have been reviewed by Eccleston.[12]

Emulsions are widely used in pharmacy and medicine, and emulsified materials can possess advantages not observed in formulations in other dosage forms. For example, certain medicinal agents that have an objectionable taste have been made more palatable for oral administration when formulated in an emulsion. The principles of emulsification have been applied extensively in the formulation of dermatological creams and lotions. Intravenous emulsions of contrast media have been developed to assist the physician in undertaking x-ray examinations of the body organs while exposing the patient to the minimum of radiation. Considerable attention has been directed towards the use of sterile, stable intravenous emulsions containing fat, carbohydrate, and vitamins all in one preparation. Such products are administered to patients unable to assimilate these vital materials by the normal oral route. Emulsions are also used to deliver nutrients via the enteral route in the form of nutritional supplements. More recently, emulsions have been used to deliver poorly water-soluble drugs, such as general anesthetics and anti-cancer compounds, via the intravenous route.

Emulsions offer potential in the design of systems capable of giving controlled rates of drug release and affording protection to drugs susceptible to oxidation or hydrolysis. There is still a need for well-characterized dermatologic products with reproducible properties, regardless of whether these products are antibacterial, sustained-release, protective, or emollient lotions, creams, or ointments. In addition, emulsions may provide a useful way to deliver poorly water-soluble drugs via enteral and parenteral routes. The principle of emulsification is also involved in an increasing number of aerosol products.

The pharmacist must be familiar with the types of emulsions and the properties and theories underlying their preparation and stability; such is the purpose of the remainder of this chapter. Microemulsions, which can be regarded as isotropic, swollen micellar systems are discussed in Chapter 39.

EMULSION TYPE AND MEANS OF DETECTION

A stable emulsion must contain at least three components: the *dispersed phase*, the *dispersion medium*, and the *emulsifying agent*. Invariably, one of the two immiscible liquids is aqueous, and the second is an oil. Whether the aqueous or the oil phase becomes the dispersed phase depends primarily on the emulsifying agent used and the relative amounts of the two liquid phases. Hence, an emulsion in which the oil is dispersed as droplets throughout the aqueous phase is termed an *oil-in-water* (O/W) *emulsion*. When water is the dispersed phase and an oil the dispersion medium, the emulsion is of the *water-in-oil* (W/O) type. Most pharmaceutical emulsions designed for oral administration are of the O/W type; emulsified lotions and creams are either O/W or W/O, depending on their use. Butter and salad creams are W/O emulsions.

So-called *multiple emulsions* have been developed with a view to delaying the release of an active ingredient. In these types of emulsions three phases are present: the emulsion has the form W/O/W or O/W/O. In these "emulsions within emulsions," any drug present in the innermost phase must now cross two phase boundaries to reach the external, continuous phase.

It is important for pharmacists to know the type of emulsion they have prepared or are dealing with, because this can affect its properties and performance. Unfortunately, the several methods available can give incorrect results, so the type of emulsion determined by one method should always be confirmed by means of a second method.

DILUTION TEST—The dilution method depends on the fact that an O/W emulsion can be diluted with water and a W/O emulsion with oil. When oil is added to an O/W emulsion or water to a W/O emulsion, the additive is not incorporated into the emulsion and separation is apparent. The test is greatly improved if the addition of the water or oil is observed microscopically.

CONDUCTIVITY TEST—An emulsion in which the continuous phase is aqueous can be expected to possess a much higher conductivity than an emulsion in which the continuous phase is an oil. Accordingly, it frequently happens that when a pair of electrodes, connected to a lamp and an electrical source, are dipped into an O/W emulsion, the lamp lights because of the passage of a current between the two electrodes. If the lamp does not light, it is assumed that the system is W/O.

DYE-SOLUBILITY TEST—The knowledge that a water-soluble dye will dissolve in the aqueous phase of an emulsion while an oil-soluble dye will be taken up by the oil phase provides a third means of determining emulsion type. Thus, if microscopic examination shows that a water-soluble dye has been taken up by the continuous phase, we are dealing with an O/W emulsion. If the dye has not stained the continuous phase, the test is repeated using a small amount of an oil-soluble dye. Coloring of the continuous phase confirms that the emulsion is of the W/O type.

FORMATION AND BREAKDOWN OF DISPERSED LIQUID DROPLETS

An emulsion exists as the result of two competing processes: the dispersion of one liquid throughout another as droplets, and the combination of these droplets to reform the initial bulk liquids. The first process increases the free energy of the system, while the second works to reduce the free energy. Accordingly, the second process is spontaneous and continues until breakdown is complete—that is, until the bulk phases are reformed.

It is of little use to form a well-dispersed emulsion if it quickly breaks down. Similarly, unless adequate attention is given to achieving an optimum dispersion during preparation, the stability of an emulsion system may be compromised from the start. Dispersion is brought about by well-designed and well-operated machinery, capable of producing droplets in a relatively short period of time. Such equipment is discussed in Chapter 39. The reversal back to the bulk phases is minimized by using those parameters that influence the stability of the emulsion once it is formed.

DISPERSION PROCESS TO FORM DROPLETS—Consider two immiscible liquid phases in a test tube. To disperse one liquid as droplets within the other, the interface between the two liquids must be disturbed and expanded to a sufficient degree so that "fingers" or threads of one liquid pass into the second liquid, and *vice versa*. These threads are unstable, and become varicosed or beaded. The beads separate and become spherical, as illustrated in Figure 22-5. Depending on the agitation or the shear rate used, larger droplets are also deformed to give small threads, which in turn produce smaller drops.

The time of agitation is important. Thus, the mean size of droplets decreases rapidly in the first few seconds of agitation. The limiting size range is generally reached within 1 to 5 min, and results from the number of droplets coalescing being equivalent to the number of new droplets being formed. It is uneconomical to continue agitation any further.

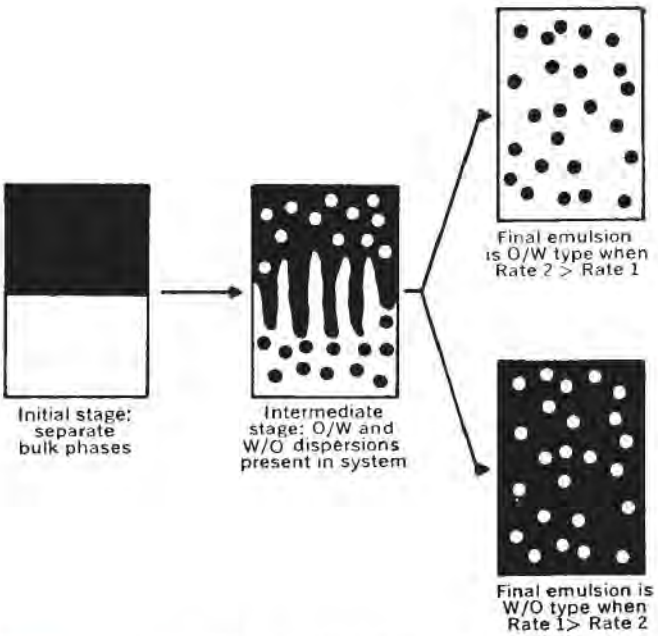


Figure 22-5. Effect of rate of coalescence on emulsion type. Rate 1: O/W coalescence rate. Rate 2: W/O coalescence rate. ●: oil. ○: water. For an explanation of Rates 1 and 2, refer to the discussion of Davies on page 329 of *Proceedings of the International Congress on Surface Activity*, 2nd ed. London: Butterworth/Academic, 1957.

The liquids may be agitated or sheared by several means. *Shaking* is employed commonly, especially when the components are of low viscosity. Intermittent shaking is frequently more efficient than continual shaking, possibly because the short time interval between shakes allows the thread that is forced across the interface time to break down into drops that are then isolated in the opposite phase. Continuous, rapid agitation tends to hinder this breakdown to form drops. A mortar and pestle is employed frequently in the extemporaneous preparation of emulsions. It is not a very efficient technique and is not used on a large scale. Improved dispersions are achieved by the use of high-speed mixers, blenders, colloid mills, or homogenizers. Ultrasonic techniques also have been employed and are described in Chapter 39.

The phenomenon of *spontaneous emulsification*, as the name implies, occurs without any external agitation. There is, however, an internal agitation arising from certain physicochemical processes that affect the interface between the two bulk liquids. For a description of this process, see Davies and Rideal in the bibliography.

COALESCENCE OF DROPLETS—*Coalescence* is a process distinct from flocculation (aggregation), which commonly precedes it. Flocculation is the clumping together of particles, but coalescence is the fusing of the agglomerates into a larger drop, or drops. Coalescence usually is rapid when two immiscible liquids are shaken together, as there is no large energy barrier to prevent fusion of drops and reformation of the original bulk phases. When an emulsifying agent is added to the system, flocculation still may occur but coalescence is reduced to an extent depending on the efficacy of the emulsifying agent to form a stable, coherent interfacial film. It is therefore possible to prepare emulsions that are flocculated yet do not coalesce. In addition to the interfacial film around the droplets acting as a mechanical barrier, the drops also are prevented from coalescing by the presence of a thin layer of continuous phase between particles clumped together. Davies[13] showed the importance of coalescence rates in determining emulsion type; this work is discussed in more detail on page 329.

EMULSIFYING AGENT

The process of coalescence can be reduced to insignificant levels by the addition of a third component—the emulsifying agent or *emulsifier*. The choice of emulsifying agent is frequently critical in developing a successful emulsion, and the pharmacist should be aware of

- The desirable properties of emulsifying agents.
- How different emulsifiers act to optimize emulsion stability.
- How the type and physical properties of the emulsion can be affected by the emulsifying agent.

Desirable Properties

Some of the desirable properties of an emulsifying agent are that it should:

1. Be surface active and reduce surface tension to below 10 dynes/cm.
2. Be adsorbed quickly around the dispersed drops as a condensed, nonadherent film that will prevent coalescence.
3. Impart to the droplets an adequate electrical potential so that mutual repulsion occurs.
4. Increase the viscosity of the emulsion.
5. Be effective in a reasonably low concentration.

Not all emulsifying agents possess these properties to the same degree; in fact, not every good emulsifier necessarily possesses all these properties. Further, there is no one ideal emulsifying agent because the desirable properties of an emulsifier depend, in part, on the properties of the two immiscible phases in the particular system under consideration.

INTERFACIAL TENSION—Lowering of interfacial tension is one way in which the increased surface free energy associated with the formation of droplets, and hence surface area, in an emulsion can be reduced (Equation 1). Assuming the droplets to be spherical, it can be shown that

$$\Delta F = \frac{6\gamma V}{d} \tag{7}$$

where V is the volume of dispersed phase in milliliters, and d is the mean diameter of the particles. To disperse 100 mL of oil as 1-μm (10^{-4}-cm) droplets in water when $\gamma_{O/W} = 50$ dynes/cm, requires an energy input of

$$\Delta F = \frac{6 \times 50 \times 100}{1 \times 10^{-4}} = 30 \times 10^7 \text{ ergs}$$

$$= 30 \text{ joules or } 30/4.184 = 7.2 \text{ cal}$$

In the above example the addition of an emulsifier that will reduce γ from 50 to 5 dynes/cm will reduce the surface free energy from 7.2 to around 0.7 cal. Likewise, if the interfacial tension is reduced to 0.5 dynes/cm (a common occurrence), the original surface free energy is reduced a hundredfold. Such a reduction can help to maintain the surface area generated during the dispersion process.

FILM FORMATION—The major requirement of a potential emulsifying agent is that it readily form a *film* around each droplet of dispersed material. The main purpose of this film—which can be a monolayer, a multilayer, or a collection of small particles adsorbed at the interface—is to form a barrier that prevents the coalescence of droplets that come into contact with one another. For the film to be an efficient barrier, it should possess some degree of surface elasticity and should not thin out and rupture when sandwiched between two droplets. If broken, the film should have the capacity to reform rapidly.

ELECTRICAL POTENTIAL—The origin of an electrical potential at the surface of a droplet has been discussed earlier in the chapter. Insofar as emulsions are concerned, the presence of a well-developed charge on the droplet surface is signif-

icant in promoting stability by causing repulsion between approaching drops. This potential is likely to be greater when an ionized emulsifying agent is employed. Electrical potential has been shown to be a significant factor for maintaining the stability of intravenous fat emulsions that are stabilized with lecithin.

CONCENTRATION OF EMULSIFIER—The main objective of an emulsifying agent is to form a condensed film around the droplets of the dispersed phase. An inadequate concentration will do little to prevent coalescence. Increasing the emulsifier concentration above an optimum level achieves little in terms of increased stability. In practice the aim is to use the minimum amount consistent with producing a satisfactory emulsion.

It frequently helps to have some idea of the amount of emulsifier required to form a condensed film, one molecule thick, around each droplet. Suppose we wish to emulsify 50 g of an oil, density = 1.0, in 50 g of water. The desired particle diameter is 1 μm. Thus,

Particle diameter = 1 μm = 1×10^{-4} cm
Volume of particle = $(\pi d^3/6) = 0.524 \times 10^{-12}$ cm^3
Total number of particles in 50 g = $(50/0.524 \times 10^{-12}) = 95.5 \times 10^{12}$
Surface area of each particle = $\pi d^2 = 3.142 \times 10^{-8}$ cm^2
Total surface area = $3.142 \times 10^{-8} \times 95.5 \times 10^{12} = 300 \times 10^4$ cm^2

If the area each molecule occupies at the oil–water interface is 30 Å^2 (30×10^{-16} cm^2), we require

$$\frac{300 \times 10^4}{30 \times 10^{16}} = 1 \times 10^{21} \text{ molecules}$$

A typical emulsifying agent might have a molecular weight of 1000. Thus, the required weight is

$$\frac{1000 \times 10^{21}}{6.023 \times 10^{23}} = 1.66 \text{ g}$$

To emulsify 10 g of oil would require 0.33 g of the emulsifying agent.

While the approach is an oversimplification of the problem, it does at least allow the formulator to make a reasonable estimate of the required concentration of emulsifier.

EMULSION RHEOLOGY—The emulsifying agent and other components of an emulsion can affect the rheologic behavior of an emulsion in several ways, as summarized in Table 22-3.[14] It should be borne in mind that the droplets of the internal phase are deformable under shear and that the adsorbed layer of emulsifier affects the interactions between adjacent droplets and also between a droplet and the continuous phase. The means by which the rheological behavior of emulsions can be controlled have been discussed by Rogers.[15]

Table 22-3. Factors Influencing Emulsion Viscosity

1. Internal phase
   a. Volume concentration (φ); hydrodynamic interaction between globules; flocculation, leading to formation of globule aggregates.
   b. Viscosity (η_1); deformation of globules in shear.
   c. Globule size, and size distribution, technique used to prepare emulsion; interfacial tension between the two liquid phases: globule behavior in shear; interaction with continuous phase; globule interaction.
   d. Chemical constitution.
2. Continuous phase
   a. Viscosity (η_0), and other rheological properties.
   b. Chemical constitution, polarity, pH; potential energy of interaction between globules.
   c. Electrolyte concentration if polar medium.
3. Emulsifying agent
   a. Chemical constitution; potential energy of interaction between globules.
   b. Concentration, and solubility in internal and continuous phases; emulsion type; emulsion inversion; solubilization of liquid phases in micelles.
   c. Thickness of film adsorbed around globules, and its rheological properties, deformation of globules in shear; fluid circulation within globules.
   d. Electroviscous effect.
4. Additional stabilizing agents
   a. Pigments, hydrocolloids, hydrous oxides.
   b. Effect on rheological properties of liquid phases, and interfacial boundary region.

From Davies JT, Rideal EK. *Interfacial Phenomena*. New York: Academic Press, 1961, Chap 8.

Mechanism of Action

Emulsifying agents may be classified in accordance with the type of film they form at the interface between the two phases.

MONOMOLECULAR FILMS—Those surface-active agents that are capable of stabilizing an emulsion do so by forming a monolayer of adsorbed molecules or ions at the oil–water interface (Fig 22-6). In accordance with Gibbs' law (Chapter 20) the presence of an interfacial excess necessitates a reduction in interfacial tension. This results in a more stable emulsion because of a proportional reduction in the surface free energy. Of itself, this reduction is probably not the main factor promoting stability. More significant is the fact that the droplets are surrounded now by a coherent monolayer that prevents coalescence between approaching droplets. If the emulsifier forming the monolayer is ionized, the presence of strongly charged and mutually repelling droplets increases the stability of the system. With un-ionized, nonionic surface-active agents, the particles may still carry a charge; this arises from adsorption of a specific ion or ions from solution.

MULTIMOLECULAR FILMS—Hydrated lyophilic colloids form multimolecular films around droplets of dispersed oil (see Fig 22-6). The use of these agents has declined in recent years because of the large number of synthetic surface-active agents available that possess well-marked emulsifying properties. Although these hydrophilic colloids are adsorbed at an interface (and can be regarded therefore as surface active), they do not cause an appreciable lowering in surface tension. Rather, their efficiency depends on their ability to form strong coherent multimolecular films. These act as a coating around the droplets and render them highly resistant to coalescence, even in the absence of a well-developed surface potential. Furthermore, any hydrocolloid not adsorbed at the interface increases the viscosity of the continuous aqueous phase; this enhances emulsion stability.

SOLID PARTICLE FILMS—Small solid particles that are wetted to some degree by both aqueous and nonaqueous liquid phases act as emulsifying agents. If the particles are too hydrophilic, they remain in the aqueous phase; if too hydrophobic, they are dispersed completely in the oil phase. A second requirement is that the particles are small in relation to the droplets of the dispersed phase (see Fig 22-6).

Chemical Types

Emulsifying agents also may be classified in terms of their chemical structure; there is some correlation between this classification and that based on the mechanism of action. For example, the majority of emulsifiers forming monomolecular films are synthetic, organic materials. Most of the emulsifiers that form multimolecular films are obtained from natural sources and are organic. A third group is composed of solid particles, invariably inorganic, that form films composed of finely divided solid particles.

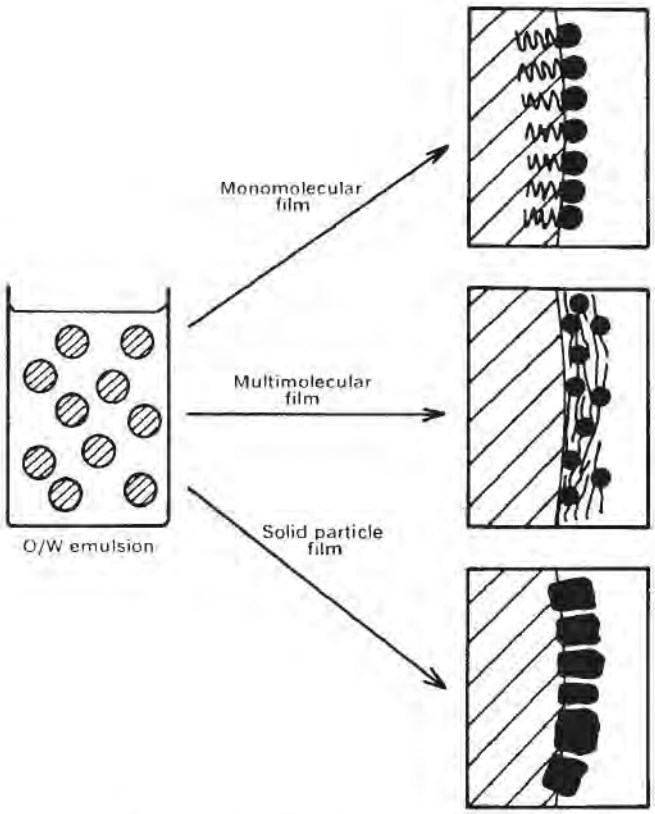


Figure 22-6. Types of films formed by emulsifying agents at the oil–water interface. Orientations are shown for O/W emulsions. ▨: oil, □: water.

Accordingly, the classification, adopted divides emulsifying agents into *synthetic, natural,* and *finely dispersed solids* (Table 22-4). A fourth group, the *auxiliary materials* (Table 22-5) are weak emulsifiers. The list of agents is not meant to be exhaustive, but rather merely illustrates the various types available.

SYNTHETIC EMULSIFYING AGENTS—Synthetic emulsifying agents, a group of surface-active agents that act as emulsifiers, may be subdivided into anionic, cationic, and nonionic, depending on the charge possessed by the surfactant.

Anionics—In the anionic subgroup, the surfactant ion bears a negative charge. The potassium, sodium, and ammonium salts of lauric and oleic acid are soluble in water and are good O/W emulsifying agents. They do, however, have a disagreeable taste and are irritating to the gastrointestinal (GI) tract; this limits them to emulsions prepared for external use. Potassium laurate, a typical example, has the structure

$$CH_3(CH_2)_{10}COO^-K^+$$

Solutions of *alkali soaps* have a high pH; they start to precipitate out of solution below pH 10 because the un- ionized fatty acid is now formed, and this has a low aqueous solubility. Further, the free fatty acid is ineffective as an emulsifier, so emulsions formed from alkali soaps are not stable at pH values less than about 10.

The calcium, magnesium, and aluminum salts of fatty acids, often termed the *metallic soaps,* are water insoluble and result in W/O emulsions.

Another class of soaps are salts formed from a fatty acid and an organic amine such as triethanolamine. These O/W emulsifiers also are limited to external preparations, but their alkalinity is considerably less than that of the alkali soaps and they are active as emulsifiers down to around pH 8. These agents are less irritating than the alkali soaps.

Sulfated alcohols are neutralized sulfuric acid esters of such fatty alcohols as lauryl and cetyl alcohol. These compounds are an important group of pharmaceutical surfactants. They are used chiefly as wetting agents, although they do have some value as emulsifiers, particularly when used in conjunction with an auxiliary agent.

Sulfonates—Sulfonates are a class of compounds in which the sulfur atom is connected directly to the carbon atom, giving the general formula

$$CH_3(CH_2)_nCH_2SO_3^-Na^+$$

A frequently used compound is sodium lauryl sulfate. Sulfonates have a higher tolerance to calcium ions and do not hydrolyze as readily as the sulfates. A widely used surfactant of this type is dioctyl sodium sulfosuccinate.

Cationics—The surface activity in the cationic group resides in the positively charged cation. These compounds have marked bactericidal properties. This makes them desirable in emulsified anti-infective products such as skin lotions and creams. The pH of an emulsion prepared with a cationic emulsifier lies in the pH 4 to 6 ranges. Because this includes the normal pH of the skin, cationic emulsifiers are advantageous in this regard also.

Cationic agents are weak emulsifiers and generally are formulated with a stabilizing or auxiliary emulsifying agent such as cetostearyl alcohol. The only group of cationic agents used extensively as emulsifying agents are the quaternary ammonium compounds. An example is cetyltrimethyl-ammonium bromide.

$$CH_3(CH_2)_{14}CH_2N^+(CH_3)_3\,Br^-$$

Cationic emulsifiers should not be used in the same formulation with anionic emulsifiers because they will interact. The incompatibility

Table 22-4. Classification of Emulsifying Agents

TYPE	TYPE OF FILM		EXAMPLES
Synthetic (surface-active agents)	Monomolecular	*Anionic*	*Cationic*
		Soaps	Quaternary ammonium compounds
		Potassium laurate	Cetyltrimethyllammonium bromide
		Triethanolamine stearate	Lauryldimethylbenzylammonium chloride
		Sulfates	*Nonionic*
		Sodium lauryl sulfate	Polyoxyethylene fatty alcohol ethers
		Alkyl polyoxyethylene sulfates	Sorbitan fatty acid esters
		Sulfonates	Polyoxyethylene sorbitan fatty acid esters
		Dioctyl sodium sulfosuccinate	Polyoxyethylene polyoxypropylene block copolymers (poloxamers)
			Lanolin alcohols and ethoxylated lalnolin alcohols
Natural	Multimolecular	*Hydrophilic colloids*	
		Acacia	
		Gelatin	
	Monomolecular	Lecithin	
		Cholesterol	
Finely divided solids	Solid particle	*Colloidal clays*	
		Bentonite	
		Veegum	
		Metallic hydroxides	
		Magnesium hydroxide	

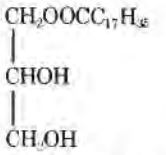
Table 22-5. Auxiliary Emulsifying Agents

PRODUCT	SOURCE AND COMPOSITION	PRINCIPAL USE
Cetyl alcohol	Chiefly $C_{16}H_{33}OH$	Lipophilic thickening agent and stabilizer for O/W lotions and ointments
Glyceryl monosterate	$C_{17}H_{35}COOCH_2CHOHCH_2OH$	Lipophilic thickening agent and stabilizer for O/W lotions and ointments
Methylcellulose	Series of methyl ethers of cellulose	Hydrophilic thickening agent and stabilizer for O/W emulsions; weak O/W emulsifier
Sodium carboxymethylcellulose	Sodium salt of the carboxymethyl esters of cellulose	Hydrophilic thickening agent and stabilizer for O/W emulsions
Stearic acid	A mixture of solid acids from fats, chiefly stearic and palmitic	Lipophilic thickening agent and stabilizer for O/W lotions and ointments. Forms a true emulsifier when reacted with an alkali

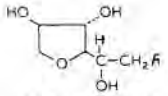
may not be immediately apparent as a precipitate, but virtually all of the desired antibacterial activity will generally have been lost.

Nonionics—Nonionics, undissociated surfactants, find widespread use as emulsifying agents when they possess the proper balance of hydrophilic and lipophilic groups within the molecule. Their popularity is based on the fact that, unlike the anionic and cationic types, nonionic emulsifiers are not susceptible to pH changes and the presence of electrolytes. The number of nonionic agents available is legion; the most frequently used are the glyceryl esters, polyoxyethylene glycol esters and ethers, and the sorbitan fatty acid esters and their polyoxyethylene derivatives. More recently, the polyoxyethylene/polyoxypropylene block copolymers have become popular surfactants and emulsifying agents.

A glyceryl ester, such as glyceryl monostearate, is too lipophilic to serve as a good emulsifier; it is used widely as an auxiliary agent (see Table 22-5) and has the structure

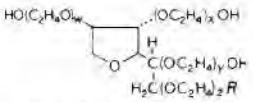


Sorbitan fatty acid esters, such as sorbitan monopalmitate



[R is $(C_{15}H_{31})COO$]

are nonionic oil-soluble emulsifiers that promote W/O emulsions. The polyoxyethylene sorbitan fatty acid esters, such as polyoxyethylene sorbitan monopalmitate

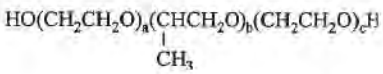


[Sum of w, x, y, and z is 20; R is $(C_{15}H_{31})COO$]

are hydrophilic water-soluble derivatives that favor O/W emulsions.

Polyoxyethylene glycol esters, such as the monostearate, $C_{17}H_{35}COO(CH_2OCH_2)_nH$, also are used widely.

Polyoxyethylene/polyoxypropylene block copolymers



also known as *poloxamers* consist of combined chains of oxyethylene with oxypropylene where the oxyethylene portion imparts hydrophilicity and the oxypropylene portion imparts lipophilicity. The molecules are synthesized as long segments of the hydrophilic portions combined with long segments of the hydrophobic portions, with each portion referred to as a *block*. This organization produces hydrophilic and hydrophobic domains that impart the surface active character to these agents. Poloxamers have been used in the formulation of intravenous emulsions and can impart structure to vehicles and interfacial films that can protect the dispersed phase against coalescence. The polymeric nature of these surfactants protects emulsions against coalescence via steric stabilization at the droplet interface.

Very frequently, the best results are obtained from blends of nonionic emulsifiers. Thus, an O/W emulsifier customarily will be used in an emulsion with a W/O emulsifier. When blended properly, the nonionics produce fine-textured stable emulsions.

NATURAL EMULSIFYING AGENTS—Of the numerous emulsifying agents derived from natural (ie, plant and animal) sources, consideration will be given only to acacia, gelatin, lecithin, and cholesterol. Many other natural materials are only sufficiently active to function as auxiliary emulsifying agents or stabilizers.

Acacia is a carbohydrate gum that is soluble in water and forms O/W emulsions. Emulsions prepared with acacia are stable over a wide pH range. Because it is a carbohydrate it is necessary to preserve acacia emulsions against microbial attack by the use of a suitable preservative.

Gelatin, a protein, has been used for many years as an emulsifying agent. Gelatin can have two isoelectric points, depending on the method of preparation. So-called Type A gelatin, derived from an acid-treated precursor, has an isoelectric point of between pH 7 and 9. Type B gelatin, obtained from an alkali-treated precursor, has an isoelectric point of approximately pH 5. Type A gelatin acts best as an emulsifier around pH 3, where it is positively charged; on the other hand, Type B gelatin is best used around pH 8, where it is negatively charged. The question as to whether the gelatin is positively or negatively charged is fundamental to the stability of the emulsion when other charged emulsifying agents are present. To avoid an incompatibility, all emulsifying agents should carry the same sign. Thus, if gums (such as tragacanth, acacia, or agar) that are negatively charged are to be used with gelatin, then Type B material should be used at an alkaline pH. Under these conditions the gelatin is similarly negatively charged.

Lecithin is an emulsifier obtained from both plant (eg, soybean) and animal (eg, egg yolk) sources and is composed of various phosphatides. The primary component of most lecithins is phosphatidylcholine and the term "lecithin" is often used to describe purified samples of phosphatidylcholine. Frequently, lecithins that are used as emulsifiers also contain mixtures of phosphatides, including phosphatidylserine, phosphatidylinositol, phosphatidylethanolamine, and phosphatidic acid in addition to phosphatidylcholine. Although phosphatidylcholine is a zwitterionic compound, the presence of other phosphatides such as phosphatidylinositol and phosphatidic acid, as well as small quantities of lysophosphatides, result in an emulsifier that imparts a net negative charge to dispersed particles.

Lecithin can be an excellent emulsifier for naturally occurring oils such as soy, corn, or safflower. Highly stable O/W emulsions can be formed with these oils. Purified lecithins from soy or egg yolk are the principal emulsifiers for intravenous fat emulsions. Lecithin provides stable emulsions with droplet sizes of less than 1 μm in diameter. It is critical that a small, uniform particle size be maintained in these emulsions to eliminate the risks of fat embolism after intravenous injection. The

excellent stability observed with these emulsions may be the result of the large negative zeta potential that results from the small quantity of charged lipids present in lecithin as well as the ability of the lecithin to form mesophases resembling liposomes. During manufacture of the emulsions, homogenization produces small droplets that are surrounded by concentric layers of phospholipids. The latter may form a protective layer that prevents coalescence of the droplets. As an emulsifier, lecithin produces the best results at a pH of around 8.

As with any natural product, the content of lecithins will vary from source to source and their emulsifying properties and toxicity may also vary. For highly critical applications, such as intravenous emulsions, the source and composition of the lecithin must be carefully controlled and monitored.

Cholesterol is a major constituent of wool alcohols, obtained by the saponification and fractionation of wool fat. It is cholesterol that gives wool fat its capacity to absorb water and form a W/O emulsion.

FINELY DISPERSED SOLIDS—Finely dispersed solids are emulsifiers that form particulate films around the dispersed droplets, producing emulsions that are coarse-grained but have considerable physical stability. It appears possible that any solid can act as an emulsifying agent of this type, provided it is reduced to a sufficiently fine powder. In practice, the group of compounds used most frequently are the colloidal clays.

Bentonite is a white to gray, odorless and tasteless powder that swells in the presence of water to form a translucent suspension with a pH of about 9. Depending on the sequence of mixing it is possible to prepare both O/W and W/O emulsions. When an O/W emulsion is desired, the bentonite is first dispersed in water and allowed to hydrate so as to form a magma. The oil phase is then added gradually with constant titration. Because the aqueous phase is always in excess, the O/W emulsion type is favored. To prepare a W/O emulsion, the bentonite is first dispersed in oil; the water is then added gradually.

Although *Veegum* is used as a solid particle emulsifying agent, it is employed most extensively as a stabilizer in cosmetic lotions and creams. Concentrations of less than 1% Veegum will stabilize an emulsion containing anionic or nonionic emulsifying agents.

AUXILIARY EMULSIFYING AGENTS—Auxiliary emulsifying agents include those compounds that are normally incapable themselves of forming stable emulsions. Their main value lies in their ability to function as thickening agents and thereby help stabilize the emulsion. Agents in common use are listed in Table 22-5. Auxiliary emulsifying agents that are amphiphilic in nature are, in some cases, capable of forming gel or liquid crystalline phases with the primary emulsifying agent when combined with water and oil. This type of behavior may help to stabilize emulsions due to an increased viscosity, as observed in topical creams. Alternatively, gel or liquid crystalline phases may prevent coalescence by reducing van der Waals forces between particles or by providing a physical barrier between approaching particles of the internal phase. This latter effect is thought to be an important function in phospholipid-stabilized emulsions that must maintain a low viscosity to permit administration via the intravenous route. Additional information is provided by Eccleston.[12]

Emulsifying Agents and Emulsion Type

For a molecule, ion, colloid, or particle to be active as an emulsifying agent, it must have some affinity for the interface between the dispersed phase and the dispersion medium. With the monolayer and multilayer films, the emulsifier is in solution, and therefore it must be soluble to some extent in one or both of the phases. At the same time it must not be overly soluble in either phase; otherwise, it will remain in the bulk of that phase and not be adsorbed at the interface. This balanced affinity for the two phases also must be evident with finely divided solid particles used as emulsifying agents. If their affinity, as evidenced by the degree to which they are wetted, is either predominantly hydrophilic or hydrophobic, they will not function as effective wetting agents.

Table 22-6. Relationship between HLB Range and Surfactant Application

HLB RANGE	USE
0–3	Antifoaming agents
4–6	W/O emulsifying agents
7–9	Wetting agents
8–18	O/W emulsifying agents
13–15	Detergents
10–18	Solubilizing agents

The great majority of the work on the relation between emulsifier and emulsion type has been concerned with surface-active agents that form interfacial monolayers. Thus, the present discussion will concentrate on this class of agents.

HYDROPHILE–LIPOPHILE BALANCE—As the emulsifier becomes more hydrophilic, its solubility in water increases and the formation of an O/W emulsion is favored. Conversely, W/O emulsions are favored with the more lipophilic emulsifiers. This led to the concept that the type of emulsion is related to the balance between hydrophilic and lipophilic solution tendencies of the surface-active emulsifying agent.

Griffin[16] developed a scale based on the balance between these two opposing tendencies. This so-called *HLB scale* is a numerical scale, extending from 1 to approximately 50. The more hydrophilic surfactants have high HLB numbers (in excess of 10), whereas surfactants with HLB numbers from 1 to 10 are considered to be lipophilic. Surfactants with a proper balance in their hydrophilic and lipophilic affinities are effective emulsifying agents because they concentrate at the oil–water interface. The relationship between HLB values and the application of the surface-active agent is shown in Table 22-6. Some commonly used emulsifiers and their HLB numbers are listed in Table 22-7. The utility of the HLB system in rationalizing the choice of emulsifying agents when formulating an emulsion will be discussed in a later section.

RATE OF COALESCENCE AND EMULSION TYPE—Davies[13] indicated that the type of emulsion produced in systems prepared by shaking is controlled by the relative coalescence rates of oil droplets dispersed in the oil. Thus, when a

Table 22-7. Approximate HLB Values for a Number of Emulsifying Agents

GENERIC OR CHEMICAL NAME	HLB	WATER DISPERSIBILITY
Sorbitan trioleate	1.8	No dispersion
Sucrose distearate	3.0	
Propylene glycol monostearate	3.4	
Glycerol monostearate (non–self-emulsifying)	3.8	Poor dispersion
Propylene glycol monolaurate	4.5	
Sorbitan monostearate	4.7	
Glycerol monostearate (self-emulsifying)	5.5	
Sorbitan monolaurate	8.6	Milky dispersion
Polyoxyethylene-4-lauryl ether	9.5	
Polyethylene glycol 400 monostearate	11.6	Translucent to clear
Polyoxyethylene-4-sorbitan monolaurate	13.3	Clear solution
Sucrose stearate	14.5	
Polyoxyethylene-20-sorbitan monopalmitate	15.6	
Polyoxyethylene-40-stearate	16.9	
Sodium oleate	18.0	
Sodium lauryl sulfate	40.0	

mixture of oil and water is shaken together with an emulsifying agent, a multiple dispersion is produced initially that contains oil dispersed in water and water dispersed in oil (see Fig 22-5).The type of the final emulsion that results depends on whether the water or the oil droplets coalesce more rapidly. If the O/W coalescence rate (Rate 1) is much greater than W/O coalescence rate (Rate 2), a W/O emulsion is formed because the dispersed water droplets are more stable than the dispersed oil droplets. Conversely, if Rate 2 is significantly faster than Rate 1, the final emulsion is an O/W dispersion because the oil droplets are more stable.

According to Davies,[13] the rate at which oil globules coalesce when dispersed in water is given by the expression

$$\text{Rate } 1 = C_1 e^{-W1/RT} \quad (8)$$

The term C_1 is a collision factor that is directly proportional to the phase volume of the oil relative to the water, and is an inverse function of the viscosity of the continuous phase (water). W_1 defines an energy barrier made up of several contributing factors that must be overcome before coalescence can take place. First, it depends on the electrical potential of the dispersed oil droplets, as this affects repulsion. Second, with an O/W emulsion, the hydrated layer surrounding the polar portion of emulsifying agent must be broken down before coalescence can occur. This hydrated layer is probably around 1 nm thick with a consistency of butter. Finally, the total energy barrier depends on the fraction of the interface covered by the emulsifying agent.

Equation 9 describes the rate of coalescence of water globules dispersed in oil:

$$\text{Rate } 2 = C_2 e^{-W2/RT} \quad (9)$$

Here, the collision factor C_2 is a function of the water–oil phase volume ratio divided by the viscosity of the oil phase. The energy barrier W_2 is, as before, related to the fraction of the interface covered by the surface-active agent. Another contributing factor is the number of—CH_2—groups in the emulsifying agent; the longer the alkyl chain of the emulsifier, the greater the gap that has to be bridged if one water droplet is to combine with a second drop.

Davies[13] showed that the HLB concept is related to the distribution characteristics of the emulsifying agent between the two immiscible phases. An emulsifier with an HLB of less than 7 will be preferentially soluble in the oil phase and will favor formation of a W/O emulsion. Surfactants with an HLB value in excess of 7 will be distributed in favor of the aqueous phase and will promote O/W emulsions.

PREPARATION OF EMULSIONS

Several factors must be taken into account in the successful preparation and formulation of emulsified products. Usually, the type of emulsion (ie, O/W or W/O) is specified; if not, it probably will be implied from the anticipated use of the product. The formulator's attention is focused primarily on the selection of the emulsifying agent, or agents, necessary to achieve a satisfactory product. No incompatibilities should occur between the various emulsifiers and the several components commonly present in pharmaceutical emulsions. Finally, the product should be prepared in such a way as not to prejudice the formulation.

Selection of Emulsifying Agents

The selection of the emulsifying agent or agents is of prime importance in the successful formulation of an emulsion. The pharmacist must ensure that, in addition to its emulsifying properties, the material chosen is nontoxic and that the taste, odor, and chemical stability are compatible with the product. Thus, an emulsifying agent that is entirely suitable for inclusion in a skin cream may be unacceptable in the formulation of an oral preparation due to its potential toxicity. This consideration is most important when formulating intravenous emulsions.

THE HLB SYSTEM—With the increasing number of available emulsifiers, particularly the nonionics, the selection of emulsifiers for a product was essentially a trial-and-error procedure. Fortunately, the work of Griffin[16,17] provided a logical means of selecting emulsifying agents. Griffin's method, based on the balance between the hydrophilic and lipophilic portions of the emulsifying agent, is now widely used and has come to be known as the HLB system. It is used most in the rational selection of combinations of nonionic emulsifiers, and we shall limit our discussion accordingly.

As shown in Table 22-6, if an O/W emulsion is required, the formulator should use emulsifiers with an HLB in the range of 8 to 18. Emulsifiers with HLB values in the range of 4 to 6 are given consideration when a W/O emulsion is desired. Some typical examples are given in Table 22-7.

Another factor is the presence or absence of any polarity in the material being emulsified, because this will affect the polarity required in the emulsifier. Again, as a result of extensive experimentation, Griffin evolved a series of "required HLB" values—that is, the HLB value required by a particular material if it is to be emulsified effectively. Some values for oils and related materials are contained in Table 22-8. Naturally, the required HLB value differs depending on whether the final emulsion is O/W or W/O.

Fundamental to the utility of the HLB concept is the fact that the HLB values are algebraically additive. Thus, by using a low HLB surfactant with one having a high HLB it is possible to prepare blends having HLB values intermediate between those of the two individual emulsifiers. The following formula serves as an example.

O/W Emulsion

Liquid petrolatum (Required HLB 10.5)	50 g
Emulsifying agents	5 g
Sorbitan monooleate (HLB 4.3)	
Polyoxyethylene 20 sorbitan monooleate (HLB 15.0)	
Water, qs	100 g

By simple algebra it can be shown that 4.5 parts by weight of sorbitan monooleate blended with 6.2 parts by weight of polyoxyethylene 20 sorbitan monooleate will result in a mixed emulsifying agent having the required HLB of 10.5. Because the formula calls for 5 g, the required weights are 2.1 and 2.9 g, respectively. The oil-soluble sorbitan monooleate is dissolved in the oil and heated to 75°; the water-soluble polyoxyethylene 20 sorbitan monooleate is added to the aqueous phase that is heated to 70°. At this point the oil phase is mixed with the aqueous phase and the whole is stirred continuously until cool.

The formulator is not restricted to these two agents to produce a blend with an HLB of 10.5. Table 22-9 shows the various proportions required, using other pairs of emulsifying agents,

Table 22-8. Required HLB Values for Some Common Emulsion Ingredients

SUBSTANCE	W/O	O/W
Acid, stearic	—	17.0
Alcohol, cetyl	—	13.0
Lanolin, anhydrous	8	15.0
Oil, cottonseed	—	7.5
Mineral oil, light	4	10–12.0
Mineral oil, heavy	4	10.5
Wax, beeswax	5	10–16.0
Microcrystalline	—	9.5
Paraffin	—	9.0

to form a blend of HLB 10.5. When carrying out preliminary investigations with a particular material to be emulsified, it is advisable to try several pairs of emulsifying agents. Based on an evaluation of the emulsions produced, it becomes possible to choose the best combination.

Occasionally, the required HLB of the oil may not be known, in which case it becomes necessary to determine this parameter. Various blends are prepared to give a wide range of HLB mixtures and emulsions are prepared in a standardized manner. The HLB of the blend used to emulsify the best product, selected on the basis of physical stability, is taken to be the required HLB of the oil. The experiment should be repeated using another combination of emulsifiers to confirm the value of the required HLB of the oil to within, say, ± 1 HLB unit.

There are methods for finding the HLB value of a new surface-active agent. Griffin[17] developed simple equations that can be used to obtain an estimate with certain compounds. It has been shown that the ability of a compound to spread at a surface is related to its HLB. In another approach a linear relation between HLB and the logarithm of the dielectric constant for a number of nonionic surfactants has been observed.

An interesting approach, developed by Davies,[13] is related to his studies on the relative rates of coalescence of O/W and W/O emulsions. According to Davies, hydrophilic groups on the surfactant molecule make a positive contribution to the HLB number, whereas lipophilic groups exert a negative effect. Davies calculated these contributions and termed them HLB Group Numbers (Table 22-10). Provided the molecular structure of the surfactant is known, one simply adds the various group numbers in accordance with the following formula:

$$\text{HLB} = \Sigma(\text{hydrophilic group numbers}) - m(\text{group number/—CH}_2\text{—group}) + 7$$

where m is the number of —CH_2— groups present in the surfactant. Poor agreement is found between the HLB values calculated by the use of group numbers and the HLB values obtained using the simple equations developed by Griffin. However, the student should realize that the absolute HLB values per se are of limited significance. The utility of the HLB approach (using values calculated by either Griffin's or Davies' equations) is to

1. Provide the formulator with an idea of the relative balance of hydrophilicity and lipophilicity in a particular surfactant.
2. Relate that surfactant's emulsifying and solubilizing properties to other surfactants. The formulator still needs to confirm experimentally that a particular formulation will produce a stable emulsion.

Later, Davies and Rideal[18] attempted to relate HLB to the C_{water}/C_{oil} partition coefficient and found good agreement for a series of sorbitan surfactants. Schott showed, however, that the method does not apply to polyoxyethylated octylphenol surfactants. Schott concluded that "so far, the search for a universal correlation between HLB and another property of the surfactant that could be determined more readily than HLB has not been successful."[19]

Table 22-9. Nonionic Blends Having HLB Values of 10.5

SURFACTANT BLEND	HLB	REQUIRED AMOUNTS (%) TO GIVE HLB = 10.5
Sorbitan tristearate	2.1	34.4
Polyoxyethylene 20 sorbitan monostearate	14.9	65.6
Sorbitan monopalmitate	6.7	57.3
Polyoxyethylene 20 sorbitan monopalmitate	15.6	42.7
Sorbitan sesquioleate	3.7	48.5
Polyoxyethylene lauryl ether	16.9	51.5

Table 22-10. HLB Group Numbers

	GROUP NUMBER
Hydrophilic groups	
—$SO_4^-Na^+$	38.7
—COO^-K^+	21.1
—COO^-Na^+	19.1
N (tertiary amine)	9.4
Ester (sorbitan ring)	6.8
Ester (free)	2.4
—COOH	2.1
Hydroxyl (free)	1.9
—O—	1.3
Hydroxyl (sorbitan ring)	0.5
Lipophilic groups	
—CH—	
—CH_2—	
CH_3—	−0.475
=CH—	
Derived groups	
—(CH_2—CH_2—O)—	+0.33
—(CH_2—CH_2—CH_2—O)—	−0.15

From Wedderburn DL. In: *Advances in Pharmaceutical Sciences*, vol 1. London: Academic Press, 1964, p 195.

The HLB system gives no information as to the *amount* of emulsifier required. Having once determined the correct blend, the formulator must prepare another series of emulsions, all at the same HLB, but containing increasing concentrations of the emulsifier blend. Usually, the minimum concentration giving the desired degree of physical stability is chosen.

When varying the amounts of emulsifier in an emulsion it is useful to consider the use of a phase diagram to select the proper ratio of oil/water/surfactant. The use of the phase diagram to aid in the formulation of emulsions has been discussed by Swarbrick.[20] This approach can provide a systematic way to optimize an emulsion formulation and help to identify the existence of liquid crystalline phases that, when present in an emulsion formulation, can enhance the stability. Because liquid crystals exhibit birefringence, observation of prototype emulsions under polarized light microscopy can be a useful tool to identify combinations of water–oil and emulsifier that produce liquid crystals. It should be noted that liquid crystals are often formed when relatively high concentrations (eg, 20% or more) of surfactant are used in a formulation. The toxicity of the emulsifier for the intended use (eg, topical, oral, or parenteral) must be considered in addition to the physical characteristics.

MIXED EMULSIFYING AGENTS—Emulsifying agents are frequently used in combination because a better emulsion usually is obtained. This enhancement may be due to several reasons, one or more of which may be operative in any one system. Thus, the use of a blend or mixture of emulsifiers may

1. Produce the required hydrophile–lipophile balance in the emulsifier.
2. Enhance the stability and cohesiveness of the interfacial film.
3. Affect the consistency and feel of the product.

The first point has been considered in detail in the previous discussion of the HLB system.

With regard to the second point, Schulman and Cockbain in 1940 showed that combinations of certain amphiphiles formed stable films at the air–water interface. It was postulated that the complex formed by these two materials (one, oil-soluble; the other, water-soluble) at the air–water interface was also present at the O/W interface. This interfacial complex was held to be responsible for the improved stability. For example, sodium cetyl sulfate, a moderately good O/W emulsifier, and elaidyl alcohol or cholesterol, both stabilizers for W/O emulsions, show evidence of an interaction at the air–water interface. Furthermore, an O/W emulsion prepared with sodium cetyl sulfate and

elaidyl alcohol is much more stable than an emulsion prepared with sodium cetyl sulfate alone.

Elaidyl alcohol is the *trans* isomer. When oleyl alcohol, the *cis* isomer, is used with sodium cetyl sulfate, there is no evidence of complex formation at the air–water interface. Significantly, this combination does not produce a stable O/W emulsion either. Such a finding strongly suggests that a high degree of molecular alignment is necessary at the O/W interface to form a stable emulsion. This high degree of molecular alignment may be a prerequisite event for the formation of lamellar liquid crystalline or gel phases. As illustrated in Figure 22-7, the combination of certain long chain acids and alcohols with water can result in the formation of micelles and liquid crystals. It has also been observed that when liquid crystals or gels form in an emulsion, increased stability is generally observed. As discussed previously, gel or liquid crystalline phases can have an important effect in inhibiting coalescence in emulsions.

When using combinations of emulsifiers, care must be taken to ensure their compatibility, as charged emulsifying agents of opposite sign are likely to interact and coagulate when mixed.

STERIC STABILIZATION—Many useful nonionic surfactants consist of hydrophobic portions composed of fatty acids or other lipophilic organic compounds and hydrophilic portions composed of polyoxyethylene chains. When used to prepare O/W emulsions, the oxyethylene chains protrude into the aqueous side of the O/W interface while the hydrophobic portion of the emulsifier will be primarily located in the oil side. As in the case of suspensions, approaching oil droplets will be influenced by van der Waals attractive forces as well as repulsive forces. For an emulsion that is stabilized by a non-ionic surfactant, the repulsive forces consist of electrostatic and non-electrostatic forces. The electrostatic repulsive forces are similar to those discussed for suspensions and depend largely upon the zeta potential of the oil droplets.

Non-electrostatic forces may also arise from a phenomenon that is frequently described as *steric stabilization*. This effect has been explained as follows. First, as emulsion droplets approach, the adsorbed layers of surfactant on each droplet begin to mix. The hydrophilic oxyethylene chains behave as soluble polymers; as their concentration increases in the region of interfacial mixing, segments of the polymers from separate droplets compete for water molecules. This results in restricted movement of the polymer chains or a loss of entropy. Likewise, a positive heat of solution (enthalpy) may result from the mixing of the polymers in the interfaces. The loss of entropy and/or increase in enthalpy results in an increase in the free energy of mixing, meaning that spontaneous mixing in the interfacial region is not favorable. The particles will tend to separate in order to reverse the temporary increase in the free energy of mixing.

An additional effect that causes repulsion of the droplets may be a result of the increased osmotic pressure that results in the area of contact between the two emulsion droplets. The concentration of oxyethylene groups in the region of overlap between the two droplets increases, necessitating an influx of water into the region. This increase in osmotic pressure has the effect of forcing the droplets apart. Thus, in addition to their favorable effect of reducing interfacial tension, nonionic surfactants that possess long, hydrophilic chains provide additional emulsion stabilization via the energetically unfavorable result of mixing of polymer chains at the droplet–droplet interface.

