Proposed New *USP* General Information Chapter, Excipient Performance ⟨1059⟩

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ABSTRACT A pharmaceutical dosage form typically consists of both active ingredient(s) and excipients, the latter of which often play a critical role in manufacturing, stability, and performance. The properties of excipients that ensure satisfactory and consistent performance often depend on the dosage form, the product, the manufacturing process, and the dosage form performance requirements. Excipient properties that are critical to dosage form performance may not be identified or specified in compendial monographs. However, general tests, procedures, and techniques may be used to evaluate the critical attributes of excipients. A recent survey conducted by the USP Excipient Expert Committees have identified industry's desire for additional information in *USP–NF* relating to excipient testing and performance (see Appendix). This *Stimuli* article presents draft General Information Chapter *Excipient Performance* ⟨1059⟩ prepared by the USP Excipient General Chapters Expert Committee. It contains sections that describe 14 of the 40 functional categories identified in *USP 30–NF 25*. Each section provides a summary of the functional mechanism as well as information about the physical and chemical properties of excipients that may be useful in ensuring consistent and desirable excipient performance. Additional sections will be added as they become available. This article seeks input from readers of *Pharmacopeial Forum* and *USP–NF* regarding the format and content of proposed ⟨1059⟩. Also included is a summary of the results of the industry survey that formed the impetus for developing this draft chapter.

INTRODUCTION

Excipients are used in virtually all drug products and are essential to product performance. Typically excipients are manufactured and supplied to comply with compendial standards. However, the development, manufacture, and performance of pharmaceutical dosage forms depend extensively upon the physical and chemical properties of the excipients. Thus, the successful manufacture of a robust product requires the use of well-defined excipients and processes that together yield a consistent product.

An excipient may have very different functional purposes (e.g., an excipient may function as a diluent, lubricant, buffer, etc.) and may fulfill various required performance characteristics (e.g., particle size, particle size distribution, surface area, etc.) depending on its use in a formulation, manufacturing process, and dosage form. The critical excipient properties that can influence product performance should therefore be evaluated and controlled to ensure that consistent product performance is achieved throughout the product's life cycle. However, not all the critical physical and chemical properties may be identified in excipient monographs via compendial tests and specifications. Because of the vast diversity of the application of excipients in product development, manufacturers must identify and control critical properties, which requires a thorough understanding of the formulation, the processing, and the physical and chemical properties of each ingredient. In addition, pharmaceutical manufacturers should anticipate lot-to-lot and supplier-to-supplier variability in excipient properties and should have in place appropriate controls to ensure consistent performance.

General Information Chapter *Excipient Performance* ⟨1059⟩ provides an overview of the key functional categories of excipients identified in *USP 30–NF 25* (*1*), along with those tests that may relate to excipient performance. It also includes test procedures that are not typically included in compendial monographs with specifications. Companies can select tests and identify appropriate specifications that are necessary to ensure consistent and reliable excipient performance only when they have a sound understanding of the function of the excipient, the manufacturing process, and the performance requirements of the dosage form.

Following are descriptions of 14 high-priority and representative functional categories that have been identified in *USP 30–NF 25*. Additional functional categories will be published as they become available. The USP Excipient General Chapters Expert Committee believes that early publication of these 14 functional categories will stimulate public discussion and contribute to the development of the remaining categories. The functional categories include lists of excipients that are commonly used to achieve the desired functionality, along with general descriptions of the excipients; discussions of the mechanisms by which the excipients achieve their activity; lists of physical properties common to these excipients; lists of chemical properties; and lists of General Chapters that may be useful as formulators develop tests and specifications relevant to the excipients in the functional categories. In some cases additional information is appended to address related topics.

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1. Functional Category: Tablet and/or Capsule Diluent

Tablet or Capsule Diluents		
Calcium Carbonate	Kaolin	Starch, Corn
Calcium Phosphate, Dibasic	Lactitol	Starch, Potato
Calcium Phosphate, Tribasic	Lactose, Anhydrous	Starch, Pregelatinized
Calcium Sulfate	Lactose, Monohydrate	Starch, Pregelatinized Modified
Cellulose, Microcrystalline	Maltitol	Starch, Tapioca
Cellulose, Powdered	Maltodextrin	Starch, Wheat
Dextrates	Maltose	Sucrose
Dextrin	Mannitol	Sugar, Compressible
Dextrose Excipient	Sorbitol	Sugar, Confectioner's
Fructose	Starch	

Description: Diluents are components that are incorporated into tablet or capsule dosage forms to increase dosage form volume or weight. Sometimes referred to as fillers, diluents often comprise a significant proportion of the dosage form, and the quantity and type of diluent selected often depends on its physical and chemical properties. Because the diluent may comprise a large portion of the dosage form, successful and robust manufacturing and dosage form performance depend on the measurement and control of these critical attributes.

Functional Mechanism: Among the most important functional roles diluents play is to impart desirable manufacturing properties (e.g., powder flow, tablet compaction strength, wet or dry granule formation, and homogeneity) and performance (e.g., content uniformity, disintegration, dissolution, tablet integrity, friability, and physical and chemical stability). Some diluents (e.g., microcrystalline cellulose) are occasionally referred to as dry binders because of the high degree of tablet strength they impart to the final compressed tablet.

Physical Properties: The primary physical properties relevant to tablet/capsule diluents are those that can have a direct effect on diluent and formulation performance. These include: (1) particle size and size distribution, (2) particle shape, (3) bulk/tapped/true density, (4) specific surface area, (5) crystallinity, (6) moisture content, (7) powder flow, (8) solubility, and (9) compaction properties for tablet dosage forms.

Chemical Properties: Tablet diluents comprise a large and diverse group of materials that include inorganics (e.g., dibasic calcium phosphate or calcium carbonate), single-component organic materials (e.g., lactose monohydrate or mannitol) and multicomponent or complex organics (e.g., microcrystalline cellulose or starch). They may be soluble or insoluble in water, and they may be neutral, acidic, or alkaline in nature. These chemical properties should be considered so formulators select diluents that will not negatively affect active ingredient physical or chemical stability and performance. Appropriate selection of excipients with desirable physical and chemical properties can enhance the physical and chemical stability as well as the performance of the active ingredient. The detailed composition of an excipient may be important because excipient function may be influenced by the presence of minor concomitant components that are essential for proper performance. Formulators may need to control the presence of undesirable components (e.g., heavy metals or peroxides) to ensure adequate dosage form stability and performance.

