

Pharmaceutical Dosage Forms: Disperse Systems volume 2

Second Edition, Revised and Expanded

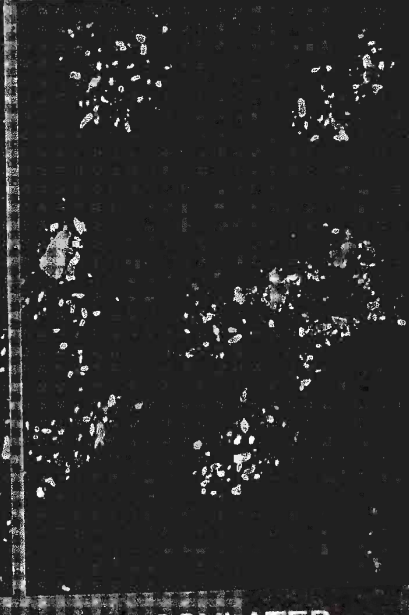
Edited by Herbert A. Lieberman, Martin M. Rieger
and Gilbert S. Banker



UNDISPERSED



DISPERSED



FLOCCULATED

PLAINTIFFS'
TRIAL EXHIBIT

PTX0177

exhibitstickler.com

PHARMACEUTICAL DOSAGE FORMS

Disperse Systems

In Three Volumes

VOLUME 2

Second Edition, Revised and Expanded

EDITED BY

Herbert A. Lieberman

H. H. Lieberman Associates, Inc.
Livingston, New Jersey

Martin M. Rieger

M. & A. Rieger Associates
Morris Plains, New Jersey

Gilbert S. Banker

University of Iowa
Iowa City, Iowa

Marcel Dekker, Inc.

New York • Basel • Hong Kong

ISBN: 0-8247-9713-2

The publisher offers discounts on this book when ordered in bulk quantities. For more information, write to Special Sales/Professional Marketing at the address below.

This book is printed on acid-free paper.

Copyright © 1996 by Marcel Dekker, Inc. All Rights Reserved.

Neither this book nor any part may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, microfilming, and recording, or by any information storage and retrieval system, without permission in writing from the publisher.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

Current printing (last digit):
10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

4

Oral Aqueous Suspensions

Clyde M. Ofner III, Roger L. Schnaare, and Joseph B. Schwartz

Philadelphia College of Pharmacy and Science, Philadelphia, Pennsylvania

I. INTRODUCTION

Oral aqueous suspensions constitute the largest percentage of pharmaceutical suspensions and are used primarily to overcome undesirable properties of the drug. The formulation of a pharmaceutical suspension is often a challenge and in most cases unique because the physical and chemical properties of drugs are different. In addition, a concern exists in all disperse systems, including suspensions, which is to develop a formulation that provides consistent doses throughout the prescribed shelf life of the product. This chapter is a summary of pertinent information to assist the formulator in the preparation of marketable oral aqueous suspension products with an emphasis on the essential principles involved in the process.

Oral aqueous suspensions can be described as two-phase systems composed of water-insoluble drug substances that are dispersed in a continuous aqueous medium. One of the most common reasons to formulate a drug as a suspension is poor aqueous solubility. Another reason for these formulations is that suspensions minimize drug degradation. Drug molecules susceptible to aqueous degradation are protected from reacting with water in the interior of the suspended drug particles. Only the very small soluble fraction of the drug is exposed to water in the solution. Suspensions are also used to mask the unpleasant taste from dissolved drug in solution, which is particularly useful for products intended for pediatric or geriatric patients.

II. CHARACTERISTICS OF ORAL AQUEOUS SUSPENSIONS

A. Efficacy

Drug suspensions are often pharmacologically very effective and they may be less complicated to manufacture than other dosage forms. Their effectiveness may be attributed to a number of factors. For example, drugs formulated as suspensions may be more bioavailable than comparable tablets or capsules [1,2]. Suspensions are often more ef-

fective than tablets or capsules in the pediatric and geriatric patient population, because these patients generally find suspensions easier to swallow. Also, dose flexibility, such as one-half or one-third of a dose, is more convenient with suspensions than with solids, and as a result, patients are more inclined to comply with their dosage instructions.

The bioavailability of oral aqueous suspensions has been studied by comparison with other oral dosage forms, by comparison with different suspending agents, and by comparison with different routes of administration. Bioavailability of some oral aqueous suspensions can be as high as that from I.V. solutions. For example, the estimated bioavailability of a methocarbamol suspension given to rats depended on the dose concentration and ranged from 7% to 112% of the drug formulated in an I.V. polyethylene glycol aqueous solution [3].

Several studies have shown bioequivalence between oral aqueous suspensions and other comparable oral formulations. For example, a suspension of the antibiotic cefuroxime axetil was slightly less bioavailable but statistically bioequivalent to the tablet formulation when tested in 12 healthy volunteers [4]. A similar comparison of propyphenazon in rabbits showed biological equivalence between suspension and tablet formulations [5]. A comparison of three oral formulations of cisapride, a gastrointestinal stimulant, demonstrated no significant differences between the bioequivalence of a suspension, tablet, and solid formulation in healthy men even though the solution produced the shortest time to attain peak plasma drug concentrations [6]. In a study involving 17 cancer patients, peak plasma drug concentrations (C_{max}) were lower from an aqueous medroxyprogesterone acetate suspension than those from a syrup formulation, but the wide intersubject spread in the plasma levels in both groups did not allow any statistical significance to be assigned to this difference [7]. Particle size reduction has produced some suspension formulations that are more bioavailable than comparable tablets or capsules [8]. Particle size reduction to submicron dimensions has been used to increase bioavailability of poorly water-soluble drugs [9].

Other oral suspension formulations have been shown to be bioequivalent to tablets and oral drug solutions. The extent of absorption of a sustained-release formulation of carbinoxamine and phenylpropanolamine was slightly less than that of an aqueous solution of the same drugs in 20 healthy subjects, but the two preparations were statistically bioequivalent [10]. The slightly greater area under the curve (AUC) value and C_{max} of a cefotaxime reconstitutable suspension compared to the values of a tablet formulation in 12 healthy volunteers were not statistically significant and indicated that the two preparations were bioequivalent [11].

The viscosity of the external or continuous phase can influence drug absorption from suspensions. The effects of several suspending agents on drug absorption from a nitrofurantoin suspension was studied in 11 subjects. A viscosity increase slowed absorption and lengthened the duration of action by 2 hours without decreasing bioavailability [12]. Viscosity enhancers, however, decreased the extent of intestinal absorption of sulfafurazole from an aqueous solution in rats; AUC decreased inversely with viscosity [13].

In some cases of poor bioavailability from oral aqueous suspensions, reformulation for alternate routes of administration may be desired. An oral aqueous suspension of artemisinin to treat plasmodium infections was rapidly but incompletely absorbed in 10 male volunteers. Its bioavailability was only 32% that of an I.M. injectable suspension of the same drug in oil. In addition, I.M. injection and rectal administration of the aqueous suspension produced very low and variable drug concentrations in serum indicating poor and erratic absorption [14]. In this case the I.M. suspension formulated with

an oil medium produced the highest bioavailability compared with three other routes of administration formulated with an aqueous medium.

Drug suspensions are subject to formulation factors that if not recognized can result in a deleterious effect on the final product and the patient. Nonuniform mixing of the product results in variations of drug concentration. Difficult redispersion of the drug from a sediment, or in the worst case, from caking, will result in over- or underdosing. An undetected polymorphism of the drug can alter its solubility and cause crystal growth. Other, less direct, parameters to be considered once the suspension leaves the manufacturer include the consequences of exposure to extreme heat or cold temperatures, risks of microbial growth, extraction of harmful container components, and change in drug concentration caused by the loss of aqueous vehicle as the result of evaporation or leaking.

B. Desired Attributes

Specific desired attributes of a suspension drug product may depend on the physical/chemical nature of the drug. Required characteristics of suspensions in general are listed in Table 1. In addition to the drug, a typical suspension may contain several other ingredients, including:

- Wetting agent
- Suspending agent
- Protective colloid
- Flocculating agent
- Sweetener
- Preservatives
- Buffer system
- Flavor
- Color
- Sequestering agent
- Antifoaming agent

The appropriate selection and combination of these ingredients are the goal of the formulator.

III. PRINCIPLES OF FORMULATION

Because the specific properties of various suspended drugs differ, no single procedure will always produce a successful suspension product. Different methods have been de-

Table 1 Requirements of Oral Suspension Formulations

- | |
|--|
| <ol style="list-style-type: none">1. The dispersed particles should be small and uniform; they should not settle fast.2. If the particles settle, they should be easily redispersed.3. There should be no excess viscosity to interfere with pouring and redispersal.4. The redispersal should produce a uniform dose for administration.5. The suspension should be chemically and physically stable for the shelf life of the product.6. The final formulation should be pleasing to the patient; it should have an agreeable odor, color, and taste. |
|--|

veloped with varying degrees of success. However, certain principles have been recognized that are fundamental for all successful formulations. This section contains a general discussion of these principles. Specific examples are discussed with sample formulas. Ingredients are discussed in more detail in the next section. For additional information on suspension formulation, see the excellent reviews by Haines and Martin [15-17], Nash [18,19], and Idson and Scheer [20]. For more information on the colloidal and surface-chemical aspects of suspensions, see the review by Schott and Martin [21].

A. Particle Size

One of the most important considerations in the formulation of a suspension is the particle size of the drug. As the insoluble drug settles, a nonuniform distribution results. A major goal of the formulator is to slow or even prevent sedimentation of the drug particle. Particle sedimentation can lead to caking, which is dense packing of the sediment. Redispersal of a caked suspension is difficult if not impossible. Redispersal of a caked sediment presents a potential danger to the patient. The patient will receive an overdose of the drug if the administered dose from the suspension contains many particles of the broken but previously caked drug sediment. It should be pointed out that as long as the sediment is easily redispersed to produce a uniform drug concentration, sedimentation is not a risk to the patient and is frequently not considered a formulation problem. The relationship of factors that describes the rate of particle settling, or sedimentation, is Stokes' law:

$$v = \frac{d^2(\rho_2 - \rho_1)g}{18\eta} \quad (1)$$

where v = sedimentation rate of an average particle

d = mean particle diameter

ρ_2 = particle density

ρ_1 = density of the dispersion medium

g = acceleration due to gravity

η = viscosity of the dispersion medium.

Equation (1) illustrates that the largest factor to influence sedimentation rate is particle diameter because the rate is directly proportional to the square of particle diameter; consequently, smaller particles settle slower than larger particles. If the particles are less than approximately 3 μm , and their density does not differ by more than 20% from that of the vehicle, then the particles could remain suspended due to Brownian motion.

In practice, there is a limit to particle size reduction. After reducing particles to a certain size, further reduction can be costly because of the time and equipment involved. Furthermore, suspensions of particles in the colloidal size range have additional problems caused by the enhanced consequences of interactions between very small particles that have an extremely large total particle surface area. One example of such problems is the change in driving force of particle motion from gravity for larger particles to the driving force of Brownian motion for colloidal-sized particles. Such particle motion can produce particle aggregation followed by settling of the aggregates and finally caking.

Equation 1 was derived under conditions not entirely applicable to pharmaceutical suspensions. More theoretical expressions have been reported [22] but Stokes' law is accurate for illustrating the factors that affect sedimentation of suspended particles.

