

# 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

PTX0192

exhibitstick.com

MEDA\_APTX03505662

CIP2113

Argentum Pharmaceuticals LLC v. Cipla Ltd.

IPR2017-00807

# 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

MEDA\_APTX03505663

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

MEDA\_APTX03505664

## 5

### Topical Suspensions

**Hridaya N. Bhargava**

*Massachusetts College of Pharmacy and Allied Health Sciences, Boston,  
Massachusetts*

**Daniel W. Nicolai**

*Stiefel Research Institute, Inc., Oak Hill, New York*

**Bharat J. Oza**

*Oza Enterprises, Summit, New Jersey*

#### I. INTRODUCTION

Pharmaceutical suspensions constitute a drug delivery system in which insoluble solid particles are dispersed as discrete units or as a network of particles in a continuous liquid medium. Pharmaceutical suspensions are used for oral, injectable, or topical applications. Nearly all pharmaceutical suspensions have particles greater than  $0.1\mu\text{m}$ , though the size and shape of individual particles may vary.

Suspensions form an important class of pharmaceutical dosage form and offer distinct advantages. Many of the more recently developed drugs are generally hydrophobic with limited aqueous solubilities. A suspension is an ideal delivery system for insoluble and bitter-tasting drugs. Suspensions allow masking of taste and thus improve patient compliance. They are a suitable form of drug delivery for the topical application of dermatologic materials to the skin and sometimes to the mucous membrane. Compared to the solubilized system, suspensions offer better chemical stability of drugs. Drugs from suspensions are more readily bioavailable than from a tablet or a capsule [1,2]. Lately, suspensions are becoming increasingly popular as intramuscular injections for depot therapy.

Formulation of a safe, effective, stable, and pharmaceutically elegant suspension is more difficult and challenging than formulation of tablets or capsules. Some of the difficulties that a formulator should overcome during the development of a suspension are nonhomogeneity of dosage, sedimentation, compaction of sediment, aggregation of suspended particles, difficulty with redispersion, and masking of taste and of undesirable odor.

For the most part, this discussion will focus on aqueous topical suspensions and theoretical considerations such as wetting, crystal growth, surface tension, zeta potential, preformulation, preparation, testing, and stability of suspensions. However, many of the areas that are covered are applicable to nonaqueous suspension or emulsion suspensions.

## II. DESIRABLE ATTRIBUTES OF A SUSPENSION

An acceptable and therapeutically effective suspension should possess the following attributes:

1. Ideally, the suspended material should not settle readily at the bottom of the container. However, suspensions, being thermodynamically unstable, do tend to settle and should therefore be readily redispersible into a uniform mixture upon shaking and must not cake.
2. Physical characteristics such as particle size and viscosity should remain fairly constant throughout the shelf life of the product.
3. Its viscosity must promote free and even flow from the container. For external application, the product should be fluid enough to spread freely over the affected area and yet must not be so mobile as to run off the intended area of application.
4. The topical suspension should dry quickly and provide a protective elastic film that will not rub off readily.
5. It should be safe, effective, stable, and pharmaceutically elegant during its shelf life.
6. Resuspension should produce a homogeneous mix of drug particles such that same amount of drug can be removed repeatedly.

## III. A SYSTEMATIC APPROACH TO SUSPENSION FORMULATION

A systematic approach to a pharmaceutical suspension, whether intended for systemic or topical usage, involves several steps. It requires:

1. Identification and knowledge of the site of drug release and its therapeutic effect
2. Preformulation studies on pure drug
3. Selection of compatible excipients and validation of their specifications
4. Identification and selection of the method of manufacturing
5. Preparation of trial formulations for in vitro and in vivo testing and evaluations
6. Pilot plant scale-up of the formula
7. Development and evaluation of in-process test methods
8. Performance of stability studies
9. In vivo safety and efficacy data
10. Validation of manufacturing process, stability data, method of analysis, and other data required for submission with an Investigational New Drug application (IND), New Drug Application (NDA), and Abbreviated New Drug Application (ANDA).

## IV. THEORETICAL CONSIDERATIONS

The difficulties in the development of a reasonably stable suspension, and problems associated with the evaluation of such products are, for the most part, related to their



nonequilibrium state. A conceptual understanding of the thermodynamics of these dispersions, particularly concerning their surfaces or interfacial free energy, will facilitate a successful formulation of such systems. A strategy that fails to utilize surface behavior to stabilize unstable formulations thermodynamically is unlikely to be productive, whereas a strategy based on an appreciation of the surface properties of the system is much more likely to succeed [3].

An understanding of interfacial properties, wetting, particle interaction, electrokinetics, aggregation, sedimentation, and rheological concepts will be of immense help to the formulator. Many of the concepts and equations presented may not be used directly for the purpose of formulation; rather, they provide an understanding of the interactions involved in the formulation of a suspension.

#### A. Interfaces

Interface is defined as the boundary between two phases [3]. Usually an interior molecule has "equal" forces pulling at it equally in all directions. However, at the interface, molecules are subjected to a highly unbalanced force field, because they are in contact with other molecules exhibiting different forces of attraction. As a result of this, molecules situated at the phase boundary contain potential forces of interaction that are not satisfied relative to the situation in the bulk phase [4]. Interfaces possess positive free energy, meaning molecules at the interface have a higher energy state than if they were located in the bulk. The greater the preference of the molecule for the bulk phase as compared to interface, the greater the interfacial free energy. The formulator attempts to reduce this positive free energy value to zero by reducing the amount of interface or varying the composition of the interface.

Although interfacial free energy is not directly measurable, interfacial tension values are obtainable. Surface or interfacial tension, however, should be looked upon as a mathematical approximations of surface or interfacial free energy.

#### B. Wetting

The introduction of solid particles into a vehicle is the critical step in the preparation of a pharmaceutical suspension and requires adequate wetting of the solid particles for a stable dispersion.

Wetting of solid materials in the most general sense implies replacement of air on a solid surface by liquid. The process of wetting involves surfaces and interfaces. Usually, slightly lyophobic powders present no major problem and can be wetted easily. Strongly lyophobic powders, however, may float in an aqueous medium because of high interfacial energy between the vehicle and the powder.

Three types of wetting have been distinguished: (a) spreading wetting, (b) adhesional wetting, and (c) immersion wetting. All types of wetting depend on the balance of surface forces [5].

In spreading wetting, a liquid in contact with substrate spreads over the substrate and displaces air from the surface. If a liquid displaces air from the surface completely, the liquid is said to wet the surface completely [5].

If the liquid L in Fig. 1 spreads from C to B, covering an area A, then the decrease in surface-free energy of the system occurs due to a decrease in area of the substrate/air interface. This decrease in surface free energy is  $A \times \gamma_{SA}$ , where  $\gamma_{SA}$  is the inter-

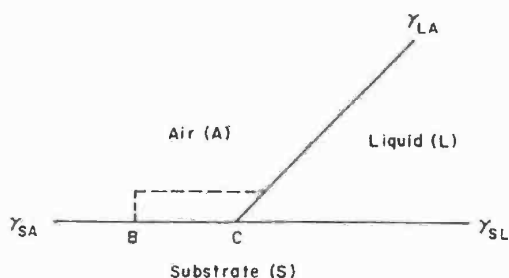


Fig. 1 Spreading wetting.

facial free energy per unit area of the substrate in equilibrium with liquid-saturated air above it.

At the same time, the free energy of the system increases because of the increase in liquid/substrate and liquid/air interfaces. The increase in surface free energy of the system due to the increase in the liquid/substrate interface is  $A \times \gamma_{SL}$ , where  $\gamma_{SL}$  is the interfacial free energy per unit area at the liquid/substrate interface. The increase in surface free energy of the system due to the increase in the liquid/air interface is  $A \times \gamma_{LA}$ , where  $\gamma_{LA}$  is the surface tension of liquid L.

The quantity, which is a measure of the driving force behind the spreading process, is usually called the spreading coefficient  $S_{L/S}$  and is defined by the equation:

$$S_{L/S} = \gamma_{SA} - (\gamma_{SL} + \gamma_{LA}) \quad (1)$$

In general, a liquid will spread spontaneously if the spreading coefficient  $S_{L/S}$  is positive, and it will not spread spontaneously if  $S_{L/S}$  is negative.

#### 1. Critical Surface Tension

Critical surface tension provides a way to characterize solid surfaces. The concept of critical surface tension ( $\gamma_c$ ) for spreading on a low energy surface was developed by Zisman and coworkers [6,7]. Generally, a liquid whose surface tension is equal to or less than the critical surface tension of a solid spreads readily. Table 1 gives the critical surface tension values of some powders [8].

Knowledge of the critical surface tension helps in determining the necessity for and the selection of a wetting agent. Usually, compounds that have a critical surface tension below 30 dynes/cm<sup>2</sup> require a wetting agent.

#### 2. Contact Angle and Its Measurement

The contact angle is an angle that a liquid makes when it is at equilibrium with other phases. A drop of liquid at rest upon a solid assumes a shape that is controlled by three forces: surface tension of the liquid, surface tension of the solid, and interfacial tension between the solid and the liquid. The contact angle ( $\theta$ ) is a measure of the relative strength of the combined forces [8]. In many applications the contact angle is the only value required for evaluating wetting properties. For applications that require determi-

**Table 1** Critical Surface Tension Values for Some Powders

Substance	Critical surface tension (dyne/cm)
Sulfadiazine	33
Aspirin	32
Salicylic acid	31
Sulfur	30
Magnesium stearate	22

Source: Ref. 8. Reprinted with permission from the publisher, the Society of Cosmetic Chemists, New York, NY.

nation of surface or interfacial energies,  $\Theta$  is analyzed in terms of vector forces using Young's equation [8], as described below:

$$\gamma_s = \gamma_{LS} + \gamma_L \cos \Theta \quad (2)$$

where  $\gamma_s$ ,  $\gamma_{LS}$ , and  $\gamma_L$  are surface tension of solid, interfacial tension of liquid/solid, and surface tension of the liquid, respectively.

Rearranging Eq. (2) gives

$$\cos \Theta = \frac{\gamma_s - \gamma_{LS}}{\gamma_L} \quad (3)$$

Complete wetting occurs if  $\cos \Theta = 1$ . For all wetting processes, reduction of the surface tension of liquid ( $\gamma_L$ ) is always beneficial and reduction of the interfacial tension between liquid and solid ( $\gamma_{LS}$ ) may also be beneficial.

To date, numerous papers on measurements of contact angle have been published [8-10]. Contact angles have been measured on macroscopic smooth planar substrates by placing a droplet of a liquid or a solution on a substrate and determining the contact angle by any of the number of techniques reviewed by Adamson [10]. The contact angle can be measured directly by the use of a microscope fitted with a goniometer or indirectly by measuring height  $h$  and diameter  $d$  of a droplet and using the Bartell relationship [11] and as given by Eq. (4).

$$\tan \frac{\Theta}{2} = 2 \frac{h}{d} \quad (4)$$

### 3. Modification of Wetting by Surfactant

Water has a rather high surface tension and generally does not spread spontaneously over substrates that have low surface free energy. For any liquid to wet the substrate, the spreading coefficient must be positive. The addition of a surfactant to water reduces its surface tension and in some instances may reduce the interfacial tension between water and the substrates well, resulting in a positive spreading coefficient. However, addition of a surfactant to water does not always increase the spreading coefficient. In cases where the substrate is porous or when adsorption of the surfactant occurs at the liquid/solid interface, the use of a surfactant may decrease wetting [5].



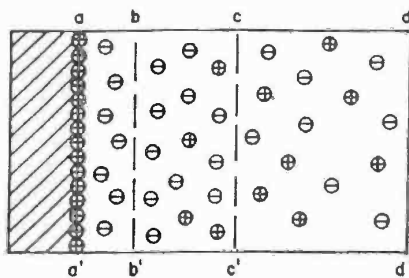
To save time in surfactant selection, a systematic scheme of identifying the relatively few surfactants, suitable for any given application was introduced in the late 1940s. This is called the HLB system (the letters HLB stand for "hydrophile-lipophile balance"). In the HLB system, each surfactant is assigned a numerical value, which is called its HLB value. A surfactant with a low HLB value tends to be oil soluble; one that has a high HLB value will tend to be water soluble. Any surfactant that lowers the surface tension of water below 30 dynes/cm<sup>2</sup> will cause spontaneous wetting [8].

### C. Zeta Potential

Electrical charges may be developed on suspended particles as the result of ionization of chemical groups on a solid surface, adsorption of the surfactant molecule on a solid surface, or adsorption of electrolytes from the solution on a solid surface. The particle charge gives rise to surface potential  $\psi_s$ . The potential will drop to zero at some distance away from the surface depending on the concentration of counterions in the external phase. The region in which the influence of the surface charge is appreciable is called the electrical double layer [12,4]. In the double layer, the first layer is tightly bound and moves with the particle; the second layer is more diffuse, as illustrated in Fig. 2.

The magnitude of charge is defined as the difference in electrical potential between the charged solid surface and the bulk of the solution. There are several potentials that can be defined but the important one for formulation of a suspension is zeta potential,  $\zeta$ . Zeta potential is defined as the difference in potential between the surface of the tightly bound layer of ions on the particle surface and the electroneutral region of the solution. The application of zeta potential measurements to the formulation of suspensions has been investigated by Haines and Martin [13].

When the zeta potential is relatively high, 25 mV or more (which depends on the particular system being used), the repulsive forces exceed the attractive London forces and particles are dispersed and the system is deflocculated. On the other hand, when the zeta potential is lowered (less than 25mV), the attractive forces exceed the repulsive forces, and the particles come together leading to flocculation.



**Fig. 2** The electrical double layer at the surface of separation between two phases showing distribution of ions. (From A. Martin, J. Swarbrick and A. Cammarata, *Interfacial phenomena*. In: *Physical Pharmacy* 4th ed., p. 387. Reprinted with permission from the publisher, Lea & Febiger, Philadelphia, PA.)

#### D. Crystal Growth, Aggregation, and Caking

The basic concern in almost all suspension systems is to decrease the rate of settling and permit easy resuspendability of any settled particulate matter. Physical instability of the suspension results from crystal growth, aggregation, or caking.

##### 1. Crystal Growth

The following factors affect the potential for crystal growth in a pharmaceutical suspension:

1. Particle size distribution
2. Dissolution and recrystallization
3. Changes in pH and temperature
4. Polymorphism and solvate formulation [14].

Small particles are more soluble than larger particles because of a higher surface energy per unit mass. The Ostwald-Freundlich equation:

$$\ln \frac{C_1}{C_2} = \left( \frac{2 M \gamma}{\rho R T} \frac{1}{R_1} - \frac{1}{R_2} \right) \quad (5)$$

where

C = solubility of particles of radii  $R_1$  and  $R_2$

M = molecular weight

$\gamma$  = surface energy of solid

$\rho$  = density of solid

R = gas constant

T = absolute temperature

The Ostwald-Freundlich equation shows that the solubility ( $C_1$ ) is higher for smaller particles ( $R_1$ ) than the solubility ( $C_2$ ) is for larger particles ( $R_2$ ). Variable particle size can also result from various factors including: (a) preparation of suspension, (b) changes in pH, and (c) temperature changes. Causes of this recrystallization phenomena include polymorphism, solvate formation, and temperature fluctuation [14].

To retard or eliminate crystal growth, the formulator must consider many factors, including the theory behind crystal growth and particle size distribution of the drug, the use of the right polymorph and solvate forms, the conducting of temperature cycling, and the selection of the appropriate viscosity of the product.

##### 2. Aggregation and Caking

Suspensions are thermodynamically unstable systems and, when left undisturbed for a long period of time, lead to aggregation of particles, sedimentation, and eventually caking. Particles held together strongly are called aggregates, and the compaction of strongly adhering aggregates that settle at the bottom of the container forms a cake. Caking is one of the most difficult problems encountered in the formulation of a suspension. Caking cannot be eliminated by reducing particle size or increasing the viscosity of the medium. Once the cake is formed it cannot be remedied. However, cake formation can be anticipated and prevented.

When particles are held together in a loose open structure, the system is said to be in the state of flocculation. The flocculated particles settle rapidly in the suspension to form sediment with large volume but are readily redispersed.

To resolve the problem of caking, one must consider forces of attraction and repulsion between particles in the suspension. Flocculation and aggregation are brought about by the forces that reside at the surface of the particles. These forces depend on the nature of the species, distance of separation, orientation of the molecule, and the nature of the medium.

Much of the present day theory regarding charge on suspended particles results from the work of four scientists, Derjaguin, Landau, Verwey, and Overbeek, and is often called the DLVO theory [15]. The theory quantitatively describes the stability of lyophobic colloids and is universally accepted. It involves the comparison of two types of forces: London and van der Waals attractive forces and forces of repulsion caused by interaction of electrical double layers surrounding each particle. The DLVO theory details the factors [16,17] involved in controlling the rate at which the particles in suspension come together or aggregate [15]. The process of aggregation of particles will accelerate the rate of sedimentation and thus affect redispersibility. The following total energy of interaction between the two particles is defined by equation:

$$V_T = V_R + V_A \quad (6)$$

where

$V_T$  = total energy of interaction

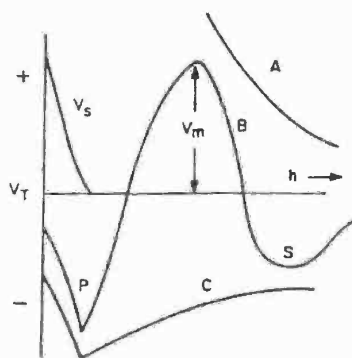
$V_R$  = total repulsive forces

$V_A$  = total attractive forces

Figure 3 shows the total energy of interaction curves between suspended particles of three general types [15,18].