General Chapters: The following General Chapters may be useful when formulators are developing tests and specifications to ensure consistent excipient performance: *Bulk and Tapped Density* ⟨616⟩, *Density* ⟨699⟩, *Crystallinity* ⟨695⟩, *Crystallinity Determination by Solution Calorimetry* ⟨696⟩, *Loss on Drying* ⟨731⟩, *Water Determination* ⟨921⟩, *Optical Microscopy* ⟨776⟩, *Particle Size Distribution Estimation by Analytical Sieving* ⟨786⟩, *Light Diffraction Measurement of Particle Size* ⟨429⟩, *Powder Fineness* ⟨811⟩, *Specific Surface Area* ⟨846⟩, and *Powder Flow* ⟨1174⟩.

2. Functional Category: Tablet and/or Capsule Binder

Tablet/Capsule Binders		
Acacia	Dextrin	Polyethylene Oxide
Alginic Acid	Ethylcellulose	Povidone
Ammonio Methacrylate Copolymer	Gelatin	Starch, Corn
Ammonio Methacrylate Copolymer Dispersion	Glucose, Liquid	Starch, Potato
	Guar Gum	Starch, Pregelatinized
Carbomer Copolymer	Low-Substituted Hydroxypropyl Cellulose	Starch, Pregelatinized Modified
Carbomer Homopolymer		Starch, Tapioca
Carbomer Interpolymer	Hypromellose	Starch, Wheat
Carboxymethylcellulose Sodium	Hypromellose Acetate Succinate	Syrup
Cellulose, Microcrystalline	Maltodextrin	
Copovidone	Maltose	
Sucrose	Methylcellulose	

Description: Tablet/capsule binders are incorporated into formulations to facilitate the agglomeration of powder into granules during mixing with a granulating fluid such as water, hydroalcoholic mixtures, or other solvents. The binder may be either dissolved or dispersed in the granulation liquid or blended in a dry state with other components and the granulation liquid added separately during agitation. Following evaporation of the granulation liquid, binders typically produce dry granules that achieve the desired properties such as granule size, size distribution, shape, content, mass, and active content. Wet granulation facilitates the further processing of the granules by improving one or more granule properties such as: flow, handling, strength, resistance to segregation, dustiness, appearance, solubility, compaction, or drug release.

Functional Mechanism: Tablet/capsule binders are soluble or partially soluble in the granulating solvent or, as in the case of native starches, can be made soluble. The concentrated binder solutions also have adhesive properties. Upon addition of liquid, binders typically facilitate the production of moist granules (agglomerates) by altering interparticle adhesion. They may also modify interfacial properties, viscosity, and/or other properties. During drying they may produce solid bridges that yield significant residual dry granule strength.

Physical Properties: Dispersion or dissolution of binder in the granulation liquid depends on its physical properties: Surface tension, particle size, size distribution, solubility, and viscosity are among the more important. Homogeneous incorporation of binder into a dry blend also depends on its physical properties such as particle size, shape, and size distribution. Viscosity is often an important property to consider for binders and, for polymer, is influenced by the nature of the polymer structure, molecular weight, and molecular weight distribution. Polymeric binders may form gels.

Chemical Properties: Tablet/capsule binders may be categorized as: (1) natural polymers, (2) synthetic polymers, or (3) sugars. The chemical nature of polymers, including polymeric structure, monomer properties and sequence, functional groups, degree of substitution, and cross-linking influence the complex interactions that can occur during granulation. Natural polymers in particular may exhibit greater variation in their properties because of variations in their sources, and therefore composition.

General Chapters: The following General Chapters may be useful when formulators develop tests and specifications to ensure consistent excipient performance: *Bulk and Tapped Density* ⟨616⟩, *Crystallinity* ⟨695⟩, *Density of Solids* ⟨699⟩, *Loss on Drying* ⟨731⟩, *Particle Size Distribution Estimation by Analytical Sieving* ⟨786⟩, *Specific Surface Area* ⟨846⟩, *Viscosity* ⟨911⟩, *Powder Flow* ⟨1174⟩, and *Chromatography* ⟨611⟩.

3. Functional Category: Lubricant

Tablet and/or Capsule Lubricants		
Calcium Stearate	Sodium Lauryl Sulfate	Talc
Glyceryl Behenate	Sodium Stearyl Fumarate	Vegetable Oil, Hydrogenated, Type I
Magnesium Stearate	Starch	Zinc Stearate
Mineral Oil, Light	Stearic Acid	
Polyethylene Glycol	Stearic Acid, Purified	

Description: Lubricants are typically used to reduce the frictional forces between particles and between particles and metal contact surfaces of manufacturing equipment such as tablet punches and dies used in the manufacture of solid dosage forms. Liquid lubricants may be absorbed into the granule matrix prior to compaction. Liquid lubricants also may be used to reduce metal–metal friction on manufacturing equipment.

Functional Mechanism: Boundary lubricants function by adhering to solid surfaces (granules and machine parts) and reducing the particle–particle friction or the particle–metal friction. The orientation of the adherent lubricant particles is influenced by the properties of the substrate surface. For optimal performance, the boundary lubricant particles should be composed of small, plate-like crystals or stacks of plate-like crystals. Fluid-film lubricants melt under pressure and thereby create a thin fluid film around particles and on the surface on punches and dies in tablet presses, which helps to reduce friction. Fluid-film lubricants re-solidify after the pressure is removed. Liquid lubricants are released from the granules under pressure and also create a fluid film. However, they do not re-solidify when the pressure is removed but are reabsorbed or redistributed through the tablet matrix over the course of time.

Physical Properties: The primary physical properties that are possibly important for boundary lubricants include particle size, surface area, hydration state, and polymorphic form. Purity (e.g., stearate/palmitate ratio) and moisture content may also be important. The primary physical properties of possible importance for fluid-film lubricants are particle size and polymorphic or pseudopolymorphic form. Purity may also be important.