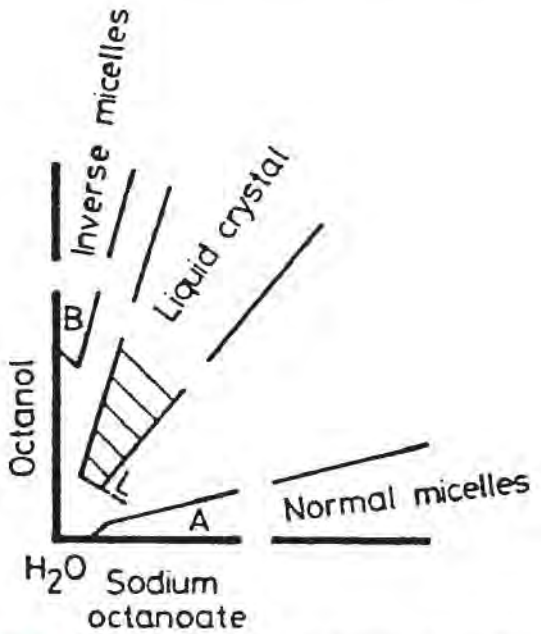


Figure 22-7. Phase diagram illustrating the formation of micellar and liquid crystalline phases in mixtures of a long-chain alcohol, long-chain acid, and water. Compositions that form the lamellar liquid crystalline phase can provide enhanced emulsion stability. (From Friberg S, Larson K. In: Brown GH, ed. *Advances in Liquid Crystals*, vol 2. New York: Academic Press, 1976, p 173.)

Method of Preparation

Different methods are employed, depending on the type of emulsifying agent used and the scale of manufacture. Traditionally, the mortar and pestle was used for the small scale preparation of emulsions stabilized by the presence of such agents as acacia and tragacanth. However, the use of these agents has declined drastically in recent years; as a result, the use of the mortar and pestle has declined as well. (Refer to the 18th edition of this text, page 306, for details of the mortar and pestle method.)

An increasing number of emulsions are being formulated with synthetic emulsifying agents, especially of the nonionic type. The components in such a formulation are separated into those that are oil-soluble and those that are water-soluble. These are dissolved in their respective solvents by heating to about 70° to 75°. When solution is complete, the two phases are mixed and the product is stirred until cool. This method, which requires nothing more than two beakers, a thermometer, and a source of heat, is necessarily used in the preparation of emulsions containing waxes and other high-melting-point materials that must be melted before they can be dispersed in the emulsion. The relatively simple methodology involved in the use of synthetic surfactant-type emulsifiers is one factor that has led to their widespread use in emulsion preparation. This, in turn, has led to a decline in the use of the natural emulsifying agents.

With hand homogenizers, an initial rough emulsion is formed by trituration in a mortar or shaking in a bottle. The rough emulsion then is passed several times through the homogenizer. A reduction in particle size is achieved as the material is forced through a narrow aperture under pressure. A satisfactory product invariably results from the use of a hand homogenizer and overcomes any deficiencies in technique. Should the homogenizer fail to produce an adequate product, the formulation, rather than the technique, should be suspected.

For a discussion of the techniques and equipment used in the large-scale manufacture of emulsions, see Chapter 39.

STABILITY OF EMULSIONS

Several criteria must be met in a well-formulated emulsion. Probably the most important and most readily apparent requirement is that the emulsion possess adequate physical stability; without this, any emulsion soon will revert back to two

separate bulk phases. In addition, if the emulsified product is to have some antimicrobial activity (eg, a medicated lotion), care must be taken to ensure that the formulation possesses the required degree of activity. Frequently, a compound exhibits a lower antimicrobial activity in an emulsion than, say, in a solution. Generally, this is because of partitioning effects between the oil and water phases, which cause a lowering of the *effective* concentration of the active agent. Partitioning has also to be taken into account when considering preservatives to prevent microbiological spoilage of emulsions. Finally, the chemical stability of the various components of the emulsion should receive some attention, as such materials may be more prone to degradation in the emulsified state than when they exist as a bulk phase.

In the present discussion, detailed consideration will be limited to the question of physical stability. Reviews of this topic have been published by Garrett[21] and Kitchener and Mussellwhite.[22] For information on the effect that emulsification can have on the biologic activity and chemical stability of materials in emulsions, see Wedderburn,[23] Burt[24] and Swarbrick.[20]

The theories of emulsion stability have been discussed by Eccleston[25] in an attempt to understand the situation in both a simple O/W emulsion and complex commercial systems. A recent review by the same author[12] has discussed the stability of multiple phase emulsions and the role of bilayer gels and liquid crystalline phases on the physical stability of these systems.

The three major phenomena associated with physical stability are

1. The upward or downward movement of dispersed droplets relative to the continuous phase, termed *creaming* or *sedimentation*, respectively.
2. The *aggregation* and possible *coalescence* of the dispersed droplets to reform the separate, bulk phases.
3. *Inversion*, in which an O/W emulsion inverts to become a W/O emulsion and *vice versa*.

CREAMING AND SEDIMENTATION—*Creaming* is the upward movement of dispersed droplets relative to the continuous phase; *sedimentation*, the reverse process, is the downward movement of particles. In any emulsion one process or the other takes place, depending on the densities of the disperse and continuous phases. This is undesirable in a pharmaceutical product where homogeneity is essential for the administration of the correct and uniform dose. Furthermore, creaming, or sedimentation, brings the particles closer together and may facilitate the more serious problem of coalescence.

The rate at which a spherical droplet or particle sediments in a liquid is governed by Stokes' law (Equation 3). Other equations have been developed for bulk systems, but Stokes' equation is still useful because it points out the factors that influence the rate of sedimentation or creaming. These are the diameter of the suspended droplets, the viscosity of the suspending medium, and the difference in densities between the dispersed phase and the dispersion medium.

Usually, only the use of the first two factors is feasible in affecting creaming or sedimentation. Reduction of particle size contributes greatly toward overcoming or minimizing creaming, because the rate of movement is a square-root function of the particle diameter. There are, however, technical difficulties in reducing the diameter of droplets to below about 0.1 μm. The most frequently used approach is to raise the viscosity of the continuous phase, although this can be done only to the extent that the emulsion still can be removed readily from its container and spread or administered conveniently.

AGGREGATION AND COALESCENCE—Even though creaming and sedimentation are undesirable, they do not necessarily result in the breakdown of the emulsion, as the dispersed droplets retain their individuality. Furthermore, the droplets can be redispersed with mild agitation. More serious to the stability of an emulsion are the processes of aggregation and coalescence. In *aggregation* (flocculation) the dispersed droplets come together but do not fuse. *Coalescence*, the complete fusion of droplets, leads to a decrease in the number of droplets and the ultimate separation of the two immiscible phases. Aggregation precedes coalescence in emulsions; however, coalescence does not necessarily follow from aggregation. Aggregation is, to some extent, reversible. Although it is not as serious as coalescence, it will accelerate creaming or sedimentation, because the aggregate behaves as a single drop.

Aggregation is related to the electrical potential on the droplets, but coalescence depends on the structural properties of the interfacial film. As discussed previously, it has been recognized that combinations of emulsifiers produce more stable emulsions than a single emulsifier alone. One reason for this synergy, as suggested by Shulman and Cockbain, is that appropriate combinations of surfactants form densely packed complex films at the oil–water interface. Additional beneficial effects of mixed emulsifier films could result from an increase in viscosity of the interfacial emulsifier film. A viscous interfacial film could enhance emulsion stability because thinning of the film at the points of droplet to droplet contact would be inhibited. An additional explanation for the beneficial effect of mixed-film emulsifiers suggests that appropriate mixtures of surfactants provide a more elastic interfacial film. A more elastic interfacial film would resist rupture upon collision of emulsion droplets.

It has also been observed that when emulsifiers are combined in certain concentrations and proportions, liquid crystalline phases can be formed. The preparation of emulsions with surfactants that form liquid crystalline states can have greater stability against coalescence compared to emulsions that are formulated in the absence of liquid crystalline states. Friberg and Larson[26] have explained the enhanced stability of emulsions due to liquid crystals in terms of a reduced van der Waals attraction between emulsion droplets. Such an effect depends upon the formation of layers or lamellae around the emulsion droplets. Each layer of liquid crystal contributes to a further reduction in the van der Waals attractive force.

An additional effect of liquid crystals may be related to the high viscosity that often is observed upon their formation. Liquid crystals possess a viscosity that is on the order of 100-fold greater than most oil–water interfaces. The high viscosity may result in reduced rates of coalescence. A key factor that may be important for the stabilizing effect of liquid crystals is the location of the liquid crystalline phase in relation to the dispersed droplets. To effectively inhibit coalescence, the liquid crystals should concentrate at the interface between the droplet and the continuous phase. This may not occur with all oil–water–surfactant combinations.

Particle-size analysis can reveal the tendency of an emulsion to aggregate and coalesce long before any visible signs of instability are apparent. The methods available have been reviewed by Groves and Freshwater.[27]

INVERSION—An emulsion is said to *invert* when it changes from an O/W to a W/O emulsion, or *vice versa*. Inversion sometimes can be brought about by the addition of an electrolyte or by changing the phase-volume ratio. For example, an O/W emulsion having sodium stearate as the emulsifier can be inverted by the addition of calcium chloride, because the calcium stearate formed is a lipophilic emulsifier and favors the formation of a W/O product.

Inversion often can be seen when an emulsion, prepared by heating and mixing the two phases, is being cooled. This takes place presumably because of the temperature-dependent changes in the solubilities of the emulsifying agents. The phase inversion temperature (PIT) of nonionic surfactants has been shown by Shinoda and Kunieda[28] to be influenced by the HLB number of the surfactant—the higher the PIT value, the greater the resistance to inversion.

Apart from work on PIT values, little quantitative work has been carried out on the process of inversion; nevertheless, it would appear that the effect can be minimized by using the proper emulsifying agent in an adequate concentration. Wherever possible, the volume of the dispersed phase should not exceed 50% of the total volume of the emulsion.

BIOAVAILABILITY FROM COARSE DISPERSIONS

All dosage forms must be capable of releasing the drug in a known and consistent manner following administration to the patient. Both the rate and extent of release are important. Ideally, the extent of release should approach 100%, while the rate of release should reflect the desired properties of the dosage form. For example, with products designed to have a rapid onset of activity, the release of drug should be immediate. With a long-acting product, the release should take place over several hours or days, depending on the type of product used. The rate and extent of drug release should be reproducible from batch to batch of the product, and should not change during shelf-life.

The principles on which biopharmaceutics is based are dealt with in some detail in Chapters 57 to 59. Although most published work in this area has been concerned with the bioavailability of solid dosage forms administered by the oral route, the rate and extent of release from both suspensions and emulsions are also important and so must be considered in some detail.

BIOAVAILABILITY FROM SUSPENSIONS—Suspensions of a drug may be expected to demonstrate improved bioavailability compared to the same drug formulated as a tablet or capsule. This is because the suspension already contains discrete drug particles, whereas tablet dosage forms must invariably undergo disintegration in order to maximize the necessary dissolution process. Frequently, antacid suspensions are perceived as being more rapid in action and therefore more effective than an equivalent dose in the form of tablets. Bates et al[29] observed that a suspension of salicylamide was more rapidly bioavailable, at least during the first hour following administration, than two different tablet forms of the drug; this study was also able to demonstrate a correlation between the initial *in vitro* dissolution rates for the several dosage forms studied and the initial rates of *in vivo* absorption. A similar argument can be developed for hard gelatin capsules, where the shell must rupture or dissolve before drug particles are released and can begin the dissolution process. Such was observed by Antal et al[30] in a study of the bioavailability of several doxycycline products, including a suspension and hard gelatin capsules. Sansom et al[31] found that mean plasma phenytoin levels were higher after the administration of a suspension than when an equivalent dose was given as either tablets or capsules. It was suggested that this might have been due to the suspension having a smaller particle size.

In common with other products in which the drug is present in the form of solid particles, the rate of dissolution, and thus potentially the bioavailability of the drug in a suspension, can be affected by such factors as particle size and shape, surface characteristics, and polymorphism. Strum *et al*[32] conducted a comparative bioavailability study involving two commercial brands of sulfamethiazole suspension (Product A and Product B). Following administration of the products to 12 normal individuals and blood samples taken at predetermined times over a period of 10 hr, the Strum study found no statistically significant difference in the extent of drug absorption from the two suspensions. The absorption rate, however, differed, and from *in vitro* studies it was concluded that product A dissolved faster than Product B, and that the former contained more particles of smaller size than the latter, differences that may be responsible for the more rapid dissolution of particles in Product A. Product A also provided higher serum levels during *in vivo* tests 0.5 hr after administration. The results showed that the rate of absorption of sulfamethiazole from a suspension depended on the rate of dissolution of the suspended particles, which in turn was related to particle size. Previous studies[33,34] had shown the need to determine the dissolution rate of suspensions to gain information as to the bioavailability of drugs from this type of dosage form.

The viscosity of the vehicle used to suspend the particles has been found to have an effect on the rate of absorption of nitrofurantoin but not the total bioavailability. Thus Soci and Parrott[35] were able to maintain a clinically acceptable urinary nitrofurantoin concentration for an additional 2 hr by increasing the viscosity of the vehicle.

BIOAVAILABILITY FROM EMULSIONS—There are indications that improved bioavailability may result when a poorly absorbed drug is formulated as an orally administered emulsion. However, little research appears to have been done to directly compare emulsions and other dosage forms such as suspensions, tablets, and capsules; thus, it is not possible to draw unequivocal conclusions as to advantages of emulsions. If a drug with low aqueous solubility can be formulated so as to be in solution in the oil phase of an emulsion, its bioavailability may be enhanced. It must be recognized, however, that the drug in such a system has several barriers to pass before it arrives at the mucosal surface of the GI tract.

For example, with an O/W emulsion, the drug must diffuse through the oil globule and then pass across the oil–water interface. This may be a difficult process, depending on the characteristics of the interfacial film formed by the emulsifying agent. In spite of this potential drawback, Wagner *et al*[36] found that indoxole, a nonsteroidal anti-inflammatory agent, was significantly more bioavailable in an O/W emulsion than in either a suspension or a hard gelatin capsule. Bates and Sequeira[37] found significant increases in maximum plasma levels and total bioavailability of micronized griseofulvin when formulated in a corn O/W emulsion. In this case, however, the enhanced effect was not due to emulsification of the drug in the oil phase *per se*, but more probably because of the linoleic and oleic acids present having a specific effect on GI motility.

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CHAPTER 37

Powders

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Powders are encountered in almost every aspect of pharmacy, both in industry and in practice. Drugs and other ingredients, when they occur in the solid state in the course of being processed into a dosage form, usually are in a more or less finely divided condition. Frequently, this is a powder whose state of subdivision is critical in determining its behavior both during processing and in the finished dosage form. Apart from their use in the manufacture of tablets, capsules, and suspensions, powders also occur as a pharmaceutical dosage form. Although the use of powders as a dosage form has declined, the properties and behavior of finely divided solid materials are of considerable importance in pharmacy. This chapter is intended to provide an introduction to the fundamentals of powder mechanics and the primary means of powder production and handling. The relationships of the principles of powder behavior to powders as dosage forms are discussed.

PRODUCTION METHODS

Molecular Aggregation

PRECIPITATION AND CRYSTALLIZATION

The precipitation and crystallization processes are fundamentally similar and depend on achieving three conditions in succession: a state of supersaturation (super cooling in the case of crystallization from a melt), formation of nuclei, and growth of crystals or amorphous particles.

Supersaturation can be achieved by evaporation of solvent from a solution, cooling of the solution if the solute has a positive heat of solution, production of additional solute as a result of a chemical reaction, or a change in the solvent medium by addition of various soluble secondary substances. In the absence of seed crystals, significant supersaturation is required to initiate the crystallization process through formation of nuclei. A nucleus is thought to consist of from 10 to a few hundred molecules having the spatial arrangement of the crystals that will be grown ultimately from them.

Such small particles are shown by the Kelvin equation to be more soluble than large crystals; therefore, they require supersaturation, relative to large crystals, for their formation and subsequent growth. It is a gross oversimplification to assume that, for a concentration gradient of a given value, the rate of crystallization is the negative of the rate of dissolution. The latter is generally somewhat greater.

Depending on the conditions of crystallization, it is possible to control or modify the nature of the crystals obtained. When polymorphs exist, careful temperature control and seeding with the desired crystal form are often necessary. The habit or shape of a given crystal form often highly depends on impurities in solution, pH, rate of stirring, rate of cooling, and the solvent. Very rapid rates of crystallization can result in impurities being included in the crystals by entrapment.

SPRAY-DRYING

Atomization of a solution of one or more solids via a nozzle, spinning disk, or other device, followed by evaporation of the solvent from the droplets is termed *spray-drying*. The nature of the powder that results is a function of several variables, including the initial solute concentration, size distribution of droplets produced, and rate of solvent removal. The weight of a given particle is determined by the volume of the droplet from which it was derived and by the solute concentration. The particles produced are aggregates of primary particles consisting of crystals and/or amorphous solids, depending on the rate and conditions of solvent removal. This approach to the powdered state provides the opportunity to incorporate multiple solid substances into individual particles at a fixed composition, independent of particle size, and avoiding difficulties that can arise in attempting to obtain a uniform mixture of several powdered ingredients by other procedures.

Particle-Size Reduction

Comminution in its broadest sense is the mechanical process of reducing the size of particles or aggregates. Thus, it embraces a wide variety of operations including cutting, chopping, crushing, grinding, milling, micronizing, and trituration, which depend primarily on the type of equipment employed. The selection of equipment in turn is determined by the characteristics of the material, the initial particle size and the degree of size reduction desired. For example, very large particles may require size reduction in stages simply because the equipment required to produce the final product will not accept the initial feed, as in crushing prior to grinding. In the case of vegetable and other fibrous material, size reduction generally must be, at least initially, accomplished by cutting or chopping.

Chemical substances used in pharmaceuticals, in contrast, generally need not be subjected to either crushing or cutting operations prior to reduction to the required particle size. However, these materials do differ considerably in melting point, brittleness, hardness, and moisture content, all of which affect the ease of particle-size reduction and dictate the choice of equipment. The heat generated in mechanical grinding, in particular, presents problems with materials that tend to liquefy or stick together and with the thermolabile products that may degrade unless the heat is dissipated by use of a flowing stream

of water or air. The desired particle size, shape, and size distribution also must be considered in the selection of grinding or milling equipment. For example, attrition mills tend to produce spheroidal, more free-flowing particles than do impact-type mills, which yield more irregular-shaped particles.

FRACTURE MECHANICS

Reduction of particle size through fracture requires application of mechanical stress to the material to be crushed or ground. Materials respond to stress by yielding, with subsequent generation of strain. Depending on the time course of strain as a function of applied stresses, materials can be classified according to their behavior over a continuous spectrum ranging from brittle to plastic. In the case of a totally brittle substance, complete rebound would occur on release of applied stress at stresses up to the yield point, where fracture would occur. In contrast, a totally plastic material would not rebound nor would it fracture.

The vast majority of pharmaceutical solids lie somewhere between these extremes and thus possess both elastic and viscous properties. Linear and, to a lesser extent, nonlinear viscoelastic theory has been developed well to account for quantitatively and explain the simultaneous elastic and viscous deformations produced in solids by applied stresses.

The energy expended by comminution ultimately appears as surface energy associated with newly created particle surfaces, internal free energy associated with lattice changes, and as heat. Most of the energy expressed as heat is consumed in the viscoelastic deformation of particles, friction, and in imparting kinetic energy to particles. Energy is exchanged among these modes and some is, of course, effective in producing fracture. It has been estimated that 1% or less of the total mechanical energy used is associated with newly created surface or with crystal lattice imperfections.

Although the grinding process has been described mathematically, the theory of grinding has not been developed to the point where the actual performance of the grinding equipment can be predicted quantitatively. However, three fundamental laws have been advanced:

Kick's Law—The work required to reduce the size of a given quantity of material is constant for the same reduction ratio regardless of the original size of the initial material.

Rittinger's Law—The work used for particulate size reduction is directly proportional to the new surface produced.

Bond's Law—The work used to reduce the particle size is proportional to the square root of the diameter of the particles produced.

In general, however, these laws have been useful only in providing trends and qualitative information on the grinding process. Usually laboratory testing is required to evaluate the performance of particular equipment. A work index, developed from Bond's Law, is a useful way of comparing the efficiency of milling operations.[1] A grindability index, which has been developed for a number of materials, also can be used to evaluate mill performance.[2]

A number of other factors also must be considered in equipment selection. Abrasion or mill wear is an important factor in the grinding of hard materials, particularly in high-speed, close-clearance equipment (eg, hammer mills). In some instances mill wear may be so extensive as to lead to highly contaminated products and excessive maintenance costs that make the milling process uneconomical. Hardness of the material, which often is related to abrasiveness, also must be considered. This usually is measured on the Moh's scale. Qualitatively, materials from 1 to 3 are considered as soft and from 8 to 10 as hard. Friability (ease of fracture) and fibrousness can be of equal importance in mill selection. Fibrous materials, such as plant products, require a cutting or chopping action and usually cannot be reduced in size effectively by pressure or impact techniques. A moisture content above about 5% will in most instances also create a problem and can lead to agglomeration or even liquefaction of the milled material. Hydrates often will release their water of hydration under the influence of a high-temperature milling process and thus may require cooling or low-speed processing.

METHODS AND EQUIPMENT

When a narrow particle-size distribution with a minimum of fines is desired, closed-circuit milling is advantageous. This technique combines the milling equipment with some type of classifier (see *Particle-Size Measurement and Classification*). In the simplest arrangement, a screen is used to make the separation, and the oversize particles are returned to the mill on a continuous basis while the particles of the desired size pass through the screen and out of the grinding chamber. Overmilling, with its subsequent production of fines, thereby is minimized. Equipment also has been designed to combine the sieving and milling steps into a single operation (see *Centrifugal-Impact Mills and Sieves*).

To avoid contamination or deterioration, the equipment used for pharmaceuticals should be fabricated of materials that are chemically and mechanically compatible with the substance being processed. The equipment should be easy to disassemble for cleaning to prevent cross-contamination. Dust-free operation, durability, simplified construction, and operation and suitable feed and outlet capacities are additional considerations in equipment selection.

Although there is no rigid classification of large-scale comminution equipment, it generally is divided into three broad categories based on feed and product size:

1. *Coarse crushers* (eg, jaw, gyratory, roll, and impact crushers).
2. *Intermediate grinders* (eg, rotary cutters, disk, hammer, roller, and chaser mills).
3. *Fine grinding mills* (eg, ball, rod, hammer, colloid, and fluid-energy mills; high-speed mechanical screen and centrifugal classifier).

Machines in the first category are employed ordinarily where the size of the feed material is relatively large, ranging from 1½ to 60 inches in diameter. These are used most frequently in the mineral crushing industry and will not be considered further. The machines in the second category are used for feed materials of relatively small size and provide products that fall between 20- and 200-mesh. Those in the third category produce particles, most of which will pass through a 200-mesh sieve, although often the particle size of the products from fine grinding mills is well into the micron range.

The comminution effect of any given operation can be described mathematically in terms of a matrix whose elements represent the probabilities of transformation of the various-size particles in the feed material to the particle sizes present in the output. The numerical values of the elements in the transition matrix can be determined experimentally and the matrix serves to characterize the mill. Matrices of this type are frequently a function of feed rate and feed particle-size distribution but are useful in predicting mill behavior. Multiplication of the appropriate comminution matrix with the feed-size distribution line-matrix yields the predicted output-size distribution.

INTERMEDIATE AND FINE GRINDING MILLS

The various types of comminuting equipment in this class generally employ one of three basic actions or, more commonly, a combination of these actions.

1. *Attrition.* This involves breaking down of the material by a rubbing action between two surfaces. The procedure is particularly applicable to the grinding of fibrous materials where a tearing action is required to reduce the fibers to powder.
2. *Rolling.* This uses a heavy rolling member to crush and pulverize the material. Theoretically, only a rolling-crushing type of action is involved, but in actual practice some slight attrition takes place between the face of the roller and the bed of the mill.
3. *Impact.* This involves the operation of hammers (or bars) at high speeds. These strike the lumps of material and throw them against each other or against the walls of the containing chamber. The impact causes large particles to split apart, the action continuing until small particles of required size are produced. In some instances high-velocity air or centrifugal force may be used to generate high-impact velocities.

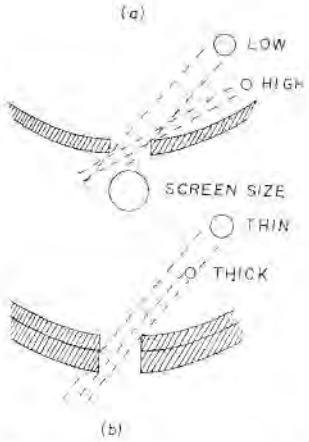

Figure 37-1. The influence of (**a**) mill speed and (**b**) screen thickness on particle size at a constant screen-opening size.[3]

Roller Mills—Roller mills in their basic form consist of two rollers revolving in the same direction at different rates of speed. This principle, which provides particle-size reduction mainly through compression (crushing) and shear, has been applied to the development of a wide variety of roller mills. Some use multiple smooth rollers or corrugated, ribbed, or saw-toothed rollers to provide a cutting action. Most allow adjustment of the gap between rollers to control the particle size of the product. The roller mill is quite versatile and can be used to crush a variety of materials.

An example of a pharmaceutical roller mill is the Crack-U-Lator, in which a series of ribbed rollers are adjusted to reduce sequentially the particle size of the product to produce the desired distribution. The design allows particles that are smaller than the gap between the rollers to pass to the next stage without unnecessary size reduction, thus reducing fines.

Hammer Mills—Hammer mills consist of a rotating shaft on which are mounted either rigid or swing hammers (beaters). This unit is enclosed with a chamber containing a grid or removable screen through which the material must pass. On the upper part is the feed hopper. As the material enters the chamber, the rapidly rotating hammers strike against it and break it into smaller fragments. These are swept downward against the screen where they undergo additional *hammering* action until they are reduced to a size small enough to pass through the openings and out. Oversize particles are hurled upward into the chamber where they also undergo further blows by the revolving hammers.

These mills operate at high speed and generally with controlled feed rate. Both impact and attrition provide the grinding action. Particle size is regulated by rotor speed, feed rate, type and number of hammers, clearance between hammers and chamber wall, and discharge openings. At a constant screen opening, the speed of the mill and the thickness of the screen will affect the particle size of the milled powder,[3] as shown in Figure 37-1. The higher the speed, the steeper the approach angle of the particle to the screen hole. Thus, for any screen size opening, the higher the blade speed, the smaller the particle obtained. Increasing the screen thickness will have a similar effect. In general flat-edged blades are most effective for pulverizing, while sharp-edged blades will act to chop or cut fibrous materials.

The FitzMill Comminutor (Fig 37-2) is an example of this type of mill. It can be used in either the hammer or knife-blade configuration and can be fitted with a wide range of screen sizes to fulfill a variety of milling specifications.

A wide range of particle sizes down to the micron size can be produced by these mills. The particle shape, however, is generally sharper and more irregular than that produced by compression methods. When very fine particles are desired, hammer mills can be operated in conjunction with an air classifier. Under such conditions a narrower particle-size distribution and lower grinding temperatures are obtained. Fine pulverizing of plastic material can be accomplished in these mills by embrittlement with liquid N_2 or CO_2 or by jacketing the grinding chamber.

Centrifugal-Impact Mills and Sieves—Centrifugal-impact mills and sieves are useful to minimize the production of fine particles, because their design combines sieving and milling into a single operation. The mill consists of a nonrotating bar or stator that is fixed within a rotating sieve basket. The particles that are smaller than the hole size of the sieve can pass through the mill without comminution; however, the particles or agglomerates larger than the hole size are directed by centrifugal force to impact with the stator. The sieve baskets also can be constructed to have a cutting edge that can aid in particle-size reduction without impact with the stator. The Quick Sieve (Fig 37-3), Turbo Sieve and CoMill are examples of this type of mill.

Cutter Mills—Cutter mills are useful in reducing the particle size of fibrous material and act by a combined cutting and shearing action. They consist of a horizontal rotor into which is set a series of knives or blades. This rotor turns within a housing, and into it are set stationary bed knives. The feed is from the top and a perforated plate or screen is set into the bottom of the housing through which the finished product is discharged. The particle size and shape is determined by the plate size, gap between rotor and bed knives, and size of the openings. A number of rotor styles are available to provide different particle shapes and sizes, though cutter mills are normally not designed to produce particles finer than 80- to 100-mesh.

Attrition Mills—Attrition mills make use of two stone or steel grinding plates, one or both of which revolve to provide grinding mainly through attrition. These mills are most suitable for friable or medium-hard, free-flowing material.

A double-runner attrition mill is an example of a mill that uses two rotating disks revolving in opposite directions. The particle-size reduction is controlled by varying the rotational speed of the disks, the space between the disks, and the size and number of ridges and indentations in the face of the disks. By appropriate combination with a classifier, particle sizes ranging from 10-mesh to 20 μm can be obtained by these attrition mills.

Figure 37-2. EZ-Clean FitzMill Comminutor (courtesy, Fitzpatrick).

Figure 37-3. Quick Sieve (courtesy, Glatt Air).

Chaser Mills—Chaser mills are so called because two heavy granite stones, or chasers, mounted vertically like wheels and connected by a short horizontal shaft, are made to revolve or chase each other upon a granite base surrounded by a curb. Revolution of the chasers produces an upward current of air; this carries over the lighter particles, which fall outside the curb and subsequently are collected as a fine powder.

Pebble or Ball Mills—Pebble or ball mills, sometimes called *pot mills* or *jar mills,* are operated on the principle of attrition and impact. The grinding is effected by placing the substance in jars or cylindrical vessels that are lined with porcelain or a similar hard substance and containing *pebbles* or *balls* of flint, porcelain, steel, or stainless steel. These cylindrical vessels revolve horizontally on their long axis and the tumbling of the pebbles or balls over one another and against the sides of the cylinder produces pulverization with a minimum loss of material. Ball-milling is a relatively slow process and generally requires many hours to produce material of suitable fineness. To keep the grinding time within reasonable limits, coarse material (>10-mesh) should be preground before introduction into a ball mill. Figure 37-4 shows a sectional view of a single jar mill. *Rod mills* are a modification in which rods about 3 inches shorter than the length of the mill are used in place of balls. This results in a lower production of fines and a somewhat more granular product.

Vibrating Ball Mills—Vibrating ball mills, which also combine attrition and impact, consist of a mill shell containing a charge of balls similar to rotating ball mills. However, in this case the shell is vibrated at some suitable frequency, rather than rotated. These mills offer the advantage of being free of rotating parts, and thus can be integrated readily into a particle classifying system or other ancillary equipment. Furthermore, there have been several studies that have demonstrated that the vibrating ball mill will grind at rates often as high as 20 to 30 times that of the conventional tumbling mill and offer a higher order of grinding rate and efficiency than other prevailing milling procedures.

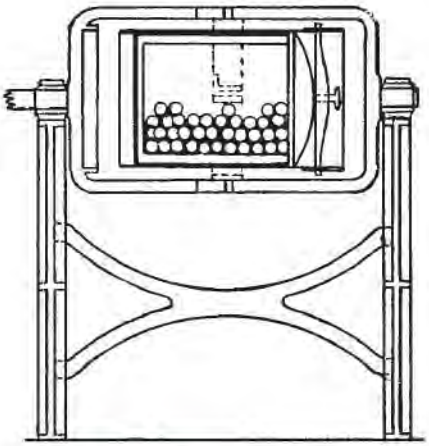

Figure 37-4. Single jar mill.

Fluid-Energy Mills—Fluid-energy mills are used for pulverizing and classifying extremely small particles of many materials. The mills have no moving parts, grinding being achieved by subjecting the solid material to streams of high-velocity elastic fluids, usually air, steam, or an inert gas. The material to be pulverized is swept into violent turbulence by the sonic and supersonic velocity of the streams. The particles are accelerated to relatively high speeds; when they collide with each other, the impact causes violent fracture of the particles.

One type of fluid-energy mill is shown in Figure 37-5. The elastic grinding fluid is introduced through nozzles in the lower portion of the mill under pressures ranging from 25 to 300 psi. In this way, a rapidly circulating flow of gas is generated in the hollow, doughnut-shaped mill. A Venturi feeder introduces the coarse material into the mill and the particles enter into the jet stream of rapidly moving gas. The raw material is pulverized

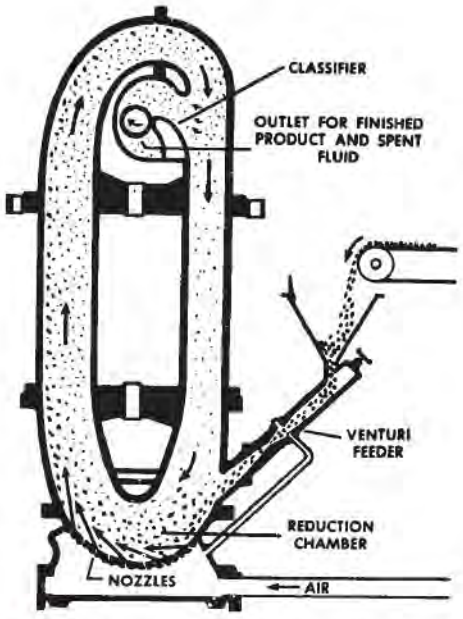

Figure 37-5. The Jet-O-Mizer fluid energy mill (courtesy, Fluid Energy).

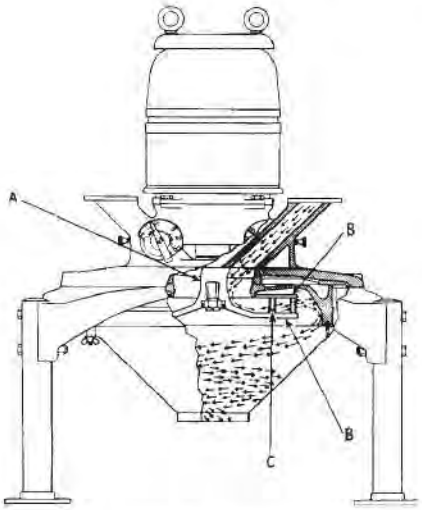

Figure 37-6. CentriMil, a centrifugal-impact mill, available in models ranging from 2 to 250 hp. **A.** Spinning roto. **B.** Rotor hub disks. **C.** Impacters (courtesy, Entoleter).

quickly by mutual impact in the reduction chamber. As the fine particles form, they are carried upward in the track. Particles are ground simultaneously and classified in this process. The smaller particles are entrapped by the drag of gas leaving the mill and are carried out to a collecting chamber or bag. Centrifugal force at the top of the chamber stratifies the larger, heavy particles and their greater momentum carries them downward and back to the grinding chamber.

A major advantage of the fluid-energy mill is that the cooling effect of the grinding fluid as it expands in the grinding chamber more than compensates for the moderate heat generated during the grinding process. Another advantage is the rather narrow range of particle sizes produced. When precise control of particle size is an important factor, the fluid-energy mill produces very narrow ranges of particles with minimum effort.

One major disadvantage is the necessity of controlling the feeding of the coarse, raw material into the jet stream. Often, the feeding device becomes clogged by a clump of material, and special feeding devices must be built to produce a uniform rate of feed.

Centrifugal-Impact Pulverizers—Centrifugal-impact pulverizers also have been found to be effective for the reduction of the particle size of a wide variety of materials ranging from very soft, organic chemicals to hard, abrasive minerals. In addition, this type of mill is suited well for the size reduction of heat-sensitive substances. Basically, in these pulverizers, the material is fed into the center of a spinning rotor that applies a high centrifugal force to the particles. The material, thus accelerated, moves toward the impactor set at the periphery of the rotor. On striking these impactors the material is hurled against the outer casing where final reduction is achieved. Processed material is removed from the bottom of the conical discharge hopper (Fig 37-6). Particle-size reduction in the range of 10- to 325-mesh can be obtained with this type of mill with a minimum of fines.

PARTICLE-SIZE MEASUREMENT AND CLASSIFICATION

Size and Distribution

STATISTICAL PARAMETERS

Monodisperse systems of particles of regular shape, such as perfect cubes or spheres, can be described completely by a single parameter: the length of a side or diameter. However, when either nonuniform size distributions or anisometric shapes exist, any single parameter is incapable of fully defining the powder. Measurements must be made over the total range of sizes present. Statistical diameters, for example, are useful measures of central size tendency and are computed from some measured property that is a function of size and related to a linear dimension. For irregular particles the assigned size will depend strongly on the method of measurement.

Table 37-1. Definition of Statistical Diameters[a]

TYPE OF MEAN DIAMETER	STATISTICAL DEFINITION	DESCRIPTION
Arithmetic	$\Sigma nd/\Sigma n$	Mean diameter weighted by number
Diameter moment	$\Sigma nd^2/\Sigma nd$	Mean diameter weighted by particle diameter
Surface moment	$\Sigma nd^3/\Sigma nd^2$	Mean diameter weighted by particle surface
Volume moment	$\Sigma nd^4/\Sigma nd^3$	Mean diameter weighted by particle volume
Surface	$(\Sigma nd^2/\Sigma n)^{1/2}$	Root mean square
Volume	$(\Sigma nd^3/\Sigma n)$	

[a] When grouped data are used, n is the number of particles in a size interval characterized by a diameter, d.

Once a method of assignment of numerical value for the diameter, surface area or other parameter has been established, the average value computed depends on the weighting given the various sizes. Mean particle diameter is the most important single statistical parameter because, if the proper diameter is chosen, the various other parameters of interest such as specific surface area, number, mean particle weight often may be calculated. Thus, the choice of the mean diameter to be measured or calculated is based on its intended use. For example, specific surface area, which may control drug dissolution, frequently can be related to the root-mean square diameter. Depending on the method of measurement, various diameters are obtained; these will be discussed later. The particle diameters most commonly used are listed in Table 37-1.

SIZE DISTRIBUTIONS

As has been pointed out, size distributions are often complex and no single particle-size parameter is sufficient to characterize or permit prediction of the many bulk properties of pharmaceutical interest, such as flow characteristics, packing densities, compressibility, or segregation tendencies. Thus, descriptions beyond the central tendency provided by the various mean diameters are needed. These generally take the form of equations or charts that describe in detail the distribution of particle size. In measuring particle size it is important first to select the parameter that is related to the ultimate use of the product, and then select the method that will measure this parameter.

Certainly, more useful information would be gained if the particle size of a powder used in a suspension were determined by sedimentation rather than by microscopy, or if the total surface area of the particles were the critical factor (as in use as an adsorbant) by the more useful method of permeability or gas adsorption.

Particles can be classified by determining the number of particles in successive size ranges. The distribution can be represented by a bar graph or histogram (Fig 37-7), where the widths of the bars represent the size range and the heights represent the frequency of occurrence in each range. A smooth curve drawn through the midpoints of the tops of the bars in this case results in a normal probability size-distribution curve. A line drawn through the center of the curve to the abscissa divides the area into two equal parts and represents the mean value. Because a number of other symmetrical distributions could have this same midpoint, a term to describe the scatter

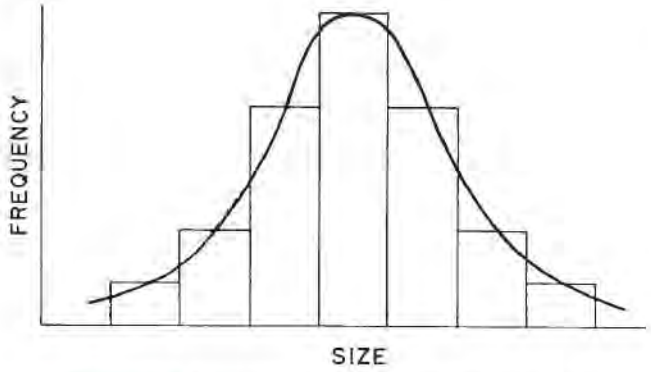

Figure 37-7. Symmetrical particle-size distribution curve.

about the mean value is needed. Standard deviation (the root-mean square deviation about the mean) serves to define the spread of the curve on either side of the midpoint.

Most particulate material cannot, however, be described by a normal distribution curve. The resultant curves are usually skewed as shown in Figure 37-8, making mathematical analysis complex. In a skewed size distribution, the mean value is affected by very large or very small values. In these cases, the median (ie, the central value of a series of observations) is a more useful average. In a symmetrical distribution the mean and the median values are the same. Most asymmetrical size distribution curves relating to powders can be converted into symmetrical curves by using the logarithm of the size—the log normal distribution curve. The symmetrical shape of the latter curve allows for simplified mathematical analysis.

Cumulative plots are also useful for particle-size distribution analysis. Here, the cumulative percent of the particles that are finer (or larger) than a given size is plotted against the size. By use of logarithmic-probability paper, the median size (geometric mean) and standard deviation (geometric standard deviation) can be obtained readily by graphical solution. The median is the 50% size and the standard deviation is the slope of the line and equal to the ratio 50% size/15.87% size (Fig 37-9).

Size Measurement

Frequently, particle-size measurements are made in conjunction with separation of the powder into fractions on the basis of size. Methods that lead primarily to size distribution analysis only are discussed first, followed by methods in which classification by size is a central feature.

The basic processes employed for measurement, classification, or fractionation of fine solid particles involve direct and indirect techniques. Direct methods measure the actual dimensions of the particle by use of a calibration scale, as in microscopy and sieving. Indirect measurements make use of some characteristic of the particle that can be related to particle size, such as sedimentation rates, permeability, and optical properties.

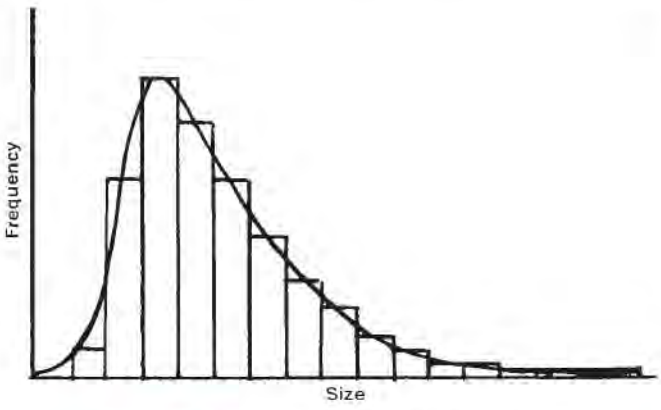

Figure 37-8. Skewed particle-size distribution curve.

MICROSCOPY

Microscopic techniques have been classified as one of the most accurate of *direct* methods. Here, particles are sized directly and individually, rather than being grouped statistically by some other means of classification. The linear measurement of particles is made by comparison with a calibrated scale usually incorporated into the microscope. For spherical particles the size is defined by the measurement of the diameter. However, for other-shaped particles some alternative single size designation is generally used, such as the diameter of a sphere with the same projected area as the nonspheroidal particle being measured. Other characteristic diameters based on various aspects of the projected particle outline as seen through the microscope also have been reported in the literature to describe nonspheroidal particles.

The method is rather tedious and other limitations are found in the techniques required for preparation of the slides and in the maximum resolution that sets the lower limits of particle size measurement using visible light. White light can resolve particles within the range of 0.2 to 100 μm. This lower limit can be decreased to about 0.1 μm by the use of ultraviolet

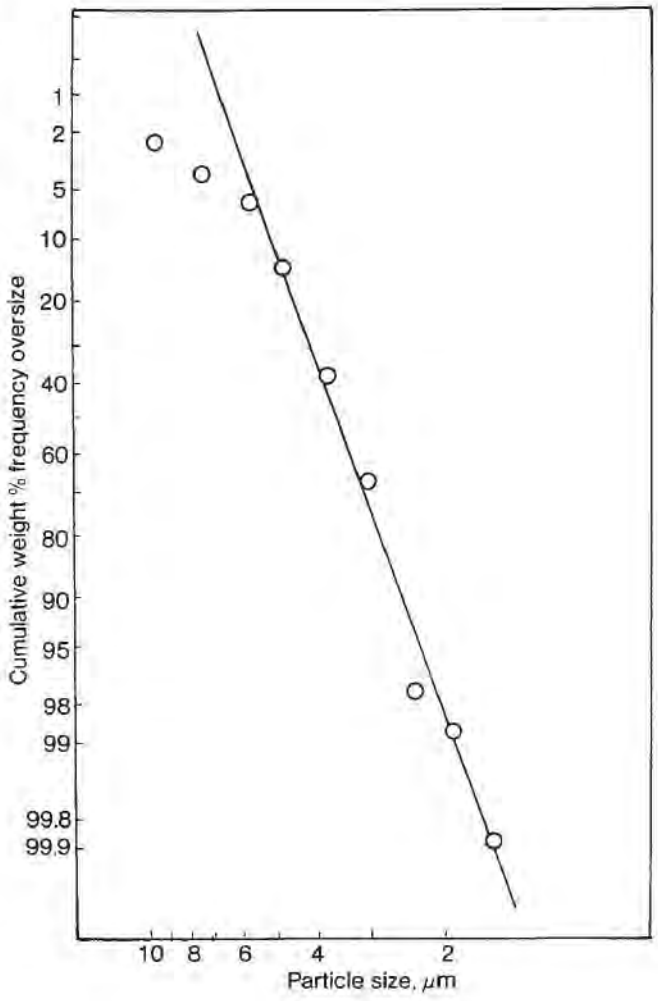

Figure 37-9. Log probability plot of particle size versus cumulative weight % frequency oversize.

light and to about 0.01 μm by the use of the ultramicroscope. The electron microscope finds its greatest usefulness in particle-size measurements in the range of 0.001 to 0.2 μm.

Although microscopic methods for particle size determination are time consuming, tedious, and generally require more skill than some of the other techniques, they offer a number of advantages. They supply information about particle shape and thickness that cannot be obtained by other methods and, in addition, supply a permanent record through use of photomicrographs.

A variety of semiautomated procedures have been developed to reduce the fatigue and tedium associated with manual counting of particles. These are represented by instruments such as the Imanco Quantimet 720 and the πMC System (*Millipore*), which scan the powder image in a manner similar to a TV scanner. The signal obtained is analyzed by a pulse-height analyzer and expressed as a particle-size distribution.

ADSORPTION OF GASES

Adsorption of a solute from solution or of a gas at low temperatures onto powdered material serves as a measure of the particle surface area, generally reported as specific surface (area/unit mass). Common adsorption techniques use the adsorption of nitrogen and krypton at low temperatures. The volume of the gas adsorbed by a powdered sample is determined as a function of gas pressure, and an appropriate plot is prepared. The point at which a monomolecular layer of adsorbate occurs is estimated from the discontinuity that shows in the curve. The specific surface area then can be calculated from knowledge of the volume of gas required to achieve this monolayer, and the area/molecule occupied by the gas, its molecular weight and density. Frequently, more complex expressions such as the Brunauer, Emmett, and Teller (BET) equation must be used to describe the surface adsorption of some materials and determine the volume of gas required to produce an adsorbed monolayer. The surface properties of a number of pharmaceuticals have been investigated by this technique.

PERMEABILITY

When a gas or liquid is allowed to flow through a powdered material, the resistance to this flow is a function of such factors as specific surface of the powder, area of the bed, pore space, pressure drop across the bed, and viscosity of the fluid. This resistance can be described and the specific surface calculated by the Kozeny–Carmen equation, which relates these factors. This method, although it does not provide a size distribution analysis, offers a rapid and convenient means of size estimation that is useful for some industrial operations.

Instruments that measure the rate of flow of a gas through a powder bed under controlled pressure differential are available commercially. The Sub-Sieve Sizer (*Fisher*) permits the reading of average particle size directly. The Blaine Permeameter (*Precision Scientific*) uses the principle of filling the void spaces in a powder with mercury and then weighing it. The void fraction is calculated from the known density of mercury at different temperatures.

The calculations involved in permeability techniques are often complicated and yield only an average size of particles. In measuring particles in the subsieve ranges, rather large deviations may be encountered. With larger mesh sizes, some good agreement is found between the results obtained by techniques employing permeability and microscopy, particularly if the powders are made up of spherical or near-spherical particles.

IMPACTION AND INERTIAL TECHNIQUES

The laws that govern the trajectories of particles in fluid streams are used in several methods of particle-size measurement. Impaction devices are based on the dynamics of deposition of fine particles in a moving air stream when directed past obstacles of defined geometric form, or when forced from a jet device onto a plane surface.

The *cascade impactor*, described by Pilcher and co-workers,[4] forces particle laden air at a very high speed and fixed rate through a series of jets (each smaller than the preceding one) onto glass slides; impaction takes place in a series of stages. The velocities of the air stream and the particles suspended in it are increased as they advance through the impactor. As a result, the particles are classified by impaction on the different slides, with the larger particles on the top slides and the smaller ones on the downstream slides. Figure 37-10 illustrates the principle of the cascade impactor. The exact size of impacted particles on each slide subsequently must be determined. Size analyses may be obtained directly by theoretical treatment or prior calibration of the instrument.

Tillotson[5] described an instrument based on inertial principles similar to those of the cascade impactor. This instrument may be adapted for automatic readout of size distribution by means of light-scattering techniques and electronic counters. The method is claimed to provide complete particle-size distribution data in a few minutes.

AUTOMATIC PARTICLE SIZE COUNTERS

The principles of electronic and light sensing and light scattering techniques have been used to develop automated particle size counters that indirectly measure particle size.

Electrozone Sensing—The *Coulter Counter* determines the particle volume distribution of materials suspended in an electrolyte-containing solution. This instrument utilizes an electrical sensing zone and measures electrical pulses caused by the passage of particles through the zones. The instrument must be calibrated with monodispersed particles of known diameter. A table of size ranges of several methods

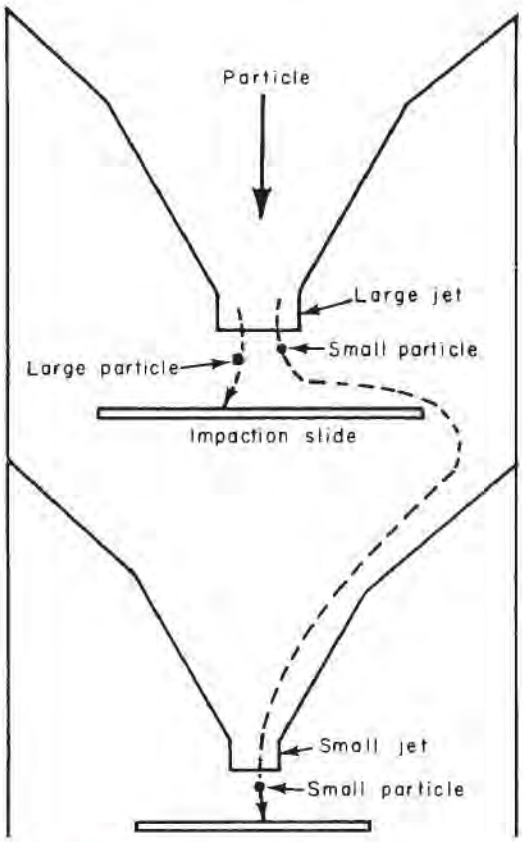

Figure 37-10. The principle of the cascade impactor.

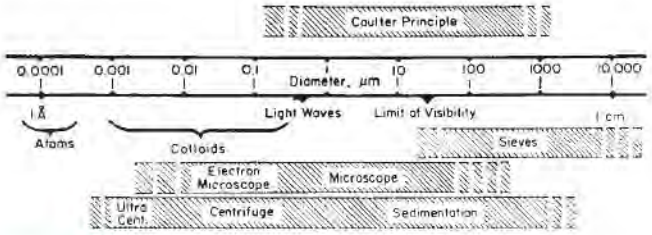

Figure 37-11. Size range of Coulter method compared with coverage of sieve, sedimentation, and microscopic methods, and overlap of electron microscope and centrifuge ranges (courtesy, Coulter).

compared with the Coulter principle is shown in Figure 37-11. Detection is limited by thermal and electrical noise and the ability to discriminate true signal pulses from background.

