# PHARMACEUTICAL DOSAGE FORMS

## Disperse Systems

*In Three Volumes*
VOLUME 2
Second Edition, Revised and Expanded

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3. Dissolve preservative in sufficient purified water and slowly add to step 1 with agitation.
4. Mix calamine, zinc oxide, and colorant together and suspend in step 1 with agitation.
5. Add fragrance and pass suspension through a colloid mill or homogenizer rinsing through with purified water.
6. Bring suspension to final volume with purified water.

**Formula 6** Barium Sulfate Oral Suspension

| | |
|---|---|
| Barium sulfate, microcrystals | 35.0% w/v |
| Docusate, sodium | 0.16% w/v |
| Colloidal microcrystalline cellulose | 1.5% w/v |
| Emulsifying wax NF | 2.0% w/v |
| Preservative blend | qs |
| Flavor | qs |
| Saccharin, sodium | qs |
| High fructose corn syrup (SpG = 1.41) | 20.0% w/v |
| Purified water, qs ad | 100% |

*Procedure*

1. Dissolve docusate, sodium, in a portion of purified water and thoroughly wet barium sulfate overnight.
2. Dissolve preservative blend and saccharin, sodium, in a separate portion of purified water.
3. Disperse colloidal microcrystalline cellulose and emulsifying wax in step 2 with agitation.
4. Add the barium sulfate slurry (step 1) to step 3 with agitation.
5. Add flavor and high fructose corn syrup to step 4.
6. Pass suspension through a colloidal mill or homogenizer, rinsing through with purified water.
7. Add purified water to final volume.

## V. FORMULATION OF SUSPENSIONS

During the preparation of physically stable pharmaceutical suspensions, a number of formulation components are employed to help keep the solid particles in a state of suspension (suspending agents), whereas other components are merely part of the liquid vehicle itself. These formulation components are classified as follows:

1. Components of the suspending system
   a. Wetting agents
   b. Dispersants or deflocculation agents
   c. Flocculating agents
   d. Thickeners
2. Components of the suspending vehicle or external phase
   e. pH control agents and buffers
   f. Osmotic agents

g. Coloring agents, flavors and fragances
h. Preservatives to control microbial growth
i. Liquid vehicles

Not all of the components listed above are required in each of the three types of pharmaceutical suspensions: oral, topical, and parenteral.

### A. Wetting Agents

According to Idson and Scheer [62], certain solids are readily wet by liquids, whereas others are not. The degree of wettability depends on the affinity of drugs for water, and whether the solids are hydrophilic or hydrophobic. Hydrophilic solids are easily wetted by water and can increase the viscosity of aqueous suspensions. Hydrophobic solids repel water but can be wetted by nonpolar liquids. When properly wetted, the latter usually do not alter the viscosity of aqueous suspensions. Hydrophilic solids usually can be incorporated into suspensions without the use of wetting agents. The majority of drugs in aqueous suspension are, however, hydrophobic. These are extremely difficult to suspend and frequently float on the surface of water and polar liquids due to entrapped air and poor wetting.

Wetting agents are surfactants that lower the interfacial tension and contact angle between solid particles and liquid vehicle. If, according to Hiestand [8], a wetting agent is present when the powder is added to the liquid vehicle, penetration of the liquid phase into powder will be sufficiently rapid to permit air to escape from the particles and the resulting wetted particles will either sink en masse or separate with low shear agitation. According to hydrophile-lipophile balance (HLB) theory [9], the best range for wetting and spreading by nonionic surfactants lies between 7 and 10.

A number of surfactants that may be used as pharmaceutical wetting agents are listed in Table 8. Note that the 7–10 HLB values listed in the table for optimum wetting are greater than the range normally recommended. The usual concentration of surfactant varies from 0.05% to 0.5% and depends on the solids content intended for suspension.