Chemical Properties: Lubricants can be classified as boundary lubricants, fluid-film lubricants, or liquid lubricants. Boundary lubricants are salts of long-chain fatty acids (e.g., magnesium stearate) or fatty acid esters (e.g., sodium stearyl fumarate) with a polar head and fatty acid tail. Fluid-film lubricants are solid fats (e.g., hydrogenated vegetable oil, type 1) or fatty acids (e.g., stearic acid) that melt when subjected to pressure. Liquid lubricants are liquid materials that are released from granules under pressure.

General Chapters: The following General Chapters may be useful to formulators when they develop tests and specifications to ensure consistent excipient performance: *Light Diffraction Measurement of Particle Size* ⟨429⟩, *Particle Size Distribution Estimation by Analytical Sieving* ⟨786⟩, *Specific Surface Area* ⟨846⟩, *X-ray Diffraction* ⟨941⟩, *Loss on Drying* ⟨731⟩, *Water Determination* ⟨921⟩, *Crystallinity* ⟨695⟩, ⟨696⟩ *Crystallinity Determination by Solution Calorimetry* ⟨695⟩, and *Optical Microscopy* ⟨776⟩.

Other Information: Certain lubricants, particularly those used in effervescent applications, do not fall into the chemical categories define above. However, these materials are used in specialist situations, and they are not suitable for universal application. Talc is an inorganic material that may have some lubricant properties. However, it is generally used in combination with fluid-film lubricants to reduce sticking to punches and dies.

4. Functional Category: Color

Colors listed in *USP–NF*		
Ferric Oxide, Red	Ferric Oxide, Yellow	Ferric Oxide Blends
Caramel		
Colors not listed in *USP–NF*		
FD&C Colors and Lakes	D&C Colors	Ext. D&C Colors (for external use only)

Description: Coloring agents are incorporated into dosage forms in order to produce a distinctive appearance that may serve to differentiate a particular formulation from others that have a similar physical appearance. These substances are subdivided into dyes (water-soluble substances), lakes (insoluble forms of a dye that result from its irreversible adsorption onto a hydrous metal oxide), inorganic pigments (substances such as titanium dioxide or iron oxides), and natural colorants (colored compounds not considered dyes per se, such as riboflavin). Coloring agents are subject to federal regulations, and consequently the current regulatory status of a given substance must be determined before its use.

In the Federal Food, Drug, and Cosmetic Act of 1938, three categories of coloring agents were created:

- FD&C colors: those certifiable for use in coloring foods, drugs, and cosmetics
- D&C colors: dyes and pigments considered safe in drugs and cosmetics when in contact with mucous membranes or when ingested
- Ext. D&C colors: colorants that, because of their oral toxicity, are not certifiable for use in ingestible products but are considered safe for use in externally applied products.

Functional Mechanism: Water-soluble dyes are usually dissolved in a granulating fluid for use, although they may also be adsorbed onto carriers such as starch, lactose, or sugar from aqueous or alcoholic solutions. These latter products are often dried and used as formulation ingredients. Owing to their insoluble character, lakes are almost always blended with other dry excipients during formulation. For this reason, direct-compression tablets are often colored with lakes.

Physical Properties: Particle size and size distribution of dyes and lakes can influence product processing times (blending and dissolution), color intensity, and uniformity of appearance.

Chemical Properties: The most important properties of a coloring agent are its depth of color and resistance to fading over time. Substances can be graded on their efficiency in reflecting desired colors of visible light, as well as on their molar absorptivities at characteristic wavelengths of absorbance. Obviously, the substance should be physically and chemically nonreactive with formulation ingredients and drug substances. The quality of a coloring agent is ordinarily measured by a determination of its strength, performance, or assay. The impurity profile is established by measurements of insoluble matter, inorganic salt content, metal content, and organic impurities.

General Chapters: Two General Chapters may be useful to formulators when they develop tests and specifications to ensure consistent excipient performance. Instrumental methods should be used to determine the absolute color of a coloring agent: *Color—Instrumental Measurement* ⟨1061⟩and *Light Diffraction Measurement of Particle Size* ⟨429⟩.

Other Information: Coloring agents are subject to federal regulations, and consequently the current regulatory status of a given substance must be determined before it is used. Following is a list of coloring agents and currently applicable sections of the Code of Federal Regulations (CFR).

Color	CFR
Ferric Oxides	21 CFR 73.1200
Titanium Dioxide	21 CFR 73.575 & 21 CFR 73.1575
FD&C Blue #1/Brilliant Blue FCF Aluminum Lake	21 CFR 82.51 & 21 CFR 82.101
FD&C Blue #2/Indigo Carmine Aluminum Lake	21 CFR 82.51 & 21 CFR 82.102
FD&C Red #40/Allura Red AC Aluminum Lake	21 CFR 74.340 & 21 CFR 74.1340
FD&C Yellow #5/Tartrazine Aluminum Lake	21 CFR 82.51 & 21 CFR 82.705
FD&C Yellow #6/Sunset Yellow FCF Aluminum Lake	21 CFR 82.51 & 21 CFR 82.706
D&C Yellow #10 Aluminum Lake	21 CFR 82.1051 & 21 CFR 82.1710
D&C Red #30/Helendon Pink Aluminum Lake	21 CFR 82.1051 & 21 CFR 82.1330
D&C Red #7/Lithol Rubin B Calcium Lake	21 CFR 82.1051 & 21 CFR 82.1307
D&C Red #27/Phloxine Aluminum Lake	21 CFR 82.1051 & 21 CFR 82.1327

5. Functional Category: Suppository Base

Suppository Bases		
Cocoa Butter	Hard Fat	Polyethylene Glycol

Description: Suppository bases are used in the manufacture of suppositories (for rectal administration) and pessaries (for vaginal administration). They can be hydrophobic or hydrophilic.

Functional Mechanism: Suppositories should melt at just below body temperature (37 °C), thereby allowing the drug to be released either by erosion and partition if the drug is dissolved in the base or by erosion and dissolution if the drug is suspended in the base. Hard fat suppository bases melt at approximately body temperature. Hydrophilic suppository bases also melt at body temperature and typically also dissolve or disperse in aqueous media. Thus release takes place via a combination of erosion and dissolution.

Physical Properties: The important physical characteristic of suppository bases is their melting range. In general suppository bases melt between 27 and 45 °C. However, individual bases usually have a much narrower melting range within these temperature boundaries, typically 2–3 °C. The choice of a particular melting range is dictated by the influence of the other formulation components on the melting range of the final product.