Photozone Sensing—The *HIAC Counter* measures the size distribution of particles suspended in either liquids or gases. The standard models will measure sizes from 2 to 2500 μm at pressures up to 3000 psi. Basically, in this instrument the particles pass a window, one by one. As each particle passes, depending on its size it interrupts some portion of a light beam. This causes an instantaneous reduction in the voltage from a photodetector that is proportional to the size of the particle. Several counting circuits with preset thresholds tally the particles by size.

Laser Diffraction—Laser diffraction or low angle laser light scattering has become one of the preferred methods for particle size characterization. The instrument consists of a laser light source (generally a He-Ne gas laser), a suitable detector such as a silicon photodiode, and a means of passing the sample through the laser beam. An ultrasonic probe may be used to improve particle dispersion. In this technique, particles are dispersed in a liquid or gaseous medium. The diffraction angle is inversely proportional to particle size. The instrument does not require calibration against a standard and dry powders may be measured directly by using pressure to pass the sample through the instrument. In addition, the method is nondestructive and samples can be recovered after testing. The latest instruments utilize the Mie theory of particle interaction with light and allow for accurate measurements over a large size range (typically 0.1 to 3000 μm)[6].

Size Classification

SIEVING

Sieving is one of the simplest and probably most frequently used methods for determining particle-size distribution. The technique basically involves size classification followed by the determination of the weight of each fraction.

In this technique, particles of a powder mass are placed on a screen made of uniform apertures. By the application of some type of motion to the screen, the particles smaller than the apertures are made to pass through. The sieve motion generally is either (1) horizontal, which tends to loosen the packing of the particles in contact with the screen surface, permitting the entrapped subsieve particles to pass through, or (2) vertical, which serves to agitate and mix the particles as well as to bring more of the subsieve particles to the screen surface.

One major difficulty associated with this method is the production of screens with uniform apertures, particularly in the very fine mesh sizes. As a result the practical lower limit for woven-wire mesh screens is about 43 μm (325-mesh). However, with the introduction of electroformed screens, sieves capable of analyzing particles in the 5-μm range are now available. In addition, "blinding" of the openings by oversized or irregular particles and inefficient presentation of the particles to the screen surface are problems associated with this technique. The use of horizontal and vertical screening motions, air jets, sudden periodic reversal of the sieve motion, and continuous cycling all have been used in an attempt to eliminate these problems.

For continuous operations, the screens are attached to mechanical or electromagnetic devices that supply the energy required to shake the particles through the openings in the screen and also to prevent accumulation of fines within the openings, as this tends to clog them and slow down the operation. The use of an electromagnetic instead of mechanical drive provides a more gentle sieving action with a resultant decrease in sieve wear, blinding, and machine noise. Sieves may be used either in a sequence of sizes through which the material must pass or singly in the required size.

This apparatus is useful in obtaining size-analysis data under controlled conditions. The sample is placed in the top of the nest of standard sieves arranged in a descending order. The length of time and force of vibration to which the sample is subjected may be preset by variable time and voltage controls. The controlled vibration causes the powder particles to pass through the sieves, each fraction coming to rest in the sieve through which it cannot pass. For the purpose of analysis, the weight of each fraction is determined and the percentage calculated.

The Sonic Sifter (*Allen-Bradley* and *ATM*) is a laboratory sifter that uses sonic oscillation to classify particles. A mechanical pulse action is used to reduce blinding and agglomeration in the subsieve sizes. This combination of sonic and mechanical agitation permits dry sifting down to 5 μm. US Standard Sieves are available for this unit from 31/2- to 400-mesh and in precision electroformed mesh sizes from 150 to 5 μm.

Industrial-size mechanical sieves are varied in design and capacity, and include the gyratory, circular rotatory, vibrating, shaking, and revolving sifters. In gyratory sifters, the motion is in a single horizontal plane, but may vary from circular to reciprocal from the feed to the discharge end. The circular sifter also confines the screen motion to a horizontal plane, but in this case the total motion applied to the sieve is circular. The material enters the top of a gyratory sifter and spreads over the first sieve. Some of the finer particles drop through and are discharged into the *throughs* channel. The remaining powder moves to the next sieve in order, the process is repeated until complete separation is accomplished (Fig 37-12).

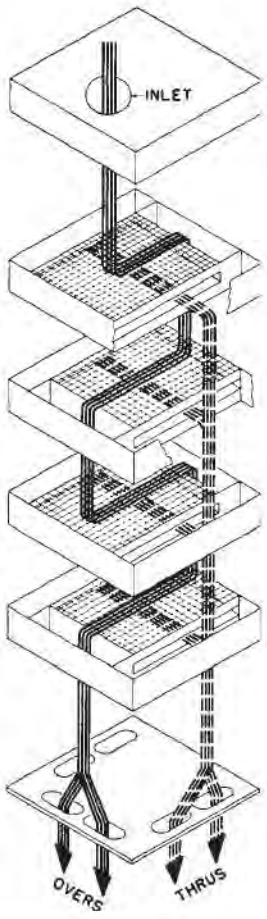

Figure 37-12. Gyratory sifter (courtesy, Sprout Waldron).

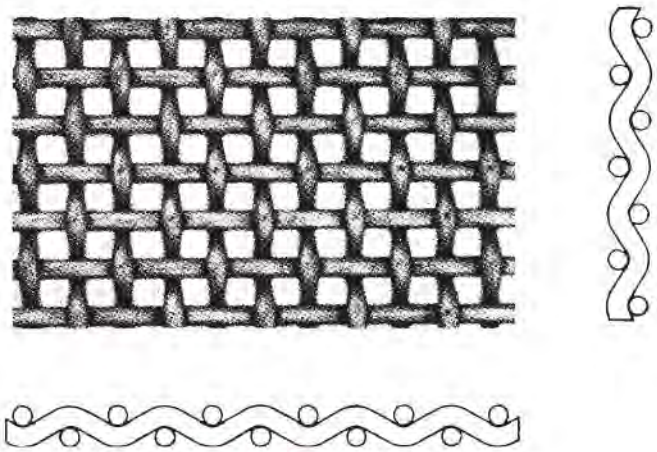

Figure 37-13. Plain weave screen.

In centrifugal screening, the material is pushed through a spinning vertical wire cloth cylinder. Sharp cuts in particle size can be obtained with this type of equipment. Downward air flow, instead of shaking and tapping, has been used to move the particles through the screen openings; alternating with a reverse air flow serves to prevent *blinding*, particularly with fine-mesh sieves.

WET SCREENING

The addition of water sometimes is employed to dissolve any unwanted binders, remove fines or surface contamination, and to reduce surface forces—particularly in micromesh sieves—that oppose the flow of particles through the sieve. Particles that tend to agglomerate or react with oxygen or moisture and thus cannot be dry-sieved often can be handled by wet-sieving. Particles in the 6- to 150-μm range have been classified with good precision using electroformed sieves. Some hydrophobic substances that resist wetting by water may be wet screened by the use of organic liquids such as petroleum ether, acetone, or alcohol. Wet screening may be accomplished by spraying both the screen surface and the material as it is fed onto the screen or by feeding a slurry of material directly onto the screen.

SCREENING SURFACES

A number of factors must be considered in selecting screening surfaces. Primary consideration is given to the size and shape of the aperture opening, the selection of which is determined by the particle size that is to be separated. Screens commonly used in pharmaceutical processing include *woven wire screens, bolting cloth, closely spaced bars,* and *punched plates.* Punched plates are used for coarse sizing; their holes may be round, oval, square, or rectangular. The plates must be sturdy and withstand rough service. Sizes in common use range upward from 1/4 inch.

Most screening, however, is accomplished with woven-wire screens ranging in size from those with 400 openings/inch to screens with 4-inch square openings or larger. There are numerous types of woven wire screens, including plain, twilled, and braided weave. An example of the plain and twilled weave is shown in Figures 37-13 and 37-14.

In the US, the two common standards are the *Tyler Standard* and *US Standard* sieves. In both these series the sieve number refers to the number of openings per linear inch. For most purposes, screens from the two series are interchangeable, though in a few instances the number designations are different. Because these numbers do not define the size of the openings, the Bureau of Standards has established specifications for *Standard Sieves,* as given in Table 37-2. These specifications also establish tolerances for the evenness of weaving, as irregularities from careless weaving might permit much larger particles to pass the sieve than would be indicated. The standard sieves used for pharmaceutical testing are of wire cloth.

SEDIMENTATION

The sedimentation method employs the settling of particles in a liquid of a relatively low density, under the influence of a gravitational or centrifugal field. In free settling (ie, no particle-particle interference), the particles are supported by hydraulic forces and their fall can be described by Stokes' law. However, in most real situations, particle–particle interference, nonuniformity, and turbulence are all present, resulting in more complex settling patterns. The Andreason pipet, which is based on sampling near the bottom of a glass sedimentation chamber, is perhaps the best known of the early instruments. With centrifugation, entrainment of particles in the currents produced by other particles also may interfere with fractionation.

Gravitational settling chambers often are used for large-scale separation of relatively coarse particles in the range of 100 μm. Centrifugal devices are useful for the separation of much smaller particles (5–10 μm).

Sedimentation balances are available that provide a means of directly weighing particles at selected time intervals as they fall in a liquid system. For continuous observations, automatic recording balances also are available. A commercially available instrument called a *Micromerograph* uses the principle of sedimentation in an air column. This instrument and others related

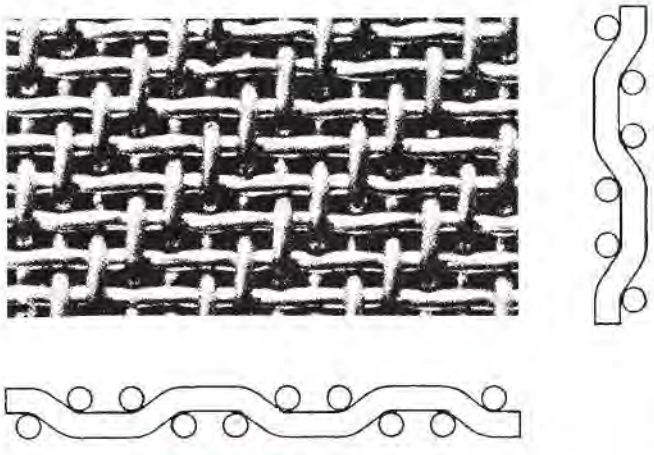

Figure 37-14. Twilled weave screen.

Table 37-2. Nominal Dimensions of Standard Sieves

NO	SIEVE OPENING mm	SIEVE OPENING μm	PERMISSIBLE VARIATION IN AVERAGE OPENING, %	PERMISSIBLE VARIATION IN MAXIMUM OPENING, %	WIRE DIAMETER, mm
2	9.52	9520	±3	+5	2.11 to 2.59
4	4.76	4760	±3	+10	1.14 to 1.68
8	2.38	2380	±3	+10	0.74 to 1.10
10	2.00	2000	±3	+10	0.68 to 1.00
20	0.84	840	±5	+15	0.38 to 0.55
30	0.59	590	±5	+15	0.29 to 0.42
40	0.42	420	±5	+25	0.23 to 0.33
50	0.297	297	±5	+25	0.170 to 0.253
60	0.250	250	±5	+25	0.149 to 0.220
70	0.210	210	±5	+25	0.130 to 0.187
80	0.177	177	±6	+40	0.114 to 0.154
100	0.149	149	±6	+40	0.096 to 0.125
120	0.125	125	±6	+40	0.079 to 0.103
200	0.074	74	±7	+60	0.045 to 0.061

to it in principle offer more rapid determinations than those that use a liquid medium. There are, however, serious uncertainties in the method that must be taken into consideration. Deviations from Stokes' law and impaction of particles against the inner wall of the settling chamber are sources of possible error.

The Carey and Stairmand *photosedimentometer* photographs the tracks of particles as they fall in a dispersion medium. The size determination is derived from the length of the photographic track, which is an indication of the distance traveled by the particles, and the time of exposure of the photograph.

ELUTRIATION

In elutriation, the particles are suspended in a moving fluid, generally water or air. In vertical elutriation at any particular velocity of the fluid, particles of a given size will move upwards with the fluid, while larger particles will settle out under the influence of gravity. In horizontal elutriation a stream of suspended particles is passed over a settling chamber. Particles that leave the stream are collected in the bottom of the chamber. Normally, for all elutriation techniques, both undersize and oversize particles appear in each fraction and recycling is required if a clean cut is desired. By varying the fluid velocities stepwise, the sample may be separated into fractions. The amount in each fraction then can be determined and the size limits calculated by the use of the Stokes' equation or measured directly by microscopy. Air elutriation usually will give a sharper fractionation in a shorter time than will water elutriation.

Centrifugal elutriation is basically the same process, except in this case the fluid stream is caused to spin so as to impart a high centrifugal force to the suspended particles. The particles that are too large to follow the direction of flow separate out on the walls or bottom of the elutriator or cyclone. The finer particles escape with the discharge stream. Separation down to about 0.5 μm can be achieved with some centrifugal classifiers.

The DorrClone (*Dorr-Oliver*) (Fig 37-15) is an example of a centrifugal-type classifier. The feed enters tangentially into the upper section. Centrifugal forces in the vortex throw the coarser particles to the wall where they collect and then drop down and out of the unit. The fine particles move to the inner spiral of the vortex and are displaced upward and finally out of the top of the unit.

Inertial elutriators, which use an abrupt change in direction of the fluid stream to produce separation, are effective down to about 200-mesh. However, as with other elutriators, a clean cut usually cannot be obtained without recycling.

Felvation is a unique process that combines elutriation and sieving along with a varying fluid flow rate and a turbulent fluidized bed to achieve particle separation. The particles are fluidized within the felvation column. With a gradual increase of the fluid flow rate, the very fine particles are brought up to and then through a sieve surface set into the upper section of the column. These fines are filtered subsequently out of the fluid stream. A further increase in the fluid flow rate causes larger and larger particles to move through the sieve. The final stage is reached when particles just larger than the sieve aperture are elutriated up to the sieve.

Because of the way in which the particles are presented to the sieve, very little blinding of the openings occur. Furthermore, because the sieve need only serve as a go/no-go gauge and not as a supporting surface for the powder, a relatively small sieve surface is required. Thus, the more-uniform but more-expensive electroform sieves, even down to a 10-μm size, can be used in this process.

MISCELLANEOUS METHODS

Numerous other methods have been applied to particle size determination, including x-ray and electron diffraction, ultrasound, flotation, and electrostatic, magnetic, and dielectrophoretic methods. Newer techniques include photon correlation spectroscopy, polarization intensity differential scattering, and fourier-transform infrared spectroscopy with diffuse reflectance. These techniques either are used principally as research tools or are industrial-scale methods of use outside the pharmaceutical industry. Detailed descriptions of their principles of operation and their applications can be found in the *Bibliography*.

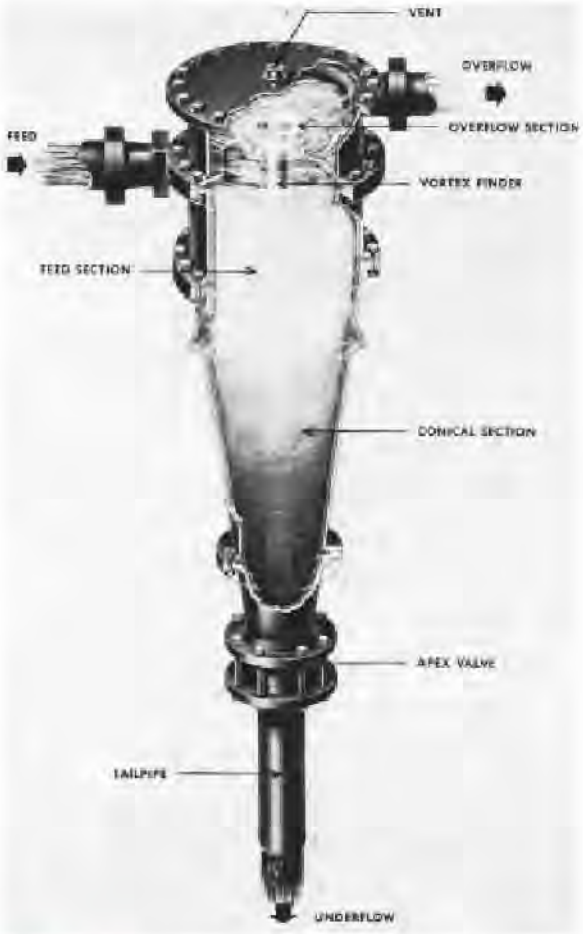

Figure 37-15. DorrClone, a hydrocentrifugal classifier (courtesy, Dorr-Oliver).

SOLIDS HANDLING

Packing and Bulk Properties

BULK DENSITY; ANGLES OF REPOSE

Systems of particulate solids are the most complex physical systems encountered in pharmacy. No two particles in a powder are identical and the nature of momentum and energy exchange between particles defies description except in the most idealized and approximate terms. Bulk properties of powders are determined in part by the chemical and physical properties of their component solids and in part by the manner in which the various components interact. These interactions in turn frequently depend on the past history of the powder bed as well as on the ambient conditions.

The static properties of a particulate bed depend on particle–particle interactions and, in particular, on the way in which applied stresses are distributed through the bed. The number of contacts between particles and, hence, the average number of interparticulate contact points per particle increases as bed-packing increases. Packing may be expressed in terms of porosity,

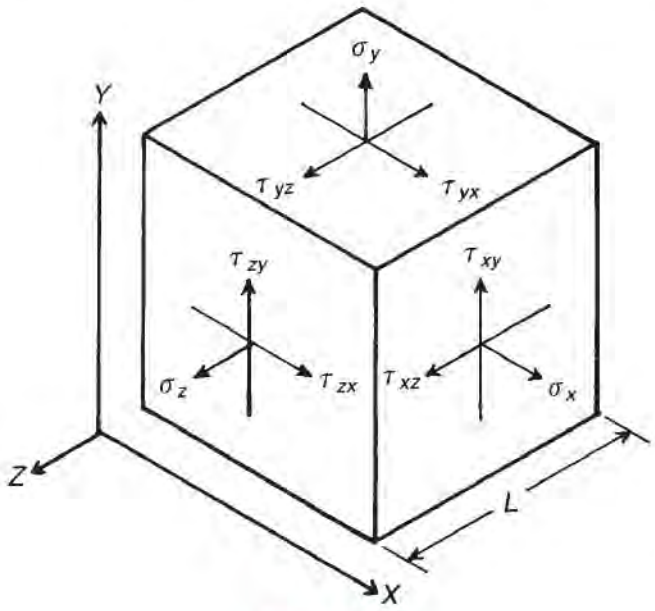

Figure 37-16.

percent voids, or fraction of solids by volume. Packings for regular arrangements of uniform spheres can be calculated and range in fractional solids from 0.53 for cubic to 0.74 for tetrahedral lattices. Powders composed of irregular-shaped particles in a distribution of sizes can pack to fractional densities approaching unity.

The manner in which stresses are transmitted through a bed and the bed's response to applied stress are reflected in the various angles of friction and repose. The most commonly used of these is the angle of repose, which may be determined experimentally by a number of methods, with slightly differing results. The typical method is to pour the powder in a conical heap on a level, flat surface and measure the included angle with the horizontal. Angles of repose range from 23° for smooth uniform glass beads to 64° for granular limestone. Cohesive materials frequently behave in an anomalous manner, yielding values in excess of 90°.

The angle of internal friction is a measure of internal stress distributions and is the angle at which an applied stress diverges as it passes through the bed. This angle together with the angle of slide are useful parameters in the design of storage/discharge bins. The latter angle is defined as the least slope at which a powder will slide down an inclined plane surface. Various other angles are in lesser use and will not be discussed here.

STATICS

Powders at rest experience stresses that vary with location throughout their volume and arise from pressures exerted by the container as well as from the weight of the bed above. Each point within the bed experiences both normal and shear stresses in general. Normal stresses may be either tensile or compressive. The powder bed will remain motionless and no flow will occur unless the normal and/or the shear strength is exceeded at some point within the bed. In general, the yield strengths, both normal and shear, are functions of the normal and shear stresses at the point of interest and depend upon the orientation of the axes of reference and the nature of the powder itself. It is apparent that to understand powder flow it is necessary to understand the conditions under which bed failure occurs and powder flow is initiated and sustained.

Consider the stresses that are applied to the faces of a small cube that is centered about a point chosen at random within a powder bed. Normal stresses are designated σ_i, where the subscript indicates the axis normal to the face and shear stresses are designated τ_{ij}, where the first subscript indicates the face and the second indicates the direction of the applied force. If the cube has an edge length, L, which is not infinitesimal, and if a stress gradient exists within the region, the corresponding stresses on opposite faces of the cube will not be equal. However, if the cube is made progressively smaller, and as L approaches zero, the stress values will converge to those at the point of interest. These forces are illustrated in Figure 37-16. It can be seen from this diagram that the state of stress at a point can be described by nine stress components.

If the system is in static equilibrium, and is not being accelerated translationally or rotationally, the forces that otherwise would result in movement must be in balance and have the effect of canceling each other. For example, τ_{xy} must equal τ_{yx} if rotation about the z-axis is not to occur. In a similar manner, shear and normal stresses, which would lead to translational movement along any of the three axes, also must balance.

Because the directions of the mutually perpendicular axes in Figure 37-16 were chosen arbitrarily, any other orientation of the cube corresponding to another set of axes also must result in a balance of forces. However, the distribution of stress among normal and shear components will depend on the particular axes selected. Thus, the stress condition of a powder can be analyzed in terms of the dependence of the normal and shear stresses on the direction chosen for the reference axes. This can be done by a method of analysis devised by Mohr, and can be visualized using a Mohr circle diagram, which permits stresses at any given point within a powder bed to be graphically resolved into normal, σ, and shear, τ, stresses for any arbitrary choice of axes.

For simplicity, assume that stress in the z-direction is not a function of z and that stress gradients exist in the x and y directions only. Stresses then can be analyzed in the xy plane without reference to the z-axis. Figure 37-17 shows the relationship between stresses relative to two xy coordinate systems at an angle θ to each other. If the condition of stress in the powder remains constant and only the angle θ between the two sets of reference axes is allowed to change, the resolution of stress into normal and shear components will be different for each set of axes and will depend on θ. By means of

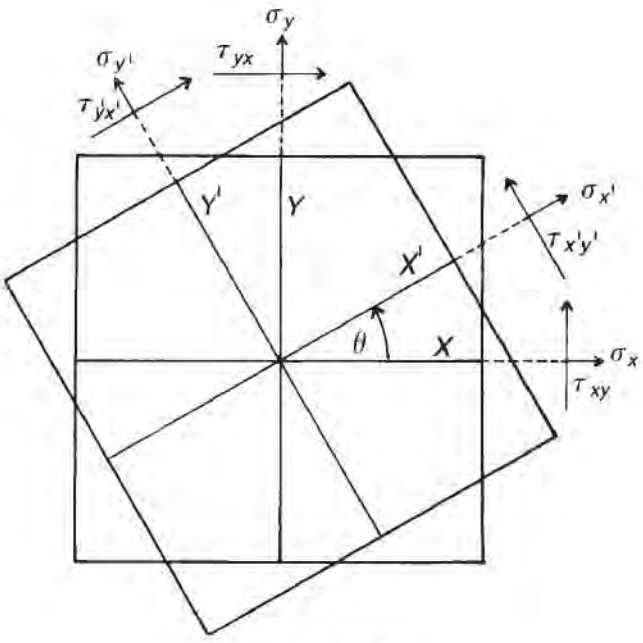

Figure 37-17.

trigonometry, the relationships between these two sets of stresses is shown to be

$$\sigma_{x'} = \frac{\sigma_x + \sigma_y}{2} + \frac{\sigma_x - \sigma_y}{2}\cos 2\theta + \tau_{xy}\sin 2\theta$$

$$\sigma_{y'} = \frac{\sigma_x + \sigma_y}{2} - \frac{\sigma_x - \sigma_y}{2}\cos 2\theta - \tau_{xy}\sin 2\theta$$

$$\tau_{x'y'} = -\frac{\sigma_x - \sigma_y}{2}\sin 2\theta - \tau_{xy}\cos 2\theta$$

These equations permit the calculation of σ and τ values for any desired set of axes if the values are known for any given set of axes. In particular, if σ is chosen properly, $\tau_{x'y'}$ can be made to vanish and normal stresses only will remain. The set of axes for which this is true are called the *principal axes* of stress and the corresponding σ's are called the *principal stresses*. All points within static beds of powders can be characterized by principal axes and stresses that will, in general, vary from point to point throughout the bed. The principal axes do not correspond necessarily to the orientation of the walls of the powder container.

These concepts can be extended to three dimensions. Thus, it is possible to find a set of three mutually perpendicular planes, on which there are no shear stresses acting, for each location within the powder. The normals to these planes are the principal axes. It also is possible to find a set of planes for which the shear stresses are a maximum and the normal stresses are equal. The associated axes are called the axes of maximum shear. These two sets of axes are important because they represent directions of bed failure were it to occur.

The relationships between stresses, as functions of θ, can be illustrated and determined graphically. Figure 37-18 is an example of a Mohr's circle diagram for stress. Such diagrams are based on the stress equations. This can be seen by comparing Figure 37-18 with the equations, noting the relationships of the stresses of θ. A Mohr diagram can be constructed for any point within the powder, permitting stresses to be resolved graphically into normal and shear components for any arbitrary choice of axes.

Steps in constructing a diagram are

1. Plot the center of the circle, p, on the σ axis at the average normal stress, $(\sigma_x + \sigma_y)/$
2. Plot point x and y with coordinates (σ_x, τ_{xy}) and (σ_y, τ_{xy}), respectively. Note that these three points lie on a diameter of the circle.
3. Draw a circle with its center at p and passing through points x and y.
4. Locate the $x'y'$ diameter using the angle 2θ.

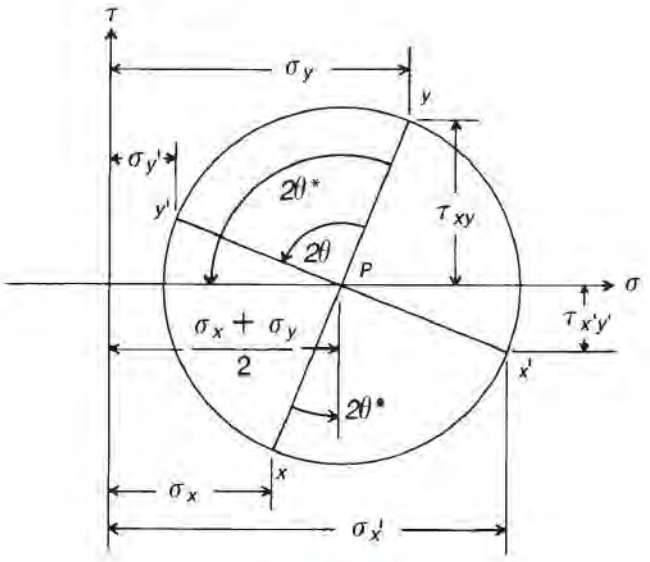

Figure 37-18.

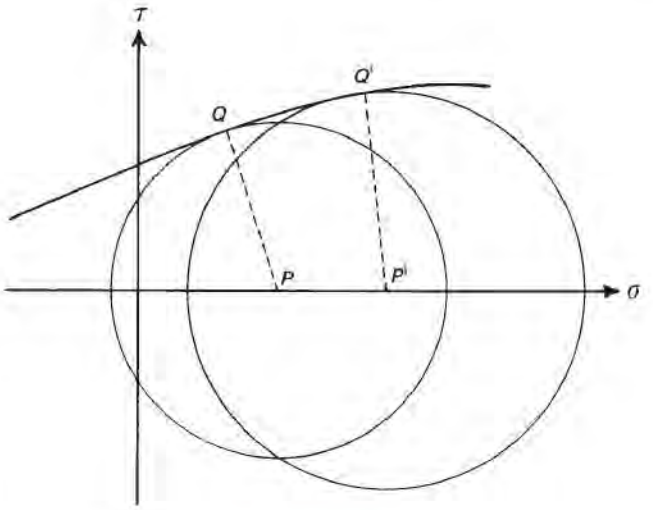

Figure 37-19.

The stress components corresponding to the new axes can be read off the graph. Both $\sigma_{x'}$ and $\sigma_{y'}$ are read off the same axes on the graph because both are normal stresses.

For the particular case in Figure 37-19, the principal axes lie at an angle of θ^* to the original axes. The axes of maximum shear stress lie at an angle of θ^- from the original axes because the xy line corresponding to maximum shear is perpendicular to the σ axis. Depending on the state of the powder, it is possible to have negative σ values, where the Mohr circle passes to the left of the τ axis.

The application of stress normal to a plane of shear influences the shear stress at which the powder fails. Because of this, a given powder will fail at various combinations of normal and shear stresses. These combinations can be expressed graphically by a line in the σ, τ plane that separates regions on the graph at which the powder either flows or is stable.

This is shown in Figure 37-19 for a typical powder. Various powders will display curves that uniquely define their failure characteristics. Each point on such a curve corresponds to a σ, τ combination at which failure occurs and can be analyzed by constructing a Mohr circle that passes through the point and is centered on the intersection of a line perpendicular to the point q and the σ axis. An example is shown in Figure 37-19.

BULK PROPERTIES

In addition to the angles of repose and friction that reflect bulk behavior, tensile and shear strength and dilatancy are of interest. Tensile strength is measured by forming a powder bed on a roughened and split plate. Half of the plate is laterally movable and the force necessary to rupture the bed by pulling the plate halves apart, minus sliding plate friction corrections, represents the bed tensile strength. Various methods of applying force to the movable plate are used, including tipping the plate from the horizontal and allowing it to react to gravity by rolling on steel balls.

Shear strength is determined from the force necessary to shear horizontally a bed of known cross-section. The Jenike shear cell is typical of those in use. It permits various loads to be applied normal to the plane of shear, whereby a shear failure locus can be determined. With the desired normal load applied, a steadily increasing shearing force is applied until failure occurs. These measurements are the basis for constructing powder-failure curves.

When packed powder beds are deformed, local expansion occurs along the failure planes, barring fracture of the particles themselves. This phenomenon is termed dilatancy and is a

direct consequence of the micromechanics of interparticulate movement. For one particle to move past another, it is necessary for it to move to the side in order to move forward when the particles are in an *interlocked* arrangement. Such arrangements predominate in packed beds with the consequence that the collective sideways movements in the failure zone produce bed expansion. Room for expansion therefore must be provided when packed beds are forced to flow.

Mixing of Powders

DEGREE OF HOMOGENEITY

Many mathematical expressions have been proposed and used to express the degree of homogeneity of powders composed of two or more components. For the most part, measures of mixture uniformity have been statistical and based on either the standard deviation or variance of the composition from its mean value. It should be recognized that these indices of mixing are scalar quantities and are incapable of uniquely describing the composition profile of a given powder bed. A practical definition of mixing uniformity should be selected to relate as closely as possible to the desired properties of the mix. The manner in which samples are taken (number, size, location of samples, and method of sampling) largely determines the validity and interpretation of the derived index[7].

The standard deviation is presented here as a representative index. It can be estimated solely from a set of n samples. If sample number i has composition x_i, and all samples are of uniform size, the sample standard deviation is defined in the usual way as

$$s = \sqrt{\sum_{i=1}^{n} (x_i - \bar{x})^2/(n-1)}$$

where $\bar{x}$ is the mean composition estimated from the samples alone.

In sampling a bed, there should be assurance that the bed is sampled uniformly over its entirety. This can be done either by use of a *sampling thief* designed to probe the bed and collect samples at selected points or serially as the powder is discharged from the mixer.

The *scale of scrutiny* at which the powder is examined for uniformity is determined by the sample size. This should be chosen based on the ultimate use of the powder. For a tablet or capsule formulation, the appropriate sample size is that of the dosage form.

Two important concepts related to mixing uniformity have been described by Danckwerts as the scale and intensity of segregation. Assuming that zones having uniform but differing compositions exist in a powder bed, the scale of segregation is a function of the size of the zones. The intensity of segregation is, in turn, a function of the composition differences among zones. Generally, the process of mixing tends to reduce the intensity of segregation, whereas the scale of segregation passes through a minimum.

MECHANISMS OF MIXING AND SEGREGATION

Three primary mechanisms are responsible for mixing:

- Convective movement of relatively large portions of the bed.
- Shear failure, which primarily reduces the scale of segregation.
- Diffusive movement of individual particles.

Most efficient mixers operate to induce mixing by all three mechanisms. Thus, mixing can be considered to be a random shuffling-type operation involving both large and small particle groups and even individual particles. However, it should be noted that the use of random motion to achieve random distribution assumes that no other factors influence this distribution. This is rarely if ever the case in practice. Instead, a variety of properties of the powders being mixed influence this approach to complete randomness. Stickiness or slipperiness of particles must be considered, among other factors. As might be expected, the stickier the material, the less readily it mixes and demixes. Electrostatic forces on the particle surface also can produce marked effects on the mixing process, and in fact may produce sufficient particle-particle repulsion to make random mixing impossible.

By enabling particles to undergo movement relative to each other, mixers also provide the conditions necessary for segregation to occur. Any manipulation of a powder bed for purposes of conveying, discharging from a hopper, and so on provides the opportunity for segregation. Thus, many of the so-called mechanisms of segregation are actually conditions under which segregation can happen.

The segregation that occurs in free-flowing solids usually does so as a result of differences in particle size and, to a lesser extent, to differences in particle density and shape. The circumstances leading to segregation can be generalized from a fundamental physical standpoint. The necessary and sufficient conditions for segregation to occur are

1. Various mixture components exhibit mobilities for interparticulate movement that differ.
2. The mixture experiences either a field that exerts a directional motive force on the particles, or a gradient in a mechanism capable of inducing or modifying interparticulate movement.

The combination of these conditions results in asymmetric particle migrations and leads to segregation.

RATES OF MIXING AND SEGREGATION

Rate expressions analogous to those of chemical kinetics can be derived using any of the various indices of mixing as time-dependent variables. When this is done, it usually is found that mixing follows a first-order approach to an equilibrium state of mixedness. More recently, mixing has been described as a stochastic process (by means of stationary and nonstationary Markov chains) in which the probabilities of particle movement from place to place in the bed are determined. When applied to a mixer, this approach is capable of indicating zones of greater and lesser mixing intensity.

LARGE-SCALE MIXING EQUIPMENT

The ideal mixer should produce a complete blend rapidly with as gentle as possible a mixing action to avoid product damage. It should be cleaned and discharged easily, be dust-tight, and require low maintenance and low power consumption. All of these assets generally are not found in any single piece of equipment, thus requiring some compromise in the selection of a mixer.

Rotating-Shell Mixers—The drum-type, cubical-shaped, double-cone, and twin-shell blenders are all examples of this class of mixers. Drum-type blenders, with their axis of rotation horizontal to the center of the drum, are used quite commonly. These, however, suffer from poor crossflow along the axis. The addition of baffles or inclining the drum on its axis increases crossflow and improves the mixing action.

Cubical-and polyhedron-shaped blenders with the rotating axis set at various angles also are available. However, in the latter, because of their flat surfaces, the powder is subjected more to a sliding than a rolling action, a motion that is not conducive to the most efficient mixing.

Double-cone blenders, an important class of rotating-shell or tumbling mixers, were developed in an attempt to overcome some of the shortcomings of the previously discussed mixers. Here, the mixing pattern provides a good crossflow with a rolling rather than a sliding motion. Normally, no baffles are required, so cleaning is simplified. The twin-shell blender is another important tumbling-type blender. It combines the

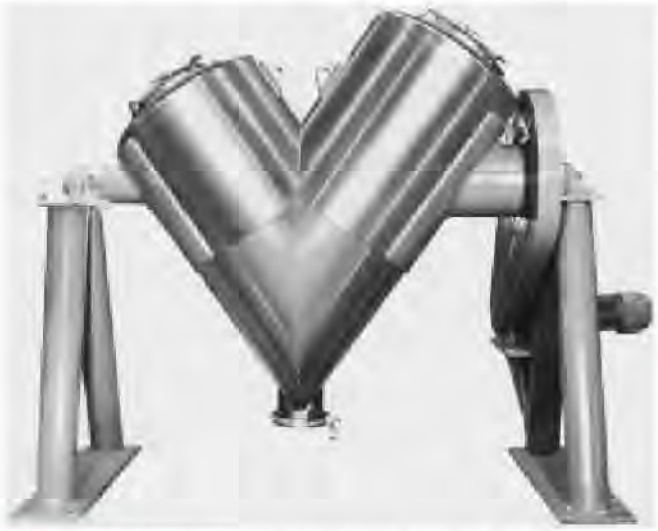

Figure 37-20. Cross-flow twin-shell blender (courtesy, Patterson-Kelley).

efficiency of the inclined drum-type with the intermixing that occurs when two such mixers combine their flow.

The Cross-Flow blender (*Patterson-Kelley*) (Fig 37-20) is an example of a twin-shell blender. The uneven length of each shell in this blender provides additional mixing action when the powder bed recombines during each revolution of the blender. The Zig-Zag blender, an extension of the twin-shell blender, provides efficient continuous precision blending.

Fixed-Shell Mixers—The ribbon mixer, one of the oldest mechanical solid–solid blending devices, exemplifies this type of mixer. It consists of a relatively long troughlike shell with a semicircular bottom. The shell is fitted with a shaft on which are mounted spiral ribbons, paddles, or helical screws, alone or in combination. These mixing blades produce a continuous cutting and shuffling of the charge by circulating the powder from end to end of the trough as well as rotationally. The shearing action that develops between the moving blade and the trough serves to break down powder agglomerates. However, ribbon mixers are not precision blenders; in addition, they suffer from the disadvantage of being more difficult to clean than the tumbler-type blenders and of having a higher power requirement.

Sigma-Blade and Planetary Paddle Mixers—Sigma-blade and planetary paddle mixers also are used for solid–solid blending, although most generally as a step prior to the introduction of liquids. Mixers with high-speed impeller blades set into the bottom of a vertical or cylindrical shell have been shown to be very efficient blenders. This type, in addition to its ability to produce precise blends, serves also to break down agglomerates rapidly. The mechanical heat buildup produced within the powder mix and the relatively high power requirement are often drawbacks to the use of this type of mixer; however; the shorter time interval necessary to achieve a satisfactory blend may offset these factors.

Vertical Impeller Mixers—Vertical impeller mixers, which have the advantage of requiring little floor space, employ a screw-type impeller that constantly overturns the batch (Fig 37-21). The fluidized mixer is a modification of the vertical impeller type. The impeller is replaced by a rapidly moving stream of air fed into the bottom of the shell. The body of the powder is fluidized, and mixing is accomplished by circulation and overtumbling in the bed (Fig 37-22). Generally, when precision solid–solid blending is required, the rotating twin-shell or the double-cone–type blenders are recommended.

Motionless Mixers—These are in-line continuous processing devices with no moving parts. They consist of a series of fixed flow-twisting or flow-splitting elements. The Blendex (*Ross & Son*), designed for blending of free-flowing solids, is constructed to operate in a vertical plane. Four pipes interconnect with successive tetrahedral chambers, the number of chambers needed depending on the quality of mix desired. The powders enter the mixer from overhead hoppers and free-fall through the mixer and are mixed by what is described as Interfacial Surface Generation. For two input streams entering this mixer the number of layers, L, emerging from each of the successive chambers, C, is $L = 2(4)^C$. Thus, for 10 chambers over 2 million layers are generated. This type provides efficient batch or continuous mixing for a wide variety of solids without particle-size reduction or heat generation with essentially no maintenance. Units are available to mix quantities ranging from 100 to 5000 lb/hour.

SMALL-SCALE MIXING EQUIPMENT

The pharmacist most generally employs the mortar and pestle for the small-scale mixing usually required for prescription compounding. However, spatulas and sieves also may be used on occasion. The mortar and pestle method combines comminution and mixing in a single operation. Thus, it is particularly useful where some degree of particle-size reduction as well as mixing is required, as in the case of mixtures of crystalline material.

The blending of powders with a spatula on a tile or paper, or spatulation, is used sometimes for small quantities of powders, often as an auxiliary blending technique or when the compaction produced by the mortar and pestle technique is

Figure 37-21. Cutaway view of the Mark II Mixer (courtesy, JH Day).

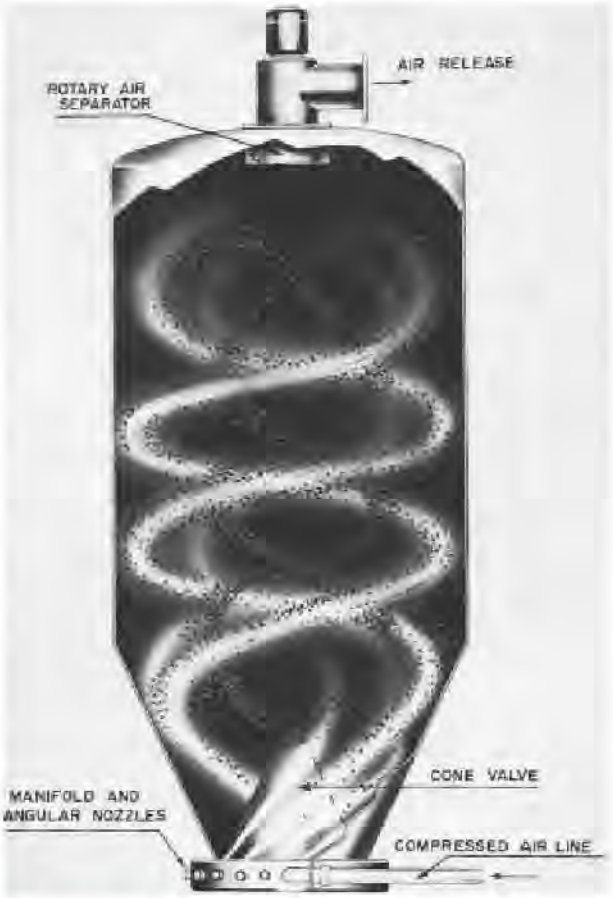

Figure 37-22. Fluidized air mixer (courtesy, Sprout, Waldron).

undesirable. Spatulation is a relatively inefficient method of mixing, thus principles of geometric dilution must be employed. Spatulation is rarely used to prepare a finished dosage form.

Sieving usually is employed as a pre- or post-mixing method to reduce loosely held agglomerates and to increase the overall effectiveness of a blending process. When used alone as a solid–solid blending technique, several passes through the sieve are required to produce a reasonably homogeneous mix.

Storage and Flow

FLOW PATTERNS

Discharge of powders from large-scale mixers, storage, bins or machine-fed hoppers primarily generates flow in the form of shear failure—the powder behaves in a manner analogous to a viscous liquid in laminar flow. The analogy ends at that point, because conditions are then present in the powder bed conducive to segregation. The overall pattern of discharge from a bin takes the form of either funnel flow or mass flow. Bin-design characteristics, which take into account the powder's angles of slide and internal friction and its yield locus in terms of normal and shear stresses, determine which flow pattern will occur.

In funnel flow the powder moves in a column down the center of the bin toward the exit orifice at the bottom. Material surrounding this relatively rapidly moving core remains stationary or is drawn slowly into the core, which is fed primarily from the top where powder moves to the center and then down in the manner of a funnel.

The powder in a mass-flow bin moves downward toward the orifice as a coherent mass. When it reaches the tapered section of the bin leading to the orifice, it is compressed and flows in shear analogous to a plastic mass being compressed. This type of bin is advantageous for use with powders having a strong tendency to segregate.

The rate of discharge from a hopper varies as a function of the cube of the orifice diameter and is nearly independent of the height of the bed. An arch forms over the orifice that in effect is a boundary between material in essentially free-fall and material in the closely packed condition of the powder bed. The rate of mass transport across this constantly renewed surface determines the rate of orifice flow. It has been shown that flow can be increased substantially if gas is pumped through the bed and across the orifice in the direction of the solids flow. Flow conditioners, an important means of improving flow, are discussed in Chapter 20.

PNEUMATIC TRANSPORT

The pneumatic transport of powders is of interest because it can be used to mix powders at the same time as they are being conveyed. The method consists of propelling a solids–gas mixture along a conduit via a gas pressure drop. The solids are held in suspension by the turbulence of the gas stream. At low-solids concentrations, where the particles are relatively small, the solids are dispersed uniformly over the pipe cross-section. However, at higher solids content or with larger particles, some stratification will occur in a horizontal pipe and solids will settle out if the pipe is overloaded.

Gas flow must be turbulent so as to suspend the solids; however, the solids behave as in laminar flow. Slippage between gas and solid occurs, particularly in vertical pipes; consequently, gas and solids flow rates are not in proportion to flow-stream composition. Further, smaller and less dense particles flow more rapidly than large and dense material and a chromatographic-like separation occurs. This is not a problem, however, once steady state is achieved. Because of the industrial importance of this process in many fields it has been investigated extensively and a number of useful theoretical and empirical expressions have been derived and may be used to predict conditions necessary for satisfactory pneumatic transport.

POWDERS AS A DOSAGE FORM

Historically, powders represent one of the oldest dosage forms. They are a natural outgrowth of the attempt to prepare crude drugs and other natural products in a more conveniently administered form. However, with declining use of crude drugs and increasing use of many highly potent compounds, powders as a dosage form have been replaced largely by capsules and tablets.

In certain situations, powders possess advantages and thus still represent a portion (although small) of the solid dosage forms currently being employed. These advantages are flexibility in compounding and relatively good chemical stability. The chief disadvantages of powders as a dosage form are they are time-consuming to prepare and they are not well suited for dispensing the many unpleasant-tasting, hygroscopic, or deliquescent drugs.

Bulk powders have another serious disadvantage when compared with divided and individually weighed powders: inaccuracy of dose. The dose is influenced by many factors, including size of measuring spoon, density of powder, humidity, degree of settling, fluffiness due to agitation, and personal judgment. Not only do patients measure varying amounts of powder when using the same spoon, but they often select one differing in size from that specified by their physician.

EXTEMPORANEOUS TECHNIQUES

In both the manufacturing and extemporaneous preparation of powders, the general techniques of weighing, measuring,

sifting, and mixing, as described previously, are applied. However, the following procedures should receive special attention.

- Use of geometric dilution for the incorporation of small amounts of potent drugs.
- Reduction of particle size of all ingredients to the same range to prevent stratification of large and small particles.
- Sieving when necessary to achieve mixing or reduction of agglomerates, especially in the preparation of dusting powders or powders into which liquids have been incorporated.
- Heavy trituration, when applicable, to reduce the bulkiness of a powder.
- Protection against humidity, air oxidation, and loss of volatile ingredients.

Powders are prepared most commonly either as divided powders and bulk powders, which are mixed with water or other suitable material prior to administration, or as dusting powders, which are applied locally. They also may be prepared as dentifrices, products for reconstitution, insufflations, aerosols, and other miscellaneous products.

The manually operated procedures usually employed by the pharmacist today are *trituration, pulverization by intervention,* and *levigation.*

Trituration—This term refers to the process of reducing substances to fine particles by rubbing them in a mortar with a pestle. The term also designates the process whereby a mixture of fine powders is intimately mixed in a mortar. The circular mixing motion of the pestle on the powders contained in a mortar blends the powders and also breaks up their soft aggregates. By means of the application of pressure on the pestle, crushing or grinding also can be effected. When granular or crystalline materials are to be incorporated into a powdered product, these materials are comminuted individually and then blended together in the mortar.

Pulverization by Intervention—This is the process of reducing the state of subdivision of solids with the aid of an additional material that can be removed easily after the pulverization has been completed. This technique often is applied to substances that are gummy and tend to reagglomerate or that resist grinding. A prime example is camphor, which cannot be pulverized easily by trituration because of its gummy properties; however, on the addition of a small amount of alcohol or other volatile solvent, this compound can be reduced readily to a fine powder. Similarly, iodine crystals may be comminuted with the aid of a small quantity of ether. In both instances the solvent is permitted to evaporate and the powdered material is recovered.

Levigation—In this process a paste is first formed by the addition of a suitable nonsolvent to the solid material. Particle-size reduction then is accomplished by rubbing the paste in a mortar with a pestle or on an ointment slab using a spatula. Levigation generally is used by the pharmacist to incorporate solids into dermatological and ophthalmic ointments and suspensions.

THE MORTAR AND PESTLE

The mortar and pestle are the most frequently used utensils in small-scale comminution. Mortars made of various materials and in diverse shapes are available; although these often are used interchangeably, the different kinds of mortars have specific utility in preparing or grinding different materials.

Modern mortars and pestles are prepared usually from Wedgwood ware, porcelain, or glass. Although pharmacists often use different mortars interchangeably, each type has a preferential range of utility.

Glass mortars are designed primarily for use in preparing solutions and suspensions of chemical materials in a liquid. They also are suitable for preparing ointments which require the reduction of soft aggregates of powdered materials or the incorporation of relatively large amounts of liquid. Glass also has the advantage of being comparatively nonporous and of not staining easily and thus is particularly useful when substances such as flavoring oils or highly colored substances are used. Glass cannot be used for comminuting hard solids.

Wedgwood mortars are suited well for comminution of crystalline solids or for the reduction in particle size of most materials used in modern prescription practice. They are capable of adequately powdering most substances that are available only as crystals or hard lumps. However, Wedgwood is relatively porous and will stain quite easily. A Wedgwood mortar is available with a roughened interior, which aids in the comminution process but which requires meticulous care in washing because particles of the drugs may be trapped in the rough surface and cause contamination of materials subsequently comminuted in the mortar.

Porcelain mortars are very similar to Wedgwood, except that the exterior surface of the former is usually glazed and thus less porous. Porcelain mortars may be used for comminution of soft aggregates or crystals but more generally are used for blending powders of approximately uniform particle size.

Pestles are made of the same material as the mortar. Pestles for Wedgwood or porcelain mortars are available with hard rubber or wooden handles screwed into the head of the pestle. Also available are one-piece Wedgwood pestles. Pestles made entirely of porcelain are objectionable, because they are broken easily.

Pestles and mortars should not be interchanged. The efficiency of the grinding or mixing operation depends largely on a maximum contact between the surfaces of the head of the pestle and the interior of the mortar. The pestle should have as much bearing on the interior surface of the mortar as its size will permit. A pestle that does not *fit* the mortar will result in a waste of labor.

Divided Powders

Divided powders (*chartula* or *chartulae*) are dispensed in the form of individual doses and generally are dispensed in papers, properly folded. They also may be dispensed in metal foil, small heat-sealed plastic bags, or other containers.

DIVIDING POWDERS

After weighing, comminuting, and mixing the ingredients, the powders must be divided accurately into the prescribed number of doses. To achieve accuracy consistent with the other steps in the preparation, *each dose should be weighed individually* and transferred to a powder paper. Following completion of this step, the powder papers are folded.

FOLDING POWDERS

The operations of folding powder papers are illustrated in Figure 37-23. Care in making the several folds, and experience gained by repetition, are necessary to obtain uniformity when the powders finally are placed in the box for dispensing. Deviation from any of the three main folds will result in powders of varying height being formed, and variations in the folded ends likewise will be noticeable when the powders are placed side by side.

PACKAGING DIVIDED POWDERS

Specially manufactured paper and boxes are available for dispensing divided powders.