B. Viscosity

Equation (1) illustrates the inverse relationship between viscosity of the dispersion medium and rate of particle settling. An increase in viscosity produces a reduced sedimentation rate and increases physical stability. Viscosity is also increased by the volume fraction of the particles [23]. The formulator must be aware that the presence of the drug itself increases viscosity. The most common method of increasing viscosity is by adding a suspending agent. Too high a viscosity, however, is undesirable if it interferes with pouring and redispersal of the settled particles.

According to Eq. (1), sedimentation rate is also lowered by reducing the density difference between particles and the dispersion medium. Increasing the vehicle density has not been a particularly successful way to control the sedimentation rate because water is the most common vehicle and the additional ingredients do not greatly increase its density. Traditionally, particle size and viscosity have been the properties of suspension products that have received the most attention by formulators.

Also illustrated in Eq. (1) is that suspending agent viscosity will slow but not prevent sedimentation. As early as 1959 Meyer and Cohen [24] suggested that yield value, or the point of an effective infinite viscosity in which there is no flow, was an important mechanism of permanent suspensions in order to prevent sedimentation. The mechanism has been examined [25]. The theoretical yield value (YV) for a suspension must balance or exceed the force of gravity on the settling particles. The equation for spherical particles is:

$$YV = \frac{V(\rho_2 - \rho_1)g}{A} \quad (2)$$

where V = particle volume

ρ_2 = density of particle

ρ_1 = density of dispersion medium

g = acceleration due to gravity

A = cross-sectional area of the particle = πR^2 for radius, R

Using Carbomer 934P as the suspending agent, Meyer and Cohen produced a sand suspension that lasted for several years. These investigators calculated a theoretical yield value for sand (density = 2.60 g/cm³ radius = 0.030 cm) and for marbles (density = 2.55 g/cm³ radius = 0.800 cm) of 63 and 1622 dynes/cm², respectively. The concentrations of the agent required to suspend the "particles" were 0.18% and 0.4%, for sand and marbles, respectively.

The yield value of a dispersion medium can be experimentally determined using a rotational viscometer by plotting shear stress (dyne/cm²) as a function of shear rate (sec⁻¹). The resulting curve, shown in Fig. 1, does not pass through the origin but intersects the axis of shear stress as in curve A, or by extrapolation of the linear portion of the curve as in curve B. The intersection, at C or D, is the yield value. The apparent viscosity of the material is the slope of the curve and for most pharmaceutical systems varies with shear rate, as in curve A. The entire curve, therefore, is usually required to describe the viscosity of these systems.

A dispersion medium in which the suspending agents has a molecular structure that entraps drug particles, thereby severely retarding or preventing sedimentation, is called a structured vehicle [26]. If sedimentation is prevented, then the material has a yield value. This structure must not be so rigid as to prevent flow during pouring from the

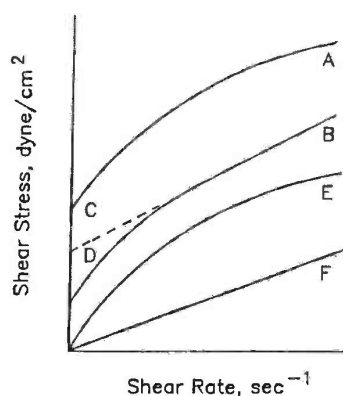


Fig. 1 Rheologic flow behavior. Key: Plastic flow, A and B, with yield values C and D; pseudoplastic flow, E; Newtonian flow, F.

container. These vehicles should be shear-thinning—that is, have high viscosities at negligible shear rates during shelf storage and low viscosities at high shear rates during shaking.

If the molecular structure of the suspending agent producing the increased viscosity is broken down by agitation during shaking but then re-forms upon aging, the suspending agent is thixotropic. The apparent viscosity of thixotropic suspensions is therefore dependent on their previous shear history, including the duration of shearing. This property is useful for pharmaceutical suspensions because the structure formed on standing produces high viscosity or even a yield value and retards or prevents sedimentation. Redispersion by shaking with shear stress greater than the yield value prior to administration temporarily breaks down the structure, reduces the yield value to practically zero, and lowers the apparent viscosity. The suspension then pours easily from the container. After administration and on standing, the structure re-forms to impede sedimentation. Colloidal clays such as bentonite are an example of suspending agents that are thixotropic.

One type of rheologic flow illustrated in Fig. 1 is plastic flow (curves A and B). If the curve passes through the origin (i.e., has no yield value), the material exhibits pseudoplastic flow (curve E). Pseudoplastic materials are shear-thinning; the viscosity varies with shear rate. If the viscosity of a material is unaffected by shear rate, then the plot is linear, the plot passes through the origin, and the material exhibits Newtonian flow (curve F). The yield value of plastic materials is an advantage in a suspending medium. The shear-thinning ability, or the lowered viscosity during shaking, is an advantage of pseudoplastic materials, but the absence of a yield value is a disadvantage. Suspending agents exhibiting Newtonian flow are used infrequently because they lack both yield value and shear-thinning properties. Additional background on the rheology of pharmaceutical materials is available in volume one of this series and in standard pharmacy texts [27,28].

C. Wetting

Most drugs are hydrophobic and, when suspended, frequently float on the vehicle surface as the result of poor wetting. A wetting agent enhances the ability of the disper-

sion medium, or suspension vehicle, to spread on the surface of the drug particle. Wettability of the drug particle can sometimes be evaluated by measuring the contact angle [29]. If poor wetting can be differentiated from moderate wetting, the number of wetting agents to be tested can be reduced. Low concentrations of surfactants are commonly used as wetting agents to aid dispersion of the particles in the suspension vehicle.

Excess wetting agent may lead to foaming or unpleasant taste. An additional caution with wetting agents is the increased possibility of caking because the coated particles resist aggregate formation, settle individually, and may form a dense or caked sediment.

D. Mixing

Although not usually considered an aspect of suspension formulation, mixing is the major operation of suspension particles and is very important because inadequate mixing results in nonhomogeneity of the drug dispersed in the vehicle. A few pertinent points directly related to formulation are discussed. Good reviews on the principles and equipment are available in other chapters of this volume and other sources [30-32].

The initial dispersion of the drug in the vehicle medium is a mixing operation. If the drug is hydrophobic, a wetting agent should be included. Sometimes shearing forces from equipment, such as a ball mill or colloid mill, are used to break up particle aggregates for enhanced wetting and dispersion of the drug.

In some cases, mixing has an unusual purpose. Restoration of the structure associated with thixotropic suspensions is slow if the suspension is viscous. Gentle agitation from low shear rates may accelerate structure restoration, producing high apparent viscosity or thixotropic gels with a yield value [26].

The addition of suspending agents, such as sodium carboxymethylcellulose, to build viscosity increases the difficulty of mixing. The equipment must have the capacity to mix viscous material, but excessive shearing and its concomitant heat production can degrade polymeric suspending agents and should be avoided. Often the completed suspension is passed through a colloid mill to break up excessive particle aggregates and to ensure adequate mixing of the final product.

E. Flocculation

Early formulation efforts were concerned with reduction of the sedimentation rate and ease of redispersing the settled particles. One approach still used is to employ a protective colloid [21]. These agents, such as proteins or gums, adsorb and coat the drug particles and impede aggregation. The result is usually an unsightly appearance of sediment and clear supernatant because the particles eventually settle. If the particles are easily redispersed, however, the appearance does not preclude use of the product. Many antacid suspensions are formulated in this manner but placed in an opaque container to hide the appearance of separated sediment.

Maintaining the drug in suspension with little or no separation results in a more elegant, permanent suspension and is more consistent with modern suspension technology. One such approach is flocculation, which is the formation of loose, low density, particle aggregates [26,33,34]. The flocs settle and produce a loose, inefficiently packed sediment that is less dense and easier to redisperse than a sediment produced by deflocculated, or individual, particles. If the flocculated particles have a sufficient concentration prior to settling, a continuous structure is produced that results in a yield value and little sedimentation. The yield value can therefore be used as an indicator for the extent of flocculation [28]. With the use of flocculating agents, adequate control of floc-

Table 2 Comparison of Properties of Flocculated and Deflocculated Suspension Particles**Deflocculated**

1. Particles exist in suspension as separate entities.
2. Sedimentation rate is slow because each particle settles separately and particle size is minimal.
3. The sediment is formed slowly.
4. The sediment eventually becomes closely packed due to weight of upper layers of sediment. Repulsive forces between particles are overcome, caking results and the sediment is difficult, if not impossible, to redisperse.
5. The suspension has a pleasing appearance because the suspended material remains suspended for a relatively long time. The supernatant also remains cloudy, even when settling is apparent.

Flocculated

1. Particles form loose aggregates.
2. Sedimentation rate is high because particles settle as a floc, which is a collection of particles.
3. The sediment is formed rapidly.
4. The sediment is loosely packed 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 in order to re-form the original suspension.
5. The suspension is somewhat unsightly because of 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 equal volume of the product.

Source: Ref. 35.

culation ideally results in a suspension that does not noticeably separate [35]. Table 2 is a comparison of the properties of flocculated and deflocculated suspension particles.

The use of electrolytes to control the extent of flocculation, known as controlled flocculation, has been used successfully in a number of systems [15–17, 33–35]. Electrolytes reduce the electrical barrier, or zeta potential, between particles and allow them to approach each other and to form flocs. The most efficient electrolytes are those with a charge opposite to that of the particle. The efficiency increases as the valence of the electrolyte increases. For example, a negatively charged particle, such as kaolin, would be very efficiently flocculated with aluminum chloride. This approach requires determinations of zeta potential of the drug particle as a function of electrolyte concentration. The concentration producing zero or a low absolute value of zeta potential should produce optimum flocculation.

Flocculation may occur unintentionally. Other ingredients such as protective colloids, wetting agents, suspending agents, and electrolytes can act as flocculating agents. Colloidally dispersed solids are also an effective method of inducing flocculation [36].

F. Chemical Incompatibilities

Formulators must be aware of the potential chemical incompatibilities between suspension ingredients. These problems may not be immediately apparent. The suspending agents, which are often large anionic molecules such as sodium carboxymethylcellulose, will usually precipitate or gel with cationic molecules. Possible cationic ingredients are the drug, wetting agents, electrolytes, and flocculating agents. Anionic surfactants are usually incompatible with cationic surfactants. Surfactants are used as wetting or flocc-

culating agents. Incompatibilities also exist between di- and trivalent electrolytes and surfactants of opposite charge. Buffers may occasionally react with the drug or suspending agent. Colorants may react with surfactants.

G. Principles of Particle Interactions in Liquid

A discussion of some theory of particle interactions is included to increase conceptual understanding of the principles in the prior sections. The topics of surface free energy, forces of attraction, surface potential, and forces of repulsion are briefly discussed. Several sources are available for more detailed information [37-40].

When a solid material is decreased in size, the total surface area of the subdivided material increases. As the surface area increases, so does the surface free energy, or the positive free energy. Basically, this means that the molecules at the surface have a higher energy state than the molecules below the surface (i.e., within the particle). In order to attain a more energetically stable state, the particles tend to aggregate, which reduces the surface area and lowers the positive free energy toward zero. The clumping of particles, particularly hydrophobic particles such as steroids or sulfur, illustrates this "natural" mechanism of a reduction in free energy.

An alternate mechanism of reducing surface free energy is the adsorption of surface-active materials such as surfactants. After this wetting step, the reduced free energy results in less tendency to reduce surface area and less, if any, clumping is observed. In practice however, the dispersed particles usually settle and caking often results.

The terminology used to describe particle aggregation varies. Some investigators differentiate between coagulation and flocculation to describe the result of specific interactions. The term flocculation is used for all "loose" particle aggregation in this brief discussion.