Chemical Properties: Hard fat suppository bases are mixtures of semisynthetic triglyceride esters of longer-chain fatty acids. They may contain varying proportions of mono- and diglycerides and may also contain ethoxylated fatty acids. They are available as many different grades differentiated by melting range, hydroxyl number, acid value, iodine value, solidification range, and saponification number.

Hydrophilic suppository bases are mixtures of hydrophilic semisolid materials that in combination are solid at room temperature and yet release the drug by melting, erosion, and dissolution when administered to the patient. Hydrophilic suppository bases have much higher levels of hydroxyl groups or other hydrophilic groups than do hard fat suppository bases. Typical hydrophilic suppository bases include polyethylene glycols that show appropriate melting behavior.

General Chapters: The following General Chapters may be useful to formulators as they develop tests and specifications to ensure consistent excipient performance: *Fats and Fixed Oils* ⟨401⟩*, Congealing Temperature* ⟨651⟩*, Melting Range or Temperature* ⟨741⟩*,* and *Pharmaceutical Dosage Forms* ⟨1151⟩.

Other Information: Some materials included in suppositories based on hard fats have much higher melting ranges. These materials are typically microcrystalline waxes that help stabilize molten suspension formulations. Suppositories also may be manufactured from glycerinated gelatin (n.b., the latter is not included in *USP* and thus is not listed in the table above).

6. Functional Category: Suspending and/or Viscosity-increasing Agent

Suspending and/or Viscosity-increasing Agents		
Acacia	Carbomer Homopolymer	Pectin
Agar	Carbomer Interpolymer	Polyethylene Oxide
Alamic Acid	Carboxymethylcellulose Calcium	Polyvinyl Alcohol
Alginic Acid	Carboxymethylcellulose Sodium	Povidone
Aluminum Monostearate	Carboxymethylcellulose Sodium 12	Propylene Glycol Alginate
Attapulgite, Activated	Carrageenan	Silicon Dioxide
Attapulgite, Colloidal Activated	Cellulose, Microcrystalline	Silicon Dioxide, Colloidal
Bentonite	Dextrin	Sodium Alginate
Bentonite, Purified	Gelatin	Starch, Corn
Bentonite Magma	Gellan Gum	Starch, Potato
Carbomer 910	Guar Gum	Starch, Tapioca
Carbomer 934	Hydroxyethyl Cellulose	Starch, Wheat
Carbomer 934P	Hydroxypropyl Cellulose	Tragacanth
Carbomer 940	Hypromellose	Xanthan Gum
Carbomer 941	Magnesium Aluminum Silicate	
Carbomer 1342	Maltodextrin	
Carbomer Copolymer	Methylcellulose	

Description: Suspending and/or viscosity-increasing agents are used in pharmaceutical formulations to stabilize disperse systems (e.g., suspensions or emulsions), to reduce the rate of solute or particulate transport therein, or to decrease the fluidity of liquid formulations.

Functional Mechanism(s): A number of mechanisms contribute to the dispersion stabilization or viscosity-increasing effect of these agents. The most common is the increase in viscosity—due to the entrapment of solvent by macromolecular chains or clay platelets—and the disruption of laminar flow. Other mechanisms include gel formation via a three-dimensional network of excipient molecules or particles throughout the solvent continuum and steric stabilization wherein the macromolecular or mineral component in the dispersion medium adsorbs to the surfaces of particles or droplets of the dispersed phase. The latter two mechanisms increase formulation stability by immobilizing the dispersed phase.

Physical Properties: Each of the mechanisms—increased viscosity, gel formation, or steric stabilization—is a manifestation of the rheological character of the excipient. Because of the molecular weights and sizes of these excipients, the rheological profiles of their dispersions are non-Newtonian. Dispersions of these excipients display viscoelastic properties. The molecular weight distribution and polydispersity of the macromolecular excipients in this category are important criteria for formulators to evaluate.

Chemical Properties: The majority of the suspending and/or viscosity-increasing agents in *USP–NF* are (a) hydrophilic carbohydrate macromolecules (acacia, agar, alginic acid, carbomers, carboxymethylcellulose, carrageenans, dextrin, gellan gum, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hypromellose, maltodextrin, methylcellulose, pectin, polyethylene oxide, polyvinyl alcohol, propylene glycol alginate, sodium alginate, starch, tragacanth, and xanthan gum) and (b) noncarbohydrate hydrophilic macromolecules, including gelatin and povidone. Minerals (e.g., attapulgite, bentonite, magnesium aluminum silicate, and silicon dioxide) comprise the second-largest group of suspending and/or viscosity-increasing agents in *USP–NF*. Aluminum monostearate is the one non-macromolecular, non-mineral excipient in this functional category. It consists chiefly of variable proportions of aluminum monostearate and aluminum monopalmitate.

General Chapter: The following General Chapter may be useful to formulators as they develop tests and specifications to ensure consistent excipient performance: *Viscosity* ⟨911⟩.

7. Functional Category: Ointment Base

Ointment Bases		
Caprylocaproyl Polyoxylglycerides	Ointment, White	Petrolatum, White
Diethylene Glycol Monoethyl Ether	Ointment, Yellow	Rose Water Ointment
Lanolin	Oleoyl Polyoxylglycerides	Squalane
Lauroyl Polyoxylglycerides	Polyethylene Glycol Monomethyl Ether	Stearoyl Polyoxylglycerides
Linoleoyl Polyoxylglycerides	Petrolatum	Vegetable Oil, Hydrogenated, Type II
Ointment, Hydrophilic	Petrolatum, Hydrophilic	

Description: An ointment is a viscous semisolid preparation used topically on a variety of body surfaces. An ointment base is the major component of an ointment and controls its physical properties.

Functional Mechanism: Ointment bases serve as vehicles for topical application of medicinal substances and also as emollients and protective agents for skin.

Physical Properties: Ointment bases are liquids with a relatively high viscosity so that solids may be suspended as a stable mixture.