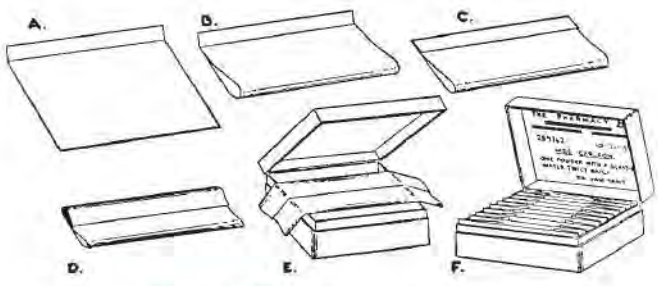

Figure 37-23. Folding powder papers.

Powder Papers—Four basic types of powder papers are available.

1. Vegetable parchment, a thin, semiopaque, moisture-resistant paper.
2. White bond, an opaque paper with no moisture-resistant properties.
3. Glassine, a glazed, transparent, moisture-resistant paper.
4. Waxed, a transparent waterproof paper.

Hygroscopic and volatile drugs can be protected best by using a waxed paper, double-wrapped with a bond paper to improve the appearance of the completed powder. Parchment and glassine papers offer limited protection for these drugs.

A variety of sizes of powder papers are available. The selection of the proper size depends on the bulk of each dose and the dimensions of the powder box required to hold the number of doses prescribed.

Powder Boxes—Various types of boxes are supplied in several sizes for dispensing divided powders. The hinged-shoulder box shown in Figure 37-23F is the most popular; these have the advantage of preventing the switching of lids with the directions for use when several boxes of the same size are in the same home. The prescription label may be pasted directly on top of the lid or inside the lid. In the latter case, the name of the pharmacy is lithographed on top of the lid.

SPECIAL PROBLEMS

The incorporation of volatile substances, eutectic mixtures, liquids, and hygroscopic or deliquescent substances into powders presents problems that require special treatment.

VOLATILE SUBSTANCES

The loss of camphor, menthol, and essential oils by volatilization when incorporated into powders may be prevented or retarded by use of heat-sealed plastic bags or by double wrapping with a waxed or glassine paper inside of a bond paper.

EUTECTIC MIXTURES

Liquids result from the combination of phenol, camphor, menthol, thymol, antipyrine, phenacetin, acetanilid, aspirin, salol, and related compounds at ordinary temperatures. These so-called eutectic mixtures may be incorporated into powders by addition of an inert diluent. Magnesium carbonate or light magnesium oxide are commonly used, effective diluents for this purpose, although kaolin, starch, bentonite, and other absorbents have been recommended. Silicic acid prevents eutexia with aspirin, phenyl salicylate, and other troublesome compounds; incorporation of about 20% silicic acid (particle size, 50 μm) prevented liquefaction even under the compression pressures required to form tablets.

In handling this problem, each eutectic compound should be mixed first with a portion of the diluent and gently blended together, preferably with a spatula on a sheet of paper. Generally, an amount of diluent equal to the eutectic compounds is sufficient to prevent liquefaction for about 2 weeks. Deliberate forcing of the formation of the liquid state, by direct trituration, followed by absorption of the moist mass, also will overcome this problem. This technique requires use of more diluent than previously mentioned methods but offers the advantage of extended product stability. Thus, the technique is useful for dispensing a large number of doses that normally would not be consumed over a period of 1 or 2 weeks.

LIQUIDS

In small amounts, liquids may be incorporated into divided powders. Magnesium carbonate, starch, or lactose may be added to increase the absorbability of the powders if necessary. When the liquid is a solvent for a nonvolatile heat-stable compound, it may be evaporated gently on a water bath. Lactose may be added during the course of the evaporation to increase the rate of solvent loss by increasing the surface area. Some fluidextracts and tinctures may be treated in this manner, although the use of an equivalent amount of a powdered extract, when available, is a more desirable technique.

HYGROSCOPIC AND DELIQUESCENT SUBSTANCES

Substances that become moist because of affinity for moisture in the air may be prepared as divided powders by adding inert diluents. Double-wrapping is desirable for further protection. Extremely deliquescent compounds cannot be prepared satisfactorily as powders.

BULK POWDERS

Bulk powders may be classified as oral powders, dentifrices, douche powders, dusting powders, insufflations, and triturations.

ORAL POWDERS

Oral powders generally are supplied as *finely divided powders* or *effervescent granules*. The finely divided powders are intended to be suspended or dissolved in water or mixed with soft foods such as applesauce prior to administration. Antacids and laxative powders frequently are administered in this form.

Effervescent granules contain sodium bicarbonate and either citric acid, tartaric acid, or sodium biphosphate in addition to the active ingredients. On solution in water, carbon dioxide is released as a result of the acid–base reaction. The effervescence from the release of the carbon dioxide serves to mask the taste of salty or bitter medications.

Granulation generally is accomplished by producing a moist mass, forcing it through a coarse sieve and drying it in an oven. The moisture necessary for massing the materials is obtained readily by heating them sufficiently to drive off the water of hydration from the uneffloresced citric acid. The completed product must be dispensed in tightly closed glass containers to protect it against the humidity of the air.

Effervescent powders may be prepared also by adding small amounts of water to the dry salts to obtain a workable mass. The mass is dried and ground to yield the powder or granule. Care must be used in this procedure to ensure that the reaction that occurs in the presence of water does not proceed too far before it is stopped by the drying process. Should this happen, the effervescent properties of the product will be destroyed.

Other preparative techniques have been reported for effervescent powders such as a fluidized-bed procedure in which the powders are blended and then suspended in a stream of air in a Wurster chamber. Water is sprayed into the chamber, resulting in a slight reaction and an expansion of the particles to form granules ranging in size from 10- to 30-mesh. This approach apparently offers a number of advantages over the older techniques. The extent of reaction and particle size are controlled during the manufacture. A drying oven, trays, or even grinding devices are not required. Furthermore, the technique lends itself to a continuous as well as a batch operation.

The heat generated from the blending and mixing operation also has been used to mass the powders by causing the release of the water of hydration from the citric acid. The massed materials can be dried and sieved through a coarse sieve. This technique thus eliminates the need of an external heat source or a granulating solution.

DENTIFRICES

Dentifrices may be prepared in the form of a bulk powder, generally containing a soap or detergent, mild abrasive, and an anticariogenic agent.

DOUCHE POWDERS

Douche powders are completely soluble and are intended to be dissolved in water prior to use as antiseptics or cleansing agents for a body cavity. They most commonly are intended for vaginal use, although they may be formulated for nasal, otic, or ophthalmic use. Generally, because aromatic oils are included in these powders, they are passed through a No 40 or 60 sieve to eliminate agglomeration and ensure complete mixing. Dispensing in wide-mouth glass jars serves to protect against loss of volatile materials and permits easy access by the patient. Bulk-powder boxes may be used for dispensing douche powders, although glass containers are preferred because of the protection afforded by these containers against air and moisture.

DUSTING POWDERS

Dusting powders are locally applied nontoxic preparations that are intended to have no systemic action. They are applied to various parts of the body as lubricants, protectives, absorbents, antiseptics, antipruritics, antibromhidrosis agents, astringents, and antiperspirants. Dusting powders always should be dispensed in a very fine state of subdivision to enhance effectiveness and minimize irritation. When necessary, they may be micronized or passed through a No 80 or 100 sieve.

Extemporaneously prepared dusting powders should be dispensed in sifter-top packages. Commercial dusting powders are available in sifter-top containers or pressure aerosols. The latter, while generally more expensive than the other containers, offer the advantage of protection from air, moisture, and contamination, as well as convenience of application. Foot powders and talcum powders are currently available as pressure aerosols.

Although in most cases dusting powders are considered nontoxic, the absorption of boric acid through large areas of abraded skin has caused toxic reactions in infants. Accidental inhalation of zinc stearate powder has led to pulmonary inflammation of the lungs of infants. The pharmacist should be aware of the possible dangers when the patient uses these compounds as well as other externally applied products. See also Chapter 65.

INSUFFLATIONS

Insufflations are finely divided powders introduced into body cavities such as the ears, nose, throat, tooth sockets, and vagina. An insufflator (powder blower) usually is employed to administer these products. However, the difficulty in obtaining a uniform dose has restricted their general use.

Specialized equipment has been developed for the administration of micronized powders of relatively potent drugs. The Norisodrine Sulfate Aerohaler Cartridge (*Abbott*) is an example. In the use of this Aerohaler, inhalation by the patient causes a small ball to strike a cartridge containing the drug. The force of the ball shakes the proper amount of the powder free, permitting its inhalation. Another device, the Spinhaler turbo-inhaler (*Fisons*), is a propeller-driven device designed to deposit a mixture of lactose and micronized cromolyn sodium into the lung as an aid in the management of bronchial asthma.

Pressure aerosols also have been employed as a means of administering insufflations, especially for potent drugs. This method offers the advantage of excellent control of dose, through metered valves, as well as product protection.

TRITURATIONS

Triturations are dilutions of potent powdered drugs, prepared by intimately mixing them with a suitable diluent in a definite proportion by weight. They were at one time official as 1 to 10 dilutions. The pharmacist sometimes prepares triturations of poisonous substances such as atropine in a convenient concentration using lactose as the diluent, for use at the prescription counter. These medicinal substances are weighed more accurately and conveniently by using this method.

The correct procedure for preparing such triturations or any similar dilution of a potent powder medicament, to ensure uniform distribution of the latter, is

1. Reduce the drug to a moderately fine powder in a mortar.
2. Add about an equal amount of diluent and mix well by thorough trituration in the mortar.
3. Successively add portions of diluent, triturating after each addition, until the entire quantity of diluent has been incorporated.

Under no circumstance should the entire quantity of diluent be added at once to the drug that is to be diluted in the expectation that uniform dispersion of the latter will be more expeditiously achieved on brief trituration of the mixture.

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CHAPTER 39

Solutions, Emulsions, Suspensions, and Extracts

Michael M Crowley, PhD

The dosage forms described in this chapter are prepared by employing pharmaceutically and therapeutically acceptable vehicles. The active ingredient(s) may be dissolved in aqueous media, organic solvent or combination of the two, by suspending the drug (if it is insoluble) in an appropriate medium, or by incorporating the medicinal agent into one of the phases of an oil and water emulsion. Such solutions, suspensions and emulsions are further defined in subsequent paragraphs but some, with similar properties and applications, are considered in greater detail elsewhere in *Remington*.

These dosage forms are useful for a number of reasons. They can be formulated for different routes of administration: orally, introduction into body cavities, or external application. The dose can easily be adjusted by dilution, making the oral liquid form ready to be administered to children or people unable to swallow tablets or capsules. Extracts eliminate the need to isolate the drug in pure form, allow several ingredients to be administered from a single source (eg, pancreatic extract), and permit the preliminary study of drugs from natural sources. Occasionally, solutions of drugs such as potassium chloride are used to minimize adverse effects in the gastrointestinal tract.

The preparation of these dosage forms involves several considerations on the part of the pharmacist, namely; purpose of the drug, internal or external use, solubility and concentration of the drug, selection of the liquid vehicle(s), physical and chemical stability of the drug and any excipients, preservation of the preparation, and use of appropriate excipients such as buffers, solubility enhancers, suspending agents, emulsifying agents, viscosity controlling agents, colors and flavors. Oral preparations require consideration be given to improving patient compliance by making an acceptable product; consequently, color, odor and taste must be considered. The viscosity of a product also must be considered so that it has the proper palatability for an oral preparation and has the appropriate suspending properties if it is an emulsion or suspension. The theory of solutions, which involves solubility, ionization, pH control through the use of buffers, and solubilization, is discussed in Chapters 16 (*Solutions and Phase Equilibria*) and 17 (*Ionic Solutions and Electrolyte Equilibria*). Because of the complexity of some manufactured products, compounding may be carried out with the aid of linear programming models to obtain the optimal product. Chapters 41 to 43 should be consulted for information on the preparation and characteristics of those liquid preparations that are intended for parenteral and ophthalmic use.

Much has been written about the biopharmaceutical properties of solid dosage forms. Many researchers begin their absorption studies of drugs administered in solution to assess the bioavailability relative to tablets and capsules. Absorption occurs when drugs are in a dissolved state, thus it is frequently observed that the bioavailability of oral dosage forms decreases in the following order: aqueous solution > aqueous suspension > tablet or capsule. Formulation may influence the bioavailability and pharmacokinetics of drugs in solution, including drug concentration, volume of liquid administered, pH, ionic strength, buffer capacity, surface tension, specific gravity, viscosity and excipients. Emulsions and suspensions are more complex systems; consequently, the bioavailability and pharmacokinetics of these systems may be affected by additional formulation factors such as surfactants, type of viscosity agent, particle size and particle-size distribution, polymorphism and solubility of drug in the oil phase.

Liquid preparations may be dispensed in one of three ways: (1) in its original container, (2) repackaging a bulk product at the time a prescription is presented by the patient or (3) compounding the solution, suspension, or emulsion in the dispensary. Compounding may involve nothing more than mixing marketed products in the manner indicated on the prescription or, in specific instances, may require the incorporation of active ingredients and excipients in a logical and pharmaceutically acceptable manner into aqueous or organic solvents that will form the bulk of the product.

The pharmacist, in the first instance, depends on the pharmaceutical manufacturer to produce a product that is safe, efficacious, elegant and stable until its expiration date when stored at conditions described on its label. Manufacturers guarantee efficacy of their products but, in some instances, consumer preference is variable. For example, cough syrups marketed by two different manufacturers may contain the same active ingredient(s), and the relative merits of the two products may appear interchangeable. In such instances the commercial advantage may be based on factors such as flavor, color, aroma, mouth feel and packaging.

SOLVENTS FOR LIQUID PHARMACEUTICAL PREPARATIONS

The pharmacist's knowledge of the physical and chemical characteristics of a given drug dictates the selection of the appropriate solvent for a particular formulation. In addition to solubility, solvent selection is also based on clarity, toxicity, viscosity, compatibility with excipients, chemical inertness, palatability, odor, color, and economy. In most cases, especially solutions for oral, ophthalmic or parenteral administration, water is the preferred solvent because it meets the majority of the

above criteria better than other available solvents. Often, an auxiliary solvent is also employed to augment the solvent action of water or to contribute to a product's chemical or physical stability. Alcohol, glycerin, and propylene glycol have been frequently used for these purposes.

Solvents such as acetone, ethyl oxide, and isopropyl alcohol are too toxic for use in oral pharmaceutical preparations, but they are useful as solvents in organic chemistry and in the preparatory stages of drug development. For purposes such as this, certain solvents are officially recognized in the compendia. A number of fixed oils such as corn oil, cottonseed oil, peanut oil, and sesame oil serve useful solvent functions particularly in the preparation of oleaginous injections and are recognized in the compendia for this purpose.

WATER

The major ingredient in most of the dosage forms described herein is water. It is used both as a vehicle and as a solvent for the desired flavoring or medicinal ingredients. Its tastelessness, freedom from irritating qualities, and lack of pharmacological activity make it ideal for such purposes. There is, however, a tendency to assume that its purity is constant and that it can be stored, handled, and used with a minimum of care. Although it is true that municipal supplies must comply with Environmental Protection Agency (EPA) regulations (or comparable regulations in other countries), drinking water must be purified before it can be used in pharmaceuticals. Water quality can have a significant impact on the stability of pharmaceutical dosage forms.[1] In manufacturing environments, the design of purified water systems must meet standards outlined in the United States Pharmacopeia (USP) and be validated.[2–5]

Five of the eight solvent waters described in the USP are used in the preparation of parenterals, irrigations, or inhalations. *Purified Water* must be used for all other pharmaceutical operations, dosage forms, and, as needed, in all USP tests and assays. It must meet rigid specifications for chemical purity. Purified Water is water obtained by deionization, distillation, ion-exchange, reverse osmosis, filtration, or other suitable procedures. For parenteral administration, Water for Injection, Bacteriostatic Water for Injection, or Sterile Water for Injection must be used. Sterile water may be sterile at the time of production but may lose this characteristic if it is stored improperly.

The major impurities in water are calcium, iron, magnesium, manganese, silica, and sodium. The cations usually are combined with the bicarbonate, sulfate, or chloride anions. Hard waters are those that contain calcium and magnesium cations. Bicarbonates are the major impurity in alkaline waters. Deionization processes do not necessarily produce Purified Water that will comply with EPA requirements for drinking water. Resin columns retain phosphates and organic debris. Either alone or in combination, these substances can act as growth media for microorganisms. Observations have shown that deionized water containing 90 organisms / mL contained 10^6 organisms / mL after 24-hour storage. Ultraviolet radiant energy (240–280 nm), heat or filtration can be used to limit the growth of, kill, or remove microorganisms in water. The latter method employs membrane filters and can be used to remove bacteria from heat-labile materials.

The phenomenon of *osmosis* involves the passage of water from a dilute solution across a semi-permeable membrane to a more concentrated solution. Flow of water can be stopped by applying pressure to the concentrated solution equal to the osmotic pressure. The flow of water can be reversed by applying a pressure greater than the osmotic pressure. The process of reverse osmosis uses the latter principle; by applying pressure greater than the osmotic pressure to the concentrated solution (eg, tap water), pure water may be obtained. Organic molecules are rejected on the basis of a sieve mechanism related to their size and shape. Small organic molecules, with a molecular weight smaller than approximately 200, will pass through the membrane material. Because there are few organic molecules with a molecular weight of less than 200 in the municipal water supply, reverse osmosis usually is sufficient for the removal of organic material. The pore sizes of the selectively permeable reverse-osmosis membranes are between 0.5 and 10 nm. Viruses and bacteria larger than 10 nm are rejected if no imperfections exist in the membrane. The membranes may and do develop openings that permit the passage of microorganisms. Because of the semi-static conditions, bacteria can grow both upstream and downstream of the membrane.

ALCOHOLS

Next to water, alcohol is the second most commonly used solvent in pharmacy for many organic compounds. When mixed with water, a hydroalcoholic mixture is formed capable of dissolving both alcohol-soluble and water-soluble substances, a feature especially useful for extraction and purification of active constituents from crude drugs and synthetic procedures. Alcohol, USP, is 94.9% to 96.0% by volume, at 15.56°C of C_2H_5OH and Dehydrated Alcohol, USP, contains not less than 99.5% C_2H_5OH by volume. Dehydrated alcohol is utilized when an essentially water-free alcohol is necessary. Alcohol is widely used for its miscibility with water and its ability to dissolve many water-insoluble ingredients including drug substances, flavors, and antimicrobial preservatives. Alcohol is used in liquid products as an antimicrobial preservative or in conjunction with parabens, benzoates, sorbates, and other agents. Diluted Alcohol, NF, is prepared by mixing equal volumes of Alcohol, USP, and Purified Water, USP. Due to contraction upon mixing, the final volume of such mixtures is not the sum of the individual volumes of the two components, but is generally about 3% less.

The United States Food and Drug Administration (FDA) has expressed concern about undesired pharmacologic and potential toxic effects of alcohol when ingested by children. For this reason, manufacturers of over-the-counter (OTC) oral drug products have been asked to restrict, if possible, the use of alcohol and include appropriate warnings in the labeling. For OTC oral products intended for children under 6 years of age, the recommended alcohol content limit is 0.5%; for products intended for children 6 to 12 years of age, the recommended limit is 5%; and for products recommended for children over 12 years of age and for adults, the recommended limit is 10%.

Rubbing Alcohol, USP must be manufactured in accordance with the requirements of the US Treasury Department, Bureau of Alcohol, Tobacco, and Firearms, Formula 23-H (8 parts by volume of acetone, 1.5 parts by volume of methyl isobutyl ketone, and 100 parts by volume of ethyl alcohol). It contains not less than 68.5% and not more than 71.5% by volume of dehydrated alcohol, the remainder consisting of water and the denaturants with or without color additives and perfume oils. Rubbing Alcohol contains in each 100 mL not less than 355 mg of sucrose octaacetate or not less than 1.40 mg of denatonium benzoate. The preparation may be colored with one or more color additives listed by the FDA for use in drugs and a suitable stabilizer may be added. The use of this denaturant mixture makes the separation of ethyl alcohol from the denaturants a virtually impossible task with ordinary distillation apparatus. This discourages the illegal removal and use of the alcoholic content of rubbing alcohol as a beverage. The product is volatile and extremely flammable and should be stored in tight containers remote from ignition sources. It is used externally as a soothing rub for bedridden patients, a germicide for instruments, and a skin cleanser prior to injection.

Isopropyl Rubbing Alcohol is about 70% by volume isopropyl alcohol, the remainder consisting of water with or without color additives, stabilizers, and perfume oils. It is used

exclusively as a vehicle in topical products and applications. This preparation and a commercially available 91% isopropyl alcohol solution are commonly employed to disinfect needles and syringes for hypodermic injections of insulin and for disinfecting the skin.

Glycerin is a clear, syrupy liquid with a sweet taste and is miscible with water and alcohol. Glycerin is used in a wide variety of pharmaceutical formulations including oral, otic, ophthalmic, topical, and parenteral preparations. In topical pharmaceutical formulations and cosmetics, glycerin is used primarily for its humectant and emollient properties. In parenteral formulations, glycerin is used mainly as a solvent. In oral solutions, glycerin is used as a solvent, sweetening agent, antimicrobial preservative, and viscosity-increasing agent.

Propylene glycol has become widely used as a solvent, extractant, and preservative in a variety of liquid pharmaceutical formulations, including parenterals. Propylene glycol is a viscous liquid and is miscible with water and alcohol. It is a useful solvent with a wide range of applications and is often used in place of glycerin. As an antiseptic it is similar to ethanol, and against molds it is similar to glycerin and only slightly less effective than ethanol. Propylene glycol is also used as a carrier for emulsifiers and as a vehicle for flavors, as opposed to ethanol, due to its lack of volatility.

STABILITY CONSIDERATIONS

The stability of the active ingredient in the final product is a primary concern to the formulator. In general, drug substances are less stable in aqueous media than solid dosage forms, and it is important to properly stabilize and preserve solutions, suspensions, and emulsions that contain water. Acid–base reactions, acid or base catalysis, oxidation, and reduction can occur in these products. These reactions can arise from ingredient–ingredient interactions or container–product interactions. For pH sensitive compounds, any of these interactions may alter the pH and cause precipitation.

Vitamins, essential oils, and almost all fats and oils can be oxidized. Formulators usually use the word *auto-oxidation* when the ingredient(s) reacts with oxygen but without drastic external interference. Such reactions can be initiated by heat, light (including ultraviolet radiant energy), peroxides, or other labile compounds or heavy metals such as copper or iron. This initiation step results in the formation of a free radical that then reacts with oxygen. The free radical is regenerated and reacts with more oxygen (propagation). The reactions are terminated when the free radicals react with one another.

The effect of trace metals can be minimized by using chelating agents such as citric acid or EDTA. Antioxidants may retard or delay oxidation by rapidly reacting with free radicals as they are formed (quenching). Common antioxidants include propyl, octyl, and dodecyl esters of gallic acid, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and the tocopherols or vitamin E. Connors and coworkers provide a detailed approach for the prevention of oxidative degradation of pharmaceuticals.[6] Common antioxidants and chelating agents used in pharmaceutical preparations are listed in Table 39-1.

Table 39-1. Common Antioxidants and Chelating Agents Used in Liquid Pharmaceutical Dosage Forms

Antioxidants	Alpha tocopherol
	Ascorbic acid
	Acorbyl palmitate
	Butylated hydroxyanisole
	Butylated hydroxytoluene
	Monothioglycerol
	Potassium metabisulfite
	Propionic acid
	Propyl gallate
	Sodium ascorbate
	Sodium bisulfite
	Sodium metabisulfite
	Sodium sulfite
Chelating Agents	Citric acid monohydrate
	Disodium edetate
	Dipotassium edetate
	Edetic acid
	Fumaric acid
	Malic acid
	Phosphoric acid
	Sodium edetate
	Tartaric acid
	Trisodium edetate

The USP states that if a product must be repackaged, the container specified by the compendium must be used. For example, a suitable opaque plastic container should be used if a light-resistant container is specified. If a product is diluted, or where two products are mixed, the pharmacist should use his or her knowledge to guard against incompatibility and instability. Oral antibiotic preparations constituted into liquid form should never be mixed with other products. If the chemical stability of extemporaneously prepared liquid preparations is unknown, their use should be minimized and every care taken to ensure that product characteristics will not change during the time it must be used by the patient.

Because of the number of excipients and additives in these preparations, it is recommended all the ingredients be listed on the container to reduce the risks that confront hypersensitive patients when these products are administered. Finally, the pharmacist should inform the patient regarding the appropriate use of the product, the proper storage conditions, and the time after which it should be discarded.

PRESERVATIVES

In addition to stabilization of pharmaceutical preparations against chemical and physical degradation, liquid and semisolid preparations must be protected against microbial contamination. Nearly all products described in this chapter contain water and thus, with certain exceptions such as aqueous acids, will support microbial growth. Aqueous solutions, syrups, emulsions, and suspensions often provide excellent growth media for microorganisms such as molds, yeast, and bacteria (typically *Pseudomonas, E. coli, Salmonella,* and *Staphylococcus*).

Kurup and Wan describe many preparations that are not preserved adequately and are not able to resist microbial contamination.[7] Products such as ophthalmic and injectable preparations are sterilized by autoclaving (20 minutes at 15 pounds of pressure at 120°C followed by dry heat at 180°C for 1 hour) or filtration. However, many of them require the presence of an antimicrobial preservative to maintain aseptic conditions throughout their stated shelf life.[8] Certain hydroalcoholic and alcoholic preparations do not require addition of a chemical preservative if the alcohol content is sufficient to prevent microbial growth. In general, an alcohol content of 15% by weight in acid solutions and 18% by weight in alkaline solutions is sufficient to prevent microbial growth. Most alcohol containing preparations such as elixirs, spirits, and tinctures are self-preserving and will not require preservation. Indeed, the formulator should challenge any new preparation by procedures described in the General Tests and Assays, parts ⟨51⟩ and ⟨61⟩ of the USP and other methods reported in the literature.[9–12]

When a preservative is required, its selection is based upon several considerations, in particular the site of use whether internal, external, or ophthalmic.[13] Several researchers have described various interactions that must be considered when preservatives are selected.[14,15] The major criteria that should be considered in selecting a preservative are as follows: It should be effective against a wide spectrum of microorganisms, stable for its shelf life, nontoxic, nonsensitizing, compatible with the ingredients in the dosage form, inexpensive, and relatively free of taste and odor.

The chosen preservative should be sufficiently stable and soluble to achieve adequate concentration to provide protection. This choice is more critical in two and three phase emulsion systems in which the preservative may be more soluble in the oil phase than in the aqueous phase.[12,16] The pH of the preparation must be considered to ensure that the preservative does not dissociate rendering it ineffective or degrade by acid or base catalyzed hydrolysis. The undissociated moiety or molecular form of a preservative possesses preservative capacity because the ionized form is unable to penetrate microorganisms. The preservative must be compatible with the formulation ingredients and the product container or closure. Finally, the preservative must not impact the safety or comfort of the patient when administered. For instance, preservatives used in ophthalmic preparations must be non-irritating. Chlorobutanol, benzalkonium chloride, and phenylmercuric nitrate are commonly used in these applications.

Although few microorganisms are viable below a pH of 3 or above pH 9, most aqueous pharmaceutical preparations are manufactured within the favorable pH range. Acidic preservatives such as benzoic acid, boric acid, and sorbic acid are less dissociated and more effective in acidic formulations. Similarly, alkaline preservatives are less effective in acidic or neutral conditions and more effective in alkaline formulations. The scientific literature is rife with examples of incompatibilities between preservatives and other pharmaceutical adjuncts.[17–19] Commonly used macromolecules including cellulose derivatives, polyethylene glycol and tragacanth gum have been reported to cause preservative failure due to binding and adsorption.[20,21]

The mode of action by which preservatives interfere with microbial growth, multiplication, and metabolism occurs through one of several mechanisms. Preservatives often alter cell membrane permeability causing leakage of cell constituents (partial lysis), complete lysis, and cytoplasmic leakage and / or coagulation of cytoplasmic constituents (protein precipitation). Other preservatives inhibit cellular metabolism by interference with enzyme systems or cell wall synthesis, oxidation of cellular constituents, or hydrolysis.

Preservatives commonly used in pharmaceutical products are listed in Table 39-2 with typical concentration levels. Preservatives may be grouped into a number of classes depending upon their molecular structure. These basic groups are discussed below.

Alcohols

Ethanol is useful as a preservative when it is used as a solvent; however, it does need a relatively high concentration, somewhat greater than 15%, to be effective. Too high a concentration may result in incompatibilities in suspension and emulsion systems. Propylene glycol also is used as a solvent in oral solutions and topical preparations, and it can function as a preservative in the range of 15% to 30%. It is not volatile like ethanol and is used frequently not only in solutions but also in suspensions and emulsions. Chlorobutanol and phenylethyl alcohol are other alcohols used in lower concentrations (about 1%) as preservatives.

Acids

Benzoic acid has a low solubility in water, about 0.34% at 25°C, but the apparent aqueous solubility of benzoic acid may be enhanced by the addition of citric acid or sodium acetate to the solution. The concentration range used for inhibitory action varies from 0.1% to 0.5%. Activity depends on the pH of the medium because only the undissociated acid has antimicrobial properties. Optimum activity occurs at pH values below 4.5; at values above pH 5, benzoic acid is almost inactive.[22] It has been reported that antimicrobial activity of benzoic acid is enhanced by the addition of the basic protein protamine.[23] Sorbic acid also has a low solubility in water, 0.3% at 30°C. Suitable concentrations for preservative action are in the range of 0.05 to 2%. Its preservative action is due to the nonionized form; consequently, it is only effective in acid media. The optimum antibacterial activity is obtained at pH 4.5, and practically no activity is observed above pH 6. Sorbic acid is subject to oxidation, particularly in the presence of light and in aqueous

Table 39-2. Common Preservatives Used in Liquid Pharmaceutical Dosage Forms and Their Typical Concentration Levels

ANTIMICROBIAL PRESERVATIVES	TYPICAL USAGE LEVEL (% W/W)	ANTIFUNGAL PRESERVATIVES	TYPICAL USAGE LEVEL (% W/W)
Benzalkonium Chloride	0.002–0.02%	Butyl Paraben	0.1–0.4%
Benzethonium Chloride	0.01–0.02%	Methyl Paraben	0.1–0.25%
Benzyl Alcohol	3.0%	Ethyl Paraben	0.1–0.25%
Bronopol	0.01–0.1%	Propyl Paraben	0.1–0.25%
Cetrimide	0.005%	Benzoic Acid	0.1–0.5%
Cetylpyridinium chloride	0.0005–0.0007%	Potassium sorbate	0.1–0.2%
Chlorhexidine	0.002–0.5%	Sodium Benzoate	0.1–0.2%
Chlorobutanol	0.5%	Sodium Propionate	5–10%
Chlorocresol	0.2%	Sorbic Acid	0.05–0.2%
Chloroxylenol	0.1–0.8%		
Cresol	0.15–0.3%		
Ethyl Alcohol	15–20%		
Glycerin	20–30%		
Hexetidine	0.1%		
Imidurea	0.03–0.5%		
Phenol	0.1–0.5%		
Phenoxyethanol	0.5–1.0%		
Phenylethyl Alcohol	0.25–0.5%		
Phenylmercuric Nitrate	0.002–0.01%		
Propylene Glycol	15–30%		
Thimerosal	0.1%		

solutions. Activity against bacteria can be variable because of its limited stability. Thus, sorbic acid is frequently used in combination with other antimicrobial preservatives or glycols in which synergistic effects occur.

Esters

Parabens are esters of *p*-hydroxybenzoic acid and include the methyl, ethyl, propyl, and butyl derivatives. The water solubility of the parabens decreases as the molecular weight increases from 0.25% for the methyl ester to 0.02% for the butyl ester. These compounds are used widely in pharmaceutical products, stable over a pH range of 4 to 8, and have a broad spectrum of antimicrobial activity, although they are most effective against yeasts and molds. Antimicrobial activity increases as the chain length of the alkyl moiety is increased, but aqueous solubility decreases; therefore, a mixture of parabens is frequently used to provide effective preservation. Preservative efficacy is also improved by the addition of propylene glycol (2–5%) or by using parabens in combination with other antimicrobial agents such as imidurea. Activity is reduced in the presence of nonionic surface active agents due to binding. In alkaline solutions, ionization takes place and this reduces their activity; in addition, hydrolytic decomposition of the ester group occurs with a loss of activity.

Quaternary Ammonium Compounds

Benzalkonium chloride is a mixture consisting principally of the homologs $C_{12}H_{25}$ and $C_{14}H_{29}$. This preservative is used at a relatively low concentration, 0.002% to 0.02%, depending on the nature of the pharmaceutical product. This class of compounds has an optimal activity over the pH range of 4 to 10 and is quite stable at room temperature. Because of the cationic nature of this type of preservative, it is incompatible with many anionic compounds such as surfactants and can bind to nonionic surfactants. It is used generally in preparations for external use or those solutions that come in contact with mucous membranes. In ophthalmic preparations, benzalkonium chloride is widely used at a concentration of 0.01–0.02% w/w. Often it is used in combination with other preservatives or excipients, particularly 0.1% w/v disodium edetate, to enhance its antimicrobial activity against strains of *Pseudomonas*. A concentration of 0.002–0.02% is used in nasal and otic formulations, sometimes in combination with 0.002–0.005% thimerosal. Benzalkonium chloride 0.01% w/v is also employed as a preservative in small-volume parenteral products.

Clearly, when the pharmacist dispenses or compounds liquid preparations, responsibility is assumed, along with the manufacturer, for the maintenance of product stability. General chapter ⟨1191⟩ of the USP describes stability considerations for dispensing, which should be studied in detail.[9] Stock should be rotated and replaced if expiration dates on the label so indicate. Products should be stored in the manner indicated on the manufacturer's label or in the compendium. Further, products should be checked for evidence of instability. With respect to solutions, elixirs, and syrups, major signs of instability are color change, precipitation, and evidence of microbial or chemical gas formation. Emulsions may cream, but if they break (ie, there is a separation of an oil phase) the product is considered unstable. Sedimentation and caking are primary indications of instability in suspensions. The presence of large particles may mean that excessive crystal growth has occurred (Ostwald Ripening). Additional details on these topics are provided in the pertinent sections of this chapter.

SOLUTIONS

A solution is a homogeneous mixture that is prepared by dissolving a solid, liquid, or gas in another liquid and represents a group of preparations in which the molecules of the solute or dissolved substance are dispersed among those of the solvent. Most solutions are unsaturated with the solute, in other words, the concentration of the solute in the solution is below its solubility limit. The strengths of pharmaceutical solutions are usually expressed in terms of % strength, although for very dilute preparations expressions of ratio strength are sometimes used. The term % when used without qualification (as with w/v, v/v, or w/w) means % weight-in-volume for solutions or suspensions of solids in liquids; % weight-in-volume for solutions of gases in liquids; % volume-in-volume for solutions of liquids in liquids; and weight-in-weight for mixtures of solids and semisolids.

Solutions also may be classified on the basis of physical or chemical properties, method of preparation, use, physical state, number of ingredients, and particle size. For the pharmacist, solutions are more defined by site of administration and composition than by physicochemical definitions. For instance, pharmaceutical solutions may be classified as an *oral solution, otic solution, ophthalmic solution,* or *topical solution*. These solutions may also be classified based upon their composition. *Syrups* are aqueous solutions containing a sugar; *elixirs* are sweetened hydroalcoholic (combinations of water and ethanol) solutions; *spirits* are solutions of aromatic materials if the solvent is alcoholic or *aromatic waters* if the solvent is aqueous. Depending on their method of preparation and concentration, *tinctures* or *fluid extracts* are solutions prepared by extracting active constituents from crude drugs.

Many pharmaceutical chemicals are only slowly soluble in a given solvent and require an extended time for complete dissolution. To increase the dissolution rate, a pharmacist may employ one or several techniques such as applying heat, reducing the particle size of the solute, utilizing of a solubilizing agent, or subjecting the ingredients to rigorous agitation. In most cases, solutes are more soluble in solvents at elevated temperatures than at room temperature or below due to the endothermic nature of the dissolution process. The pharmacist should ensure that the materials are heat stabile and non-volatile when using heat to facilitate the dissolution rate.

AQUEOUS SOLUTIONS

The narrower definition in this subsection limits the solvent to water and excludes those preparations that are sweet and/or viscid in character and nonaqueous solutions. This section includes those pharmaceutical forms that are designated as *Aromatic Waters, Aqueous Acids, Solutions, Douches, Enemas, Gargles, Mouthwashes, Juices, Nasal Solutions, Otic Solutions,* and *Irrigation Solutions.*

Aromatic Waters

The USP defines Aromatic Waters as clear, saturated aqueous solutions (unless otherwise specified) of volatile oils or other aromatic or volatile substances.[9] Their odors and tastes are similar, respectively, to those of the drugs or volatile substances from which they are prepared, and they are free from empyreumatic and other foreign odors. Aromatic waters may be prepared by distillation or solution of the aromatic substance, with or without the use of a dispersing agent. They are used principally as flavored or perfumed vehicles.

Peppermint Water USP and Stronger Rose Water USP are examples of aromatic waters. Concentrated waters, such as peppermint, dill, cinnamon, and caraway, may be prepared as follows:

> Dissolve 20 mL of the volatile oil in 600 mL of 90% ethanol. Add sufficient purified water in successive small portions to produce 1000 mL. Shake vigorously after each addition. Add 50 g of sterilized purified talc, shake occasionally for several hours, and filter.

The aromatic water is prepared by diluting the concentrate with 39 times its volume of water.

The chemical composition of many of the volatile oils is known, and suitable synthetic substances may be used in preparing pharmaceuticals and cosmetics. Similarly, many synthetic aromatic substances have a characteristic odor; for example, geranyl phenyl acetate has a honey odor. Such substances, either alone or in combination, can be used in nonoffi-cial preparations.

The principal difficulty experienced in compounding prescriptions containing aromatic waters is *salting out* certain ingredients such as very soluble salts. A replacement of part of the aromatic water with purified water is permissible when no other function is being served than that of a vehicle. Aromatic waters will deteriorate with time and should, therefore, be made in small quantities, protected from intense light and excessive heat, and stored in airtight, light-resistant containers.

Aqueous Acids

Inorganic acids and certain organic acids, although of minor significance as therapeutic agents, are of great importance in pharmaceutical manufacturing and analysis. This is especially true of acetic, hydrochloric, and nitric acids. Many of the more important inorganic acids are available commercially in the form of concentrated aqueous solutions. The percentage strength varies from one acid to another and depends on the solubility and stability of the solute in water and on the manufacturing process. Thus, Hydrochloric Acid contains from 36.5% to 38.0% by weight of HCl, whereas Nitric Acid contains from 69% to 71% by weight of HNO_3.

Because the strengths of these concentrated acids are stated in terms of percent by weight, it is essential that specific gravities also be provided if one is to be able to calculate conveniently the amount of absolute acid contained in a unit volume of the solution as purchased. The mathematical relationship involved is given by the equation $M = V \times S \times F$, where M is the mass in g of absolute acid contained in V mL of solution having a specific gravity S and a fractional percentage strength F.

As an example, Hydrochloric Acid containing 36.93% by weight of HCl has a specific gravity of 1.1875. Therefore, the amount of pure HCl supplied by 100 mL of this solution is given by:

$$M = 100 \times 1.1875 \times 0.3693 = 43.85 \text{ g HCl}$$

Although many of the reactions characteristic of acids offer opportunities for incompatibilities, only a few are of sufficient importance to require more than casual mention. Acids and acid salts decompose carbonates with liberation of carbon dioxide; in a closed container, sufficient pressure may be developed to produce an explosion. Inorganic acids react with salts of organic acids to produce the free organic acid and a salt of the inorganic acid. If insoluble, the organic acid will be precipitated. Thus, salicylic acid and benzoic acid are precipitated from solutions of salicylates and benzoates. Boric acid likewise is precipitated from concentrated solutions of borates. By a similar reaction, certain soluble organic compounds are converted into an insoluble form. Phenobarbital sodium, for example, is converted into phenobarbital that will precipitate in aqueous solution.

The ability of acids to combine with alkaloids and other organic compounds containing a basic nitrogen atom is used in preparing soluble salts of these substances. Certain solutions, syrups, elixirs, and other pharmaceutical preparations, may contain free acid, which causes these preparations to exhibit the incompatibilities characteristic of the acid. Acids also possess the incompatibilities of the anions that they contain and, in the case of organic acids, these are frequently of prime importance. These are discussed under the specific anions.

Diluted Acids

The diluted acids in the USP are aqueous solutions of acids of a suitable strength (usually 10% *w/v* but Diluted Acetic Acid is 6% *w/v*) for internal administration or for the manufacture of other preparations.

The strengths of the official undiluted acids are expressed as percentages in weight (*w/w*), whereas the strengths of the official diluted acids are expressed as percent in volume (*w/v*). It, therefore, becomes necessary to consider the specific gravities of the concentrated acids when calculating the volume required to make a given quantity of diluted acid. The following equation will give the number of milliliters required to make 1000 mL of diluted acid:

$$\frac{\text{Strength of diluted acid} \times 1{,}000}{\text{Strength of undiluted acid} \times \text{Specific gravity of undiluted acid}}$$

Thus, if one wishes to make 1000 mL of Diluted Hydrochloric Acid USP (10% w/v) using Hydrochloric Acid that assays 37.5% HCl (sp gr 1.18), the amount required is

$$\frac{10 \times 1{,}000}{37.5 \times 1.18} = 226 \text{ mL}$$

Diluted Hydrochloric Acid, USP has been used in the treatment of achlorhydria. However, it may irritate the mucous membrane of the mouth and attack the enamel of the teeth. The usual dose is 2 to 4 mL, well-diluted with water. In the treatment of achlorhydria no attempt is made to administer more than a relief-producing dose.

Douches

A douche is an aqueous solution directed against a part or into a cavity of the body. It functions as a cleansing or antiseptic agent. An *eye douche*, used to remove foreign particles and discharges from the eyes, is directed gently at an oblique angle and allowed to run from the inner to the outer corner of the eye. *Pharyngeal douches* are used to prepare the interior of the throat for an operation and cleanse it in suppurative conditions. Similarly, there are *nasal douches* and *vaginal douches*. Douches usually are directed to the appropriate body part by using bulb syringes.

Douches are often dispensed in the form of a powder with directions for dissolving in a specified quantity of water (usually warm). However, tablets for preparing solutions are available (eg, Dobell's Solution Tablets) or the solution may be prepared by the pharmacist. If powders or tablets are supplied, they must be free from insoluble material in order to produce a clear solution. Tablets are produced by the usual processes but any lubricants or diluents used must be readily soluble in water. Boric acid may be used as a lubricant and sodium chloride normally is used as a diluent. Tablets deteriorate on exposure to moist air and should be stored in airtight containers.

Douches are not official as a class of preparations but several substances in the compendia frequently are employed as such in weak solutions. *Vaginal douches* are the most common type of douche and are used for cleansing the vagina and hygienic purposes. Liquid concentrates or powders, which may be prepared in bulk or as single-use packages, should be diluted or dissolved in the appropriate amount of warm water prior to use.

The ingredients used in vaginal douches include antimicrobial agents such as benzalkonium chloride, the parabens or chlorothymol, and anesthetics or antipruritics such as phenol or menthol. Astringents such as zinc sulfate or potassium alum, surface-active agents such as sodium lauryl sulfate, and chemicals to alter the pH such as sodium bicarbonate or citric acid also are used.

Enemas

A number of solutions are administered rectally for the local effects of the medication (eg, hydrocortisone) or for systemic absorption (eg, aminophylline). In the case of aminophylline, the rectal route of administration minimizes the undesirable gastrointestinal reactions associated with oral therapy.[24] Clinically effective blood levels of the agents are usually obtained within 30 minutes following rectal instillation. Corticosteroids are administered as retention enemas or continuous drip as adjunctive treatment of some patients with ulcerative colitis.

Enema preparations are rectal injections employed to evacuate the bowel (evacuation enemas), influence the general system by absorption, or to affect a local disease. The latter two are called retention enemas. They may possess anthelmintic, nutritive, sedative, or stimulating properties, or they may contain radiopaque substances for roentgenographic examination of the lower bowel.

Sodium chloride, sodium bicarbonate, sodium monohydrogen phosphate, sodium dihydrogen phosphate, glycerin, docusate potassium, and light mineral oil are used in enemas to evacuate the bowel. These substances may be used alone, in combination with each other, or in combination with irritants such as soap. Evacuation enemas usually are given at body temperature in quantities of 1 to 2 pt injected slowly with a syringe.

An official retention enema used for systemic purposes is aminophylline. Retention enemas are to be retained in the intestine and should not be used in larger quantities than 150 mL for an adult. Usually, the volume is considerably smaller, such as a few mL. *Microenema* is a term used to describe these small-volume preparations. Vehicles for retention microenemas have been formulated with small quantities of ethanol and propylene glycol, and no significant difference in irritation, as compared with water, was found. A number of other drugs such as valproic acid, indomethacin, and metronidazole have been formulated as microenemas for the purpose of absorption.

Gargles

Gargles are aqueous solutions frequently containing antiseptics, antibiotics, and/or anesthetics used for treating the pharynx and nasopharynx by forcing air from the lungs through the gargle that is held in the throat; subsequently, the gargle is expectorated. Many gargles must be diluted with water prior to use. Although mouthwashes are considered as a separate class of pharmaceuticals, many are used as gargles either as is, or diluted with water.

A gargle/mouthwash containing the antibiotic tyrothricin has been shown to provide levels of gramicidin, a component of tyrothricin, in saliva when used as a gargle rather than a mouthwash.[25] Higher saliva levels of gramicidin were obtained when a lozenge formulation was employed. Rapid relief of pharyngeal and oral pain was obtained when Cepacaine solution, which contains a topical anesthetic, was used as a gargle.[26]

Nystatin is administered in both powder and liquid form to treat oral fungal infections.[27] The medication is taken by placing one-half of the dose in each side of the mouth, swishing it around as long as possible, then gargling and swallowing. Hydrogen peroxide is a source of nascent oxygen and a weak topical antibacterial agent. Hydrogen peroxide topical solution has been used as a mouthwash or gargle in the treatment of pharyngitis or Vincent's stomatitis.[28,29] Hydrogen peroxide has also been applied in root canals of teeth or other dental pulp cavities. While used topically as a 1.5–3% solution for cleansing wounds, hydrogen peroxide is usually diluted with an equal volume of water for use as a mouthwash or gargle. Hydrogen peroxide gel is used topically as a 1.5% gel for cleansing minor wounds or irritations of the mouth or gums. A small amount of the gel is applied to the affected area, allowed to remain in place for at least 1 minute, and then expectorated; the gel may be used up to 4 times daily (after meals and at bedtime).

Mouthwashes

Mouthwashes are aqueous solutions often in concentrated form containing one or more active ingredients and excipients described below. They are used by swishing the liquid in the oral cavity. Mouthwashes can be used for two purposes, therapeutic and cosmetic. Therapeutic rinses or washes can be formulated to reduce plaque, gingivitis, dental caries, and stomatitis. Cosmetic mouthwashes may be formulated to reduce bad breath through the use of antimicrobial and/or flavoring agents.

Recent information indicates that mouthwashes are being used as a dosage form for a number of specific problems in the oral cavity; for example, mouthwashes containing a combination of antihistamines, hydrocortisone, nystatin, and tetracycline have been prepared from commercially available suspensions, powders, syrups, or solutions for the treatment of stomatitis, a painful side effect of cancer chemotherapy. Other drugs include allopurinol, also used for the treatment of stomatitis,[30] pilocarpine for xerostoma (dry mouth),[31] amphotericin B for oral candidiasis,[32] and chlorhexidine gluconate for plaque control.[33] Mouthwashes may be used for diagnostic purposes. For example, oral cancer and lesions are detected using toluidine blue mouth rinse.[34]

Commercial products (eg, Cepacol, Listerine, Micrin, or Scope) vary widely in composition. Tricca has described the excipients generally found in Mouthwashes as alcohols, surfactants, flavors, and coloring agents.[35] Alcohol is often present in the range of 10% to 20%. It enhances the flavor, provides sharpness to the taste, aids in masking the unpleasant taste of active ingredients, functions as a solubilizing agent for some flavoring agents, and may function as a preservative. Humectants such as glycerin and sorbitol may form 5% to 20% of the mouthwash. These agents increase the viscosity of the preparation and provide a certain *body* or *mouth feel* to the product. They enhance the sweetness of the product and, along with the ethanol, improve the preservative qualities of the product.

Surfactants of the nonionic class such as polyoxyethylene/polyoxypropylene block copolymers or polyoxyethylene derivatives of sorbitol fatty acid esters may be used. The concentration range is 0.1% to 0.5%. An anionic surfactant occasionally used is sodium lauryl sulfate. Surfactants are used because they aid in the solubilization of flavors and in the removal of debris by providing foaming action. Cationic surfactants such as cetylpyridinium chloride are used for their antimicrobial properties, but these tend to impart a bitter taste.

Flavors are used in conjunction with alcohol and humectants to overcome disagreeable tastes, at the same time flavors must be safe to use. The principle flavoring agents are peppermint, spearmint, cinnamon, wintergreen oils, menthol, or methyl salicylate. Other flavoring agents may be used singly or in combination. Finally, coloring agents also are used in these products.

Juices

A juice is prepared from fresh ripe fruit, is aqueous in character, and is used in making syrups that are employed as vehicles. The freshly expressed juice is preserved with benzoic acid and allowed to stand at room temperature for several days, until the pectins that naturally are present are destroyed by enzymatic action, as indicated by the filtered juice yielding a clear solution

with alcohol. Pectins, if allowed to remain, would cause precipitation in the final syrup.

Cherry Juice and Tomato Juice are described in the USP. Artificial flavors now have replaced many of the natural fruit juices. Although they lack the flavor of the natural juice, they are more stable and easier to incorporate into the final pharmaceutical form. Commercial juices such as orange, apple, grape, and mixed vegetables have been used recently to prepare extemporaneous preparations of cholestyramine[36] and nizatidine.[37] Information on cranberry juice indicates that it may be effective in controlling some urinary tract infections and urolithiasis.[38]

Nasal Solutions

Nasal solutions are usually aqueous solutions designed to be administered to the nasal passages in drops or sprays. Other nasal preparations may be in the form of emulsions or suspensions. The adult nasal cavity has about a 20 mL capacity with a large surface area (about 180 cm^2) for drug absorption afforded by the microvilli present along the pseudo-stratified columnar epithelial cells of the nasal mucosa.[39] The nasal tissue is highly vascularized making it an attractive site for rapid and efficient systemic absorption. Another advantage of nasal delivery is that it avoids first-pass metabolism by the liver. For some peptides and small molecular compounds, intranasal bioavailability has been comparable to that of injections. However, bioavailability decreases as the molecular weight of a compound increases, and for proteins composed of more than 27 amino acids bioavailability may be low.[40] Various pharmaceutical techniques and functional excipients, such as surfactants, have been shown to be capable of enhancing the nasal absorption of large molecules.[41,42]

Many drugs are administered for their local sympathomimetic effects to reduce nasal congestion, such as Ephedrine Sulfate Nasal Solution, USP or Naphazoline Hydrochloride Nasal Solution, USP. A few other preparations, Lypressin Nasal Solution USP and Oxytocin Nasal Solution USP, are administered in spray form for their systemic effect for the treatment of diabetes insipidus and milk letdown prior to breast feeding, respectively. Examples of commercial products for nasal use are listed in Table 39-3.