Curve A applies when  $V_R$  is greater than  $V_A$ ; that is, the term  $V_T$  is always positive because of high potential at the double layer. In such cases the suspension would exhibit good resistance to aggregation and indefinite stability, provided particles are not sufficiently large to sediment under gravity.

Curve B shows a high potential energy barrier  $V_M$ , which must be surmounted if particles are to approach one another sufficiently close to enter the deep primary en-



**Fig. 3** The total energy of interaction between two particles, as a function of interparticle distance  $h$ . (From Ref. 18. Reproduced with permission of the copyright owner, the American Pharmaceutical Association.)

ergy minimum at P. The value  $V_M$  required to just prevent this is probably equivalent to a zeta potential of about 50 mV. Aggregates that do form at P are likely to be very tightly bound together because  $h$ , the interparticulate distance, is small. Thus, to redisperse the product, vigorous shaking is required. Curve B also has a secondary minimum S. Aggregations formed by particles in this region can break up readily with shaking [18].

Curve C prevails when attractive forces completely overwhelm the electrostatic repulsion (i.e.,  $V_A > V_R$ ) and rapid coagulation occurs [18].

Curve  $V_S$  exhibits the stabilizing effect of the surfactants adsorbed on the substrate. It shows a sharp cutoff point at a distance equal to  $2d$ , where  $d$  is the thickness of the adsorbed surfactant layer. The strongly hydrated nature of the surfactant head group impedes particle-particle contact, which would result in aggregation and thus stabilize the suspension [15]. In such suspensions, which are stabilized by adsorbed surfactant molecules, the total energy of interaction,  $V_T$ , existing between two particles is obtained by adding the contribution from repulsion  $V_S$ ,  $V_A$ , and  $V_R$ . The total energy of interaction,  $V_T$ , is then given by Eq. (7).

$$V_T = V_A + V_R + V_S \quad (7)$$

Schneider et al. [19] have prepared a computer program to calculate the repulsion and attraction energies in pharmaceutical suspensions.

Several differences between flocculated and deflocculated suspensions are evident and summarized in Table 2. Overflocculation is undesirable as it leads to the growth of excessively large particles that interfere with uniformity in the viscosity and appearance of the suspension. The concept of "controlled flocculation" applies to a pharmaceuti-

**Table 2** Relative Properties of Flocculated and Deflocculated Particles in Suspension

Deflocculated	Flocculated
1. Particles exist in suspension as separate entities	Particles form loose aggregates
2. Rate of sedimentation is slow because each particle settles separately and particle size is minimal.	Rate of sedimentation is high because particles settle as a floc, which is a collection of particles.
3. A sediment is formed slowly.	A sediment is formed rapidly.
4. The sediment eventually becomes very closely packed as the result of weight of upper layers of sedimenting material. Repulsive forces between particles are overcome and a hard cake is formed that is difficult, if not impossible, to redisperse.	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, so as to reform the original suspension.
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.	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 encompass the volume of the suspension.

Source: Ref. 4. Reprinted with permission from the publisher, Mack Publishing Co., Easton, PA.

cal suspension. The theory and technique of controlled flocculation was first introduced by Haines and Martin [13]. Scientists have tested and advanced the concept, finding it to be helpful in the formulation of suspensions. Mathews and Rhodes, in a series of papers [20-25] dealing with physicochemical factors involved in suspension formulation, evaluated the use of "controlled flocculation" for suspension stability. Various therapeutic agents such as hydrocortisone and norgestrel were formulated using a controlled flocculation technique to stabilize the suspension [24]. The theory of controlled flocculation is still the subject for further investigation, and certain aspects of the theory have been criticized [26].

### E. Flocculents

Particle flocculation affects sedimentation rate, as well as the degree of compaction that takes place within the sediment. Flocculents function either by reducing the electrostatic repulsive forces or by providing additional interparticle attraction. Electrolytes function as flocculating agents in a suspension containing charged particles by reducing interparticulate repulsion; thus, the balance shifts in favor of the attractive van der Waals forces bringing particles together [8]. Formula adjuvants such as surface-active agents and polymers, chosen for their effect on wetting and rheological behavior, respectively, may also influence flocculation.

#### 1. Electrolytes

The electrolytes needed to effect optimum flocculation depend on the valence and type of interacting ion; the Schulze-Hardy rule [27] summarizes this, stating that the valence of the ions having a charge opposite to that of the lyophobic particle determines the effectiveness of an electrolyte in aggregating the particle. The aggregating efficiency increases with the valence of the ion. Trivalent ions are more efficient than divalent ions, which in turn are more efficient than monovalent ions.

Mathews and Rhodes [21] studied the influence of several salts and anionic wetting agents on the flocculation characteristics of suspensions. In the absence of a salt the suspension was deflocculated, but the addition of a salt flocculated the system. Their studies found aluminum chloride to be a much more efficient flocculent than calcium chloride, which was found to be more efficient than sodium chloride. They further extended their work on the flocculation of sulfamerazine hydrocortisone and griseofulvin suspensions and found the efficiency of the electrolytes to be of the same order in all three suspensions and in agreement with the Schulze-Hardy rule.

#### 2. Surface-Active Agents

Ionic and nonionic surface-active agents have been reported to produce flocculation [28-32]. The flocculation produced by a surfactant depends on its physicochemical properties and its concentration. The surface-active agent is adsorbed on the electrical double layer, causing neutralization or reversal of the charges, thus lowering the zeta potential. Otsuka et al. [30] studied adsorption of nonionic polyethoxylated octyl and nonylphenols on sulfathiazole and naphthalene and observed that the surfactant with a large hydrophilic chain length significantly influenced flocculation of sulfathiazole, but there was little influence of the hydrophobic chain length on the flocculation behavior of naphthalene. Liao and Zatz [29,30] investigated the effect of nonionic surfactants on the flocculation behavior of a suspension containing benzocaine and butamben. Assessing



the apparent viscosity, sedimentation volume and refiltration as a flocculation probe they reported that the flocculation of benzocaine was a function of the surfactant concentration, polyoxyethylene chain length, and particle size.

### 3. Polymers

Polymers are considered to differ from surfactants because polymers have a very high molecular weight with many active centers spaced along the chain. On the other hand, a surfactant has low molecular weight with few active centers on a single molecule [28]. The polymers act as flocculating agents by adsorption as well as by liquid bridging of particles. In the case of polymers, a part of the polymer chain is adsorbed at the solid-liquid interface with the remaining part projecting out into the dispersion medium. The adsorption phenomenon of polymers is independent of changes in temperature, solvent, and even the adsorbent surface [28].

Zatz et al. [34] studied flocculation of negatively charged sulfamerazine by a cationic polymer and reported that at low concentration of the polymer, the sedimentation volume was not affected, but at a critical value a significant rise in sedimentation volume was observed, indicating the suspension had flocculated. Their findings suggest that at a small concentration or in the absence of a polymer, particles were separated by their negative charge. Flocculation occurred at a critical polymer concentration and was caused by the bridging of particles by the polymer [33]. Felmeister, Reiss, and Healy separately [34-36] studied the influence of xanthan gum, an anionic polysaccharide, on the flocculation characteristics of suspensions of sulfaguanidine and bismuth subcarbonate. Addition of xanthan gum resulted in a flocculated suspension. Tiempo and Zatz [37,38] studied the effect of xanthan gum on the flocculation properties of aluminum hydroxide and magnesium carbonate suspensions. Addition of xanthan gum increased the extent of the flocculation. They studied flocculation mechanism and concluded that a number of factors influence the adsorption of a polymer at the solid-liquid interface.

Zatz [39] reported that a magnesium carbonate suspension became highly flocculated in the presence of xanthan gum but deflocculated on addition of docusate sodium, an anionic surfactant. The nonionic surfactant polysorbate 40 had no effect on the flocculation state of a suspension. If xanthan gum and docusate sodium both were present, the flocculation state depended on the relative concentration of the two substances, as both are anionic and compete for the same surface site on the magnesium carbonate particle.

### F. Sedimentation

The majority of factors that govern the physical stability of a suspension are the result of unequal gravitational pull on the suspended particles and the medium, and are depicted by Stokes' equation:

$$V = \frac{d^2(\rho - \rho_0)g}{18\eta} \quad (8)$$

Where

$V$  = sedimentation velocity

$d$  = particle diameter

$\rho$  = particle density

$\rho_0$  = medium density

$g$  = gravitational constant

$\eta$  = viscosity of continuous external phase.

Thus, physical stability of a suspension can be improved by increasing the viscosity of the external phase as the rate of sedimentation is an inverse function of viscosity. However, too high a viscosity is undesirable, especially if the suspending medium is Newtonian, because in such a system it is difficult to redisperse the material that has settled. Also, the rate of sedimentation is proportional to the particle diameter and a reduction in particle size will reduce the rate of sedimentation significantly.

According to Stokes' law the rate of sedimentation is reduced if the difference in densities ( $\rho - \rho_0$ ) of the dispersed phase and the continuous phase can be reduced significantly. It is possible to increase the density of the liquid by using polyols like glycerin or sorbitol and thus bringing it closer to the dispersed solid, but this technique is rarely used to stabilize pharmaceutical suspensions.

### G. Rheology

The rheological behavior of a pharmaceutical suspension furnishes the formulator with a means of exercising the greatest control over sedimentation and optimization of the physical stability of the system. The choice of the type of rheology depends to a large extent on the type of bodying agent and its intended application. If the medium is viscous enough, like castor oil or glycerin, a bodying agent may not be necessary to enhance the viscosity. However, if the medium is nonviscous, like alcohol or water, a bodying agent may be necessary to impart the desired viscosity to the medium. For example, a suspension for topical application should be fluid enough to permit proper shaking and pourability yet should not flow readily from the skin. It should also provide sufficient resistance against the gravitational settling while in the container.

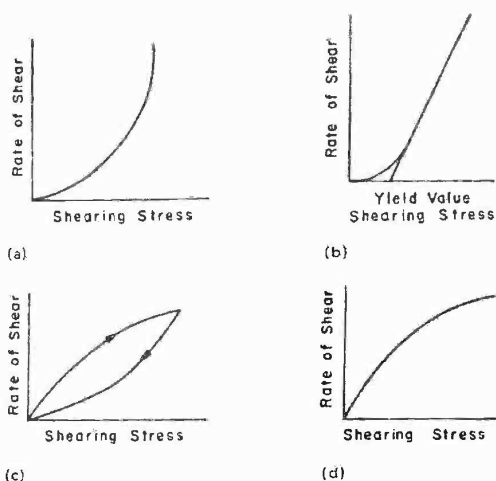
A fluid may exhibit Newtonian or non-Newtonian flow. The non-Newtonian type of behavior includes pseudoplastic, plastic thixotropic, or dilatant flow characteristics, as shown in Fig. 4. The combination of desired attributes requires careful selection of an additive that will impart non-Newtonian flow characteristics to the suspension.

#### 1. Pseudoplasticity

The viscosity of a system exhibiting pseudoplastic flow is inversely proportional to the shear rate. As shear stress is increased, the resistance to flow decreases (Fig. 4a), and the system becomes more fluid. This shear-thinning behavior is called pseudoplasticity. The apparent viscosity of such a system therefore cannot be defined in terms of one value. Many colloidal systems, especially polymer solutions, exhibit pseudoplastic flow.

#### 2. Plasticity

Plastic behavior is characterized by the presence of a yield value (Fig. 4b). Some materials such as semisolids do not flow at low shear stress. A Bingham body does not flow until shearing stress equals or exceeds the yield value. Once the shear stress equals or exceeds the yield value, the composition begins to flow. This system exhibits solid-like behavior under quiescent conditions. This property of plastic flow may effectively inhibit sedimentation altogether in a suspension. Agitation temporarily disrupts the rigid network of solids, making it possible to pour or apply the suspensions to the skin.



**Fig. 4** Plots of rate of shear as a function of shearing stress for: (a) simple pseudoplastic; (b) plastic; (c) thixotropic; and (d) dilatant flow. (Reprinted from Ref. 15, p. 333, by courtesy of Marcel Dekker, Inc., New York, New York.)

### 3. Thixotropy

Thixotropy, which may be seen in both plastic and pseudoplastic systems, is characterized by the fact that the rate of shear at any given shearing stress can vary depending on whether the rate of shear is increasing or decreasing. Thixotropy is a measure of the breakdown and then rebuilding of the structure of the system. Thixotropic systems contain a structural network of colloidal particles. At rest, this structure confers some degree of rigidity on the system, but when disrupted by shear, the system begins to flow. Upon removal of shear stress, the structure begins to re-form. The reformation of structure is time dependent and can take from several minutes to hours or days. During this time, the product can be poured from the container. The apparent viscosity of a thixotropic system depends not only on the shear rate and shear stress, but also on duration under shear.

The most apparent characteristic of a thixotropic system is the presence of a hysteresis loop, which is formed by the up and down curve of the rheogram (Fig. 4c). The area of a hysteresis loop has been proposed as a measure of thixotropic breakdown and rebuilding of the structure and can be easily obtained [40].

### 4. Dilatancy

A dilatant system exhibits an increase in the resistance to flow when stress is exerted; thus, the system returns to its original state of fluidity when the stress is removed (Fig. 4d). A dilatant system is the reverse of a pseudoplastic system and is a shear-thickening system.

Pharmaceutical suspensions that exhibit plastic or thixotropic rheological behavior generally exhibit good physical stability. Such a suspension may prevent sedimentation, aggregation, and caking by virtue of its high yield value at rest, yet reduce viscosity significantly to permit its application. On the other hand, pseudoplastic or dilatant flow characteristics are undesirable in a suspension as they impart physical instability to the product.

## V. PREFORMULATION

The first step in the systematic development of any pharmaceutical dosage form is the careful examination of preformulation test results. The compilation of physicochemical properties is known as preformulation. In today's environment of drug development, it is imperative that the formulator have a complete profile of the physicochemical properties of the drug substance available before initiating formulation development. The use of preformulation parameters maximizes the chances of success in formulating an acceptable, safe, efficacious, and stable product and at the same time provides the basis for optimization of the drug product quality.

A typical preformulation program should begin with the description of the organoleptic qualities of the drug substance. The color, odor, and taste are of immense value in developing an aesthetically acceptable suspension. Appropriate flavor, dyes, and adjuvants can be used to alleviate problems of unpalatable taste, unsightly appearance, or unpleasant odor, but only if they do not compromise efficacy or stability of the drug in the suspension. Some descriptive terms for organoleptic attributes of a drug product are listed in Table 3.

Other significant preformulation parameters include purity of the drug, particle size, shape and surface area, static charge, solubility, dissolution, partition coefficient, ionization constant, crystal properties and polymorphism, chemical and physical stability, solid state and aqueous stability, absolute and bulk density, hygroscopicity, flowability, and excipient compatibility [41]. Of these, crystal properties, particle size and surface area, dissolution, flow characteristics, and drug excipient compatibility are of prime importance in the formulation of suspensions.

### A. Crystal Properties

Most organic drug substances exist in more than one crystalline form or lattice configuration, a feature called polymorphism. Polymorphs may exhibit differing physical properties; for example, x-ray diffraction patterns, solubility, dissolution, density, vapor pressure, melting point, crystal form, compaction behavior, flow properties, solid state

**Table 3** Suggested Terminology to Describe Organoleptic Properties of Pharmaceutical Powders

Color	Odor	Taste
Off white	Pungent	Acidic
Cream yellow	Sulfurous	Bitter
Tan	Fruity	Bland
Shiny	Aromatic; odorless	Intense; sweet; tasteless

Source: Ref. 41

stability, and absorption rate [42]. Though a drug can exist in more than one polymorphic form, only one of these forms is thermodynamically stable, and the other unstable (metastable) forms will revert to the stable form in time [43]. Many solids can be prepared in the desirable polymorphic form by selecting an appropriate solvent for recrystallization and the appropriate rate of cooling.

Polymorphs of several drugs have been extensively investigated. Cortisone acetate exists in four polymorphic forms but only one is stable in aqueous medium. Amorphous penicillin exhibits less chemical stability than the crystalline salt [43]; metastable sulfathiazole dissolves more rapidly than the more stable sulfathiazole [42].

The use of a metastable polymorph may result in the following: (a) crystal growth; (b) caking; (c) reduced bioavailability; (d) crystal transition, which produces changes in physical and biological characteristics; and (e) reduced chemical stability.

The transition from one structural arrangement to another can be achieved by temperature fluctuations. One polymorphic form of the drug can be reversibly changed to another one. The crystal habit (external shape of crystal), although not as important as polymorphism, also plays a role in product properties, especially if the particle size is small. An increase in temperature during shipment and storage of a suspension may lead to increased solubility, with subsequent dissolution of small crystals. When the temperature decreases, however, the dissolved drug tends to recrystallize to larger crystals. Thus, fluctuations in temperature may change the particle size distribution and crystal habit and may lead to caking. The crystal growth of some drugs has been significantly retarded by the use of a surface-active agent or a polymer. They seem to act by adsorbing at the surface of the crystal [4].

Various techniques are available to study crystal properties. These include microscopy, infrared spectrophotometry, x-ray powder diffraction, and thermal analysis [42].