Ointment bases are classified as:

- Oleaginous ointment bases that are anhydrous, do not absorb water readily, are insoluble in water, and are not removable by water (e.g., paraffins)
- Absorption ointment bases that are anhydrous and absorb some water but are insoluble in water and are not water removable (e.g., wool fat)
- Emulsion ointment bases that are water/oil or oil/water emulsions and are hydrous, absorb water, and are insoluble in water (e.g., creams of water, oils, waxes, and/or paraffins)
- Water soluble ointment bases that are anhydrous and absorb water and are soluble in water and are water removable (e.g., polyethylene glycol)

Chemical Properties: Ointment bases are selected to be inert and chemically stable.

General Chapter: The following General Chapter may be useful to formulators when they develop tests and specifications to ensure consistent excipient performance: *Viscosity* ⟨911⟩.

8. Functional Category: Glidant and/or Anticaking Agent

Glidant and/or Anticaking Agents	
Calcium Silicate	Silicon Dioxide, Colloidal
Magnesium Silicate	Talc

Description: Glidants and anticaking agents are used to promote powder flow and to reduce the caking or clumping that can occur when powders are stored in bulk. In addition, glidants and anticaking agents reduce the incidence of bridging during the emptying of powder hoppers and during powder processing.

Functional Mechanism: Glidants probably work by a combination of adsorption onto the surface of larger particles and reduction of particle–particle adhesive and cohesive forces, thus allowing particles to move more easily relative to one another. In addition, glidants may be dispersed between larger particles and may thus reduce friction between larger particles. Anticaking agents probably work by absorbing free moisture that otherwise would allow the development of particle–particle bridges that are implicated in caking phenomena.

Physical Properties: Primary physical properties of potential importance for glidants and anticaking agents are particle size, particle size distribution, and surface area. They may be slightly hygroscopic.

Chemical Properties: Glidants and anticaking agents typically are finely divided inorganic materials. They are insoluble in water but are not hydrophobic. Some of these materials are complex hydrates.

General Chapters: The following General Chapters may be useful to formulators who develop tests and specifications to ensure consistent excipient performance: *Light Diffraction Measurement of Particle Size* ⟨429⟩, *Particle Size Distribution Estimation by Analytical Sieving* ⟨786⟩, *Specific Surface Area* ⟨846⟩, *Loss on Drying* ⟨731⟩, and *Water Determination* ⟨921⟩.

9. Functional Category: Surfactant (Emulsifying, Wetting, and/or Solubilizing Agent)

Emulsifying, Wetting and Solubilizing Agents		
Acacia	Mono- and Diglycerides	Polysorbate 60
Benzalkonium Chloride	Monoethanolamine (Adjunct)	Polysorbate 80
Benzethonium Chloride	Nonoxynol 9	Propylene Glycol Monostearate
Carbomer Copolymer	Octoxynol 9	Sodium Cetostearyl Sulfate
Carbomer Interpolymer	Oleic Acid (Adjunct)	Sodium Lauryl Sulfate
Cetylpyridinium Chloride	Oleyl Alcohol (Stabilizer)	Sodium Stearate
Cholesterol	Poloxamer	Sorbitan Monolaurate
Diethanolamine (Adjunct)	Polyoxyethylene 50 Stearate	Sorbitan Monooleate
Diethylene Glycol Stearates	Polyoxyl 10 Oleyl Ether	Sorbitan Monopalmitate
Docusate Sodium	Polyoxyl 20 Cetostearyl Ether	Sorbitan Monostearate
Ethylene Glycol Stearates	Polyoxyl 35 Castor Oil	Sorbitan Sesquioleate
Glyceryl Distearate	Polyoxyl 40 Hydrogenated Castor Oil	Sorbitan Trioleate
Glyceryl Monolinoleate	Polyoxyl 40 Stearate	Stearic Acid
Glyceryl Monooleate	Polyoxyl Lauryl Ether	Trolamine
Glyceryl Monostearate	Polyoxyl Stearyl Ether	Tyloxapol
Lanolin Alcohols	Polysorbate 20	Wax, Emulsifying
Lecithin	Polysorbate 40	

Description: Surfactants, or surface-active agents, are amphiphilic molecules that contain both a polar and nonpolar region. Surfactants have diverse functionality and serve as emulsifying, wetting, or solubilizing agents in pharmaceutical dosage forms and delivery systems. Other diverse materials, including, but not limited to suspending and/or viscosity-increasing agents, have been used to facilitate emulsion formation or to stabilize emulsion systems. The latter materials, in contrast to surfactants, are sometimes referred to as secondary emulsifiers or emulsion stabilizers.

Functional Mechanism: The amphiphilic nature of surfactants is responsible for two important properties of these compounds that account for a variety of interfacial phenomena: One is the ability of surfactant molecules to adsorb at gas–liquid, liquid–liquid, and solid–liquid interfaces, thereby reducing interfacial tension. The other is their tendency to self-associate and form aggregates or micelles when the surfactant concentration exceeds the critical micelle concentration. The ability of amphiphiles to reduce interfacial tension is critical to emulsification and wetting, and aggregation or micelle formation enables the solubilization of lyophobic compounds. Secondary emulsifiers such as lyophilic macromolecules or finely divided solids may accumulate or adsorb at an interface, thereby forming condensed films that are more mechanically stable and resistant to coalescence.

Physical Properties: The hydrophile–lipophile balance (HLB) number, often used to describe surfactant functionality, particularly in emulsion systems, is influenced by the presence of other adjuvants, temperature, surfactant concentration, emulsion phase volume, the nature of the immiscible phase, and the processing method. The HLB concept was originally developed to characterize polyoxyethylene-based surfactants but has been extended to a broader array of surfactant molecules. Nonetheless, surfactants with an HLB ranging from 0 to10 are characterized as lipophilic surfactants and are used for their antifoaming or water-in-oil emulsifying properties. Surfactants with an HLB ranging from 10 to 20 are characterized as hydrophilic surfactants and often serve as emulsifiers for oil-in-water systems. Other important physical properties include pH of aqueous surfactant dispersions, saponification value, acid value, and trace impurity levels (such as heavy metals and organic volatile impurities).