The forces of attraction between these hydrophobic particles originate at the molecular level and are predominately van der Waals forces of attraction. The rate of particle flocculation caused by these forces can be measured under controlled conditions. Comparison of measured rates constants with theoretical rates constants reveals many examples in which flocculation occurs much slower than expected [40]. These cases indicate a component of repulsion that opposes and reduces attraction.

The forces of repulsion are the result of the presence of an electrical charge on the surface of the particles. Charges of the same sign produce forces of electrostatic repulsion. The charge may originate from different sources. The material may have an ionic composition, such as insoluble salts; or electrolytes from the continuous liquid phase may adsorb to the particles; or surfactant ions may adsorb to the particles.

The charge on the particle results in a surface potential, ψ_0 , at the particle surface. Counterions, or ions of a charge opposite to that on the particle, must be present for electro-neutrality and consequently can counteract the potential. The distance at which the potential drops to zero depends on the concentration of counterions. This region of decreasing potential ends gradually at a distance where its ionic composition approaches that of the bulk liquid and is called the electrical double layer. It ranges in thickness from 10 to 1000 Å and decreases as the concentration of electrolyte increases. It is illustrated by the dashed circle and line D in Fig. 2 (a). The Stern layer is within the double layer and represents a first layer of charge. It is composed of counterions adsorbed directly to the surface of the particle and is represented by line S. Line P represents the sur-

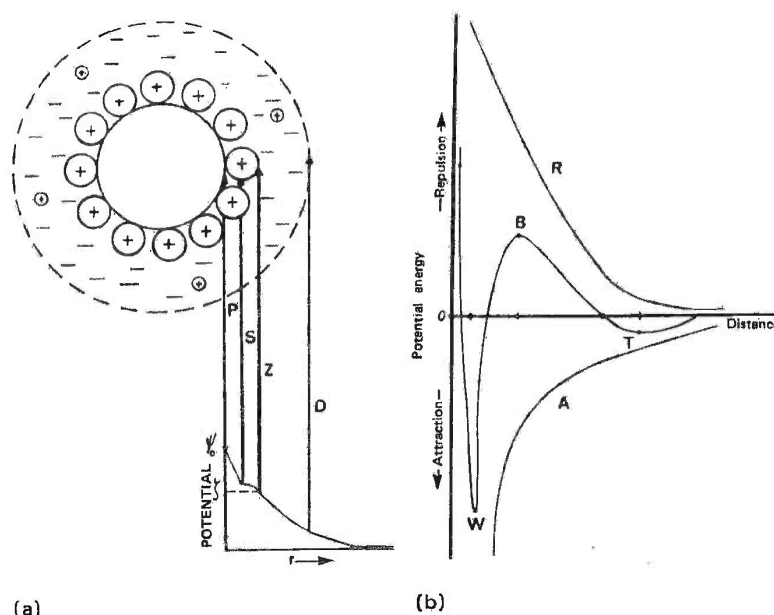


Fig. 2 Components of particle interactions. (a) Decreasing potential at various points: particle surface, P; Stern layer, S; plane of shear, Z; electrical double layer, D. (b) Potential energies between two identically charged particles: curve of electrostatic energy of repulsion, R; van der Waals energy of attraction, A; and net interaction energy, WBT. (From Refs. 37 and 38.)

face of the particle. The potentials at the corresponding distances from the particle surface are also shown in Fig. 2(a).

The electrokinetic or ζ (zeta) potential has practical importance because it can be experimentally measured. A charged particle suspended in water will migrate toward an electrode of the opposite charge in an electrical field. Ions in the Stern layer and bound water of hydration are carried along with the particle. The plane of shear that separates the bound water from the free bulk water is represented by line Z in Fig. 2 (a). This plane is a small distance from the particle surface and therefore has a lower potential than the surface. The zeta potential is frequently used to describe energies of interactions between particles because it can be measured directly.

The energies of attraction and repulsion were used to develop a quantitative theory of particle interactions known as the DLVO theory. The forces of electrostatic repulsion and van der Waals attraction are compared. While the theory does not explain all of the experimental data, it provides a very useful basis for understanding particle interactions in suspensions (and in emulsions).

Figure 2 (b) illustrates the DLVO theory in which the potential energy of interaction between two identically charged particles is plotted as a function of the interparticle distance. If the y-axis is viewed as the plane of a particle surface, then the x-axis measures the distance of an approaching particle and the curves describe the forces encountered. The upper curve, labeled R, represents the electrostatic energy of repul-

sion and curve A represents the van der Waals energy of attraction. Both forces, and their resultant energies, decrease as interparticle distance increases but they do not decrease in an identical manner. The algebraic sum of these curves is the middle curve labeled with the points, W, B, T; it gives the total or net energy of interaction between two like charged particles. If the particles are of opposite charge then electrostatic attraction is added to van der Waals attraction to easily overcome repulsion and rapidly aggregate the particle.

The chemical nature and particle size of the material primarily determines the extent of interparticle attraction. Electrostatic repulsion, however, is subject to more variables. It is largely influenced by surface potential and thickness of the double layer. Zeta potential is also governed by these factors and its magnitude is therefore an indicator of interparticle repulsion. As a consequence of these factors, and probably because it can be measured directly, this parameter has been correlated to the stability of dispersion [39]. Electrolytes and ionic surfactants are among the additives that influence zeta potential.

Curve WBT of net interaction energy illustrates aspects of an energy barrier and an energy well regarding particle aggregation. A shallow well, or secondary minimum, exists at the distance corresponding to point T on the curve. At a closer interparticle distance corresponding to point B, an energy barrier repels any approaching particle with less kinetic energy than the potential energy at B. If the approaching particle has sufficient energy to overcome the barrier, then van der Waals attraction dominates up to point W in the primary minimum where the particles touch. Energetically, this point represents a very stable situation.

Although the DLVO theory enjoys almost universal acceptance, disagreement exists on some details. Some investigators believe that flocculation exists in the secondary minimum, others believe it to exist in the primary minimum. The variables of major influence, however, are well described and their effects can be used to advantage by the formulator.

If a hydrophobic particle is wetted with an anionic surfactant to aid dispersion, then the adsorbed charges give the particle a sufficient zeta potential such that interparticle repulsion dominates to prevent flocculation. As an electrolyte is added in increasing concentrations, the thickness of the repulsive double layer is reduced and consequently, the zeta potential is reduced which allows closer approach of particles to each other. Flocculation occurs as the absolute value of the zeta potential shifts to a certain range closer to zero. Generally, this occurs at zeta potentials less than 25 mV. Most of the zeta potential and electrostatic repulsion from the anionic surfactant is countered because of electrolyte cation adsorption and van der Waals attraction then dominates. The flocs, as voluminous particle aggregates, have a high sedimentation volume and are easily redispersed. An example of this system is described in a study that uses the DLVO theory to interpret suspension stability [41]. The investigators used griseofulvin as the drug particle, ammonium dodecyl polyoxyethylene sulfate as the anionic surfactant, and aluminum chloride as the electrolyte.

In some situations, the continued addition of the electrolyte after the zeta potential was shifted to near zero leads to further adsorption of the counterion in which a charge gradually builds. The magnitude of the zeta potential then increases, which promotes repulsion and deflocculation. An example of this is the addition of phosphate anions to suspensions of positively charged particles of bismuth subnitrate. The zeta potential of the particle starts as positive, is reduced to zero, and builds a negative charge from the

continued addition of the phosphate anion. When the zeta potential is near zero the sediment of such a suspension is voluminous, with no caking. When the magnitude of the zeta potential is high, the sediment is small, and a high tendency for caking exists.

IV. COMMONLY USED INGREDIENTS

This section contains material on the ingredients used in suspension formulation, including the primary ingredient—the drug. Many ingredients are presented in tabular form for ease of comparison. Suspending, flocculating, and wetting agents are discussed separately and the remaining ingredients are discussed collectively.

A. Drug Particles

Some drugs are known to pose specific problems to the formulator. Particle size reduction and characteristics of the drug, such as polymorphism and crystal growth, are discussed.

In most pharmaceutical suspensions the range of particle diameters is between 1 and 50 μm . Common methods of particle size reduction include dry-milling, spray-drying, micropulverization, and fluid-energy grinding, of which the last two are considered industry standards [18,42]. Recent reviews of particle size reduction are available [43,44].

Particles are micropulverized by a high-speed attrition impact mill. Because the particles are seldom less than 10 μm , a buildup of electrostatic charge on the powder surface is not routinely a problem. The distribution of particle sizes obtained usually ranges from 10 to 50 μm . This broad range is the primary disadvantage of micropulverization, but the particles are suitable for most oral suspensions.

Micronizing with a fluid-energy mill readily reduces particle size below 5 μm . The primary disadvantage of this method is the electrostatic charge built up on the powder surface; powder collection is, therefore, very difficult. The cost of a fluid-energy source and dust collection equipment in addition to that of the mill might be considered a second disadvantage.

Colloidal particles can be prepared by precipitation. Three methods used are organic solvent precipitation, precipitation by pH changes of the medium, and chemical reaction. A precipitation reaction is illustrated in an example formula in a subsequent section. The interested reader is referred to a review for additional information on precipitation methods [45].

The unrecognized existence of different polymorphic forms of the drug can present several problems. Polymorph conversion is usually from a less stable and more soluble form to a more stable form. The more stable polymorph is less soluble and may produce crystal growth, unanticipated sedimentation, and possibly caking. A slow conversion rate may result in adverse consequences after manufacture. The different solubilities of the polymorphs can produce changes in concentration of the administered dose. Changes in bioavailability can occur because solubility changes alter absorption [1]. Cortisone, prednisolone, riboflavin, sulfathiazole, many barbiturate derivatives, and chloramphenicol palmitate [46] are examples of drugs that exhibit polymorphism. The temperature, solvent for crystallization, and cooling rate are important factors in obtaining both the desired polymorph and in controlling its rate of formation. A change in the particle shape is also important and can influence the rate of sedimentation [47]. Melt-

ing point and x-ray diffraction patterns are other physical properties that differ between polymorphs.

Crystal growth often occurs in the absence of polymorphism [48]. Drugs frequently formulated as suspensions in which crystal growth was investigated include sulfathiazole and methylprednisolone [49]. Protective colloids that inhibit crystal growth provide one means of preventing caking. Polymers employed to inhibit crystal growth include polyvinylpyrrolidone [50] and methylcellulose [51]. The effect of several surfactants on carbamazepine crystal growth and aqueous solubility has also been examined. The authors of these studies concluded that benzalkonium chloride [52] and polysorbate 80 [53] stopped crystal growth at a certain level, but sodium lauryl sulfate [53] and poloxamer 184 [54] accelerated growth and could produce very large crystals.

B. Suspending Agents

Several classes of suspending agents are discussed in this section. Suspending agents are used to impart increased viscosity and retard sedimentation. The formulator must select the most appropriate agent, alone or in combination, and at the appropriate concentration. Factors to consider during selection include suspending ability in the system; chemical compatibility with all ingredients, especially the drug; effect of pH range on the drug; length of time for hydration; appearance; source; reproducibility of these considerations from batch to batch; and cost. Even if chemically compatible, the suspending agent and drug may interact. For example, reduced dissolution behavior of nitrofurantoin was reported in the presence of methylcellulose [55].