## B. Particle Size and Surface Area

Several chemical, physical, and biological properties of drug substances are influenced by particle size and surface area. The rate of sedimentation, content uniformity, taste, texture, and chemical stability are dependent on the particle size. Control of particle size is directly related to flow properties, segregation, and demixing. The relationship between particle size and particle surface area is an inverse one; that is, reduction in particle size leads to an increase in the surface area. Although a decrease in particle size favors suspendability, the high surface energy of a micronized powder caused by the large surface area may result in poor wettability and agglomeration in suspension.

In most pharmaceutical suspensions, the particle diameter is between 1 and 50  $\mu\text{m}$ ; a topical suspension should have a particle size less than 35  $\mu\text{m}$  to be impalpable to the touch—otherwise, grittiness results.

The most efficient method of producing particles of optimum size is by dry milling prior to incorporation into the dispersion medium. However, this method is not appropriate when processing potentially explosive ingredients such as benzoyl peroxide for which wet milling or homogenization of the finished product may be more desirable. Among the several methods of producing small uniform drug particles are micropulverization, fluid energy grinding, spray drying, and controlled precipitation [44]. Micropulverizers, using high speed attrition, or impact mills are capable of reducing the particle size to an acceptable range for most oral or topical suspensions. Fluid energy grinding is quite effective in producing particles less than 10  $\mu\text{m}$  in size. Particles of



extremely small dimensions and desired shape can also be produced by the spray-drying technique. It produces free-flowing monodispersible powder. Particles of less than 5  $\mu\text{m}$  can be prepared by controlled precipitation with the aid of ultrasound. This involves shock cooling of a hot, saturated solution of the drug in conjunction with ultrasonic insonation of its solvent environment [45].

Several techniques and tools are used to monitor particle size. The most widely used technique is microscopy, which is capable of measuring particles of 0.3  $\mu\text{m}$  or larger. Sieving is another technique for particles in the 40  $\mu\text{m}$  or higher range. Screen analysis data serves as a qualitative guideline in evaluating raw materials. A variety of instruments is available (see listing in Appendix, p. 199). These instruments are based on light scattering<sup>a</sup> (see Appendix), light blockage,<sup>b</sup> or blockage of electrical conductivity<sup>c</sup> [41]. Most of these instruments measure the numbers and sizes of particles and readily convert them to weight and size distribution. The most widely used technique to measure surface area utilizes the Brunauer, Emmet, Teller (BET) theory of adsorption using an inert gas as an adsorbate at a specific partial pressure [41].

### C. Dissolution

Several *in vivo*/*in vitro* correlation studies have shown that the absorption of many poorly soluble drugs, administered in suspension form, is dissolution rate limited, thus confirming the necessity for dissolution rate determination of suspensions [46].

Therefore, knowledge of the intrinsic dissolution rate of the drug aids in determining whether a drug is absorbed easily. The intrinsic dissolution rate of a drug is its own dissolution rate in a given solvent and is expressed as mg dissolved per minute per square centimeter [41]. Usually, drugs with intrinsic dissolution rate in water of less than 0.1 mg per minute per square centimeter exhibit absorption rates [47] and would require modification in their dissolution rate for adequate bioavailability. The dissolution rate of a drug can be improved by reducing particle size, coprecipitation, or by the addition of small quantities of an appropriate surface-active agent.

### D. Flow Properties

The flow properties of a drug in powder form are an important parameter for the manufacturing of a suspension and should be studied at an early stage of development. Good flow of powder is essential for mixing and for homogeneous drug content. Powders with low density and static charge exhibit poor flow and may be modified to achieve proper flow.

Flow characteristics of a powder are commonly expressed by the "static angle of repose." Most pharmaceutical powders have angle of repose values between 25 and 45° [41]. A low angle of repose is indicative of superior flow properties. There are a number of methods available to measure angle of repose. The method of Pilpel [48] uses a container with a platform. First, the container is filled with the powder. Then the powder is drained out from the bottom, leaving a cone. The angle of repose is then measured using a cathetometer [41].

### E. Drug-Excipient Compatibility

Drug-excipient studies are designed to select the basic list of excipients that may be used to develop a final suspension formulation. Some commonly used excipients in a suspen-

sion include a dispersing agent, wetting agent, suspending agent, flocculent, preservative, sequestrant, antioxidant, color, and fragrance, and these should be tested for their compatibility with the drug.

An aqueous suspension containing drug, dispersion medium, and an excipient should be stored at elevated temperature of 50°C or 60°C and at 6000 foot-candle lights, with constant agitation for 2 to 12 weeks. The ratio of drug to the excipient concentration is at the discretion of the preformulation scientist and should be consistent with the ratio most likely to be encountered in the final formulation.

The samples are drawn at predetermined time intervals and examined for physical and chemical integrity of the drug and the excipient. Parameters such as color change, crystal shape, caking, pH, and quantitative assay for the drug should be examined by commonly used techniques; for example, thin layer chromatography, differential thermal analysis, and diffuse reflectance spectroscopy [41]. The excipients that show minimal or no degradation of the drug after 8 to 12 weeks at elevated temperatures are chosen, as they are compatible with the drug and the product probably would exhibit satisfactory stability for about 2 years at ambient temperatures. A change in physical attributes (pH, color, crystal shape, etc.) of the drug-excipient mixture, on the other hand, is indicative of physicochemical change and suggests incompatibility. This, too, will aid in the selection of an appropriate colorant, buffer, and other excipients of the formulation.

## VI. SUSPENSION EXCIPIENTS

A pharmaceutical suspension seldom contains a drug and a vehicle alone. Usually, it contains several formula adjuvants. These excipients may enhance its physical and chemical stability, microbiological integrity, and aesthetic attributes. Today, formulators have a large number of raw materials to choose from to develop a safe, effective, and stable suspension.

The main considerations for excipient selection are compatibility with the drug, stability at a specific pH and temperature, compatibility with other adjuvants of the formula, ease of processing, and cost. All excipients preferably should be selected from the Generally Recognized As Safe (GRAS) list.

### A. Dispersing Agents

There are four general classes of dispersing agents that can be used to prepare an optimum dispersion. Their use depends on the type of dispersion, their required concentration, and the physicochemical properties of the solid to be dispersed. They are classified as (a) wetting agents, (b) deflocculant or true dispersing agents, (c) protective colloids, and (d) inorganic electrolytes.

#### 1. Wetting Agents

Wetting agents are surfactants that lower the contact angle between the solid surface and the wetting liquid. Surfactants that adsorb significantly to the vapor-liquid and solid-liquid interface facilitate wetting. Sometimes alcohol, glycerin, or other polyols such as poly-

ethylene glycol or propylene glycol are used in the initial stages to disperse the solid particles, thereby allowing the vehicle to penetrate.

Ionic as well as nonionic surfactants have been used as wetting agents. Anionic surfactants are most effective for drugs with negative zeta potential, and cationic surfactants are most effective for drugs with positive zeta potential. Good examples of anionic wetting agents are dioctyl sodium sulfosuccinate (docusate sodium) and sodium lauryl sulfate (SLS). Table 4 indicates the effect of increasing concentration of a surfactant, dioctyl sodium sulfosuccinate, on the surface tension and the contact angle of water with magnesium stearate, a hydrophobic tablet lubricant [4].

Two groups of nonionic surfactants used as wetting agents are ethoxylates and poloxamers. A large variety of ethoxylated surfactants exist. In principle, any compound with a reactive hydroxyl group can serve as a starting material for the preparation of an ethoxylated surfactant by reacting it with ethylene oxide.



Most frequently used starting materials are fatty acids, fatty alcohols, phenols, sterols, sucrose, fatty esters, and fatty amides. Ethoxylation allows control of the physicochemical properties of nonionic surfactants resulting in a diverse range of HLB values; for example, sorbitan mono-oleate has a HLB value of 4.3 and polyoxyethylene sorbitan mono-oleate (polysorbate 80) with 20 moles of ethylene oxide has a HLB value of 15.0.

Nonionics are favorite wetting agents because of their insensitivity to pH, presence of electrolytes, and low toxicity potential.

Although using an ethoxylated surfactant offers many advantages, it has disadvantages as well. Some of the disadvantages include complexation with phenolic/ester preservatives such as parabens and their inactivation and degradation as the result of oxidation.

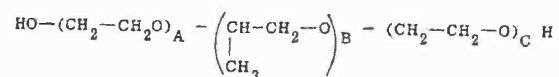
Poloxamers are synthetic block copolymers of ethylene oxide and propylene oxide. Their molecular weight ranges from 1,000 to 150,000. In a molecule the hydrophilic

**Table 4** Effect of Dioctyl Sodium Sulfosuccinate Concentration on the Surface Tension of Water and the Contact Angle of Water with Magnesium Stearate

Concentration, $m \times 10^6$	Surface tension	Contact angle
1.0	6.01	120°
3.0	49.8	113°
5.0	45.1	104°
8.0	40.6	89°
10.0	38.6	80°
12.0	37.9	71°
15.0	35.0	63°
20.0	32.4	54°
25.0	29.5	50°

Source: Ref. 4. Reprinted with permission from the publisher, Mack Publishing Co., Easton, PA.

poly(oxyethylene) sandwiches the hydrophobic poly(oxypropylene). The poly(oxyethylene) on the ends of the molecule constitutes 10% to 80% of the final molecule. The general structure of poloxamer is:



where A and C are statistically equal.

High molecular weight poloxamers are ideal for viscosity control and have excellent dispersing power. The hydrophobic group here is polypropylene oxide polymer, whose multiple ether linkage promotes adsorption on to the particle surface [3].

Table 5 lists some selected wetting and solubilizing agents [49].

Irrespective of the type of wetting agent selected, it should be compatible and should be used in the minimum amount necessary to produce adequate dispersion. Excessive amounts may lead to foaming, solubilization, and unpleasant taste or odor.

## 2. Deflocculants or True Dispersing Agents

Invariably, as a result of wetting, the particles are deflocculated. True dispersing agents or deflocculants are polymerized organic salts of sulfonic acid of both the aryl-alkyl as well as the alkyl-aryl type that alter the charges through physical adsorption [45]. However, most of these polyelectrolytes are not generally considered safe for internal use. One deflocculating agent, lecithin, has been widely used.

**Table 5** Wetting and Solubilizing Agents

Benzalkonium chloride
Benzethonium chloride
Cetylpyridinium chloride
Docusate sodium
Nonoxynol 10
Octoxynol 9
Poloxamer
Polyoxyl 50 stearate
Polyoxyl 10 oleyl ether
Polyoxyl 20 cetostearyl ether
Polyoxyl 40 stearate
Polysorbate 20
Polysorbate 40
Polysorbate 60
Polysorbate 80
Sodium lauryl sulfate
Sorbitan monolaurate
Sorbitan mono-oleate
Sorbitan monopalmitate
Sorbitan monostearate

Source: Ref. 49.

### 3. Protective Colloids

Protective colloids that are adsorbed by solid particles increase the strength of the double layer through hydrogen bonding and thus reduce the molecular interaction and aid in dispersion. These agents do not reduce the interfacial or surface tension. These are discussed in detail under suspending agents.

### 4. Inorganic Electrolytes

Inorganic electrolytes can be used to disperse drug particles. Though they are relatively inexpensive, they are not very efficient. Their efficiency as dispersing agents varies with the size and valence of the electrolyte. Some commonly used inorganic electrolytes are trisodium phosphate, alum (aluminum potassium sulfate), aluminum chloride, and sodium chloride.

## B. Suspending Agents

Suspending agents are used to prevent sedimentation by affecting the rheological behavior of a suspension. There are many factors that determine the selection of pseudoplastic and plastic suspending agents for a particular preparation.

An ideal suspending agent should have the following attributes:

1. It should produce a structured vehicle.
2. It should have high viscosity at low shear.
3. Its viscosity should not be altered by temperature or on aging.
4. It should be able to tolerate electrolytes and should be applicable over a wide pH range.
5. It should exhibit "yield stress."
6. It should be compatible with other formula excipients.
7. It should be nontoxic.

Modern technology has provided the pharmaceutical scientist with a variety of suspending materials for formulating and developing superior suspensions. Among the suspending agents, hydrocolloids have played an important role. All hydrocolloids increase the viscosity of water. They do so by binding the water molecule or by trapping the water molecule between their intertwined macromolecular chain, thus limiting the mobility of water. This increase in viscosity has a significant effect on the rate of sedimentation at low shear and is responsible for the improved physical stability of the suspension.

There are numerous hydrocolloids approved for pharmaceutical use and they may be used as suspending agents either alone or in combination. They can be broadly classified into four categories:

1. *Cellulose derivatives*: microcrystalline cellulose (MCC), carboxymethyl cellulose, hydroxypropyl methylcellulose, etc.
2. *Polysaccharides and gums*: alginates, carrageenan, xanthan gum, acacia, tragacanth, avicel, etc.
3. *Synthetic polymers*: carbomer, polyvinylpyrrolidone, poloxamer, etc.
4. *Clays*: magnesium aluminum silicate (veegum), bentonite, etc.

Lately, synthetic suspending agents are preferred because of their batch-to-batch consistency and superior microbial integrity.



### 1. Cellulose

a. *Sodium Carboxymethylcellulose.* Carboxymethylcellulose (CMC), an anionic polymer, is a long-chain cellulose ether prepared by reacting alkali and cellulose with sodium monochloroacetate (Fig. 5). It is available in low, medium, or high viscosity grades.

It dissolves rapidly in hot or cold water, giving a clear solution, but forms aggregates when first wet with water. Its solution characteristics depend on the average chain length and degree of substitution [50]. As the molecular weight of CMC increases, the viscosity of its solutions increases. The high or medium viscosity type of CMC in solution exhibits pseudoplastic flow characteristics. However, solutions of low molecular weight CMC are less pseudoplastic than those of high molecular weight CMC.

The viscosity of CMC solution is influenced by the temperature and pH. On prolonged exposure to heat, the polymer degrades with a permanent reduction in viscosity. CMC solutions exhibit maximum viscosity and stability at pH 7 through 9. At a pH above 10, there is an increase in viscosity and at a pH below 4.0, the viscosity decreases significantly due to hydrolysis of the polymer [50].

Carboxymethylcellulose solutions have poor tolerance for electrolytes especially di- and trivalent cations, as they precipitate the polymer. CMC is compatible with other nonionic cellulose derivatives, clays, and commonly used preservatives but is incompatible with cationic drugs [50].

b. *Microcrystalline Cellulose.* Some forms of microcrystalline cellulose (MCC), such as Avicel (FMC Corp.), provide for a smoother, more uniform suspension vehicle. MCC is a linear, long-chain cellulose polymer. The Avicel MCC grades used in aqueous dispersions are Avicel RC/CL. These products are made by adding sodium carboxymethyl cellulose of medium viscosity (89%) to MCC.

Avicel RC 591 is not water soluble, but disperses quickly in water. Avicel RC 591 gels are highly thixotropic with finite yield values at low concentrations. Its use in a formulation results in a well-structured suspension vehicle that will retard phase separation.

Avicel RC 591 dispersions are stable over a wide pH range (4 to 11), and show little change in their viscosity after exposure to increased temperatures, or after being subjected to freeze and thaw cycles. Avicel RC 591 is compatible with other hydrocolloid clays, and most preservatives and colorants, but is incompatible with cationic drugs and electrolytes [51].

c. *Hydroxypropyl Methylcellulose.* Hydroxypropyl methylcellulose (HPMCs) are linear polymers consisting of polymeric anhydro-glucose (cellulose) units to which a methyl and hydroxypropyl substitution have been attached (Fig. 6). Commercial designations of HPMC products are based on their viscosity values at room temperature [52].

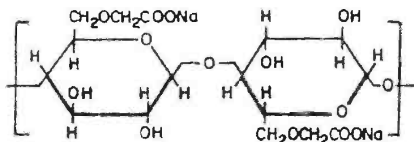


Fig. 5 Structure of sodium carboxymethylcellulose.

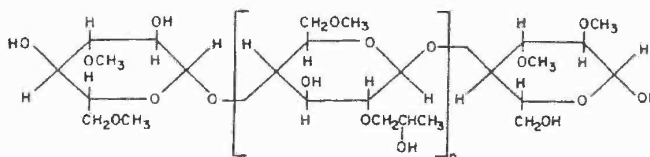


Fig. 6 Structure of hydroxypropyl methylcellulose.

Hydroxypropyl methylcellulose swells in water with successive hydration and its solutions are prepared by dispersion in hot water (about 80°C) with agitation to assure better wetting, followed by the addition of cold water or even ice to obtain proper temperature (0 to 5°C) for optimal hydration. [52]. HPMC forms a clear solution and the apparent viscosity is proportional to the molecular weight or chain length of the polymer. In general, the solution of a high molecular weight HPMC exhibits pseudoplastic flow.

The rheology of an aqueous solution of HPMC is affected by temperature, pH, and the presence of other solutes. Because HPMC is nonionic, the viscosity of its solution is generally stable over a wide pH range. On prolonged exposure to a pH above 10 or below 3, HPMC solutions exhibit a permanent reduction of viscosity caused by hydrolysis of the polymer. It also degrades at high temperatures as well, a factor that should be considered for the shelf life of the product.

HPMC solutions have better tolerance for electrolytes than CMC solutions do, but electrolytes in large concentration precipitate HPMC from solution [52]. HPMC is compatible with preservatives, other celluloses, and clay-type suspending agents as well as other excipients used in pharmaceutical suspensions.