Chemical Properties: Surfactants may be classified on the basis of charge and chemical structures: Anionic surfactants carry a negative charge in the hydrophilic part and often contain carboxylate (calcium and sodium stearate), sulfate (sodium lauryl sulfate), or sulfonate (docusate sodium) ions. Cationic surfactants, typified by quaternary ammonium salts (e.g., benzalkonium chloride or cetrimonium bromide), are infrequently used as emulsifying agents because of potential tissue irritation. They are, however, often used as preservatives because of their bactericidal properties. Nonionic surfactants have many pharmaceutical applications because of their nonionic character, their low toxicity, and their ability to solubilize poorly soluble compounds. Nonionic surfactants can be further classified based on their chemical structure: a) polyol esters, which can be subdivided into glycols and glycerol esters (glyceryl stearate or propylene glycol stearate) and sorbitan derivatives (sorbitan monolaurate, monooleate and monostearate, or polysorbate-20, -60, and -80); b) polyoxyethylene esters [polyoxyl esters or macrogol esters such as polyethylene glycol–40 (PEG-40)] and ethers; c) poloxamers (poloxamer 188 and 407); and d) sucrose esters. Other surfactants include amphoteric molecules and biomolecules such as bile salts, cholesterol, and phospholipids (e.g., lecithins). The heterogeneity of secondary emulsifiers precludes characterization based on charge and chemical structure alone.

General Chapters: The following General Chapters may be useful to formulators who develop tests and specifications to ensure consistent excipient performance: *pH* ⟨791⟩*, Saponification Value* ⟨401⟩*,* and *Acid Value* ⟨401⟩.

10. Functional Category: Plasticizer

Plasticizers		
Acetyltributyl Citrate	Diethyl Phthalate	Sorbitol Sorbitan Solution
Acetyltriethyl Citrate	Glycerin	Triacetin
Castor Oil	Polyethylene Glycol	Tributyl Citrate
Diacetylated Monoglycerides	Polyethylene Glycol Monomethyl Ether	Triethyl Citrate
Dibutyl Sebacate	Propylene Glycol	Chlorbutanol*
Sorbitol*	Benzyl Benzoate*	Other solvents*
Dextrin*	Water*	

* Additional plasticizers for consideration are listed in texts such as the *Handbook of Pharmaceutical Excipients* and the *Handbook of Pharmaceutical Additives Handbook* (Rowe RC, Sheskey PJ, Owen SC eds. *Handbook of Pharmaceutical Excipients*. 5th ed. Chicago: Pharmaceutical Press; 2006; Ash M, Ash I eds. *Handbook of Pharmaceutical Additives*. 3rd ed. Endicott, NY: Synapse Information Resources; 2007).

Description: A plasticizer is a low molecular weight substance that, when added to another material—usually a polymer—makes the latter flexible, resilient, and easier to handle. Modern plasticizers are synthetic organic chemicals, the majority of which are esters such as citrates and phthalates. They are key components that determine the physical properties of polymeric pharmaceutical systems such as tablet film coatings and capsule shells.

Functional Mechanism: Plasticizers function by increasing the inter- and intramolecular mobility of the macromolecules that comprise polymeric materials. They achieve this by interfering with the normal inter- and intramolecular bonding mechanisms in such systems. The most effective plasticizers exert their effect at low concentrations, typically less than 5% w/w. Plasticizers commonly are added to film coatings (aqueous and nonaqueous systems) and capsule shells (hard and soft varieties) to improve their workability and mechanical ruggedness. Without the addition of plasticizers such materials can split or fracture prematurely. Plasticizers are also added to semisolid pharmaceutical preparations such as creams and ointments to enhance their rheological properties.

Physical Properties: The most common plasticizers are low molecular weight (<500 Da) solids or liquids. They typically have low melting points (<100 °C) and can be volatile (i.e., exert an appreciable vapor pressure) at ambient temperature. Plasticizers can significantly reduce the glass transition temperature of the system to which they are added

Chemical Properties: As noted, many modern plasticizers are synthetic esters such as citrates and phthalates. Traditional pharmaceutical plasticizers include oils, sugars, and their derivatives.

General Chapters: The following General Chapters may be useful to formulators who develop tests and specifications to ensure consistent excipient performance: *Melting Range or Temperature* ⟨741⟩*, Water Determination* ⟨921⟩*, Residual Solvents* ⟨467⟩*, Specific Gravity* ⟨841⟩*, Refractive Index* ⟨831⟩*,* and *Thermal Analysis* ⟨891⟩

Other Information: The choice of an appropriate plasticizer often is guided by reference to its ''solubility parameter,'' which is related to its cohesive energy density. Solubility parameter values for many common materials are tabulated in standard reference texts. To ensure maximum effectiveness the solubility parameter of the plasticizer and the polymeric system being plasticized should be matched as closely as possible.

11. Functional Category: Tonicity Agent

Tonicity Agents		
Dextrose	Mannitol	Sodium Chloride
Glycerin	Potassium Chloride	

Description: To avoid crenation or hemolysis of red blood cells and to mitigate pain and discomfort if solutions are injected or introduced into the eyes and nose, solutions should be made isotonic. This means that the effective osmotic pressure of solutions for injection is approximately the same as that in the blood. When drug products are prepared for administration to membranes such as eyes or nasal or vaginal tissues, etc., the formulator should ensure that solutions are isotonic with respect to these tissues.

Functional Mechanism: Tonicity is the effective osmolality. It is equal to the sum of the concentrations of the solutes that have the capacity to exert an osmotic force across a membrane. Tonicity applies to the impermeant solutes within a solvent—in contrast to osmolarity, which takes into account both permeant and impermeant solutes. For example, urea is a permeant solute, meaning it can pass through the cell membrane freely and is not factored when one determines the tonicity of a solution. In contrast NaCl is impermeant and cannot pass a membrane without the help of a concentration gradient and will therefore contribute to a solution's tonicity.

Physical Properties: Solutions of sodium chloride, dextrose, and Lactated Ringer's are common examples of pharmaceutical preparations that contain tonicity agents. Not all solutes contribute to the tonicity, which in general depends only on the number of solute particles present in a solution, not the kinds of solute particles. For example, mole for mole, sodium chloride solutions display a higher *osmotic pressure* than do glucose solutions of the same molar concentration. This is because when glucose dissolves it remains one particle, but when NaCl dissolves, it becomes two particles: Na^+ and Cl^-.