The use of surfactants as wetting agents will also retard crystal growth in the range of 0.05% to 0.5%. On the other hand, employing surfactants at concentrations less than about 0.05% can result in incomplete wetting. Concentrations greater than 0.5% surfactant may solubilize ultrafine particles and lead eventually to changes in particle size distribution and crystal growth.

The high HLB surfactants are also foaming agents; however, foaming is an undesirable property during wetting of a suspension formulation. In addition, the ionic types, even though claimed to be more effective at the preferred concentration range than nonionic types, are considered pH sensitive and incompatible with many excipients.

Most of the surfactants, except poloxamers, have a bitter taste that often rules against their use in oral suspensions. Nevertheless, polysorbate 80 is still the most widely used surfactant for suspension formulation because of its lack of toxicity and compatibility with most formulation ingredients. Steric stabilization of suspensions with poloxamers was reviewed by Rawlins and Kayes [63]. Nonoxynols and poloxamers were also found to be effective agents below their critical micelle concentration.

The rate of wetting is often determined by placing a measured amount of powder on the undisturbed surface of water containing a given concentration of surfactant and measuring the time required to completely wet and sink the powder. For example, Carino and Mollet [64] found the most rapid sinking time for a hydrophobic solid (SpG > 1)

**Table 8** Surfactants Used as Pharmaceutical Wetting Agents

| Surfactant | HLB[a] value | Surface tension (dynes $cm^{-1}$ at 0.1% w/v in water) | Comment |
|---|---|---|---|
| Anionic type | | | |
| docusate sodium | >24 | 41 | Bitter taste, foaming agent |
| sodium lauryl sulfate | 40 | 43 | Bitter taste, foaming agent |
| Nonionic type | | | |
| polysorbate 65 | 10.5 | 33 | Bitter taste |
| octoxynol-9 | 12.2 | 30 | Bitter taste |
| nonoxynol-10 | 13.2 | 29 | Bitter taste |
| polysorbate 60 | 14.9 | 44 | Bitter taste |
| polysorbate 80 | 15.0 | 42 | Most widely used, bitter taste |
| polysorbate 40 | 15.6 | 41 | Low toxicity, bitter taste |
| poloxamer 235 | 16 | 42 | Low toxicity, good taste |
| polysorbate 20 | 16.7 | 37 | Bitter taste |
| polyoxamer 188 | 29 | 50 | Foaming agent |

[a]Term introduced by W. Griffin to describe the hydrophilic-lipophilic balance or properties of nonionic surfactants; it has a numerical value between 1 and 20.

was at a concentration of 0.018% docusate sodium USP in water, which is above the critical micelle concentration of the surfactant. The authors also showed that wetting proceeds via liquid penetration into powder pores followed by spreading of wetted powder aggregates prior to sinking.

The addition of smaller amounts of neutral electrolyte, such as potassium chloride, has been found [65] to lower the critical micelle concentration and the interfacial tension of surfactant solutions and thus improve wetting. The resultant suspensions, however, are more susceptible to aggregate or floc formation.

Two simple tests have been devised by the paint industry for wetting agent evaluation.

1. The *wet point* method, which measures the amount of suspending vehicle required to just wet all of the powder. The reduction of the wet point by an additive, such as a wetting agent at a particular concentration, is a practical test of wettability.
2. The *flow point* method measures the amount of suspending vehicle used to achieve *pourability*, i.e., rheologic flow beyond the yield-stress value. The extent to which the flow point of a powder-vehicle system is reduced by a particular concentration of wetting agent is related to the wetting agent's ability to deflocculate the system or its ability to inhibit the buildup of networklike structures (agglomerates).

Both these test methods are best designed for high solids containing topical suspensions.

### B. Deflocculants or True Dispersing Agents

Mitsui and Takada [66] showed that the dispersibility of a powder in water depends largely on the magnitude of its surface charge and particle density, whether the powder was forcibly dispersed by applying mechanical shear or not. Deflocculating agents are polymerized organic salts of sulfonic acid of both alkyl-aryl or aryl-alkyl types that

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