## 2. Xanthan Gum

Xanthan gum is a high molecular weight, specially designed anionic polysaccharide that functions as a hydrocolloid and suspending agent. Xanthan gum contains three different monosaccharides: mannose, glucose, and glucuronic acid (as salt). Each repeating block of polymer chain has five sugar units (two glucose, two mannose, one glucuronic acid). The main chain is made of  $\beta$ -D-glucose units linked through the 1 and 4 positions. The two mannose units and glucuronic acid units make up the side chain. The terminal  $\beta$ -D-mannose unit is glycosidically linked to the 4 position of  $\beta$ -D-glucuronic acid, which in turn is linked to the 2 position of  $\alpha$ -D-mannose. This side chain is linked to the 3 position of every other glucose residue on average in the polymer main chain. Roughly half of the terminal D-mannose residue carries a pyruvic acid residue linked ketolically to the 4 and 6 positions. The non-terminal D-mannose unit on the side chain has an acetyl group at the 6 position (Fig. 7).

Xanthan gum is soluble in hot and cold water and imparts high viscosity at low concentration with pseudoplastic flow characteristics [53]. Aqueous xanthan gum systems exhibit gel behavior at a very low pH. Gel persistence under shear, viscosity, and pseudoplasticity all increase with xanthan gum concentration [54]. Compared to other cellulosic agents and or polysaccharides, xanthan gum solutions are unusually resistant

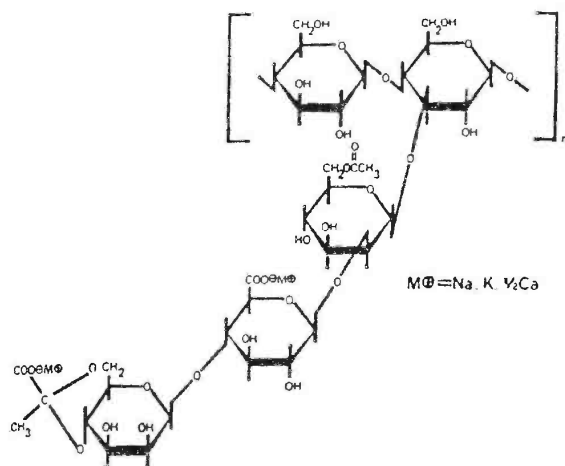


Fig. 7 Structure of xanthan gum. (Reproduced from the *Kelco Xanthan Gum Booklet*, 5th ed., with permission of proprietor Merck & Co., Inc., Kelco Division, San Diego.)

to prolonged shear. A 1% xanthan gum solution sheared at 46,000 reciprocal seconds for 1 hour exhibited no significant loss of viscosity [53].

Temperature has very little effect on the viscosity of xanthan gum solutions. The small change in viscosity that does occur with temperature is reversible [53]. This temperature independence of viscosity is unique to xanthan gum and is a very desirable attribute for product shelf life. Products containing xanthan gum stored at elevated temperatures are stable and exhibit minimal loss of viscosity. There is no significant change in the viscosity of a solution over a wide pH range of 1 to 10.

Solutions of xanthan gum are compatible with virtually all mono- and divalent cations like sodium, calcium, and magnesium over a wide pH range and with many pharmaceutical adjuvants such as polyols, alcohol, acidulants, chelating agents, and preservatives. Because of its anionic nature, xanthan gum is incompatible with cationic drugs and preservatives. It is not influenced by a freeze-thaw cycle and is resistant to enzymatic degradation. However, xanthan gum solutions are susceptible to microbiological degradation on prolonged storage and do require a preservative to maintain the microbial integrity of the product.

### 3. Carbomer

Carbomer resins are high molecular weight polymers of acrylic acid (Fig. 8). They are available in several grades. The choice of the proper carbomer resin may require evaluation of all grades because formulations must often meet several requirements.

Carbomers represent a family of polymers that impart plastic behavior to aqueous systems at a relatively low concentration. Nearly any required level of viscosity can be achieved by simply adjusting the concentration of polymer. Initial viscosity development

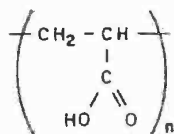


Fig. 8 Structure of polyacrylic acid.

occurs as a result of partial swelling of the polymer by water molecules. Final swelling along with the development of viscosity and yield value occurs when the acid polymer is neutralized with an organic or inorganic base [55]. Irrespective of the type of carbomer resin, neutralization is essential to develop the unique rheological properties of these resins. Much of the work on carbomer rheology has been summarized by Barry [56]. At low concentration, carbomer solutions are pseudoplastic, becoming plastic at higher concentrations. The combination of yield value and high consistency accounts for their good suspending properties. Meyer and Cohen [57] made permanent suspensions of silica and using 0.25% carbomer. For the same stability of suspension, 3% polysaccharide gum concentration was required. Their work showed that the formation of a permanent suspension is dependent on the critical yield value and not the viscosity. Berney and Deasy [58] indicated the suitability of carbomer<sup>®</sup> to prepare a pharmaceutically stable, nonsedimenting, readily pourable suspension of 10% sulfadimidine [58]. Swafford and Nobles [59] successfully developed a topical suspension of calamine and neocalamine using carbomer.

The viscosity of carbomer resin is influenced by temperature and pH. Carbomer resins are not subject to hydrolysis or oxidation under normal conditions and resist thinning at elevated temperatures when exposed for a short period of time but there is a loss of viscosity after prolonged exposure. Carbomer resin solutions offer maximum viscosity control at pH 5.5, but loss of viscosity and precipitation of acrylic acid polymer occur at a lower pH.

Even a small amount of soluble electrolyte decreases the viscosity and the efficiency of carbomer solutions. Salts cause deswelling, and divalent salts cause more drastic loss of viscosity than monovalent salts. Carbomer resins are compatible with commonly used formula excipients and hydrocolloids.

The stability of carbomer resin solutions is sensitive to ultraviolet (UV) light, which causes a significant reduction in the viscosity. The combination of a chelating agent such as the sodium salt of ethylenediaminetetraacetic acid and a water-soluble UV absorber is an effective stabilizer for carbomer resin against UV light [55]. Carbomer resin solutions are not attacked by bacteria and fungi; however, they do not prevent their growth in aqueous system [55].

New entries into the market are the new water-swellaable, high molecular weight cross-linked polymers and copolymers of acrylic acid marketed by BF Goodrich under the trade names Pemulen<sup>®</sup> and Noveon<sup>®</sup>. By modifying cross-link types and levels as well as hydrophilic comonomer characteristics in cross-linked polymers, a wide range of performance characteristics can be achieved [60]. Pemulen are high molecular weight polymers with larger hydrophilic and smaller oleophilic portions. Pemulen are compatible with a broad spectrum of raw materials used in topical formulations. Pemulen require

neutralization to desired pH with water-soluble base to impart swelling properties. Pemetals have limited tolerance for electrolytes and are incompatible with cationics.

#### 4. Magnesium Aluminum Silicate

Various inorganic clays have the property of swelling in water. Important representatives of this group are colloidal aluminum silicates, bentonite, and magnesium aluminum silicate (MAS), which are differentiated by their crystal structure.

Magnesium aluminum silicate is derived from natural smectite clays characterized by an expanding lattice structure [61]. It is preferable to other clays because of its whiter color and greater uniformity. Several grades of MAS are available that differ in viscosity, particle size, acid demand, and salt stability.

Water dispersions of 1% to 2% MAS are thin but increase in viscosity with an increased concentration of MAS. These dispersions exhibit pseudoplastic rheological behavior with yield value and impart thixotropy to the suspension. Hence, MAS functions well as a suspending agent. It is a superior suspending agent because it prevents caking without affecting pourability or spreadability of the suspension.

Magnesium aluminum silicate dispersions are influenced by heat, and the viscosity of the dispersion increases on prolonged exposure to elevated temperatures. Magnesium aluminum silicate is stable over a wide pH range of 6 to 11.

Electrolytes also thicken MAS dispersions because MAS is partially flocculated by electrolytes [61]. This increases both the viscosity and the yield value.

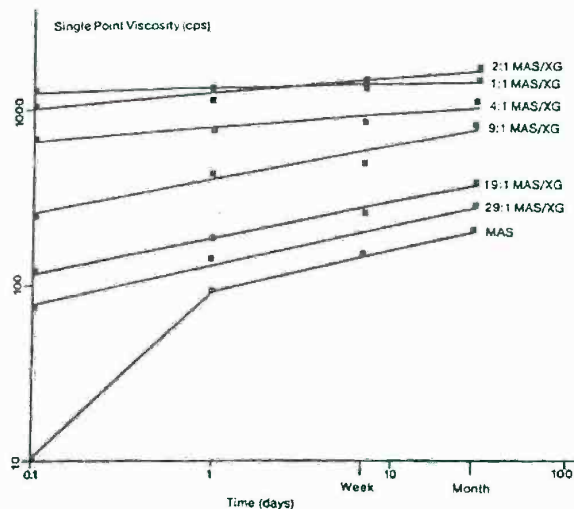
Magnesium aluminum silicate is compatible with many commonly used formula adjuvants, especially anionic and nonionic hydrocolloids. Syman observed that blends of MAS and CMC provide synergistic viscosity and excellent electrolyte tolerance, combining the high yield value of MAS and the smooth flow properties of CMC [62]. Schumacher [63] uses blends of MAS with CMC and other gums in an antacid suspension and observed that MAS in the flocculated state enhanced the stability of the antacid suspensions. For a synergistic effect, MAS/CMC ratios of 9:1 to 2:1 are most commonly used. Ciullo [64] investigated rheological properties of MAS and xanthan gum combinations (Fig. 9). A minor inclusion of xanthan gum in MAS dispersions provided synergism in both the viscosity and the yield value. The combination showed a modification of the thixotropy of MAS in the presence of xanthan gum. The excellent yield value obtained suggest superior stabilization of the suspension [64].

Magnesium aluminum silicate dispersions allow the growth of bacteria, and need a bacteriostat to maintain their microbiological integrity. Magnesium aluminum silicate possesses cation exchange capacity and drug adsorption properties for various cationic and nonionic drugs. Anionic drugs are found to be weakly bound [65].

#### C. Buffers

A large number of modern therapeutic agents are either weak acids or weak bases. Their physicochemical properties, therapeutic efficacy, and stability can be influenced by a change in the pH of their environment. The same is true of organic excipients, such as preservatives, suspending agents, and chelating agents, used in the formulation of a suspension. Furthermore, buffer salts may also act as flocculating agents. Thus, the selection of a proper buffer to maintain optimum pH is critical. The selection of a buffer should meet the following criteria [66]:





**Fig. 9** Three percent magnesium aluminum silicate/xanthan gum dispersions showing progressive flattening of the MAS aging curve with increasing levels of XG. (From Ref. 64. Reprinted with permission from the publisher, the Society of Cosmetic Chemists, New York.)

1. A buffer must have adequate buffer capacity in the desired pH range.
2. A buffer must be compatible with the flocculating agent.
3. A buffer must be biologically safe for the intended use.
4. A buffer should have little or no deleterious effect on the stability or efficacy of the product.
5. A buffer should permit incorporation of an acceptable flavor, fragrance, and color in the product.

Windheuser [67] has reported commonly used buffers and their effective buffer ranges (Fig. 10).

#### D. Humectants and Cosolvents

Humectants and cosolvents are used as formula adjuvants in oral as well as in topical suspensions. Humectants such as glycerin, sorbitol, and polyethylene glycol retard the crystallization of solubilized solids in an aqueous suspension. They impart desired consistency and good taste and help prevent "cap locking." Cosolvents increase the solubility of weak electrolytes or nonpolar molecules in water. These nonpolar molecules may include the preservatives, antioxidants, flavors, or fragrances. Generally, the drugs in suspension should exhibit practically no solubility in the cosolvent or humectant chosen. Commonly used cosolvents are alcohol, polyethylene glycol, propylene glycol and 1,3-butylene glycol. These are acceptable for use in oral as well as in topical preparations.

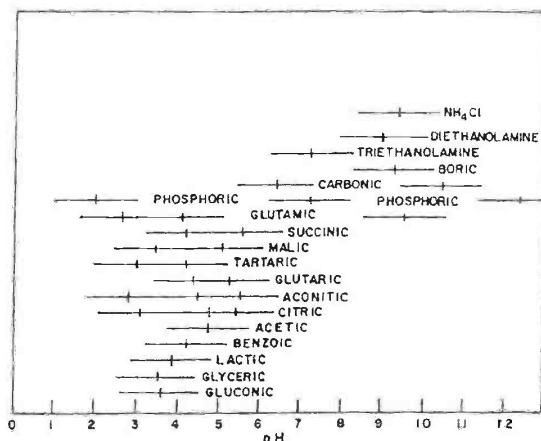


Fig. 10 Commonly used pharmaceutical buffers and their effective buffer ranges. (From Ref. 67. Reprinted with permission from the publisher, Parenteral Drug Association, Philadelphia.)

### E. Preservatives

Stringent regulatory and compendial limits coupled with numerous product recalls have increased the importance of formulating a well-preserved suspension. Injectable and ophthalmic suspensions must be sterile, but oral and topical suspensions that come into prolonged contact with tissues and organs of the human body must meet very high standards of microbial integrity. Microbial growth is a potential health hazard and a source of infection. All oral and topical suspensions must be free of pathogens such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Candida albicans*, *Aspergillus niger*, and *Salmonella* species [49].

The presence of microorganisms is not only hazardous to the health of patients but can also bring about undesirable physicochemical changes in the suspension. The physical changes may include discoloration, loss of viscosity and modification of rheological behavior, and gas and odor formation. The chemical changes may include hydrolysis of drug or formula excipients such as hydrocolloid and preservative, inactivation of the preservative system, change in pH, and so forth.

Preservation of a suspension poses several problems to a formulator. Suspensions may contain carbohydrates, clay, polysaccharides, electrolytes, gum, cellulose derivatives, surfactant, polar solvent, and other excipients, many of which are excellent nutrients for the growth of microorganisms. Processing containers, equipment, packaging components, and operators may also contribute to the microbial contamination of the product.

Therefore, pharmaceutical suspensions should contain an antimicrobial preservative that will eliminate infecting microorganisms (bacteria, yeast, and fungi) and should be manufactured and packaged in accordance with current Good Manufacturing Practices.

Factors affecting the efficacy of a preservative include solubility in aqueous phase, partitioning between polar and nonpolar phases, dissociation due to change in pH, and

interaction with the other ingredients in the formula. Though none exists, an ideal preservative should have a broad spectrum of activity; be capable of sustained action; have few chemical or physical incompatibilities; be effective over a wide pH range and not influence the pH of product; be nontoxic, nonirritant, and nonsensitizing; be colorless and odorless (or nearly so); be economical; and be easily formulated [68].

From a large number of available preservatives, a formulator chooses a preservative system for a particular product. The formulator is aided by the knowledge of a few basic guidelines during each stage of development such as the history of similar raw materials and formulas, routes of administration, package design, frequency of use, manufacturing process and product life.

A preservative system usually consists of a combination of preservatives to ensure microbial integrity of the product in case one of the preservatives is inactivated either by a contaminant in the product or by one of the challenge organisms.

In a broad chemical sense, a preservative may be an alcohol, acid, ester, quaternary ammonium compound, phenol and its derivatives including halogenated phenols, or aldehyde and formaldehyde donors. The formaldehyde donors in combination with parabens are the most frequently used preservatives in topical suspensions. However, many of the aldehyde and formaldehyde donors are not approved for internal use. Table 6 gives a classification of some commonly used preservatives [68].

#### F. Sequestrants

The presence of metal ions causes oxidative degradation of many drugs and excipients used in suspensions. Metal ions in such cases act as catalysts in the degradation processes. Removal of these free metal ions from the formulation improves its integrity, acceptability, and stability. For the most part, sequestrants react with metal to form metal-sequestant complexes and thereby block the reaction site of metal ions. In order to form a sequestant-metal complex, two general conditions must be satisfied [69].

1. A sequestant must have proper steric and electronic configuration in relation to the metal being complexed.
2. The surrounding environment—such as pH, ionic strength, and solubility—must be conducive to complex formation.

The rate at which the metal-sequestant complex is formed depends on the rate of rupture of the proceeding complex. In a well-defined system, relative inefficiency of different sequestrants for a given metal can be compared by inspecting the stability constant of each metal complex. Generally, the higher the stability constant ( $\log K$ ), the more stable is the metal-sequestant complex. The stability constants of some metal-sequestant complexes have been reported [69].

Some commonly used sequestrants in pharmaceuticals are ethylenediaminetetraacetic acid (EDTA) and its salts, citric acid, glutamic acid, 8-hydroxyquinoline, etc. The theoretical quantity of sequestant required can be calculated but actual usage levels in the particular formula should be established in the laboratory by the formulator.

#### G. Antioxidants

Many polydisperse preparations deteriorate on storage because the therapeutic agent or the adjuvant is subject to oxidative degradation. The degradation can result in reduced potency of the drug or a change in the color, odor, taste, viscosity, or other characteristic of the product.

**Table 6** Limited Chemical Classification of Some Contemporary Preservatives

Acids and their salts	Esters	Quaternary compounds	Phenols	Formaldehyde and formaldehyde donors	Miscellaneous
Benzoic acid and its salt	Methylparaben	Benzalkonium chloride	Ottasept		
Formaldehyde	Benzyl alcohol	Cetylpyridinium chloride	Irgasan DP 300	Bronopol	Ethyl alcohol
Sorbic acid and its salts	Propylparaben			Ucarcide	Myacide SP
	Butylparaben	Benzethonium chloride		MDMH	Kathon CG
				Dowicil 200	Oxadine A
				Germall II	Omadine
				Germall 115	Phenoxetox
				Glydant	

Source: Ref. 68.