Chemical Properties: Tonicity agents may be present as ionic and/or nonionic types. Examples of ionic tonicity agents are alkali metal or earth metal halides such as $CaCl_2$, KBr, KCl, LiCl, NaI, NaBr or NaCl, Na_2SO_4, or boric acid. Nonionic tonicity agents include, e.g., glycerol, sorbitol, mannitol, propylene glycol, or dextrose.

General Chapters: The following General Chapters may be useful to formulators who develop tests and specifications to ensure consistent excipient performance: *Injections* ⟨1⟩*, Biotechnology-Derived Articles—Product Formulation* ⟨1045⟩*, Pharmaceutical Dosage Forms—Ophthalmic Preparations* ⟨1151⟩*,* and *Pharmaceutical Calculations in Prescription Compounding* ⟨1160⟩.

12. Functional Category: Sweetening Agent

Sweetening Agents		
Acesulfame Potassium	Maltitol	Sucralose
Aspartame	Maltose	Sucrose
Aspartame Acesulfame	Mannitol	Sugar, Compressible
Dextrates	Saccharin	Sugar, Confectioner's
Dextrose	Saccharin Calcium	Syrup
Dextrose Excipient	Saccharin Sodium	Tagatose
Fructose	Sorbitol	
Galactose	Sorbitol Solution	

Description: Sweetening agents are used to sweeten oral dosage forms and to mask unpleasant flavors.

Functional Mechanism: Sweetening agents bind to receptors on the tongue that are responsible for the sensation of sweetness. The longer the sweetener molecule remains attached to the receptor, the sweeter the substance is perceived to be. The standard for sweetness is sucrose.

Physical Properties: The primary physical properties relevant to sweeteners relate to their compatibility with the other ingredients in the formulation (e.g., acidic ingredients), processing conditions (e.g., heating), particle size and distribution, moisture content, isomerism, sweetness, and taste-masking capability, which may be formulation dependent.

Chemical Properties: Sweeteners can be divided into 3 main groups: sugars (which have a ring structure), sugar alcohols (sugars that do not have a ring structure), and artificial sweeteners. All sweeteners are water soluble. The stability of many sweeteners is affected by pH and other ingredients in the formulation. Some sweeteners may catalyze the degradation of some active ingredients, especially in liquids and in cases when the manufacturing processes involve heating.

General Chapters: The following General Chapters may be useful to formulators who develop tests and specifications to ensure consistent excipient performance: *Optical Rotation, Specific Rotation* ⟨781⟩*, Water Determination* ⟨921⟩*, Loss on Drying* ⟨731⟩, and *Melting Range* ⟨741⟩.

Other Information: Products that contain aspartame must include a warning on the label stating that the product contains phenylalanine.

Sugar alcohols have a glycemic index well below that of glucose. However, sorbitol is slowly metabolized to fructose and glucose, which raises blood sugar levels. Sugar alcohols in quantities generally greater than 20 g/d act as an osmotic laxative, especially when they are contained in a liquid formulation.

Preservative systems should be carefully chosen to avoid incompatibility with the sweetener—some sweeteners are incompatible with certain preservatives.

13. Functional Category: Coating Agent

Coating Agents		
Ammonio Methacrylate Copolymer	Ethylcellulose	Methylcellulose
Ammonio Methacrylate Copolymer Dispersion	Ethylcellulose Aqueous Dispersion	Polyethylene Glycol
Carboxymethylcellulose, Sodium	Gelatin	Polyvinyl Acetate Phthalate
Cellaburate	Glaze, Pharmaceutical	Shellac
Cellacefate (formerly Cellulose Acetate Phthalate)	Hydroxypropyl Cellulose	Starch, Pregelatinized Modified
Cellulose Acetate	Hypromellose	Sucrose
Cellulose Acetate Phthalate (see Cellacefate)	Hypromellose Acetate Succinate	Titanium Dioxide
Copovidone	Hypromellose Phthalate	Wax, Carnauba
	Maltodextrin	Wax, Microcrystalline
	Methacrylic Acid Copolymer	Zein
	Methacrylic Acid Copolymer Dispersion	

Description: Reasons for coating pharmaceutical drug delivery systems include masking unpleasant tastes or odors, improving ingestion, improving appearance, protecting active ingredients from the environment, controlling the rate of release of the active ingredient, and controlling drug release in the gastrointestinal tract (by means of enteric coating). The materials used in coating systems include natural and synthetic or semisynthetic materials. All the materials applied have been prepared for use in a highly purified state. Some coating materials are used as colloidal dispersions. Titanium dioxide, an inorganic compound, is used in coatings as an opacifier.

Functional Mechanism: The coating system forms a layer on the substrate, e.g., a particle or unit dosage form, and changes its appearance. On contact with the aqueous secretions of the gastrointestinal tract, the coating makes the product slide more easily over mucosal surfaces and helps control the rate and site of drug release. Coating materials

must have the ability to form a complete and stable film or coating around the product. The coating material must be applied uniformly and must dry at the proper evaporative rate. The coating system must spread out or coalesce to form a smooth film. This is most important for all polymeric materials, whether they are derived from natural or synthetic sources. Some of the coating materials listed are designed for polishing the final surface, and they also must form a complete film for application.

Physical Properties: The necessary physical properties for a coating system include adequate mechanical strength. The film must be strong enough to withstand tumbling during the coating process and to resist film erosion. The solubility of the coating material must be adequate in either aqueous or nonaqueous solvents, depending on the nature of the material. Coating systems that are aqueous dispersions must retain their uniformity during coat formation. Enteric coating materials must retain their integrity in gastric acid.

Chemical Properties: The materials used as coating systems have different chemical natures that vary from natural products to various cellulosic derivatives. The purity of both types of materials must be closely monitored, as noted in the official monographs. Solid–solid interactions may take place between the pharmaceutical product and the coating, necessitating preformulation studies to ensure compatibility. For example, trace acid content from a coating may interact with the surface of a susceptible drug substance.

General Chapters: The following General Chapters may be useful to formulators who develop tests and specifications to ensure consistent excipient performance: *Residual Solvents* ⟨467⟩, *Heavy Metals* ⟨231⟩, *Bulk and Tapped Density* ⟨616⟩, *Density* ⟨699⟩, *Crystallinity* ⟨695⟩, *Loss on Drying* ⟨731⟩, *Water Determination* ⟨921⟩, *Particle Size Distribution Estimated by Analytical Sieving* ⟨786⟩, *Powder Fineness* ⟨811⟩, *Gel Strength of Gelatin* ⟨1081⟩, *Intrinsic Dissolution* ⟨1087⟩, *Phase-Solubility Analysis* ⟨1171⟩, and *Powder Flow* ⟨1174⟩.