Nasal solutions are formulated to be similar to nasal secretions with regard to toxicity, pH, and viscosity so that normal ciliary action is maintained. Thus, aqueous nasal solutions usually are isotonic and slightly buffered to maintain a pH of 5.5 to 6.5. In addition, antimicrobial preservatives, similar to those used in ophthalmic preparations, and appropriate drug stabilizers, if required, are included in the formulation.

Current studies indicate that nasal sprays are deposited mainly in the atrium and cleared slowly into the pharynx with the patient in an upright position. Drops spread more extensively than the spray, and three drops cover most of the walls of the nasal cavity with the patient in a supine position and head tilted back and turned left and right.[43,44] It is suggested that drop delivery, with appropriate movement by the patient, leads to extensive coverage of the walls of the nasal cavity.

Most nasal solutions are packaged in dropper or spray bottles, usually containing 15 to 30 mL of medication. The formulator should ensure the product is stable in the containers and the pharmacist should keep the packages tightly closed during periods of nonuse. The patient should be advised that should the solution become discolored or contain precipitated matter, it must be discarded.

Otic Solutions

These solutions occasionally are referred to as ear or aural preparations. Other otic preparations include suspensions and ointments for topical application in the ear. Ear preparations are usually placed in the ear canal by drops or in small amounts for the removal of excessive cerumen (ear wax) or for the treatment of ear infections, inflammation, or pain.

The main classes of drugs used for topical administration to the ear include analgesics, such as benzocaine; antibiotics, such as neomycin; and anti-inflammatory agents, such as cortisone (Table 39-4). The USP preparations include Antipyrine and Benzocaine Otic Solution. The Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Solutions may contain appropriate buffers, solvents, and dispersants usually in an aqueous solution. The main solvents used in these preparations include glycerin or water. The viscous glycerin vehicle permits the drug to remain in the ear for a long time. Anhydrous glycerin, being hygroscopic, tends to remove moisture from surrounding tissues, thus reducing swelling. Viscous liquids such as glycerin or propylene glycol are used either alone or in combination with a surfactant to aid in the removal of cerumen (ear wax). To provide sufficient time for aqueous preparations to act, it is necessary for patients to remain on their side for a few minutes so the drops do not run out of the ear. Otic preparations are dispensed in a container that permits the administration of drops.

Irrigation Solutions

Irrigation solutions are sterile, non-pyrogenic solutions used to wash or bathe surgical incisions, wounds, or body tissues. Because they come in contact with exposed tissue, they must meet stringent USP requirements for sterility, total solids, and bacterial endotoxins. These products may be prepared by dissolving the active ingredient in Water for Injection. They are packaged in single-dose containers, preferably Type I or Type II glass, or suitable plastic containers, and then sterilized. A number of irrigations are described in the USP, including Acetic

Table 39-3. Examples of Commercial Nasal Preparations

PRODUCT NAME	MANUFACTURER	ACTIVE INGREDIENT	INDICATION
Atrovent Nasal Spray	Boehringer Ingelheim	Ipratropium bromide 0.06%	Seasonal or Allergic Rhinitis
Beconase AQ Nasal Spray	GlaxoSmithKline	Beclomethasone dipropionate, monohydrate 42 mcg	Seasonal or Allergic Rhinitis
Miacalcin	Novartis	Calcitonin-salmon, 2200 I.U. per mL	Postmenopausal osteoporosis
Nasalcrom Nasal Spray	Pharmacia	Cromolyn sodium 5.2 mg	Seasonal or Allergic Rhinitis
Nasarel Nasal Spray	IVAX	Flunisolide	Seasonal or perennial rhinitis
Nicotrol Nasal Spray	Pfizer	Nicotine 0.5 mg	Smoking Cessation
Neo-Synephrine	Bayer	Oxymetazoline hydrochloride 0.05%	Decongestion
Rhinocort Aqua Nasal Spray	Astra-Zeneca	Budesonide 32mcg	Seasonal or Allergic Rhinitis
Stadol Nasal Spray	Bristol-Myers Squibb	Butorphanol tartrate, 1 mg	Pain Relief, Migraines
Stimate Nasal Spray	Aventis	Desmopressin Acetate 1.5 mg/mL	Hemophilia A or von Willebrand disease
Synare Nasal Solution	Searle	Nafarelin acetate 2 mg/mL	Endometriosis
Tyzine	Bradley Pharmaceuticals	Tetrahydrozoline hydrochloride	Decongestion

Table 39-4. Examples of Commercial Otic Preparations

PRODUCT NAME	MANUFACTURER	ACTIVE INGREDIENT	INDICATION
Americaine-Otic	Celltech	Benzocaine	Local anesthetics
Cerumenex Ear Drops	Purdue	Triethanolamine polypeptide oleate-condensate	Removal of earwax
Chloromycetin Otic	Pfizer	Chloramphenicol	Antiinfective
Cipro HC Otic	Alcon	Ciprofloxacin hydrochloride and hydrocortisone	Acute otitis externa
Cortisporin	GlaxoSmithKline	Neomycin and Polymyxin B Sulfates and Hydrocortisone	Antibacterial and anti-inflammatory
Debrox Drops	GlaxoSmithKline	Carbamide peroxide	Removal of earwax
Floxin Otic	Daiichi	Ofloxacin	Antiinfective
Tympagesic	Savage	Antipyrine, Benzocaine, and Phenylephrine Hydrochloride	Topical anesthetic

Acid Irrigation for bladder irrigation, Dimethyl Sulfoxide Irrigation for relief of internal cystitis, Glycine Irrigation for transurethral prostatic resection, Ringer's Irrigation for general irrigation, Neomycin and Polymyxin B Sulfates Solution for Irrigation for infection, and Sodium Chloride Irrigation for washing wounds.

Extemporaneous formulations frequently are prepared using an isotonic solution of sodium chloride as the solvent. For example, cefazolin or gentamicin in 0.9% sodium chloride are used as anti-infective irrigations[45] and 5-fluororacil in 0.9% sodium chloride is employed for bladder irrigation.[46] Alum, either potassium or ammonium, in either sterile water or 0.9% sodium chloride for irrigation has been used for bladder hemorrhage. Amphotericin in sterile water has been used for the treatment of localized infections on the dermis, the bladder, and urinary tract.[47] All the extemporaneous preparations should meet the general requirements noted above for USP irrigations.

PREPARATION OF SOLUTIONS

The method of preparation for many solutions is given in the compendia. These procedures fall into three main categories: simple solutions, solution by chemical reaction, and solution by extraction.

Simple Solutions are prepared by dissolving the solute in most of the solvent, mixing until dissolved, then adding sufficient solvent to bring the solution up to the proper volume. The solvent may contain other ingredients that stabilize or solubilize the active ingredient. Calcium Hydroxide Topical Solution USP (Lime Water), Sodium Phosphates Oral Solution USP, and Strong Iodine Solution USP are examples.

Calcium Hydroxide Topical Solution USP contains, in each 100 mL, not less than 140 mg of $Ca(OH)_2$. The solution is prepared by agitating vigorously 3 g of calcium hydroxide with 1000 mL of cool, purified water. Excess calcium hydroxide is allowed to settle out and the clear, supernatant liquid dispensed. An increase in solvent temperature usually implies an increase in solute solubility. This rule does not apply, however, to the solubility of calcium hydroxide in water, which decreases with increasing temperature. The official solution is prepared at 25°C.

Solutions containing hydroxides react with the carbon dioxide in the atmosphere.

$$OH^- + CO_2 \rightarrow HCO_3^-$$

$$OH^- + HCO_3^- \rightarrow CO_3^{2-} + H_2O$$

Calcium Hydroxide Topical Solution, therefore, should be preserved in well-filled, tight containers, at a temperature not exceeding 25°C.

Strong Iodine Solution USP contains, in each 100 mL, 4.5 to 5.5 g of iodine, and 9.5 to 10.5 g of potassium iodide. It is prepared by dissolving 50 g of iodine in 100 mL of purified water containing 100 g of potassium iodide. Sufficient purified water then is added to make 1000 mL of solution. One g of iodine dissolves in 2950 mL of water. However, solutions of iodides dissolve large quantities of iodine. Strong Iodine Solution is, therefore, a solution of polyiodides in excess iodide.

$$I^- + nI_2 \rightarrow I_{(2n+1)}^-$$

Doubly charged anions may be found also.

$$2I^- + nI_2 \rightarrow I_{(2n+2)}^{2-}$$

Strong Iodine Solution is used in the treatment of iodide deficiency disorders such as endemic goiter.

Several antibiotics (eg, cloxacillin sodium, nafcillin sodium, and vancomycin), because they are relatively unstable in aqueous solution, are prepared by manufacturers as dry powders or granules in combination with suitable buffers, colors, diluents, dispersants, flavors, and/or preservatives. These preparations, Cloxacillin Sodium for Oral Solution, Nafcillin for Oral Solution, and Vancomycin Hydrochloride for Oral Solution meet the requirements of the USP. Immediately prior to dispensing to the patient, the pharmacist adds the appropriate amount of water. The products are stable for up to 14 days when refrigerated.[48] This period usually provides sufficient time for the patient to complete the administration of all the medication.

Solutions by chemical reaction are prepared by reacting two or more solutes with each other in a suitable solvent. An example is Aluminum Subacetate Topical Solution USP. Aluminum sulfate (145 g) is dissolved in 600 mL of cold water. The solution is filtered, and precipitated calcium carbonate (70 g) is added, in several portions, with constant stirring. Acetic acid (160 mL) is added slowly and the mixture set aside for 24 hours. The product is filtered and the magma on the Buchner filter washed with cold water until the total filtrate measures 1,000 mL.

The solution contains pentaquohydroxo- and tetraquodihydroxoaluminum(III) acetates and sulfates dissolved in an aqueous medium saturated with calcium sulfate. The solution contains a small amount of acetic acid. It may be stabilized by the addition of not more than 0.9% boric acid. The reactions involved in the preparation of the solution are given below. The hexaquo aluminum cations first are converted to the nonirritating

$$[Al(H_2O)_5(OH)]^{2+} \text{ and } [Al(H_2O)_4(OH)_2]^+ \text{ cations.}$$

$$[Al(H_2O)_6]^{3+} + CO_3^{2-} \rightarrow [Al(H_2O)_5(OH)]^{2+} + HCO_3^-$$

$$[Al(H_2O)_6]^{3+} + HCO_3^- \rightarrow [Al(H_2O)_5(OH)]^{2+} + H_2O + CO_2$$

As the concentration of the hexaquo cations decreases, secondary reactions involving carbonate and bicarbonate occur.

$$[Al(H_2O)_5(OH)]^{2+} + CO_3^{2-} \rightarrow [Al(H_2O)_4(OH)_2]^+ + HCO_3^-$$

$$[Al(H_2O)_5(OH)]^{2+} + HCO_3^- \rightarrow [Al(H_2O)_4(OH)_2]^+ + H_2CO_3$$

The pH of the solution now favors the precipitation of dissolved calcium ions as the insoluble sulfate. Acetic acid now is added.

The bicarbonate that is formed in the final stages of the procedure is removed as carbon dioxide.

Aluminum Subacetate Topical Solution is used in the preparation of Aluminum Acetate Topical Solution USP (Burow's Solution). The latter solution contains 15 mL of glacial acetic acid, 545 mL of Aluminum Subacetate Topical Solution and sufficient water to make 1000 mL. It is defined as a solution of aluminum acetate in approximately 5%, by weight, of acetic acid in water. It may be stabilized by the addition of not more than 0.6% boric acid.

Often, drugs or pharmaceutical necessities of vegetable or animal origin often are extracted with water or with water containing other substances. Preparations of this type may be classified as solutions but, more often, are classified as extracts and are described at the end of this chapter.

SWEET AND OTHER VISCID AQUEOUS SOLUTIONS

Solutions that are sweet or viscid include syrups, honeys, mucilages, and jellies. All of these are viscous liquids or semisolids. The basic sweet or viscid substances giving body to these preparations are sugars, polyols, and / or polysaccharides.

Syrups

Syrups are concentrated, viscous, aqueous solutions of sugar or a sugar substitute with or without flavors and medical substances. When Purified Water alone is used in making the solution of sucrose, the preparation is known as *syrup,* or *simple syrup* if the sucrose concentration is 85%. Syrups are also used to apply sugar coatings to tablets, particularly those with disagreeable aromas or acrid taste. In addition to sucrose, certain other polyols, such as glycerin or sorbitol, may be added to retard crystallization of sucrose or to increase the solubility of added ingredients. Alcohol often is included as a preservative and also as a solvent for flavors; further resistance to microbial attack can be enhanced by incorporating antimicrobial agents. When the aqueous preparation contains some added medicinal substance, the syrup is called a *medicated syrup. Flavored* syrups are usually not medicated, but rather contain various aromatic or pleasantly flavored substances and are intended to be used as a vehicle or flavor for prescriptions, such as Acacia, Cherry, Cocoa, Orange, and Raspberry USP.

Flavored syrups offer unusual opportunities as vehicles in extemporaneous compounding and are accepted readily by both children and adults. Because they contain no, or very little, alcohol they are vehicles of choice for many of the drugs that are prescribed by pediatricians. Their lack of alcohol makes them superior solvents for water-soluble substances. However, sucrose-based medicines continuously administered to children apparently cause an increase in dental caries and gingivitis; consequently, alternate formulations of the drug either unsweetened or sweetened with noncariogenic substances should be considered. A knowledge of the sugar content of liquid medicines is useful for patients who are on a restricted calorie intake; a list has been prepared by Greenwood.[49]

As noted above, sucrose-based syrups may be substituted in whole or in part by other agents in the preparation of medicated syrups. A solution of sorbitol, or a mixture of polyols, such as sorbitol and glycerin, is commonly used. Sorbitol Solution, USP, which contains 64% by weight of the polyhydric alcohol sorbitol, is often used in sugar-free and children's preparations. However, reports of adverse reactions to sorbitol are largely due to its action as an osmotic laxative when ingested orally.[50] Ingestion of large quantities of sorbitol (> 20 g/day in adults) should therefore be avoided.

Syrups possess remarkable taste-masking properties for bitter or saline drugs. Syrups flavored with Glycyrrhizin, a triterpene glycoside extracted from licorice root, has been recommended for disguising the salty taste of bromides, iodides, and chlorides.[51] This has been attributed to its colloidal character and its double sweetness—the immediate sweetness of the sugar and the lingering sweetness of the glycyrrhizin. This syrup is also of value in masking bitterness in preparations containing the B complex vitamins. Acacia Syrup USP is of particular value as a vehicle for masking the disagreeable taste of many medicaments because of its colloidal character. Raspberry Syrup, USP is one of the most efficient flavoring agents and is especially useful in masking the taste of bitter drugs. Many factors, however, enter into the choice of a suitable flavoring agent. Literature reports are often contradictory and there appears to be no substitute for the taste panel when developing new formulations.[52]

It is important that the concentration of sucrose approach but not quite reach the saturation point. In dilute solutions sucrose provides an excellent nutrient for molds, yeasts, and other microorganisms. In concentrations of 65% by weight or more, the solution will retard the growth of such microorganisms. However, a saturated solution may lead to crystallization of a part of the sucrose under conditions of changing temperature. Several commercial medicated syrups are available for a variety of indications (Table 39-5).

Preparation of Syrups

Syrups are generally prepared using one of four techniques: solution with heat, solution by agitation, addition of sucrose to a liquid medication or flavored liquid, and percolation. The method of choice depends on the physical and chemical characteristics of the substances entering into the preparation. In many cases, syrups may be successfully prepared by more than one of the above methods, and the selection may simply be a matter of preference on the part of the pharmacist. Many of the compendial syrups do not have a designated method for preparation because most are commercially available and are not prepared extemporaneously by the pharmacist.

Solution with Heat is a suitable preparation method if the constituents are not volatile or degraded by heat, and when it is desirable to make the syrup rapidly. Purified water is heated to 80°–85°C, removed from its heat source, and sucrose is added with vigorous agitation. Then, other required heat-stable components are added to the hot syrup, the mixture is allowed to cool, and its volume is adjusted to the proper level by the addition of purified water. In instances in which heat labile agents or volatile substances, such as flavors and alcohol, are to be

Table 39-5. Examples of Commercial Medicated Syrups

PRODUCT NAME	MANUFACTURER	ACTIVE INGREDIENT & DOSE	INDICATION
Chlor-Trimeton	Schering-Plough	2 mg chlorpheniramine maleate / 5 mL	Allergic rhinitus
Children's Benadryl	Pfizer	12.5 mg diphenhydramine HCl / 5 mL	Allergic rhinitus
Demerol Syrup	Sanofi	50 mg meperidine HCl / 5 mL	Narcotic analgesic
Ditropan Syrup	Ortho-McNeil	5 mg Oxybutynin chloride / 5 mL	Overactive bladder
Dramamine	Pfizer	12.5 mg dimenhydrinate / 5 mL	Antiemitic
Phenergan Syrup	Wyeth-Ayerst	25 mg promethazine HCl / 5 mL	Antiemitic
Symmetrel Syrup	Endo	50 mg amantadine HCl / 5 mL	Antiviral

added, they are generally incorporated into the syrup after cooling to room temperature.

When heat is used in the preparation of syrups, there is almost certain to be an inversion of a slight portion of the sucrose. Sucrose, a disaccharide, may be hydrolyzed into monosaccharides, dextrose (glucose), and fructose (levulose). This hydrolytic reaction is referred to as *inversion*, and the combination of the two monosaccharide products is *invert sugar*. Sucrose solutions are dextrorotary, but as hydrolysis proceeds, the optical rotation decreases and becomes negative when the reaction is complete. The rate of inversion is increased greatly by the presence of acids; the hydrogen ion acts as a catalyst in this hydrolytic reaction. Invert sugar is more readily fermentable than sucrose and tends to be darker in color. Nevertheless, its two reducing sugars are of value in retarding the oxidation of other substances.

The fructose formed during inversion is sweeter than sucrose, and thus the resulting syrup is sweeter than the original syrup. The relative sweetness of fructose, sucrose, and dextrose is in the ratio of 173:100:74. Thus, invert sugar is $1/100\,(173 + 74)1/2 = 1.23$ times as sweet as sucrose. Fructose is responsible for the darkening of syrup, as it is amber in color. If the syrup is significantly overheated, sucrose is carmelized and becomes darker. Excessive heating of syrups is undesirable because inversion occurs with an increased tendency to ferment. Syrups cannot be sterilized in an autoclave without some caramelization.

Agitation without Heat is used in cases in which heat would cause degradation or volatilize formulation constituents. On a small scale, sucrose and other formulation ingredients may be dissolved in purified water by placing the ingredients in a vessel of greater capacity than the volume of syrup to be prepared, allowing intense agitation without spillage. This process is more time-consuming than solution with heat, but the product has greater stability. Large glass-lined and stainless steel tanks equipped with mechanical mixers are employed in the large scale preparation of syrups.

Often, simple syrup or some other non-medicated syrup, rather than sucrose, is employed as the sweetening agent and vehicle. When solid agents are to be added to a syrup, it is best to dissolve them in a minimal amount of purified water and then incorporate the resulting solution into the syrup. When solid substances are added directly to syrups, they dissolve slowly because the viscous nature of the syrup does not permit the solid substance to distribute readily.

This method and that previously described are used for the preparation of a wide variety of preparations that are described popularly as syrups. Most cough syrups, for example, contain sucrose and one or more active ingredients. Many other active ingredients (eg, ephedrine sulfate, dicyclomine hydrochloride, chloral hydrate, or chlorpromazine hydrochloride) are marketed as syrups. Like cough syrups, these preparations are flavored, colored, and recommended in those instances where the patient cannot swallow the solid dosage form.

Addition of sucrose to a liquid medication or flavored liquid is often used with fluidextracts, tinctures. Syrups made in this way usually develop precipitates because alcohol is often an ingredient of the liquids thus used, and the resinous and oily substances solubilized by the alcohol precipitate when water is added. A modification of this process entails mixing the fluidextract or tincture with the water, allowing the mixture to stand to permit the separation of insoluble constituents, filtering, and then dissolving the sucrose in the filtrate. It is obvious that this procedure is not permissible when the precipitated ingredients are the valuable medicinal agents.

In the *percolation* method, either purified water or the source of the medicinal component is passed slowly through a bed of crystalline sucrose, thus dissolving it and forming a syrup. This latter method really involves two separate procedures: first the preparation of the extractive of the drug and then the preparation of the syrup. To be successful in using this process, technique is critical: (1) the percolator used should be cylindrical or semicylindrical and cone-shaped as it nears the lower orifice; (2) a coarse granular sugar must be used, otherwise it will coalesce into a compact mass, which the liquid cannot permeate. The percolation method is applied on a commercial scale for the making of compendial syrups as well as those for confectionary use.

Ipecac syrup is prepared by percolation by adding glycerin and syrup to an extractive of powdered ipecac obtained by percolation. The drug ipecac consists of the dried rhizome and roots of *Cephaelis ipecacuanha* and contains the medicinally active alkaloids, emetine, cephaeline, and psychotrine. These alkaloids are extracted from the powdered ipecac by percolation with a hydroalcoholic solvent. The syrup is categorized as an emetic with a usual dose of 15 mL. This amount of syrup is commonly used in the management of poisoning in children when the evacuation of stomach contents is desirable. About 80% of children given this dose will vomit within a half hour. Bulimics have used ipecac to bring on attacks of vomiting in an attempt to lose more weight.[53] Pharmacists must be aware of this abuse and warn these individuals because one of the active ingredients is emetine. With chronic abuse of the syrup, emetine builds up toxic levels within body tissues and in 3 to 4 months can do irreversible damage to heart muscles resulting in symptoms mimicking a heart attack.

Syrups should be made in quantities that can be consumed within a few months, except in those cases where special facilities can be employed for their preservation; a low temperature is the best method. Concentration without super-saturation is also a condition favorable to preservation. The USP states that syrups may contain preservatives. Glycerin, methylparaben, benzoic acid, and sodium benzoate may be used to prevent bacterial and mold growth. Combinations of alkyl esters of *p*-hydroxybenzoic acid are effective inhibitors of yeasts that have been implicated in the contamination of commercial syrups. Syrups should be preserved in well-dried bottles, preferably those that have been sterilized. These bottles should not hold more than is likely to be required during 4 to 6 weeks and should be filled completely, carefully closed, and stored in a cool, dark place.

Some examples of syrup formulations are noted below:

Ferrous Sulfate Syrup

Ferrous Sulfate	40.0 g
Citric Acid	2.1 g
Peppermint Spirit	2 mL
Sucrose	825 g
Purified Water	to make 1000.0 mL

Dissolve the Ferrous Sulfate, Citric Acid, Peppermint Spirit, and 200 g of the Sucrose in 450 mL of Purified Water, and filter the solution until clear. Dissolve the remainder of the Sucrose in the clear filtrate, and add Purified Water to make 1000 mL. Mix, and filter, if necessary, through a pledget of cotton.

Amantadine Hydrochloride Syrup

Amantadine Hydrochloride	10.0 g
Citric Acid	2.1 g
Artifical Raspberry Flavor	2 mL
Methyl paraben	2 g
Propyl paraben	0.5 g
Sorbitol Solution	to make 1000 mL

Dissolve the amantadine hydrochloride, the Citric Acid, flavor and preservatives in the sorbitol solution.

Syrups are useful for preparing liquid oral dosage forms from not only the pure drug, as described above, but also injections, capsules, or tablets if the pure drug is not readily available. If the drug and all the excipients in the preparation, such as injectables or capsules, are water-soluble, a solution should result if a syrup is prepared. On the other hand, if the preparation to be used contains water-insoluble ingredients, as is usually the case with tablets and some capsules, a suspension will be formed. Several of these preparations have been described in

the literature, in regard to their formulation, stability, and bioavailability. Some drugs that have been prepared from either the pure drug or an injectable form include midazolam, atropine, aminocaproic acid, terbutaline, procainamide, chloroquine, propranolol, and citrated caffeine.[54,55] If the appropriate salt of the drug is used, a solution will result.

When tablets are introduced to a syrup formulation, a suspension is often formed because there are water-insoluble ingredients used in tablet preparations. Examples of medicated syrups prepared from tablets are clonidine hydrochloride, cefuroxime axetil, famotidine, terbutaline sulfate, spironolactone, ranitidine, and rifampin.[56,57] The resulting suspensions should have a uniform distribution of particles so that a consistent dose is obtained. If the materials are not distributed uniformly, more appropriate suspending formulations should be considered, which are described later in the chapter. If pharmaceutical preparations contain a liquid that is insoluble in water, such as valproic acid or simethicone, to be incorporated into syrups, an emulsion will form and it will be difficult to prepare a uniform product.

Honeys

Honeys are thick liquid preparations somewhat allied to the syrups, differing in that honey, instead of syrup, is used as a base. They are unimportant as a class of preparations today, but at one time, before sugar was available and honey was the most common sweetening agent, they were used widely. Honey and sugar pastes are used to a small extent and have been discussed in the pharmaceutical literature for topical application for the treatment of certain types of ulcers and abscesses.[58]

Mucilages

Mucilages are thick, viscid, adhesive liquids, produced by dispersing gum in water, or by extracting the mucilaginous principles from vegetable substances with water. The mucilages all are prone to decomposition, showing appreciable decrease in viscosity on storage; they should never be made in quantities larger than can be used immediately, unless a preservative is added. Mucilages are used primarily to aid in suspending insoluble substances in liquids; their colloidal character and viscosity help prevent immediate sedimentation. Examples include sulfur in lotions, resin in mixtures, and oils in emulsions. Both tragacanth and acacia either are partially or completely insoluble in alcohol. Tragacanth is precipitated from solution by alcohol, but acacia, on the other hand, is soluble in diluted alcoholic solutions. A 60% solution of acacia may be prepared with 20% alcohol, and a 4% solution of acacia may be prepared even with 50% alcohol.

Recent research on mucilages includes the preparation of mucilage from plantain and the identification of its sugars, the preparation and suspending properties of cocoa gum, the preparation of glycerin ointments using flaxseed mucilage, and the consideration of various gums and mucilages obtained from several Indian plants for pharmaceutical purposes.

Several synthetic mucilage-like substances such as *polyvinyl alcohol, methylcellulose, carboxymethylcellulose,* and related substances are used at the appropriate concentration as mucilage substitutes, and emulsifying and suspending agents. Methylcellulose is used widely as a bulk laxative because it absorbs water and swells to a hydrogel in the intestine, in much the same manner as *psyllium* or *karaya* gum. Methylcellulose Oral Solution USP is a flavored solution of the agent. It may be prepared by adding slowly the methylcellulose to about one-third the amount of boiling water, with stirring, until it is thoroughly wetted. Cold water then should be added and the wetted material allowed to dissolve while stirring. The viscosity of the solution will depend upon the concentration and the specifications of the methylcellulose. The synthetic gums are non-glycogenetic and may be used in the preparation of diabetic syrups. Sodium carboxymethyl cellulose of a medium grade in water (0.25–1%) is generally suitable for preparing a suspending vehicle. Several formulas for such syrups, based on sodium carboxymethylcellulose, have been proposed.

Uniformly smooth mucilages sometimes are difficult to prepare because of the uneven wetting of the gums. In general, it is best to use fine gum particles and disperse them with agitation in a small quantity of 95% alcohol or in cold water (except for methylcellulose). The appropriate amount of water then can be added with constant stirring. A review of the chemistry and properties of acacia and other gums has been prepared.[59]

Jellies

Jellies are a class of gels in which the structural coherent matrix contains a high portion of liquid, usually water. They are similar to mucilages, in that they may be prepared from similar gums, but they differ from the latter in having a jelly-like consistency. A whole gum of the best quality, rather than a powdered gum, is desirable to obtain a clear preparation of uniform consistency. Although the specific thickening agent in the USP jellies is not indicated, reference usually is made in the monograph to a water-soluble, sterile, viscous base. These preparations also may be formulated with water from acacia, chondrus, gelatin, carboxymethylcellulose, hydroxyethylcellulose, and similar substances.

Jellies are used as lubricants for surgical gloves, catheters, and rectal thermometers. Lidocaine Hydrochloride Jelly USP is used as a topical anesthetic. Therapeutic vaginal jellies are available and certain jelly-like preparations are used for contraceptive purposes, which often contain surface-active agents to enhance the spermatocidal properties of the jelly. Aromatics, such as methyl salicylate and eucalyptol, often are added to give the preparation a desirable odor.

Jellies are prone to microbial contamination and therefore contain preservatives; for example, methyl *p*-hydroxybenzoate is used as a preservative in a base for medicated jellies. One base contains sodium alginate, glycerin, calcium gluconate, and water. The calcium ions cause a cross-linking with sodium alginate to form a gel of firmer consistency. A discussion of gels is provided later in the chapter.

NONAQUEOUS SOLUTIONS

It is difficult to evaluate fairly the importance of nonaqueous solvents in pharmaceutical processes. That they are important in the manufacture of pharmaceuticals is an understatement. However, pharmaceutical preparations, and, in particular, those intended for internal use, rarely contain more than minor quantities of the organic solvents that are common to the manufacturing or analytical operation. Products of commerce for internal use may contain solvents such as ethanol, glycerin, propylene glycol, certain oils, and liquid paraffin. Preparations intended for external use may contain solvents in addition to those just mentioned, namely isopropyl alcohol, polyethylene glycols, various ethers, and certain esters.

Although the lines between aqueous and nonaqueous preparations tend to blur in those cases where the solvent is water-soluble, it is possible to categorize a number of products as nonaqueous. This section is, therefore, devoted to groups of non-

aqueous solutions: the alcoholic or hydroalcoholic solutions (eg, elixirs and spirits), ethereal solutions (eg, collodions), glycerin solutions (eg, glycerins), oleaginous solutions (eg, liniments, oleovitamins, and toothache drops), inhalations, and inhalants.

Although the above list is limited, a wide variety of solvents are used in various pharmaceutical preparations. Solvents such as glycerol formal, dimethylacetamide, and glycerol dimethylketal have been suggested for some products produced by the industry. However, the toxicity of many of these solvents is not well established and, for this reason, careful clinical studies should be carried out on the formulated product before it is released to the marketplace. It is essential that the toxicity of solvents be tested appropriately and approved to avoid problems; for example, lives were lost in 1937 when diethylene glycol was used in an elixir of sulfanilamide. The result of this tragedy was the 1938 Federal Food, Drug, and Cosmetic Act, which required that products be tested for both safety and effectiveness.

COLLODIONS

Collodions are liquid preparations containing pyroxylin, a partially nitrated cellulose, in a mixture of ethyl ether and ethanol. They are applied to the skin by means of a soft brush or other suitable applicator and, when the ether and ethanol have evaporated, leave a film of pyroxylin on the surface. Salicylic Acid Collodion USP, contains 10% *w/v* of salicylic acid in Flexible Collodion USP and is used as a keratolytic agent in the treatment of corns and warts. Collodion USP and Flexible Collodion USP are water-repellent protectives for minor cuts, scratches, and chigger bites. Collodion is made flexible by the addition of castor oil and camphor. Collodion has been used to reduce or eliminate the side effects of fluorouracil treatment of solar keratoses.[60] Vehicles other than flexible collodion, such as a polyacrylic base, have been used to incorporate salicylic acid for the treatment of warts with less irritation.

ELIXIRS

Elixirs are clear, pleasantly flavored, sweetened hydroalcoholic liquids intended for oral use. The main ingredients in elixirs are ethanol and water but glycerin, sorbitol, propylene glycol, flavoring agents, preservatives, and syrups often are used in the preparation of the final product. The solvents are often used to increase the solubility of the drug substance in the dosage form. Elixirs are more fluid than syrups, due to the use of less viscous ingredients such as alcohol and the minimal use of viscosity-improving agents such as sucrose. They are used as flavors and vehicles such as Aromatic Elixir USP for drug substances; when such substances are incorporated into the specified solvents, they are classified as medicated elixirs, such as Dexamethasone Elixir USP and Phenobarbital Elixir USP.

The distinction between some of the medicated syrups and elixirs is not always clear. For example, Ephedrine Sulfate Syrup USP contains between 20 and 40 mL of alcohol in 1000 mL of product. Definitions are sometimes inconsistent and, in some instances, not too important with respect to the naming of the articles of commerce. To be designated as an elixir, however, the solution must contain alcohol. The alcoholic content will vary greatly, from elixirs containing only a small quantity to those that contain a considerable portion as a necessary aid to solubility. For example, Aromatic Elixir USP contains 21% to 23% alcohol; Compound Benzaldehyde Elixir USP, on the other hand, contains 3% to 5%.

Elixirs also may contain glycerin and syrup. These may be added to increase the solubility of the medicinal agent, for sweetening purposes, or to decrease the pharmacological effects of the alcohol. Some elixirs contain propylene glycol. Claims have been made for this solvent as a satisfactory substitute for both glycerin and alcohol.

Although alcohol is an excellent solvent for some drugs, it does accentuate the saline taste of bromides and similar salts. It often is desirable, therefore, to substitute some other solvent that is more effective in masking such tastes for part of the alcohol in the formula. In general, if taste is a consideration, the formulator is more prone to use a syrup rather than a hydroalcoholic vehicle.

Because only relatively small quantities of ingredients have to be dissolved, elixirs are more readily prepared and manufactured than syrups, which frequently contain considerable amounts of sugar. An elixir may contain both water- and alcohol-soluble ingredients. If such is the case, the following procedure is indicated:

> Dissolve the water-soluble ingredients in part of the water. Add and solubilize the sucrose in the aqueous solution. Prepare an alcoholic solution containing the other ingredients. Add the aqueous phase to the alcoholic solution, filter, and make to volume with water.

Sucrose increases viscosity and decreases the solubilizing properties of water and so must be added after the primary solution has been effected. A high alcoholic content is maintained during preparation by adding the aqueous phase to the alcoholic solution. Elixirs always should be brilliantly clear. They may be strained or filtered and, if necessary, subjected to the clarifying action of purified talc or siliceous earth.

Elixirs, and many other liquid preparations intended for internal use, such as the diabetic syrups thickened with sodium carboxymethylcellulose or similar substances, contain saccharin, aspartame, acesulfame potassium, and other sweeteners. Cyclamates and saccharin have been banned in some countries as ingredients in manufactured products. Much research has been done to find a safe synthetic substitute for sucrose.

Research concerning the preparation of a dry elixir has been conducted by Kim and co-workers.[61] Dry Elixirs containing a nonsteroidal anti-inflammatory drug and ethanol were encapsulated in a dextrin. The dissolution rate constant of the drug from the microcapsules usually increased considerably compared to the drug alone, possibly due to the cosolvent ethanol. It is suggested that this type of dosage form may be useful to improve the solubility, dissolution rate, and bioavailability of the drug.

Because elixirs contain alcohol, incompatibilities of this solvent are an important consideration during formulation. Alcohol precipitates tragacanth, acacia, and agar from aqueous solutions. Similarly, it will precipitate many inorganic salts from similar solutions. The implication here is that such substances should be absent from the aqueous phase or present in such concentrations that there is no danger of precipitation on standing.

If an aqueous solution is added to an elixir, a partial precipitation of alcohol soluble ingredients may occur. This is due to the reduced alcoholic content of the final preparation. Usually, however, the alcoholic content of the mixture is not sufficiently decreased to cause separation. As vehicles for tinctures and fluidextracts, the elixirs generally cause a separation of extractive matter from these products due to a reduction of the alcoholic content. Many of the incompatibilities between elixirs, and the substances combined with them, are due to the chemical characteristics of the elixir per se, or of the ingredients in the final preparation. Thus, certain elixirs are acid in reaction while others may be alkaline and will, therefore, behave accordingly.

Some example formulations of medicated elixirs are as follows:

Phenobarbital Elixir

Phenobarbital	4.00 g
Propylene Glycol	50 mL
Alcohol	200 mL
Sorbitol Solution	600 mL
Saccharin Sodium	5.0 g
Flavor	qs
Purified Water, to make	1000 mL

Theophylline Elixir

Theophylline	5.3 g
Citric Acid	10.0 g
Syrup	132.0 mL
Glycerin	50.0 mL
Sorbitol Solution	324.0 mL
Alcohol	200.00 mL
Flavor	q.s
Purified Water, to make	1000.0 mL

GLYCERINS

Glycerins or glycerites are solutions or mixtures of medicinal substances in not less than 50% by weight of glycerin. Most of the glycerins are extremely viscous and some are of a jelly-like consistency. Few of them are used extensively. Glycerin is a valuable pharmaceutical solvent forming permanent and concentrated solutions not otherwise obtainable. Glycerin is used as the sole solvent for the preparation of Antipyrine and Benzocaine Otic Solution USP. Glycerins are hygroscopic and should be stored in tightly closed containers.

INHALATIONS AND INHALANTS

Inhalation preparations are so used or designed that the drug is carried into the respiratory tree of the patient. The vapor or mist reaches the affected area and gives prompt relief from the symptoms of bronchial and nasal congestion. The USP defines Inhalations in the following way:

> "Inhalations are drugs or solutions or suspensions of one or more drug substances administered to the nasal or oral respiratory route for local or systemic effect. Solutions of drug substances in sterile water for inhalation or in sodium chloride inhalation solution may be nebulized by the use of inert gases. Nebulizers are suitable for the administration of inhalation solutions only if they give droplets sufficiently fine and uniform in size so that the mist reaches the bronchioles. Nebulized solutions may be breathed directly from the nebulizer, or the nebulizer may be attached to a plastic face mask, tent or intermittent positive pressure breathing (IPPB) machine."

Another group of products, also known as metered-dose inhalers (MDIs) are propellant-driven drug suspensions or solutions in liquefied gas propellant (chlorofluorocarbons and hydrofluoroalkanes) with or without a cosolvent and are intended for delivering metered doses of the drug to the respiratory tract. An MDI contains multiple doses, often exceeding several hundred. The most common single-dose volumes delivered are from 25 to 100 μL (also expressed as mg) per actuation. Examples of MDIs containing drug solutions are Epinephrine Inhalation Aerosol, USP and Isoproterenol Hydrochloride and Phenylephrine Bitartrate Inhalation Aerosol, respectively. Both the solubility and stability of the drug in the propellant mixture must be investigated during formulation development. Ethanol is commonly used as a cosolvent hydrofluoroalkane propellants, and was reported to significantly increase the solubility of steroids.[62]

As stated in the USP, particle size is of major importance in the administration of this type of preparation. The various mechanical devices that are used in conjunction with inhalations are described in Chapter 50 (*Aerosols*). It has been reported that the optimum particle size for penetration into the pulmonary cavity is of the order of 0.5 to 7.0 μm.[63] Fine mists are produced by pressurized aerosols and hence possess basic advantages over the older nebulizers; in addition, metered aerosols deliver more uniform doses. A number of inhalations are described in the USP.

The USP defines "inhalants" as follows:

> "A special class of inhalations termed "inhalants" consists of drugs or combinations of drugs that, by virtue of their high vapor pressure, can be carried by an air current into the nasal passage where they exert their effect. The container from which the inhalant is administered is known as an inhaler."

Amyl nitrate USP and Propylhexedrine Inhalant USP are two examples. Amyl nitrite is a clear, yellowish, volatile liquid that acts as a vasodilator when inhaled. The drug is prepared in sealed glass vials that are covered with a protective gauze cloth. Upon use, the glass vial is broken in the fingertips and the cloth soaks up the liquid which is then inhaled. The vials generally contain 0.3 mL of the drug substance. The effects of the drug are rapid and are used in the treatment of anginal pain.

Propylhexedrine is the active ingredient in the widely used Benzedrex Inhaler. Propylhexedrine is a liquid, vasoconstrictor agent that volatilizes slowly at room temperature. This quality enables it to be effectively used as an inhalant. The official inhalant consists of cylindrical rolls of suitable fibrous material impregnated with propylhexedrine, usually aromatized to mask its amine-like odor, and contained in a suitable inhaler. The vapor of the drug is inhaled into the nostrils when needed to relieve nasal congestion due to colds and hay fever. It may also be employed to relieve ear block and the pressure pain in air travelers. Each plastic tube of the commercial product contains 250 mg of propylhexedrine with aromatics. The containers should be tightly closed after each opening to prevent loss of the drug vapors.

LINIMENTS

Liniments are alcoholic or oil-based solutions or emulsions containing therapeutic agents intended for external application. These preparations may be liquids or semisolids that are rubbed onto the affected area; because of this, they were once called *embrocations*.

Liniments usually are applied with friction and rubbing of the skin, the oil or soap base providing for ease of application and massage. Alcoholic liniments are used generally for their rubefacient, counterirritant, mildly astringent, and penetrating effects. Such liniments penetrate the skin more readily than do those with an oil base. The oily liniments, therefore, are milder in their action but are more useful when massage is required. Depending on their ingredients, such liniments may function solely as protective coatings. Liniments should not be applied to skin that is bruised or broken.

Other liniments contain antipruritics, astringents, emollients, or analgesics and are classified on the basis of their active ingredient. Dermatologists prescribe products of this type but only those containing the rubefacients are advertised extensively and used by consumers for treating minor muscular aches and pains. It is essential that these applications be marked clearly "For External Use Only". Liniments containing a capsaicin are being investigated for treatment of pruritus.[64]

OLEOVITAMINS

Oleovitamins are fish liver oils diluted with edible vegetable oil or solutions of the indicated vitamins or vitamin concentrates (usually vitamin A and D) in fish liver oil. The definition is broad enough to include a wide variety of marketed products.

In oleovitamin A and D, USP, vitamin D may be present as ergocalciferol or cholecalciferol obtained by the activation of ergosterol or 7-dehydrocholesterol, or may be obtained from natural sources. Synthetic vitamin A, or a concentrate, may be used to prepare oleovitamin A. The starting material for the concentrate is fish liver oil, the active ingredient being isolated by molecular distillation or by a saponification and extraction procedure. These vitamins are unstable in the presence of rancid oils; therefore, these preparations should be stored in small, tight containers, preferably under vacuum or under an atmosphere of an inert gas, protected from light and air.

SPIRITS

Spirits, sometimes known as essences, are alcoholic or hydroalcoholic solutions of volatile substances. Like the aromatic waters, the active ingredient in the spirit may be a solid, liquid, or gas. The genealogical tree for this class of preparations begins with a distinguished pair of products, Brandy (*Spiritus Vini Vitis*) and Whisky (*Spiritus Frumenti*), and ends with a wide variety of products that comply with the definition given above. Physicians have debated the therapeutic value of the former products, and these are no longer compendial.

Generally, the alcohol concentration of spirits is rather high, usually over 60%. Because of the greater solubility of aromatic or volatile substances in alcohol than in water, spirits can contain a greater concentration of these materials than the corresponding aromatic waters. When mixed with water or with an aqueous preparation, the volatile substances present in spirits generally separate from solution and form a milky preparation. Salts may be precipitated from their aqueous solutions by the addition of spirits due to their lesser solubility in alcoholic liquids. Some spirits show incompatibilities characteristic of the ingredients they contain. For example, Aromatic Ammonia Spirit cannot be mixed with aqueous preparations containing alkaloids (eg, codeine phosphate). An acid–base reaction (ammonia-phosphate) occurs, and if the alcohol content of the final mixture is too low, codeine will precipitate. Spirits should be stored in tight, light-resistant containers and in a cool place. This tends to prevent evaporation and volatilization of either the alcohol or the active principle and to limit oxidative changes.

Spirits may be used pharmaceutically as flavoring agents and medicinally for the therapeutic value of the aromatic solute. As flavoring agents they are used to impart the flavor of their solute to other pharmaceutical preparations. For medicinal purposes, spirits may be taken orally, applied externally, or used by inhalation, depending upon the particular preparation. When taken orally, they are generally mixed with a portion of water to reduce the pungency of the spirit. Depending on the materials utilized, spirits may be prepared by simple solution, solution by maceration, or distillation. The spirits still listed in the USP/NF are aromatic ammonia spirit, camphor spirit, compound orange spirit, and peppermint spirit.

EMULSIONS

An emulsion is a two-phase system prepared by combining two immiscible liquids, in which small globules of one liquid are dispersed uniformly throughout the other liquid. The liquid that is dispersed into small droplets is called the dispersed, internal, or discontinuous phase. The other liquid is the dispersion medium, external phase, or continuous phase. Where oil is the dispersed phase and an aqueous solution is the continuous phase, the system is designated as an oil-in-water (O/W) emulsion. Conversely, where water or an aqueous solution is the dispersed phase and oil or oleaginous material is the continuous phase, the system is designated as a water-in-oil (W/O) emulsion. Emulsions may be employed orally, topically, or parenterally depending upon on the formulation ingredients and the intended application. Many pharmaceutical emulsions may not be classified as such because they are described by another pharmaceutical category more appropriately. For instance, certain lotions, liniments, creams, ointments, and commercial vitamin drops may be emulsions but may be preferentially referred to in these terms.

Emulsions possess a number of important advantages over other liquid forms:

- In an emulsion, poorly water-soluble drugs may be easily incorporated with improved dissolution rates and bioavailability.
- The unpleasant taste or odor of oils can be masked partially or wholly, by emulsification.
- The absorption rate and permeation of medicaments are can be controlled.
- Absorption may be enhanced by the diminished size of the internal phase.
- Formulation and technology for organ targeted delivery is available.
- Various particle sizes of the internal phase can be achieved by preparation technique, from micro emulsions (micron-sized particles) to nanoparticles.
- Water is an inexpensive diluent and a good solvent for the many drugs and flavors that are incorporated into an emulsion.

It is possible to prepare emulsions that are basically nonaqueous. For example, investigations of the emulsifying effects of anionic and cationic surfactants on the nonaqueous immiscible system, glycerin and olive oil, have shown that certain amines and three cationic agents produced stable emulsions. Although the USP definition is broad enough to encompass nonaqueous systems, emphasis is placed on those emulsions that contain water, as they are by far the most common in pharmacy.

When it is necessary to administer oils by the oral route, patient acceptance is enhanced when the oil is prepared in emulsion form. Thus, mineral oil (a laxative), valproic acid (an anticonvulsant), oil-soluble vitamins, vegetable oils, and preparations for enteral feeding are formulated frequently in an O/W emulsion form to enhance their palatability.

The bioavailability of oils for absorption may be enhanced when the oil is in the form of small droplets. Furthermore, the absorption of some drugs, such as griseofulvin may be enhanced when they are prepared in the form of an O/W emulsion.[65] Emulsion formulations of drugs such as erythromycin and physostigmine salicylate have been considered, in order to improve their stability.[66,67] Finally, the greatest use of emulsions is for topical preparations. Both O/W and W/O emulsions are used widely, depending upon the effect desired. Emulsion bases of the W/O type tend to be more occlusive and emollient than O/W emulsion bases, which tend to be removed more easily by water. The effects of viscosity, surface tension, solubility, particle size, complexation, and excipients on the bioavailability of emulsions have been reported.[68]

Although this section on emulsions focuses primarily on those for oral use and to a lesser degree those for topical application, it should be noted that there are a number of emulsions used parenterally that are described in specialized textbooks on this topic. For example, emulsions of the O/W type are used for intravenous feeding of lipid nutrients. These are used to provide a source of calories and essential fatty acids. These emulsions must meet exacting standards in regard to particle size, safety, and stability. Examples of commercial products include Diprivan Injectable Emulsion (*AstraZeneca*), EMLA Cream (*AstraZeneca*), Renova 0.02% Cream (*OrthoNeutrogena*), Bactroban Cream (*GlaxoSmithKline*), Cordran Lotion (*Watson*), Differin Cream (*Galderma*) and Renova 0.05% Cream (*OrthoNeutrogena*). Other specialized uses of emulsions include radiopaque emulsions that are used as diagnostic agents for x-ray examination.

THEORIES OF EMULSIFICATION

Several theories have been proposed to explain how emulsifying agents act in producing the multi-phase dispersion and in maintaining the stability of the resulting emulsion. Some of these theories apply to specific types of emulsifying agents and to certain conditions, such as pH of the system and the physicochemical nature and proportions of the internal and external phases). The most prevalent theories are the *surface-tension theory*, the *oriented-wedge theory*, and the *interfacial film theory*.

Liquids assume a shape to minimize their surface area, which is spherical for a small drop. In a spherical drop of liquid, there are attractive forces between the molecules, resisting distortion into a less spherical form. If two or more drops of the same liquid come into contact with one another, it is more thermodynamically favorable for them to coalesce, making a larger drop with a decreased surface area compared to the total surface area of the individual drops. The tendency of liquids to minimize their surface area can be measured quantitatively, and when the liquid is surrounded by air, the measurement is called the surface tension.

When a liquid is in contact with another liquid in which it is insoluble and immiscible, the force causing each liquid to resist breaking up into smaller particles is called interfacial tension. Surface active agents, or surfactants, are substances that reduce the resistance of a droplet to form smaller droplets. Surfactants are also called emulsifiers and wetting agents. According to the surface tension theory of emulsification, the use of surfactants results in a reduction in the interfacial tension of the two immiscible liquids, reducing the repellent force between the liquids and diminishing each liquid's attraction for its own molecules. Thus, surfactants enable large globules to break into smaller ones, and prevent small globules from coalescing into larger ones.

The oriented wedge theory proposes that the surfactant forms monomolecular layers around the droplets of the internal phase of the emulsion. The theory is based on the assumption that emulsifying agents orient themselves about and within a liquid relative to their solubility in that particular liquid. In a system containing two immiscible liquids, the emulsifying agent is preferentially soluble in one of the two liquids and becomes more embedded with that phase relative to the other. Many surfactants have a hydrophilic or water loving portion and a hydrophobic or water hating portion (but usually lipophilic or oil-loving), and the molecules will position or orient themselves into each phase. Depending upon the shape and size of the molecules, their solubility characteristics, and thus their orientation, the wedge shape theory proposes that emulsifiers will surround either oil globules or water globules.

Generally an emulsifying agent having a greater hydrophilic character than hydrophobic character will promote oil in water emulsions. On the other hand, water in oil emulsions result with the use of an emulsifyer that is more hydrophobic than hydrophilic. Putting it another way, the phase in which the emulsifying agent is more soluble will become the continuous or external phase of the emulsion. Although this theory does not represent a completely accurate depiction of the molecular arrangement of the emulsifier molecules, the concept that water soluble emulsifiers generally form oil in water emulsions is important.

The interfacial film theory proposes that the emulsifier forms an interface between the oil and water, surrounding the droplets of the internal phase as a thin layer of film adsorbed on the surface of the drops. The film prevents the contact and coalescing of the dispersed phase; the tougher and more pliable the film, the greater the stability of the emulsion. Naturally, the surfactant must be available to coat the entire surface of each drop of internal phase. Similar to the oriented wedge theory, the formation of an oil in water or a water in oil emulsion depends upon the degree of solubility of the emulsifier in the two phases, with water soluble agents encouraging oil in water emulsions and oil-soluble emulsifiers promoting water in oil emulsions.

In reality, none of the emulsion theories can individually explain the mechanism by which the many and varied emulsifiers promote emulsion formation and stability. It is more than likely that even within a given emulsion system, more than one of the theories of emulsification are applicable. For instance, reducing the interfacial tension is critical during initial formation of an emulsion, but the formation of a protective wedge of molecules or film of emulsifier is equally important for continued emulsion stability. Undoubtedly, many emulsifiers are capable of both tasks.

EMULSION FORMULATION INGREDIENTS

The first step in preparation of an emulsion is the selection of the emulsifier. The emulsifier must be compatible with the formulation ingredients and the active pharmaceutical ingredient. It should be stable, nontoxic, and promote emulsification to maintain the stability of the emulsion for the intended shelf life of the product. The selection of the oil phase for oral preparations depends upon the purpose of the product. For example, mineral oil is used as a laxative and corn oil is used for its nutrient properties. Vegetable oils can be used to dissolve or suspend pharmaceuticals such as oil-soluble vitamins.