Many pharmaceuticals are prone to autoxidation, a free radical reaction initiated by UV radiation in the presence of a trace amount of oxygen. The autoxidation may be catalyzed by metal ions. The addition of a small amount of an antioxidant inhibits the formation of highly reactive free radicals and the chain reaction by providing a hydrogen atom or an electron to the free radical.

Antioxidants are classified into two major groups. True antioxidants such as butylated hydroxyanisole (BHA), tocopherols, and alkyl gallates perform by blocking and breaking the free radical chain reaction. These antioxidants are generally oil soluble. A second group of antioxidants is composed of reducing agents such as sodium bisulfate and ascorbic acid, which have a lower redox potential than the chemical they protect. They are preferentially oxidized and also react with free radicals. They are generally water soluble.

An ideal antioxidant should be nontoxic, nonirritant, and nonsensitizing as well as effective in low concentration. It should be odorless, tasteless, colorless, stable over a wide pH range, and compatible with formula excipients. Its decomposition products should be nontoxic and nonirritant.

The selection of an antioxidant can be made on sound theoretical grounds based on the difference of redox potential between the drug and the antioxidant. In practice, however, a combination of two antioxidants and a chelating agent or a weak acid has been found to be more effective [56]. The comparative value of an antioxidant's efficiency is measured by subjecting the pharmaceutical system to standard oxidative conditions and periodically analyzing for the drug and the antioxidants [70].

#### H. Colors

Colors are incorporated into pharmaceutical oral or topical suspensions for several reasons. First, colors give aesthetic appeal and impart pleasing appearance to the product, thereby providing it with a marketing advantage. Second, colors may be used to identify products or similar appearance or to mask the discolored degraded excipient or drug, thereby maintaining the appearance of the formulation for its entire shelf life. Finally, colors help minimize the possibility of a mix-up during manufacture.

Dyes and other organic colorants may degrade via oxidation, hydrolysis, photolysis, or other routes, and their solubility and stability may be pH dependent. Before selecting a dye for a particular formulation, its physicochemical properties should be examined.

Dyes are incorporated into a suspension as aqueous solutions. At times it may be necessary to utilize a combination of a water-soluble dye and an inorganic pigment to obtain homogeneity of color and the desired shade.

A formulator should use only FD&C colors or D&C colors in oral suspensions. Additionally, one can use D&C external colors for topical suspensions. However, not all colorants are universally approved and each country has its own list of approved colorants. For example, FD&C Red No. 40 is an approved colorant for food, drugs, and cosmetics in the United States, but its use is not approved in Canada. On the other hand, FD&C Red No. 2 (amaranth) is approved in Canada but its use is prohibited in the United States. The list of approved colors and dyes is revised on a continuing basis.

Hence, before formulating a product that may be marketed in several countries, it would be wise to check the current status of each dye in each country. Dye suppliers



are excellent sources of information on this subject. Such information may also be obtained from the Division of Colors & Cosmetics of the Food and Drug Administration. Colorants currently in use are listed in CTFA International Color Handbook [71].

#### I. Fragrances

Even a well-designed topical pharmaceutical suspension with optimum efficacy, safety, and stability requires the aesthetic appeal necessary to ensure patient acceptability. An unpleasantly scented product may result in patient noncompliance and in the possibility of the patient switching to a competitive product. Odor of the product can be a determining factor between commercial success or failure for an OTC product. Although consumers may not apply as stringent criteria of acceptability to a pharmaceutical suspension as to a cosmetic suspension, one would still prefer a product that has a pleasant odor—or at least no unpleasant odor. Fragrances are used to mask an unpleasant odor and impart aesthetic appeal to the product.

### VII. PREPARATION OF A SUSPENSION

A suspension can be prepared by the precipitation method or by the dispersion method. The precipitation method is tedious, complex, and time consuming. The precipitation of a drug can be accomplished by controlling the pH or by the use of appropriate solvents. This method is not widely used for the preparation of oral or topical suspensions. The dispersion method utilizes dispersion of fine particles in an appropriate vehicle.

The development of a suspension formula involves some degree of trial and error. Several trial formulations are produced to include the optimum level of excipients needed to impart the desired physical attributes. Suspensions can be formulated by any of the following three methods [4] as illustrated in Fig. 11.

1. Deflocculated suspension in a structured vehicle as the final product
2. Flocculated suspension as the final product
3. Flocculated suspension in a structured vehicle as the final product

All three methods of preparation require uniform dispersion of the deflocculated particles and preparation of an appropriate vehicle. The decision of whether to develop a deflocculated or flocculated suspension will be determined by the physicochemical properties of the drug and its application. Generally, suspensions developed with controlled flocculation in a structured vehicle are preferred. As a rule, the steps involved in the preparation of such formulations on laboratory batch or small pilot batch scale are:

1. Preparation of a dispersion of the drug
2. Preparation of a structured vehicle, followed by addition of the drug dispersion
3. Addition of other formula adjuncts
4. Deaeration, followed by making up to final volume
5. Homogenization

#### A. Drug Dispersion

In the preparation of a suspension, particle-particle attractive forces among powder particles may be overcome by high shear action of a colloid mill or by the use of a wetting agent. Normally, an anionic surfactant is preferred but nonionics may also be

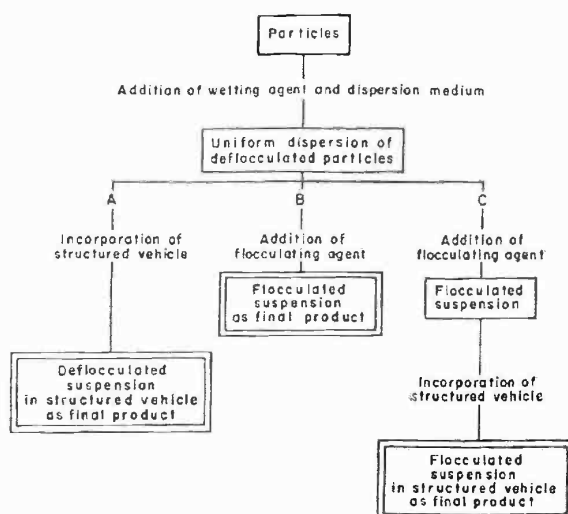


Fig. 11 Alternative approaches to the formulation of suspensions. (From Ref. 4, p. 296, Reprinted with permission from the publisher, Mack Publishing Co., Easton, PA.)

used. The minimum amount of wetting agent should be used. A concentrated solution of the wetting agent in the vehicle may be used to prepare the slurry. The drug-dispersion slurry may be prepared through a colloid mill<sup>f</sup> (Gaulin type) to provide optimum wetting. Alcohol or glycerin may be used in the initial stages to disperse the particles and facilitate the penetration of the vehicle into the powder mass. Alternately, the drug can be dispersed by slow addition to the water or to a water-glycerol system containing a wetting agent.

#### B. Preparation of Structured Vehicle and Addition of Drug Dispersion

Structured vehicles are aqueous solutions of suspending agents: hydrocolloids, polysaccharides, clays, or a combination of these. The vehicle suspension may be water, glycerin alone, or a combination of several solvents. Usually a structured vehicle is preferred.

The uniform dispersion of hydrocolloids or clays in water is the key to rapid preparation of the vehicle. Generally speaking, a warm medium hydrates hydrocolloids/clays more readily and is preferred over a cold medium, though not all hydrocolloids require a warm medium. A solution of hydrocolloid or drug can be made in short time if the dry hydrocolloid is dispersed properly. Clays however, take more time to hydrate. Subsequent to the preparation of a structured vehicle, the drug dispersion may be added to it. Any one of the following methods can be employed to obtain good dispersions of hydrocolloids or clays: high shear mixer, use of an eductor, or dry mixing.

### 1. High-Shear Mixing

Good dispersion can be achieved with a high-shear mixture that develops a good vortex. Alternatively, a rotor-stator processing system can be utilized. The powdered hydrocolloid should be sifted slowly into the upper wall of the vortex so that individual granules are wetted. The addition should be completed before thickening destroys the vortex and starts to incorporate air into the system.

### 2. Use of an Eductor

Possibly the best dispersion of a hydrocolloid can be obtained by using a funnel and mixing eductor (Fig. 12). Sufficient water is added to the tank fitted with a high-shear mixer. The mixer is turned on, and the hydrocolloid is poured into a funnel that is attached to the top of an aspirator while the water is running. In this process, individual particles are coated with water before reaching the bulk of water in the tank and subsequent lumping of the hydrocolloid is prevented.

### 3. Dry Mix Dispersion

Often a formulation contains other water-soluble ingredients like citric acid that can be preblended with a hydrocolloid to facilitate dispersion. A blend of hydrocolloid and other dry ingredients is added slowly to water with high-shear mixing, and dispersion of the hydrocolloid is attained in a short time.

### 4. Addition of Other Formula Adjuncts

Formula adjuncts such as a chelating agent, antioxidant, humectant, preservative, color, and fragrance are added to the vehicle directly or are presolubilized in an appropriate

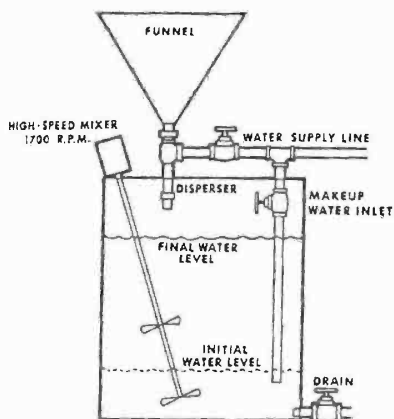


Fig. 12 Typical installation of Kelco funnel and mixing eductor. (Reproduced from the *Kelco Xanthan Gum Booklet*, 5th ed., with permission of proprietor Merck & Co., Inc., Kelco Division, San Diego.)

cosolvent. Generally, preservatives such as propylparaben, fragrances, and antioxidants require presolubilization in a cosolvent such as propylene glycol or alcohol before their addition to the aqueous medium. The time of addition and the temperature at the time of addition of some excipients will depend on their physicochemical properties. Usually, temperature-sensitive materials such as fragrances are added at a relatively low temperature and generally toward the end of the manufacturing process.

#### **C. Deaeration and Making Up to Final Volume**

The batch is processed through deaerating equipment just prior to making up to final volume. A suspension with a large amount of entrapped air will not be pharmaceutically acceptable because excess air will affect the rheological properties, drug dosage, color, density, and fill volume.

#### **D. Homogenization**

Finally, the suspension is passed through a homogenizer to efficiently reduce the particles dispersed phase.

### **VIII. PILOT PLANT SCALE-UP**

Scientists expend large amounts of time developing topical suspension formulations that not only meet the criteria of safety, efficacy, and stability, but also conform to exacting specifications. In addition, the laboratory formulas should be reproducible on large-scale production equipment at a reasonable cost. To be acceptable, a formula must be capable of being manufactured and packaged in commercial quantities, often with equipment that only remotely resembles the laboratory equipment.

Often it is necessary and advisable to scale up laboratory formulas in a pilot plant. The goal, then, of a pilot plant is to facilitate the transfer of the product from laboratory into mass production. The ease with which a new product and its manufacturing processes are brought into routine production reflect the effectiveness of the pilot plant [72].

Suspensions require more attention during scale-up than do simple solutions because of additional processing. Variability in the quality of a product may result from:

1. Raw materials
2. Equipment
3. Processing

Early intelligent decisions to define and control these variables can yield significant economic benefits, as well as prevent unnecessary headaches and delays. If necessary, it is not unusual to make slight modifications in product formulas and processes in order to meet the demands of production equipment.

#### **A. Raw Materials**

One of the responsibilities of pilot plant function is approval and validation of active and inactive raw materials in a given formula. Even a slight change in morphology, particle size and particle size distribution, or rate of solubility may result in different bulk den-

sity, density ratio change, flow properties and handling properties, or raw materials and ultimately may alter the quality and integrity of the product [72]. Reliance on a single source of a raw material may leave a company vulnerable with respect to supplies and price. Evaluation of alternate suppliers, approval of raw material, or any change in the specifications of raw material require that several batches of the product be prepared with each raw material and their performance in the formulation and stability of finished product be compared to standard product [72].

### B. Processing Equipment

Formulation development work on a topical suspension is usually carried out with relatively simple equipment. For example, addition and dispersion of suspending agents—which on a laboratory scale—may merely involve sprinkling the material into a liquid vortex may require the use of a vibrating feeder or other novel approaches of dispersion in the pilot plant and manufacturing procedure [73].

Additionally, the manufacturing of topical suspensions requires several pieces of equipment. Many types and variations of mixing, dispersion, particle size reduction, and filling equipment can be used to manufacture a suspension. By selecting a given type of equipment, not only are certain operating techniques made possible as a result of the individual capabilities of the equipment, [72] but also there is the opportunity to produce a product with desirable physical and chemical attributes while maintaining economical production.

It is essential that the equipment used during scale-up be the same as that which would be used in the final manufacturing process of the product. Pilot plant design and equipment are available from manufacturers of full-sized production equipment. Ideally, the pilot plant laboratory will have the equipment to prepare batches in volumes in the 10 to 100 liter range.

Based on known characteristics of processing, types of mixers, homogenizers, filters, and filling equipment, each with its own advantages and limitations, should be critically examined. The selection of each piece of equipment will depend on the state of matter of the dispersed phase. Tabibi [74] has listed various mixers and mills generally used in the preparation of disperse systems.

### C. Processing

Once the manufacturing process has been proposed and accepted, and various pieces of equipment needed to mix, mill, homogenize, filter, and fill have been evaluated and selected, the next step in the scale-up and transfer of laboratory formula to production is to analyze "process parameters flexibility."

Process parameters flexibility analyzes a number of operating parameters such as [75]:

1. Rate and order of addition of components
2. Mixing rate and intensity
3. Mixing time
4. Rate of heating and overall time
5. Rate of cooling and overall time



6. Homogenization (particle size reduction, condition and effectiveness)
7. Filter screen size

All these process parameters can be critical to the production of a stable product. Experience has shown that a vast number of process parameters will ultimately affect the physicochemical or microbiological attributes of topical suspensions. Knowledge of the effects of these critical process parameters on "in-process" and finished product quality is the basis for process optimization and validation. For example, mixing at too high a speed may result in an incorporation of excessive air into the product—which if not removed can influence the stability of the product. The temperature, rate of addition, and time required to hydrate suspending agents are often critical; unless this hydration process is complete, the suspension may not conform to its specifications. Topical suspensions should be constantly agitated or recirculate these during transfer, otherwise solids may "settle out," resulting in loss of homogeneity of drug in the product.

During the scale-up process, critical process parameters, (mixing rate, mixing time, rate of cooling, rate of heating, homogenization, etc.) should be altered intentionally to ascertain the resultant effects on product quality and yield. Such process data should be accumulated from a series of batches. For example, if a colloid mill is used for homogenization in the scale-up process, several variations in experimental variables should be considered to determine the aperture setting, RPM, length of process time required, and so on. If the data show that the homogenization process parameters repeatedly produced a similar product that conforms to specifications, then the process has been validated.

Current Good Manufacturing Practice regulations require that manufacturing processes be validated so as to demonstrate quantitatively that a manufacturing process does what it purports to do.

To initiate the validation process, a set of specification ranges of desired characteristics should be established. For a topical suspension, for example, a specification range should be established for important characteristics including appearance, pH, density, viscosity, particle size, sedimentation volume, zeta potential, total drug content, and drug content uniformity.

It is necessary that all the information from each of these validation runs be documented in order to know what was done and to provide a record of the conditions under which the experiment was conducted. Validation runs should include a condition that puts the most stress on the process (worst case), thereby making it most likely that the product characteristic will fall outside specifications. Process specifications can then be established to ensure that this "worst case" condition will not occur.

A checklist of GMP items that should be part of scale-up includes the following:

1. Equipment qualification
2. Process validation
3. Regularly scheduled preventive maintenance of equipment
4. Regular process review and revalidation
5. Relevant Standard Operating Procedure
6. Use of competent technically qualified personnel
7. Adequate provision for training of personnel
8. A well-developed technology transfer system
9. Validated cleaning procedures
10. Orderly arrangement of equipment so as to ease material flow and prevent cross-contamination

Table 7 details some problems and suggested remedies in preparation, scale-up, and production of topical suspensions [51].

## IX. EVALUATION OF A SUSPENSION

There are many dimensions of a suspension dosage form that are indicative of its quality, stability, acceptance, and performance. Appearance, color, odor, pH, density, viscosity, sedimentation parameters, ease of redispersibility, particle size, zeta potential, dissolution, labeled potency, microbial integrity, and human safety are all important parameters to consider in evaluating suspensions.

### A. Sedimentation Parameters

The study of sedimentation includes two different parameters: sedimentation volume and degree of flocculation.

#### 1. Sedimentation Volume

In an acceptable suspension the sediment formed should be easily redispersed to yield a homogeneous (uniform) product. The sedimentation volume  $F$  is defined as the ratio of the final, equilibrium volume of the sediment,  $V_u$  to the total volume,  $V_o$ , before settling, as expressed in Eq. 9 [40].

$$F = \frac{V_u}{V_o} \times 100 \quad (9)$$

where

$F$  = sedimentation volume

$V_u$  = volume of sediment and

$V_o$  = volume of suspension before settling

For example, if 200 ml ( $V_o$ ) of a well-shaken formulation is placed in a graduated cylinder and it is found that the equilibrium volume of sediment  $V_u$  is 40 ml then

$$F = \frac{40}{200} = 0.2$$

Calculated as percentage sedimentation,

$$F = \frac{40}{200} \times 100 = 20\%$$

Usually, the higher the value of  $F$ , the more acceptable the product.