14. Functional Category: Pharmaceutical Water

Pharmaceutical Waters	
Purified Water (PW)	Bacteriostatic WFI
Sterile PW	Water for Hemodialysis
Water for Injection (WFI)	Sterile Water for Inhalation
Sterile WFI	Sterile Water for Irrigation

Description: Water is used as a solvent, vehicle, diluent, or filler for many drug products, especially those supplied in liquid form. These can include injectable drugs, ophthalmic drugs, oral solutions, inhalation solutions, and others. Water is also a vehicle for buffers and antimicrobial agents and is a volume expander for infusion solutions. Its use in dosage form preparation also can include granulation preparation for solid oral dosage forms and applications in the preparation of ointments and gels.

USP includes monographs for eight grades of pharmaceutical waters. One of these types of *USP* water is always the water of choice when formulators prepare a pharmaceutical dosage form for human or animal use. However, *USP* also contains references to other types of water, such as distilled water, deionized water, etc. according to its specific use as summarized in General Information Chapter *Water for Pharmaceutical Purposes* ⟨1231⟩.

Functional Mechanism: A solvent is able to dissolve materials because it is able to disrupt the intermolecular attractive forces and to allow the individual molecules to become dispersed throughout the bulk solvent. Water is a favored solvent and vehicle in the majority of applications because it is easy to handle, safe, and inexpensive.

Physical Properties: Water is liquid at normal temperature and pressure. It forms ice at the freezing temperatures of 0 °C or lower and it vaporizes at a normal boiling temperature of 100 °C, depending upon atmospheric pressure. Vaporized water in the form of steam is used for sterilization purposes because the latent heat of steam is significantly higher than that of boiling water.

Chemical Properties: Water in its pure form is neutral in pH and has very low conductivity and Total Organic Carbon (TOC). However, pH, conductivity, and TOC are affected by storage conditions and exposure of water to gases in the air. Exposure of water to atmospheric CO_2 lowers the pH of water. Storage of water in plastic containers may increase the TOC content of water over time. Water stored in glass containers may result in an increase in pH and conductivity of water over time.

General Chapters: The following General Chapters may be useful to formulators who develop tests and specifications to ensure consistent excipient performance: *Injections* ⟨1⟩, *Water for Pharmaceutical Purposes* ⟨1231⟩, *Water for Health Applications* ⟨1230⟩, *Bacterial Endotoxin Test* ⟨85⟩, *Total Organic Carbon* ⟨643⟩, and *Water Conductivity* ⟨645⟩.

REFERENCE

1. USP. *USP 30–NF 25, Excipient Performance* ⟨1059⟩. USP, Rockville, MD: 2007; 1045–1049.

APPENDIX: EXCIPIENT MONOGRAPHS AND PERFORMANCE TESTING SURVEY CONDUCTED AT THE USP 2005 ANNUAL SCIENTIFIC MEETING, SEPTEMBER 2005, SAN DIEGO, CA

Approximately 75 Respondents

Demographics	
Research-based Pharmaceutical Companies	33%
Generic Pharmaceutical Companies	9%
OTC Manufacturers	3%
Nutraceutical Manufacturers	4%
Excipient Manufacturers	29%
Excipient Distributors	7%
Academia	3%
Regulatory	0%
Compendial	1%
Other	10%

Primary Responsibility

Formulation	Analytical	Regulatory	Other
21%	24%	26%	29%

	Agree	Disagree	Did Not Respond
1. Do current excipient monographs need revision?	52	13	10
1a. Do the following areas require revision?			
Existing Acceptance Criteria (AC)	35	20	20
1b. Test methods	62	10	3
1c. Reduce number of unnecessary methods?	68	5	2
2. Should methods (but not AC) be added to distinguish grades of excipients?	44	29	2
3a. Will Question #2 above help users address: Manufacturing process variability or reliability?	39	32	4
3b. Lot-to-lot variability?	38	35	2
3c. Multisource excipients?	44	22	9
3d. Other?	0	3	72
4. Should AC be included with test methods in excipient monographs?	55	16	4
5a. How will additional test methods impact excipient supply and suppliers? Increase excipient cost?	63	10	2
5b. Increase number of excipient suppliers?	25	46	4
5c. Improve excipient quality?	45	30	0
5d. Facilitate communication between supplier and user?	49	22	4
5e. Increase competition between suppliers?	36	33	6
6. Should additional tests (not AC) that relate to excipient function (sometimes called functionality) such as lubricity, compressibility, or disintegrant efficiency be included in monographs?	35	40	0
7. Would a *USP* general information chapter discussing excipient characterization, including functionality, be beneficial?	62	12	1
8. Would it be desirable to include functionality tests as General Chapters but not include them in monographs unless they were needed to differentiate between different grades of the same excipient?	57	16	2
11. How would additional excipient test methods in USP be beneficial?			
11a. Improve excipient quality?	43	23	9
11b. Simplify regulatory filings?	40	30	5
11c. Decrease drug product costs?	18	47	10
11d. Increase drug product quality?	37	25	13

11e. Do you currently test excipients to distinguish grades?

Yes	No	Don't Know	Other
34	18	N/A	20

11f. For your specific needs, would you pay to have additional tests done by the excipient supplier?

27	10	N/A	36

11g. If there are additional tests included in excipient monographs to distinguish grades, would you do the tests or pay to have them done?

Do Test	Pay	Don't Know	Other
36	10	22	10

13. How many excipients does your Company/Division multisource?

Answered	No Response	Don't Know	Other
28	8	25	11

14. How many different excipients/grades does your Company/Division routinely hold in stock?

Answered	No Response	Don't Know	Other
30	9	24	10

15. Does your Company purchase custom grades (i.e., grades specifically produced for your Company and not generally available in the market) of any excipient?

Yes	No	Don't Know	Other
22	24	18	9

16. Are the terms *additive, impurity, processing aid, concomitant component, contaminant,* and *co-processing* adequately defined?

Yes	No	Don't Know	Other
11	30	23	11