Table 3 is a compilation of some pertinent characteristics of most suspending agents currently used. The agents are divided into classes of cellulose derivatives, clays, natural gums, synthetic gums, and miscellaneous agents. Although a few little-used agents are included in the table, a suspending agent such as calcium carboxymethylcellulose is not, because it is very similar to an agent that is included. Not all agents listed are suitable for individual use; some must be used in combinations. For each agent the rheologic flow behavior, maximum viscosity, pH range, ionic charge, range of useful concentration, and references are listed. The types of rheologic behavior listed are plastic, pseudoplastic, Newtonian, and thixotropic. An agent may exhibit more than one type of rheology; changes are listed in the order of concentration exhibiting that behavior. The viscosity range is designated by the maximum value reported from pertinent concentrations and grades at room temperatures. These values are dependent on the conditions of measurement such as shear rate, concentration, spindle size, and the instrument. They are intended only for general comparison. Stable pH ranges of the agents and common concentrations are listed. One value is listed if no range was reported. The concentration units of percent vary but they are usually weight per volume (w/v) or weight per weight (w/w). Additional details of the values in this table are available in the listed references. For incompatibilities and proprietary preparations of many suspending agents consult the monographs in Martindale [56].

1. Cellulose Derivatives

Cellulose derivatives are semisynthetic and have good batch-to-batch reproducibility of their characteristics. Excluding sodium carboxymethylcellulose, these agents are nonionic and, therefore, are chemically compatible with most ingredients. Most are available in grades of different viscosities. These agents usually exhibit pseudoplastic flow and have

Table 3 Summary of Suspending Agents^a

	Agent	Class	Rheologic behavior
1	Microcrystalline cellulose	Cellulose	Plastic/thixotropic
2	Microcrystalline cellulose with carboxymethylcellulose sodium	Derivative	Plastic/thix ^b
3	Powdered cellulose		Pseudoplastic
4	Ethylmethylcellulose		Pseudoplastic
5	Carboxymethylcellulose sodium		Pseudoplastic
6	Hydroxypropyl methylcellulose		Pseudo/plastic
7	Methylcellulose		Pseudoplastic ^b
8	Ethylcellulose		Pseudoplastic
9	Ethylhydroxyethylcellulose		Plastic
10	Hydroxyethylcellulose		Pseudoplastic
11	Hydroxypropyl cellulose		Plastic/thix ^b
12	Attapulgit	Clay	Plastic/thix
13	Bentonite		Plastic/thix
14	Hectorite		Plastic/thix
15	Montmorillonite		Plastic/thix
16	Magnesium aluminum silicate		Pseudo/plastic ^b
17	Silica gel	Colloidal	Plastic/thix ^b
18	Silicon dioxide, colloidal		Newtonian
19	Acacia	Natural	Plastic
20	Agar	Gum	Newt/pseudo
21	Carrageenan		Newt/pseudo
22	Guar gum		Pseudoplastic
23	Locust bean gum		Newt/pseudo
24	Pectin		Pseudoplastic
25	Na alginate		Pseudoplastic
26	Propylene glycol alginate		Pseudoplastic
27	Tamarind gum		Newt/pseudo
28	Tragacanth		Plastic
29	Xanthan gum		Plastic
30	Carbomer 934	Synthetic	Newt/pseudo
31	Povidone	Gum	Plastic
32	Gelatin	Miscellaneous	Pseudoplastic
33	Glycyrrhizin		Plastic
34	Pregelatinized starch		Pseudoplastic ^b
35	Sodium starch glycolate		

	Viscosity range (cps)	pH range	Ionic charge	Concentration range (%)	References
1	<25	5-7	0	1-5	[59],[60]
2	<200	3.5-11	-	0.5-2	[59],[61],[62]
3	—	5-7.5	0	10	[56],[63],[64]
4	<60	7	0	2.5	[56]
5	<6000	3-11.5	-	1-2	[18],[24],[65],[66],[67]
6	<5250	6-8	0	0.3-2	[21],[56],[66]
7	<8000	2-12	0	1-5	[18],[65],[66]
8	<100	7	0	5	[56]

Table 3 Continued

	Viscosity range (cps)	pH range	Ionic charge	Concentration range (%)	References
9	—	—	0	0.1-2	[56]
10	<4000	6.5-8.5	0	0.5-2	[59],[66],[67],[68]
11	<6500	5-8.5	0	1-10	[69],[70]
12	—	6-8.5	—	10	[71],[72]
13	<800	3-10	—	1-6	[60],[73]
14	<120	—	—	3-5.5	[74]
15	—	3-10	—	1-5	[72]
16	<2200	3-11	—	0.5-5	[18],[59],[61]
17	—	4-8	0	5	[56]
18	low	3.5-4.4	0	0.25-1.0	[60],[75],[76]
19	<10	4-10	—	2.0	[77],[78]
20	—	4.5-9	—	0.1-2	[79]
21	<1000	4-10	—	1-2	[18],[56],[64],[73]
22	<12000	1-10.5	0	0.6-1.5	[12],[75],[80]
23	<6000	3-11	0	0.4-2.5	[24],[81]
24	<1000	2-9	—	1-3	[18],[71],[73]
25	<10000	4-11.5	—	0.5-2.5	[12],[18],[24],[65]
26	<10000	2.5-7	—	1.5-3	[59],[73]
27	—	2.5-9.5	0	0.5-2	[82]
28	<9700	2.5-9	—	0.2-4	[24],[59],[66]
29	<8000	2-13	—	0.3-3	[83]
30	<40000	5-11	—	0.1-0.4	[24],[60],[84],[85]
31	<95	5.5-11.5	0	5-10	[86],[87]
32	—	3-8	+/-	<1	[88]
33	<370	3.5-5.5	—	0.5-2	[89]
34	—	—	0	1	[59],[90]
35	<6	3-7.5	—	1-2	[59],[90]

*See text for explanation of column headings.

^bView of authors based on behavior of similar agents.

no yield value. However, microcrystalline and powdered cellulose are not water soluble and produce dispersions that exhibit plastic flow and have yield values. A good review of the pharmaceutical uses of these cellulose derivatives is available [57].

Combinations are used to increase suspending ability. Microcrystalline cellulose has been used in combination with hydroxypropyl methylcellulose, sodium carboxymethylcellulose, and methylcellulose. The combination of microcrystalline cellulose and sodium carboxymethylcellulose is used extensively. It disperses quickly in cold water and needs little hydration time. The presence of sodium carboxymethylcellulose adds sufficient structuring to retard sedimentation of the cellulose, and, at total concentrations of the combination above 1%, its presence results in thixotropic gels. The presence of the anionic derivative also extends the usefulness over a larger pH range.

Methylcellulose also produces gels and is available in several viscosity grades. This agent is soluble in cold and insoluble in hot water. It is dispersed in hot water and a subsequent temperature reduction dissolves the agent. Agents with properties and uses

similar to those of methylcellulose include ethylmethylcellulose, and ethylhydroxyethylcellulose.

Table 3 includes other suspending agents with uses similar to those of methylcellulose. Hydroxypropyl methylcellulose is often used in ophthalmic preparations because of its clarity; a high viscosity grade is available for use in suspensions. Ethylcellulose is insoluble in water and rarely used as a suspending agent. Less insoluble grades with a lower degree of substitution are available. Hydroxyethylcellulose is soluble in cold or hot water but is reported to have poor suspending ability [58,59].

Sodium carboxymethylcellulose is extensively employed as a suspending agent. Because it is anionic it is usually incompatible with cationic drugs. Solutions are usually pseudoplastic but certain grades exhibit thixotropy. Hydroxypropyl cellulose is soluble in both water and alcohol. This agent is pseudoplastic at high shear and has been used as a protective colloid. Water-soluble cellulose derivatives are all subject to microbial degradation and require preservatives.

2. *Clays*

The second class of suspending agents in Table 3 is the clays. They are hydrated aluminum and/or magnesium silicates, which in water hydrate further to form viscous colloidal dispersions. They exhibit thixotropy and are very useful for stabilizing suspensions. These agents should be dispersed in water with high shear for optimum dispersion and hydration. Clays are most stable between pH 9 and 11 but can be used within a broader pH range. Ethanol and electrolytes may reduce the viscosity of these agents.

Magnesium aluminum silicate is used extensively. Its innocuous taste often produces a more acceptable suspension than other suspending agents. Bentonite is recognized for its swelling ability. Equal concentrations of bentonite and sodium carboxymethylcellulose for a total of 5% produce a good structure vehicle with both pseudoplastic and thixotropic behavior [27]. Hectorite possesses greater swelling ability than bentonite, but its disadvantage is cost and supply. Attapulgit, bentonite, and magnesium aluminum silicate in concentrations of 0.1% to 1% have been used as flocculating agents to aid the suspension of many drugs in a sorbitol or syrup base [18].

Silicon dioxide and its hydrate, silica gel, are considered in this section because their colloidal nature is similar to that of clays. Like the clays, these agents are water insoluble. At sufficient concentrations their dispersions gel and exhibit thixotropy. These agents are usually employed in combination with other suspending agents. For example, colloidal silicon dioxide, used alone at a concentration of 1%, was reported to be an unsatisfactory suspending agent for chalk and sulfamethazine [59].

3. *Natural Gums*

The natural gums are common suspending agents. This group, listed in Table 3, includes those of tree exudate, seed or root, and seaweed origin. These agents are nontoxic, readily available, and inexpensive. They are water soluble and produce solutions of high viscosity. Most are anionic and therefore are incompatible with cationic ingredients. These agents, however, are susceptible to bacterial and mold growth. In the past, many imported tree gums and seed pods were so heavily contaminated that they overwhelmed any added preservative [69]; this problem does not usually occur today. Another disadvantage is batch variation in color, viscosity, gel strength, and hydration rate. Because of these disadvantages and the anionic charge of natural gums, other agents such as the cellulose derivatives are often preferred.

Acacia, tragacanth, and pectin have been employed as suspending agents for many years. Tragacanth solutions are very viscous and have been employed to suspend dense particles. Several different viscosity grades are available. Pectin solutions have low viscosity; use of this agent is decreasing. Guar gum and locust bean (or carob) gum are nonionic. Guar gum is recognized as producing solutions of very high viscosity; locust bean gum is infrequently used because of its limited water-thickening and swelling properties at room temperatures. Tamarind gum, or specifically tamarind seed polysaccharide, is seldom used in the pharmaceutical industry although it is nonionic, disperses readily in cold water, and forms viscous solutions at concentrations less than 2%. This agent is relatively unaffected by the pH of the solution.

Agar, the alginates, and carrageenan are seaweed extracts. Agar is resistant to microbial growth and produces strong gels. It has been used to suspend barium sulfate. The alginates form solutions of high viscosity. They exhibit Newtonian flow at concentrations below those listed in Table 3. The propylene glycol form is used at low pH values and is available in a grade for dispersal by vigorous hand shaking. Carrageenans are water soluble and anionic. The commercially available types are kappa, iota, and lambda. The kappa and iota types form gels; gels from the latter type are thixotropic. Lambda carrageenan does not gel.

Use of xanthan gum is increasing for several reasons. It is a high molecular weight natural polysaccharide produced from microbial fermentation by an organism originally isolated from the rutabaga plant [83]. It has good batch-to-batch uniformity, few microbial contamination problems because it is unusually resistant to enzymes, and it is soluble in both hot and cold water. Xanthan gum is particularly useful as a suspending agent because of its shear-thinning or pseudoplastic behavior and because it has a yield value (the combination being plastic behavior). The apparent yield value of a 1% solution was reported as 20 to 50 dyne/cm² [83]. At low rates of shear, but high enough to exceed the yield value, the solution has a high viscosity. At high shear rates, such as mixing or pumping, the solution has a low viscosity. Another very useful property of xanthan gum is that its solution viscosity is almost independent of temperature and pH. In addition, it is usually more resistant to degradation or fracture from prolonged shearing than other polymeric suspending agents. For example, a 1% solution was sheared at 46,000 sec⁻¹, which is comparable to that encountered in a colloid mill, and no viscosity loss was reported after 1 hour [83].