#### 2. Degree of Flocculation

A more useful parameter to measure sedimentation is the degree of flocculation ( $\beta$ ). Sedimentation volume  $F$  gives only a qualitative account of flocculation. The degree of flocculation is calculated by using Eq. (10)

$$\beta = \frac{\text{Ultimate sediment volume of flocculated suspension}}{\text{Ultimate sediment volume of deflocculated suspension}} \quad (10)$$

**Table 7** Some Problems, Causes, and Suggested Remedies in Production of Suspensions

Problem	Cause	Remedy
Caking	Crystal growth, fusing of crystals, to form aggregates	Modify particle size characteristic Increase density and viscosity of vehicle Check zeta potential
	Deflocculated systems	Formulate a flocculated system Apply controlled flocculation concept (See details in chapter)
Crystal growth	Polymorphism: combination of crystalline and amorphous entities	Lower interfacial tension to reduce free surface energy of particles
	Too much surfactant, causing drug to be solubilized and precipitated	Modify drug precipitation procedure Check surfactant concentration and HLB
	Extreme differences in crystal size	Change content of suspension vehicle Modify particle size reduction procedure to yield narrow particle size range
	Temperature changes resulting in cooling of an already saturated solution	Create protective coating around particles with protective colloids (barriers to free energy)
Deflocculation	Excessive electrolyte concentration	Check drug properties, surfactant, polymer content, electrolyte level
		Check ionic charge of drug, flocculating and suspending agents
Drug potency (decrease)	Crystal growth	Try controlled flocculation
	Suspension is not homogeneous	Check ionic charge of drug and suspending agent
	Variations in particle size	Check particle size and distribution
	Too large particle size	Check ionic charge of flocculating and suspending agents
	Suspension is air-filled	Check mixing technique methods, filling methods

pH change	Insufficient buffer system	Maximize buffer system, avoiding overuse of salts and buffers
	Altered surface charge of particles Drug decomposition	Check ionic character of drug, surfactant and polymers Check drug stability, route of degradation, and decomposition products
Redispersibility (poor)	Bacteriological	Check preservative system
	Deflocculation	Formulate a flocculated system Apply controlled flocculation system
Settling	Particle size uniformity questionable	Modify particle size characteristics
	Insufficient quantity of suspending agent—low yield value	Increase concentration of suspending agent in small increments to increase yield value
Flotation agent	Electrolyte effect	Check electrolyte quantities and ionic charges
	Hydrophobic drug is not adequately wetted by suspension vehicle due to air adhering to the wetted or insufficiently unwetted particle	Use appropriate hydrophobic wetting—a nonionic surfactant to reduce contact angle at particle interface
Physical breakdown of suspension system (sudden, severe)	Severe flocculation of suspending agent	Check electrolyte content
	Change in suspending agent; characteristics not detected by quality control check of specifications	Check with raw material supplier to confirm lot conformity and method of manufacture
Color change	Change in raw material manufacturing method	Check reactivity properties of dye (colorant)
	Dye reaction with drug or any excipient or formula	Dye may decompose in light or air or at pH of vehicle
Fragrance change	Poor color retention of colorant	Deaerate product
	Suspension extremely air-filled	Check electrolyte content
	Suspending agent is flocculating	Reexamine fragrance components relative to their organic chemical class
	Reactive fragrance constituents (Aldehydes oxidize, react easily with amines; esters hydrolyze at high pH, phenol aromatic amine, etc.)	

Source: Ref. 51.

that is,

$$\beta = \frac{F}{F_{\infty}}$$

where  $F_{\infty}$  is sedimentation volume of the deflocculated suspension.

The degree of flocculation is therefore an expression of increased sediment volume resulting from flocculation. If, for example,  $\beta$  has a value of 5.0 (Fig. 13), this means that the volume of sediment in a flocculated system is five times that in the deflocculated state. If a second flocculated formulation results in a value of  $\beta$  of, say, 6.5, this latter suspension obviously is preferred if the aim is to produce as flocculated a product as possible [4].

### B. Ease of Dispersibility

Stanko and Dekay [76] first proposed the use of redispersibility to evaluate a pharmaceutical suspension. Various modifications of their basic principle have been described. Stanko and Dekay [76] placed a sedimented suspension in a 100 mL graduated cylinder and rotated it through 360° at 20 rpm. The end point was taken when the base of the graduated cylinder was free of sediment. The number of revolutions necessary to achieve the end point was recorded [76]. Matthews evaluated the above method to measure redispersibility of suspensions [77]. Dekay and Lesschaft [78] measured redispersibility by shaking in a 90° arc and not a complete revolution. The ultimate test of redispersibility is the uniformity of the suspended drug delivered from the product.

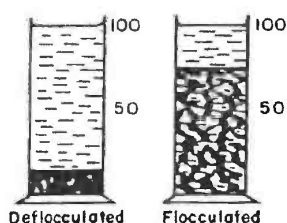
### C. Rheological Measurements and Viscosity

The viscosity of suspensions can be of particular importance, especially for a topical suspension. It is important to measure viscosity at a low shear rate to evaluate the structure achieved on storage.

Viscometers are used to measure the viscosity of high shear rate systems as well as low shear rate systems. They are divided into two types:

1. Those that operate at a single rate of shear
2. Those that allow more than one shear rate to be examined

The first type is a useful quality-control tool. However, to measure the rheological behavior of plastic, pseudoplastic, or thixotropic materials, it has limited value as it only



**Fig. 13** Sedimentation parameters of suspensions. Deflocculated suspension:  $F = 0.15$ . Flocculated suspension:  $F = 0.75$ ;  $B = 5.0$ . (From Ref. 4, p. 296. Reprinted with permission from the publisher, Mack Publishing Co., Easton, PA.)



provides a single point measurement on the rheogram. The second type of viscometer<sup>1</sup> is capable of operating at several shear rates and is therefore preferred because it develops the entire rheogram.

#### D. Zeta Potential Measurement

Zeta potential measurements are of significant importance to the physical stability of suspensions. Zeta potential can be measured in a microelectrophoresis cell. A sample of the disperse system is mounted on a special microscope slide across which a known potential is applied. The speed of movement of the particles across the field is a function of the zeta potential and is determined visually. The zetameter is a commercial micro-electrophoresis apparatus for easy, fast, and reproducible operations. This apparatus should be standardized using particles of known zeta potential [79].

#### E. Particle Size Measurement

Particle size measurements permit evaluation of aggregation or crystal growth. Any change in particle size affects the sedimentation rate, ease of redispersibility, caking, and efficacy properties of a disperse system. Commonly used techniques to estimate and detect changes in particle size are microscopy and use of the Coulter counter.<sup>1</sup> Particle size measurement can be rapid and simple or detailed and complex, depending upon the exact nature of the product.

#### F. Centrifugation

Centrifugation has been explored as a possible method of evaluating suspensions because sedimentation rate is influenced by the gravitational force. However, to date, no reliable correlation has been established to justify its application in establishing the performance or the stability of the suspension over its shelf life. However, it serves as an excellent tool to monitor batch to batch variation.

#### G. pH Measurement

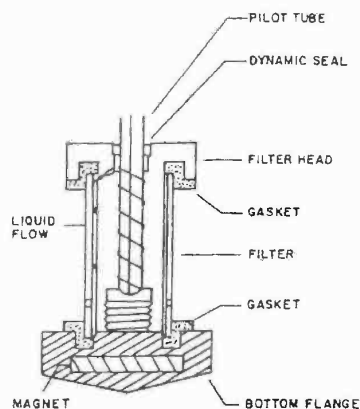
pH is an important physical parameter as some drugs exhibit maximum stability at a specific pH value, and fluctuation in pH is not desirable. The measurement of the pH value provides good control over the manufacturing process and shelf life of the product.

#### H. Density Measurement

The density measurement provides qualitative information on the amount of air entrapped in a suspension during manufacture, floating of sedimentation, and lumping of dispersed particles. These measurements provide for better product control during production. There are several methods to measure density but the most widely used employ the precision hygrometer or a pycnometer.

#### I. Dissolution

In general, most dissolution apparatuses that are used for tablets or capsules can be employed to determine the dissolution rate of drug in suspension. The USP apparatus II (paddle) has been used frequently at a rotation speed of 25 to 50 rpm [47]. However, a rotating filter apparatus by Shah [80], as shown in Fig. 14, has gained wide accep-



**Fig. 14** Rotating filter assembly. (From Ref. 80. Reproduced with permission of the copyright owner, the American Pharmaceutical Association.)

tance for suspension testing because it provides mild laminar liquid agitation and functions as an in situ nonclogging filter [46].

#### **J. Preservative Efficacy Test**

A suspension is adequately preserved if it withstands a laboratory challenge test and resists microbial insults during manufacturing and use. Preservative efficacy testing enables the formulator to ensure microbial integrity of the product. In recognition of the importance of preservative efficacy testing, several official and nonofficial guidelines have been developed such as the guidelines of the United States Pharmacopeia [49] and the guidelines of the Cosmetics, Toiletries and Fragrance Association [81].

#### **K. Safety Tests**

According to federal regulations administered by the Food & Drug Administration, pharmaceutical manufacturers must substantiate the safety of the pharmaceutical products they market and each ingredient contained in the product. The first stage of safety substantiation is preclinical toxicity testing, which includes acute oral toxicity; acute, subacute, and chronic dermal toxicity; skin irritation; eye irritation; and skin sensitization tests. These tests are performed using various species of animals, followed by human testing [81]. Each product must be individually tested for dermal toxicity, eye or skin irritation, photoallergic reaction, or other toxic side effects. To obtain information on toxicity, the test should be performed in a well-planned manner on the final product [81].

#### **X. STABILITY**

Drug stability is a critical element in the accurate and appropriate delivery of drug therapy. Both the therapeutic adequacy of treatment and safety of therapy can be ad-

versely affected by drug instability. The necessity and importance of stability testing during the development of pharmaceutical testing is well recognized, not only by regulatory agencies, but also by the pharmaceutical industry. From regulatory considerations, there are several sections of the Federal Food and Drug & Cosmetics Act that relate to the stability of drug products [83].

A New Drug Application (NDA) requires a complete description of stability studies indicating the methods of analysis for the drug substance. If the drug does not meet criteria of stability and purity, it is considered adulterated [83].

It is required that all prescription drug products for human use have an "expiration date" with storage conditions on the labels. It is also required that the company producing the drug include a written description of the testing program to cover stability characteristics of the drug substance and drug product, and that this program be followed [84].

The purpose of stability testing is to provide evidence of the quality of the drug substance or drug product, and how it varies with time under the influence of a variety of environmental conditions (heat, humidity, light, air, etc.). Information gathered from stability testing enables the establishment of recommended storage conditions, retest periods, and shelf life [85]. A good stability program exposes the weaknesses of a product, demonstrates that weaknesses can be protected by a "barrier," and demonstrates that this barrier has no effect on the safety of efficacy of the dosage form.

The diversity of topical suspensions and the complexity of stability parameters precludes the existence of simple, rigid, and universally accepted stability guidelines. No single stability protocol could reasonably be expected to ensure the quality and integrity of every topical suspension from every manufacturer.

An important document relating to the stability testing of pharmaceuticals was first developed in 1984 and later updated in 1987 [86]. The FDA guidelines for submitting documentation for the stability of human drugs and biologicals are designed to give one an understanding of the stability performance of a given product. The process begins in the early development phases and continues through registration and monitoring of a marketed product. The guidelines give common definitions, such as the following:

*Bulk drug substance:* The pharmacologically active component of drug product before formulation [87].

*Batch:* A defined quantity of product processed in a single process or series of processes, so that the resultant product could be expected to be homogeneous [87].

*Expiration date:* The date placed on the immediate container label of drug product that designates the date through which the product is expected to remain within specifications, if stored correctly [88].

*Accelerated stability testing:* Studies designed to increase the rate of chemical and physical change of a drug by using exaggerated storage conditions (elevated and below normal temperatures, heat, high humidity, and light) as part of a formal stability-testing program [88].

*Shelf life:* The period during which a pharmaceutical product, if stored correctly, is expected to comply with specifications, as determined by stability studies on a number of batches of product. The shelf life is used to establish the expiration date of each batch [89].

*Real-time stability studies:* Evaluation of experiments to determine physical, chemical, biological and microbiological characteristics of a drug product during and

beyond the expected time of shelf life and storage of samples at expected storage conditions in the intended market. The results are used to establish shelf life, as well as to confirm projected shelf life and recommended storage conditions [89].

*Stability-indicating methodology:* Quantitative analytical methods that are based on the characteristic structural, chemical, and biological properties of each active ingredient of the drug product, and that will distinguish each active ingredient from its degradation products, so that active ingredient content can be accurately measured [88]. The method should be specific, accurate, precise, reproducible, and rugged.

The guidelines include various phases of stability testing, reflecting the development of a suspension. Table 8 shows the phases and their activities.

Mounting concerns over duplication of data and continued debate over what constitutes sufficient data for registration of a pharmaceutical in different countries prompted the formation of an International Conference on Harmonization (ICH). It consists of a working group of experts from the European Community (EC), Japan, and the United States. ICH developed "The Guidelines on Stability of New Drug Substances and Products" in October 1993 [85]. Recognizing the potential of harmonization, the ICH has recommended adoption of the Guidelines by the regulatory agencies of all three Conference groups. The document has already been accepted in the EC, and is under review by the FDA and its counterpart in Japan.

Some advantages of harmonizing protocol design are:

1. Inherent simplicity for worldwide filing
2. Decreased stability testing for global products
3. Bracketing and matrix design permitted
4. Detailed photosensitivity testing

FDA guidelines, as well as the ICH Tripartite Guidelines, primarily address the information required in the registration applications for new molecular entities and associated drug products. Generally, these are prescription drug products that progress from IND status through NDA status. However, there are different storage conditions (such as the addition of RH to established temperatures) and minimum time requirements, as well as defined parameters for long-term accelerated testing for the generation of stability data required in the preparation of dossiers for registration in ICH guidelines.

Once the ICH Guidelines are adopted by the United States and Japan, the stability data generated in one country will be mutually acceptable to the EC, Japan, and the United States.

The stability testing protocols of generic and OTC products differ from studies of a product containing a New Chemical Entity (NCE). Manufacturers of generic products are not required to perform stability tests on the individual drug substances, only on the finished products. Such companies have access to (once) privileged information concerning drug substances and their stability. In reviewing an ANDA, the regulatory authorities may be able to establish a tentative shelf life for a potential product on the basis of minimal core data. The World Health Organization (WHO) has developed guidelines for stability testing of generic and OTC products for global distribution [88]. The guidelines primarily address the information required in the registration applications.

MEDA\_APTX03505708

**Table 8** Phase of Stability Testing

Protocol elements	Activities or results
<b>Preformulation [87]</b>	
Objectives	Determine any reactivities of the new drug substance Establish storage conditions and packaging requirements for the new drug substance
Study design	Short-term studies under accelerated conditions, looking for gross changes
Tests	Potency, appearance, physical properties, degradation products, etc.
Schedules	Storage conditions geared to possible degradative conditions of heat, light, moisture, oxidants, catalysts, pH, etc.
Samples	As appropriate to allow estimates of stability parameters Representative of the batch
Evaluation	Review of data to estimate relevant stability parameters
<b>Excipient Compatibility [90]</b>	
Objective	Delineate any interaction between probable formulation excipient and the drug substance
Study design	Short-term; accelerated studies designed to elucidate gross changes
Tests	Assay for potency and appearance; other tests
Storage conditions	Environment geared to probable degradative sensitivities—exaggerated heat, light, humidity, etc.
Schedules	Established on rate of degradation
Samples	Representative batch of the drug and selected excipients
Evaluation	Flexible and comparative
Study design	Short-term; accelerated studies designed to elucidate gross changes
Tests	Assay for potency and appearance; other tests
Storage conditions	Environment geared to probable degradative sensitivities—exaggerated heat, light, humidity, etc.
Schedules	Established on rate of degradation
Samples	Representative batch of the drug and selected excipients
Evaluation	Flexible and comparative

(continued)



Table 8 Continued

Protocol elements	Activities or results
<b>Toxicology [90]</b>	
Objectives	Ensure that potency and level of significant degradation products are documented throughout the life of the supplies Develop supporting data for subsequent stability studies of the formulated drug
Study design	Generally short to medium term
Tests	Assay for potency, significant degradation products and significant physical characteristics
Storage conditions	Under the same conditions as storage of clinical supplies
Schedule	More frequent testing for unstable drug
Samples	Representative of each formulation of toxicology supplies
Evaluation	Regular evaluation of data to ascertain continued suitability of the supplies, usually involving direct comparison with established criteria
<b>Formulation Comparison [89]</b>	
Objectives	Determine any physical formulation changes and significant drug substance degradation products Collect preliminary information on possible stability-limiting factors
Study design	Short-term studies under accelerated conditions, looking for gross changes
Tests	Potency, significant degradation products, physical properties, plus individual tests relevant to specific dosage forms
Storage conditions	Geared to possible degradative conditions of heat, light, moisture, etc.
Schedules	As appropriate to allow estimation of stability parameters
Samples	Representative of the batch
Evaluation	Direct comparison of raw data, comparison of rates, etc., to estimate relative stability parameters
<b>Clinical Supplies [89]</b>	
Objectives	Determine the values of the critical quality parameters of formulations utilized to establish safety and efficacy Ensure that only satisfactory material is used
Study design	Medium-term studies looking for changes in critical quality parameters
Tests	Basic attributes such as potency, significant degradation products, physical properties plus individual tests relevant to specific dosage form
Storage conditions	Conforming to label storage conditions
Schedules	More frequent for less stable formulations
Samples	Representative of each formulation and container-closure system
Evaluation	Periodic evaluation to ensure continued suitability of supplies by direct comparison to established specifications or statistical evaluation

Proposed Product [89]	
Objectives	Assess stability performance to define stability-limiting parameter factors and storage conditions Confirm degradation pathways in the market formulation Establish initial expiration-dating period
Study design	Both short-term studies at accelerated conditions and long-term studies at proposed label storage conditions
Tests	Potency, significant degradation products, physical properties, plus individual tests relevant to specific dosage form
Storage conditions	Accelerated: geared to known reactivities
Schedules	More frequent testing for less stable formulations
Samples	Representatives of the formulation and container-closure systems; the least protective container-closure should be included
Evaluation	Direct comparison of raw data with proposed standards or statistical analysis with a determined confidence level
Established Product [89]	
Objectives	Confirmation of stability performance determined in preceding stages
Study design	Long-term studies
Tests	Significant quality attributes as determined in preceding stages
Storage conditions	Consistent with the label storage conditions
Schedules	Based on relative stability of the product and the relative sensitivities of the various stability parameters
Samples	Representatives of the product Lot selection rotated among the various marketed container-closure systems
Evaluation	Periodic evaluations to allow timely decision making Evaluation by comparison of results with the established statistical profile

### A. Stability Protocol

Design of stability testing protocols varies from product to product. A good protocol should allow a degree of flexibility that encompasses a variety of different practical situations and the various characteristics of the topical suspension being evaluated.