Emulsions are thermodynamically unstable because of the large increase in surface energy that results from the combination of interfacial tension and large surface area of the dispersed phase and the different densities of the two phases. Thus, emulsions tend to cream—the less dense phase rises and the more dense phase falls in the container. Subsequently, the droplets can coalesce with a considerable reduction in surface free energy. Consequently, considerable research has been conducted on their preparation and stabilization. To prepare suitable emulsions that remain stable, a number of excipients are used in their preparation.

Emulsifiers often have a hydrophilic portion and a lipophilic portion with one or the other being more or less predominant. Griffin devised a method whereby emulsifying or surface-active agents may be categorized on the basis of their *hydrophilic-lipophilic balance or HLB value*. By this method, each agent is assigned an HLB value or number which is indicative of the substance's polarity, which may vary from 40 for sodium lauryl sulfate to 1 for oleic acid. Although the numbers have been assigned up to about 40, the usual range is between 1 and 20. Examples of HLB values for common emulsifiers used in pharmaceutical applications are listed in Table 39-6. HLB values have also been useful in describing the functional properties of materials. For example, HLB values from 1 to 3 typically exhibit anti foaming properties, values from 7 to 10 exhibit good wetting properties, values from 13 to 20 act as solubilizers, and values from 13 to 15 function as

Table 39-6. HLB Values of Common Emulsifiers Used in Pharmaceutical Systems

AGENT	HLB	CLASS
Oleic Acid	1.0	Anionic
Ethylene glycol distearate	1.5	Nonionic
Sorbitan tristearate (Span 65)	2.1	Nonionic
Glyceryl monooleate	3.3	Nonionic
Propylene glycol monostearate	3.4	Nonionic
Glyceryl monostearate	3.8	Nonionic
Sorbitan monooleate (Span 80)	4.3	Nonionic
Sorbitan monostearate (Span 60)	4.7	Nonionic
Diethylene glycol monolaurate	6.1	Nonionic
Sorbitan monopalmitate (Span 40)	6.7	Nonionic
Acacia	8.0	Anionic
Polyoxyethylene lauryl ether (Brij 30)	9.7	Nonionic
Polyoxyethylene monostearate (Myrj 45)	11.1	Nonionic
Triethanolamine oleate	12.0	Anionic
Polyoxyethylene sorbitan monostearate (Tween 60)	14.9	Nonionic
Polyoxyethylene sorbitan monooleate (Tween 80)	15.0	Nonionic
Polyoxyethylene sorbitan monolaurate (Tween 20)	16.7	Nonionic
Pluronic F 68	17.0	Nonionic
Sodium oleate	18.0	Anionic
Potassium oleate	20.0	Anionic
Cetrimonium Bromide	23.3	Cationic
Cetylpyridinium chloride	26.0	Cationic
Poloxamer 188	29.0	Nonionic
Sodium lauryl sulfate	40.0	Anionic

detergents. Oil in water emulsions typically have a weighted HLB value ranging from 8 to 16 while water in oil emulsions have weighted HLB values ranging from 3 to 8.

Materials that are highly polar or hydrophilic have been assigned higher numbers than materials that are less polar and more lipophilic. Generally, lipophilic surfactants have an HLB value from 0 to 10 and are known for their antifoaming, water in oil emulsifying or wetting properties. Hydrophilic surfactants have HLB values ranging from 10 to 20 and form oil in water emulsions. The HLB system also assigns values to oils and oil like substances. In using the HLB concept in the preparation of an emulsion, one selects emulsifying agents having the same or nearly the same HLB value as the oleaginous phase of the intended emulsion. When needed, two or more emulsifiers may be combined to achieve the proper HLB value.

The ionic nature of a surfactant is an important consideration when selecting a surfactant for an emulsion. Nonionic surfactants are effective over pH range 3 to 10; cationic surfactants are effective over pH range 3 to 7; and, anionic surfactants require a pH of greater than 8.[69]

Emulsifying agents may be divided into three classes: *natural emulsifying agents*, *finely divided solids*, and *synthetic emulsifying agents*.

1. **Natural Emulsifying Agents** are substances derived from vegetable sources and include acacia, tragacanth, alginates, chondrus, xanthan, and pectin. These materials form hydrophilic colloids when added to water and generally produce o/w emulsions. Although their surface activity is low, these materials achieve their emulsifying power by increasing the viscosity of the aqueous phase. Examples of emulsifying agents derived from animal sources include gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin. Because of the widely different chemical constitution of these compounds, they have a variety of uses, depending upon the specific compound, in both oral and topical preparations. All naturally occurring agents show variations in their emulsifying properties from batch to batch.
2. **Finely Divided Solids** are the colloidal clays: bentonite (aluminum silicate) and Veegum (magnesium aluminum silicate). These compounds are good emulsifiers and tend to be absorbed at the interface, increase the viscosity in the aqueous phase, and are often used in conjunction with a surfactant to prepare O/W emulsions. However, both O/W and W/O preparations can be prepared by adding the clay to the external phase. They are used frequently for external purposes such as a lotion or cream.
3. **Synthetic Emulsifying Agents** are very effective at lowering the interfacial tension between the oil and water phases because the molecules possess both hydrophilic and hydrophobic properties. These emulsifying agents are available in different ionic types: anionic, such as sodium dodecyl sulfate; cationic, such as benzalkonium chloride; nonionic, such as polyethylene glycol 400 monostearate; and ampholytic, such as long-chain amino acid derivatives. In addition to the emulsifying agents, *viscosity agents* are employed, namely the hydrophilic colloids such as naturally occurring gums, noted above, and partially synthetic polymers such as cellulose derivatives (eg, methylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose) or a number of synthetic polymers that may be used, such as carbomer polymers. These materials are hydrophilic in nature and dissolve or disperse in water to give viscous solutions and function as emulsion stabilizers.

Other functional excipients are often utilized in emulsions. High molecular weight alcohols such as stearyl alcohol, cetyl alcohol, and glyceryl monostearate are employed primarily as thickening agents and stabilizers for o/w emulsions of certain lotions and ointments used externally. Cholesterol and cholesterol derivatives may also be employed in externally used emulsions and to promote w/o emulsions.

The aqueous phase of the emulsion favors the growth of microorganisms; because of this, a preservative usually is added to the product. Some of the preservatives that have been used include chlorocresol, chlorobutanol, mercurial preparations, salicylic acid, the esters of *p*-hydroxybenzoic acid, benzoic acid, sodium benzoate, or sorbic acid. The preservative should be selected with regard for the ultimate use of the preparation and possible incompatibilities between the preservative and the ingredients in the emulsion (eg, binding between the surfactant and the preservative). Low pH values of 5 to 6 and low concentrations of water are characteristics also likely to inhibit microbiological growth in emulsions.

Emulsions consist of an oil or lipid phase and an aqueous phase, thus the preservative may diffuse from the aqueous phase into the oil phase. It is in the aqueous phase that microorganisms tend to grow. As a result, water-soluble preservatives are more effective because the concentration of the unbound preservative in the aqueous phase assumes a great deal of importance in inhibiting the microbial growth. Esters of *p*-hydroxybenzoic acid appear to be the most satisfactory preservatives for emulsions.

Many mathematical models have been used to determine the availability of preservatives in emulsified systems. One model takes into account the O/W partition coefficient of the preservative, interaction of the preservative with the surfactant, interfacial tension and membrane permeability. However, because of the number of factors that reduce the effectiveness of the preservative, a final microbiological evaluation of the emulsion must be performed.

While emphasis concerning preservation of emulsions deals with the aqueous phase, microorganisms can reside also in the lipid phase. Consequently, it has been recommended that pairs of preservatives be used to ensure adequate concentration in both phases. Esters of *p*-hydroxybenzoic acid can be used to ensure appropriate concentrations in both phases because of their difference in oil and water solubilities.

The oxidative decomposition of certain excipients, the oil phase, and some pharmaceuticals is possible in emulsions, not only because of the usual amount of air dissolved in the liquid and the possible incorporation of air during the preparation of the product, but also the large interfacial area between the oil and water phase. The selection of the appropriate antioxidant briefly described at the beginning of the chapter depends on factors such as stability, compatibility with the ingredients of the emulsion, toxicity, effectiveness in emulsions, odor, taste, and distribution between the two phases.

PREPARATION OF EMULSIONS

After the purpose of the emulsions has been determined (eg, oral or topical use), the type of emulsions (O/W or W/O) and appropriate ingredients selected, and the theory of emulsification considered, then experimental formulations may be prepared. One method is suggested by Griffin[70]:

1. Group the ingredients on the basis of their solubilities in the aqueous and nonaqueous phases.
2. Determine the type of emulsion required and calculate an approximate HLB value.
3. Blend a low HLB emulsifier and a high HLB emulsifier to the calculated value. For experimental formulations, use a higher concentration of emulsifier (eg, 10% to 30% of the oil phase) than that required to produce a satisfactory product. Emulsifiers should, in general, be stable chemically, nontoxic, and suitably low in color, odor, and taste. The emulsifier is selected on the basis of these characteristics, as well as the type of equipment being used to blend the ingredients and the stability characteristics of the final product. Emulsions should not coalesce at room temperature, or when frozen and thawed repeatedly, or at elevated temperatures of up to 50°C. Mechanical energy input varies with the type of equipment used to prepare the emulsion. The more the energy input, the less the demand on the emulsifier. Both process and formulation variables can affect the stability of an emulsion.
4. Dissolve the oil-soluble ingredients and the emulsifiers in the oil. Heat, if necessary, to approximately 5° to 10°C over the melting point of the highest melting ingredient or to a maximum temperature of 70° to 80°C.
5. Dissolve the water-soluble ingredients (except acids and salts) in a sufficient quantity of water.
6. Heat the aqueous phase to a temperature that is 3° to 5°C higher than that of the oil phase.

7. Add the aqueous phase to the oily phase with suitable agitation.
8. If acids or salts are employed, dissolve them in water and add the solution to the cold emulsion.
9. Examine the emulsion and make adjustments in the formulation if the product is unstable. It may be necessary to add more emulsifier, to change to an emulsifier with a slightly higher or lower HLB value, or to use an emulsifier with different chemical characteristics.

The technique of emulsification of pharmaceutical preparations has been described by Nielloud and Marti-Mestres.[71] The preparation of an emulsion requires work to reduce the internal phase into small droplets and disperse them throughout the external phase. This can be accomplished by a mortar and pestle or a high-speed emulsifier. The addition of emulsifying agents not only reduces this work but also stabilizes the final emulsion.

Emulsions are prepared by four principal methods.

ADDITION OF INTERNAL PHASE TO EXTERNAL PHASE—This is usually the most satisfactory method for preparing emulsions as there is always an excess of the external phase present that promotes the type of emulsion desired. If the external phase is water and the internal phase is oil, the water-soluble substances are dissolved in the water and the oil-soluble substances mixed thoroughly in the oil. The oil mixture is added in portions to the aqueous preparation with agitation. To give a better shearing action during the preparation, sometimes all of the water is not mixed with the emulsifying agent until the primary emulsion with the oil is formed; subsequently, the remainder of the water is added. An example using gelatin Type A is given below.

ADDITION OF THE EXTERNAL PHASE TO THE INTERNAL PHASE, THE DRY GUM TECHNIQUE—Using an O/W emulsion as an example, the addition of the water (external phase) to the oil (internal phase) will promote the formation of a W/O emulsion due to the preponderance of the oil phase. After further addition of the water, phase inversion to an O/W emulsion should take place. This method is especially useful and successful when hydrophilic agents such as acacia, tragacanth, or methylcellulose are first mixed with the oil, effecting dispersion without wetting. Water is added, and eventually an O/W emulsion is formed. This "dry gum" technique is a rapid method for preparing small quantities of emulsion. The ratio 4 parts of oil, 2 parts of water and 1 part of gum provides maximum shearing action on the oil globules in the mortar. The emulsion then can be diluted and triturated with water to the appropriate concentration. The preparation of Mineral Oil Emulsion described below is an example.

MIXING BOTH PHASES AFTER HEATING—This method is used when waxes or other substances that require melting are used. The oil-soluble emulsifying agents, oils, and waxes are melted and mixed thoroughly. The water-soluble ingredients dissolved in the water are warmed to a temperature slightly higher than the oil phase. The two phases then are mixed and stirred until cold. For convenience, but not necessity, the aqueous solution is added to the oil mixture. This method frequently is used in the preparation of ointments and creams. An example of an oral preparation containing a poorly soluble drug is given below.

ALTERNATE ADDITION OF THE TWO PHASES TO THE EMULSIFYING AGENT—A portion of the oil, if an O/W emulsion is being prepared, is added to all of the oil-soluble emulsifying agents with mixing, then an equal quantity of water containing all the water-soluble emulsifying agents is added with stirring until the emulsion is formed. Further portions of the oil and water are added alternately until the final product is formed. The high concentration of the emulsifying agent in the original emulsion makes the initial emulsification more likely and the high viscosity provides effective shearing action leading to small droplets in the emulsion. This method often is used successfully with soaps.

Examples of some emulsions are given below.

Type A gelatin is prepared by acid-treated precursors and is used at a pH of about 3.2. It is incompatible with anionic emulsifying agents such as the vegetable gums. The following formula was recommended.

Type A Gelatin Emulsion

Gelatin (Type A)	8 g
Tartaric Acid	0.6 g
Flavor	q.s
Alcohol	60 mL
Oil	500 mL
Purified Water,	to make 1000 mL

Add the gelatin and the tartaric acid to about 300 mL of purified water, allow to stand for a few minutes, heat until the gelatin is dissolved, then raise the temperature to about 98°C and maintain this temperature for about 20 min. Cool to 50°C, add the flavor, the alcohol, and sufficient purified water to make 500 mL. Add the oil, agitate the mixture thoroughly, and pass it through a homogenizer or a colloid mill until the oil is dispersed completely and uniformly. This emulsion cannot be prepared by trituration or by the use of the usual stirring devices.

Type B gelatin is prepared from alkali-treated precursors and is used at a pH of about 8. It may be used with other anionic emulsifying agents but is incompatible with cationic types. If the emulsion contains 50% oil, 5 g of Type B gelatin, 2.5 g of sodium bicarbonate and sufficient tragacanth or agar should be incorporated into the aqueous phase to yield 1,000 mL of product of the required viscosity.

An emulsion that may be prepared by the mortar and pestle method is the following Mineral Oil Emulsion USP.

Mineral Oil Emulsion, USP

Mineral Oil	500 mL
Acacia, in very fine powder	125 g
Syrup	100 mL
Vanillin	40 mg
Alcohol	60 mL
Purified Water,	to make 1000 mL

The mineral oil and acacia are mixed in a dry Wedgwood mortar. Purified water (250 mL) is added and the mixture triturated vigorously until an emulsion is formed. A mixture of the syrup, 50 mL of purified water, and the vanillin dissolved in alcohol is added in divided portions with trituration; sufficient purified water is then added to the proper volume; the mixture is mixed well and homogenized.

An Oral Emulsion (O/W) Containing an Insoluble Drug[72]

Cottonseed Oil	460 g
Sulfadiazine	200 g
Sorbitan Monostearate	84 g
Polyoxyethylene 20 Sorbitan Monostearate	36 g
Sodium Benzoate	2 g
Sweetener	qs
Flavor Oil	qs
Purified Water	1000 g

Heat the first three ingredients to 50°C and pass through colloid mill. Add the next four ingredients at 50°C to the first three ingredients at 65°C and stir while cooling to 45°C. Add the flavor oil and continue to stir until room temperature is reached.

PROPERTIES AND STABILITY OF EMULSIONS

The type of emulsion (O/W or W/O) depends, to some extent, on the phase to volume ratio. The higher the fraction of one phase, the greater likelihood it will form the external phase. Thus, O/W emulsions are favored if water forms a greater fraction of the volume than the oil phase. However, it is possible for the internal phase of an emulsion to occupy up to 74% of the volume of the emulsion and still form a stable product.

The consistency of emulsions can be increased by increasing the viscosity of the continuous phase, increasing the fractional volume of the internal phase, reducing the particle size of the internal phase, increasing the proportion of the emulsifying agent, or adding hydrophobic emulsifying agents to the oil phase of the emulsion.

The physical stability of emulsions may be defined by a number of expressions. The first of these, which is called *creaming*, is the movement of the droplets either upward or downward, depending upon their density. This gives a product that is not homogenous and can lead to poor content uniformity. Generally, creaming is not a serious problem because a moderate amount of shaking will redisperse the droplets uniformly. The rate of creaming may be decreased by considering the theory of creaming using Stokes' law. This equation relates the rate of creaming to the size of the droplets, the difference in densities, and the viscosity of the external phase. Thus, the rate of creaming may be decreased by decreasing the size of the droplets and increasing the viscosity of the external phases, both of which were discussed above. Minimizing the difference between densities is more challenging due to a number of practical difficulties.

When the droplets aggregate, they come together and act as a single unit, but do not fuse. As a result of the larger size, they tend to cream faster and further provoke physical instability. Aggregation is to some extent reversible and may be controlled by choosing a somewhat different surfactant system and controlling the electrical potential of the droplets. Coalescence of an emulsion is the fusion of the droplets, leading to a decrease in their numbers and eventually the complete separation of the two phases, yielding an unsatisfactory product that should be reformulated.

General methods are available for testing and challenging the stability of emulsions including bulk changes, centrifugal and ultracentrifugal studies, dielectric measurement, surface area measurement, temperature cycling, preservative effectiveness, and accelerated motion studies. Low-shear rheological studies measuring viscoelasticity are suggested as the optimal method of stability testing.

MULTIPLE EMULSIONS

A recent innovation in emulsion technology is the development of multiple emulsions. The dispersed phase of these emulsions contains even smaller droplets that are miscible with the continuous phase. Thus, the multiple emulsion may be O/W/O, where the aqueous phase is between two oil phases, or W/O/W, where the internal and external aqueous phases are separated by an oil phase. In these systems both hydrophobic and hydrophilic emulsifiers are used, and both have an effect on the yield and stability.[73,74]

It appears that O/W/O emulsions are formed better by lipophilic, nonionic surfactants using acacia emulsified simple systems, whereas W/O/W multiple emulsions are formed better by nonionic surfactants in a two-stage emulsification procedure. A specific formulation for a W/O/W emulsion may be prepared by forming the primary (W/O) emulsion from isopropyl myristate (47.5%), sorbitan monooleate (2.5%), and distilled water to 100%. This primary emulsion (50%) is added to a polyoxyethylene sorbitan monooleate (2% *w/v*) solution in water.[74] Other formulations of multiple emulsions include carboxymethylcellulose sodium, microcrystalline cellulose, sorbitan monooleate, and sorbitan trioleate.

Although the technique of preparing these emulsions is more complicated, research indicates potential use of these emulsions for prolonged action, taste-masking, more effective dosage forms, improved stability, parenteral preparations, protection against the external environment, and enzyme entrapment. These emulsions also may be used to separate two incompatible hydrophilic substances in the inner and outer aqueous phases by the middle oil phase. Some drugs that have been investigated in these types of emulsions are vancomycin[75] and prednisolone.[124]

MICROEMULSIONS

The coarse pharmaceutical macroemulsions appear white and tend to separate on standing. Microemulsions are translucent or transparent, do not separate, and typically have a droplet diameter from 10 to 200 nanometers. The microemulsions are not always distinguishable from micellar solutions. Both O/W and W/O emulsions are possible, and one may be converted to the other by addition of more internal phase or by altering the type of emulsifier. As the internal phase is added, the emulsion will pass through a viscoelastic gel stage; with further addition, an emulsion of the opposite type will occur.

The most obvious benefit of microemulsions is their stability. Usually, the emulsifier should be 20% to 30% of the weight of the oil used. The W/O systems are prepared by blending the oil and emulsifier with a little heat, if required, and then adding the water. The order of mixing for O/W systems is more flexible. One of the simplest methods is to blend the oil and the emulsifier and pour this into water with a little stirring.

If the emulsifier has been selected properly, microemulsification will occur almost spontaneously, leading to a satisfactory and stable preparation. The details of various preparations and the relationship between microemulsions and micellar solutions have been reviewed by Bourrel.[77] Other authors suggest that the preparation of microemulsions is considerably more difficult than the preparation of coarse emulsions. Rosano and colleagues discuss the use of a primary surfactant adsorbed at the interface that influences the curvature of the dispersed phase.[78] The amount of surfactant required may be estimated from the surface area of the droplets and the cross-sectional area of the surfactant molecule. The authors propose the use of a co-surfactant to form a duplex film and the order of mixing is important.

PROCESSING EQUIPMENT FOR EMULSIONS

The preparation of emulsions requires a certain amount of energy to form the interface between the two phases, and additional work must be done to stir the system to overcome resistance to flow. In addition, heat often is supplied to the system to melt waxy solids and/or reduce viscosity. Consequently, the preparation of emulsions on a large scale requires considerable amounts of energy for heating and mixing. Careful consideration of these processes has led to the development of low energy emulsification equipment that uses an appropriate emulsification temperature and selective heating of the ingredients. This process, described by Lin, involves the preparation of an emulsion concentrate subsequently diluted with the external phase at room temperature.[79,80]

Because of the variety of oils used, emulsifier agents, phase to volume ratios, and the desired physical properties of the product, a wide selection of equipment is available for preparing emulsions, and the main classes of equipment are discussed below. Homogenization speed and time and rate of cooling may influence the viscosity of the product. Further information may be obtained from the *Bibliography*.

Special techniques and equipment in certain instances will produce superior emulsions, including rapid cooling, reduction in particle size, or ultrasonic devices. A wide selection of equipment for processing both emulsions and suspensions has been described.[71] A number of improvements have been made to make the various processes more effective and energy efficient.

The mortar and pestle may be used to prepare small quantities of an emulsion in the pharmacy or laboratory, and it is one of the simplest and least expensive methods. It may be used for most of the different techniques of preparing emulsions. Generally, the final particle size is considerably larger than is achieved by the equipment described below. In addition, it is necessary for the ingredients to have a certain viscosity prior to trituration to achieve a satisfactory shear. Satisfactory

emulsions of low viscosity ingredients and small volumes may be prepared using the appropriate equipment described below.

Agitators

Ordinary agitation or shaking may be used to prepare the emulsion. This method frequently is employed by the pharmacist, particularly in the emulsification of easily dispersed, low-viscosity oils. Under certain conditions, intermittent shaking is considerably more effective than ordinary continuous shaking. Continuous shaking tends to break up not only the phase to be dispersed but also the dispersion medium, thus impairing the ease of emulsification. Laboratory shaking devices may be used for small-scale production.

Mechanical Mixers

Emulsions may be prepared by using one of several mixers that are available. Propeller and impeller type mixers that have a propeller attached to a shaft driven by an electric motor are convenient and portable and can be used for both stirring and emulsification. This type operates best in mixtures that have low viscosity, that is, mixtures with a viscosity of glycerin or less. They are also useful for preparing emulsions. A turbine mixer has a number of blades that may be straight or curved, with or without a pitch, mounted on a shaft. The turbine tends to give a greater shear than propellers. The shear can be increased by using diffuser rings that are perforated and surround the turbine so that the liquid from the turbine must pass through holes. The turbines can be used for both low-viscosity mixtures and medium-viscosity liquids. The degree of stirring and shear by propeller or turbine mixers depends upon several factors, such as the speed of rotation, pattern of liquid flow, position in the container, and baffles in the container.

Production sized mixers include high-powered propeller, shaft stirrers immersed in a tank, or self-contained units with propeller and paddle systems. The latter usually are constructed so that the contents of the tank either may be heated or cooled during the production process. Baffles often are built into a tank to increase mixing efficiency. Examples of two production dispersion mixers are shown in Figures 39-1 and 39-2.

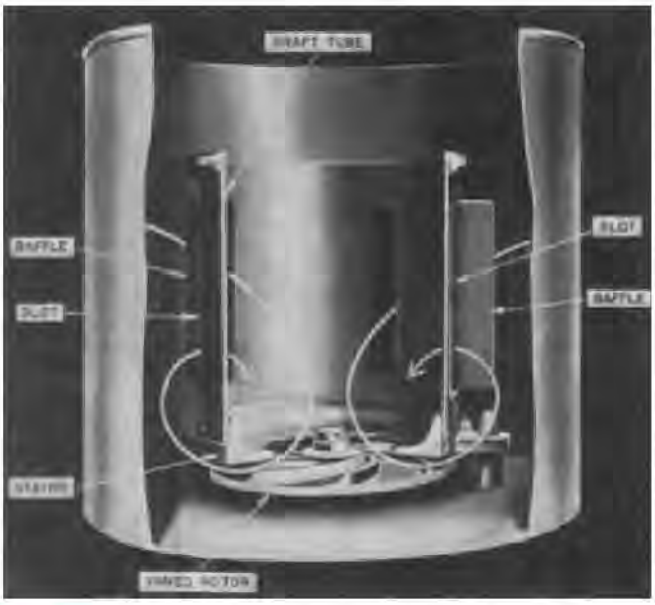

Figure 39-1. Standard slurry-type dispersal mixer with vaned-rotor mixing element and slotted draft-tube circulating element (courtesy, Abbe Eng).

Figure 39-2. Standard paste-type dispersal mixer with cupped-rotor milling element and double-rotating mixing arm circulating element (courtesy, Abbe Eng).

Small electric mixers may be used to prepare emulsions at the prescription counter. They will save time and energy and produce satisfactory emulsions when the emulsifying agent is acacia or agar. The commercially available *Waring Blender* disperses efficiently by means of the shearing action of rapidly rotating blades. It transfers large amounts of energy and incorporates air into the emulsion. If an emulsion first is produced by using a blender of this type, the formulator must remember that the emulsion characteristics obtained in the laboratory will not necessarily be duplicated by the production-size equipment.

Colloid Mills

The principle of operation of the colloid mill is the passage of the mixed phases of an emulsion formula between a stator and a high-speed rotor revolving at speeds of 2,000 to 18,000 rpm. The clearance between the rotor and the stator is very small, but adjustable from 0.001 inches and up. The emulsion mixture, in passing between the rotor and stator, is subjected to a tremendous shearing action that effects a fine dispersion of uniform size. A colloid mill and various rotors are shown in Figures 39-3 and 39-4. The operating principle is the same for all, but each manufacturer incorporates specific features that result in changes in operating efficiency. The shearing forces applied in the colloid mill usually result in a temperature increase within the emulsion. It may be necessary, therefore, to use jacketed equipment to cool the emulsion during processing. Maa and Hsu have shown that droplet size of emulsions was mainly determined by shear force within the gap between the spinning rotor and stationary rotor.[81] Droplet size decreased with homogenization intensity and duration, increasing viscosity of the continuous phase, and with decreasing viscosity of the dispersed phase.

Colloid mills are used frequently for the comminution of solids and for the preparation of suspensions, especially suspensions containing solids that are not wetted by the dispersion medium, which are discussed later in this chapter.

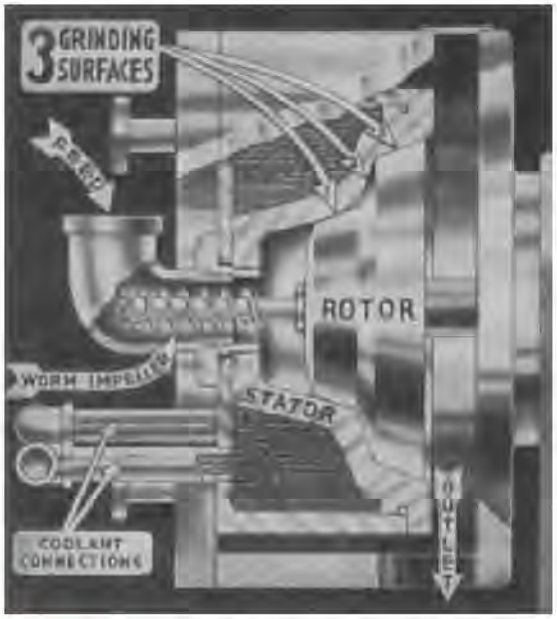

Figure 39-3. A cross section of a colloid mill (courtesy, Tri-Homo).

Homogenizers

Impeller types of equipment frequently produce a satisfactory emulsion; however, for further reduction in particle size, homogenizers may be employed.[82] Homogenizers may be used in one of two ways:

1. The ingredients in the emulsion are mixed and then passed through the homogenizer to produce the final product.
2. A coarse emulsion is prepared in some other way and then passed through a homogenizer for the purpose of decreasing the particle size and obtaining a greater degree of uniformity and stability.

The mixed phases or the coarse emulsion are subjected to homogenization and are passed between a finely ground valve and seat under high pressure. This, in effect, produces an atomization that is enhanced by the impact received by the atomized mixture as it strikes the surrounding metal surfaces. They operate at pressures of 1,000 to 5,000 psi and produce some of the finest dispersions obtainable in an emulsion.

Figure 39-5 shows the flow through the homogenizing valve, the heart of the high pressure, APV Gaulin homogenizer. The product enters the valve seat at high pressure, flows through the region between the valve and the seat at high velocity with

Figure 39-4. Types of rotors used in colloid mills. These may be smooth (for most emulsions), serrated (for ointments and very viscous products), or of vitrified stone (for the paints and pigment dispersions) (courtesy, Tri-Homo).

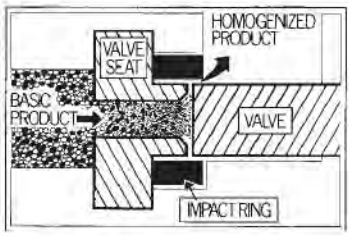

Figure 39-5. Material flow through a homogenizer (courtesy, APV Gaulin).

a rapid pressure drop, causing cavitation; subsequently, the mixture hits the impact ring causing further disruption and then is discharged as a homogenized product. It is postulated that circulation and turbulence are responsible mainly for the homogenization that takes place. Different valve assemblies, two-stage valve assemblies, and equipment with a wide range of capacities are available.

Two-stage homogenizers are constructed so that the emulsion, after treatment in the first valve system, is conducted directly to another where it receives a second treatment. A single homogenization may produce an emulsion that, although its particle size is small, has a tendency to clump or form clusters. Emulsions of this type exhibit increased creaming tendencies. This is corrected by passing the emulsion through the first stage of homogenization at a high pressure (eg, 3,000–5,000 psi) and then through the second stage at a greatly reduced pressure (eg, 1,000 psi). This breaks down any clusters formed in the first step.

For small-scale extemporaneous preparation of emulsions, the inexpensive hand-operated homogenizer is particularly useful. It is probably the most efficient emulsifying apparatus available to the prescription pharmacist. The two phases, previously mixed in a bottle, are hand-pumped through the apparatus. Recirculation of the emulsion through the apparatus will improve its quality.

A homogenizer does not incorporate air into the final product. Air may ruin an emulsion because the emulsifying agent is adsorbed preferentially at the air–water interface, followed by an irreversible precipitation termed *denaturization*. This is particularly prone to occur with protein emulsifying agents. Homogenization may spoil an emulsion if the concentration of the emulsifying agent in the formulation is less than that required to accommodate the increase in surface area produced by the process.

The temperature rise during homogenization is not very large. However, temperature does play an important role in the emulsification process. An increase in temperature will reduce the viscosity and, in certain instances, the interfacial tension between the oil and the water. There are, however, many instances, particularly in the manufacturing of cosmetic creams and ointments, where the ingredients will fail to emulsify properly if they are processed at too high a temperature. Emulsions of this type are processed first at an elevated temperature and then homogenized at a temperature not exceeding 40°C.

Homogenizers have been used most frequently with liquid emulsions, but now they may be used with suspensions, as the metal surfaces are formed from wear-resistant alloys that will resist the wear of solid particles contained in suspensions.

Ultrasonic Devices

The preparation of emulsions by the use of ultrasonic vibrations also is possible. An oscillator of high frequency (100–500 kHz) is connected to two electrodes between which is placed a piezoelectric quartz plate. The quartz plate and electrodes are immersed in an oil bath and, when the oscillator is operating, high-frequency waves flow through the fluid. Emulsification is accomplished by simply immersing a tube containing the

emulsion ingredients into this oil bath. Considerable research has been done on ultrasonic emulsification, particularly with regard to the mechanism of emulsion formation. The method has not been proven to be practical for large-scale production of emulsions, but evaluations are underway.[83]

Microfluidizers

Microfluidizers have been used to produce very fine particles. The process subjects the emulsion to an extremely high velocity through micro-channels in to an interaction chamber; as a result, particles are subjected to shear, turbulence, impact, and cavitation. Two advantages of this type of equipment are lack of contamination in the final product and ease of production scale up.

LIPOSOMES

Liposomes have been one of the most extensively studied drug delivery systems.[84–87] Liposomes, meaning lipid body, may be broadly described as small vesicles of a bilayer of phospholipid encapsulating an aqueous space ranging from about 0.03 to 10 μm in diameter. Generally, the lipid membrane of a liposome consists of a bilayer-forming amphiphile, cholesterol, and a charge-generating molecule. The lipid membrane encloses a discrete aqueous compartment. This structure presents an overall hydrophilic membrane-like assembly, in which the apolar or lipophilic portion of the amphiphilic molecule points inward while the polar or hydrophilic portion points outward of the lamellar structure. These characteristics make liposomes useful as drug delivery systems. The enclosed vesicles can encapsulate water soluble drugs in the aqueous spaces or lipid soluble drugs in the membranes. Liposomes have been administered parenterally, topically, and by inhalation.

Liposomes offer several advantages as drug delivery systems: (1) they are biologically inert and completely biodegradable; (2) they can be prepared in various sizes, charge, compositions, and surface morphology; (3) liposomes can encapsulate both water-soluble and water-insoluble drugs, including enzymes, hormones, and antibiotics; (4) encapsulated drugs are less susceptible to degradation; (5) organ-targeted drug delivery is possible since the entrapped drug is delivered intact to various tissues and cells after the liposome is destroyed; and (6) other tissues and cells of the body are protected from the drug until it is released by the liposomes, thus decreasing the drug's toxicity. The primary disadvantage of liposomes is their rapid removal from the blood following intravenous administration by cells of the reticuloendothelial system, particularly by Kupfer cells in the liver. Drug release is slowed by phagocytes through endocytosis, fusion, surface adsorption, or lipid exchange.

Several different amphiphiles have been investigated to create liposomal structures (vesicles). Only the bilayer-forming lipid is the essential part of the lamellar structure, and the other components are to impart specific characteristics. For example, cholesterol adds rigidity to the vesicular structure rendering it less permeable. Phospholipids such as phosphatidyl choline (lecithin) were the first amphiphiles used to produce bilayer structures to mimic cell membranes.

Liposomes can be prepared into several morphologies, which have been classified according to the vesicular shape. *Multilamellar vesicles* (MLV) were first prepared by Bangham and have multiple bilayer structures surrounding a relatively small internal core, much like an onion.[88] *Oligolamellar vesicles* (OLV) have large central aqueous cores surrounded by 2 to 10 bilayers. *Unilamellar vesicles* (ULV) have a single bilayer structure surrounding an internal aqueous core. Unilamellar vesicles can be prepared in a variety sizes: small unilamellar vesicles (20–40 nm), medium unilamellar vesicles (40–80 nm), large unilamellar vesicles (10–1,000 nm), and giant unilamellar vesicles (> 1,000 nm).

Drug release in the blood following intravenous administration ranges from a few minutes to several hours depending upon the nature and composition of the lipids, surface properties, and size. In general, smaller unilamellar vesicles show much longer half-lives than multilamellar vesicles and large unilamellar vesicles. Negatively charged liposomes are cleared more rapidly from the circulation than neutral or positively charged liposomes. Circulation can be prolonged by blocking the reticuloendothelial system and allowing the liposomes to interact with vascular endothelial cells and blood cells. These "stealth liposomes" were developed by coating the liposomes with polymers such as polyethylene glycol, enabling liposomes to evade detection by the body's immune system.

Preparation of Liposomes

Liposomes have been prepared using a number of techniques including solvent evaporation, sonication, supercritical fluid techniques, spray drying, extrusion, and homogenization. A combination of these methods is often used, and the drug is added during the formation process. In this method, the lipid is dissolved in an organic solvent such as acetone or chloroform. The solvent is evaporated leaving a thin, lipid film on the walls of the container. An aqueous solution of the drug is added and placed in an ultrasonic bath. The sound waves displace the lipid from the container walls, and they self-assemble into spheres or cylinders entrapping the aqueous drug solution inside. If the drug is lipophilic, it is incorporated into the lipid phase and will reside within the lipophilic bilayers. Several advances have been made in liposome preparation to better control stability and size.

Liposomal products are now commercially available. Amphotec (distributed by *InterMune*, manufactured by *Ben Venue Laboratories*) is Amphotericin B Cholesteryl Sulfate Complex for Injection. It is a sterile, pyrogen-free, lyophilized powder for reconstitution and intravenous (IV) administration. Amphotec consists of a 1:1 (molar ratio) complex of amphotericin B and cholesteryl sulfate. Upon reconstitution, Amphotec forms a colloidal dispersion of microscopic disc-shaped particles. Each 50 mg single dose vial contains amphotericin B, 50 mg; disodium edetate dihydrate, 0.372 mg; lactose monohydrate, 950 mg; and hydrochloric acid, qs. Amphotec is indicated for the treatment of invasive aspergillosis in patients where renal impairment or unacceptable toxicity precludes the use of amphotericin B deoxycholate in effective doses and in aspergillosis patients where prior amphotericin B deoxycholate therapy has failed. The drug is reconstituted with Sterile Water for Injection by rapidly adding the water to the vial; it is shaken gently by hand, rotating the vial until all the solids have dissolved. The fluid may be opalescent or clear.[89] For infusion, it is further diluted in 5% dextrose injection. The product should not be reconstituted with any fluid other than Sterile Water for Injection; do not reconstitute with dextrose or sodium chloride solutions. Also, for further dilution, it should not be admixed with sodium chloride or electrolytes. Solutions containing benzyl alcohol or any other bacteriostatic agent should not be used as they may cause precipitation. An inline filter should not be used, and the infusion admixture should not be mixed with other drugs. If infused using a y-injection site or similar device, flush the line with 5% dextrose injection before and after infusion of Amphotec. After reconstitution, the drug should be refrigerated and used within 24 hours; do not freeze. If further diluted with 5% dextrose injection, it should be refrigerated and used within 24 hours.

Doxil (*Ortho Biotech*) is doxorubicin hydrochloride encapsulated in stealth liposomes for intravenous administration. The product is provided as a sterile, translucent, red liposomal dispersion in a 10 mL glass, single use vial. Each vial contains 20 mg of doxorubicin HCl at a concentration of 2 mg/mL and a pH of 6.5. The stealth liposome carriers are composed of N-(carbonyl-methoxypolyethylene glycol 2000) - 1,2–distearoyl–

sn–glycerol–3 - phosphoethanolamine sodium salt (MPEG-DSPE), 3.19 mg/mL; fully hydrogenated soy phosphatidylcholine (HSPC), 9.58 mg/mL; and cholesterol, 3.19 mg/mL. Each mL also contains ammonium sulfate, approximately 2 mg; histidine as a buffer; hydrochloric acid and/or sodium hydroxide for pH control; and sucrose to maintain isotonicity. Greater than 90% of the drug is encapsulated in the Stealth liposomes. The stealth liposomes are specially formulated to circulate in the body "undetected" by the mononuclear phagocyte system for a prolonged circulation time of about 55 hours. This is accomplished by pegylation, or binding methoxypolyethylene glycol on the surface of the liposomes. These liposomes are small, in the range of 100 nm in diameter. Doxil must be diluted in 250 mL of 5% dextrose injection prior to administration; once diluted it should be refrigerated and administered within 24 hours. It should not be mixed with any other diluent or any preservative-containing solution. It should not be used with in-line filters. The product is not a clear solution but a red, translucent liposomal dispersion. Unopened vials should be stored in a refrigerator but freezing should be avoided, even though short-term freezing (less than 1 month) does not appear to adversely affect the product.

SUSPENSIONS

The physical chemist defines the word "suspension" as a two-phase system consisting of an undissolved or immiscible material dispersed in a vehicle (solid, liquid, or gas). A variety of dosage forms fall within the scope of this definition, but emphasis is placed on solids dispersed in liquids. In more specific terms, the pharmaceutical scientist differentiates between such preparations as suspensions, mixtures, magmas, gels, and lotions. In these preparations, the substance distributed is referred to as the dispersed phase and the vehicle is termed the dispersing phase or dispersion medium. In a general sense, each of these preparations represents a suspension, but the state of subdivision of the insoluble solid varies from particles that settle gradually on standing to particles that are colloidal in nature.

The particles of the dispersed phase vary widely in size, from large, visible particles to colloidal dimensions, which fall between 1.0 nm and 0.5 μm in size. Course dispersions contain particles usually 10–50 μm in size, and include suspensions and emulsions. Fine dispersions contain particles of smaller size, usually 0.5–10 μm. Magmas and gels represent such fine dispersions. Particles in a coarse dispersion have a greater tendency to separate from the dispersion medium than do the particles of a fine dispersion. Most solids in a dispersion tend to settle to the bottom of the container because their density is higher than the dispersion medium.

Suspensions have a number of applications in pharmacy. They are used to supply drugs to the patient in liquid form. Many people have difficulty swallowing solid dosage forms; consequently a liquid preparation has an advantage for these people. In addition, the dose of a liquid form may be adjusted easily to meet the patient's requirements. Thus, if the drug is insoluble or poorly soluble, a suspension may be the most suitable dosage form. If a drug is unstable in an aqueous medium, a different form of the drug, such as an ester or insoluble salt that does not dissolve in water, may be used in the preparation of a suspension. Drugs, such as antibiotics, that are unstable in the presence of an aqueous vehicle for extended periods of time are most frequently supplied as dry powder mixtures for reconstitution at the time of dispensing. This type of preparation is designated in the USP by the title "for Oral Suspension." Suspensions that do not require reconstitution at the time of dispensing are simply designated as an "Oral Suspension." Examples of commercial products are presented in Table 39-7.

To improve the stability of an antibiotic such as ampicillin, formulations are made in such a way that the dispersion medium, water, is added upon dispensing to form a satisfactory suspension. Generally, the taste of pharmaceuticals can be improved if they are supplied in suspension form, rather than solutions; thus, chloramphenicol palmitate is used instead of the more soluble form, chloramphenicol. Another method to decrease the solubility of the drug is to replace part of the water with another appropriate liquid such as alcohol or glycerin. Insoluble drugs may be formulated as suspensions for topical use such as calamine lotion. Other preparations of suspensions, in addition to those noted above, include parenteral preparations (Chapter 41), ophthalmic preparations (Chapter 43), aerosol suspensions (Chapter 50), and medicated topicals (Chapter 44).

PHYSICAL CHARACTERISTICS OF SUSPENSIONS

Formulation of suspensions involves more than mixing a solid in a liquid. Knowledge of the behavior of particles in liquids, suspending agents, wetting agents, polymers, buffers, preservatives, flavors, and colors is required to produce an acceptable and satisfactory suspension. Suspensions should possess several basic chemical and physical properties. The dispersed phase should settle slowly, if at all, and be re-dispersed readily upon shaking. The solid particles should have a narrow particle size distribution, which does not cake on settling, and the viscosity should be such that the preparation pours easily. In addition, the product should have an elegant appearance, be resistant to microbial growth, and maintain its chemical stability.

Several factors influence the sedimentation rate of particles in a suspension. Stokes' law relates the diameter of the

Table 39-7. Examples of Commercial Suspensions

PRODUCT NAME	MANUFACTURER	ACTIVE INGREDIENT & DOSE	INDICATION
Carafate	Aventis	1 g sucralfate / 10 mL.	Antiulcer
Maalox	Novartis	225 mg aluminum hydroxide and 200 mg magnesium hydroxide / 5 mL	Antacid
Mepron	GlaxoSmithKline	750 mg atovaquone / 5 mL	Antiprotozoal
Mylanta Liquid	J&J-Merck	200 mg Aluminum Hydroxide, 200 mg Magnesium Hydroxide, and 20 mg simethicone / 5 mL	Antacid
Nystastin	Teva	100,000 units mycostatin / mL	Antifungal
Pepto-Bismol Liquid	Proctor & Gamble	262 mg bismuth subsalicyalte / 15 mL	Antidiarrheal
Pred-G ophthalmic suspension	Allegan	0.3% gentamicin and 1.0% prednisolone acetate	topical anti-inflammatory/ anti-infective
Viramune	Boehringer Ingelheim	50 mg of nevirapine / 5 mL	Antiviral

particles, the density of the particles and the medium, and the viscosity of the of the medium to the sedimentation rate:

$$\frac{dS}{dt} = \frac{d^2(\rho_P - \rho_M)g}{18\eta}$$

where
dS/dt is the sedimentation rate,
d is the diameter of the particles,
ρ_P is the density of the particles,
ρ_M is the density of the medium,
g is the gravitational constant,
η is the viscosity of the medium.

Stokes' equation was derived for an ideal situation with perfectly spherical particles in a very dilute suspension. It assumes the spherical particles settle without causing turbulence, without particle-to-particle collision, and without chemical or physical attraction or affinity for the dispersion medium. Obviously, the typical pharmaceutical suspension contains particles are irregularly shaped with a range of sizes, settling results in both turbulence and collision, and there is a reasonable affinity between the particles and suspension medium. However, the basic concepts of the equation offer an indication of the important variables for suspension of the particle and clues to formulation adjustments to decrease the rate of particle sedimentation.

Clearly, the sedimentation rate of large particles is greater than smaller particles, assuming all other factors remain constant. A slower rate of settling can be achieved by reducing particle size. Density also has a direct relationship with sedimentation rate: dense particles settle more rapidly than less dense particles. Most pharmaceutical suspensions are aqueous, and the density of the particles is generally greater than water; a desirable feature, since if they were less dense, they would float making a uniform product difficult to achieve.

The sedimentation rate is indirectly related to the medium viscosity, allowing the pharmaceutical scientist to manipulate settling by adjusting the viscosity of the medium. Settling is reduced by increasing the viscosity of the dispersion medium. One must keep in mind, a very high viscosity is not generally desirable, because it pours with difficulty and it is equally difficult to re-disperse. The viscosity characteristics of a suspension may be altered not only by the vehicle used, but also by the solids content. As the proportion of solid particles is increased in a suspension, so is the viscosity. In most cases, the physical stability of a pharmaceutical suspension is adjusted by the dispersed phase rather than through the dispersion medium. Generally, the dispersion medium supports the adjusted dispersed phase.

The most important consideration in formulation of suspensions is the size of the drug particles. In most pharmaceutical suspensions, the particle diameter is between 1 and 50 μm. The reduction in the particle size is beneficial to the stability of the suspension in that the rate of sedimentation is reduced as the particles are decreased in size. The reduction in particle size produces slow, more uniform rates of settling. However, reduction of the particle size to too great a degree of fineness should be avoided, since fine particles have a tendency to form a compact cake upon settling. The result may be that the cake resists breakup upon shaking and forms rigid aggregates of particles. Particle shape can also affect caking and product stability.[90]

Actions must be taken to prevent the agglomeration of particles into larger crystals or into masses, to avoid the formation of a cake. A common method to prevent rigid cohesion of small particles is through the intentional formation of a less rigid or loose aggregation of the particles by particle-to-particle bonding forces. An aggregation of this type is called a *floc* or *floccule*, in which particles form a lattice structure that resists complete settling and compaction. Flocs form a higher sediment volume than unflocculated particles, and the loose structure permits the aggregates to break up easily and redistribute with agitation. There are several methods of preparing flocculated suspensions, the choice depending on the drug and type of product desired. For example, clays such as bentonite are commonly used as flocculating agents in oral suspensions. The structure of bentonite and of other clays assists the suspension by helping to support the floc once formed. When clays are unsuitable, as in a parenteral suspension, a floc of the dispersed phase can be produced by an alteration in the pH of the preparation, generally to a region of low drug solubility. Electrolytes can also act as flocculating agents by reducing electrostatic interactions between the particles. Nonionic and ionic surfactants can also induce particle flocculation and increase the sedimentation volume.

Particle growth or *Ostwald ripening* is also a destabilizing process resulting from temperature fluctuations during storage. Temperature fluctuations may change particle size distribution and polymorphic form of a drug, if the solubility of the drug is temperature dependent. For example, if the temperature is raised, drug crystals may dissolve and form a supersaturated solution, which favor crystal growth on cooling. As the dissolved drug crystallizes out of solution, it will preferentially occur on the surface of a crystal in the suspension.

SUSPENSION INGREDIENTS

The external phase is usually water for oral preparations; however, other polar liquids such as glycerin or alcohol may be considered to control solubility, stability, and taste. The selection of the external phase is based upon taste, viscosity, density, and stability. Nonpolar liquids such as aliphatic hydrocarbons and fatty esters may be considered if the preparation is used for external purposes.

The main ingredients in a suspension are the drug and functional excipients that wet the drug, influence flocculation, control viscosity, adjust pH, and the external medium, usually water. In addition, flavoring, sweetening, and coloring agents and preservatives are employed. A *wetting agent* is a surfactant with an HLB value between 7 and 9. Surfactants with higher HLB values are recommended sometimes, such as polysorbates and poloxamers. They are employed at a low concentration (0.05–0.5%) to allow the displacement of air from hydrophobic material and permit the liquid, usually water, to surround the particles. If it is desirable to flocculate the particles, then flocculating agents are employed. Usually low concentrations, less than 1%, of electrolytes such as sodium or potassium chloride are employed to induce flocculation. Water-soluble salts possessing divalent or trivalent ions may be considered if the particles are highly charged.

Viscosity producing agents are generally polymers, including natural gums (acacia, xanthan) and cellulose derivatives, such as sodium carboxymethylcellulose and hydroxypropyl methylcellulose. These excipients are used at low concentrations to function as protective colloids, but at higher concentrations they function as viscosity increasing agents. At higher viscosity, the rate of settling of deflocculated particles is decreased providing additional stability to the flocculated suspension. The choice of an appropriate viscosity agent depends upon the use of the product (external or internal), processing equipment, and the duration of storage. Suspension preparations for internal use exhibiting good flow and suspending properties often contain sodium carboxymethylcellulose 2.5%, tragacanth 1.25%, or guar gum 0.5%. For external applications, Carbopol polymers have been successfully used. Other common viscosity-producing agents include acacia, methylcellulose, sodium alginate, or tragacanth.

Ideally, a suspension should be stable over a wide pH range. The chemical and / or physical stability of an active compound may occasionally require the pH of the medium to be maintained within a specified range. *Buffers* must be carefully considered so that they produce their intended effects without interference with other ingredients in the formulation. Buffers can influence the solubility of the active, preservative ionization and its activity, and ionic viscosity agents.

PREPARATION OF SUSPENSIONS

The preparation of suspensions involves several steps; the first is to obtain particles of the proper size, typically in the lower micrometer range. Oral preparations should not feel gritty, topical preparations should feel smooth to the touch, and injectables should not produce tissue irritation. Particle size and distribution also should be considered in terms of bioavailability, or from an in vitro perspective, the rate of release. Very small particles, less than 1 μm, will have a higher solubility than larger particles, but also have a faster *rate* of dissolution. Thus, particle size of the dispersed solid in a suspension can influence the rate of sedimentation, flocculation, solubility, dissolution rate, and ultimately, bioavailability.