4. *Synthetic Gums*

The synthetic agents have the advantage of good batch-to-batch uniformity and no microbial contamination. Carbomer is widely used because its solutions have a very high viscosity and a yield value. At concentrations above 0.4% it forms gels. Povidone, which is polyvinylpyrrolidone, should be used with other suspending agents because it has a low solution viscosity. It is used more often as a protective colloid.

5. *Miscellaneous*

The starches are not widely used but were evaluated as comparable or better than several other suspending agents, including alginates, tragacanth, and magnesium aluminum silicate [59]. Glycyrrhizin is reported to have good suspending characteristics [89]. Its solution is pseudoplastic and exhibits thixotropy. Gelatin may be anionic or cationic, depending on the pH of the medium and the type of gelatin. Interactions between this agent and drugs have been investigated [91]. Under appropriate conditions, this agent

is compatible with most ingredients. It has a disadvantage in that it lacks good batch-to-batch uniformity.

C. Flocculating Agents

Flocculating agents enable particles to link together in loose aggregates or flocs. As described previously, these flocs settle rapidly but are easily redispersed. These agents can be divided into four classes: surfactants, hydrophilic polymers, clays, and electrolytes. Typical agents are listed in Table 4.

Both ionic and nonionic surfactants have been used as flocculating agents. Concentrations employed range from 0.001% to as high as 1.0% (w/v). Nonionic surfactants are preferred because they are chemically compatible with more ingredients. The flocculating agent may be the same material as the wetting agent. Excess concentrations may produce a bad taste, foaming, or caking.

Hydrophilic polymers have wide use as flocculating agents. These substances have a high molecular weight with long carbon chains and include many materials that at higher concentrations (> 0.1%) are employed as suspending agents. Xanthum gum has been used to flocculate sulfaguanidine, bismuth subcarbonate, and other drugs [92,93]. Hydrophilic polymers may act both as protective colloids to prevent caking and as flocculating agents to form loose flocs. The use of surfactants alone or in combination with a protective colloid in conjunction with a structured suspending vehicle is reported as a common and successful method of flocculation [61]. Bentonite, at 1.7%, produces very good flocculation of bismuth subnitrate suspensions [36]. Clays at concentration equal to or above 0.1% are reported to successfully flocculate most drugs suspended in a sorbitol or syrup base [18].

The presence of electrolytes can enhance flocculation and lower the necessary surfactant concentration. For example, sulfamerazine suspensions were flocculated with sodium dodecyl polyoxyethylene sulfate. Addition of the appropriate amount of sodium

Table 4 Typical Flocculating Agents

Agent	Class	Ionic charge
Sodium lauryl sulfate	Surfactant	Anionic
Docusate sodium		Anionic
Benzalkonium chloride		Cationic
Cetylpyridinium chloride		Cationic
Polysorbate 80		Nonionic
Sorbitan monolaurate	Hydrophilic polymer	Nonionic
Carboxymethylcellulose sodium		Anionic
Xanthan gum		Anionic
Tragacanth		Anionic
Methylcellulose		Nonionic
Polyethylene glycol	Clay	Nonionic
Magnesium aluminum silicate		Anionic
Attapulgate		Anionic
Bentonite		Anionic
Potassium dihydrogen phosphate	Electrolyte	Anionic
Aluminum chloride		Cationic
Sodium chloride		Anionic/cationic

chloride increased flocculation and reduced the required surfactant concentration [94]. An electrolyte may be the sole flocculating agent. Sulfaguanidine, wetted by a suitable surfactant, was flocculated by aluminum chloride [95]. Electrolytes as flocculating agents are apparently not routinely utilized in the industry, yet offer a means of attaining optimum flocculation.

D. Wetting Agents

Surfactants, hydrophilic polymers, and certain clays are used as wetting agents to aid in the dispersion of hydrophobic drugs. The USP 23 [96] includes 24 surfactants as official wetting and/or solubilizing agents. Sodium carboxymethylcellulose, bentonite, aluminum magnesium silicate, and colloidal silicon dioxide are also reported to aid dispersion of hydrophobic drugs. Glycerin, propylene glycol, and alcohol are widely employed. Concentrations of alcohol used as a wetting agent include 0.008%, 0.1%, and 0.26%.

The formulator selects the wetting agent for optimum dispersion of the drug at the lowest effective concentration. The agent selected will vary depending on its ability to wet the surface of the drug. The Hiestand [34] method of selecting a wetting agent provides a comparison of their wetting ability. A narrow hydrophobic trough holds the powder at one end while a solution of the wetting agent is placed at the other end. The better agents will have a faster rate of penetration through the powder. Another test evaluates the wetting ability by dripping a solution of the wetting agent onto the drug powder spread over a piece of gauze. The better wetting agents carry more powder through the gauze than the poorer agents.

E. Sweeteners

Frequently sweeteners are included in suspensions to produce a more palatable medication. Drugs may have a bitter taste, and suspending agents, particularly clays, may have a bland taste. A viscous sweetener, such as sorbitol solution, or syrup (sucrose) also can be used to impart viscosity to retard sedimentation. High-fructose corn syrup has also been used for this dual purpose. Other common sweetening agents include mannitol, sodium saccharin, and aspartame. Aspartame is used extensively at low concentrations because of its high potency.

F. Additional Ingredients

Table 5 contains some typical buffers, flavoring agents, colorants, and preservatives. Buffers are used to control the pH of the formulation. Suspension pH is often adjusted to ensure that the drug remains insoluble. If too much drug is in solution the drug may recrystallize and alter the particle size, shape, and distribution. The tendency of particles to fuse together is also increased. In addition, the poor taste of a drug in solution may be amplified.

The optimum pH for each ingredient may not coincide. The pH may be selected on the basis of solubility or stability of the drug. The polymeric suspending agents, however, have the greatest viscosity at the pH of their maximum solubility. The suspending agent should be stable at the pH of the system for the shelf life of the product. Certain preservatives, such as sodium benzoate, are effective only at low pH values in which the molecule is predominately un-ionized.

Table 5 Typical Buffering Agents, Flavors, Colorants, and Preservatives Used in Suspensions

Agent	Class
Ammonia solution, strong	Buffering
Citric acid	
Fumaric acid	
Sodium citrate	Flavor
Cherry	
Grape	
Methyl salicylate	
Orange	
Peppermint	Colorant
D&C Red No. 33	
FD&C Red No. 3	
FD&C Red No. 40	
D&C Yellow No. 10	
FD&C Yellow No. 6	Preservative
Butylparaben	
Methylparaben	
Propylparaben	
Sodium benzoate	

Flavoring agents also enhance patient acceptance of the product; they are a necessity in suspensions intended for pediatric patients. Some prevalent flavors used in formulations intended for children include raspberry, pineapple, and bubble gum. To maintain full effectiveness of the flavoring agent in some commercial suspensions, the manufacturer recommends that the product be stored at refrigerator temperatures. In such cases, the formulator must consider both the positive and adverse consequences of the increased viscosity caused by the temperature reduction. Flavoring agents are usually oils and require solvents.

Colorants are intended to provide a more aesthetic appearance to the final suspension. As relatively large cations or anions, these agents may be chemically incompatible with other ingredients. For example, anionic D&C Yellow No. 10 interacts with quaternary ammonium compounds such as surfactants. Some colorants have been implicated as a potential source of cancer, and the formulator must realize that a selected agent, in the future, may be banned by the Food and Drug Administration. FD & C Yellow No. 5 is a noted allergen, and its presence must be listed on the label.

Preservatives are required in most suspensions because the suspending agents and sweeteners are often good growth media for microorganisms. Some natural gums are sources of contamination, and the preservative must be effective against these contaminating organisms. Clays are susceptible to mold growth. In some suspensions the drug imparts a pH at which no preservative is stable. An example is magnesium hydroxide suspension. Antimicrobial surfactants, such as cetylpyridinium chloride, must be used with caution because of their potential incompatibilities.

The parabens are frequently employed as preservatives. These agents may require small concentrations of a solvent to remain in solution. Alcohol, glycerin, or propylene glycol are often used as these solvents at concentrations $\leq 10\%$. These solvents can also

be used for other water-insoluble ingredients such as flavors. Other, less common, excipients include a sequestering, or chelating, agent, such as edetate disodium, an antifoaming agent such as simethicone, or bitterness modifiers such as sodium chloride.

V. PREPARATION OF SUSPENSIONS

A. General Guidelines

There are three general approaches to the formulation of suspensions, as illustrated in Fig. 3. All three have the common preliminary step of dispersing the wetted particles in the medium to achieve a uniform dispersion of deflocculated particles. The approach labeled A in Fig. 3 is to suspend the deflocculated particles in a viscosity-enhancing agent or a structured vehicle. This approach produces individual particles that settle slowly but are seldom completely suspended.

The second approach, labeled B in Fig. 3, incorporates a flocculating agent to produce a flocculated suspension as the final product. In practice, this approach is not commonly used because the flocs settle rapidly leaving a clear supernatant. Usually a suspending agent, with properties of a structured vehicle, is added to the flocculated suspension. The flocculated particles are suspended better than deflocculated particles in a structured vehicle, often yielding no noticeable separation. Upon shaking, the high shear thins the vehicle, and the suspension is easily poured from the container. After use, the vehicle regains its structure, producing a high viscosity to retard, if not prevent, sedimentation of the flocculated particle. The approach of combining flocculated particles and structured vehicle is labeled C in Fig. 3.

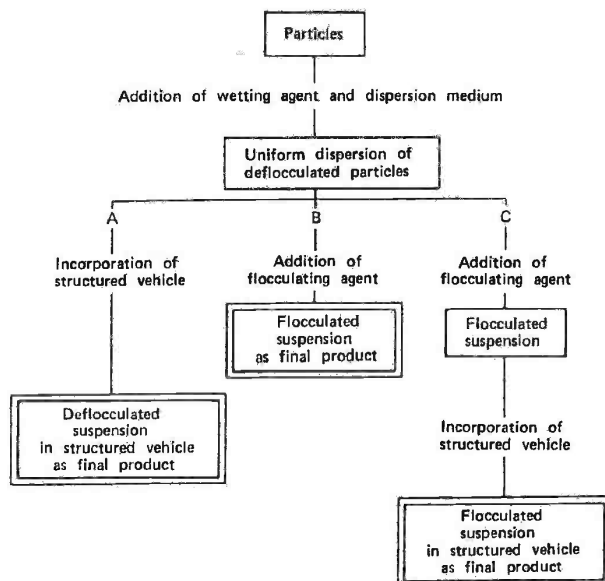


Fig. 3 General guidelines to suspension formulation. (From Ref. 35.)

B. Specific Guidelines

Each procedure requires some trial and error. The following guidelines have been recommended [20].