A stability protocol should be a written document that will demonstrate trends and provide predictive power in settling the choice of storage conditions. The program should include specifications and reliable and specific test methods, sample size, test intervals, storage conditions, and number of batches. For a topical suspension, physical, chemical, and microbiological characteristics should be examined: appearance, odor, density, total drug content, uniformity of drug content, redispersibility, dissolution, sedimentation volume, crystal size, pH, rheological behavior, and preservative efficacy.

The above specifications should cover features that are susceptible to change during storage conditions and that may influence quality, safety, and efficacy of the product.

#### Test Samples

For registration purposes of the product, samples from three production batches, or two production and one pilot lot, should be tested. Batches should be representative of the manufacturing process of pilot or production scale. Where possible, batches should be manufactured using different lots of drug substance as well as excipients.

### B. Storage Test Conditions and Testing Frequency

The time length of studies and the storage conditions should be sufficient to reveal any possible instabilities caused by storage, shipment, and subsequent use. Current FDA guidelines and ICH Tripartite guidelines include different storage conditions. The details of storage conditions and testing frequency specifications are listed in Tables 9 and 10.

#### 1. Accelerated (Stress) Stability Studies

Because most pharmaceutical suspensions contain organic drugs or excipients that may degrade via oxidation, photolysis, hydrolysis, racemization, or decarboxylation, their rate

**Table 9** Current FDA Guidelines

Conditions	Storage time (months)											
	0	1	2	3	6	9	12	18	24	36	48	60
50°C		x	x	x								
40°C		x	x	x	x							
30°C	x	x	x	x	x	x	x	x	x	x	x	x
40°C & 75% RH		x	x	x								
30°C/Light		x	xx or as necessary									
Cold (2 and 8°C)				x	x		x	x		x	x	x

Cyclic Testing: Three freeze-and-thaw cycles

1. Long-term testing at 30°C with ambient RH.
2. Accelerated testing at 40°C and 75% RH with 3 months' data required for submission.

Source: Ref. 84.

Table 10 ICH Guidelines

Conditions	Storage time (months)										
	0	1	2	3	6	9	12	24	36	48	60
50°C		x	x	x							
40°C & 75% RH		x	x	x	x						
30°C & 60% RH			x	x	x	x					
25°C & 60% RH		x	x	x	x	x	x	x	x	x	x
Light		To be determined									
Temperature $\pm 2^{\circ}\text{C}$											
RH $\pm 5^{\circ}\text{C}$											
Cyclical Testing: Three freeze-and-thaw cycles											
1. Long-term testing at 25°C and 60% RH.											
2. Accelerated testing at 40°C and 75% RH with 6 months' data required for submission.											
3. 30°C and 60% RH with 12 months' data required for submission if significant changes at 40°C and 75% RH.											
4. 12-month data at 25°C and 60% RH required for submission.											

Source: Ref. 85.

of degradation can be influenced by heat, moisture, light, or air. Accelerated stability studies are designed to increase the rate of chemical or physical degradation of drugs or excipients by using exaggerated storage conditions with the purpose of determining kinetic parameters of degradation reactions and to predict the shelf life of a product at normal storage conditions. Results from accelerated stability studies help to establish inherent stability conditions [88] and support the suitability of the analytical method [85].

For suspensions, centrifugation as well as freeze-and-thaw cycles should be integral parts of stress in monitoring of crystal growth, caking, and redispersibility phenomena. Generally, for accelerated stability testing, suspensions are stored inverted and straight at 45°C or 50°C, 35°C or 40°C, room temperature or 30°C, 40°C & 75%, light and at 4°C. Additionally, they are subjected to three freeze-and-thaw cycles, and centrifuged for 30 minutes at 3000 rpm.

## 2. Microbial Stability

Topical suspensions generally contain a preservative or preservative system to control microbial contamination of the product. Preservative content should be monitored, at least at the beginning and end of the projected expiration dating period [86]. This may be accomplished by performing a chemical assay for preservatives or by performing the Antimicrobial Preservative Effectiveness Test of the USP. This includes subjecting the product to the microbial limit test, USP, which is designed to confirm the absence of pathogenic organisms in the product [86].

## 3. Analytical Methods

All analytical methods should be validated for precision, accuracy, reproducibility, and specificity and should be stability indicating. Where applicable, the standard deviation should be recorded [91].

#### 4. Stability Report

A stability profile is established for internal use, registration purposes, and so forth, detailing the design and concept of the study as well as results and conclusions. The results should be presented as tables and graphs for each batch. Testing results should be given both at the time of manufacture and at different times during storage of the product [92].

#### C. Predicting Shelf Life

The use of kinetic and predictive studies for establishing tentative expiration dates is well accepted by regulatory agencies worldwide. Techniques for estimating shelf life of a suspension from accumulated data at elevated temperatures utilizes Arrhenius' equation to extrapolate shelf life of the product at lower temperatures. Application of Arrhenius' equation only applies when the stability-limiting factor is of a chemical nature. It is not applicable for physical parameters such as caking, viscosity, or redispersibility. Usually, a product exhibiting satisfactory stability for 3 months at 50°C or 6 months at 40°C has a potential of 2 years of shelf life.

Tingstad and his coworkers [93] have developed a simplified method for determining the stability of a drug substance in a suspension. The approach is based on the assumption that degradation takes place only in solution and is of a first order rate process. Also, the effect of temperature on drug solubility and reaction rate conforms with classical theory, and dissolution is not rate-limiting for degradation [94].

A simple means of estimating shelf life using a set of computer-prepared tables is described by Lintner [95]. The method has proved to be quite reliable in predicting the shelf life of active ingredients in the product.

To make a shelf-life prediction from elevated temperatures, three or more storage temperatures are necessary. One could measure intact drug by a highly selective method, measure total drug content nonselectively and estimate the decomposition products, or selectively measure both drug and decomposition products [96]. As a general rule, the FDA accepts the data from accelerated stability testing on three pilots for a tentative expiration date of up to 2 years. Currently a product with adequate stability for 3 months at 40°C and 75% relative humidity (RH) is generally granted an expiration date of 2 years. However, if the FDA agrees with ICH guidelines, minimum stability for 6 months at 40°C and 75% RH would be required. Final determination of an expiration date is based on real-time data from several batches that have been stored at storage conditions and assayed at regular intervals per recommendation of the Food and Drug Administration. If results of a real-time study do not conform to the predictive studies, an appropriate adjustment in expiration date must be made.

#### XI. ILLUSTRATIVE EXAMPLES

This section includes a number of formulas that illustrate the use of some of the excipients discussed in this chapter.

A patent by Young includes the following examples of suspending benzoyl peroxide in a hydro-alcoholic vehicle [97]

Formula No. 1	% by weight
Benzoyl peroxide (on an anhydrous basis)	5.00
Water	57.95
Ethyl alcohol	30.00
Polyoxyethylene (9) lauryl ether	3.00
Colloidal magnesium aluminum silicate	2.50
Hydroxypropyl methylcellulose	1.50
Citric acid	0.05

PROCEDURE: Water is heated to approximately 70°C. While stirring, add the colloidal magnesium silicate to the water and continue to stir for approximately 1 1/2 hours. While continuing to stir, add the hydroxypropyl methylcellulose. Continue to stir for an additional 15 minutes. Then cool to 50°C and add the polyoxethylene [9] lauryl ether. While continuing to stir, cool to 35°C and successively add the ethyl alcohol, citric acid, and benzoyl peroxide (70%) aqueous slurry. Continue to stir for an additional 10 minutes and mill to obtain a smooth suspension of finely divided benzoyl peroxide.

Mixing may be accomplished in a stainless steel tank equipped with a propeller mixer, or preferably in a processing tank equipped with a rotorstator and paddle sweep that can be independently operated. Homogenization may be substituted for milling to obtain the final smooth dispersion.

Young's patent also illustrates the use of several other suspending agents in formulating a topical benzoyl peroxide suspension. The following are examples.

Formula No. 2	% by weight
Benzoyl peroxide (on an anhydrous basis)	15.00
Water	49.35
Ethyl alcohol	25.00
Polyoxyethylene (40) stearate	8.50
Colloidal magnesium aluminum silicate	1.50
Sodium carboxymethylcellulose	0.60
Citric acid	0.05

Formula No. 3	% by weight
Benzoyl peroxide (on an anhydrous basis)	5.00
Water	76.97
Isopropyl alcohol	10.00
Polysorbate 20	5.00
Hydroxypropyl methylcellulose	1.50
Xanthan gum	1.50
Phosphoric acid	0.03

Formula No. 4	% by weight
Benzoyl peroxide (on an anhydrous basis)	3.00
Water	68.94
Ethyl alcohol	15.00
Poloxamer 188	10.00
Hydroxypropyl methylcellulose	1.50
Guar gum	1.50
Tartaric acid	0.06



Formula No. 5	% by weight
Benzoyl peroxide (on an anhydrous basis)	15.00
Water	46.93
Ethyl alcohol	15.00
Polyoxyethylene laurate	20.00
Hydroxyethyl cellulose	2.50
Sodium carboxymethylcellulose	0.50
Citric acid	0.07

Formula No. 6	% by weight
Benzoyl peroxide (on an anhydrous basis)	7.50
Water	62.95
Isopropyl alcohol	15.00
Polyoxyethylene (20) oleyl ether	3.00
Colloidal aluminum magnesium silicate	1.00
PEG/PPG-18/4 copolymer	10.50
Citric acid	0.05

The following is an example of a topical suspension of benzoyl peroxide in an aqueous gel base in which a carbomer resin is the suspending agent.

Formula No. 7	% by weight
Water	81.50
Carbomer 940	2.00
Di-isopropanolamine	1.50
Propylene glycol	5.00
Benzoyl peroxide (on an anhydrous basis)	10.00

**PROCEDURE:** Heat the water to approximately 70°C in a stainless steel processing tank equipped with a propeller or rotor-stator mixer. Add the Carbomer 940 to the water through the eductor while mixing and continue mixing for approximately 1 hour until a lump-free suspension is obtained.

Successively add the di-isopropanolamine and propylene glycol while continuing to mix. Cool the batch to 35 to 40°C. Add the benzoyl peroxide (70%) slurry and mill or homogenize to obtain a smooth suspension.

Because this suspension does not contain alcohol, some air entrapment may occur. It is desirable to utilize a processing tank in which a vacuum can be drawn.

Although the active ingredient in this formulation has antibacterial properties it would be prudent to conduct a microbial challenge test on the finished formulation. Addition of preservative may be required.

Another carbomer resin (934) has been used to formulate a smooth nongreasy aqueous suspension of zinc oxide [98]

Formula No. 8	% by weight
Water, purified	76.0
Carbomer, 934	0.8
Sodium hydroxide (10% solution)	3.2
Zinc oxide	20.0

**PROCEDURE:** With the use of an eductor disperse the carbomer in the water. Add the sodium hydroxide solution with slow-speed agitation to minimize air-entrapment. Add the zinc oxide in the same manner. Continue mixing until homogeneous.

In order to avoid flocculation of the zinc oxide it is important to neutralize the carbomer aqueous dispersion prior to the addition of the zinc oxide.

Zinc pyrithione is the most commonly used antidandruff agent. It has very low solubility in water and therefore it is usually suspended and formulated as a cream or lotion shampoo.

Magnesium aluminum silicate is the suspending agent of choice for zinc pyrithione formulations.

Neutralized carbomer, hydroxypropyl methylcellulose, methylhydroxy ethylcellulose, cellulose gum, sodium chloride, and alkanolamides, alone or in combination, have been effectively used as thickeners in zinc pyrithione formulations.

The inclusion of EDTA and amphoteric or cationic surfactants in zinc pyrithione formulations may cause chemical instability.

If color additives are to be included in the formulation, it is desirable to use a combination that will impart a blue color, because zinc pyrithione will react with any ferric ion present to impart a blue-gray color to the formulation.

The following is a suggested formulation for a zinc pyrithione lotion shampoo:

Formula No 9	% by weight
A. Water, purified	25.40
Magnesium aluminum silicate	0.25
Cellulose gum	0.10
Zinc pyrithione (48%)	2.10
B. Disodium oleamido PEG-2 sulfosuccinate (30%)	29.00
Lanolin oil	1.00
Sodium lauryl sulfate (29%)	34.00
Lauramide DEA	7.50
C. Citric acid (0.4%)	0.25
FD&C Blue No. 1 (0.5%)	0.40
Fragrance	qs

**PROCEDURE:** Heat water to 70°C. While rapidly stirring successively add magnesium aluminum silicate, cellulose gum, and zinc pyrithione at intervals of approximately 15 minutes. Cool to approximately 45°C and return to weight by adding back any water lost by evaporation. In a separate suitable vessel, successively add the ingredients in B. While stirring heat to 40 to 45°C and stir until uniform. Add A to B while stirring and cool to 25 to 30°C. Add fragrance and color solution and stir until uniform. Add citric acid to adjust pH to approximately 7.9.

The following is a suggested formulation for a zinc pyrithione cream shampoo:

Formula No. 10	% by weight
A. Sodium lauryl sulfate paste (30%)	40.00
Lanolin oil	1.00
Glyceryl stearate	5.00
B. Water, purified	50.15
Sodium chloride	1.35
C. Zinc pyrithione (48%)	2.10
FD&C Blue No. 1 (0.5%)	0.40
Fragrance	qs

PROCEDURE: While stirring slowly, heat the ingredients of A to 70°C. Add the sodium chloride to the water (B) and heat to 70°C. When the sodium chloride is dissolved add A to B while stirring slowly. Add the zinc pyrithione (C) and continue to stir while cooling to approximately 40°C. Add color solution and fragrance and continue to stir while cooling to approximately 25°C.

Selenium sulfide is another widely used antidandruff ingredient. Because it is also virtually insoluble in water it is customarily formulated as a suspension in shampoo bases.

The following is a suggested formulation from a Baldwin and Young patent [99].

Formula No. 11	% w/v
Composition of equal parts of selenium sulfide and bentonite	5.0
Bentonite	4.0
Monobasic sodium phosphate	1.0
Glyceryl monoricinoleate	1.0
Triethanolamine lauryl sulfate	17.0
Citric acid	0.2-0.5
Fragrance	0.5
Water, purified	qs to 100.0

PROCEDURE: Wet the bentonite with water and add the triethanolamine lauryl sulfate while stirring. Successively add the glyceryl monoricinoleate and monobasic phosphate while continuing to stir. After the solution has become uniform add the selenium sulfide-bentonite powder in small increments. Continue stirring until a uniform suspension is obtained. Add the citric acid in sufficient quantity to adjust the pH of the composition to about 4.5. While continuing to stir add fragrance and bring water up to volume.

The following formulation is another example of a selenium sulfide suspension:

Formula No. 12	% by weight
Ammonium laureth sulfate (29%)	15.0
Ammonium lauryl sulfate (29%)	15.0
Citric acid	0.4
Cocamide DEA	4.0
Cocamidopropyl betaine (30%)	0.25
DMDM hydantoin (50%)	0.25
FD&C Blue No. 1 (1%)	0.04
Hydroxypropyl methylcellulose	0.4
Magnesium aluminum silicate	0.4
Fragrance	0.4
Sodium chloride	0.4
Titanium dioxide	0.5
Selenium sulfide	1.0
Water, purified	qs 100.0

PROCEDURE: Heat water to approximately 60°C. While stirring, add and disperse the magnesium aluminum silicate. When completely hydrated, slowly add the hydroxypropyl methylcellulose with continued stirring. Maintain temperature of approximately 60°C and continue to stir while successively adding the cocamide DEA, ammo-

nium laureth sulfate, ammonium lauryl sulfate, cocamidopropyl betaine, DMDM hydantoin, citric acid, sodium chloride, and FD&C No. 1 solution.