Particle size reduction is generally accomplished by dry milling prior to the incorporation of the dispersed phase into the dispersion medium. *Milling* is the mechanical process of reducing particle size, which may be accomplished by a number of different types of machines. Hammer mills grind the powders by impact (Fig 39-6). Centrifugally rotating hammers or blades contact the particles and direct them against a screen, typically in the range of 4 to 325 mesh. The particles are forced through the screen, which regulates final particle size at the outlet of the milling chamber. The blade and screen act in conjunction to determine final product sizing, typically in the range of 10–50 μm.

Fluid energy or jet mills produce particles under 25 μm through violent turbulence in high velocity air (Fig 39-7). Compressed air forms a high speed, jet stream which passes the feed funnel and draws powders into grinding chamber. Pulverizing nozzles are installed around the grinding chamber and inject additional high-speed air into the grinding chamber in a rotational direction. The centrifugal air-flow accelerates particles and reduces particle size by particle to particle impaction and friction. The air-flow drives large particles toward the perimeter, but small particles move toward the center where they exit through the outlet.

A ball mill contains a number of steel or ceramic balls in a rotating drum. The balls reduce the particle size to a 20 to 200 mesh by both attrition and impact. Roller mills have two or more rollers that revolve at different speeds, and the particles are reduced to a mesh of 20 to 200 by means of compression and a shearing action. See Chapter 37 (Powders) for a more detailed discussion on particle size reduction of solids.

In the pharmacy, ceramic mortar and pestle are better for grinding and reducing particle size than glass. After reducing particle size, the drug powder is wetted thoroughly with a small quantity of water miscible solvent, such as glycerin or alcohol, which reduces the interfacial tension. The suspending agent in the aqueous medium is then added. Alternately, the suspending agent can be triturated with the drug particles using a small quantity of glycerin or alcohol and then brought up to volume with the diluent water and triturated to a smooth uniform product.

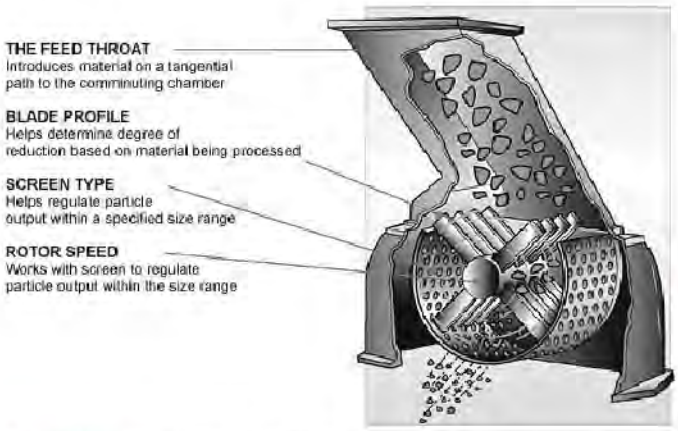

Figure 39-6. Material Flow through a Hammer Mill. Hammer mills operate by feeding material uniformly into a chamber in which a rotating blade assembly reduces the particles of the material by cutting or impacting them. The material discharges through a screen which regulates final particle size at the outlet of the milling chamber (courtesy, The Fitzpatrick Company).

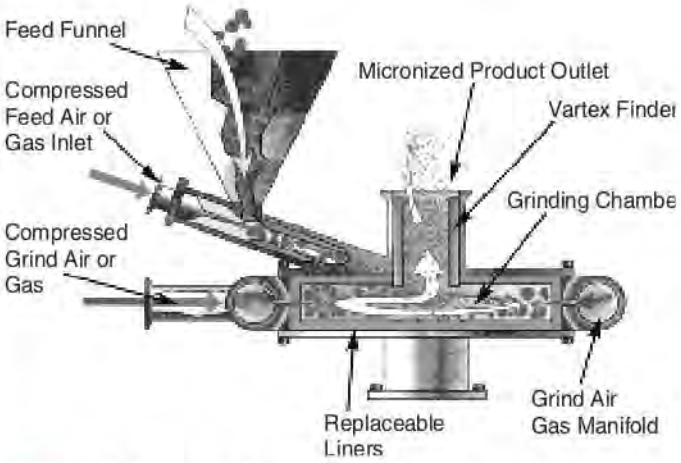

Figure 39-7. Schematic of particle size reduction in a fluid energy or jet mill (courtesy, Sturtevant Inc.).

On a large scale, the fine drug particles are treated with a small portion of water that contains the wetting agent and allowed to stand for several hours to release entrapped air. At the same time, the suspending agent should be dissolved or dispersed in the main portion of the external phase and allowed to stand until complete hydration takes place. Subsequently, wetted drug particles should be added slowly to the main portion of the dissolved suspending agent. Other excipients such as electrolytes or buffers should be carefully introduced. The preservatives, flavoring agents, and coloring agents are added last. Finally, the formulation is processed with homogenizers, ultrasonic devices, or colloid mills to produce a uniform product.

A procedure for the preparation of Trisulfapyrimidines Oral Suspension is given below.

Trisulfapyrimidines Oral Suspension

Veegum	1.00 g
Syrup USP	90.60 g
Sodium Citrate	0.78 g
Sulfadiazine	2.54 g
Sulfamerazine	2.54 g
Sulfamethazine	2.54 g

Add the Veegum slowly and with continuous stirring to the syrup. Incorporate the sodium citrate into the Veegum–syrup mixture. Premix the sulfa drugs, add to the syrup, stir, and homogenize. Add sufficient 5% citric acid to adjust the pH of the product to 5.6. A preservative and a flavoring agent may be added to the product.

QUALITY CONSIDERATIONS

The quality of the suspension can be determined in a number of ways. Particle size, particle size distribution, and particle shape are often determined using photo microscopy or laser light diffraction techniques. Physical stability, the degree of settling, or flocculation may be determined using a device to measure the zeta potential. Viscosity may be determined by instruments such as the Brookfield viscometer or of the cone and plate configuration. Microbiological as well as stability testing according to ICH guidelines should be performed to determine the efficiency of the preservative and the appropriateness of the formulation with respect to time, temperature, and relative humidity.[91]

EXTEMPORANEOUS PREPARATIONS FROM TABLETS AND CAPSULES

Occasionally, it is necessary to prepare a liquid formulation of a drug to meet certain patient requirements. Consequently, patients who are unable to swallow solid medications, require a different route of administration or different dosing strength present a special need. Thus, the pharmacist may have to extemporaneously compound a liquid product. If the pure drug is available, it should be used to prepare the liquid dosage form. If it is necessary to prepare a liquid dosage form from tablets or capsules, a suspension is formed if either the drug or one of the excipients in the tablets or capsules is insoluble. Insoluble excipients in these dosage forms include disintegrants, lubricants, glidants, colors, diluents, and coatings. Consequently, although the drug may be soluble in water, many excipients are not. It is preferable to use the contents of capsules, or tablets that are not coated. If coated, tablets with a water-soluble coat are preferred to those with functional enteric coatings and the like. In any case, the contents of the capsules or the tablets should be ground finely with a ceramic mortar and pestle and then wetted using alcohol or glycerin.

Preservatives may be included in the liquid formulation to enhance the stability. However, preservatives have been found to cause serious adverse effects in infants. Benzyl alcohol should be omitted from neonatal formulations because it can cause a gasping syndrome characterized by a deterioration of multiple organ systems and eventually death. Propylene glycol has also been implicated to cause seizures and stupor in some preterm infants. Thus, formulations for neonates should be purposely kept simple, and not compounded to supply more than just a few days of medicine

Finally, it may be desirable to use a hand homogenizer to prepare a more suitable product. Some drugs that have been formulated in this manner include clonidine hydrochloride and simple syrup,[92] cefuroxime axetil in an orange syrup vehicle,[93] and famotidine in cherry syrup.[94] Many other examples may be found in current hospital and community pharmacy journals such as the *American Journal of Hospital Pharmacy, Canadian Journal of Hospital Pharmacy, U.S. Pharmacist, International Journal of Pharmaceutical Compounding,* and *Drug Development and Industrial Pharmacy*. Frequently, stability data and, occasionally, bioavailability and/or taste data are provided.

To minimize stability problems of the extemporaneously prepared product, it should be placed in air-tight, light-resistant containers and stored in the refrigerator by the patient. Because it is a suspension, the patient should be counseled to shake it well prior to use and to be aware of any change that might indicate a stability problem with the formulation.

Tortorici reports an example of an extemporaneous suspension of cimetidine tablets that retained its potency at 40° over 14 days.[95] Twenty-four, 300 mg cimetidine tablets are compounded with 10 mL of glycerin and 120 mL of simple syrup. The tablets are triturated to a fine powder using a mortar, the mixture is levigated with the glycerin, and the simple syrup added. The suspension is mixed well, placed in a blender until smooth, and then refrigerated.

SUSTAINED RELEASE SUSPENSIONS

Sustained release suspensions represent a very specialized class of preparation. Sustained release, oral suspensions with morphine,[96] nonsteroidal anti-inflammatory agents,[97] and other drugs[98] have been described in the literature. However, limited commercial success has been achieved due to the difficulty in maintaining the stability. Formulation research for sustained release suspensions has focused on the similar technologies used in preparing sustained release tablets and capsules. *Celltech* licenses the Tussionex Pennkinetic system, which uses a combination of ion exchange resin and particle coating.[99] This novel system exploits the likelihood of complexation between ionic drugs and ion-exchange resins, which are then coated with ethyl cellulose. When administered orally, the coated particles with encapsulated drug adsorbed onto the resin are slowly released by an ion exchange process.

Durect markets the SABER system for sustained release suspension applications. SABER uses a non-polymeric, non-water-soluble high-viscosity liquid carrier material (>5,000 cPs. at 37°C), such as sucrose acetate isobutyrate (SAIB), to provide controlled release of active ingredients.[100] The drug is mixed with a small amount of a pharmaceutically acceptable solvent to form a low viscosity solution or suspension, which is then mixed with the high viscosity carrier. The resulting suspension can be administered via injection, orally, or as an aerosol, forming an adhesive, biodegradable depot upon contact with tissues. After administration of the SABER formulation, the solvent diffuses away, leaving a viscous, adhesive matrix of the three components—SAIB, drug, and any additives. The release rate can be easily modified by the ratio of non-polymeric, non-water-soluble high-viscosity liquid carrier material present in the formulation. Extended systemic and local delivery for durations of 1 day to 3 months from a single injection has been demonstrated.

GELS AND MAGMAS

Gels are defined by the USP as:

> "...semisolid systems consisting of either suspensions made up of small inorganic particles or large organic molecules interpenetrated by a liquid. Where the gel mass consists of a network of small discrete particles, the gel is classified as a two-phase system. In a two-phase system, if the particle size of the dispersed phase is relatively large, the gel mass is sometimes referred to as a magma. Both gels and magmas may be thixotropic, forming semisolids on standing and becoming liquid on agitation.
>
> Single-phase gels consist of organic macromolecules uniformly distributed throughout a liquid in such a manner that no apparent boundaries exist between the dispersed macromolecules and the liquid. Single-phase gels may be made from synthetic macromolecules or from natural gums. The latter preparations are also called mucilages. Although these gels are commonly aqueous, alcohols and oils may be used as the continuous phase. For example, mineral oil can be combined with a polyethylene resin to form an oleaginous ointment base.
>
> Gels can be used to administer drugs topically or into body cavities."

Gels are also defined as semi-rigid systems in which the movement of the dispersing medium is restricted by an interlacing three-dimensional network of particles or solvated macromolecules in the dispersed phase. Physical and / or chemical cross-linking may be involved. The interlacing and consequential internal friction is responsible for increased viscosity and the semisolid state.

Some gel systems are clear and others are turbid, since the ingredients involved may not be completely soluble or insoluble, or they may form aggregates, which disperse light. The concentration of the gelling agents is generally less than 10%, and usually in 0.5 to 2.0% range. Gels in which the macromolecules are distributed throughout the liquid in such a manner that no apparent boundaries exist between them and the liquid are called single-phase gels. In instances in which the gel mass consists of floccules of small distinct particles, the gel is classified as a two-phase system and frequently called a magma or a milk. Gels and magmas are considered colloidal dispersions since they each contain particles of colloidal dimension

Different types of colloidal dispersions have been given specific names. For instance, *sol* is a general term designating a dispersion of a solid substance in a liquid, a solid, or a gaseous

dispersion medium. However, more often than not it is used to describe the solid liquid dispersion system. A prefix such as hydro- for water (*hydrosol*) or alco- for alcohol (*alcosol*) is used to specify the medium. Similarly, *aerosol* has similarly been developed to indicate a dispersion of a solid or a liquid in a gaseous phase.

The generally accepted size range for a substance "colloidal" is when particles fall between 1 nm and 0.5 μm. One difference between colloidal dispersions and true solutions is the larger particle size of the dispersed phase in colloidal systems. The optical properties of the two systems are also different. True solutions do not scatter light and therefore appear clear, but colloidal dispersions contain discrete particles scatter light.

Gelling Agents

Several compendial materials function as gelling agents, including acacia, alginic acid, bentonite, carbomer, carboxymethylcellulose sodium, cetostearyl alcohol, colloidal silicon dioxide, ethylcellulose, gelatin, guar gum, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium aluminum silicate, maltodextrin, methylcellulose, polyvinyl alcohol, povidone, propylene carbonate, propylene glycol alginate, sodium alginate, sodium starch glycolate, starch, tragacanth, and xanthan gum.

Alginic acid is refined from seaweed. It is a tasteless, practically odorless, white to off-white colored, fibrous powder. It is used in concentrations between 1% and 5% as a thickening agent, and swells in water to about 200 times its own weight without dissolving. Alginic acid can be cross-linked by addition of calcium salts, resulting in substantially higher viscosity. Sodium alginate produces a gel at concentrations up to 10%. Aqueous preparations are most stable between pH values of 4–10; below pH 3, alginic acid is precipitated. Sodium alginate gels for external use should be preserved.

Carbomer resins are high molecular weight, acrylic acid-based polymers. The pH of 0.5% and 1.0% aqueous dispersions are 2.7–3.5 and 2.5–3.0, respectively. There are many carbomer resins, with viscosity ranges available from 0 to 80,000 cPs., depending upon the pH to which it is neutralized. In addition to thickening, suspending, and emulsifying in both oral and topical formulations, carbomers are also used to provide sustained release properties in both the stomach and intestinal tract for commercial products. Alcohol is often added to carbomer gels to decrease their viscosity. Carbomer gel viscosity is also dependent upon the presence of electrolytes and the pH. Generally, a rubbery mass forms if greater than 3% electrolytes are added. Carbomer preparations are primarily used in aqueous systems, although other liquids can be used. In water, a single particle of carbomer will wet very rapidly but, like many other powders, carbomer polymers tend to form clumps of particles when haphazardly dispersed in polar solvents. Rapid dispersion of carbomers can be achieved by adding the powder very slowly into the vortex of the liquid that is very rapidly stirred. A neutralizer is added to thicken the gel after the carbomer is dispersed. Sodium hydroxide or potassium hydroxide can be used in carbomer dispersions containing less than 20% alcohol. Triethanolamine will neutralize carbomer resins containing up to 50% ethanol.

Carboxymethylcellulose (CMC) produces gels when used in concentrations of 4% to 6% of the medium viscosity grade. Glycerin may be added to prevent drying. Precipitation will occur at pH values less than 2, it is most stable at pH levels between 2 and 10, with maximum stability at pH 7 to 9. It is incompatible with ethanol. Sodium carboxymethylcellulose (NaCMC) is soluble in water and should be dispersed with high shear in cold water before the particles hydrate and swell. Once the powder is well dispersed, the solution is heated with moderate shear to about 60°C for fastest dissolution. These colloidal dispersions are sensitive to pH and the viscosity of the product decreases below pH 5 or above pH 10.

Tragacanth gum has been used to prepare gels that are stable at a pH range of 4–8. These gels must be preserved or sterilized by autoclaving. Tragacanth often lumps when added to water, thus, aqueous dispersions are prepared by adding the powder to rapidly mixed water. Also, lumps are also prevented by wetting the gum with ethanol, glycerin, or propylene glycol.

Colloidal silicon dioxide can be used to prepare transparent gels when used with other ingredients of similar refractive index. Colloidal silicon dioxide adsorbs large quantities of water without liquefying, and its viscosity is largely independent of temperature. Changes in pH affect the viscosity; it is most effective at pH values up to about 7.5. Colloidal silicon dioxide (fumed silica) will form a hydrophobic gel when combined with 1-dodecanol and n-dodecane. These are prepared by adding the silica to the vehicle and sonicating for about 1 minute to obtain a uniform dispersion, sealing, and storing at about 40°C overnight.

Gelatin gels are prepared by dispersing gelatin in hot water followed by cooling. Alternatively, gelatin can be wetted with an organic liquid such as ethyl alcohol or propylene glycol followed by the addition of the hot water and cooling. Magnesium aluminum silicate forms thixtropic gels at concentrations of about 10%. The material is inert and has few incompatibilities but is best used above pH 3.5. It may bind to some drugs and limit their availability.

Methylcellulose forms gels at concentrations up to about 5%. Since methylcellulose hydrates slowly in hot water, the powder is dispersed with high shear at 80–90°C in a portion of water. Once the powder is finely dispersed, the remaining water is added with moderate stirring. Alcohol or propylene glycol is often used to help wet the powders. High electrolyte concentrations will salt out the polymer, ultimately precipitating the polymer.

Poloxamer gels are made from selected forms of polyoxyethylene-polyoxypropylene copolymers in concentrations ranging from 15% to 50%. Poloxamers are white, waxy, free-flowing granules that are practically odorless and tasteless. Aqueous solutions of poloxamers are stable in the presence of acids, alkalis, and metal ions. Polyvinyl alcohol (PVA) is used at concentrations of about 2.5% in the preparation of various jellies, which dry rapidly when applied to the skin. Borax is a often used to gel PVA solutions. For best results, disperse PVA in cold water, followed by hot water. It is less soluble in the cold water.

Povidone, in the higher molecular weight forms, can be used to prepare gels in concentrations up to about 10%. It has the advantage of being compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It has also been used to increase the solubility of a number of poorly soluble drugs.

Two-Phase Gels

Two-phase gels containing bentonite may be used as a base for topical preparations such as plaster and ointment. Aluminum Hydroxide Gel, USP is an example of a two-phase gel. The USP states that "Aluminum Hydroxide Gel is a suspension of amorphous aluminum hydroxide in which there is a partial substitution of carbonate for hydroxide." The gel is usually prepared by the interaction of a soluble aluminum salt, such as a chloride or sulfate, with ammonia solution, sodium carbonate, or bicarbonate. The reactions that occur during the preparation are

$$3CO_3^{2-} + 3H_2O \rightarrow 3HCO_3^- + 3OH^-$$

$$[Al(H_2O)_6]^{3+} + 3OH^- \rightarrow [Al(H_2O)_3(OH)_3] + 3H_2O$$

$$2HCO_3 - \rightarrow CO_3^{2-} + H_2O + CO_2$$

The physical and chemical properties of the gel will be affected by the order of addition of reactants, pH of precipitation, temperature of precipitation, concentration of the reactants, the reactants used, and the conditions of aging of the precipitated gel.

Aluminum Hydroxide Gel is soluble in acidic (or very strongly basic) media. The mechanism in acidic media is

$$\text{Aluminum Hydroxide Gel} + 3H_2O \rightarrow [Al(H_2O)_3(OH)_3]^0$$

$$[Al(H_2O)_3(OH)_3]^0 + H_3O^+ \rightarrow [Al(H_2O)_4(OH)_2]^+ + H_2O$$

$$[Al(H_2O)_4(OH)_2]^+ + H_3O^+ \rightarrow [Al(H_2O)_5(OH)]^{2+} + H_2O$$

$$[Al(H_2O)_5(OH)]^{2+} + H_3O^+ \rightarrow [Al(H_2O)_6]^{3+} + H_2O$$

It is unlikely that the last reaction given proceeds to completion. Because the activity of the gel is controlled by its insolubility. Further, because a certain quantity of insoluble gel always is available, the neutralizing capability of the gel extends over a considerable period of time.

Aluminum hydroxide gels also may contain peppermint oil, glycerin, sorbitol, sucrose, saccharin, and various preservatives. Sorbitol improves the acid-consuming capacity by inhibiting a secondary polymerization that takes place on aging. In addition, polyols such as mannitol, sorbitol, and inositol have been shown to improve the stability of aluminum hydroxide and aluminum hydroxycarbonate gels.[101]

Single-Phase Gels

Single-phase gels are used more frequently in pharmacy for several reasons: semisolid state, high degree of clarity, ease of application, and ease of removal and use. The gels often provide a faster release of drug substance, independent of the water solubility of the drug, as compared to creams and ointments.

Some recent gel formulations include ophthalmic preparations of pilocarpine, carbachol, and betamethasone valerate; topical preparations for burn therapy, anti-inflammatory treatment, musculoskeletal disorders, and acne; peptic ulcer treatment with sucralfate gel; and bronchoscopy using lidocaine. Gels may be used as lubricants for catheters and bases for patch testing, and sodium chloride gels are used for electrocardiography.

Some gel formulation examples are provided below.

Methylcellulose and Carbomer Gel Base

Methylcellulose, 4000 cps	1.0 %
Carbomer 934	0.35 %
1 N Sodium hydroxide solution	qs to pH 7
Propylene glycol	16.7 %
Methyl paraben	0.015%
Purified water,	qs 100%

Disperse the methylcellulose in a portion of hot (80–90°C) water. Cool to room temperature, and disperse the Carbomer 934 in the gel using a bladed impeller. Adjust the pH of the dispersion to 7.0 by adding sufficient 1 N sodium hydroxide solution. Dissolve the methylparaben in the propylene glycol. Mix the methylcellulose, Carbopol 934 and propylene glycol fractions using caution to avoid incorporating air.

Sodium Alginate Gel Base

Sodium Alginate	10 g
Glycerin	10 g
Methyl Hydroxybenzoate	0.2 g
A soluble calcium salt (calcium gluconate)	0.5 g
Purified Water,	to make 100 mL

Place a portion of water in a beaker and add the glycerin and preservative. Stir this solution with a high speed mixer and add the sodium alginate. The calcium salt is added next, which increases the viscosity. Continue mixing until the preparation is homogeneous. The preparation should be stored in a tightly sealed wide mouth jar or tube.

Carbomer Gel

Carbomer 934	2 g
Triethanolamine	1.65 mL
Methyl Paraben	0.2 g
Propyl Paraben	0.05 g
Purified Water,	to make 100 mL

The parabens are dissolved in 95 mL of water with the aid of heat and allowed to cool. Carbomer 934 is added in small amounts to the solution using a high speed mixer until a smooth dispersion is obtained. The preparation is allowed to stand, permitting entrapped air to separate. Then the neutralizing agent, triethanolamine, is added very slowly to avoid entrapping air. Finally, the remaining water is then incorporated.

LOTIONS

Lotions are not defined specifically in the USP, but a broad definition describes them as either liquid or semi-liquid preparations that contain one or more active ingredients in an appropriate vehicle. Lotions may contain antimicrobial preservatives and other appropriate excipients such as stabilizers. Lotions are intended to be applied to the unbroken skin without friction. Lotions are usually suspensions of solids in an aqueous medium. Some lotions are, in fact, emulsions or solutions.

Even though lotions usually are applied without friction, the insoluble matter should be divided very finely. Particles approaching colloidal dimensions are more soothing to inflamed areas and effective in contact with infected surfaces. A wide variety of ingredients may be added to the preparation to produce better dispersions or to accentuate its cooling, soothing, drying, or protective properties. Bentonite is a good example of a suspending agent used in the preparation of lotions. Methylcellulose or sodium carboxymethylcellulose, for example, will localize and hold the active ingredient in contact with the affected site and at the same time be rinsed off easily with water. A formulation containing glycerin will keep the skin moist for a considerable period of time. The drying and cooling effect of a lotion may be accentuated by adding alcohol to the formula.

Dermatologists frequently prescribe lotions containing anesthetics, antipruritics, antiseptics, astringents, germicides, protectives, or screening agents, to be used in treating or preventing various types of skin diseases and dermatitis. Antihistamines, benzocaine, calamine, resorcin, steroids, sulfur, zinc oxide, betamethasone derivatives, salicylic acid, safflower oil, minoxidil, and zirconium oxide are ingredients common in lotions.

Lotions may be prepared by triturating the ingredients to a smooth paste and then adding the remaining liquid phase with trituration. High-speed mixers or colloid mills produce better dispersions and, therefore, are used in the preparation of larger quantities of lotion. Calamine Lotion USP is the classic example of this type of preparation and consists of finely powdered, insoluble solids held in more or less permanent suspension by the presence of suspending agents and/or surface-active agents. The formula and the method of preparation of Calamine Lotion, USP follows.

Calamine Lotion, USP

Calamine	80 g
Zinc Oxide	80 g
Glycerin	20 mL
Bentonite Magma	250 mL
Calcium Hydroxide Topical Solution	qs 1,000 mL

Dilute the bentonite magma with an equal volume of calcium hydroxide topical solution. Mix the powder intimately with the glycerin and about 100 mL of the diluted magma, triturating until a smooth, uniform paste is formed. Gradually incorporate the remainder of the diluted magma. Finally add enough calcium hydroxide topical solution to make 1000 mL, and shake well. If a more viscous consistency in the Lotion is desired, the quantity of bentonite magma may be increased to not more than 400 mL.

Many investigators have studied Calamine Lotion, and this has led to the publication of many formulations, each possessing certain advantages over the others, but none satisfying the col-

lective needs of all dermatologists. Formulations containing hydrated microcrystalline cellulose and carboxymethylcellulose have a slower rate of sedimentation than the official preparation.

Although most lotions are prepared by trituration, some lotions are formed by chemical interaction in the liquid. White Lotion, USP is an example.

White Lotion

Zinc Sulfate	40 g
Sulfurated Potash	40 g
Purified Water,	qs 1,000 mL

Dissolve the zinc sulfate and the sulfurated potash separately, each in 450 mL of purified water, and filter each solution. Add slowly the sulfurated potash solution to the zinc sulfate solution with constant stirring. Then add the required amount of purified water, and mix.

Benzyl Benzoate Lotion USP is an example of a lotion that is also an emulsion. The formula and method of preparation are:

Benzyl Benzoate	250 mL
Triethanolamine	5 g
Oleic Acid	20 g
Purified Water	qs 1,000 mL

Mix the triethanolamine with the oleic acid, add the benzyl benzoate, and mix. Transfer the mixture to a suitable container of about 2000 mL capacity, add 250 mL of purified water, and shake the mixture thoroughly. Finally add the remaining purified water, and again shake thoroughly.

Triethanolamine forms a soap with the oleic acid and functions as the emulsifying agent to form a stable product. This type of emulsifying agent is almost neutral in water and gives a pH of about 8 and thus should not irritate the skin.

Certain lotions tend to separate or stratify on long standing, and they require a label directing that they be shaken well before each use. All lotions should be labeled "For External Use Only." Microorganisms may grow in certain lotions if no preservative is included. Care should be taken to avoid contaminating the lotion during preparation, even if a preservative is present.

Milk of Magnesia USP is a suspension of magnesium hydroxide containing approximately 80 mg of $Mg(OH)_2$ per milliliter. The specifications for double strength or triple strength are that these products should contain approximately 160 mg or 240 mg of $Mg(OH)_2$ per mL, respectively. It has an unpleasant, alkaline taste that can be masked with 0.1% citric acid (to reduce alkalinity) and 0.05% of a volatile oil or a blend of volatile oils. Magnesium hydroxide is prepared by the hydration of magnesium oxide.

For the most part, magmas are intended for internal use, although Bentonite Magma is used primarily as a suspending agent for insoluble substances for local application and occasionally for internal use. All magmas require a "Shake Well" label and "Avoid Freezing."

EXTRACTS

Extraction, as the term is used pharmaceutically, involves the separation of medicinally active portions of plant or animal tissues from the inactive or inert components by using selective solvents in standard extraction procedures. The products obtained from plants are relatively impure liquids, semisolids, or powders intended only for oral or external use. These include classes of preparations known as decoctions, infusions, fluidextracts, tinctures, pilular (semisolid) extracts, and powdered extracts. Such preparations popularly have been called galenicals, after Galen, the 2nd century Greek physician.

Extraction continues to be of considerable interest in order to obtain improved yields of drugs derived from plant and animal sources. For example, extraction of digitalis glycosides has been carried out using super critical carbon dioxide.[102] Other techniques include ultrasonics, rotary-film evaporators, hydrodistillation, liquid chromatography, multiple-solvent extraction, countercurrent extraction, and gravitation dynamics.

This discussion is concerned primarily with basic extraction procedures for crude drugs to obtain the therapeutically desirable portion and eliminate the inert material by treatment with a selective solvent, known as the menstruum. Extraction differs from solution in that the presence of insoluble matter is implied in the former process. The principal methods of extraction are maceration, percolation, digestion, infusion, and decoction. The quality of the finished product can be enhanced by standardizing primary extracts and carrying out analytical assays during production on the raw materials, intermediate products, and manufacturing procedures.

The processes of particular importance, insofar as the USP is concerned, are those of maceration and percolation, as described specifically for Belladonna Extract USP and Cascara Sagrada Extract USP. Most pharmacopeias refer to such processes for extraction of active principles from crude drugs. The USP provides general directions for both maceration and percolation under the heading of *Tinctures*.

Techniques of extraction continue to be investigated and applied to obtain higher yields of the active substance from natural sources. Some of these methods include the use of different grinding and shearing processes of plants, use of specific membranes for extraction, and different extraction procedures such as distillation, digestion, percolation, and microwaves.

MACERATION—In this process the solid ingredients are placed in a stoppered container with 750 mL of the prescribed solvent and allowed to stand for a period of at least 3 days in a warm place with frequent agitation, until soluble matter is dissolved. The mixture is filtered and, after most of the liquid has drained, the residue on the filter is washed with sufficient quantity of the prescribed solvent or solvent mixture; the filtrates are combined to produce 1000 mL.

PERCOLATION—The ground solids are mixed with the appropriate quantity of the prescribed solvent to make it evenly and uniformly damp. It is allowed to stand for 15 min, then transferred to a percolator and packed. Sufficient prescribed solvent is added to saturate the solids. The top is placed on the percolator, and when the liquid is about to drip from the apparatus, the lower opening is closed. The solids are allowed to macerate for 24 hours or for the specified time. If no assay is directed, the percolation is allowed to proceed slowly or at the specified rate gradually adding sufficient solvent to produce 1000 mL of solution. If an assay is required, only 950 mL of percolate are collected and mixed and a portion assayed as directed. The rest of the percolate is diluted with the solvent to produce a solution that conforms to the required standard and then mixed.

DIGESTION—This is a form of maceration in which gentle heat is used during the process of extraction. It is used when moderately elevated temperature is not objectionable and the solvent efficiency of the menstruum is increased thereby.

INFUSION—An infusion is a dilute solution of the readily soluble constituents of crude drugs. Fresh infusions are prepared by macerating the solids for a short period of time with either cold or boiling water. The USP has not included infusions for some time.

DECOCTION—This once popular process extracts water-soluble and heat stable constituents from crude drugs by boiling in water for 15 min, cooling, straining, and passing sufficient cold water through the drug to produce the required volume.

EXTRACTIVE PREPARATIONS

After a solution of the active constituents of a crude drug is obtained by maceration or percolation, it may be ready for use as a medicinal agent, as with certain tinctures or fluidextracts, or it may be processed further to produce a solid or semisolid extract.

Tinctures

Tinctures are defined in the USP as being alcoholic or hydroalcoholic solutions prepared from vegetable materials or from chemical substances, an example of the latter being Iodine Tincture. Traditionally, tinctures of potent vegetable drugs essentially represent the activity of 10 g of the drug in each 100 mL of tincture, the potency being adjusted following assay. Most other tinctures of vegetable drugs represent the extractive from 20 g of the drug in 100 mL of tincture.

The USP specifically describes two general processes for preparing tinctures, one by percolation and the other by maceration. Percolation includes a modification so that tinctures that require assay for adjustment to specified potency thus may be tested before dilution to final volume. Belladonna Tincture, USP is prepared in this manner. Compound Benzoin Tincture USP and Sweet Orange Peel Tincture, USP are prepared by the maceration procedure.

Fluidextracts

The USP defines fluidextracts as being liquid preparations of vegetable drugs, containing alcohol as a solvent or as a preservative, or both, so made that, unless otherwise specified in an individual monograph, each milliliter contains the therapeutic constituents of 1 g of the standard drug that it represents.

Extracts

Extracts are defined in the USP as concentrated preparations of vegetable or animal drugs obtained by removal of the active constituents of the respective drugs with suitable menstrua, evaporation of all or nearly all of the solvent, and adjustment of the residual masses or powders to the prescribed standards. There are three forms of extracts: semiliquids or liquids of syrupy consistency, plastic masses (known as *pilular* or *solid extracts*), and dry powders (known as *powdered extracts*). Extracts, as concentrated forms of the drugs from which they are prepared, are used in a variety of solid or semisolid dosage forms. The USP states that pilular extracts and powdered extracts of any one drug are interchangeable medicinally, but each has its own pharmaceutical advantages. Pilular extracts, so-called because they are of a consistency to be used in pill masses and made into pills, are also suited for use in ointments and suppositories. Powdered extracts are better suited for incorporation into a dry formulation, as in capsules, powders, or tablets. Semiliquid extracts, or extracts of a syrupy consistency, may be used in the manufacture of some pharmaceutical preparations.

Most extracts are prepared by extracting the drug by percolation. The percolate is concentrated, generally by distillation under reduced pressure. The use of heat is avoided where possible because of potential injurious effect on active constituents. Powdered extracts that are made from drugs that contain inactive oily or fatty matter may have to be defatted or prepared from defatted drug. Pure Glycyrrhiza Extract USP is an example of a pilular extract and Belladonna Extract USP is an example of a powdered extract.

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CHAPTER 52

Stability of Pharmaceutical Products

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Stability of a pharmaceutical product may be defined as the capability of a particular formulation, in a specific container/closure system, to remain within its physical, chemical, microbiological, therapeutic, and toxicological specifications. Assurances that the packaged product will be stable for its anticipated shelf life must come from an accumulation of valid data on the drug in its commercial package. These stability data involve selected parameters that, taken together, form the stability profile. Pharmaceutical products are expected to meet their specifications for identity, purity, quality, and strength throughout their defined storage period at specific storage conditions.

The stability of a pharmaceutical product is investigated throughout the various stages of the development process. The stability of a drug substance is first assessed in the preformulation stage. At this stage, pharmaceutical scientists determine the drug substance and its related salts stability/compatibility with various solvents, buffered solutions, and excipients considered for formulation development. Optimization of a stable formulation of a pharmaceutical product is built upon the information obtained from the preformulation stage and continues during the formulation development stages.

Typically, the first formulation development stage is the preparation of a "first in human" formulation which is often a non-elegant formulation optimized for short-term dose-ranging clinical studies. The second major formulation development stage occurs to support Phase II and early Phase III clinical studies. The pharmaceutical product developed at this stage is usually the prototype for the commercial product. Therefore, the pharmaceutical product will be formulated based in part on the stability information obtain from the previous formulations and must meet stability requirements for longer-term clinical studies. The final formulation development stage is for the commercial pharmaceutical product. In addition to building on the clinical requirements of the drug, the commercial pharmaceutical product must also incorporate the commercial or the final market image of the product, which includes the container closure system. The stability of this product must be demonstrated to the appropriate regulatory agencies in order to assign an expiration date for the product.

Once a pharmaceutical product has gained regulatory approval and is marketed, the pharmacist must understand the proper storage and handling of the drug. In some cases, a pharmacist may need to prepare stable compounded preparations from this product. It is the responsibility of the pharmacist, via the information of the manufacturer, to instruct the patient in the proper storage and handling of the drug product. The impact of a drug product with a poor stability profile could delay approval, affect the safety and efficacy of the drug, and/or cause product recall.

Much has been written about the development of a stable pharmaceutical product. Comprehensive treatments of all aspects of pharmaceutical product stability has been published by Lintner,[1] Connors et al,[2] and more recently Carstensen[3]. This chapter will outline the appropriate steps from preformulation to drug approval to assure that the pharmaceutical product developed is stable. Requirements for compounded products will also be discussed.

The USP defines the stability of a pharmaceutical product as "extent to which a product retains, within specified limits, and throughout its period of storage and use (ie, its shelf-life), the same properties and characteristics that it possessed at the time of its manufacture." There are five types of stability that must be considered for each drug.

Type of Stability	Conditions Maintained Throughout the Shelf-Life of the Drug Product
Chemical	Each active ingredient retains its chemical integrity and labeled potency, within the specified limits.
Physical	The original physical properties, including appearance, palatability, uniformity, dissolution, and suspendability are retained.
Microbiological	Sterility or resistance to microbial growth is retained according to the specified requirements. Antimicrobial agents that are present retain effectiveness within the specified limits.
Therapeutic	The therapeutic effect remains unchanged.
Toxicological	No significant increase in toxicity occurs.

Stability of a drug also can be defined as the time from the date of manufacture and packaging of the formulation until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously. Although there are exceptions, 90% of labeled potency generally is recognized as the minimum acceptable potency level. Expiration dating is defined, therefore, as the time in which a drug product in a specific packaging configuration will remain stable when stored under recommended conditions.

An expiration date, which is expressed traditionally in terms of month and year, denotes the last day of the month. The expiration date should appear on the immediate container and the outer retail package. However, when single-dose containers are packaged in individual cartons, the expiration date may be

placed on the individual carton instead of the immediate product container. If a dry product is to be reconstituted at the time of dispensing, expiration dates are assigned to both the dry mixture and the reconstituted product. Tamper-resistant packaging is to be used where applicable.

One type of time-related stability failure is a decrease in therapeutic activity of the preparation to below labeled content. A second type of stability failure is the appearance of a toxic substance, formed as a degradation product upon storage of the formulation. The numbers of published cases reflecting this second type are few. However, it is possible, though remote, for both types of stability failures to occur simultaneously within the same pharmaceutical product. Thus, the use of stability studies with the resulting application of expiration dating to pharmaceuticals is an attempt to predict the approximate time at which the probability of occurrence of a stability failure may reach an intolerable level. This estimate is subject to the usual Type 1 or alpha error (setting the expiration too early so that the product will be destroyed or recalled from the market appreciably earlier than actually is necessary) and the Type 2 or beta error (setting the date too late so that the failure occurs in an unacceptably large proportion of cases). Thus, it is obligatory that the manufacturer clearly and succinctly define the method for determining the degree of change in a formulation and the statistical approach to be used in making the shelf-life prediction. An intrinsic part of the statistical methodology must be the statements of value for the two types of error. For the safety of the patient a Type 1 error can be accepted, but not a Type 2 error.

REGULATORY REQUIREMENTS

Stability study requirements and expiration dating are covered in the Current Good Manufacturing Practices (cGMPs),[4] the USP,[5] and the FDA guidelines.[6]

GOOD MANUFACTURING PRACTICES—The GMPs[4] state that there shall be a written testing program designed to assess the stability characteristics of drug products. The results of such stability testing shall be used to determine appropriate storage conditions and expiration dating. The latter is to ensure that the pharmaceutical product meets applicable standards of identity, strength, quality, and purity at time of use. These regulations, which apply to both human and veterinary drugs, are updated periodically in light of current knowledge and technology.

COMPENDIA—The compendia also contain extensive stability and expiration dating information. Included are a discussion of stability considerations in dispensing practices and the responsibilities of both the pharmaceutical manufacturer and the dispensing pharmacist. It now is required that product labeling of official articles provide recommended storage conditions and an expiration date assigned to the specific formulation and package. Official storage conditions as defined by the USP 26[5] are as follows: *Cold* is any temperature not exceeding 8°C, and *refrigerator* is a cold place where the temperature is maintained thermostatically between 2 and 8°C. A *freezer* is a cold place maintained between −25 and −10°C. *Cool* is defined as any temperature between 8 and 15°C, and *room temperature* is that temperature prevailing in a working area. *Controlled room temperature* is that temperature maintained thermostatically between 20 and 25°C. *Warm* is any temperature between 30 and 40°C, while *excessive heat* is any heat above 40°C. Should freezing subject a product to a loss of potency or to destructive alteration of the dosage form, the container label should bear appropriate instructions to protect the product from freezing. When no specific storage instructions are given in a USP monograph, it is understood that the product's storage conditions shall include protection from moisture, freezing, and excessive heat.

As is noted above in USP 26, the definition of controlled room temperature was a "temperature maintained thermostatically between 20 and 25°C (68 and 77°F)." This definition was established to harmonize with international drug standards efforts. The usual or customary temperature range is identified as 20 to 25°C, with the possibility of encountering excursions in the 15 to 30°C range and with the introduction the mean kinetic temperature (MKT).

The mean kinetic temperature is calculated using the following equation:

$$T_k = \left[\frac{\Delta H/R}{-In\left(\frac{e^{-\Delta H/RT_1} + e^{-\Delta H/RT_2} + \ldots + e^{-\Delta H/RT_{n-1}} + e^{-\Delta H/RT_n}}{n} \right)} \right]$$

in which T_k is the mean kinetic temperature; ΔH is the heat of activation, 83.144kJ·mole^{-1}; R is the universal gas constant, 8.3144×10^{-3} kJ· mole^{-1}· degree^{-1}; T_1 is the value for the temperature (in degrees Kelvin [°K]) recorded during the first time period, T_2 is the value for the temperature recorded during the second time period, eg, second week; T_{n-1} is the value of the second to last time period, and T_n is the value for the temperature recorded during the nth time period. Typically, the time period is in days or weeks. The mean kinetic temperature determines the thermal exposure of a material. This allows an acceptable estimation to assess if a temperature excursion (or series of excursions) adversely affected a material.

FDA Guidelines provide recommendations for:

1. The design of stability studies to establish appropriate expiration dating periods and product storage requirements
2. The submission of stability information for investigational new drugs, biologicals, new drug applications, and biological product license applications

Thus, the guidelines represent a framework for the experimental design and data analysis as well as the type of documentation needed to meet regulatory requirements in the drug-development process.

Table 52-1. Stability Protocols

CONDITIONS	MINIMUM TIME PERIOD AT SUBMISSION
Long-term testing 25°C ± 2°C/60% ± 5% RH	12 mo
Accelerated testing 40°C ± 2°C/75% ± 5% RH	6 mo
Alternate testing[a] 30°C ± 2°C/65% ± 5% RH	12 mo

[a]Required if *significant change* occurs during 6-mo storage under conditions of accelerated testing.

Example Stability Pull Schedule for a Solid Oral Dose for Zone I and II

STORAGE CONDITIONS	DURATIONS (MONTHS)								
	0	1	3	6	9	12	18	24	36
25°C/60% RH	R*		X	X	X	X, Y	X	X	X
30°C/65% RH			O	O	O	O			
40°C/75% RH		X	X	X, Y					

*From Release testing if testing is within 30 days of stability set down.

R = Release Tests
- Appearance (visual)
- Identity
- Assay (HPLC)
- Impurities (HPLC)
- Dissolution (USP <711>)
- Moisture Content (Karl Fischer)
- Uniformity of Dosage Unit

X = Tests at Every Stability Pull
- Appearance (visual)
- Assay (HPLC)
- Impurities (HPLC)
- Dissolution (USP <711>)

O = Pull and test only after 40°C/75% is out of specification
- Appearance (visual)
- Assay (HPLC)
- Impurities (HPLC)
- Dissolution (USP <711>)

Y = Additional tests periodically performed
- Moisture Content (Karl Fischer)

FDA Guidelines, however, has been reevaluated and revised significantly in the last few years, with the aim of harmonizing the technical requirements for the registration of pharmaceuticals worldwide. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brought together regulatory authorities and experts from the pharmaceutical industry from three regions of the world; Europe, Japan, and the US. The first conference (ICH1) took place in November 1991 in Brussels, and the second conference (ICH2) in Orlando, FL, in October 1993. These conferences provided an open forum for discussion and resulted in the creation of an extensive set of guidelines dealing with the many aspects of safety, quality, and efficacy of medicinal products. The ICH Harmonized Tripartite Guideline provides a general indication on the requirements for *Stability Testing of New Drug Substances and Products*. The main thrust of the stability guideline centers around criteria for setting up stability protocols, shown in Table 52-1 and the example Stability Pull Schedule.

The guidelines were published in a draft form in the *Federal Register*, April 16, 1993. The final guidelines were published in 1994, with implementation of the guidelines occurring with Registration Applications after January 1, 1998. Revision 1 of the guidance was published in August 2001. Online computer can now access a complete listing of FDA publications and guidances. To view the publications, go to http://www.fda.gov/cder/guidance/index.htm.

PRODUCT STABILITY

Many factors affect the stability of a pharmaceutical product and include the stability of the active ingredient(s), the potential interaction between active and inactive ingredients, the manufacturing process, the dosage form, the container-liner-closure system, and the environmental conditions encountered during shipment, storage and handling, and length of time between manufacture and usage.

Classically, pharmaceutical product stability evaluations have been separated into studies of chemical (including biochemical) and physical stability of formulations. Realistically, there is no absolute division between these two arbitrary divisions. Physical factors, such as heat, light, and moisture, may initiate or accelerate chemical reactions, while every time a measurement is made on a chemical compound. Physical dimensions are included in the study.

In this treatment, physical and chemical stability are discussed along with those dosage form properties that can be measured and are useful in predicting shelf life. The effect of various physical and chemical phenomena of pharmaceuticals also is treated.

Knowledge of the physical stability of a formulation is very important for three primary reasons. First, a pharmaceutical product must appear fresh, elegant, and professional, for as long as it remains on the shelf. Any changes in physical appearance such as color fading or haziness can cause the patient or consumer to lose confidence in the product. Second, since some products are dispensed in multiple-dose containers, uniformity of dose content of the active ingredient over time must be ensured. A cloudy solution or a broken emulsion can lead to a non-uniform dosage pattern. Third, the active ingredient must be available to the patient throughout the expected shelf life of the preparation. A breakdown in the physical system can lead to non-availability or "dose dumping" of the medication to the patient. In the case of metered-dose inhaler pulmonary aerosols, particle aggregation may result in inadequate lung deposition of the medication.

The chemical causes of drug deterioration have been classified as incompatibility, oxidation, reduction, hydrolysis, racemization, and other mechanisms. In the latter category, decarboxylation, deterioration of hydrogen peroxide and hypochlorites, and the formation of precipitates have been included.

PHARMACEUTICAL DOSAGE FORMS

As the various pharmaceutical dosage forms present unique stability problems, they are discussed separately in the following section.

TABLETS—Stable tablets retain their original size, shape, weight, and color under normal handling and storage conditions throughout their shelf life. In addition, the *in vitro* availability of the active ingredients should not change appreciably with time.

Excessive powder or solid particles at the bottom of the container, cracks or chips on the face of a tablet, or appearance of crystals on the surface of tablets or on container walls are indications of physical instability of uncoated tablets. Hence, the effect of mild, uniform, and reproducible shaking and tumbling of tablets should be studied. The recommended test for such studies is the determination of tablet friability as described in the USP. Tablet Friability <1216> describes the recommended apparatus and the test procedure. After visual observation of the tablets for chips, cracks, and splits, the intact tablets are sorted and weighed to determine the amount of material worn away by abrasion. In general a maximum weight loss of not more than 1% of the weight of the tablets being tested is considered acceptable for most products. The results of these tests are comparative rather than absolute and should be correlated with actual stress experience. Packaged tablets also should be subjected to cross-country shipping tests as well as to various *drop tests*.

Tablet hardness (or resistance to crushing or fracturing) can be assessed by commercially available hardness testers. As results will vary with the specific make of the test apparatus used, direct comparison of results obtained on different instruments may not necessarily be made. Thus, the same instrument should be used consistently throughout a particular study.

Color stability of tablets can be followed by an appropriate colorimeter or reflectometer with heat, sunlight, and intense artificial light employed to accelerate the color deterioration. Caution must be used in interpreting the elevated temperature data, as the mechanism for degradation at that temperature may differ from that at a lower temperature. It is not always proper to assume that the same changes will occur at elevated temperatures as will be evidenced later at room temperature. Cracks, mottling, or tackiness of the coating indicates evidence of instability of coated tablets.

For tablets containing the more insoluble active ingredients, the results of dissolution tests are more meaningful than disintegration results for making bioavailability predictions. Dissolution-rate tests should be run in an appropriate medium such as artificial gastric and/or intestinal fluid at 37°. When no significant change (such as a change in the polymorphic form of the crystal) has occurred, an unaltered dissolution-rate profile of a tablet formulation usually indicates constant *in vivo* availability.

Uniformity of weight, odor, texture, drug and moisture contents, and humidity effect also are studied during a tablet stability test.

GELATIN CAPSULES—Hard gelatin capsules are the type used by pharmaceutical manufacturers in the production of the majority of their capsule products. The pharmacist in the extemporaneous compounding of prescriptions may also use hard gelatin capsules. Soft gelatin capsules are prepared from shells of gelatin to which glycerin or a polyhydric alcohol such as sorbitol has been added to render the gelatin elastic or plastic-like. Gelatin is stable in air when dry but is subject to microbial decomposition when it becomes moist or when it is maintained in aqueous solution. Normally hard gelatin capsules contain between 13% and 16% moisture. If stored in a high humidity environment capsule shells may soften, stick together, or become distorted and lose their shape. On the other hand, in an environment of extreme dryness gelatin capsules may harden and crack under slight pressure. Gelatin capsules should be protected from sources of microbial contamination.

Encapsulated products, like all other dosage forms, must be packaged properly.

Because moisture may be absorbed or released by gelatin capsules depending on the environmental conditions, capsules offer little physical protection to hygroscopic or deliquescent materials enclosed within a capsule when stored in an area of high humidity. It is not uncommon to find capsules packaged in containers along with a packet of desiccant material as a precautionary measure.

Both hard and soft gelatin capsules exposed to excessive heat and moisture may exhibit delayed or incomplete dissolution due to cross-linking of the gelatin in the capsule shell. The cross-linking of gelatin capsules is an irreversible chemical reaction. Cross-linking may also occur in capsules that are exposed to aldehydes and peroxides. Although cross-linked capsules may fail dissolution due to pellicle formation, digestive enzymes will dissolve the capsules. For hard or soft gelatin capsules that do not conform to the dissolution specification, the dissolution test may be repeated with the addition of enzymes. Where water or a medium with a pH less than 6.8 is specified as the medium in the individual monograph, the same medium specified may be used with the addition of purified pepsin that results in an activity of 750,000 units or less per 1000 mL. For media with a pH of 6.8 or greater, pancreatin can be added to produce not more than 1750 USP units of protease activity per 1000 mL.

SUSPENSIONS—A stable suspension can be redispersed homogeneously with moderate shaking and can be poured easily throughout its shelf life, with neither the particle-size distribution, the crystal form, nor the physiological availability of the suspended active ingredient changing appreciably with time.

Most stable pharmaceutical suspensions are flocculated; that is, the suspended particles are bonded together physically to form a loose, semi rigid structure. The particles are said to uphold each other while exerting no significant force on the liquid. Sedimented particles of a flocculated suspension can be redispersed easily at any time with only moderate shaking.

In nonflocculated suspensions, the particles remain as individuals unaffected by neighboring particles and are affected only by the suspension vehicle. These particles, which are smaller and lighter, settle slowly, but once they have settled, often form a hard, difficult-to-disperse sediment. Nonflocculated suspensions can be made acceptable by decreasing the particle size of the suspended material or by increasing the density and viscosity of the vehicle, thus reducing the possibility of settling.