1. Disperse the drug by slow addition to a water, water-glycol, or glycol system containing the wetting agent. Addition of wetting system to the powder requires prolonged levigation and is more difficult on a large scale.
2. Add all other excipients that require solution in as dilute a system as possible. Concentrated solutions can cause reactions or precipitation on the liquid surface of the bulk phase.
3. Ensure that the solvent system maintains ingredients in solution. Precipitation can occur if the bulk vehicle cannot dissolve the solute.
4. Provide sufficient water for ease of dispersion and hydration of suspending agent(s) and protective colloids.
5. If the suspension is to contain more than one drug, ascertain mutual compatibility.
6. Use sufficient drug excess to compensate for loss during manufacture and to maintain the labeled amount during the shelf life of the product.
7. Flavors (as oils) can be added to most suspension vehicles if the final batch is processed through a colloid mill.
8. Process the batch through a colloid mill to ensure dispersion of the drug. The mill will break up large soft agglomerates.
9. Process the batch through deaerating equipment. Suspensions may contain large quantities of air from the surface of the drug particles or from incorporation during milling and mixing. These suspensions are unsatisfactory.
10. Avoid excessive water loss, particularly if prolonged heating is required. Use an excess of water to compensate for a significant loss.
11. Avoid excessive shearing and high temperatures, which can degrade colloids.
12. Consider the percentages of un-ionized preservatives at various pH values.
13. Follow Good Manufacturing Practices as published by the FDA and described in Chapter 12, "Drug Regulatory Affairs," in Volume 3 of *Disperse Systems*.

VI. STABILITY

Determining the stability of a suspension entails evaluation of the complete product. The batch should be evaluated in the final package. More than one batch should be evaluated to compare different lots of drug and other ingredients to the criteria established with the first batch. The product should be evaluated after manufacture, after storage at all test temperatures, and after all conditions of stress testing.

A. Chemical Stability

The drug within suspended particles is not likely to undergo chemical degradation; only the small but finite fraction of drug in solution is susceptible to degradation. A method of determining the stability of drugs in suspension has been reported [97]. The method is based on three assumptions which are: (a) degradation takes place only in solution and is first order, (b) the effect of temperature on drug solubility conforms to classical theory, and (c) dissolution is not rate limiting on degradation.

Suspending agents are also subject to degradation with age. The functional parameter, viscosity, can be examined at elevated temperatures to determine aging characteristics [98]. The viscosity change for sodium alginate followed first-order degradation. Concentration of the agent had a negligible influence on the stability. An increase in concentration of sodium carboxymethylcellulose, however, produced a decrease in the rate of viscosity change.

The antimicrobial activity can be reduced by chemical degradation or incompatibility of the preservative. If an unexpected pH change occurs, the effectiveness of the preservative may be reduced substantially. A loss of activity may also occur from adsorption of the preservative onto the drug particle [99].

B. Physical Stability

Several physical tests are employed to evaluate physical ability of suspensions. Tables 6 and 7 list these tests, which are divided into passive and active types [20]. The most common tests are evaluations of sedimentation by sedimentation volume and degree of flocculation [100]. Flocculation and deflocculation of suspension particles can be evaluated by rate of filtration [101], rate of settling, and the filtration of suspension and refiltration of filtrate through the formed filter bed [102].

Not all tests listed in Tables 6 and 7 are required to evaluate suspension stability. Fewer tests than these, as well as additional tests, have been used. The stability of suspensions containing primidone and prednisone was well characterized by the following common tests: turbidity measurements, viscosity measurements, sedimentation volumes, and redispersibility of sediments [103].

Stability testing of suspensions is a difficult problem faced by formulators. There are no standardized tests available to determine stability and shelf life. Evaluation of suspension physical stability is an area of ongoing research. For example, the effects of surface charge on dye adsorption and suspension stability were examined in a titanium dioxide aqueous suspension. Both suspension stability and dye adsorption were dependent on the pH of the suspension and the point of zero charge (PZC) of the suspended titanium dioxide [104]. Another example is the evaluation of a spreading coefficient parameter as a method of predicting the aggregation of powders dispersed in

Table 6 Passive Tests for Evaluation of Physical Stability of Suspensions

1. Aesthetic appeal (appearance, color, odor, taste)
2. pH
3. Specific gravity
4. Sedimentation rate
5. Sedimentation volume
6. Zeta potential measurement
7. Compatibility with container
8. Compatibility with cap-liner
9. Microscopic examination (photomicrographs)
10. Determine crystal size
11. Determine uniform drug distribution

Source: Adapted from Ref. 20.

Table 7 Active Tests for Evaluation of Physical Stability of Suspensions

-
1. Redispersibility
 2. Centrifuge
 3. Rheological measurements
 4. Stress tests (vibration to simulate transportation)
 5. Accelerated shock cycles
 6. Freeze-thaw cycles
 7. Use tests
-

Source: Adapted from Ref. 20.

aqueous suspensions [105]. The remainder of this section on stability concerns strategies for the evaluation of suspensions. For additional information see the excellent review by Weiner [106].

It should be clear what type of stability is under investigation because not all formulations use the same system of stabilization. The factors affecting rate of settling, flocculation, and caking are different. Different types of instabilities require different testing procedures and will result in different degrees of reliability for determining a shelf life.

Protocols for stability testing should consider special properties of the product that may be troublesome as well as special conditions the product may encounter. If controlled flocculation is the strategy used to stabilize a suspension, it must be made certain that the energy barrier (which stabilizes the product) will protect the product from destabilizing factors such as vibration caused by shipping. Therefore, a reciprocating shaker is useful to test this type of product.

Accelerated stability testing is difficult and risky. Testing at elevated temperatures ($>25^{\circ}\text{C}$) is often used but the higher temperatures cause large changes in physical properties of the so-called inactive ingredients. Irreversible changes may occur from the precipitation or breakdown of polymers in the dispersion that can substantially alter viscosity. Higher temperatures will dramatically change the solubility of the suspended drug. During cycling from hot to cold temperatures, the saturated layer around the suspended particles will change, resulting in a greater tendency for aggregation of particles, particularly in suspensions that do not have a uniform particle size [106]. Higher temperatures will also affect the hydration of polymer additives, which affects the ability of the polymer to stabilize the suspension.

VII. TYPICAL FORMULAS

Examples of formulations that illustrate systems of suspensions are described in this section. The systems range from those with no suspending agents to those with combinations of agents. The objective of the suspending agents may vary. Ease of redispersal and good flow properties are the goals of some formulations such as the antacid-demulcent suspension in part F. The absence of sedimentation is the goal of other formulations such as the sulfamethazine suspension in part D.

A. Drug Particles from Precipitation Reaction**1. Milk of Magnesia, USP**

This simple formulation illustrates a precipitation reaction to produce the drug in a colloidal size range and the subsequent preparation of the suspension. The reaction between a magnesium salt and sodium hydroxide yields magnesium hydroxide as a colloidal precipitate. The ingredients for this reaction and the preparation of the suspension [107] follow.

Magnesium sulfate	300 g
Sodium hydroxide	100 g
Distilled water, qs	1000 mL

The magnesium salt is dissolved in about 650 mL of distilled water in a large container and heated to boiling. The sodium hydroxide is dissolved in 1000 mL of distilled water and added slowly to the boiling solution of magnesium sulfate; continue the boiling for 30 minutes. Transfer the mixture to a cylindrical container of not less than 5000 mL and fill with hot distilled water. Allow the mixture to stand until a separation occurs and remove the supernatant liquid. Wash repeatedly with hot distilled water until sulfates have practically been eliminated, as indicated by testing the supernatant liquid with barium chloride T.S. Concentrate the mixture by evaporation until it contains not less than 7% magnesium hydroxide [107].

Current preparations usually employ a suspending agent because caking has been known to occur. A nonionic suspending agent, such as methylcellulose, could be used. A flavoring oil or blend of oils is often used but the amount is limited to 0.5 mL for each 1000 mL of product. The addition of 0.1% of citric acid reduces the interaction between the magnesium hydroxide and the glass. If a plastic container is used, then citric acid is not required. An opaque container is preferred so that the sediment is not visible. A preservative should be used.

B. Viscous Sweetener as Suspending Agent**1. Antacid Aluminum Hydroxide**

A viscous solution of the sweetener such as syrup or sorbitol solution may supply sufficient viscosity to suspend the drug. The following formula employs syrup and sorbitol solution for both sweetness and viscosity [108]. The preservatives are methylparaben and propylparaben.

Aluminum hydroxide compressed gel	362.8 g
Sorbitol solution, USP	282.0 mL
Syrup, NF	93.0 mL
Glycerin, USP	25.0 mL
Methylparaben, NF	0.9 g
Propylparaben, NF	0.3 g
Flavor	qs
Purified water, USP to	1000.0 mL

The parabens are dissolved in a heated mixture of the sorbitol solution, glycerin, syrup and a part of the water. The mixture is cooled and the aluminum hydroxide is added

with stirring. The flavor is added followed by sufficient purified water to volume. A hand homogenizer, homomixer, or colloid mill is then used to homogenize the suspension.

The preparation of aluminum hydroxide compressed gel can be divided into two parts. The first part is the preparation of the aluminum hydroxide gel. The gel is then dried, or compressed, at a low temperature until it has the required amount of Al_2O_3 . One process for the preparation of aluminum hydroxide gel follows. Dissolve 1000 g of $\text{Na}_2\text{CO}_3 \cdot 10\text{H}_2\text{O}$ in 400 mL of hot water and filter. Dissolve 800 g of ammonium alum in 2000 mL of hot water and filter into the carbonate solution with constant stirring. Then add 4000 mL of hot water and remove all gas. Dilute to 80,000 mL with cold water. Collect and wash the precipitate and suspend it in 2000 mL of purified water flavored with 0.01% peppermint oil and preserve with 0.1% of sodium benzoate. Homogenize the resulting gel [109].

C. Viscosity from Active Ingredients

1. Kaolin Mixture with Pectin

Kaolin and pectin, the active ingredients, provide some viscosity of the system. Glycerin is the wetting agent. Sodium saccharin is the sweetener, peppermint oil is for flavor. The preservative is benzoic acid. The formula follows.

Kaolin	200 g
Pectin	10 g
Tragacanth	5 g
Sodium saccharin	1 g
Glycerin	20 mL
Benzoic acid	2 g
Peppermint oil	0.75 mL
Purified water, qs	1000 mL

Mix kaolin with 500 mL of the purified water. Triturate pectin, powdered tragacanth, and sodium saccharin with glycerin. Add to this mixture, with constant stirring, benzoic acid dissolved in 300 mL of boiling purified water. Continue mixing until all the pectin is dissolved and allow the mixture to stand until it cools to room temperature. Add peppermint oil and the kaolin-water mixture, thoroughly mix, and finally add sufficient purified water to make 1000 mL. The quantity of tragacanth and pectin may be altered in order to obtain a product with suitable consistency in the preparation of larger amounts. If, however, the proportion of pectin in the formula is altered by more than 10%, then the pectin content of the preparation must be clearly stated on the label [109].

D. Plastic Suspending Agent

1. Sulfamethazine suspension

Carbomer 934 is used in this formula as the suspending agent to produce good suspensions with practically no sedimentation [84]. The wetting agent is sodium lauryl sulfate. The sweeteners are sodium saccharin and sugar (sucrose). Citric acid and sodium hydroxide are used to control pH. The preservatives are the sodium salts of methyl and propylparaben, which are not listed in the USP. Substitution with methyl and propylparaben at the same concentrations may be acceptable.