Premix the titanium dioxide and the selenium sulfide. Cool batch to approximately 45°C and add the titanium dioxide-selenium sulfide blend while stirring rapidly. Add fragrance. Process through a colloid mill.

The following is an example of an antiacne suspension.

Formula No. 13	% by weight
A. Water	80.0
Sodium carboxymethyl cellulose, LP	0.2
Sodium benzoate	0.1
Carbowax 400	3.0
B. Oleic acid	2.0
Resorcinol	1.25
C. Triethanolamine	1.5
D. Sulfur, sublimed	2.5
Color blend	5.0
E. Propylene glycol	2.0
Perfume	0.25
Antifoam 60	0.2
Sulfuric acid	2.0
F. Alcohol	11.0

PROCEDURE: Heat water to 70°C. While stirring, rapidly add ingredients A (sodium CMC, Carbowax 400, and sodium benzoate). Heat ingredients B to 70°C and add to A while stirring rapidly. Add C (triethanolamine) and slowly cool to 30°C. Add D and mix. Presolubilize perfume in propylene glycol and add to bulk. Adjust pH to 3.5. Add F at about 25 to 28°C. Homogenize or mill to form a smooth suspension.

The following is a formulation for an antidandruff suspension shampoo.

Formula No. 14	% by weight
A. Water	75.725
Disodium EDTA	0.075
Xanthan gum	0.05
Sodium lauryl ether sulfate	7.5
Disodium monolauryl ether sulfo-succinate	7.5
Coconut fatty acid diethanolamine	3.0
Imidurea	0.3
Sodium chloride	0.5
B. Propylene glycol	3.0
Perfume	0.25
Propylparaben	0.03
Methylparaben	0.1
C. Ketoconazole	2.0

PROCEDURE: Heat water to 70°C. While rapidly stirring, add xanthan gum. Cool to 50°C. While stirring slowly, add remaining ingredients of A, one after the other. Cool to 35°C. In a separate container, heat propylene glycol to 35°C and add propylparaben. Mix until a clear solution is formed. Add perfume and then add

other ingredients of B to A. Adjust pH to 6.2 to 6.8 with HCl or sodium hydroxide. Add C to the bulk and mix slowly. Homogenize to make smooth suspension.

Adapted from U. S. Patent #4,335,125 [100].

The following is an example of a sunscreen suspension.

Formula No. 15	% by weight
A. Octyl dimethyl PABA	7.0
Benzophenone	3.5
Mineral oil-lanolin alcohol	7.0
C <sub>12</sub> -C <sub>15</sub> alcohol benzoate	7.5
Stearic acid, triple pressed	2.0
B. Water	61.2
Glycerin	3.0
C. Propylene glycol	3.0
Methyl paraben	0.1
Propyl paraben	0.03
Perfume	0.25
D. Zinc oxide, micronized	2.5
Titanium dioxide, micronized	3.0

PROCEDURE: While stirring slowly, heat the ingredients of A to 70°C. Add ingredients of B, heating to 72°C, and stir vigorously for 10 minutes. Slowly cool to 35°C. Add phase C while mixing slowly. Add ingredients of D one after the other and mix for 10 minutes. Homogenize or mill to obtain smooth suspension.

#### ACKNOWLEDGMENTS

The authors wish to thank Ms. Patricia Leonard for her numerous helpful discussions and editorial assistance, and Elgie Ginsburgh and Cheryl Flynn for typing the manuscript.

#### APPENDIX

##### Instruments Discussed and Their Manufacturers

Serial No.	Description of instrument	Manufacturer
1	<sup>a</sup> Light-scattering Royco	HiAC/Royco, Ins., Pacific Scientific Silver Spring, MD
2	<sup>b</sup> Light blockage Hiac	HiAC/Royco, Ins., Pacific Scientific Silver Spring, MD
3	<sup>c</sup> Electrical conductivity Coulter Counter	Coulter Electronics, Hialeah, FL
4	<sup>d</sup> Quantasorb	Quantachrome, Inc., Syosset, NY
5	<sup>e</sup> Carbopol resins	B. F. Goodrich Cleveland, OH
6	<sup>f</sup> Colloid mill	APV Gaulin Wilmington, MA

Serial No.	Description of instrument	Manufacturer
7	<sup>a</sup> Lightnin mixer	Mixing Equipment Co. Rochester, NY
8	<sup>b</sup> Deaerator	Cornell Machine Co. Springfield, NJ
9	<sup>c</sup> Rotostator homogenizer	Cherry Burrel, Inc. Louisville, KY
10	<sup>d</sup> Viscometer, Haake	Haake, Inc. Paramus, NJ
11	<sup>e</sup> Zetameter	Zetameter, Inc. New York, NY

## REFERENCES

1. T. R. Bates, D. A. Lambert, and W. H. Johns, *J. Pharm. Sci.*, 58:1468 (1969).
2. M. C. Meyer, A. B. Straughn, and G. Ramchander, J. C. Cavagnol, and A. F. Biola Mabadeje, *J. Pharm. Sci.*, 67:1659 (1978).
3. N. Weiner, *Drug Dev. Ind. Pharm.*, 12(7):933 (1986).
4. G. Zografis, et al. Interfacial phenomena. In: *Remington's Pharmaceutical Sciences* (A. Gennaro, ed.), 18th ed., Mack Publishing Co., Easton, PA, 1990, pp. 257-270.
5. J. Rosen, Wetting and its modification by surfactants. In: *Surfactant and Interfacial Phenomenon*, John Wiley & Sons, New York, 1978, pp. 174-176, 262-269.
6. W. A. Zisman, *Advances in Chemistry*, #43, American Chemical Society, Washington, D.C., 1964, pp. 33-37.
7. E. G. Sharfin and W. A. Zisman, *J. Phys. Chem.*, 64:519 (1960).
8. J. L. Zatz, *J. Cosmet. Chem.*, 36:393 (1985).
9. *Use of Contact Angle in Surface Science*, Ramehart Inc., Technical Bulletin, TB100, Mountainlake, N.J., 1983, p. 1.
10. A. W. Adamson, *Physical Chemistry of Surfaces*, 3rd ed., John Wiley & Sons, New York, 1976, p. 342.
11. E. F. Bartell and H. H. Zuidema, *J. Am. Chem. Soc.*, 58:1449 (1936).
12. A. N. Martin, *J. Pharm. Sci.*, 50:513 (1961).
13. B. A. Haines and A. N. Martin, *J. Pharm. Sci.*, 50:228 (1961).
14. M. J. Akers and R. L. Robinson, *J. Pharm. Sci. Tech.*, 41(3):88 (1987).
15. C. T. Rhodes, Disperse systems. In: *Modern Pharmaceutics*, (G. S. Banker and C. T. Rhodes, eds.) 2nd ed., Marcel Dekker, New York, 1990, pp. 327-354.
16. B. Derjaguin and L. Landau, *Acta Physiol. Chem.*, 14:633 (1941).
17. E. J. Verwey and T. T. G. Overbeek, *Theory of Stability of Lyophobic Colloids*, Elsevier, New York (1948).
18. B. A. Matthews and C. T. Rhodes, *J. Pharm. Sci.*, 59:518 (1970).
19. W. Schneider, S. Starchansky, and A. N. Martin, *Am. J. Pharm. Educ.*, 42:280 (1978).
20. B. A. Matthews and C. T. Rhodes, *J. Pharm. Pharmacol.*, 20:204S (1968).
21. B. A. Matthews and C. T. Rhodes, *Pharm. Acta Helv.*, 45:52 (1969).
22. B. A. Matthews and C. T. Rhodes, *J. Pharm. Sci.*, 59:521 (1970).
23. B. A. Matthews and C. T. Rhodes, *J. Pharm. Sci.*, 59:1360 (1970).
24. M. P. Short and C. T. Rhodes, *Can. J. Pharm. Sci.*, 8:46 (1973).
25. B. A. Matthews, *J. Pharm. Sci.*, 62:172 (1973).
26. R. G. Wilson and B. Ecanow, *J. Pharm. Sci.*, 52:757 (1963).
27. N. K. Patel, L. Kennon, and R. S. Levinson, Pharmaceutical suspensions. In: *The Theory and Practice of Industrial Pharmacy* (H. A. Lieberman, L. Lachman and J. Kanig, eds.), 3rd ed., Lea & Febiger, Philadelphia, 1986, pp. 479-482.

MEDA\_APTX03505721



28. E. N. Hiestand, *J. Pharm. Sci.*, 53:1 (1964).
29. E. N. Hiestand, *J. Pharm. Sci.*, 61:268 (1972).
30. A. Otsuka, H. Sunada, and Y. Yonezawa, *J. Pharm. Sci.*, 62:751 (1973).
31. W. C. Liao and J. L. Zatz, *J. Soc. Cosmet. Chem.*, 31:107 (1980).
32. W. C. Liao, *J. Soc. Cosmet. Chem.*, 31:123 (1980).
33. J. L. Zatz, L. Schnitzer, and P. Sarpordar, *J. Pharm. Sci.*, 68:1491 (1979).
34. A. Felmeister, G. M. Kuchtyak, S. Kozioi, and C. J. Felmeister, *J. Pharm. Sci.*, 62:2026 (1973).
35. H. E. Reiss, Jr. and B. L. Meyer, *Science* 160:1449 (1968).
36. T. W. Healy and V. K. Lamer, *J. Phys. Chem.*, 33:149 (1982).
37. J. S. Tempio and J. L. Zatz, *J. Pharm. Sci.*, 69:1209 (1980).
38. J. S. Tempio and J. L. Zatz, *J. Pharm. Sci.*, 70:554 (1981).
39. J. L. Zatz, et al., *Int. J. Pharm.*, 9:315 (1981).
40. A. Martin, J. Swarbrick, and A. Cammarata, Rheology. In: *Physical Pharmacy*, 4th ed., Lea & Febiger, Philadelphia, 1993, pp. 387, 455-458.
41. D. A. Wadke, T. M. Serajuddin, and H. Jacobson, Preformulation testing. In: *Pharmaceutical Dosage Forms: Tablets*, Vol. 1, (H. A. Lieberman, and L. Lachman, eds.), 2nd ed., Marcel Dekker, New York, 1986, pp. 1-73.
42. E. F. Fieser and T. A. Hagen, Preformulation. In: *Theory and Practice of Industrial Pharmacy* (L. Lachman, H. A. Lieberman, and J. L. Kanig, eds.), 3rd ed., Lea & Febiger, Philadelphia, 1986, pp. 171-195.
43. T. J. Macek, *Am. J. Pharm.*, 137:217 (1965).
44. H. P. Fletcher, et al., *J. Pharm. Sci.*, 57:2101 (1968).
45. R. A. Nash, *Drug Cosmet. Ind.*, 65:97 (1965).
46. H. M. Abdou, Dissolution. In: *Remington's Pharmaceutical Sciences* (A. Gennaro, ed.), 18th ed., Mack Publishing Co., Easton, PA, 1990, pp. 600-601.
47. S. A. Kaplan, *Drug Metab. Rev.*, 1:15 (1972).
48. N. Pipel, *Chem. Process. Eng.*, 46:167 (1965).
49. United States Pharmacopeia XXIII and National Formulary XVIII, U.S. Pharmacopeial Convention, Inc., Rockville, 1995, pp. 1681, 2207.
50. *Cellulose Gums Chemical and Physical Properties*, Hercules, Inc., Wilmington (1984).
51. B. Idson and A. J. Scheer, Suspensions. In: *Problem Solver and Reference Manual*, FMC Corp., Philadelphia (1984).
52. *Methocel Cellulose Ether*, Dow Chemical Co., Midland (1988).
53. *Xanthan Gum/Keltrol/Kelzan—A Natural Biopolysaccharide for Scientific Water Control*, 5th ed., Kelco, Division of Merck & Co., Inc., San Diego.
54. J. L. Zatz, *Ind. Eng. Prod. Res. Dev.* 23:12 (1984).
55. *Carbopol® Water Soluble Resin Service Bulletin*, CP25, BF Goodrich, Cleveland (1993).
56. B. W. Barry, *Dermatological Formulations*, Marcel Dekker, New York, 1983, pp. 301-304.
57. R. J. Meyer and L. Cohen, *J. Soc. Cosmet. Chem.*, 10:143 (1959).
58. B. M. Berney and P. B. Deasy, *Int. J. Pharm.*, 3:73 (1979).
59. W. B. Swafford and W. L. Nobles, *J. Am. Pharm. Assoc.*, 16:171 (1955).
60. *Pemulen Polymeric Emulsifier #TDS114-118*, BF Goodrich Company, Cleveland (1990).
61. *Veegum Booklet*, R. T. Vanderbilt Co., Norwalk, CT (1993).
62. J. C. Symyn, *J. Pharm. Sci.*, 50(6):517 (1961).
63. G. E. Schumacher, *Am. J. Hosp. Pharm.*, 26:70 (1979).
64. P. A. Ciullo, *J. Soc. Cosmet. Chem.*, 32:275 (1981).
65. J. W. McGinity and J. L. Lach, *J. Pharm. Sci.*, 65:896 (1976).
66. J. C. Boylan, Liquids. In: *Theory and Practice of Industrial Pharmacy* (L. Lachman, H. A. Lieberman, and J. L. Kanig, eds.), 3rd ed., Lea & Febiger, Philadelphia, 1986, pp. 457-460.
67. J. Windheuser, *Bull. Parenteral Drug Assoc.*, 17:1 (1963).
68. H. N. Bhargava and A. Anaebonam, *Soap Cosmet. Chem., Specialties*, 59(10):39 (1983).

69. *Keys to Chelation*, Dow Chemical Co., Midland, 1979, pp. 49-69.
70. S. Das and B. N. Dutta, *Eastern Pharmacist*, 8:31 (1964).
71. *CTFA International Color Handbook*, 2nd ed., Cosmetic Toiletries and Fragrance Association, Washington, DC (1992).
72. S. Harder and G. Van Buskirk, Pilot plant scale-up. In: *Theory and Practice of Industrial Pharmacy* (L. Lachman, et al., eds.), 3rd ed., Lea & Febiger, Philadelphia, 1986, pp. 681-689.
73. D. T. Hansford, *Powder Tech.*, 26:119 (1980).
74. I. Tabibi, Production of dispersed delivery systems. In: *Specialized Drug Delivery Systems* (P. Tyle, ed), Marcel Dekker, New York, 1990, pp. 321-323.
75. G. A. Van Buskirk, et al., *Pharm. Res.*, 11(8):1217 (1994).
76. G. L. Stanko and H. G. Dekay, *J. Am. Pharm. Assoc., Sci. Ed.*, 47:104 (1958).
77. B. A. Matthews and C. T. Rhodes, *J. Pharm. Sci.*, 57:569 (1968).
78. C. T. Lesschaft and H. G. Dekay, *Drug Standards*, 22:155 (1954).
79. A. P. Black and A. L. Smith, *Water Works Assoc.*, 58:445 (1966).
80. A. C. Shah, C. B. Peot, and J. F. Ochs, *J. Pharm. Sci.*, 62:671 (1973).
81. *CTFA Technical Guidelines*, Cosmetics, Toiletries and Fragrance Assn., Washington, DC (1992).
82. B. Idson, *J. Pharm. Sci.*, 57:1 (1967).
83. L. Lachman, P. Deluca, and M. J. Akens, Kinetic principles and stability testing. In: *Theory and Practice of Industrial Pharmacy* (L. Lachman et al., eds.), 3rd ed., Lea & Febiger, Philadelphia, 1986, p. 778.
84. P. Guirag, AAPS Workshop on Stability Guidelines for Testing Pharmaceutical Products, Washington, DC (1994).
85. International Conference on Harmonization Steering Committee Guidelines on Stability Testing of Pharmaceuticals (1993).
86. FDA Guidelines for Submitting Documentation for the Stability of Human Drugs and Biologics, February 1987, p. 15.
87. J. T. Carstensen, Overview. In: *Drug Stability Principles and Practice*, Marcel Dekker, New York, 1990, pp. 7-9.
88. Stability of Drug Dosage Forms: World Health Organization Report, Pharm 88.82, 1988.
89. G. R. Duke, General considerations for stability testing of topical pharmaceutical formulations. In: *Topical Drug Delivery Formulations* (D. W. Osborne and A. H. Amann, eds.), Marcel Dekker, New York, 1990, pp 197-211.
90. Stability Concepts, PMA Joint OC-PDC Stability Committee Report, *Pharm. Tech.*, 8(6):42, (1984).
91. D. M. Winship and R. McCormack, Manufacturing and control requirements of the NDA and ANDA. In: *New Drug Approved Process* (RA Guarino ed.), Marcel Dekker, New York, 1993, p. 346.
92. "Guidelines on Stability Testing of Pharmaceutical Product," WHO Expert Committee 31st Report, Technical Report Series #790 (1990).
93. J. Tingstad, et al., *J. Pharm. Sci.*, 63:1361 (1973).
94. PMA's Joint OC-PDC Stability Committee, *Pharm. Tech.*, 15, (9):92-96 (1991).
95. C. J. Lintner, et al., *Am. Perfum. Cosmet.*, 85:31 (1970).
96. L. Chafetz, *Pharm. Res.*, 5(4):249 (1988).
97. H. Young, U.S. Patent #4,056,611 (1977).
98. *Carbopol Water Soluble Resin Service Bulletin* GC 36, Revised 1993, BF Goodrich, Cleveland.
99. Baldwin & Young, US Patent 2,694,669 (1954).
100. J. Heeves, L. J. J. Backx, and J. H. Mostmanf, U.S. Patent #4,335,125 (1992).

MEDA\_APTX03505723