When studying the stability of a suspension, first determine with a differential manometer if the suspension is flocculated. If the suspension is flocculated, the liquid will travel the same distance in the two side arms. With nonflocculated suspensions, the hydrostatic pressures in the two arms are unequal; hence, the liquids will be at different levels.

The history of settling of the particles of a suspension may be followed by a Brookfield viscometer fitted with a Helipath attachment. This instrument consists of a rotating T-bar spindle that descends slowly into the suspension as it rotates. The dial reading on the viscometer is a measure of the resistance that the spindle encounters at various levels of the sedimented suspension. This test must be run only on fresh, undisturbed samples.

An electronic particle counter and sizer, such as a Coulter counter, or a microscope may be used to determine changes in particle-size distribution. Crystal form alterations may be detected by microscopic, near-IR or Raman examination and, when suspected, must be confirmed by x-ray powder diffraction.

All suspensions should be subjected to cycling temperature conditions to determine the tendency for crystal growth to occur within the suspension. Shipping tests, ie, transporting bottles across the country by rail or truck are also used to study the stability of suspensions.

SOLUTIONS—A stable solution retains its original clarity, color, and odor throughout its shelf life. Retention of clarity of a solution is a main concern of a physical stability program. As visual observation alone under ordinary light is a poor test of clarity, a microscope light should be projected through a diaphragm into the solution. Undissolved particles will scatter the light, and the solution will appear hazy. While the Coulter counter also can be used, light-scattering instruments are the most sensitive means of following solution clarity.

Solutions should remain clear over a relatively wide temperature range such as 4 to 47°C. At the lower range an ingredient may precipitate due to its lower solubility at that temperature, while at the higher temperature the flaking of particles from the glass containers or rubber closures may destroy homogeneity. Thus, solutions should be subjected to cycling temperature conditions.

The stability program for solutions also should include a study of pH changes, especially when the active ingredients are soluble salts of insoluble acids or bases. Among other tests are observations for changes in odor, appearance, color, taste, light-stability, redispersibility, suspendibility, pourability, viscosity, isotonicity, gas evolution, microbial stability, specific gravity, surface tension, and pyrogen content, in the case of parenteral products.

When solutions are filtered, the filter medium may absorb some of the ingredients from the solution. Thus, the same type of filter should be used for preparing the stability samples as will be used to prepare the production-size batches.

For dry-packaged formulations reconstituted prior to use, the visual appearance should be observed on both the original dry material and on the reconstituted preparation. The color and odor of the cake, the color and odor of the solution, the moisture content of the cake, and the rate of reconstitution should be followed as a part of its stability profile.

EMULSIONS—A stable emulsion can be redispersed homogeneously to its original state with moderate shaking and can be poured at any stage of its shelf life. Although most of the important pharmaceutical emulsions are of the oil in water (O/W) type, many stability test methods can be applied to either an O/W or water in oil (W/O) emulsion.

Two simple tests are used to screen emulsion formulations. First, heating to 50 to 70°C and observing its gross physical stability either visually or by turbidimetric measurements can determine the stability of an emulsion. Usually the emulsion that is the most stable to heat is the one most stable at room temperature. However, this may not be true always, because an emulsion at 60°C may not be the same as it is at room temperature. Second, the stability of the emulsion can be estimated by the *coalescence time* test. Although this is only a rough quantitative test, it is useful for detecting gross differences in emulsion stability at room temperature.

Emulsions also should be subjected to refrigeration temperatures. An emulsion stable at room temperature has been found to be unstable at 4°C. It was reasoned that an oil-soluble emulsifier precipitated at the lower temperature and disrupted the system. An emulsion chilled to the extent that the aqueous base crystallizes is damaged irreversibly.

The ultracentrifuge also is used to determine emulsion stability. When the amount of separated oil is plotted against the time of centrifugation, a plateau curve is obtained. A linear graph results when the oil flotation (creaming) rate is plotted versus the square of the number of centrifuge revolutions per minute. The flotation rate is represented by the slope of the line resulting when the log distance of emulsion-water boundary from the rotor center is plotted against time for each revolution per minute.

For stability studies, two batches of an emulsion should be made at one time on two different sizes of equipment. One should be a bench-size lot and the other a larger, preferably production-size, batch. Different types of homogenizers produce different results, and different sizes of the same kind of homogenizer can yield emulsions with different characteristics.

OINTMENTS—Ointments have been defined as high-viscosity suspensions of active ingredients in a non-reacting

vehicle. A stable ointment is one that retains its homogeneity throughout its shelf-life period. The main stability problems observed in ointments are *bleeding* and changes in consistency due to aging or changes in temperature. When fluid components such as mineral oil separate at the top of an ointment, the phenomenon is known as *bleeding* and can be observed visually. Unfortunately, as there is no known way to accelerate this event, the tendency to *bleed* cannot be predicted.

An ointment that is too soft is messy to use, while one that is very stiff is difficult to extrude and apply. Hence, it is important to be able to define quantitatively the consistency of an ointment. This may be done with a penetrometer, an apparatus that allows a pointed weight to penetrate into the sample under a measurable force. The depth of the penetration is a measure of the consistency of an ointment. Consistency also can be measured by the Helipath attachment to a high-viscosity viscometer or by a Burrell Severs rheometer. In the latter instrument, the ointment is loaded into a cylinder and extruded with a measured force. The amount extruded is a measure of the consistency of the ointment.

Ointments have a considerable degree of structure that requires a minimum of 48 hours to develop after preparation. As rheological data on a freshly made ointment may be erroneous, such tests should be performed only after the ointment has achieved equilibrium. Slight changes in temperature (1 or 2°C) can affect the consistency of an ointment greatly; hence, rheological studies on ointments must be performed only at constant and controlled temperatures.

Among the other tests performed during the stability study of an ointment are a check of visual appearance, color, odor, viscosity, softening range, consistency, homogeneity, particle-size distribution, and sterility. Undissolved components of an ointment may change in crystal form or in size with time. Microscopic examination or an x-ray diffraction measurement may be used to monitor these parameters.

In some instances it is necessary to use an ointment base that is less than ideal, to achieve the required stability. For example, drugs that hydrolyze rapidly are more stable in a hydrocarbon base than in a base containing water, even though they may be more effective in the latter.

TRANSDERMAL PATCHES—A typical transdermal patch consists of a protective backing, a matrix containing active drug, an adhesive that allows the patch to adhere to the skin, and a release liner to protect the skin adhering adhesive. Therefore, the transdermal patch must deliver drug as labeled, adhere properly to both the backing and to the patient's skin. In addition, the transdermal patch must be pharmaceutically elegant through the shelf life of the product. For a transdermal patch, this means that the release line peels easily with minimal transfer of adhesive onto the release liner and that the adhesive does not ooze from the sides of the patch. Therefore, the typical stability related tests for transdermal patches are, appearance, assay, impurities, drug release USP<724> and, backing peel force.

METERED-DOSE AEROSOLS DRUG PRODUCTS—A metered dose inhalation product consists of an aerosol can containing a propellant, a drug and a mouthpiece used to present an aerosolized drug to the patient. There are many drug contact components in a metered-dose inhalation product. Therefore, the drug may be in contact with materials that could allow plasticizer leach into the drug. The typical stability related tests for metered-dose aerosols include appearance, assay, impurities, plume geometry, emitted dose, particle size distribution of the emitted dose, and number of doses per unit. In addition, stability studies on leachables may be required. Shelf life of metered-dose aerosols drug products may also be dependent on the orientation that the drug product is stored. Typically most canisters type product are tested at least in the upright orientation.

DRY-POWDERED INHALATION PRODUCTS—A dry-powdered inhalation product consists of drug with excipients delivered in a dry powdered form. The delivery system for a dry-powdered inhalation product may be a separate device or integrated with the active. A dry-powdered dosage must reproducibly deliver a specific amount of drug at a particle size that can be deposited into the lungs. Particles too large will get trapped in the throats and particles too small will just be carried out of the lungs on the next expiration. The typical stability related tests for dry powder inhalation products include appearance, assay, impurities, emitted dose, particle size distribution of the emitted dose, and water content.

NASAL INHALATION PRODUCTS—A nasal inhalation product consists of drug with excipients delivered from a delivery system. The delivery system for a nasal inhalation product may be a separate device or integrated with the active. A nasal inhalation product must reproducibly deliver a specific amount of drug at a particle size and plume that can be deposited into the nasal membrane. Particles too large will not be absorbed into nasal membrane or run out of the nose; and poor spray pattern will deposit the drug ineffective in the nasal cavity. The typical stability related tests for nasal inhalation products include appearance, assay, impurities, spray content uniformity, particle (droplet) size distribution of the emitted dose, spray pattern or /and plume geometry, leachables, weight loss and preservative content. Sterility and microbial testing may be required periodically for stability testing.

INCOMPATIBILITY

Typically, physicochemical stability is assessed at the preformulation stage of development. A drug substance candidate is treated with acid, base, heat, light, and oxidative conditions to assess its inherit chemical stability. Binary mixtures of the drug substance with individual excipients are also investigated at the preformulation stage. These tests are performed to determine the drug substance sensitivity to degrade or react with common pharmaceutical excipients. The most common reactions observed for drug substances from these tests include: hydrolysis, epimerization (racemization), decarboxylation, dehydration, oxidation, polymerization, photochemical decomposition, and addition. All drug substances have the potential to degrade by at least one of the reactions mentioned above. With an understanding of the stability/reactivity of a drug substance in the preformulation stage, it is possible to formulate the drug product to minimize drug decomposition. Numerous examples are described in other sections of this book, and the literature is replete with illustrations.

While undesirable reactions between two or more drugs are said to result in a *physical, chemical,* or *therapeutic* incompatibility, physical incompatibility is somewhat of a misnomer. It has been defined as a physical or chemical interaction between two or more ingredients that leads to a visibly recognizable change. The latter may be in the form of a gross precipitate, haze, or color change.

On the other hand, a chemical incompatibility is classified as a reaction in which a visible change is not necessarily observed. Since there is no visible evidence of deterioration, this type of incompatibility requires trained, knowledgeable personnel to recognize it.

A therapeutic incompatibility has been defined as an undesirable pharmacological interaction between two or more ingredients that leads to

1. Potentiation of the therapeutic effects of the ingredients
2. Destruction of the effectiveness of one or more of the ingredients
3. Occurrence of a toxic manifestation within the patient.

REACTION KINETICS

An understanding of reaction kinetics is important in determining the shelf life of a product.

CHEMICAL REACTIONS

The most frequently encountered chemical reactions, which may occur within a pharmaceutical product, are described below.

OXIDATION-REDUCTION—Oxidation is a prime cause of product instability, and often, but not always, the addition of oxygen or the removal of hydrogen is involved. When molecular oxygen is involved, the reaction is known as auto-oxidation because it occurs spontaneously, though slowly, at room temperature.

Oxidation, or the loss of electrons from an atom, frequently involves free radicals and subsequent chain reactions. Only a very small amount of oxygen is required to initiate a chain reaction. In practice, it is easy to remove most of the oxygen from a container, but very difficult to remove it all. Hence, nitrogen and carbon dioxide frequently are used to displace the headspace air in pharmaceutical containers to help minimize deterioration by oxidation.

As an oxidation reaction is complicated, it is difficult to perform a kinetic study on oxidative processes within a general stability program. The redox potential, which is constant and relatively easy to determine, can, however, provide valuable predictive information. In many oxidative reactions, the rate is proportional to the concentration of the oxidizing species but may be independent of the concentration of the oxygen present. The rate is influenced by temperature, radiation, and the presence of a catalyst. An increase in temperature leads to an acceleration in the rate of oxidation. If the storage temperature of a preparation can be reduced to 0 to 5°C, usually it can be assumed that the rate of oxidation will be at least halved.

The molecular structures most likely to oxidize are those with a hydroxyl group directly bonded to an aromatic ring (eg, phenol derivatives such as catecholamines and morphine), conjugated dienes (eg, vitamin A and unsaturated free fatty acids), heterocyclic aromatic rings, nitroso and nitrite derivatives, and aldehydes (eg, flavorings). Products of oxidation usually lack therapeutic activity. Visual identification of oxidation, for example, the change from colorless epinephrine to its amber colored products, may not be visible in some dilutions or to some eyes.

Oxidation is catalyzed by pH values that are higher than optimum, polyvalent heavy metal ions (eg, copper and iron), and exposure to oxygen and UV illumination. The latter two causes of oxidation justify the use of antioxidant chemicals, nitrogen atmospheres during ampul and vial filling, opaque external packaging, and transparent amber glass or plastic containers.

Trace amounts of heavy metals such as cupric, chromic, ferrous, or ferric ions may catalyze oxidation reactions. As little as 0.2 mg of copper ion per liter considerably reduces the stability of penicillin. Similar examples include the deterioration of epinephrine, phenylephrine, lincomycin, isoprenaline, and procaine hydrochloride. Adding chelating agents to water to sequester heavy metals and working in special manufacturing equipment (eg, glass) are some means used to reduce the influence of heavy metals on a formulation. Parenteral formulations should not come in contact with heavy metal ions during their manufacture, packaging, or storage.

Hydronium and hydroxyl ions catalyze oxidative reactions. The rate of decomposition for epinephrine, for example, is more rapid in a neutral or alkaline solution with maximum stability (minimum oxidative decomposition) at pH 3.4. There is a pH range for maximum stability for any antibiotic and vitamin preparation, which usually can be achieved by adding an acid, alkali, or buffer.

Oxidation may be inhibited by the use of antioxidants, called negative catalysts. They are very effective in stabilizing pharmaceutical products undergoing a free-radical-mediated chain reaction. These substances, which are easily oxidizable, act by possessing lower oxidation potentials than the active ingredient. Thus, they undergo preferential degradation or act as chain inhibitors of free radicals by providing an electron and receiving the excess energy possessed by the activated molecule.

The ideal antioxidant should be stable and effective over a wide pH range, soluble in its oxidized form, colorless, nontoxic, nonvolatile, nonirritating, effective in low concentrations, thermostable, and compatible with the container-closure system and formulation ingredients.

The commonly used antioxidants for aqueous systems include sodium sulfite, sodium metabisulfite, sodium bisulfite, sodium thiosulfate, and ascorbic acid. For oil systems, ascorbyl palmitate, hydroquinone, propyl gallate, nordihydroguaiaretic acid, butylated hydroxytoluene, butylated hydroxyanisole, and alpha-tocopherol are employed.

Synergists, which increase the activity of antioxidants, are generally organic compounds that complex small amounts of heavy metal ions. These include the ethylenediamine tetraacetic acid (EDTA) derivatives, dihydroethylglycine, and citric, tartaric, gluconic, and saccharic acids. EDTA has been used to stabilize ascorbic acid, oxytetracycline, penicillin, epinephrine, and prednisolone.

Reduction reactions are much less common than oxidative processes in pharmaceutical practice. Examples include the reduction of gold, silver, or mercury salts by light to form the corresponding free metal.

HYDROLYSIS—Drugs containing esters (eg, cocaine, physostigmine, aspirin, tetracaine, procaine and methyldopa), amides (eg, dibucaine), imides (eg, amobarbital), imines (eg, diazepam) and lactam (eg, penicillins, cephalosporins) functional groups are among those prone to hydrolysis.

Hydrolysis reactions are often pH dependent and are catalyzed by either hydronium ion or hydroxide ions (specific-acid or specific-base catalysis, respectively). Hydrolysis reactions can also be catalyzed by either a Brønsted acid or a Brønsted base (general-acid or general-base catalysis, respectively). Sources of Brønsted acid or base include buffers and some excipients. Sometimes, it is necessary to compromise between the optimum pH for stability and that for pharmacological activity. For example, several local anesthetics are most stable at a distinctly acid pH, whereas for maximum activity they should be neutral or slightly alkaline. Small amounts of acids, alkalines, or buffers are used to adjust the pH of a formulation. Buffers are used when small changes in pH are likely to cause major degradation of the active ingredient.

Obviously, the amount of water present can have a profound effect on the rate of a hydrolysis reaction. When the reaction takes place fairly rapidly in water, other solvents sometimes can be substituted. For example, barbiturates are much more stable at room temperature in propylene glycol–water than in water alone.

Modification of chemical structure may be used to retard hydrolysis. In general, as it is only the fraction of the drug in solution that hydrolyzes, a compound may be stabilized by reducing its solubility. This can be done by adding various substituents to the alkyl or acyl chain of aliphatic or aromatic esters or to the ring of an aromatic ester. In some cases less-soluble salts or esters of the parent compound have been found to aid product stability. Steric and polar complexation have also been employed to alter the rate of hydrolysis. Caffeine reduces the rate of hydrolysis and thus promotes stability by complexation with local anesthetics such as benzocaine, procaine, or tetracaine.

Esters and β-lactams are the chemical bonds that are most likely to hydrolyze in the presence of water. For example, the acetyl ester in aspirin is hydrolyzed to acetic acid and salicylic acid in the presence of moisture, but in a dry environment the hydrolysis of aspirin is negligible. The aspirin hydrolysis rate increases in direct proportion to the water vapor pressure in an environment.

The amide bond also hydrolyzes, though generally at a slower rate than comparable esters. For example, procaine (an ester) will hydrolyze upon autoclaving, but procainamide will not. The amide or peptide bond in peptides and proteins varies

in the labiality to hydrolysis. The lactam and azomethine (or imine) bonds in benzodiazepines are also labile to hydrolysis. The major chemical accelerators or catalysts of hydrolysis are adverse pH and specific chemicals (eg, dextrose and copper in the case of ampicillin hydrolysis).

The rate of hydrolysis depends on the temperature and the pH of the solution. A much-quoted estimation is that for each 10°C rise in storage temperature, the rate of reaction doubles or triples. As this is an empiricism, it is not always applicable.

When hydrolysis occurs, the concentration of the active ingredient decreases while the concentration of the decomposition products increases. The effect of this change on the rate of the reaction depends on the order of the reaction. With zero-order reactions the rate of decomposition is independent of concentration of the ingredient. Although dilute solutions decompose at the same absolute rate as more concentrated solutions, the more dilute the solution, the greater the proportion of active ingredient destroyed in a given time; ie, the percentage of decomposition is greater in more dilute solutions. Increasing the concentration of an active ingredient that is hydrolyzing by zero-order kinetics will slow the percentage decomposition.

With first-order reactions, which occur frequently in the hydrolysis of drugs, the rate of change is directly proportional to the concentration of the reactive substance. Thus, changes in the concentration of the active ingredient have no influence on the percentage decomposition.

The degradation of many drugs in solution accelerates or decelerates exponentially as the pH is decreased or increased over a specific range of pH values. Improper pH ranks with exposure to elevated temperature as a factor most likely to cause a clinically significant loss of drug, resulting from hydrolysis and oxidation reactions. A drug solution or suspension, for example, may be stable for days, weeks, or even years in its original formulation, but when mixed with another liquid that changes the pH, it degrades in minutes or days. It is possible that a pH change of only one unit (eg, from 4 to 3 or 8 to 9) could decrease drug stability by a factor of ten or greater.

A pH-buffer system, which is usually a weak acid or base and its salt, is a common excipient used in liquid preparations to maintain the pH in a range that minimizes the drug degradation rate. The pH of drug solutions may also be either buffered or adjusted to achieve drug solubility. For example, pH in relation to pKa controls the fractions of the usually more soluble ionized and less soluble nonionized species of weak organic electrolytes.

INTERIONIC (ION N+ −ION N−) COMPATIBILITY— The compatibility or solubility of oppositely charged ions depends mainly on the number of charges per ion and the molecular size of the ions. In general, polyvalent ions of opposite charge are more likely to be incompatible. Thus, an incompatibility is likely to occur upon the addition of a large ion with a charge opposite to that of the drug.

As many hydrolytic reactions are catalyzed by both hydronium and hydroxyl ions, pH is an important factor in determining the rate of a reaction. The pH range of minimum decomposition (or maximum stability) depends on the ion having the greatest effect on the reaction. If the minimum occurs at about pH 7, the two ions are of equal effect. A shift of the minimum toward the acid side indicates that the hydroxyl ion has the stronger catalytic effect and *vice versa* in the case of a shift toward the alkaline side. In general, hydroxyl ions have the stronger effect. Thus, the minimum is often found between pH 3 and 4. The influence of pH on the physical stability of two-phase systems, especially emulsions, is also important. For example, intravenous fat emulsion is destabilized by acidic pH.

DECARBOXYLATION— Pyrolytic solid-state degradation through decarboxylation usually is not encountered in pharmacy, as relatively high heats of activation (25 to 30 kcal) are required for the reaction. However, solid *p*-aminosalicylic acid undergoes pyrolytic degradation to *m*-aminophenol and carbon dioxide. The reaction, which follows first-order kinetics, is highly pH-dependent and is catalyzed by hydronium ions. The decarboxylation of *p*-aminobenzoic acid occurs only at extremely low pH values and at high temperatures.

Some dissolved carboxylic acids, such as *p*-aminosalicylic acid, lose carbon dioxide from the carboxyl group when heated. The resulting product has reduced pharmacological potency. β-Keto decarboxylation can occur in some solid antibiotics that have a carbonyl group on the β-carbon of a carboxylic acid or a carboxylate anion. Such decarboxylations will occur in the following antibiotics: carbenicillin sodium, carbenicillin free acid, ticarcillin sodium, and ticarcillin free acid.

RACEMIZATION— Racemization, or the action or process of changing from an optically active compound into a racemic compound or an optically inactive mixture of corresponding *R* (*rectus*) and *S* (*sinister*) forms, is a major consideration in pharmaceutical stability. Optical activity of a compound may be monitored by polarimetry and reported in terms of specific rotation. Chiral HPLC has been used in addition to polarimetry to confirm the enantiomeric purity of a sample.

In general, racemization follows first-order kinetics and depends on temperature, solvent, catalyst, and the presence or absence of light. Racemization appears to depend on the functional group bound to the asymmetric carbon atom, with aromatic groups tending to accelerate the process.

EPIMERIZATION— Members of the tetracycline family are most likely to incur epimerization. This reaction occurs rapidly when the dissolved drug is exposed to a pH of an intermediate range (higher than 3), and it results in the steric rearrangement of the dimethylamino group. The epimer of tetracycline, epitetracycline, has little or no antibacterial activity.

PHOTOCHEMICAL REACTIONS

Photolytic degradation can be an important limiting factor in the stability of pharmaceuticals. A drug can be affected chemically by radiation of a particular wavelength only if it absorbs radiation at that wavelength and the energy exceeds a threshold. Ultraviolet radiation, which has a high energy level, is the cause of many degradation reactions. Exposure to, primarily, UV illumination may cause oxidation (photo-oxidation) and scission (photolysis) of covalent bonds. Nifedipine, nitroprusside, riboflavin, and phenothiazines are very labile to photo-oxidation. In susceptible compounds, photochemical energy creates free radical intermediates, which can perpetuate chain reactions.

If the absorbing molecule reacts, the reaction is said to be photochemical in nature. When the absorbing molecules do not participate directly in the reaction, but pass their energy to other reacting molecules, the absorbing substance is said to be a photosensitizer.

As many variables may be involved in a photochemical reaction, the kinetics can be quite complex. The intensity and wavelength of the light and the size, shape, composition, and color of the container may affect the velocity of the reaction.

The photodegradation of chlorpromazine through a semiquinone free-radical intermediate follows zero-order kinetics. On the other hand, alcoholic solutions of hydrocortisone, prednisolone, and methylprednisolone degrade by reactions following first-order kinetics.

Colored-glass containers most commonly are used to protect light-sensitive formulations. Yellow-green glass gives the best protection in the ultraviolet region, while amber confers considerable protection from ultraviolet radiation but little from infrared. Riboflavin is best protected by a stabilizer that has a hydroxyl group attached to or near the aromatic ring. The photodegradation of sulfacetamide solutions may be inhibited by an antioxidant such as sodium thiosulfate or metabisulfite.

A systematic approach to photostability testing is recommended covering, as appropriate, studies such as tests on the drug substance, tests on the exposed drug product outside of the immediate pack; and if necessary, tests on the drug product

in the immediate pack. ICH Q1B discusses the minimum requirements for assessing photostability. Drug substance is first assessed by exposing sample powder having a depth of not more than 3 mm to an overall illumination of not less than 1.2 million lux hours and an integrated near ultraviolet energy of not less than 200 watt hours/square meter. If the drug substance shows sensitivity to photodegrations, then the drug product will need to be tested as well. The testing of drug product uses the same light exposure that was used to test drug substance. The drug product should be tested directly exposed to light and in its container closure system.

ULTRASONIC ENERGY

Ultrasonic energy, which consists of vibrations and waves with frequencies greater than 20,000 Hz, promotes the formation of free radicals and alters drug molecules. Changes in prednisolone, prednisone acetate, or deoxycorticosterone acetate suspensions in an ultrasonic field have been observed spectrometrically in the side chain at C-17 and in the oxo group of the A ring. With sodium alginate, in an ultrasonic field, it has been reported that above a minimum power output, degradation increased linearly with increased power.

IONIZING RADIATION

Ionizing radiation, particularly gamma rays, has been used for the sterilization of certain pharmaceutical products. At the usual sterilizing dose, 2.5 mRad, it seldom causes appreciable chemical degradation. In general, formulations that are in the solid or frozen state are more resistant to degradation from ionizing radiation than those in liquid form. For example, many of the vitamins are little affected by irradiation in the solid state but are decomposed appreciably in solution. On the other hand, both the liquid- and solid-state forms of atropine sulfate are affected seriously by radiation.

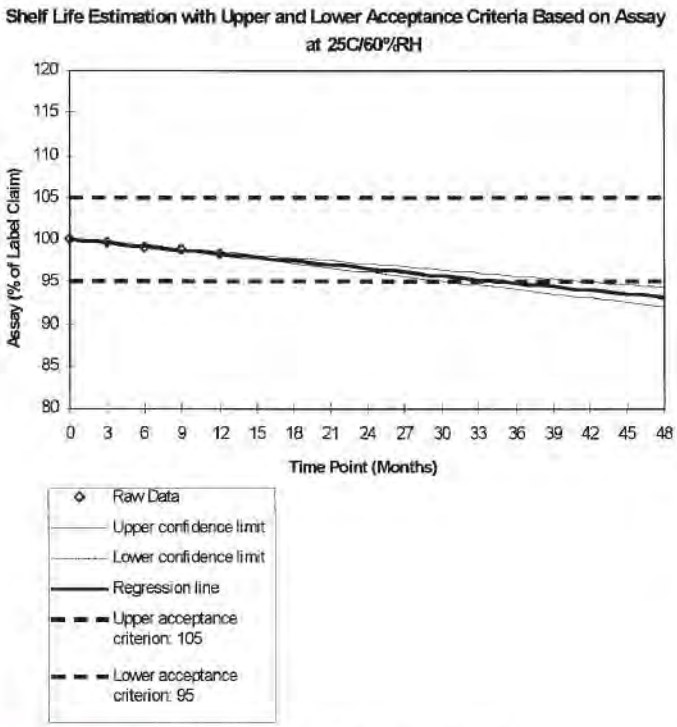

Figure 52-1. Typical two-sided shelf-life estimation plot.

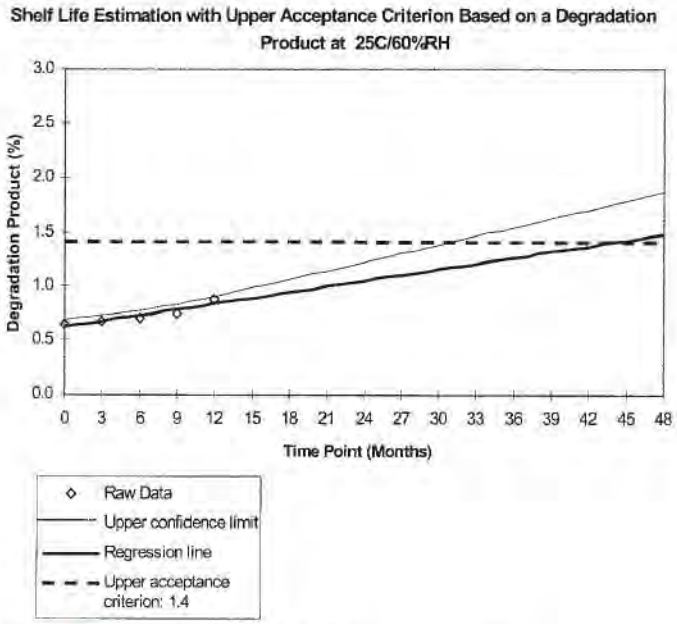

Figure 52-2. Typical one-sided shelf-life estimation plot.

PREDICTING SHELF LIFE

ICH Recommended Evaluation

The shelf life of a commercial drug product must be determined in the commercial container closure at the defined storage conditions. ICH requires at least 12 months stability data at the time of NDA submission. Most products require at least 24 months to be commercially viable. The ICH Q1E recommends how the 12 months data may be used to predict long-term stability. Figures 52-1 and 52-2 show trending graphs with double-sided and single-sided 95% confidence limits plots, respectively.

Figure 52-1 shows a plot of 12 months of assay (potency) results versus time. The acceptance criteria for this test have a lower and an upper limit of 95% and 105%, respectively. The extrapolated line from this data set intersects the lower acceptance limit at about 35 months. However, there is always statistical uncertainty when extrapolating a data set. The 95% confidence limit is used to take this uncertainty into account. The lower 95% confidence intersects the lower acceptance limit at about 29 months. Therefore, this product would be assessed an expiration date of 29 months.

Figure 52-2 shows a plot of 12 months of degradation product results. In this case, the acceptance criterion is an upper limit of not more than 1.4%. The extrapolated line from this data set intersects the acceptance limit at about 44 months. The upper 95% confidence limit curve intersects the acceptance limit at about 30 months. Therefore, this product would be assessed an expiration date of 30 months. The expiration of a product is the time where the confidence line intersects with the acceptance limit. Trend analysis of data need only be performed on test data that shows a change related to time.

Approximations in Assessing Product Stability—Estimation of Temperature Effect

In early development, a shelf life prediction of a clinical material, especially a Phase I material, may be based on a very limited amount of sample and limited amount of time to make the evaluation. One way to estimate long-term storage for a material is by extrapolating data from studies performed at elevated conditions. An understanding of potential activation energy is needed to estimate long-term stability. Many may have heard

of the estimate that for every 10°C decrease in storage temperature the shelf-life doubles. This is only true, however, if the activation energy of the reaction(s) that causes degradation is 15 kcal/moles. The activation energy, E_a, for many chemical processes related to the degradation of a drug substance/product is typically within the range of 10 to 25 kcal/moles.

The equation below shows a way of calculating the $Q_{\Delta T}$ value that may be used to estimate the affect of temperature on shelf life.

$$Q_{\Delta T} = \exp\left[\frac{E_a}{R}\left(\frac{\Delta T}{T + \Delta T(T)}\right)\right] \quad (1)$$

where, $Q_{\Delta T}$ is a factor (multiplier/divisor) used to estimate the change in the reaction rate constant with change in temperature, ΔT. E_a is the activation energy established for a reaction

An approximation for the change in reaction rate constants due to the temperature effects are shown in the table below.

Ea (kcal/mole)	Q_5 (25 to 30°C)	Q_{10} (25 to 35°C)	Q_{15} (25 to 40°C)
10	1.32	1.73	2.24
15	1.52	2.27	3.36
20	1.75	2.99	5.04
25	2.01	3.93	7.55

Therefore, the old rule of thumb that a reaction rate doubles with every 10°C is only true if the reaction has an activation energy between 10 to 15 kcal/mole (Q_{10} = 1.73 and 2.27, respectively). Q_{15} is useful for understanding the relationship of ICH accelerated temperature of 40°C has with controlled room temperature at 25°C. Materials made and packaged for clinical studies are usually tested at an accelerated condition in order to predict that the packaged material will be stable for the duration of the clinical study. A material stable for one month at accelerated temperature (40°C) supports that the material stored at room temperature should be stable for at least 3 months. This true only when the activation energy of the degradation process is about 15 kcal/mole (Q_{15} factor = 3.36) [In other words, a reaction at 40°C should be 3.36 times faster than the same reaction at 25°C; or the reaction will take 3.36 times longer at 25°C than at 40°C)].

The technique of estimating the shelf life of a formulation from its accumulated stability data has evolved from examining the data and making an educated guess through plotting the time-temperature points on appropriate graph paper and crudely extrapolating a regression line to the application of rigorous physical-chemical laws, statistical concepts, and computers to obtain meaningful, reliable estimates.

A simple means of estimating shelf life from a set of computer-prepared tables has been described by Lintner et al.[6] This system was developed to select the best prototype formulation on the basis of short-term stability data and predict both estimated and minimum shelf-life values for the formulation. It is a middle-ground approach between the empirical methods and the modern, rigorous statistical concepts. All calculations can be made readily by hand, and the estimated values can be obtained easily from appropriate tables. The system assumes that

1. Shelf-life predictions can be made satisfactorily for lower temperatures using the classical Arrhenius model from data obtained at higher temperatures.
2. The energy of activation of the degradation reaction is between 10 and 20 kcal/mol (this is a safe assumption, as Kennon[8] has noted that rarely are drugs with energies of activation below 10 kcal/mol used in pharmacy, and for values as high as 20 kcal/mol, the error in the shelf-life prediction will be on the conservative side).
3. The rate of decomposition will not increase beyond that already observed.
4. The standard deviation of the replicated assays is known or can be estimated from the analytical data.

This concept further assumes that the degradation reaction follows zero- or pseudo-zero-order kinetics. For data corresponding to a zero-, first-, or second-order degradation pattern, it is impossible to distinguish one order from another with usual analytical procedures, when the total degraded material is not large. In addition, shelf-life calculations assuming zero-order kinetics are more conservative than those for higher orders.

This middle-ground system is useful in creating the experimental design for the stability study. The formulator has the opportunity to study various combinations of parameters to try to optimize the physical-statistical model. One can check the effect of improving the assay standard deviation, running additional replicates, using different time points, and assuming various degradation rates and energies of activation on the stability of the test formulation.

McMinn and Lintner later developed and reported on an information-processing system for handling product stability data.[9] This system saves the time of formulators in analyzing and interpreting their product stability data, in addition to minimizing the amount of clerical help needed to handle an ever-increasing assay load. For products such as those of vitamins, for example, where large overages are required, the statistical portions of this advanced technique aid the manufacturer to tailor the formula composition to obtain the desired and most economical expiration dating.

This system stores both physical and chemical data and retrieves the information in three different formats (one of which was designed specifically for submitting to regulatory agencies). It analyzes single-temperature data statistically by analysis of covariance and regression or multiple-temperature data by weighted or unweighted analysis using the Arrhenius relationship; provides estimates of the shelf life of the preparation with the appropriate confidence intervals; preprints the assay request cards that are used to record the results of the respective assay procedures and to enter the data into the system; and produces a 5-yr master-stability schedule as well as periodic 14-day schedules of upcoming assays.

As mentioned above, a portion of the advanced system analyzes the stability data obtained at a single temperature by analysis of covariance and regression. This analysis is based on the linear (zero-order) model

$$Y_{ij} = \beta_i X_{ij} + \alpha_i + \varepsilon_{ij} \quad (2)$$

where Y_{ij} is the percentage of label of the jth stability assay of the ith lot, X_{ij} is the time in months at which Y_{ij} was observed, β_i and α_i are the slope and intercept, respectively, of the regression line of the ith lot, and ε_{ij} is a random error associated with Y_{ij}. The random errors are assumed to be identically and independently distributed normal variables with a zero mean and a common variance, σ^2.

A summary of the regression analysis for each individual lot and for the combination of these lots, plus a summary of the analyses of covariance and deviation from regression is prepared by the computer.

Because the computer combines, or pools, the stability data from the individual lots, irrespective of the statistical integrity of this step, the pooled data are examined for validity by the F test. The mean square of the regression coefficient (slope) is divided by the mean square of the deviation within lots, and similarly, the adjusted mean (y intercept) is divided by the common mean square to give the respective F ratios. The latter values then are compared with the critical 5% F values. When the calculated F values are smaller than the critical F values, the data may be combined, and the pooled data analyzed.

A printout for the combined lots as well as for each individual lot provides the estimated rate of degradation and its standard error in percentage per month for each ingredient. The *Student t* value is calculated from these estimates and tested for significance from zero. When the t value is significant, the printout contains an estimate of the shelf life with the appropriate confidence interval. When the t value is not significantly different from zero, estimates of the minimum and projected shelf-life values are made. In addition, coordinates of the calculated least-squares regression line with ap-

propriate confidence limits for the mean and individual predicted assays are printed.

Plots of the resulting least-squares line containing the individual data points also are printed by the computer. For the calculation of X_0, $\hat{Y}$ equals $\overline{Y} + \hat{\beta}(X_0 - \overline{X..})$, where $\hat{\beta}$ is the least-squares estimate of the slope, and $\overline{X..}$ is the mean time of assay.

The sample variance for this estimate, $S^2(Y)$ is equal to

$$S_{y \cdot x}{}^2 \left[\frac{1}{N} + \left[\frac{(X_0 - \overline{X..})^2}{\sum (X_{ij} - \overline{X..})^2} \right] \right] \quad (3)$$

where N is the number of assays. The 95% confidence interval is equal to $Y \pm t_{0.05S(\hat{Y})}$.

For cases in which the slope of the best fitting line is positive and significantly different from zero (resulting, eg, from solvent evaporation), the statement "no degradation has been detected and hence no shelf-life estimate is made" is printed. When the computed line has a positive slope but not significantly different from zero, only the minimum shelf-life value is calculated.

Traditionally, extensive stability data are collected at the recommended storage temperatures (usually refrigerator and/or room temperature) to be placed on the label of the package. However, elevated-temperature data are very valuable in determining the shelf life of a product. In practice, multiple levels of thermal stress are applied to the formulation so that appropriate shelf-life estimates can be made for normally expected marketing conditions. In cases in which data from accelerated studies are used to project a tentative expiration date that is beyond the date supported by actual shelf-life studies, testing must continue until the tentative expiration date is verified.

The effect of temperature variation on the rate of a reaction can be expressed by an integrated form of the Arrhenius equation

$$k = se^{-E_A/RT} \quad (4)$$

where, k is the rate constant, E_A is the energy of activation in kcal/mole, R is the universal gas constant of 1.987 cal/deg mole, T is the temperature in degrees in Kelvin, and S is a constant that is related to the specific reaction.

$$\log \frac{k_2}{k_1} = \frac{E_a}{2.303R}\left(\frac{T_2 - T_1}{T_2 * T_1}\right) \quad (5)$$

where, k_1 is the rate constant at temperature T_1 and k_2 is the rate constant at temperature T_2.

A weighted modification of this model has been incorporated into the previously described computerized system. Each printout contains a statement concerning the acceptability of the Arrhenius assumption with its appropriate probability level, the slope and intercept for the Arrhenius line, the estimated apparent energy of activation with its 95% confidence limits, plus the estimated shelf-life values at selected temperatures.

The analysis of first-order stability data is based on the linear model

$$Y_{ij} = \alpha_i + \beta_i X_{ij} + \varepsilon_{ij} \quad (6)$$

where Y_{ij} is the natural logarithm of the assay value for the jth observation of the ith temperature, X_{ij} is the elapsed time in months for the assay sample for the ith temperature, β_i and α_i are the slope and intercept, respectively, and ε_{ij} is a random error associated with Y_{ij}. The errors are assumed to be distributed identically and independently, normally with a zero mean and variance σ^2.

For orders other than first, Y_{ij} represents the concentration raised to the power of 1 minus the order.

The estimated rate constant (ie, the negative slope) is

$$-b_i = -\sum_j (Y_{ij} - Y_i)(X_{ij} - X_i) / \sum_j (X_{ij} - X_i)^2 \quad (7)$$

The standard error of the estimated rate constant is

$$S_{-b_i} = \frac{S(X/Y)}{[\sum (X_{ij} - X_i)^2]^{1/2}} \quad (8)$$

where $S(Y/X)$, the residual standard error, is equal to

$$S(X/Y) = \left\{ \frac{1}{N-2} \left[\sum_{j=1}^{12} (Y_{ij} - Y_i)^2 - \frac{[\sum (X_{ij} - X_i)(Y_{ij} - Yi)^2]}{\sum (X_{ij} - X_i)^2} \right] \right\}^{1/2} \quad (9)$$

According to the Arrhenius relationship, faster degradation occurs at the higher temperatures; hence, assays for the high-temperature data usually are run more often but for a shorter period of time. The effect of simple least-squares analysis of this type of data is to force the Arrhenius equation through the low temperature data and essentially ignore the high-temperature information. Thus, much more credence is placed in the point estimates of the low temperature than is warranted. In addition, the usual confidence limits on extrapolated degradation rates at refrigerator or room temperature cannot be made validly. For these reasons, Bentley[10] presented a method based on a weighted least-squares analysis to replace the unweighted approximation. He also developed a statistical test for the validity of the Arrhenius assumption, which is computed easily from the results of the unweighted method.

To make shelf-life estimates from elevated temperature data, two storage temperatures are obviously the minimum. As the accuracy of the extrapolation is enhanced by using additional temperatures, a minimum of four different temperatures is recommended for most product stability studies. With the current use of computers to do the bulk of stability calculations, including weighted least-squares analysis, the temperatures and storage conditions need not be selected for arithmetic convenience.

It is not necessary to determine the mechanism of the degradation reaction. In most cases, it is necessary only to follow some property of degradation and to linearize this function. Either the amount of intact drug or the amount of a formed degradation product may be followed. It usually is impractical to determine the exact order of the reaction. With assay errors in the range of 2 to 5%, at least 50% decomposition must occur before the reaction order can be determined. As the loss with pharmaceuticals generally is less, zero-order kinetics should be assumed, unless the reaction order is known from previous work. In any case, replication of stability assays is advisable.

The batches of drugs used for a stability study should be representative of production run material or at least material of a known degree of purity. The quality of the excipients also should be known, as their impurities or even their moisture content can affect product stability deleteriously. Likewise, the samples of the formulation taken for the stability study must be representative of the lot.

Specific, stability-indicating assay methods must be used, to make meaningful shelf-life estimates. The reliability and specificity of the test method on the intact molecule and on the degradation products must be demonstrated.

ADDITION OF OVERAGE

The problem of declining potency in an unstable preparation can be ameliorated by the addition of an excess or overage of the active ingredient. Overages, then, are added to pharmaceutical formulations to keep the content of the active ingredient within the limits compatible with therapeutic requirements, for a predetermined period of time.

The amount of the overage depends upon the specific ingredient and the galenical dosage form. The International Pharmaceutical Federation has recommended that overages be limited to a maximum of 30% over the labeled potency of an ingredient.

PHARMACEUTICAL CONTAINERS

The official standards for containers apply to articles packaged by either the pharmaceutical manufacturer or the dispensing

pharmacist unless otherwise indicated in a compendial monograph. In general, repackaging of pharmaceuticals is inadvisable. However, if repackaging is necessary, the manufacturer of the product should be consulted for potential stability problems.

A pharmaceutical container has been defined as a device that holds the drug and is, or may be, in direct contact with the preparation. The immediate container is described as that which is in direct contact with the drug at all times. The liner and closure traditionally have been considered to be part of the container system. The container should not interact physically or chemically with the formulation so as to alter the strength, quality, or purity of its contents beyond permissible limits.

The choice of containers and closures can have a profound effect on the stability of many pharmaceuticals. Now that a large variety of glass, plastics, rubber closures, tubes, tube liners, etc are available, the possibilities for interaction between the packaging components and the formulation ingredients are immense. Some of the packaging elements themselves are subject to physical and chemical changes that may be time-temperature dependent.

Frequently, it is necessary to use a well-closed or a tight container to protect a pharmaceutical product. A *well-closed container* is used to protect the contents from extraneous solids or a loss in potency of the active ingredient under normal commercial conditions. A *tight container* protects the contents from contamination by extraneous materials, loss of contents, efflorescence, deliquescence, or evaporation and is capable of tight re-closure. When the packaging and storage of an official article in a well-closed or tight container is specified, water-permeation tests should be performed on the selected container.

In a stability program, the appearance of the container, with special emphasis on the inner walls, the migration of ingredients onto/into the plastic or into the rubber closure, the migration of plasticizer or components from the rubber closure into the formulation, the possibility of two-way moisture penetration through the container walls, the integrity of the tac-seal, and the back-off torque of the cap, must be studied.

GLASS—Traditionally, glass has been the most widely used container for pharmaceutical products to ensure inertness, visibility, strength, rigidity, moisture protection, ease of re-closure, and economy of packaging. While glass has some disadvantages, such as the leaching of alkali and insoluble flakes into the formulation, these can be offset by the choice of an appropriate glass. As the composition of glass may be varied by the amounts and types of sand and silica added and the heat treatment conditions used, the proper container for any formulation can be selected.

According to USP 26, glass containers suitable for packaging pharmacopeial preparations may be classified as either Type I, Type II, Type III, or type NP. Containers of Type I borosilicate glass are generally used for preparations that are intended for parenteral administration, although Type II treated soda-lime glass may be used where stability data demonstrates its suitability. Containers of Type III and Type NP are intended for packaging articles intended for oral or topical use.

New, unused glass containers are tested for resistance to attack by high-purity water by use of a sulfuric acid titration to determine the amount of released alkali. Both glass and plastic containers are used to protect light-sensitive formulations from degradation. The amount of transmitted light is measured using a spectrometer of suitable sensitivity and accuracy.

Glass is generally available in flint, amber, blue, emerald green, and certain light-resistant green and opal colors. The blue-, green-, and flint-colored glasses, which transmit ultraviolet and violet light rays, do not meet the official specifications for light-resistant containers.

Colored glass usually is not used for injectable preparations, since it is difficult to detect the presence of discoloration and particulate matter in the formulations. Light-sensitive drugs for parenteral use usually are sealed in flint ampuls and placed in a box. Multiple-dose vials should be stored in a dark place.

Manufacturers of prescription drug products should include sufficient information on their product labels to inform the pharmacist of the type of dispensing container needed to maintain the identity, strength, quality, and purity of the product. This brief description of the proper container, e.g., light- resistant, well-closed, or tight, may be omitted for those products dispensed in the manufacturer's original container.

PLASTICS—Plastic containers have become very popular for storing pharmaceutical products. Polyethylene, polystyrene, polyvinyl chloride, and polypropylene are used to prepare plastic containers of various densities to fit specific formulation needs.

Factors such as plastic composition, processing and cleaning procedures, contacting media, inks, adhesives, absorption, adsorption, and permeability of preservatives also affect the suitability of a plastic for pharmaceutical use. Hence, biological test procedures are used to determine the suitability of a plastic for packaging products intended for parenteral use and for polymers intended for use in implants and medical devices. Systemic injection and intracutaneous and implantation tests are employed. In addition, tests for nonvolatile residue, residue on ignition, heavy metals, and buffering capacity were designed to determine the physical and chemical properties of plastics and their extracts.

The high-density polyethylene (HDPE) containers, which are used for packaging capsules and tablets, possess characteristic thermal properties, a distinctive infrared absorption spectrum, and a density between 0.941 and 0.965 g/cm^3. In addition, these containers are tested for light transmission, water-vapor permeation, extractable substances, nonvolatile residue, and heavy metals. When a stability study has been performed to establish the expiration date for a dosage form in an acceptable high-density polyethylene container, any other high-density polyethylene container may be substituted provided that it, too, meets compendial standards and that the stability program is expanded to include the alternative container.

Materials from the plastic itself can leach into the formulation, and materials from the latter can be absorbed onto, into, or through the container wall. The barrels of some plastic syringes bind various pharmaceutical preservatives. However, changing the composition of the syringe barrel from nylon to polyethylene or polystyrene has eliminated the binding in some cases.

A major disadvantage of plastic containers is the two-way permeation or *breathing* through the container walls. Volatile oils and flavoring and perfume agents are permeable through plastics to varying degrees. Components of emulsions and creams have been reported to migrate through the walls of some plastics, causing either a deleterious change in the formulation or collapse of the container. Loss of moisture from a formulation is common. Gases, such as oxygen or carbon dioxide in the air, have been known to migrate through container walls and affect a preparation.

Solid dosage forms, such as penicillin tablets, when stored in some plastics, are affected deleteriously by moisture penetration from the atmosphere into the container.

Single unit does packaging in the form of blister packages are often used to package capsule and tablet dosage forms. A typical blister package is comprised of a polymeric film that is molded to have a cavity into which the dosage form is placed. The polymer film is then heat bonded to a paper backed foil liner.

As with plastic bottles, the blister package will allow a certain amount of moisture vapor permeation to occur, and this must be a consideration when selecting the type of film used for the package. The choice of packaging materials used depends on the degree to which the product needs to be protected from light, heat and moisture. Each material has different resistance to each of these elements and will affect the shelf life and storage conditions of the packaged pharmaceutical.

Polyvinylchloride (PVC) offers the least resistance to moisture vapor permeation. Polyvinylidenechloride (PVdC) has characteristics similar to PVC but offers superior resistance to moisture vapor permeation. Aclar, which is a polychlorotrifluo-

roethylene (PVC-CTFE) film has the lowest water vapor permeability and thus offers the best protection from moisture.

METALS—The pharmaceutical industry was, and to a degree still is, a tin stronghold. However, as the price of tin constantly varies, more-collapsible aluminum tubes are being used. Lead tubes tend to have pinholes and are little used in the industry.

A variety of internal linings and closure fold seals are available for both tin and aluminum tubes. Tin tubes can be coated with wax or with vinyl linings. Aluminum tubes are available with epoxy or phenolic resin, wax, vinyl, or a combination of epoxy or phenolic resin with wax. As aluminum is able to withstand the high temperatures required to cure epoxy and phenolic resins adequately, tubes made from this metal presently offer the widest range of lining possibilities.

Closure fold seals may consist of unmodified vinyl resin or plasticized cellulose and resin, with or without added color.

Collapsible tubes are available in many combinations of diameters, lengths, openings, and caps. Custom-use tips for ophthalmic, nasal, mastitis, and rectal applications also are available. Only a limited number of internal liners and closure seals are available for tubes fitted with these special-use tips.

Lined tubes from different manufacturers are not necessarily interchangeable. While some converted resin liners may be composed of the same base resin, the actual liner may have been modified to achieve better adhesion, flow properties, drying qualities, or flexibility. These modifications may have been necessitated by the method of applying the liner, the curing procedure, or, finally, the nature of the liner itself.

CLOSURES

The closures for the formulations also must be studied as a portion of the overall stability program. While the closure must form an effective seal for the container, the closure must not react chemically or physically with the product. It must not absorb materials from the formulation or leach its ingredients into the contents.

The integrity of the seal between the closure and container depends on the geometry of the two, the materials used in their construction, the composition of the cap liner, and the tightness with which the cap has been applied. Torque is a measure of the circular force, measured in inch-pounds, which must be applied to open or close a container. When pharmaceutical products are set up on a stability study, the formulation must be in the proposed market package. Thus, they should be capped with essentially the same torque to be used in the manufacturing step.

Rubber is a common component of stoppers, cap liners, and parts of dropper assemblies. Sorption of the active ingredient, preservative, or other formulation ingredients into the rubber and the extraction of one or more components of the rubber into the formulation are common problems.

The application of an epoxy lining to the rubber closure reduces the amount of leached extractives but essentially has no effect on the sorption of the preservative from the solution. Teflon-coated rubber stoppers may prevent most of the sorption and leaching.

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