Sulfamethazine	10.00 g
Carbomer 934	0.50 g
Sodium lauryl sulfate	0.02 g
Sodium saccharin	0.08 g
Sugar (sucrose, granular)	40.00 g
Methyl sodium hydroxy benzoate	0.20 g
Propyl sodium hydroxy benzoate	0.02 g
Flavor mixture	1.00 g
Citric acid	0.20 g
1.0 N sodium hydroxide solution to pH 5.5	(approx. 10 mL)
Purified water, qs	100.00 mL

The flavor mixture consists of vanilla 1.00 mL, caramel 3.00 mL, and glycerin 100.00 g. Carbomer 934 is hydrated for 24 hours in a solution of the sodium lauryl sulfate in 30 mL of water. The sulfamethazine powder is suspended in the vehicle and the aid of a mixer. The preservatives and sugar are dissolved in the remaining 40 mL of water by heating. After the solution has cooled to room temperature, the sodium saccharin and citric acid are added to the cooled solution. The solution is then added to the suspension, the flavor mixture added, the pH adjusted to 5.5, and the final suspension mixed in a homogenizer.

E. Pseudoplastic Suspending Agents

Two formulas in this section illustrate the use of different pseudoplastic suspending agent. Methylcellulose is used in the first formula and sodium carboxymethylcellulose is used in the second formula.

1. Kaolin-Pectin Suspension

This formula has a slightly lower solids concentration than the similar formula in part C, and uses methylcellulose 4000 cps as the suspending agent [110].

Kaolin	20.00%
Pectin	0.50%
Methylcellulose 4000 cps	0.75%
Methylparaben	0.20%
Propylparaben	0.04%
Butterscotch imitation flavor	0.01%
Vanillin	0.01%
Sorbitol solution USP	20.00%
Distilled water, qs	100.00%

Minor modifications in procedure were tested without the butterscotch imitation flavor in three preparations of 100 g [111]. The differences between these preparations are not large but the suspension prepared by the third procedure was considered the most elegant.

Mix the kaolin with half the water. In another container, disperse the pectin in the remaining half of the water and heat to near boiling. To this hot solution of pectin, add the parabens and disperse the methylcellulose while mixing. Allow the methylcellulose mixture to hydrate and cool for 4 hours followed by 5 minute's exposure to ice bath temperatures. To this solution, add the kaolin-water mixture, sorbitol solution, and fla-

vors using an electrical mixer to complete the preparation. After 7 days standing, the suspension was a thixotropic gel with a yield value but no supernatant.

The second procedure eliminates the exposure of the methylcellulose to cold temperature but extends the hydration time to overnight. An additional minor change is to mix the pectin in water for 1 hour with a magnetic stirrer prior to heating. After 7 days, the sediment of this suspension appeared clumpy, represented approximately 93% of total suspension volume, and did not flow upon inversion (indicating a yield value).

The third procedure eliminated both the cold temperatures and overnight hydration. The methylcellulose mixture was hydrated for only 4 hours. After 7 days, the sediment flowed smoothly and represented approximately 93% of total volume.

Ease of redispersal of the three suspensions after seven days decreased from procedure 3 > procedure 2 > procedure 1. After 30 days, the suspension prepared by the third procedure exhibited a sediment volume of 99% and could be poured, although slowly. The order of redispersability did not change and the remaining two preparations did not flow upon inversion. Because viscosity was somewhat high the formulator may wish to reduce the concentration of methylcellulose.

2. Antacid Suspension

The suspending agent used in this formula [110] is low-viscosity, pharmaceutical grade, sodium carboxymethylcellulose.

Aluminum hydroxide	4.00%
Magnesium hydroxide	4.00%
Sodium carboxymethylcellulose, 7LP	1.00%
Methylparaben	0.20%
Propylparaben	0.04%
Saccharin calcium	0.02%
Peppermint oil	0.01%
Distilled water, qs	100.00%

Hydrate the suspending agent in some hot water and allow it to stand overnight. The hydroxides are mixed in some water to which the saccharin and the parabens, as a propylene glycol solution, are added. The slurry is added to the solution of NaCMC with mixing. Add the flavor and the remaining water. Homogenize the suspension by passing it through a colloid mill.

F. Combination of Pseudoplastic and Thixotropic Agents

In many cases, these combinations produce suspensions with more stability, better flow properties, and equal redispersion capacity to suspensions using either agent alone.

1. Sulfamethazine Suspension

The formula in part D is modified to use the combination of sodium carboxymethylcellulose and magnesium aluminum silicate as the suspending agents [84]. The viscosity of a 2% solution of the cellulose derivative was reported as 72 cp. The suspension is prepared in the same manner as described in part D except that the pH is not adjusted; the final pH of the suspension is 7.4. In addition, the preservatives, as described in part D, may be replaced with methyl- and propylparaben.

Oral Aqueous Suspensions

Sulfamethazine	10.00 g
Magnesium aluminum silicate	0.60 g
Sodium carboxymethylcellulose	1.30 g
Sodium lauryl sulfate	0.02 g
Sodium saccharin	0.08 g
Sugar (sucrose, granular)	40.00 g
Sodium methyl hydroxy benzoate	0.20 g
Sodium propyl hydroxy benzoate	0.02 g
Flavor mixture	1.00 g
Purified water, qs	100.00 g

2. Antacid-Demulcent Suspension

Caking is a major problem in suspensions containing a high concentration of solids. Suitable redispersion and flow properties are attained with different concentrations of the suspending agents illustrated above [110]. A medium-viscosity type of the cellulose derivative is used.

Aluminum hydroxide	4.00%
Magnesium trisilicate	12.00%
Magnesium aluminum silicate	0.80%
Sodium carboxymethylcellulose, 7MP	0.60%
Methylparaben	0.20%
Propylparaben	0.04%
Peppermint oil	0.01%
Sorbitol solution, USP	20.00%
Distilled water, qs	100.00%

Hydrate the magnesium aluminum silicate and the sodium carboxymethylcellulose in some hot water and allow them to stand overnight. The hydroxide is mixed in some water; the sorbitol and parabens are added. The slurry is pumped into the gelled suspending agents and mixed. The trisilicate is added slowly with vigorous agitation and mixed until it is well dispersed. The flavor is added with agitation and the suspension brought to full volume. Pass the suspension through a colloid mill into a tank fitted with a strainer.

Combinations of similar agents are used in other successful formulations. Examples include magnesium aluminum silicate and sodium alginate in a griseofulvin suspension [112] and bentonite and carboxymethylcellulose in a sulfamethoxazole/trimethoprim suspension [113]. The exact ratio of suspending agents will vary with processing conditions and selection of other ingredients.

REFERENCES

1. M. Gibaldi, *Introduction to Biopharmaceutics*, Lea & Febiger, Philadelphia, 1971, p. 37.
2. L. N. Sansom, W. J. O'Reilly, C. W. Wiseman, L. Stern, and J. Derham, *Med. J. Aust.*, 2:593-595 (1975).
3. R. Obach, J. Prunonosa, A. Menargues, M. Nomen, and J. Valles, *Biopharm. Drug Dispos.*, 9:501-511 (1988).
4. F. Kees, U. Lukassek, K. G. Naber, and H. Grobecker, *Arzneim. Forsch.*, 41:843-846 (1991).

5. R. Shekerdjiski, V. Paskov, N. Larnbov, P. Gencheva, D. Rachev, S. Titeva, and E. Minkov, *Pharmazie* 42:184-186 (1987).
6. J. A. Barone, Y. C. Huang, R. H. Bierman, J. L. Colaizzi, J. F. Long, D. A. Ker, A. Van Peer, R. Woestenborghs, and J. Heykants, *Clin. Pharm.* 6:640-645 (1987).
7. F. Pannuti, E. Strocchi, A. Longhi, R. Comparsi, and C. M. Camaggi, *Chemioterapia*, 5:237-239 (1987).
8. J. D. Strum, J. L. Colaizzi, T. S. Gochl, J. M. Jaffe, and R. I. Poust, *J. Pharm. Sci.*, 67:1399-1402 (1978).
9. N. Kondo, T. Iwao, H. Masuda, K. Yamanouchi, Y. Ishihara, N. Yamada, T. Haga, Y. Ogawa, and K. Yokoyama, *Chem. Pharm. Bull.*, 41:737-740 (1993).
10. A. Stockis, E. Lebacqz, S. Deroubaix, A. M. Allemon, and H. Laufen, *Arzneim Forsch.*, 42:1478-1481 (1992).
11. F. Kees, K. G. Naber, G. Sigl, W. Ungethum, and H. Grobecker, *Arzneim. Forsch.*, 40:293-297 (1990).
12. M. M. Soci and E. L. Parrott, *J. Pharm. Sci.*, 69:403-406 (1980).
13. M. Marvola, J. Pirjola, and A. Huikari, *Int. J. Pharm.*, 3:13-22 (1979).
14. H. A. Titulaer, J. Zuidema, P. A. Kager, J. C. Weisteyn, C. B. Lugt, and F. W. Merkus, *J. Pharm. Pharmacol.*, 42:810-813 (1990).
15. B. A. Haines and A. N. Martin, *J. Pharm. Sci.*, 50:228-232 (1961).
16. B. A. Haines and A. N. Martin, *J. Pharm. Sci.*, 50:753-756 (1961).
17. B. A. Haines and A. N. Martin, *J. Pharm. Sci.*, 50:756-759 (1961).
18. R. A. Nash, *Drug Cosmet. Ind.*, 97:843-951 (1965).
19. R. A. Nash, *Drug and Cosmetic Ind.*, 98:39-43, 128-133 (1966).
20. B. I. Idson and A. J. Scheer, Suspensions. In: *Problem Solver* (J. Wallace, ed.), FMC Corporation, 1984, pp. 1-31.
21. H. Schott and A. N. Martin, Colloidal and surface-chemical aspects of dosage forms. In: *American Pharmacy* (L. W. Dittert, ed.), Lippincott, Philadelphia, 1974, pp. 103-174.
22. J. T. Carstenson and K. S. E. Su, *J. Pharm. Sci.*, 59:666-670 (1970).
23. P. C. Hiemenz, *Principles of Colloid and Surface Chemistry*, Marcel Dekker, New York, 1986, pp. 193-200.
24. R. J. Meyer and L. Cohen, *J. Soc. Cosmet. Chem.* 10:143-154 (1959).
25. S. L. Hem, J. R. Feldkamp, and J. L. White, Basic chemical principles related to emulsion and suspension dosage forms. In: *Theory and Practice of Industrial Pharmacy* (L. Lachman, H. A. Lieberman, J. L. Kanig, eds.), Lea & Febiger, Philadelphia, 1986, pp. 140-143.
26. E. N. Hiestand, *J. Pharm. Sci.*, 53:1-18 (1964).
27. H. Schott, Rheology. In: *Remington: The Science and Practice of Pharmacy* (A. R. Gennaro, ed.), Mack, Easton, PA, 1995, pp. 292-311.
28. A. Martin, *Physical Pharmacy*, Lea & Febiger, Philadelphia, 1993, pp. 453-476.
29. A. Martin, *Physical Pharmacy*, Lea & Febiger, Philadelphia, 1993, p. 384.
30. J. Y. Oldshue, *Pharm. Sci.*, 50:523-530 (1961).
31. R. J. Lantz and J. B. Schwartz, Mixing. In: *Pharmaceutical Dosage Forms: Tablets*, Vol. 2 (H. A. Lieberman, L. Lachman, J. B. Schwartz, eds.), Marcel Dekker, New York, 1990, pp. 1-70.
32. E. G. Rippie, Mixing. In: *The Theory and Practice of Industrial Pharmacy* (L. Lachman, H. A. Lieberman, J. L. Kanig, eds.), Lea & Febiger, Philadelphia, 1986, pp. 3-20.
33. A. Martin, *J. Pharm. Sci.*, 50:513-517 (1961).
34. E. N. Hiestand, *J. Pharm. Sci.*, 61:268-272 (1972).
35. W. Higuchi, J. Swarbrick, N. Ho, A. Simonelli, A. Martin, Particle phenomena and coarse dispersions. In: *Remington's Pharmaceutical Sciences* (A. R. Gennaro, ed.), Mack, Easton, PA, 1985, pp. 311-317.

36. H. Schott, *J. Pharm. Sci.*, 65:855-861 (1976).
37. H. Schott, Colloidal dispersions. In: *Remington: The Science and Practice of Pharmacy* (A. R. Gennaro, ed.), Mack, Easton, PA, 1995, pp. 261-269.
38. W. Higuchi, J. Swarbrick, N. Ho, A. Simonelli, A. Martin, Particle phenomena and coarse dispersions. In: *Remington's Pharmaceutical Sciences* (A. R. Gennaro, ed.), Mack, Easton, PA, 1985, pp. 308-311.
39. K. J. Mysels, *Introduction to Colloid Chemistry*, Wiley-Interscience, New York, 1959.
40. P. C. Hiemenz, *Principles of Colloid and Surface Chemistry*, Marcel Dekker, New York, 1986, pp. 611-731.
41. B. A. Mathews and C. T. Rhodes, *J. Pharm. Sci.*, 59:521-525 (1970).
42. A. J. Scheer, *Drug Cosmet. Ind.*, 128:40-44 (1981).
43. R. J. Lantz, Size reduction. In: *Pharmaceutical Dosage Forms: Tablets*, Vol. 2 (H. A. Lieberman, L. Lachman, J. B. Schwartz, ed.), Marcel Dekker, New York, 1990, pp. 107-200.
44. E. L. Parrott, Milling. In: *The Theory and Practice of Industrial Pharmacy* (L. Lachman, H. A. Lieberman, J. L. Kanig, eds.), Lea & Febiger, Philadelphia, 1986, pp. 21-46.
45. K. N. Patel, L. Kennon, and S. R. Levinson, Pharmaceutical suspensions. In: *The Theory and Practice of Industrial Pharmacy* (L. Lachman, H. A. Lieberman, J. L. Kanig, eds.), Lea & Febiger, Philadelphia, 1986, p. 487.
46. S. Banerjee, A. Bandyopadhyay, R. C. Bhattacharjee, A. K. Mukherjee, and A. K. Halder, *J. Pharm. Sci.*, 60:153-155 (1971).
47. A. Heyd and D. Dhabhar, *Drug Cosmet. Ind.*, 125:42-45, 146 (1979).
48. C. M. G. Macie and A. J. W. Grant, *Pharm. Int.*, 7:233-237 (1986).
49. S. C. Mehta, P. D. Bernardo, W. I. Higuchi, and A. P. Simonelli, *J. Pharm. Sci.*, 59:638-644 (1970).
50. A. P. Simonelli, S. C. Mehta, and W. I. Higuchi, *J. Pharm. Sci.*, 59:633-637 (1970).
51. J. D. Mullins and T. J. Macek, *J. Am. Pharm. Assoc. (Sci. Ed.)*, 49:245-248 (1960).
52. S. Luhtala, P. Kahela, and E. Kristofferson, *Acta Pharm. Fenn.*, 99:59-67 (1990).
53. S. Luhtala, *Acta Pharm. Nordica*, 4:85-90 (1992).
54. S. Luhtala, *Acta Pharm. Nordica*, 4:271-276 (1992).
55. N. B. Shah and B. B. Sheth, *J. Pharm. Sci.*, 65:1618-1623 (1976).
56. *Martindale, The Extra Pharmacopoeia*, 30th ed., The Pharmaceutical Press, London, 1993, pp. 1217-1221.
57. V. Kumar and G. S. Banker, *Drug Dev. Ind. Pharm.*, 19:1-33 (1993).
58. J. H. Chapman and E. L. Neustadter, *J. Pharm. Pharmacol.*, 17:S138 (1965).
59. C. A. Farley, *Pharm. J.*, 216:562-566 (1976).
60. H. Schott, *J. Pharm. Sci.*, 59:1492-1496 (1970).
61. A. Scheer, *Drug Cosmet. Ind.*, 128:53-55, 102-105 (1981).
62. B. A. Miller, *Pharm. J.*, 231:384 (1983).
63. National Formulary, 18th ed., United States Pharmacopoeial Convention, Rockville, MD, 1995, p. 2232.
64. L. G. Galt and R. V. Josephson, *Am. J. Hosp. Pharm.*, 39:1009-1012 (1982).
65. S. Kabre, H. DeKay, G. Banker, *J. Pharm. Sci.*, 53:495-499 (1964).
66. D. Johnston, M. R. Gray, C. S. Reed, F. W. Bonner, and N. H. Anderson, *Drug Dev. Ind. Pharm.*, 16:1893-1909 (1990).
67. H. Asche, *Pharm. Acta Helv.*, 49:277-284 (1974).
68. C. Chauveau, H. Maillols, H. Delonca, *Pharm. Acta Helv.*, 61:292-297 (1978).
69. B. Idson and M. O. Bachynsky, *Drug Cosmet. Ind.*, 122:38-46, 153-155 (1986).
70. R. W. Butler and E. D. Klug, Hydroxypropylcellulose. In: *Handbook of Water-Soluble Gums and Resins* (R. L. Davidson, ed.), McGraw-Hill, New York, 1980, pp. 13-3.
71. B. Joynt and D. Zuck, *Can. J. Pharm. Sci.*, 3:93-96 (1968).

72. J. A. Polon, *J. Soc. Cosmet. Chem.*, 21:347-363 (1970).
73. P. W. Gerding and G. J. Spierandio, *J. Am. Pharm. Assoc. Pract. Ed.*, 15:356-359 (1954).
74. J. E. Carless and J. Ocran, *J. Pharm. Pharmacol.*, 24:637-644 (1972).
75. G. Catacajos and J. Wood, *J. Pharm. Sci.*, 53:1089-1093 (1964).
76. G. Dondi and A. Zanotti Gerosa, *Boll. Chim. Farm.*, 120:606-617 (1981).
77. V. Das Gupta, *Am. J. Hosp. Pharm.*, 38:363-264 (1981).
78. B. Meer, Gum arabic. In: *Handbook of Water-Soluble Gums and Resins* (R. L. Davidson, ed.), McGraw-Hill, New York, 1980, pp. 8-1-8-24.
79. W. Meer, Gum agar. In: *Handbook of Water-Soluble Gums* (R. L. Davidson, ed.), McGraw-Hill, New York, 1980, p. 7-5.
80. A. M. Goldstein, E. N. Alter, and J. K. Seaman, Guar gum. In: *Industrial Gums*, (R. L. Whistler, ed.), Academic Press, New York, 1973, pp. 303-321.
81. F. Rof, Locust bean gum. In: *Industrial Gums* (R. L. Whistler, ed.), Academic Press, New York, 1973, pp. 323-337.
82. P. S. Rao and H. C. Srivastava, Tamarind. In: *Industrial Gums* (R. L. Whistler, ed.), Academic Press, New York, 1973, pp. 394-411.
83. I. W. Cottrell, K. S. Kang, and P. Kovacs, Xanthan gum. In: *Handbook of Water-Soluble Gums and Resins* (R. L. Davidson, ed.), McGraw-Hill, New York, 1980, pp. 24-1-24-30.
84. M. C. B. Van Oudtshoorn and F. J. Potgieter, *Pharm. Weekblad*, 106:909-915 (1971).
85. A. Delgado, V. Gallardo, A. Perera, and F. Gonzalez Caballero, *J. Pharm. Sci.*, 79:709-715 (1990).
86. M. Barzegar-Jalali and J. R. Richards, *Int. J. Pharm.*, 2:195-201 (1979).
87. M. A. Kassem and A. G. Mattha, *Pharm. Acta Helv.*, 45:18-27 (1970).
88. N. Patel, L. Kennon, R. Levinson, Pharmaceutical suspensions. In: *The Theory and Practice of Industrial Pharmacy* (L. Lachman, H. A. Lieberman, J. L. Kanig, eds., Lea & Febiger, Philadelphia, 1986, p. 490.
89. E. Azaz and R. Segal, *Pharm. Acta Helv.*, 55:183-188 (1980).
90. K. Sabra and D. B. Deasy, *J. Pharm. Pharmacol.*, 35:275-278 (1983).
91. C. M. Ofner III and H. Schott, *J. Pharm. Sci.*, 76:715-723 (1987).
92. A. Felmeister, S. Kuchtyak, S. Koziol, C. J. Felmeister, *J. Pharm. Sci.*, 62:2026-2027 (1973).
93. J. S. Tempio and J. L. Zatz, *J. Pharm. Sci.*, 70:554-558 (1981).
94. J. V. Bondi, R. L. Schnaare, P. J. Niebergall, and E. T. Sugita, *J. Pharm. Sci.*, 62:1731-1733 (1973).
95. R. D. C. Jones, R. A. Matthews, and C. T. Rhodes, *J. Pharm. Sci.*, 59:518-520 (1970).
96. *United States Pharmacopeial/National Formulary*, 23rd ed., United States Pharmacopeial Convention, Inc., Rockville, MD, 1995, p. 2207.
97. J. Tingstad, J. Dudzinski, L. Lachman, E. Shami, *J. Pharm. Sci.*, 62:1361-1363 (1973).
98. G. Levy, *J. Pharm. Sci.*, 50:429-435 (1961).
99. A. A. H. Khalil and R. N. Nasipuri, *J. Pharm. Pharmacol.*, 25:138-142 (1973).
100. J. Swarbrick, Coarse dispersions: Suspensions, emulsions, and lotions. In: *American Pharmacy* (L. W. Dittert, ed.), Lippincott, Philadelphia, 1974, pp. 196-197.
101. V. K. La Mer, R. H. Smellie, and P. Lee, *J. Colloid Sci.*, 12:230-239 (1957).
102. A. Dakkuri and B. Ecanow, *J. Pharm. Sci.*, 65:420-423 (1976).
103. H. Schott and A. E. Royce, *Colloids Surfaces*, 19:399-418 (1986).
104. T. T. Oryl and G. E. Peck, *Drug Dev. Ind. Pharm.*, 17:2245-2268 (1991).
105. S. A. Young and G. Buckton, *Int. J. Pharm.*, 60:235-241 (1990).
106. N. Weiner, *Drug Dev. Ind. Pharm.*, 12:933-951 (1986).
107. A. Osol and G. Farrar, eds., *United States Dispensatory*, Lippincott, Philadelphia, 1955, p. 771.
108. H. C. Ansel, *Introduction to Pharmaceutical Dosage Forms*, Lea & Febiger, Philadelphia, 1985, p. 213.

Oral Aqueous Suspensions

181

109. K. G. Tolman, Gastrointestinal and liver drugs. In: *Remington: The Science and Practice of Pharmacy* (A. R. Gennaro, ed.), Mack, Easton, PA, 1995, p. 887.
110. G. E. Schmacher, *Am. J. Hosp. Pharm.* 26:85 (1969).
111. C. M. Ofner III and R. L. Schnaare, Unpublished data.
112. *Grifulvin V, Package Insert*, Ortho Pharmaceutical Corporation, Raritan, NJ, 1985.
113. H. J. Von Dechow, D. Dolcher, G. Hubner, S. Kim, K. Lammerhirt, C. H. Pich, and E. Schmidt-Bothelt, *Arzneim. Forsch.*, 26:596-613 (1976).